Genetic Determinants of Antiplatelet Therapy

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Disclosures

Research Grants/Support

Pozen

AstraZeneca

Nanosphere

Accumetrics

Helena

Multiplate

Portola

Daiichi

Honoraria/Consulting

Pozen

Novartis

Bayer

AstraZeneca

Eli Lilly

Accumetrics

Nanosphere

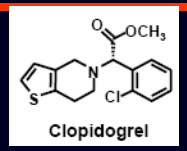
Sanofi Aventis

Boehringer

Merck

Medtronic

Metabolism of $P2Y_{12}$ Receptor Blockers: Clopidogrel



P-Glycoprotein

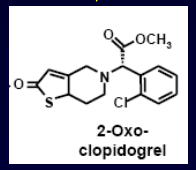
Intestinal Absorption

h-Esterase

85%

15%

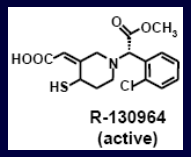
Inactive metabolite



2C19
1A2
2B6

2 Step Hepatic CYP Conversion

PON-1 ?



2C19
2C9
3A4
2B6

Variable and inefficient active metabolite generation

Slow, Variable IPA

Gurbel PA et al. *Curr Opin Investig Drugs.* 2008;9:324-36. Gurbel PA et al. *Expert Opin Pharmacother*. 2010;11:2251-9.

Pharmacogenomics-CYP2C19 Common SNP's

***17* = Gain-of- Function SNP**
(~34% Caucasians, 30% African Americans, 4% Asians)

***2*,*3 = Loss-of- Function SNP**
(~25% Caucasians, ~33% African Americans, ~55% Asians)

***1* = Wild type**

Common *CYP2C19* Genotypes	Phenotypes	
*17/*17 *17/*1	Extensive Metabolizer (EM)	34% Caucasians, 30 % African Americans, 4% Asians
*1/*1 *17/*2	Normal Metabolizer (NM)	
*1/*2	Intermediate Metabolizer (IM)	24% Caucasians, 30% African Americans, 46% Asians,
*2/*2	Poor Metabolizer (PM)	2% Caucasians, 3.5% African Americans, 10% Asians

Gurbel PA et al. *Am Heart J.* 2011;161:598-604.;Beitelshees AL et al. *Clin Ther.* 2011:89:455-459

Influence of Genetics

FDA Drug Safety Communication: Reduced effectiveness of Plavix (clopidogrel) in patients who are poor metabolizers of the drug

PLAVIX (clopidogrel bisulfate) tablets
Initial U.S. Approval: 1997

WARNING: DIMINISHED EFFECTIVENESS IN POOR METABOLIZERS

See full prescribing information for complete boxed warning.

- **Effectiveness of Plavix depends on activation to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19. (5.1)**
- **Poor metabolizers treated with Plavix at recommended doses exhibit higher cardiovascular event rates following acute coronary syndrome (ACS) or percutaneous coronary intervention (PCI) than patients with normal CYP2C19 function. (12.5)**
- **Tests are available to identify a patient's CYP2C19 genotype and can be used as an aid in determining therapeutic strategy. (12.5)**
- **Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers. (2.3, 5.1)**

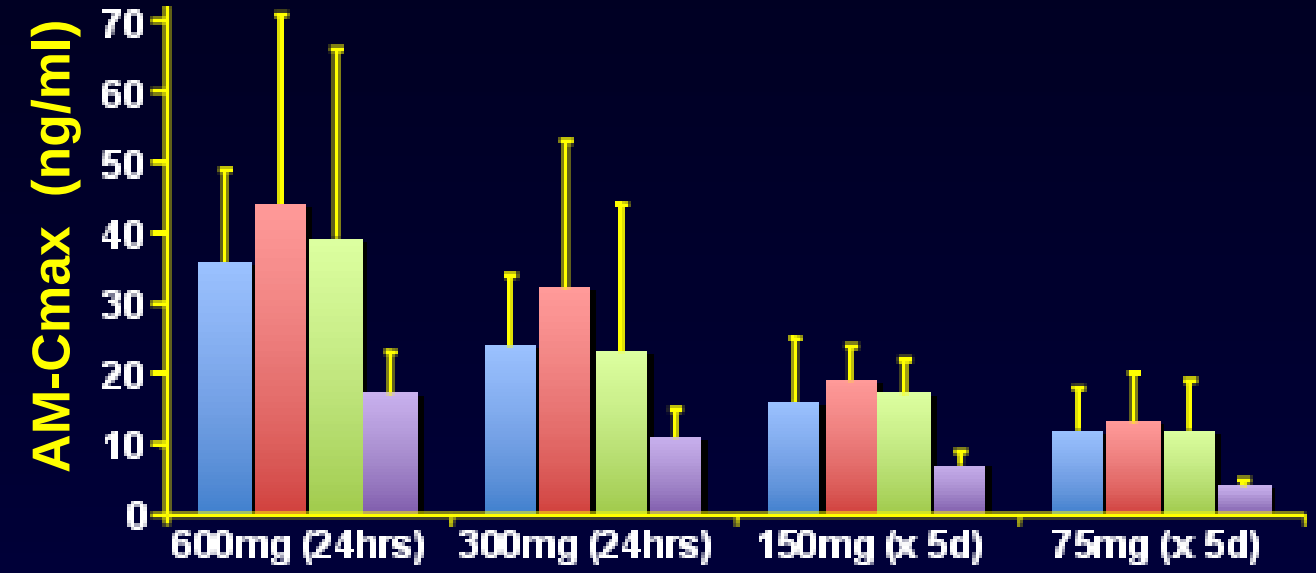
----------RECENT MAJOR CHANGES----------

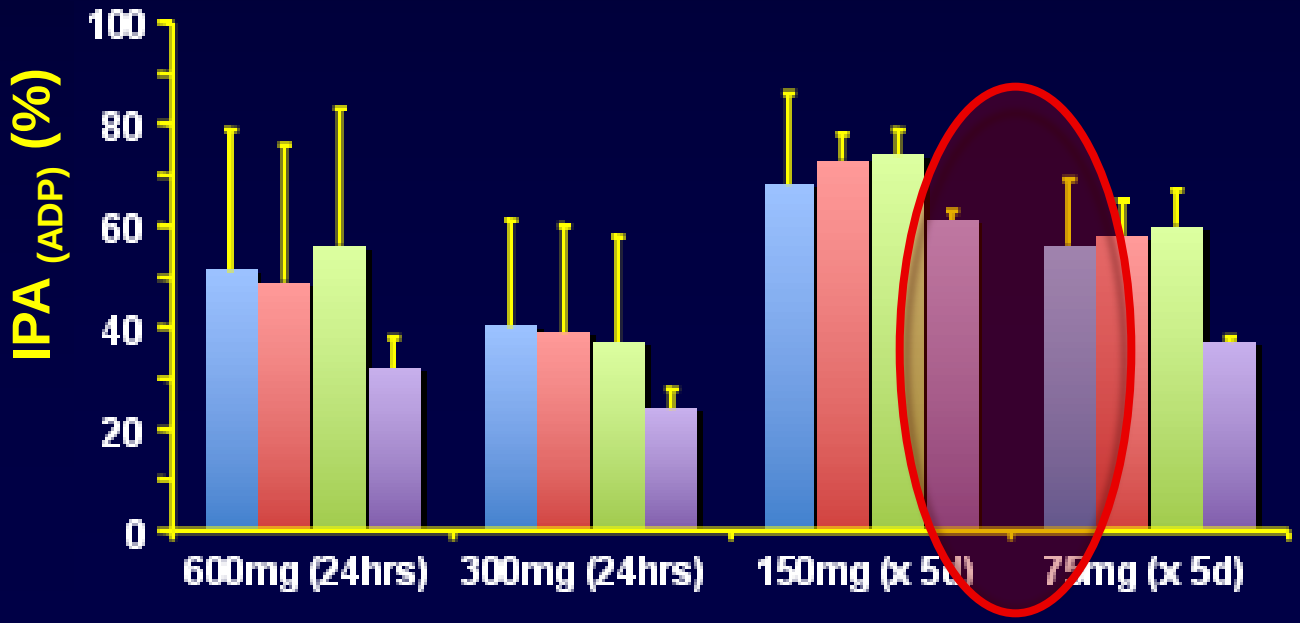
Boxed Warning	03/2010
Dosage and Administration (2.3)	03/2010
Warnings and Precautions (5.1, 5.2, 5.3)	03/2010

http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020839s042lbl.pdf

CYP2C19 Metabolizer Status & Clopidogrel PK/PD

Healthy Volunteers Study



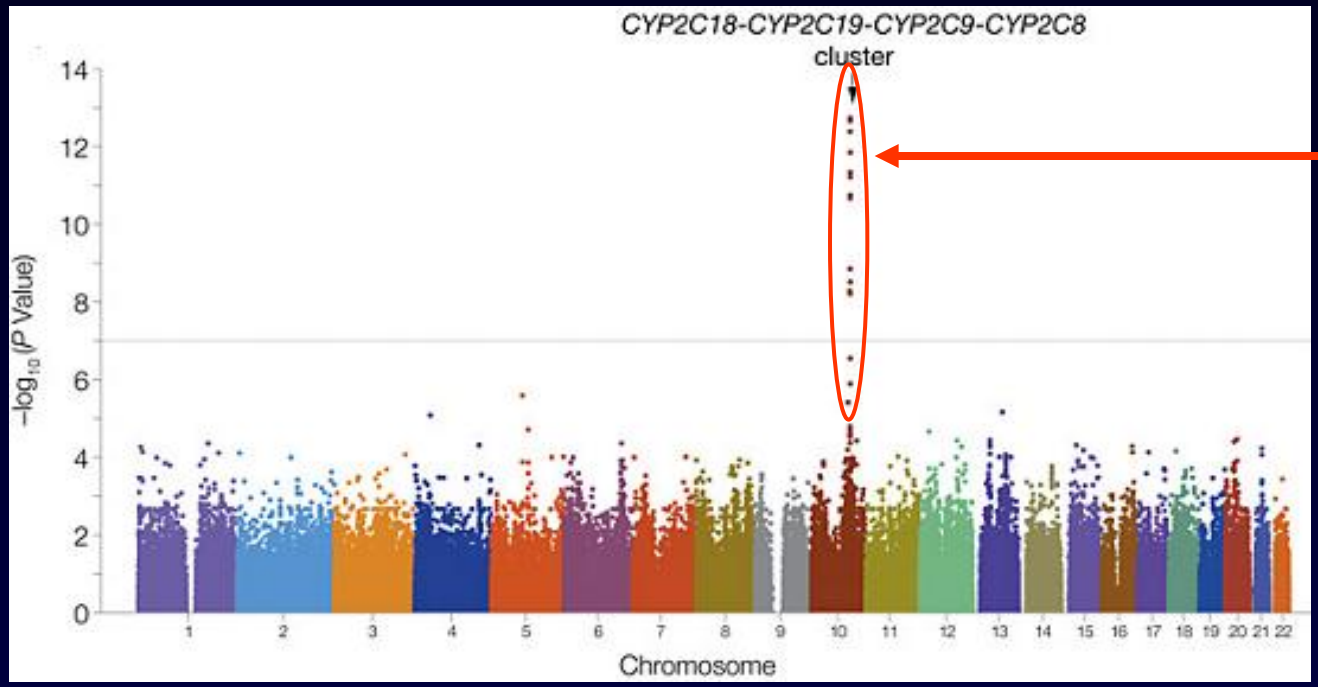


- Ultra-rapid (n=10)
- Extensive (n=10)
- Intermediate (n=10)
- Poor (n=10)

http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020839s042lbl.pdf

A genetic locus unequivocally associated with clopidogrel response variability has been identified: *we have come a long way from thinking that response variability is "normal"*

Genome Wide Association Study ~ 500,000 SNP's



13 SNP's cluster (1.5 mb on 10q24)

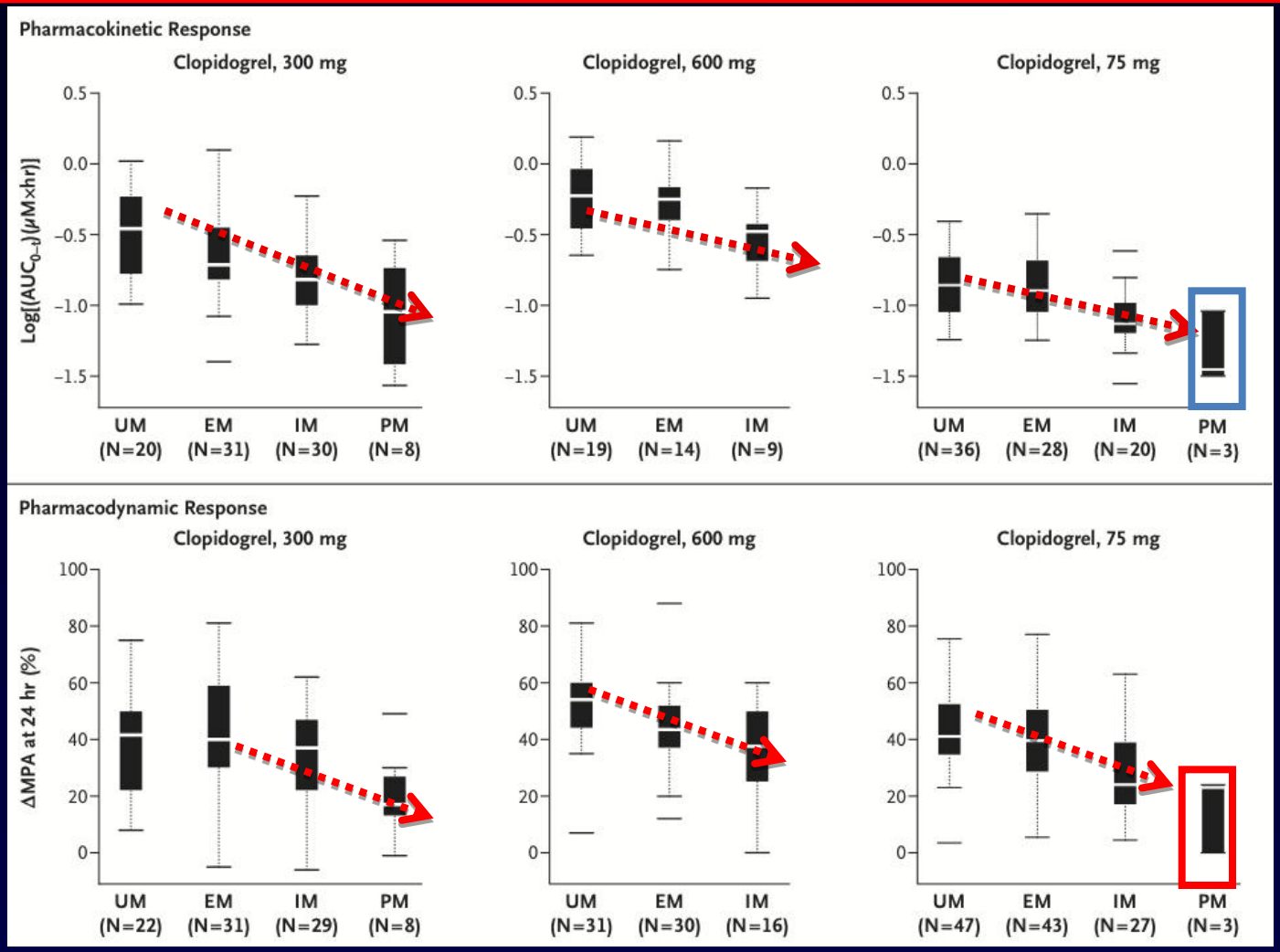
- Healthy Amish subjects (n=429) with extensive family relationships treated with 75mg x7d clopidogrel
- Contribution of genetic component to clopidogrel response variability ~70%
- Contribution of *CYP2C19 locus* to clopidogrel response variability is only ~12%
- Majority of clopidogrel response variability remains unexplained

  (rare/other genetic variants that escaped detection with GWAS)

Shuldiner AR and Gurbel PA et al. *JAMA*. 2009;302:849-57

Relation of Metabolizer Status to PK/PD Response:

Pooled Healthy Volunteers +/- Aspirin (n=162)



- 20μm ADP-induced MPA
- ΔMPA at 24 hours

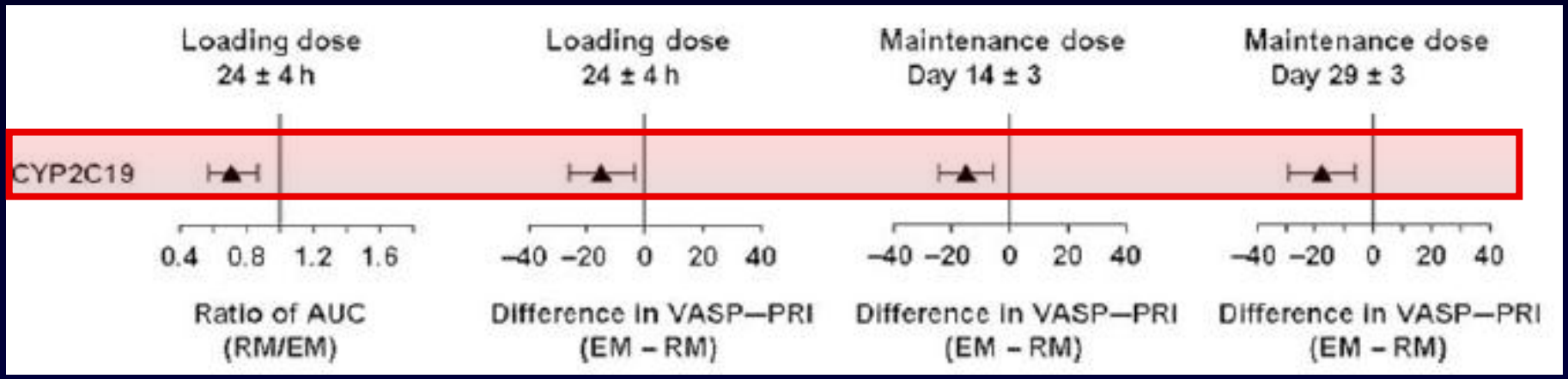
Carriers - 32% relative reduction In plasma exposure to AM

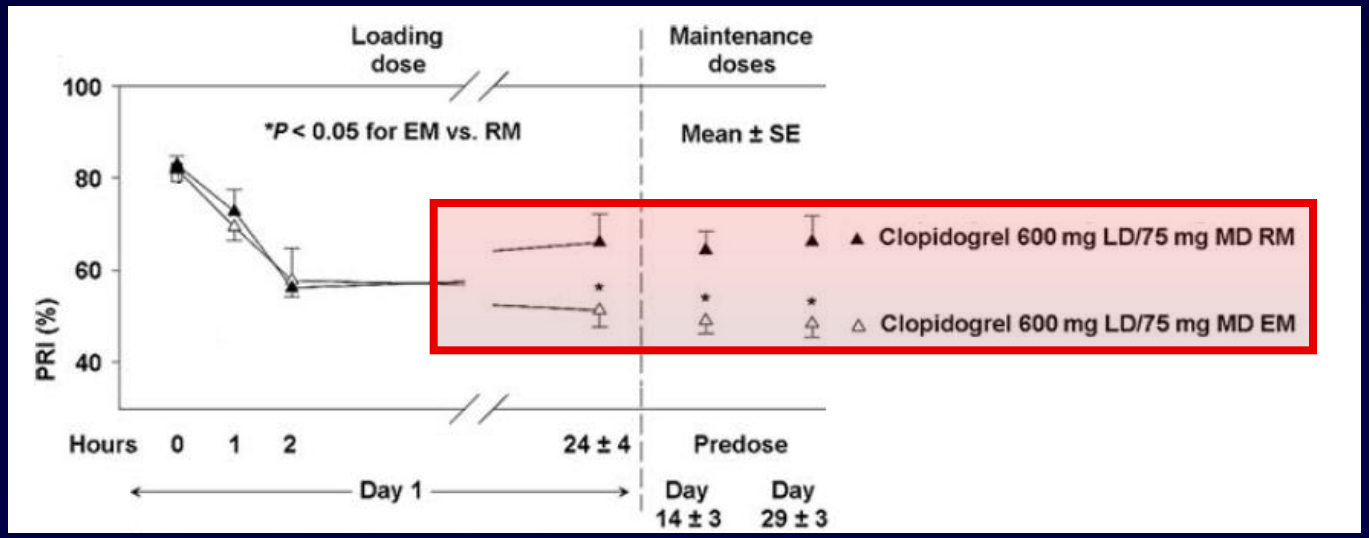
25% relative reduction in ΔMPA

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

Relation of Metabolizer Status to Clopidogrel PK/PD Response: CAD Patients + Aspirin (n=47)

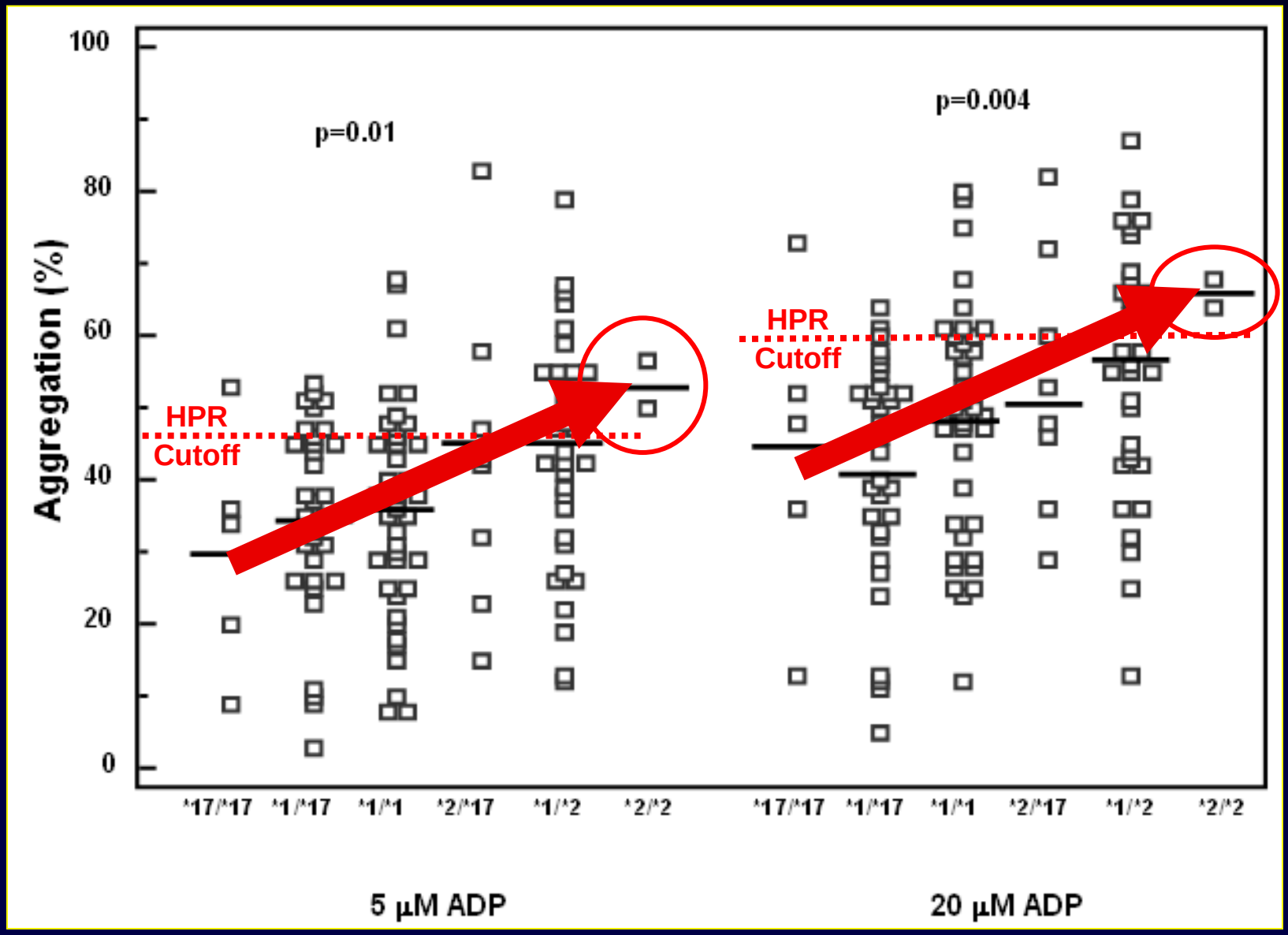
EM = extensive metabolizer : *17/*17, *17/*1, *1/*1
RM = reduced metabolizer : *1/*2, *2/*2, *1/*8





Adapted from Varenhorst et al. *Eur Heart J.* 2009; 30:1744-1752

Relation of Genotype to PD Response:
Stented Patients + Aspirin (n=118)

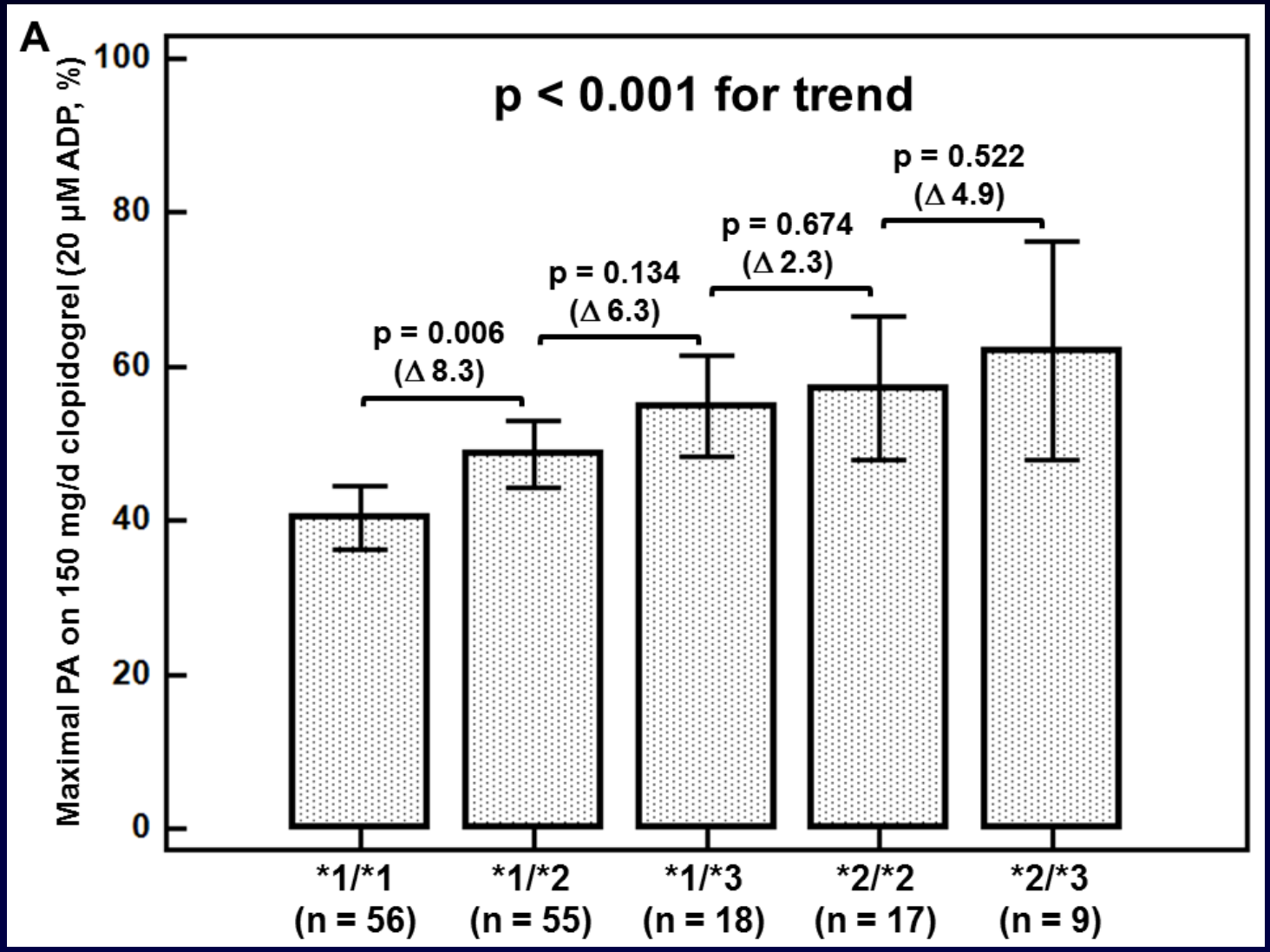


Gurbel PA et al. *Am Heart J* . 2011;161:598-604

Influence of *CYP2C19* *2 and *3 on Clopidogrel Response

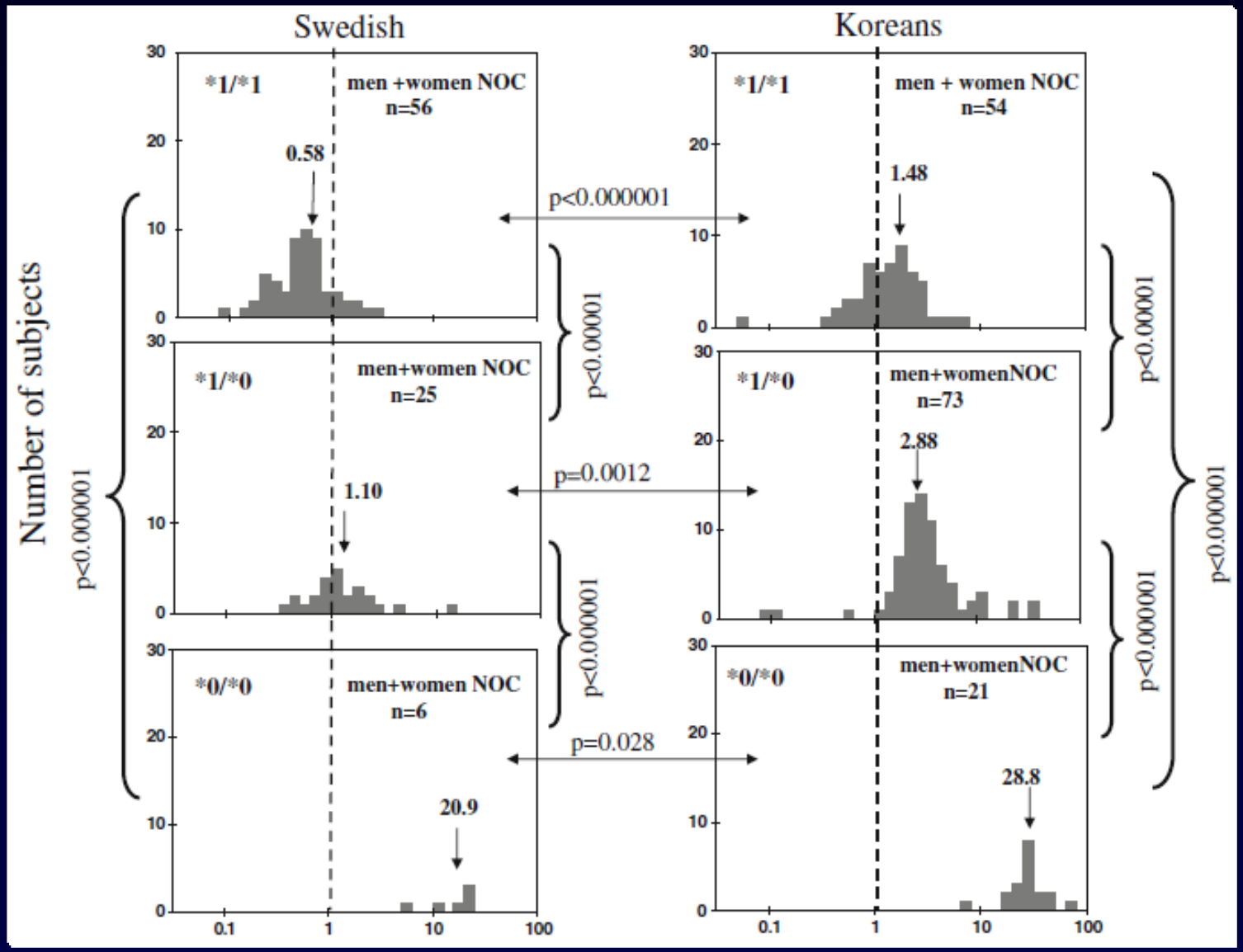
155 East Asians Undergoing Percutaneous Coronary Intervention

High maintenance-dose (150 mg/d) clopidogrel for ≥30 days



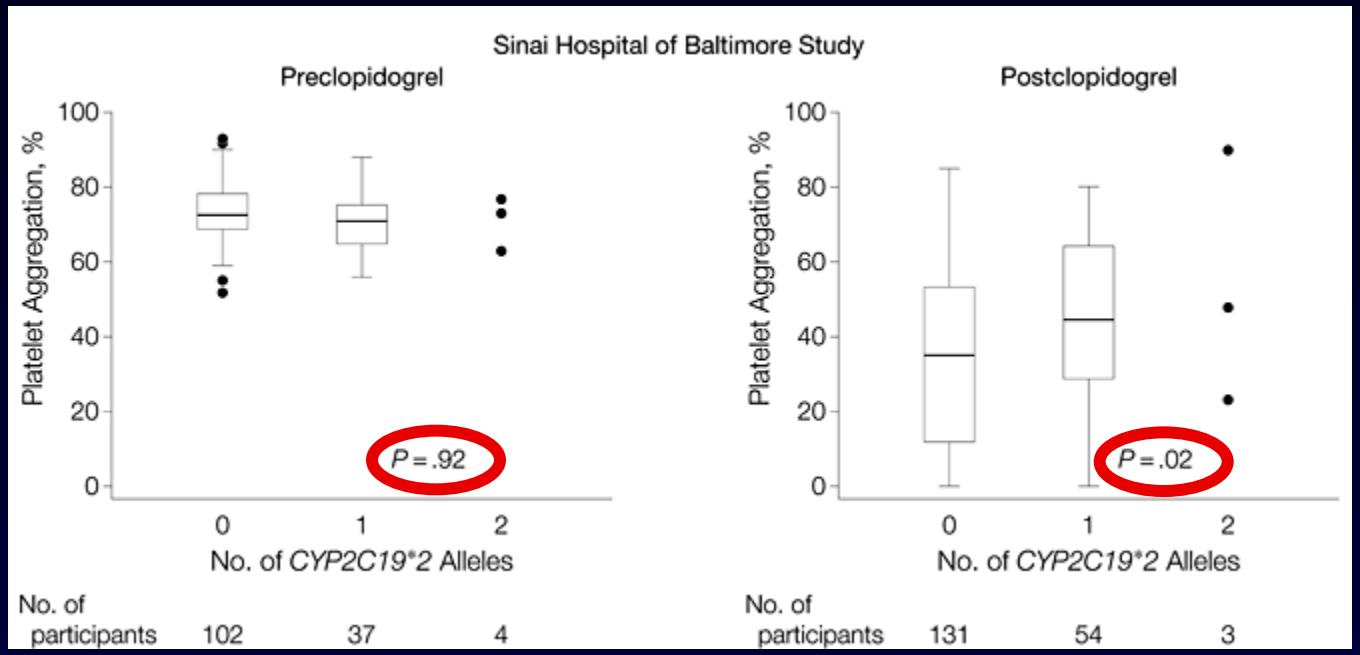
Jeong YH et al. Presented at TCT 2011

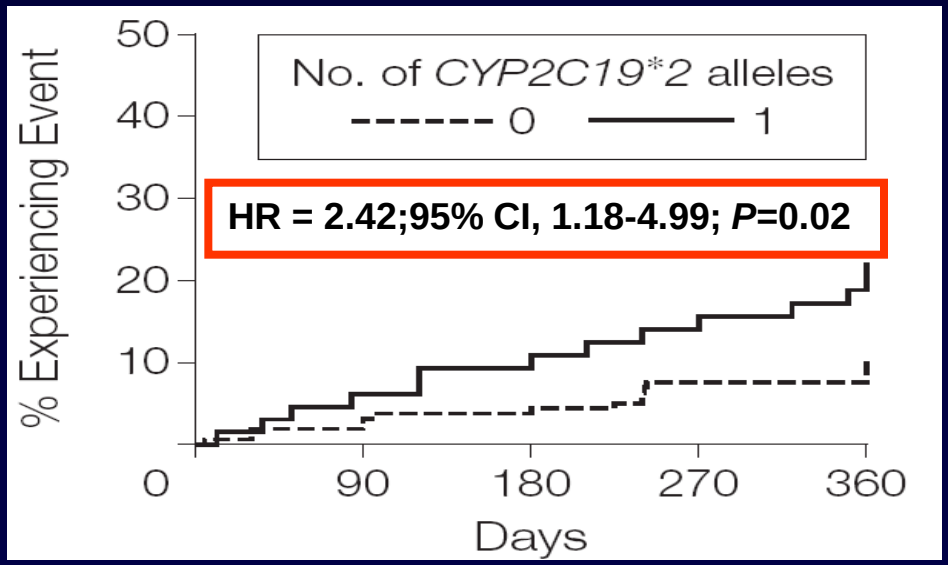
Distribution of Omeprazole/5-Hydroxyomeprazole Ratio in Swedish and Koreans Without *17 allele



Ramsjö M et al. *Eur J Clin Pharmacol* . 2010;66:871–877

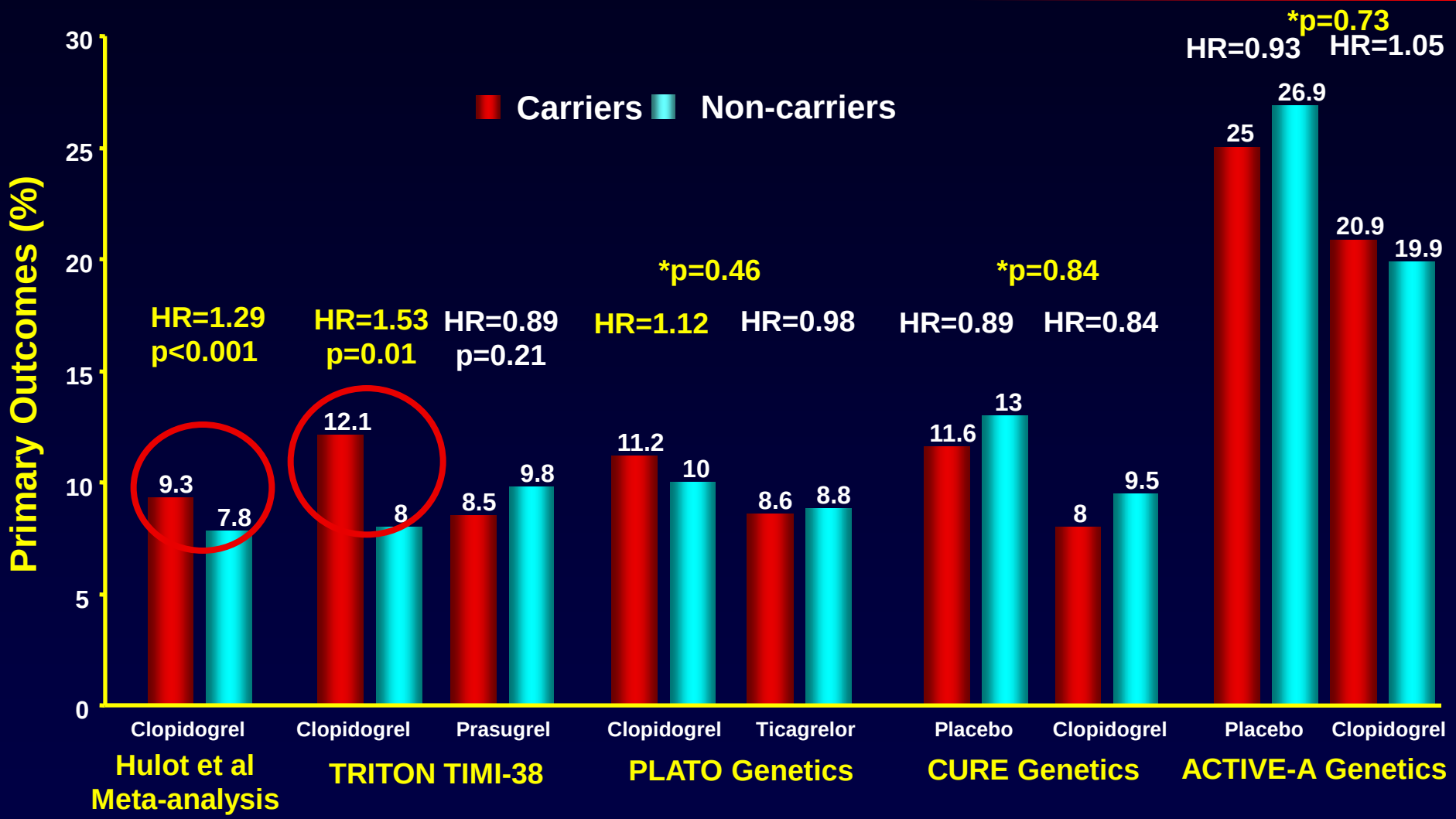
Relation of *CYP2C19*2* Allele to PD Response and Clinical Outcome





Shuldiner AR and Gurbel PA et al. *JAMA*. 2009;302:849-57

CYP2C19 LOF Carrier Status Has Only Been Linked to Risk: in the PCI Population



J Am Coll Cardiol. 2010;56:134-43

N Engl J Med. 2009;360:354-62
Circulation. 2009;119:2553-60

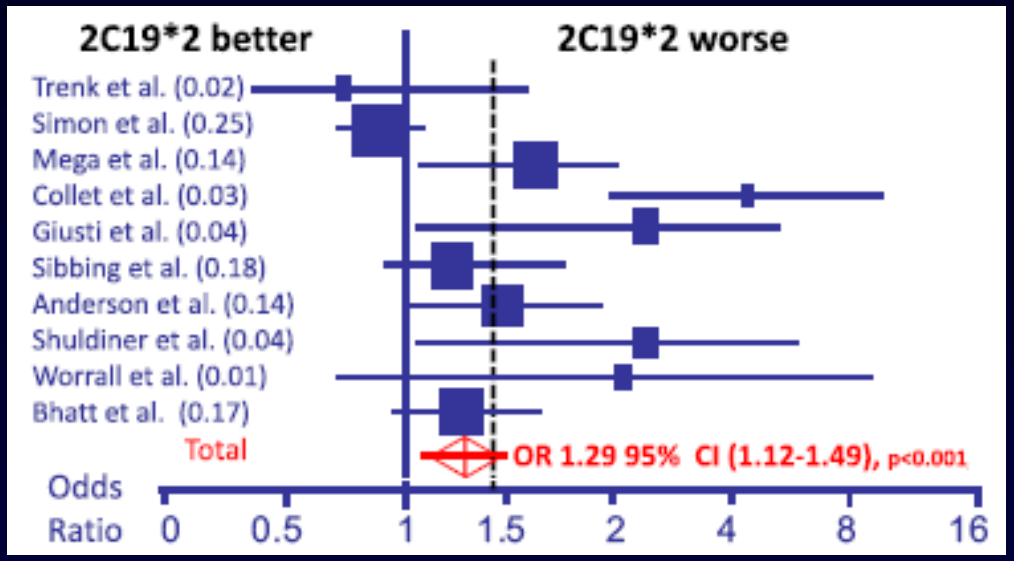
Lancet 2010;376:1320-28

N Engl J Med 2010;363:1704-14

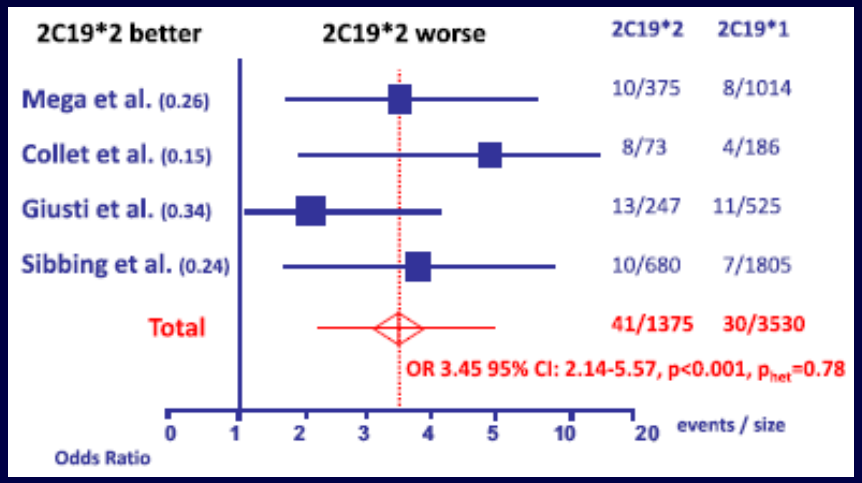
* p value of interaction indicates significance of effects of genotype groups on the results of comparisons between treatment groups.

Reduced Function *CYP2C19* SNP is a Risk Factor in Patients Treated with Clopidogrel Undergoing PCI: Collaborative Meta-analysis

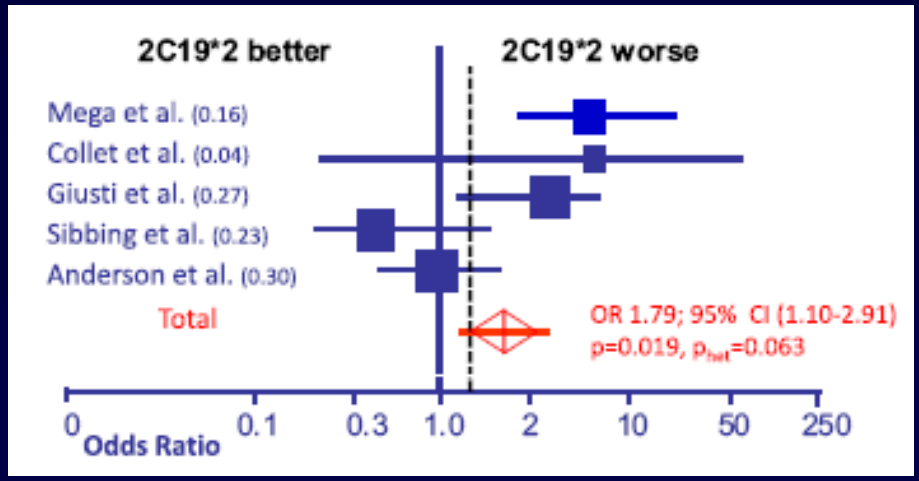
MACE



Stent Thrombosis



Death



Hulot J-S et al. *J Am Coll Cardiol*. 2010;56:134-43

Conflicting Data on Clinical Significance of *CYP2C19 GOF* Carrier Status

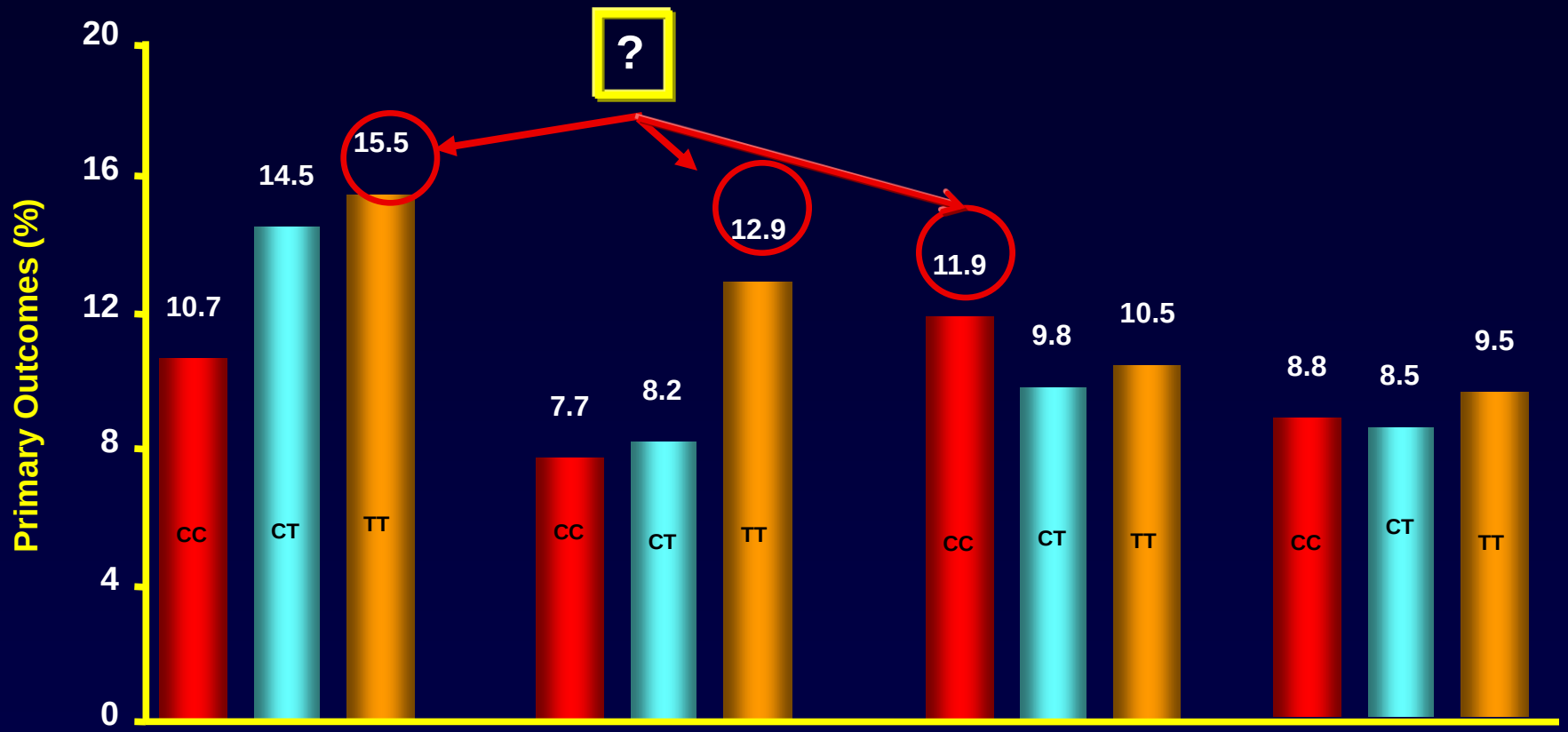
Study	Treatment	CV Events Carrier vs. Non-Carrier	Bleeding Events Carrier vs. Non-Carrier
CHARISMA Genetics	Placebo Clopidogrel	1.49; (1.00-2.21); p=0.052 No signal	No signal No signal
PLATO Genetics	Clopidogrel Ticagrelor	Not reported	GOF vs. non-GOF or LOF, p= 0.02
CURE Genetics	Placebo Clopidogrel	No signal 7.7% vs. 10.0%; HR=0.77	No signal
ACTIVE A	Placebo Clopidogrel	No signal	No signal
Sibbing et al.	Clopidogrel	No signal	OR= 1.8; 1.03-3.14; p=0.01

Bhatt DL et al. Presented at TCT 2009;
Pare G et al. *N Engl J Med* 2010;363:1704-14;
Wallentin L et al. *Lancet* 2010;376:1320-28
Sibbing D et al. *Circulation* 2010;121:512-8

Conflicting Data on Clinical Significance of *ABCB1* Carrier Status

ABCB1 Gene Frequency	Japanese	Caucasians	African Americans
High Expression - CC	5-8	25	44
Intermediate Expression - CT	14-17	50	13
Low Expression - TT	15-17	25	0

Ozawa S et al
Drug Metab Pharmacokin
2004l;19:83-95

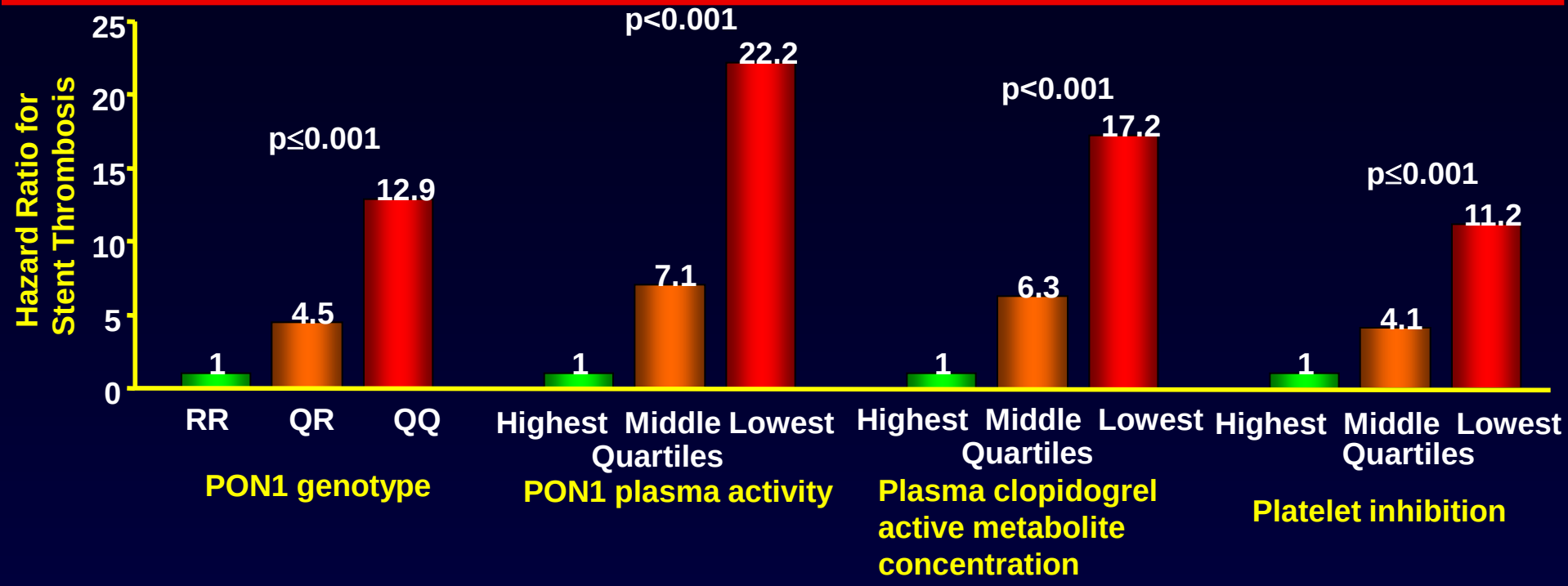


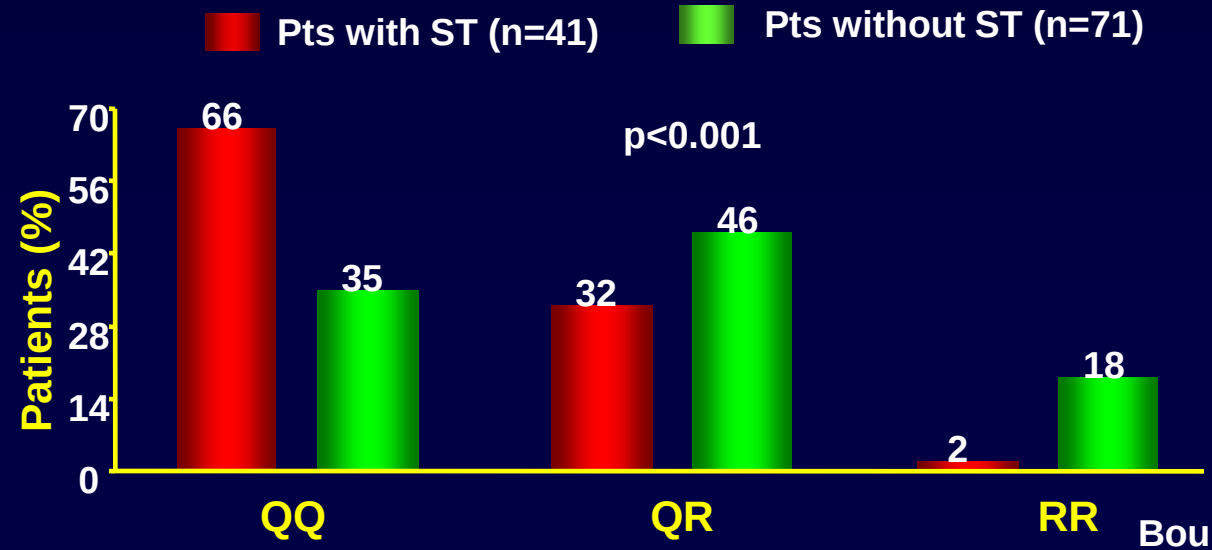
Simon et al
N Engl J Med. 2009;360:363-75

Triton TIMI-38
Mega J et al. *Lancet.* 2010;376:1312-9

PLATO Genetics
Wallentin L et al. *Lancet.* 2010;376:1320-28.

Influence of PON1 (Hepatic Esterase) on Clopidogrel Response and Clinical Outcome (n=112)



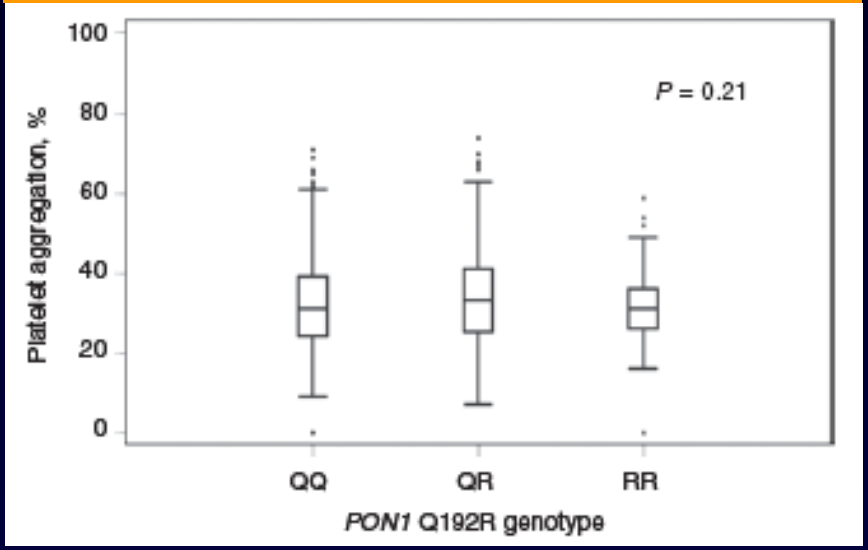


* No effect of *CYP2C9, 2C19, 3A4, 3A5, ABCB1* genotypes

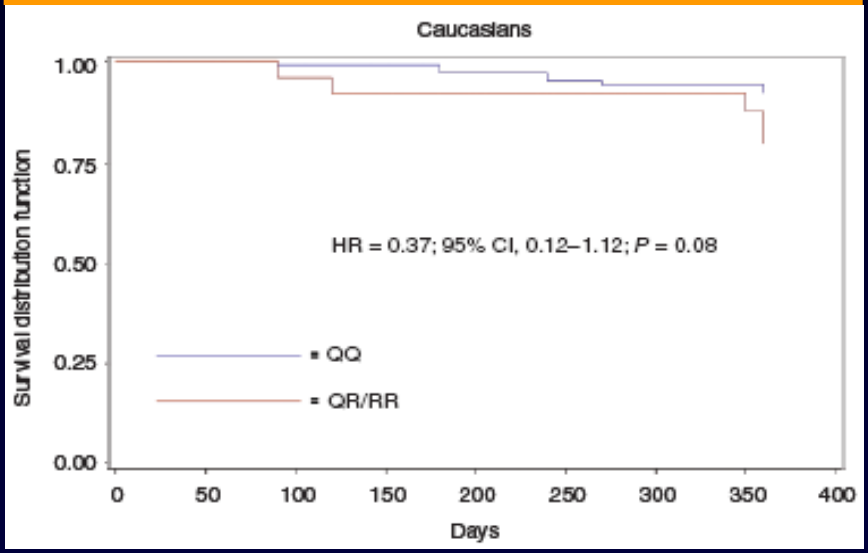
Bouman HJ, et al. *Nat Med* 2011;17:110-116

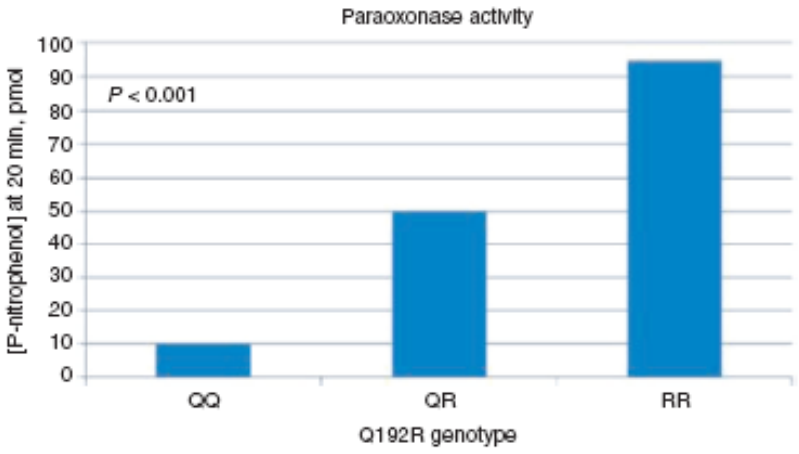
Lack of Influence of PON1 on Clopidogrel Response and Clinical Outcome

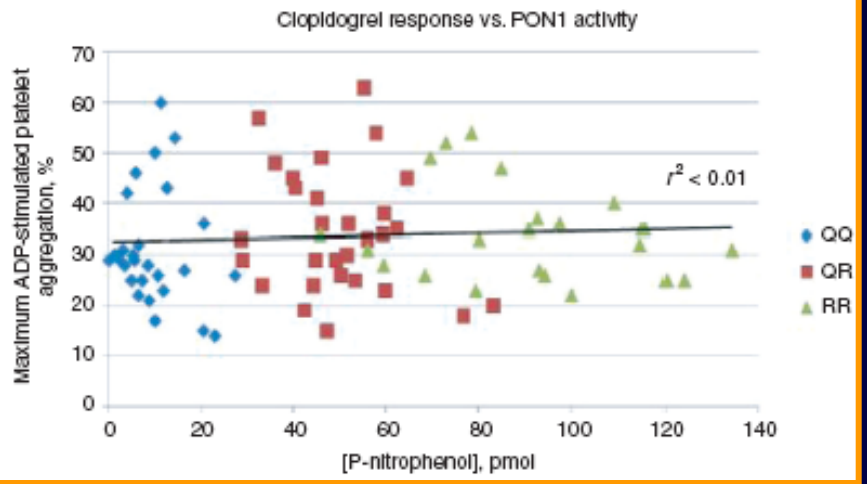
566 Amish Subjects:
300mg LD + 75mg/day for 7 days



227 Nonemergent PCI Patients
600/300mg LD + 75mg/d for 1 year

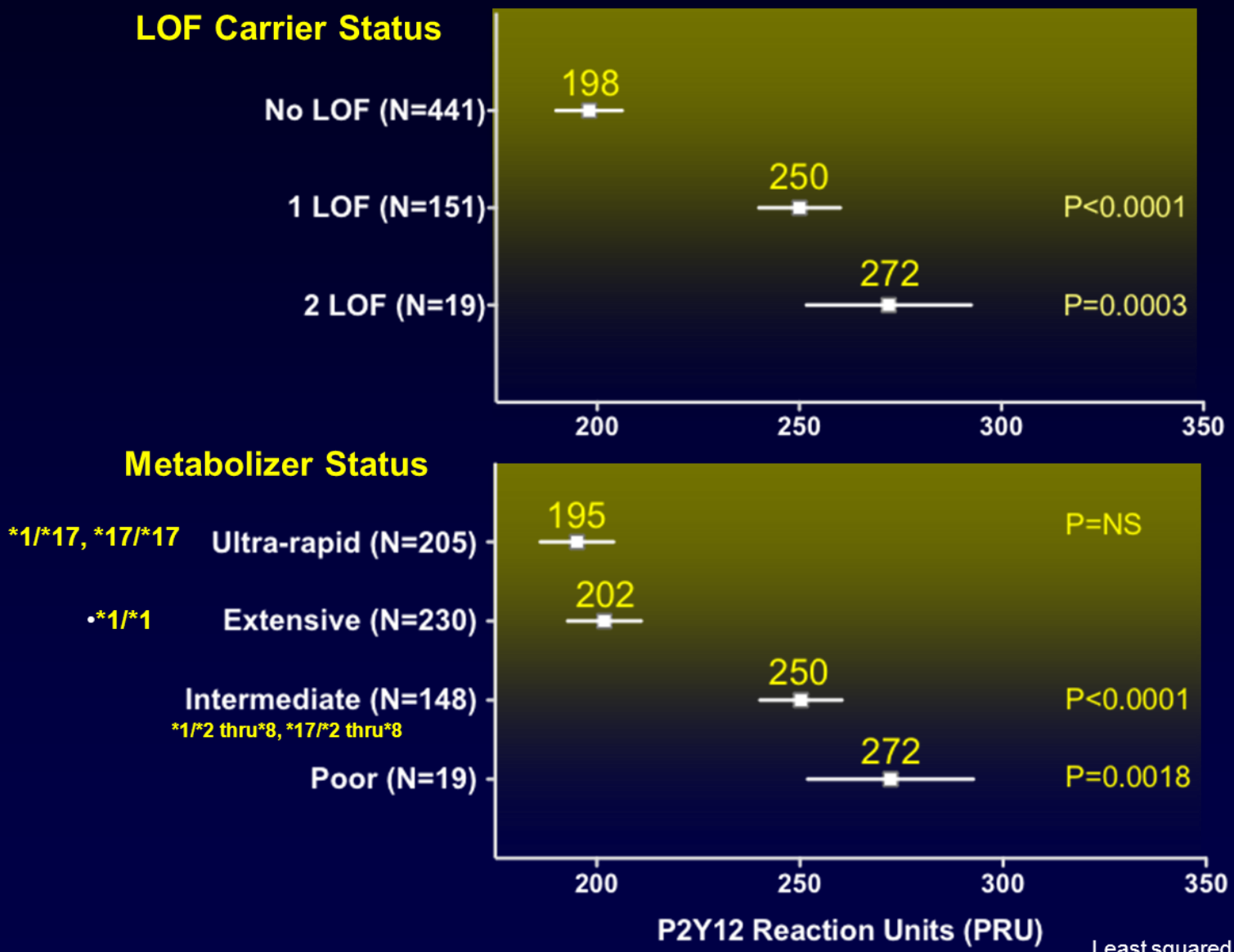






Lewis JP, Gurbel PA and Shuldiner AR et al. *Clin Pharmacol Ther*. 2011;90:568-74.

Relation of *LOF* Carrier and Metabolizer Status to Phenotype: *GIFT Study*: Post-PCI Clopidogrel-Treated Patients

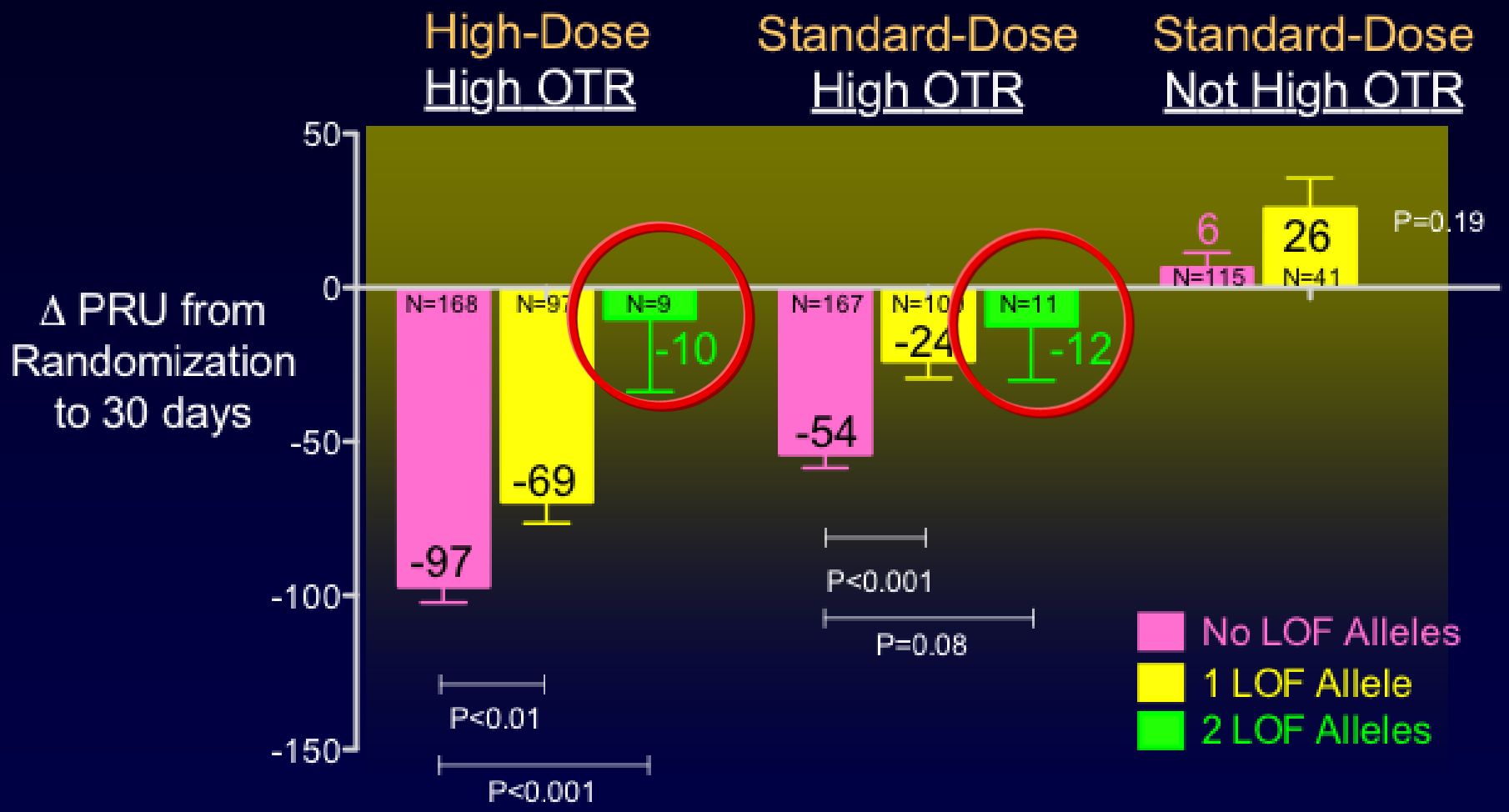


η^2=6.7%

Price MJ et al. *ACC 2011*

Least squared means.
P values compared to No LOF/Extensive.

CYP2C19 Genotype is Associated With the PD Effect of Clopidogrel at 30 Days In Patients with High OTR Regardless of Dosing Strategy



High-dose: clopidogrel 600 re-load then 150 mg/day; Standard-dose: clopidogrel 75 mg/day.
High OTR: ≥ 230 PRU at enrollment (12-24 hrs post-PCI)
P values adjusted for multiple comparisons

Price MJ et al. *ACC 2011*

ELEVATE
TIMI 56

Study Design

Investigator-Initiated Study
IND #: 107635

335 Patients Enrolled
Stable CAD Pts on Clopidogrel 75 mg daily
(>4 Weeks and <6 Months Post-MI or PCI)

2 Not Genotyped

333 Blinded Genotyping

247 *CYP2C19*2* Non-Carriers

86 *CYP2C19*2* Carriers
(80 Heterozygotes; 6 Homozygotes)

Randomized to various blinded sequences of daily doses of clopidogrel

75 mg | 150 mg | 75 mg | 150 mg

Randomized to various blinded sequences of daily doses of clopidogrel

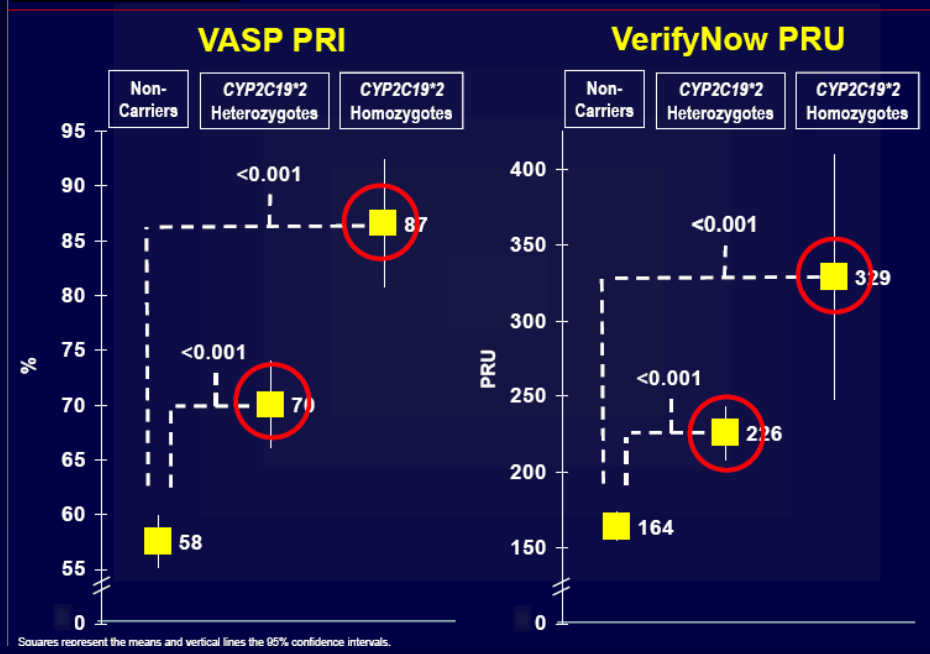
75 mg | 150 mg | 225 mg | 300 mg

Each dose given for ~14 days followed by platelet function testing (VASP and VerifyNow $P2Y_{12}$ assays) and assessment for events

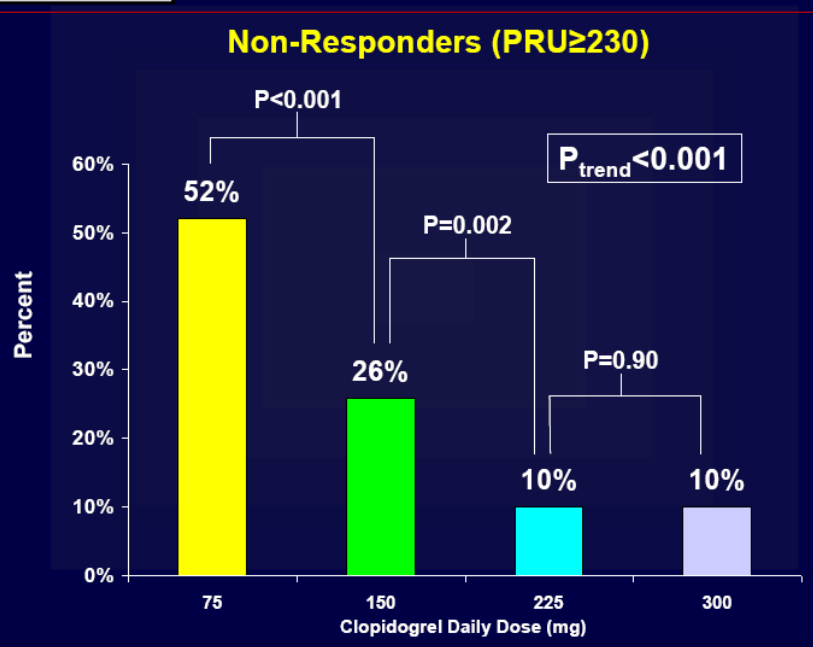
Mega JL et al. *JAMA.* 2011;306:2221-8.

ELEVATE - PCI

75 mg Clopidogrel Daily



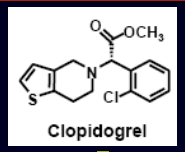
*CYP2C19*2* Heterozygotes

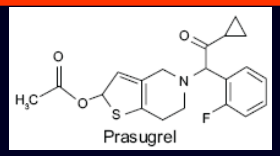


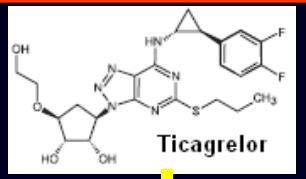
Mega JL et al. *JAMA*. 2011;306:2221-8.

New $P2Y_{12}$ Inhibitors

Metabolism of $P2Y_{12}$ Receptor Blockers:







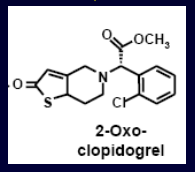
P-Glycoprotein

Intestinal Absorption

h-Esterase 85%

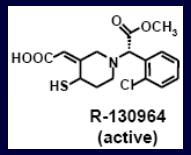
15%

Inactive metabolite



2C19
1A2
2B6

2 Step Hepatic CYP Conversion



2C19
2C9
3A4
2B6

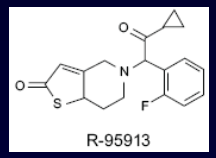
Variable and inefficient active metabolite generation

Slow, Variable IPA

P-Glycoprotein

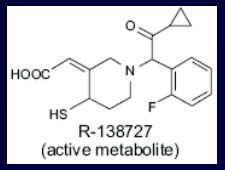
Intestinal Absorption

Intestinal Esterases 85%



1 Step Intestinal/hepatic CYP-Conversion

55%



3A4
2B6
2C9
2C19

Efficient active metabolite generation

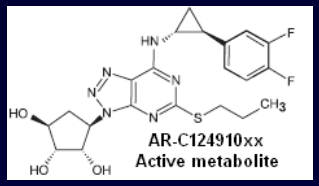
Rapid Consistent /Greater IPA

P-Glycoprotein

Intestinal Absorption

Hepatic CYP3A4

30%

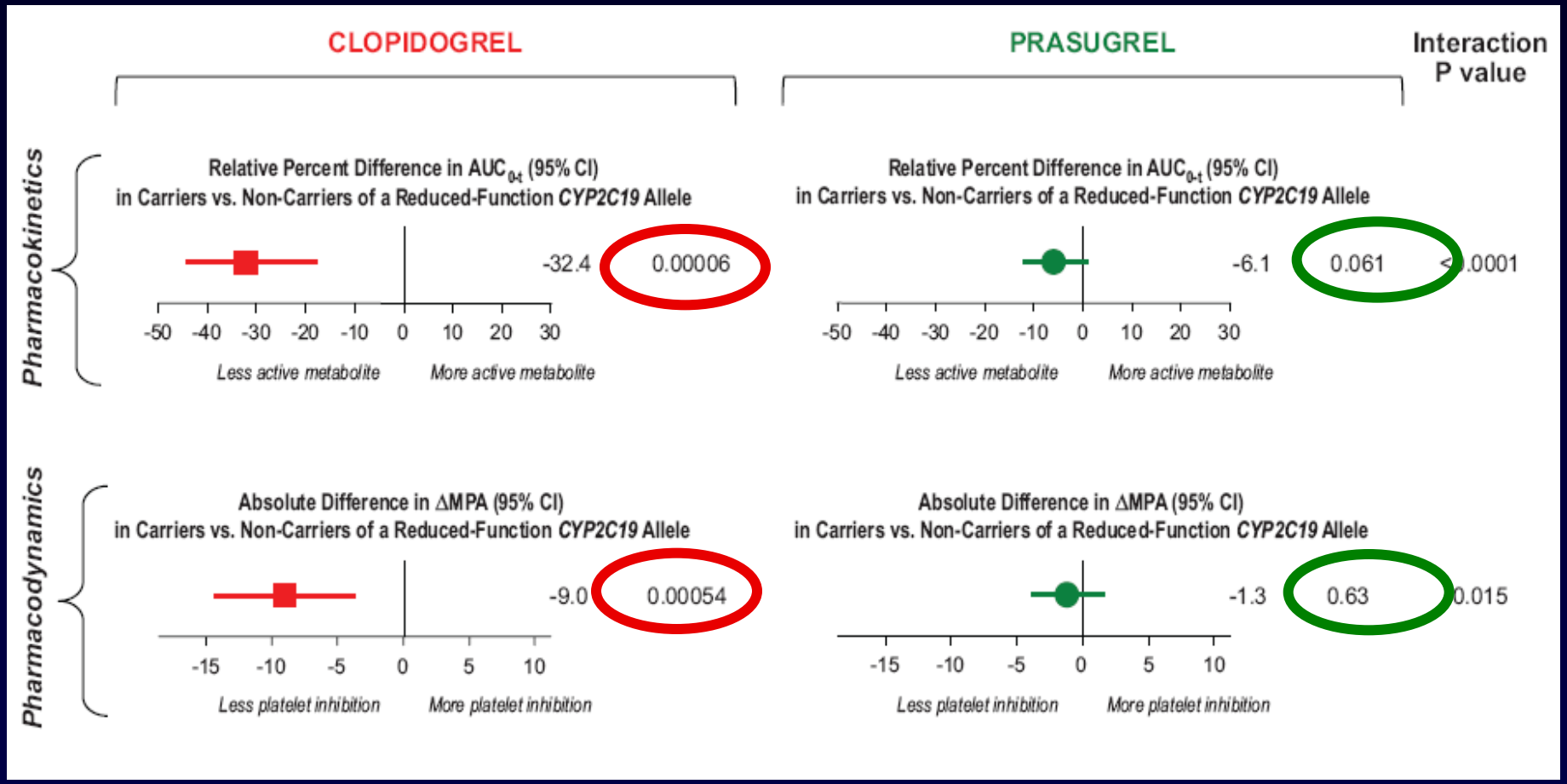


Rapid Consistent /Greater IPA

Gurbel PA et al. *Curr Opin Investig Drugs.* 2008;9:324-36. Gurbel PA et al. *Expert Opin Pharmacother*. 2010;11:2251-9.

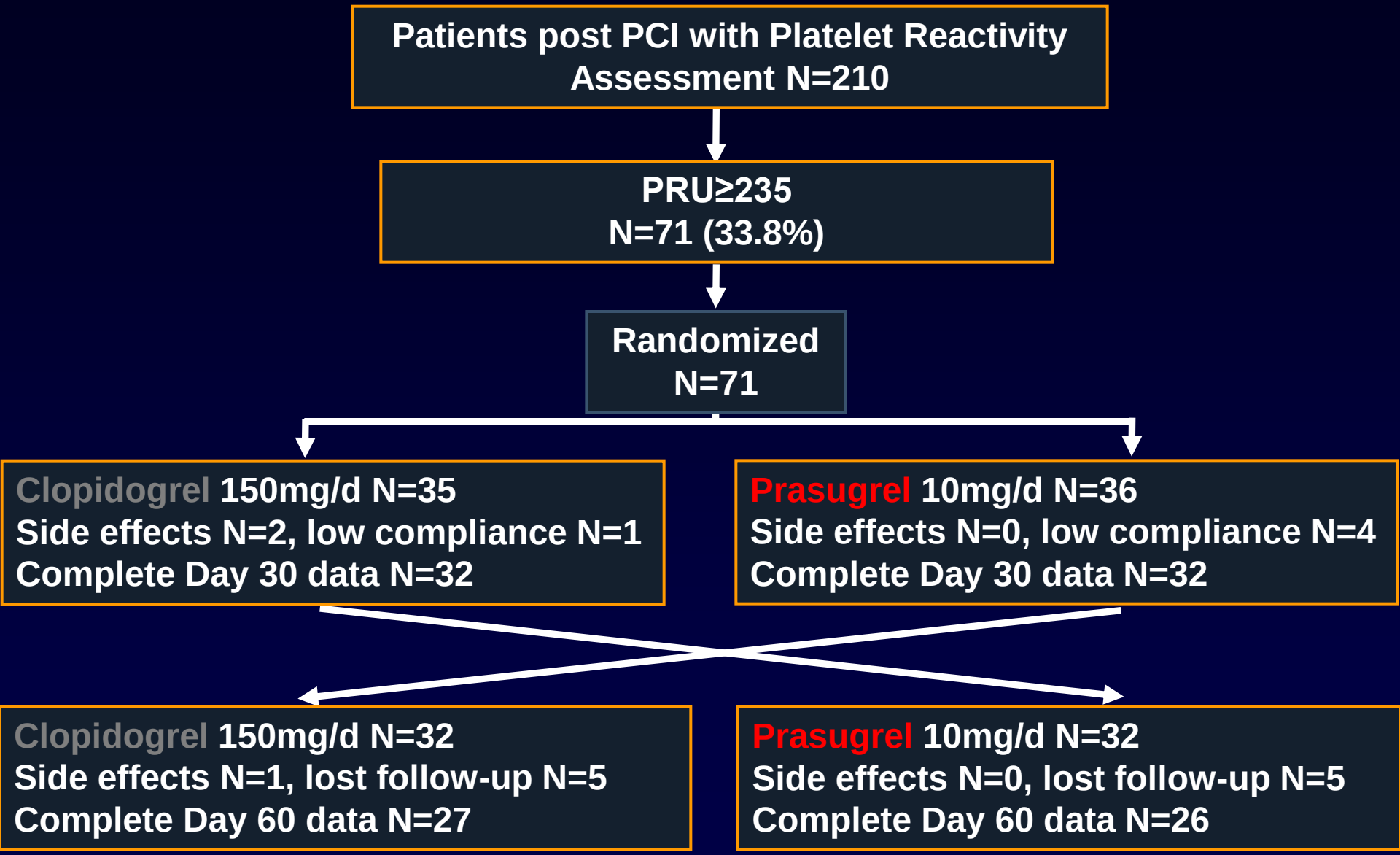
PG vs. PK and PD: Clopidogrel and Prasugrel

Healthy Subjects +/- Aspirin



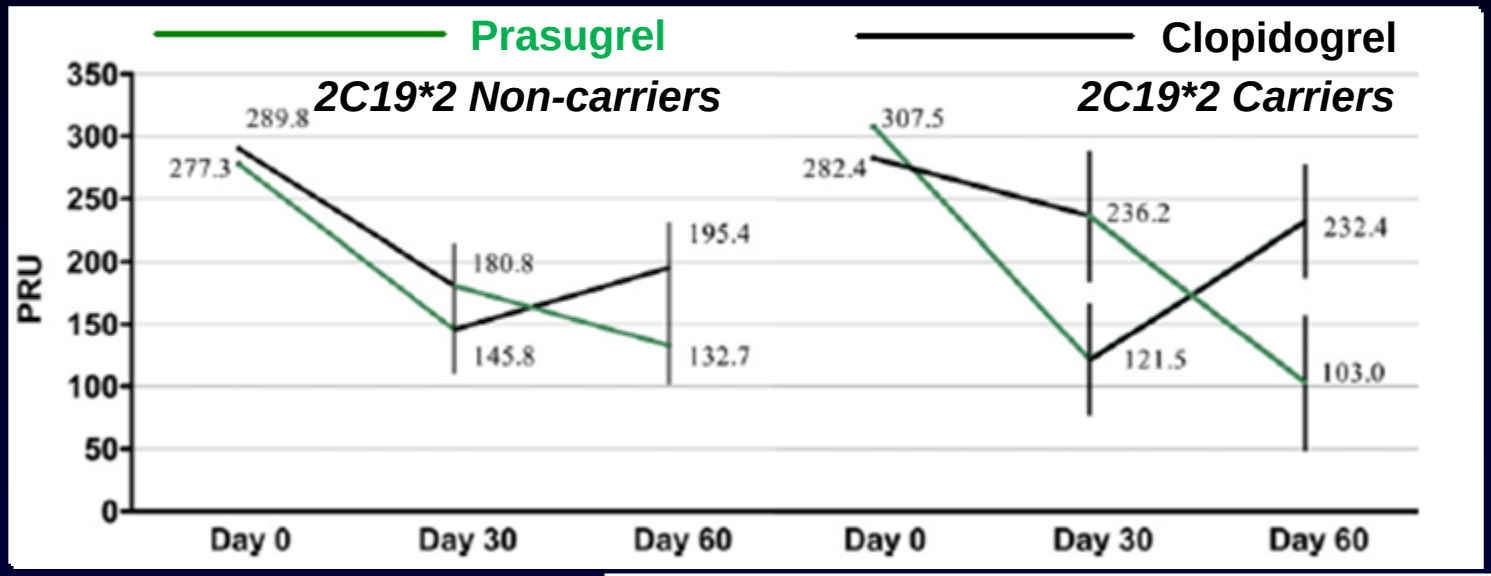
Mega J et al. *N Engl J Med*. 2009;360:354-62

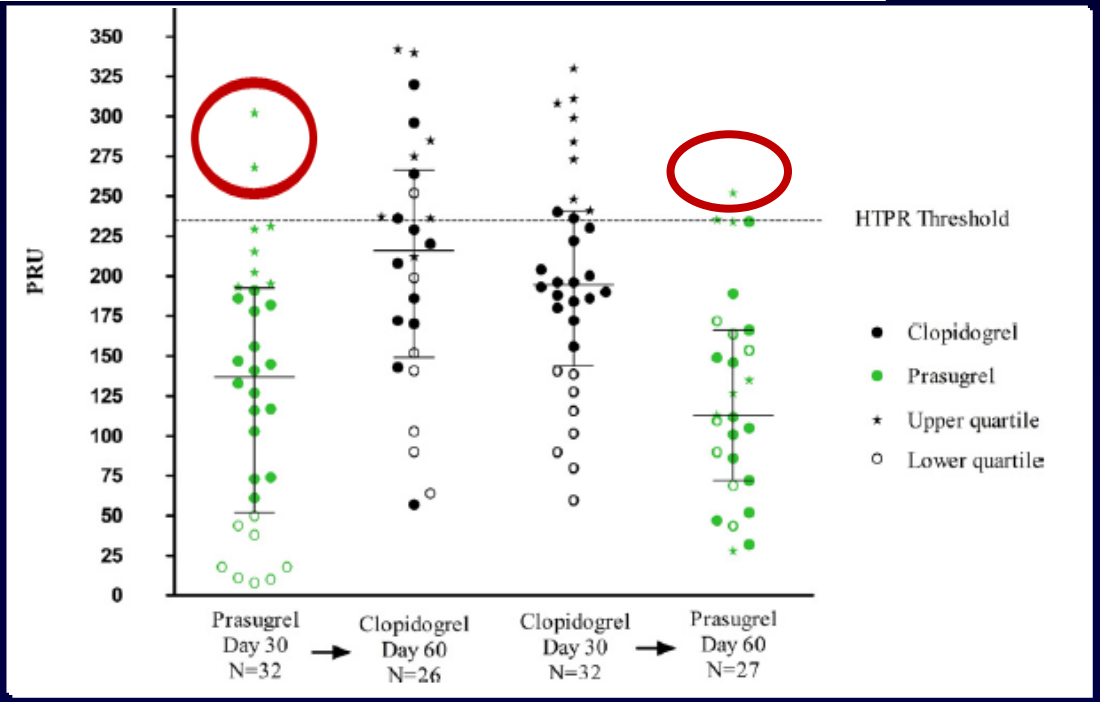
PRO-GR: Study Design



Alexopoulos D. *JACC Cardiovasc Interv*. 2011;4:403-10

Platelet Reactivity in Patients CYP2C19*2 Carriers and Non-carriers

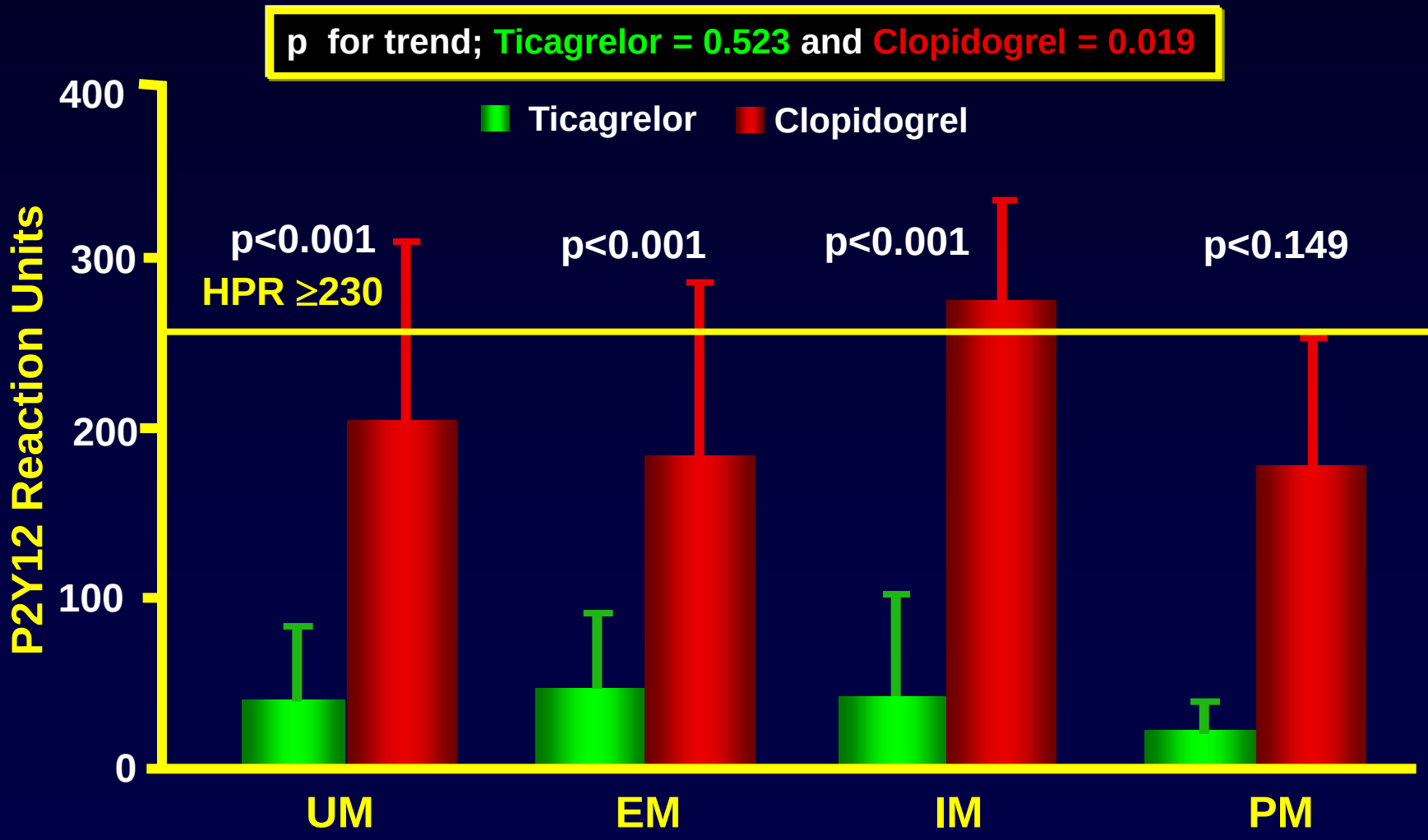




Alexopoulos D. *JACC Cardiovasc Interv*. 2011;4:403-10

Relation of Metabolizer Status to Pharmacodynamics: Clopidogrel vs. Ticagrelor

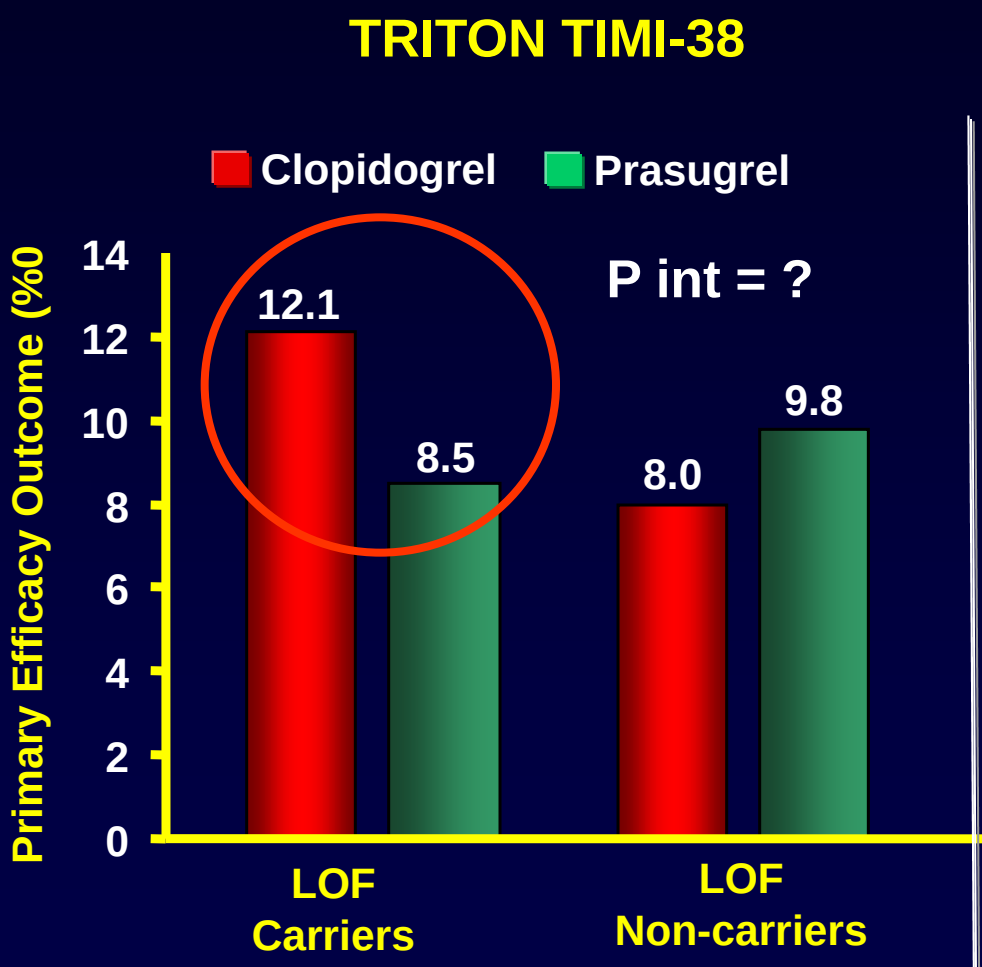
Ticagrelor Eliminates the Worrisome Phenotype (HPR) in All Genotypes

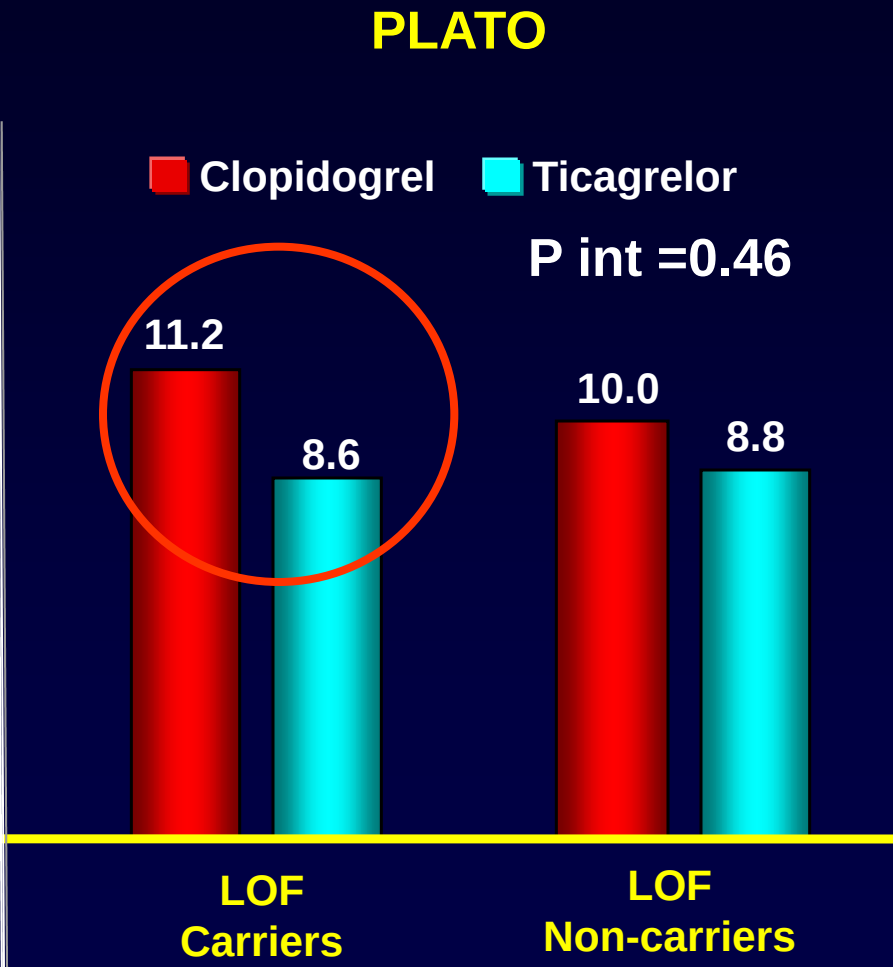


Tantry US and Gurbel PA et al. *Circ Cardiovasc Genet.* 2010;3:556-66

Alternative antiplatelet therapy (prasugrel or ticagrelor) may reduce the risk associated with LOF carriage.

Blanket Use of the New $P2Y_{12}$ Inhibitors as Proposed by Some May Not Be a Cost-Effective Strategy:

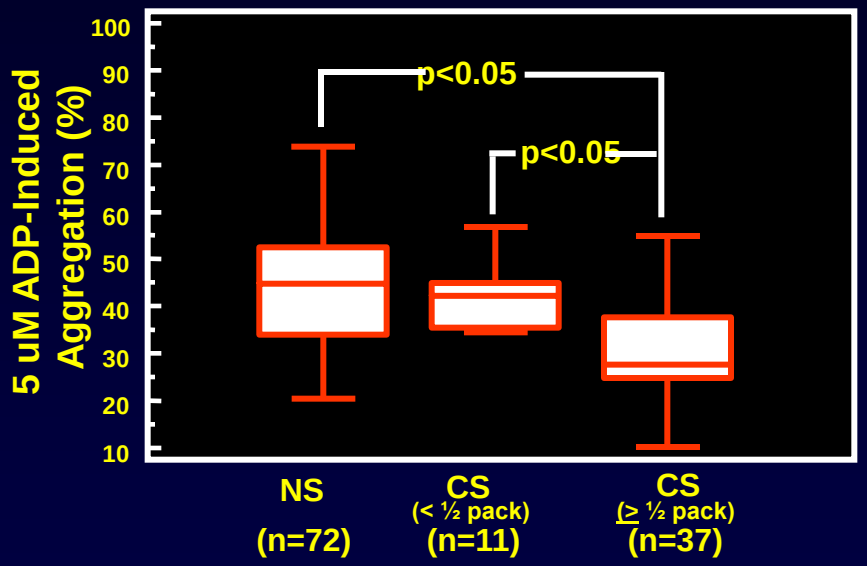


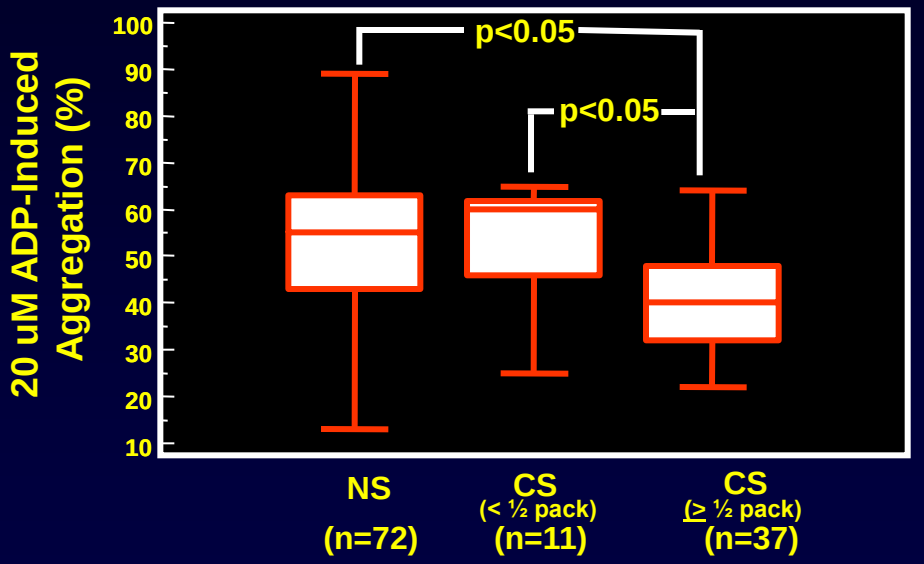


Mega J et al. *Circulation* 2009;119:2553-60
Mega J et al. *N Engl J Med* 2009;360:354-62

Wallentin L et al *Lancet* 20010;376:1320-28

CYP1A2: Clopidogrel-Smoking Interaction



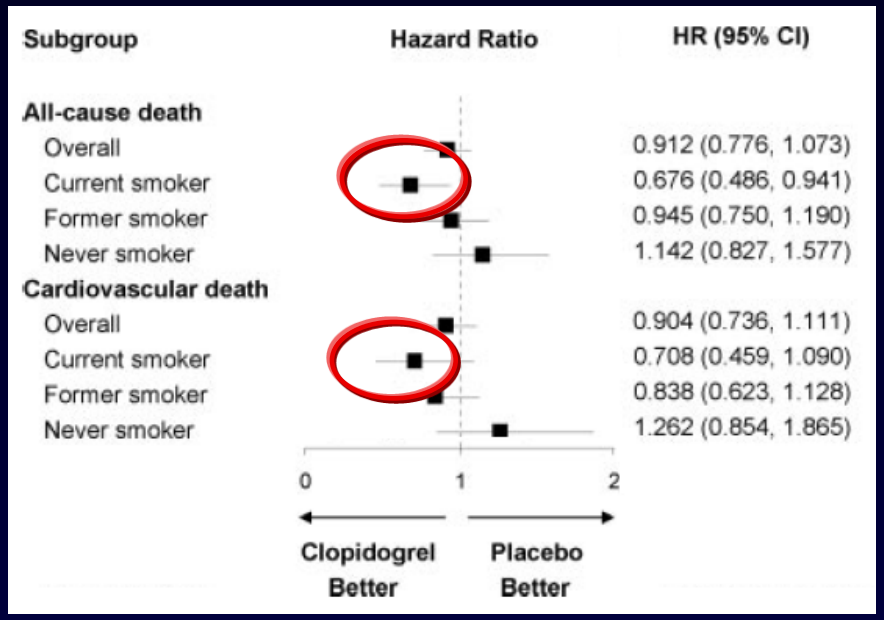


Bliden KP et al. *J Am Coll Cardiol* 2008;52:531–3

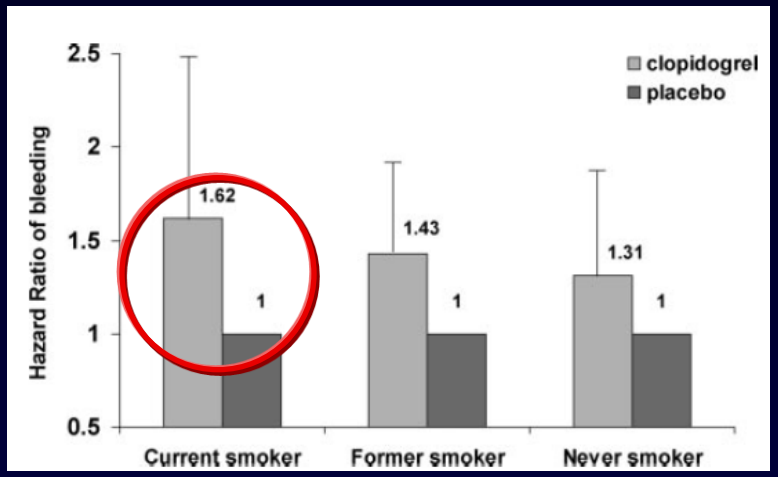
CYP1A2: Smoking - Clopidogrel Interaction

CHARISMA Trial: Berger J et al. *Circulation*. 2009;120:2337-2344

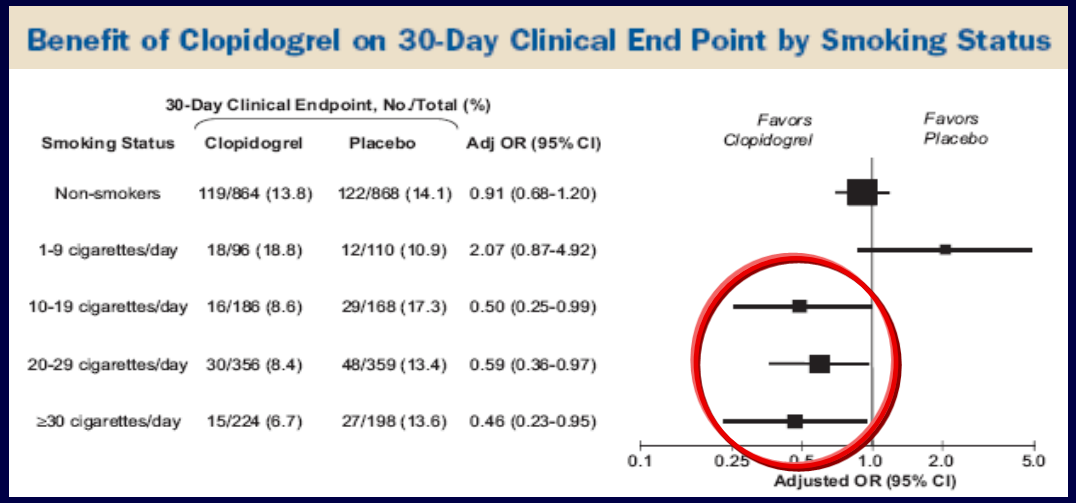
All Cause and CV Death



Bleeding



CLARITY-TIMI 28 STUDY: Desai NR et al. *J Am Coll Cardiol.* 2009;53:1273–8



CURE: Incidence of CV Death, MI and Stroke by Subgroup

Smoking Status	Clopidogrel/ASA (N=6259)	Placebo/ASA (N=6303)	Hazard Ratio (95% CI)
Current (N=2893)	89 (6.1%)	135 (9.4%)	0.63 (0.48, 0.83)
Former (N=4738)	240 (10.3%)	316 (13.1%)	0.77 (0.65, 0.91)
Never (N=4928)	252 (10.2%)	268 (10.9%)	0.93 (0.79, 1.11)

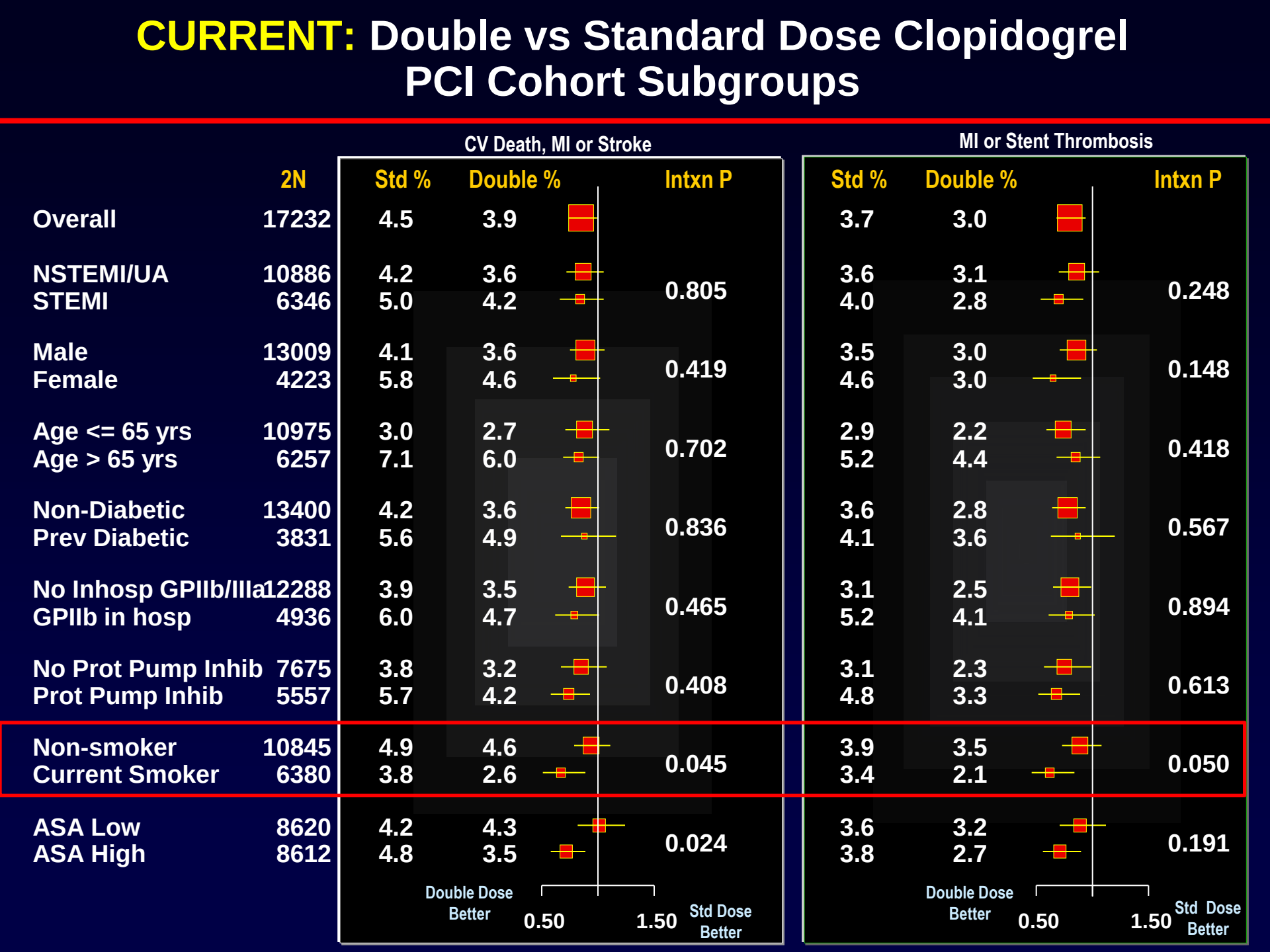
CREDO: Smoking Influences the Effectiveness of Dual Antiplatelet Therapy on Long-Term Outcomes Following PCI

Smoking Status	Smokers (n=647)		Nonsmokers (n=1433)	
Treatment	ASA only (n=312)	ASA + Clop (n=335)	ASA only (n=737)	ASA + Clop (n=696)
28 Day Outcome[1]	10.58%* (33/312)	5.37%* (18/335)	6.78% (50/737)	6.75% (47/696)
1 Year Outcome[2]	13.78%† (43/312)	6.27%† (21/335)	10.72% (79/737)	9.77% (68/696)

Salek F. Et al. Abstract 8. *Pharmacotherapy. 2010;30:154e.*

Saraff KY et al. *J Am Coll Cardiol.* 2006;36B (Abstract 2920-122)

CURRENT: Double vs Standard Dose Clopidogrel PCI Cohort Subgroups



5 Major Clinical Trials Suggest :

Non-Smokers Don’t Benefit From Clopidogrel Therapy !

SNP's of *CYP1A2* and Risk for HPR

Patients Undergoing Angjography (n=1123)

CYP1A2*1A **= wild type, 15 SNPs (*1B to *16)**

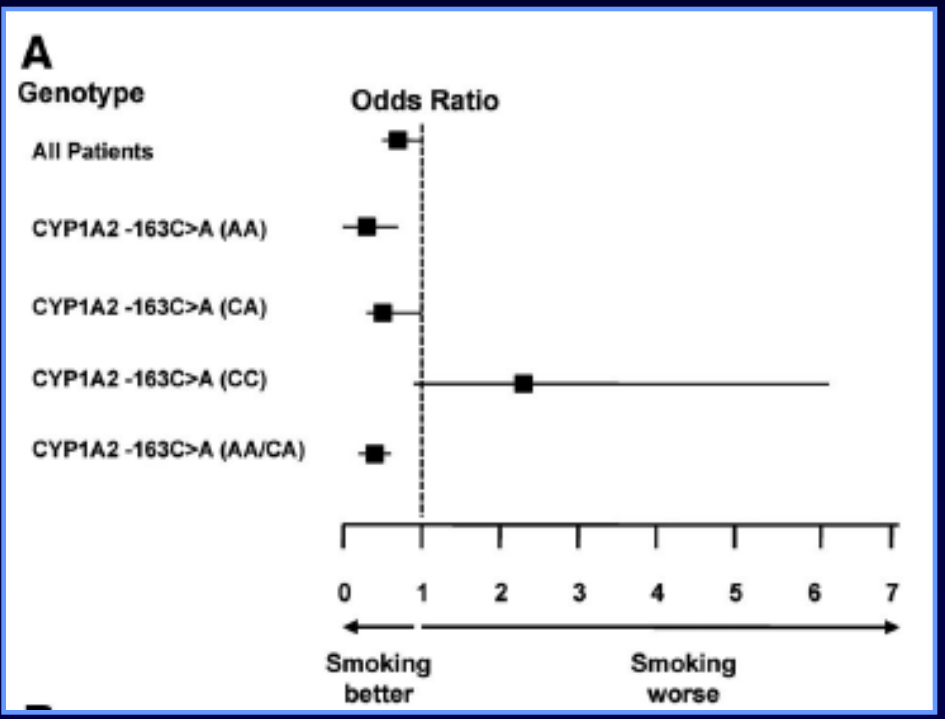
Important : ***CYP1A2*1C*** **(-3860G>A, decreased activity;Asians <24%, Caucasians <8%)**

CYP1A2*1F **(-163C>A, inducibility, all ethnicities 60%-80%)**

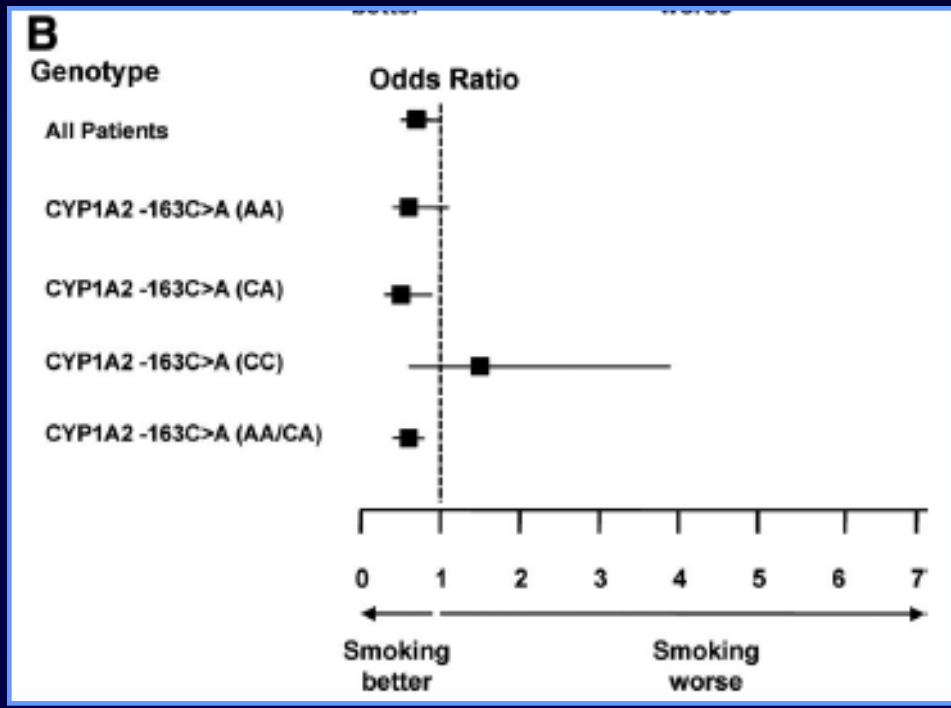
Zhou SF et al. *Drug Metab Rev*. 2010;42:268-354

*CYP1A2*1F* (163C>A)

HPR>275PRU



HPR>235PRU



Park KW et al. *Arterioscler Thromb Vasc Biol*. 2011;31:665-671

The Future is Now for Genotyping: Verigene System

Bench top instrumentation

Single-use disposable cartridges

Results available in 3 hours

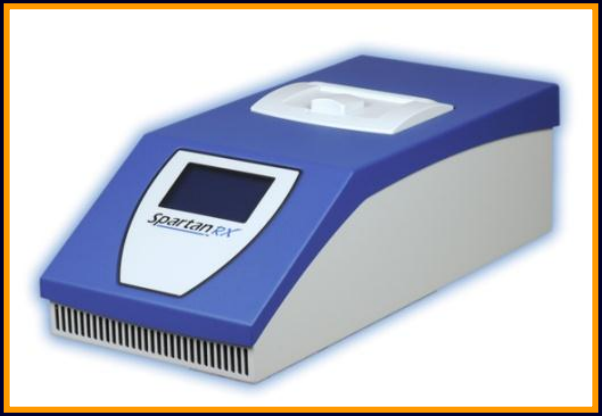
Verigene® *CYP2C19* Test Performance

Blinded Methods Comparison Study		Bi-Directional DNA Sequencing							
		*1/*1	*2/*1	*2/*2	*8/*1	*9/*1	*10/*1	*17/*1	*17/*17
Verigene® Test (*2-*10, *13, *17 alleles)	*1/*1	38							
	*2/*1		26						
	*2/*2			2					
	*8/*1				1				
	*9/*1					1			
	*10/*1						1		
	*17/*1							29	
	*17/*17								2

100% concordance,
100% sensitivity,
100% specificity

Gurbel PA et al., Presented at ACC 2011, New Orleans

The RAPID Program: Spartan RX CYP2C19 System



- Buccal Swab/Real Time PCR
- ½ hour course on machine
- 1 step insertion into machine
- 60 minutes to identify:
  - *CYP2C19*2* carrier status
  - Heterozygous vs. Homozygous

	Rapid Genotyping (N=91)	Standard Therapy (N=96)
Carriers of *CYP2C19*2* allele no.(%)	23(25.3)	23(24.0)
Heterozygous *CYP2C19*2* no.(%)	19(20.9)	20(20.8)
Homozygous *CYP2C19*2* no.(%)	4(4.4)	3(3.1)

Performance Characteristics of rapid Testing vs. Direct DNA Sequencing

- **Sensitivity – 100%**
- **Specificity – 99.4%**
- **Conclusive Rate – 93.6%**

So D , On behalf of the RAPID GENE Investigators, Presented at TCT 2011

Patient Enrollment

Patients undergoing PCI for non ST-ACS or stable CAD
N=200

Excluded patients
After Procedure:
- 2 did not undergo PCI
- 2 withdrawn from study by treating physician
- 1 had coronary dissection and underwent urgent CABG

Rapid Genotyping
N=102

Standard Therapy
N=98

***CYP2C19*2* Carriers**
N=23

Non-Carriers
N=74

Clopidogrel 75 mg OD

Excluded patients
- 1 refused to return for Day 7 blood work
- 1 loss to follow-up

Prasugrel 10 mg OD

Clopidogrel 75 mg OD

Platelet Function Testing at 1 week

Excluded patients
- 4 refused to return for Day 7 blood work
- 2 inconclusive readings on platelet function measurements

Point-of-Care Genotyping

***CYP2C19*2* Carriers**
N=23

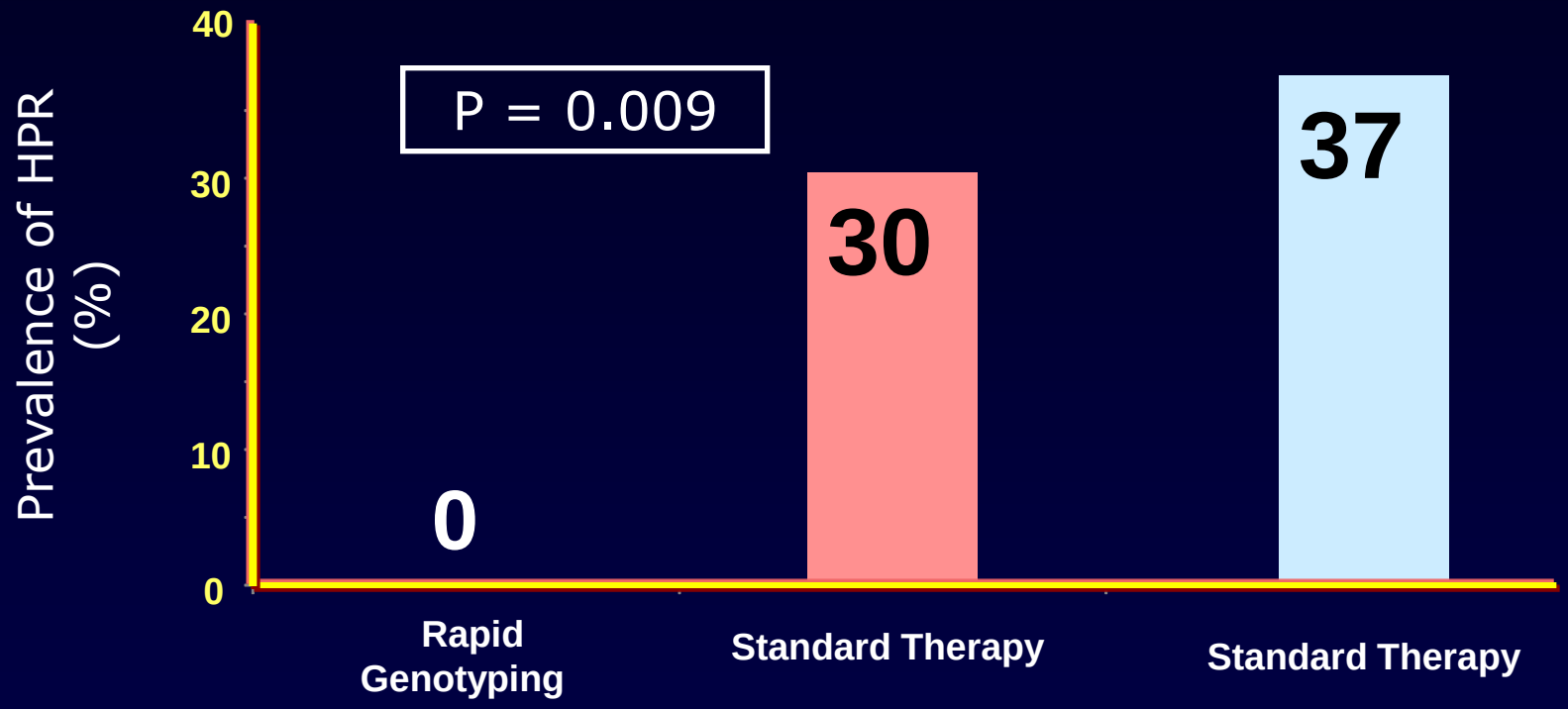
Non-Carriers
N=68

***CYP2C19*2* Carriers**
N=23

Non-Carriers
N=73

So D , On behalf of the RAPID GENE Investigators, Presented at TCT 2011

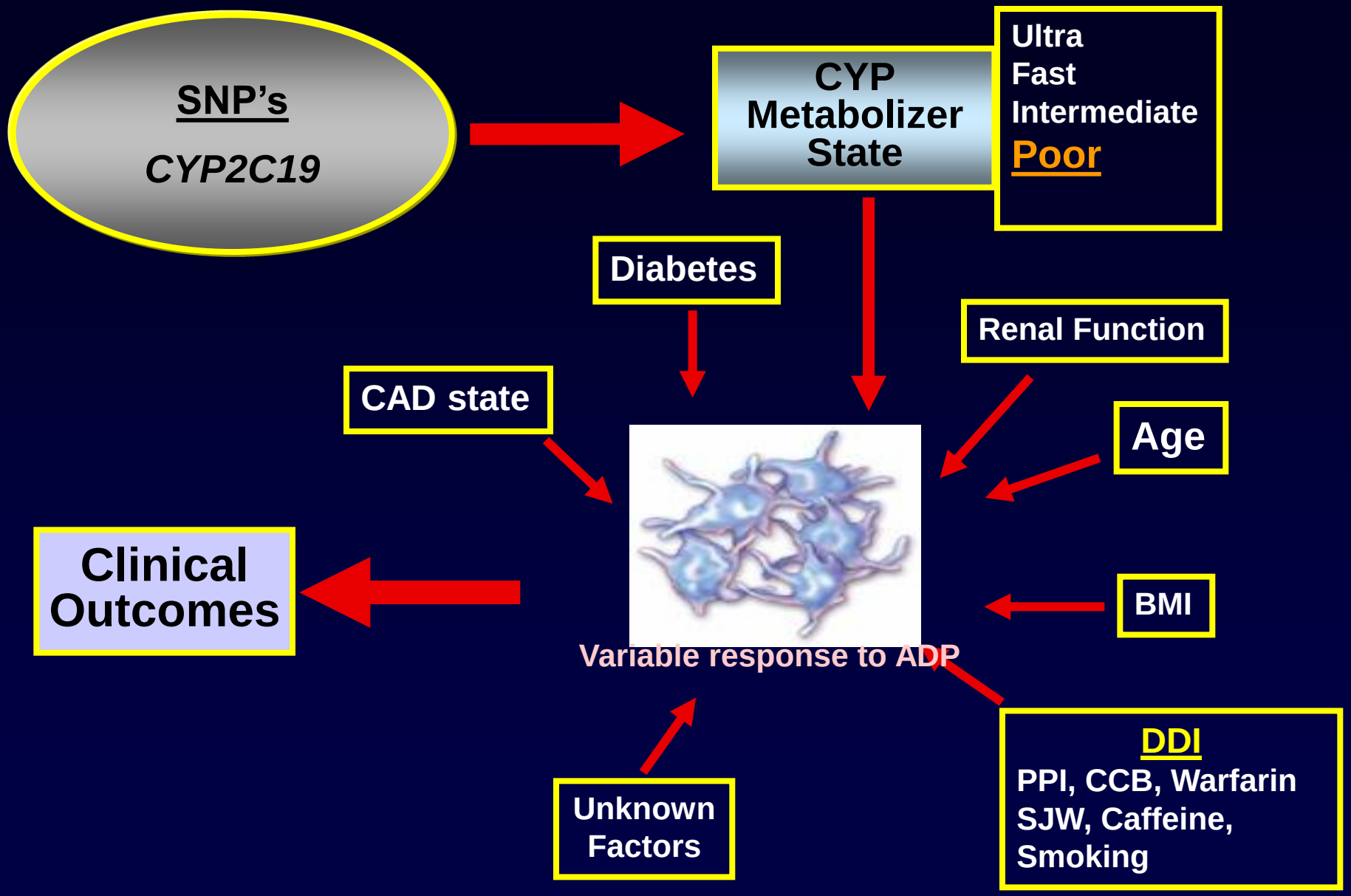
Primary Endpoint: Proportion of *CYP2C19*2* Carriers with High On-treatment Platelet Reactivity (PRU>234)



So D , On behalf of the RAPID GENE Investigators, Presented at TCT 2011

Gurbel PA et al. *Am Heart J* . 2011;161:598-604

Clopidogrel Metabolism Through the Eyes of a Geneticist



Adapted from Gurbel PA, et al. *J Am Coll Cardiol.* 2010;56:112-6

Consensus/Guidelines/Alerts/FDA Statements Addressing Platelet Function/Genetic Testing

CLINICAL ALERT

ACCF/AHA Clopidogrel Clinical Alert: Approaches to the FDA "Boxed Warning"

A Report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the American Heart Association

Endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons

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ACCF/AHA FOCUSED UPDATE

2011 ACCF/AHA Focused Update of the Guidelines for the Management of Patients With Unstable Angina/ Non–ST-Elevation Myocardial Infarction (Updating the 2007 Guideline)

European Heart Journal Advance Access published August 26, 2011

ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation

PRACTICE GUIDELINE

2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention

III-No Benefit:
Routine Analysis

IIb

Conclusions

In the PCI/ACS pts. (most prothrombotic state) treated with clopidogrel:

1) The rationale for genotyping is to Identify the High Risk Phenotype

2) A link exists between clinical risk and:
   a) high platelet reactivity (PD) b) LOF carrier state (PG)

3) HOWEVER, a link between:
   PG → PD → clinical outcomes not yet confirmed in a single study.

4) PK and PD are highly variable in any PG (except poor metabolizers):

   genotyping ≠ phenotyping

5) Only one genotype (*2/*2) correlates well with the worrisome phenotype
   Otherwise, genotyping poorly identifies the individual patient with HPR

6) The influence of *ABCB1*, *CYP 2C19*17* and *PON1* are inconclusive

7) The new $P2Y_{12}$ blockers are effective in overcoming the PG limitations of clopidogrel.

No prospective study demonstrated the utility of genotype in improving clinical outcome

Pharmacogenomics of Anti-platelet Intervention-2 (PAPI-2) Study

A Prospective, Multicenter, Randomized Trial of Genotype-directed (G-D) versus Standard of Care (SOC) Anti-platelet Therapy