Gene Guided Anti-Platelet Therapy in the Era of Prasugrel

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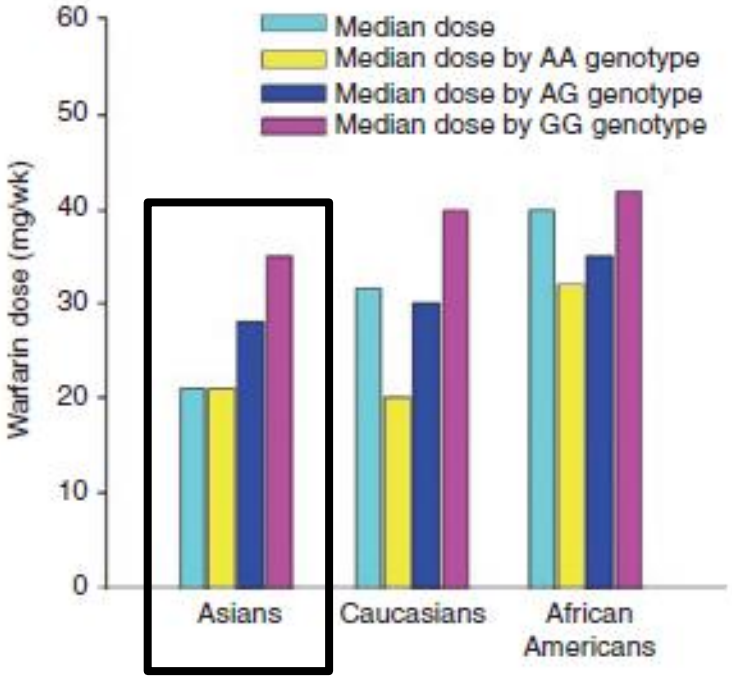
Cardiovascular Drug with Phamarcogenomic Labeling

Drug	Gene/biomarker	Label sections
Atorvastatin	*LDLR*	Warnings and precautions; clinical pharmacology; clinical studies
Carvedilol	*CYP2D6*	Drug interactions; clinical pharmacology
Clopidogrel	*CYP2C19*	Boxed warning; dosage and administration; warnings and precautions; drug interactions; clinical pharmacology
Isosorbide dinitrate/ hydralazine	*NAT1; NAT2*	Clinical pharmacology
Metoprolol	*CYP2D6*	Precautions; clinical pharmacology
Propafenone	*CYP2D6*	Clinical pharmacology
Propranolol	*CYP2D6*	Precautions; drug interactions; clinical pharmacology
Warfarin	*CYP2C9; VKORC1*	Dosage and administration; precautions; clinical pharmacology

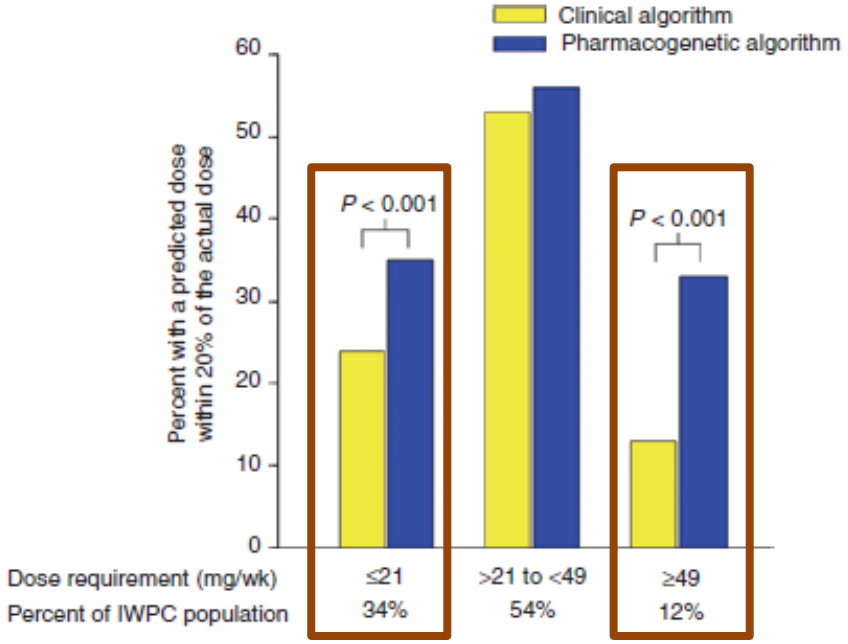
From http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm.

Johnsons JA et al. Clin Phamacol Ther 2011

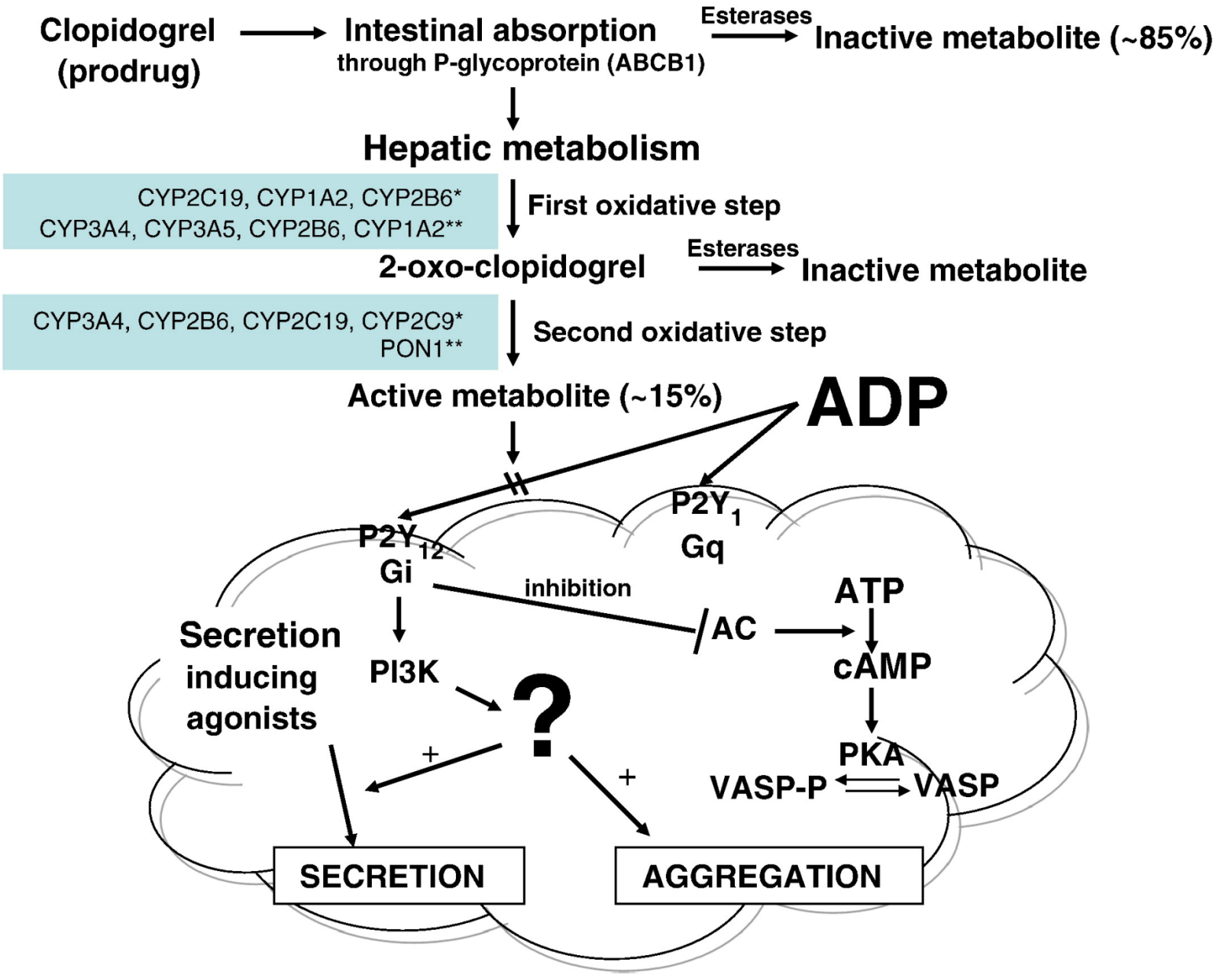
Median Warfarin Dose according to VKORC1 Genotype



Clinical or The Pharmacogenetic Dosing Algorithm



Johnsons JA et al. Clin Phamacol Ther 2011



Yin T, Miyata T. Thrombosis Research 2011

Pharmacogenomics - Common SNP's (2C19)

*17 = Gain-of-function SNP
(18% Americans, 16% Africans, 2% East Asians)

*2 = Loss-of-function SNP
(~12% Americans, 15% Africans, 29% East Asians)

*3 = Loss-of-Function SNP
(.02% Americans, .5% Africans, 9% East Asians)

*1 = Wild type

Common *CYP2C19* Genotypes	Genetically Predicted Phenotypes
*17/*17, *17/*1	**Extensive metabolizer (EM)**
*1/*1, *17/*2, *17/*3	**Normal metabolizer (NM)**
*1/*2, *1/*3	**Intermediate metabolizer (IM)**
*2/*2, *2/*3	**Poor metabolizer (PM)** ~2-5% Caucasians and African Americans, ~15% Asians

SNP, single-nucleotide polymorphism.
Scott SA et al, Clin Pharmacol Ther. 2011 Jun 29. doi: 10.1038/clpt.2011.132. [Epub ahead of print]

GENETIC VARIATIONS OF THE *CYP2C19 GENE*

- Genetic variations of CYP2C19 gene result in a spectrum of metabolic phenotypes:

Metabolic Phenotype		Genotype
Ultra-rapid Metabolizer	UM	*17/*17; *1/*17
Extensive Metabolizer	EM	*1/*1;
Intermediate Metabolizer	IM	*1/*2; *1/*3;
Poor Metabolizer	PM	*2/*2; *3/*3; *2/*3

- It remains open if the genotypes *2/*17 and *3/*17 result in an EM phenotype or an IM phenotype
- The *CYP2C19*2 and *3 polymorphisms are seen in
  - **more than 55% of Asians**
  - approximately 40% of African-Americans
  - approximately 30% of Caucasians
- The *CYP2C19*17 polymorphism frequency is upwards of 30-42% in Europeans and Africans, with approximately 2 to 8% being homozygous mutant.

PHARMACOGENETIC INFORMATION

- ***Plavix -2010 FDA: Black Box Warning***

WARNING: DIMINISHED EFFECTIVENESS IN POOR METABOLIZERS

The effectiveness of Plavix is dependent on its activation to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19 [see Warnings and Precautions (5.1)]. Plavix at recommended doses forms less of that metabolite and has a smaller effect on platelet function in patients who are CYP2C19 poor metabolizers. Poor metabolizers with acute coronary syndrome or undergoing percutaneous coronary intervention treated with Plavix at recommended doses exhibit higher cardiovascular event rates than do patients with normal CYP2C19 function. Tests are available to identify a patient's CYP2C19 genotype; these tests can be used as an aid in determining therapeutic strategy [see Clinical Pharmacology (12.5)]. Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers [see Dosage and Administration (2.3)].

Plavix PI, Bristol Meyers Squibb / Sanofi Pharmaceuticals, March 2010

PHARMACOGENETIC INFORMATION

- **2010 ESC Guidelines on Myocardial Revascularization**

  - The presence of the CYP2C19 loss-of-function allele seems to be associated with an increased risk of atherothrombotic complications in clopidogrel-treated patients. This allele does not influence the action of prasugrel on platelet function.

- **2011 ACCF/AHA Update on Management of patients with UA/NSTEMI**

2011 Focused Update Recommendations – Table 3	
Class IIb	Platelet function testing to determine platelet inhibitory response in patients with UA/NSTEMI (or, after ACVS and PCI) on thienopyridine therapy may be considered if results of testing may alter management (Level of Evidence: B)
Class IIb	Genotyping for CYP2C19 loss-of-function variant in patients with UA/NSTEMI (or, after ACVS and PCI) on thienopyridine therapy might be considered if results of testing may alter management (Level of Evidence: C)

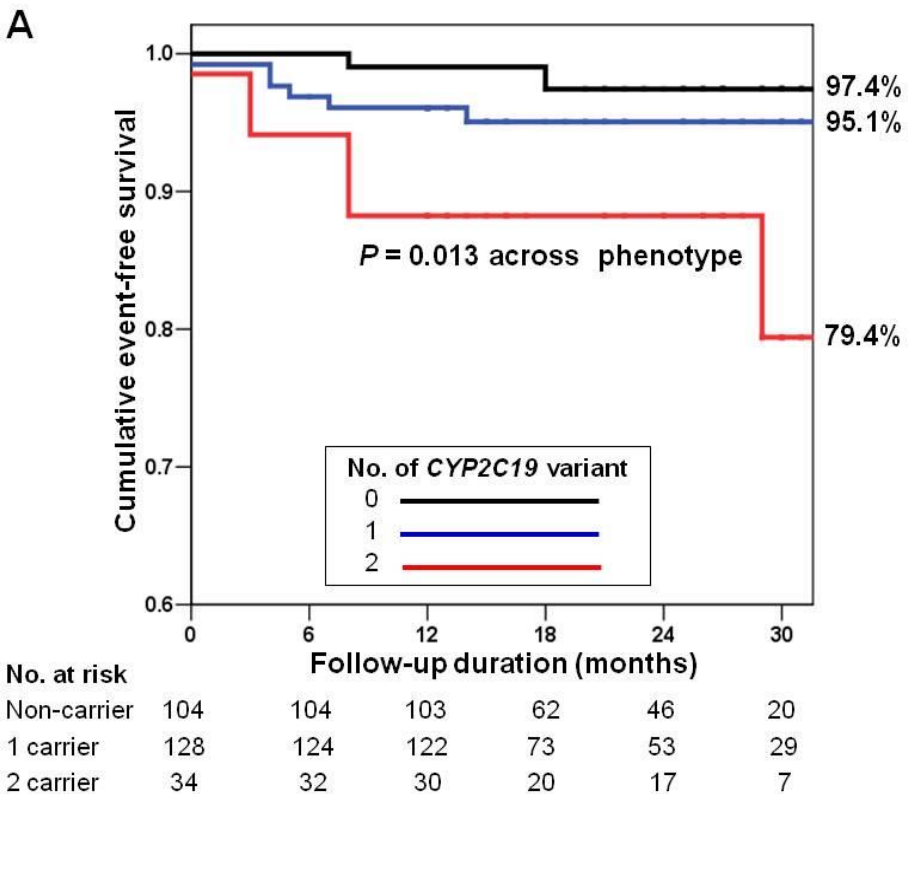
Flower, Andy Warhol

CYP450 2C19 Gene **Carrier**

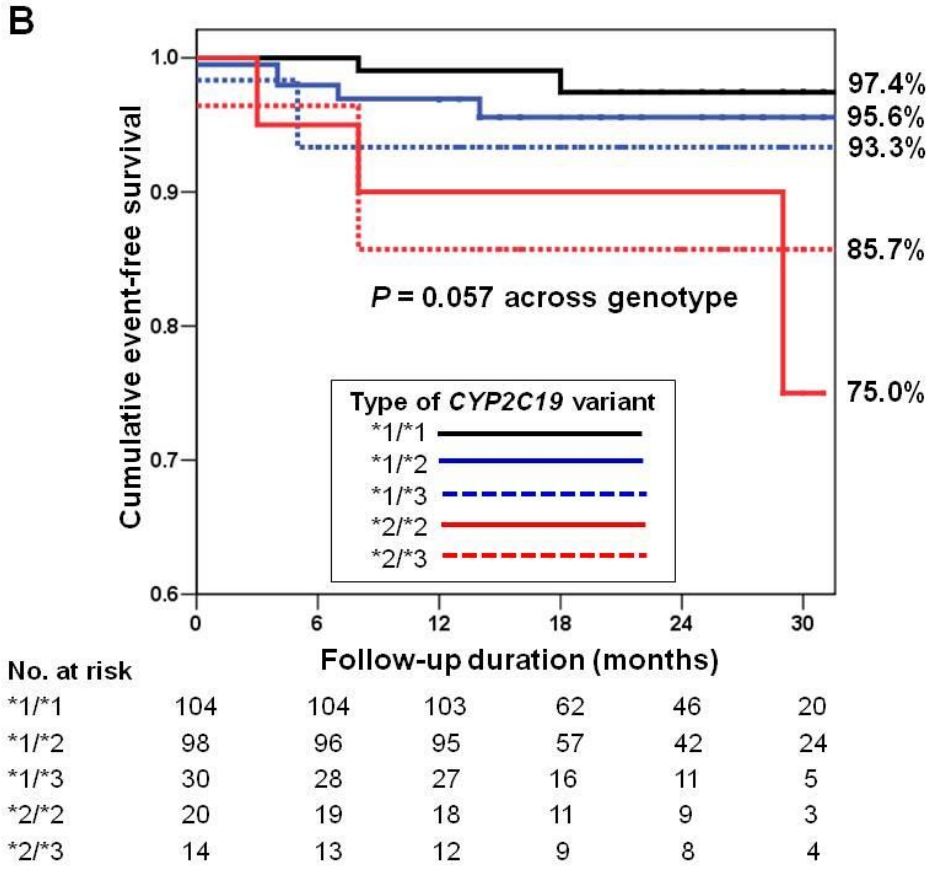
- Healthy volunteer
  - 32.4% RR of active-metabolite concentration
  - 25% RR of platelet function
- TIMI-TRITON 38
  - HR 1.53 for ischemic event
  - HR 3.09 for stent thrombosis (ST)
- Sibbing et al.
  - HR 3.81 for ST
- Mega et al.
  - HR 1.61 vs 1.81 events (hetero vs homozygote)

Effect of *CYP2C19*2* and **3* Loss-of-Function Alleles on Adverse CV Events in Korean AMI Patients (n=266)

Cumulative risk of MACE according to *CYP2C19* phenotype (A) and genotype (B) (Kaplan-Meier Estimates))



No. at risk						
Non-carrier	104	104	103	62	46	20
1 carrier	128	124	122	73	53	29
2 carrier	34	32	30	20	17	7



No. at risk						
*1/*1	104	104	103	62	46	20
*1/*2	98	96	95	57	42	24
*1/*3	30	28	27	16	11	5
*2/*2	20	19	18	11	9	3
*2/*3	14	13	12	9	8	4

- Risk factor of MACE: *CYP2C19* LOF allele

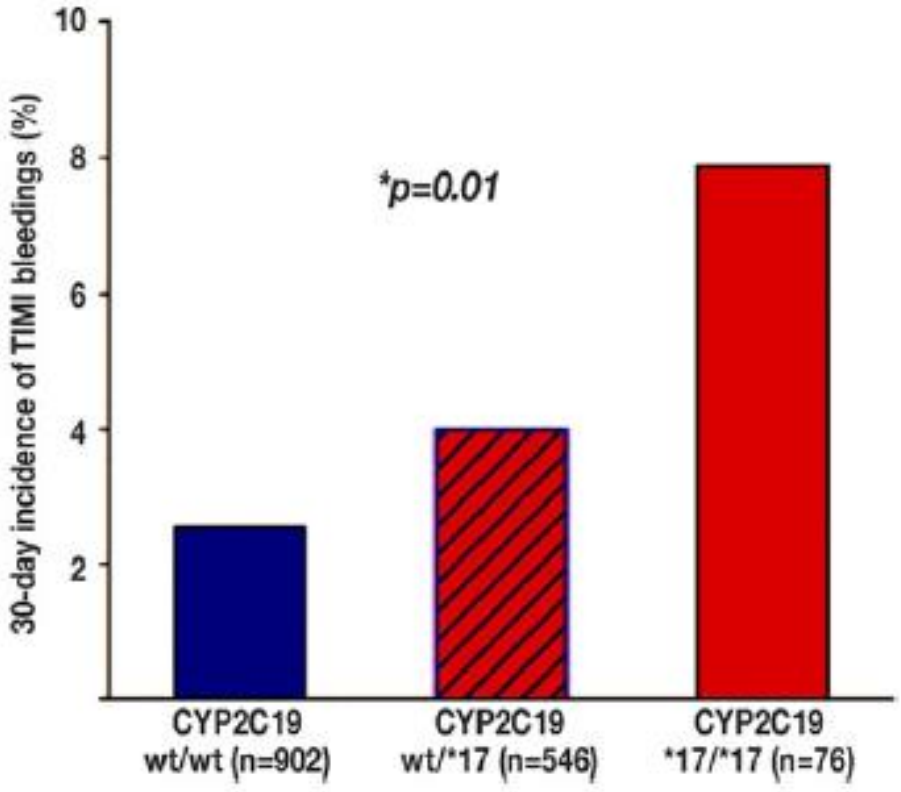
1 LOF (HR 3.1, 95% CI 0.8 to 11.6, *P* = 0.089) and 2 LOF (HR 10.1, 95% CI 1.8 to 58.8, *P* = 0.008)

Jeong YH and Gurbel PA et al. ISTH 2011

CYP2C19*17 Genotypes & Incidence of TIMI Bleedings

- 1524 PCI patients treated with clopidogrel with 30-day follow-up for stent thrombosis and TIMI bleeding
- **Stent Thrombosis**: No significant influence of *17 allele on the occurrence of stent thrombosis
- **Bleeding**: *17 allele carriage significantly associated with increased risk of bleeding with highest risk for homozygous patients

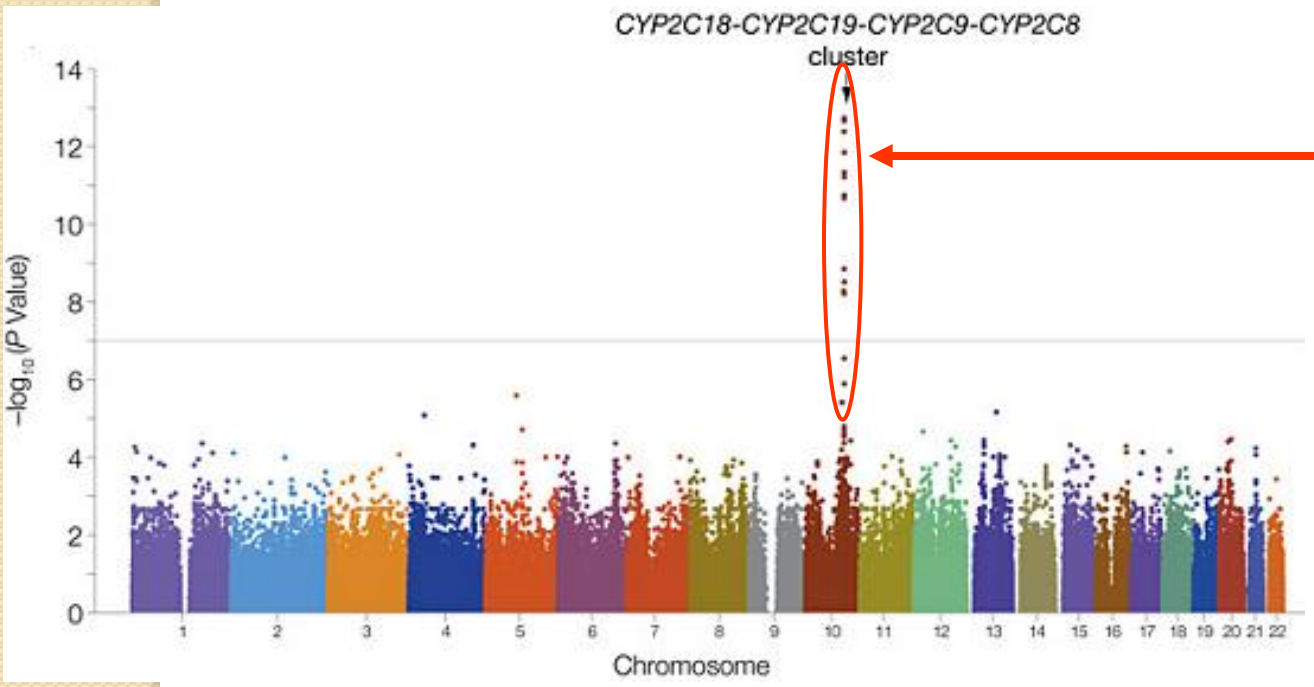
Sibbing et.al. Circulation 2010



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)

- 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

Contribution of Factors to Interindividual Variability

- Genetic influences
  - CYP2C19
  - Others:
    - CYP3A4 & CYP3A5
    - P2RY12 encoding the platelet ADP receptor
    - ABCB1encoding P-glycoprotein for clopidogrel absorption
    - PON1

- Environmental, cellular, and pathophysiological clinical factors
  - Environmental: age, smoking, diet, and drug-drug interactions involving CYP2C19,CYP3A4, CYP1A2, and CYP2C9 isoenzymes
    - Proton-pump inhibitors (PPIs), lipophilic statins, calcium channel blockers, caffeine, St. John's wort, and warfarin
  - Cellular: the life span of platelets, increased platelet sensitivity or reaction to ADP, and upregulation of the P2Y1 and P2Y2 pathways
  - Pathophysiological clinical factors such as diabetes, acute coronary syndrome, patient compliance, underdosing or inappropriate clopidogrel dosing, triglycerides, high-density lipoprotein cholesterol and body mass index

Genotyping Provides Risk Assessment Data Independent From and Possibly Synergistic with Platelet Function Tests

How Do the 2 Methods Differ?

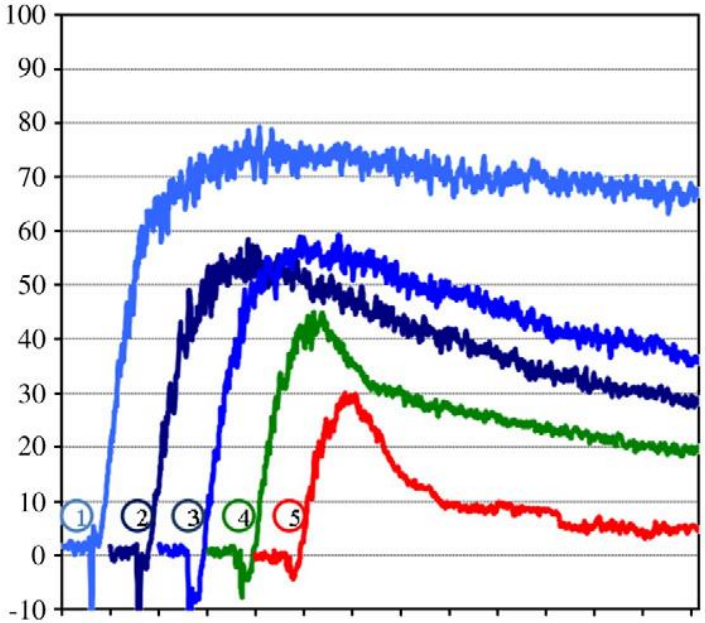
Genotyping

- Stable Risk Factor
- No Method Variability
- Assists in Choosing Initial Therapy
- Provides “Yes” or “No” Readout
- Supported by Multicenter Trial Data
- No Prospective Data on Efficacy

Phenotyping

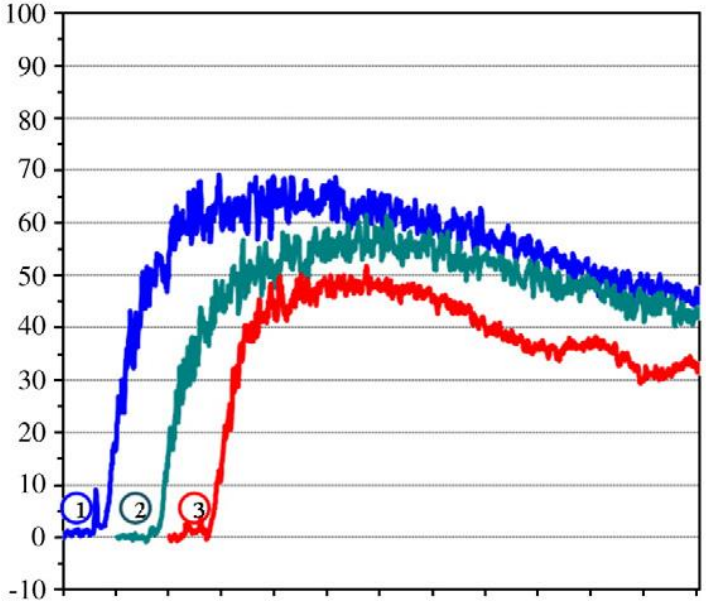
- Labile Risk Factor
- Method Variability
- No Assistance in Choosing Initial Therapy
- Provides Continuous Readout
- Supported by Mostly Single Center Trial Data
- No Prospective Data on Efficacy

A



	Treatment	ADP 10µM		VASP PRI(%)
		MPA (%)	RPA (%)	
1	clopidogrel 75 mg	75	69	76
2	clopidogrel 150 mg	54	28	73
3	clopidogrel 225 mg	56	35	67
4	ticlopidine 250 mgx2	46	18	45
5	prasugrel 10 mg	34	3	16

B



	Treatment	ADP 10µM		VASP PRI(%)
		MPA (%)	RPA (%)	
1	clopidogrel 75 mg	66	47	71
2	clopidogrel 150 mg	61	43	60
3	clopidogrel 300 mg	46	30	32

Szymezak J Thrombosis Research 2011

What scenario can we expect for this patient ?

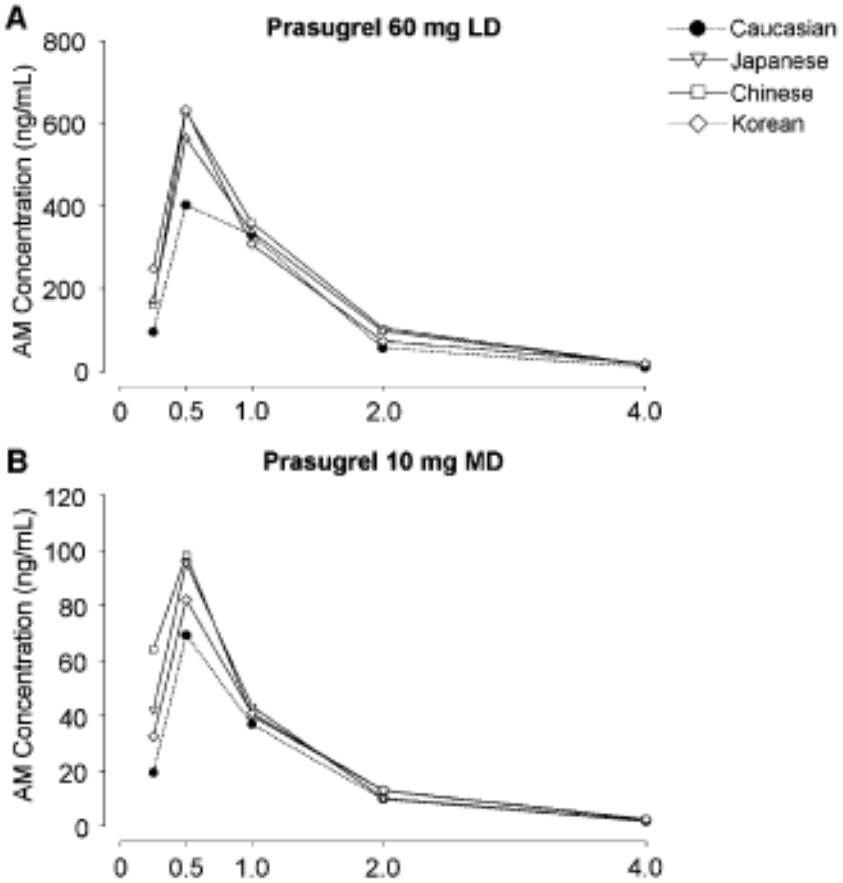
- *Do as usual*

- *Use an alternative antiplatelet agent in all patients*
- *Platelet-function guided therapy*
  - *GRAVITAS, TRIGGER-PCI, ADJUST*
- *Genotyping guided therapy*
  - *PAPI-2*

1. Use an alternative anti-platelet agent in all patients: Prasugrel

- Superior to clopidogrel : HR 0.81
- It can not be substituted for all patients
  1. *A higher associated risk of bleeding: HR 1.32*
  2. *Lower doses of prasugrel have not been adequately studied*
  3. *Larger number of conditions : clopidogrel is approved*
  4. *Lower expense of clopidogrel*

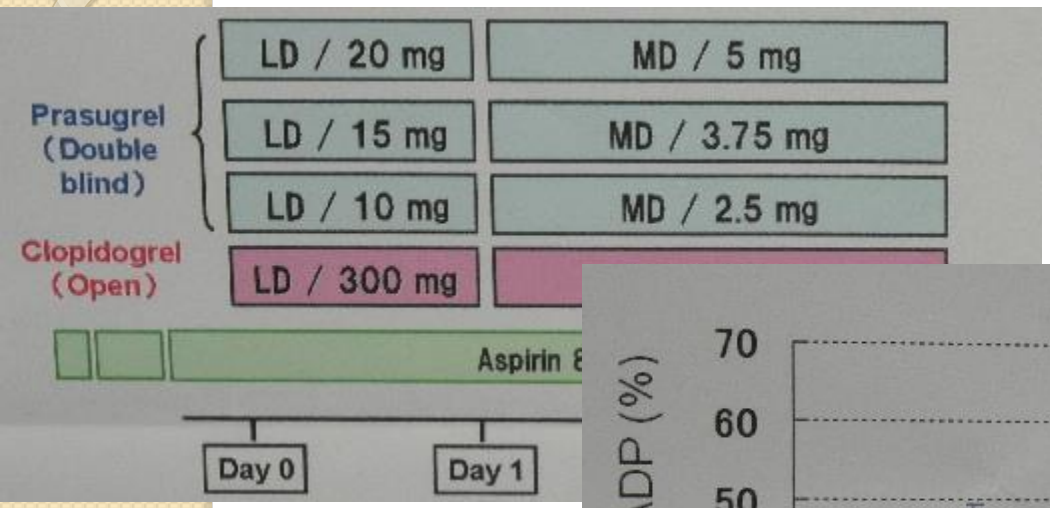
Plasma concentration-Time profiles of Prasugrel's Active Metabolite

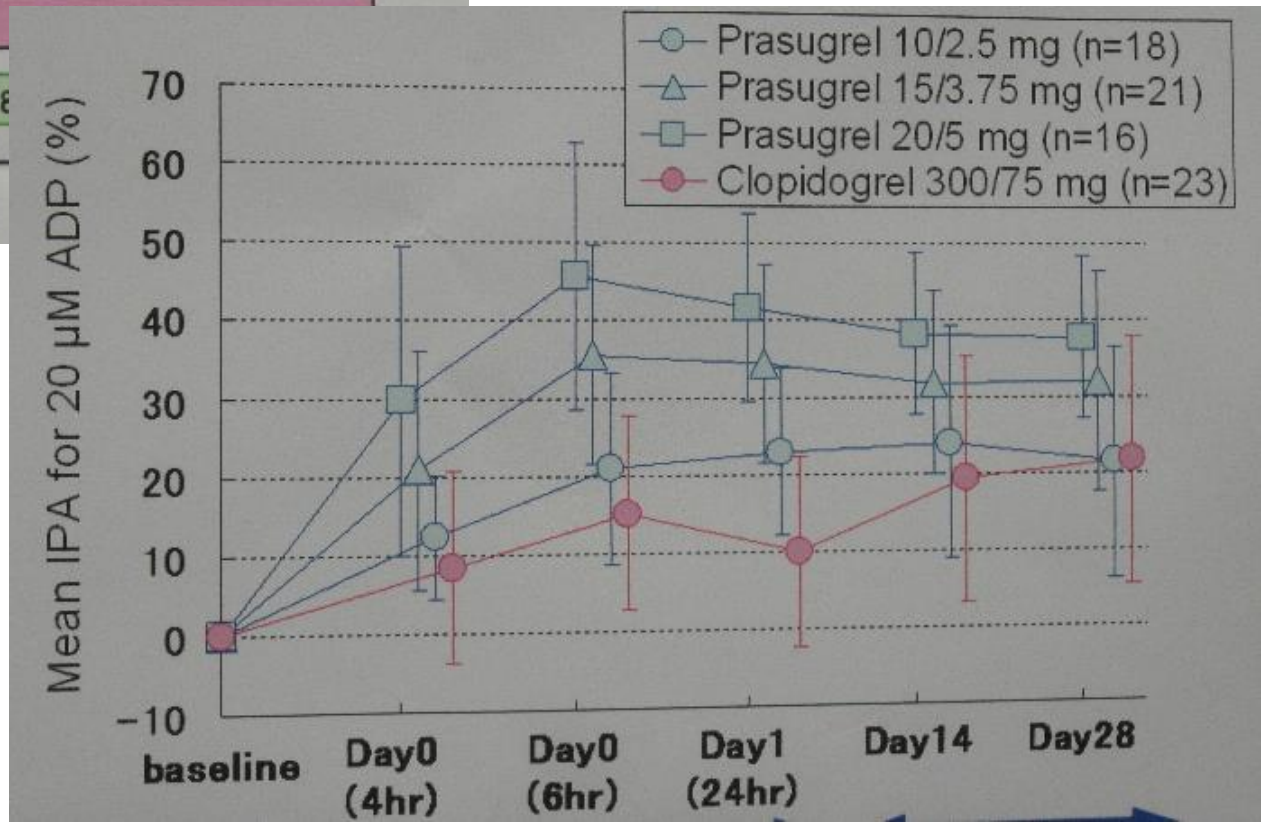


Asians have 20-30% higher concentration of active-metabolite than Caucacian !!

Small DS, et al. Eur J Clin Pharmacol 2010

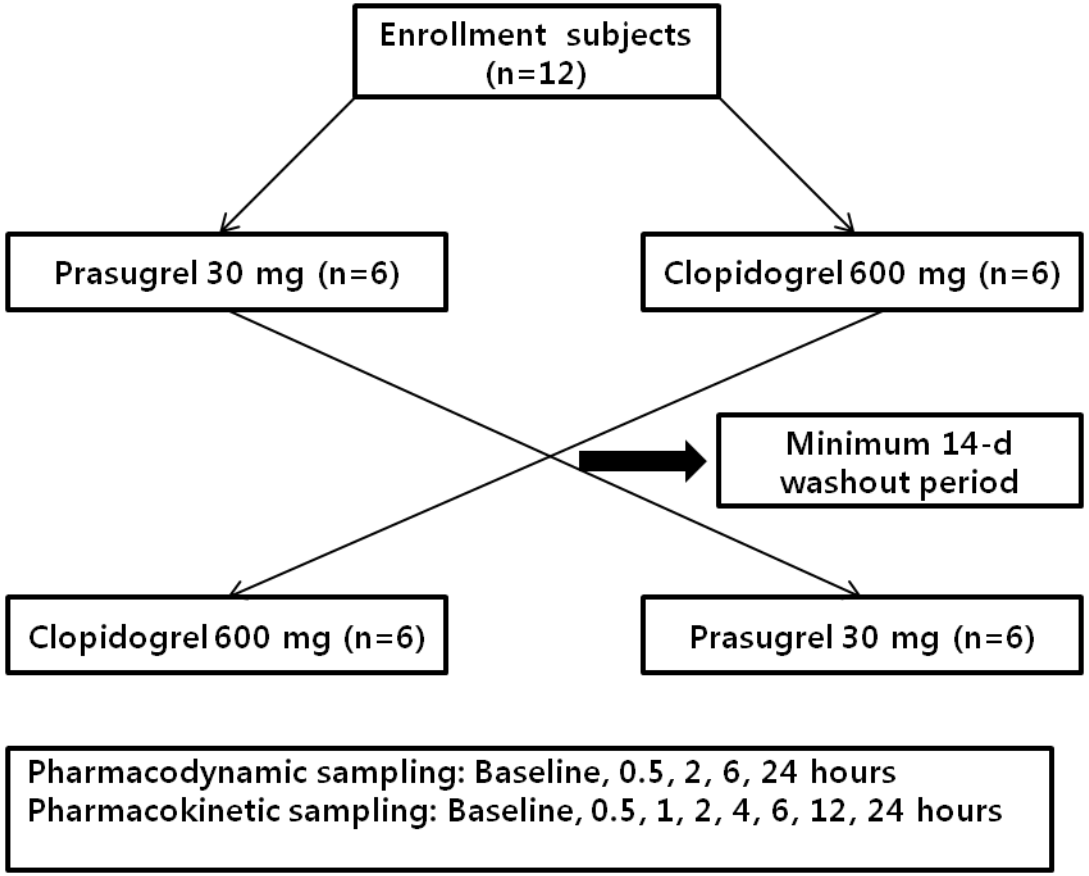
PD Effect of Low Dose Prasugrel



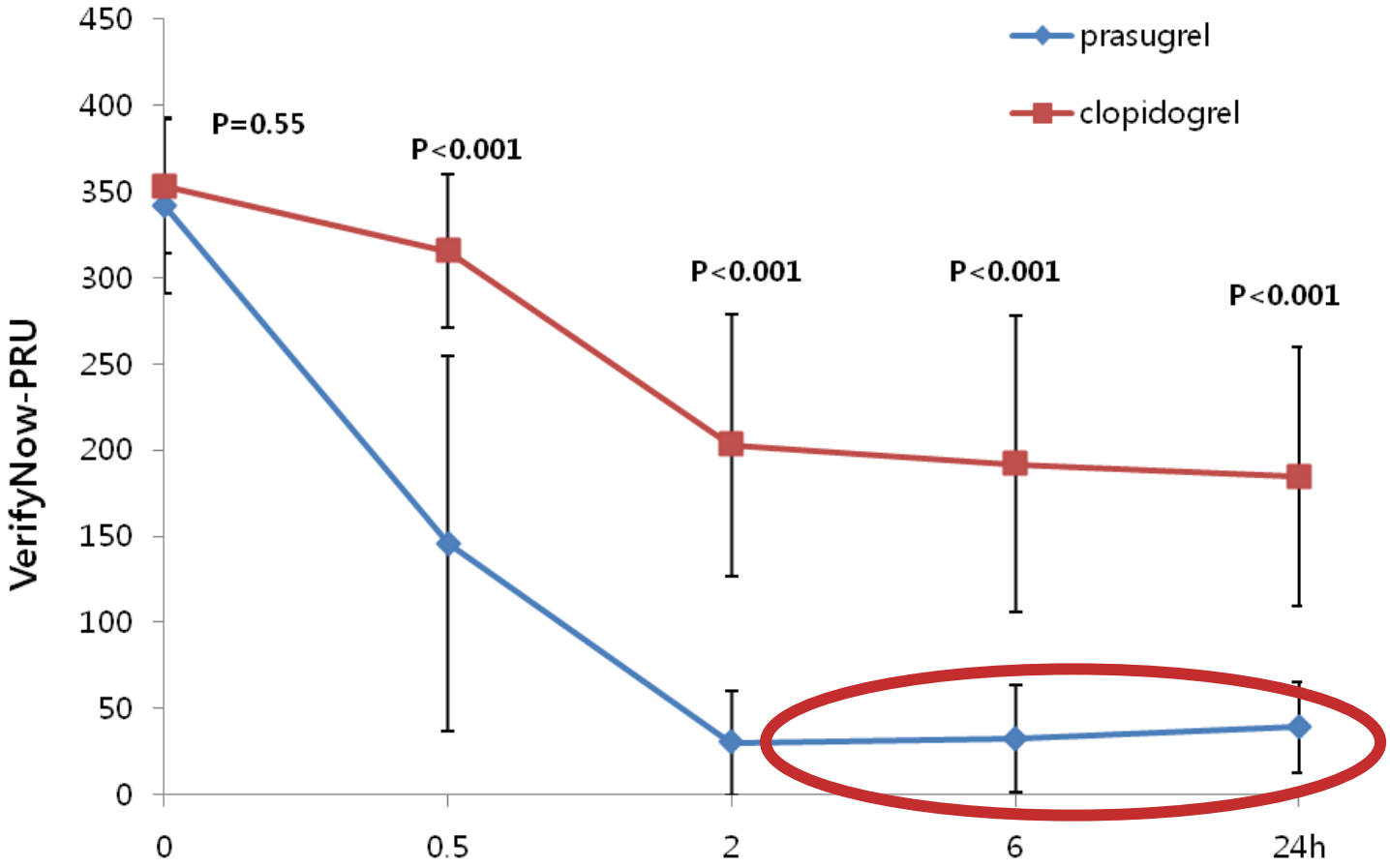


ISTH2011

Clopidogrel & Prasugrel : Loading Effect in Healthy Volunteer



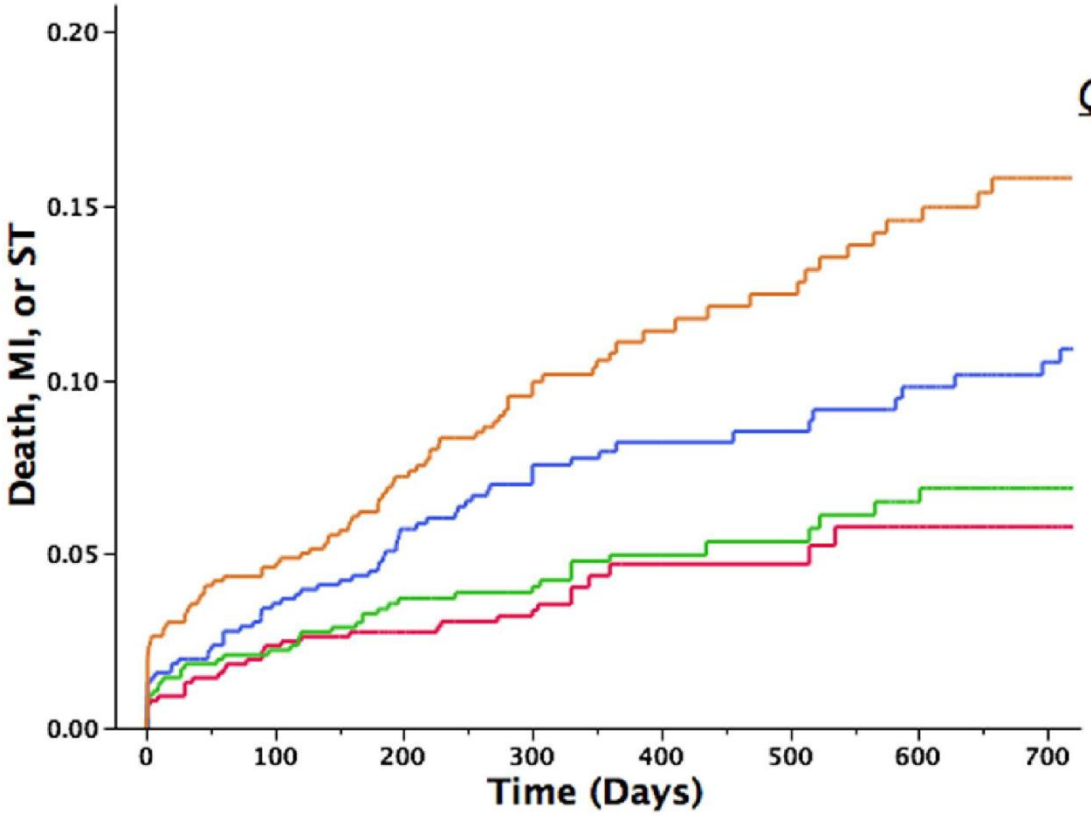
PD of Clopidogrel & Prasugrel Single LD



2. Platelet-function test guided therapy

- Platelet aggregation is “closer” to the final phenotype (i.e.,cardiovascular outcomes)
- Takes into account environmental factors that may influence platelet aggregation in addition to “all” genetic factors
- PLT testing might be more useful than CYP2C19 genotype testing for individualizing therapy
- Difficult to interpret during periods of acute physiological stress (e.g., ACS & MI) : would probably need to be repeated over time

MACE Rate by PRU Quartiles: Meta-Analysis



Quartile	Event Rate	P-value*
Q4	15.8%	<0.001
Q3	10.9%	0.02
Q2	6.9%	0.97
Q1	5.8%	–

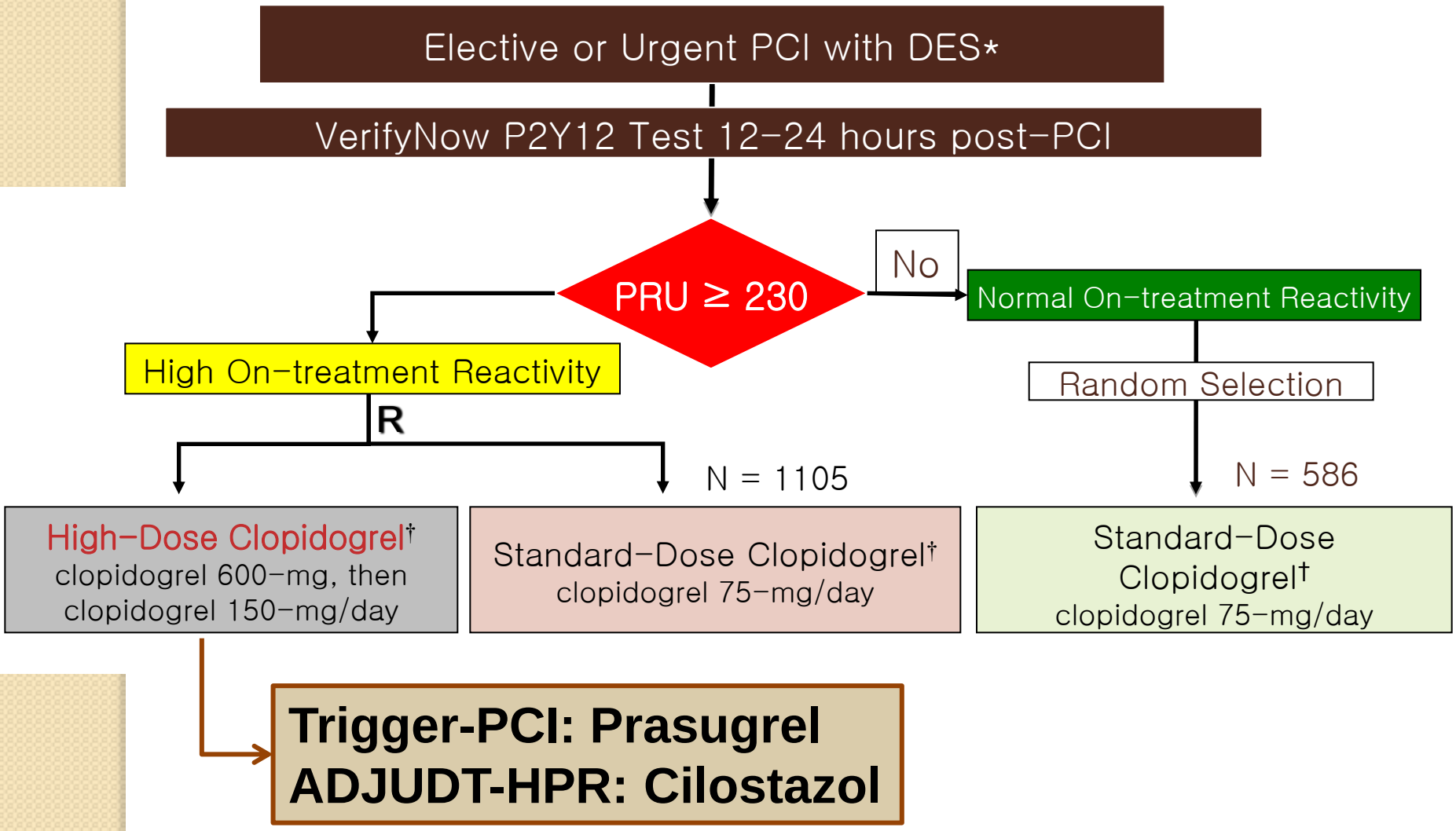
No. at risk

Q1	765	639	401	171
Q2	761	611	370	237
Q3	757	595	341	271
Q4	758	588	278	224

Brar SS et al. JACC 2011

GENOTYPE INFORMATION & FUNCTIONAL TESTING

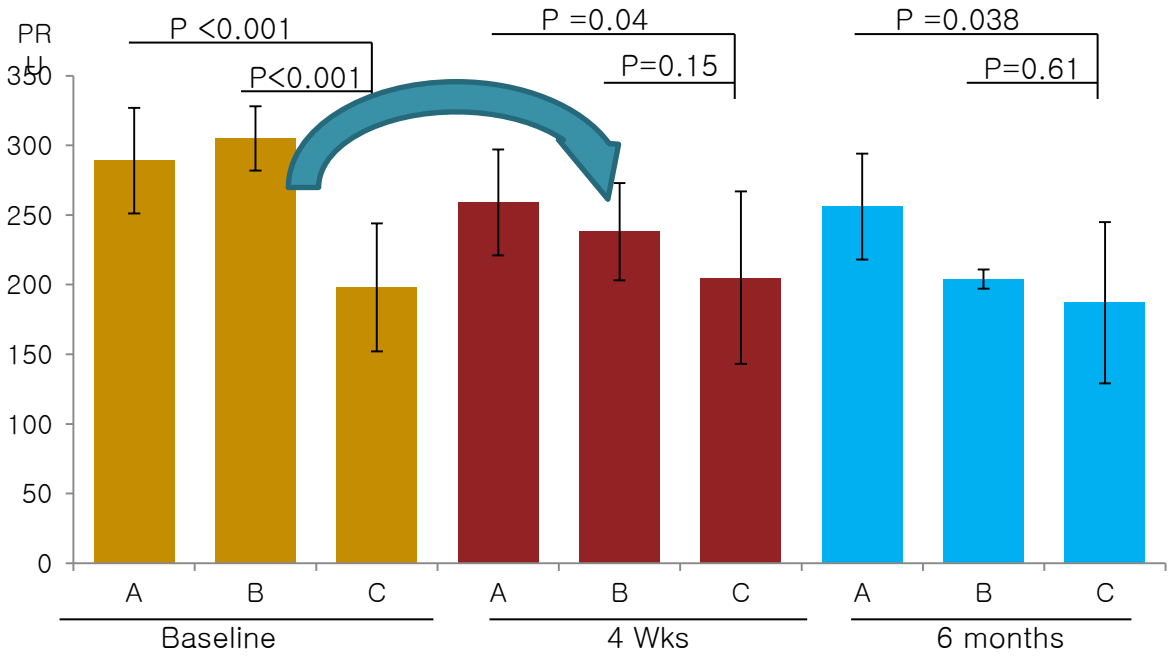
GRAVITAS Study Design



*Peri-PCI clopidogrel per protocol-mandated criteria to ensure steady-state at 12–24 hrs

†placebo-controlled

ADJUST-HPR

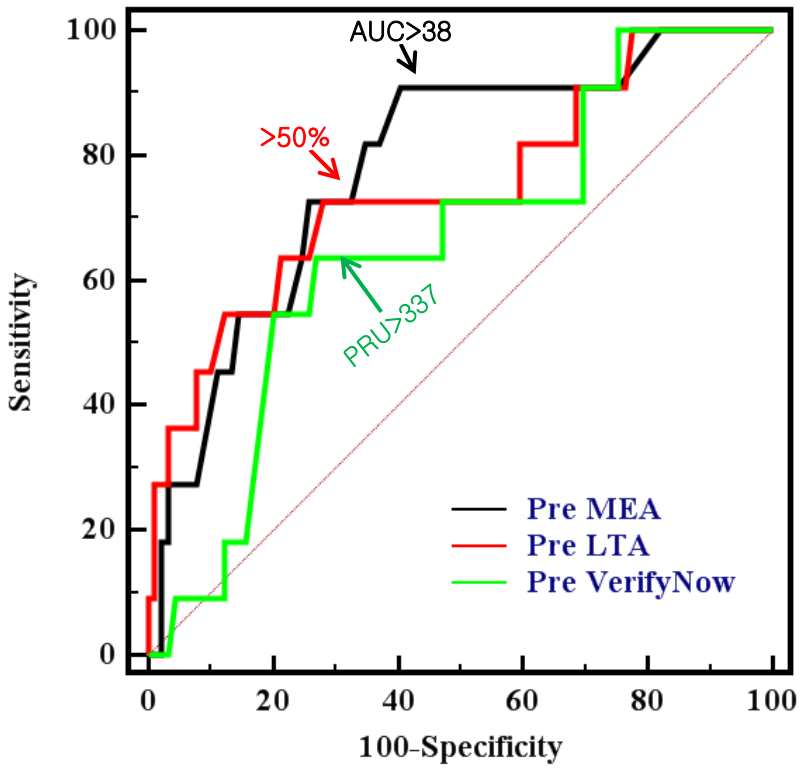


A: HPR>240 PRU, Dual
B: HPR>240 PRU, Tri
C: no HPR <240 PRU, Dual

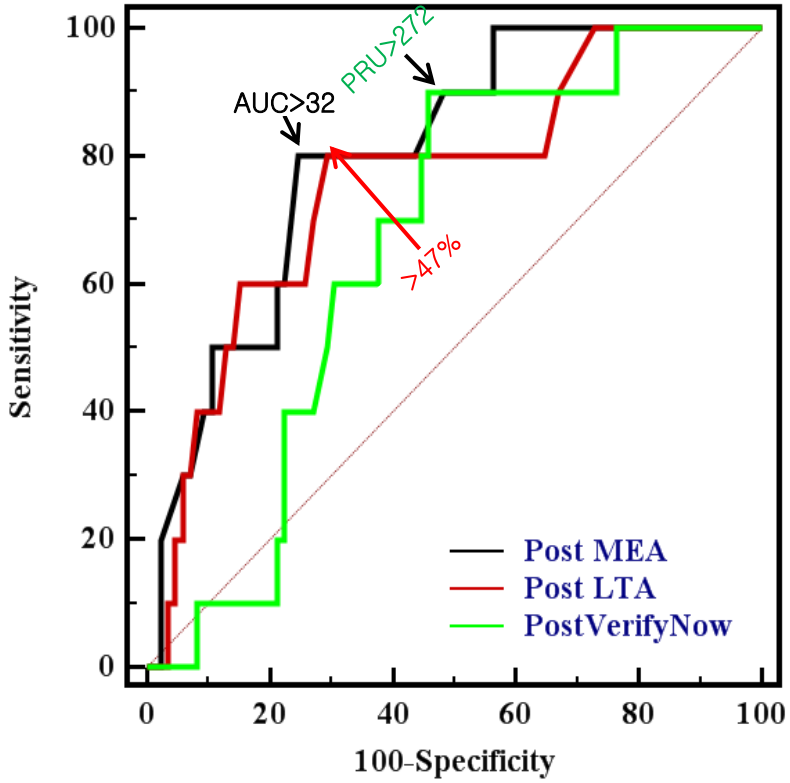
VerifyNow	Mean ± SD (PRU)	P-value
A	289 ± 38	<0.001
B	305 ± 23	
C	198 ± 46	
A	259 ± 38	0.083
B	238 ± 35	
C	205 ± 62	

Detection of Carriers of CYP2C19 Poor Metabolizer Allele : ROC Curve Analysis

Pre-PCI



Post-PCI <24hr



3. Genotyping guided therapy

- Genetic test before PCI
- Moderate to high clinical risks
  - *Multi-vessel PCI*
  - *Hx of Stent thrombosis*
  - *Clinical (ACS, DM, CKD)*
  - *Angiographic features (Thrombus, bifurcation)*

Genotyping

- Usually require several days to get information……
- However…

POC(Point of Care) Genotyping

- AmpliChip CYP450 test (Roche Diagnostics GmbH, Mannhein, Germany)
- Verigene (Nanospere, Inc., North Brook, Illinois)
- Infinity (Autogenomics, Inc., Charlsbad, California)
  - 3-8 hrs….

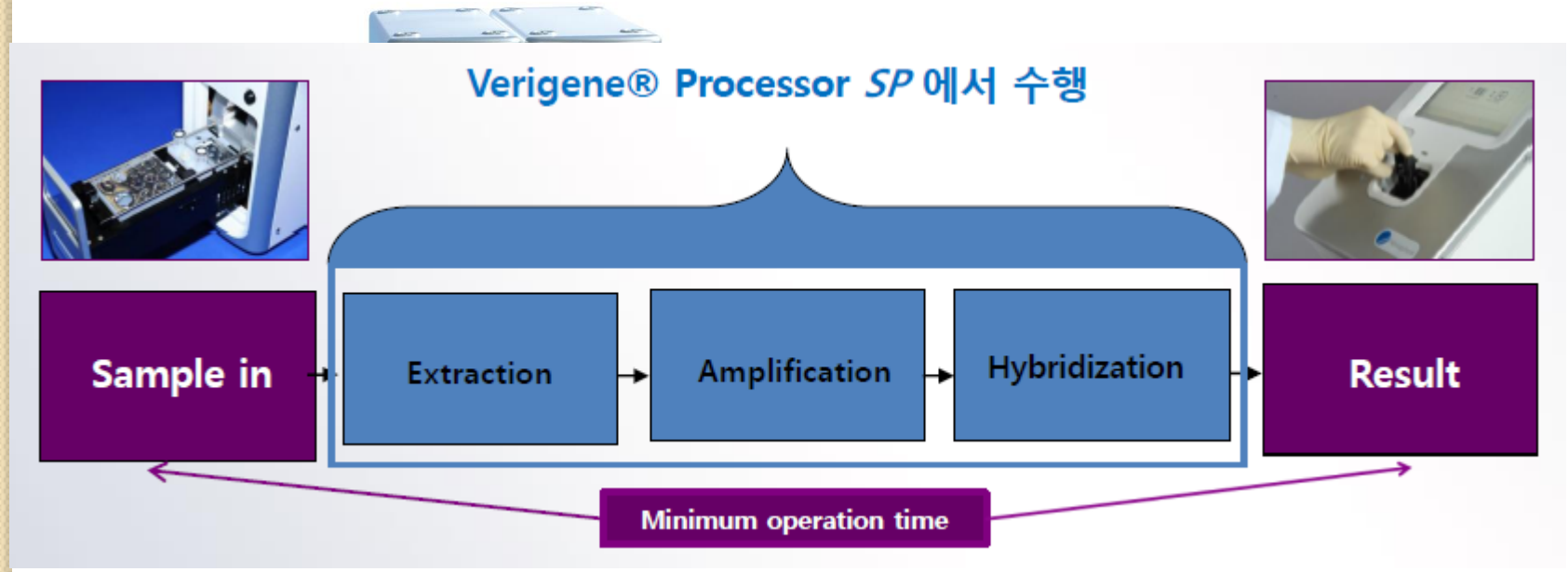
Current Genotyping Methods

- Conventional PCR
- Real-time PCR
- Gene sequencing

- Separate instrument
- Batch system
- Incovenience for multiplex

The Verigene® System *CYP2C19* Nucleic Acid Test

- Multiplex molecular test for the detection of 3 *CYP2C19* Alleles:
  - ✓ *2, *3, and *17



- Nanosphere / HANDOK offer a range of tests for Pharmacogenetics, Infectious Diseases and Human Genetics

The Verigene® System

Pharmacogenetics in Cardiology

➢ Pharmacogenetic Testing from Whole Blood

- Identification of patients who may not respond properly to drug treatment.
- Sample input: 1 mL of EDTA-anticoagulated whole blood

➢ On-Demand Random Access Testing

- Cartridge-based testing with built-in controls and calibrators enables 24/7 emergency service based on patient demand which allows to state the patients genotype earlier than with all other molecular-lab based methods.
- Enables the cardiology team within a 3 hour time period to determine whether their patient is a carrier of gene mutations responsible for drug response or not.

➢ Accurate – Fast

- Genotype results for risk stratification are available at an early stage in the acute clinical settings.
- With this solution clinicians may better select the drug of choice and/or make adjustments to each patient´s dose regimen as needed which may improve patient´s outcome.

Rapid Multiplexed Genotyping

CYP2C19 GENOTYPING

- Verigene® *CYP2C19* (CLO+) Nucleic Acid Test (CE-IVD)
  - Multiplex testing of two *CYP2C19* loss-of-function alleles (**2, *3),* and one *CYP2C19* gain-of-function allele *(*17)*
- Verigene® CBS Nucleic Acid Test (IUO)
  - Multiplex testing of the following allelic variants in the *CYP450 2C19* gene: *2, *3, *4, *5, *6, *7, *8, *9, *10, *13, and *17

Comparison Data (Verigene vs. Sequencing)

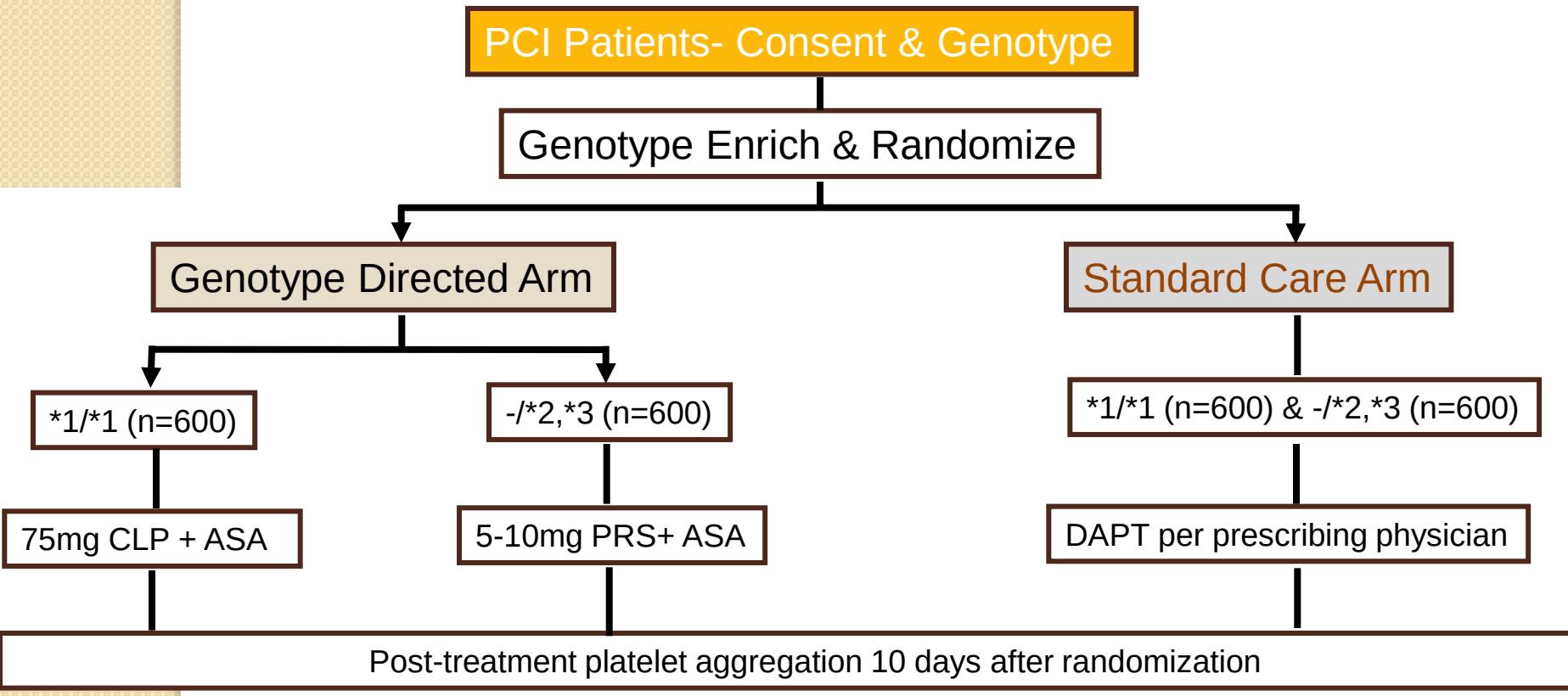
- Method Comparison – Genotype Distribution
  - The following tables represent the genotype distribution tested in the methods comparison study and the call accuracy.
  - There was a 100% agreement between the Processor SP and the comparative method.

Method Comparison Results – Genotype Distribution				
CYP2C19*2		**Verigene® System**		
		Wild Type	**Heterozygous**	**Mutant**
Sequencing	**Wild Type**	218	0	0
	Heterozygous	0	154	0
	Mutant	0	0	30

Source: Verigene® *CYP2C19* (CLO+) Nucleic Acid Test – Package Insert

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

A Prospective, Multicenter, Randomized, Comparative Effectiveness Trial



Monitor CV Events Every 3 Months

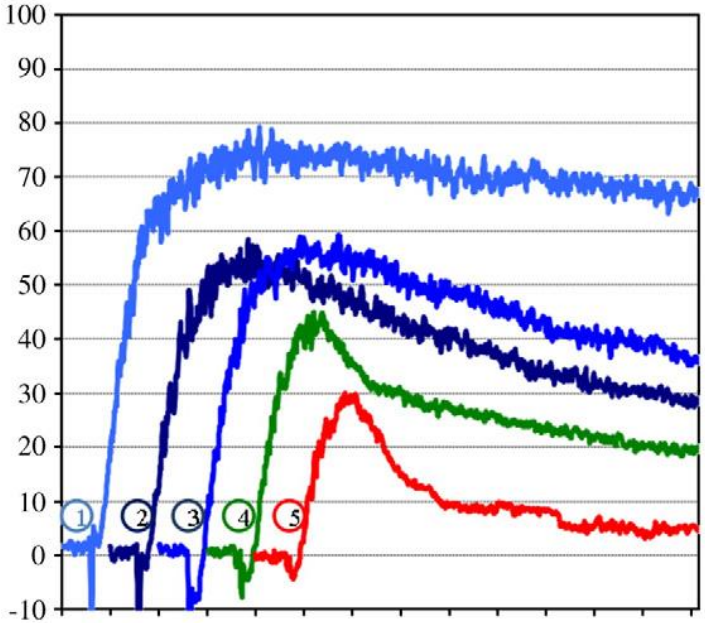
1^0 CV events = Nonfatal MI, non-fatal stroke, Definite or probable stent thrombosis, Death secondary to any cardiovascular cause

Post-treatment platelet aggregation

Pharmacoeconomic analysis

GWAS and exome **sequencing-new** gene discovery

A



*CYP2C19*2 (CYP2C19*2/*2),*

	Treatment	ADP 10µM		VASP PRI(%)
		MPA (%)	RPA (%)	
1	clopidogrel 75 mg	75	69	76
2	clopidogrel 150 mg	54	28	73
3	clopidogrel 225 mg	56	35	67
4	ticlopidine 250 mgx2	46	18	45
5	prasugrel 10 mg	34	3	16

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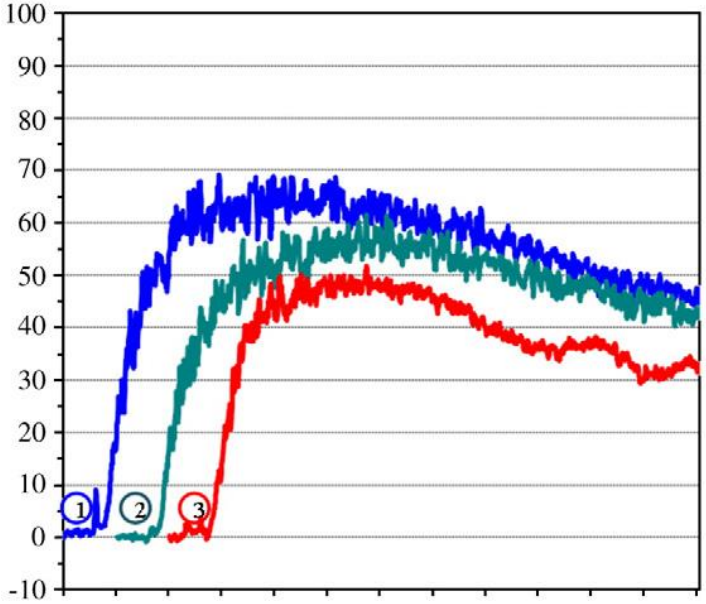

*CYP2C19 (CYP2C19*1/*1) P2Y12 H2 (P2Y12 H2/H2)*

	Treatment	ADP 10µM		VASP PRI(%)
		MPA (%)	RPA (%)	
1	clopidogrel 75 mg	66	47	71
2	clopidogrel 150 mg	61	43	60
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Szymezak J Thrombosis Research 2011

Is Gene Guided Anti-Platelet Therapy Necessary in the Era of Prasugrel ?

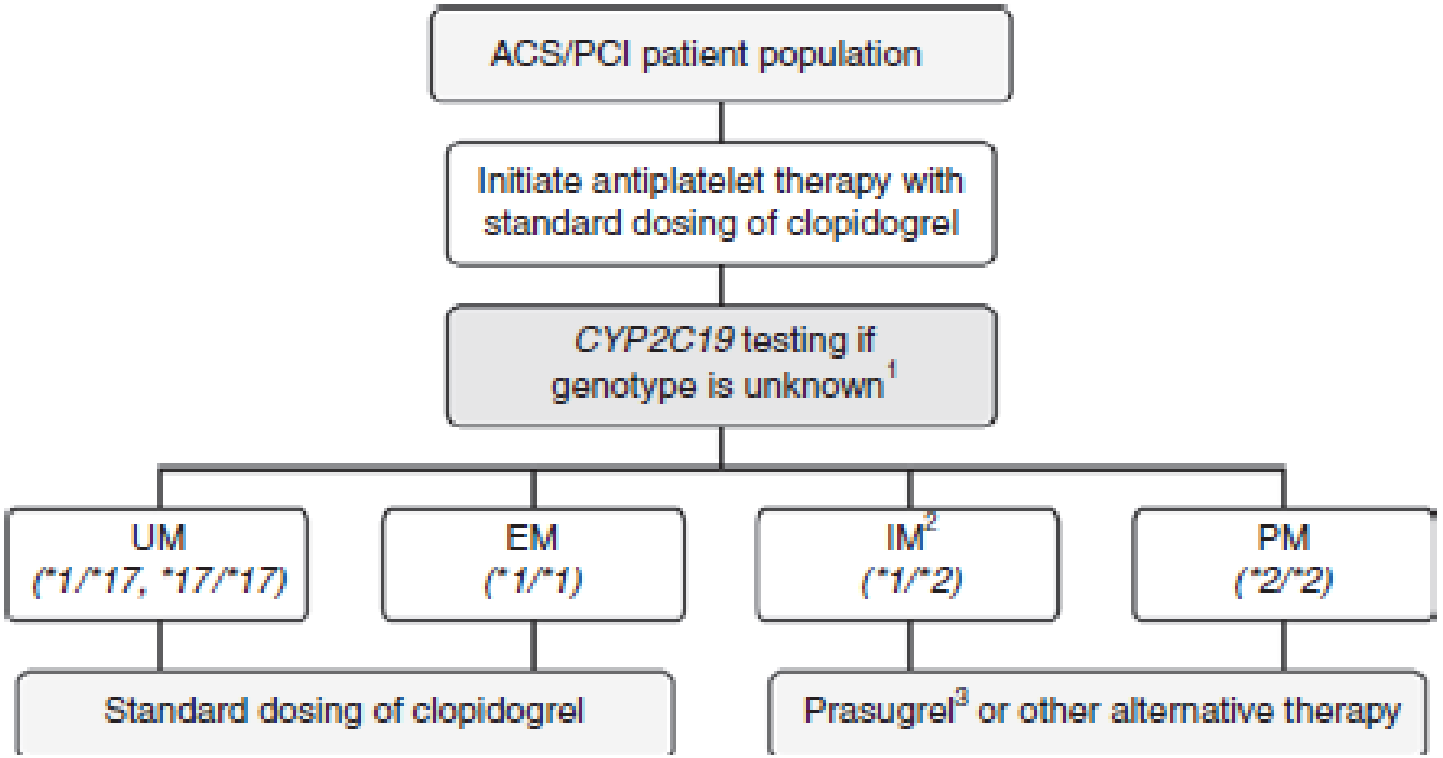
YOUR CHOICE


GET MORE INFORMATION!
Genetic information
PLT function
Clinical factors
Drug-Drug Interaction

DECISION


ULTIMATE
SUCCESS

Algorithm for suggested clinical actions based on *CYP2C19* genotype in patients with acute coronary syndromes initiating antiplatelet therapy.



Clinical Pharmacogenetics Implementation Consortium Guidelines

Scott SA et al. Clin Phamacol Ther 2011

Thank you for your attention