

Sustained Release Nitrate Agents ; A Determinant of Clopidogrel Lower Responsiveness in Patients with Dual Antiplatelet Maintenance therapy.

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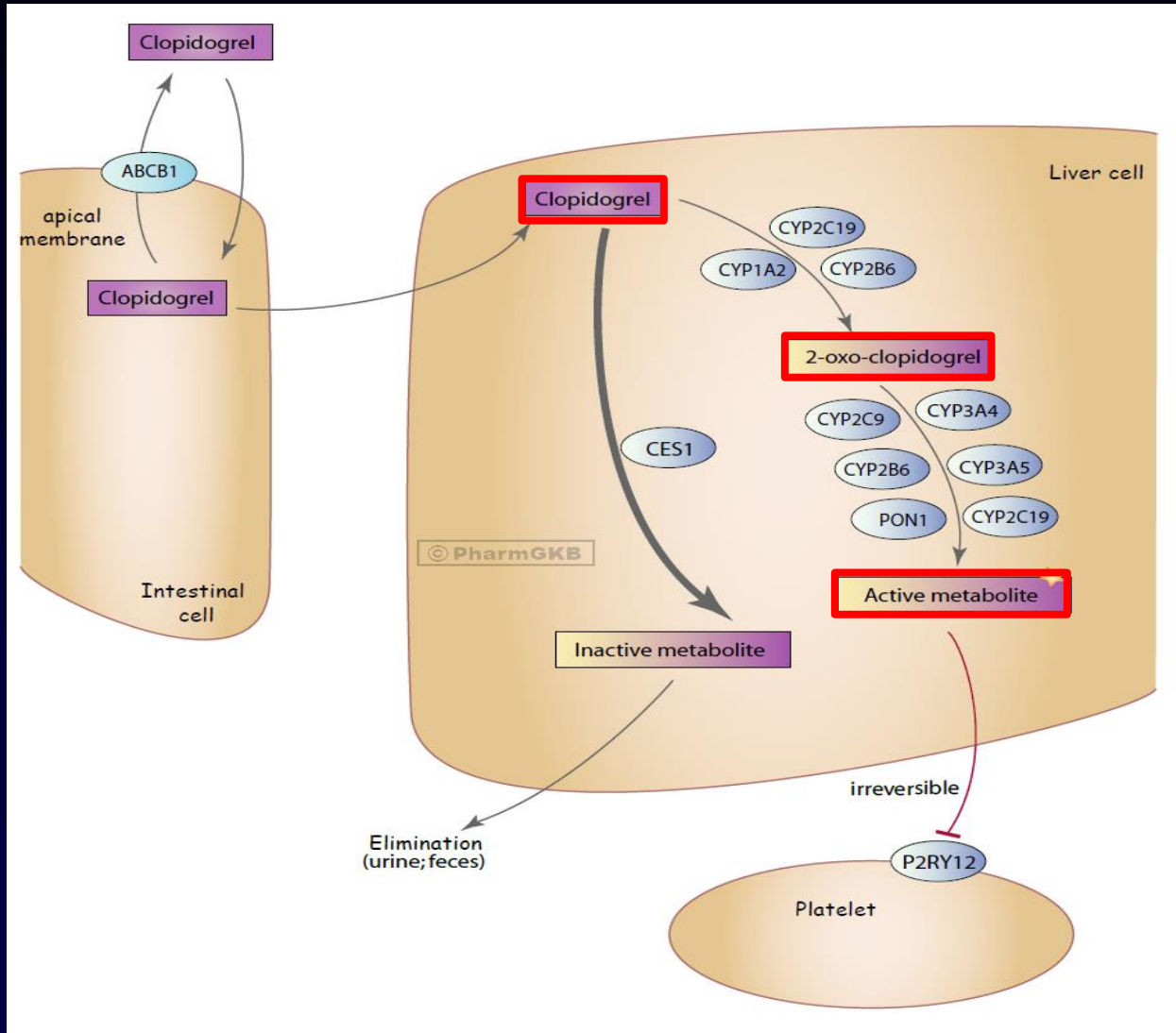
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Background

- Clopidogrel



Clopidogrel Metabolism



CYP2C19

CYP3A4

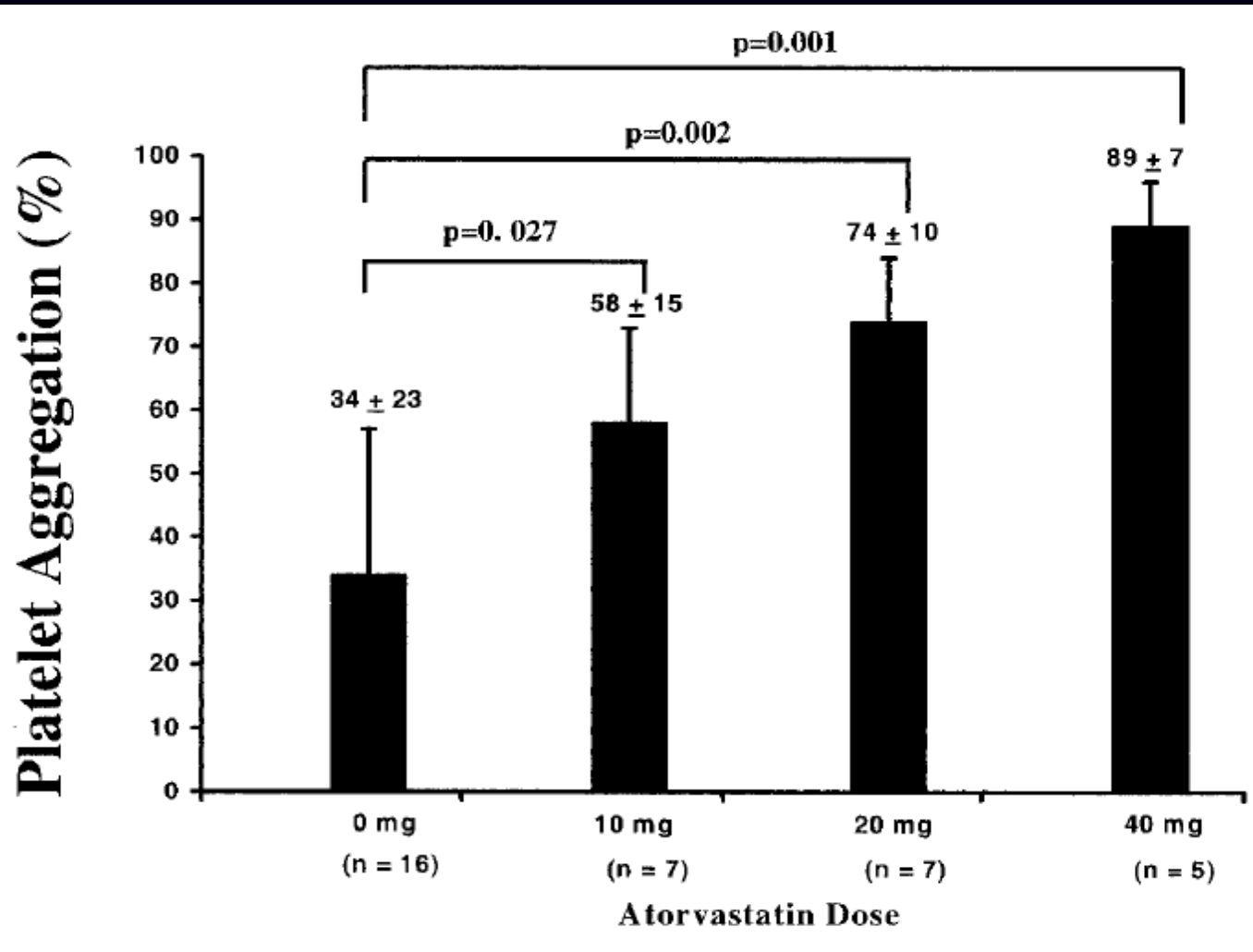
A Number of Drugs for IHD patients

- Aspirin
- Clopidogrel
- Beta blocker
- ACEi / ARB
- Diuretics
- Nitrates
- Cilostazol
- Nicorandil
- Digoxin
- PPIs / H2 blocker

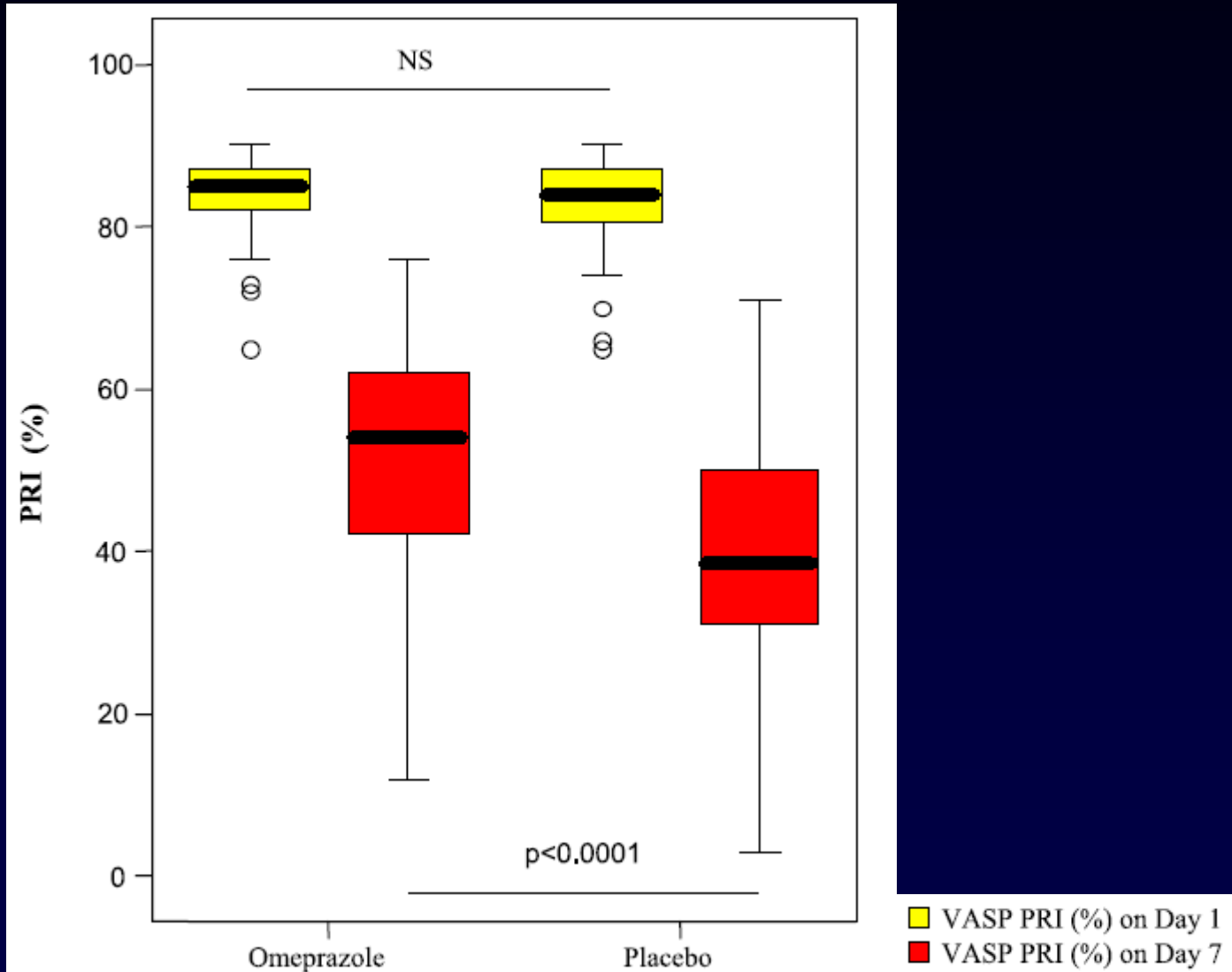
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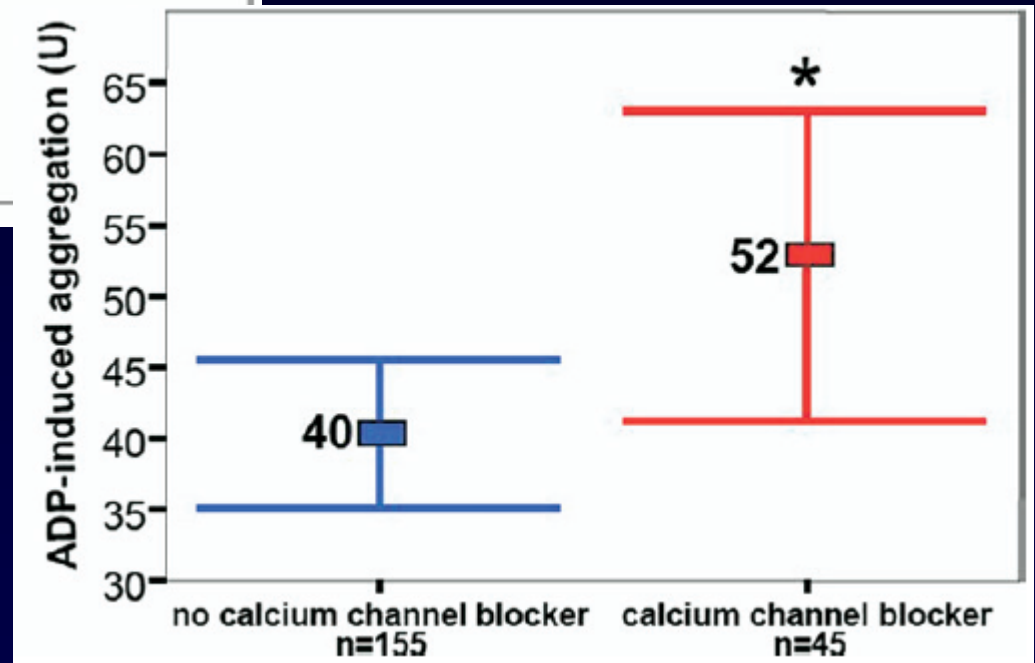
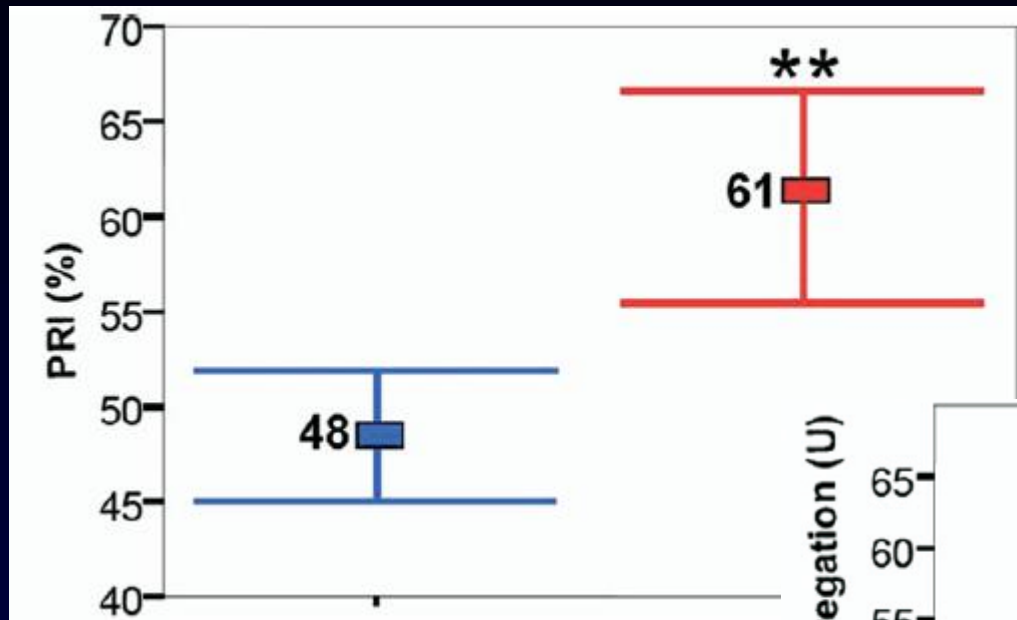
Clopidogrel with Atorvastatin



Clopidogrel with Omeprazole

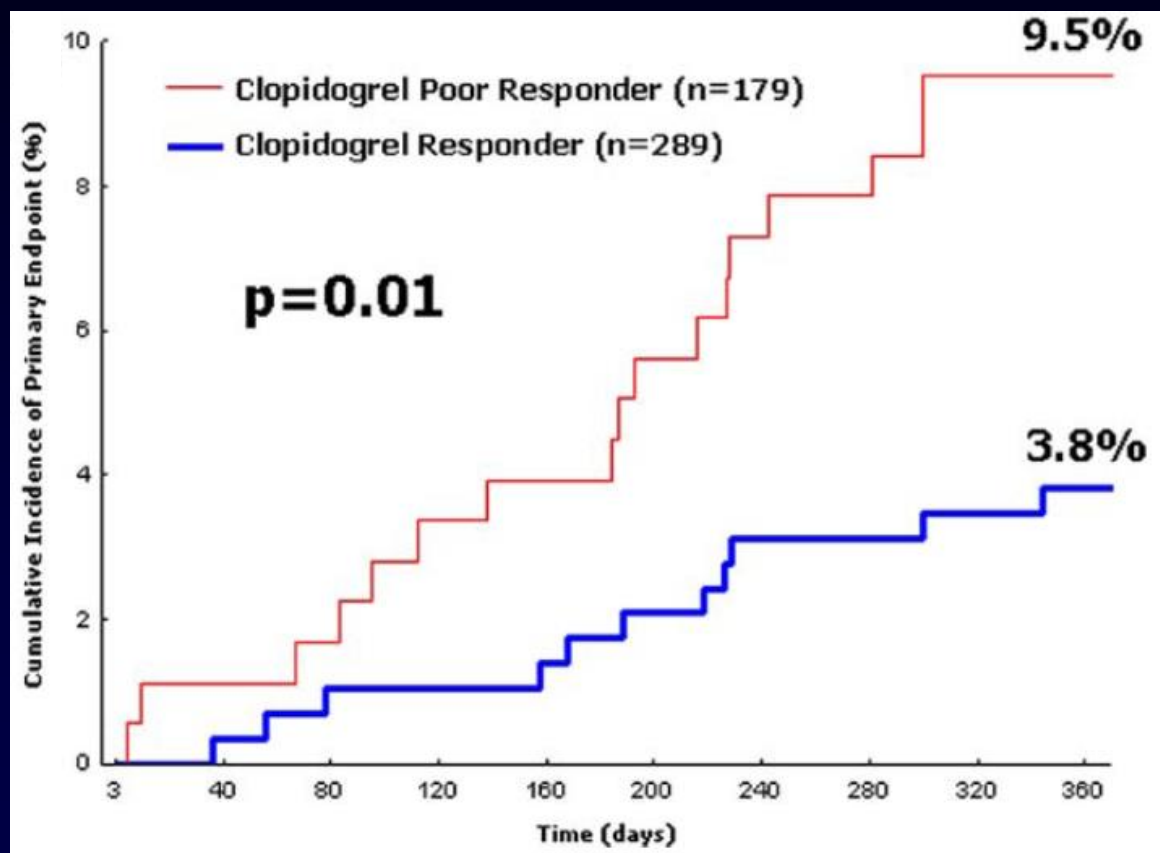


Clopidogrel with CCBs



Drug-Drug Interaction with Clopidogrel

- Clopidogrel **lower responsiveness**

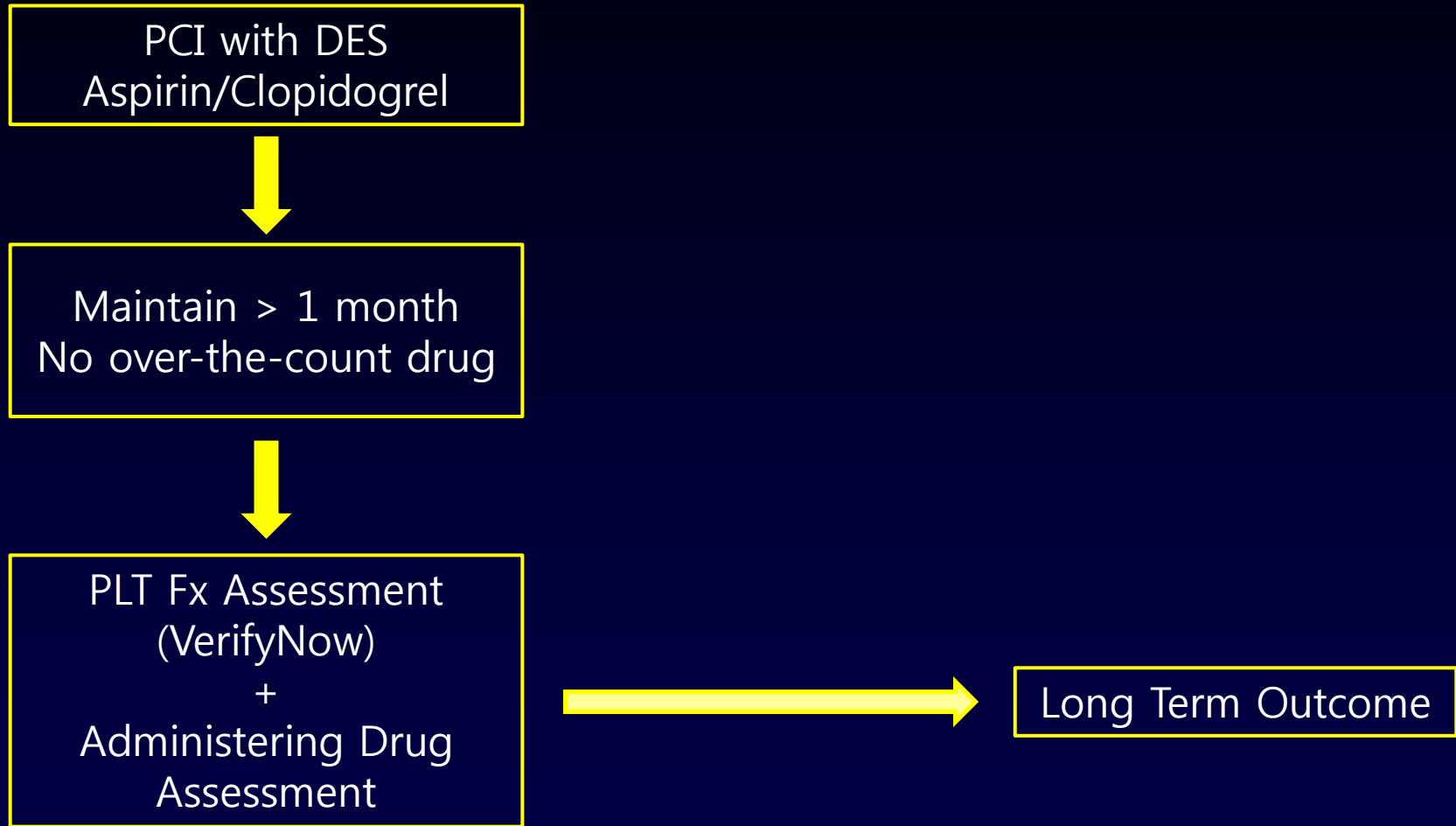


Adverse Cardiovascular Outcome

METHODS

- **Prospective observational Cohort study**
 - Drug-Drug Interaction with Clopidogrel
“In Real World”
- Eligibility
 - Previous history of **PCI with DES** within 1 year
 - Aspirin & Clopidogrel **maintain**
> 1 month
 - Normal renal / hepatic function

METHODS

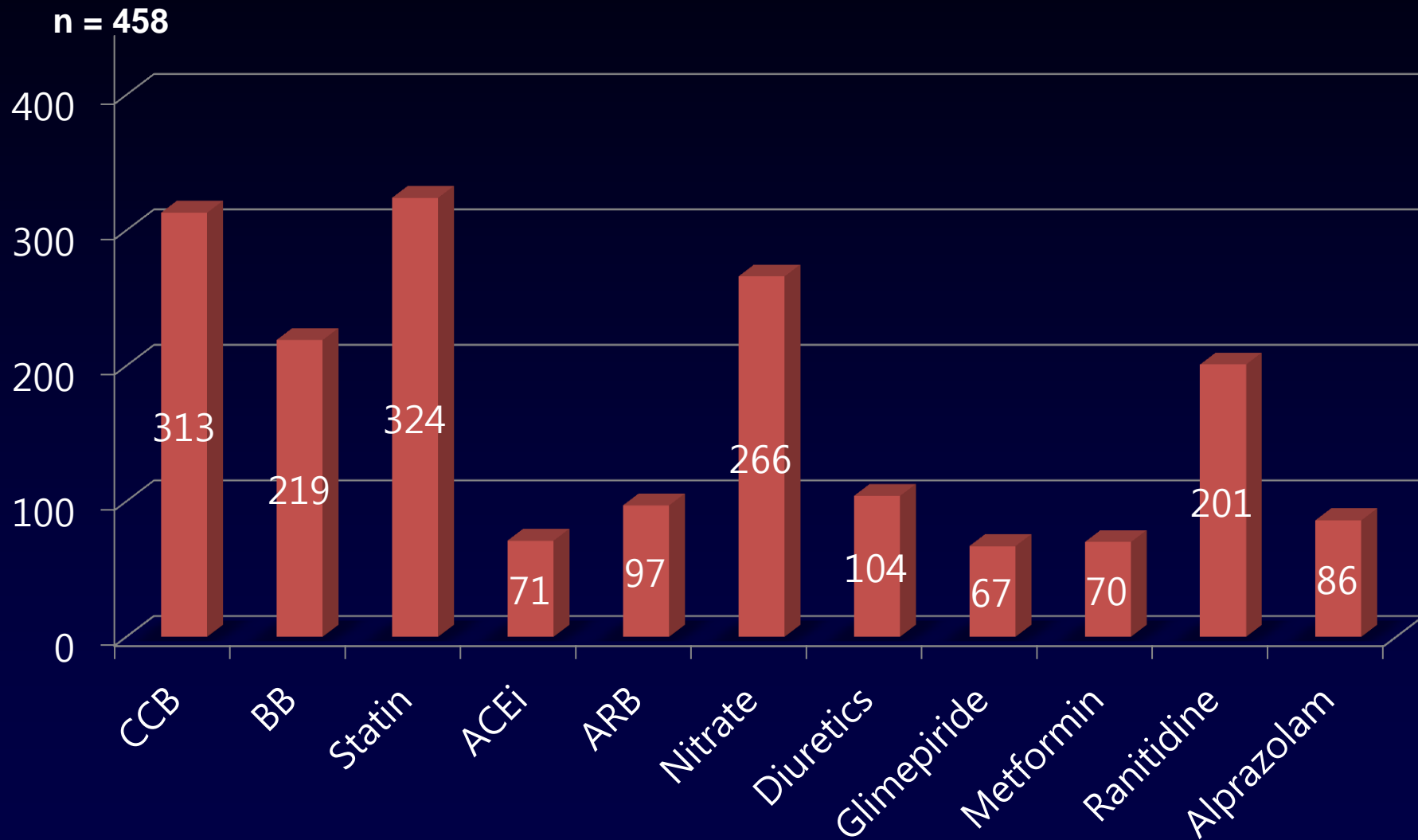


Baseline Characteristics

n = 458

Variables	Mean \pm SD or n (%)
Male (n, %)	336 (73.4)
Age (years)	64.5 \pm 9.6
Weight (kg)	66.3 \pm 11.2
Hb (g/dL)	13.3 \pm 1.7
PLT (k/mL)	234 \pm 70
Cr (mg/dL)	1.1 \pm 1.0
EF (%)	55 \pm 11
No. of kinds of taking drugs	6.8 \pm 1.7
Mean f/u duration (months)	17.7 \pm 8.1

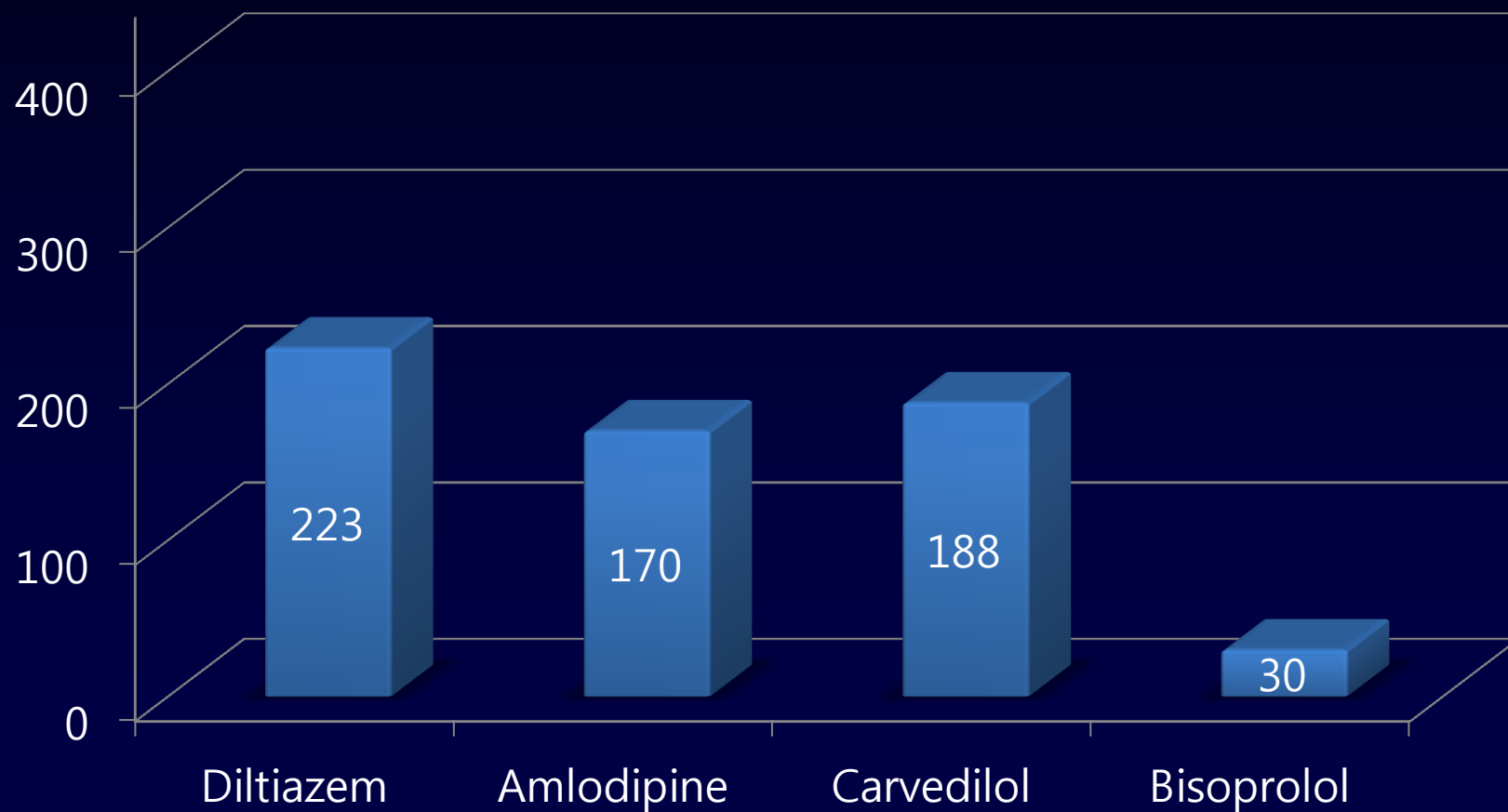
RESULTS (n=458)



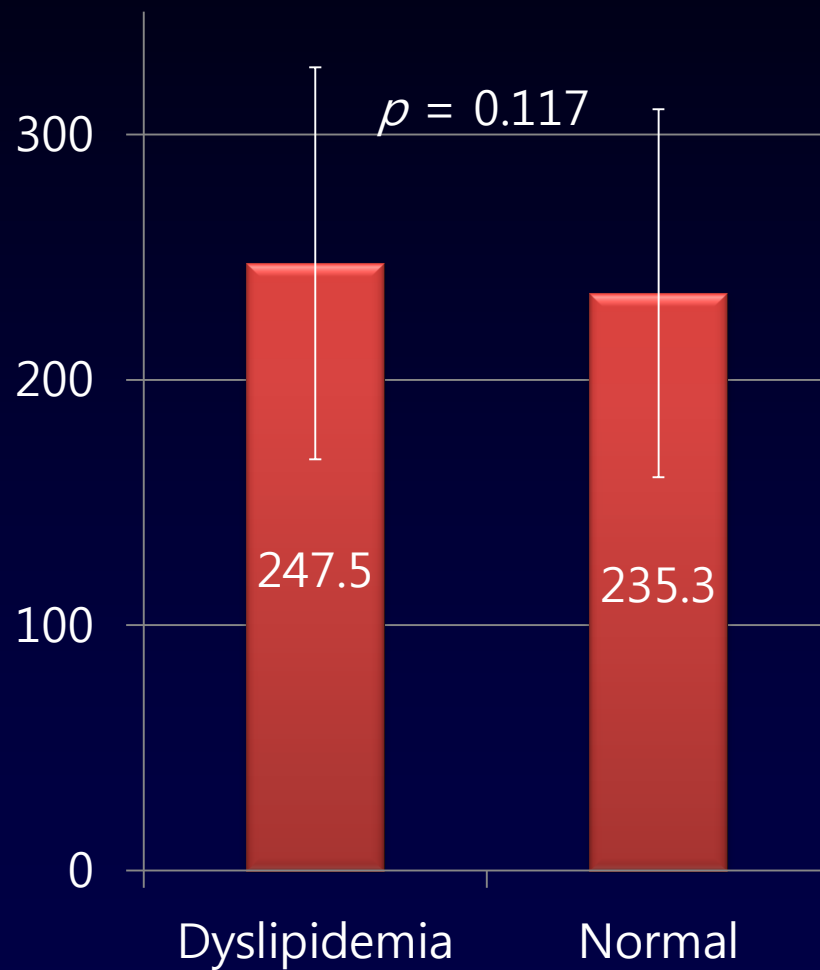
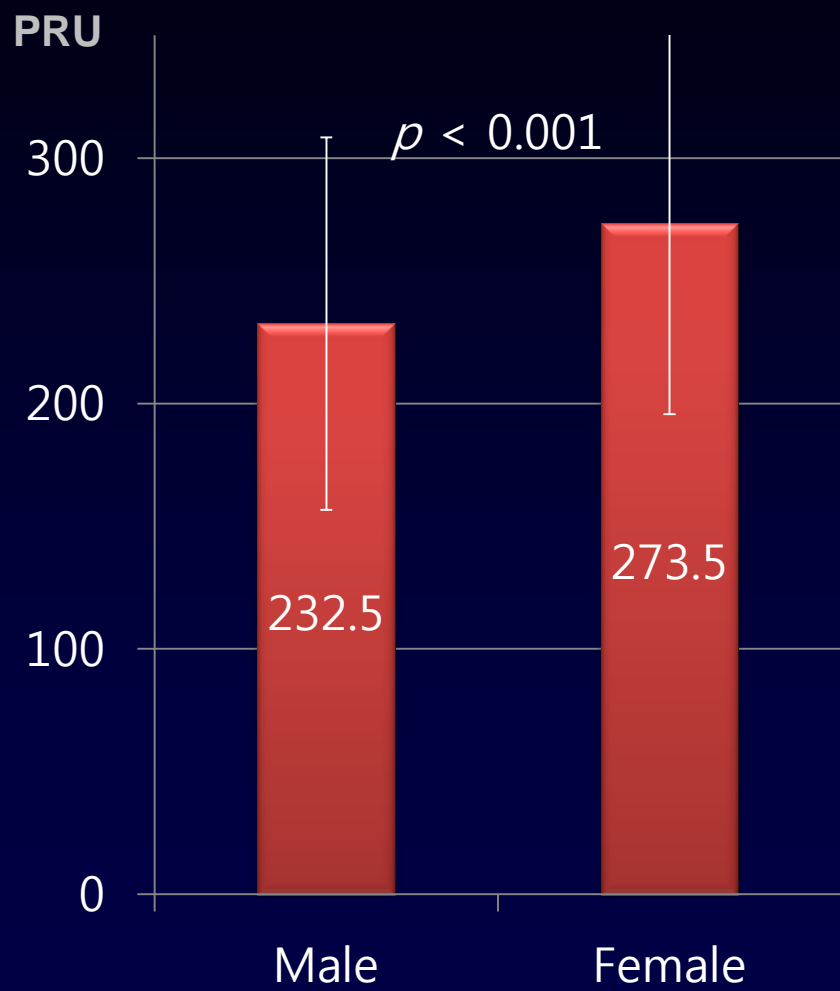
RESULTS

n = 458

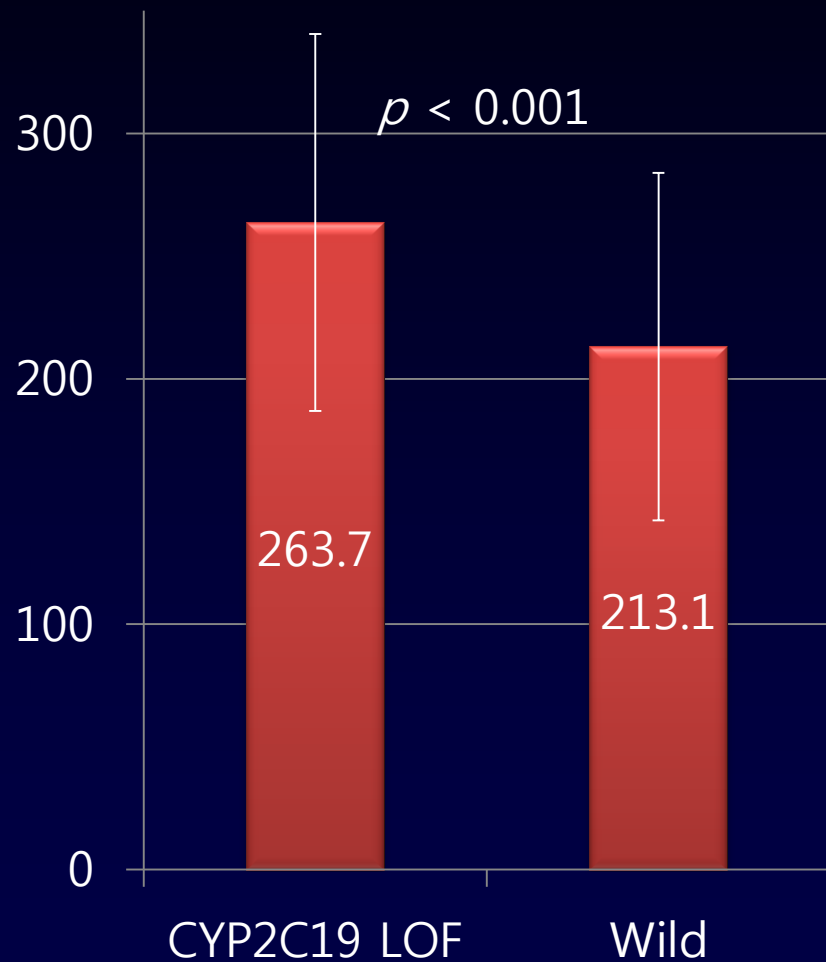
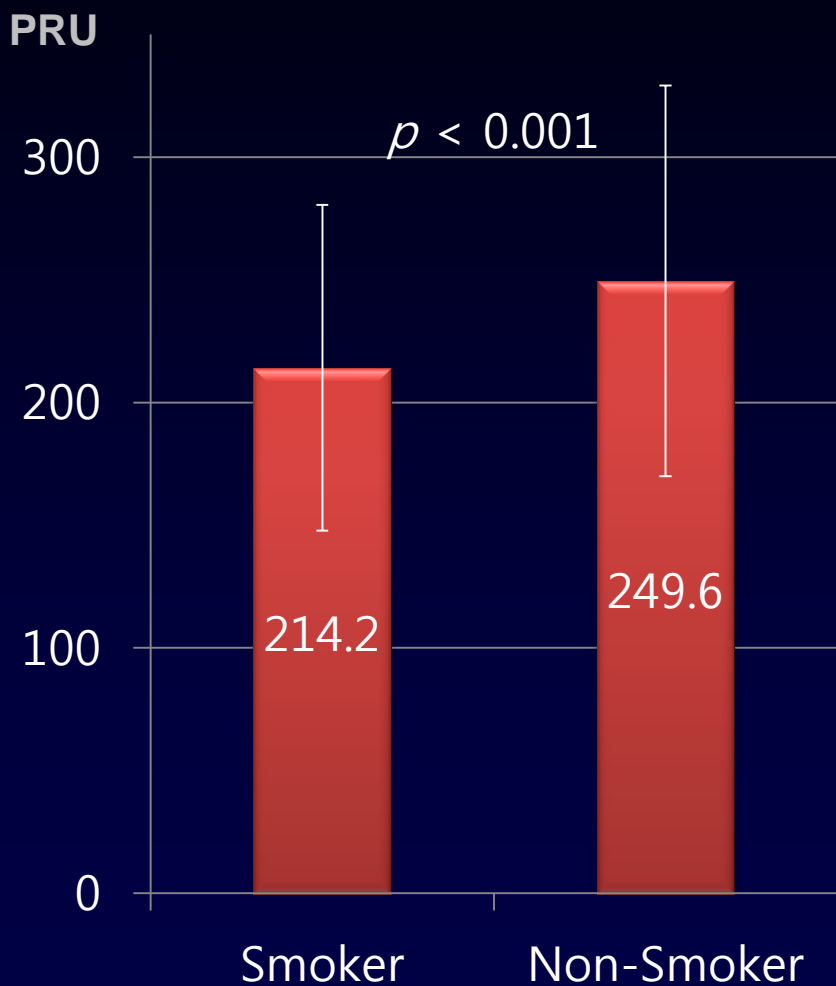
CCB & BB



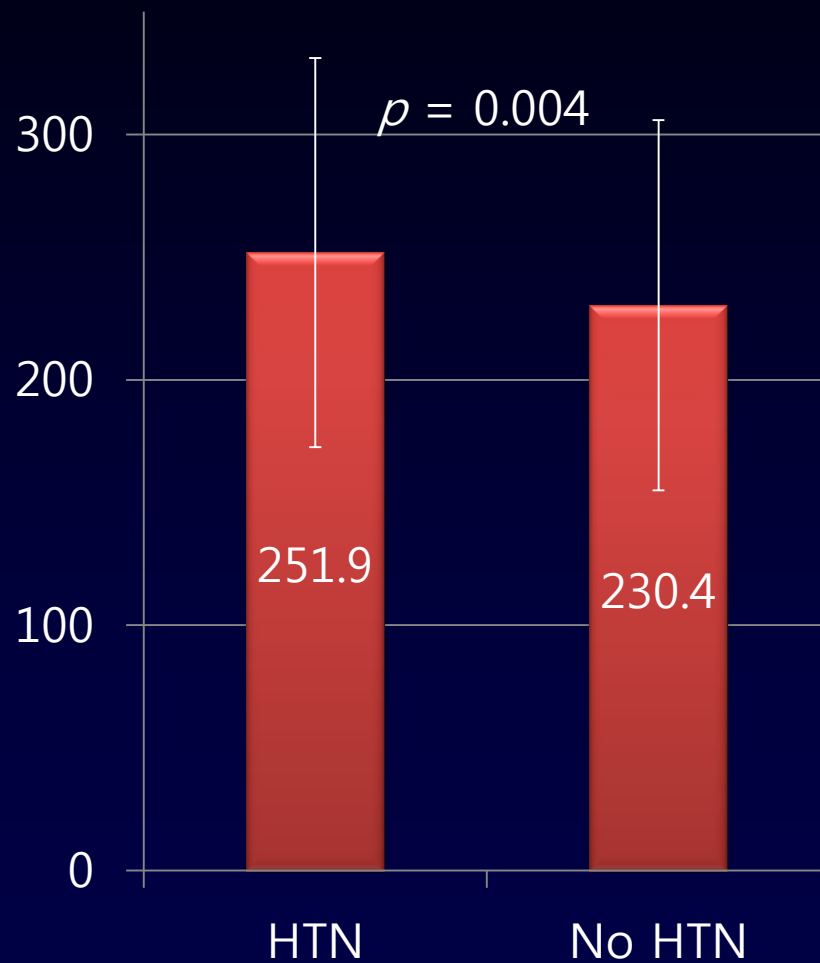
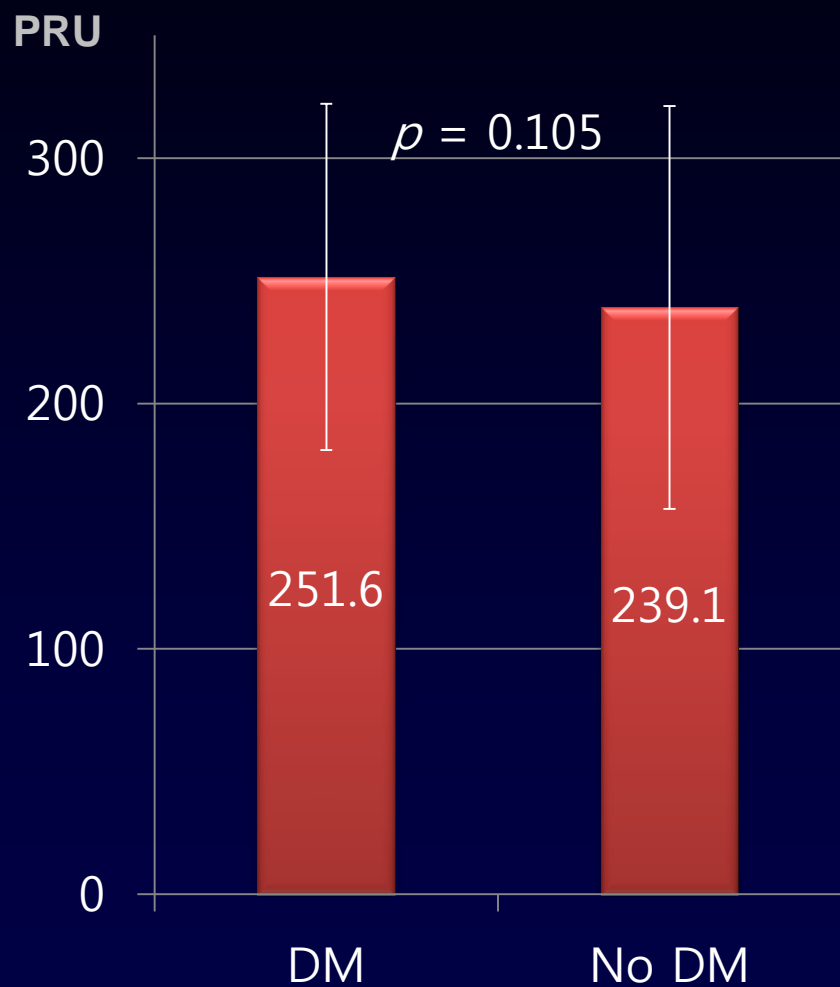
RESULTS



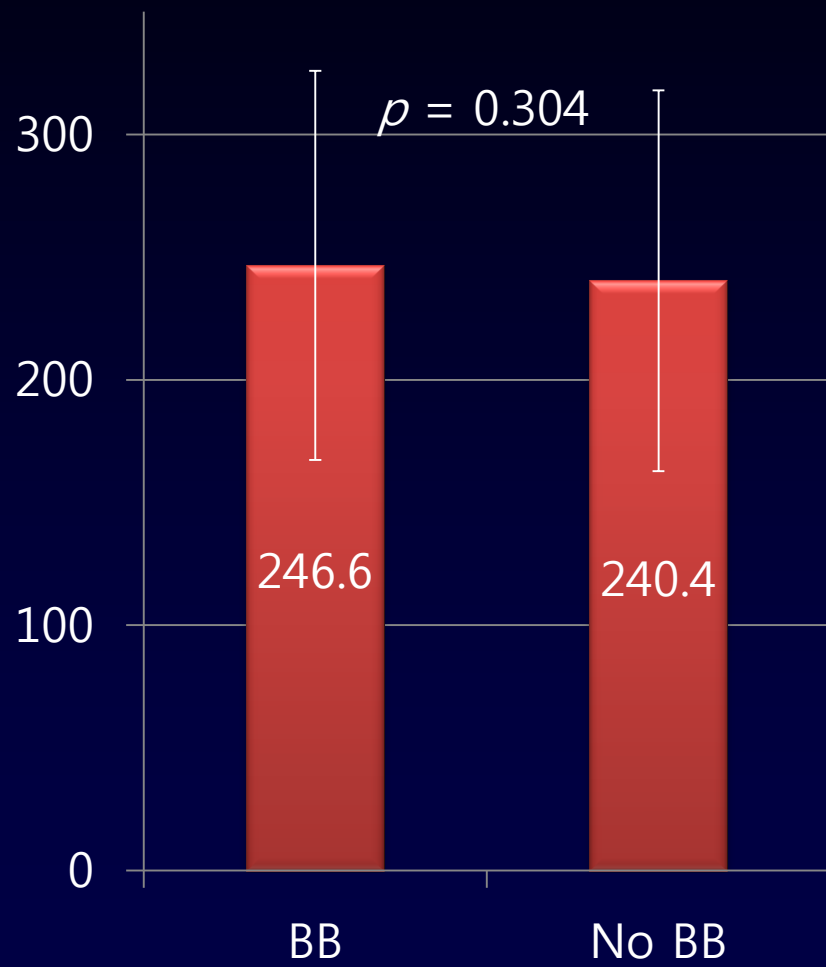
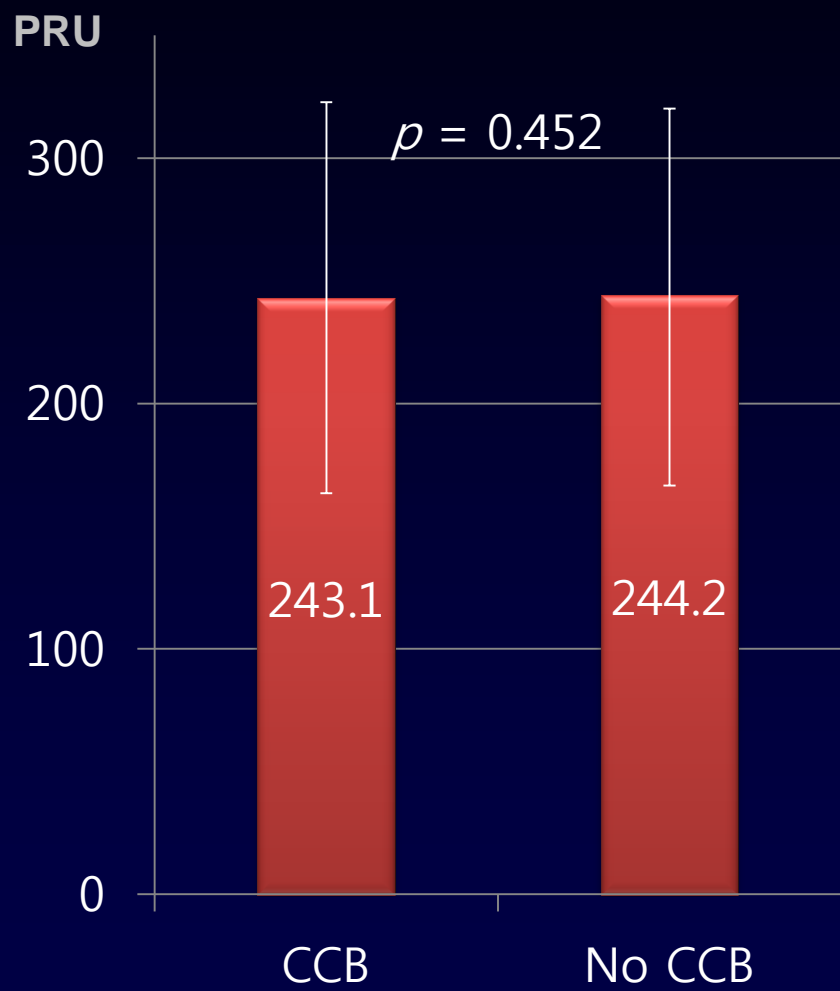
RESULTS



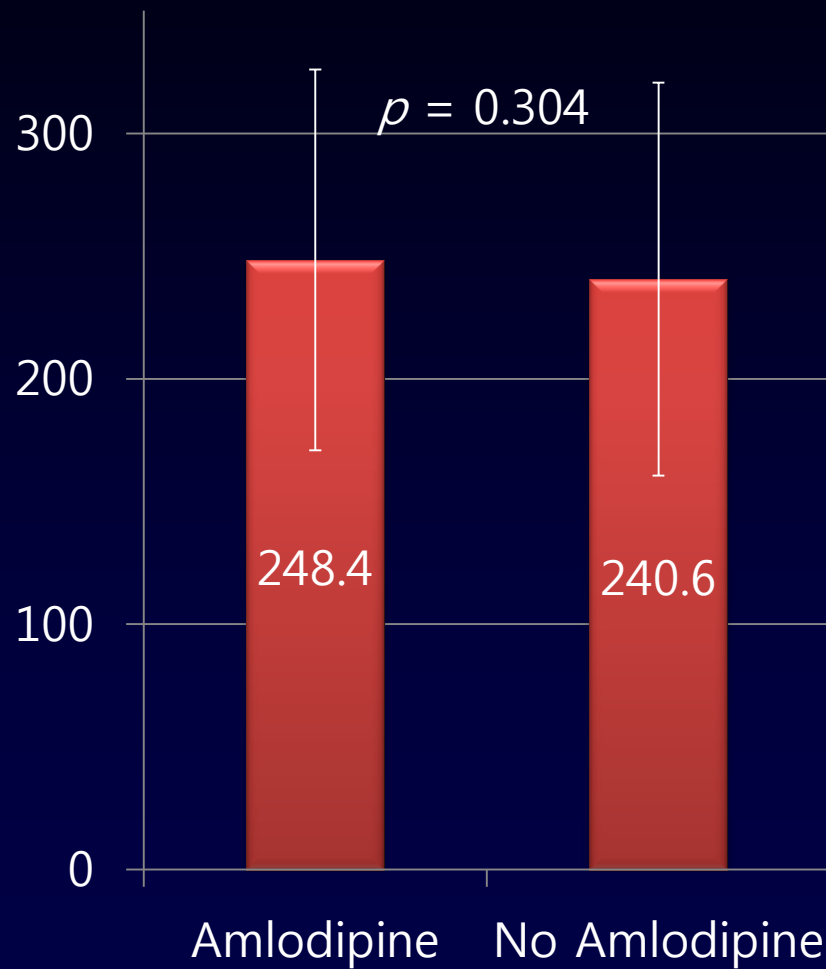
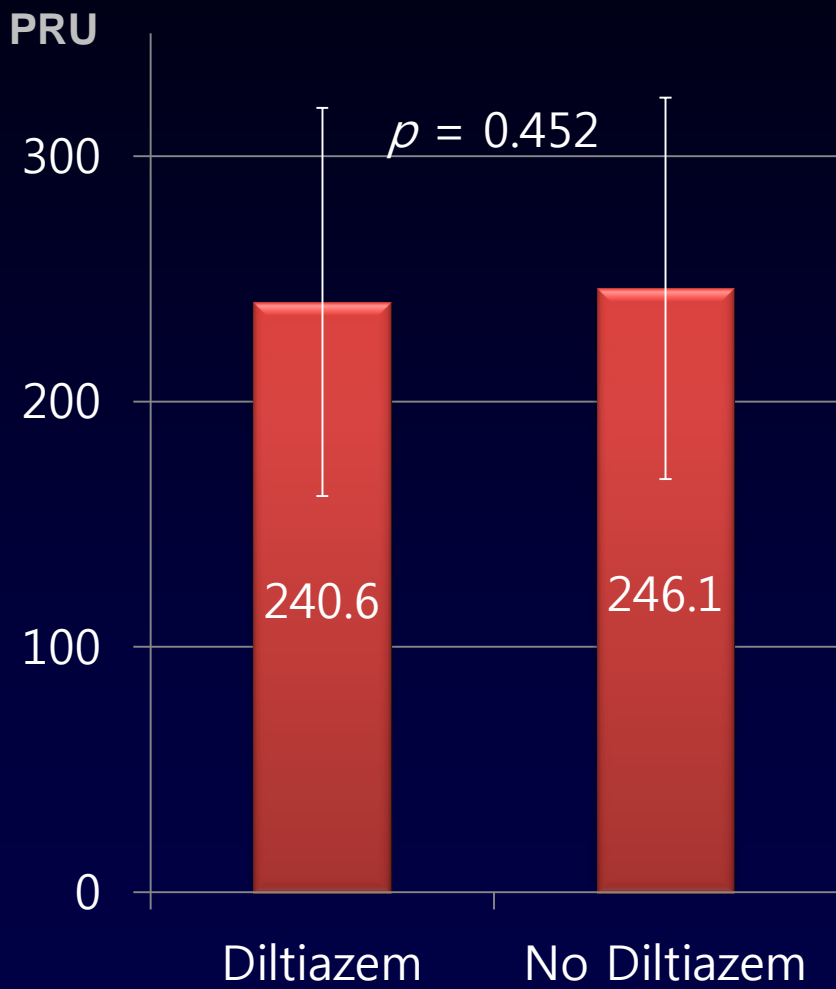
RESULTS



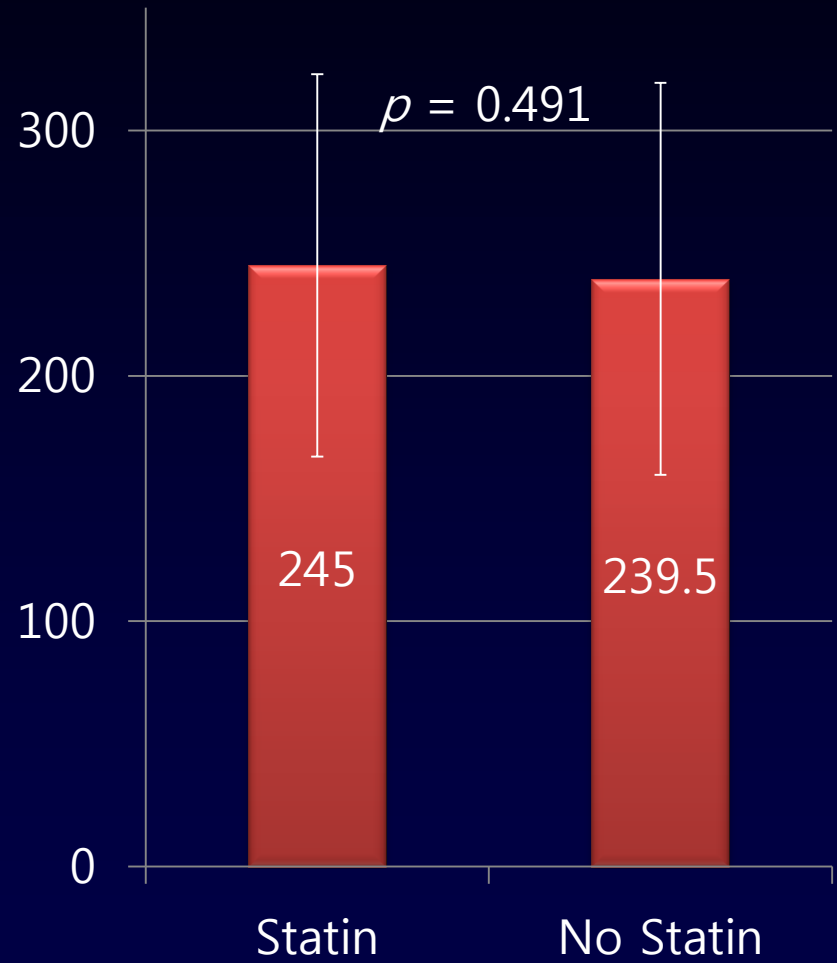
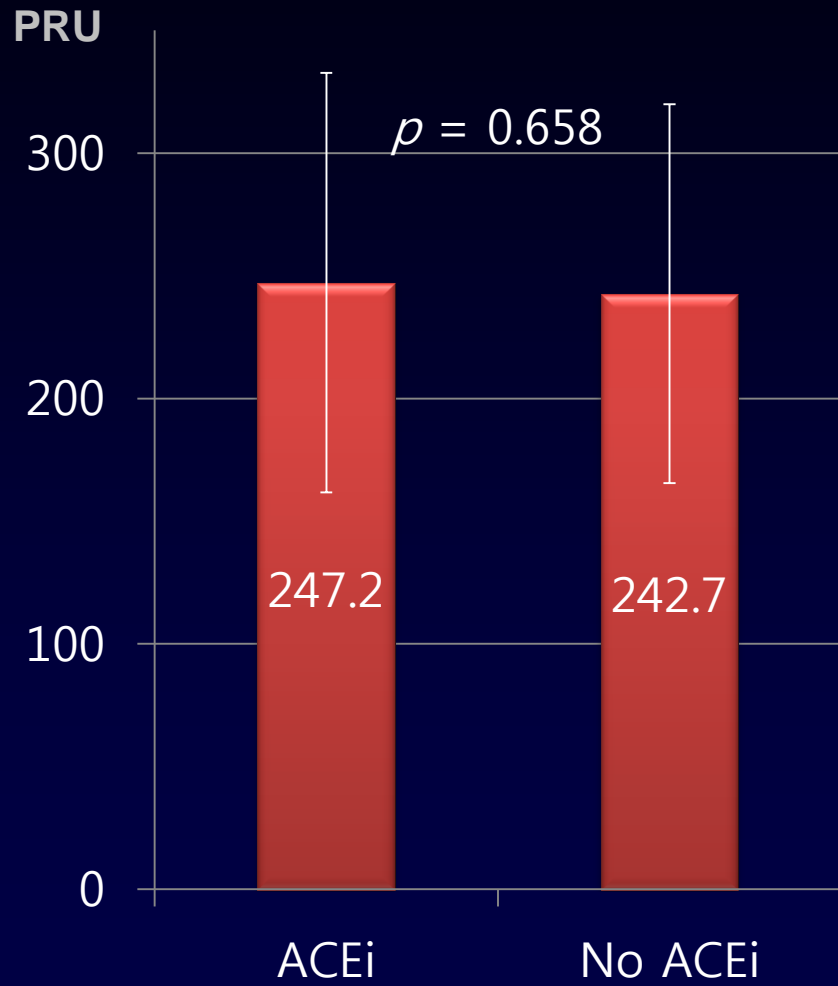
RESULTS



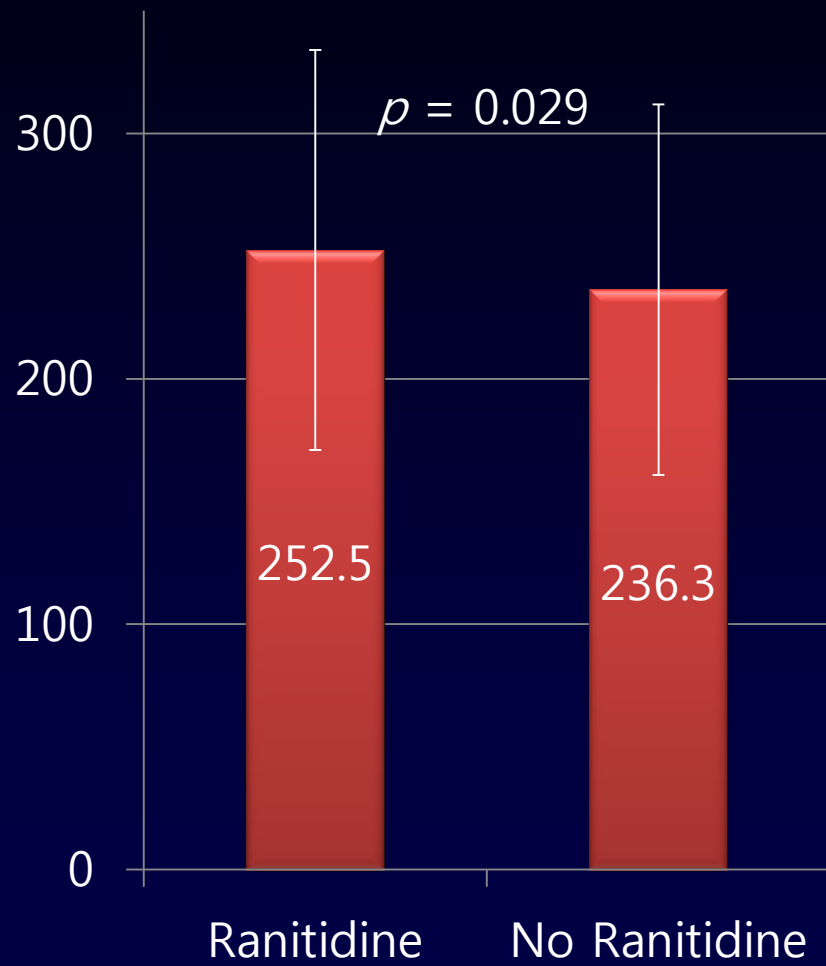
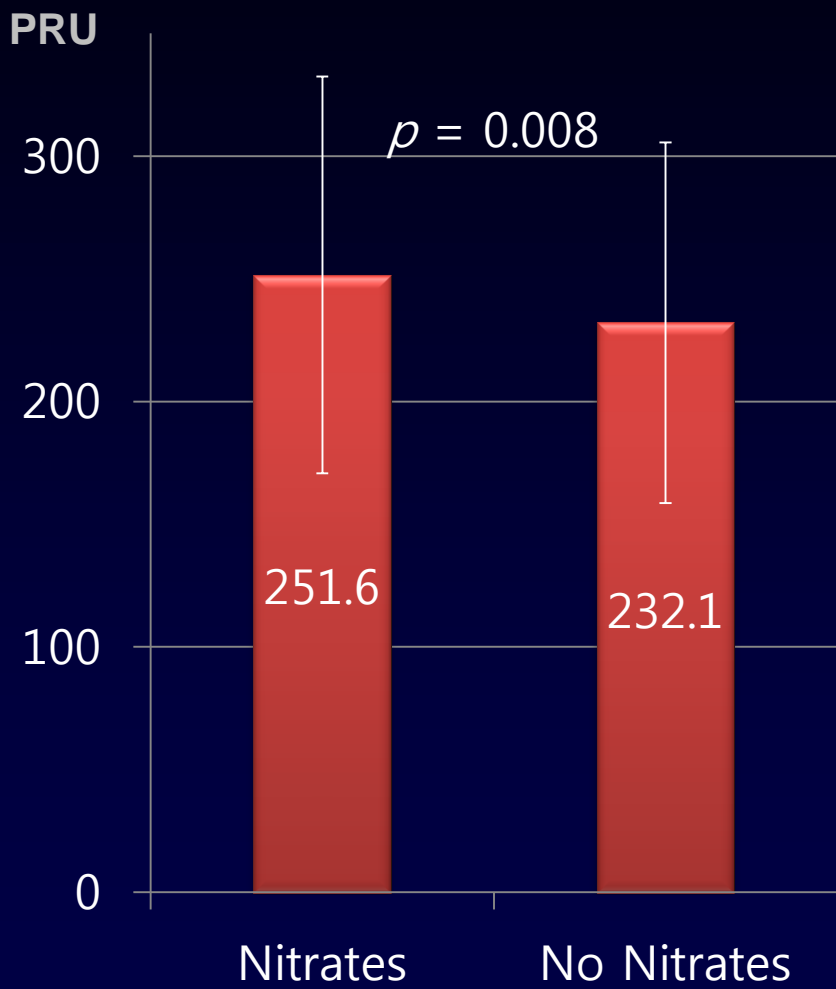
RESULTS



RESULTS

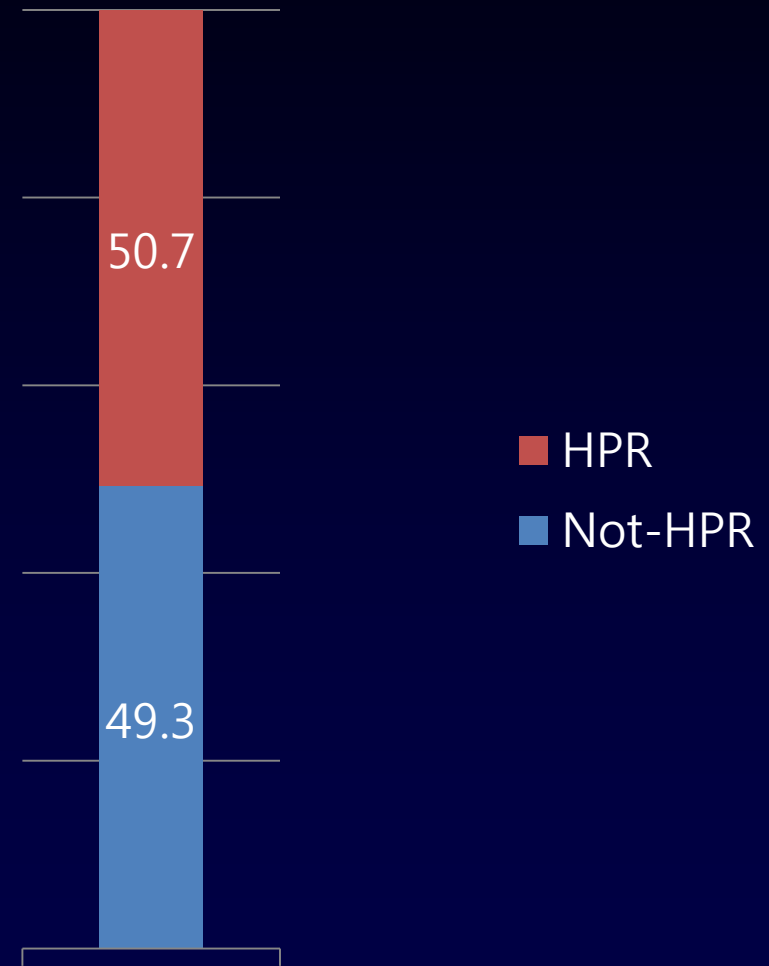


RESULTS



HPR

- HPR
 - PRU \geq **242**
 - 232 patients

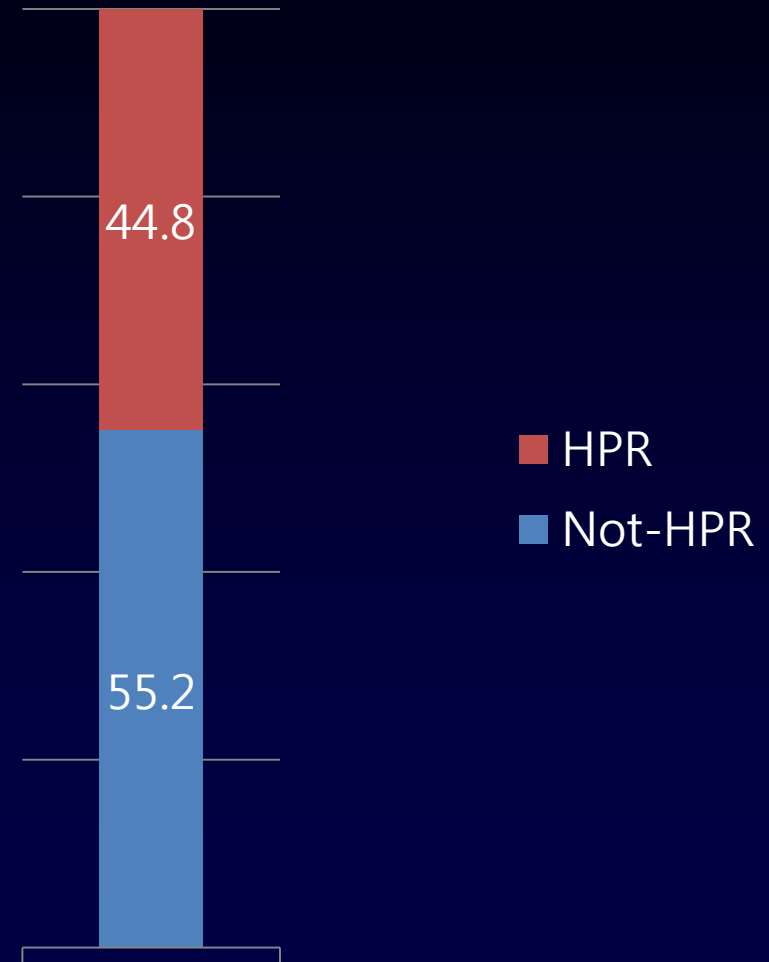


Regressions Analysis for HPR (242)

	Univariate Logistic Regression			Multivariate Logistic Regression		
	OR	95% CI	<i>P</i>	OR	95% CI	<i>p</i>
Female gender	2.4	1.6 – 3.7	<0.001			
Age (decade)	1.63	1.34 – 2.00	<0.001	1.39	1.09 – 1.77	0.006
Weight	1.97	0.96 – 0.99	0.001			
DM	0.59	0.40 – 0.88	0.008	1.57	1.00 – 2.47	0.046
HTN	1.92	1.32 – 2.81	0.001			
Current smoking	0.35	0.21 – 0.59	<0.001	0.47	0.26 – 0.82	0.011
CYP 2C19 LOF allele	2.93	1.97 – 4.36	<0.001	3.08	1.99 – 4.76	<0.001
CKD (GFR<30)	3.50	1.27 – 9.64	0.015			
Nitrates	1.87	1.28 – 2.72	0.001	1.74	1.14 – 2.65	0.010
Ranitidine	1.49	1.03 – 2.16	0.036			

HPR with different definition

- HPR
 - PRU \geq **253**
 - 205 patients



Regressions Analysis for HPR (253)

	Univariate Logistic Regression			Multivariate Logistic Regression		
	OR	95% CI	<i>P</i>	OR	95% CI	<i>p</i>
Female gender	2.65	1.73 – 4.06	<0.001	1.97	1.10 – 3.50	0.022
Age (decade)	1.51	1.24 – 1.84	<0.001			
Weight	0.97	0.95 – 0.99	0.001			
DM	1.65	1.12 – 2.43	0.012			
HTN	2.40	1.62 – 3.55	<0.001	1.60	1.01 – 2.53	0.048
Current smoking	0.32	0.19 – 0.56	<0.001	0.48	0.26 – 0.87	0.015
CYP 2C19 LOF allele	3.39	2.26 – 5.11	<0.001	3.66	2.31 – 5.79	<0.001
CKD (GFR<30)	3.08	1.07 – 8.90	0.037			
Nitrates	1.73	1.18 – 2.53	0.005	1.64	1.06 – 2.53	0.026
Alprazolam	1.63	1.02 – 2.62	0.042			

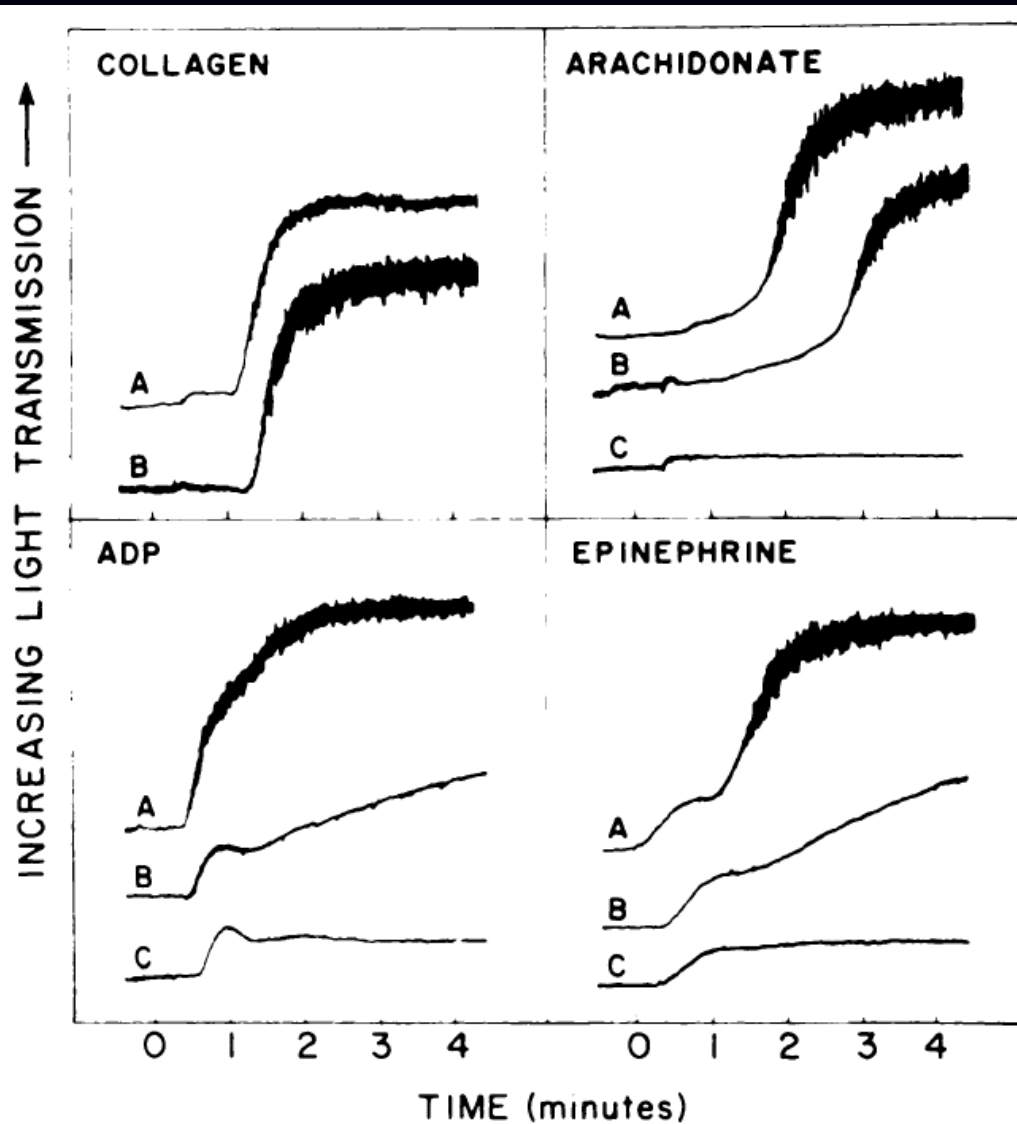
Clinical Outcomes

	PRU < 242	PRU ≥ 242	Total
MACE	6	10	16
Death	0	4	4

Mean F/U duration
17.7 ± 8.1 months

- 4 death
 - 2 SCD
 - 1 Stent thrombosis & cardiogenic shock
 - 1 Septic shock

Platelet Inhibition by Organic Nitrate



Effect of isosorbide dinitrate (ISDN) on PLT.

Collagen

- (A) No addition
- (B) Collagen 8 mM

Arachidonic acid

- (A) No addition
- (B) 800 μ M
- (C) 2.4 mM

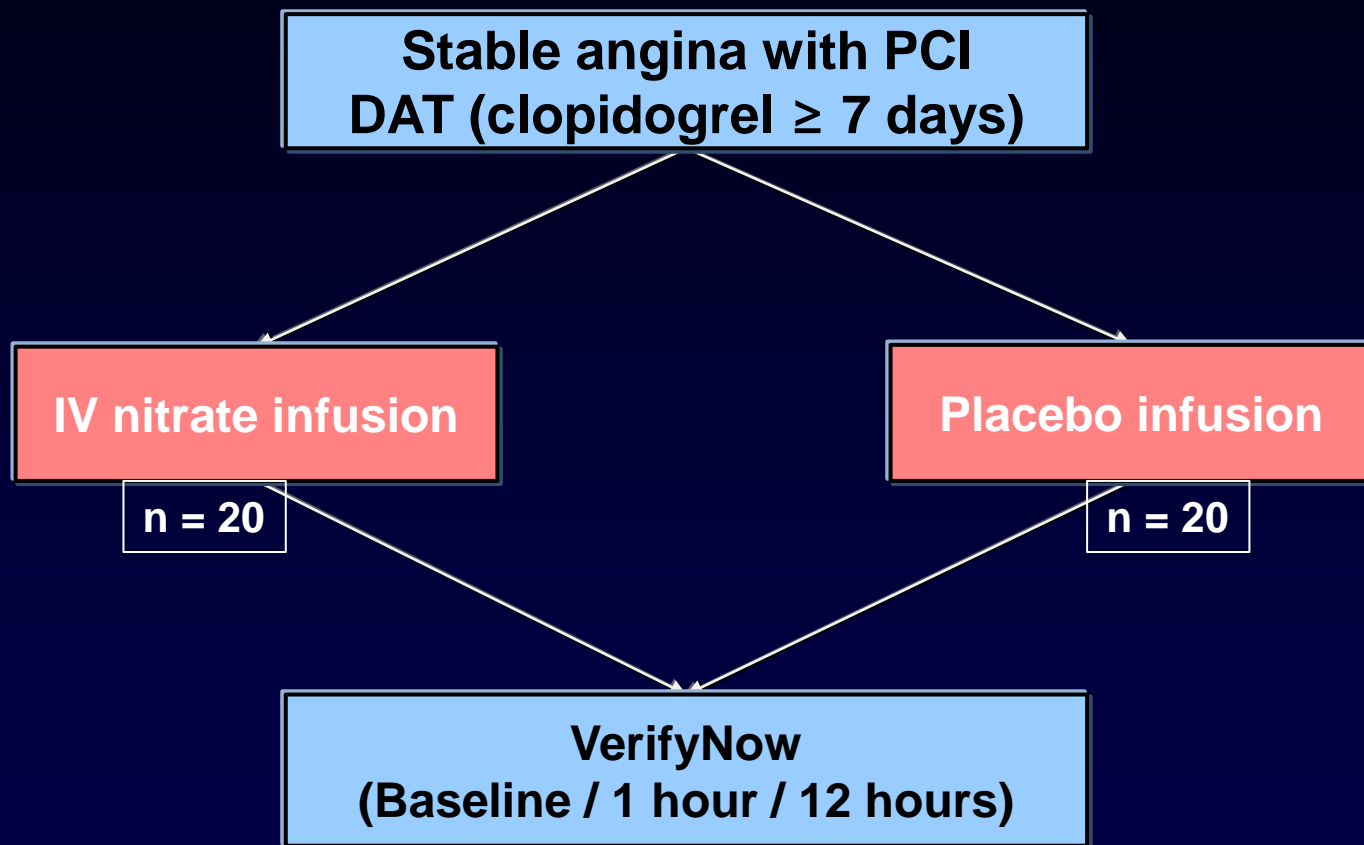
ADP aggregation

- (A) no addition
- (B) 200 μ M
- (C) 800 μ M

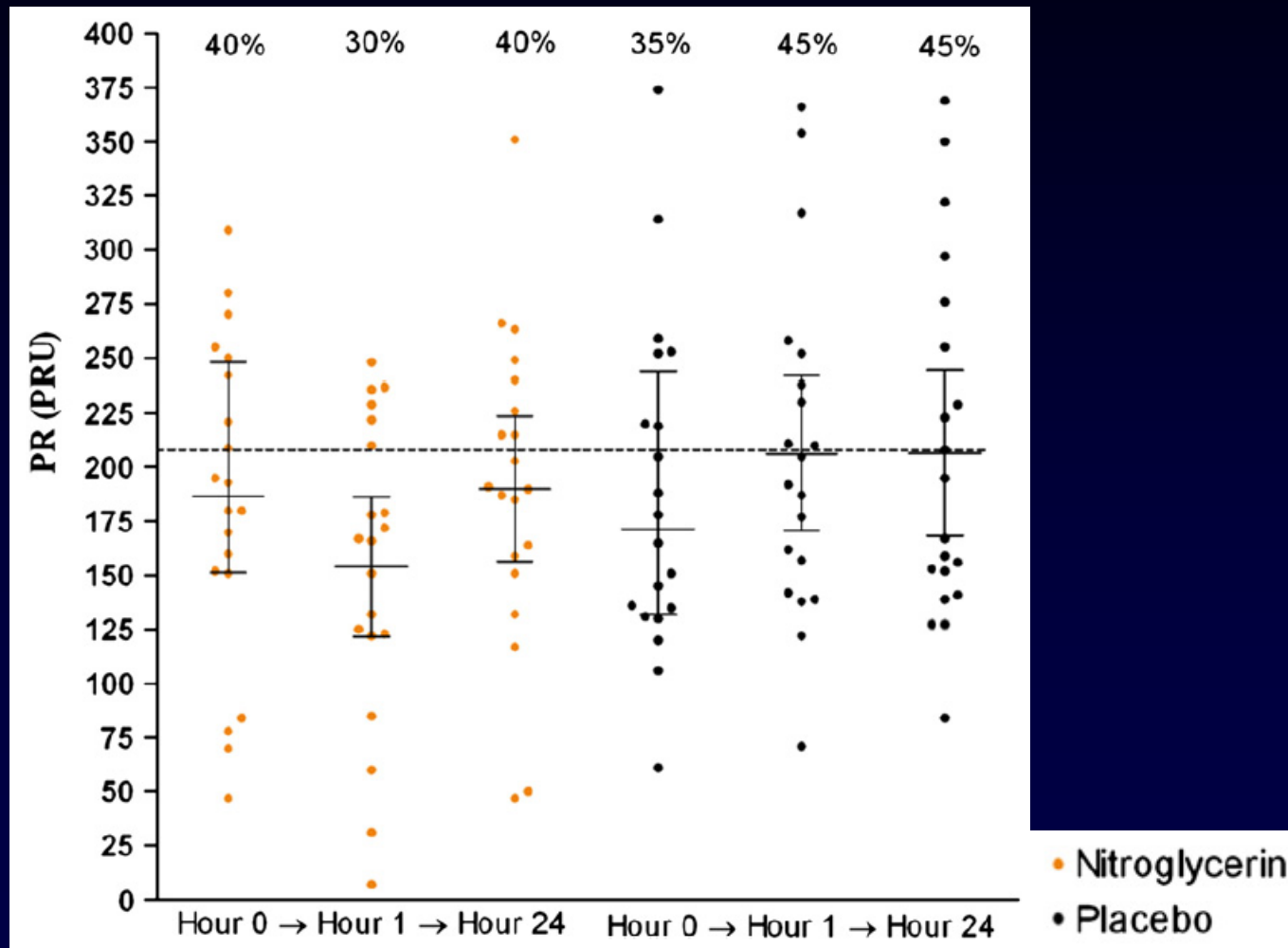
Epinephrine aggregation

- (A) No addition
- (B) 1.4 mM
- (C) 8 mM

PLT Inhibition by IV Nitrate



PLT Inhibition by IV Nitrate



Nitrate and Platelet

- 377 patients with SA
 - SA
 - MD/LD of clopidogrel
- VerifyNow
- HPR \geq 235

Characteristic	Mean Residual Platelet Reactivity (PRU)		p Value
	Characteristic Present	Characteristic Absent	
Age \geq 75 yrs	214 \pm 77	201 \pm 79	0.161
Men	200 \pm 77	220 \pm 82	0.041
Non-Caucasian ethnicity	229 \pm 79	202 \pm 78	0.047
Previous myocardial infarction	198 \pm 78	209 \pm 79	0.159
Previous stroke/transient ischemic attack	203 \pm 83	205 \pm 78	0.924
Peripheral vascular disease	212 \pm 87	203 \pm 77	0.491
History of hypertension	204 \pm 79	208 \pm 74	0.781
Hypercholesterolemia	202 \pm 79	223 \pm 68	0.106
Diabetes mellitus	220 \pm 73	196 \pm 80	0.005
Concomitant medications			
β Blocker	209 \pm 75	194 \pm 84	0.091
Calcium channel blocker	209 \pm 74	203 \pm 80	0.519
Angiotensin-converting enzyme inhibitor	198 \pm 79	209 \pm 78	0.168
Angiotensin receptor blocker	213 \pm 79	201 \pm 78	0.190
Nitrates	223 \pm 70	200 \pm 80	0.018
Proton-pump inhibitor	218 \pm 79	198 \pm 78	0.020
Statin	204 \pm 79	204 \pm 72	0.986
Lipophilic statin	204 \pm 78	205 \pm 79	0.937
Hormone replacement therapy	243 \pm 84	203 \pm 78	0.139
Body mass index $>$ 25 kg/m ²	204 \pm 77	202 \pm 83	0.840
Creatinine clearance $<$ 60 ml/min	215 \pm 79	201 \pm 77	0.107
Current smoker	168 \pm 82	208 \pm 77	0.006
Aspirin nonresponsive	215 \pm 90	203 \pm 77	0.334

Nitrate and Platelet

Result of Multivariate Logistic Regression Analysis

Variables	OR	CI	<i>p</i>
Non-Caucasian ethnicity	3.05	1.49 - 6.28	0.002
Female gender	1.91	1.14 - 3.19	0.014
PPI	1.64	1.14 - 3.19	0.014
Current smoking	0.37	0.14 - 0.94	0.037

Continuous Administration of Nitrate

0022-3656/04/3002-729-7\$18.00

THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS

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JPET 308:729-735, 2004

Vol. 308, No. 2

67877/1129089

Printed in U.S.A.

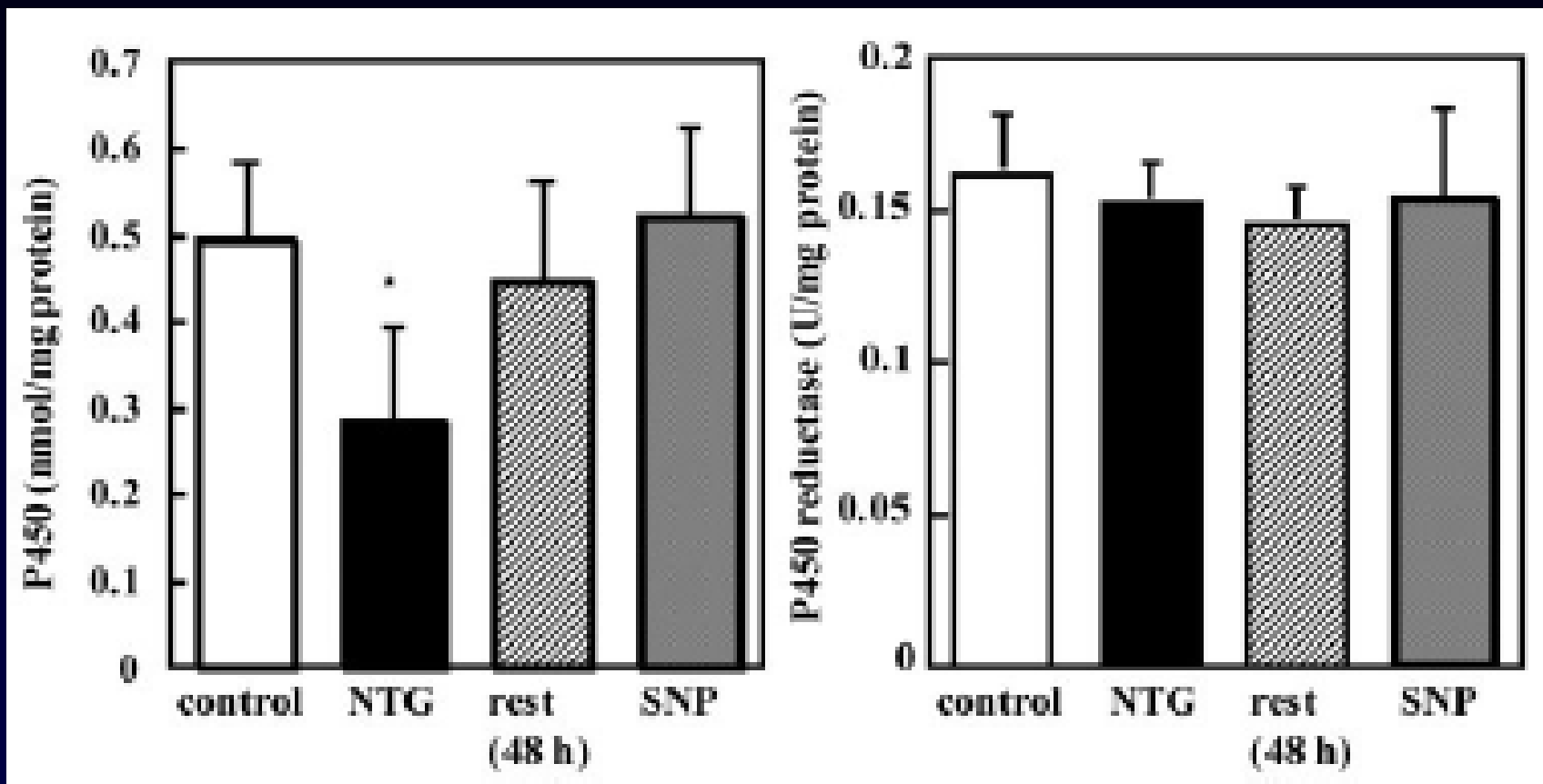
Continuous Administration of Organic Nitrate Decreases Hepatic Cytochrome P450

Yukiko Minamiyama, Shigekazu Takemura, Keiichi Yamasaki, Seikan Hai, Kazuhiro Hirohashi, Yoshihiko Funae, and Shigeru Okada

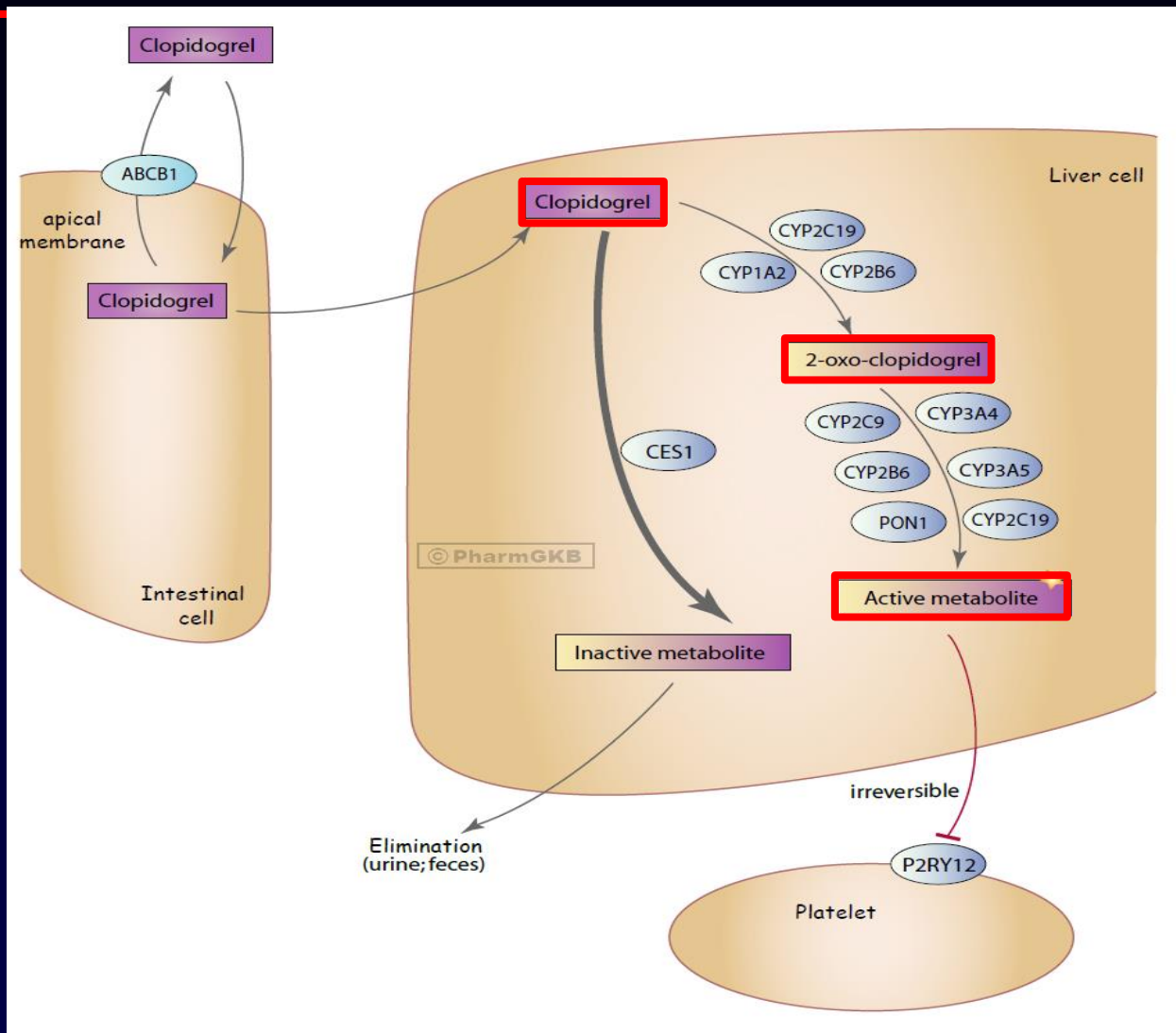
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Received July 30, 2003; accepted October 28, 2003

Continuous Administration of Nitrate



Continuous Administration of Nitrate



CYP2C19

CYP3A4

Limitations

- Not directly comparing
- Unidentified confounder
- Type of Nitrates
- Maintenance dose

CONCLUSION

Sustained Release Nitrate Agents



Long-term Administration



Clopidogrel Hypo-Responsiveness