CYP genetic polymorphisms, varying response to clopidogrel, and link to clinical outcomes: Is it real? A Korean perspective

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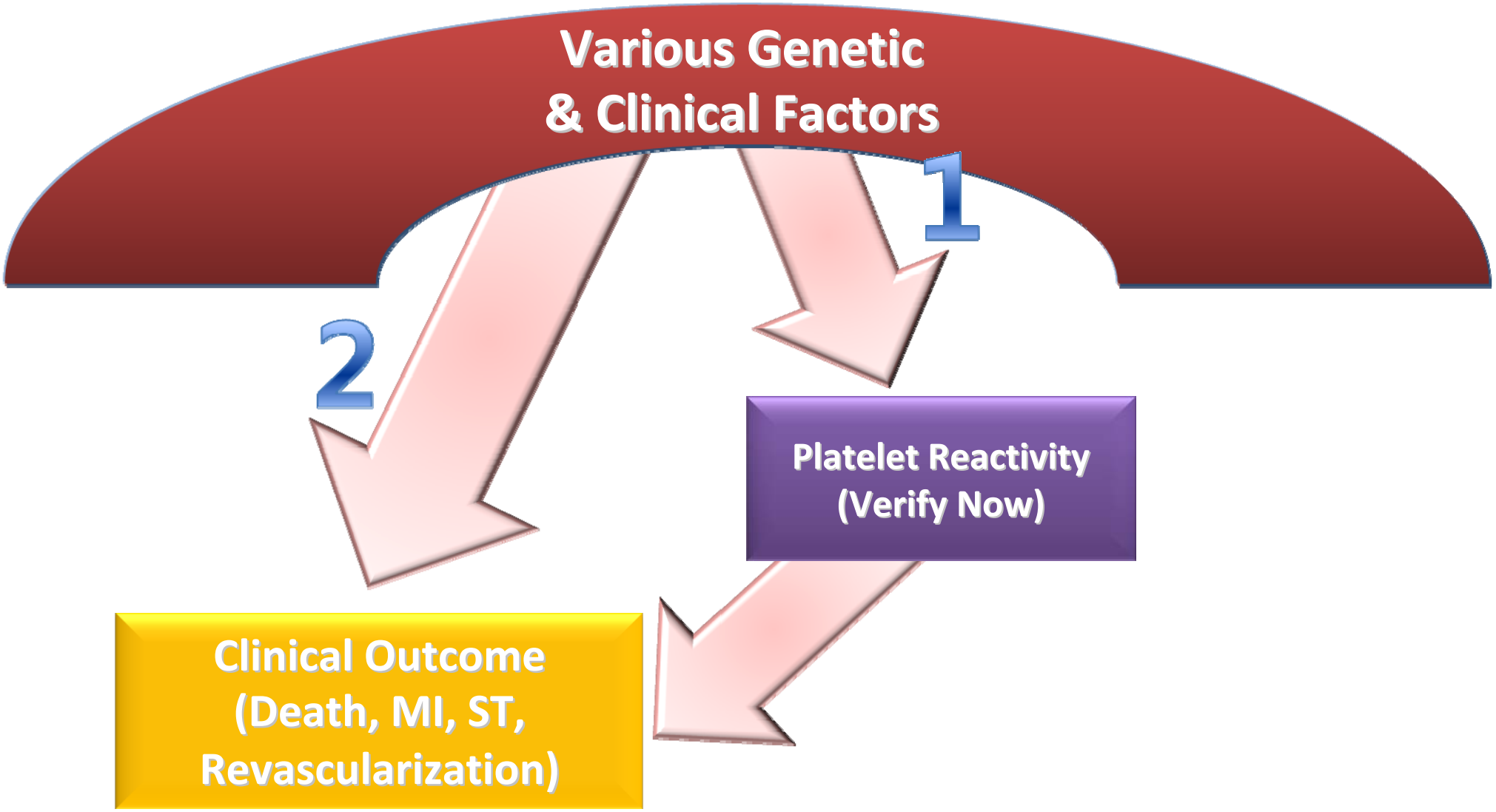
1. CYP genetic PM – Clopidogrel response variability?

2. CYP genetic PM – Clinical Outcome?

1. **CYP genetic PM – Clopidogrel response variability?**

2. **CYP genetic PM – Clinical Outcome?**

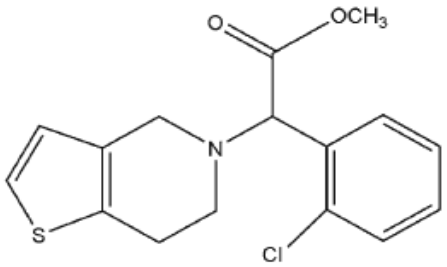
Genetics, Platelet reactivity and outcome



Clopidogrel Metabolism & Cytochrome Enz.

1. Step

Oxidation by
- CYP1A2 (35.8%)
- CYP2B6 (19.4%)
- CYP2C19 (44.9%)

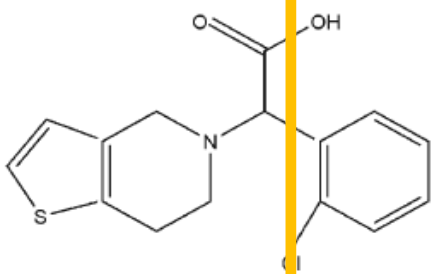


clopidogrel

CYP450s (CYP3A)

Competition between esterase and CYP pathway. Slowing CYP pathway results in inactivation via esterase pathway

Hydrolysis by esterases accounts For approximately 85% of clopidogrel metabolism



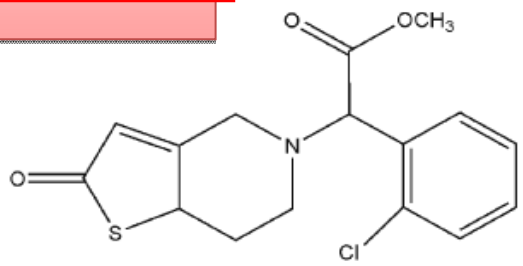
inactive

3.

Inactivation by serum esterase

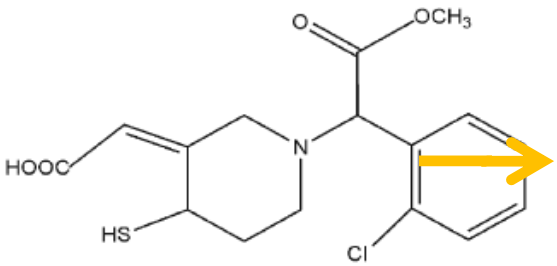
2.Step

Hydrolysis by
- CYP3A4 (39.8%)
- CYP2C9 (6.8%)
- CYP2B6 (32.9%)
- CYP2C19 (20.6%)



2-oxo-clopidogrel (inactive)

CYP450s

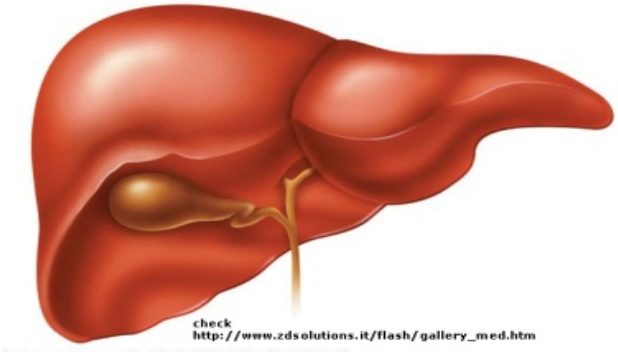


SR26334 (active)

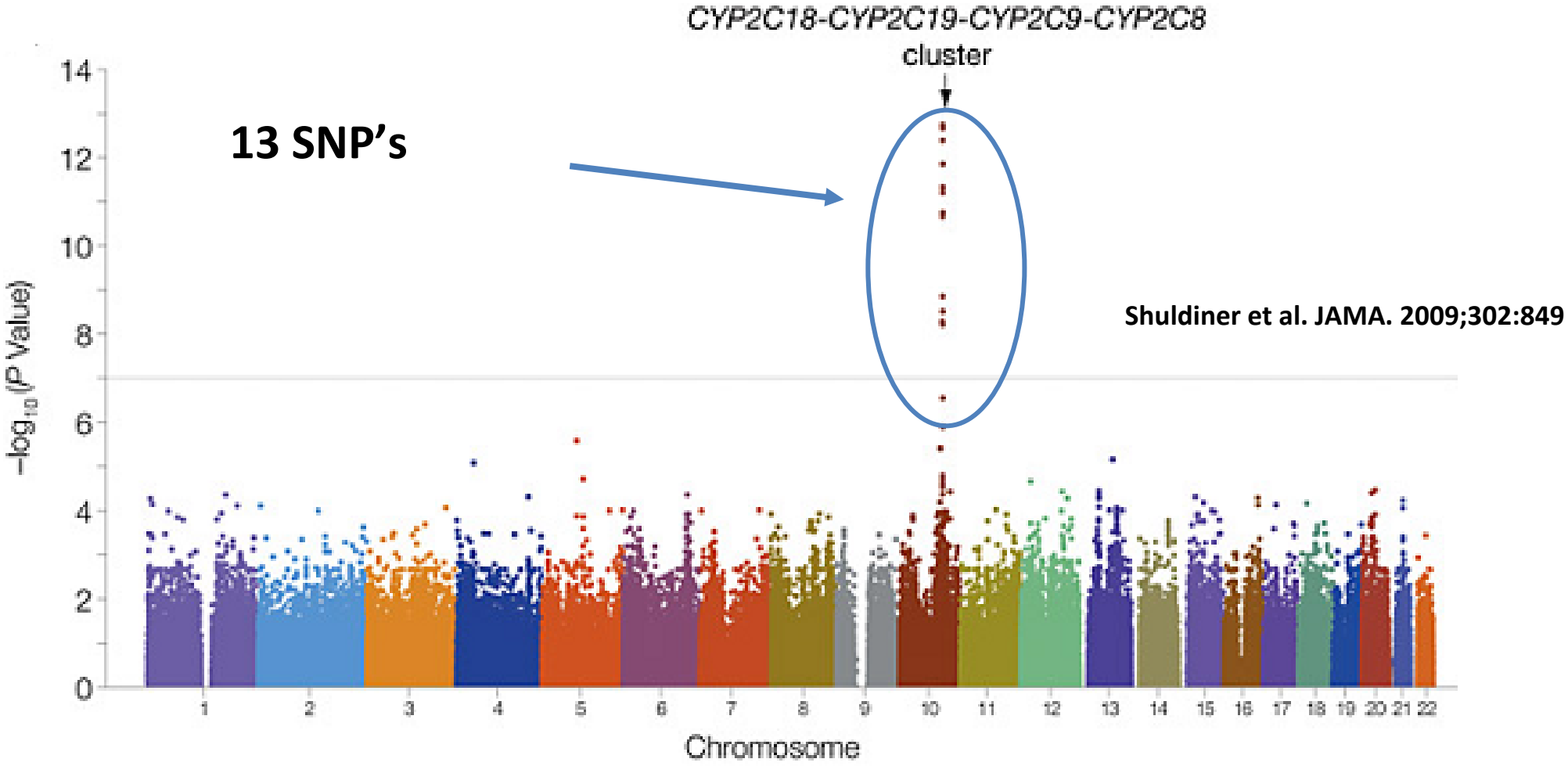
Ford et al. J. Clin. Pharmacol. 2009
Kazui et al. DMD 2009:

CYP2C19

- 10% of commonly used drug metabolism
- 490 Amino acid
- Gene on Chromosome 10
- 9 Exons, 26 non-synomymous SNPs
  - **Wild type CYP2C19*1/*1**
  - Splicing defect (null alleles) with **complete enzyme function loss**
    - ✓**CYP2C19 *2**
    - ✓**CYP2C19 *3** (almost exclusive in Asian)
  - Ultra-rapid phenotype CYP2C19*17
    - ✓99C>T
    - ✓991A>G



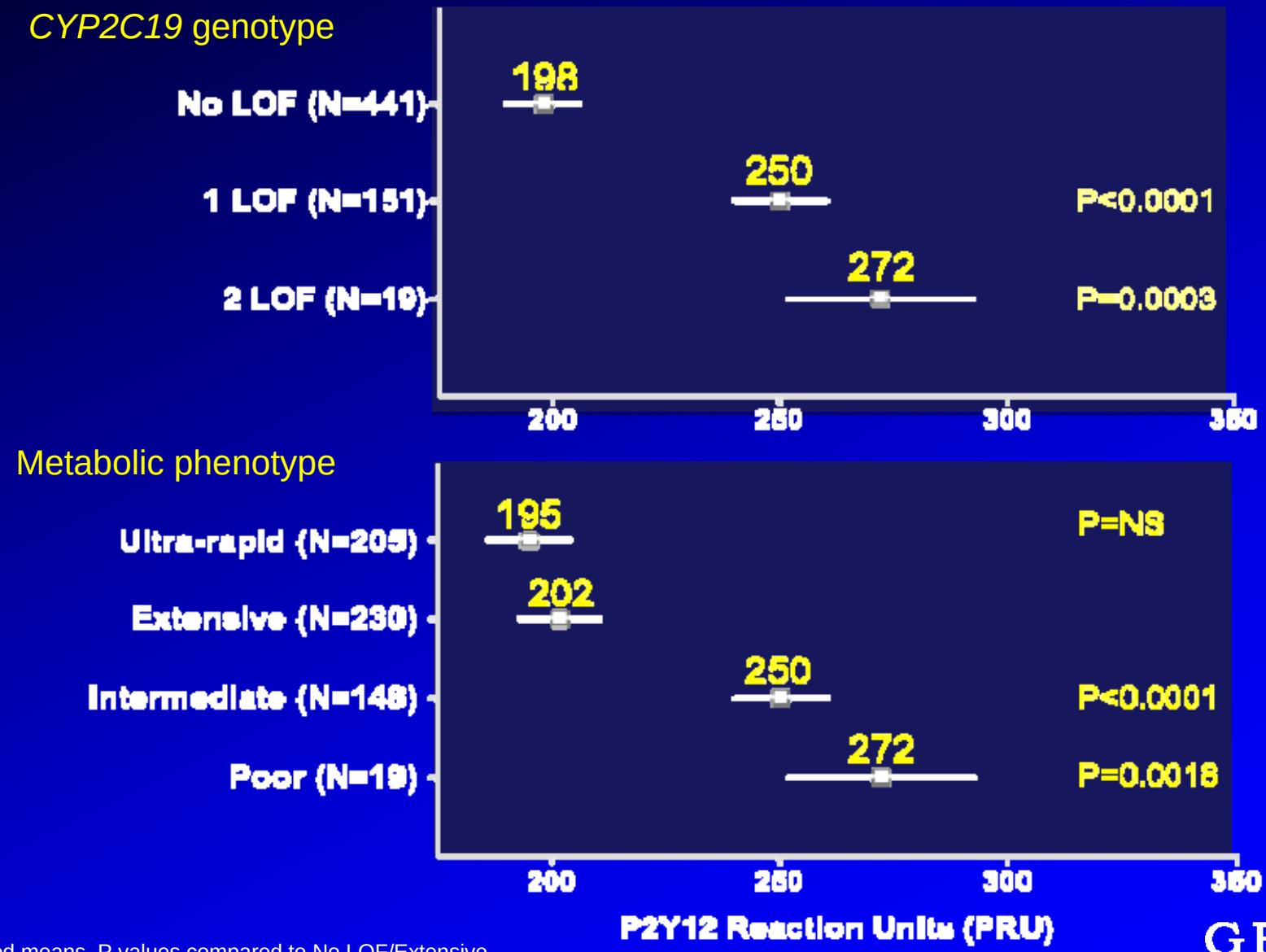
Decreased Response to Clopidogrel: GWAS Data



Shuldiner et al. JAMA. 2009;302:849

1) **Clopidogrel response was highly heritable.**
2) **Cluster of 13 SNP's <u>strongly associated</u> with clopidogrel response ($p < 10^{-7}$). (locus on 10q24)**
3) **CYP2C19*2 accounted for most or all of the 10q24 association signal (~12% of response variability)**
4) **Majority of variation in clopidogrel response remains unexplained.**

Platelet Reactivity on Clopidogrel Post-PCI Is Associated With *CYP2C19* Genotype & Phenotype

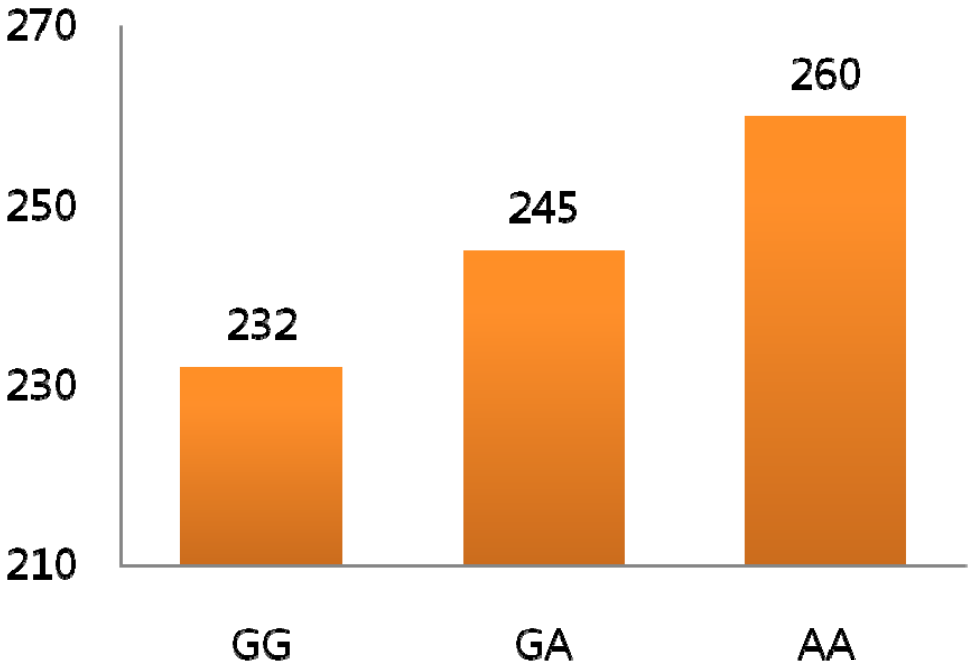


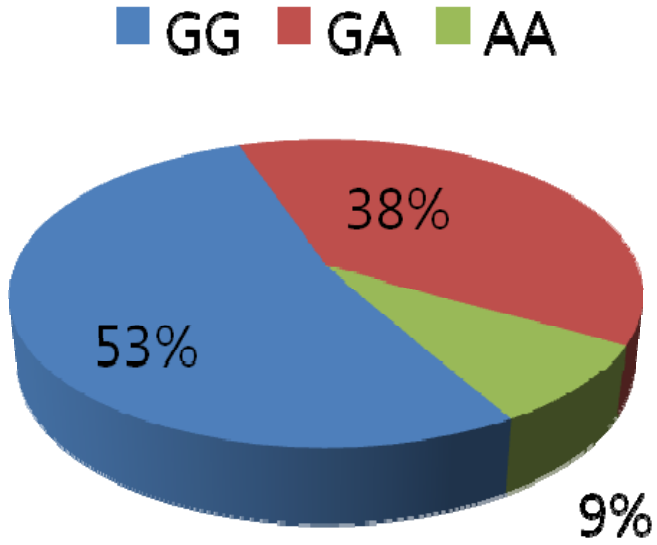
Least squared means. P values compared to No LOF/Extensive.

η^2 : portion of variance explained by the genotype or phenotype in the multivariate generalized linear model

Courtesy of M. Price. Price M et al. ACC 2011

CYP2C19*2

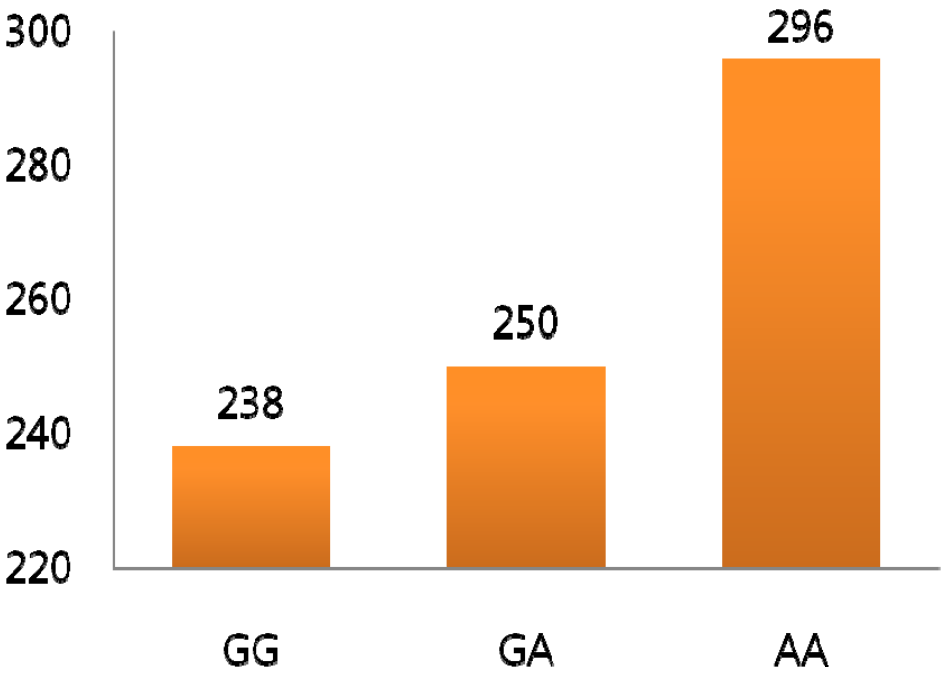


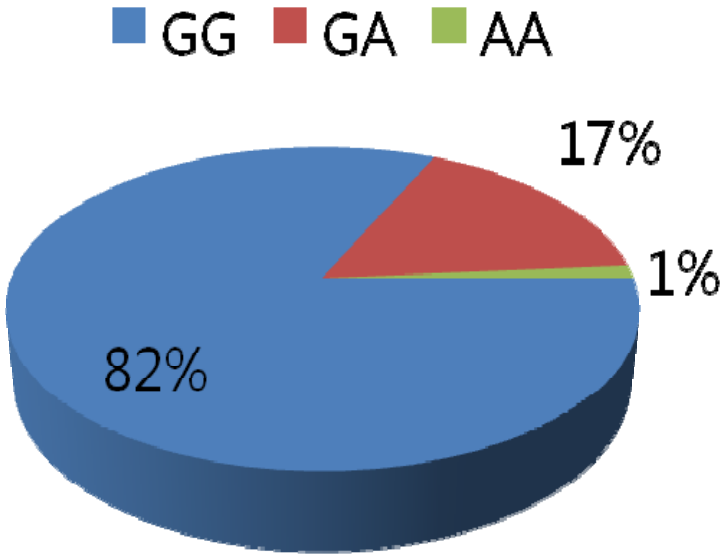


	GG	GA	AA	All	p-value
Freq	848	613	139	1600	
Expected	833.0	642.9	124.0		
PRU	232.5±82.6	245.7±79.4	260.3±72.0	240.0±81.0	P<0.001

Major G 0.72 (wild), Minor A 0.28 (mutant), X^2 = 5.463, p = 0.062)

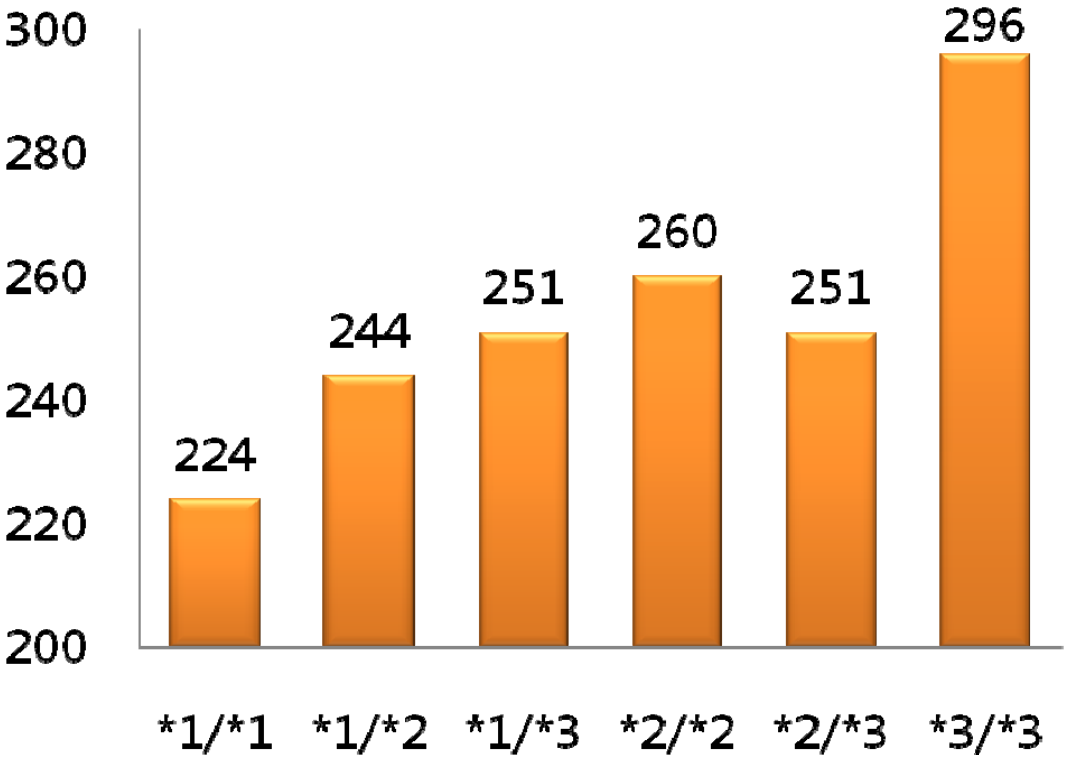
CYP2C19*3

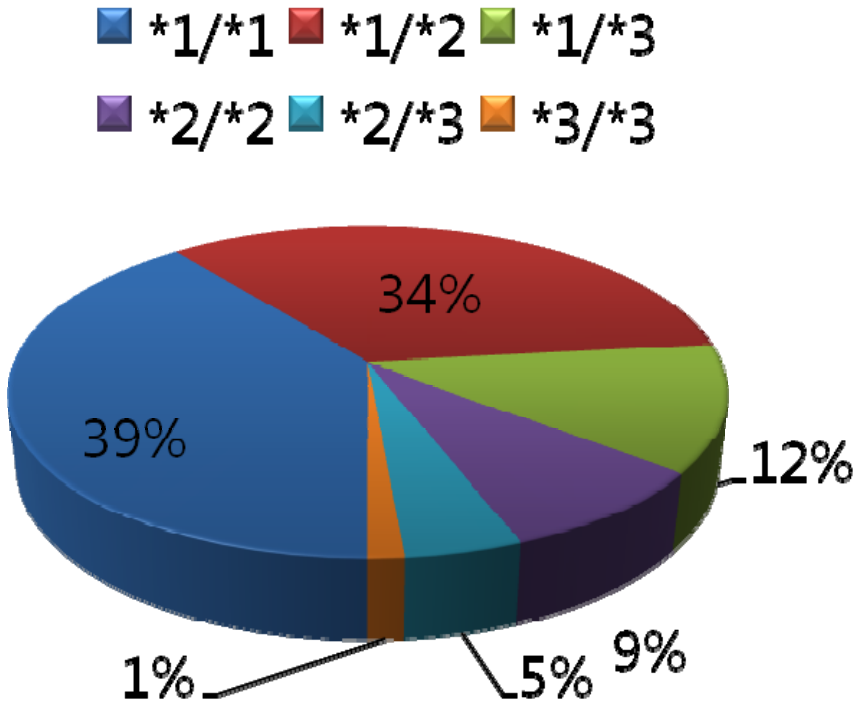




	GG	GA	AA	All	p-value
Freq	1308	267	22	1597	
Expected	1301.1	280.7	15.1		
PRU	236.8.5±81.7	250.8±76.9	296.2±58.4	240.0±81.0	P<0.001
				Major G 0.90 (wild), Minor A 0.10 (mutant), X^2 = 3.813, p = 0.050)	

CYP2C19 *2 & *3 combined : CROSS VERIFY cohort



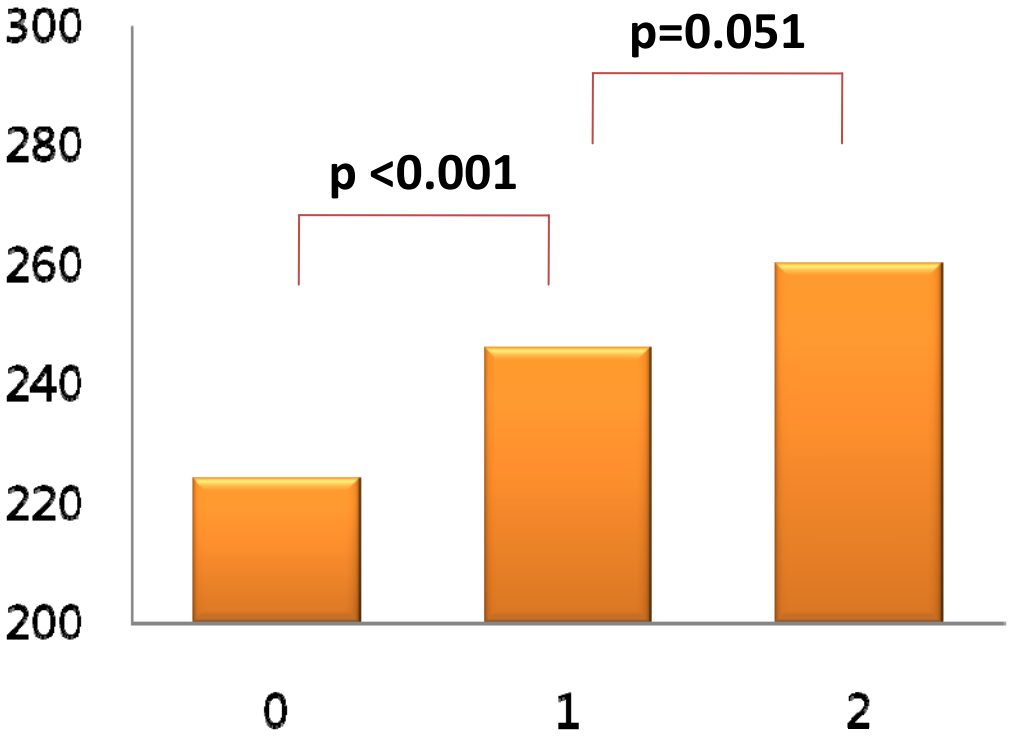


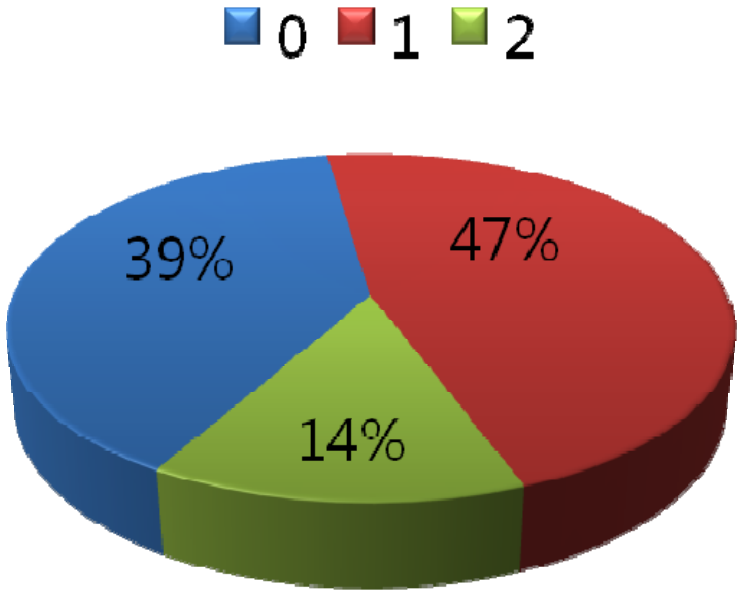
	*1/*1	*1/*2	*1/*3	*2/*2	*2/*3	*3/*3	p-value
Freq	625	540	195	139	71	22	
PRU	224.7±82.3	244.8±81.1	251.4±80.7	260.3±72.0	251.0±64.9	296.2±58.4	<0.001

Unpublished data from the CROSS VERIFY cohort

Number of 'loss of fxn' alleles & PRU:

CROSS VERIFY cohort

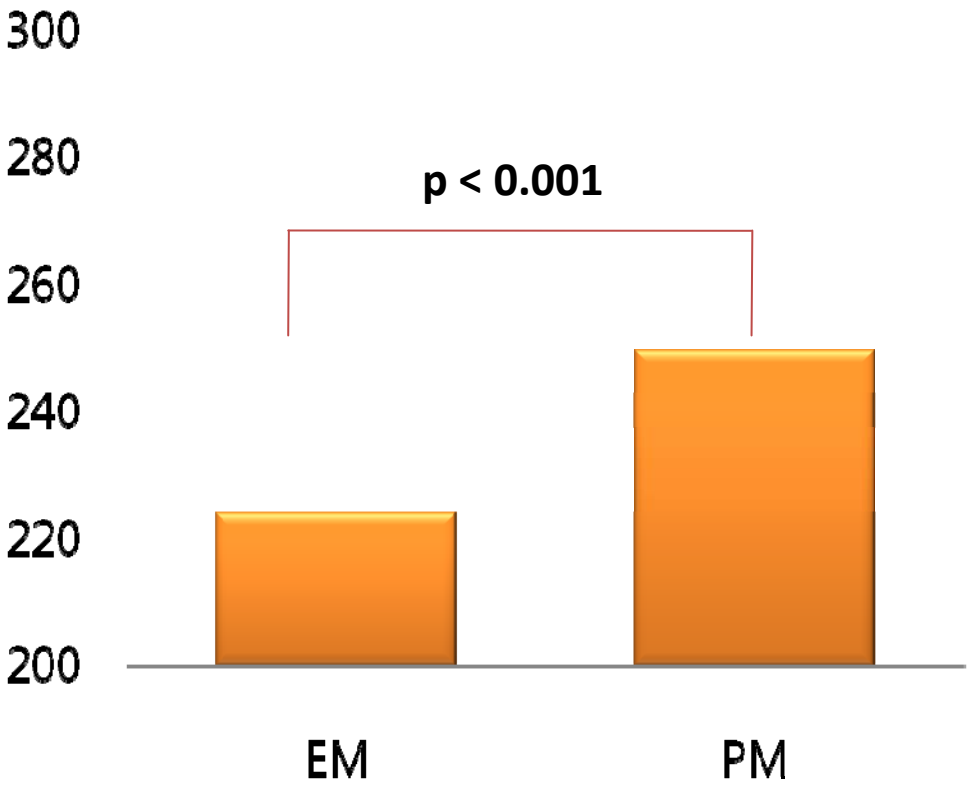




	Zero (*1/*1)	One (*1/*2, *1/*3)	Two (*2/*2, *2/*3, *3/*3)	p-value
Freq	625	735	232	
PRU	224.7±82.4	246.5±81.0	260.9±69.5	<0.001

Unpublished data from the CROSS VERIFY cohort

Extensive (EM) vs. Poor (PM) Metabolizer



Extensive Metabolizer

CYP2C19 *1/*1

Poor Metabolizer

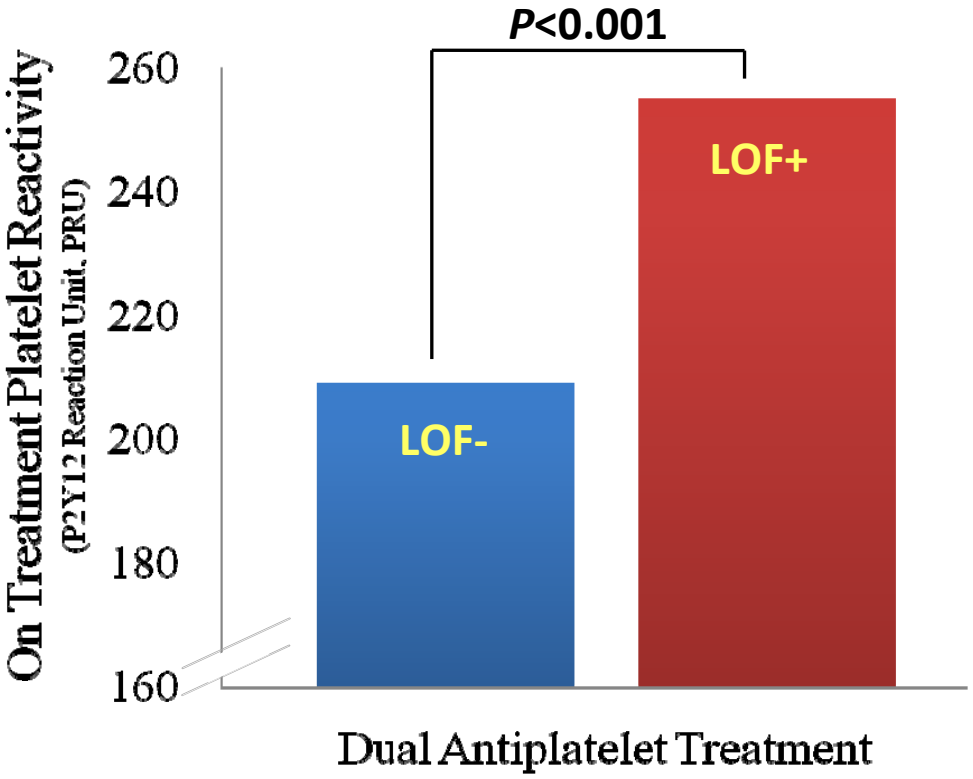
CYP2C19 *1/*2, *1/*3, *2/*2, *2/*3, *3/*3

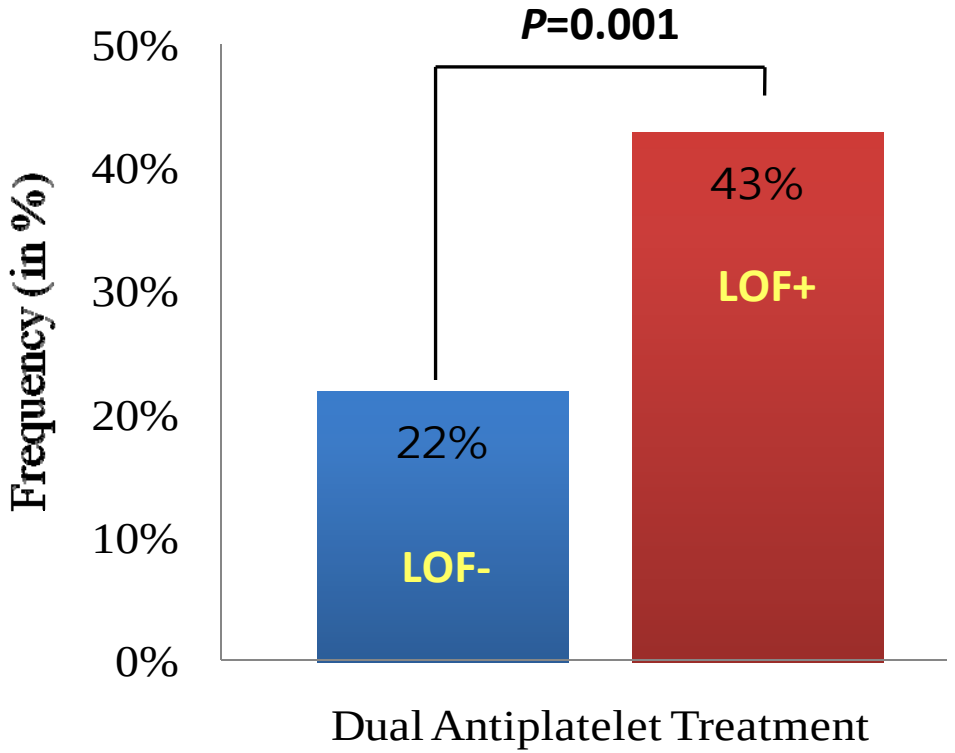
	EM	PM	p-value
Freq	625	967	
PRU	224.67±82.36	249.96±78.62	<0.001

Unpublished data from the CROSS VERIFY cohort

CYP2C19 LOF associated with HOPR in Koreans

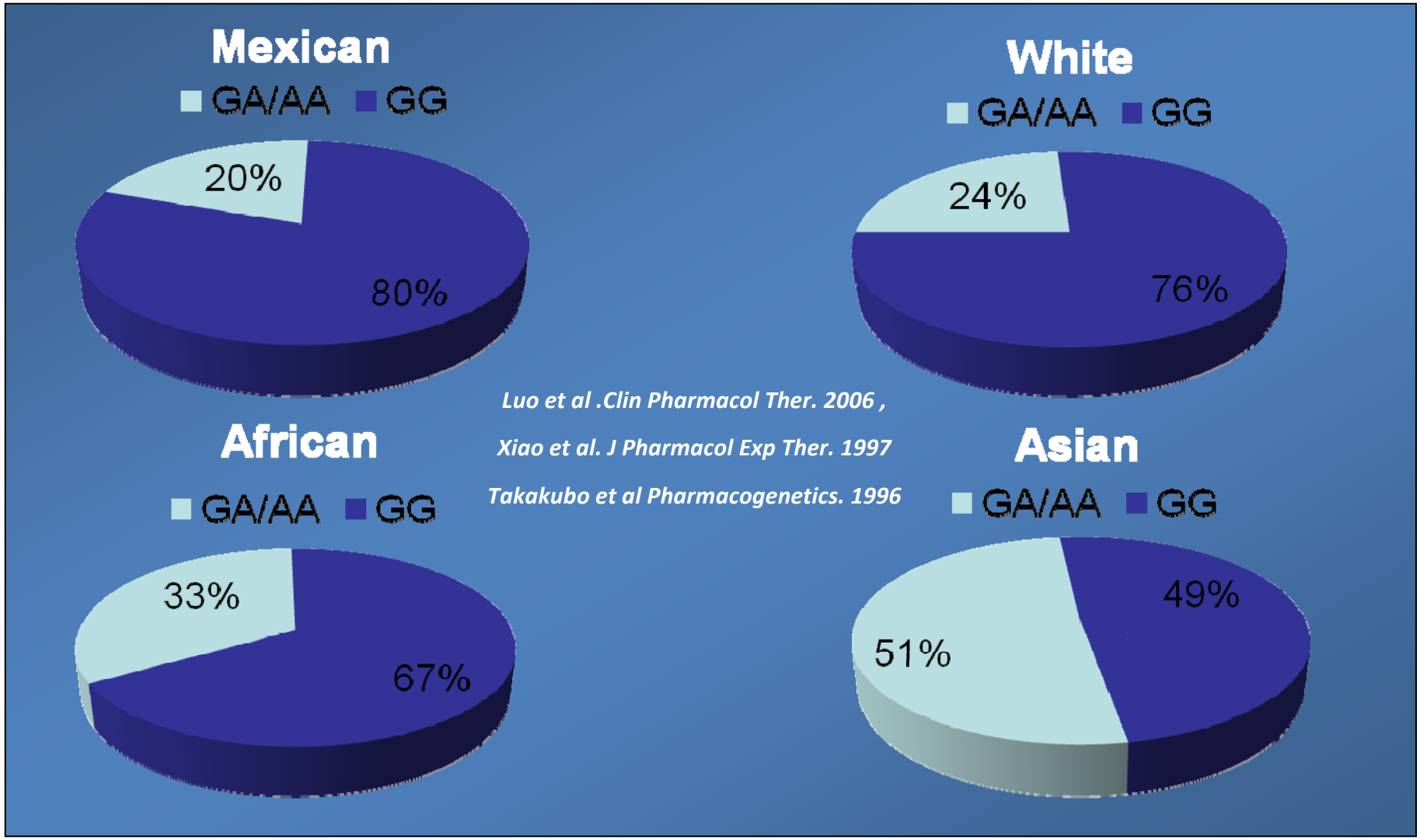
Genetic subanalysis of the CILON-T trial





Park KW, Kim HS et al. Heart 2011

Different CYP2C19 *2 Allele Frequency



Luo et al .Clin Pharmacol Ther. 2006 ,

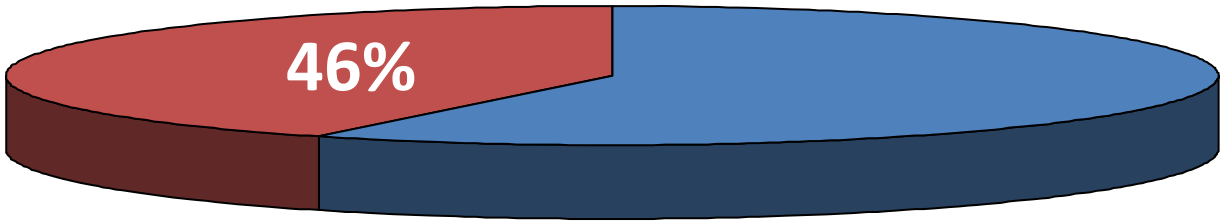
Xiao et al. J Pharmacol Exp Ther. 1997

Takakubo et al Pharmacogenetics. 1996

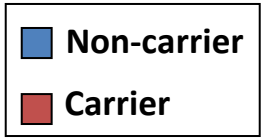
Different CYP2C19 LOF Frequency

: according to Asian Ethnicity

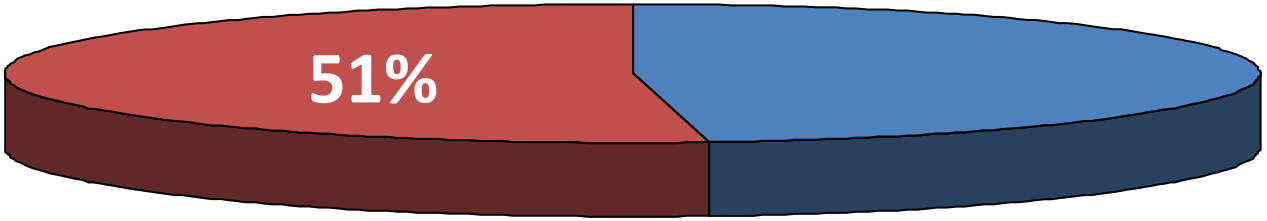
Japanese Population



Sawada T et al. Circulation J 2011.



Chinese Population



Zhou Q et al. Pharmacogenomics J 2009

HPR and Platelet Reactivity According to CYP2C19 genotyping

	Wild (*1/*1) (n =57)	One mutant (*1/*2, *1/*3) (n=59)	Two Mutant (*2/*2, *2/*3) (n = 20)	*P* value
	41.9%	58.1%		
Rate of HPPR	16 (28.1%)	27 (45.8%)	12 (60.0%)	*0.024*
LTA				
5μM ADP Agg_{max}	43±14	49±14	52±17	*0.012*
20μM ADP Agg_{max}	54±15	62±12	64±15	*0.002*
VerifyNow				
PRU	226±90	259±74	284±84	*0.018*
% inhibition	28±23	20±18	13±16	*0.016*

HPPR: *5 μM ADP induced MPA > 50%*

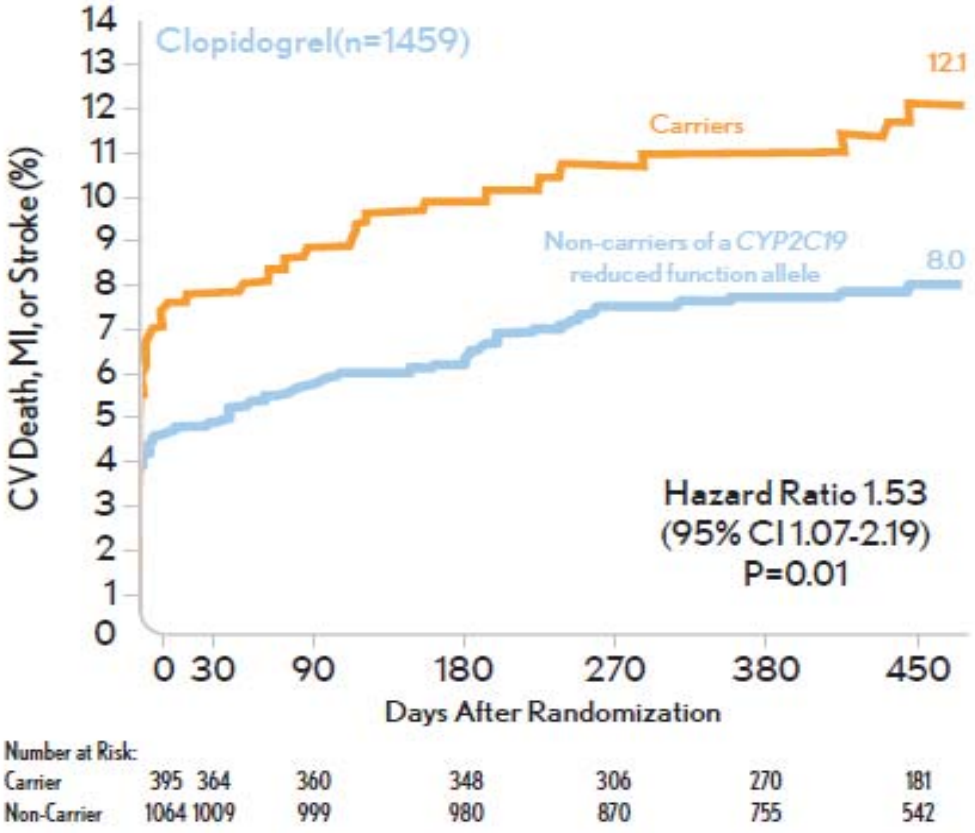
Kim IS, et al. J Thromb Haemost 2009;7:897.

1. CYP genetic PM – Clopidogrel response variability?

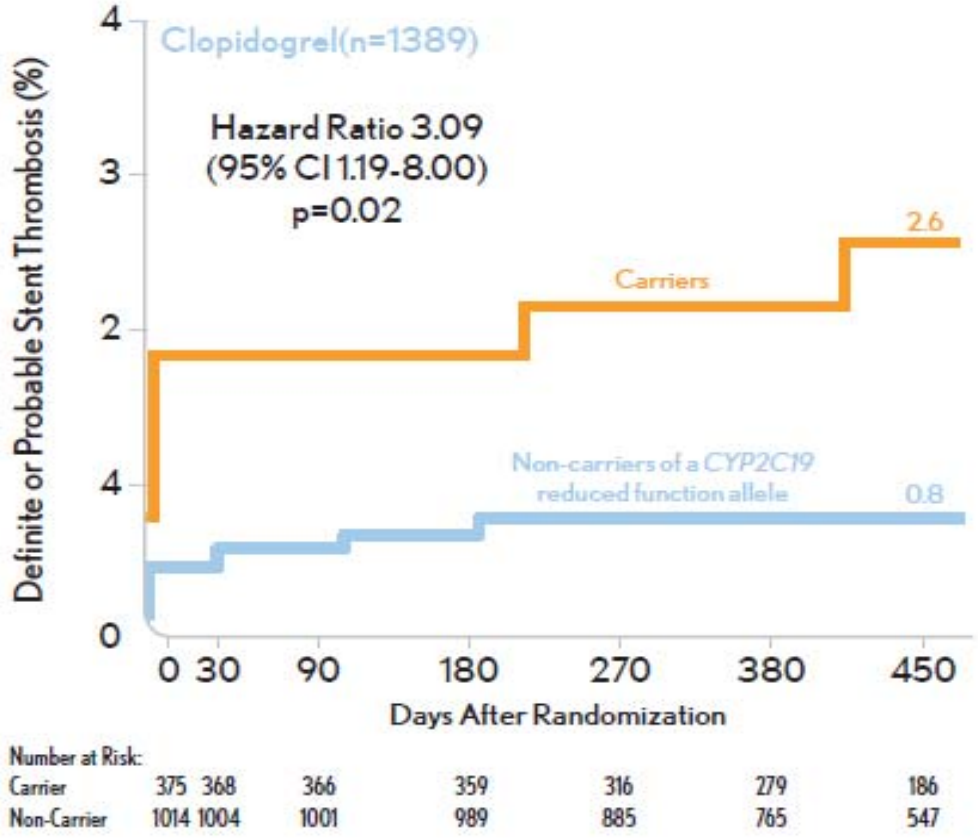
2. **CYP genetic PM – Clinical Outcome?**

Cumulative Incidence of CV ischemic Events

Pre-specified subgroup analyses of TRITON TIMI 38

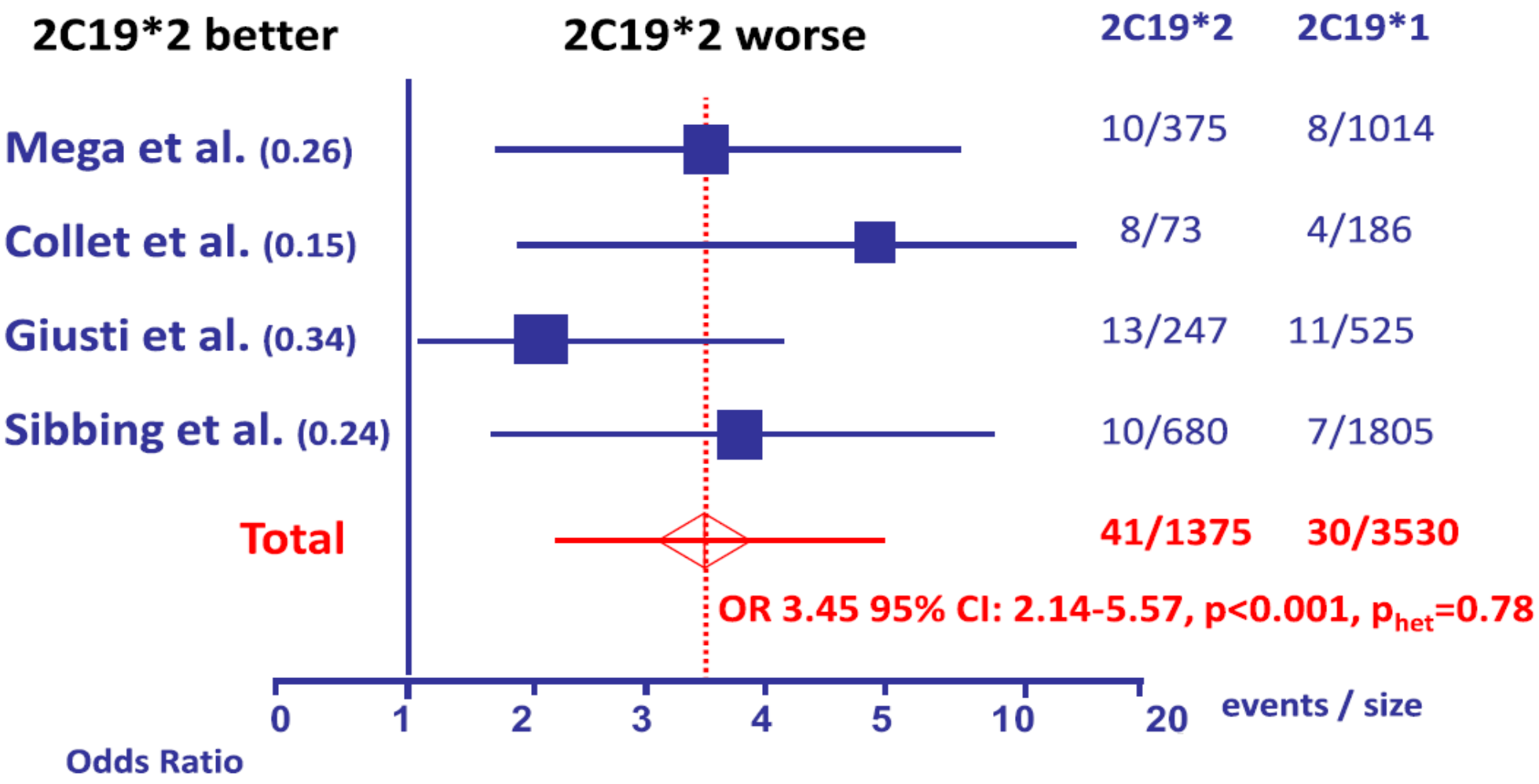


Data From Mega JL. et al. *N Engl J Med. 2009;360:354-62.*



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

Risk of ST according to CYP2C19*2 allele (n = 11,959)



Hulot JS, et al. J Am Coll Cardiol 2010;56:134-43.

Impact of Cytochrome P450 2C19*2 Polymorphism on Intra-Stent Thrombus After Drug-Eluting Stent Implantation in Japanese Patients Receiving Clopidogrel

Takahiro Sawada, MD; Toshiro Shinke, MD; Junya Shite, MD; Tomoyuki Honjo, MD; Yoko Haraguchi, MD; Ryo Nishio, MD; Masakazu Shinohara, MD; Ryuji Toh, MD; Tatsuro Ishida, MD; Hiroyuki Kawamori, MD; Amane Kozuki, MD; Takumi Inoue, MD; Hirotoshi Hariki, MD; Ken-ichi Hirata, MD

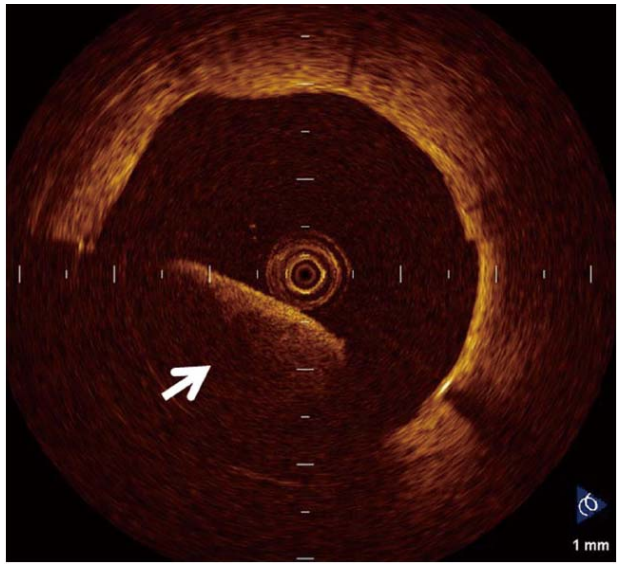
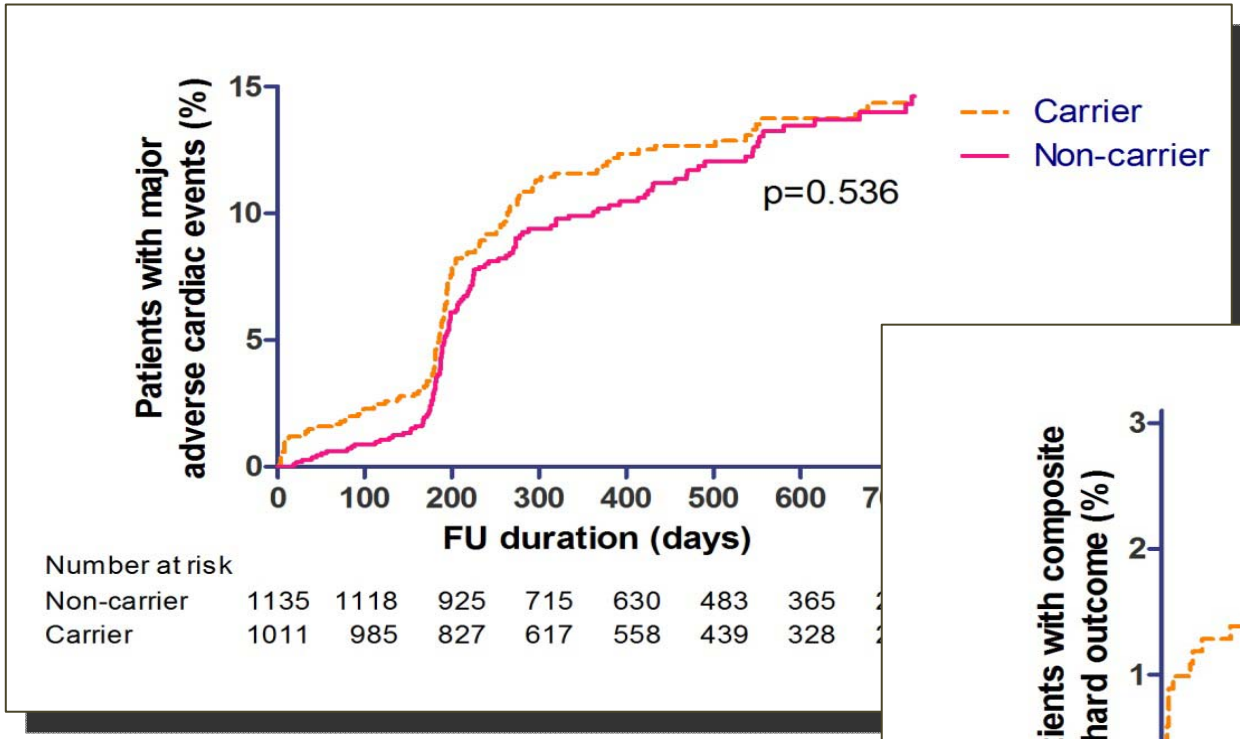


Table 3. Optical Coherence Tomography Data

	Non-carriers (n=58)	*2 carriers (n=42)	P value
Mean number of struts (n)	183.7±116.1	182.7±100.5	0.97
Frequency of malapposed stent struts (%)	2.5±3.2	1.8±2.5	0.27
Mean number of malapposed stent struts (n)	4.4±4.7	3.0±3.7	0.17
Frequency of uncovered stent struts (%)	7.0±7.5	6.2±7.2	0.63
Mean number of uncovered stent struts (n)	12.8±12.4	10.9±10.8	0.49
Minimum stent diameter (mm)	2.80±0.55	2.66±0.70	0.30
Mean stent eccentricity index	0.89±0.10	0.91±0.16	0.76
Mean neointimal thickness (mm)	0.12±0.10	0.15±0.18	0.36
Mean neointimal unevenness score	1.85±0.47	1.78±0.46	0.53
Mean stent area (mm^2)	6.70±2.4	6.59±2.59	0.78
Minimum stent area (mm^2)	5.22±2.08	5.06±2.14	0.73
Presence of intra-stent thrombus (n)	9 (15.5)	22 (52.3)	0.0002

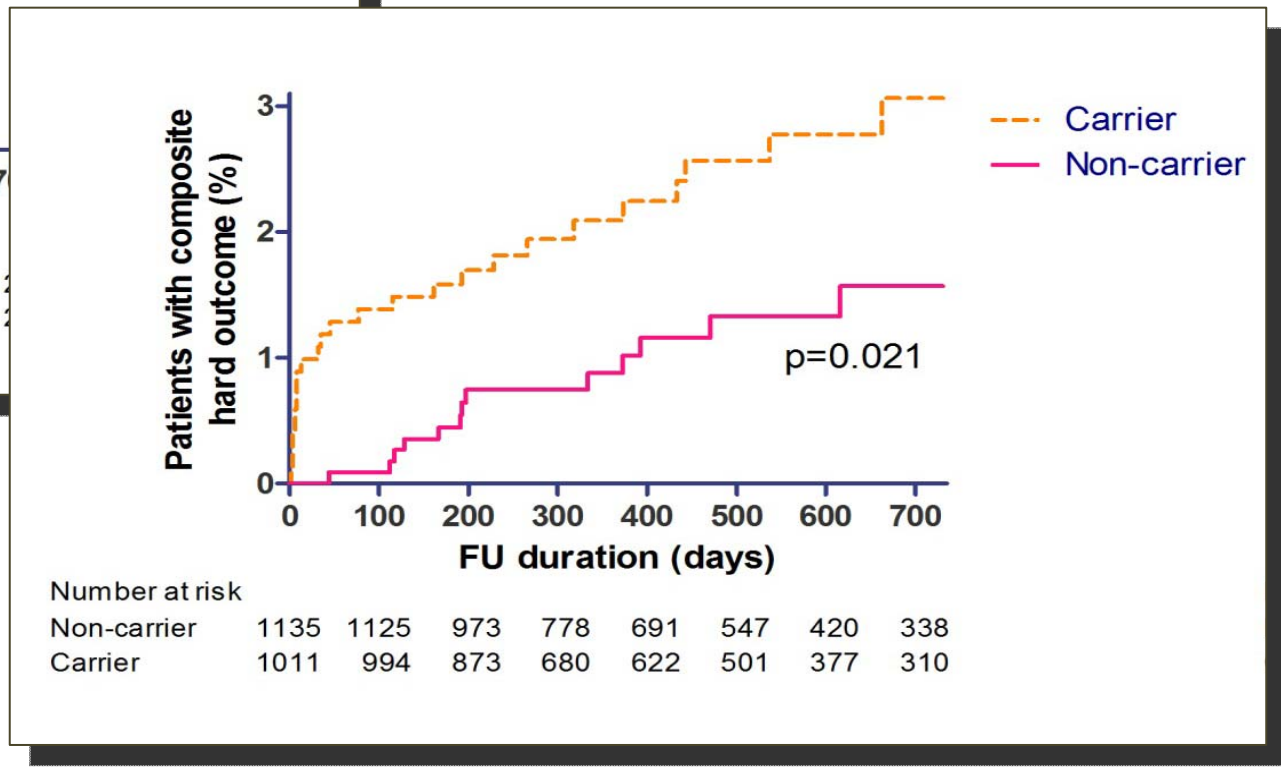
Sawada T et al. Circulation J 2011.

Association of genotype with only hard outcomes (SKY registry)



All MACE
(including revascularization)

Hard outcome
(CD, MI, and ST)



From the SKY registry, in submission to Heart

What are the possible solutions to patients with genetic risk of clopidogrel response variability?

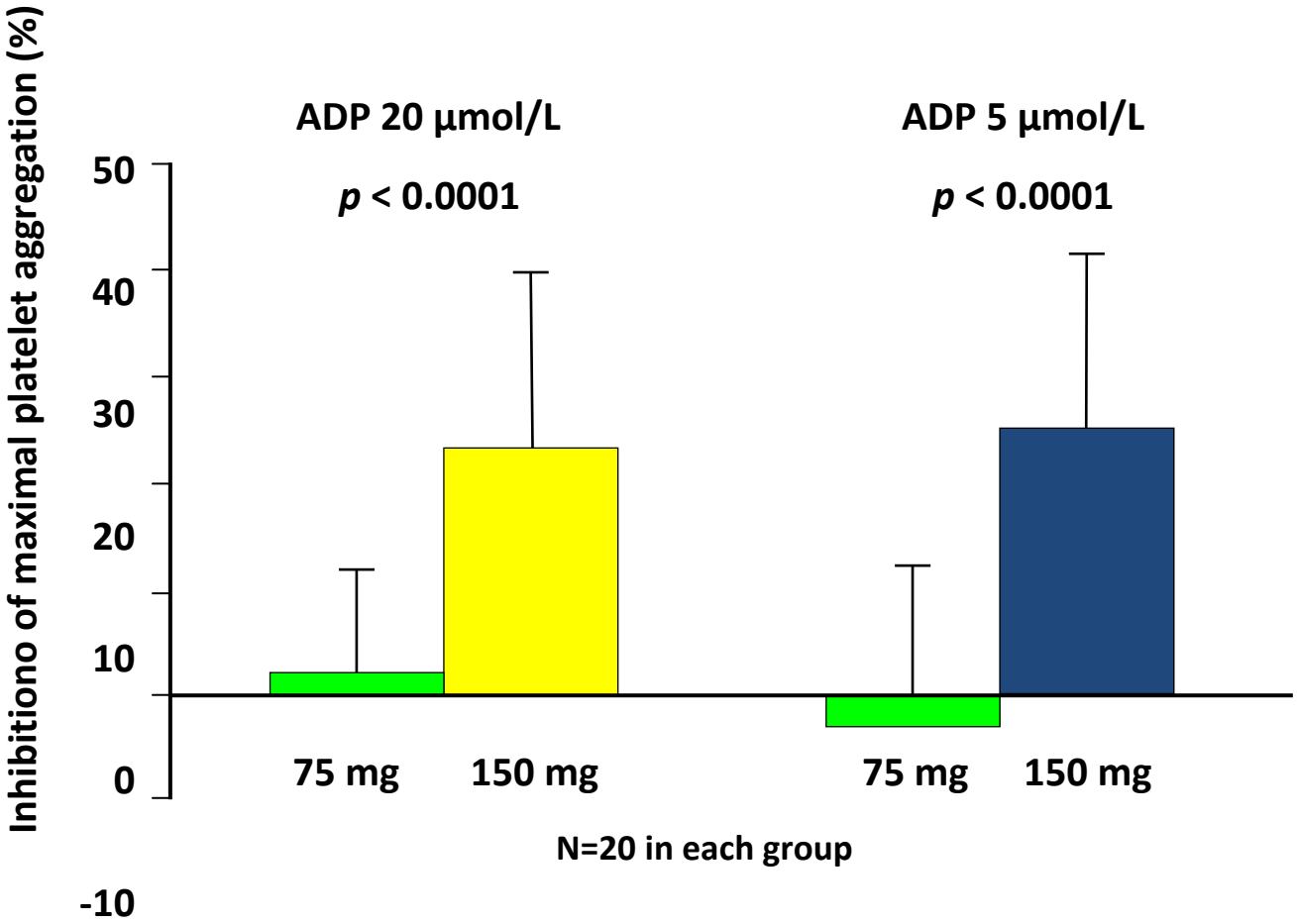
1. Increase dose of plavix?

2. Add cilostazol?

3. Use newer agents with less variability?

Increase dose of clopidogrel: OPTIMUS

Randomized comparison of a high clopidogrel maintenance dose in patients with diabetes mellitus and coronary artery disease



Angiolillo DJ, et al. Circulation 2007

Increase dose of clopidogrel: GRAVITAS

Dr. Price will talk about this topic next

Multicenter Randomized Trial Evaluating the Efficacy of Cilostazol on Ischemic Vascular Complications After Drug-Eluting Stent Implantation for Coronary Heart Disease

Results of the CILON-T (Influence of CILostazol-based triple antiplatelet therapy ON ischemic complication after drug-eluting stenT implantation) Trial

Jung-Won Suh, MD,*† Seung-Pyo Lee, MD,* Kyung-Woo Park, MD,* Hae-Young Lee, MD,* Hyun-Jae Kang, MD,* Bon-Kwon Koo, MD,* Young-Seok Cho, MD,† Tae-Jin Youn, MD,† In-Ho Chae, MD,† Dong-Ju Choi, MD,† Seung-Woon Rha, MD,‡ Jang-Ho Bae, MD,§ Taek-Geun Kwon, MD,§ Jang-Whan Bae, MD,‖ Myeong-Chan Cho, MD,‖ Hyo-Soo Kim, MD*

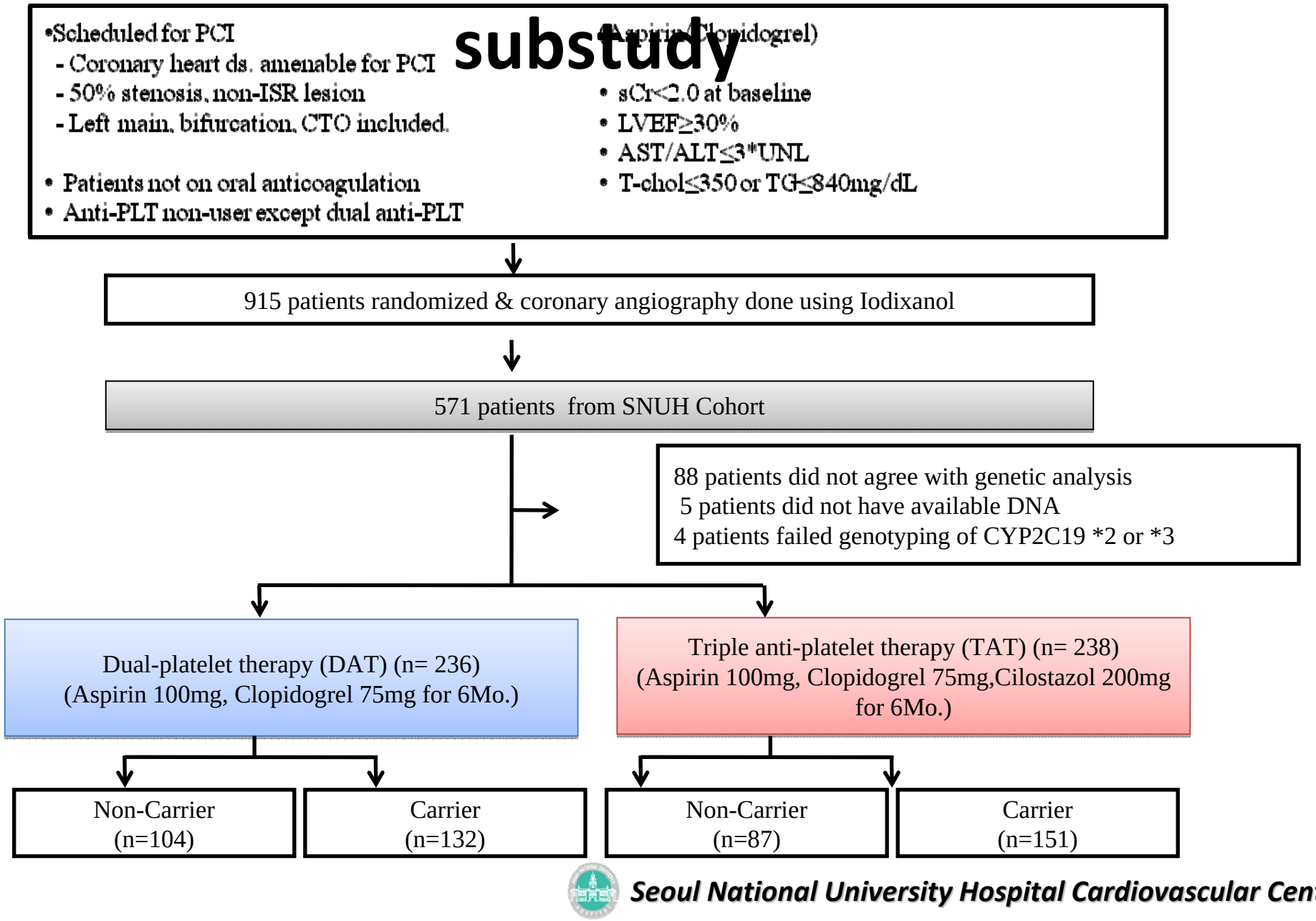
Seoul, Seongnam, Daejon, and Cheongju, Korea

Objectives We aimed to test whether cilostazol has beneficial effects in the real-world patients treated with intracoronary drug-eluting stents (DES).

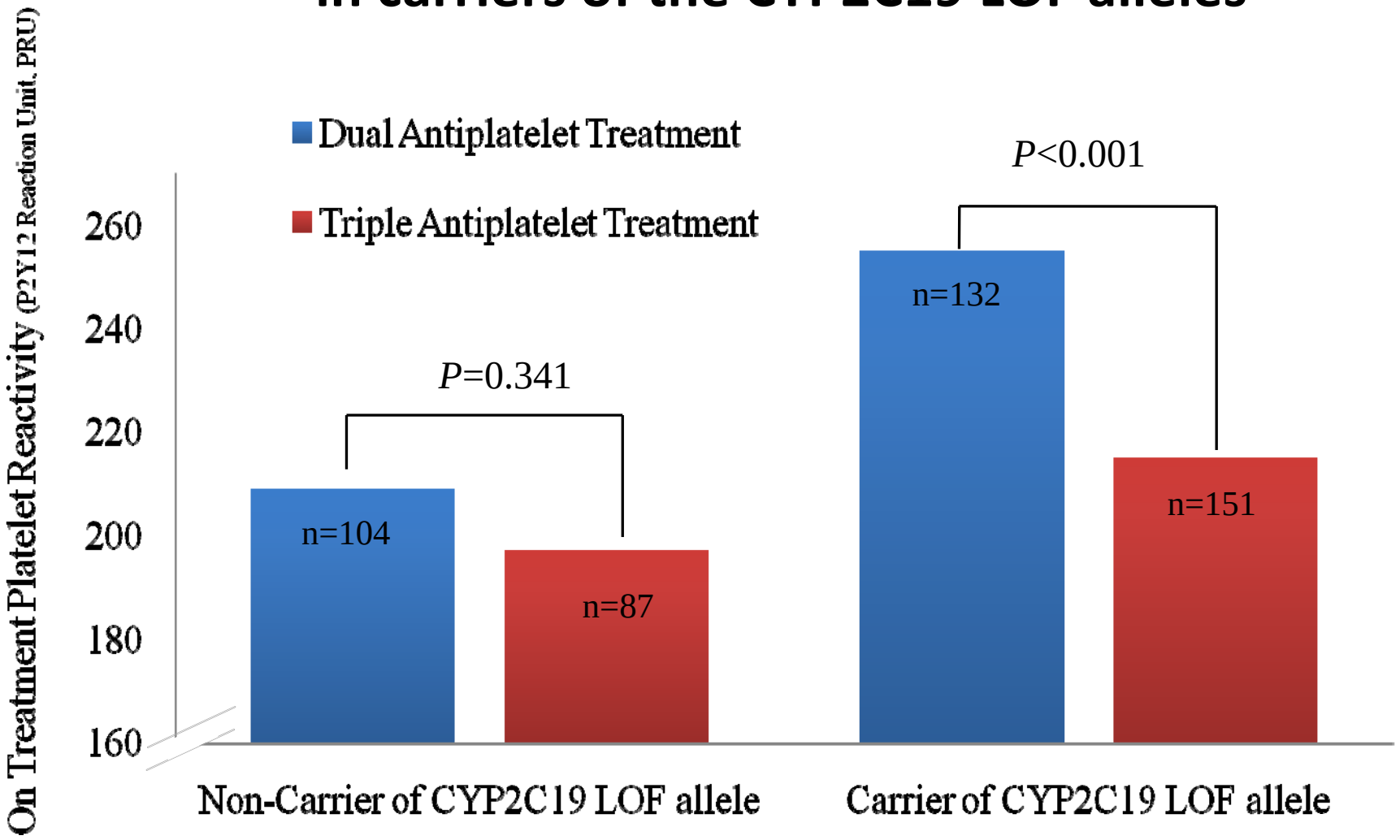
Background The addition of cilostazol on the conventional dual antiplatelet therapy has been reported to reduce platelet reactivity and to improve clinical outcomes after percutaneous coronary intervention in previous studies.

Methods In a randomized multicenter trial, we enrolled 960 patients who received DES. They were randomized to receive either dual antiplatelet therapy (DAT) (aspirin and clopidogrel) or triple antiplatelet therapy (TAT) (aspirin, clopi-

Add Cilostazol: CILON-T genetic substudy



TAT significantly reduces mean OPR
in carriers of the CYP2C19 LOF alleles



Park KW, Kim HS et al. Heart 2011

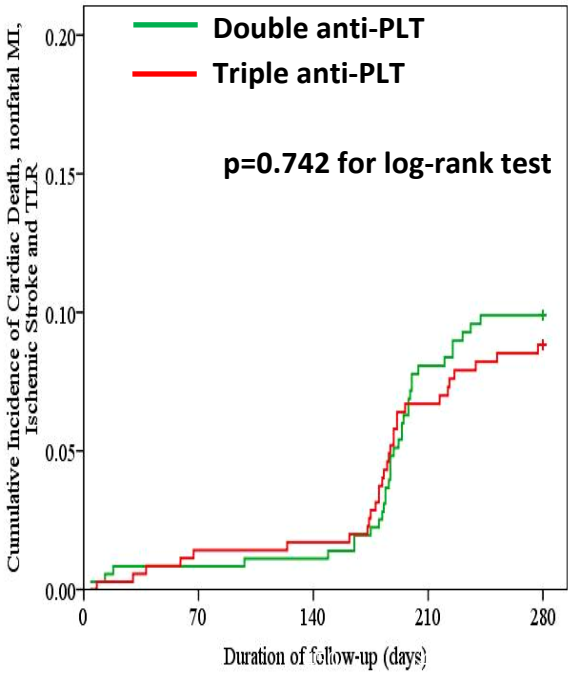
Add Cilostazol: CILON-T Trial

	TAT (n=457)	DAT (n=458)	p
Primary endpoint			
CD, nonfatal MI, ischemic stroke and TLR	39 (8.5%)	42 (9.2%)	0.73
Secondary endpoint			
Death from any cause	4 (0.9%)	6 (1.3%)	0.75
Cardiac death	0	3 (0.7%)	0.25
Nonfatal MI	4 (0.9%)	3 (0.7%)	0.73
Ischemic stroke	5 (1.1%)	4 (0.9%)	0.75
TLR	30 (6.6%)	32(7.2%)	0.79
Stent thrombosis	3 (0.7%)	5 (1.1%)	0.73
Death, nonfatal MI, ischemic stroke	13 (2.8%)	13 (2.8%)	1.0
CD, nonfatal MI, ischemic stroke	9 (2.0%)	10 (2.0%)	1.0

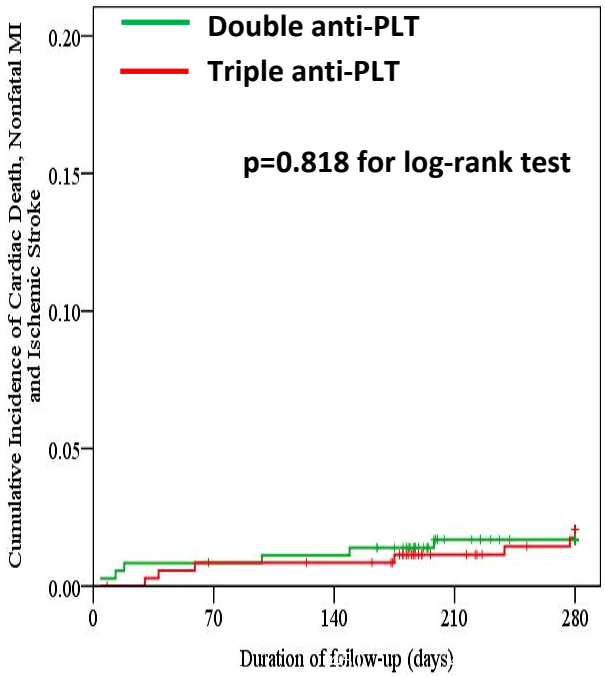
Suh JW, Park KW, Kim HS, et al. JACC 2011

Add Cilostazol: CILON-T Trial

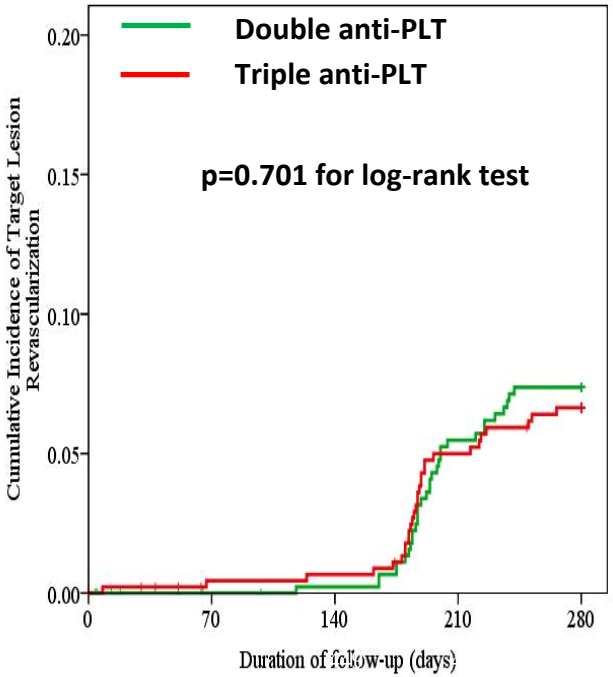
Composite of CD, nonfatal MI, ischemic stroke & TLR



Composite of CD, nonfatal MI & ischemic stroke

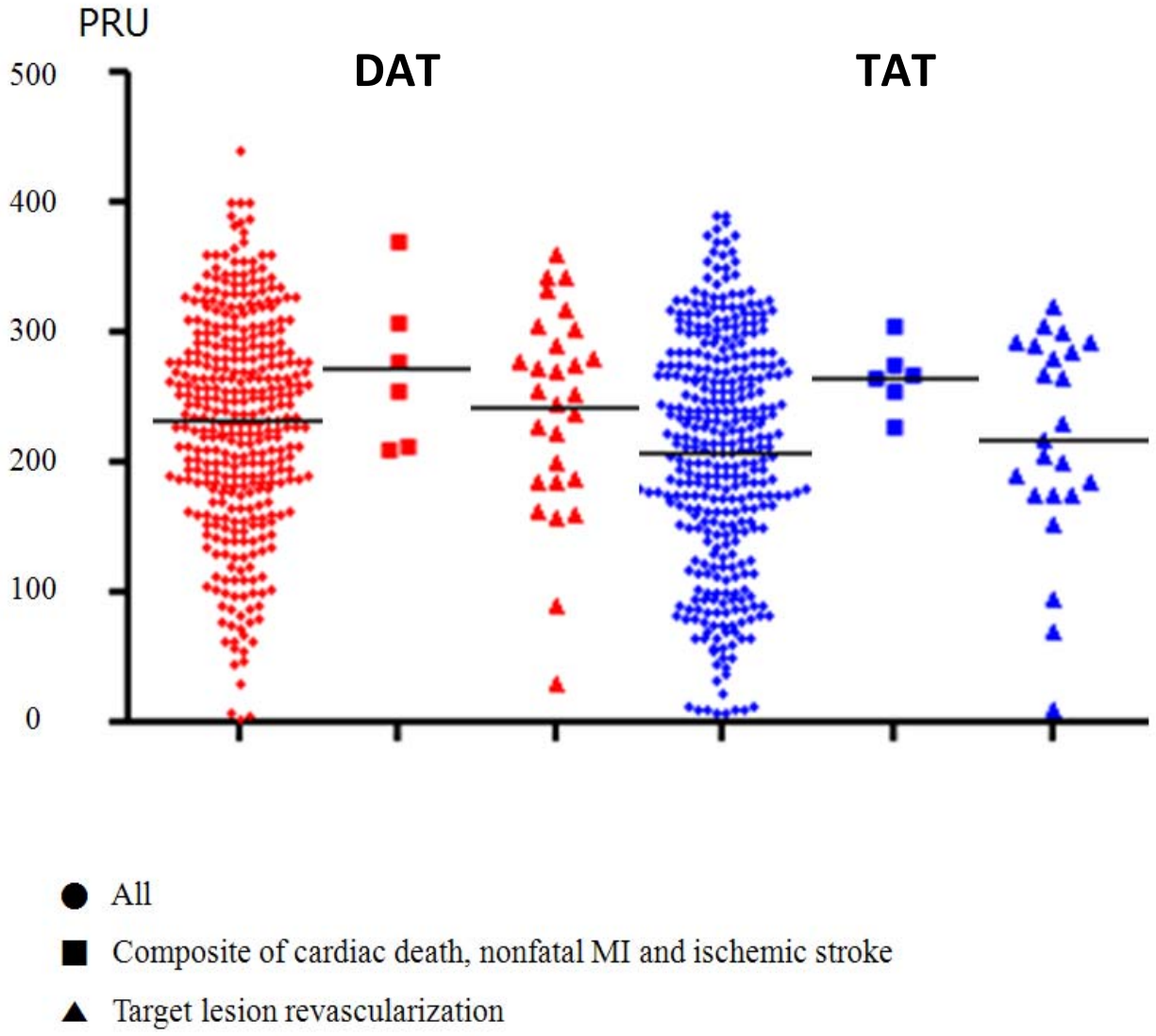


TLR



Suh JW, Park KW, Kim HS, et al. JACC 2011

CILON-T: *Platelet function and outcome*



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CILON-T: *Platelet function and outcome*

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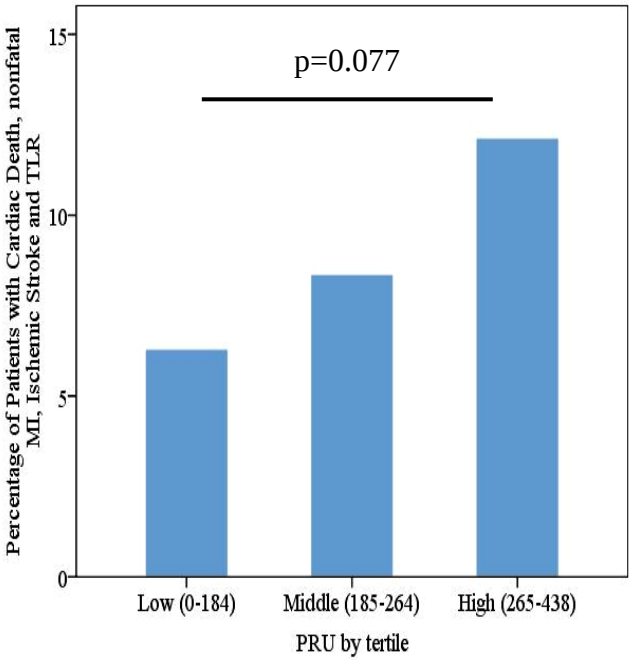
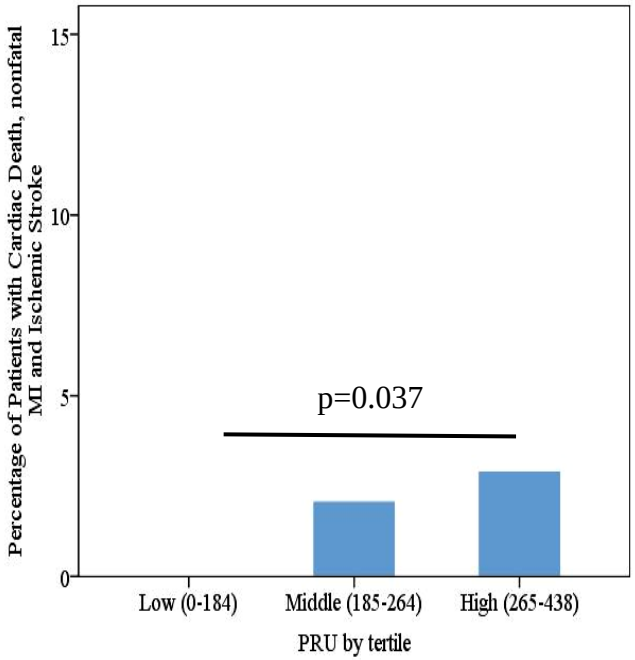


CD, nonfatal MI & ischemic stroke



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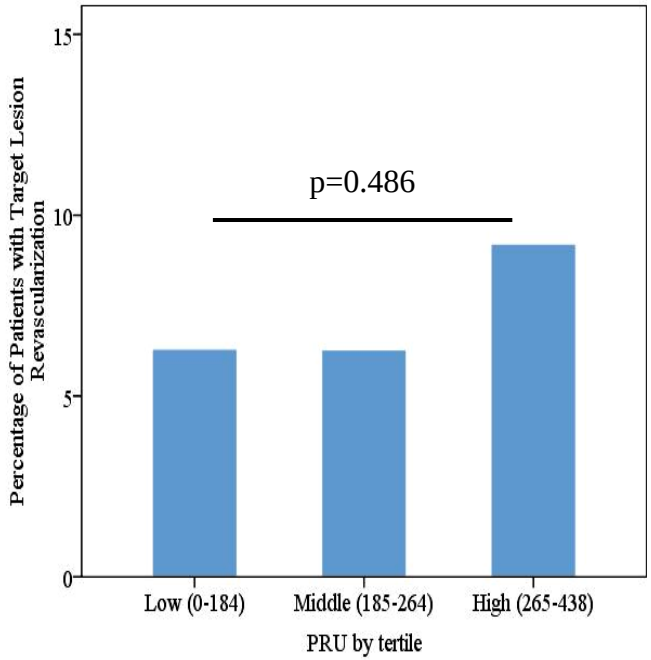

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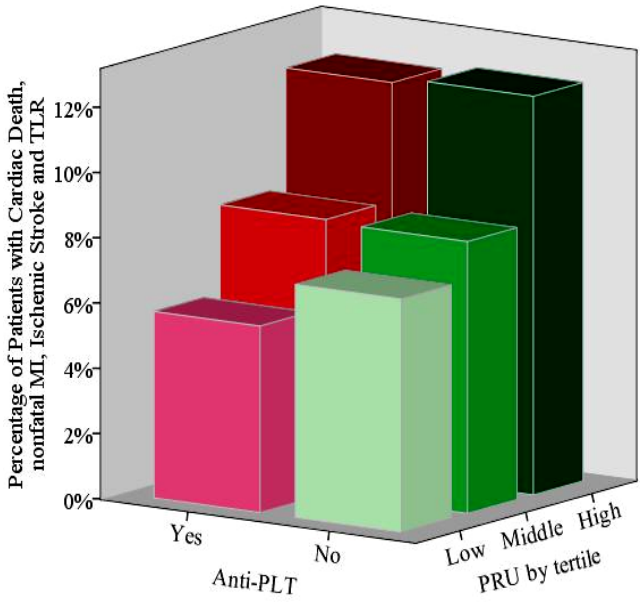
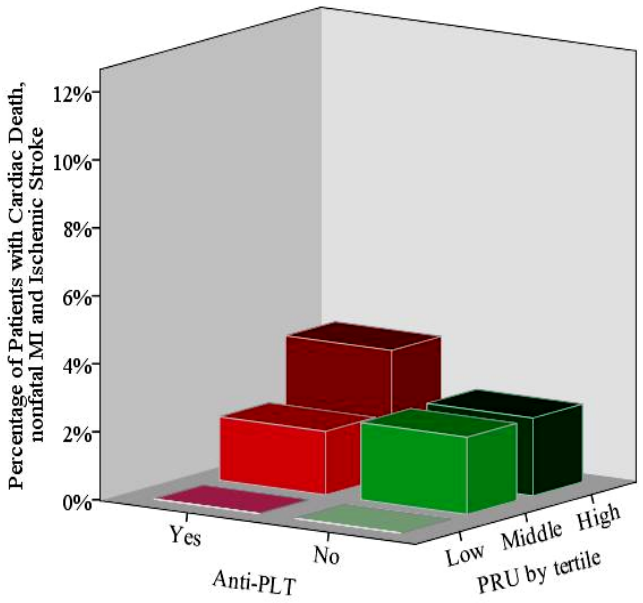
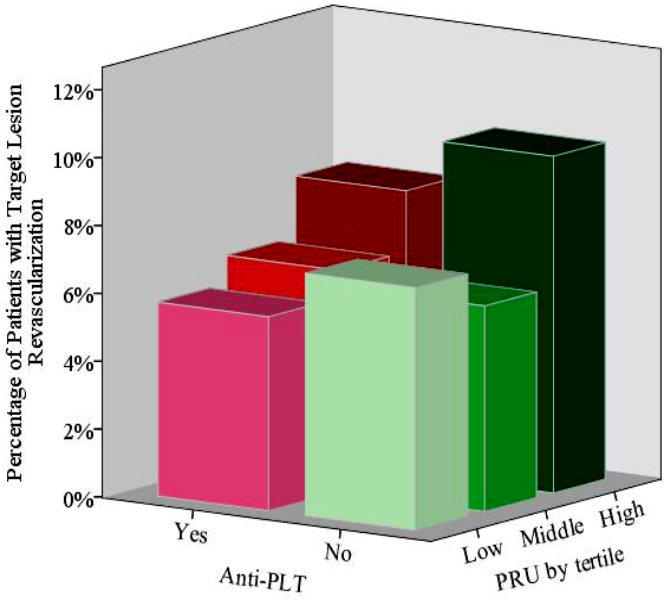


CD, nonfatal MI & ischemic stroke



TLR



Suh JW, Park KW, Kim HS, et al. JACC 2011

Is it REAL?? –Korean Perspective

1. Yes, LOF genetic polymorphisms of the CYP2C19 is associated with on-treatment platelet reactivity in Koreans

2. Yes, LOF genetic polymorphisms of the CYP2C19 is associated with clinical outcome after PCI (hard outcome yes, but soft outcome no)

3. Genetic risk patients constitute at least 50% of the PCI population in Koreans. (Higher prevalence of CYP2C19*2, *3)

CAVEATS

1. Higher proportion of genetic at risk population, but similar absolute clinical outcomes compared with Western populations

2. CYP2C19 LOF polymorphism can only predict 10-20% of the clopidogrel response variability. Magnitude of effect on individual patient is very difficult to measure.