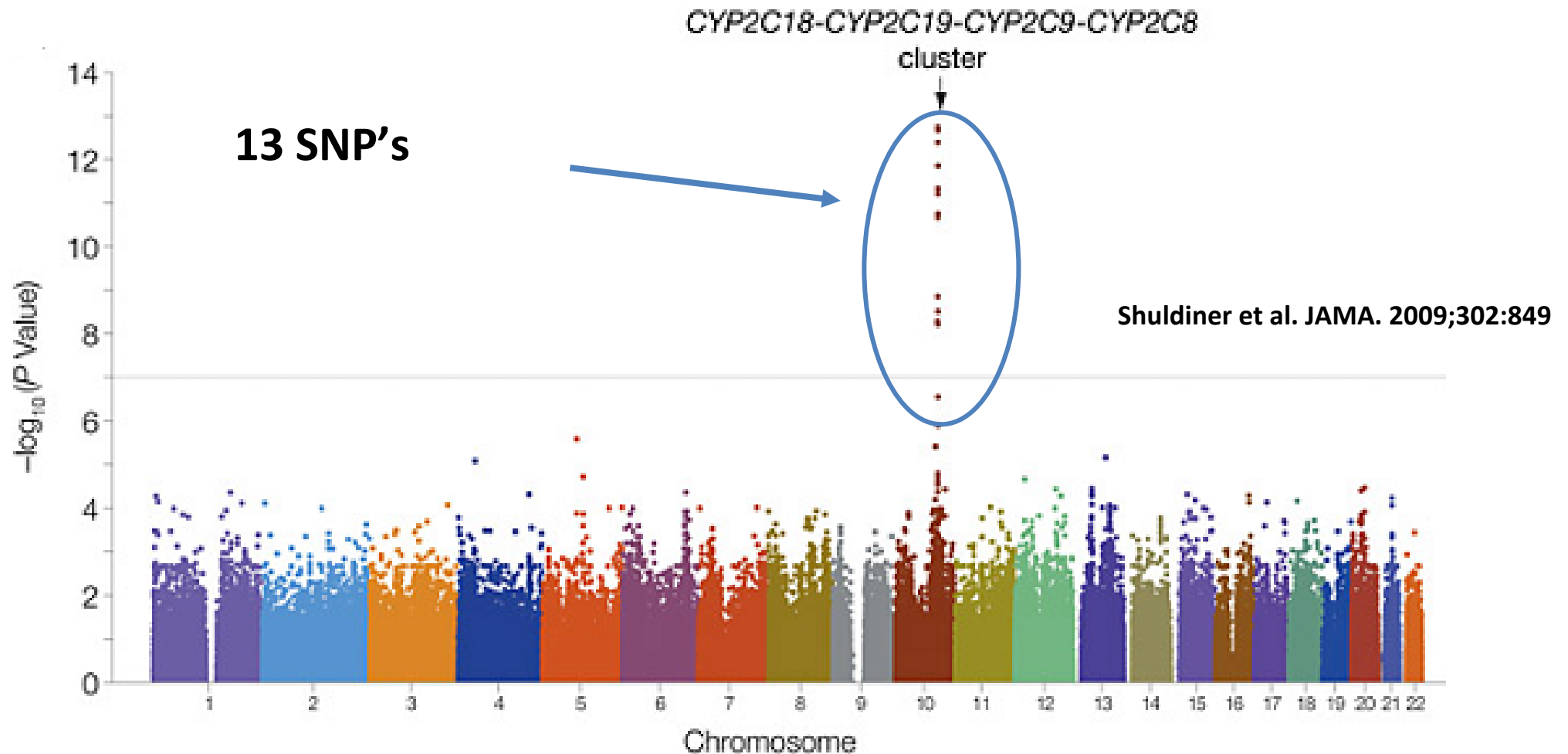# Genetic Risk of Clopidogrel Response Variability: Cilostazol as a possible solution

Kyung Woo Park, MD, PhD

Cardiovascular Center,

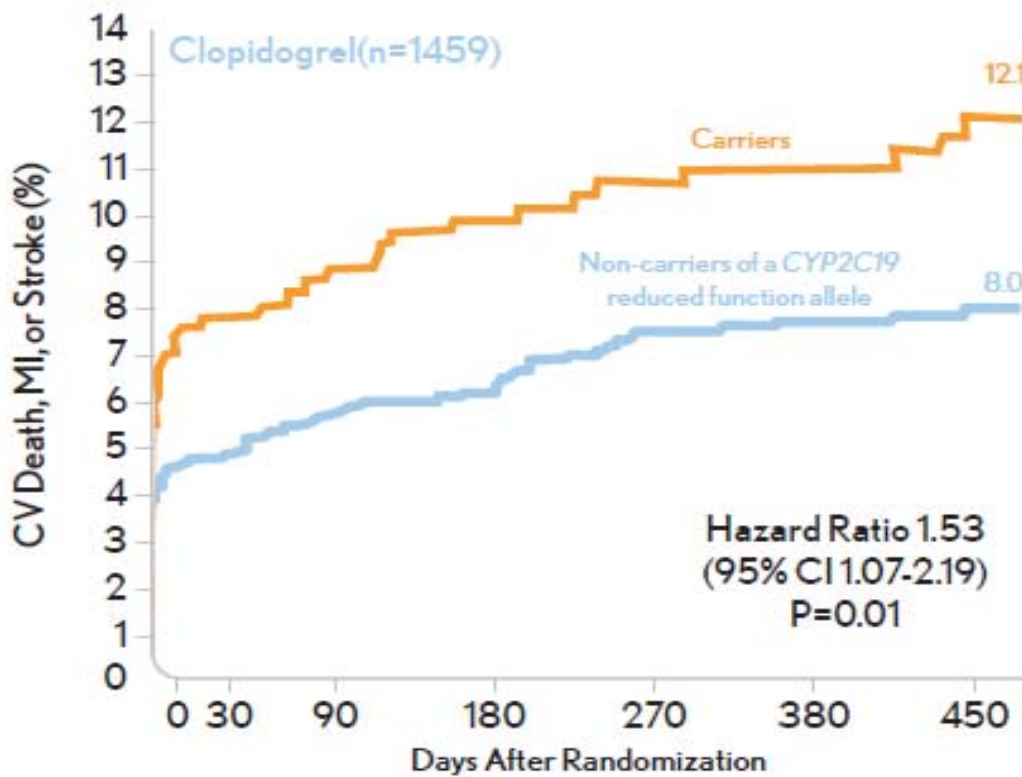**Seoul National University Hospital**

Decreased Response to Clopidogrel: GWAS Data

CYP2C18-CYP2C19-CYP2C9-CYP2C8 cluster
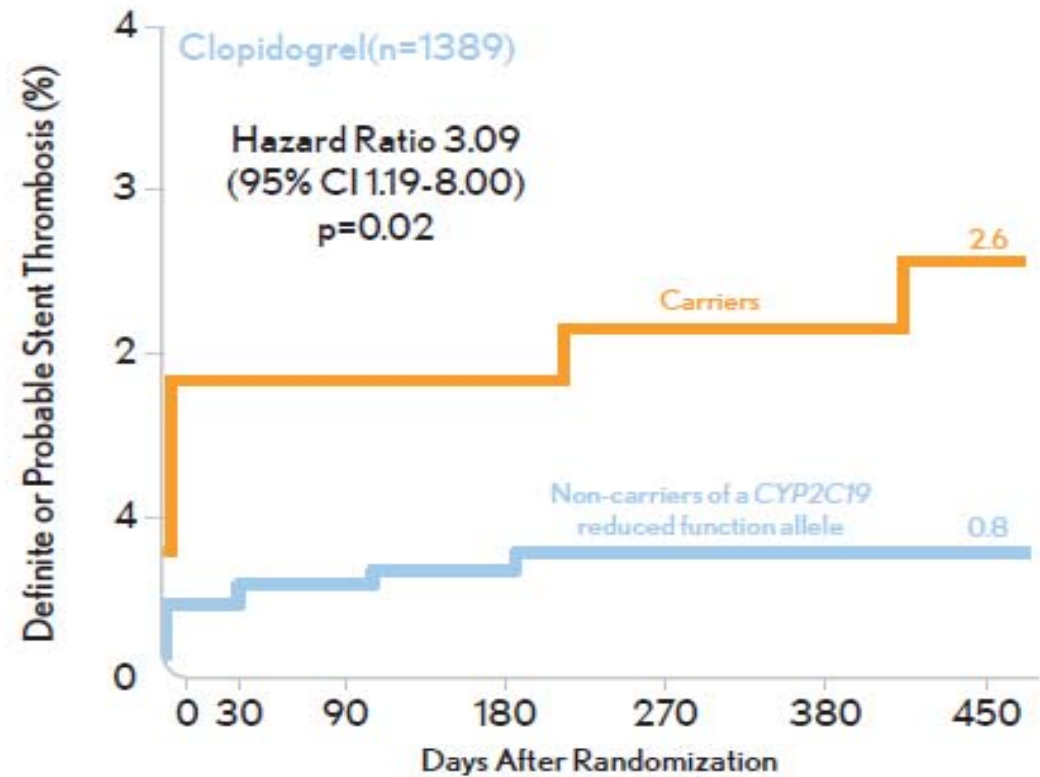
13 SNP's

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.

CYP2C19 LOF allele as a genetic risk of Ischemic Events
Pre-specified subgroup analyses of TRITON TIMI 38

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

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Ethnicity as a risk of HOPR?

Characteristic	Mean Residual Platelet Reactivity (PRU)		P Value
	Characteristic present	Characteristic absent	
Age > 75 yrs	214 ±77	201±79	0.161
Men	200±77	220±82	0.041
Non-Caucasian ethnicity	229±79	202±78	0.047
Diabetes mellitus	220±73	196±80	0.005
⋮	⋮	⋮	⋮

Price MJ et al, Circulation 2009

- **Non-Caucasian ethnicity :**

  1. has higher residual platelet activity

  2. an independent predictor of high on-treatment plt reactivity

     (OR: 3.05, 95% CI: 1.49 to 6.28, p=0.002)

Different CYP2C19 *2 Allele Frequency

Mexican
- GA/AA
- GG
- 20%
- 80%

White
- GA/AA
- GG
- 24%
- 76%

Luo et al .Clin Pharmacol Ther. 2006 ,
Xiao et al. J Pharmacol Exp Ther. 1997
Takakubo et al Pharmacogenetics. 1996

African
- GA/AA
- GG
- 33%
- 67%

Asian
- GA/AA
- GG
- 49%
- 51%

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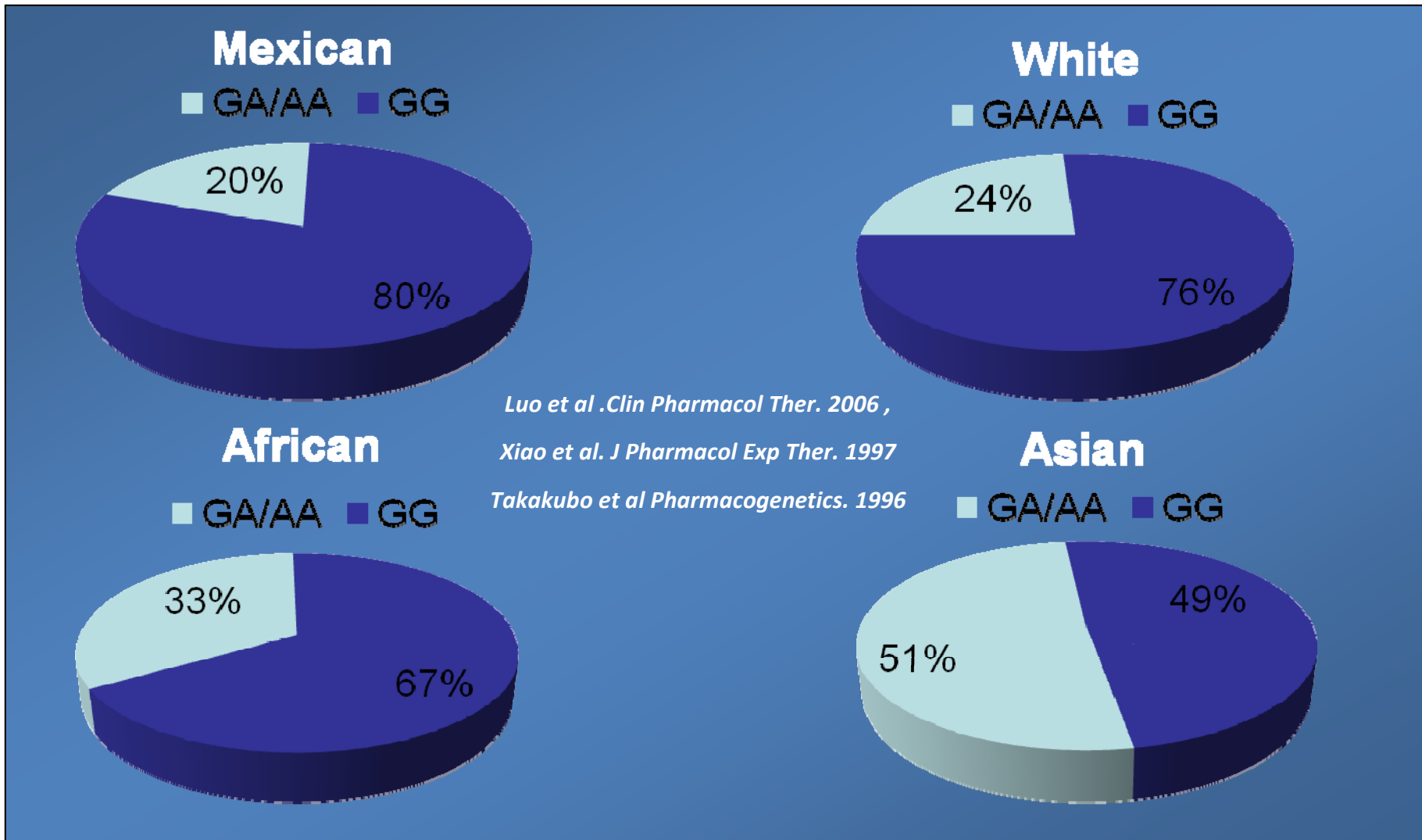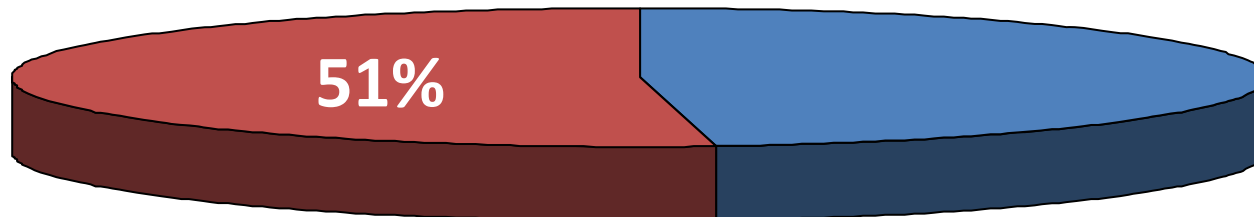
Different CYP2C19 LOF Frequency
: according to Asian Ethnicity

Japanese Population

46%
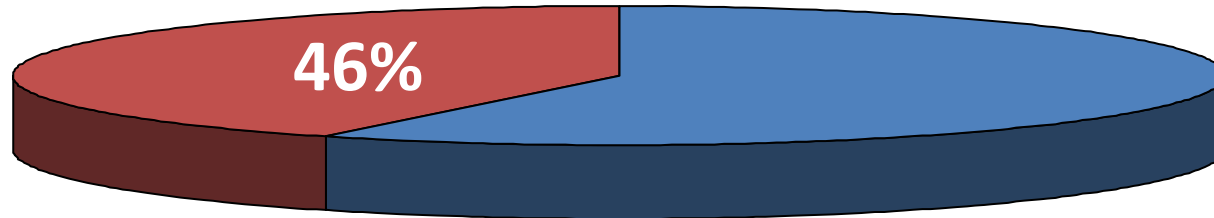
Sawada T et al. Circulation J 2011.

Non-carrier
Carrier

Chinese Population

51%

Zhou Q et al. Pharmacogenomics J 2009

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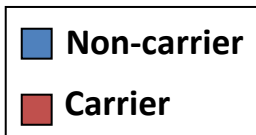
CYP2C19*2
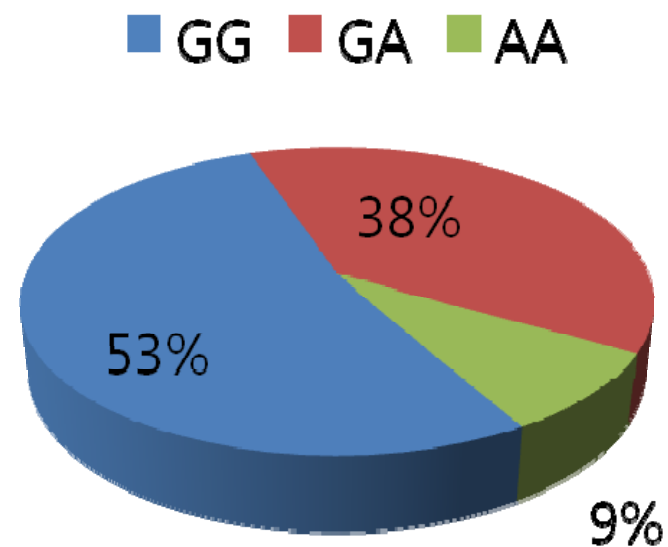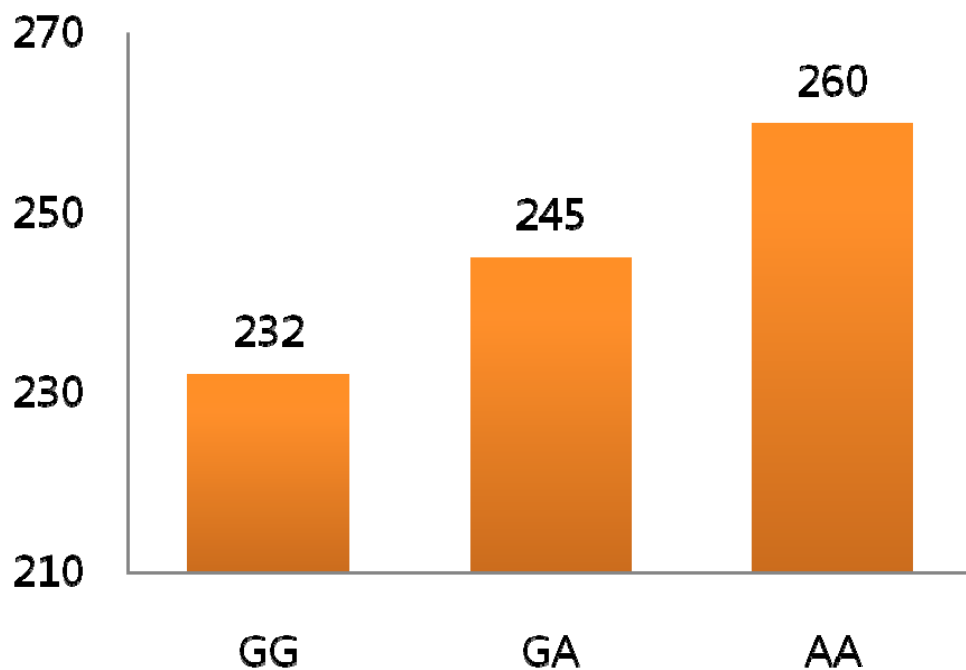
	GG	GA	AA	All	p-value
Freq	848	613	139	1600	
Expected	833.0	642.9	124.0		
PRU	232.5±82.6	245.7±79.4	260.3±72.0	240.0±81.0	**P<0.001**

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

Unpublished data from the CROSS VERIFY cohort

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CYP2C19*3
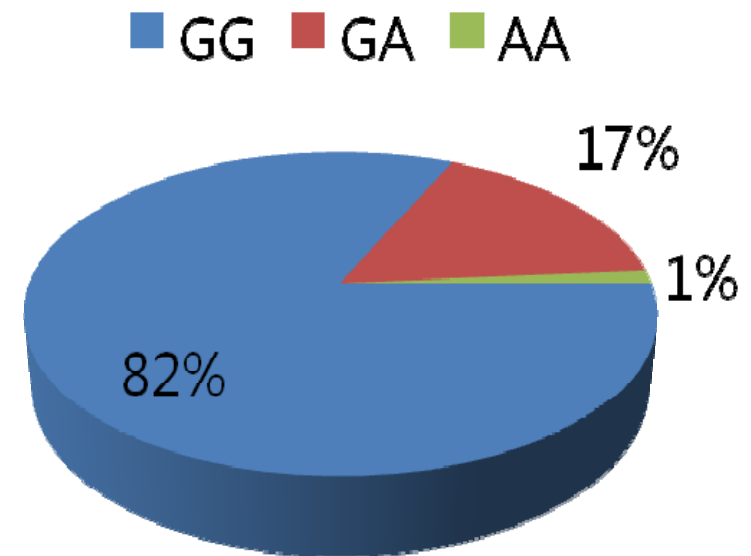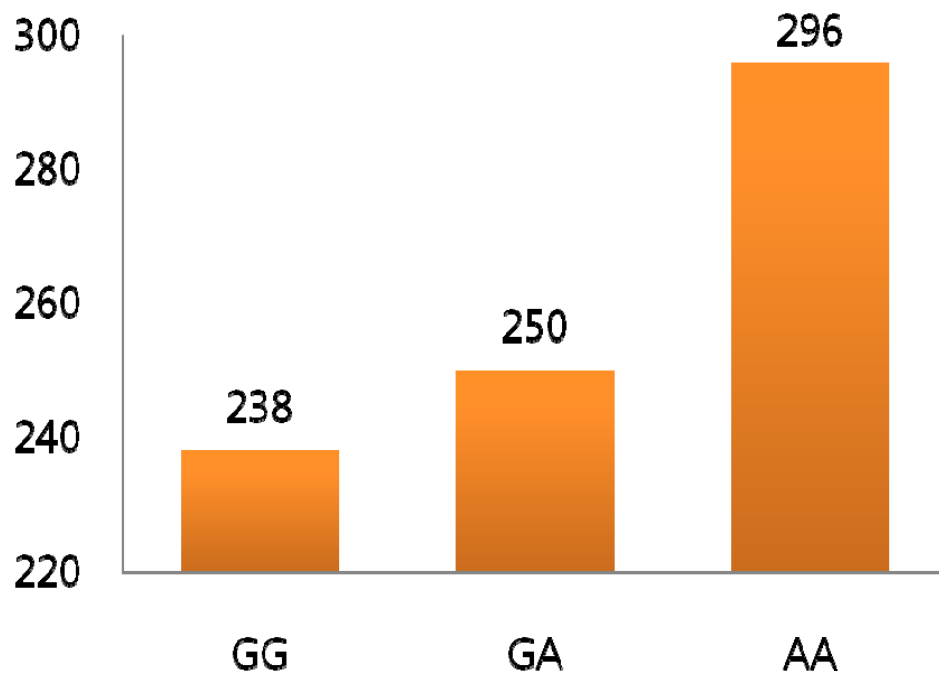
	GG	GA	AA	All	p-value
Freq	1308	267	22	1597	
Expected	1301.1	280.7	15.1		
PRU	236.8.5±81.7	250.8±76.9	296.2±58.4	240.0±81.0	**P<0.001**

Major G 0.90 (wild), Minor A   0.10 (mutant), X^2 = 3.813, p = 0.050)

Unpublished data from the CROSS VERIFY cohort

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CYP2C19 *2 & *3 combined : CROSS VERIFY cohort
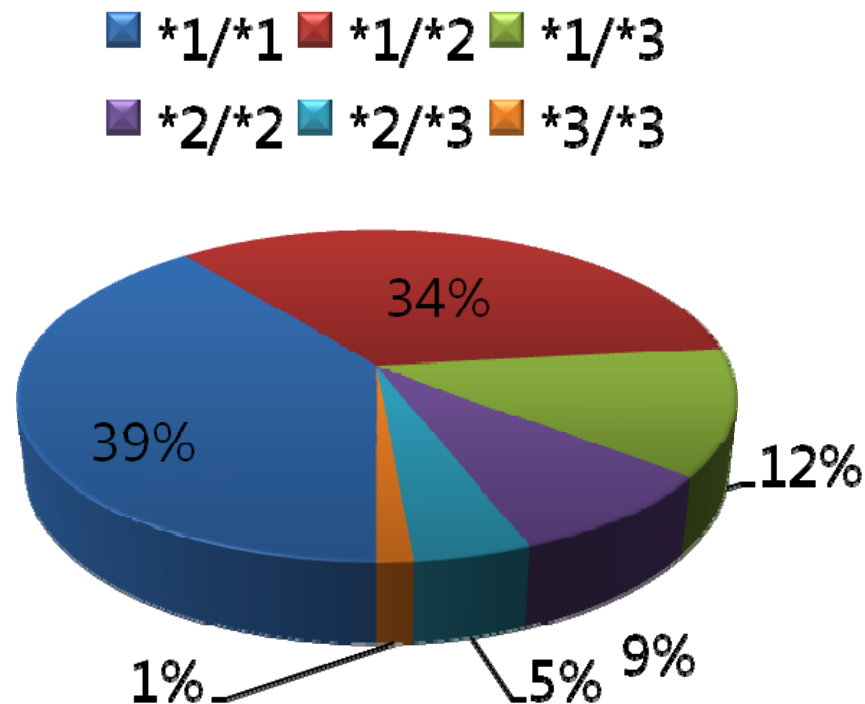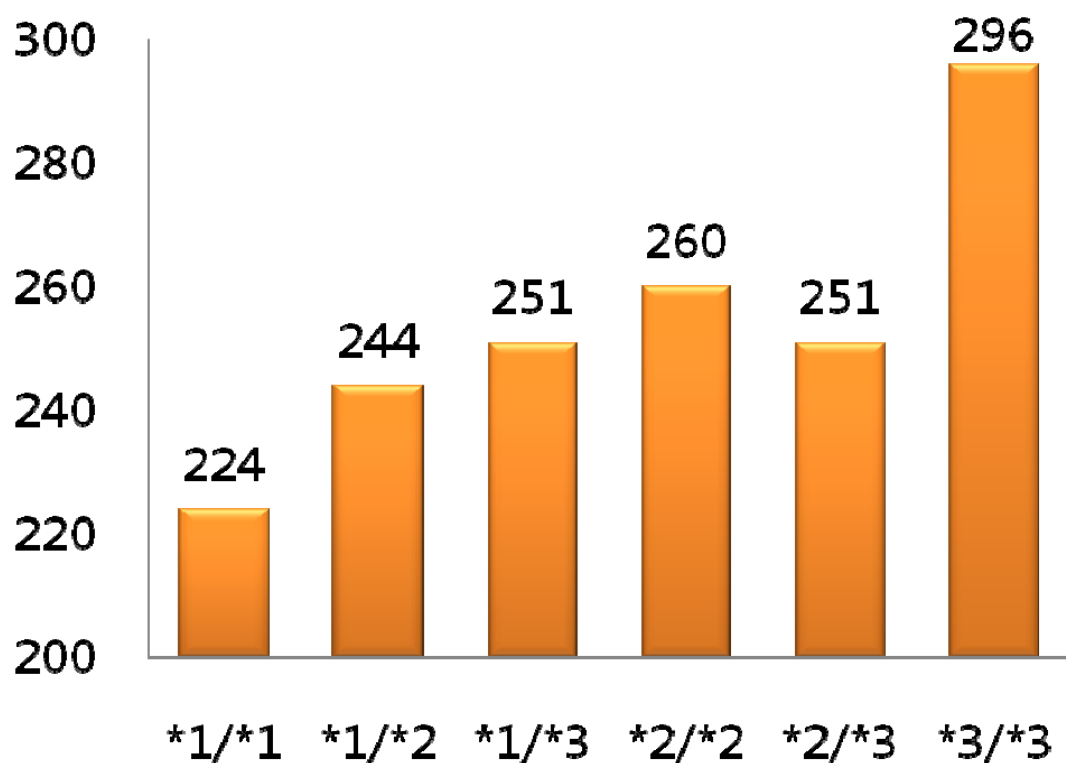
	*1/*1	*1/*2	*1/*3	*2/*2	*2/*3	*3/*3	p-value
Freq	625	540	195	139	71	22	
PRU	224.7±82.3	244.8±81.1	251.4±80.7	260.3±72.0	251.0±64.9	296.2±58.4	<0.001

Unpublished data from the CROSS VERIFY cohort

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Number of 'loss of fxn' alleles & PRU:

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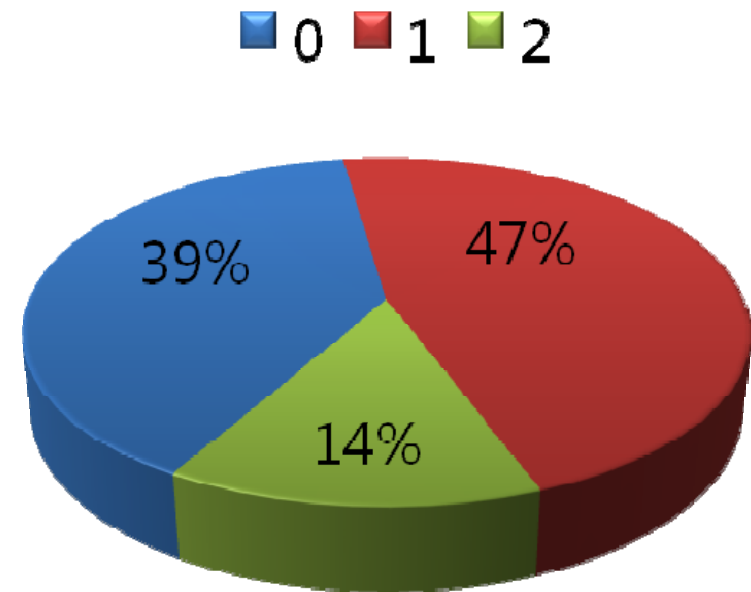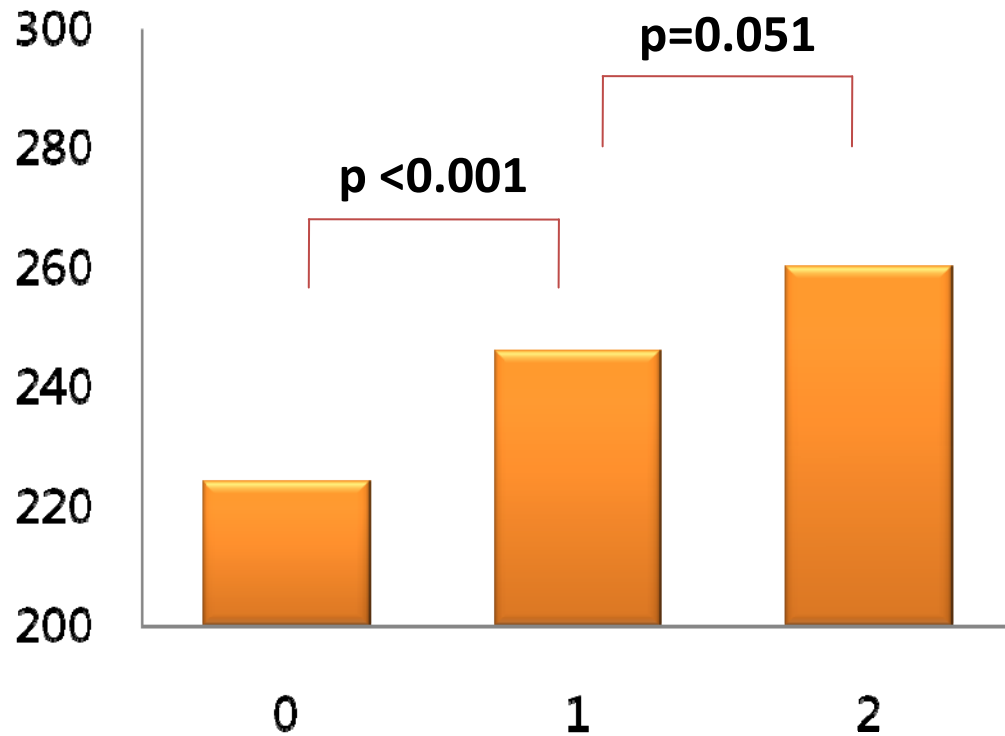
	Zero (*1/*1)	One (*1/*2, *1/*3)	Two (*2/*2, *2/*3, *3/*3)	p-value
Freq	625	735	232	
PRU	224.7±82.4	246.5±81.0	260.9±69.5	<0.001

Unpublished data from the CROSS VERIFY cohort

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Relationship btw genetic risk and outcome in Koreans:
Associated with only hard outcomes (from the SKY registry)
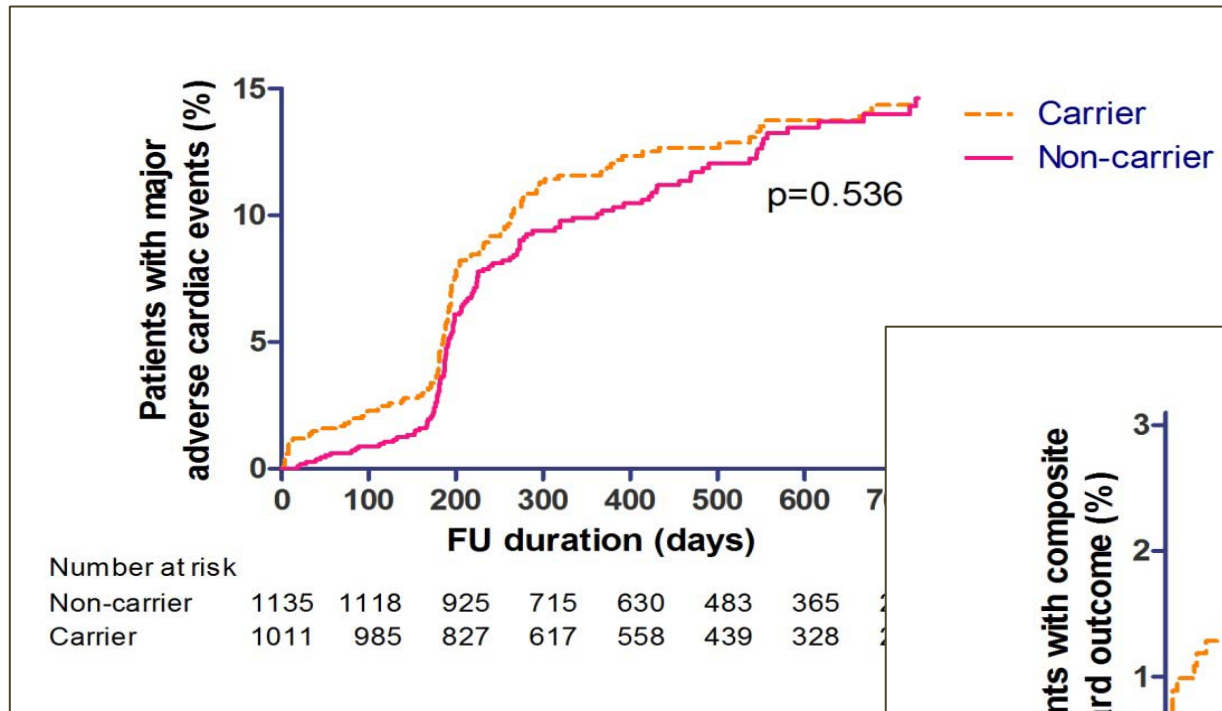
**Hard outcome
(CD, MI, and ST)**
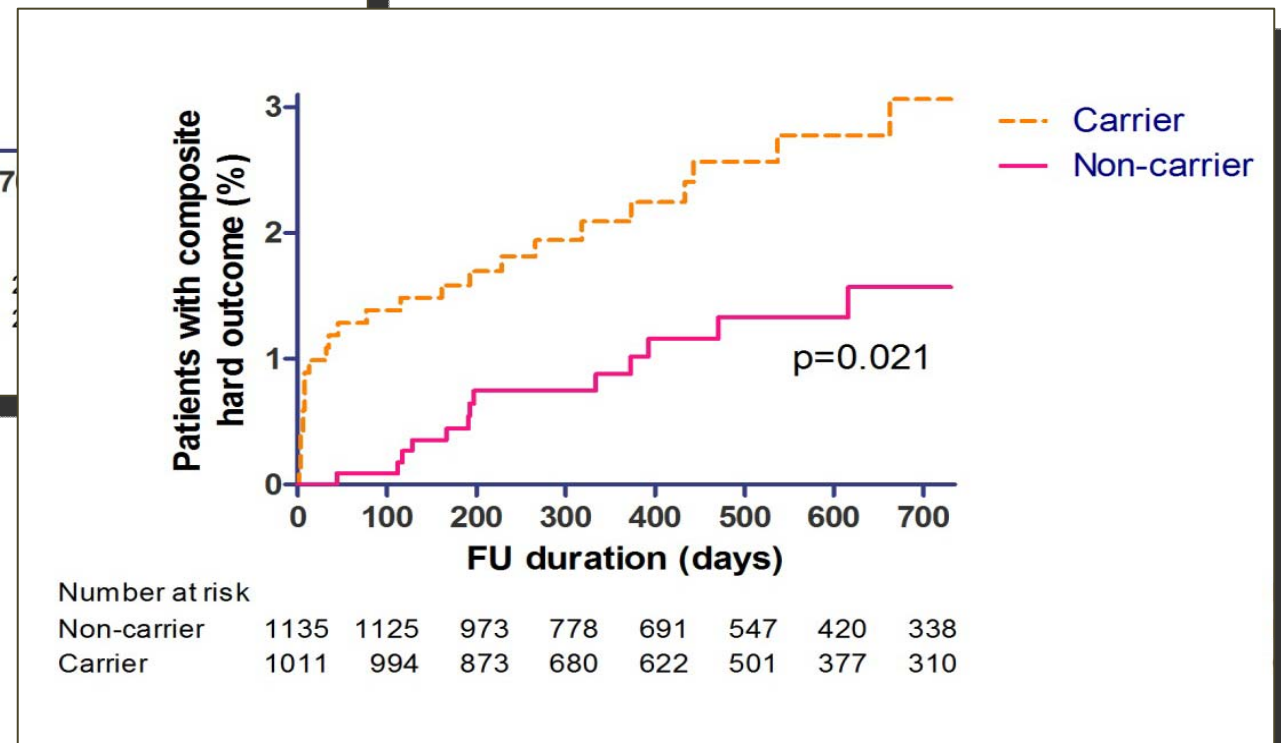
**All MACE
(including revascularization)**

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Doubling the dose of plavix??

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
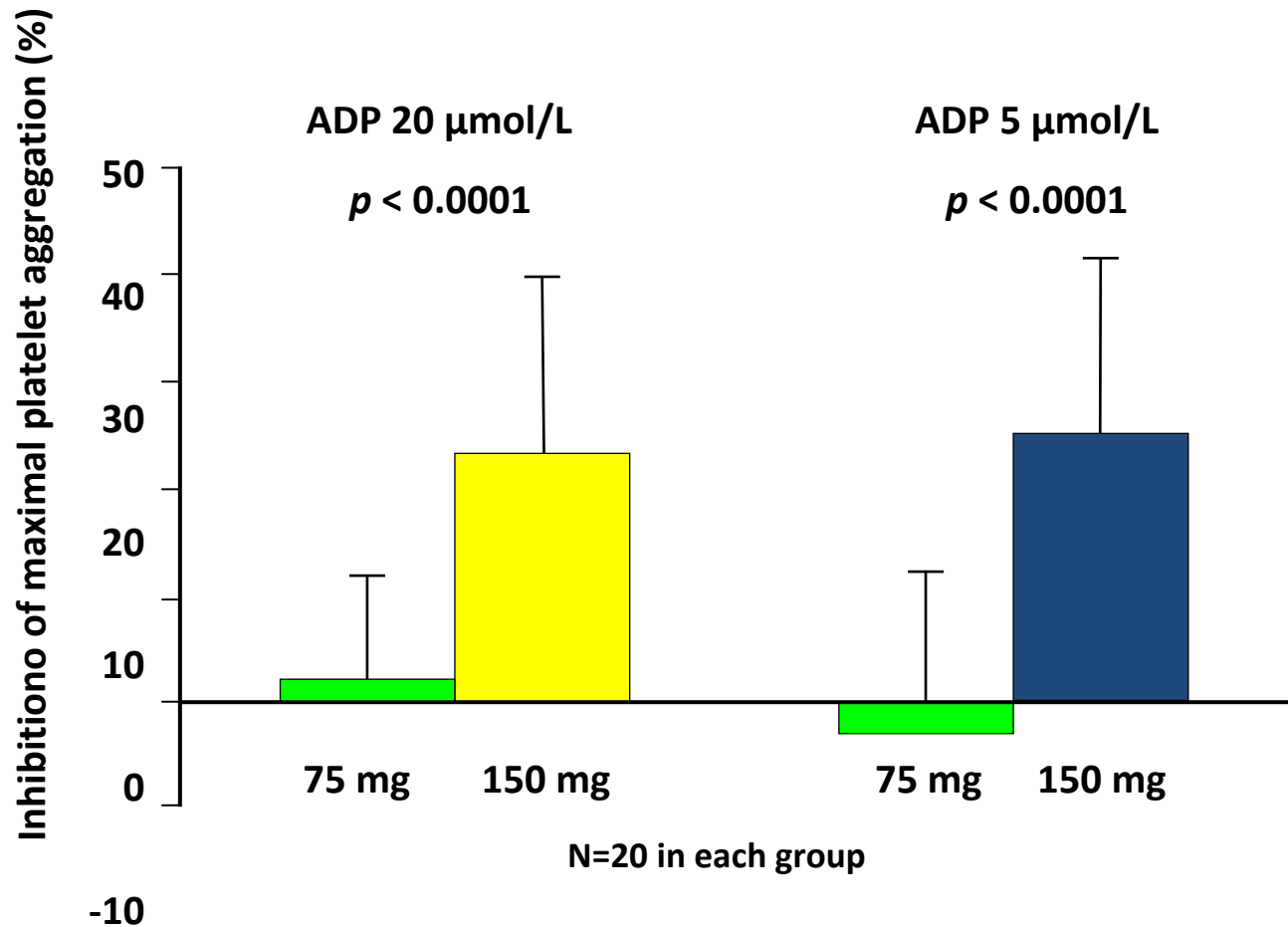
Platelet Reactivity on Clopidogrel Post-PCI Is Associated With *CYP2C19* Genotype & Phenotype
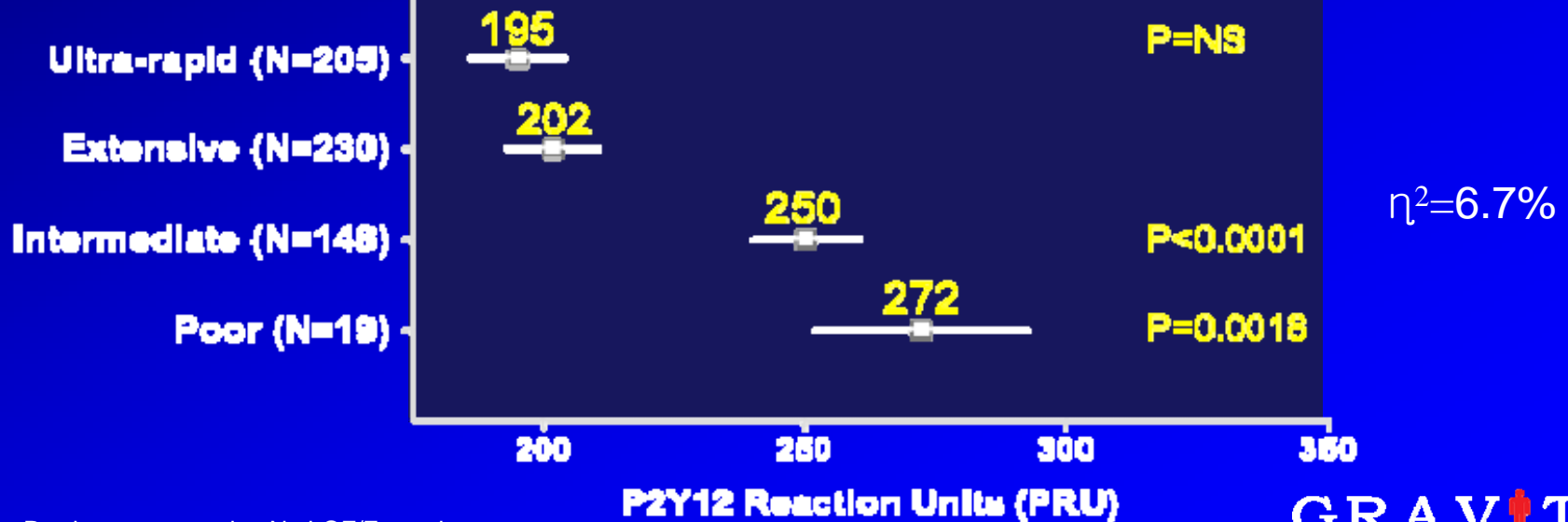
Least squared means. P values compared to No LOF/Extensive.
η^2 : portion of variance explained by the genotype or phenotype in the multivariate generalized linear model

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

CYP2C19 LOF Allele Is Associated With Higher Risk of Persistently High OTR at 30 Days Regardless of Dose

Therefore, doubling the dose of Clopidogrel cannot be a solution to overcome the genetic risk of clopidogrel response variability.
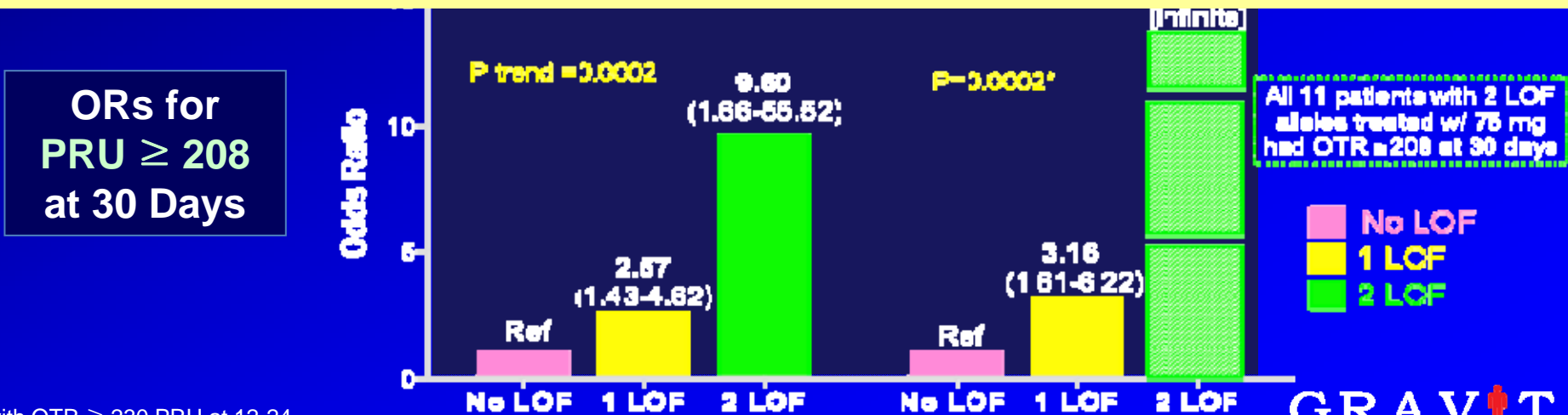
Patients with OTR ≥ 230 PRU at 12-24 hours after PCI. Adjusted ORs.

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

Adding cilostazol as a third agent??

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-
dogrel, and cilostazol) for 6 months. Primary end point was the composite of cardiac death, nonfatal myocardial

CILON-T Trial Design

Assessed for Eligibility
And Randomized (n=960)

TAT (n=477)

DAT (n=483)

Atorvastatin
(n=241)

Rosuvastatin
(n=236)

Atorvastatin
(n=242)

Rosuvastatin
(n=241)

3 Withdrawal at patient request
14 Withdrawal at clinician's judgment
3 Failed PCI

2 Withdrawal at patient request
19 Withdrawal at clinician's judgment
4 Failed PCI

TAT (n=457)

DAT (n=458)

915 patients with successful PCI & follow-up

** Primary endpoint : at 6 month

- Cardiovascular death, nonfatal MI, ischemic stroke, TLR

- Platelet (P2Y12) reaction unit

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Add Cilostazol: CILON-T genetic substudy

- Scheduled for PCI
  - Coronary heart ds. amenable for PCI
  - 50% stenosis, non-ISR lesion
  - Left main, bifurcation, CTO included.

- Patients not on oral anticoagulation
- Anti-PLT non-user except dual anti-PLT

(Aspirin/Clopidogrel)
- sCr<2.0 at baseline
- LVEF≥30%
- AST/ALT≤3*UNL
- T-chol≤350 or TG≤840mg/dL

↓

915 patients randomized & coronary angiography done using Iodixanol

↓

571 patients from SNUH Cohort

→ 88 patients did not agree with genetic analysis
5 patients did not have available DNA
4 patients failed genotyping of CYP2C19 *2 or *3

Dual-platelet therapy (DAT) (n= 236)
(Aspirin 100mg, Clopidogrel 75mg for 6Mo.)

Triple anti-platelet therapy (TAT) (n= 238)
(Aspirin 100mg, Clopidogrel 75mg,Cilostazol 200mg for 6Mo.)

Non-Carrier
(n=104)

Carrier
(n=132)

Non-Carrier
(n=87)

Carrier
(n=151)

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Genotyping & Analysis

- **Genotyping of 3 SNPs of CYP2C19**
  - TaqMan^{TM} Assay :
    - CYP2C19*2 (P227P, rs4244285)
    - CYP2C19*3 (W212X, rs4986893

  - SNaPshot^{TM} Multiplex Analysis
    - CYP2C19*17(806C/T, rs12248560)

- **Statistical Analysis**
  - Frequency
    - Categorical : count (%)
    - Continuous : mean $\pm$ SD
  - Testing differences between groups
    - Categorical : chi-square test or Fisher's exact test
    - Continuous : unpaired Student's test or 1-way ANOVA

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Baseline Characteristics I

|	DAT		TAT		p-value*
	Non-Carrier	Carrier	Non-Carrier	Carrier	
Demographic characteristics					
Age (yr)	63.25±8.34	62.83±8.30	62.82±9.14	64.11±9.02	0.601
Men	74 (71.2%)	101 (76.5%)	58 (65.9%)	97 (64.2%)	**0.045**
Body mass index (kg/m^2)	25.96±7.19	27.68±8.11	27.00±6.52	27.03±7.43	0.882
Smoker	22 (21.2%)	32 (24.2%)	16 (18.2%)	28 (18.5%)	0.251
Hypertension	73 (70.2%)	87 (65.9%)	59 (67.0%)	103 (68.2%)	0.917
Diabetes	25 (24.0%)	44 (33.3%)	30 (34.1%)	60 (39.7%)	0.054
Dyslipidemia	41 (39.4%)	51 (38.6%)	50 (56.8%)	68 (45.0%)	**0.026**
Chronic kidney disease	1 (1.0%)	1 (0.8%)	3 (3.4%)	3 (2.0%)	0.285
H/O PCI	14 (13.5%)	12 (9.1%)	8 (9.1%)	16 (10.6%)	0.695
H/O CABG	5 (4.8%)	5 (3.8%)	3 (3.4%)	4 (2.6%)	0.428
H/O Myocardial infarction	3 (2.9%)	8 (6.1%)	4 (4.5%)	9 (6.0%)	0.722
Congestive heart failure	0 (0%)	1 (0.8%)	0 (0%)	0 (0%)	0.494
Cerebrovascular accident	6 (5.8%)	7 (5.3%)	5 (5.7%)	7 (4.6%)	0.767
Peripheral artery disease	3 (2.9%)	3 (2.3%)	1 (1.1%)	3 (2.0%)	0.540

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Baseline Characteristics II

	DAT		TAT		p-value*
	Non-Carrier	Carrier	Non-Carrier	Carrier	
Laboratory finding					
Hematocrit	39.9±4.42	40.04±6.15	40.20±4.67	39.87±4.84	0.829
Creatinine (mg/dL)	1.06±0.18	1.17±0.32	1.09±0.23	1.07±0.22	0.572
Cholesterol (mg/dL)	174.43±46.25	165.86±36.53	173.36±37.05	174.18±38.20	0.222
- Triglyceride	153.05±94.34	134.51±76.87	151.15±102.02	144.91±73.20	0.597
- HDL-Cholesterol	42.92±10.84	42.11±10.38	44.00±11.68	42.72±10.53	0.481
- LDL-Cholesterol	106.63±39.34	103.00±34.36	101.32±32.59	105.81±34.58	0.968
CRP (mg/L)	3.70±4.92	3.41±5.82	54.9±450.78	7.64±34.67	0.243
Concomitant Medication					
ACEi	25 (24.3%)	20 (15.4%)	16 (18.2%)	28 (18.7%)	0.860
ARB	14 (13.6%)	20 (15.4%)	11 (12.5%)	20 (13.3%)	0.498
Beta-blocker	41 (39.8%)	56 (43.1%)	39 (44.3%)	68 (45.3%)	0.487
Calcium channel blocker	25 (24.3%)	34 (26.2%)	26 (29.5%)	47 (31.3%)	0.231
Statin	36 (35%)	39 (30%)	35 (39.8%)	58 (38.6%)	0.199
Proton pump inhibitor	0 (0%)	1 (0.8%)	0 (0%)	3 (2%)	0.624

TAT has higher antiplatelet activity

DAT vs. TAT, p<0.001
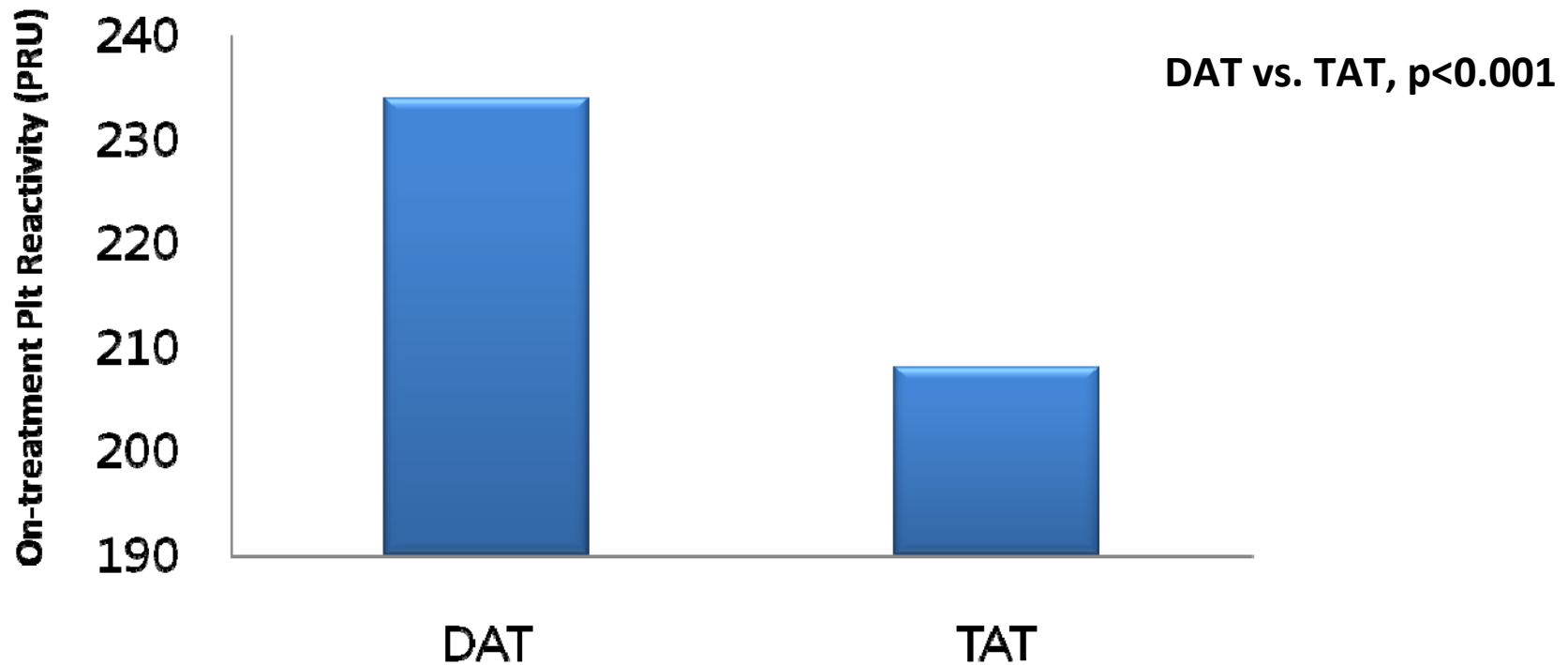
PRU	n	mean PRU
All patients	474	221.71 $\pm$ 86.09
DAT	236 (49.8%)	234.15 $\pm$ 78.85
TAT	238 (50.2%)	208.86 $\pm$ 90.32

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Genotype Distribution
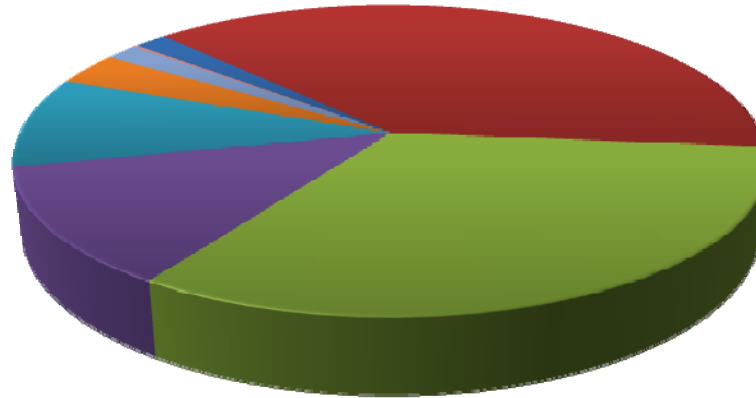
	LOF allele (-)		LOF allele (+)
*1/*17	8 (1.7%)	*1/*2	156 (32.9%)
*1/*1	183 (38.6)	*1/*3	58 (12.2%))
		*2/*2	44 (9.3%)
		*2/*3	16 (3.4%)
		*3/*3	8 (1.7%)
		*2/*17	1 (0.2%)
Total	191 (40.3%)		283 (59.7%)

CYP2C19 LOF associated with increased mean OPR
in DAT, but not in TAT group

On Treatment Platelet Reactivity (P2Y12 Reaction Unit, PRU)

■ Non-carrier of CYP2C19 LOF allele
■ Carrier of CYP2C19 LOF allele

P<0.001

P=0.142

n=104 n=132 n=87 n=151

Dual Antiplatelet Treatment Triple Antiplatelet Treatment

Seoul National University Hospital Cardiovascular Center
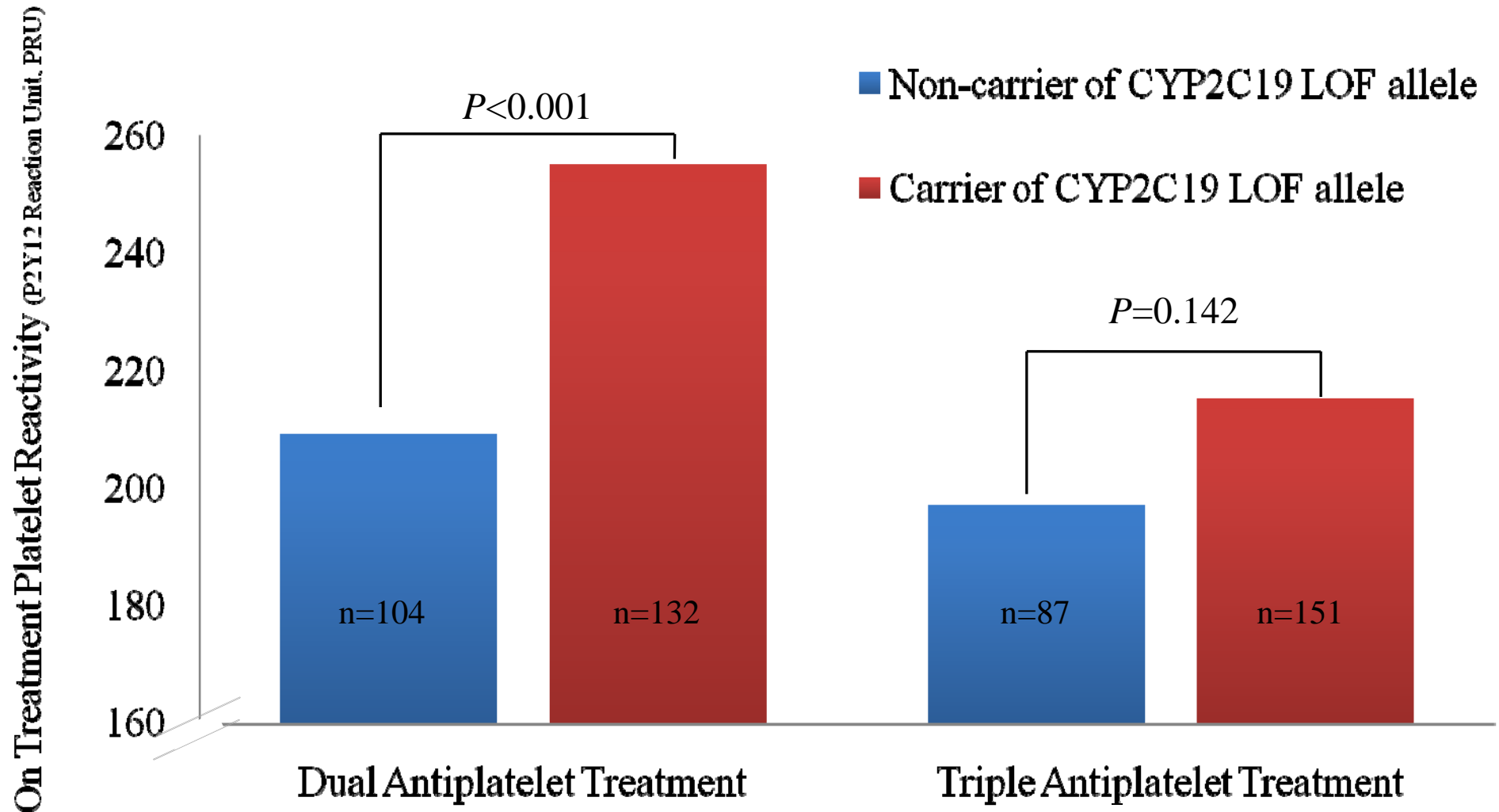
CYP2C19 LOF associated with HOPR
in DAT, but not in TAT group

Non-carrier of CYP2C19 LOF allele

Carrier of CYP2C19 LOF allele

P=0.001

P=0.905

43%

22%

26%

27%

Frequency (in %)

50%

40%

30%

20%

10%

0%

Dual Antiplatelet Treatment

Triple Antiplatelet Treatment

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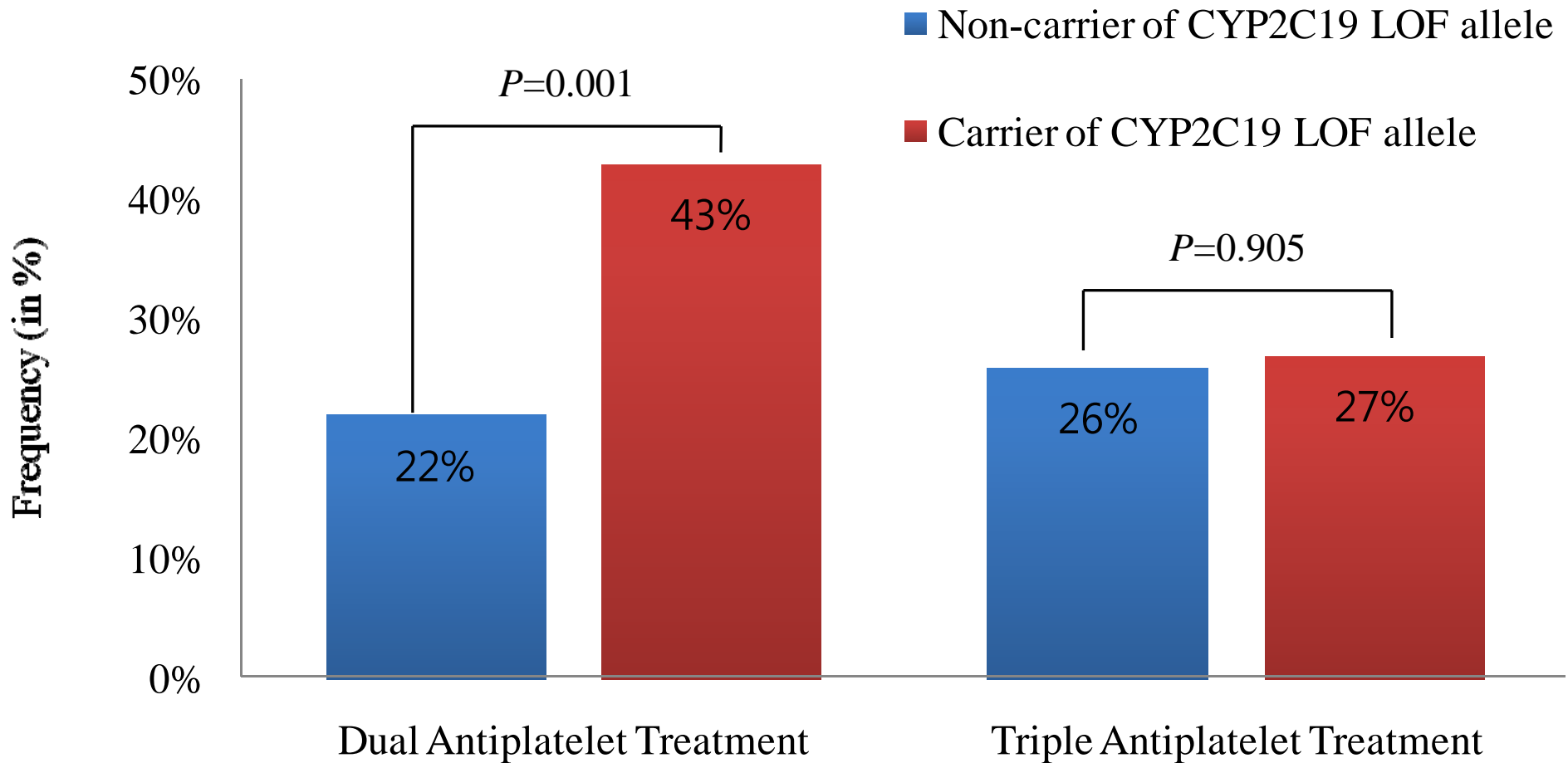
CYP2C19 LOF associated with HOPR in Koreans
Genetic subanalysis of the CILON-T trial

Park KW, Kim HS et al. Heart 2011

Seoul National University Hospital Cardiovascular Center
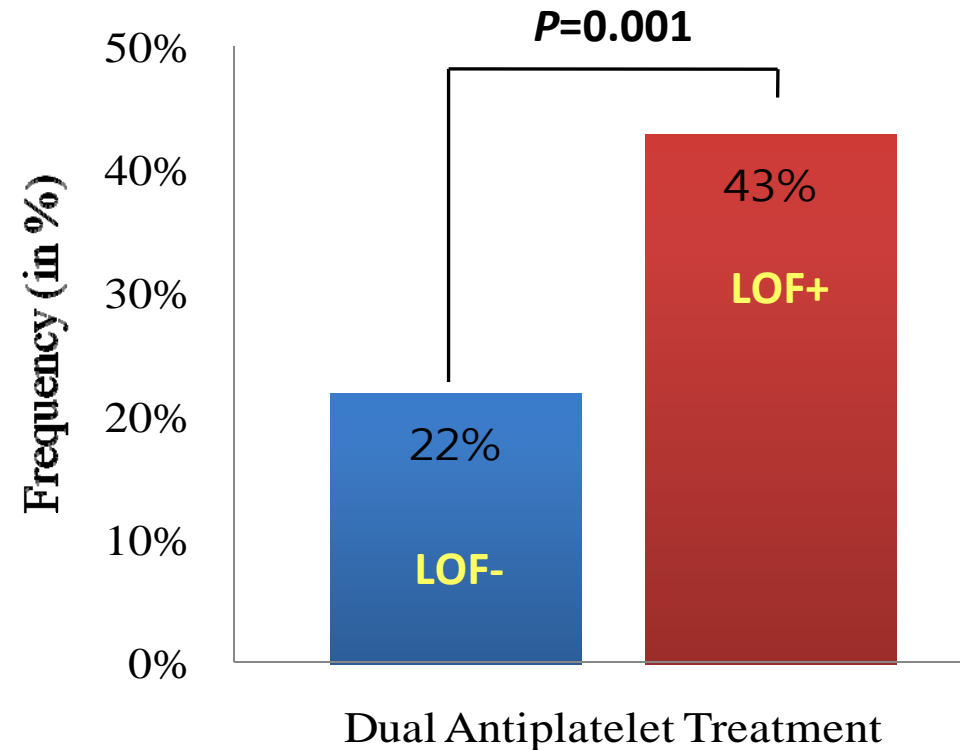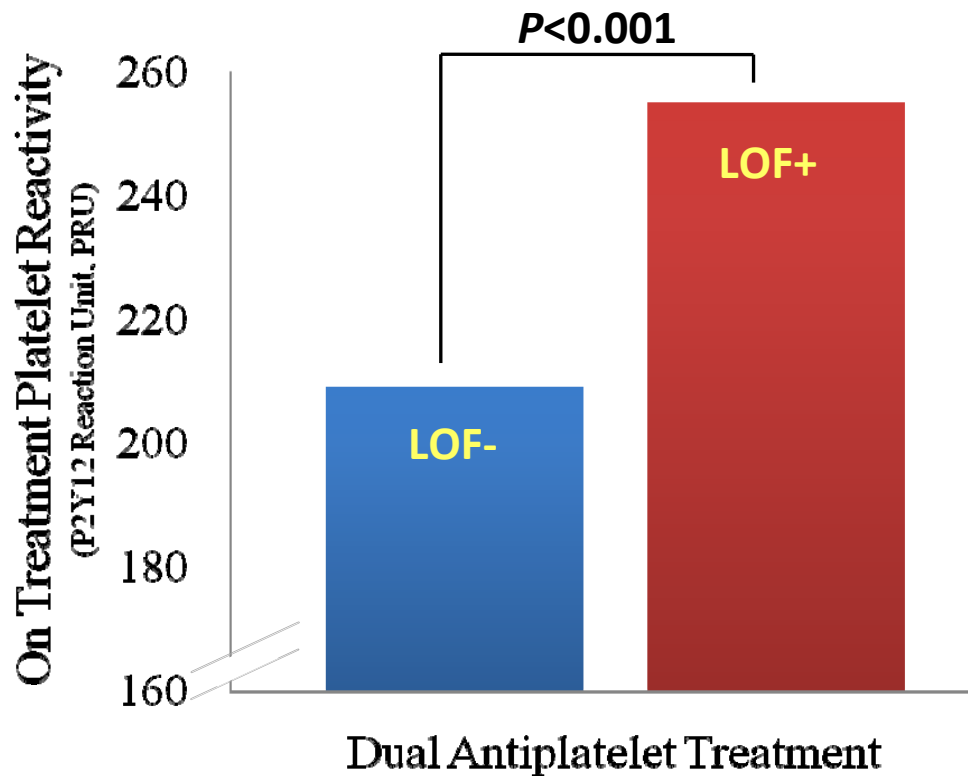
TAT significantly reduces mean OPR
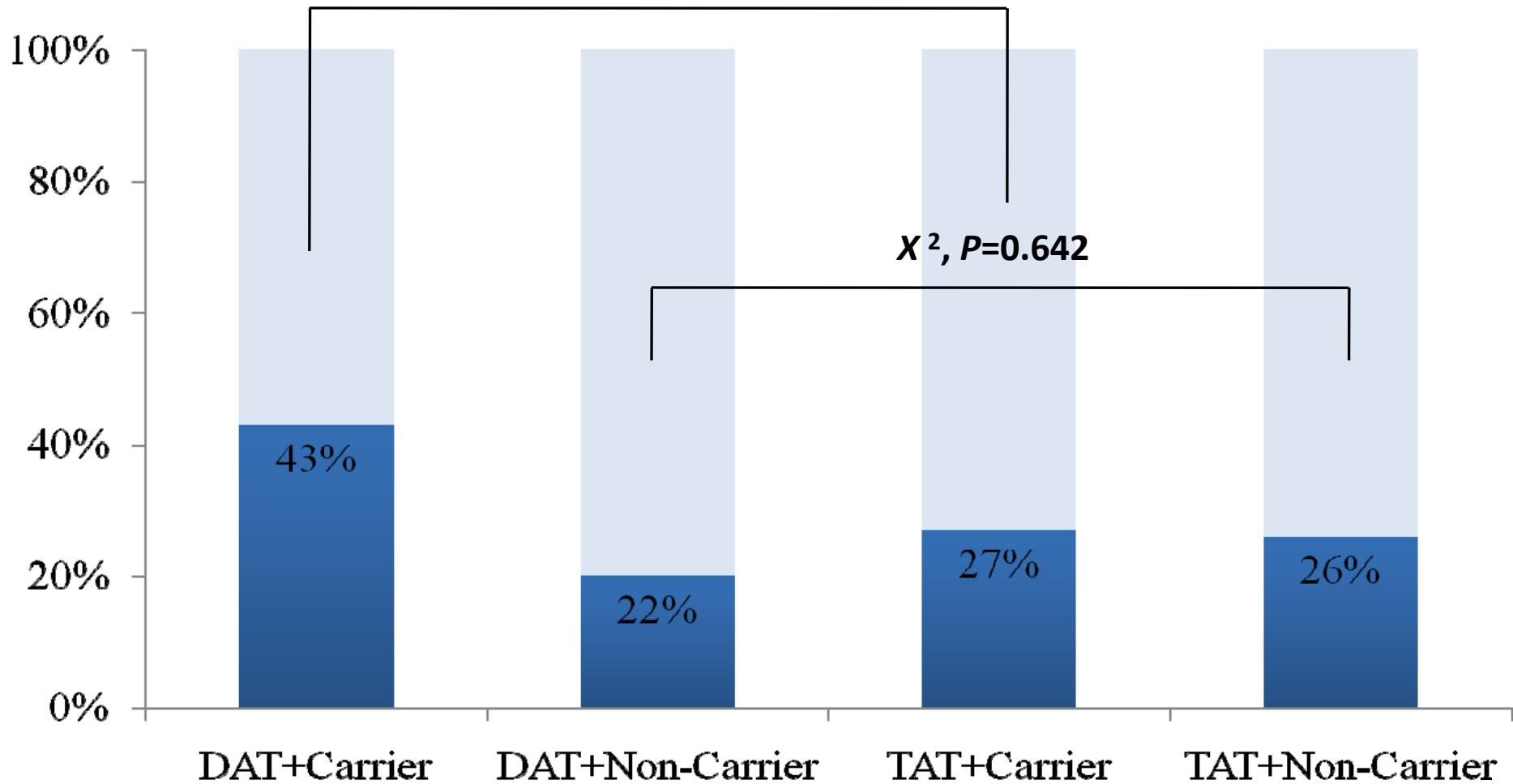## in carriers of the CYP2C19 LOF alleles
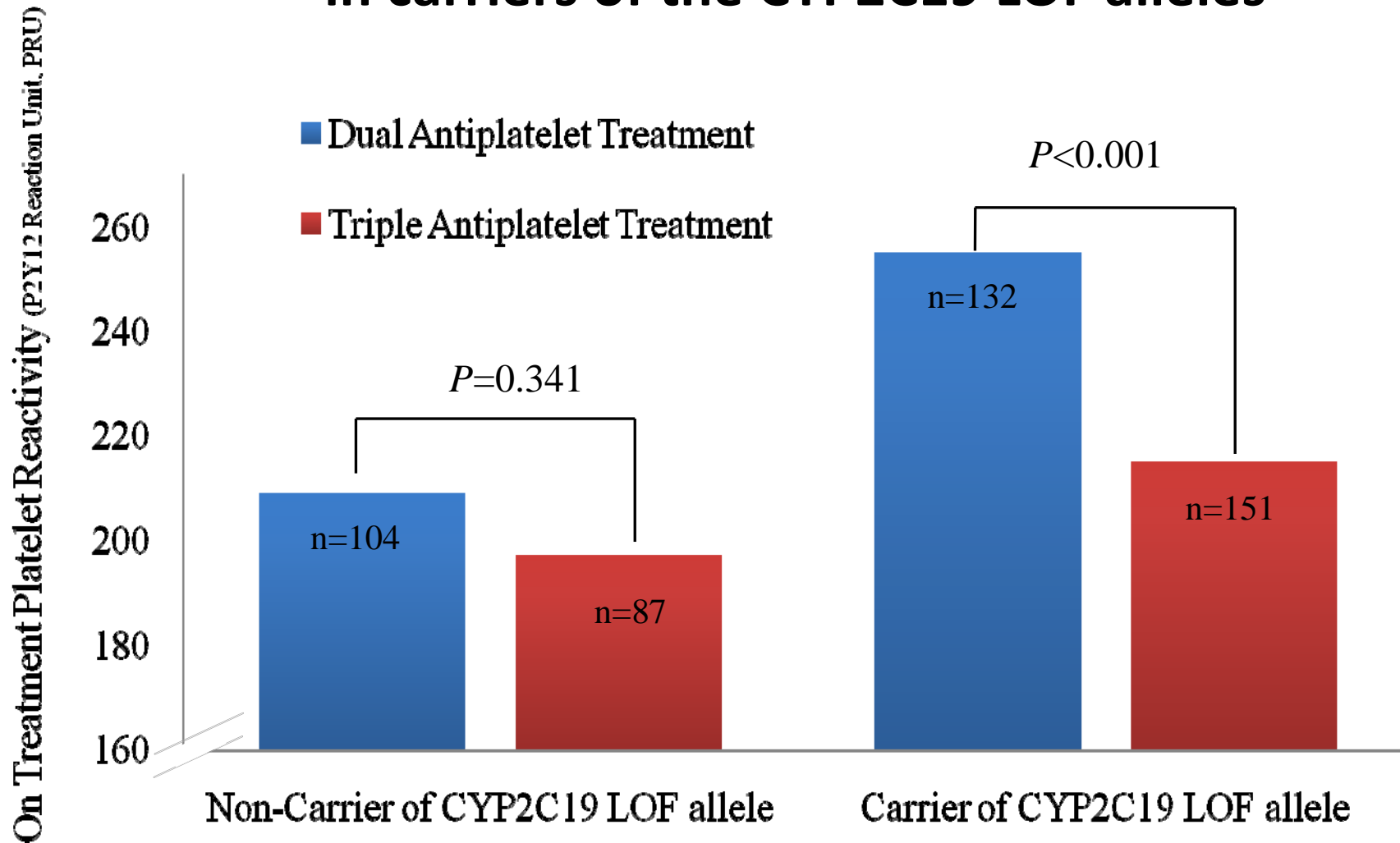
TAT significantly reduces the frequency of HOPR
in carriers of the CYP2C19 LOF alleles
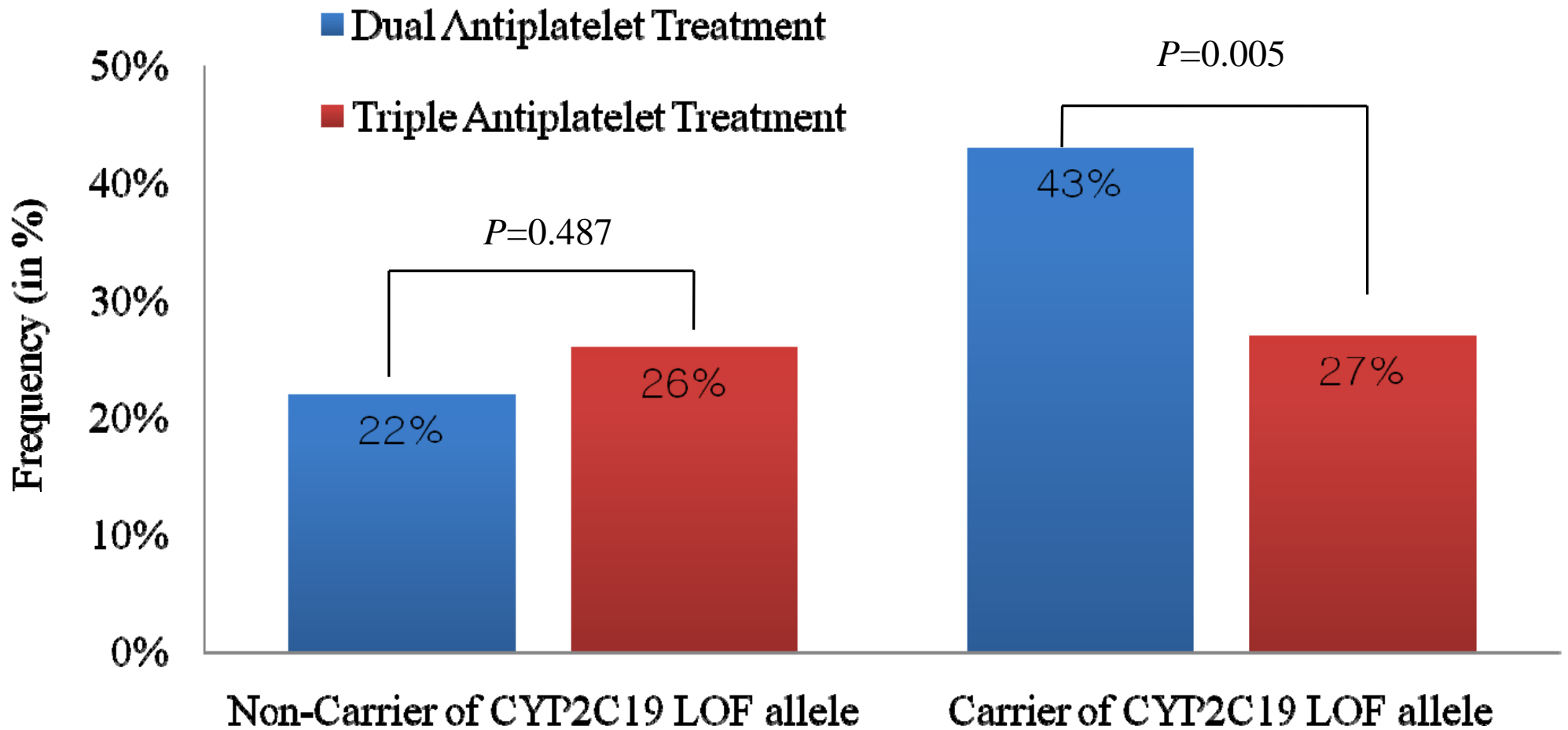
Frequency of HOPR
according to treatment and genotype
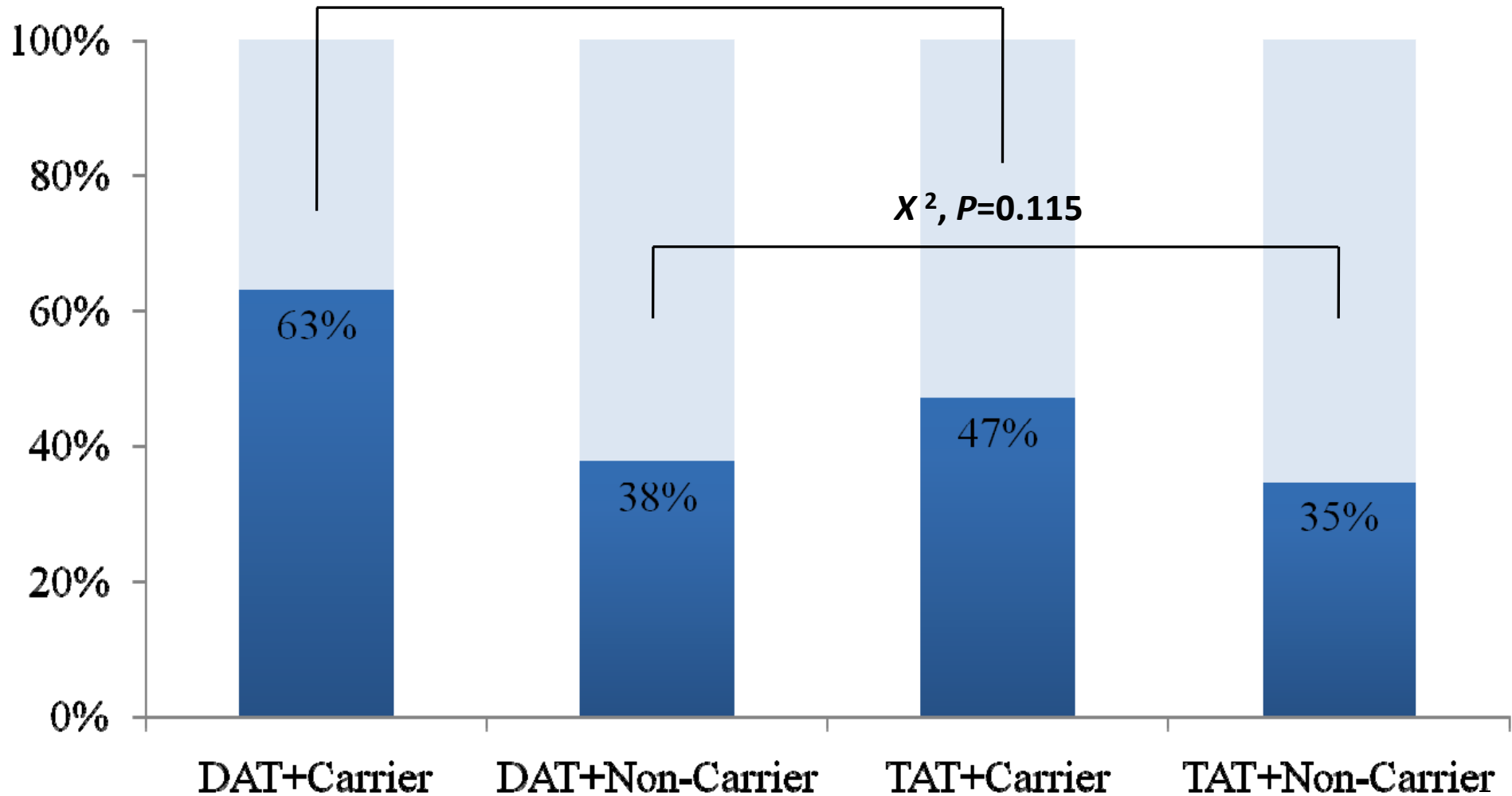## (using PRU>275 as definition of HOPR)

X^2, P<0.001

X^2, P=0.642

43%	22%	27%	26%
DAT+Carrier	DAT+Non-Carrier	TAT+Carrier	TAT+Non-Carrier

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Frequency of HOPR
according to treatment and genotype (using PRU>230 as definition of HOPR)

X^2, $P<0.001$

X^2, $P=0.115$

DAT+Carrier: 63%
DAT+Non-Carrier: 38%
TAT+Carrier: 47%
TAT+Non-Carrier: 35%

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Independent predictors of HOPR

	OR	95% Confidence Interval		P-value
		Lower limit	Upper Limit	
Age in decade	1.34	1.03	1.73	0.029
Female gender	2.53	1.56	4.12	< 0.001
Antiplatelet regimen according to genotype				
DAT + Carrier	3.13	1.65	5.94	< 0.001
TAT + Non-Carrier	1.12	0.54	2.33	0.760
TAT + Carrier	1.25	0.66	2.36	0.491

Input variables: age (in decade), gender, cigarette smoking, diabetes, chronic kidney disease, antiplatelet treatment regimen according to CYP2C19 genotype

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Summary and Conclusion

1. *CYP2C19 LOF PM are associated with higher mean OPR and increased risk for HOPR, and with increased risk of hard outcome after PCI.*

2. *The frequency of CYP2C19 LOF alleles are significantly higher in the Asian population.*

3. *The addition of cilostazol resulted in lower mean OPR and reduction of risk for HOPR in patients with CYP2C19 LOF alleles.*