# PK/PD of Clopidogrel and Prasugrel

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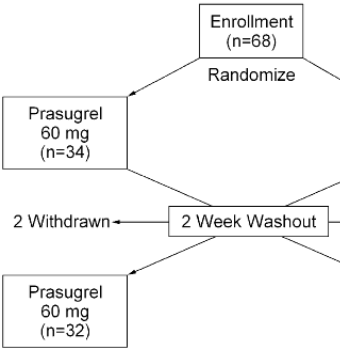
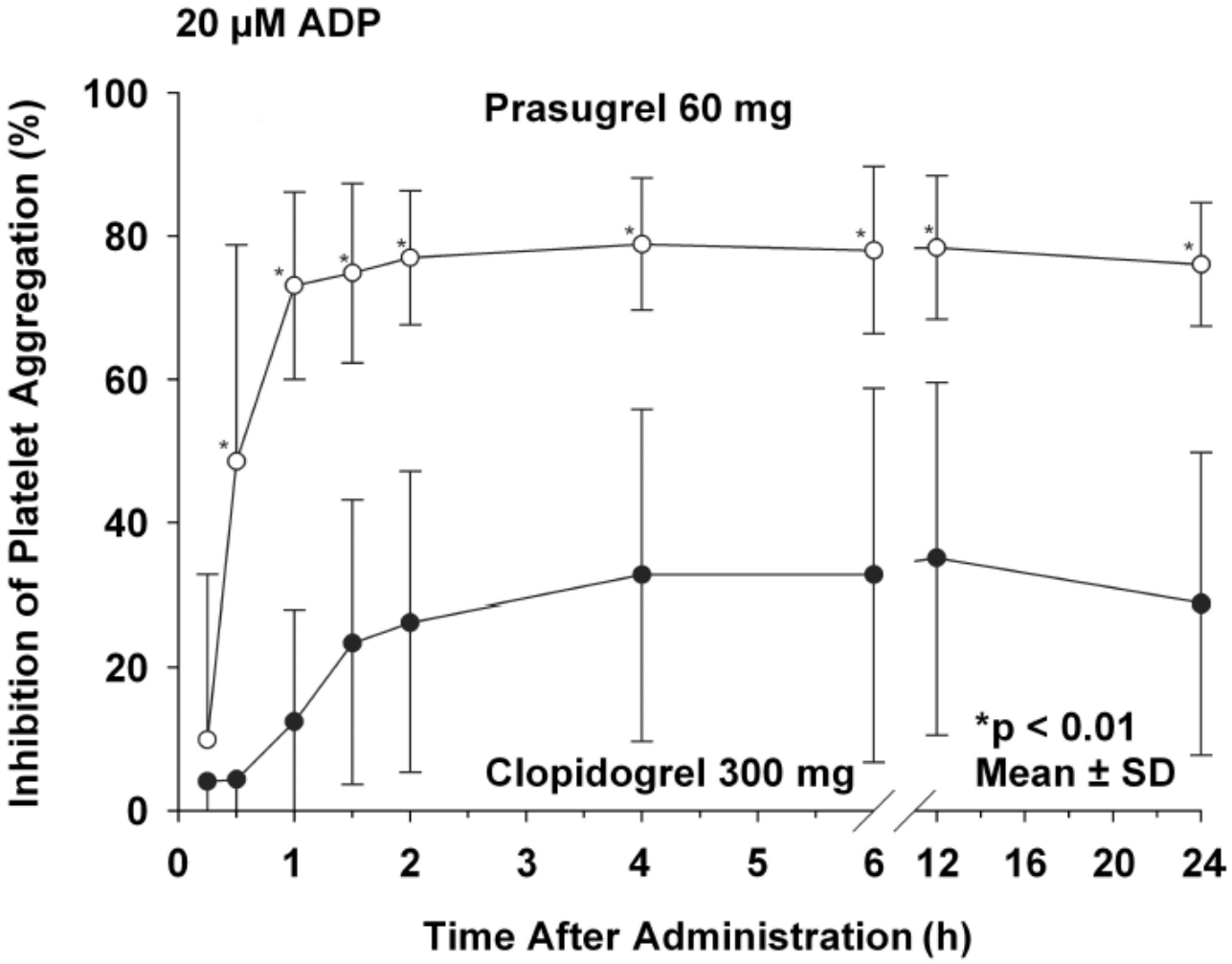
# Prasugrel vs. Clopidogrel

- 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*

# Inhibition of Platelet Aggregation

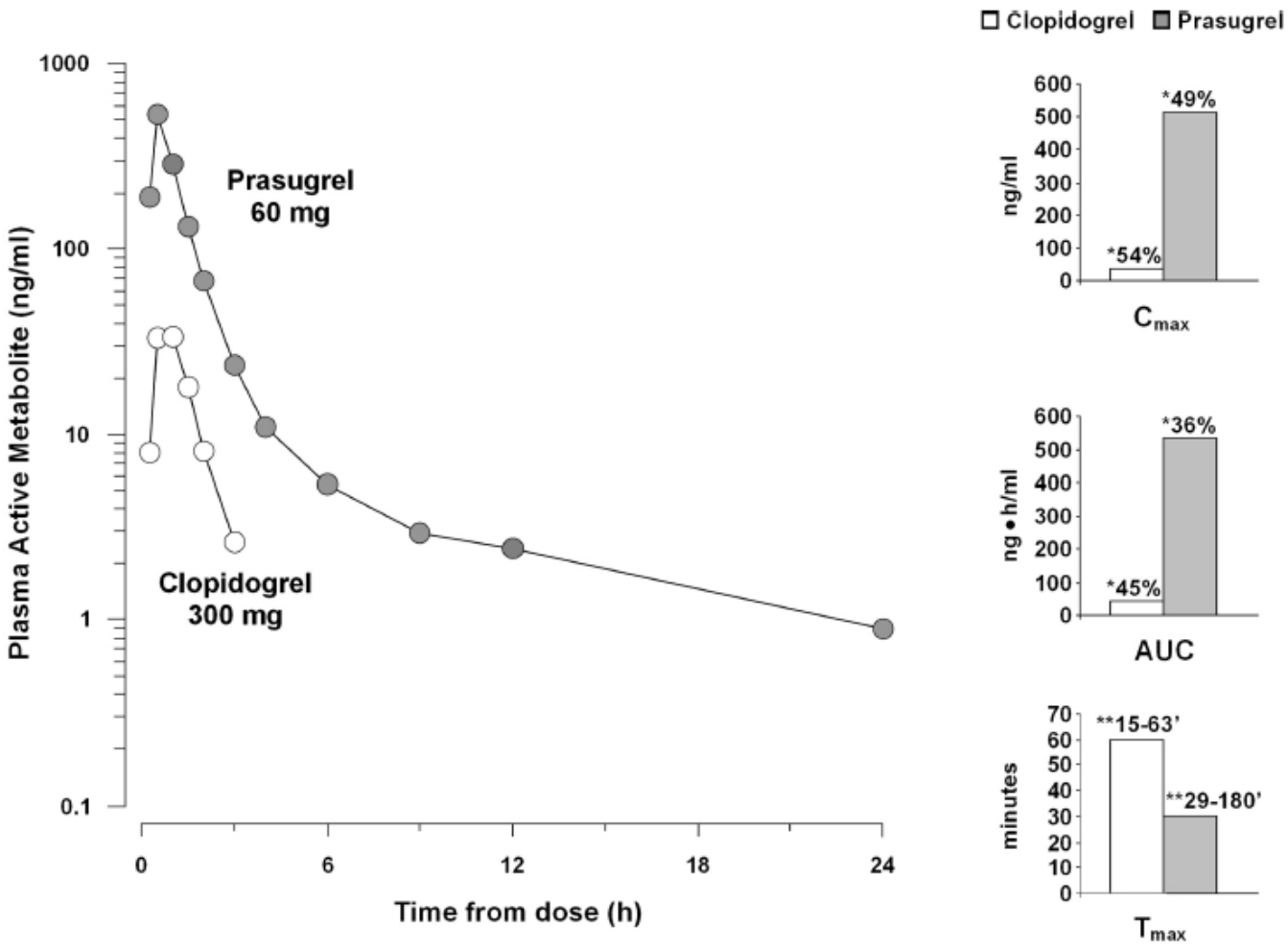



Subject flow diagram.




Brandt JT, el al. Am Heart J. 2007 Jan;153(1):66.e9-16.

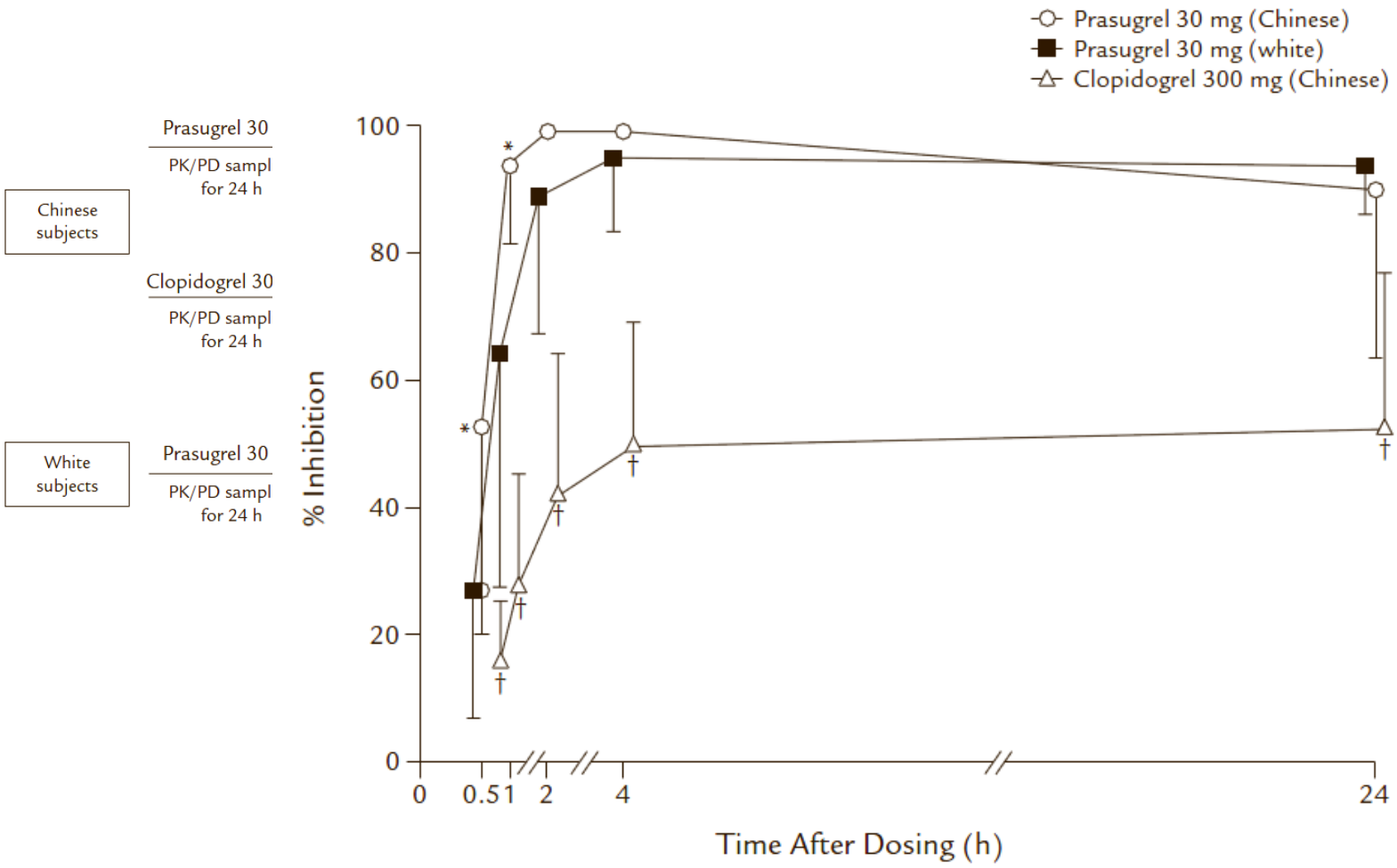
# Plasma Active Metabolite Concentration




Brandt JT, el al. Am Heart J. 2007 Jan;153(1):66.e9-16.

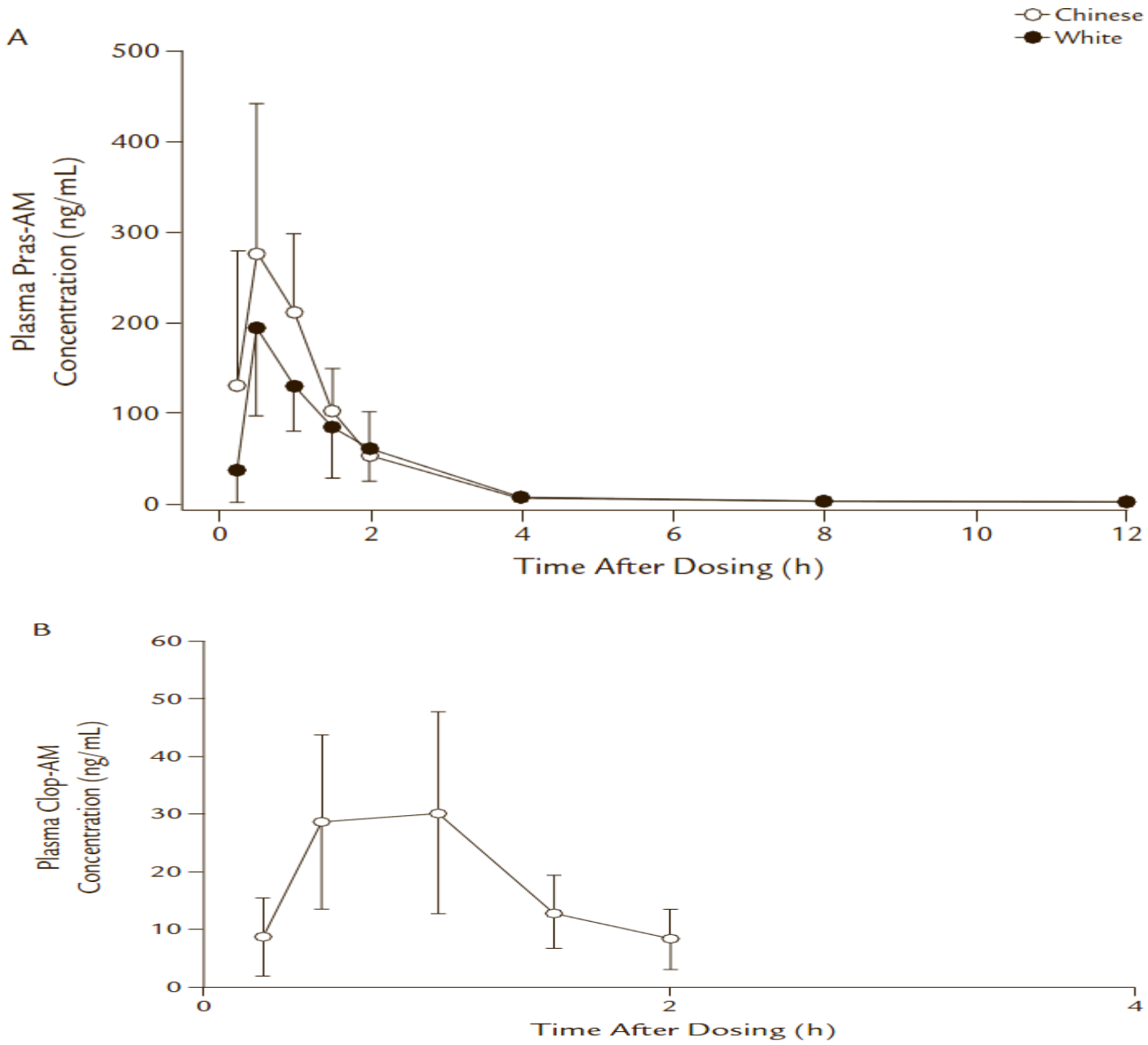
- Prasugrel 60 mg LD results in more rapid, potent, and consistent inhibition of platelet function than clopidogrel 300 mg LD.
- Lower IPA responses to clopidogrel were associated with lower concentrations of its active metabolite.

*Brandt JT, el al. Am Heart J. 2007 Jan;153(1):66.e9-16.*




LTA, VASP, VerifyNow platelet function test
HPLC-MS/MS-**Pharmacokinetic Assessments**
Samples- 0.25,0.5, 1, 1.5, 2, 4, 8, 12, and 24 hours

*Small DS, et al. Clin Ther. 2010 Feb;32(2):365-79.*




Small DS, et al. Clin Ther. 2010 Feb;32(2):365-79.

Table I. Estimated pharmacokinetic parameters for the active metabolites of prasugrel (Pras-AM) and clopidogrel (Clop-AM) after single doses of 30 and 300 mg, respectively, in Chinese and white subjects. Values are geometric mean (%CV), unless otherwise specified.

| | Pras-AM | | | |
|---|---|---|---|---|
| Parameter Estimate | Chinese Subjects (n = 16) | White Subjects (n = 14) | Geometric Least Squares Mean Ratio, Chinese/White (90% CI) | Clop-AM, Chinese Subjects (n = 17) |
| Actual | | | | |
| $AUC_{0-t}$, ng · h/mL | 361 (26) | 246 (29) | 1.47 (1.24–1.73) | 33.6 (61) |
| $C_{max}$, ng/mL | 320 (39) | 192 (40) | 1.67 (1.32–2.11) | 30.7 (56) |
| $T_{max}$, median (range), h | 0.50 (0.25–1.10) | 0.50 (0.50–2.00) | – | 1.00 (0.50–2.00) |
| Weight normalized* | | | | |
| $AUC_{0-t}$, ng · h/mL | 324 (19) | 279 (19) | 1.16 (1.02–1.33) | NA |
| $C_{max}$, ng/mL | 294 (39) | 211 (35) | 1.39 (1.08–1.80) | NA |

NA = not applicable.

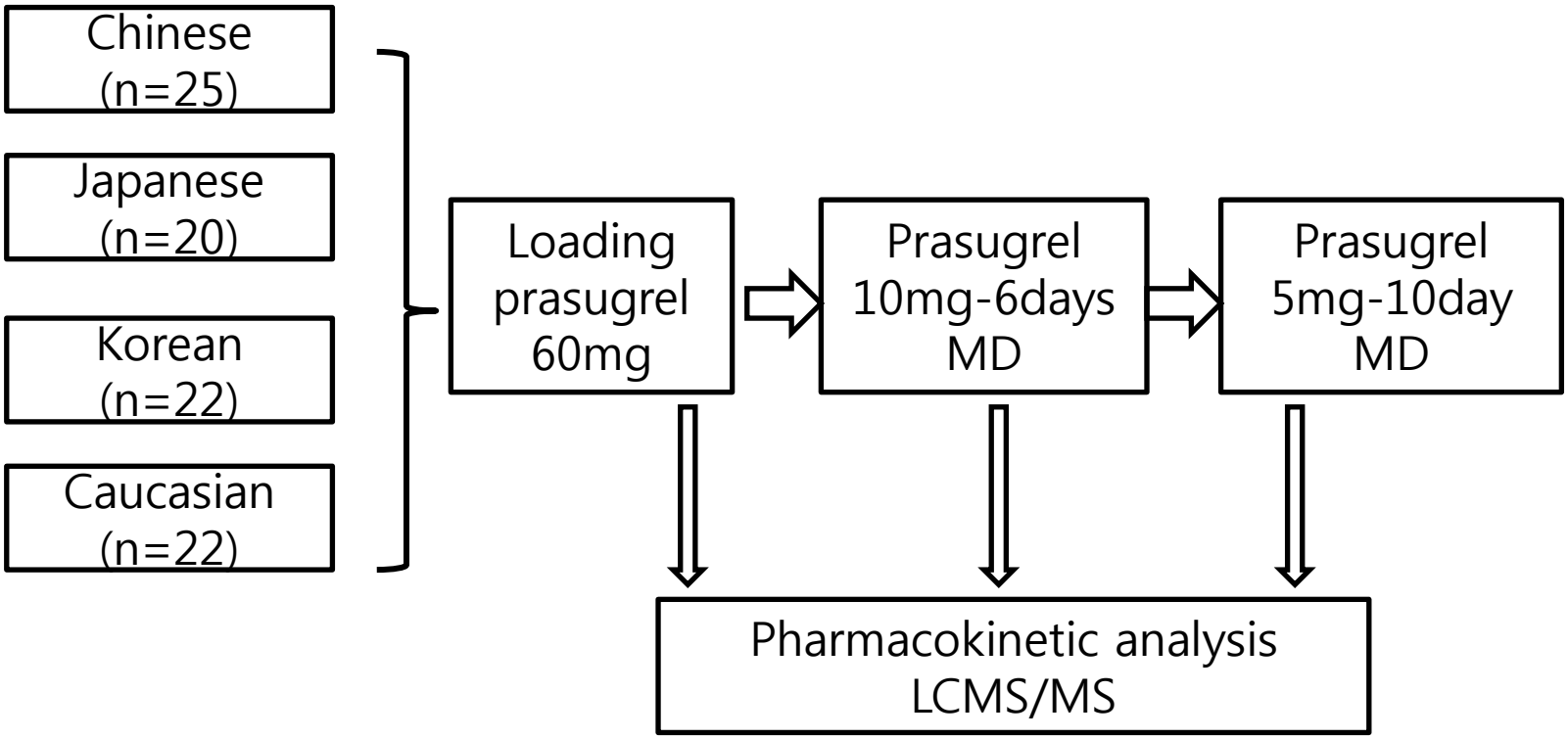
*Weight-normalized estimates were calculated using a linear mixed-effect model with weight as a covariate.

Small DS, et al. Clin Ther. 2010 Feb;32(2):365-79.

- The prasugrel 30-mg dose produced greater platelet inhibition and higher concentrations of Pras-AM in Chinese subjects than in white subjects.
- In Chinese subjects, prasugrel 30 mg produced greater platelet inhibition and higher Pras-AM concentrations than did clopidogrel 300 mg.
- The pharmacodynamic results were consistent across LTA, the VN-P2Y12 assay, and the VASP phosphorylation assay.

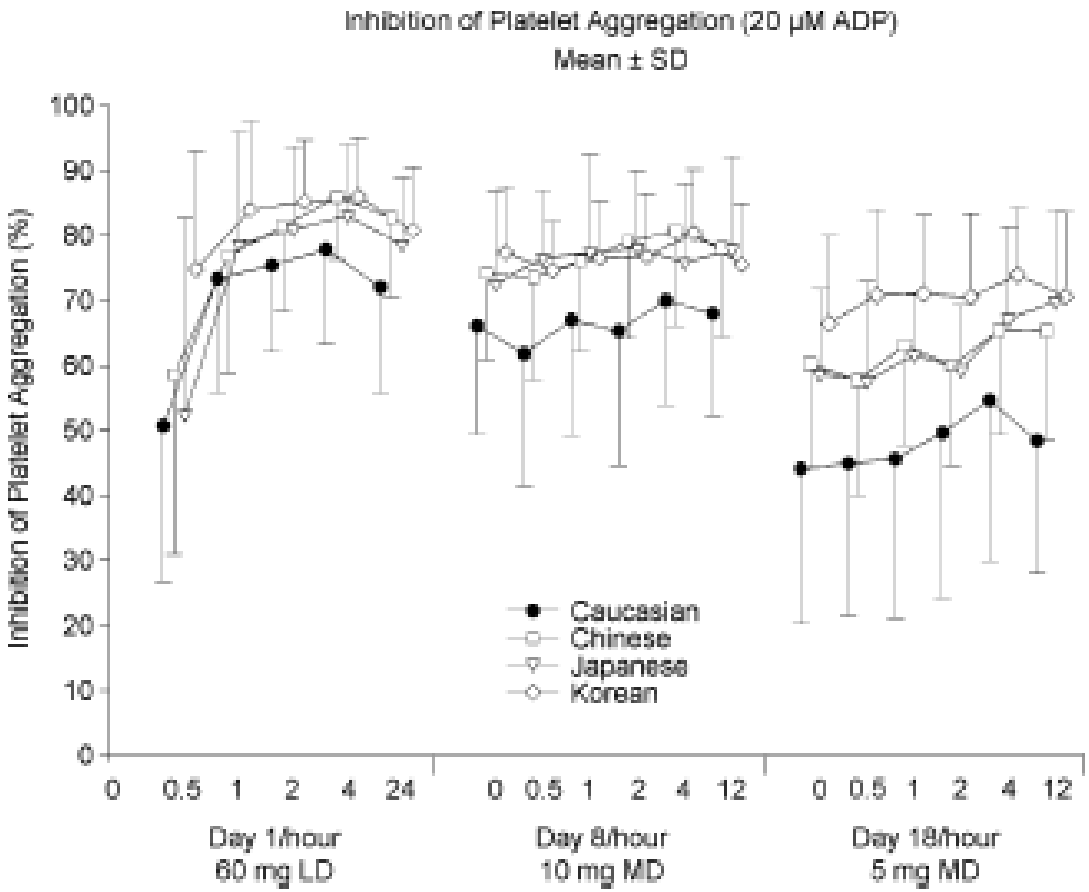
*Small DS, et al. Clin Ther. 2010 Feb;32(2):365-79.*

# The pharmacokinetics and pharmacodynamics of prasugrel in healthy Chinese, Japanese, and Korean subjects compared with healthy Caucasian subjects




*Small DS, et al. Eur J Clin Pharmacol 2010*

# Inhibition of Platelet Aggregation using 20 μM ADP following a Prasugrel 60-mg LD and 10mg / 5mg MD

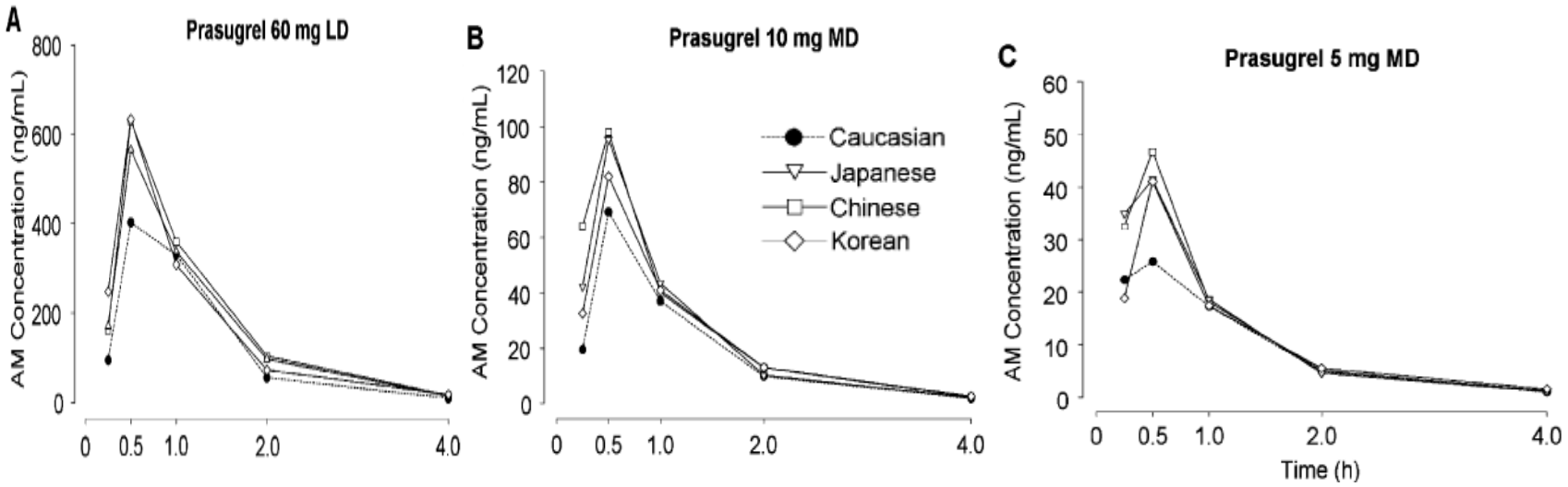



**IPA**
**66% in Caucacian**
**vs. 75% in Asian**

*Small DS, et al. Eur J Clin Pharmacol 2010*

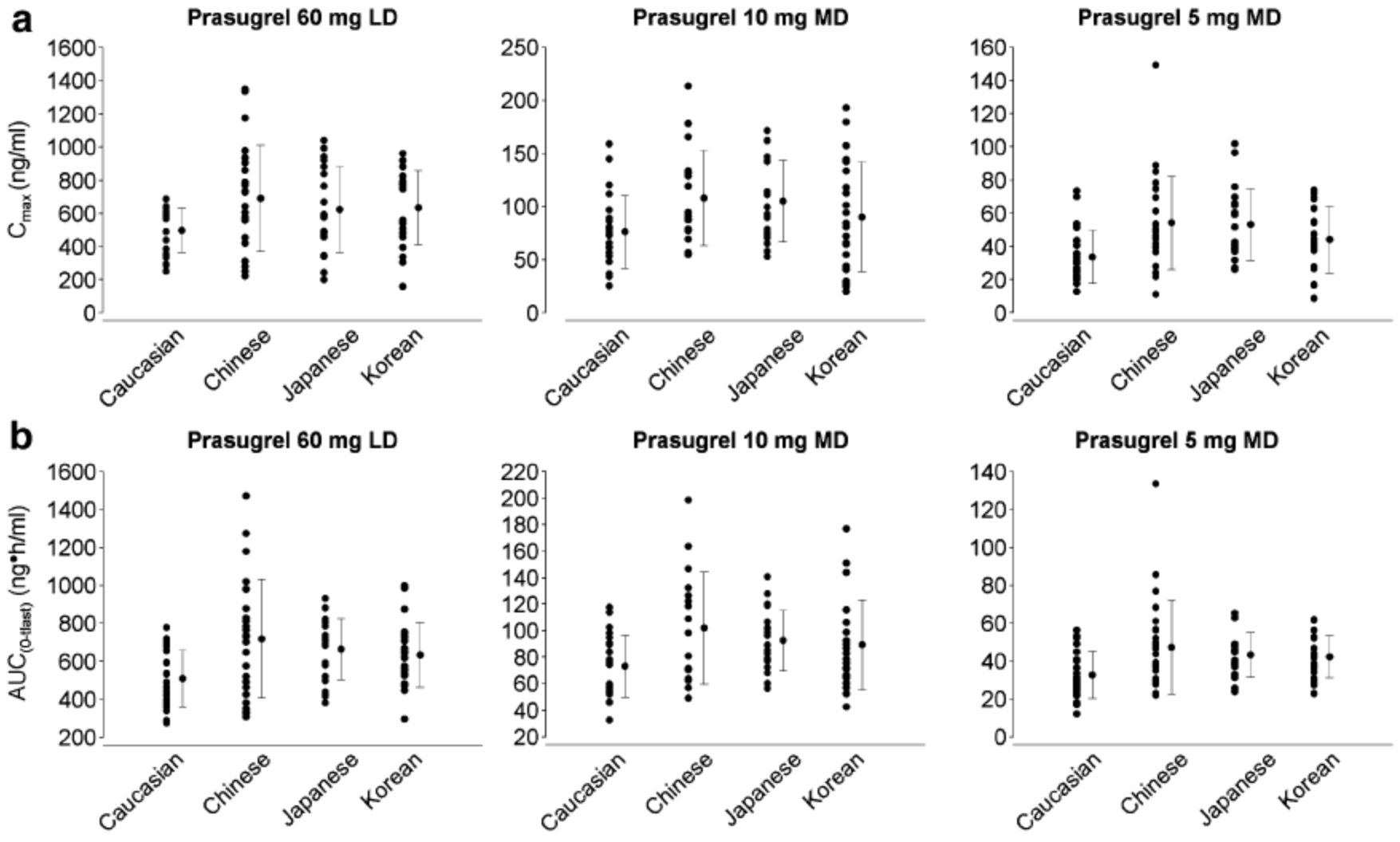
**Table 1** Demographics for Caucasian, Chinese, Japanese and Korean subjects

| Ethnicity | Subjects (*n*) | Male (*n*) | Female (*n*) | Age (years) (mean ± SD) | Body weight (kg) (mean ± SD) | Time in the UK (months) (median) |
|---|---|---|---|---|---|---|
| Caucasian | 22 | 12 | 10 | 28±10 | 66.5±11.5 | |
| Chinese | 25 | 20 | 5 | 31±8 | 67.5±13.3 | 9.11 |
| Japanese | 20 | 16 | 4 | 25±4 | 60.8±9.1 | 7.05 |
| Korean | 22 | 12 | 10 | 26±3 | 63.2±9.0 | 7.27 |




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

*Small DS, et al. Eur J Clin Pharmacol 2010*

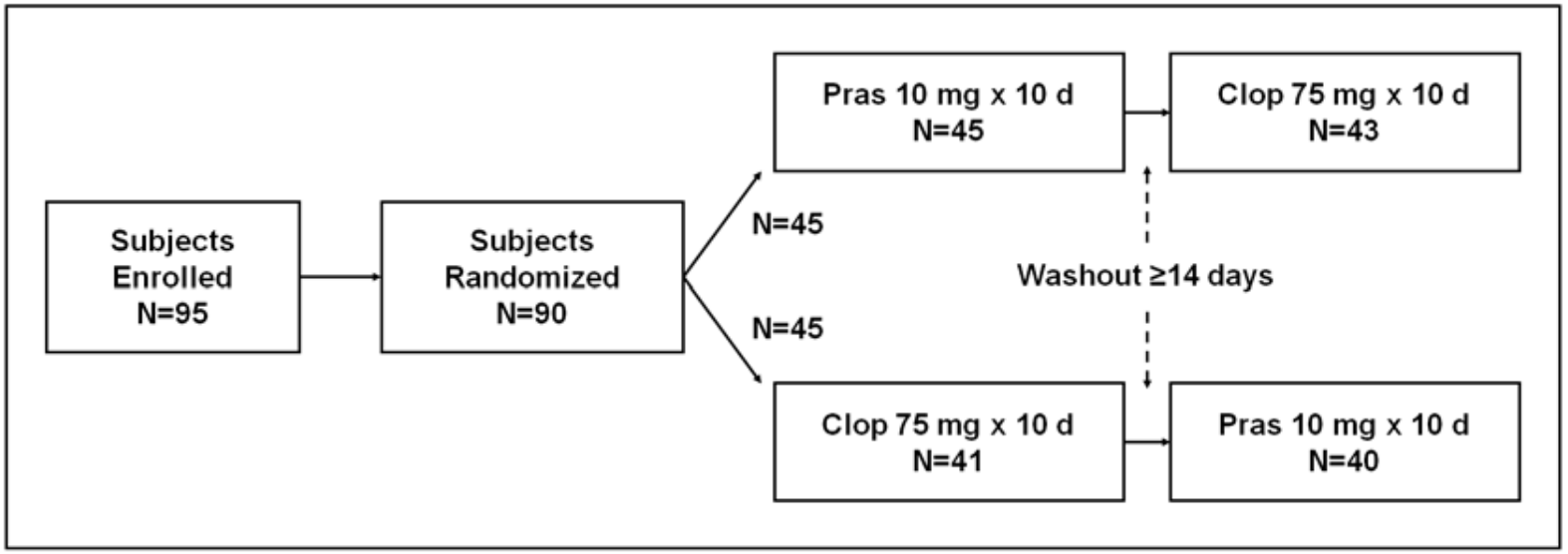



*Small DS, et al. Eur J Clin Pharmacol 2010*

- Mean exposure to the prasugrel active metabolite following prasugrel 60-mg LD and during daily 10-mg or 5-mg MD was higher in each of the Asian groups than in the Caucasian group, which resulted in greater platelet inhibition.

# Pharmacokinetics and Pharmacodynamics Following Maintenance Doses of Prasugrel and Clopidogrel in Chinese Carriers of CYP2C19 Variants

# Study Design (Chinese)




**DEMOGRAPHIC CHARACTERISTICS**
N=90 randomised subjects; 51 men, 39 women

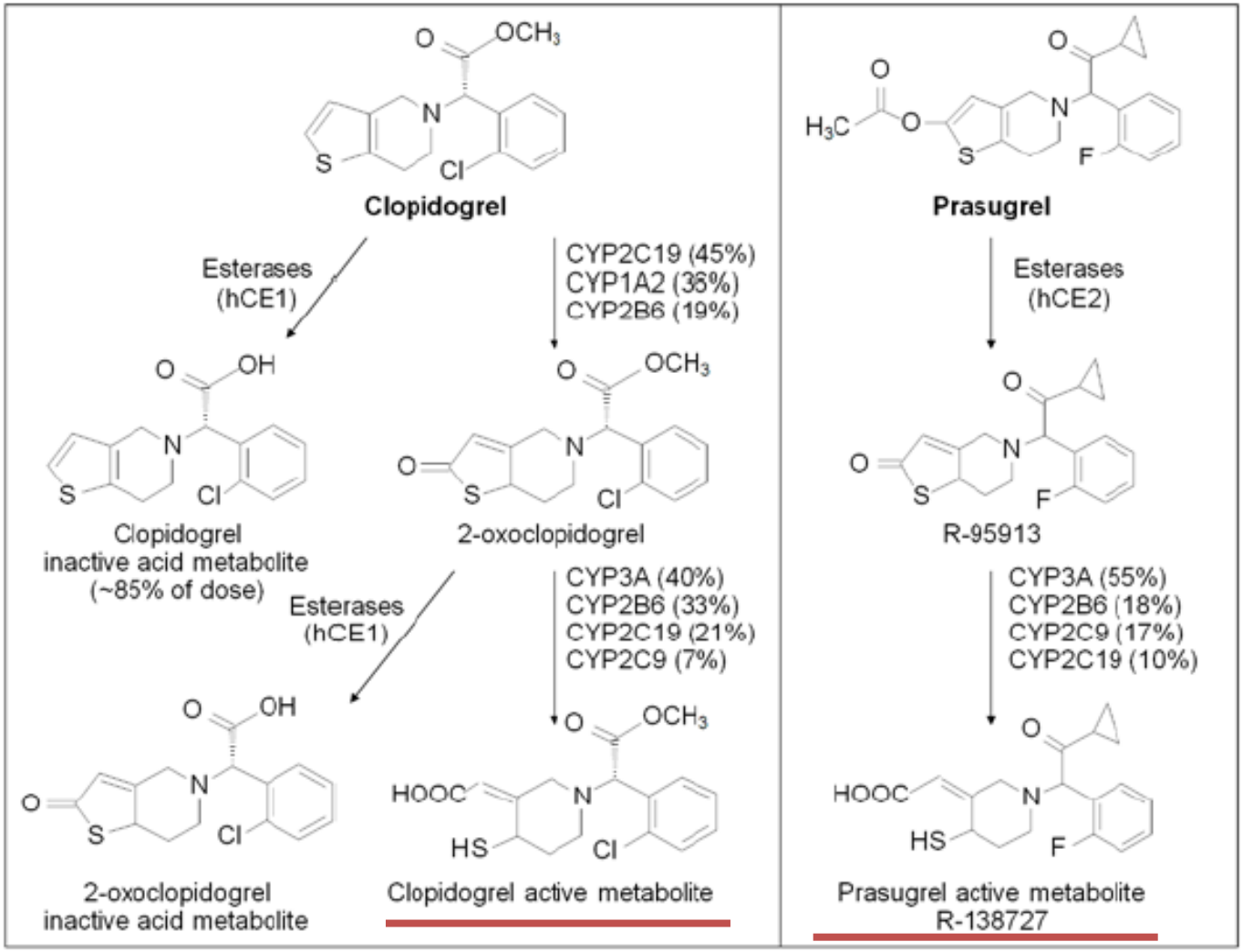
| | Age (years) | Body Weight (kg) | BMI ($kg/m^2$) |
|---|---|---|---|
| Mean (SD) | 34 (11.2) | 63.0 (9.7) | 22.6 (2.4) |
| Range | 21-60 | 43.4-101 | 21.8-29.6 |

**GENETIC RESULTS**

| CYP2C19 predicted phenotype | RM | IM | PM |
|---|---|---|---|
| CYP2C19-predicted phenotype | *1/*1 | *1/*2 | *2/*2 |
| CYP2C19 genotype | | *1/*3 | *2/*3 |
| Number of completing subjects (N=83) | 34 (41%) | 38 (46%) | 11 (13%) |

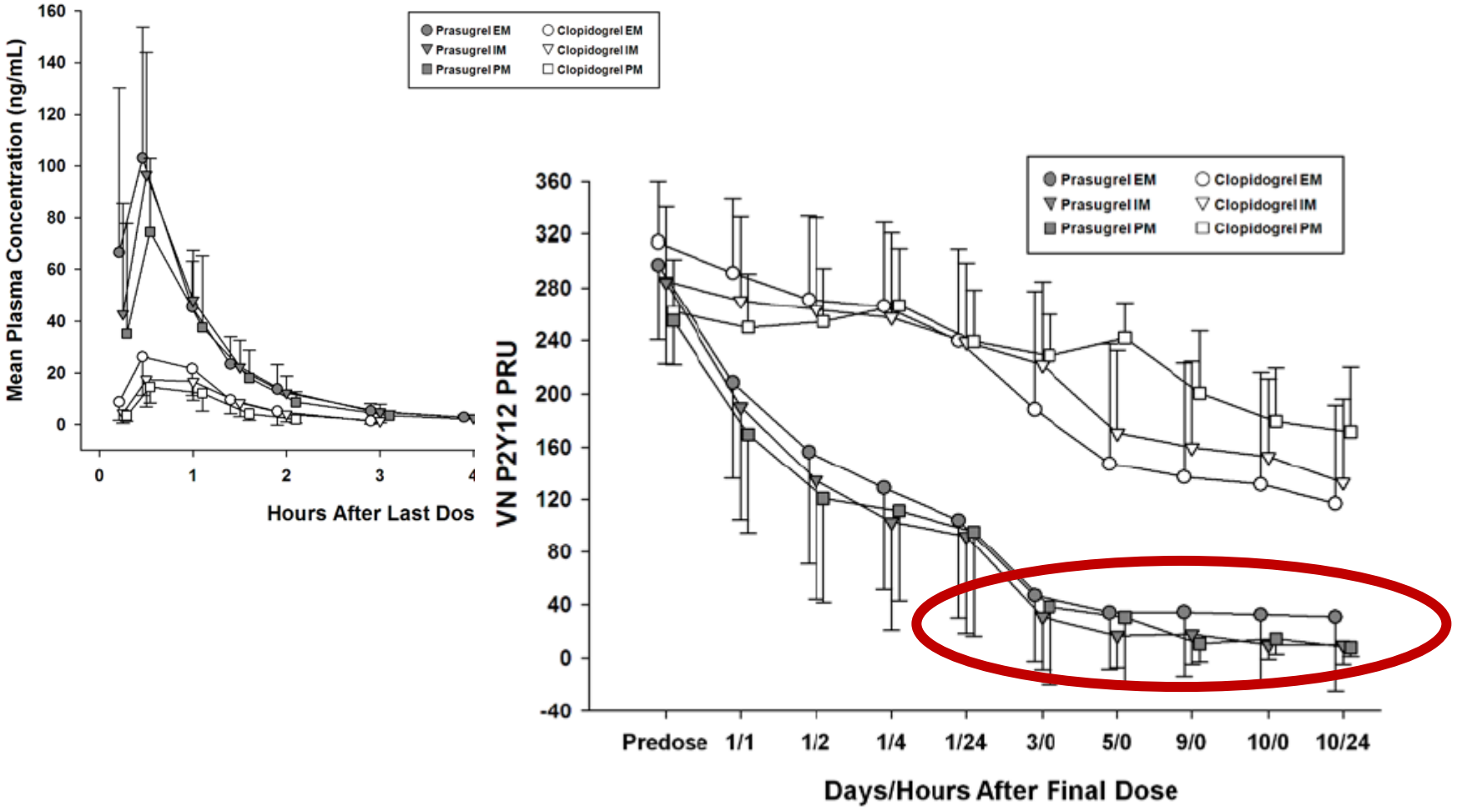
*Kelly RP et al. British J Clinical Pharmacology 2011*

# Metabolic Pathway of the Clopidogrel and Prasugrel



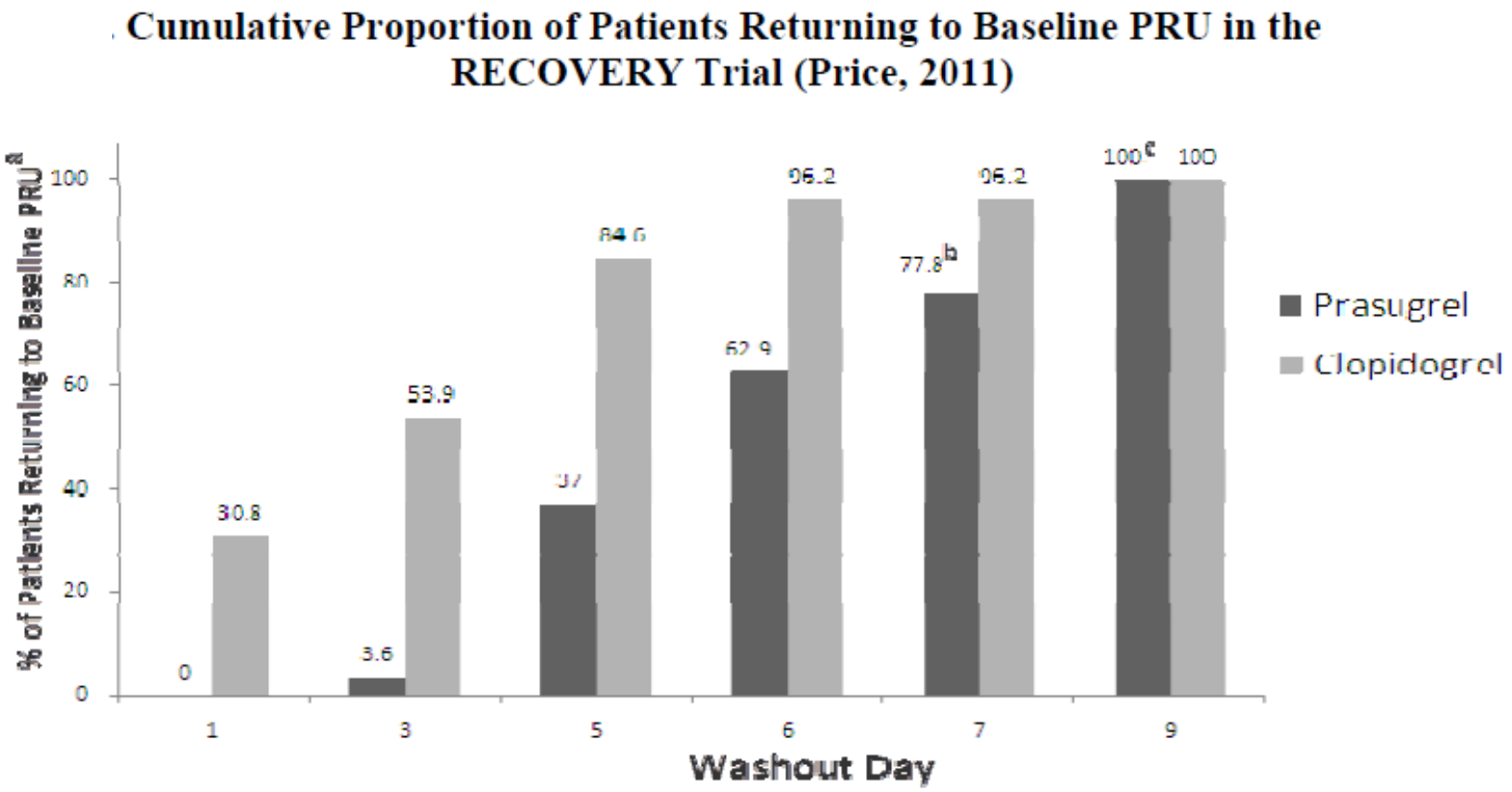

*Kelly RP et al. British J Clinical Pharmacology 2011*

# PK & PD Study of Clopidogrel & Prasugrel : Phamacogenomic relationship




*Kelly RP et al. British J Clinical Pharmacology 2011*

# Offset of the Clopidogrel and Prasugrel

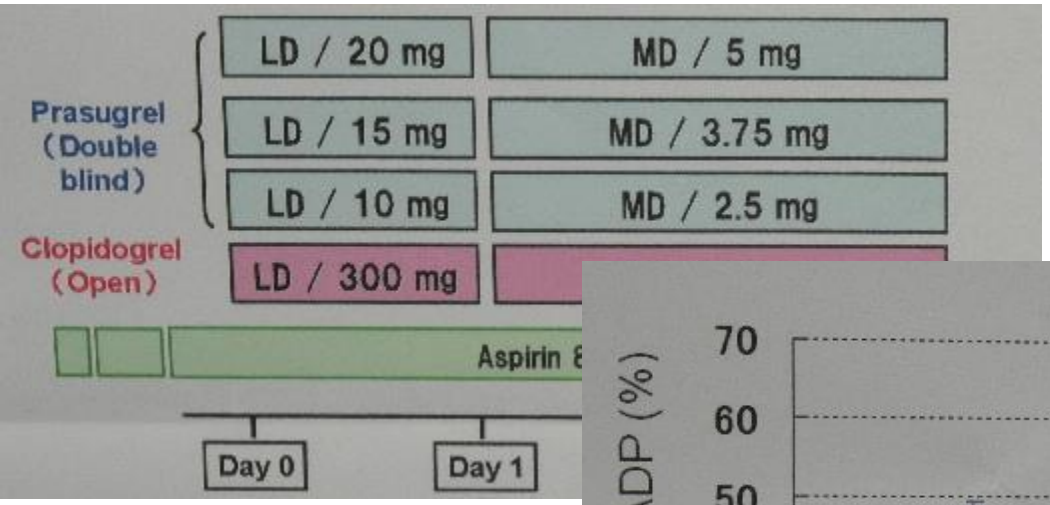


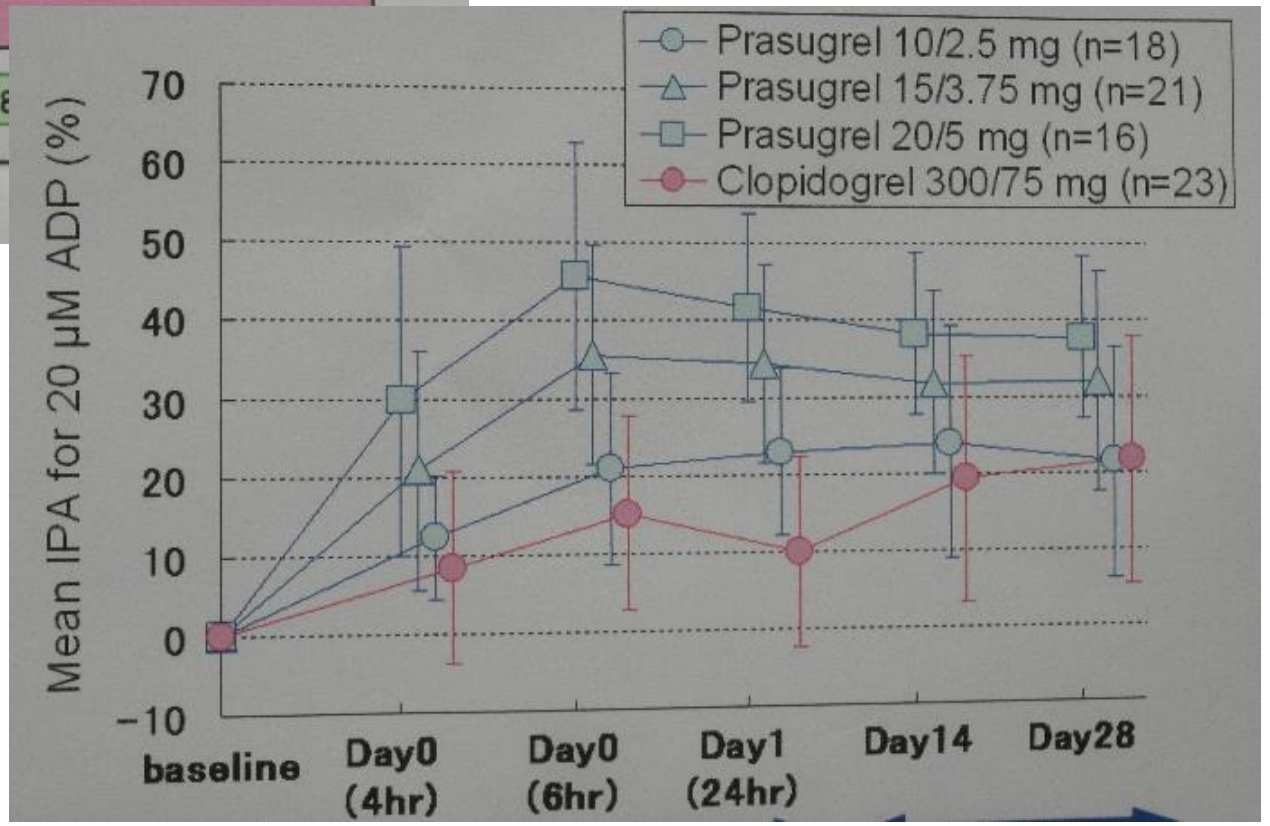
# Body Weight and Age

- Body weight <60 kg: 30-40% higher exposure to AM of prasugrel
- >Age 75: 19% higher exposure of AM
- Asian: 20-30% higher than Caucacian

# Japanese Data (Lower Dose)

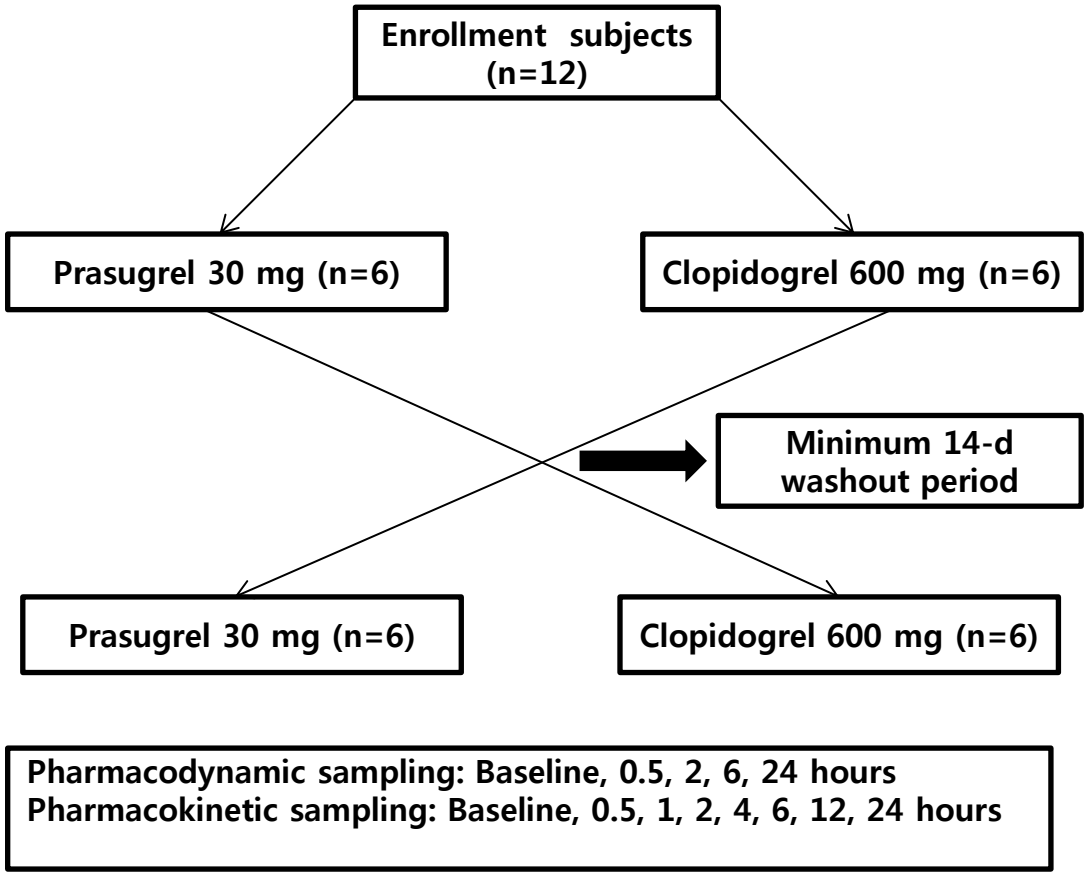
# PD Effect of Low Dose Prasugrel



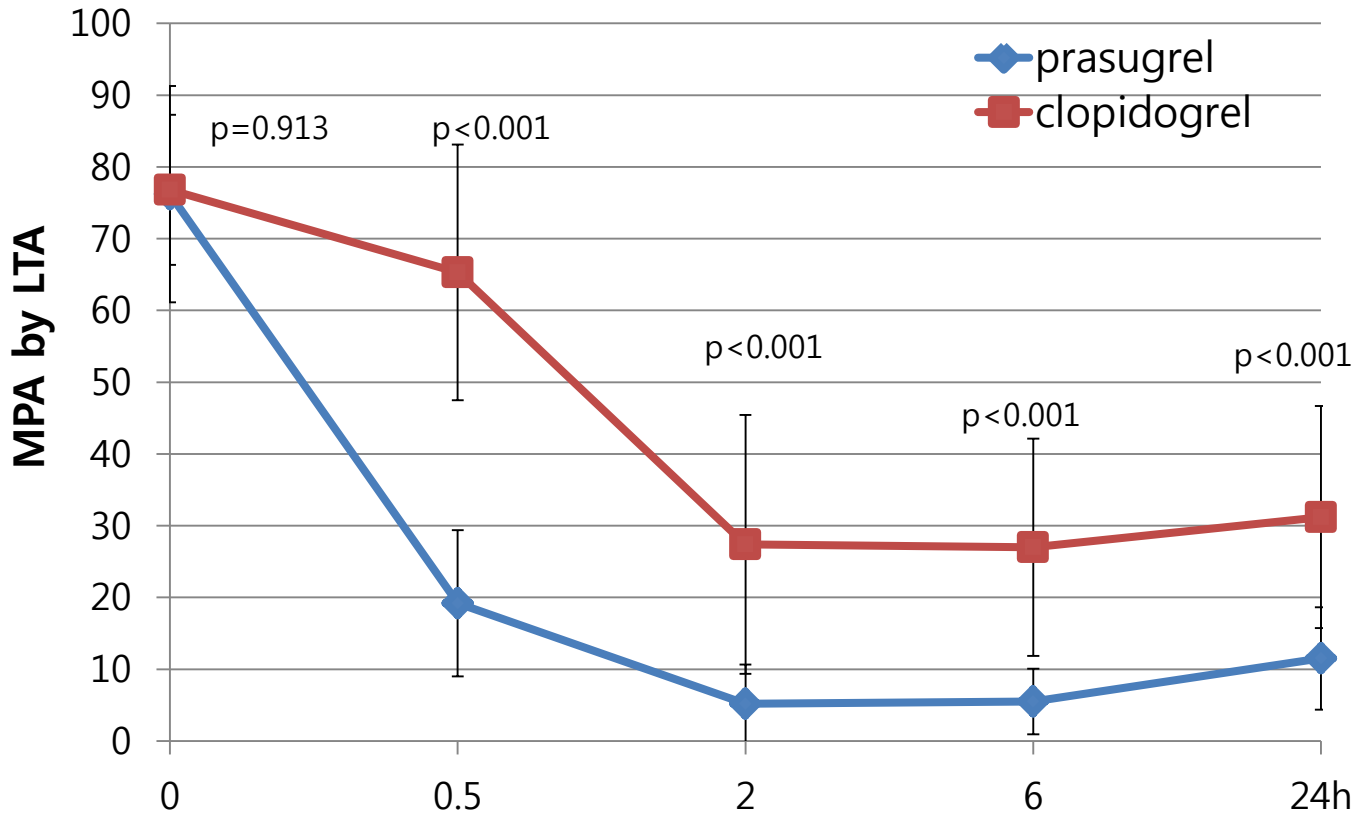




*ISTH2011*

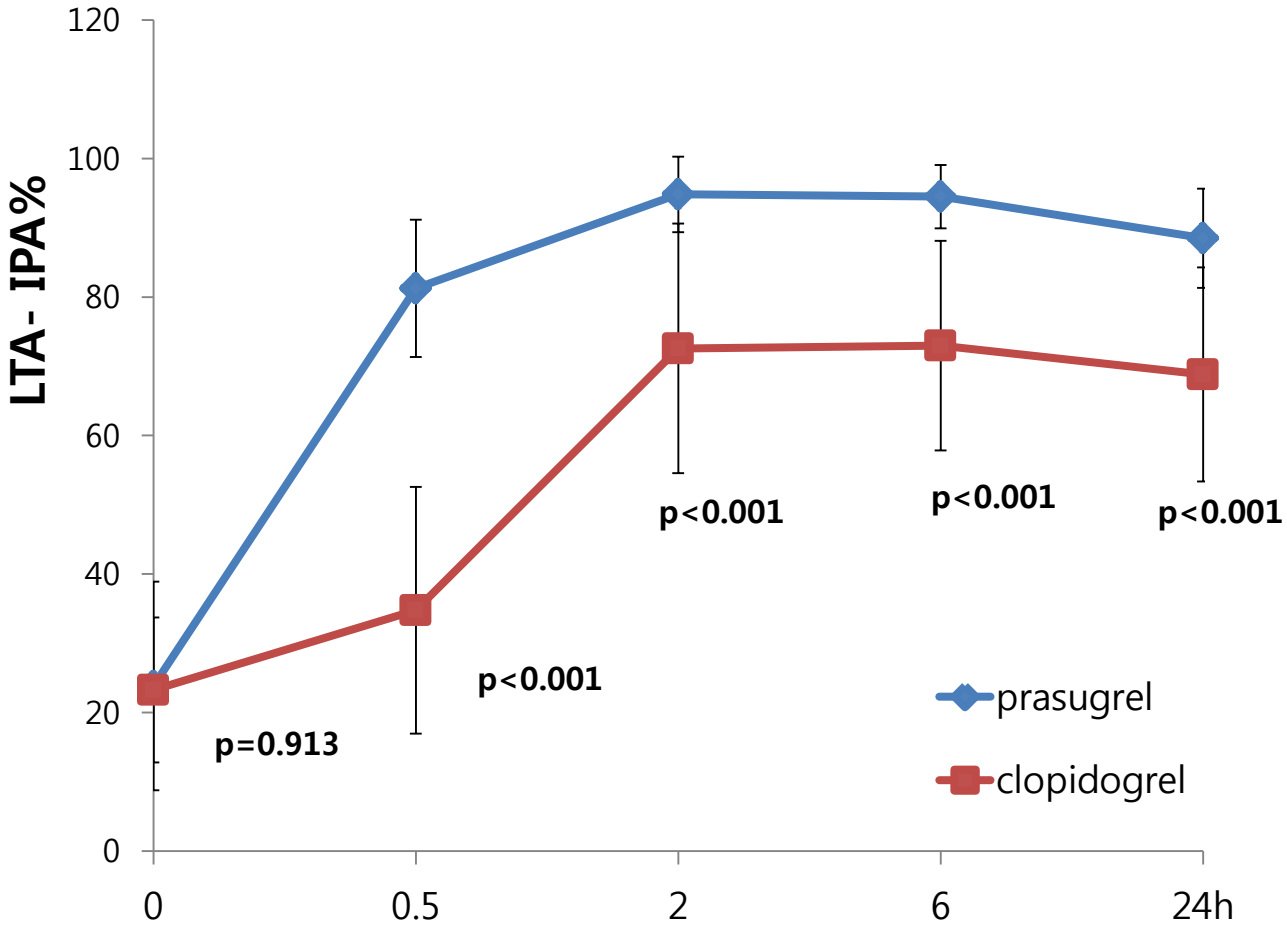
# Clopidogrel & Prasugrel
# : Loading Effect in Healthy Volunteer



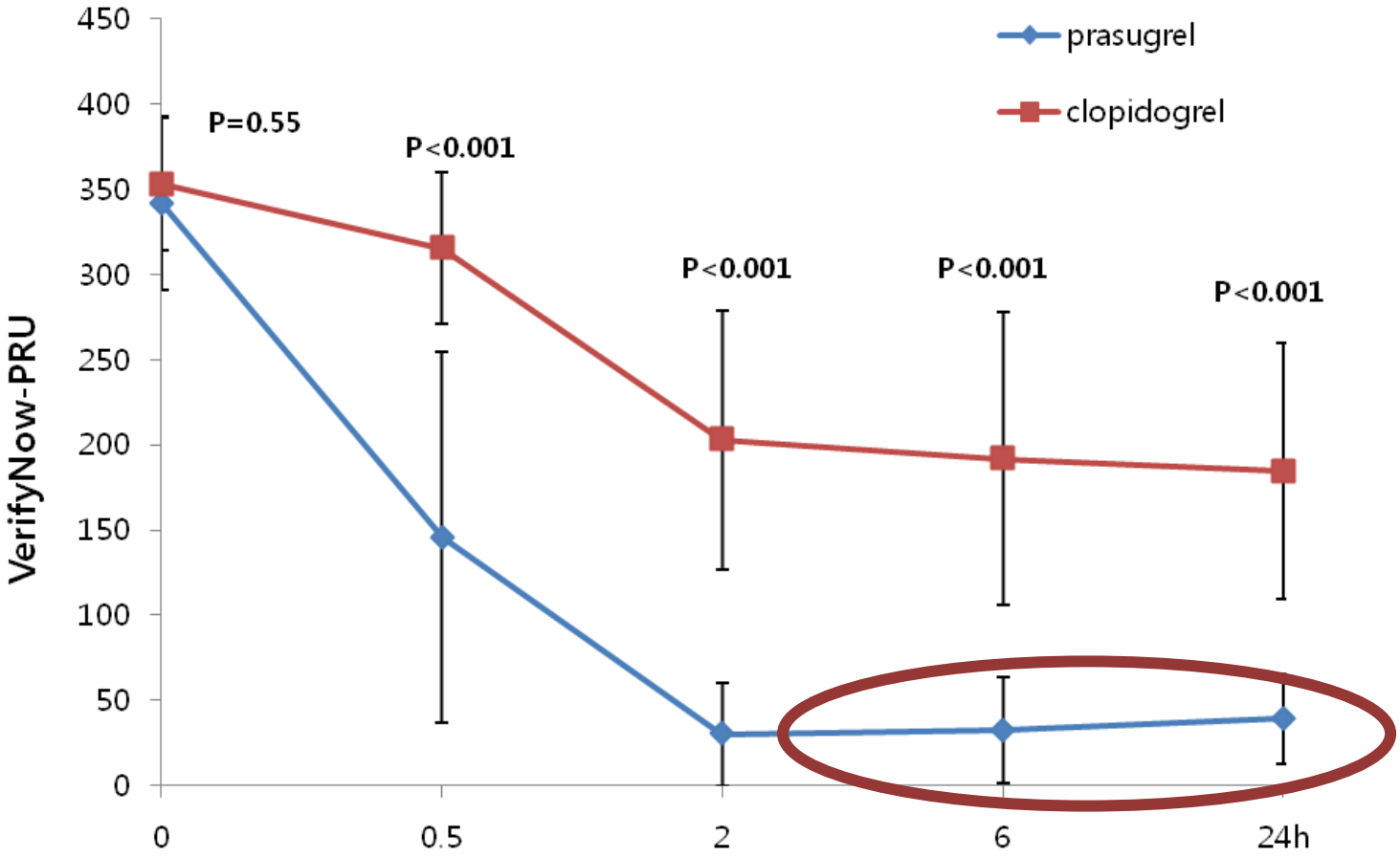
# PD of Clopidogrel & Prasugrel Single LD
## : Light Transmission Aggregometry: 10 μM ADP



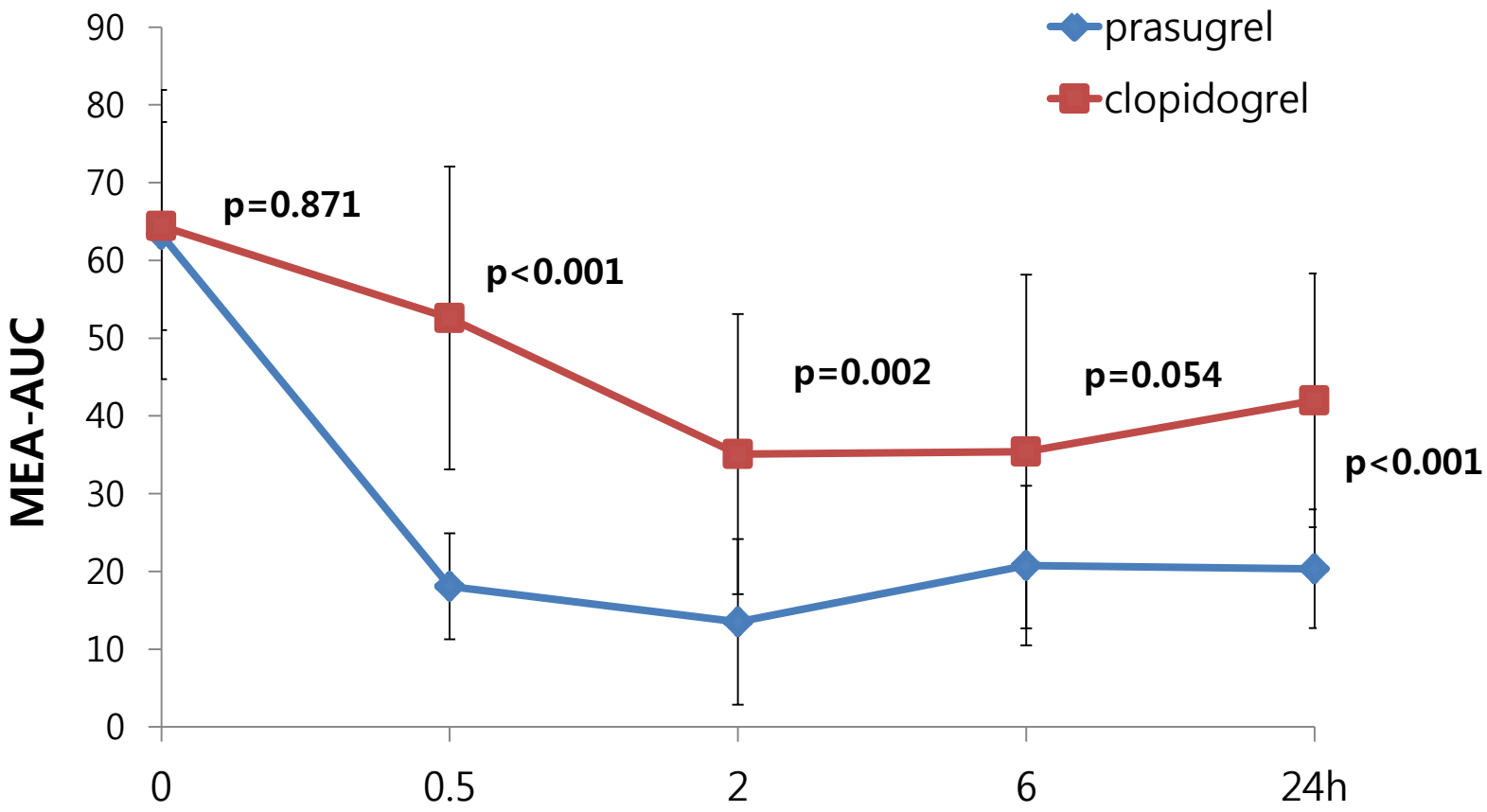
# PD of Clopidogrel & Prasugrel Single LD
## Light Transmission Aggregometry - IPA%



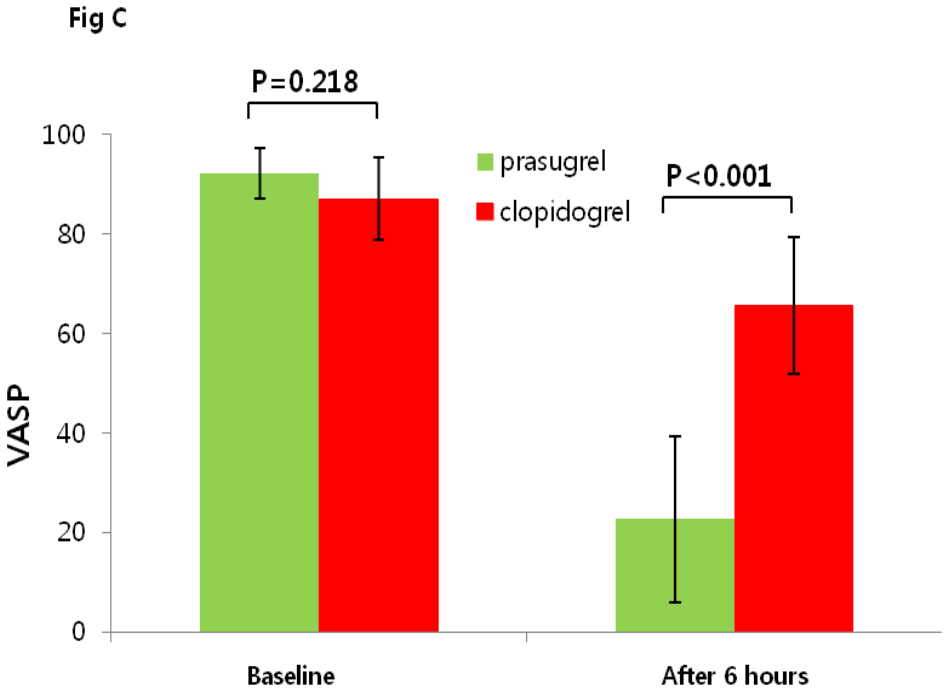
# PD of Clopidogrel & Prasugrel Single LD
## : VeryfyNow (PRU)

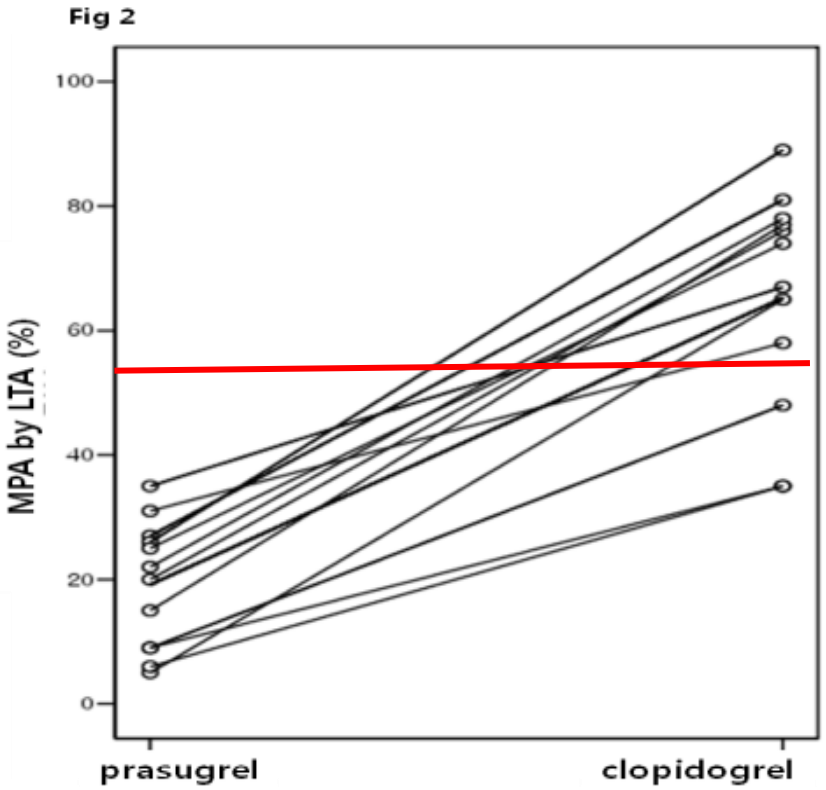


# PD of Clopidogrel & Prasugrel Single LD : MEA (AUC)



# PD of Clopidogrel & Prasugrel LD



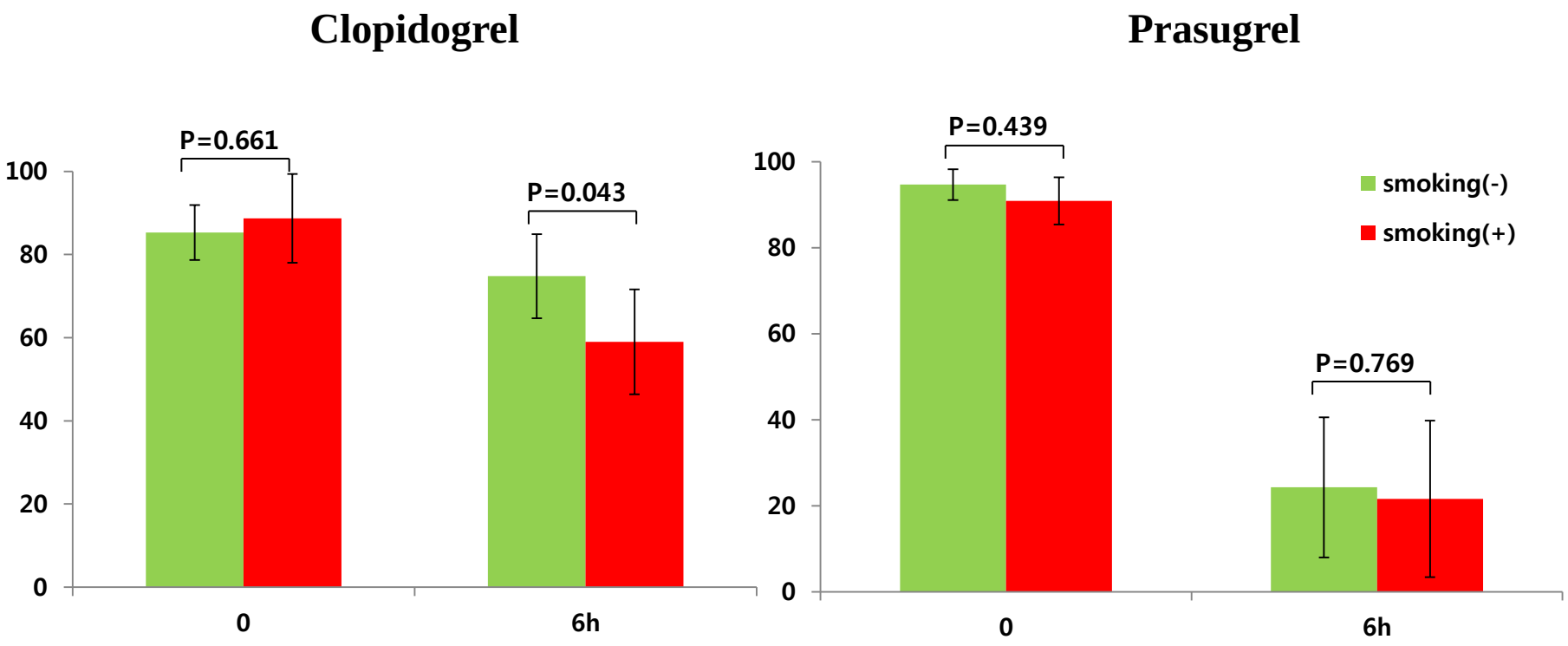




Loading dose after
0.5h

# Summary of PD with Prasugrel & Clopidogrel

| | Prasugrel | Clopidogrel | p-value |
|---|---|---|---|
| MPA, 2 hr (%) | 14 ± 11 | 35 ± 18 | 0.002 |
| MPA, 24 hr (%) | 20 ± 8 | 42 ± 16 | 0.001 |
| IPA, 2 hr (%) | 94 ± 6 | 66 ± 21 | 0.001 |
| IPA, 24 hr (%) | 86 ± 8 | 60 ± 18 | 0.001 |
| MEA, 2 hr (U) | 18 ± 7 | 53 ± 19 | 0.001 |
| MEA, 24 hr (U) | 20 ± 8 | 42 ±16 | 0.001 |
| VN, 2 hrs (PRU) | 30 ± 30 | 203 ± 76 | < 0.001 |
| VN, 24 hr (PRU) | 39 ± 26 | 185 ± 75 | < 0.001 |
| VASP, Base (PRI) | 92 ± 5 | 87 ± 8 | 0.218 |
| VASP, 6 hr (PRI) | 23 ± 17 | 66 ± 14 | < 0.001 |

# Smoking Effect - VASP



| | | ng/mL | P/C ratio | | | ng/mL |
|---|---|---|---|---|---|---|
| prasugrel | 60mg/LD | 611 | 3.7 | clopidogrel | 600mg/LD | 163 |
| prasugrel | 60mg/LD | 611 | 4.3 | Clopidogrel | 300mg/LD | 142 |
| prasugrel | 30mg/LD | 320 | 2 | Clopidogrel | 600mg/LD | 163 |
| prasugrel | 30mg/LD | 320 | 2.2 | clopidogrel | 300mg/LD | 142 |
| prasugrel | 15mg/LD | ? | 1? | clopidogrel | 600mg/LD | 163 |
| prasugrel | 15mg/LD | ? | 1.1? | clopidogrel | 300mg/LD | 142 |

| Genotype | | | ng/ml | P/C ratio | | | |
|---|---|---|---|---|---|---|---|
| EM | Prasugrel | 10mg/MD | 102.4 | 3 | clopidogrel | 75mg/MD | 27.6 |
| IM | Prasugrel | 10mg/MD | 92.9 | 4.4 | Clopidogrel | 75mg/MD | 19.9 |
| PM | prasugrel | 10mg/MD | 85.9 | 5.6 | clopidogrel | 75mg/MD | 15.1 |
| EM | Prasugrel | 2.5mg/MD | ? | 0.75? | clopidogrel | 75mg/MD | ? |
| IM | Prasugrel | 2.5mg/MD | ? | 1.1? | Clopidogrel | 75mg/MD | ? |
| PM | prasugrel | 2.5mg/MD | ? | 1.4? | clopidogrel | 75mg/MD | ? |

# Summary

- Prasugrel 60 mg LD results in more rapid, potent, and consistent inhibition of platelet function than clopidogrel 300/600 mg LD
- The prasugrel 30/60mg LD dose produced greater platelet inhibition and higher concentrations of Pras-AM in Asian subjects than in white subjects
- Prasugrel 10/2.5mg(LD/MD) is mostly equivalent to clopidogrel 300/75mg (LD/MD) in Asian subjects

*Thank you for your Attendtion*