

# Smokers' Paradox to Clopidogrel: Is it fiction?

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# Cigarette Smoking



- Proven hazardous effect on public health
- Well known independent cardiac risk factor
- But there are reports that habitual smokers present lower mortality rate after AMI, called as “smokers’ paradox”
- The mechanism is unknown.

# Conflicting literature regarding Smoker's Paradox



1977 Sparrow et al.

...

1993 Barbash et al., Gomez et al.

1995 Grines et al., Barbash et al.

1996 De Chillou et al., Gottlieb et al.

1997 Ishihara et al.

1999 Hasdai et al.

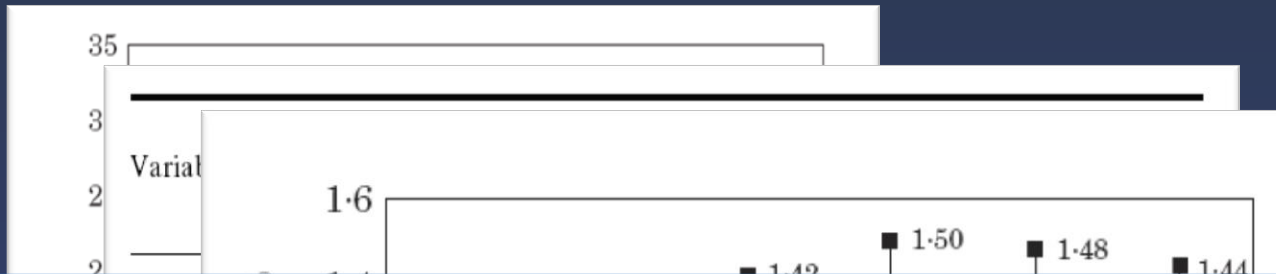
2001 Andrikopoulos et al. Euro Heart J

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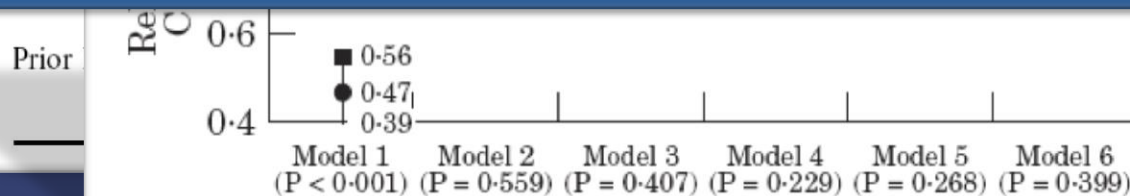
2009 Desai et al. JACC / Berger et al. Circulation

# Smoker's Paradox: Just a selection bias?

7433 AMI patients from 76 centers, 3853 smokers, In-hospital mortality rate



Smoker's Paradox: **Mere selection bias** ?



## Adjustment for

model 1: smoking

model 2: smoking, **age**

model 3: smoking, age, gender

model 4: smoking, age, gender, DM

model 5: smoking, age, gender, DM, previous MI

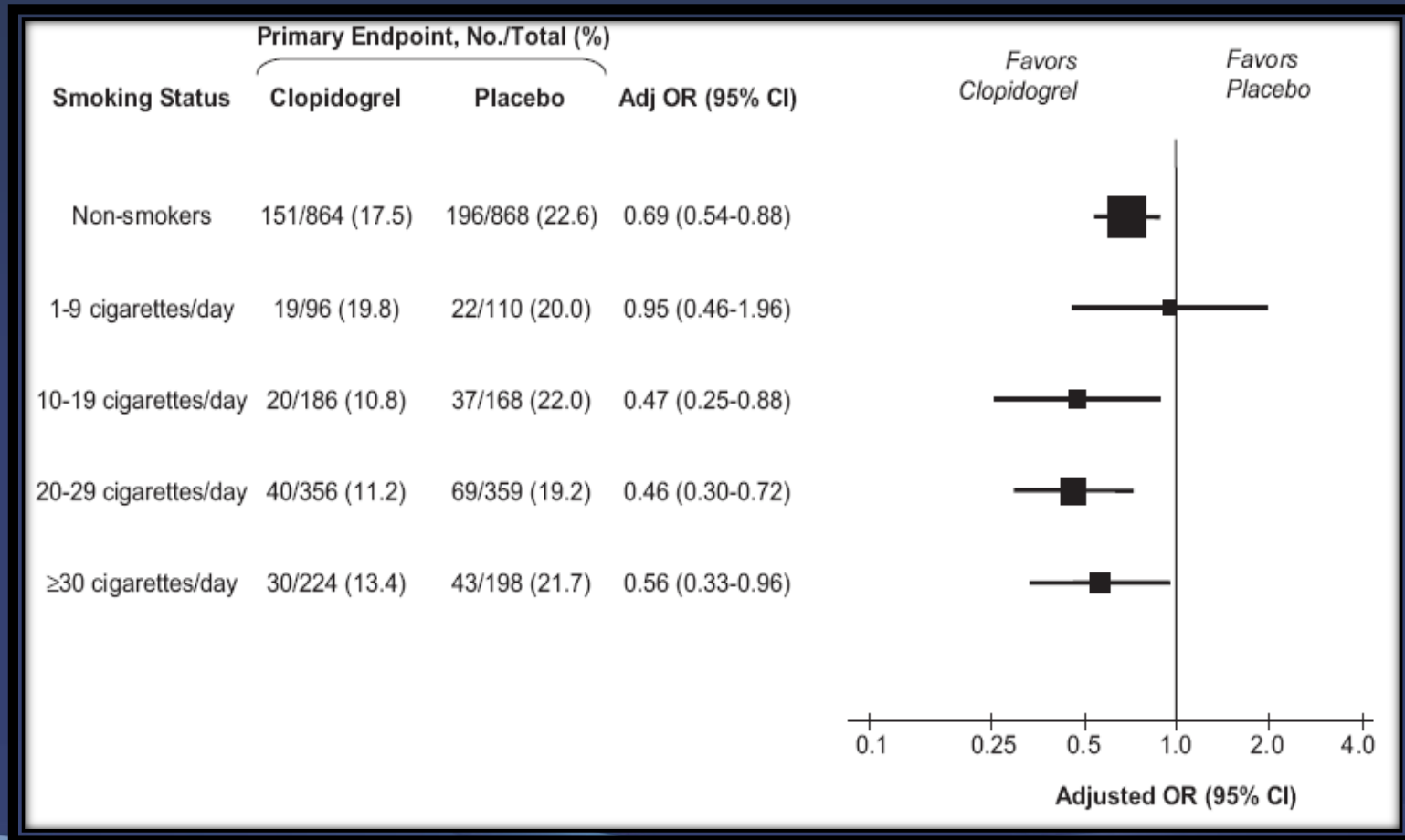
model 6: smoking, age, gender, DM, previous MI, HTN

drikopoulos et al. *Euro Heart J* 2001

# Smoker's Paradox

## Exaggerated Effect of Clopidogrel

CLARITY-TIMI 28, 3249 patients, 1517 smokers, 30-day MACE



ORs *adjusted* for age, sex, region, hypertension, diabetes, infarct location, time to fibrinolytic therapy, and type of fibrinolytic.



# Exaggerated Effect of Clopidogrel from CHARISMA

Hazard ratio of all-cause death with clopidogrel vs. placebo

Group	Hazard ratio	95% CI
Current smokers	0.68	0.49–0.94
Former smokers	0.95	0.75–1.19
Never-smokers	1.14	0.83–1.58

Hazard ratio of moderate or severe bleeding with clopidogrel vs. placebo

Group	Hazard ratio	95% CI
Current smokers	1.62	1.02-2.58
Never-smokers	1.31	0.90–1.90

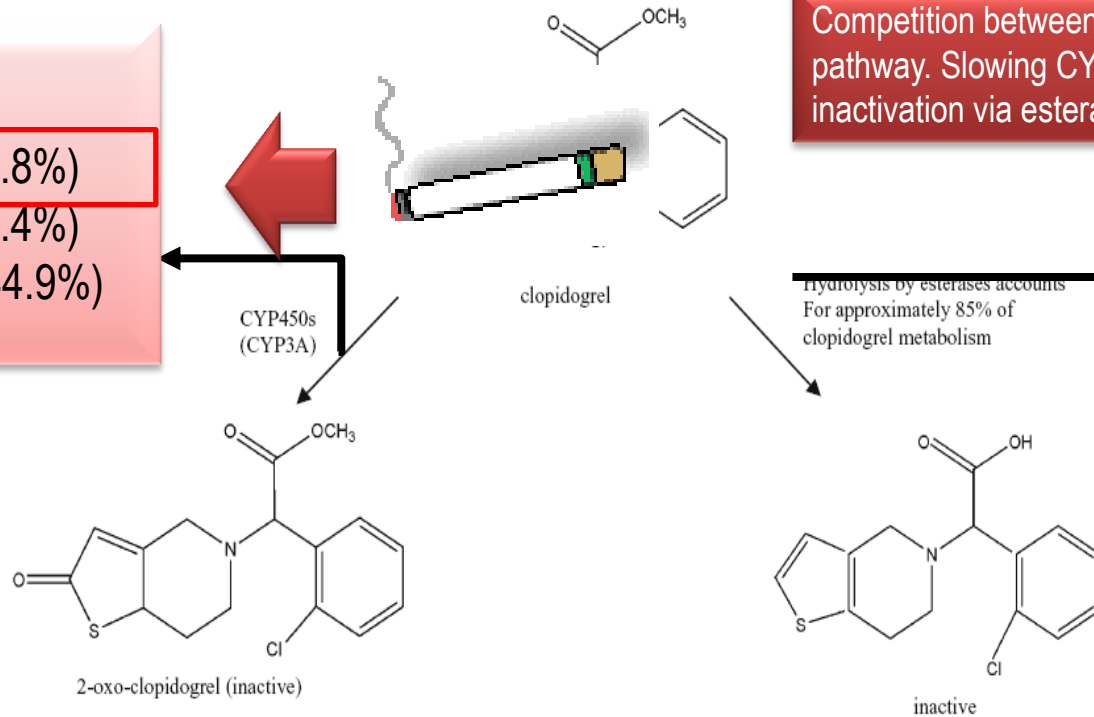
# Activation of Clopidogrel

## 1. Step

### Oxidation by

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

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



## 2. Step

### Hydrolysis by

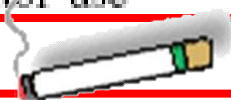
- CYP3A4 (39.8%)
- CYP2C9 (6.8%)
- CYP2B6 (32.9%)
- CYP2C19 (20.6%)

Inactivation by serum esterase

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

# Smoking as a Protective Factor of High On-treatment Platelet Reactivity?

Relations between clinical characteristics and high residual platelet reactivity (HRPR)

Characteristic	Rate of HRPR		p Value
	Characteristic Present	Characteristic Absent	
Men	32.3%	47.5%	0.012
Non-Caucasian ethnicity	55.6%	33.4%	0.008
Diabetes mellitus	42.5%	32.0%	0.044
$\beta$ -Blocker use	38.6%	28.8%	0.065
Nitrate use	41.3%	34.1%	0.242
Proton-pump inhibitor use	42.1%	32.3%	0.061
Current smoker 	19.4%	37.0%	0.049



## Clinical Predictors of High Posttreatment Platelet Reactivity to Clopidogrel in Koreans

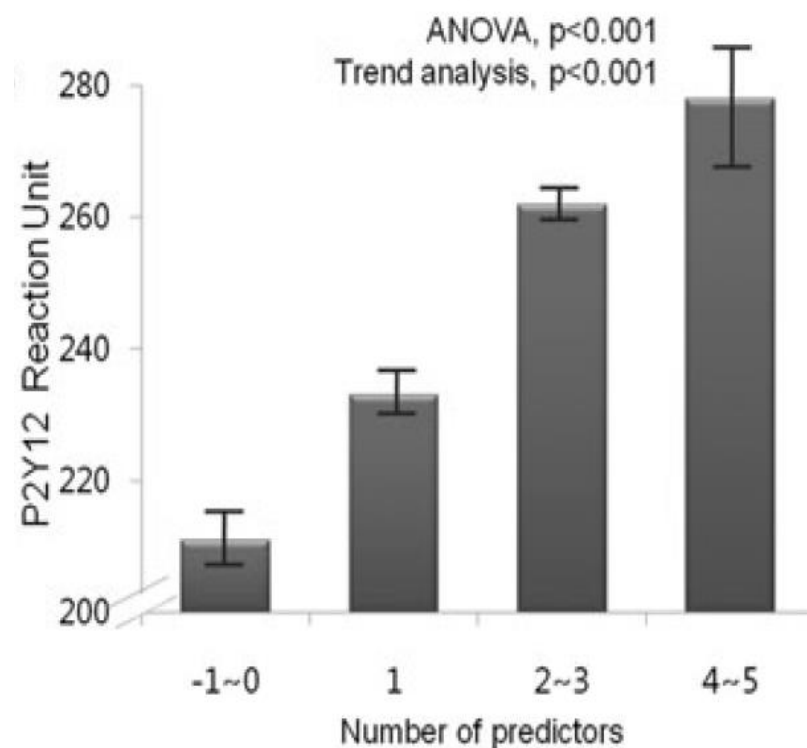
Kyung Woo Park\*, Jin Joo Park\*, Ki-Hyun Jeon, Si-Hyuk Kang, Il-Young Oh, Han-Mo Yang, Hyun-Jai Cho, Hae-Young Lee, Hyun-Jae Kang, Bon-Kwon Koo, Byung-Hee Oh, Young-Bae Park & Hyo-Soo Kim

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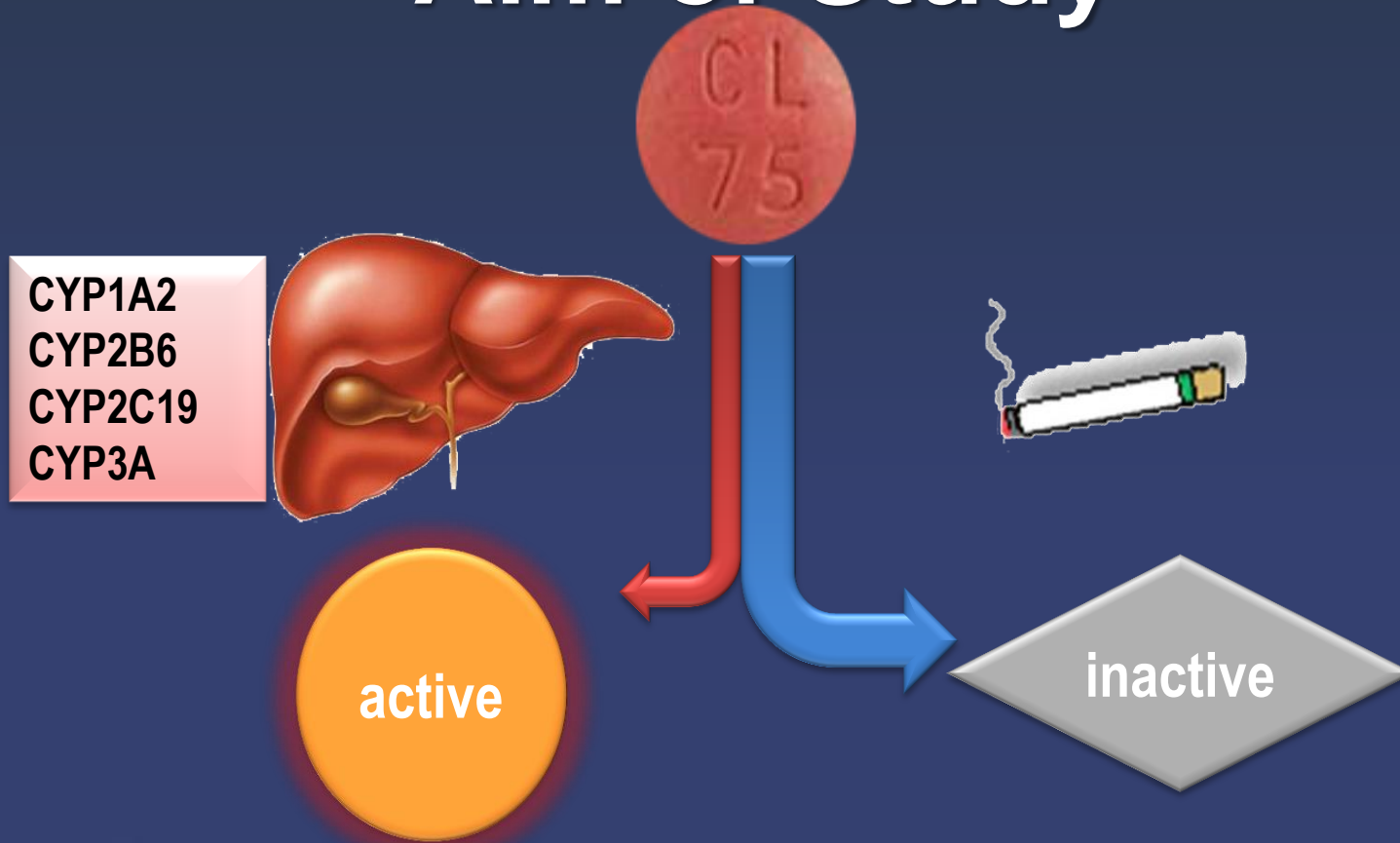
**Table 2** Multivariate analysis for independent predictors of HPPR

	OR	95% Confidence interval		P-value
		Lower limit	Upper limit	
Female gender	1.90	1.46	2.46	<0.001
Chronic kidney disease	1.51	1.14	1.99	0.004
Diabetes mellitus	1.35	1.04	1.75	0.024
CRP $\geq$ 2.0 mg/L	1.31	1.02	1.69	0.036
Age (decade)	1.21	1.06	1.39	0.005
Cigarette smoking	0.63	0.44	0.92	0.015

Input variables: age (in decade), gender, cigarette smoking, hypertension, diabetes mellitus, chronic kidney disease stage, congestive heart failure, hs-CRP  $\geq$  2.0 mg/L, beta-blocker, dihydropyridine calcium channel blocker, statin.



# Aim of Study



1. Does **SMOKING** influence **CLOPIDOGREL RESPONSE**?
2. Can it be applied to **ALL SMOKERS**?
3. What is the **CLINICAL IMPLICATION**?

# Study population

The **CROSSVerfiy** Cohort (measuring Clopidogrel Resistance tO a Ssure Safety after percutaneous coronary intervention using **VERIFY**now)

A prospective cohort including all patients undergoing CAG/PCIa

## Inclusion Criteria

✓ patients undergoing coronary angiography and/or PCI

## Exclusion Criteria

- ✓ Contraindication to aspirin, clopidogrel and heparin
- ✓ Use of iv gp-IIb/IIIa inhibitor within the previous 5 days of clopidogrel reactivity test
- ✓ Concomitant use of cilostazol
- ✓ Uncontrolled malignancy
- ✓ Bleeding tendency
- ✓ Ethnicity other than Korean heritage

# Platelet Reactivity Test & Genotyping

## I. Timing of blood sampling

- Patients on clopidogrel maintenance: within 24hr after CAG/PCI
- Clopidogrel naïve patients : within 24hr after 300 - 600mg clopidogrel loading

## II. Point-of-care Platelet reactivity assays

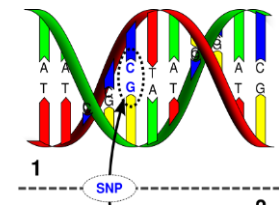
- The inhibitory effect of clopidogrel was measured by using the VerifyNow P2Y12 assay (Accumetrics Inc.)

### TaqMan™ Assay

- CYP1A2\*1F (-163C>A, rs762551)
- CYP2C19\*2 (P227P, rs4244285)
- CYP2C19\*3 (W212X, rs4986893)
- CYP3A4 (IVS10+12G/A, rs2242480)
- CYP3A5 (CYP3A5\*3, rs776746),
- ABCB1 (C1236T, rs1128503)
- ABCB1 (C3435T, rs1045642)

### SNaPshot™ Multiplex Analysis

- CYP2B6\*6 (K262R, rs2279343)
- CYP2C19\*17 (-806C/T, rs12248560)



# Study Population

1549 Patients  
undergoing CAG±PCI



1431 Patients



1115 Available for  
analysis

## Excluded:

- 1: Caucasian
- 3: Use of GP IIb/IIIa inhibitor
- 114: Use of Cilostazol

316: **Did not agree to or failed** genotyping

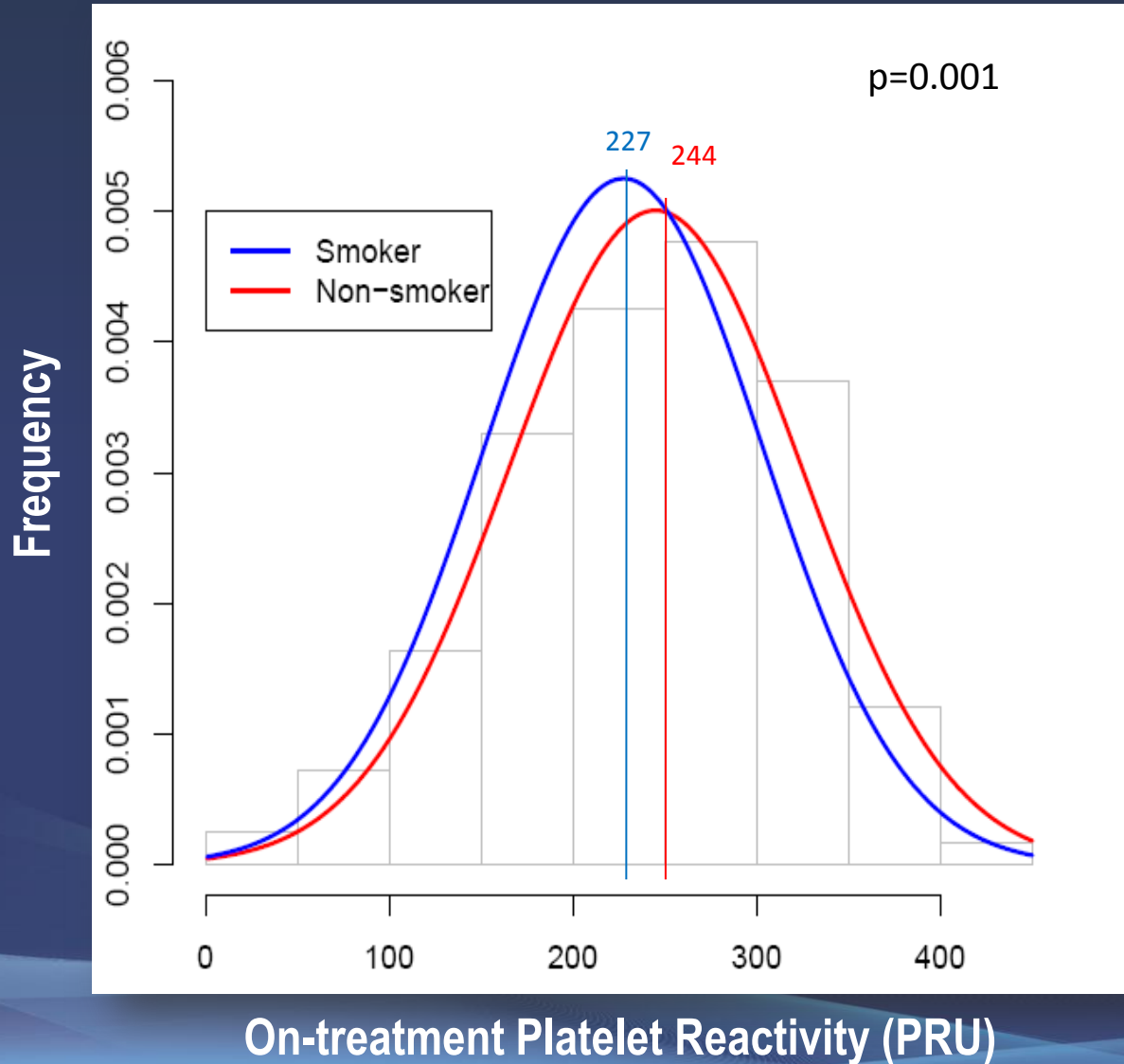
# Baseline Characteristics

	Non-smoker	Smoker	p-value
Age (years)	64.1 (9.4)	59.7 (10.1)	<0.001
Male	714 (60.4%)	232 (93.2%)	<0.001
Hypertension	785 (66.4%)	136 (54.4%)	0.001
Diabetes	377 (31.9%)	67 (26.9%)	0.122
Dyslipidemia	580 (49.1%)	92 (36.9%)	<0.001
Chronic kidney disease	29 (2.5%)	5 (2.0%)	0.675
Previous PCI	432 (36.5%)	64 (25.7%)	0.001
Previous CABG	72 (6.1%)	6 (2.4%)	0.020
Previous Myocardial infarction	105 (8.9%)	19 (7.6%)	0.523
Congestive heart failure	7 (0.6%)	3 (1.2%)	0.292
Cerebrovascular accident	95 (8.0%)	14 (5.6%)	0.192
Peripheral artery disease	14 (1.2%)	7 (2.8%)	0.075
BMI	25.1 (3.0)	24.5 (3.2)	0.013
<i>Laboratory finding</i>			
Platelet (1000/ $\mu$ L)	220 (62)	224 (58)	0.286
Creatinine (mg/dL)	1.18 (0.08)	1.24 (0.75)	0.931

# Questions

1. Does Smoking Influence Clopidogrel Response?
2. Can It Be Applied To All Smokers?
3. What Is The Clinical Implication?

# Smokers have lower On-treatment Platelet Reactivity (OPR)





# Questions

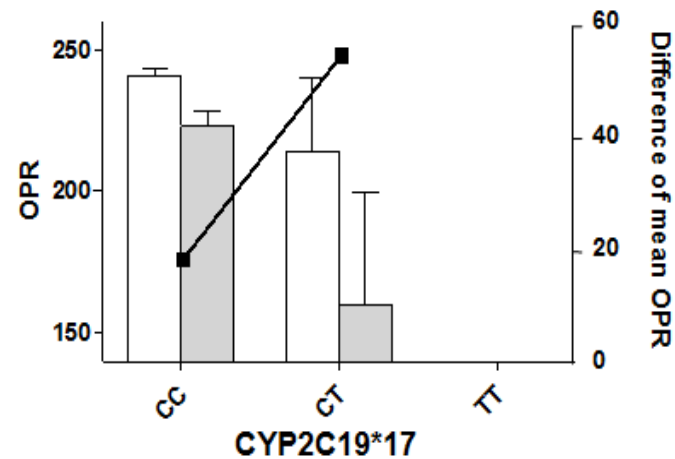
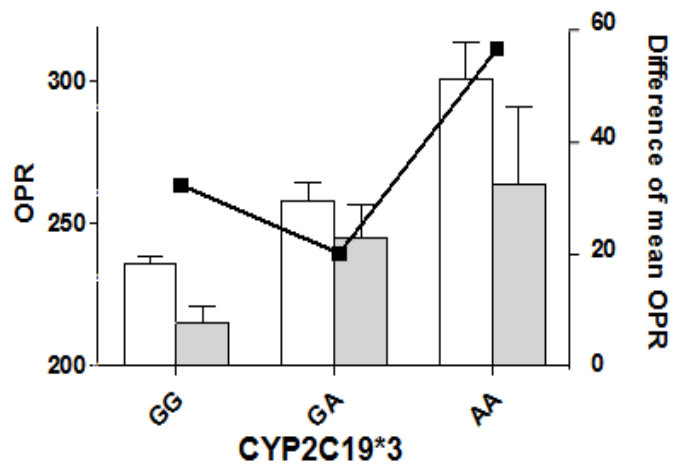
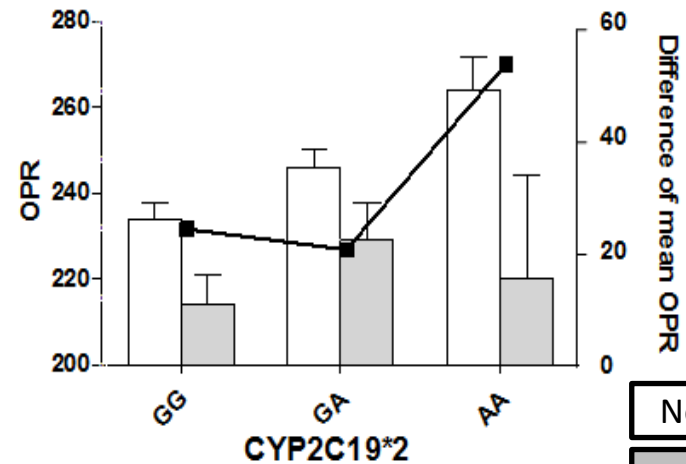
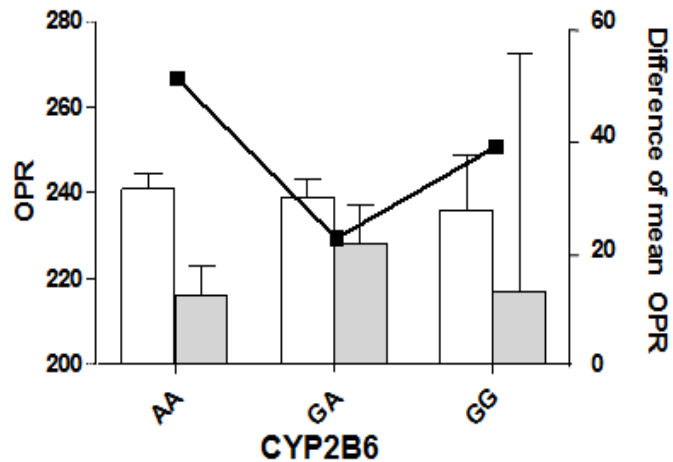
1. Does Smoking Influence Clopidogrel Response?
2. Can It be Applied To All Smokers?
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# Genotype distribution

Gene	SNP	Call Rate	Frequency		HWE
			Major	Minor	X <sup>2</sup> -test
CYP1A2	rs762551	99.4%	0.63	0.37	0.046
CYP2B6	rs2279343	98.1%	0.78	0.22	0.076
CYP2C19	rs4244285	99.3%	0.73	0.27	0.207
CYP2C19	rs4986893	99.7%	0.90	0.10	<0.001
CYP2C19	rs12248560	97.8%	0.99	0.01	0.783
CYP3A4	rs2242480	99.3%	0.79	0.21	0.729
CYP3A5	rs776746	99.4%	0.76	0.24	0.561
ABCB1	rs1128503	99.0%	0.54	0.46	<0.001
ABCB1	rs1045642	99.0%	0.64	0.36	0.895

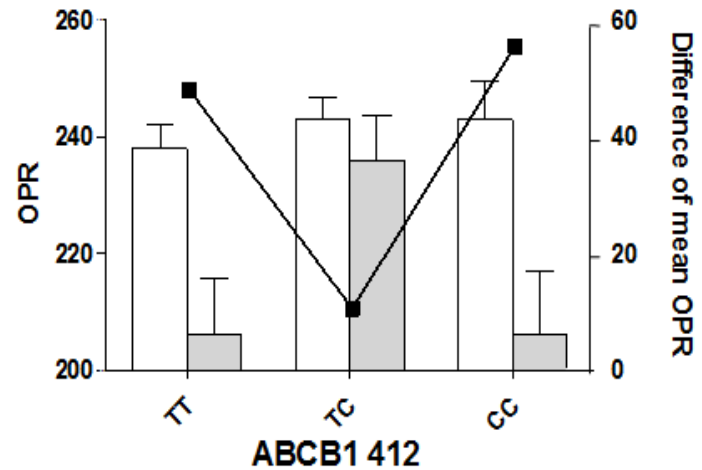
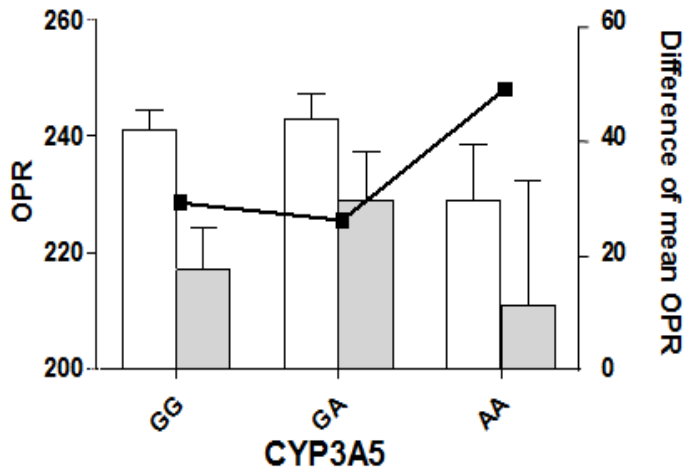
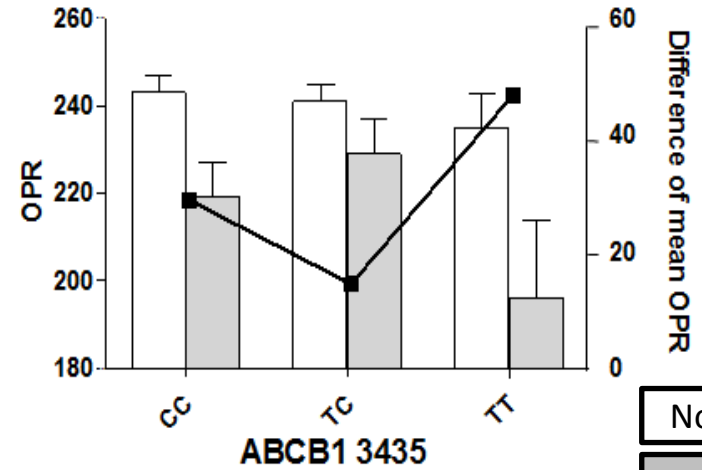
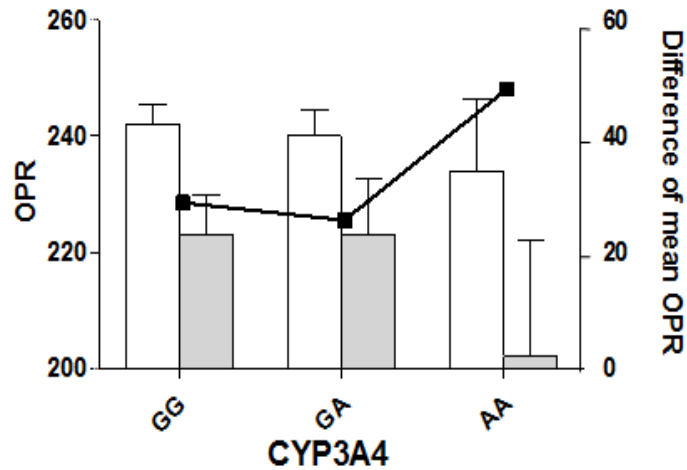
# OPR according to smoking and genotype (i)



Non-smokers  
Smokers

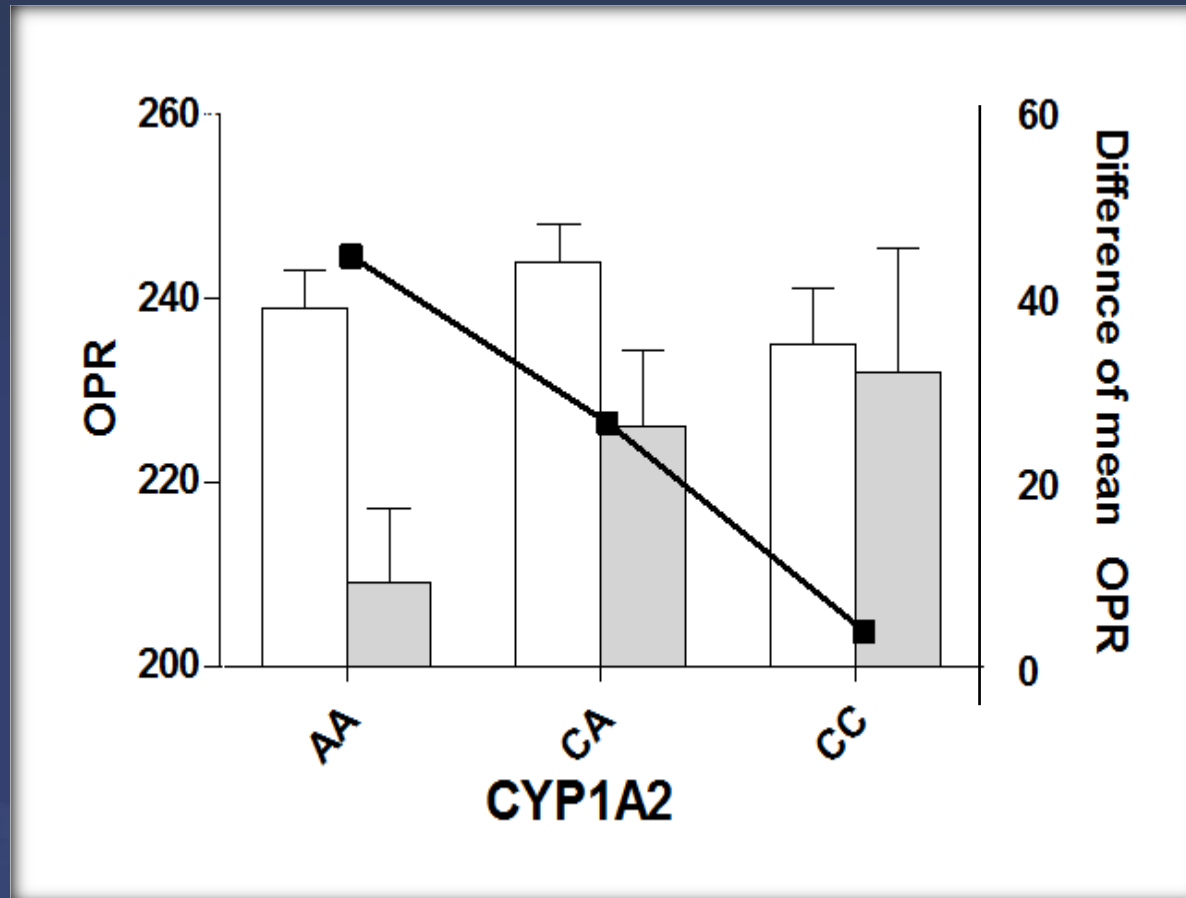


# OPR according to smoking and genotype (ii)



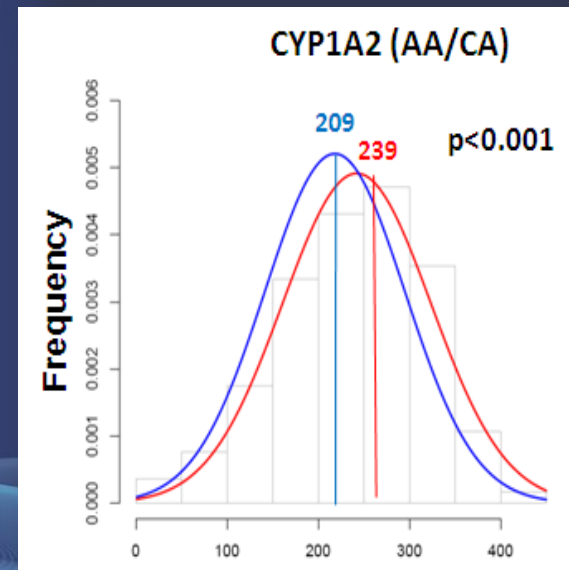
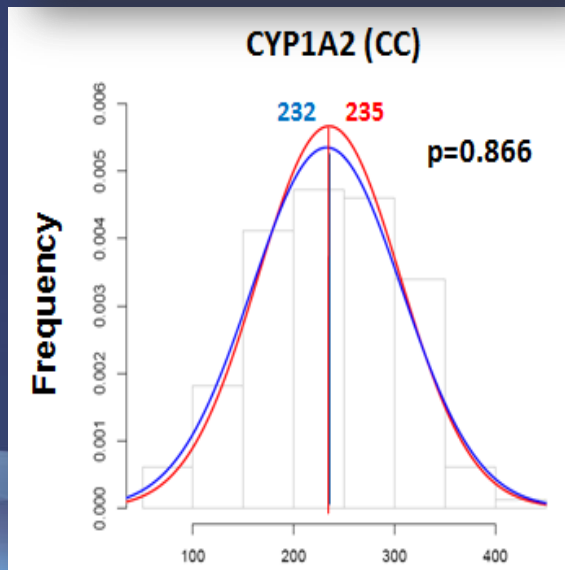
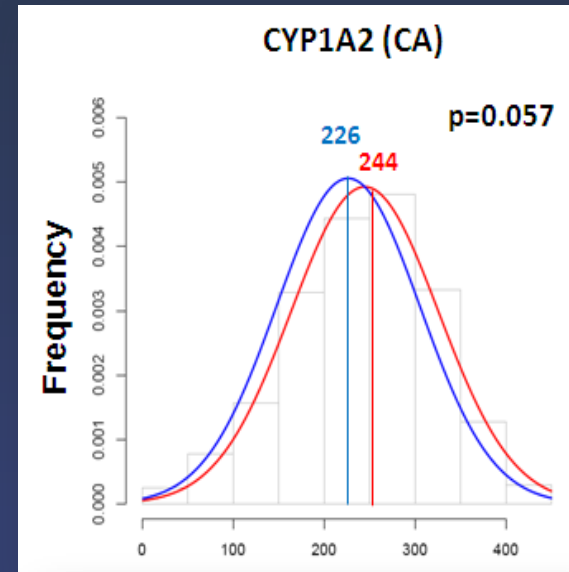
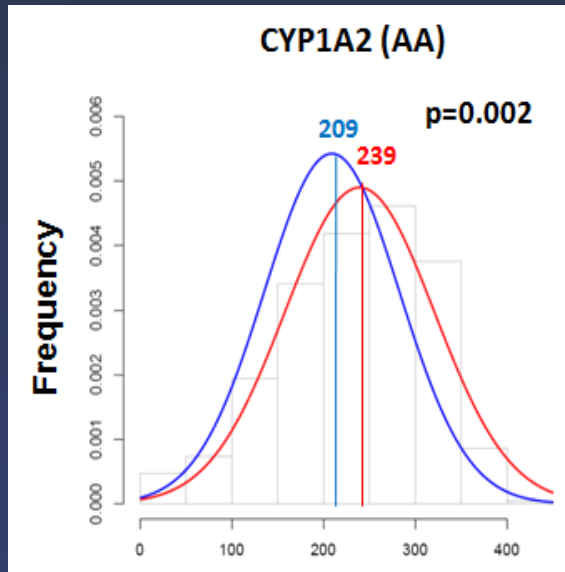
Non-smokers  
Smokers

# OPR according to smoking and genotype (iii)



# OPR distribution according to CYP1A2 genotype

— Smoker  
— Non-smoker

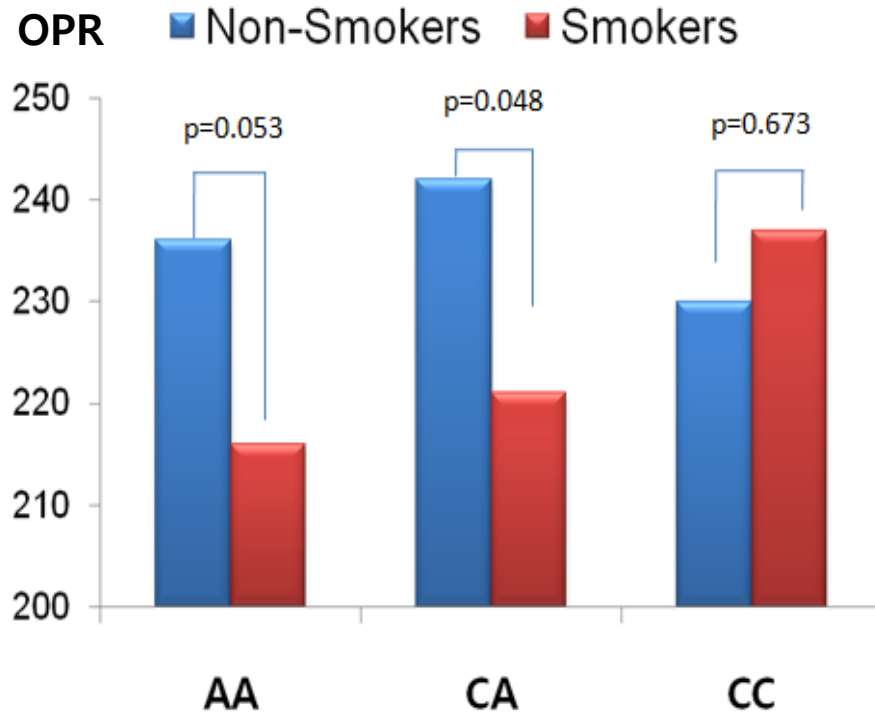


# Effect of Smoking on OPR according to CYP1A2 (-163 C>A) status : Multivariate analysis

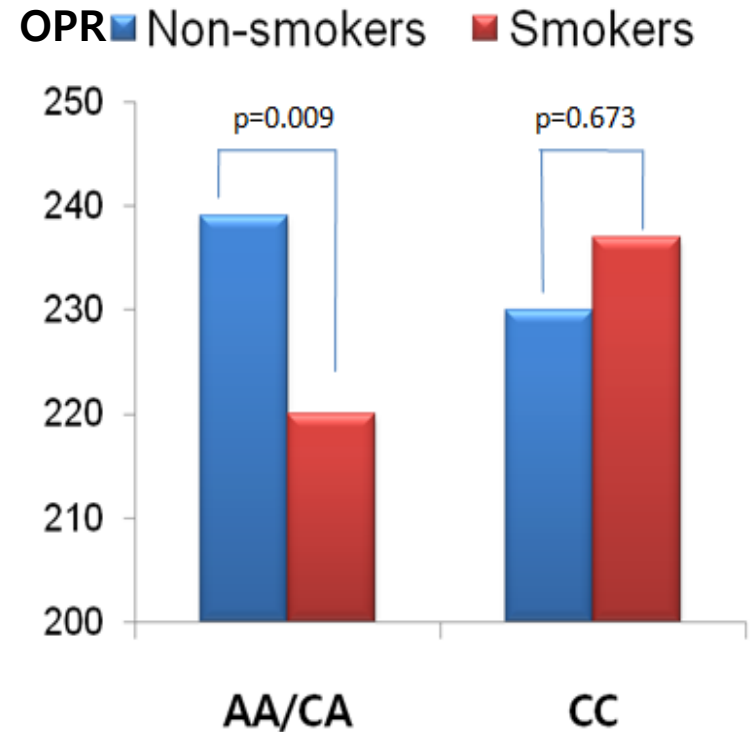
CYP1A2 (-163 C>A)	OPR-Difference	p-value	95% CI
All (AA/CA/CC)	- 12.0	0.037	-0.70 ~ -23.36
AA	- 20.0	0.053	0.23 ~ -40.25
CA	- 20.4	0.048	-0.17 ~ -40.58
AA/CA	- 19.0	0.009	-4.77 ~ -33.23
CC	+ 6.5	0.673	+36.64 ~ -23.71

**Adjusted** for age, hypertension, calcium channel blocker, serum creatinine, low density lipoprotein, high density lipoprotein

# Impact of smoking on OPR according to CYP1A2 (-163 C>A) status



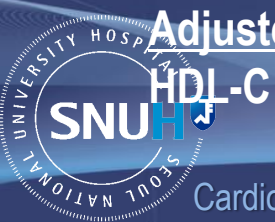
A. Co-dominant model



B. Dominant model

Adjusted for age, hypertension, calcium channel blocker, serum creatinine, LDL-C,

HDL-C



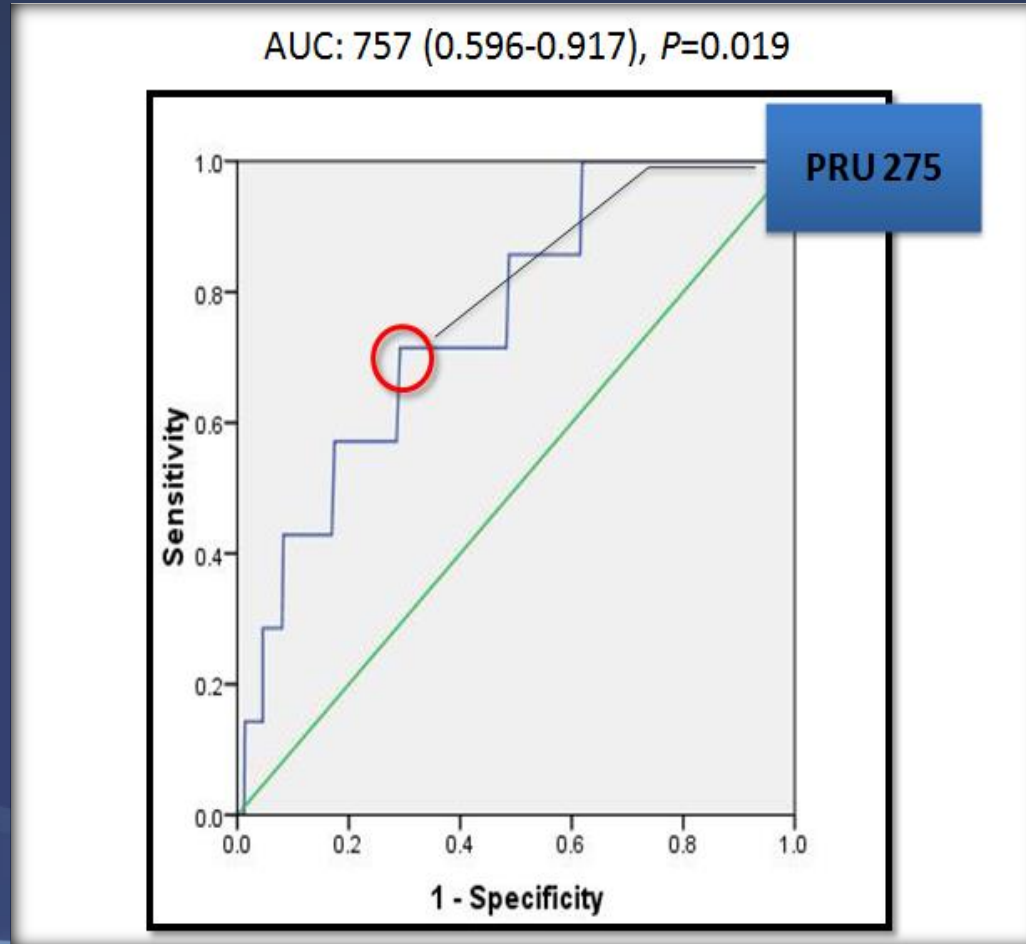


# Questions

1. Does Smoking Influence Clopidogrel Response?
2. Can It be Applied To All Patients?
3. Does It Have Any Clinical Implication?

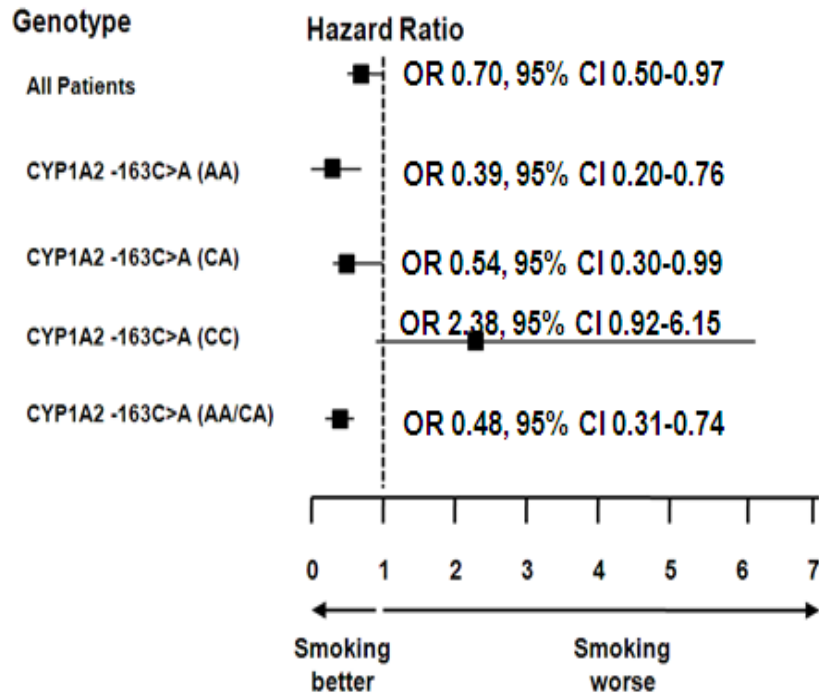


# Definition of High On-treatment Platelet Reactivity (Stent Thrombosis)

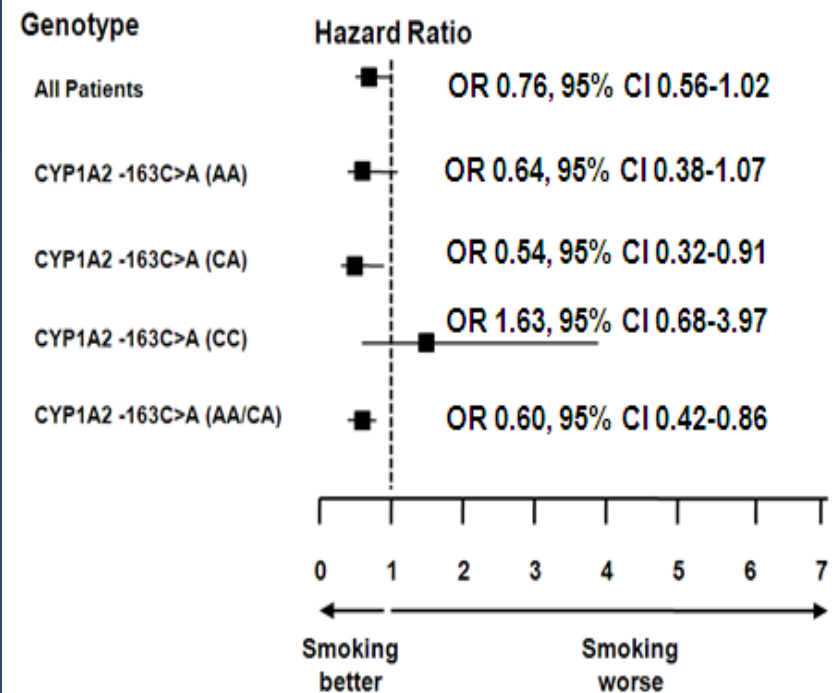


# CYP1A2 (-163C>A) Status and Risk for HOPR

## HOPR defined as PRU>275



## HOPR defined as PRU>235



# Smokers' paradox

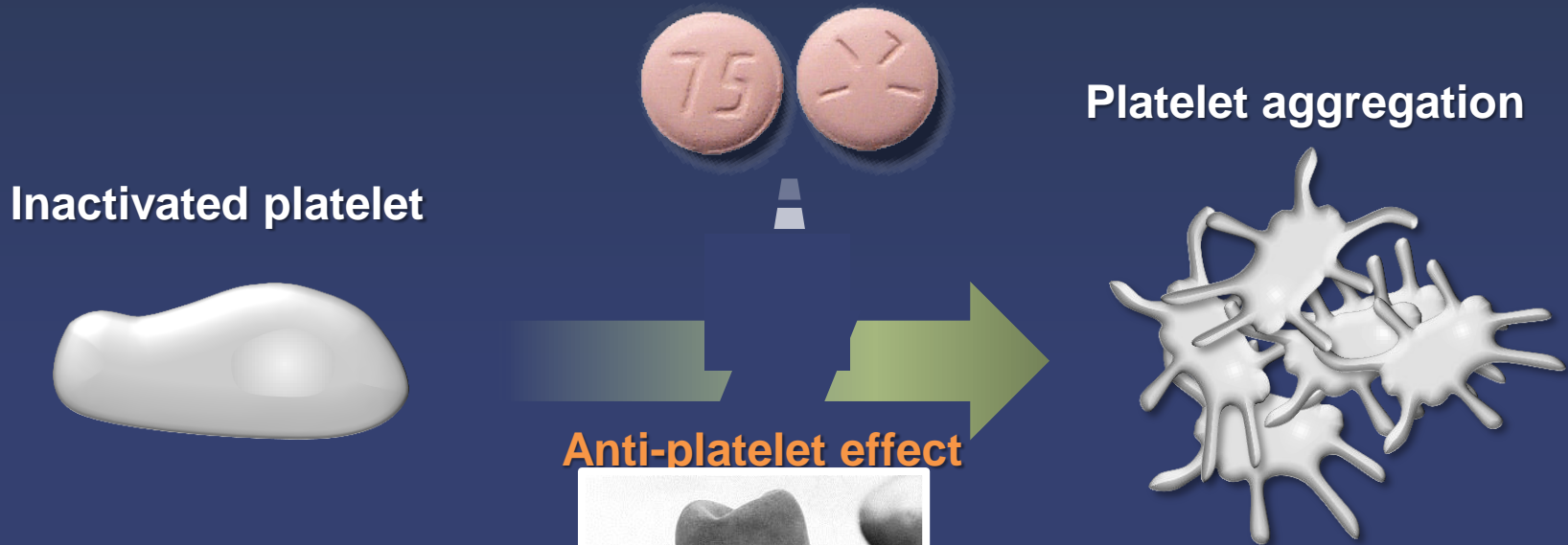
1. Smoking was associated with lower on-treatment platelet reactivity (by 12 PRU) .
2. Of the 9 genotypes that may influence clopidogrel metabolism and thus activation, only the CYP1A2 \*1F SNP was associated with a differential effect in smokers vs. non-smokers.
3. Smoking was associated with decreased mean OPR (-19 PRU) and 52% reduced risk for high OPR in only A-allele carriers, suggesting genotype dependence.

# Smoking & Enhanced Clopidogrel Effect



1. There should be an association
2. A should occur before B
3. The reverse should hold true
4. A dose response could help

# Causation or Chance Finding?



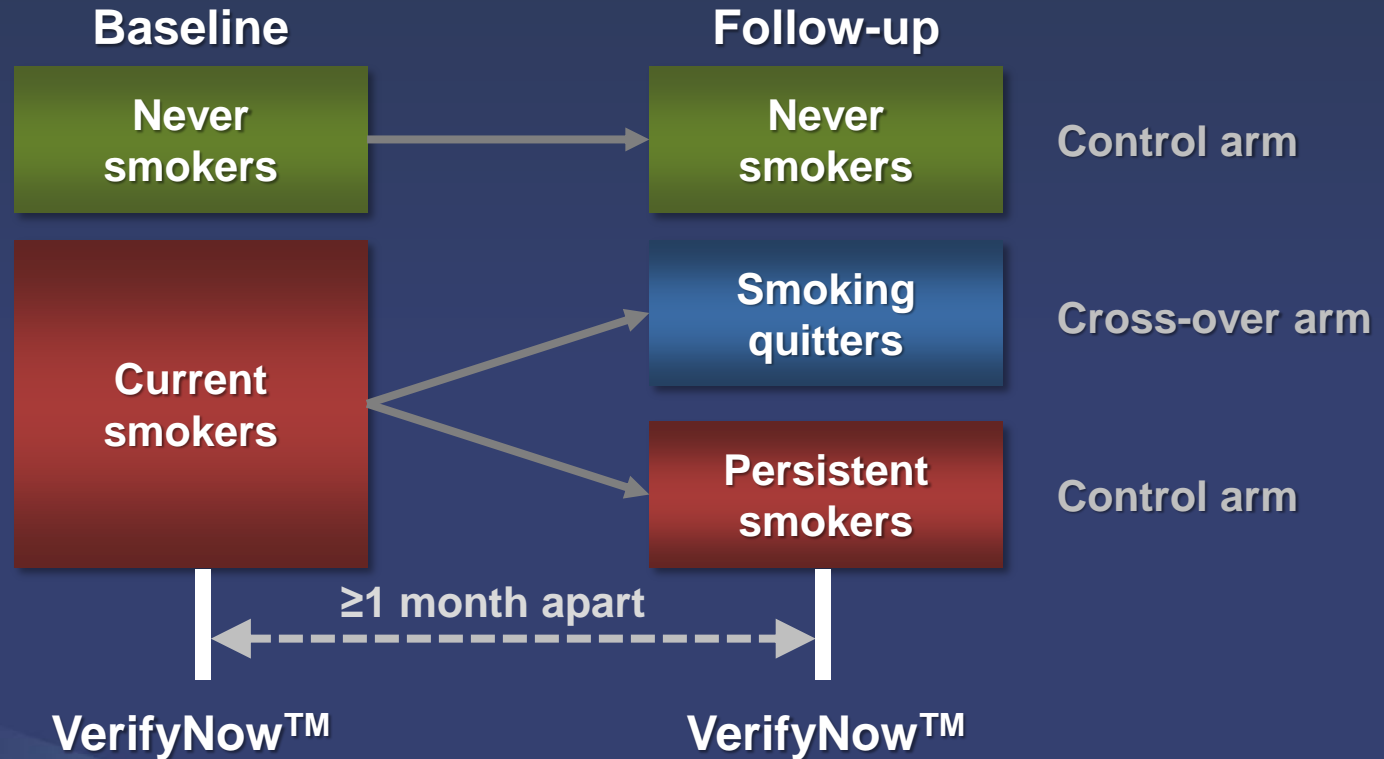
# Question



What happens if he quits smoking cigarettes?



# Study Design





# Methods

- **Definitions**

- Never smoker: never smoked & has not smoked
- Smoking quitter: not smoked for at least 1 month
- Persistent smoker: smoked at baseline and till the F/U survey

- **Major dependent variables**

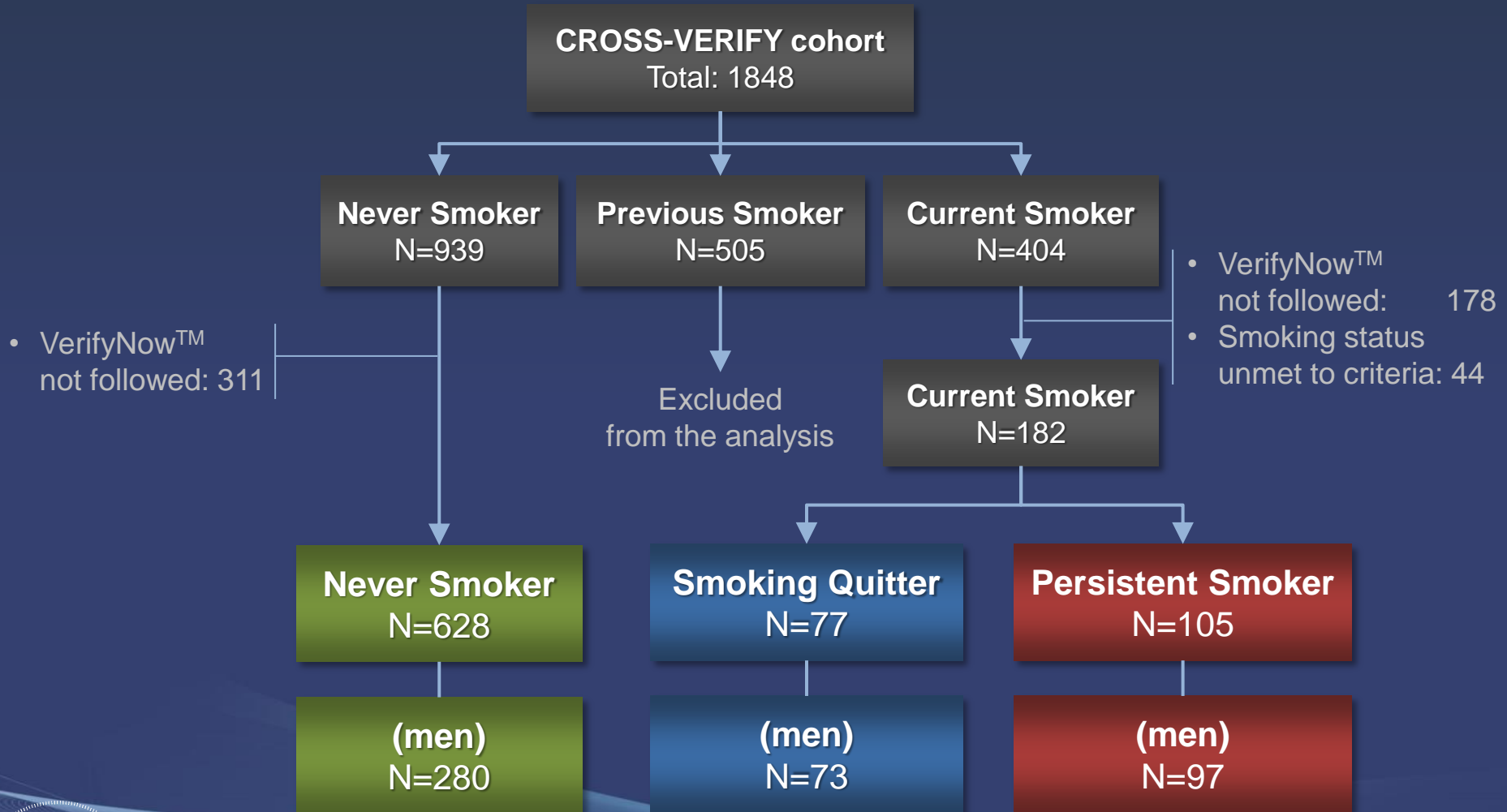
- **OPR** (on-clopidogrel platelet reactivity)
- Frequency of patients with **HOPR** (high OPR):  $OPR \geq 235$  PRU

- **Statistical analysis**

- Continuous variables: with ANOVA
- Categorical variables: with  $\chi^2$  test and logistic regression
- Main analysis: generalized estimating equation
- p-value  $< 0.05$ : significant



# Study Scheme



# Baseline Characteristics (1)

	Never smoker (N=628)	Smoking quitter (N=77)	Persistent smoker (N=105)	Overall p-value	Pairwise p-value		
					N vs. Q	N vs. P	Q vs. P
Smoking amount – per day	-	20.4±9.8	19.4±10.4	-	-	-	NS
Men	44.6%	94.8%	92.4%	<0.001	<0.001	<0.001	NS
Age – year	65.7±8.76	57.2±9.9	58.6±9.5	<0.001	<0.001	<0.001	NS
Body mass index – kg/m <sup>2</sup>	25.1±3.2	24.9±3.8	24.9±2.9	NS	NS	NS	NS
Hypertension	73.1%	49.4%	57.1%	<0.001	<0.001	0.001	NS
Diabetes mellitus	35.7%	23.4%	31.4%	NS	NS	NS	NS
Dyslipidemia	42.8%	44.2%	43.8%	NS	NS	NS	NS
Chronic renal failure	3.5%	1.3%	1.9%	NS	NS	NS	NS
Previous PCI	27.9%	15.6%	20.0%	0.024	0.024	NS	NS



# Baseline Characteristics (2)

	Never smoker (N=628)	Smoking quitter (N=77)	Persistent smoker (N=105)	Overall p-value	Pairwise p-value		
					N vs. Q	N vs. P	Q vs. P
<b>Laboratory findings</b>							
Hemoglobin – mg/dL	12.9±1.5	14.4±1.7	14.2±2.2	<0.001	<0.001	<0.001	NS
Platelet – 1,000/μL	218±60	213±47	219±60	NS	NS	NS	NS
Creatinine – mg/dL	1.14±0.90	1.07±0.23	1.19±0.82	NS	NS	NS	NS
Total cholesterol – mg/dL	160±42	158±37	163±41	NS	NS	NS	NS
Triglyceride – mg/dL	135±79	166±103	161±87	<0.001	0.005	0.008	NS
HDL-cholesterol – mg/dL	44±11	41±11	40±9	0.002	NS	0.003	NS
LDL-cholesterol – mg/dL	93±36	92±32	99±36	NS	NS	NS	NS



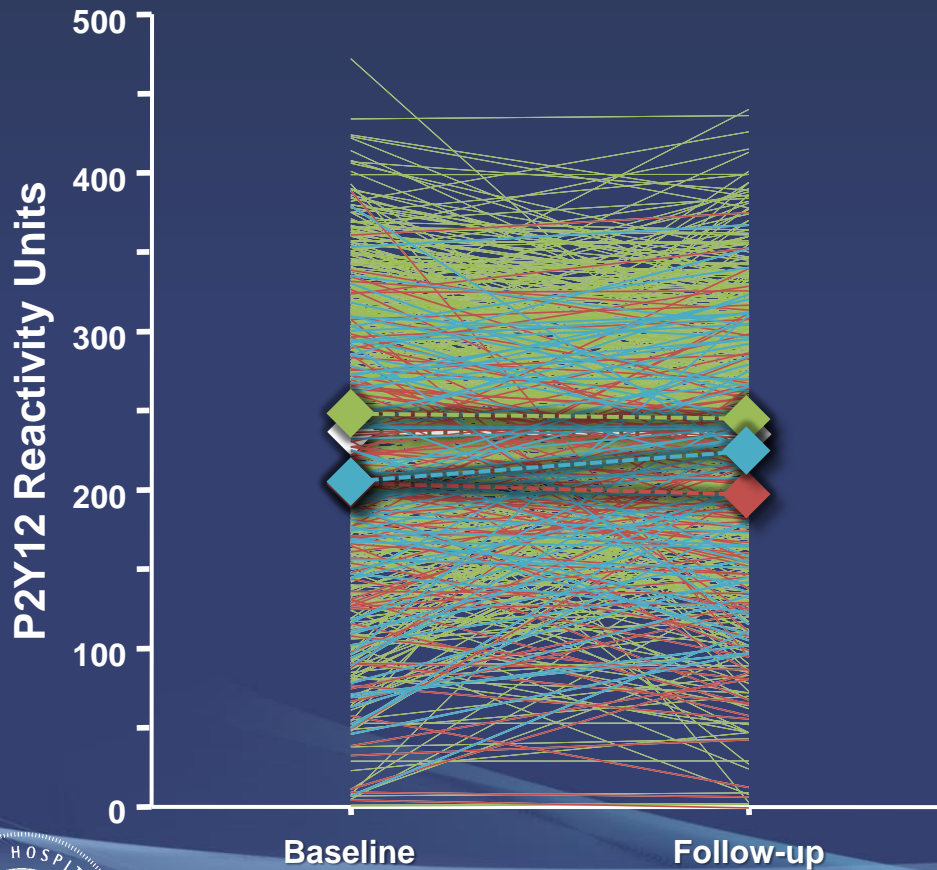
# Baseline Characteristics (3)

	Never smoker (N=628)	Smoking quitter (N=77)	Persistent smoker (N=105)	Overall p-value	Pairwise p-value		
					N vs. Q	N vs. P	Q vs. P
ACE inhibitors	11.9%	18.2%	10.5%	NS	NS	NS	NS
Angiotensin receptor blockers	31.4%	15.6%	21.0%	<b>0.003</b>	<b>0.005</b>	<b>0.032</b>	NS
β-blockers	51.1%	44.2%	44.8%	NS	NS	NS	NS
Calcium channel blockers	32.6%	19.5%	21.9%	<b>0.009</b>	<b>0.021</b>	<b>0.029</b>	NS
Dihydropyridine	20.5%	9.1%	17.1%	<b>0.047</b>	<b>0.020</b>	NS	NS
Non-dihydropyridine	12.1%	10.4%	6.7%	NS	NS	NS	NS
Hydrochlorothiazide	7.3%	5.2%	4.8%	NS	NS	NS	NS
Statin	62.1%	57.1%	60.0%	NS	NS	NS	NS
Lipophilic statin	41.2%	35.1%	39.0%	NS	NS	NS	NS
Hydrophilic statin	20.9%	22.1%	21.0%	NS	NS	NS	NS
Proton pump inhibitors	1.6%	1.3%	0.0%	NS	NS	NS	NS



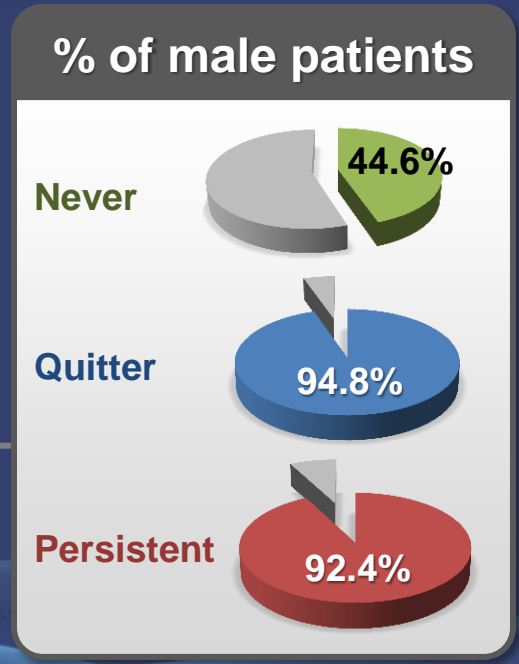
# Changes in OPR

- Never smoker (N=628)
- Smoking quitter (N=77)
- Persistent smoker (N=105)

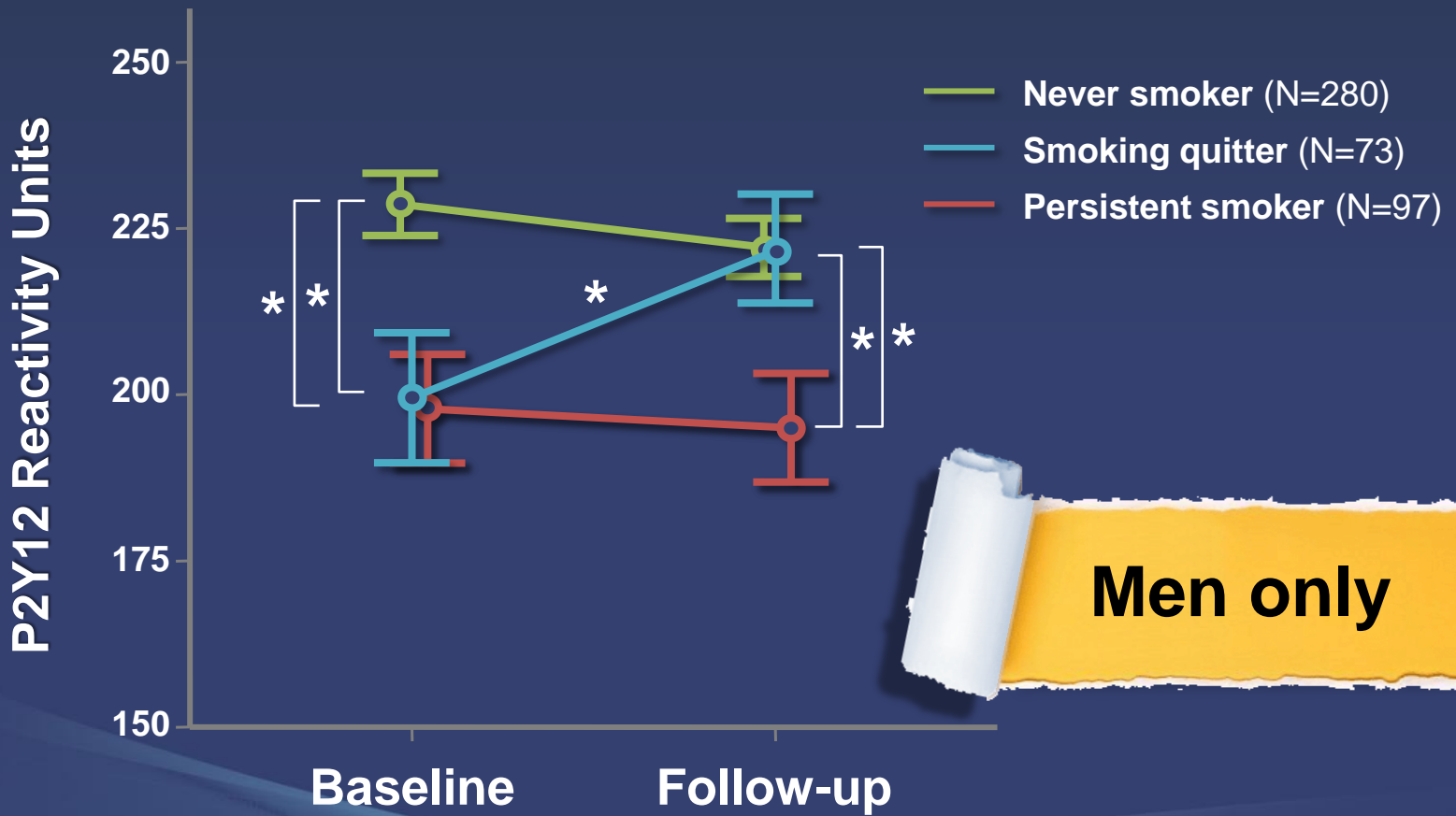


- **Median F/U duration**  
: 2.9 mo (IQ: 1.0-6.2 mo)
- **Correlation between OPR at baseline & at F/U**  
:  $R^2=0.386$ ;  $p<0.001$
- **Mean  $\pm$  SD**  
(baseline vs. F/U)  
:  $236 \pm 86$  vs.  $234 \pm 80$   
( $p=0.578$ )

# Changes in OPR



# Changes in OPR



**Men only**





# Changes in OPR

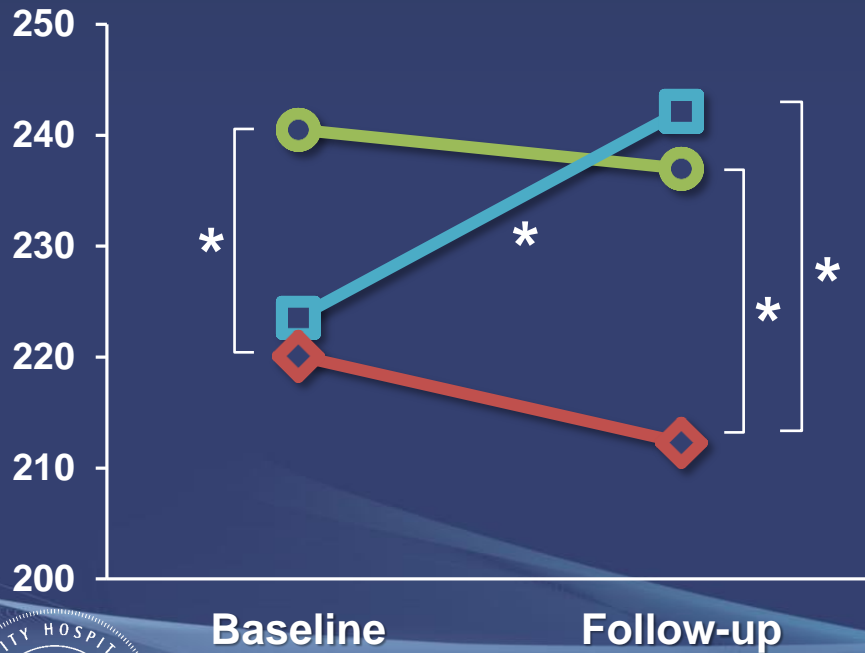
	Never smoker	Smoking quitter	Persistent smoker	Pairwise p-value		
				N vs. Q	N vs. P	Q vs. P
<b>All patients</b>	(N=628)	(N=77)	(N=105)			
Baseline PRU	246±85 ↓ Δ-3	203±83 ↓ Δ+19	202±83 ↓ Δ-7	<0.001	<0.001	0.932
Follow-up PRU	243±79	222±69	195±81	0.015	<0.001	0.010
p-value	0.311	0.013	0.275	<b>0.007</b>	<b>0.546</b>	<b>0.010</b>
<b>Men only</b>	(N=280)	(N=73)	(N=97)			
Baseline PRU	229±78	200±83	198±80	0.007	0.001	0.895
Follow-up PRU	222±73	222±70	195±81	0.955	0.003	0.021
p-value	0.099	0.005	0.662	<b>0.001</b>	<b>0.632</b>	<b>0.015</b>

interaction p-values calculated with the use of generalized estimating equation.

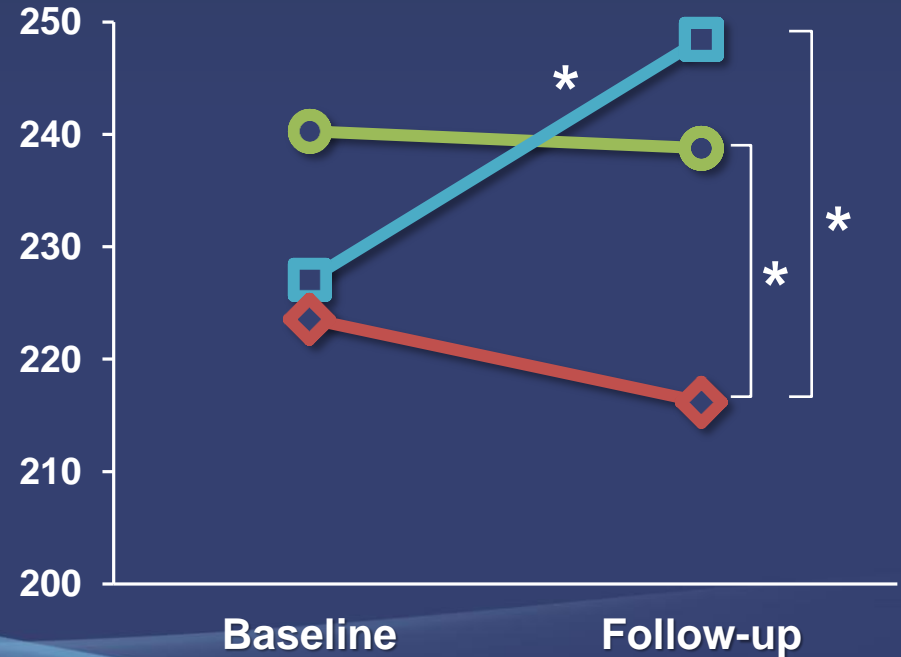
# Changes in OPR

## Multivariable Adjustment

adjusted for age & sex



adjusted for age, sex, baseline risk factors, and medications

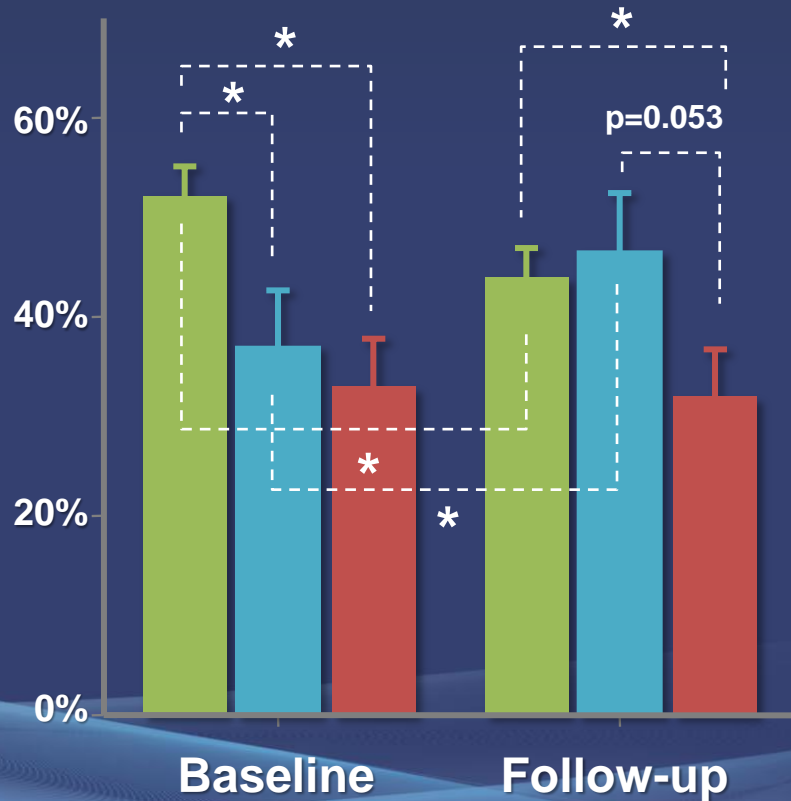
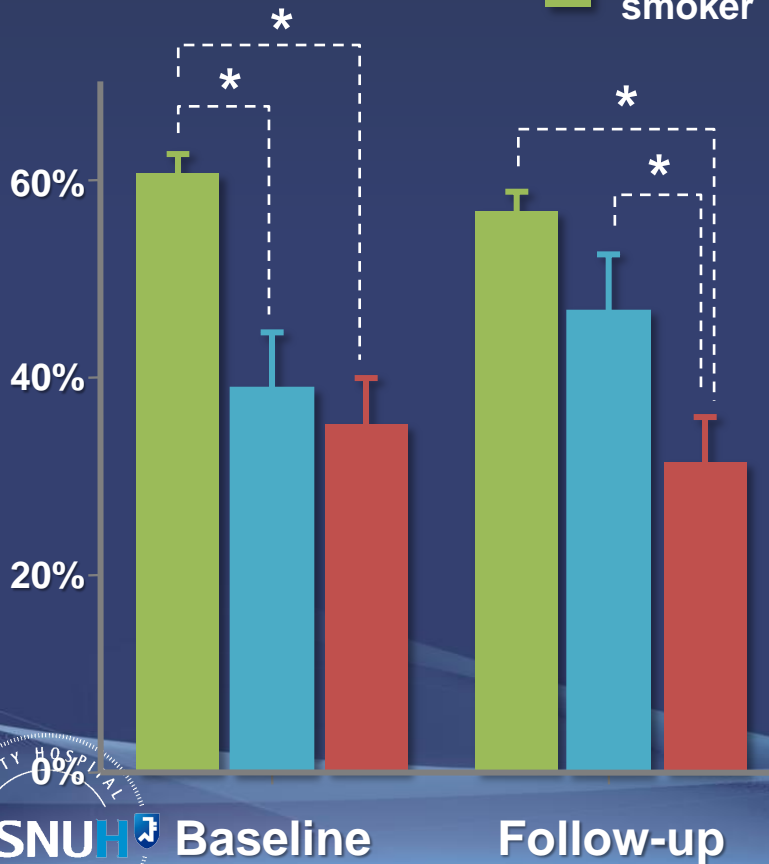


# Frequency of HOPR

All patients

Men only

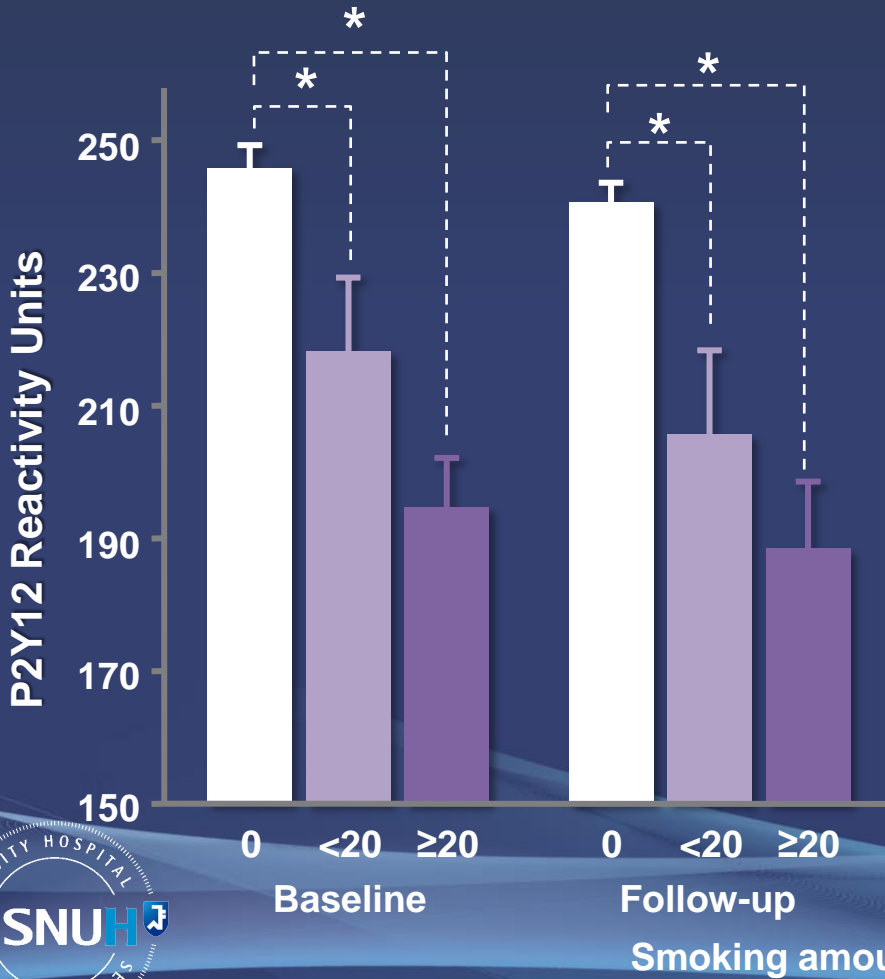
Never smoker Smoking quitter Persistent smoker



# Association with smoking amount

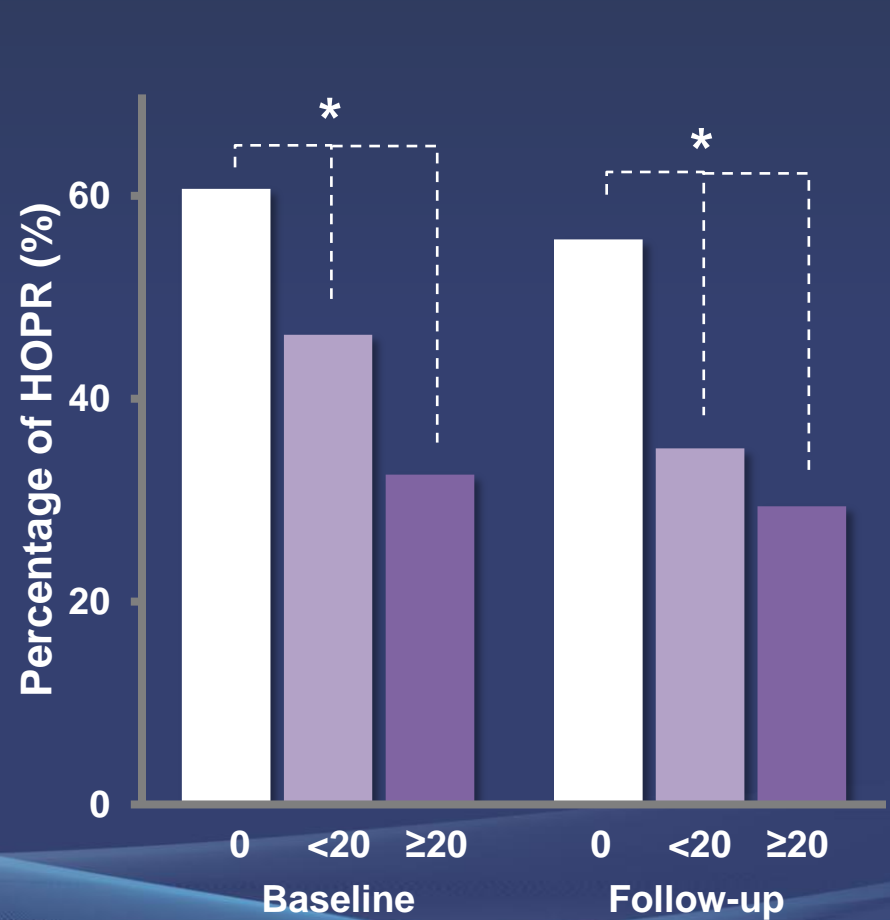
OPR

p for linearity < 0.001



HOPR

p for linearity = 0.001



# Summary

	OPR		% HOPR	
	baseline	changes at F/U	baseline	changes at F/U
Never smokers	high	→	high	→
Smoking quitters	low	↑↑	low	↑↑
Persistent smokers	low	→	low	→

- Temporal relationship
  - Smoking → enhanced response to clopidogrel
  - Quitting → reversal of enhanced response
- Dose-response relationship
  - : Smoking amount  $\propto$  antiplatelet effect of clopidogrel

# Smokers' Paradox to Clopidogrel: Is it fiction?

Our data suggests that there exists a causal relationship between smoking and enhanced response to clopidogrel.



**Thank You for Your Attention**