Genotype and platelet function test guided anti-platelet therapy in acute coronary syndrome

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Disclosure

- This study is supported by the Cardiovascular Research Foundation (CVRF).

Background

Background

- High on-treatment platelet reactivity after clopidogrel administration is linked to the loss-of-function CYP 2C19 allele and accompanied by an increased risk of adverse events.
- Prasugrel is more effective in reducing platelet reactivity, in CYP 2C19*2 carriers

– JACC intervention. 2011;4(4):403-10.

Recommendations for oral antiplatelet agents

Recommendations	Class[a]	Level[b]	Ref[c]
Aspirin should be given to all patients without contraindications at an initial loading dose of 150–300 mg, and at a maintenance dose of 75–100 mg daily long-term regardless of treatment strategy.	I	A	107, 108
A $P2Y_{12}$ inhibitor should be added to aspirin as soon as possible and maintained over 12 months, unless there are contraindications such as excessive risk of bleeding.	I	A	110, 130, 132
A proton pump inhibitor (preferably not omeprazole) in combination with DAPT is recommended in patients with a history of gastrointestinal haemorrhage or peptic ulcer, and appropriate for patients with multiple other risk factors (*H. elicobacter pylori* infection, age ≥65 years, concurrent use of anticoagulants or steroids).	I	A	125–127
Prolonged or permanent withdrawal of $P2Y_{12}$ inhibitors within 12 months after the index event is discouraged unless clinically indicated.	I	C	-
Ticagrelor (180-mg loading dose, 90 mg twice daily) is recommended for all patients at moderate-to-high risk of ischaemic events (e.g. elevated troponins) , regardless of initial treatment strategy and including those pre-treated with clopidogrel (which should be discontinued when ticagrelor is commenced).	I	B	132
Prasugrel (60-mg loading dose, 10-mg daily dose) is recommended for $P2Y_{12}$-inhibitor-naïve patients (especially diabetics) in whom coronary anatomy is known and who are proceeding to PCI unless there is a high risk of life-threatening bleeding or other contraindications.[d]	I	B	130
Clopidogrel (300-mg loading dose, 75-mg daily dose) is recommended for patients who cannot receive ticagrelor or prasugrel.	I	A	110, 146, 147
A 600-mg loading dose of clopidogrel (or a supplementary 300-mg dose at PCI following an initial 300-mg loading dose) is recommended for patients scheduled for an invasive strategy when ticagrelor or prasugrel is not an option.	I	B	108, 114, 115
A higher maintenance dose of clopidogrel 150 mg daily should be considered for the first 7 days in patients managed with PCI and without increased risk of bleeding.	IIa	B	108
Increasing the maintenance dose of clopidogrel based on platelet function testing is not advised as routine, but may be considered in selected cases.	IIb	B	124
Genotyping and/or platelet function testing may be considered in selected cases when clopidogrel is used.	IIb	B	119, 121
In patients pre-treated with $P2Y_{12}$ inhibitors who need to undergo non-emergent major surgery (including CABG), postponing surgery at least for 5 days after cessation of ticagrelor or clopidogrel, and 7 days for prasugrel, if clinically feasible and unless the patient is at high risk of ischaemic events should be considered.	IIa	C	-
Ticagrelor or clopidogrel should be considered to be (re-) started after CABG surgery as soon as considered safe.	IIa	B	134
The combination of aspirin with an NSAID (selective COX-2 inhibitors and non-selective NSAID) is not recommended.	III	C	-

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
[d]Prasugrel is not recommended by the guidelines as a class I recommendation as the overall indication including clopidogrel-pre-treated patients and/or unknown coronary anatomy. The class I recommendation here refers to the specifically defined subgroup.

ESC Guidelines for the ACS without STEMI. Eur Heart J. 2011 Dec;32(23):2999-3054.

Background

- Phenotyping of platelet response to clopidogrel was better predictor of stent thrombosis than genotyping. *– J Thromb Haemost 2012;10(4):529-42.*
- Personalized anti-platelet treatment for anti-platelet resistance was found to be associated with less occurrence of death or stent thrombosis. *– Heart 2013 Nov 5. [Epub ahead of print]*

Background

- The clinical evidence regarding the influence of tailored anti-platelet strategy on adverse outcomes has been controversial.

– Heart 2013 Nov 5. [Epub ahead of print]

Purpose

- The present study was designed to assess the effect of genotype and platelet function test guided anti-platelet therapy in patients with acute coronary syndrome (ACS).

Methods

Method

- Forty-six ACS patients undergoing percutaneous coronary intervention (PCI) were screened with CYP 2C19 *2*3 loss-of-function (LOF) polymorphism and VerifyNow® P2Y12 assay, defining high on-treatment platelet reactivity (HTPR) as platelet reaction unit (PRU) > 230.
- Before randomization step, in all cases, clopidogrel was administered. (600mg loading and then 75mg/day)

Method

- Those with homozygous LOF allele and HTPR (PRU>230), we switched clopidogrel over to prasugrel (10mg/day) (Group 1).
- Those with normal genotyping (*1*1) and normal platelet function test (PRU<230), we maintained clopidogrel (75mg/day) (Group 4).
- Others (intermediate characteristics) were randomized to prasugrel (Group 2) or clopidogrel (Group 3).

Clinical endpoints

- Primary endpoint was 1 month HTPR.
- Secondary endpoints included

  12 month death or MI

  12 month TLR, 12 month binary ISR, CV admission

  GUSTO bleeding

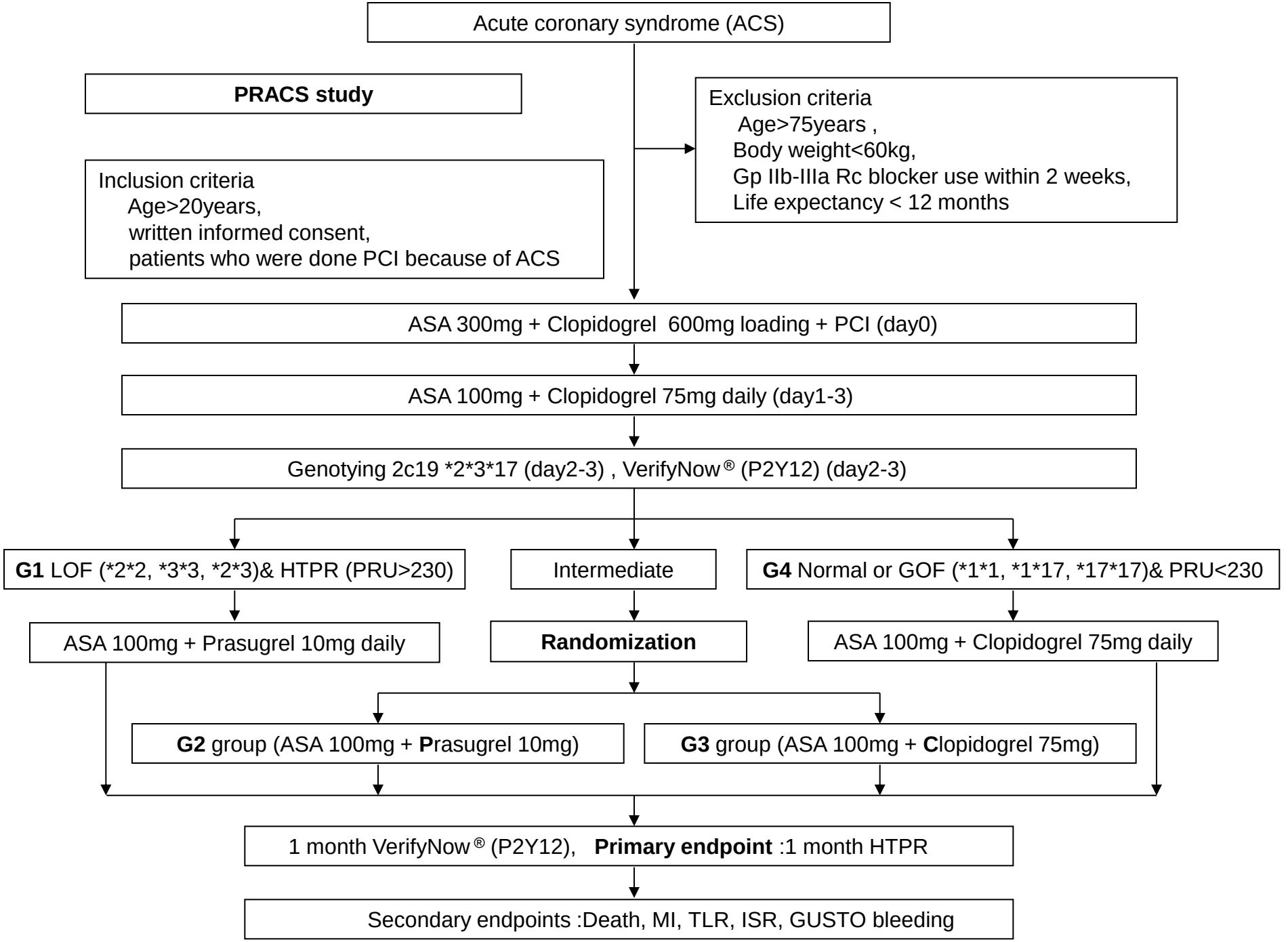
1) Severe : Intracranial hemorrhage,

   Bleeding that causes hemodynamic compromise and requires intervention

2) Moderate : Bleeding that requires blood transfusion but does not lead to

   hemodynamic instability.

3) Mild : Bleeding that does not meet criteria for severe or moderate bleeding.

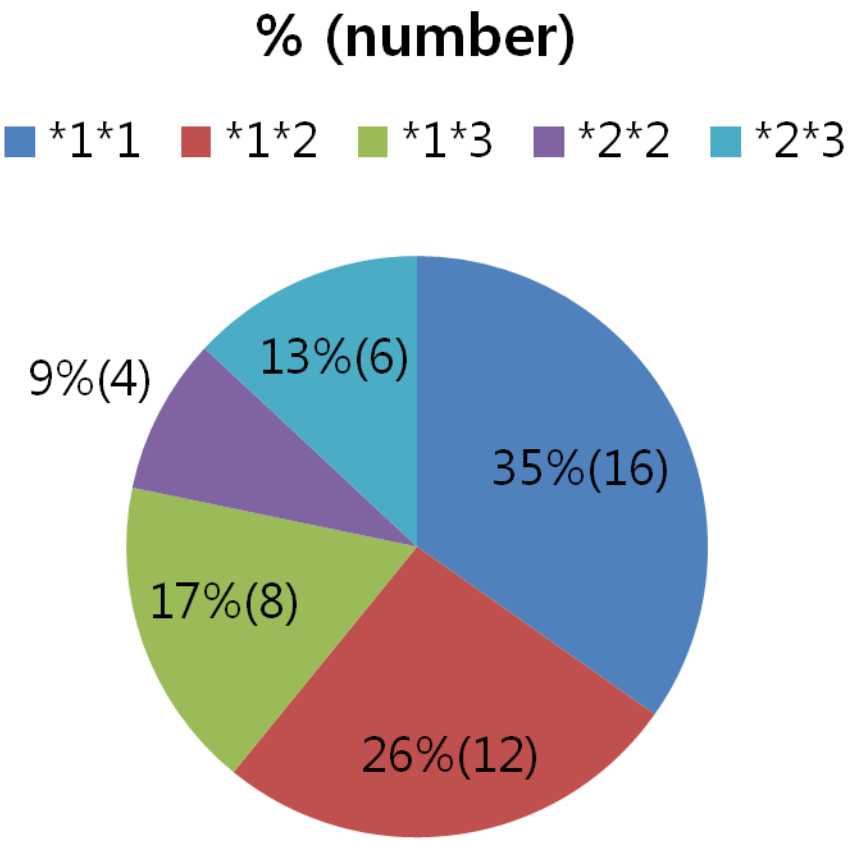

Acute coronary syndrome (ACS)
PRACS study
Exclusion criteria
Age>75years ,
Body weight<60kg,
Gp IIb-IIIa Rc blocker use within 2 weeks,
Life expectancy < 12 months
Inclusion criteria
Age>20years,
written informed consent,
patients who were done PCI because of ACS
ASA 300mg + Clopidogrel 600mg loading + PCI (day0)
ASA 100mg + Clopidogrel 75mg daily (day1-3)
Genotying 2c19 *2*3*17 (day2-3) , VerifyNow® (P2Y12) (day2-3)
G1 LOF (*2*2, *3*3, *2*3)& HTPR (PRU>230)
Intermediate
G4 Normal or GOF (*1*1, *1*17, *17*17)& PRU<230
ASA 100mg + Prasugrel 10mg daily
Randomization
ASA 100mg + Clopidogrel 75mg daily
G2 group (ASA 100mg + Prasugrel 10mg)
G3 group (ASA 100mg + Clopidogrel 75mg)
1 month VerifyNow® (P2Y12), Primary endpoint :1 month HTPR
Secondary endpoints :Death, MI, TLR, ISR, GUSTO bleeding

Results

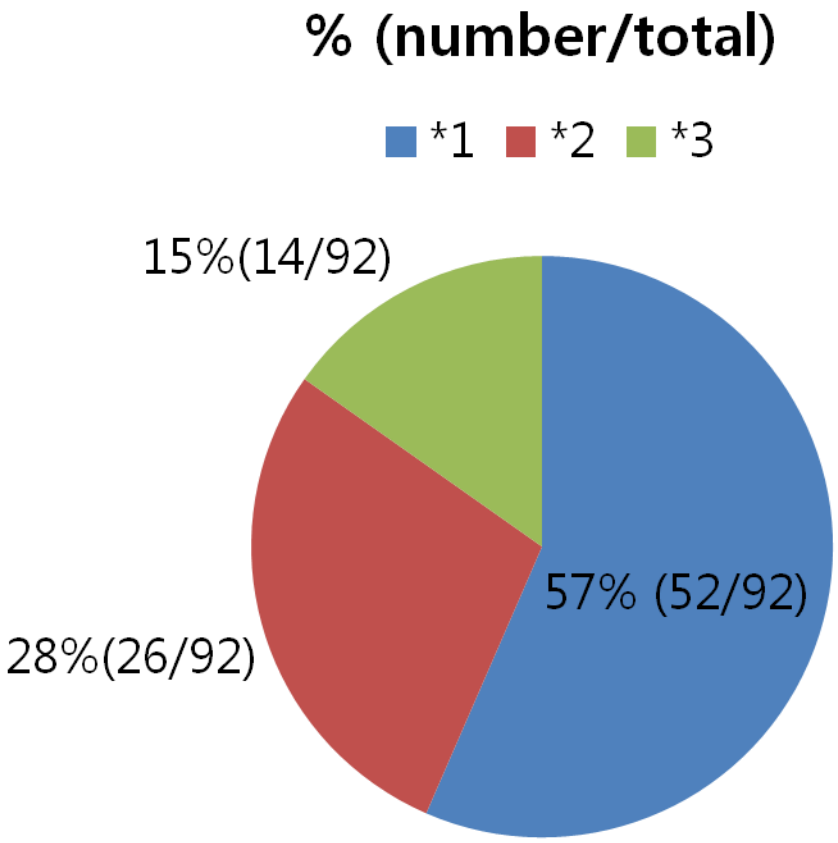
Baseline Characteristics (n=46)

Variables	Group1 Prasugrel (N=8)	Group 2 random Prasugrel (N=13)	Group 3 random Clopidogrel (N=15)	Group 4 Clopidogrel (N=10)	p value
Age (mean±SD)	57.0 ± 8.9	54.9 ± 12.0	61.0 ± 11.6	58.1± 8.9	0.522
Male sex (number)	7 (87.5%)	13 (100%)	14 (93.3%)	10 (100%)	0.472
Diagnosis (number)					0.637
STEMI	3 (37.5%)	5 (38.5%)	5 (33.3%)	1 (10%)	
NSTEMI	3 (37.5%)	5 (38.5%)	4 (26.7%)	6 (60%)	
Unstable angina	2 (25%)	3 (23.1%)	6 (40.0%)	3 (30%)	
Diabetes Mellitus (number)	2(25%)	5 (38.5%)	2 (13.3%)	2 (20%)	0.471
Hypertension (number)	3(37.5%)	5 (38.5%)	7 (46.7%)	6 (60%)	0.724
Current smoking (number)	7(87.5%)	8 (61.5%)	5 (33.3%)	7 (70%)	0.063
Family History (number)	0	0	1 (6.7%)	0	0.549
Previous MI (number)	0	0	0	0	
Previous CVA (number)	0	0	1 (6.7%)	0	0.549
Previous PCI (number)	0	0	0	2 (20%)	0.057
Previous CABG (number)	0	0	0	0	
Chronic renal failure (number)	1 (12.5%)	0	0	0	0.183

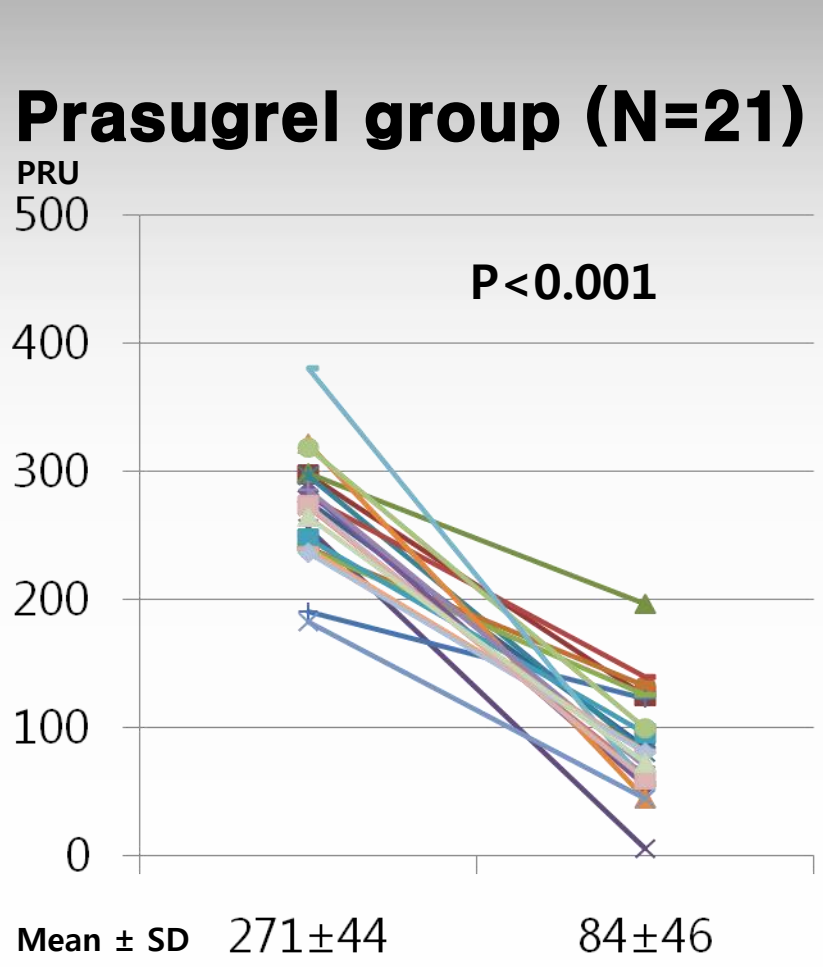
2C19 Polymorphism (N=46)

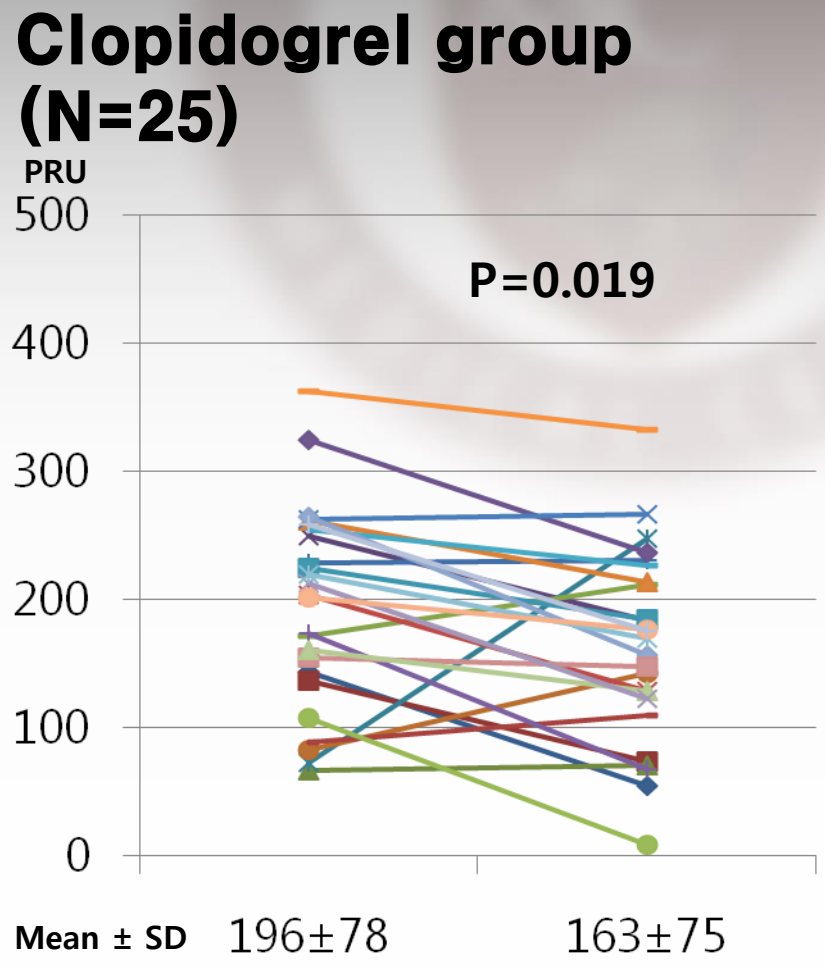


Allele frequency (N=46)



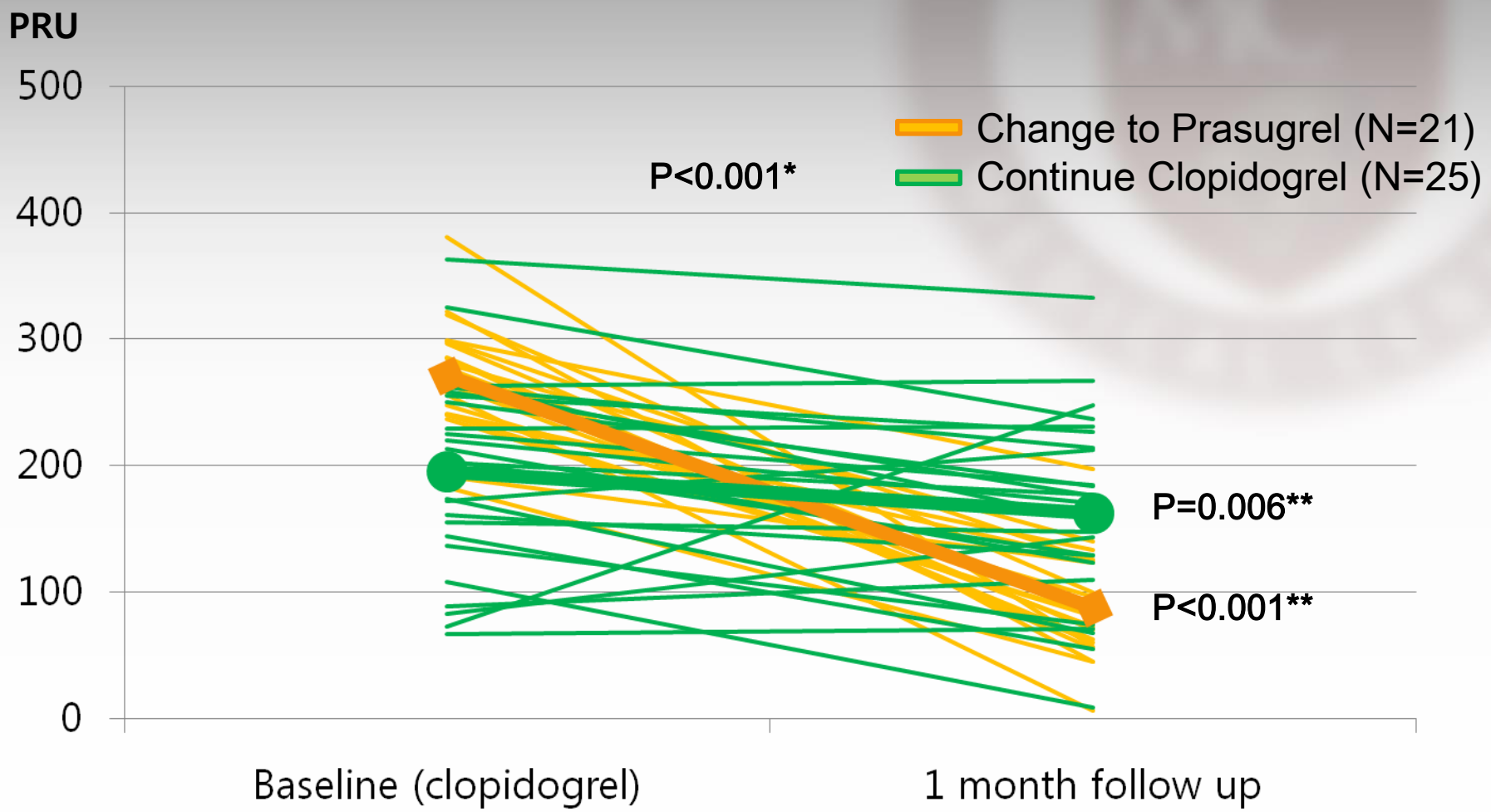
Changes of platelet inhibition





* P value by Wilcoxon's signed-ranks test

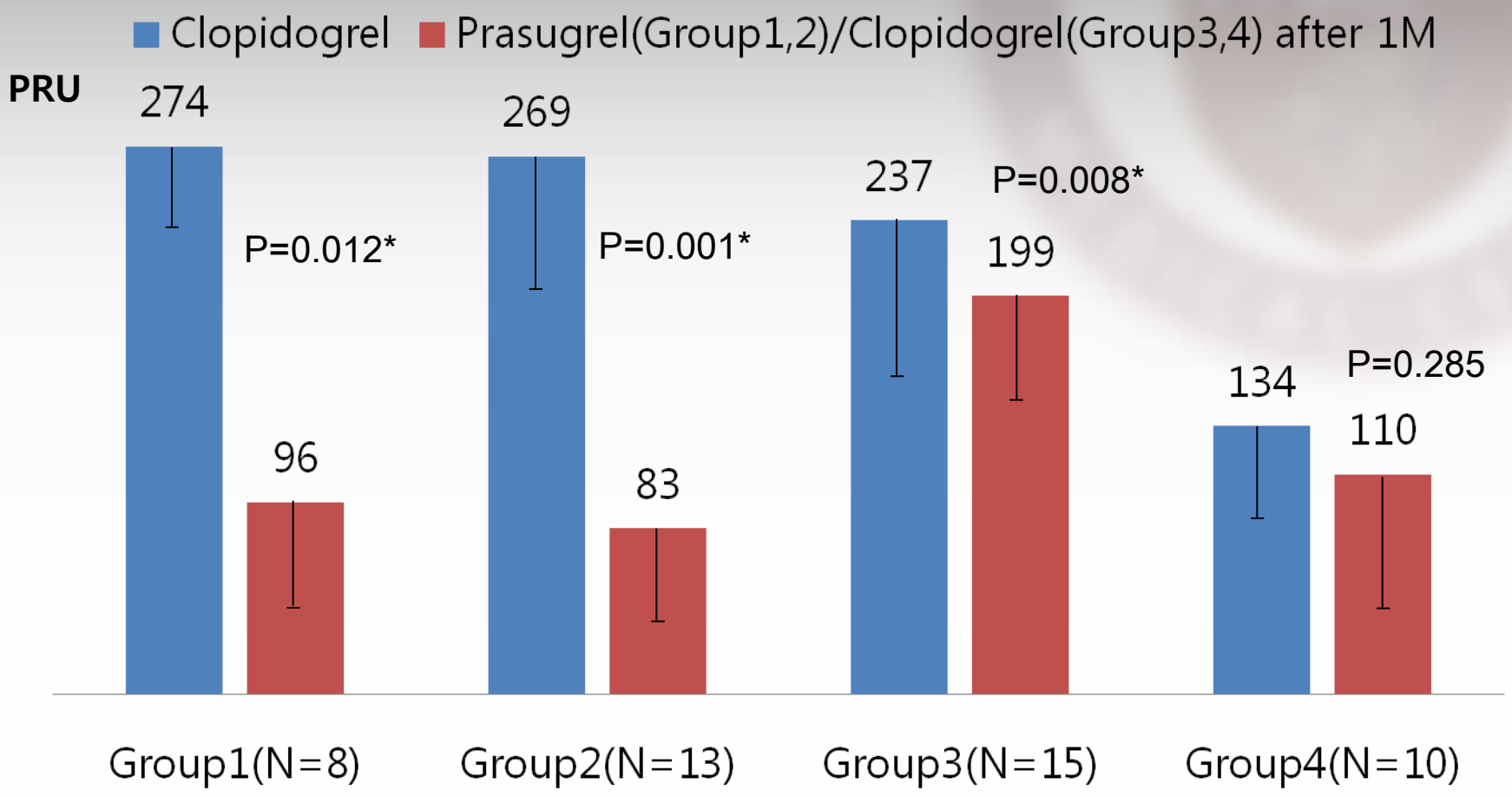
Prasugrel Versus Clopidogrel



* P value by independent t-test

** P value by Wilcoxon's signed-ranks test

Changes of platelet activity (PRU)



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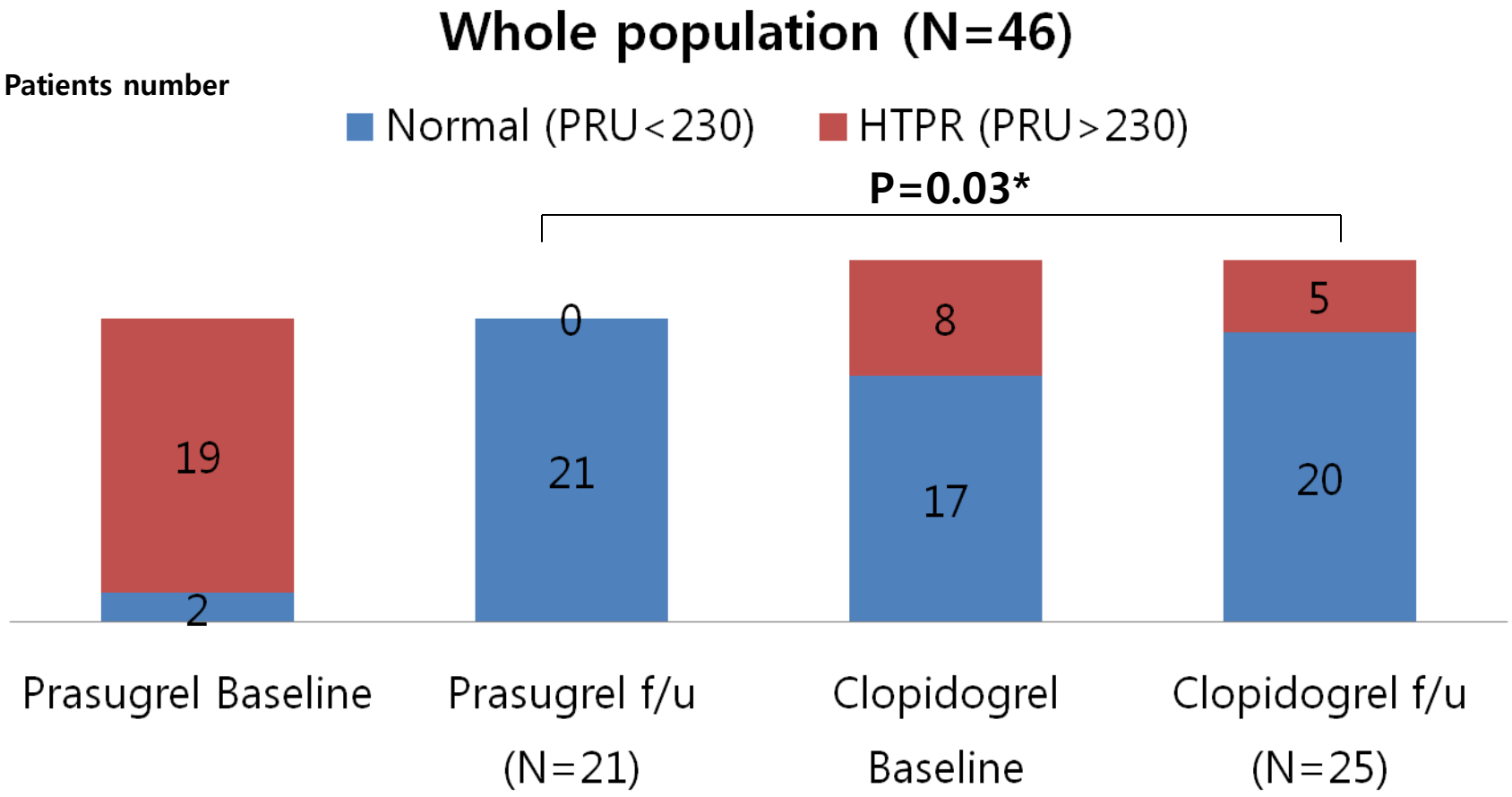
* P value by Wilcoxon's signed-ranks test

Primary endpoint : 1 month HTPR



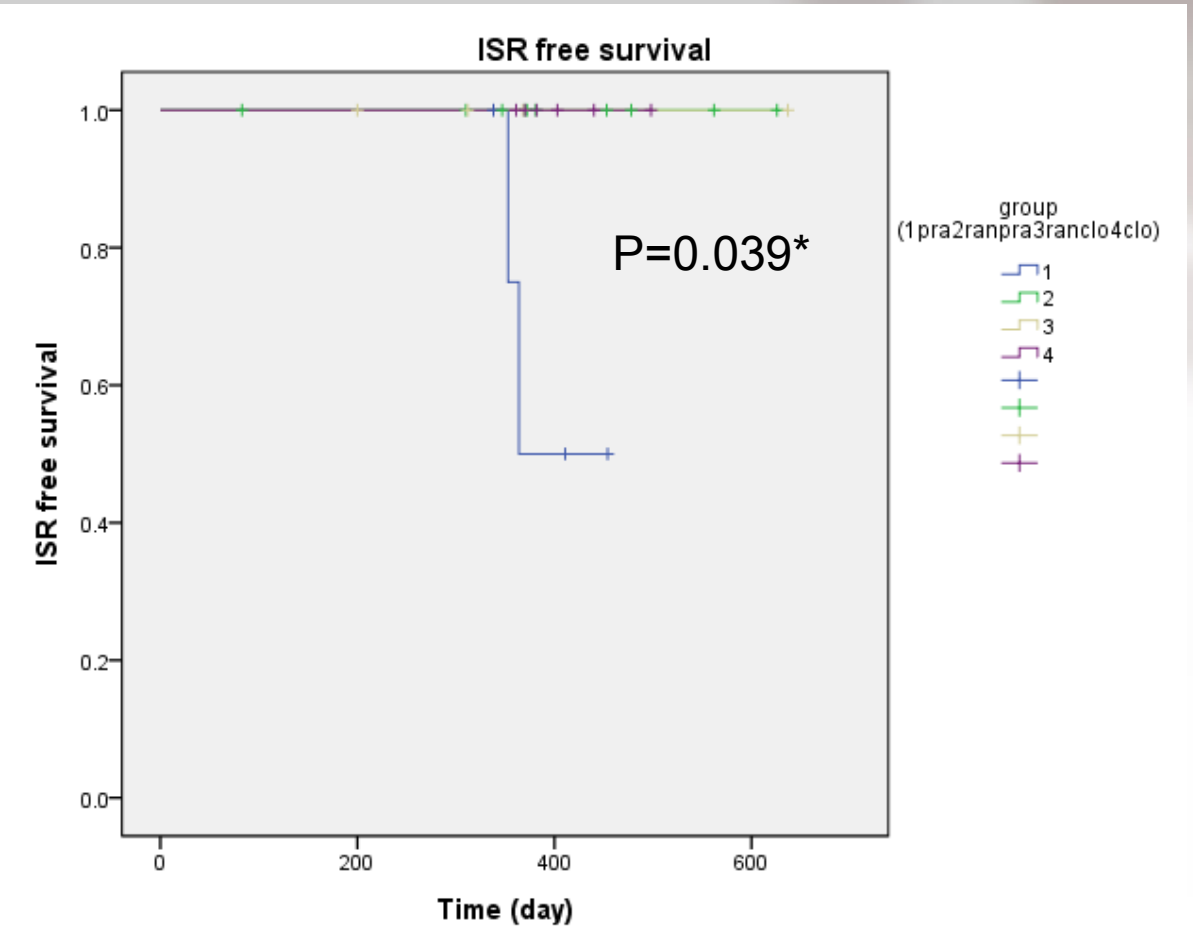
* P value by Chi-square test

Clinical outcomes (n=46)

Variables	Group1 Prasugrel (N=8)	Group 2 random Prasugrel (N=13)	Group 3 random Clopidogrel (N=15)	Group 4 Clopidogrel (N=10)	p value
Death (number)	0	0	0	0	
MI (number)	0	0	0	0	
TLR (number)	1 (12.5%)	0	0	0	0.183
ISR, binary (number)	2 (25%)	0	0	0	**0.039***
CV admission (number)	1 (12.5%)	1 (7.7%)	0	2 (20%)	0.362
GUSTO Bleeding, moderate ~ severe	0	0	0	2 (20%)	0.057
GUSTO Bleeding, mild	2 (25%)	5 (38.5%)	1 (6.7%)	0	0.054
Cross-over (number)	0	2 (15.4%)	0	0	0.151

* Mean follow up duration was 269 ± 93 (days)

Binary ISR free survival



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Summary I

- Prasugrel was associated with a significantly lower platelet reactivity than clopidogrel (PRU 271±44 to 88±42 vs 196±78 to 163±75 ; $p<0.001$).
- And, there was no HTPR patient in prasugrel group compared to clopidogrel after 1 month (19/21 to 0/21 vs 8/25 to 5/25; $p=0.03$).
- We achieved similar anti-platelet effects of prasugrel in the HTPR and LOF carriers compared to clopidogrel in the normal group.

Summary II

- There was no death or MI events in whole study population.
- There were two binary restenosis cases in Group 1 (HTPR and homozygous LOF allele carrier) (p=0.019)
- Our tailored anti-platelet strategy did not increase GUSTO moderate to severe bleeding.

Conclusions

- Genotype and platelet function test guided anti-platelet therapy is effective and safe in controlling platelet reactivity in patients with ACS.
- And, prasugrel showed excellent anti-platelet effects in patients with 2C19 LOF allele or HTPR.

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Thank you for your attention.

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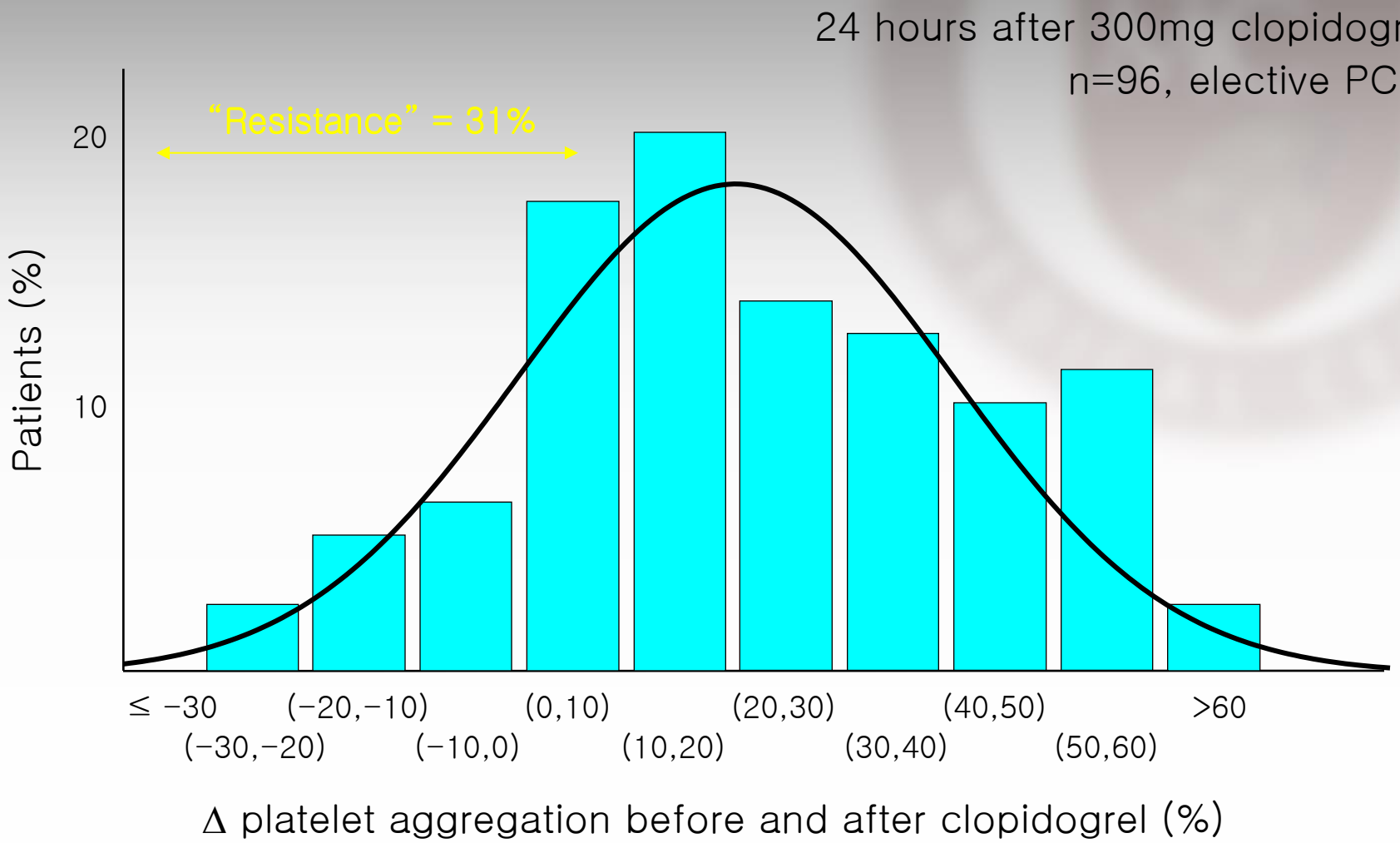
심혈관 건강증진 연구원
Cardiovascular Welfare & Research Institute

Interpatient Variability to Clopidogrel

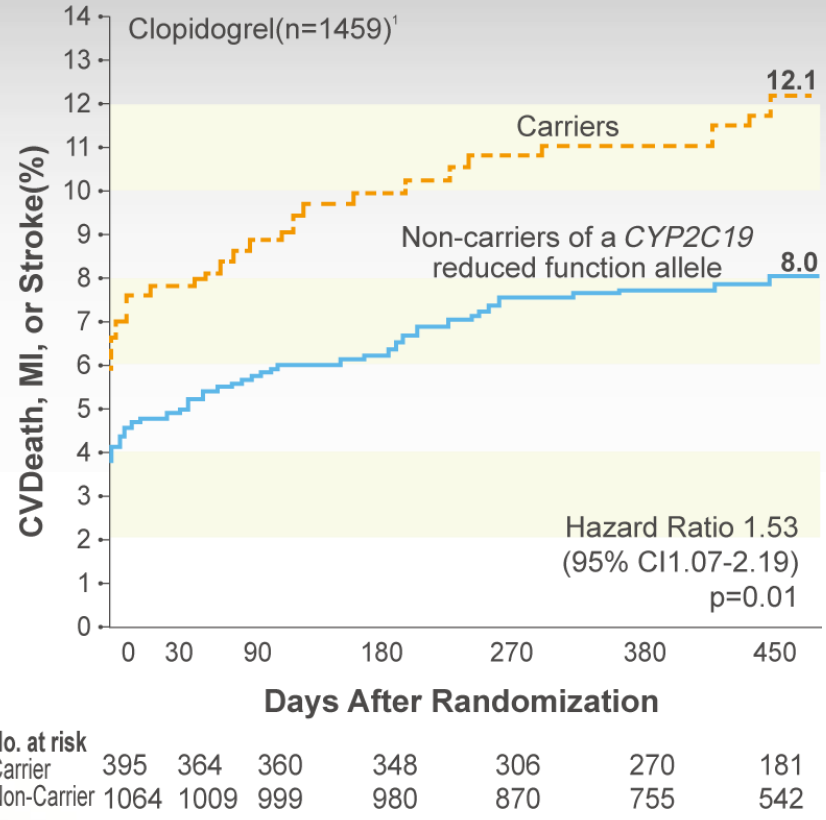


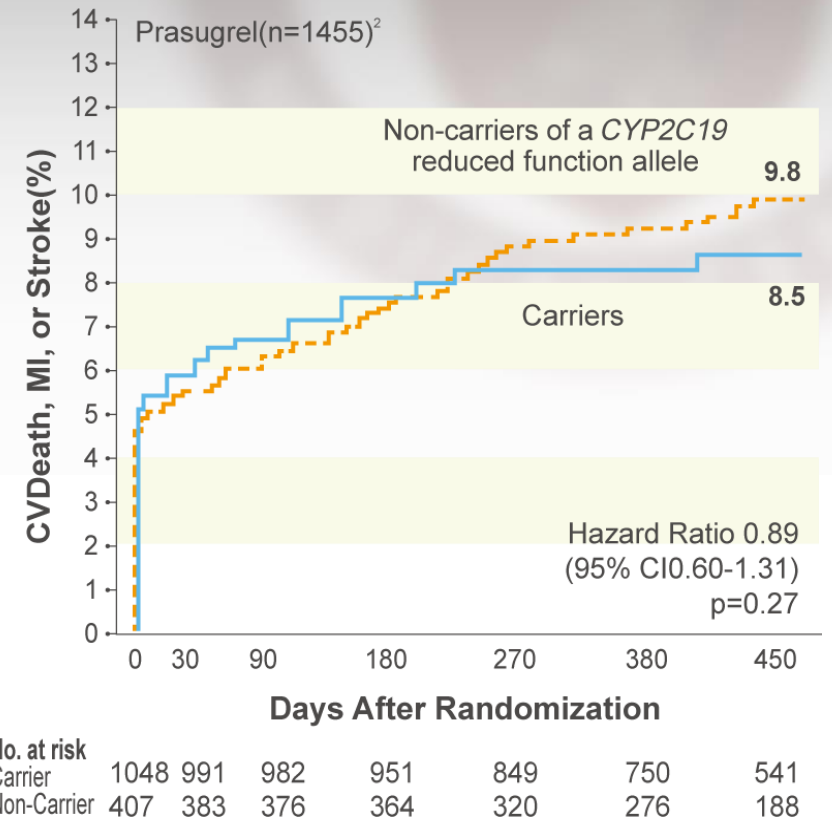
"Resistance" = ≤10% Δ platelet aggregation

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

Effient: No impact of reduced function CYP2C19 Alleles

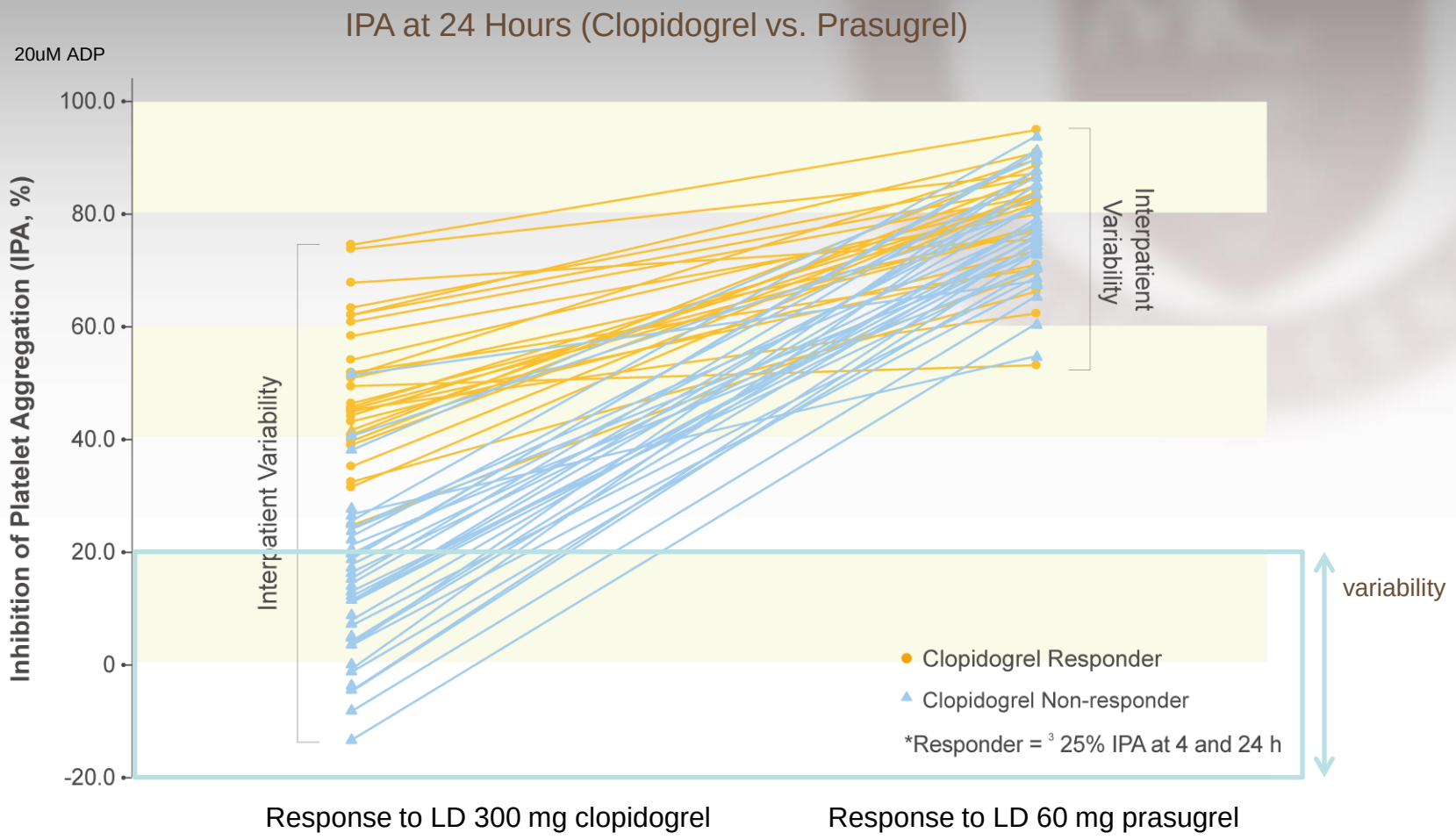
Cumulative incidence curves for the primary efficacy outcome
(composite of cardiovascular death, myocardial infaction, or stroke)





Data from 1. Mega JL et al. *N Engl J Med* 2009;360:354-62.
Data from 2. Mega JL et al. *Circulation*. 2009;119:2553-2560

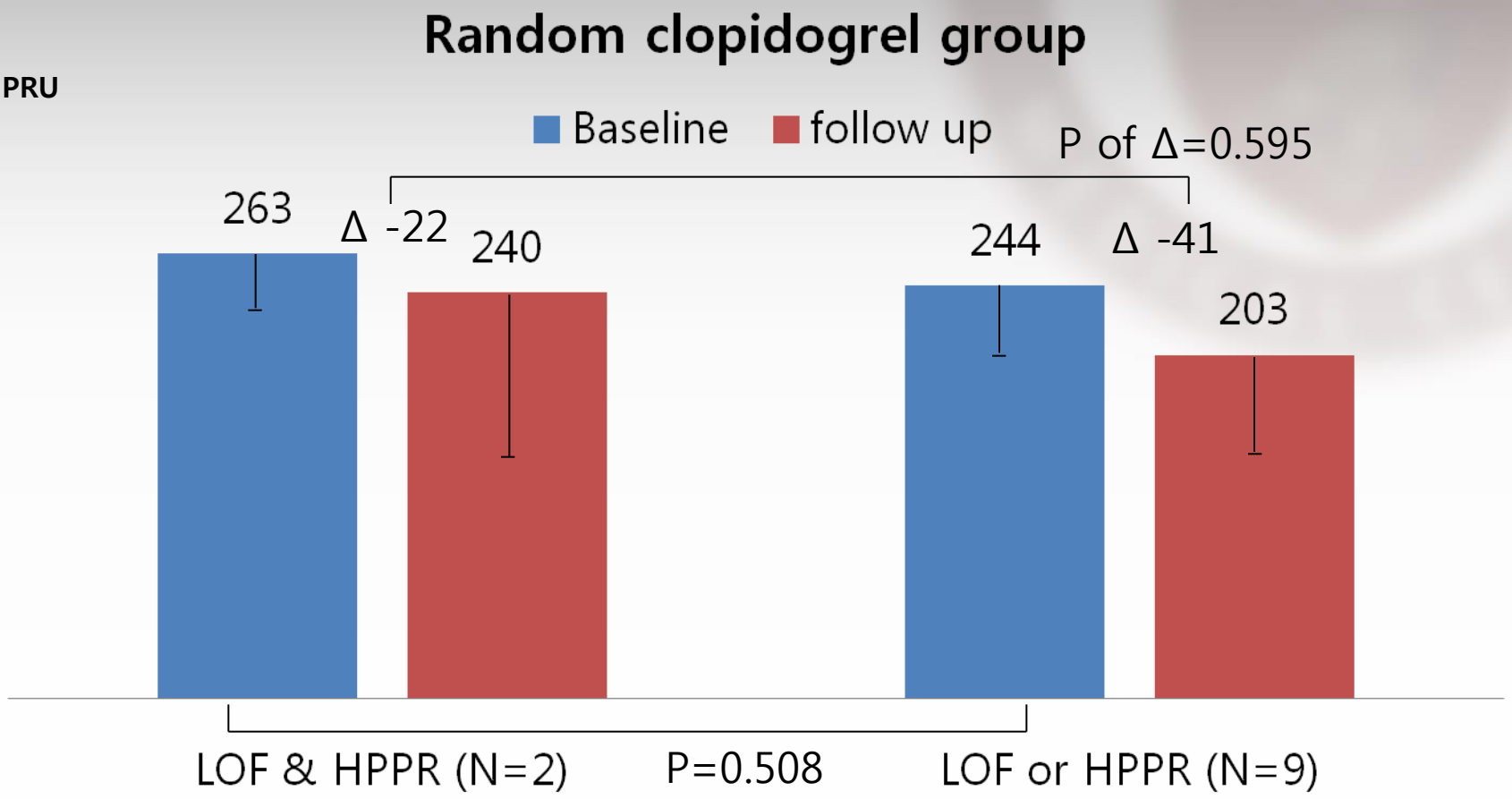
Effient: Less Variable Platelet Inhibition



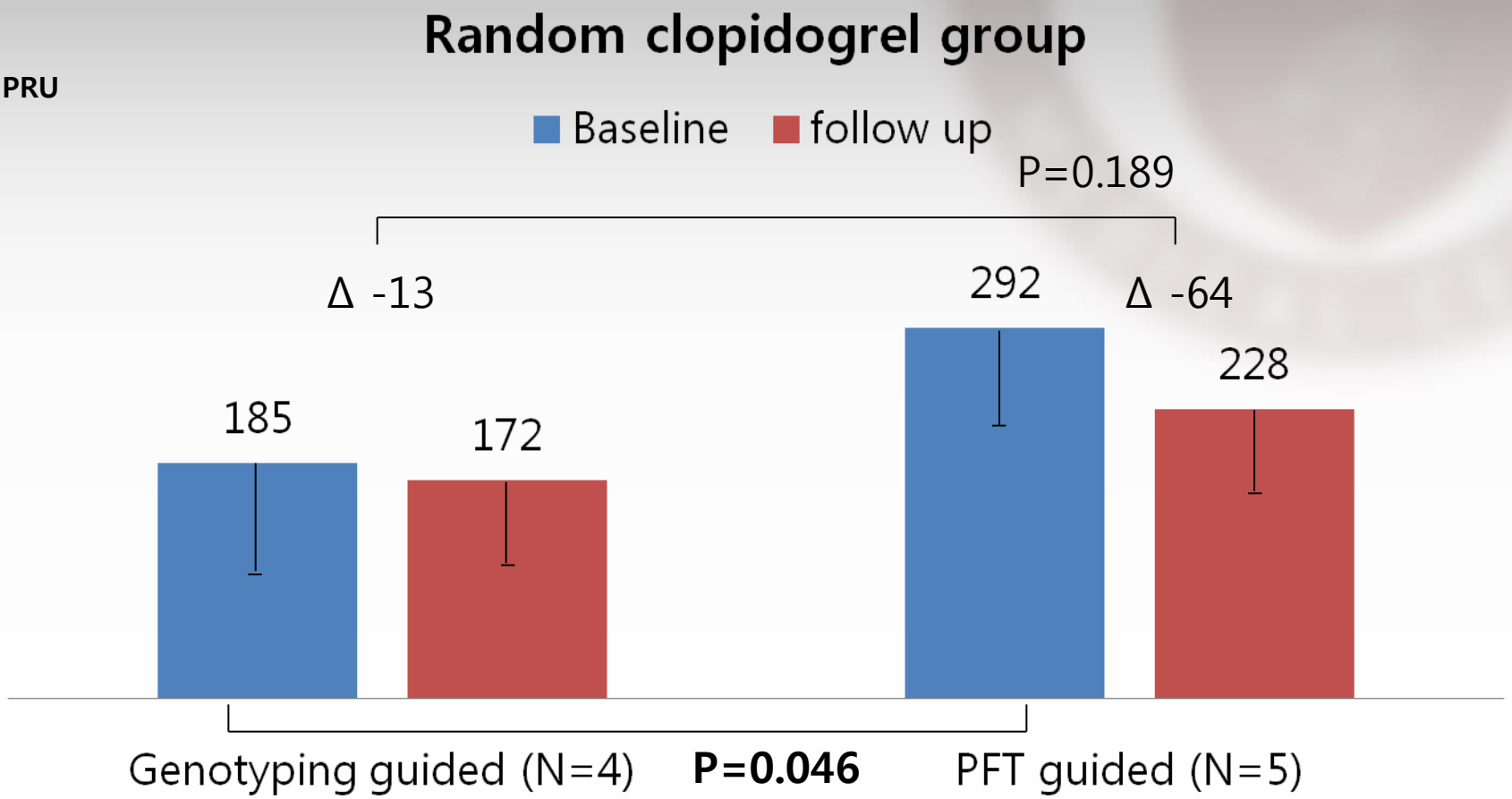
Healthy Volunteers, N=68 administered both clopidogrel and prasugrel in a crossover fashion

Data from Brandt JT et al. *Am Heart J* 2007;153:66.e9-66.e16

Changes of platelet inhibition



Changes of platelet inhibition



Changes of platelet inhibition