

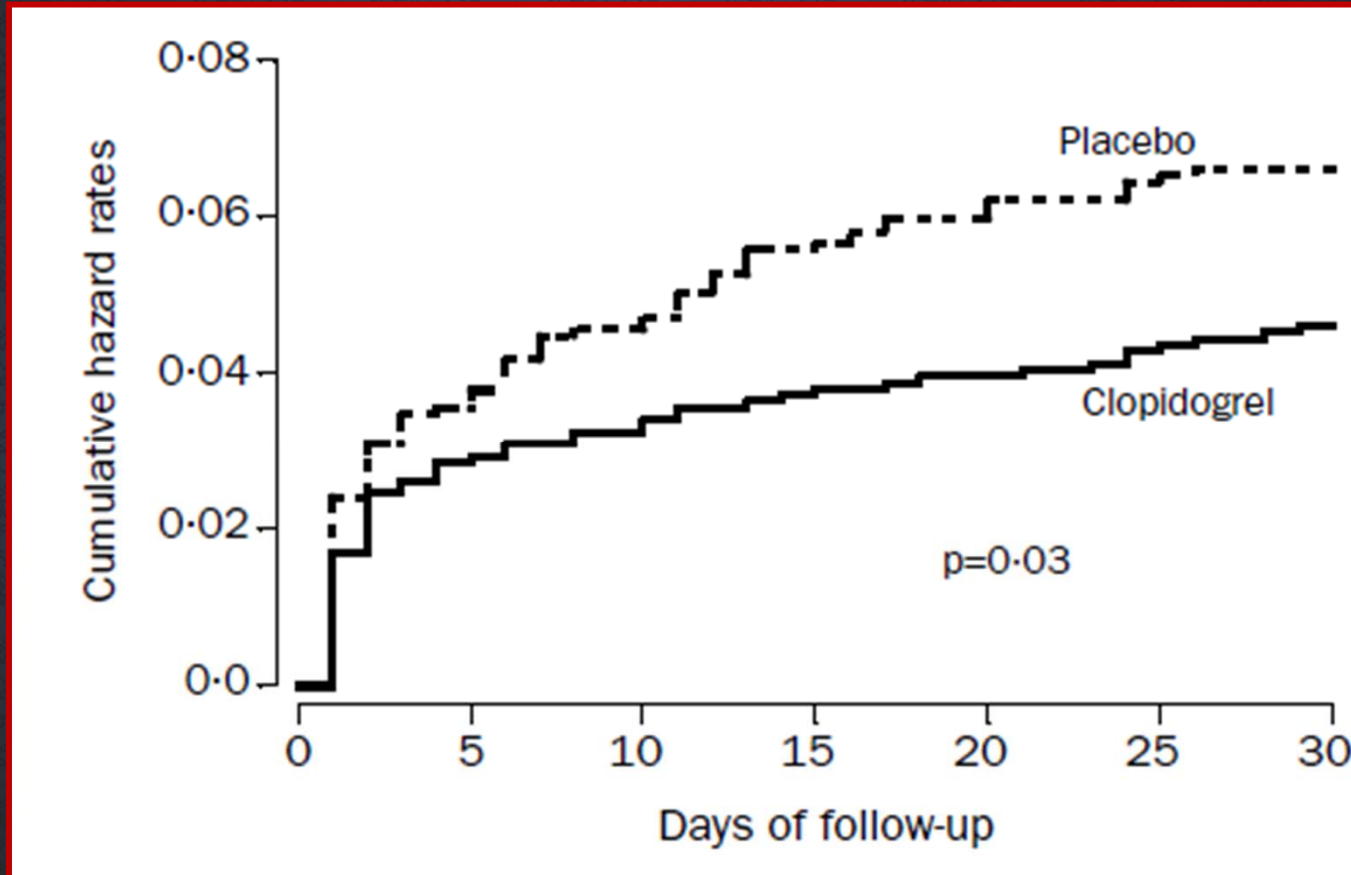
Platelet Function Testing vs Genotyping : Focus on Pharmacogenomics of Clopidogrel

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Seoul St. Mary's Hospital
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PCI-CURE

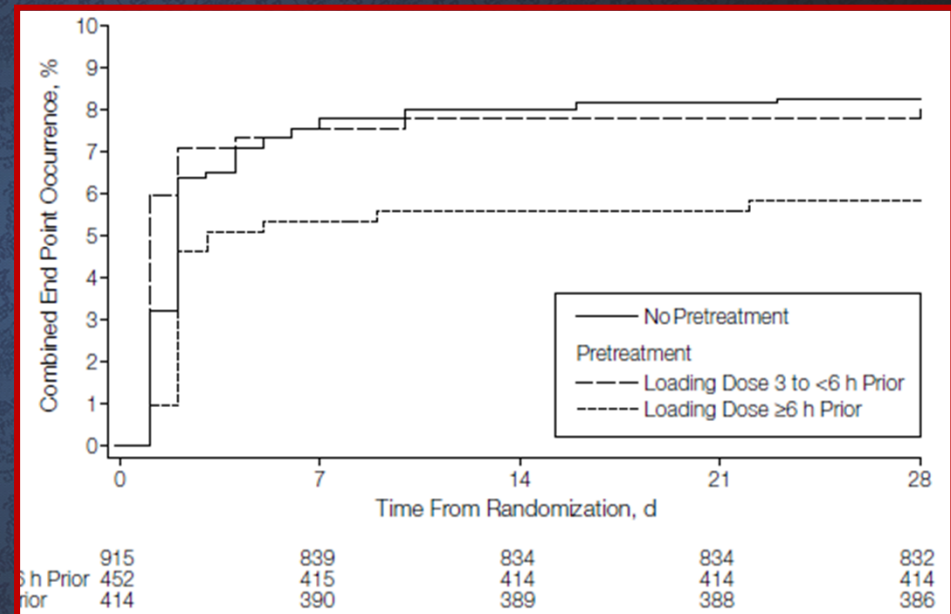
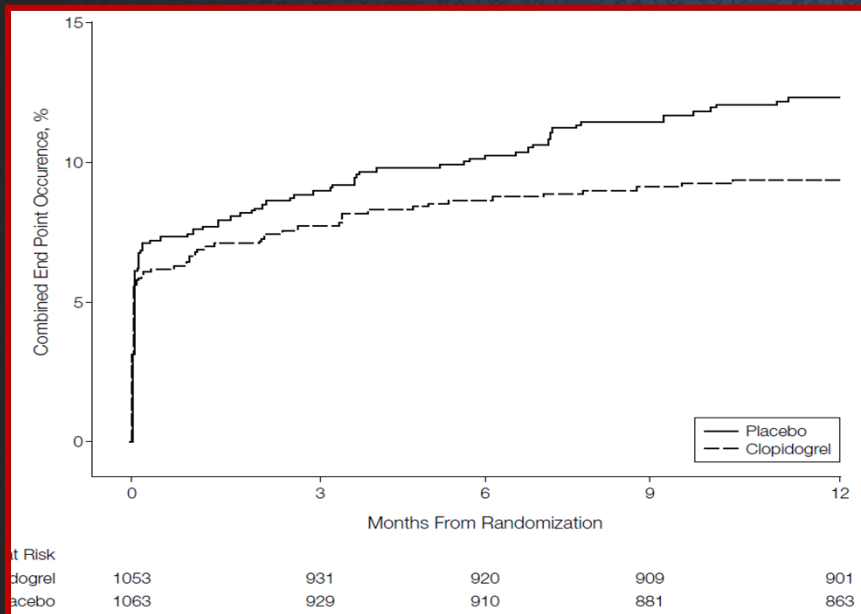
Pretreatment with clopidogrel before PCI



CURE investigators. Lancet 2001;358:527

CREDO

Duration of DAT after PCI : 1 month vs 1 year? 300 mg loading 6 hours before PCI



Steinhubl SR, et al. JAMA 2002;288:2411

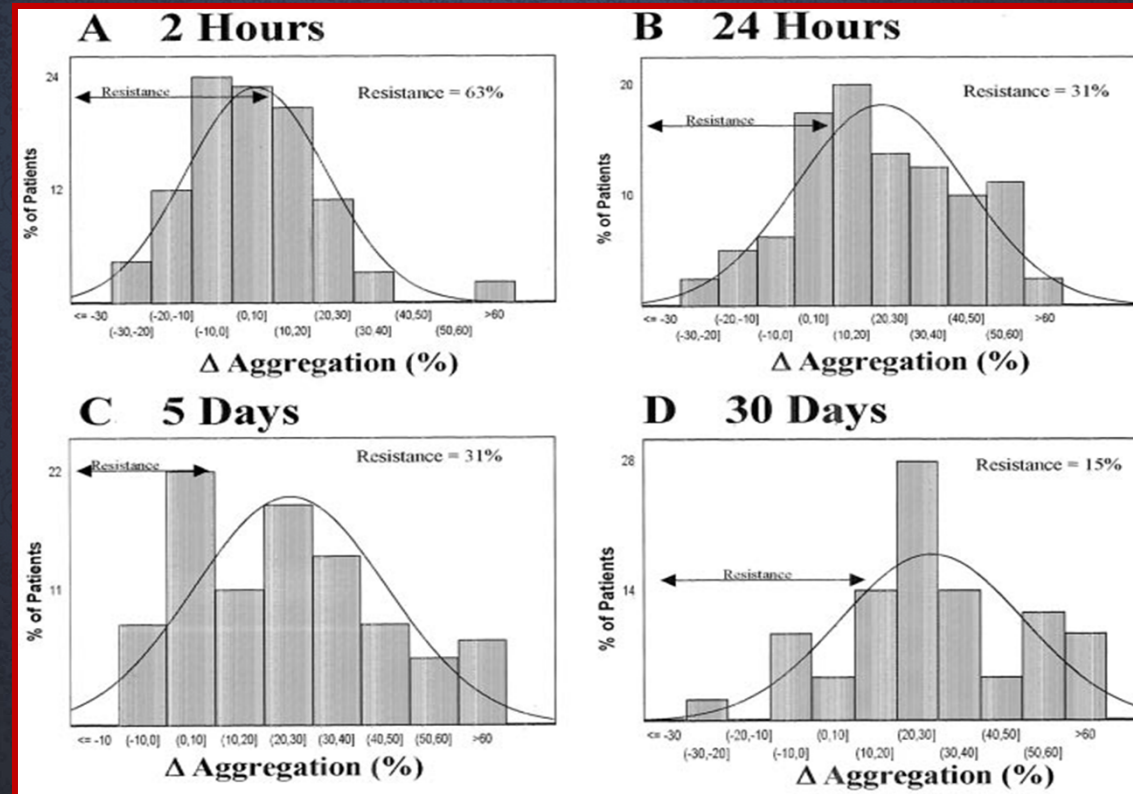
2009 Focused Updates: ACC/AHA Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction (Updating the 2004 Guideline and 2007

- **In patients receiving a stent (BMS or DES) during PCI for ACS, clopidogrel 75 mg daily should be given for at least 12 months (C).**

Clopidogrel Resistance

Clopidogrel response variability

- Δ Aggregation (%) = Baseline aggregation (%) – posttreatment aggregation (%)
- Resistance : Δ Aggregation (%) \leq 10% in 5 μ mol/L ADP response



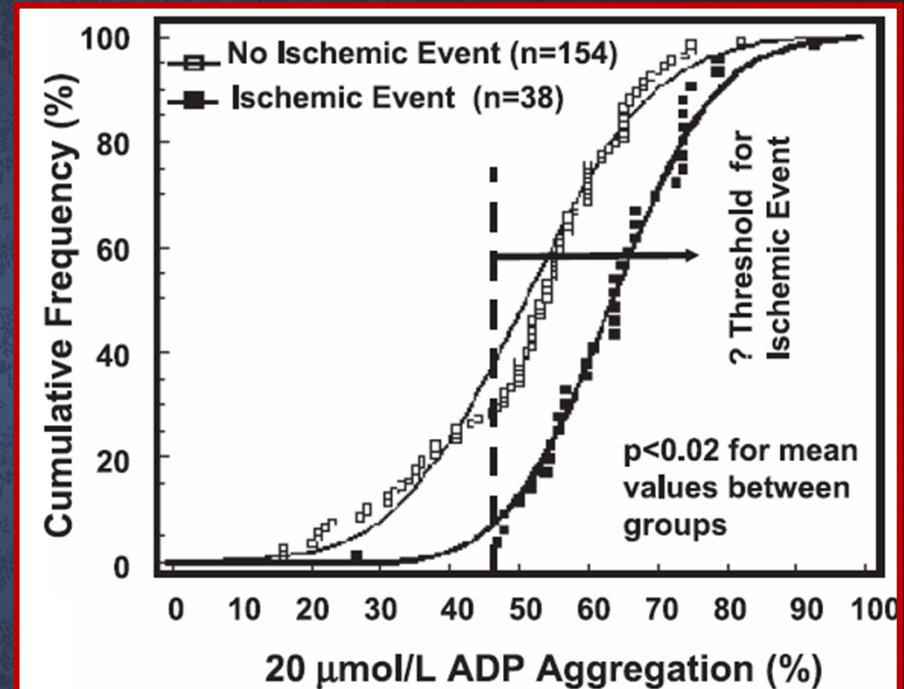
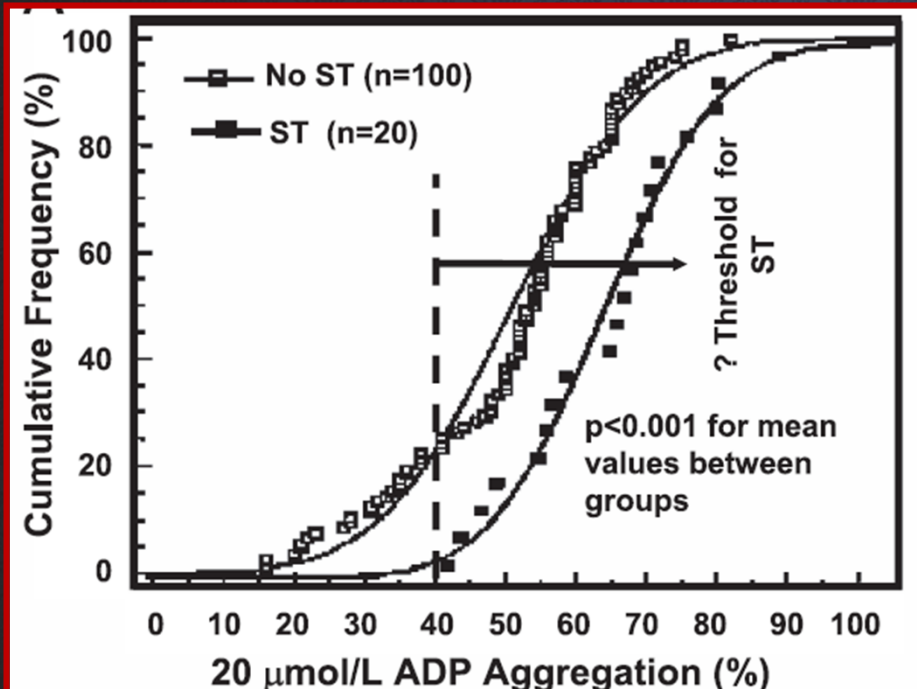
Gurbel PA, et al. *Circulation* 2003;107:2908

Clopidogrel Response Variability

논문	환자 수	Clopidogrel loading/유지량	정의	측정시간	빈도
JACC 2003	92	300/75 mg	5 μ mol/L ADP -LTA, \leq 10% absolute change	24 h	35%
Eur Heart J 2006	379	600 mg	20 μ mol/L ADP -LTA, <30% absolute inhibition	6 h	6%
Thromb Res 2005	48	300/75 mg	6 μ mol/L ADP -LTA, <40% relative inhibition	10 min, 4 h, 24h	44%

Gurbel PA, et al. J Am Coll Cardiol 2007;50:1822

Link between high on-treatment platelet reactivity & adverse clinical events



Gurbel PA, et al. *J Am Coll Cardiol* 2005;46:1827

Gurbel PA, et al. *J Am Coll Cardiol* 2005;46:1820

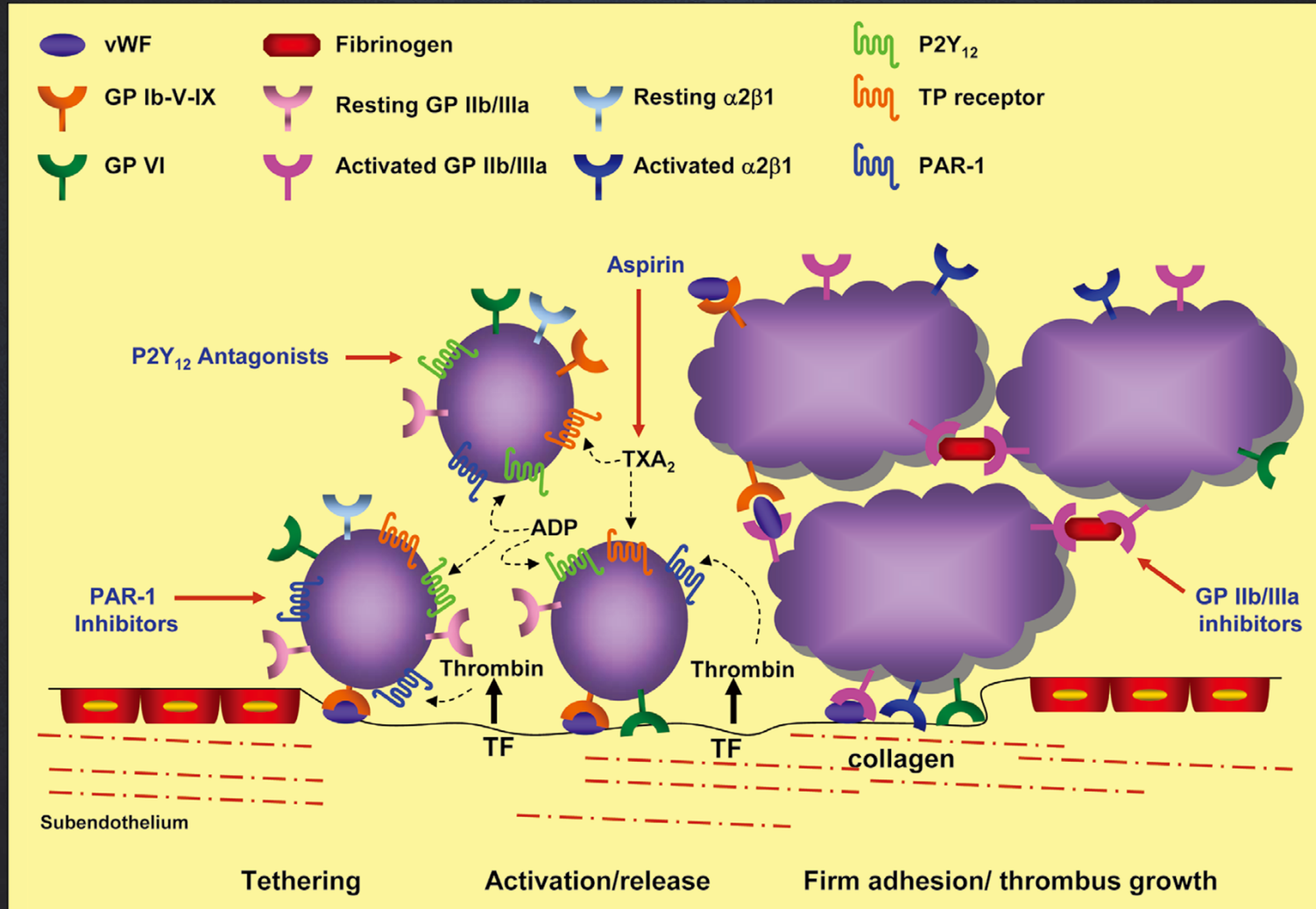
Definition of Clopidogrel Resistance

- Failure of clopidogrel to inhibit P2Y₁₂ receptor activation
: no or little change in platelet reactivity to ADP
between pre- and post-clopidogrel intake
- **Clopidogrel resistance = Laboratory resistance
≠ Clinical resistance?**

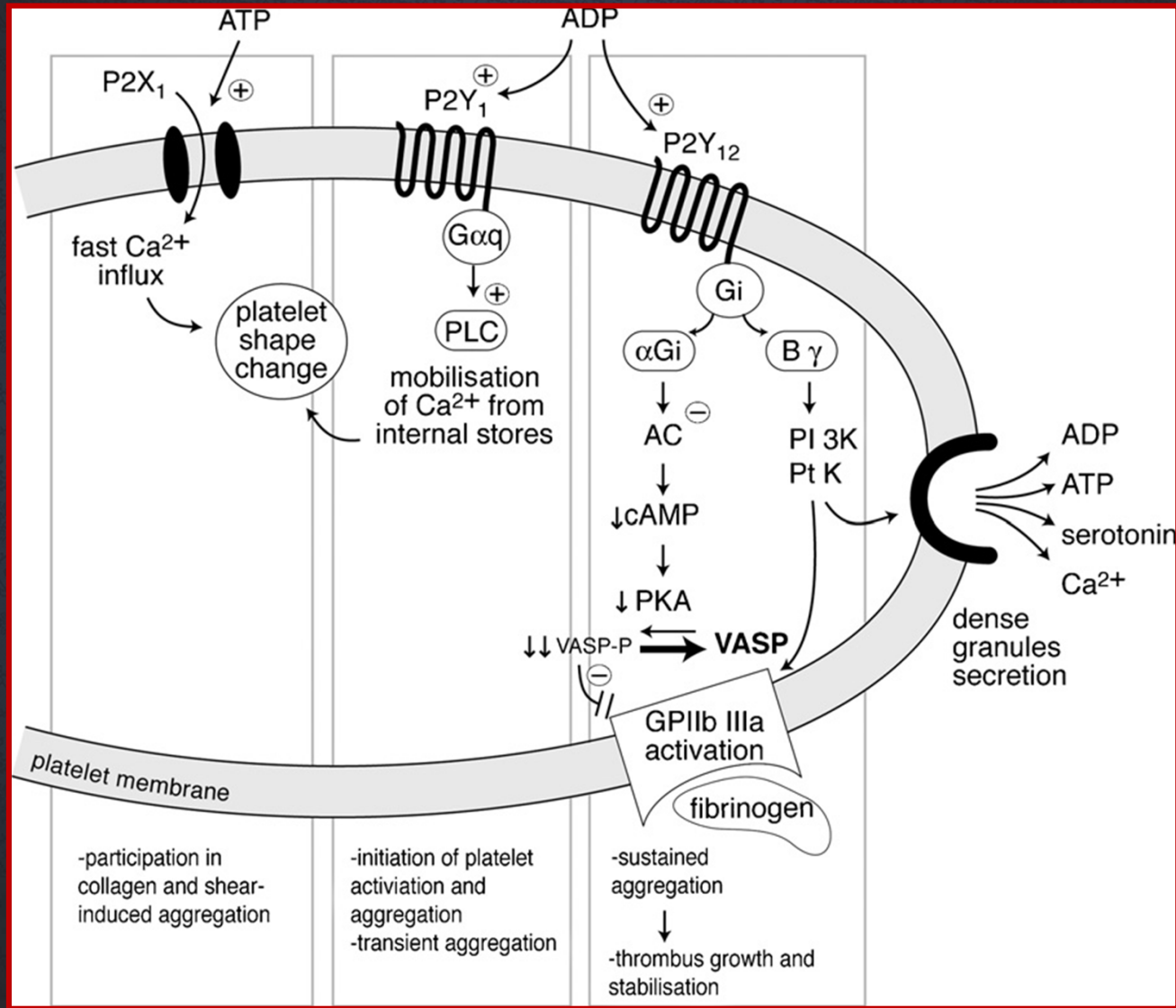
Which is the most reliable indicator of clopidogrel resistance? High On-Treatment Platelet Reactivity

- Absolute difference between baseline and post-clopidogrel platelet reactivity
 - Low pre-treatment platelet reactivity with little change
 - : **stable angina with CYP2C19 poor metabolizer**
 - High post-treatment platelet reactivity with greater change
 - : **acute MI with diabetes & CYP2C19 EM**
- Absolute level of platelet reactivity during treatment
 - : **On-treatment platelet reactivity**

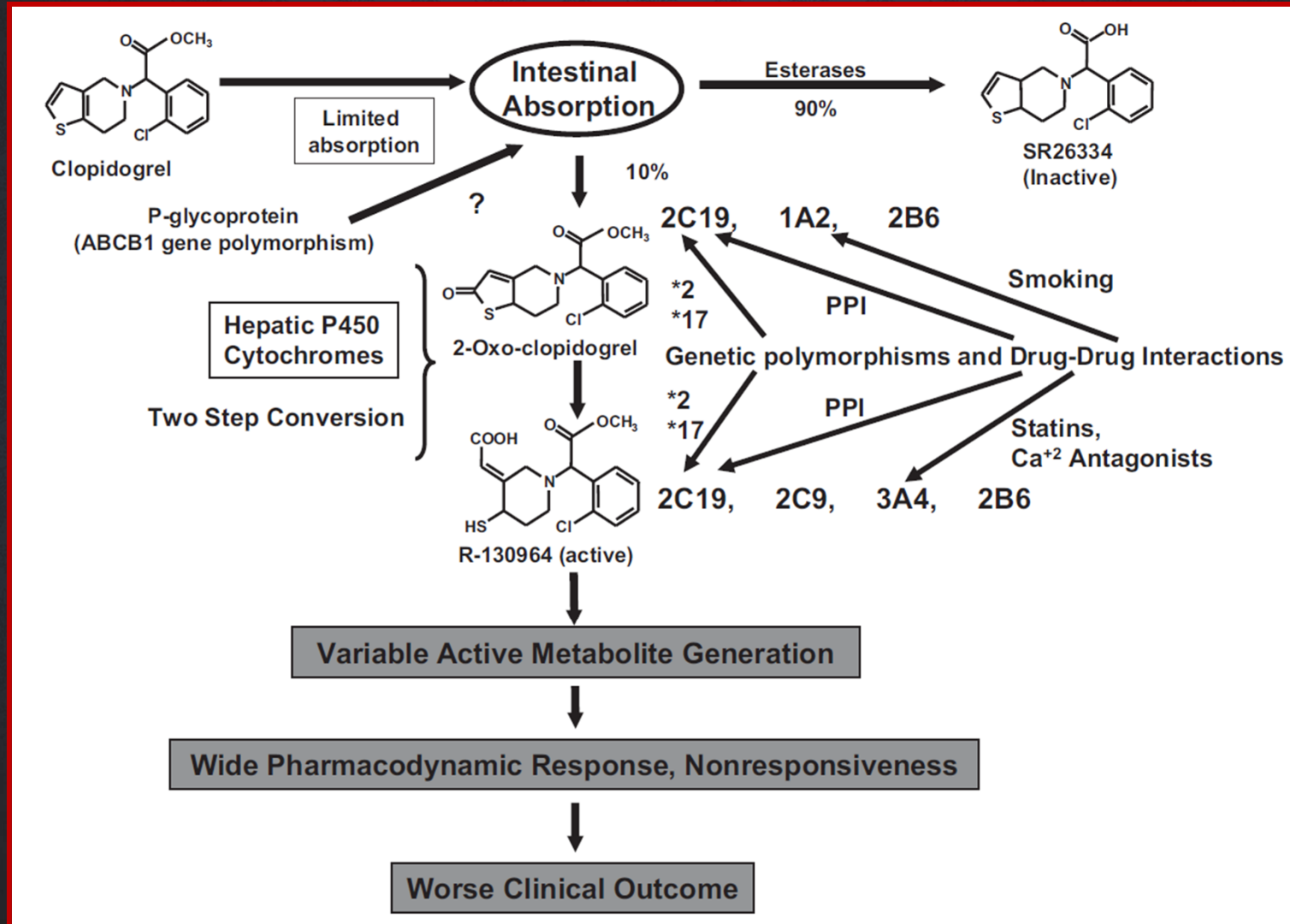
ADP-P2Y₁₂ receptor interaction



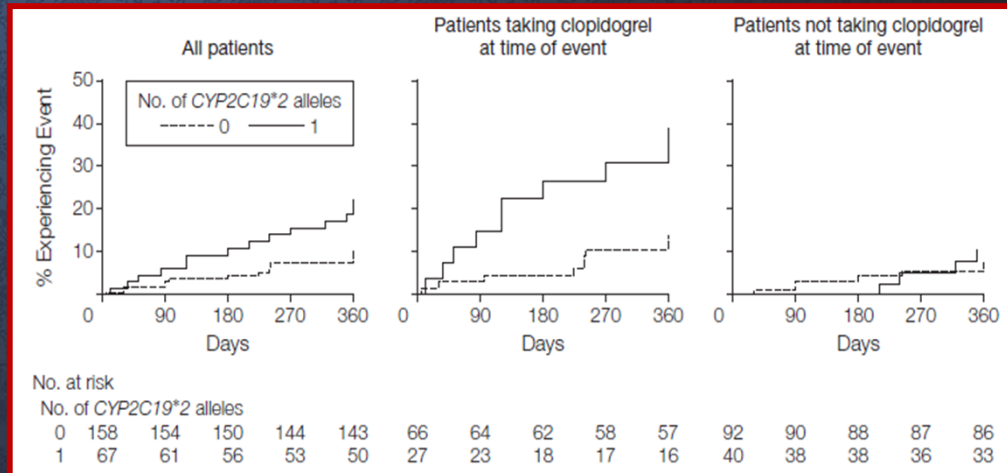
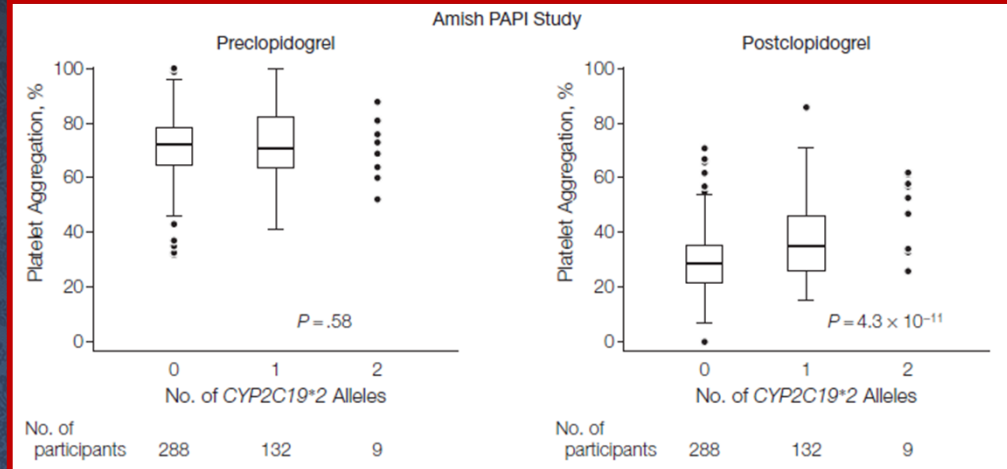
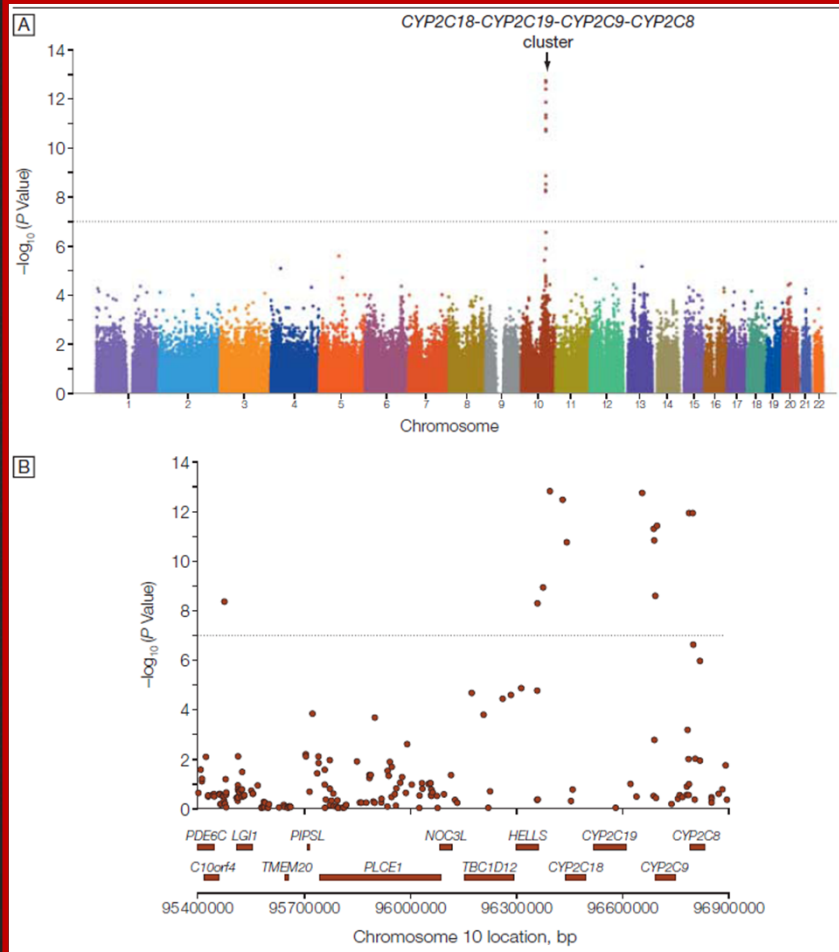
ADP-P2Y₁₂ receptor interaction



Clopidogrel Metabolism



Association of CYP 2C19 genotype with antiplatelet effect & clinical efficacy of clopidogrel therapy



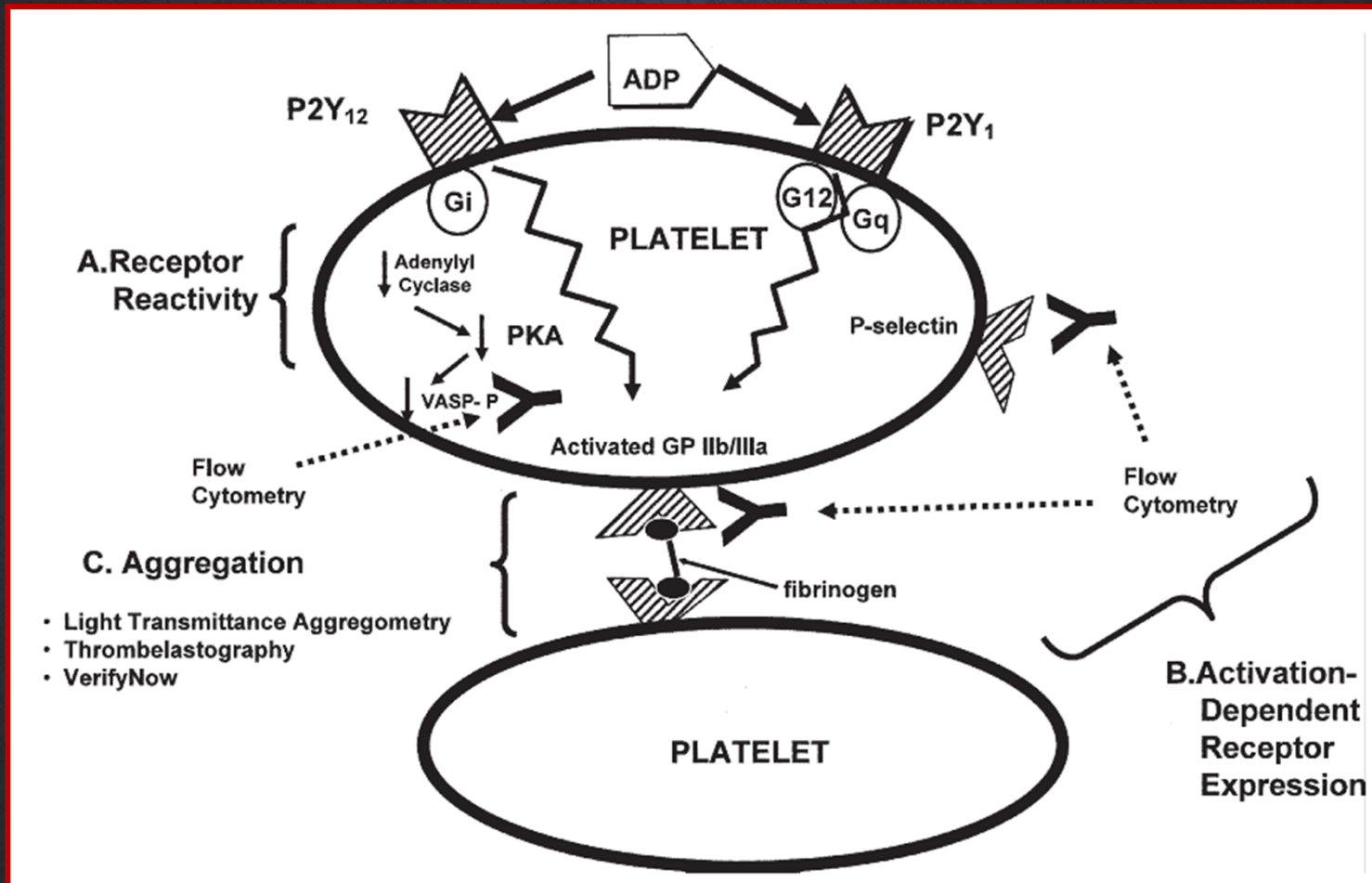
Shuldiner AR, et al. JAMA 2009;302:849

Causes of Clopidogrel Resistance

- Loss-of-function (LOF) genetic polymorphism
 - CYP2C19 LOF allele : *2, *3
 - ABCB1 3435 C->T

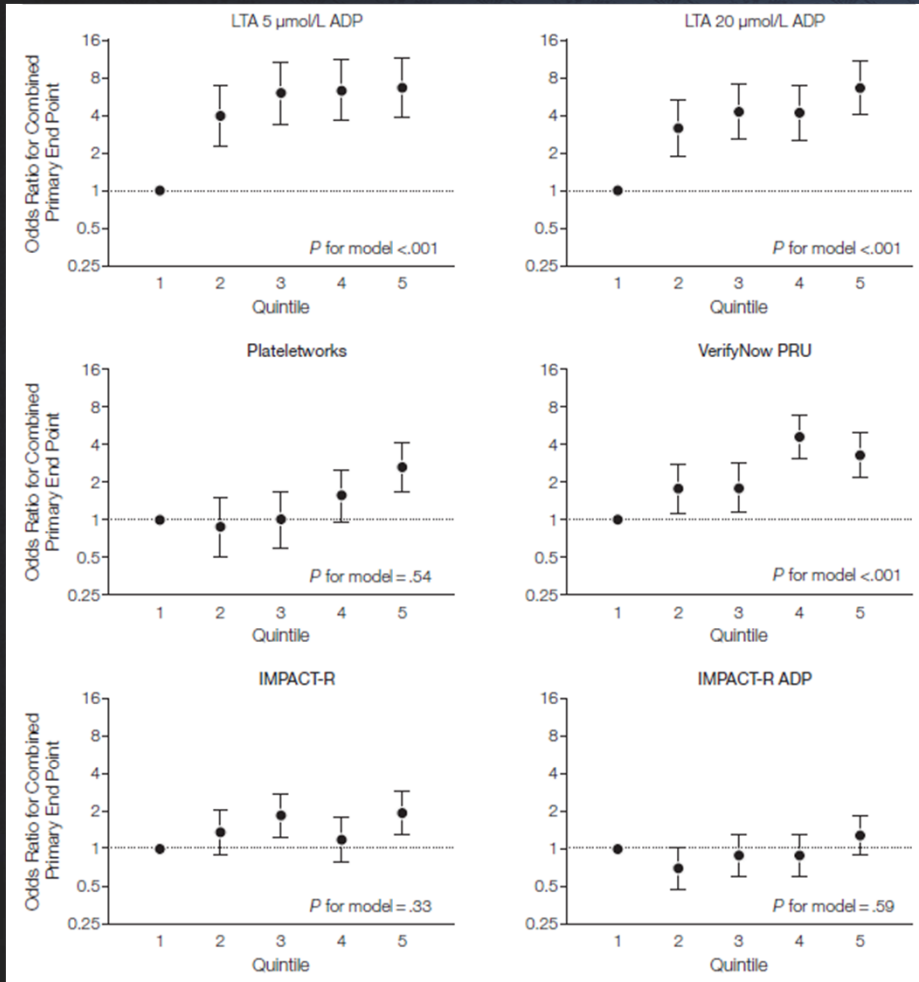
Allele	Trivial Name	Effect of Nucleotide Changes	Enzyme Activity	0 200 400 600 800 1000 1200 1400 1600 bp
<i>CYP2C19*1A</i>	<i>CYP2C19_{wt1}</i>		Active	
<i>CYP2C19*1B</i>	<i>CYP2C19_{wt2}</i>	Ile ₃₃₁ Val	Active	
<i>CYP2C19*2A</i>	<i>CYP2C19_{m1A}</i>	Splicing Defect	Inactive	
<i>CYP2C19*2B</i>	<i>CYP2C19_{m1B}</i>	Glu ₉₂ Asp Splicing Defect	Inactive	
<i>CYP2C19*3</i>	<i>CYP2C19_{m2}</i>	Stop Codon	Inactive	
<i>CYP2C19*4</i>	<i>CYP2C19_{m3}</i>	GTG Initiation Codon	Inactive	
<i>CYP2C19*5A</i>	<i>CYP2C19_{m4}</i> <i>CYP2C19_{TRP433}</i>	Arg₄₃₃Trp	Inactive	
<i>CYP2C19*5B</i>		Ile ₃₃₁ Val; Arg₄₃₃Trp		
<i>CYP2C19*6</i>	<i>CYP2C19_{m5}</i>	Arg₁₃₂Gln; Ile ₃₃₁ Val	Inactive	

Platelet function testing for clopidogrel responsiveness



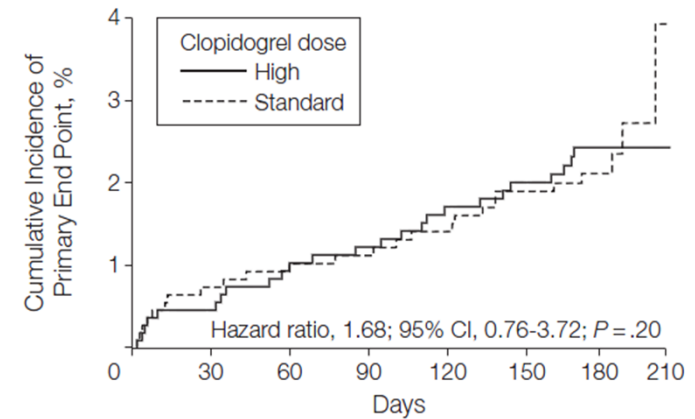
Gurbel PA, et al. *J Am Coll Cardiol* 2007;50:1822

High on-treatment platelet reactivity & Adverse clinical outcomes



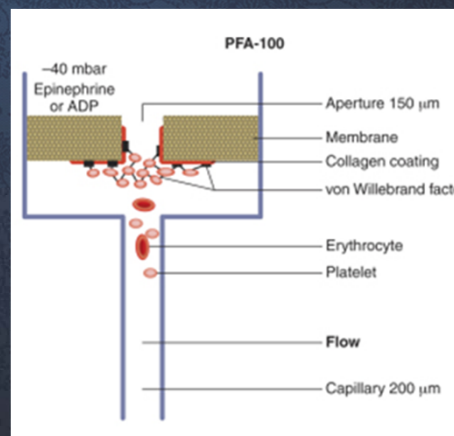
GRAVITAS

Patients with high on-treatment platelet reactivity receiving high- or standard-dose clopidogrel

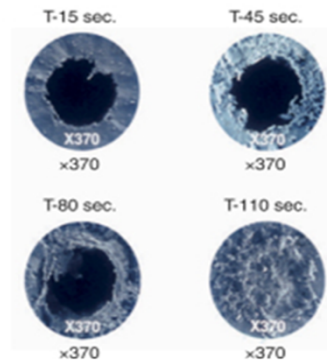


No. at risk

High-dose clopidogrel	1109	1056	1029	1017	1007	998	747	54
Standard-dose clopidogrel	1105	1057	1028	1020	1015	1005	773	53



Occlusion process
Collagen/epinephrine closure time: 110 sec.



Breet NJ, et al. JAMA 2010;303:754

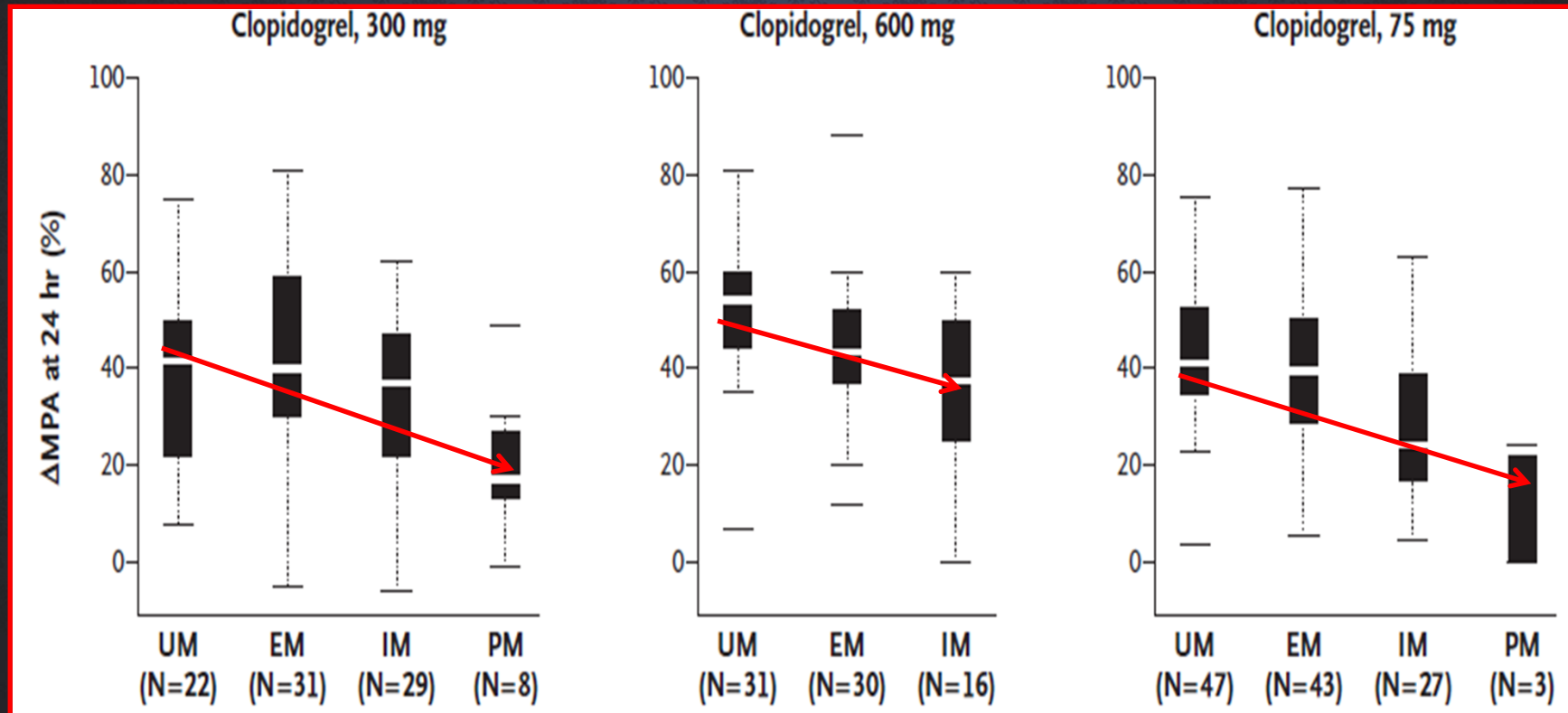
Routine platelet function testing in PCI?

- **Lack of consensus on the optimal PFT**
 - ✓ which method of aggregation
 - ✓ which agonist used
 - ✓ which concentration
 - ✓ absolute aggregation vs relative aggregation
 - ✓ when is the optimal timing for PTF?
- **Lack of cutoff values associated with clinical risk**
- **ESC guideline (2009)**
 - ✓ monitoring of PLT function in clinical practice is premature

Genotype and phenotype of CYP2C19

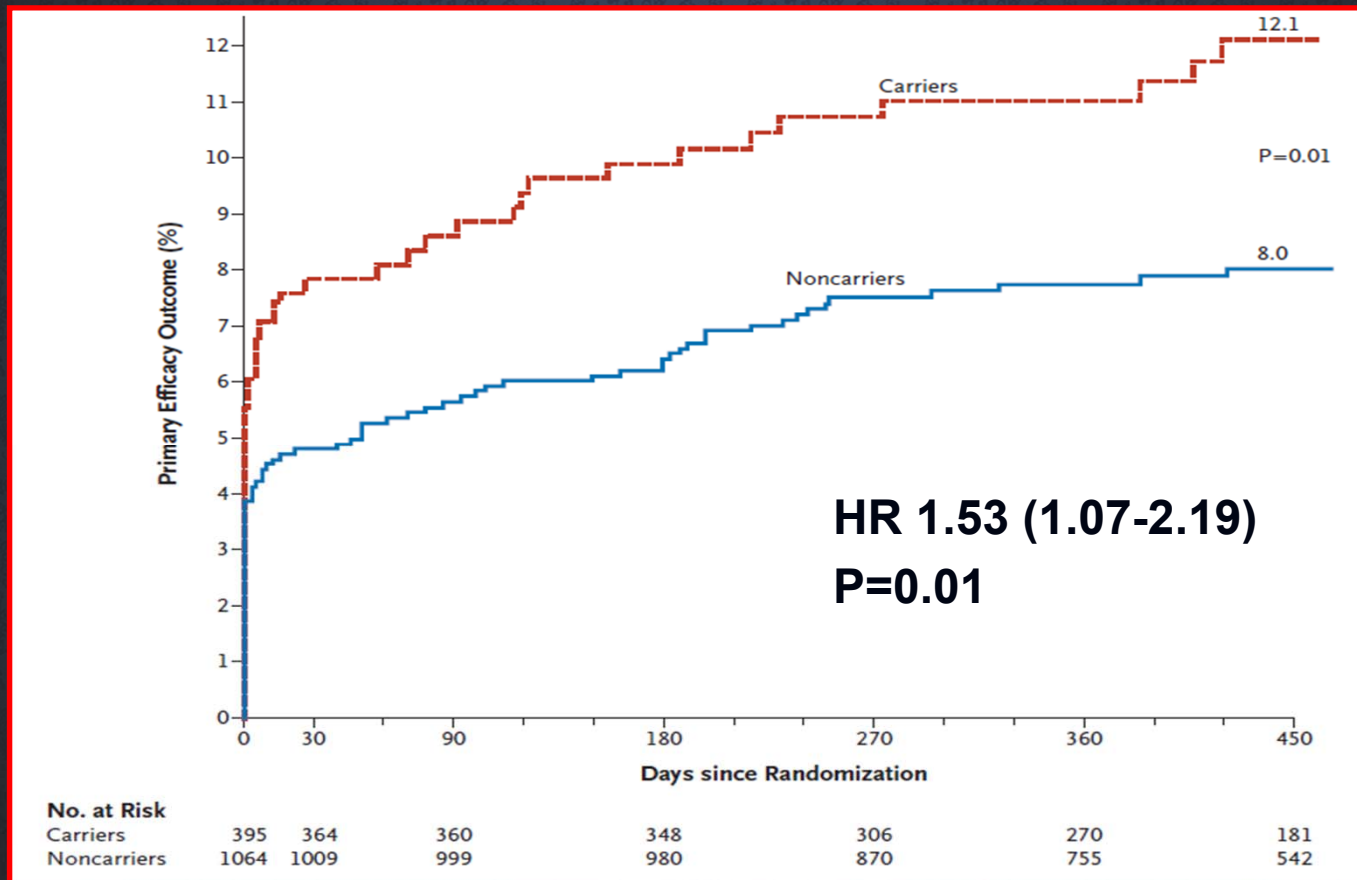
- UM (ultra-rapid metabolizer) : *1/*17
- EM (extensive metabolizer) : *1/*1
- IM (intermediate metabolizer): *1/*2, *1/*3
- PM (poor metabolizer) : *2/*2, *2/*3, *3/*3

Gene-dose response



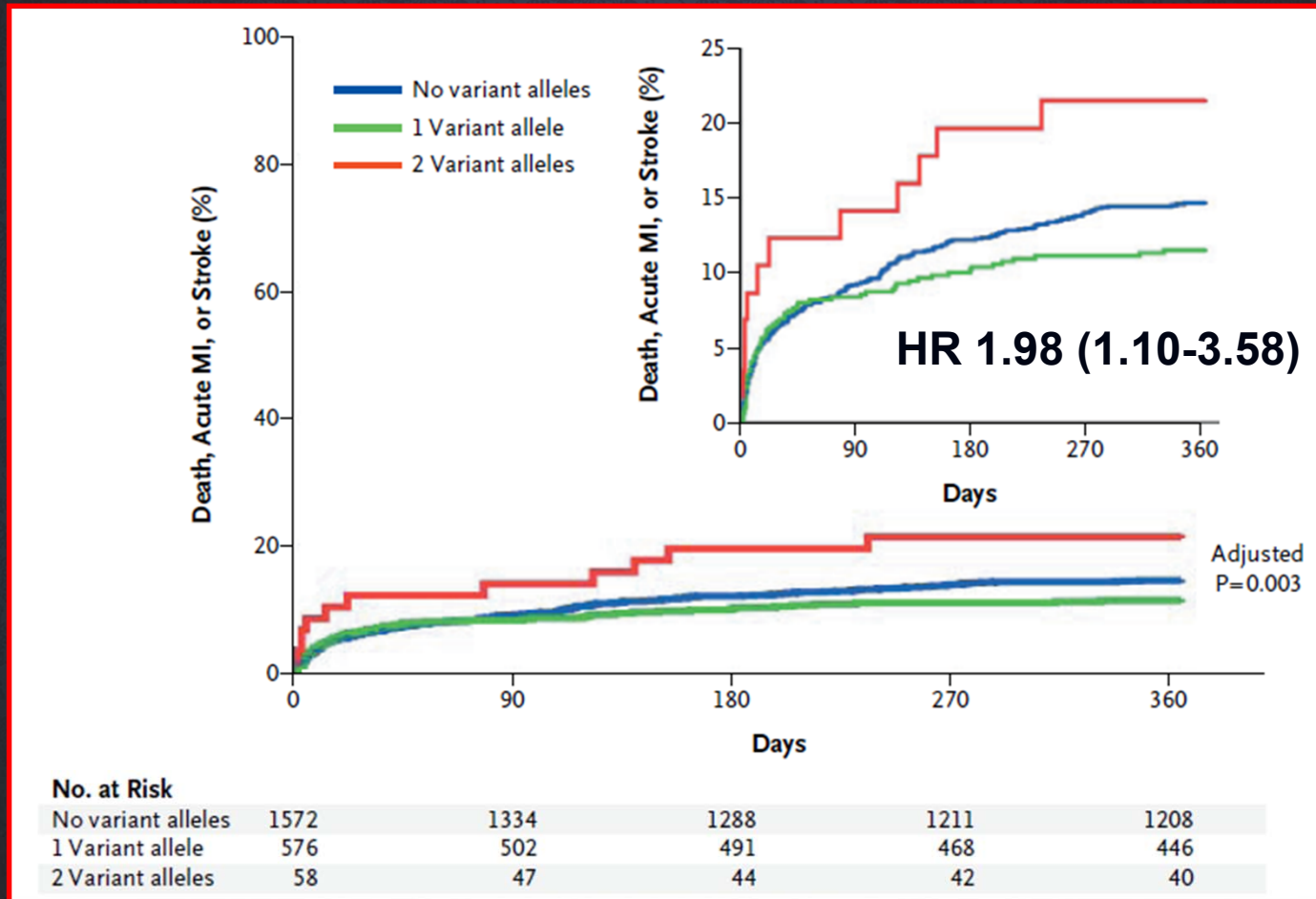
Mega JL, et al. N Engl J Med 2009;360:354

CYP2C19 LOF alleles (*2 or *3) & clinical outcomes in ACS (TRITON-TIMI 38)



Mega JL, et al. N Engl J Med 2009;360:354

CYP2C19 LOF alleles (*2 or *3) & clinical outcomes in AMI (FAST-MI)



Simon T, et al. *N Engl J Med* 2009;360:363

CYP2C19*2 or *3 & clopidogrel resistance

- CYP2C19 *2 or *3

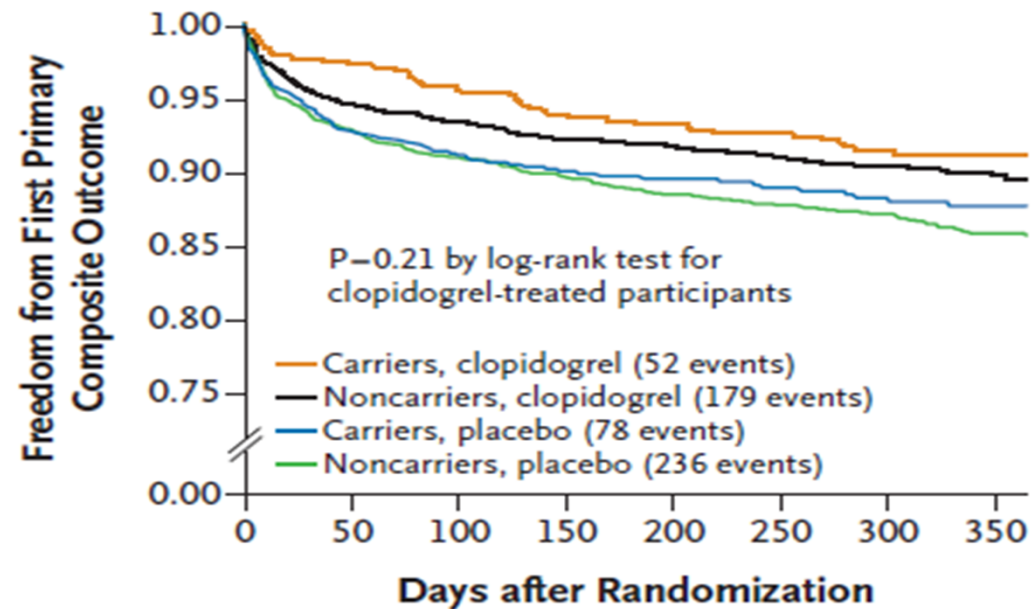
- Less clopidogrel active metabolite generation (reduced PK response)

- Poor P2Y12 receptor blocking activity (reduced PD response)

- Worse clinical outcomes

CYP2C19 LOF alleles (*2 or *3) & clinical outcomes (CURE+ACTIVE 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 Engl J Med 2010;363:1704

Racial difference in distribution of CYP2C19 genotype and phenotype

➤ In TRITON study population (manly Caucasians)

Gene	Dichotomous classification	Predicted Phenotype	Observed Genotypes ^a	Number of Subjects (%)	
				PK/PD	TRITON-TIMI 38
CYP2C19	Non-carrier	UM	*17/*17, *1A/*17	44 (30)	1064 (73) ^b
		EM	*1A/*1A	53 (36)	
	Carrier	IM	*1A/*2A, *1A/*3, *1A/*4, *1A/*8	43 (29)	357 (24)
		PM	*2A/*2A, *2A/*3, *2A/*4 *2A/*5A, *2A/*8	8 (5)	38 (3)
	n/a	Unknown ^c	*1A/*9, *1A/*10, *2A/*17, *6/*17	NI ^c	NI ^c

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

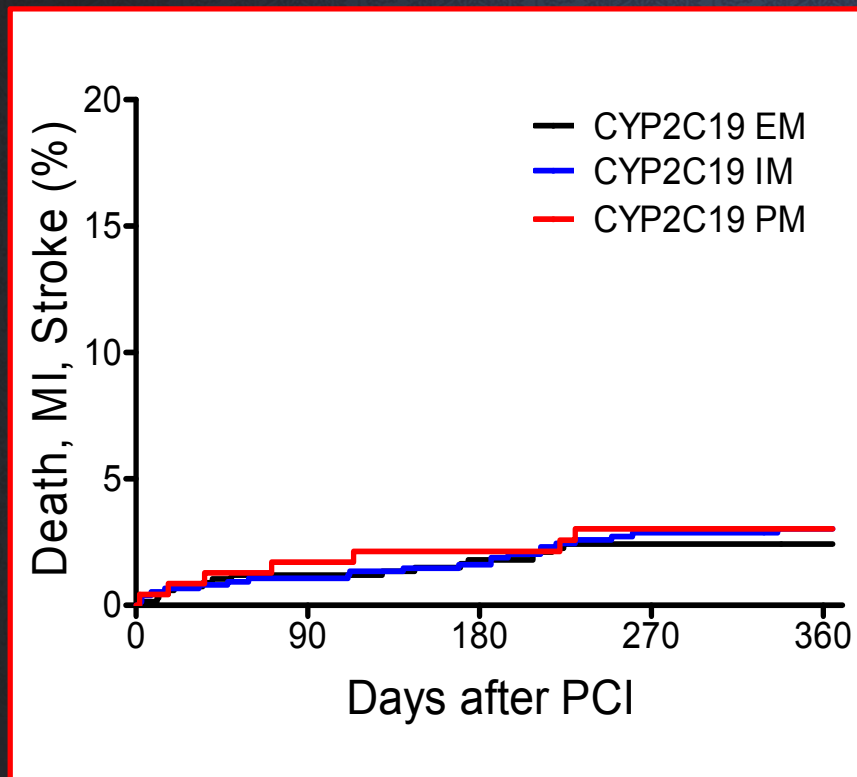
➤ In Korean population (CMC data)

Gene	Dichotomous classification	Predicted Phenotype	Observed Genotypes	Number of Subjects (%)
CYP2C19	Non-carrier	EM	*1/*1	872 (40)
	Carrier	IM	*1/*2, *1/*3	1003 (46)
		PM	*2/*2, *2/*3, *3/*3	313 (14)

CYP2C19 genotype-guided antiplatelet therapy in the future?

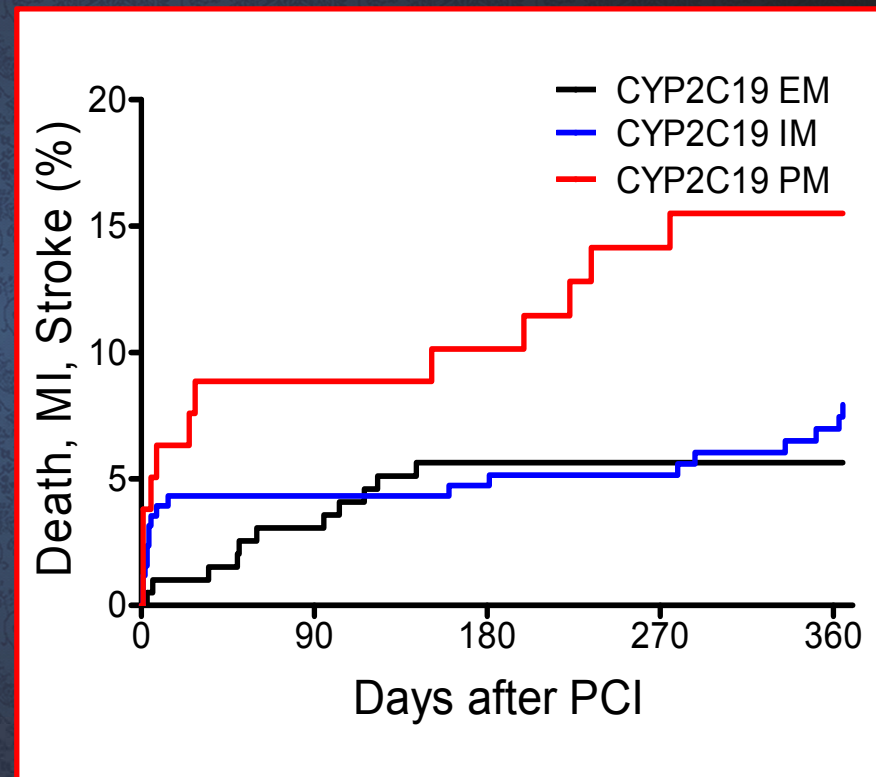
- **Which disease subsets will be greatly benefitted from genotype-guided antiplatelet therapy?**
- **What will intermediate metabolizer affect clinical outcome of clopidogrel therapy?**

Clinical outcomes according to CYP2C19 phenotype and disease subset



Angina patients

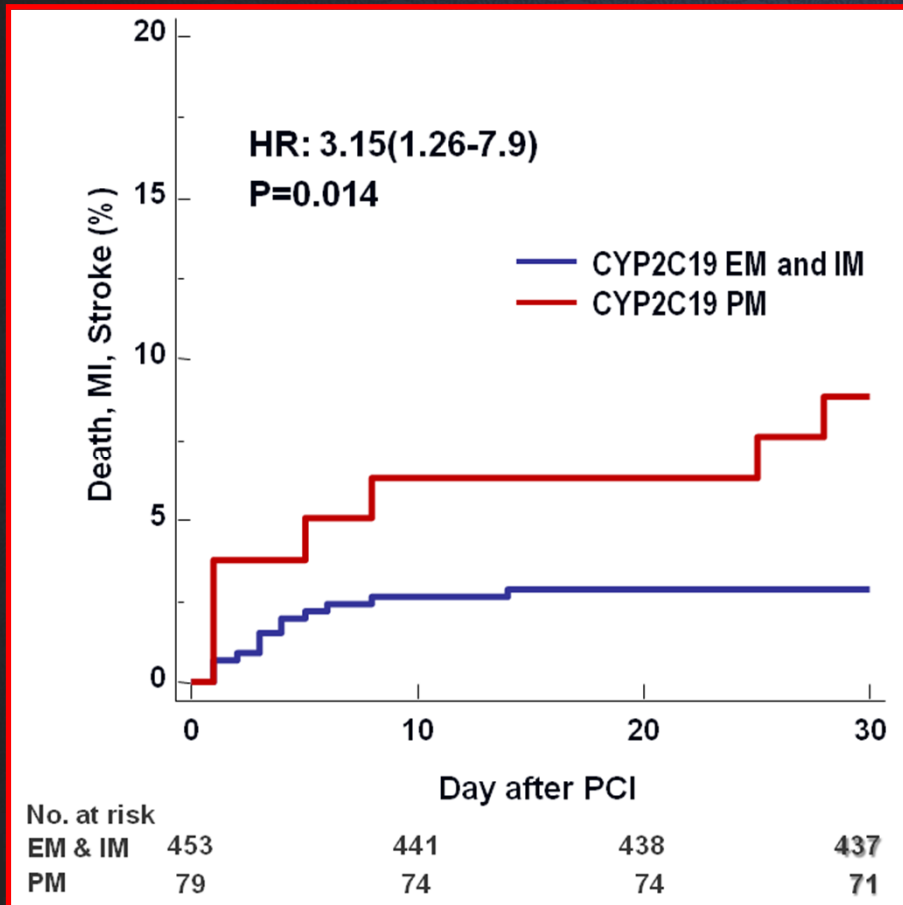
P for interaction <0.001



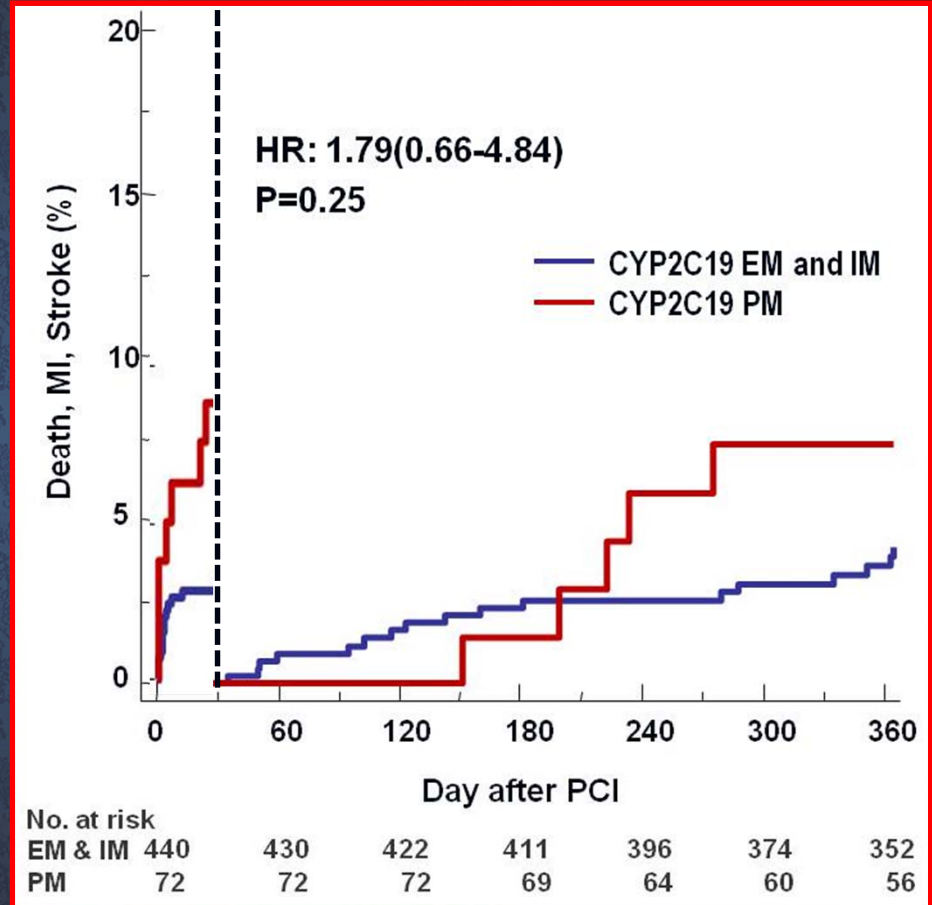
AMI patients

COACT-gene registry data

Landmark analysis in COACT-gene registry



AMI patients



COACT-gene registry data

Suggestion

- **High-risk patients undergoing PCI will be greatly benefitted from genotype-guided anti-platelet therapy.**
- **Currently, platelet function testing or genotyping in routine clinical practice is not recommended but CYP2C19 genotype-guided selection of alternative antiplatelet regimen should be considered for patients with high risk before PCI.**

In the near future

- **Future utility of PFT vs genotyping for personalized therapy**
 - Complementary strategy of Genotyping + PFT
 - Genotyping only
 - Genotyping with PFT at the early stage of events
 - PFT only
- **Prospective randomized clinical trial will be needed to evaluate whether genotype-guided antiplatelet therapy will improve clinical outcomes.**
 - Availability of more potent drugs
 - : prasugrel, ticagrelor, new PAR-1 antagonist
 - Clopidogrel generics : economical concern
 - Balance between efficacy & safety (bleeding)



Thank you for your attention