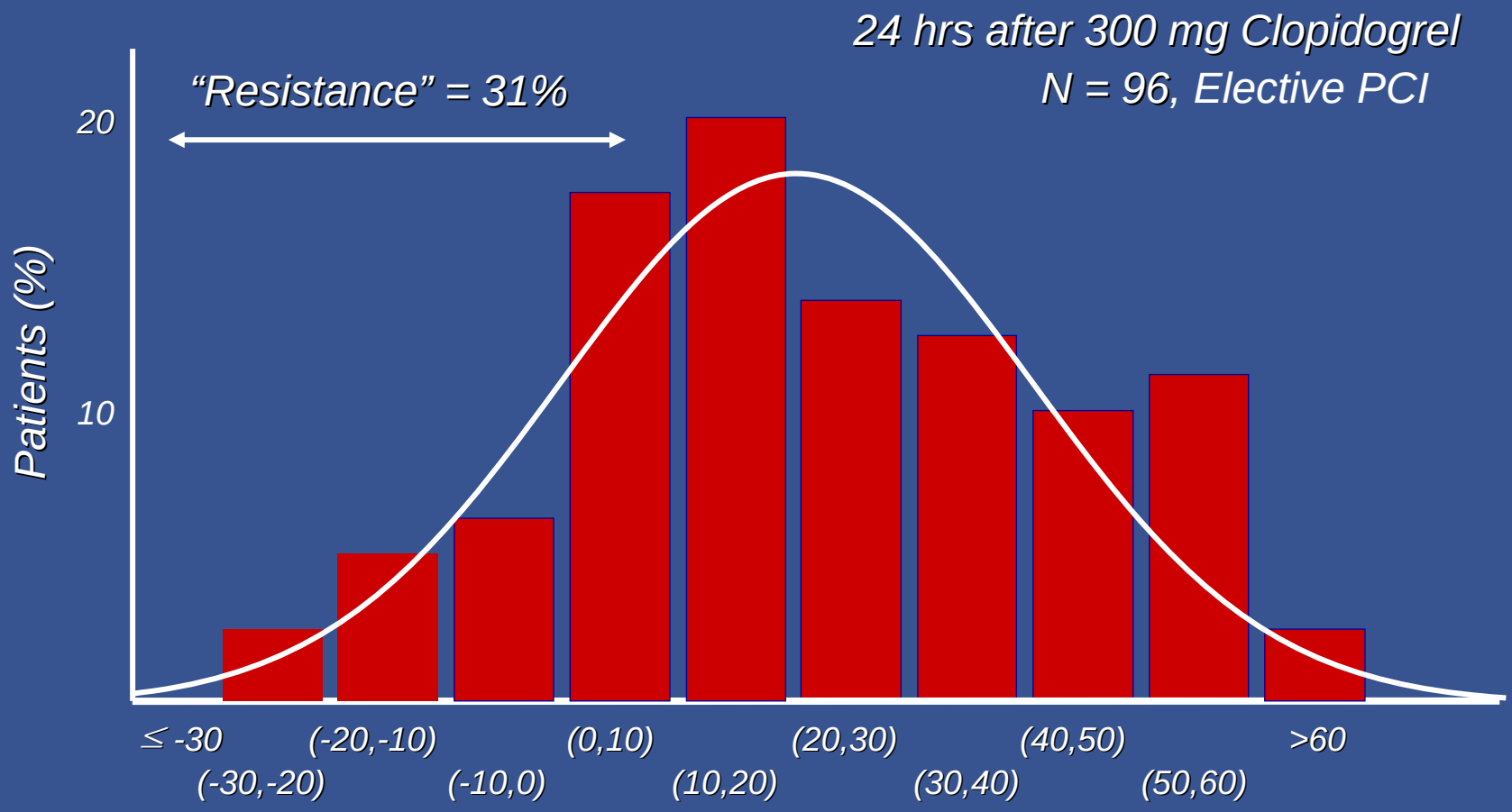
Is It Real? CYP450 Genetic Polymorphisms, Varying Response to Clopidogrel, and Link to Clinical Outcomes: Global Perspective

Alan C. Yeung, MD
Li Ka Shing Professor of Medicine
Director, Interventional Cardiology
Chief, Division of Cardiovascular Medicine (Clinical)
Stanford University School of Medicine

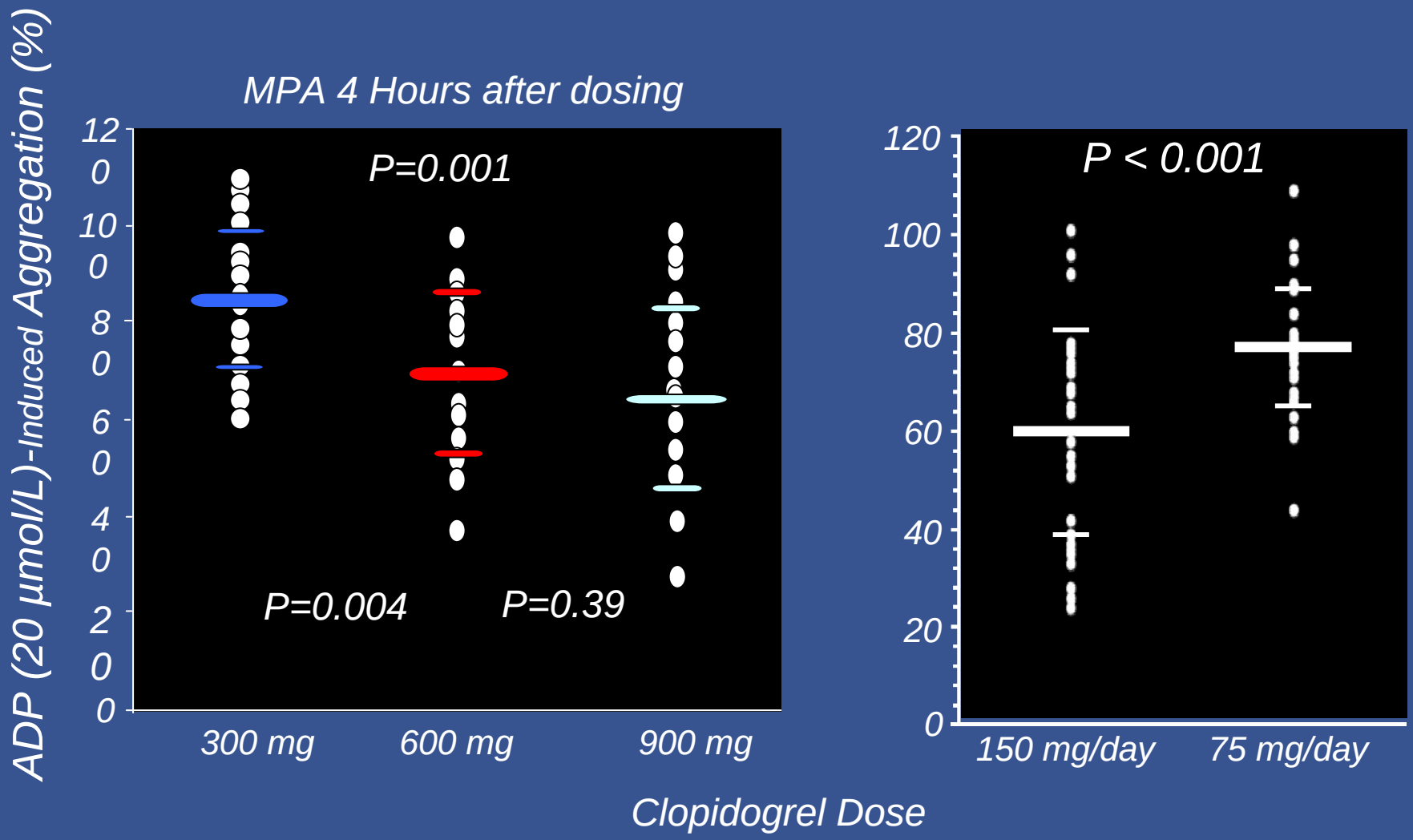
Variable Response to Clopidogrel



"Resistance" = ≤ 10% Δ platelet aggregation

Gurbel PA et al. Circulation 2003; 107: 2908-2913

Persistent Variability in Platelet Inhibition (MPA) With High Dose Clopidogrel

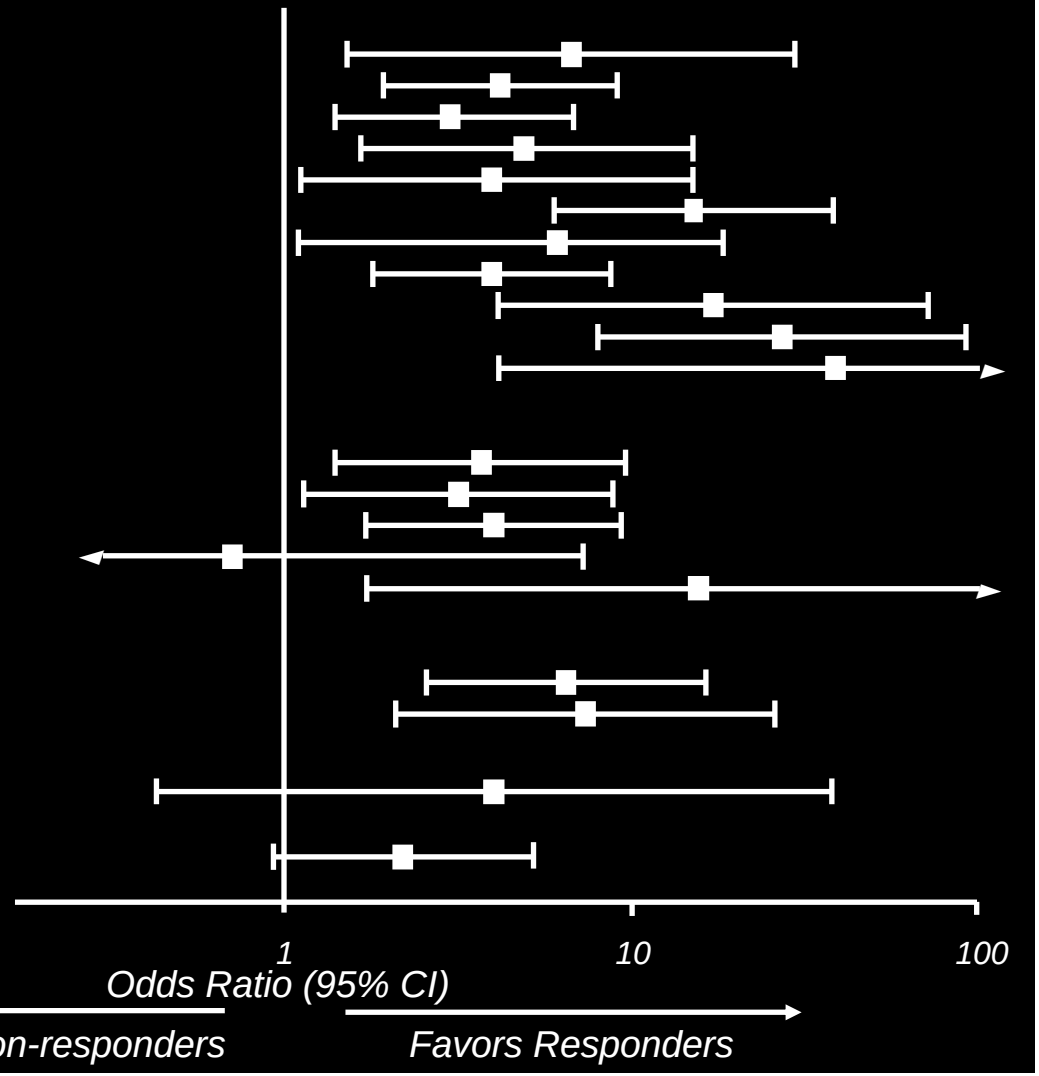


MPA=Maximum Platelet Aggregation

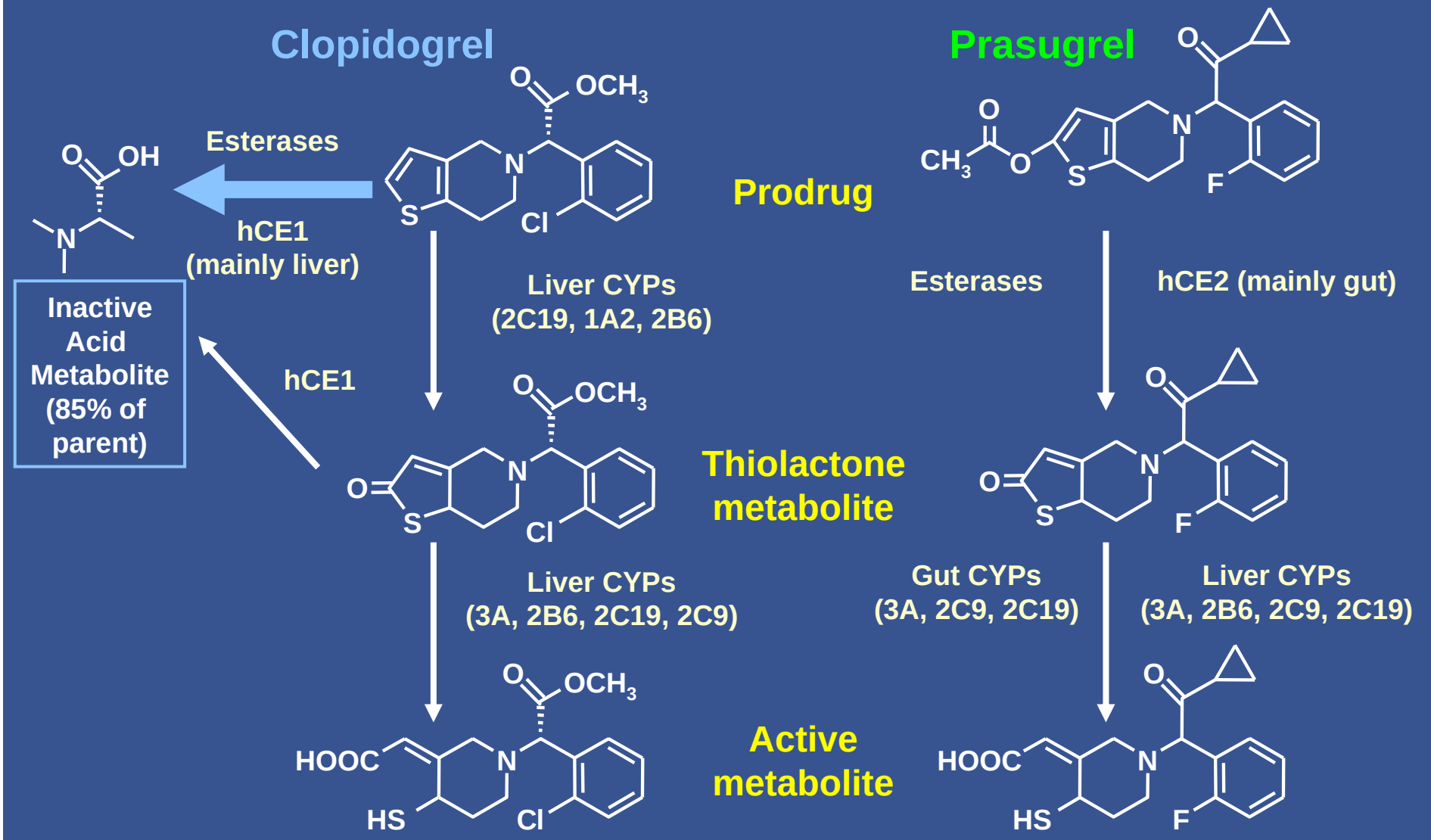
von Beckerath N, et al. Circulation 2005;112(19):2946-2950

Pharmacodynamic Non-response to Clopidogrel is Associated With an Increase in Ischemic Events

	N	Event rate Responders	Non-responders
COMPOSITE ISCHEMIC ENDPOINTS			
Hochholzer 2006	*802*	*0.5*	*3.3*
Buonamici 2007	*804*	*2.7*	*10.5*
Trenk 2008	*765*	*2.0*	*6.0*
Geisler 2006	*363*	*5.6*	*22.7*
Suh 2006	*348*	*1.9*	*7.3*
Cuisset JACC 2006	*292*	*3.0*	*31.0*
Patti 2008	*160*	*10.0*	*30.0*
Angiolillo 2008	*173*	*13.2*	*37.8*
Cuisset JTH 2006	*106*	*4.0*	*39.0*
Bliden 2007	*100*	*9.0*	*72.0*
Matetzky 2004	*60*	*2.0*	*47.0*
STENT THROMBOSIS			
Trenk 2008	*765*	*1.3*	*4.6*
Gori 2008	*746*	*2.6*	*13.3*
Buonamici 2007	*804*	*2.3*	*8.6*
Wenewaser 2005	*73*	*31.2*	*25.0*
Klamroth 2004	*40*	*36.7*	*90.0*
CARDIOVASCULAR DEATH			
Buonamici 2007	*804*	*1.4*	*8.6*
Geisler 2006	*363*	*2.9*	*18.2*
MYOCARDIAL INFARCTION			
Geisler 2006	*363*	*1.2*	*4.5*
MYONECROSIS/ELEVATED ENZYME			
Lev 2006	*150*	*17.3*	*32.4*



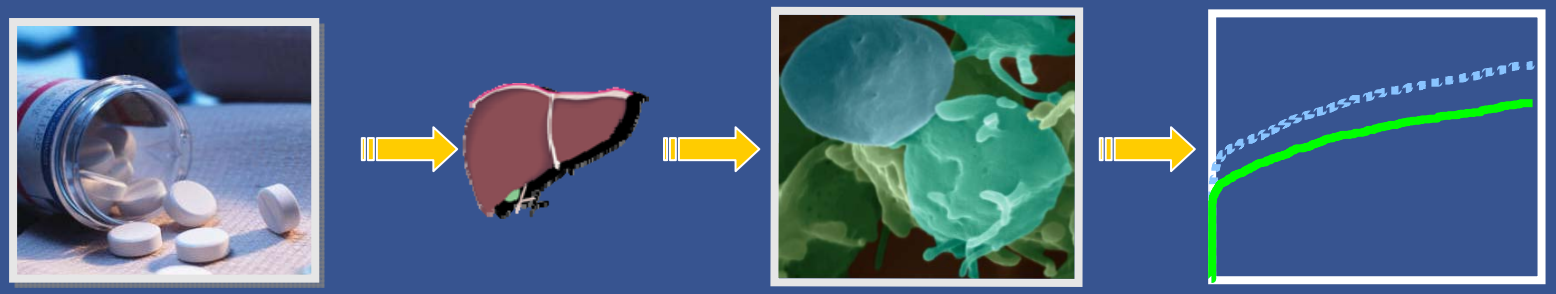
Active Metabolite Formation



Plavix® package insert, 2008
Kurihara A et al. *Drug Metab Rev* 2005;37(S2):99
Tang M et.al. *J Pharmacol Exp Ther* 2006;319(3):1467-1476

Farid NA et al. *Drug Metab Dispos* 2007;35(7):1096-1104
Rehmel JL et al. *Drug Metab Dispos* 2006;34(4):600-607
Williams ET et al. *Drug Metab Dispos* 2008;36(7):1227-1232

Genetic Hypothesis



Prodrug *Conversion to active metabolite (PK)* *Platelet response (PD)* *Clinical response*

CYP Genotypes

- Does CYP variation effect generation of AM? PD?
- If so, does this affect clinical outcome rates?
  - Efficacy: increased cardiovascular event rate in those unable to effectively generate active metabolite.
  - Bleeding: decreased bleeding in those unable to generate AM.

Investigating Variation in CYP450 Enzymes

5 Genes: CYP 3A5, 2B6, 2C19, 2C9, 1A2
Genetic Variation: SNPs, in/del, STR

↓

48 DNA Variants

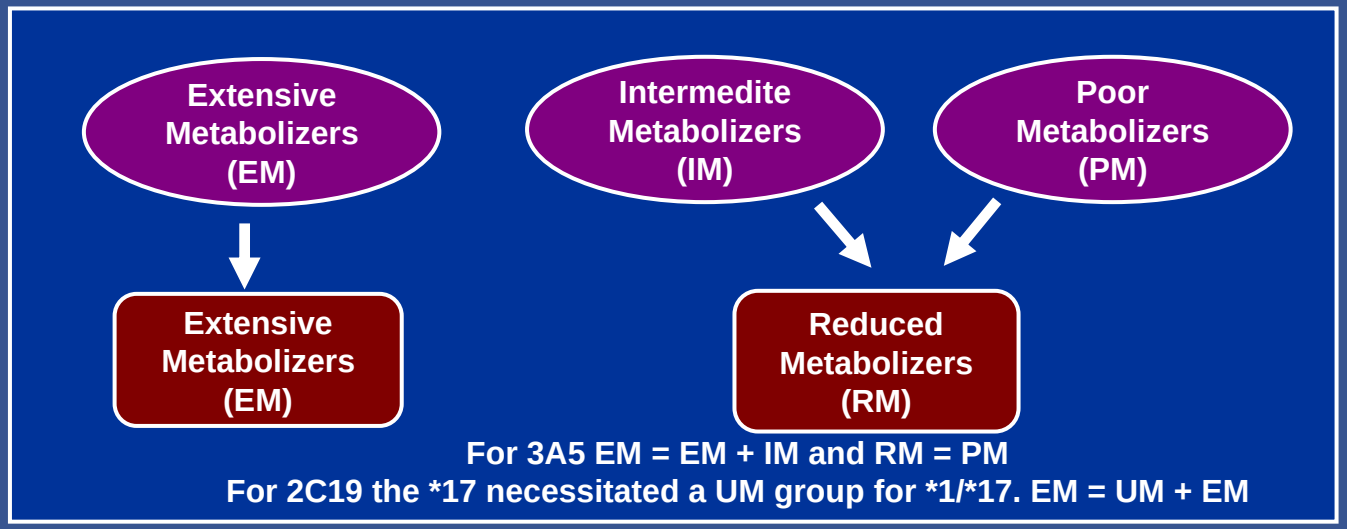
↓

Translation into Star Allele Nomenclature
eg. CYP2C19 *2
54 Different Allele ("normal" by default)

↓

Predicted Genetic Functional Group

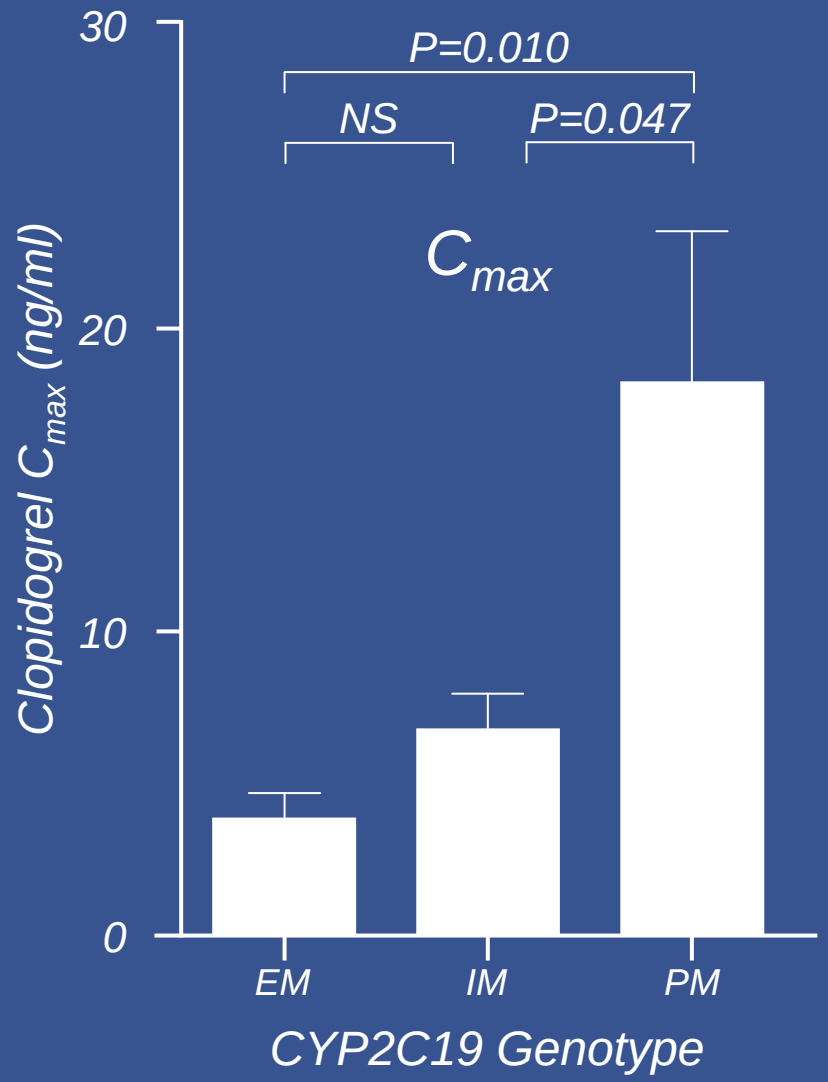
Comparison by predicted metabolic function

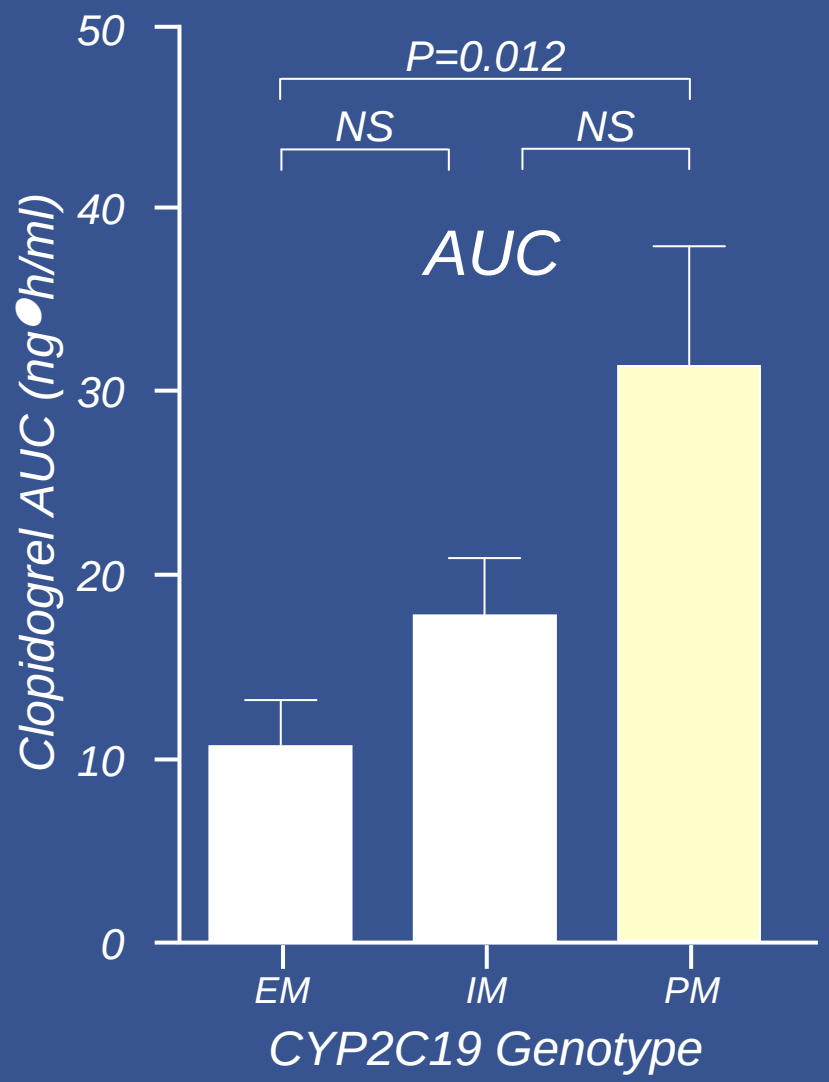


Daly TM et al. *Clin Chem* 2007;53(7):1222-1230

Close SL et al. *Eur Heart J* 2008;29(S1):759

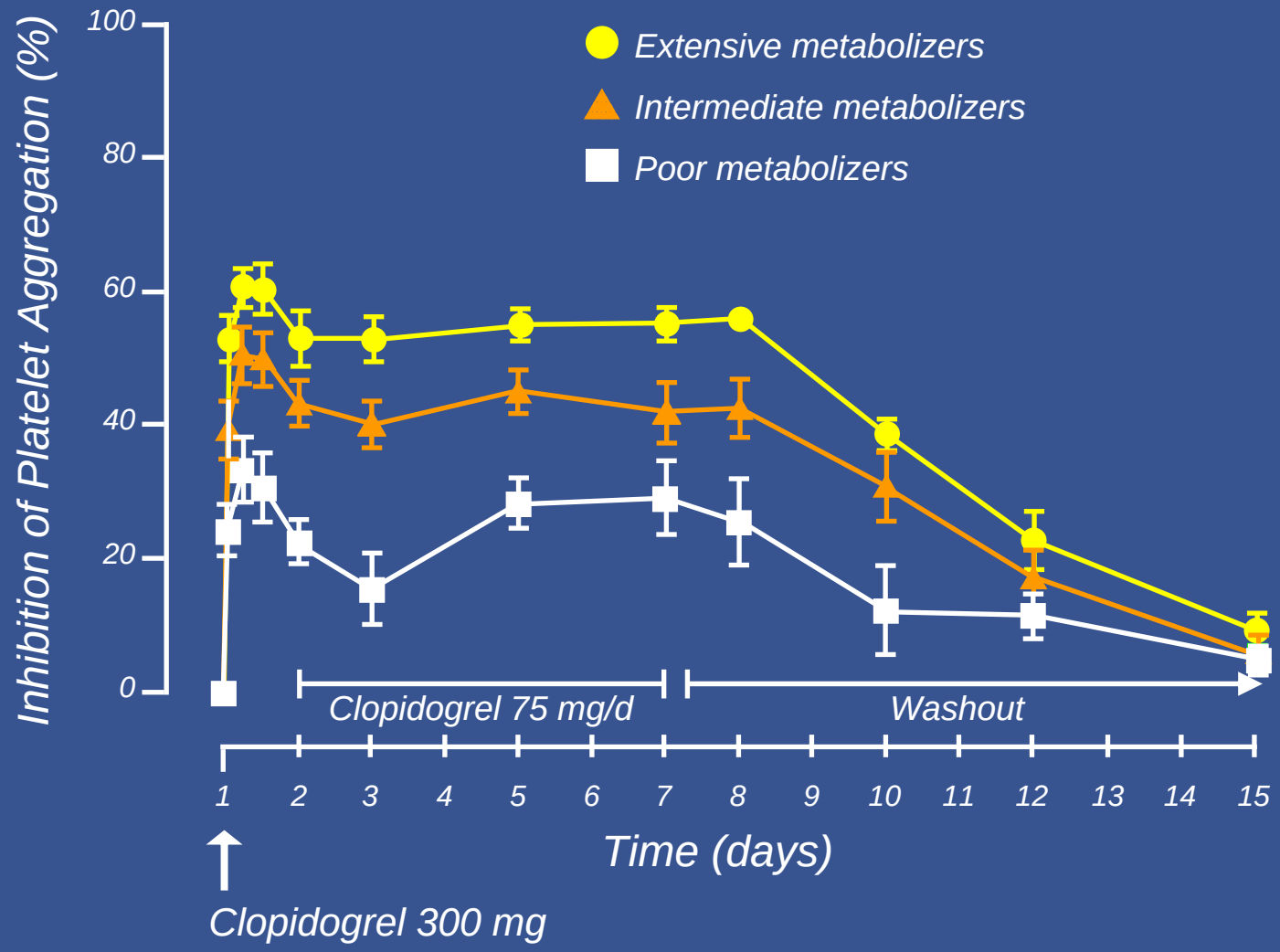
Pharmacokinetics of the Parent Compound by *CYP2C19* Genotype for Clopidogrel





Kim KA et al. Clin Pharmacol Ther 2008; 84(2):236-242

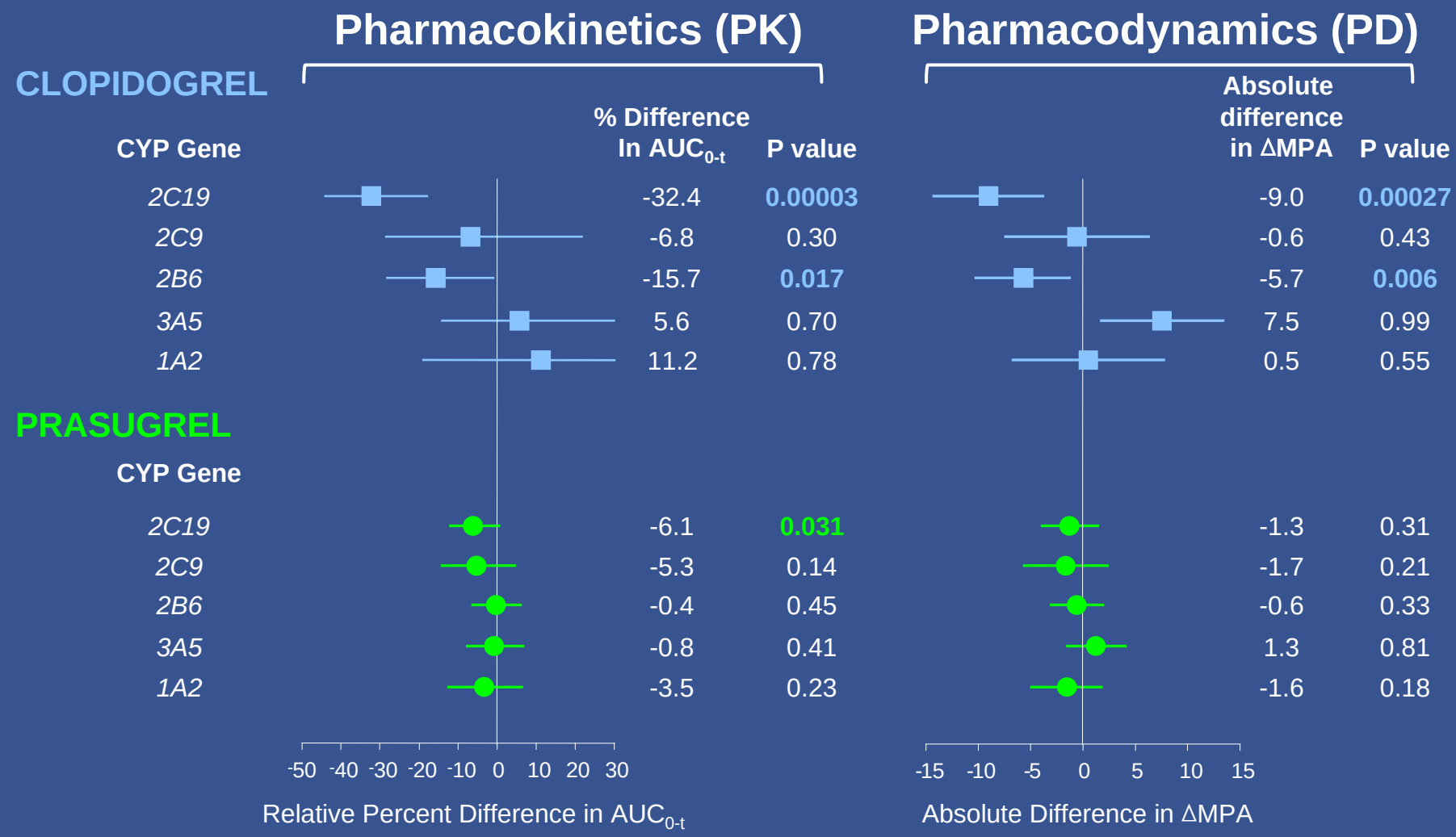
Mean IPA in Relation to *CYP2C19* Genotype for Clopidogrel



Adapted from Kim KA et al. Clin Pharmacol Ther 2008; 84(2):236-242

Investigation in Healthy Subjects

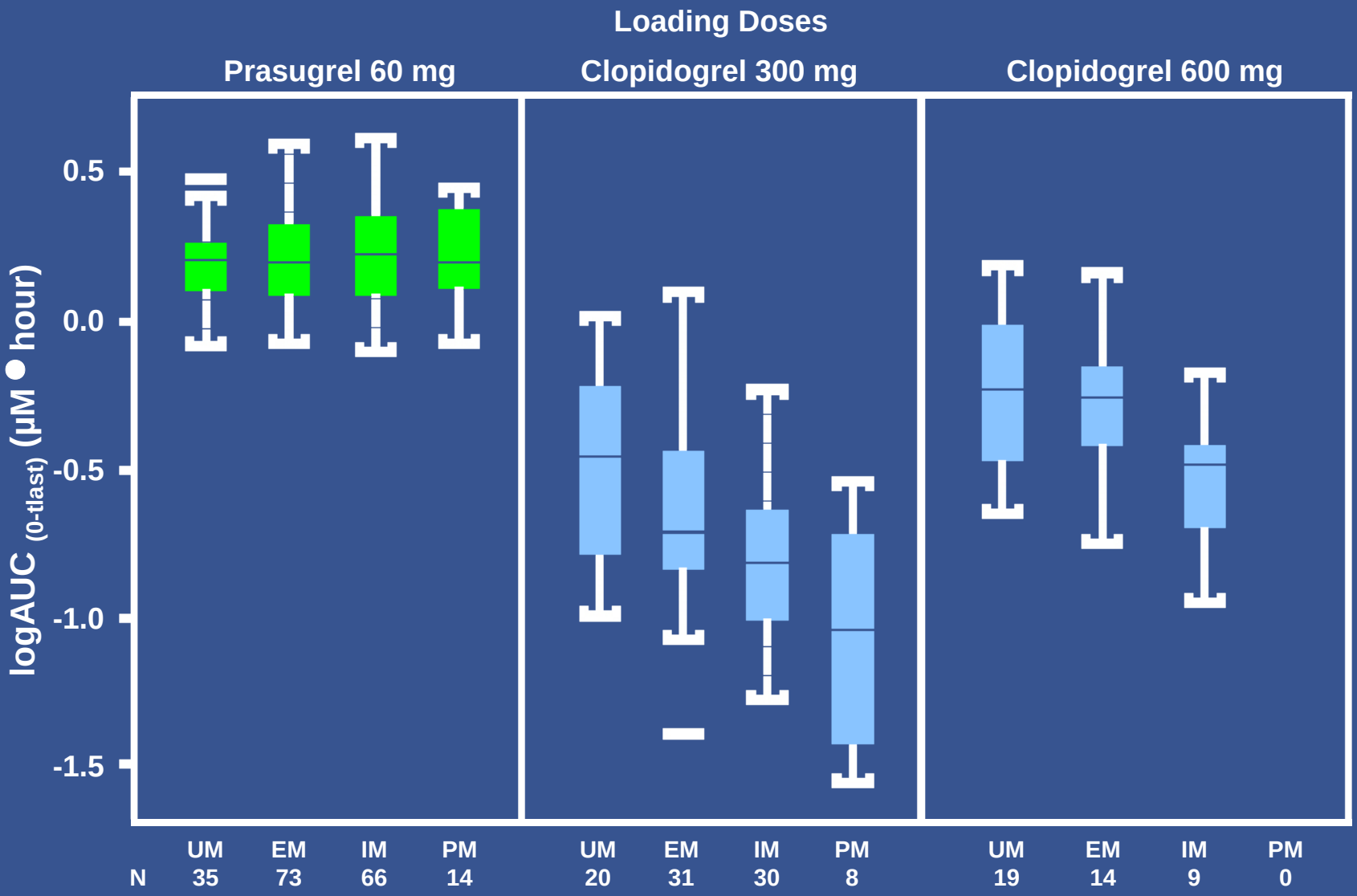
Genetic Effects on Pharmacokinetic and Pharmacodynamic Parameters



- **Model-based mean estimates and 95% confidence intervals for genetic effects in carriers vs. non-carriers of reduced function alleles in 346 healthy subjects (includes LD and MD data)**

Mega JL et al. *Circulation* 2008;118(18)(S2):S325-S326; Mega JL et al. *N Engl J Med* 2009;360(4):354-362

Relationship Between CYP2C19 and Exposure to Active Metabolite

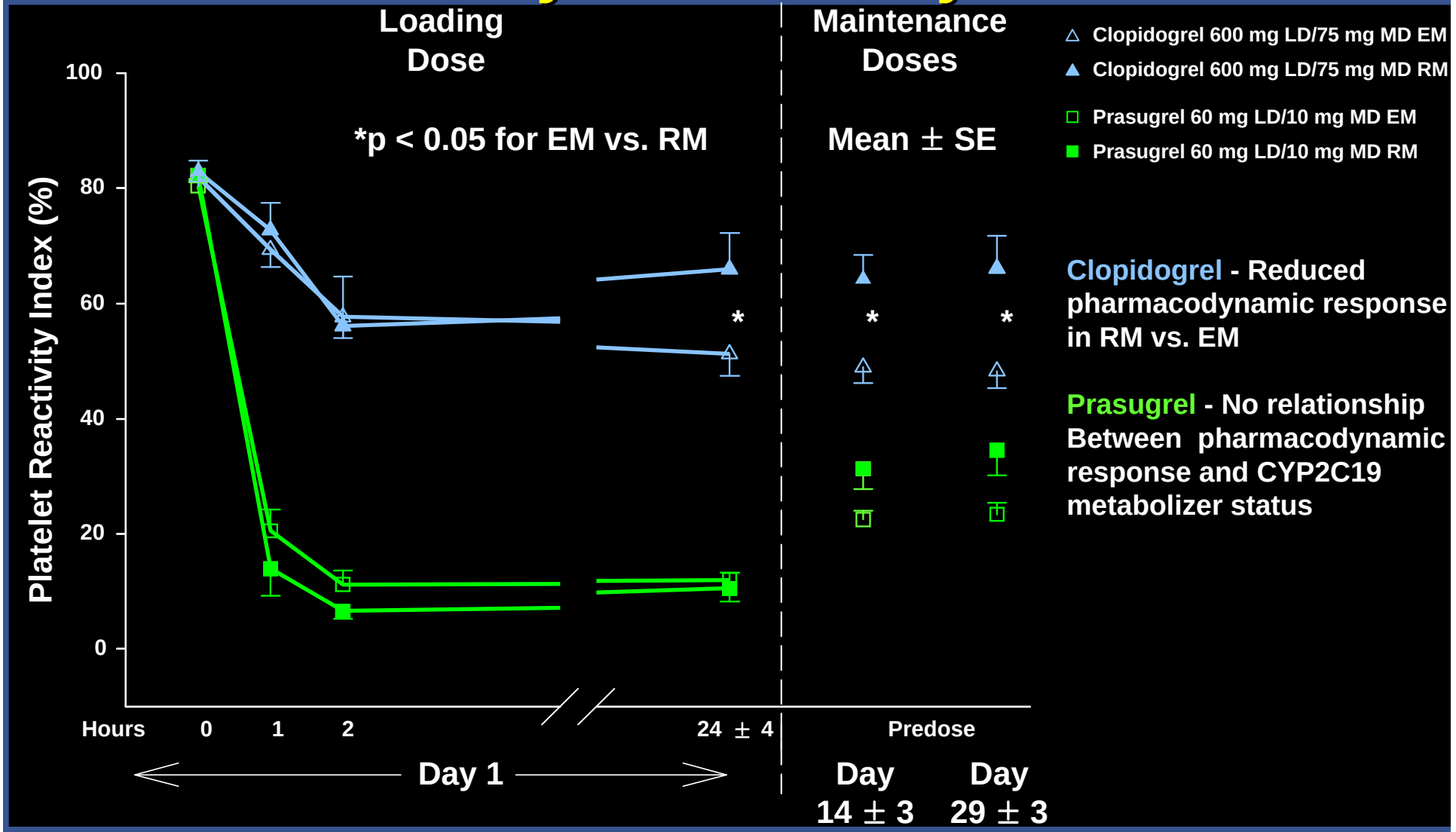


Box represents median, 25th, and 75th percentiles; whiskers represent the most extreme values within 1.5 times inter-quartile range of the box and individual lines represent outlying values

Close SL et al. *Eur Heart J* 2008;29(S):759

Investigations in Patients

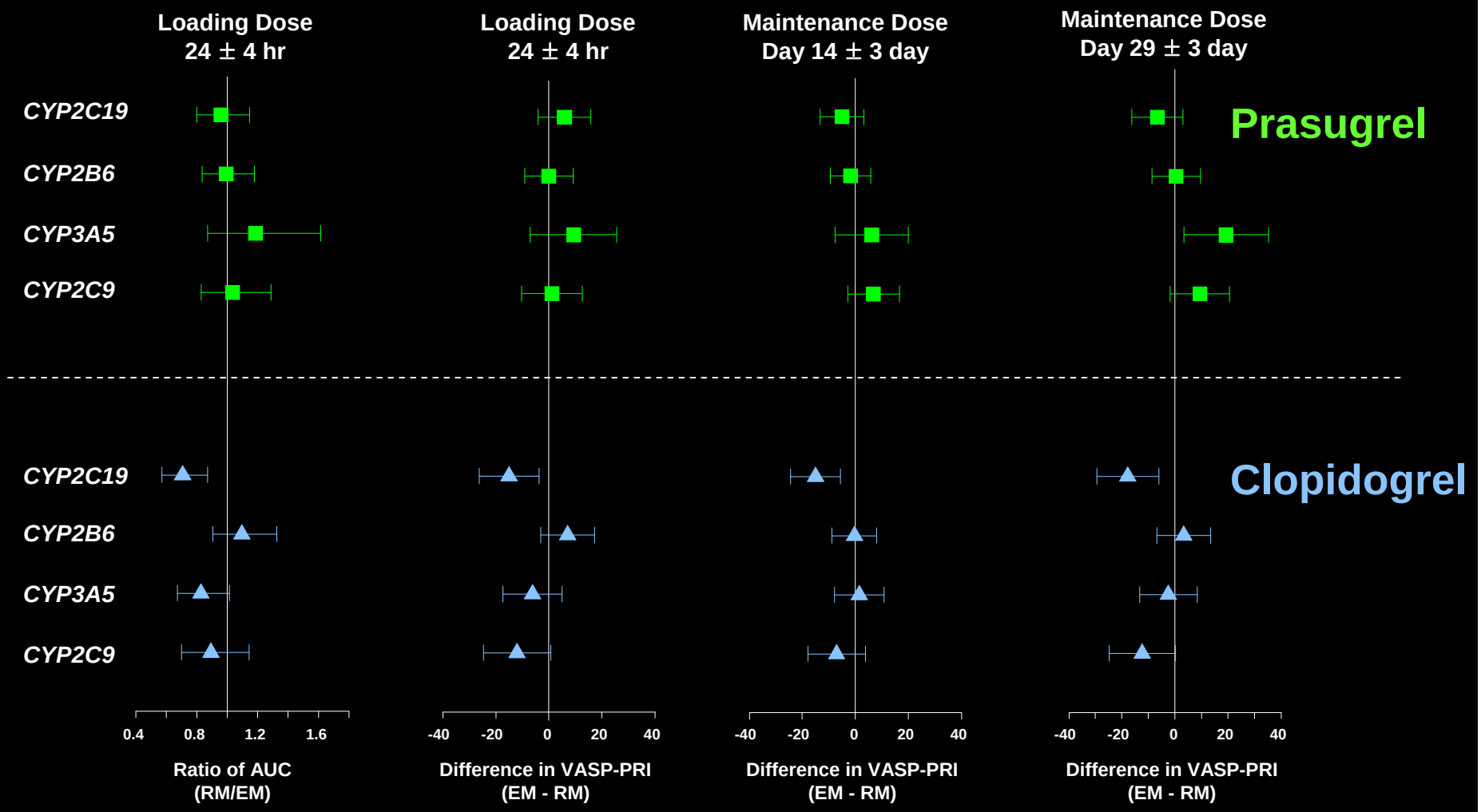
Platelet Inhibition by CYP2C19 Function as Measured by VASP Assay



EM=extensive metabolizer; RM=reduced metabolizer;
PRI=platelet reactivity index; VASP=vasodilator-stimulated phosphoprotein

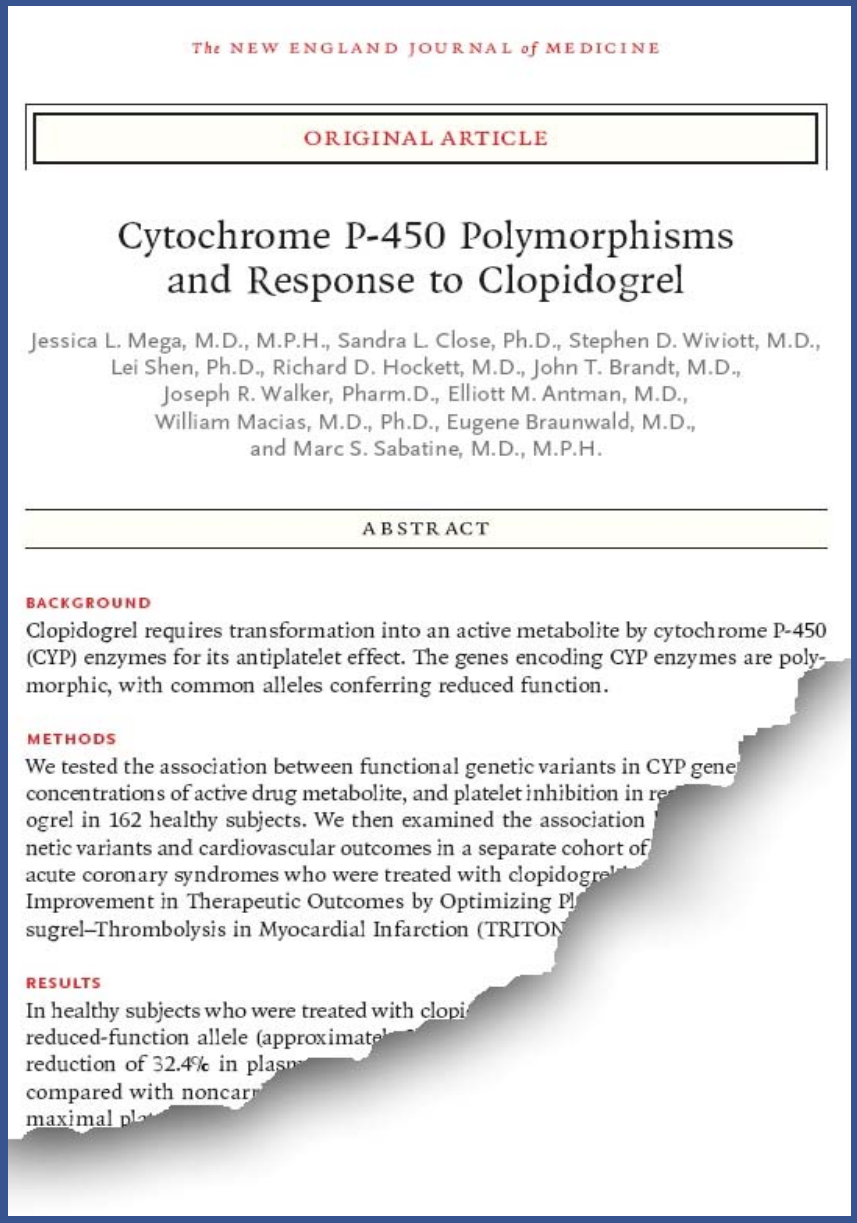
Varenhorst C et al. *Eur Heart J* 2009;30(14):1744-1752

Pharmacokinetic and Pharmacodynamic Responses for Other Cytochrome P450 Genes



AUC=area under the concentration-time curve
EM=extensive metabolizer; RM=reduced metabolizer
PRI=platelet reactivity index; VASP=vasodilator-stimulated phosphoprotein

Varenhorst C et al. *Eur Heart J* 2009;30(14):1744-1752



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cytochrome P-450 Polymorphisms and Response to Clopidogrel

Jessica L. Mega, M.D., M.P.H., Sandra L. Close, Ph.D., Stephen D. Wiviott, M.D., Lei Shen, Ph.D., Richard D. Hockett, M.D., John T. Brandt, M.D., Joseph R. Walker, Pharm.D., Elliott M. Antman, M.D., William Macias, M.D., Ph.D., Eugene Braunwald, M.D., and Marc S. Sabatine, M.D., M.P.H.

ABSTRACT

BACKGROUND

Clopidogrel requires transformation into an active metabolite by cytochrome P-450 (CYP) enzymes for its antiplatelet effect. The genes encoding CYP enzymes are polymorphic, with common alleles conferring reduced function.

METHODS

We tested the association between functional genetic variants in CYP gene
concentrations of active drug metabolite, and platelet inhibition in re
ogrel in 162 healthy subjects. We then examined the association
netic variants and cardiovascular outcomes in a separate cohort of
acute coronary syndromes who were treated with clopidogre
Improvement in Therapeutic Outcomes by Optimizing Pl
sugrel–Thrombolysis in Myocardial Infarction (TRITON

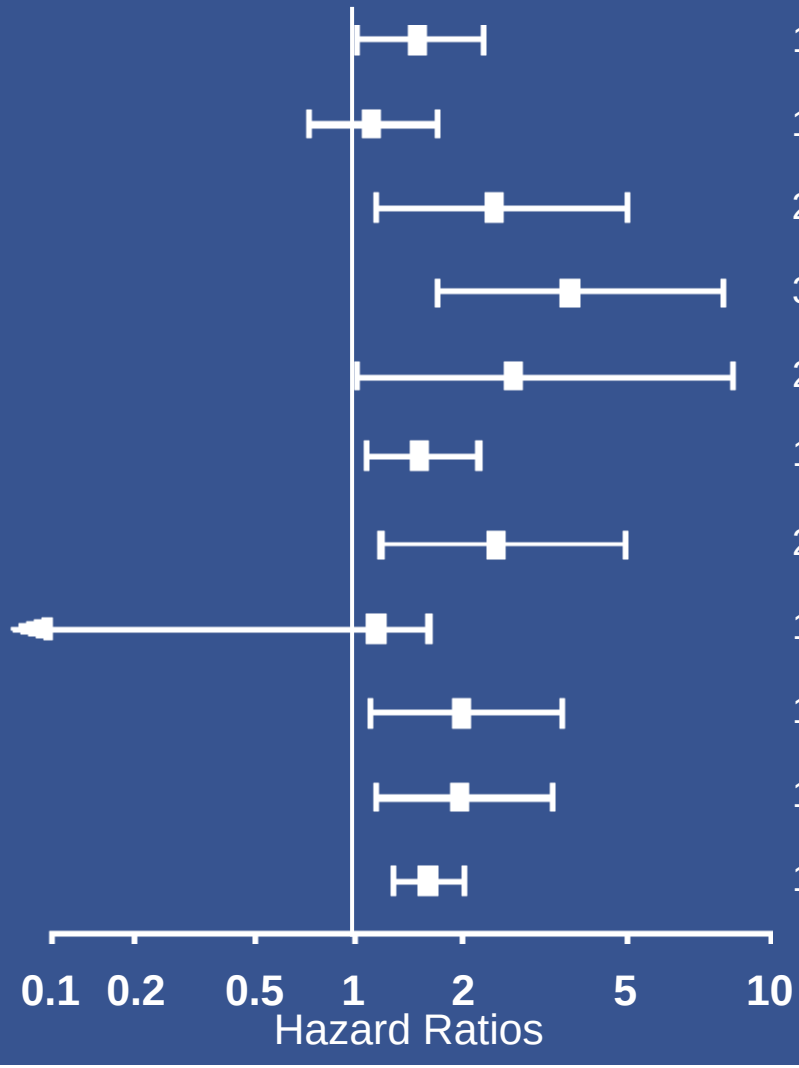
RESULTS

In healthy subjects who were treated with clopi
reduced-function allele (approximate
reduction of 32.4% in plasm
compared with noncarr
maximal pla

Papers published in *New England Journal of Medicine, Lancet, and European Heart Journal* show similar PGx associations (Collet 2009, Simon 2009, Guisti 2009)

Genetics and Cardiovascular Event Rates

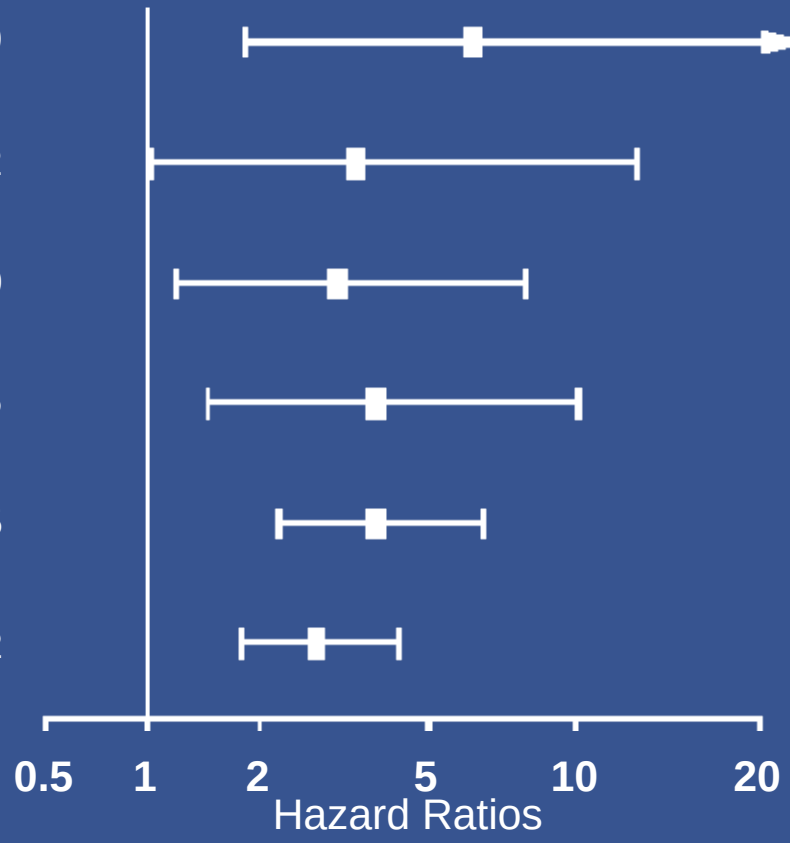
Study	N	HR
Anderson et al, *J Am Coll Cardiol* 2009	1250	1.50 (1.00-2.24)
Bhatt et al, 2010, wt/*2 vs *2/*2	2424	1.11 (0.72-1.71)
Bhatt et al, 2010, wt/wt vs *2/*2	2424	2.38 (1.14-5.00)
Collet et al, *Lancet* 2009	259	3.69 (1.69-8.05)
Giusti et al, *Am J Cardiol* 2009	772	2.70 (1.00-8.42)
Mega et al, *N Engl J Med* 2009	1459	1.53 (1.07-2.19)
Shuldiner et al, *JAMA* 2009	429	2.42 (1.18-4.99)
Sibbing et al, *Eur Heart J* 2009	2485	1.15 (0.08-1.61)
Simon et al, *N Engl J Med* 2009	2208	1.98 (1.10-3.58)
Sofi et al, *Pharmacogen J* 2010*	8043	1.96 (1.14-3.37)
Mega et al, *Circulation* 2009*	9684	1.61 (1.28-2.02)



***meta-analysis**

Genetics and Stent Thrombosis Rates

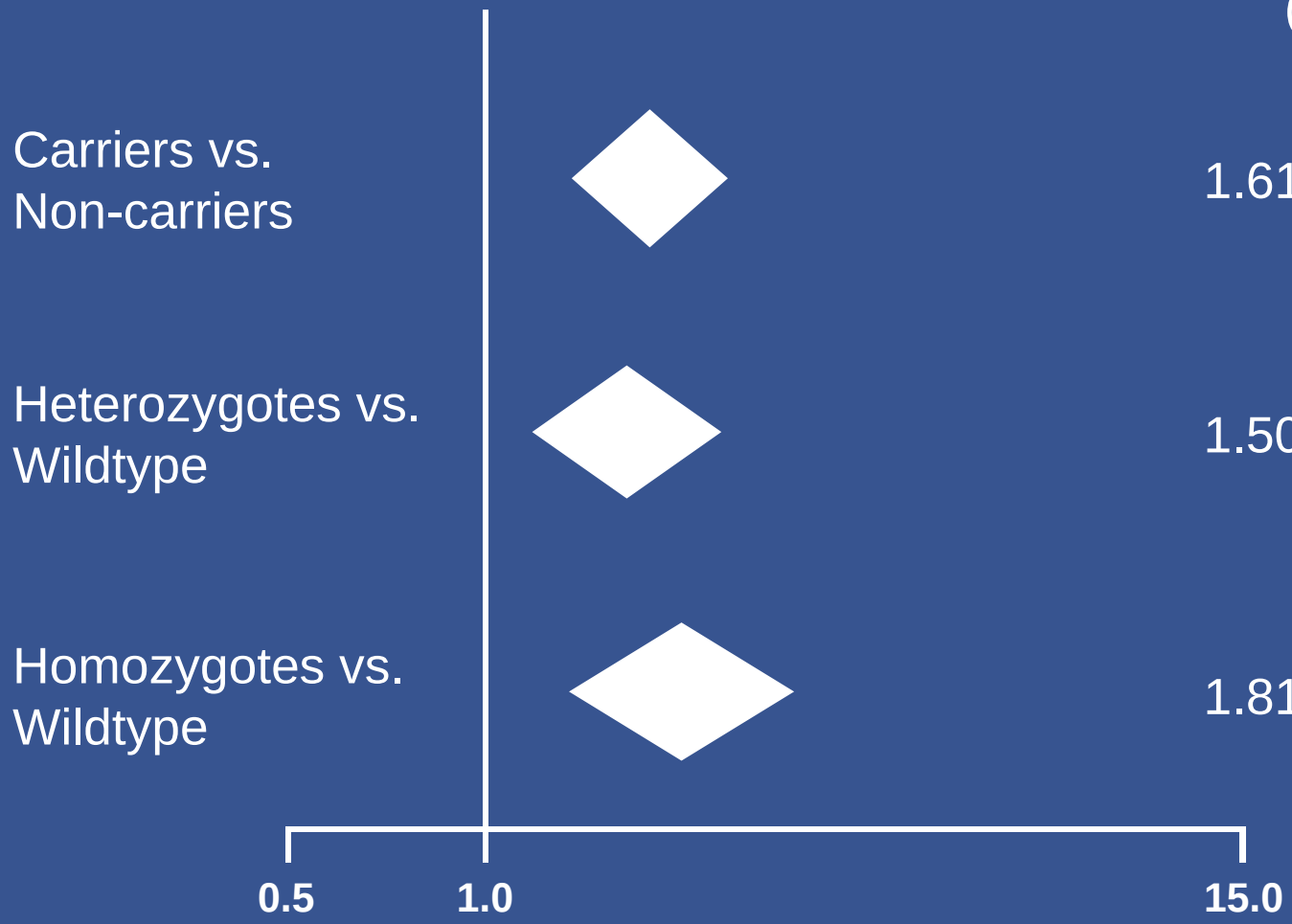
Study	N	HR
Collet et al, *Lancet* 2009	259	6.20 (1.81-20.04)
Giusti et al, *Am J Cardiol* 2009	772	3.43 (1.01-12.78)
Mega et al, *N Engl J Med* 2009	1459	3.09 (1.19-8.00)
Sibbing et al, *Eur Heart J* 2009	2485	3.81 (1.45-10.02)
Sofi et al, *Pharmacogen J* 2010*	4975	3.82 (2.23-6.54)
Mega et al, *Circulation* 2009*	5772	2.76 (1.77-4.30)



***meta-analysis**

Is it one allele or two that drives the genetic effect?

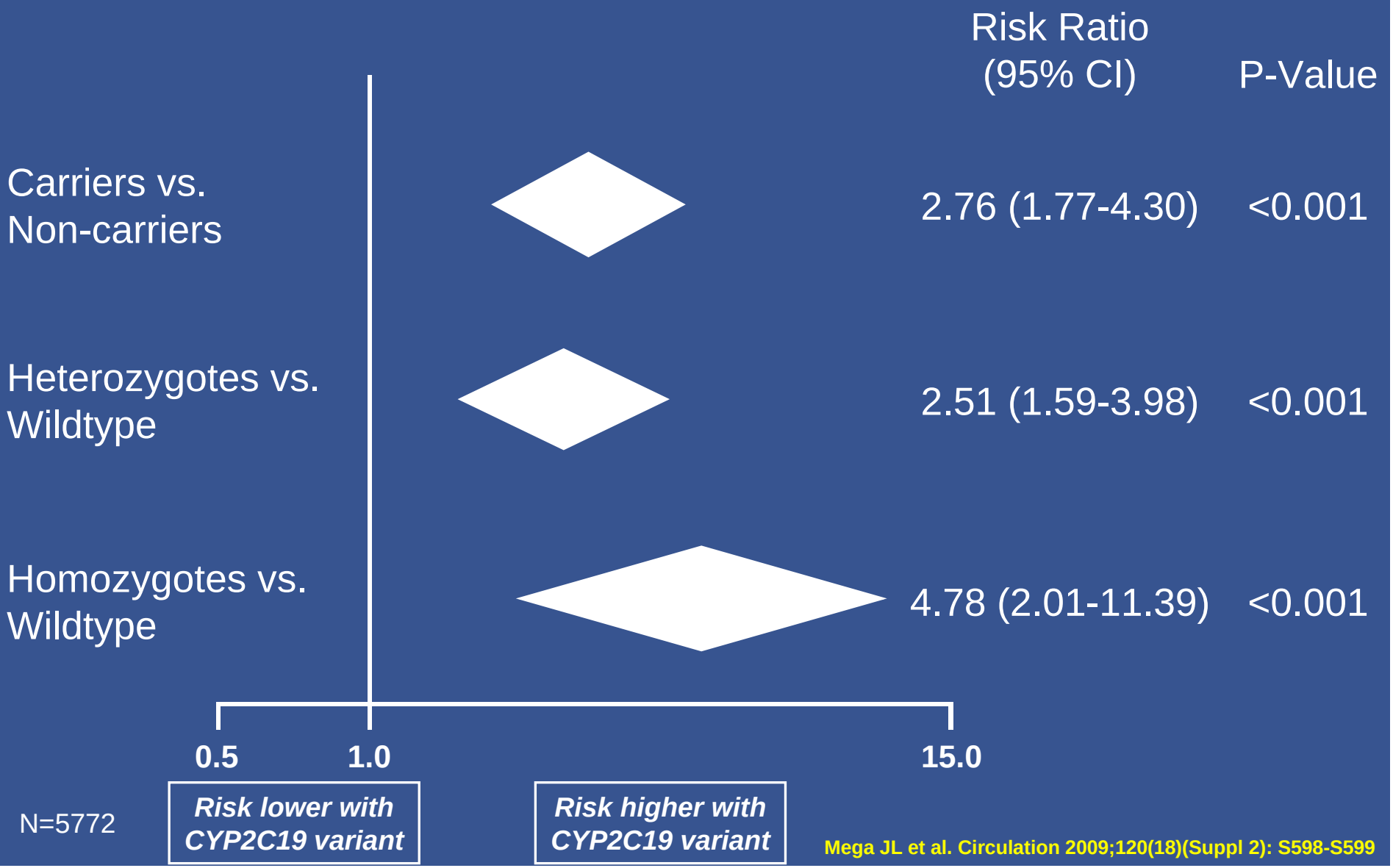
Major Adverse Cardiovascular Events



N=9684

Mega JL et al. Circulation 2009;120(18)(Suppl 2): S598-S599

Stent Thrombosis



N=5772

Mega JL et al. Circulation 2009;120(18)(Suppl 2): S598-S599

Unmet Medical Need in ACS/PCI