# Old and New Antiplatelet Agents

*Kyung Woo Park, MD, PhD*

*Cardiovascular Center,*

*Seoul National University Hospital*

# Sometimes “Old” can be “Classic”?

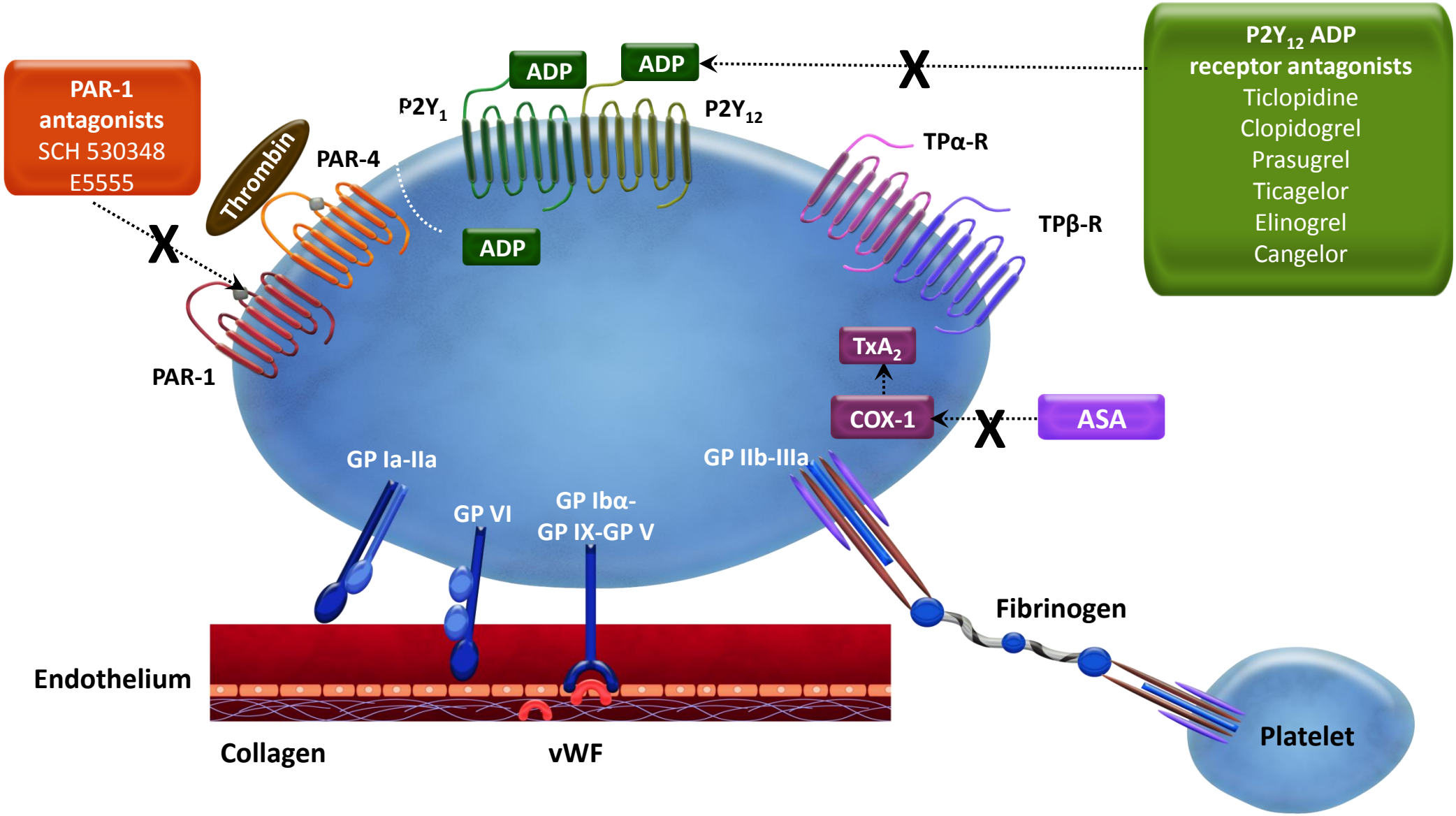


***…. something that is a perfect example of a particular style,***

***something of lasting worth or with a timeless quality.***

***(Wikipedia)***

# Platelet Agonists and Antiplatelet Agents



# Clopidogrel is still the classic thienopyridine

1. *Medical Management of ACS*
2. *Alternative to aspirin as single therapy in aspirin intolerant patients*
3. *Post elective PCI of stable angina*
4. *For 2ndary prevention of stroke*
5. *To prevent CVA in patients with Atrial fibrillation in warfarin intolerant patients (ACTIVE-A)*

# HOWEVER ….
# Clopigrel is not PERFECT!!

# *Why do we need newer agents?*

1. Wide variability in Clopidogrel response

    a. genetic variation

    b. possible drug interactions (Cytochrome enzymes): PPIs, lipophilic statins, CCBs etc

2. Unmet needs in thrombosis

3. Patients awaiting surgery : reversible agents

# *Why do we need newer agents?*

**1. Wide variability in Clopidogrel response**

a. genetic variation

b. possible drug interactions (Cytochrome enzymes): PPIs, lipophilic statins, CCBs etc

2. Unmet needs in thrombosis

3. Patients awaiting surgery : reversible agents

# What is the scope of the problem in Korea?

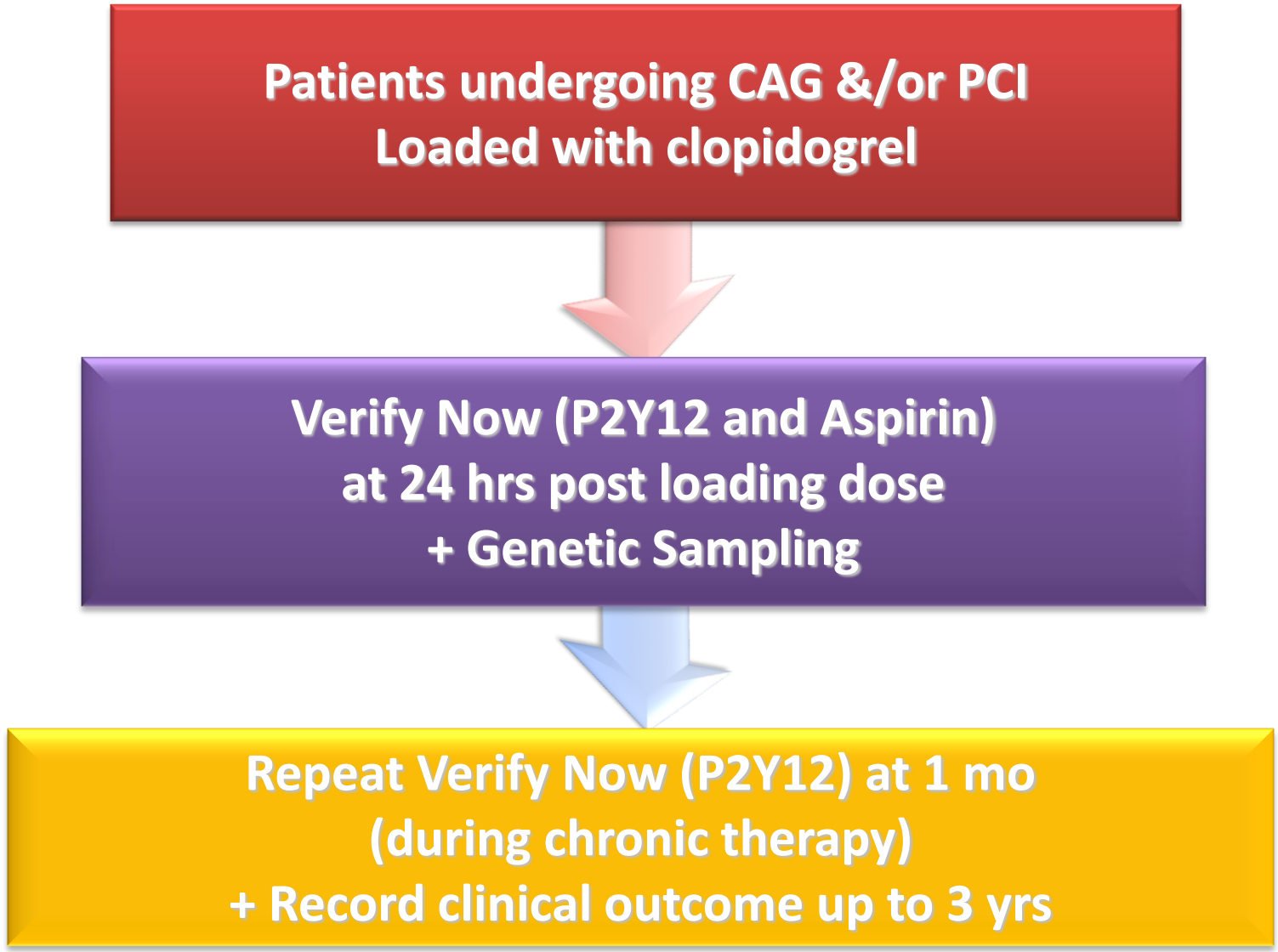
1. Wide variability in OPR in Koreans, with higher mean OPR

2. HOPR associated with clinical outcome.

3. Higher frequency of the CYP2C19 LOF allele in Koreans

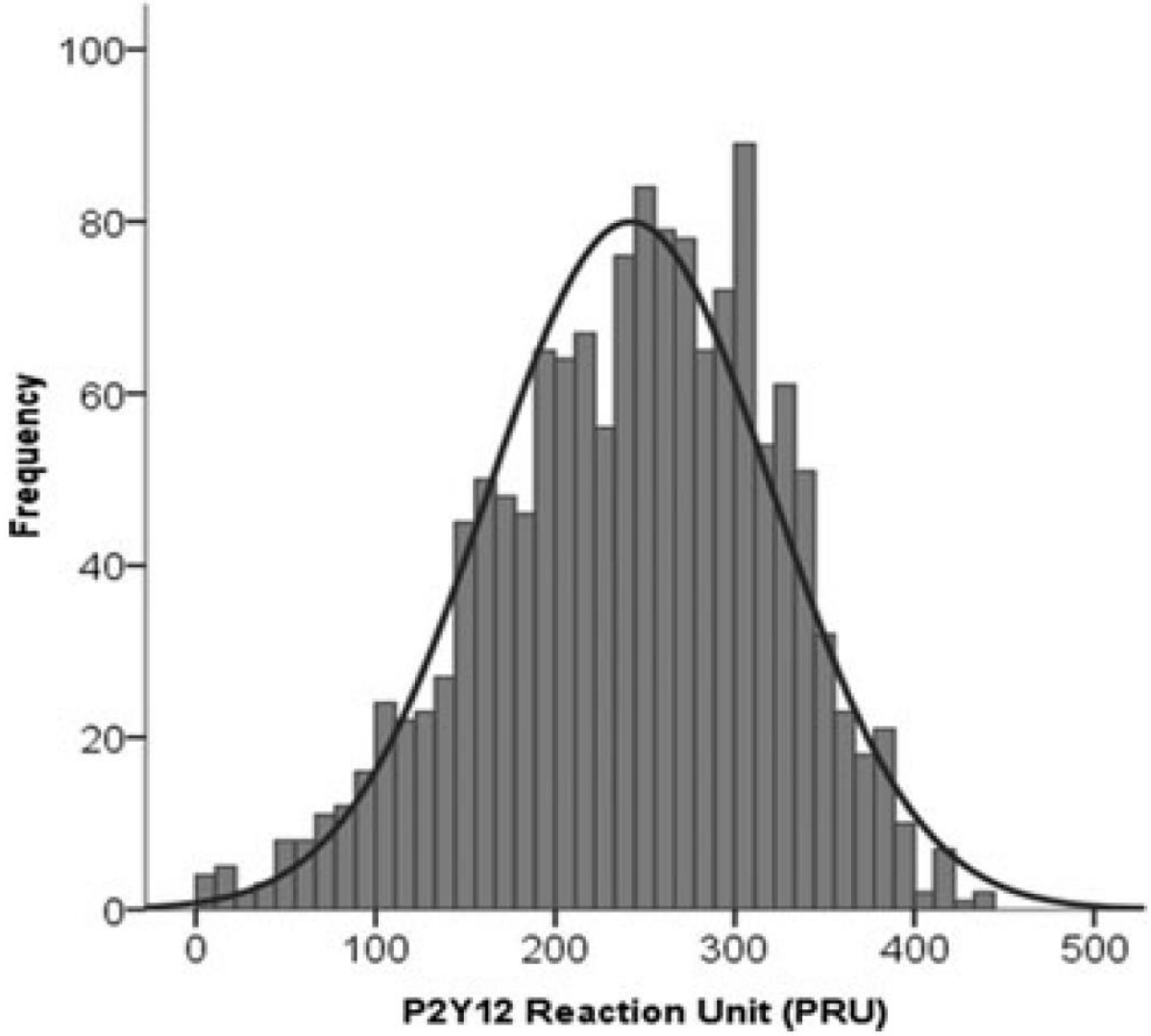
4. Genetic risk is also related with outcome in Koreans?

# The SNUH CROSS-VERIFY cohort : Scheme



# Response variability to Clopidogrel in Koreans

## Data from the SNUH CROSS-VERIFY cohort




**Mean On-treatment Platelet Reactivity:**

**241.9 ± 70.3 PRU**

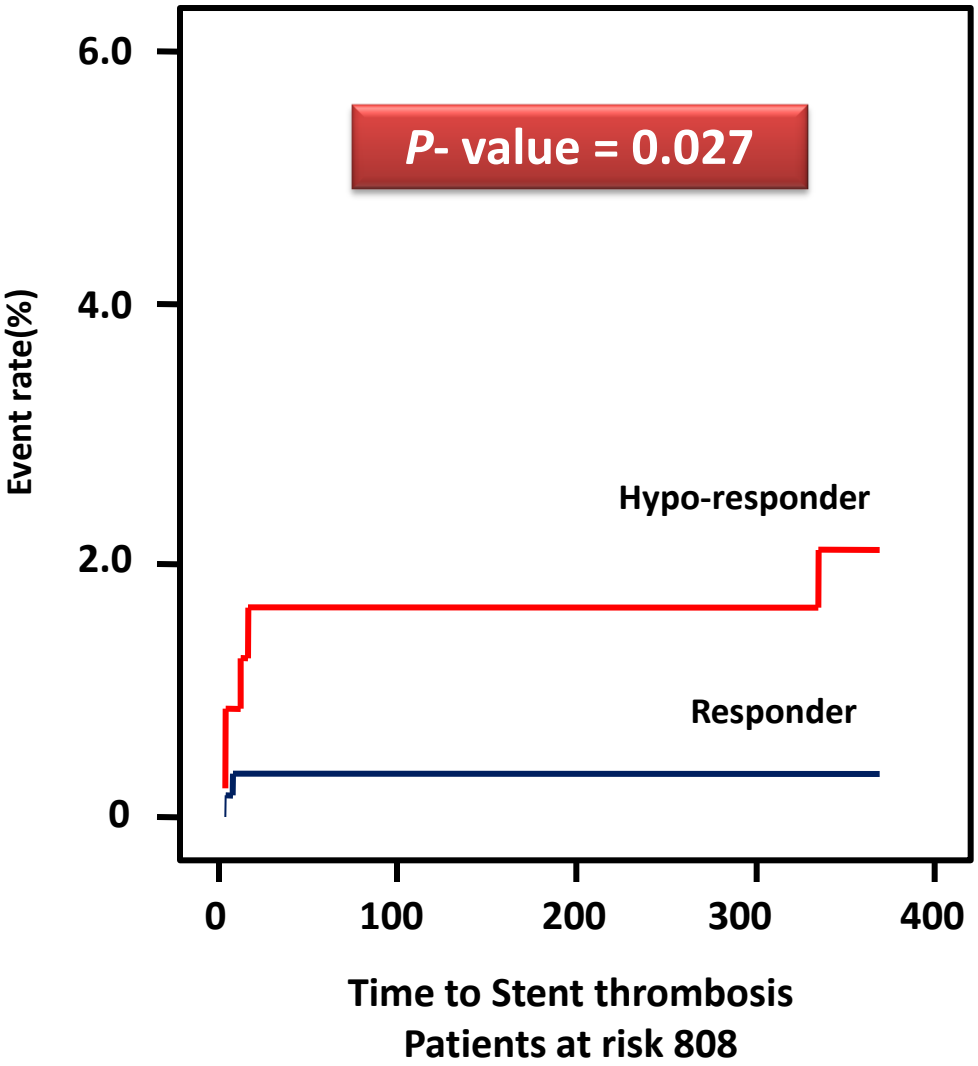
**(N=1431)**

*Park KW, Kim HS et al. Cardiovascular Therapeutics 2010*

*Seoul National University Hospital Cardiovascular Center*

# Clopidogrel Response and Outcome:

## CROSS-VERIFY cohort: Stent Thrombosis (1 Yr)




**Stent Thrombosis**

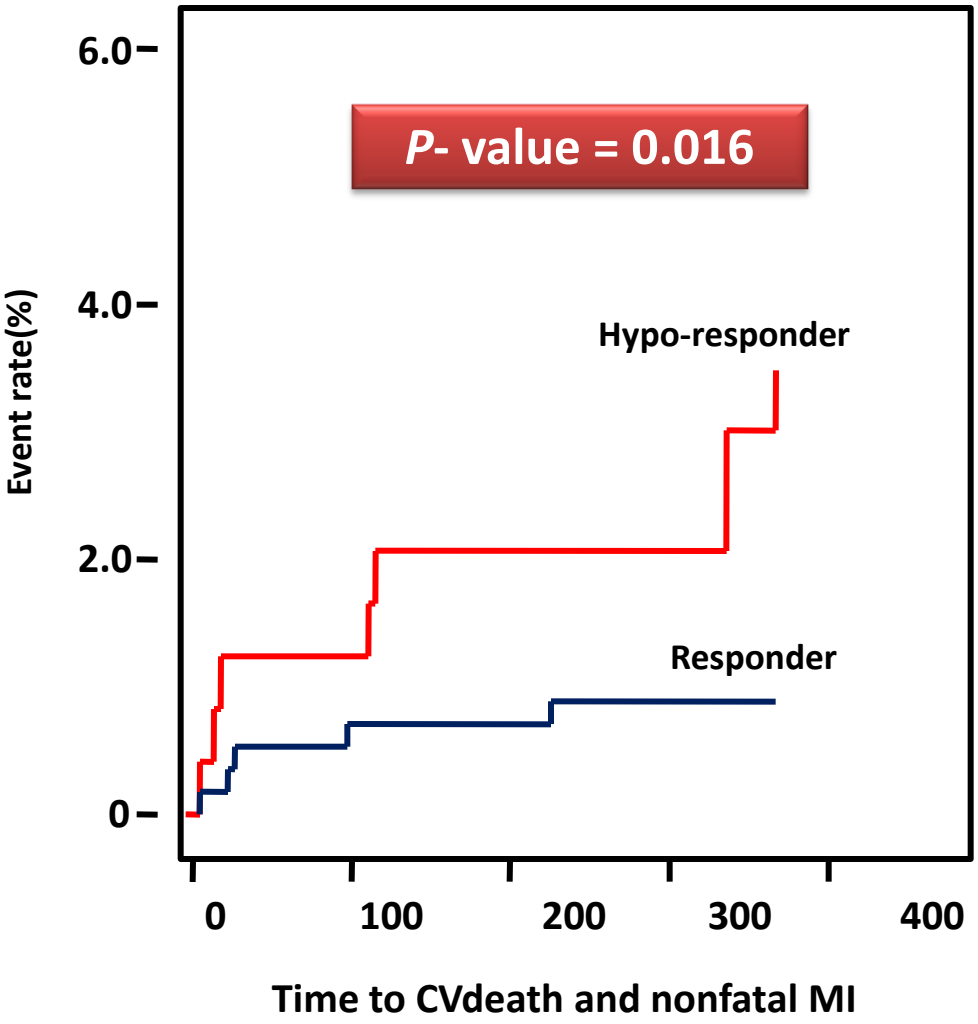
- Non-responder : 5 / 241 (2.1%)
- Responder : 2 / 574 (0.3%)

- HR : **6.059** ( 95% CI 1.167 to 31.451)

*Park KW, Jeon KH, Kim HS et al. Am J Cardiol 2011*

# Clopidogrel Response and Outcome:

## CROSS-VERIFY cohort: CV Death + MI (1 Yr)




**Hard End point**
**(CV death or nonfatal MI)**

- Hypo-responder : 8 / 241 (3.3%)
- Responder : 5 / 574 (0.9%)

- HR : **3.907** ( 95% CI 1.265 to 12.068)

*Park KW, Jeon KH, Kim HS et al. Am J Cardiol 2011*

# Study Overview

**1676 patients received PCI initially enrolled in CROSS-VERIFY during study period**

- 38 patients: non-DES implantation
- 2 patients: non-Korean ethnicity
- 229 patients: refused genetic sampling
- 143 patients : usage of cilostazol

**1264 patients available for genotyping**

| TaqMan™ Assay | SNaPshot™ Multiplex Analysis |
|---|---|
| • CYP1A2*1F (-163C>A, rs762551)<br>• CYP2C19*2 (P227P, rs4244285)<br>• CYP2C19*3 (W212X, rs4986893)<br>• CYP3A4 (IVS10+12G/A, rs2242480)<br>• CYP3A5 (CYP3A5*3, rs776746),<br>• ABCB1 (C3435T, rs1045642)<br>• PON-1 (Q192R, rs662) | • CYP2B6*6 (K262R, rs2279343)<br>• CYP2C19*17 (-806C/T, rs12248560) |

# Does ethnicity matter?

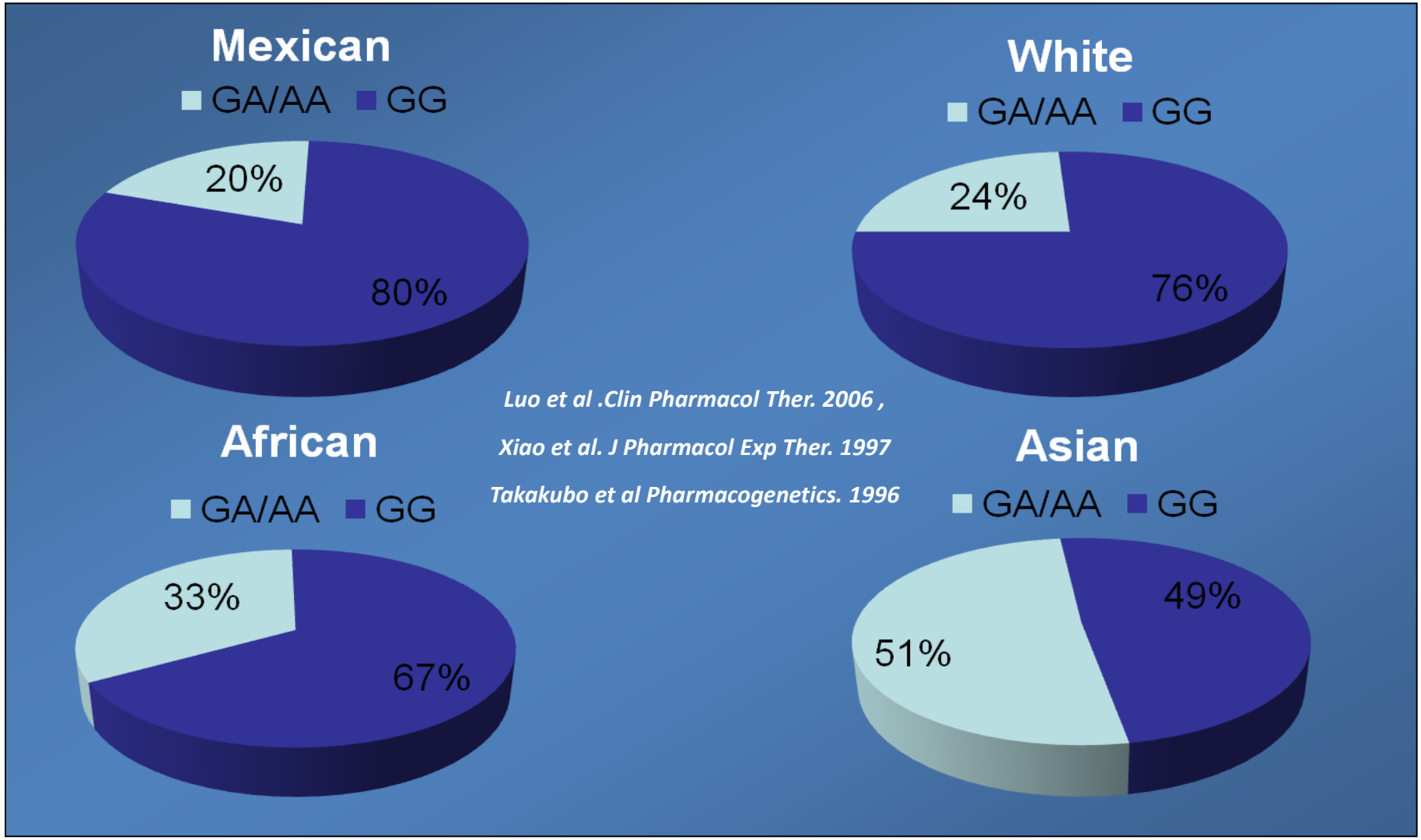
| Characteristic | Mean Residual Platelet Reactivity (PRU) | | P Value |
|---|---|---|---|
| | Characteristic present | Characteristic absent | |
| Age > 75 yrs | 214 ±77 | 201±79 | 0.161 |
| Men | 200±77 | 220±82 | 0.041 |
| Non-Caucasian ethnicity | 229±79 | 202±78 | 0.047 |
| Diabetes mellitus | 220±73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



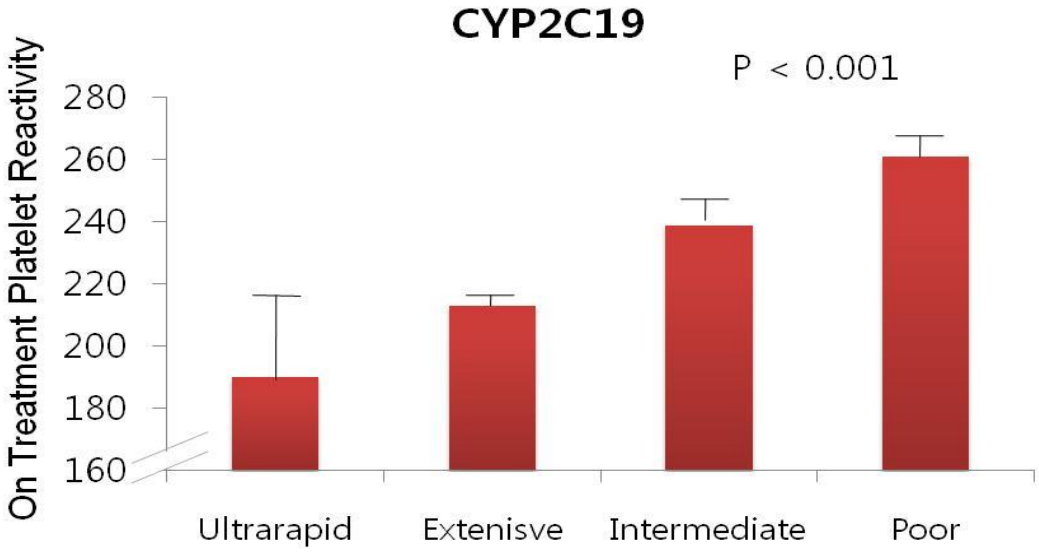

*Luo et al .Clin Pharmacol Ther. 2006 ,*

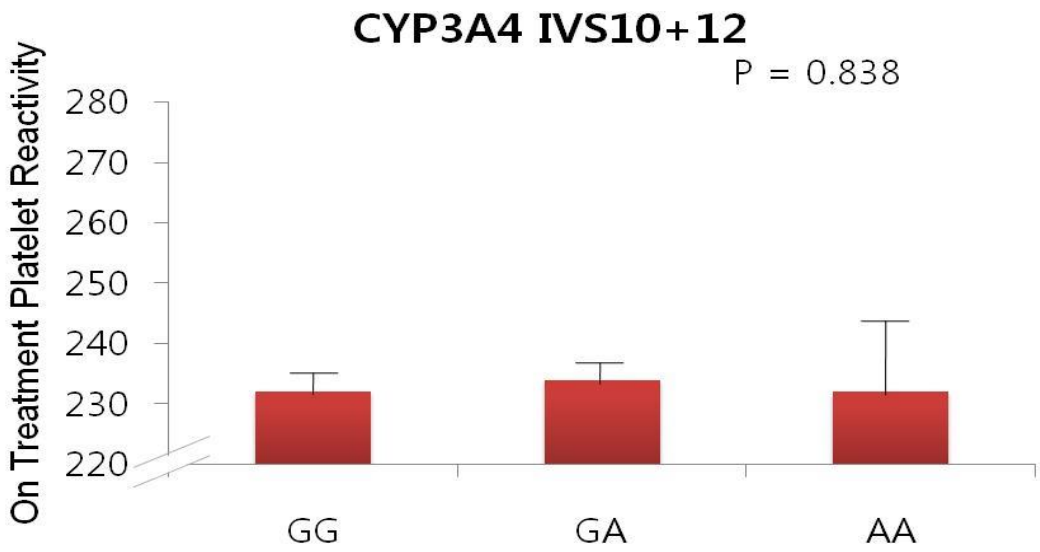
*Xiao et al. J Pharmacol Exp Ther. 1997*

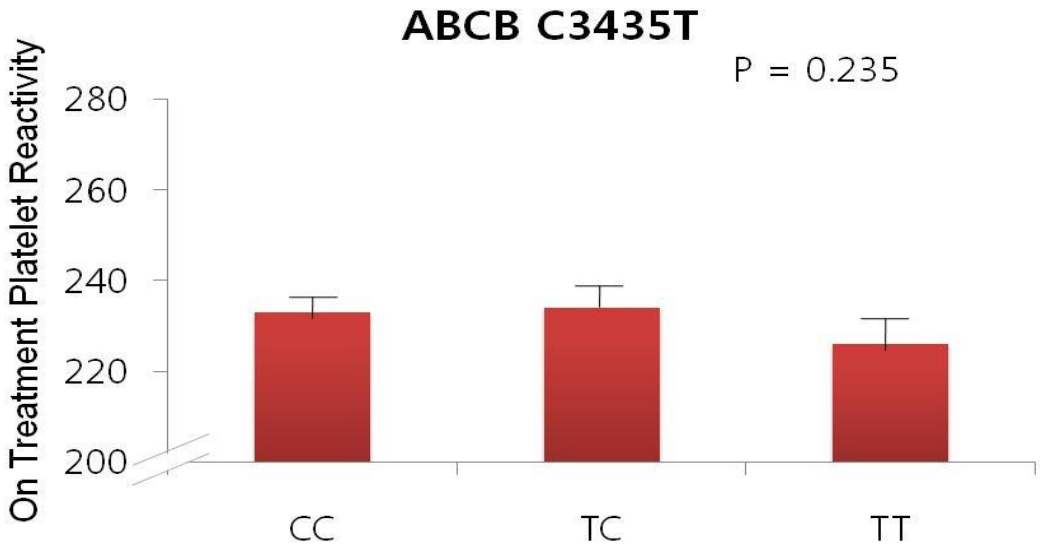
*Takakubo et al Pharmacogenetics. 1996*

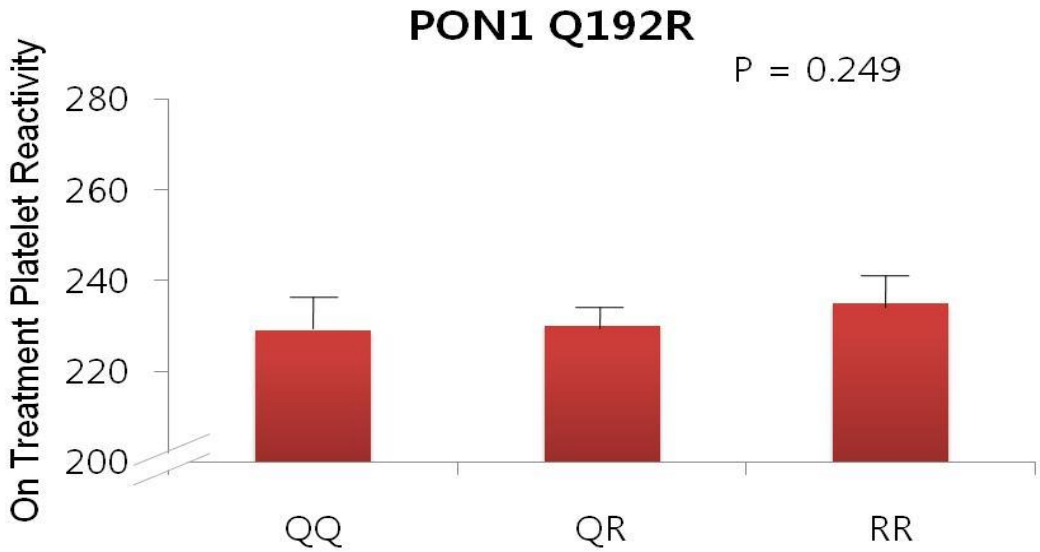
# Genetic Determinants of HOPR

## CROSS-VERIFY cohort: N=1264



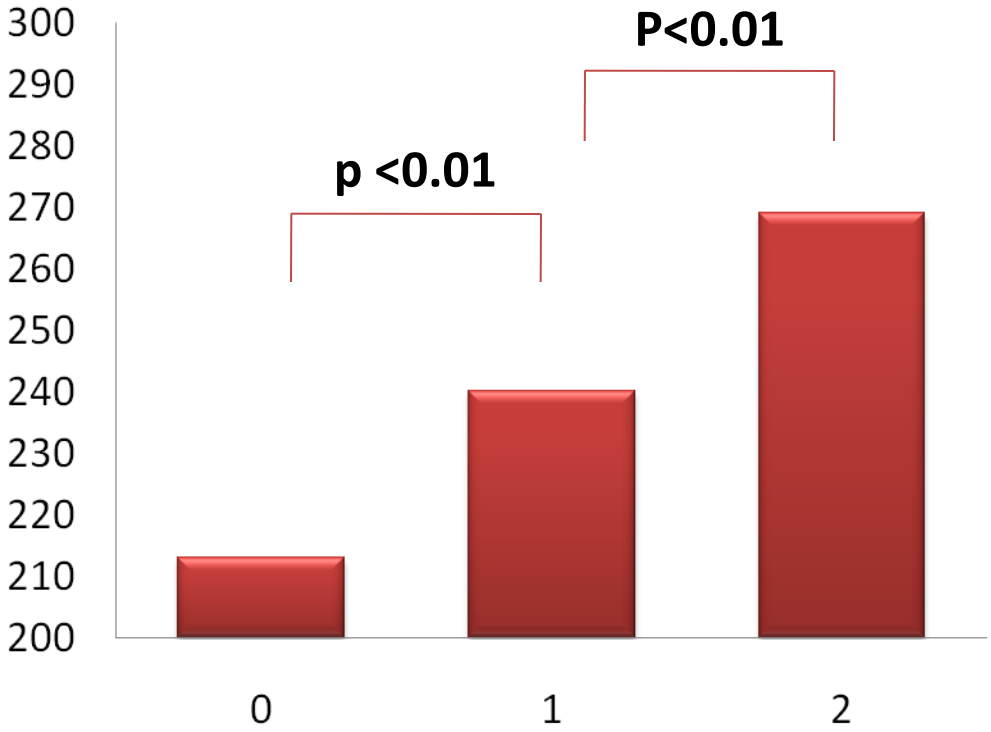



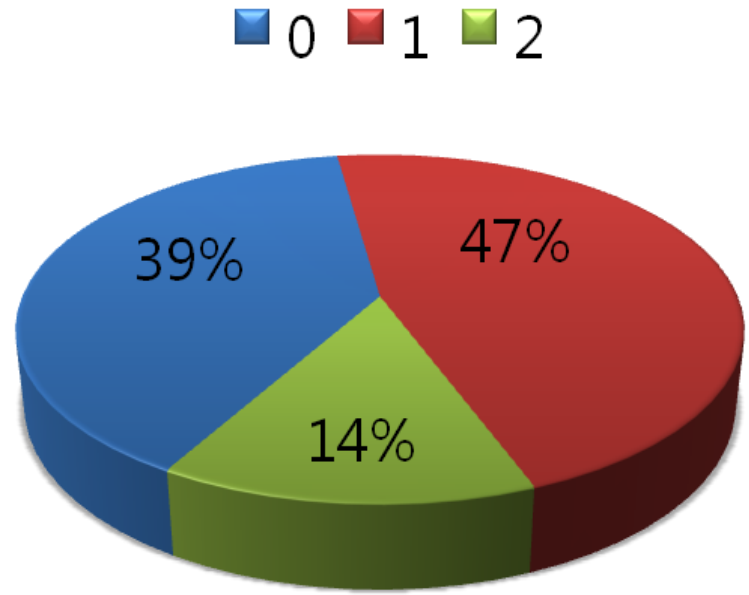

*Park KW, Kim HS et al. Circ CV Int in revision*

***Seoul National University Hospital Cardiovascular Center***

# CYP2C19 LOF alleles : CROSS VERIFY cohort

## Number of LOF alleles



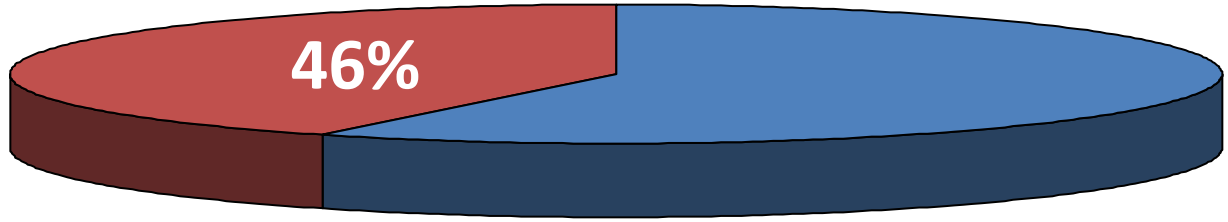

| | Zero ( *1/*1) | One (*1/*2, *1/*3) | Two (*2/*2, *2/*3, *3/*3) | p-value |
|---|---|---|---|---|
| Freq | 523 | 622 | 134 | |
| PRU | 213.4±81.1 | 240.2±83.3 | 269.2±76.0 | <0.001 |

*Park KW, Kim HS et al. Circ CV Int in revision*

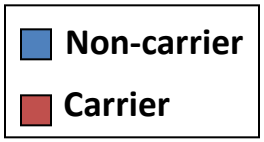
# *Different CYP2C19 LOF Frequency*

## *: according to Asian Ethnicity*

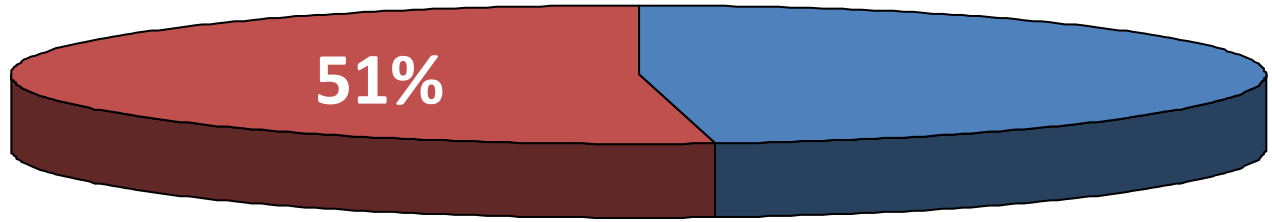
**Japanese Population**




*Sawada T et al. Circulation J 2011.*




**Chinese Population**




*Zhou Q et al. Pharmacogenomics J 2009*

# Association of cytochrome P450 2C19*2 polymorphism with clopidogrel response variability and cardiovascular events in Koreans treated with drug-eluting stents

Il-Young Oh,[1,2] Kyung Woo Park,[1] Si-Hyuk Kang,[1] Jin Joo Park,[1] Sang-Hoon Na,[1] Hyun-Jae Kang,[1] Bon-Kwon Koo,[1] Young-Hoon Jeong,[3] Jin-Yong Hwang,[3] Choong Hwan Kwak,[3] Yongwhi Park,[3] Seok-Jae Hwang,[3] Young-Guk Ko,[4] Dong Jik Shin,[4] Yangsoo Jang,[4] Hyo-Soo Kim[1]

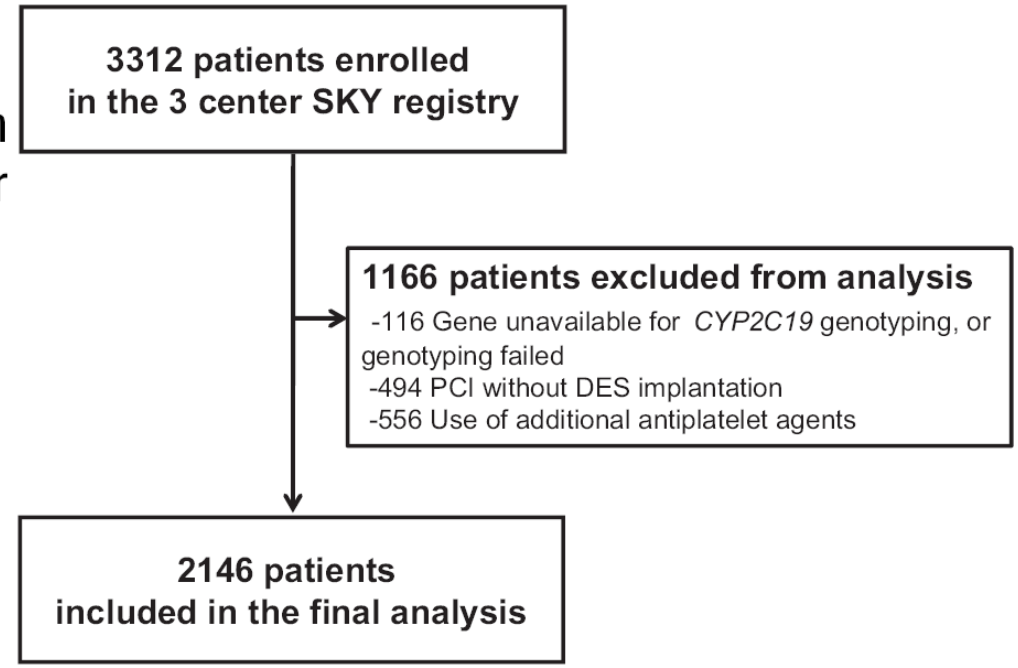


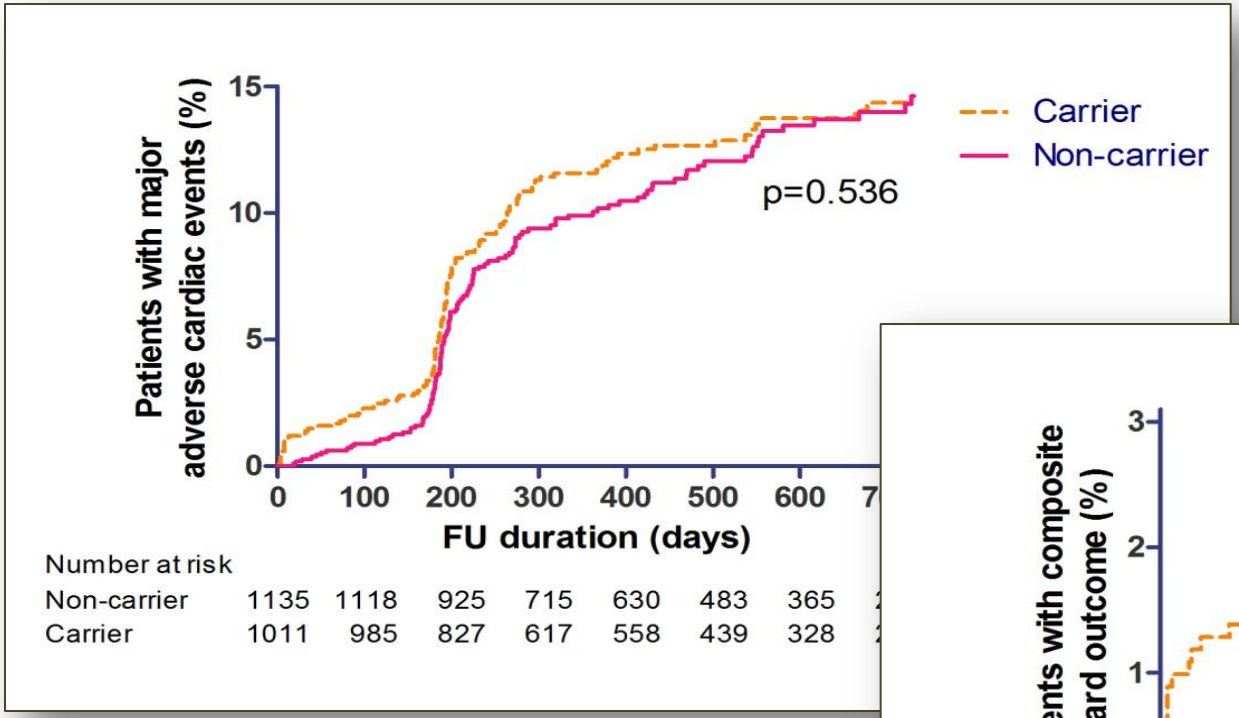

**Table 3** Independent predictors of composite hard outcome up to 1 year

| Variable | Univariate HR (95% CI) | p Value | Adjusted HR (95% CI) | p Value |
|---|---|---|---|---|
| Carrier of *CYP2C19*2* variant (carrier vs non-carrier) | 2.61 (1.24 to 5.48) | 0.01 | 2.53 (1.20 to 5.32) | 0.01 |
| Dyslipidaemia (dyslipidaemia vs non-dyslipidaemia) | 2.69 (1.28 to 5.66) | <0.01 | 2.50 (1.16 to 5.39) | 0.02 |
| Chronic kidney disease (GFR <60 vs ≥60) | 2.07 (1.02 to 4.21) | 0.04 | 2.45 (1.15 to 5.22) | 0.02 |
| Smoking (current smoker vs non-smoker) | 1.53 (0.74 to 3.16) | 0.25 | 1.69 (0.81 to 3.54) | 0.16 |
| Diabetes (diabetes vs non-diabetes) | 1.37 (0.67 to 2.78) | 0.39 | 1.07 (0.51 to 2.24) | 0.85 |
| Use of proton-pump inhibitor (yes vs no) | 1.40 (0.34 to 5.87) | 0.64 | 1.18 (0.28 to 4.05) | 0.82 |
| Hypertension (hypertensive vs normotensive) | 1.18 (0.58 to 2.39) | 0.65 | 0.86 (0.41 to 1.83) | 0.70 |
| Old age (age ≥65 vs <65) | 0.74 (0.35 to 1.56) | 0.43 | 0.66 (0.30 to 1.44) | 0.30 |
| Long length of DES (sum of DES length ≥60 vs <60) | 1.11 (0.48 to 2.57) | 0.80 | 1.02 (0.81 to 3.54) | 0.97 |

HR were adjusted for age, hypertension, diabetes, dyslipidaemia, smoking, chronic kidney disease, sum of length of DES, carrier of *CYP2C19*2*.
DES, drug-eluting stent; GFR, glomerular filtration rate.

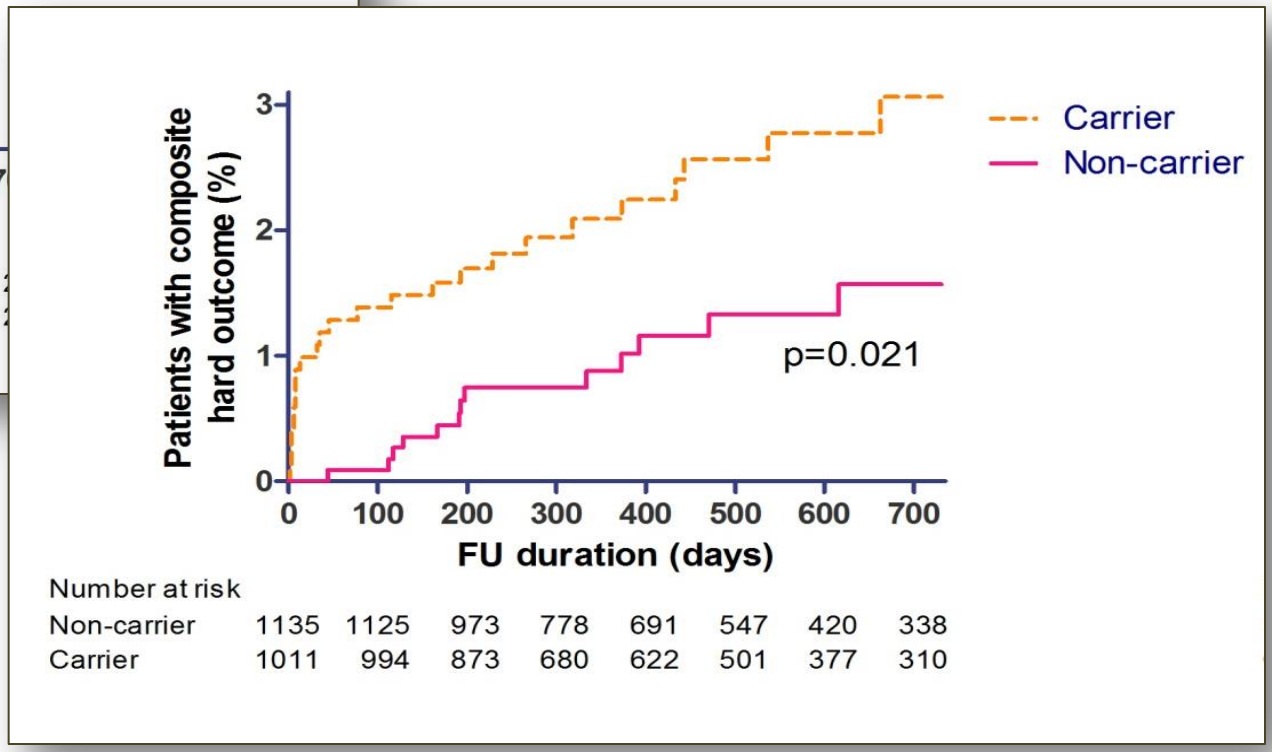
*Oh IY, Park KW et al. Heart 2011*

# Association of genotype with only hard outcomes (SKY registry)




All MACE
(including revascularization)

Hard outcome
(CD, MI, and ST)




*Oh IY, Park KW et al. Heart 2011*

# *Why do we need newer agents?*

1. Wide variability in Clopidogrel response

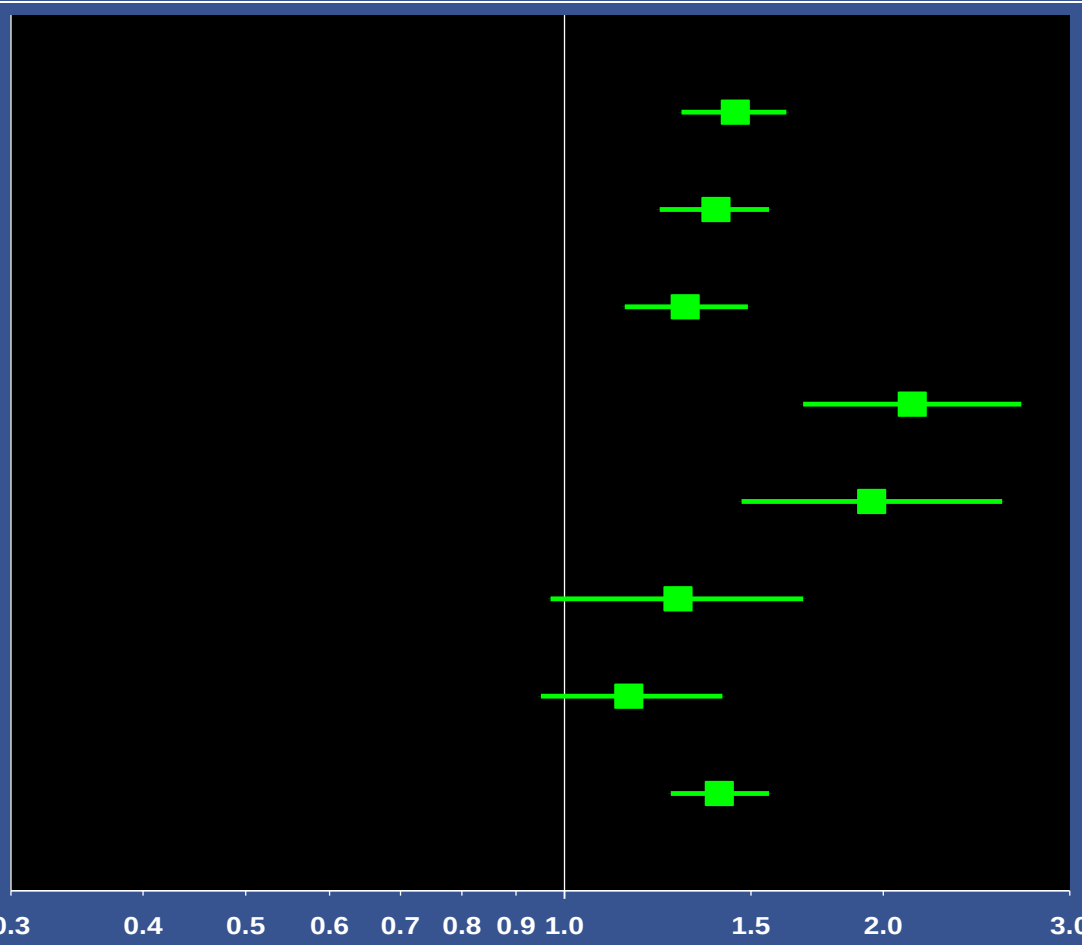
   a. genetic variation

   b. possible drug interactions (Cytochrome enzymes): PPIs, lipophilic statins, CCBs etc

**2. Unmet needs in thrombosis**

3. Patients awaiting surgery : reversible agents

# Results – Clinical Events by DM Status (DM vs. No DM)

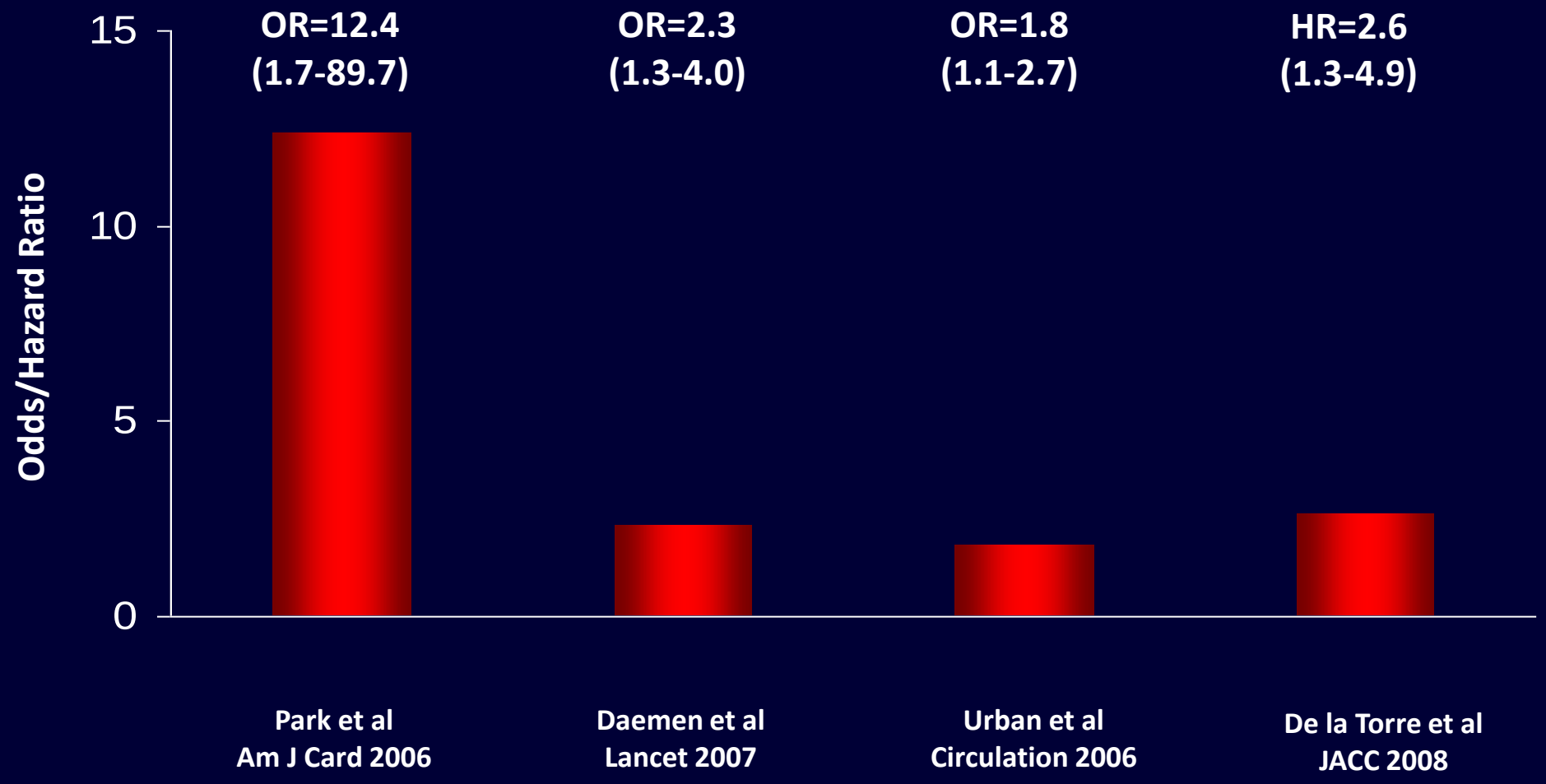



| | DM (%) | No DM (%) |
|---|---|---|
| CVD/MI/CVA* | 14.6 | 9.9 |
| CVD/MI | 13.1 | 9.2 |
| MI† | 10.7 | 8.0 |
| CVD | 3.8 | 1.8 |
| Stent thrombosis | 2.8 | 1.4 |
| Major bleed‡ | 2.6 | 2.0 |
| Major or minor bleed‡ | 4.8 | 4.2 |
| D/MI/CVA*/Major bleed‡ | 16.9 | 11.9 |

CVD,cardiovascular death; MI, myocardial infarction;
CVA, cerebrovascular accident; D, death; DM, diabetes mellitus
*The composite of cardiovascular death, nonfatal MI, or nonfatal stroke
†Any MI (fatal or nonfatal)
‡Not related to CABG

Data from Wiviott SD, et al. *Circulation*. 2008;118(16):1626-1636

# ACS as Predictor of Stent Thrombosis

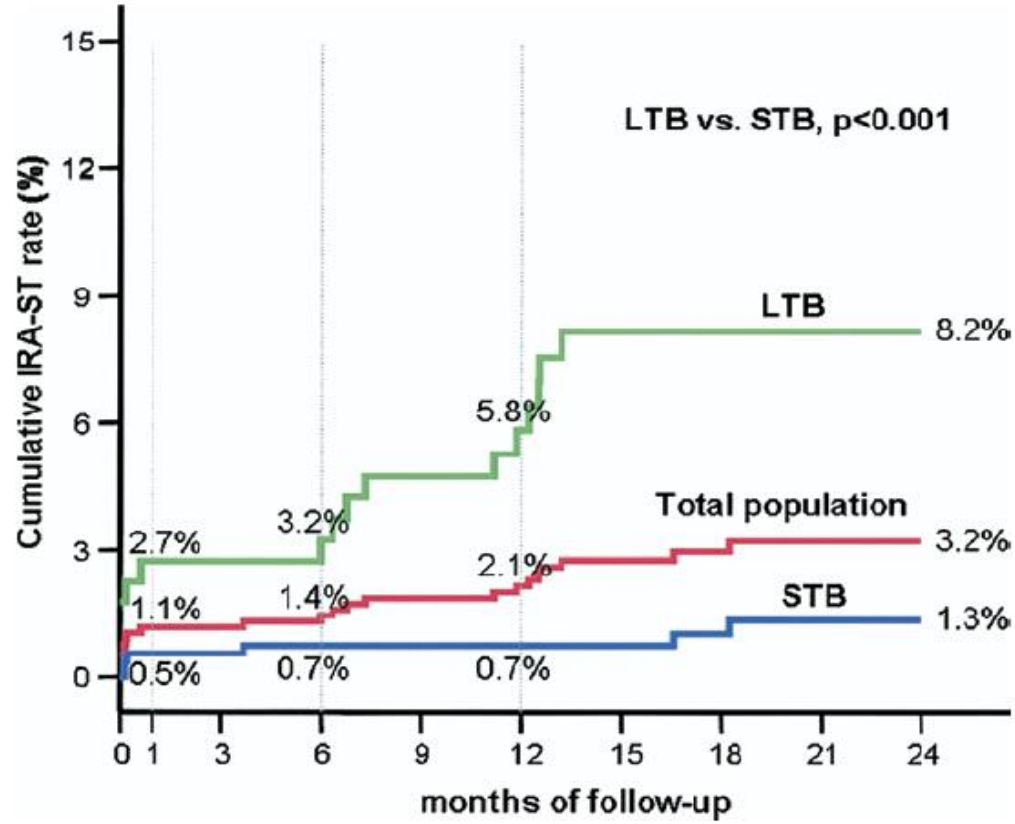


# Impact of Thrombus Burden on Risk of Stent Thrombosis With DES in Patients With STEMI

Sianos G et al. *J Am Coll Cardiol* 2007;50:573-83

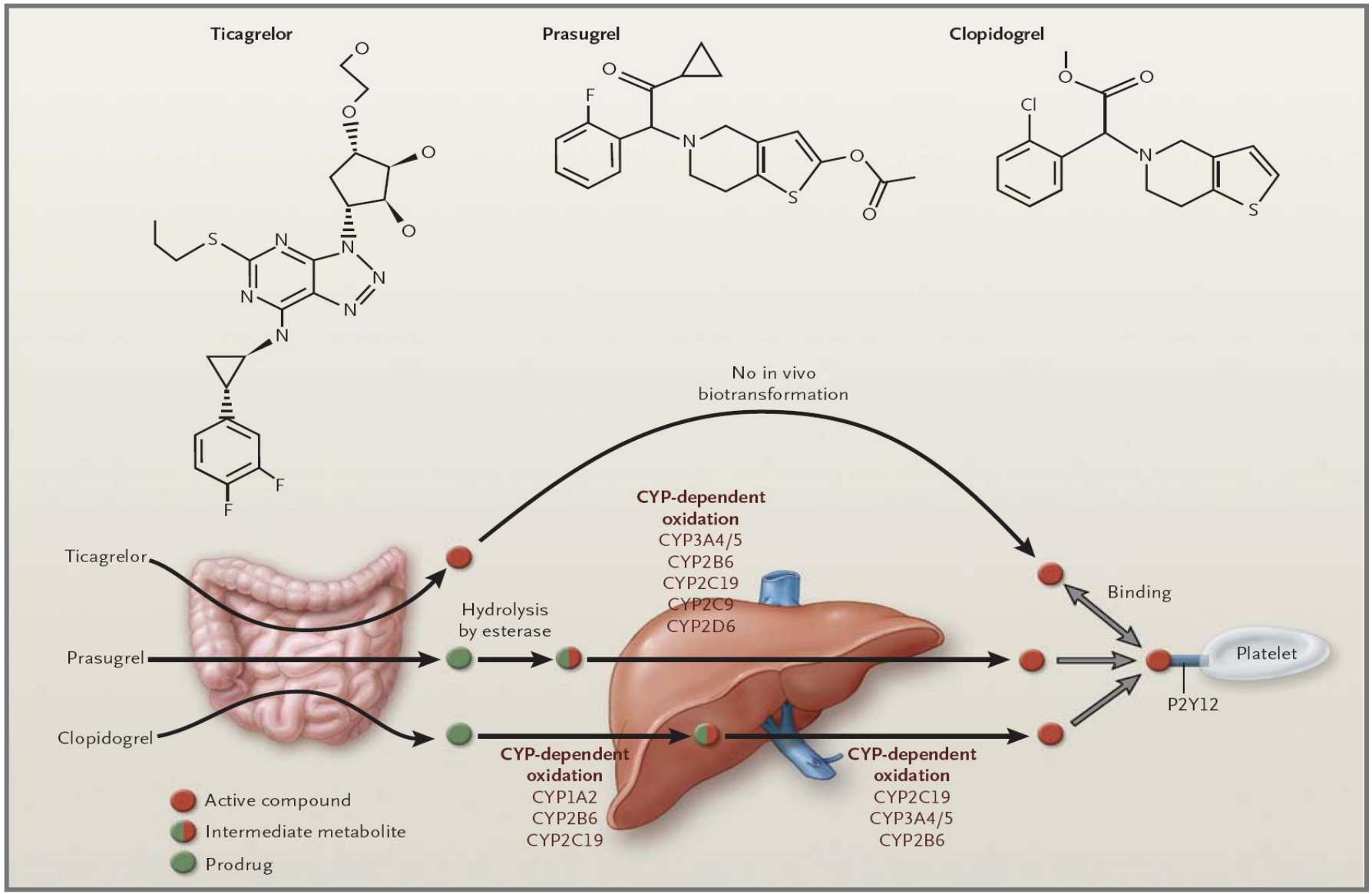
## Independent Predictors of ST

| *Variable* | *Hazard Ratio* | *95% CI* |
|---|---|---|
| Age | 0.6 | 0.4-0.8 |
| Index ST | 6.2 | 2.1-18.9 |
| Bifurcation | 4.1 | 1.6-10.0 |
| Thrombectomy | 0.1 | 0.01-0.8 |
| Large thrombus | 8.7 | 3.4-22.5 |



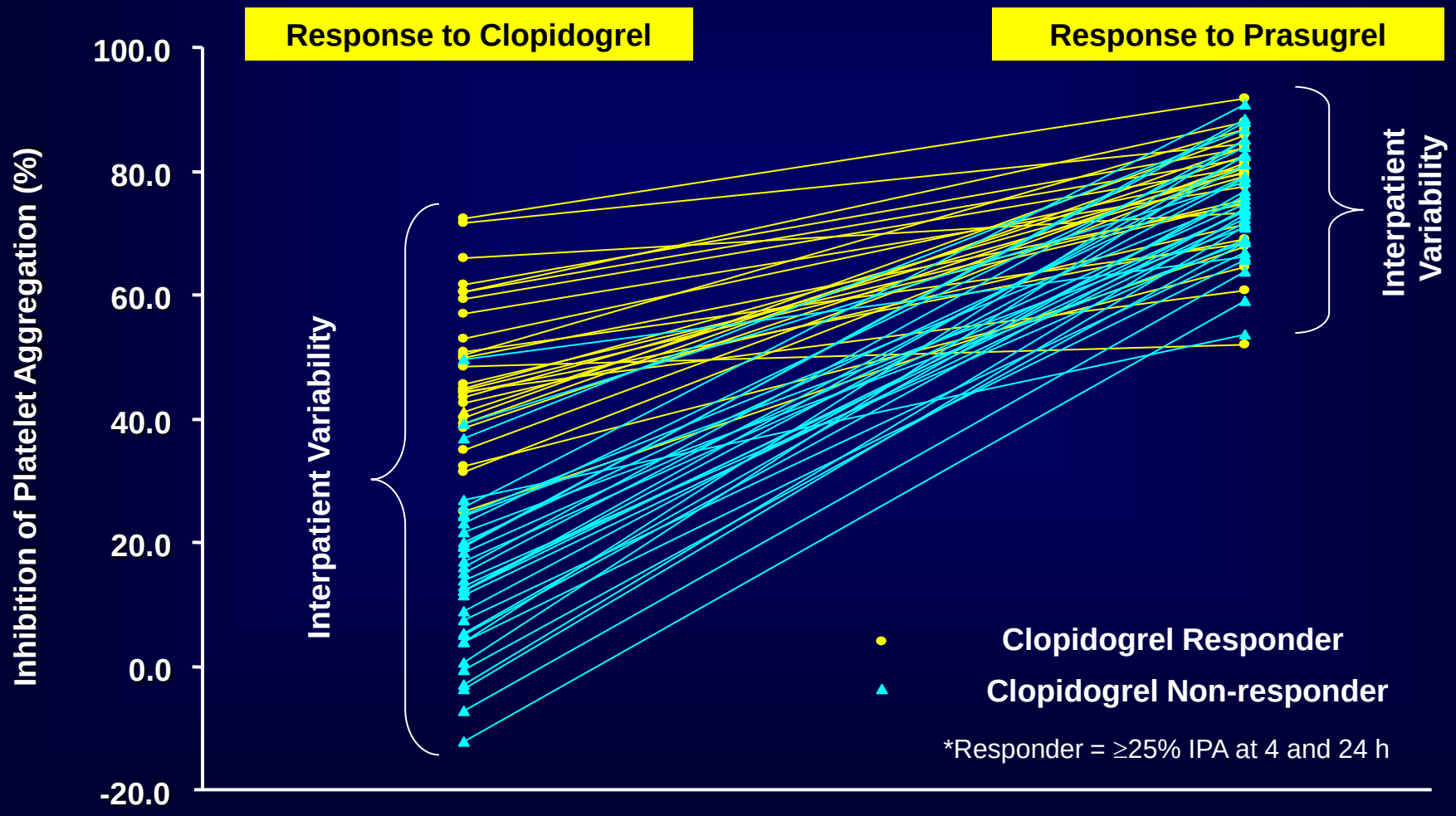
# So, what are the new agents with better efficacy?

# P2Y12 Receptor Antagonists



# Inhibition of Platelet Aggregation:
## Clopidogrel and Prasugrel

Healthy Volunteers at 24 Hours, N=68




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

TRITON TIMI-38

# Study Design

ACS (STEMI or UA/NSTEMI) & Planned PCI

ASA

N= 13,600

Double-blind

**CLOPIDOGREL**
**300 mg LD/ 75 mg MD**

**PRASUGREL**
**60 mg LD/ 10 mg MD**

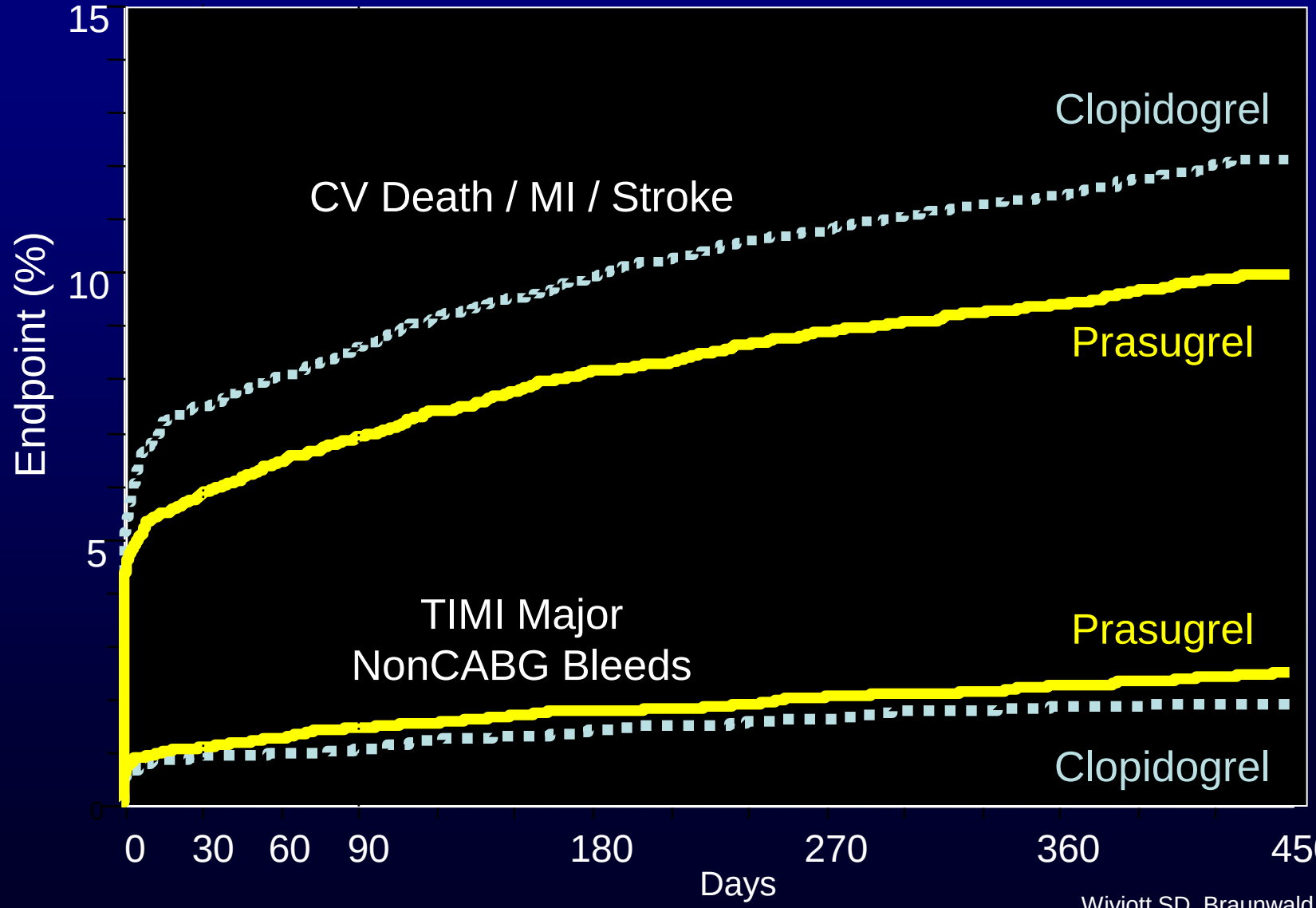
Median duration of therapy - 12 months

| | |
|---|---|
| 1º endpoint: | CV death, MI, Stroke |
| 2º endpoints: | CV death, MI, Stroke, Rehosp-Rec Isch |
| | CV death, MI, UTVR |
| | Stent Thrombosis (ARC definite/prob.) |
| Safety endpoints: | TIMI major bleeds, Life-threatening bleeds |

Wiviott SD, AHJ 2006

TRITON TIMI-38

# Balance of Efficacy and Safety




12.1

9.9

↓138 events

HR 0.81
(0.73-0.90)
P=0.0004

NNT = 46

2.4

1.8

↑35 events

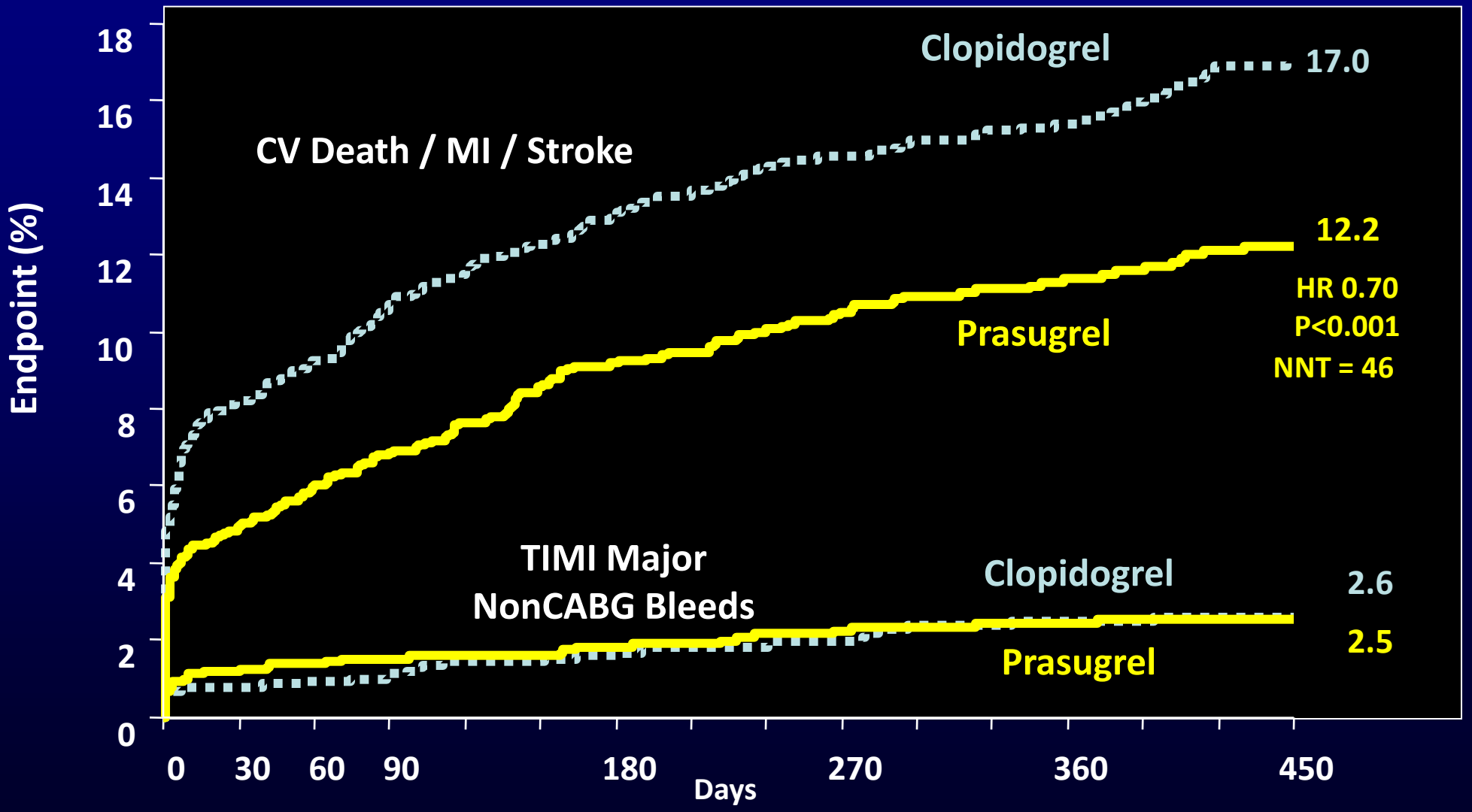
HR 1.32
(1.03-1.68)
P=0.03

NNH = 167

Wiviott SD, Braunwald E, McCabe CH et al NEJM2007

TRÎTON TIMI·38

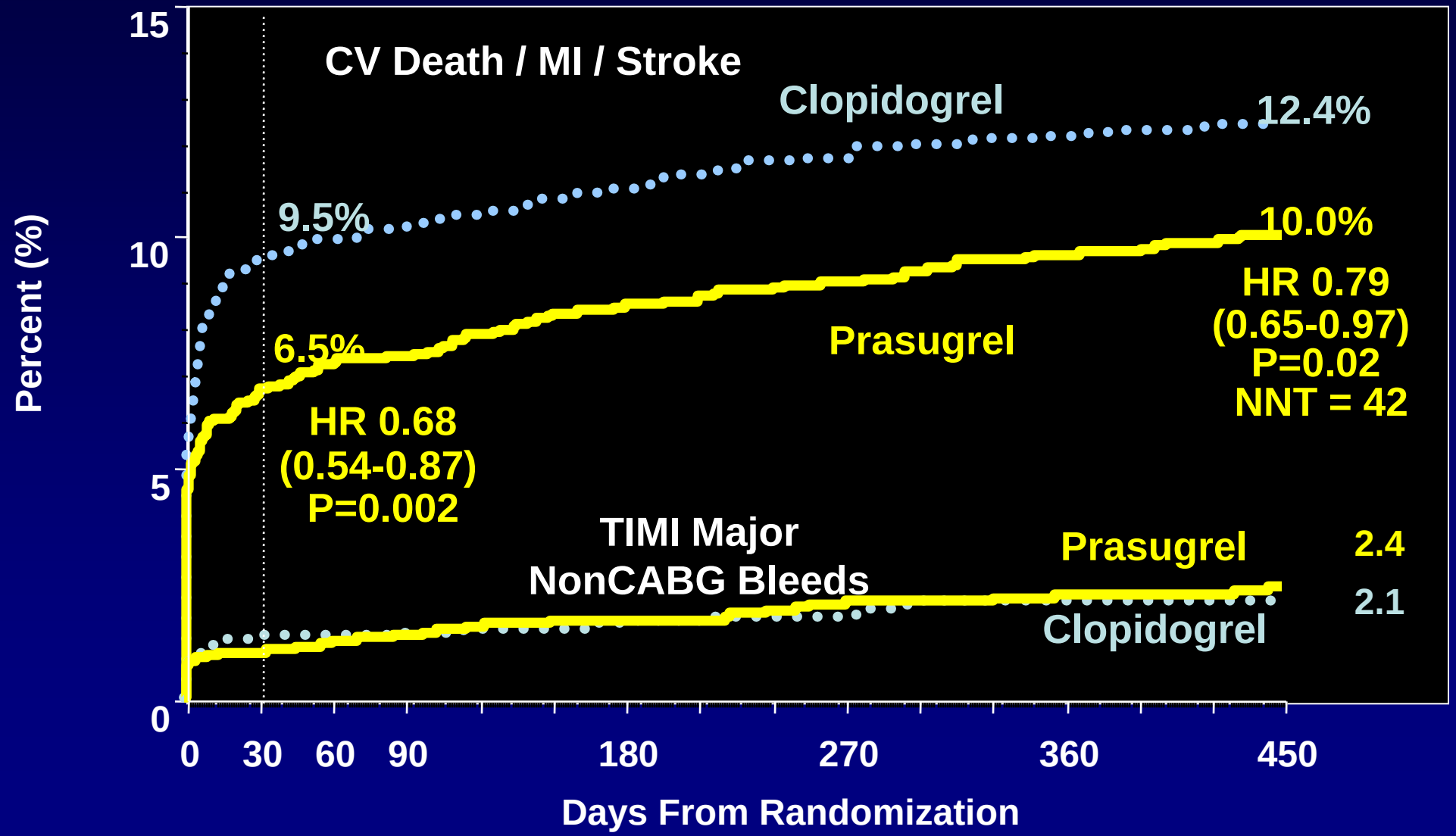
# Diabetic Subgroup
## N=3146




*Wiviott SD, Circulation 2008*

TRÎTON TIMI·38

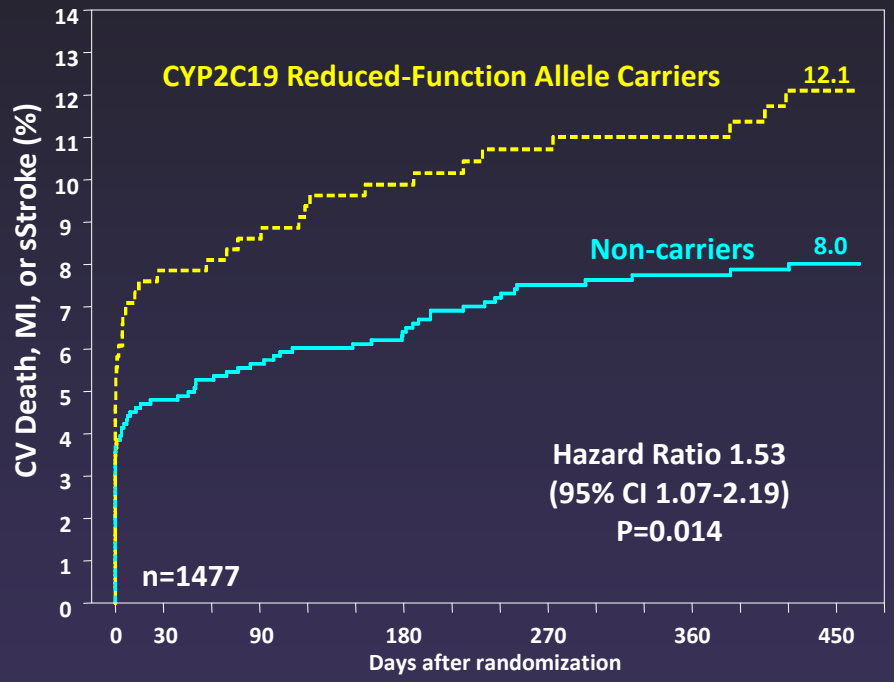
# STEMI Cohort N=3534




*Montalescot et al Lancet 2008*

# CYP2C19 and CVD, MI, or Stroke

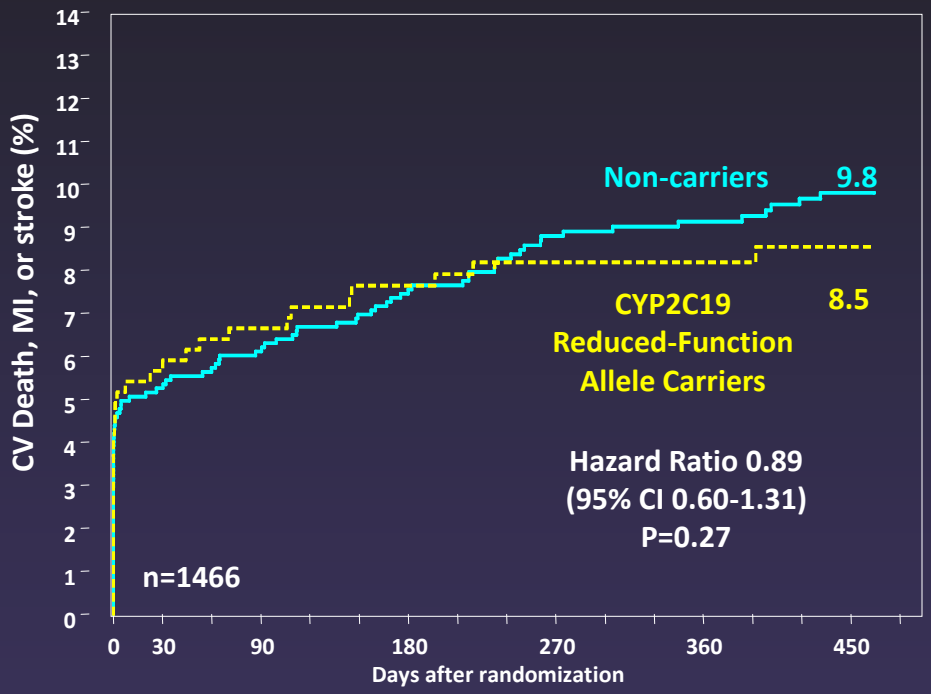
## Clopidogrel




Number at Risk:

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Non-Carrier | 1064 | 1009 | 999 | 980 | 870 | 755 | 542 |
| Carrier | 395 | 364 | 360 | 348 | 306 | 270 | 181 |

## Prasugrel




Number at Risk:

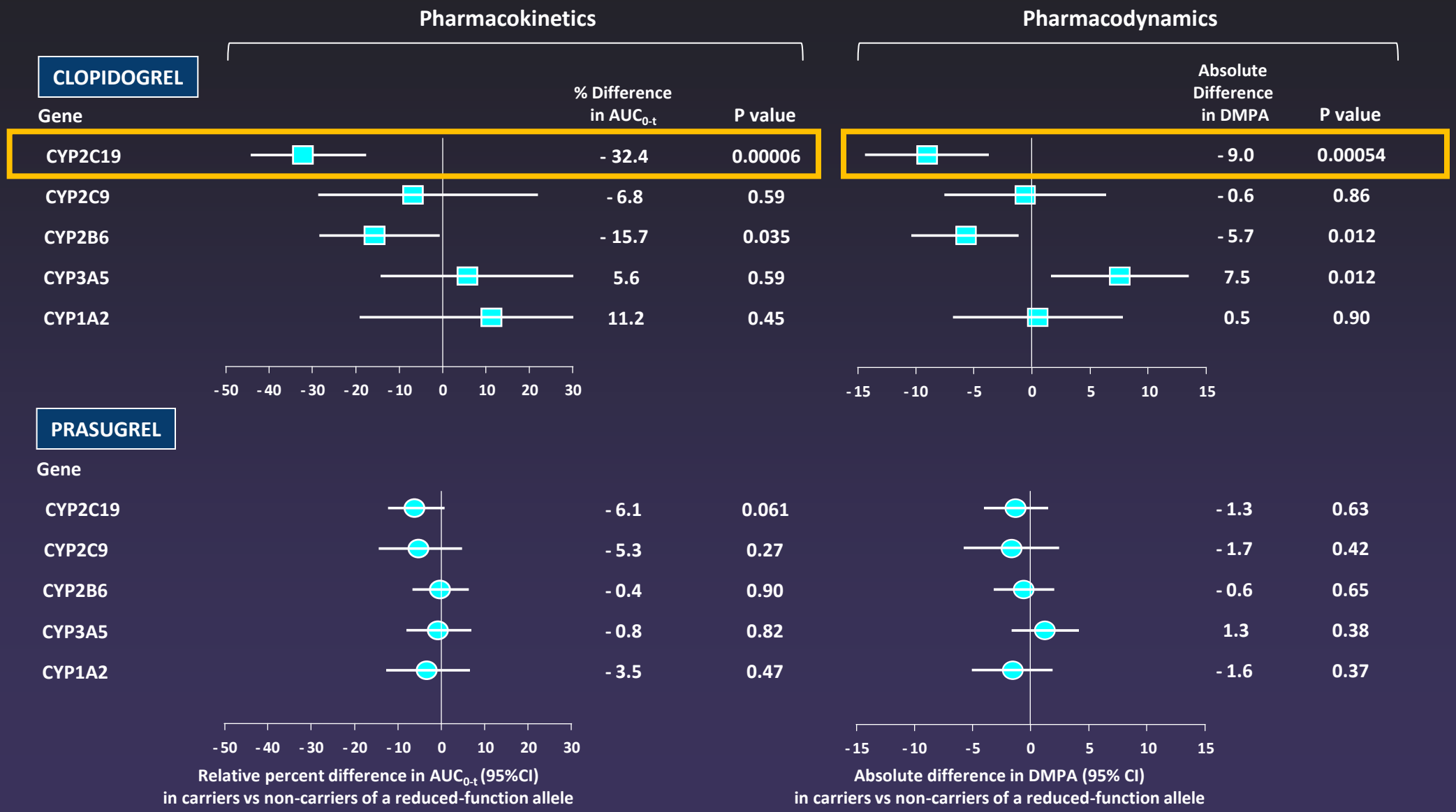
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Non-Carrier | 1048 | 991 | 982 | 951 | 849 | 750 | 541 |
| Carrier | 407 | 383 | 376 | 364 | 320 | 276 | 188 |

* Carriers ~30% of the population

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

Mega JL et al. Circulation 2009

# Genetic Effects on PK/PD

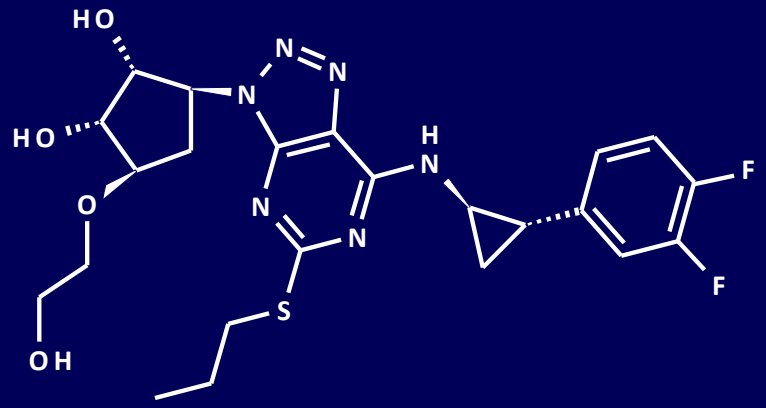



Mega JL et al. N Engl J Med. 2009;360:354-62.

Mega JL et al. Circulation 2009

# *Ticagrelor (AZD 6140): an oral reversible $P2Y_{12}$ antagonist*

PLATO

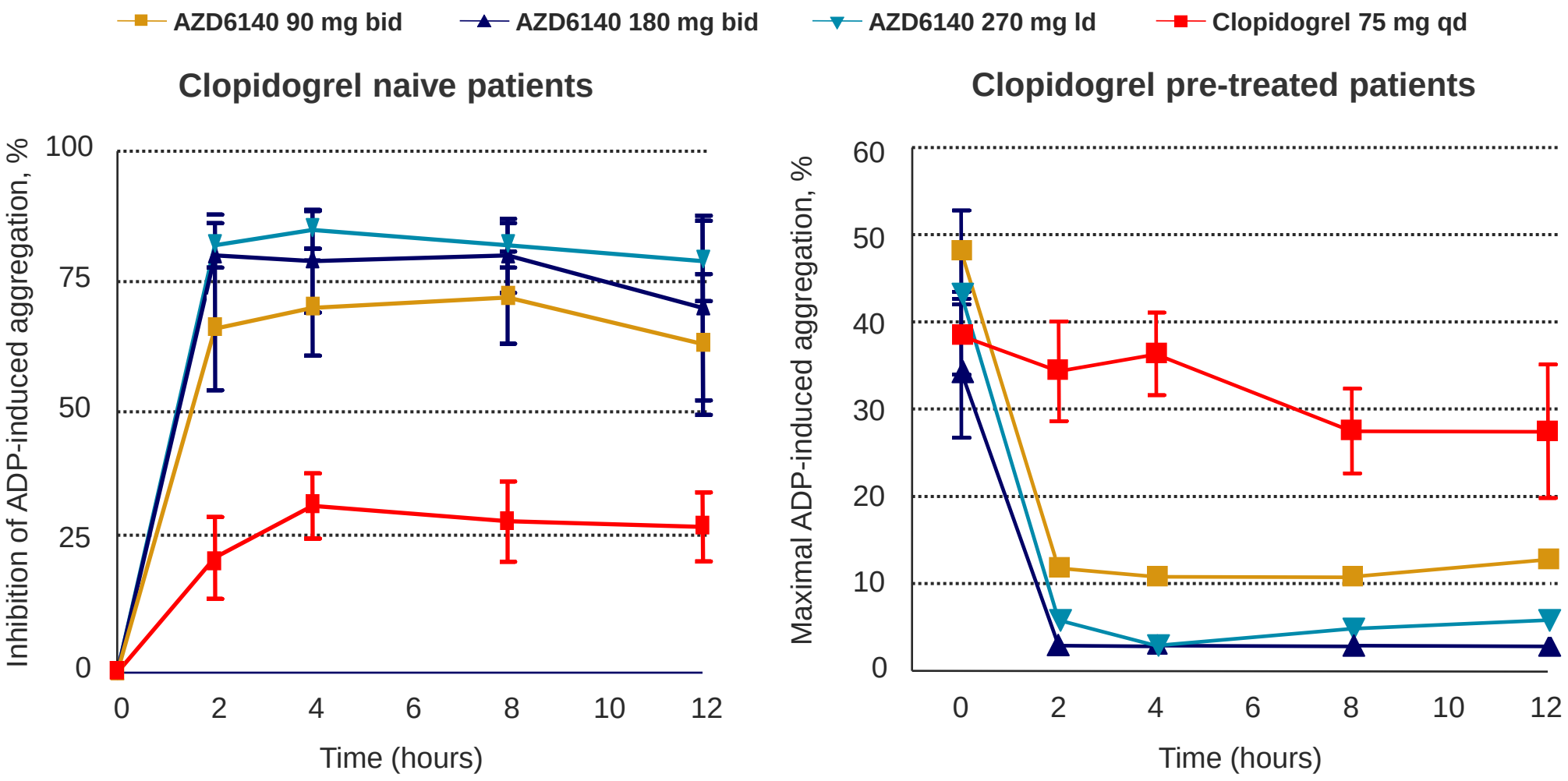



**Ticagrelor is a cyclo-pentyl-triazolo-pyrimidine (CPTP)**

- **Direct acting**
  - **Not a prodrug; does not require metabolic activation**
  - **Rapid onset of inhibitory effect on the $P2Y_{12}$ receptor**
  - **Greater inhibition of platelet aggregation than clopidogrel**
- **Reversibly bound**
  - **Degree of inhibition reflects plasma concentration**
  - **Faster offset of effect than clopidogrel**
  - **Functional recovery of all circulating platelets**

# DISPERSE2 platelet function substudy: more rapid, greater and more consistent IPA with ticagrelor

PLATO




IPA = inhibition of platelet aggregation; ld = loading dose

Storey R et al. *J Am Coll Cardiol.* 2007;50:1852–1860

# Study design

PLATO

NSTE-ACS (moderate-to-high risk) STEMI (if primary PCI)
Clopidogrel-treated or -naive;
randomised within 24 hours of index event
(N=18,624)

**Clopidogrel**
If pre-treated, no additional loading dose;
if naive, standard 300 mg loading dose,
then 75 mg qd maintenance;
(additional 300 mg allowed pre PCI)

**Ticagrelor**
180 mg loading dose, then
90 mg bid maintenance;
(additional 90 mg pre-PCI)

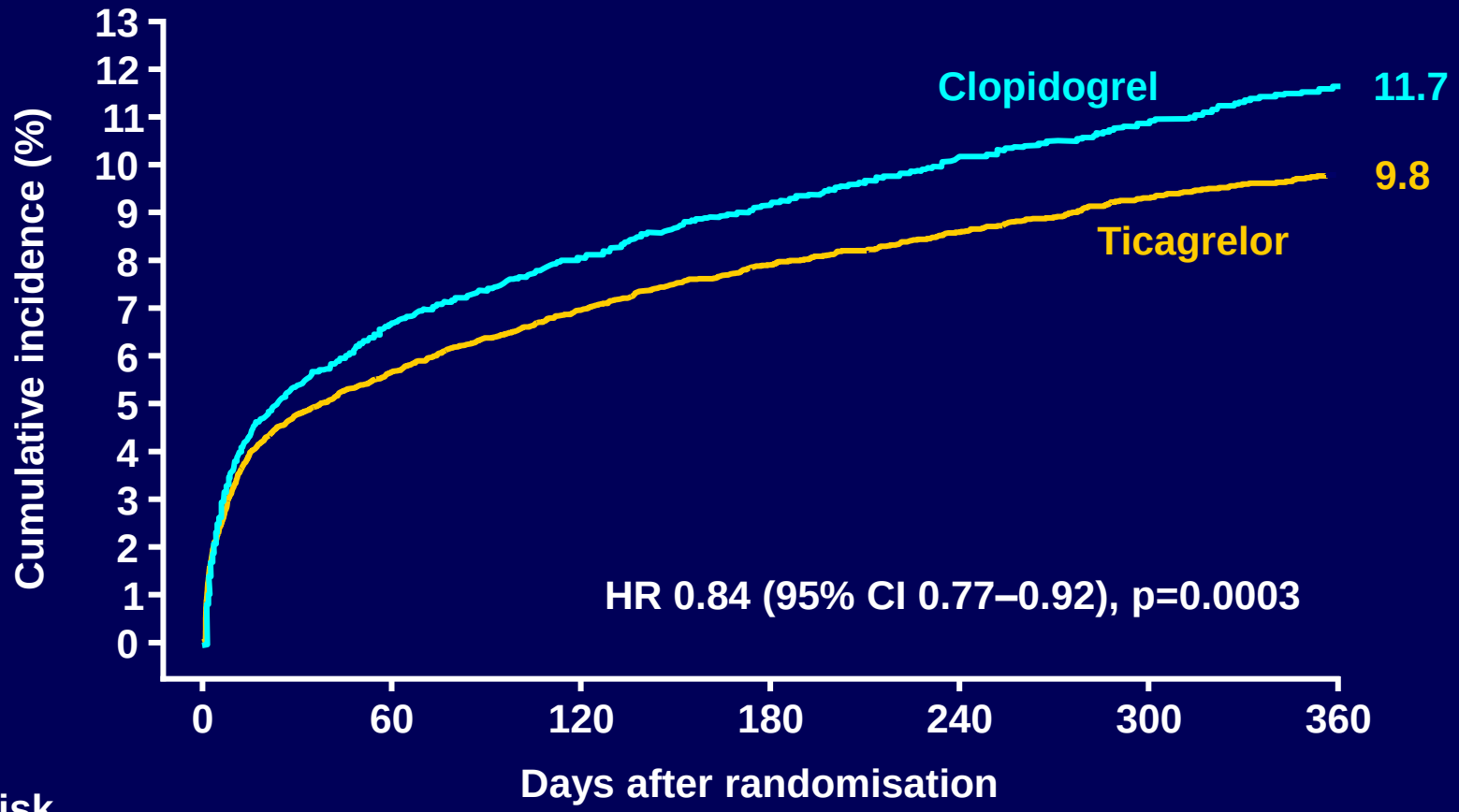
6–12-month exposure

Primary endpoint: CV death + MI + Stroke
Primary safety endpint: Total major bleeding

PCI = percutaneous coronary intervention; ASA = acetylsalicylic acid;
CV = cardiovascular; TIA = transient ischaemic attack

# *Primary efficacy event (composite of CV death, MI or stroke)*

PLATO




| No. at risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| Ticagrelor | 9,333 | 8,628 | 8,460 | 8,219 | 6,743 | 5,161 | 4,147 |
| Clopidogrel | 9,291 | 8,521 | 8,362 | 8,124 | 6,743 | 5,096 | 4,047 |

K-M = Kaplan-Meier; HR = hazard ratio; CI = confidence interval

*Adapted from Wallentin L, et al. N Engl J Med. 2009;361:1045-1057.*

# Hierarchical testing major efficacy endpoints

PLATO

| All patients* | Ticagrelor (n=9,333) | Clopidogrel (n=9,291) | HR for (95% CI) | p value† |
|---|---|---|---|---|
| **Primary objective, n (%)** | | | | |
| CV death + MI + stroke | 864 (9.8) | 1,014 (11.7) | 0.84 (0.77–0.92) | <0.001 |
| **Secondary objectives, n (%)** | | | | |
| Total death + MI + stroke | 901 (10.2) | 1,065 (12.3) | 0.84 (0.77–0.92) | <0.001 |
| CV death + MI + stroke + ischaemia + TIA + arterial thrombotic events | 1,290 (14.6) | 1,456 (16.7) | 0.88 (0.81–0.95) | <0.001 |
| Myocardial infarction | 504 (5.8) | 593 (6.9) | 0.84 (0.75–0.95) | 0.005 |
| CV death | 353 (4.0) | 442 (5.1) | 0.79 (0.69–0.91) | 0.001 |
| Stroke | 125 (1.5) | 106 (1.3) | 1.17 (0.91–1.52) | 0.22 |
| Total death | 399 (4.5) | 506 (5.9) | 0.78 (0.69–0.89) | <0.001 |

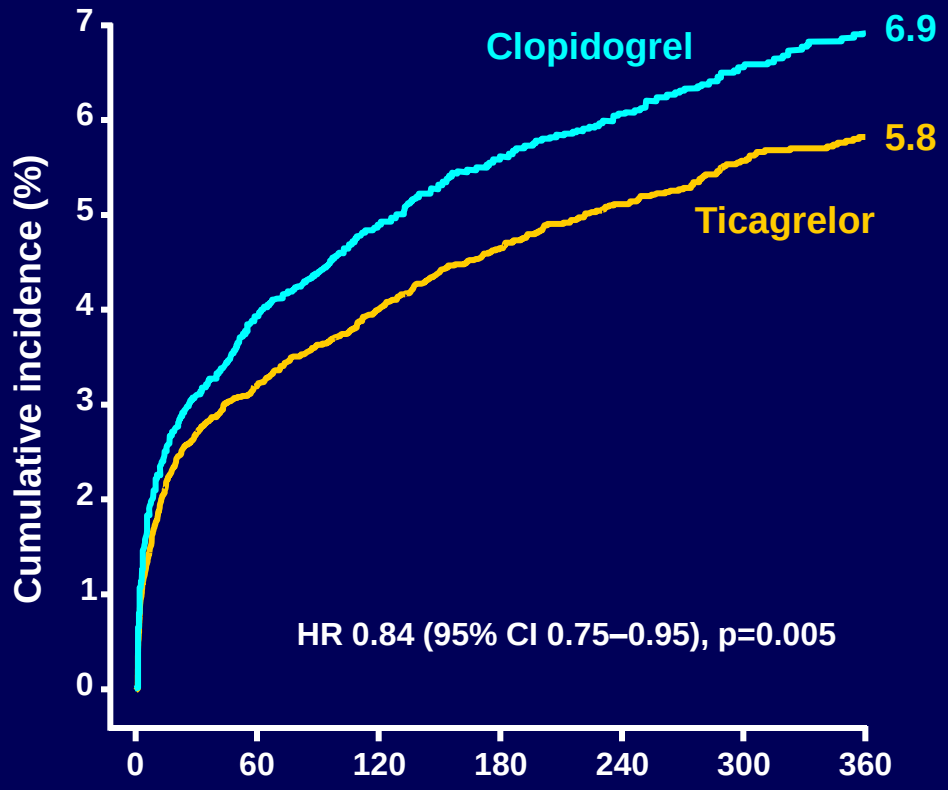
The percentages are K-M estimates of the rate of the endpoint at 12 months.

Adapted from Wallentin L, et al. *N Engl J Med.* 2009;361:1045-1057.

# Secondary efficacy endpoints over time

PLATO

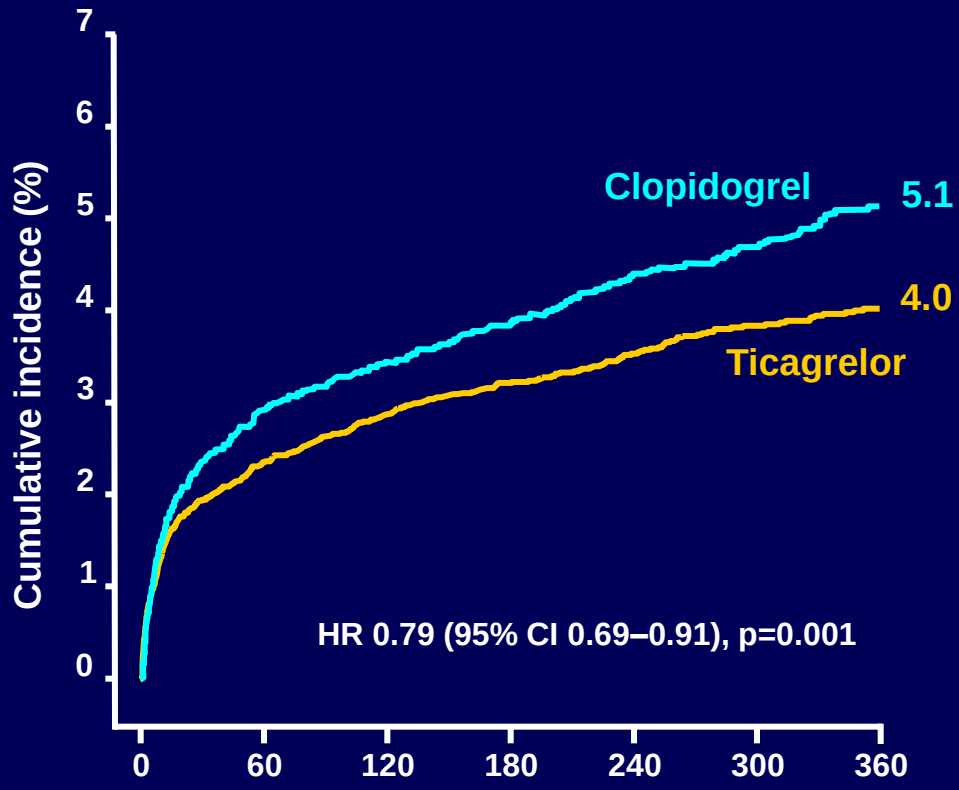
## Myocardial infarction




No. at risk

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Ticagrelor | 9,333 | 8,678 | 8,520 | 8,279 | 6,796 | 5,210 | 4,191 |
| Clopidogrel | 9,291 | 8,560 | 8,405 | 8,177 | 6,703 | 5,136 | 4,109 |

## Cardiovascular death

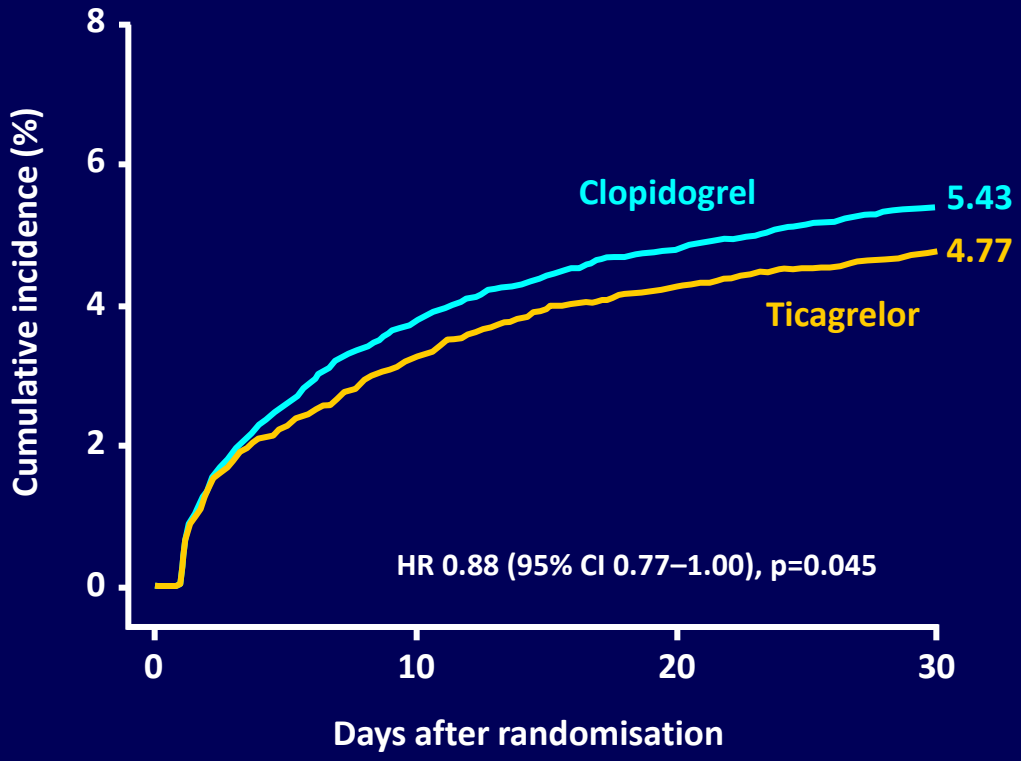


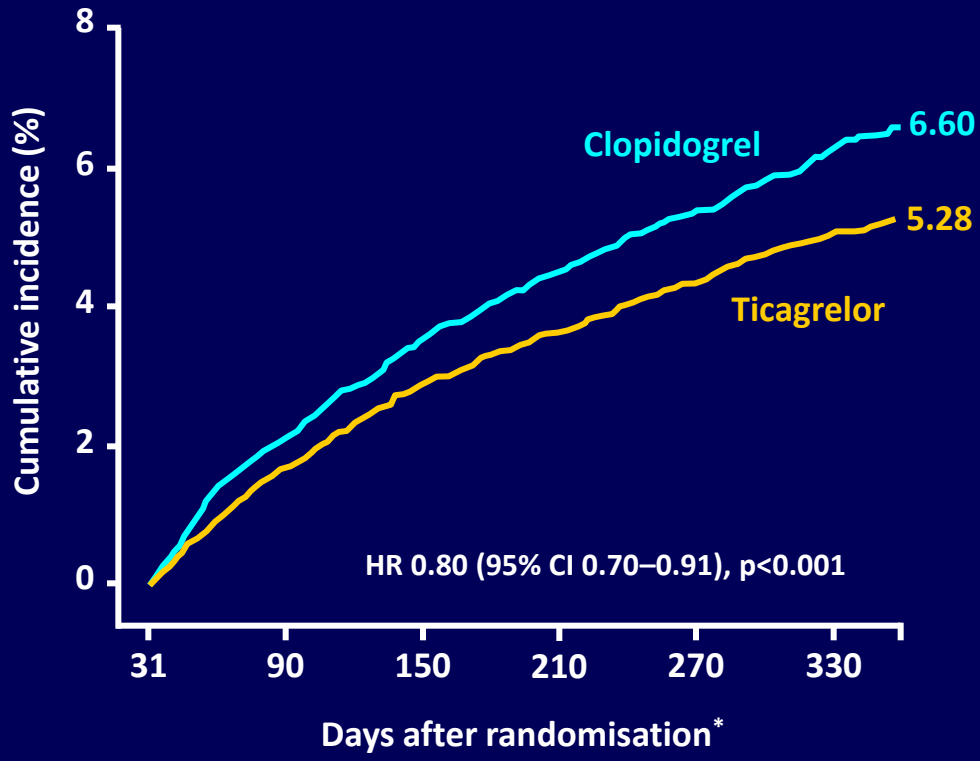

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | 9,333 | 8,294 | 8,822 | 8,626 | 7119 | 5,482 | 4,419 |
| | 9,291 | 8,865 | 8,780 | 8,589 | 7079 | 5,441 | 4,364 |

Adapted from Wallentin L, et al. *N Engl J Med.* 2009;361:1045-1057.

# *Primary efficacy endpoint (landmark analysis)*
## *(composite of CV death, MI or stroke)*

PLATO




| No. at risk | | | | |
|---|---|---|---|---|
| Ticagrelor | 9,333 | 8,942 | 8,827 | 8,763 |
| Clopidogrel | 9,291 | 8,875 | 8,763 | 8,688 |

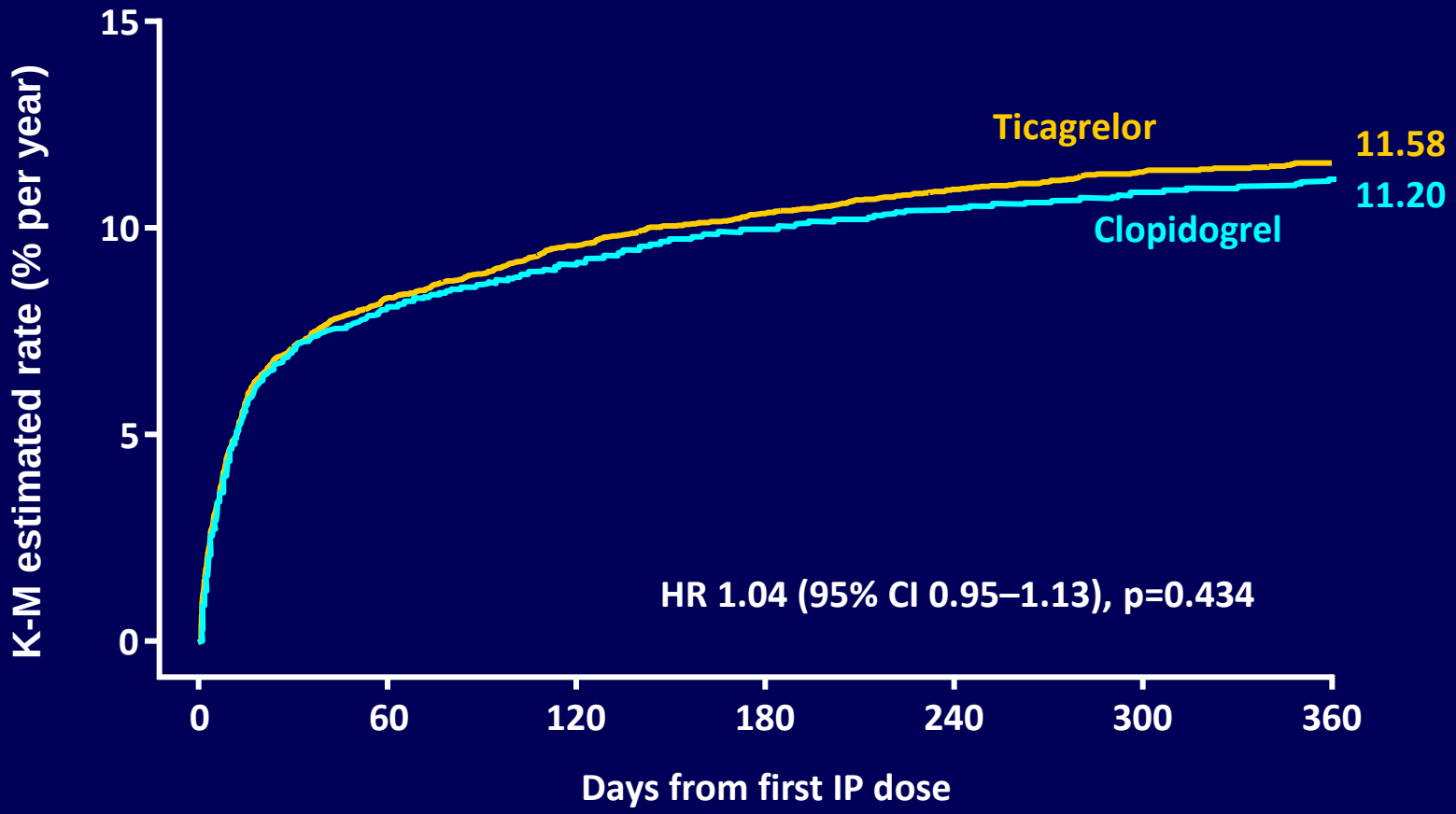
| | | | | | |
|---|---|---|---|---|---|
| 8,673 | 8,543 | 8,397 | 7,028 | 6,480 | 4,822 |
| 8,688 | 8,437 | 8,286 | 6,945 | 6,379 | 4,751 |

*Excludes patients with any primary event during the first 30 days

# Time to major bleeding

## Primary safety event

PLATO

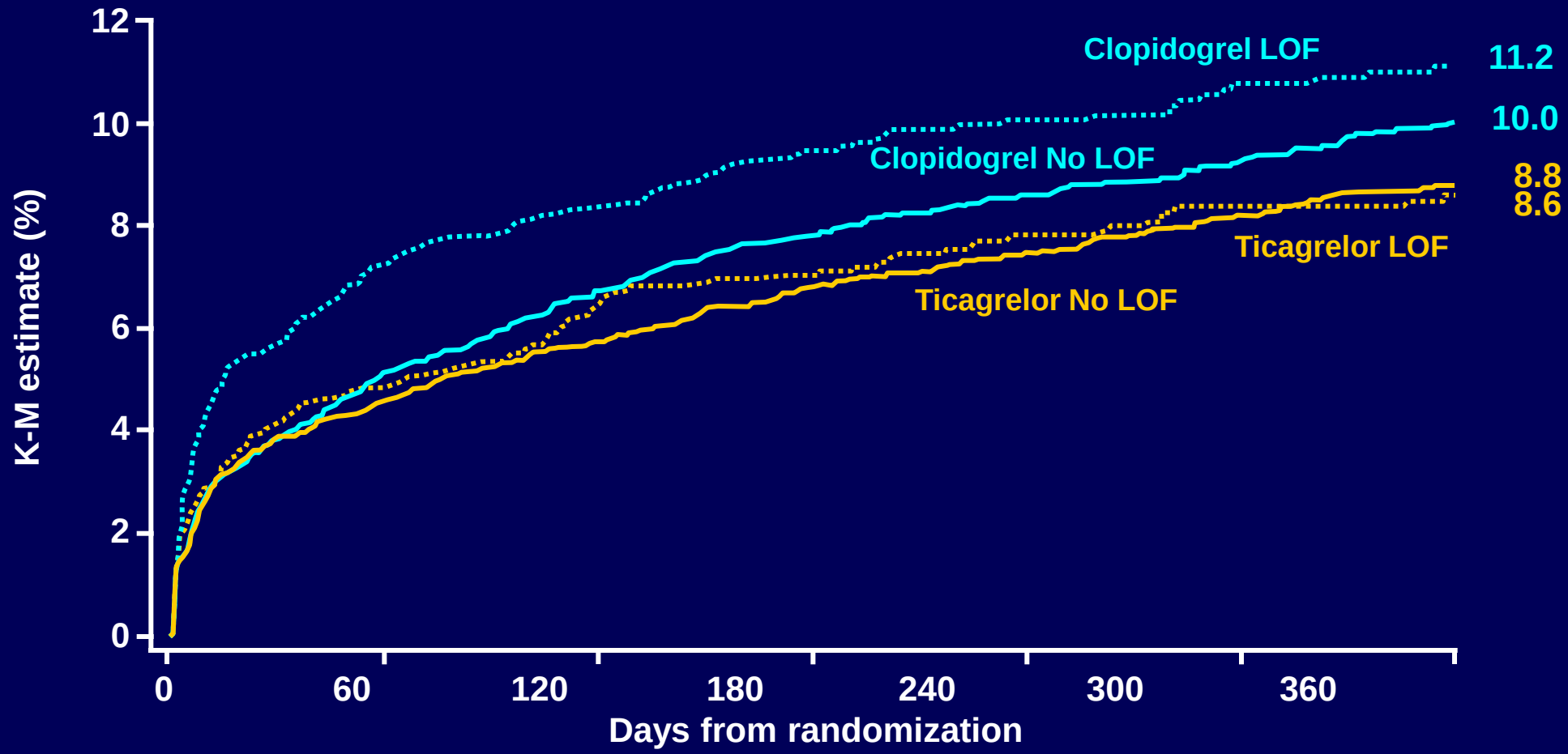



| No. at risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| Ticagrelor | 9,235 | 7,246 | 6,826 | 6,545 | 5,129 | 3,783 | 3,433 |
| Clopidogrel | 9,186 | 7,305 | 6,930 | 6,670 | 5,209 | 3,841 | 3,479 |

*Adapted from Wallentin L, et al. N Engl J Med. 2009;361:1045-1057.*

# K-M estimate of the primary endpoint in relation to any CYP2C19 LOF allele

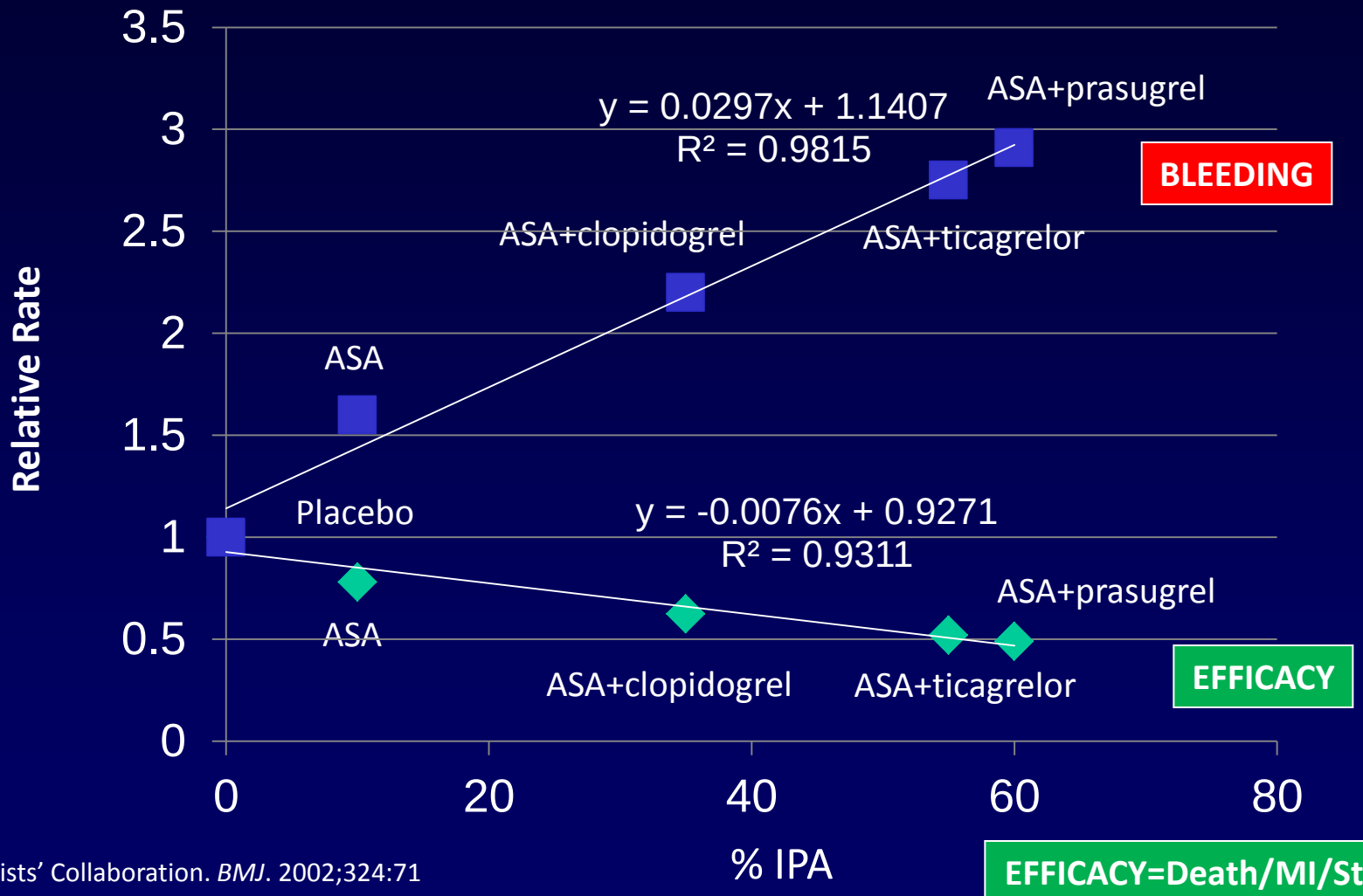
PLATO




| No. at risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| Clopidogrel LOF | 1,388 | 1,275 | 1,259 | 1,226 | 1,027 | 801 | 658 |
| Clopidogrel No LOF | 3,516 | 3,321 | 3,256 | 3,186 | 2,691 | 2,123 | 1,757 |
| Ticagrelor LOF | 1,384 | 1,305 | 1,274 | 1,250 | 1,053 | 834 | 683 |
| Ticagrelor No LOF | 3,554 | 3,352 | 3,301 | 3,222 | 2,718 | 2,127 | 1,761 |

Wallentin L et al Lancet 2010: 376, Online Aug 29, 2010

# Efficacy and Safety Correlated with IPA

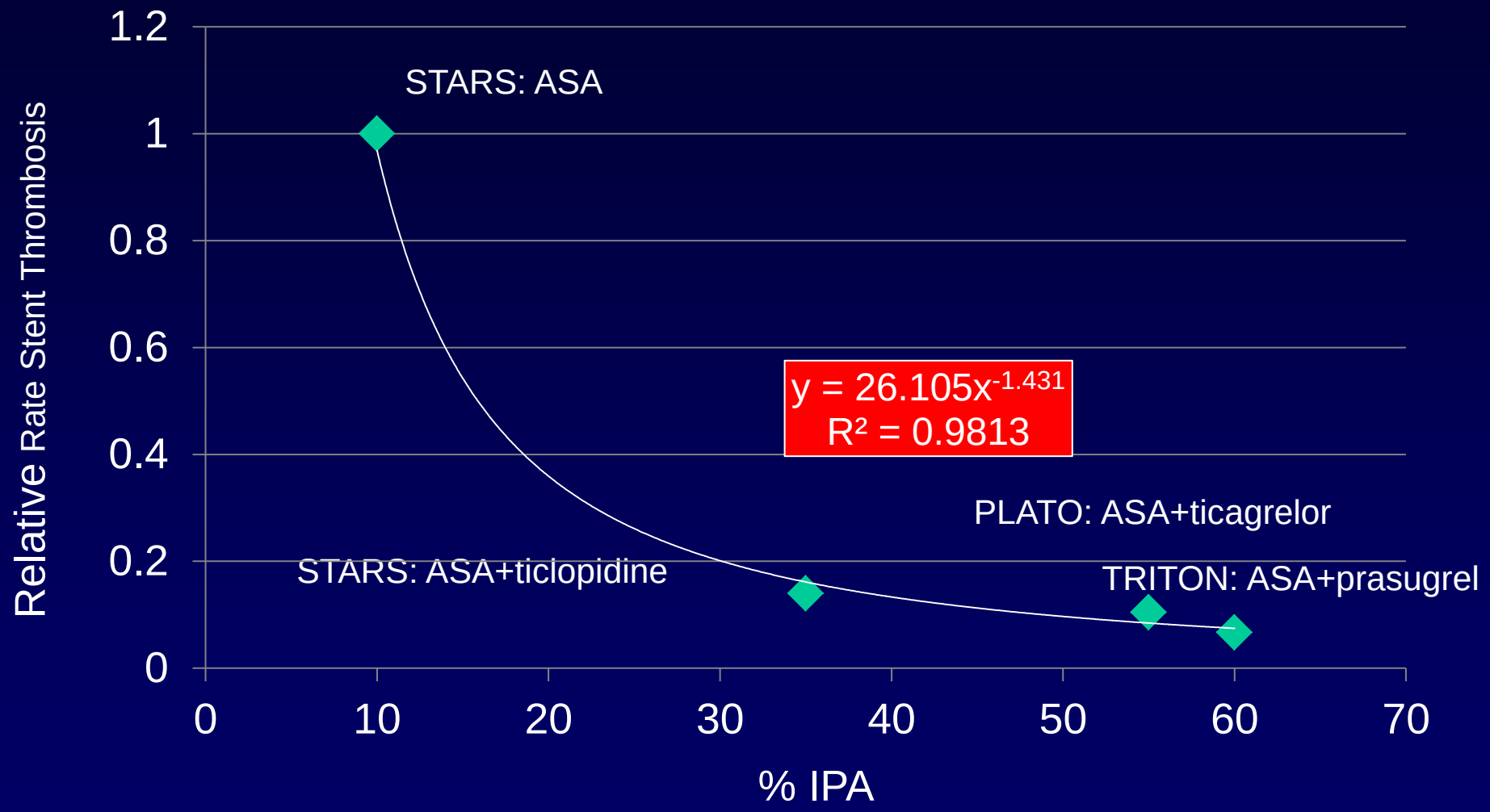



Antithrombotic Trialists' Collaboration. *BMJ*. 2002;324:71
Yusuf et al. *N Engl J Med.* 2001;345:494
Wiviott et al. *N Engl J Med* 2007;357:2001-2015
Wallentin et al. N Engl J Med 2009;361:1-13

**EFFICACY=Death/MI/Stroke**

**BLEEDING=Non-CABG Major**

# Stent Thrombosis Correlated with IPA

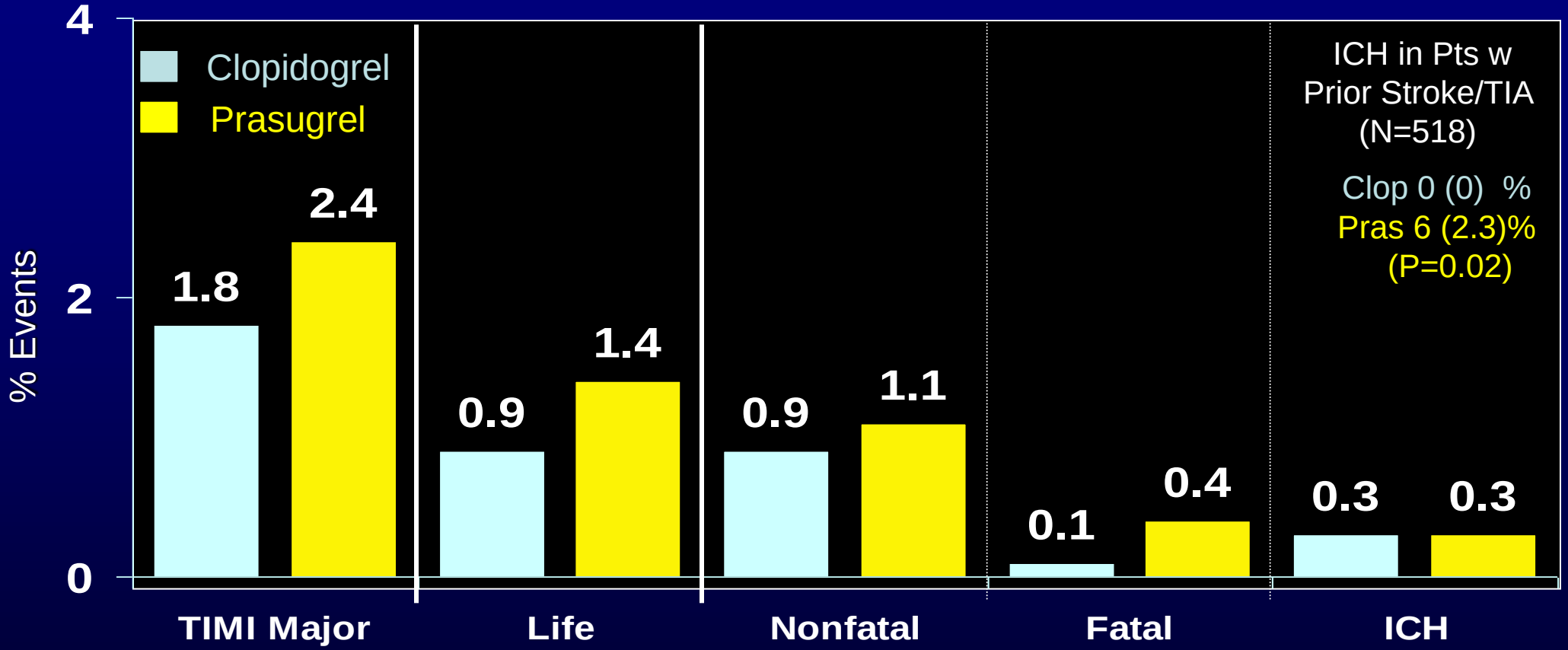




Leon et al. *N Engl J Med* 1998;339:1665-71
Wiviott et al. *N Engl J Med* 2007;357:2001-2015
Wallentin et al. *N Engl J Med* 2009;361:1-13

TRÎTON TIMI·38

# Bleeding Events Safety Cohort (N=13,457)




ARD 0.6%
HR 1.32
P=0.03
NNH=167

ARD 0.5%
HR 1.52
P=0.01

ARD 0.2%
P=0.23

ARD 0.3%
P=0.002

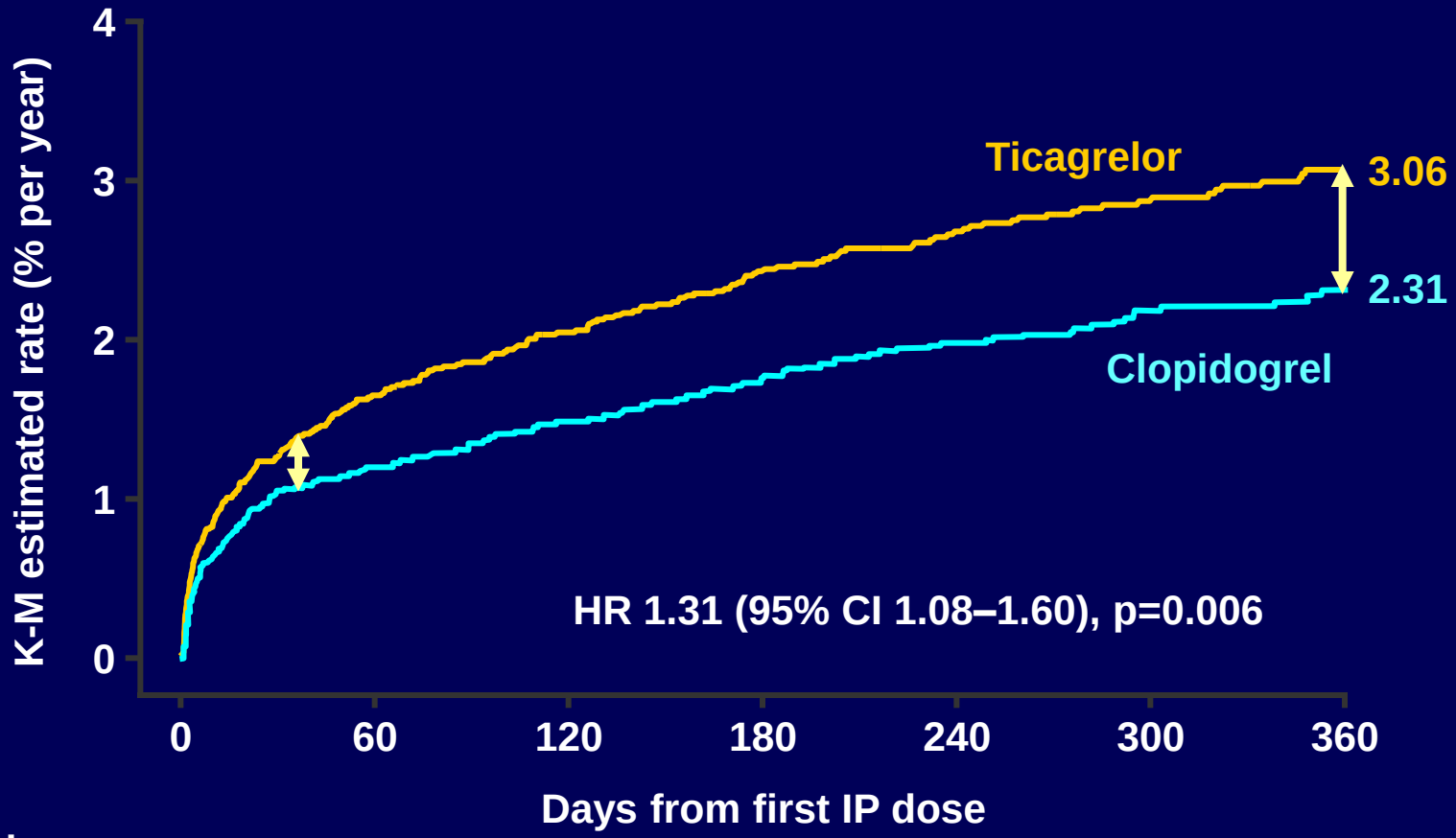
ARD 0%
P=0.74

Wiviott SD, Braunwald E, McCabe CH et al NEJM2007

# Time to non-procedure-related PLATO major bleeding

PLATO

Completeness of follow-up 99.97% = five patients lost to follow-up




| No. at risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| Ticagrelor | 9,235 | 7,641 | 7,247 | 6,979 | 5,496 | 4,067 | 3,698 |
| Clopidogrel | 9,186 | 7,718 | 7,371 | 7,134 | 5,597 | 4,147 | 3,764 |

# *Why do we need newer agents?*

1. Wide variability in Clopidogrel response

   a. genetic variation

   b. possible drug interactions (Cytochrome enzymes): PPIs, lipophilic statins, CCBs etc

2. Unmet needs in thrombosis

**3. Patients awaiting surgery : reversible agents**

# Reversible $P2Y_{12}$ receptor antagonist

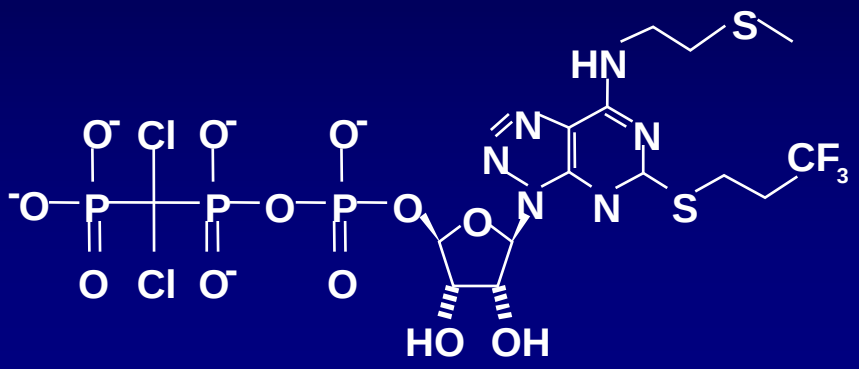
**Ticagrelor**

**Cangrelor**

**Elinogrel**

# Cangrelor (AR-C69931MX)

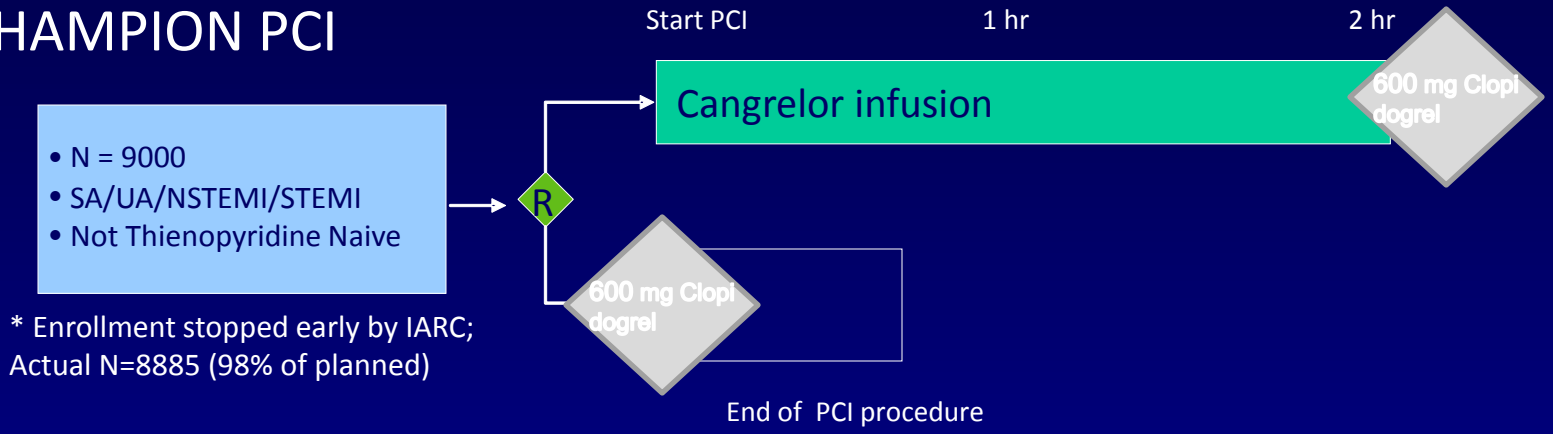
- **Parenteral** ADP-$P2Y_{12}$ receptor antagonist
- ATP analogue




- **Direct** and **Reversible** $P2Y_{12}$ inhibitor
- **More potent** than clopidogrel ~90% inhibition of platelet aggregation at 1 - 4 mcg/kg/min iv
- Plasma half-life of 5-9 min.; 20 min. for return to normal platelet function

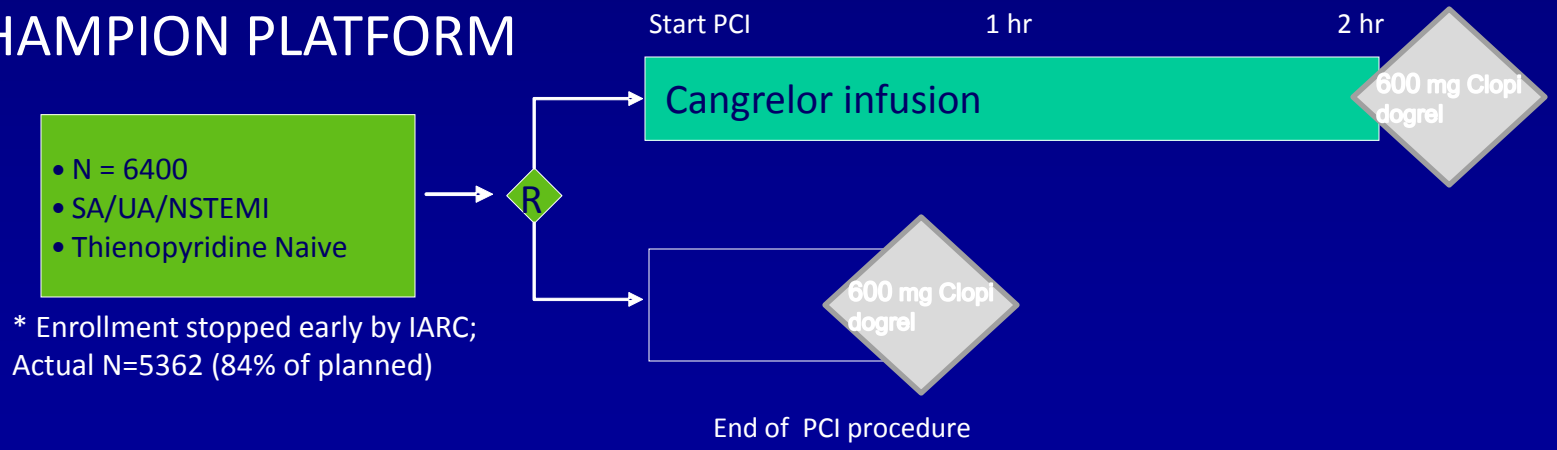
# Trial Design: CHAMPION PCI and PLATFORM

## CHAMPION PCI




* Enrollment stopped early by IARC; Actual N=8885 (98% of planned)

## CHAMPION PLATFORM

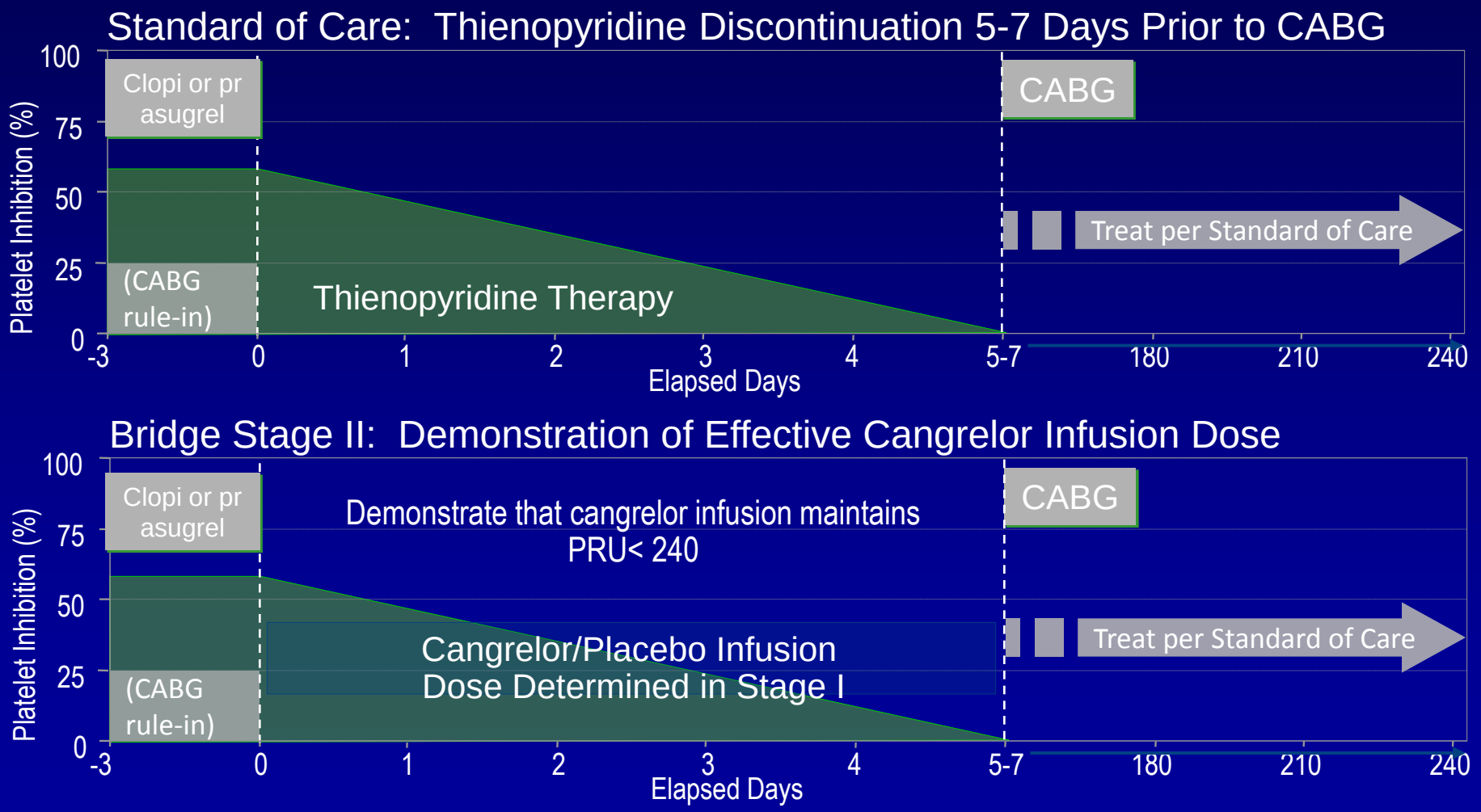



* Enrollment stopped early by IARC; Actual N=5362 (84% of planned)


Bhatt DL, et al. NEJM 2009; 361.

Harrington RA, et al. NEJM 2009; 361.

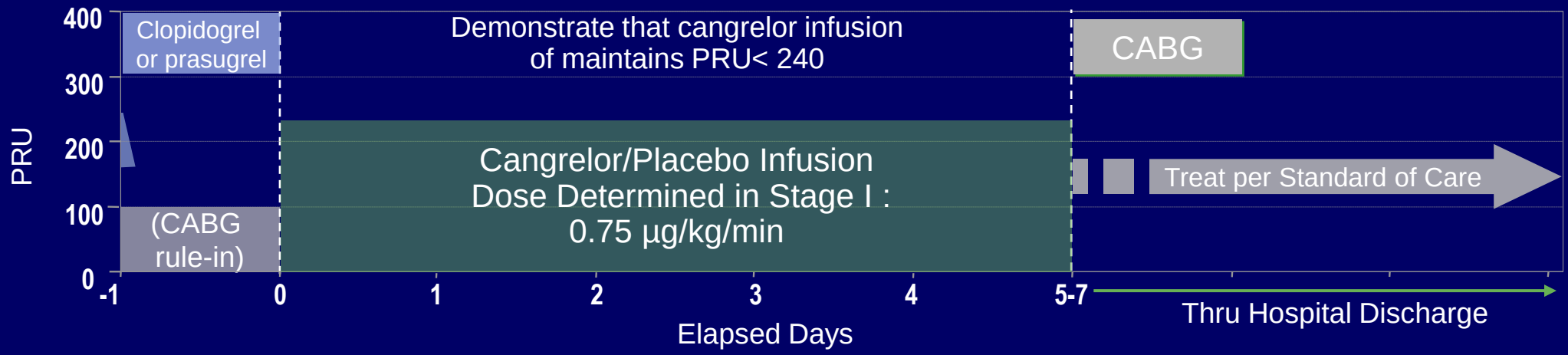
# BRIDGE Trial Design: Stage II - blinded




Angiolillo DJ. TCT 2011.

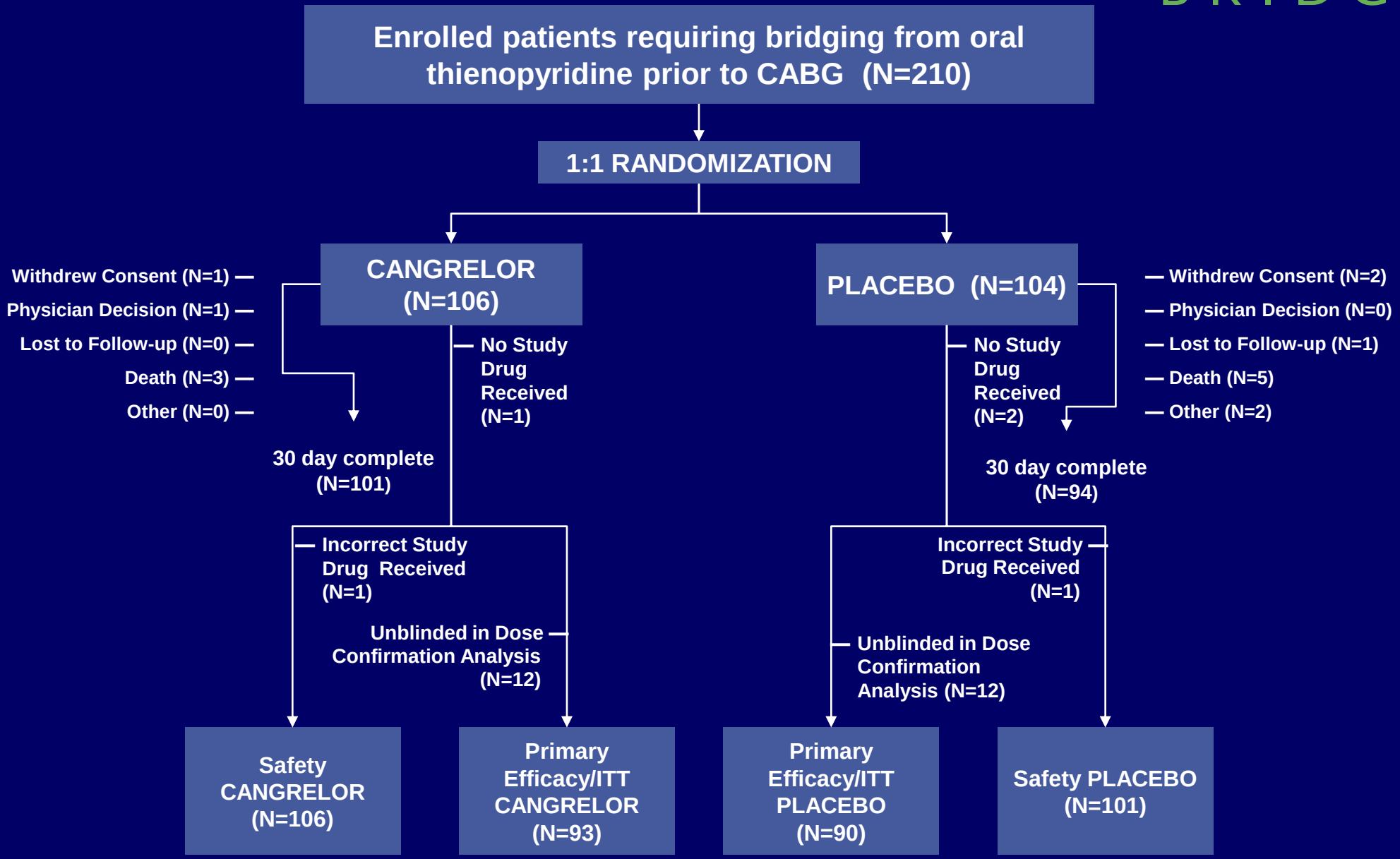
# Trial design: Stage II Randomized, Double-Blind, Placebo-Controlled

**Bridge Stage II: Demonstration of Effective Cangrelor Infusion Dose**



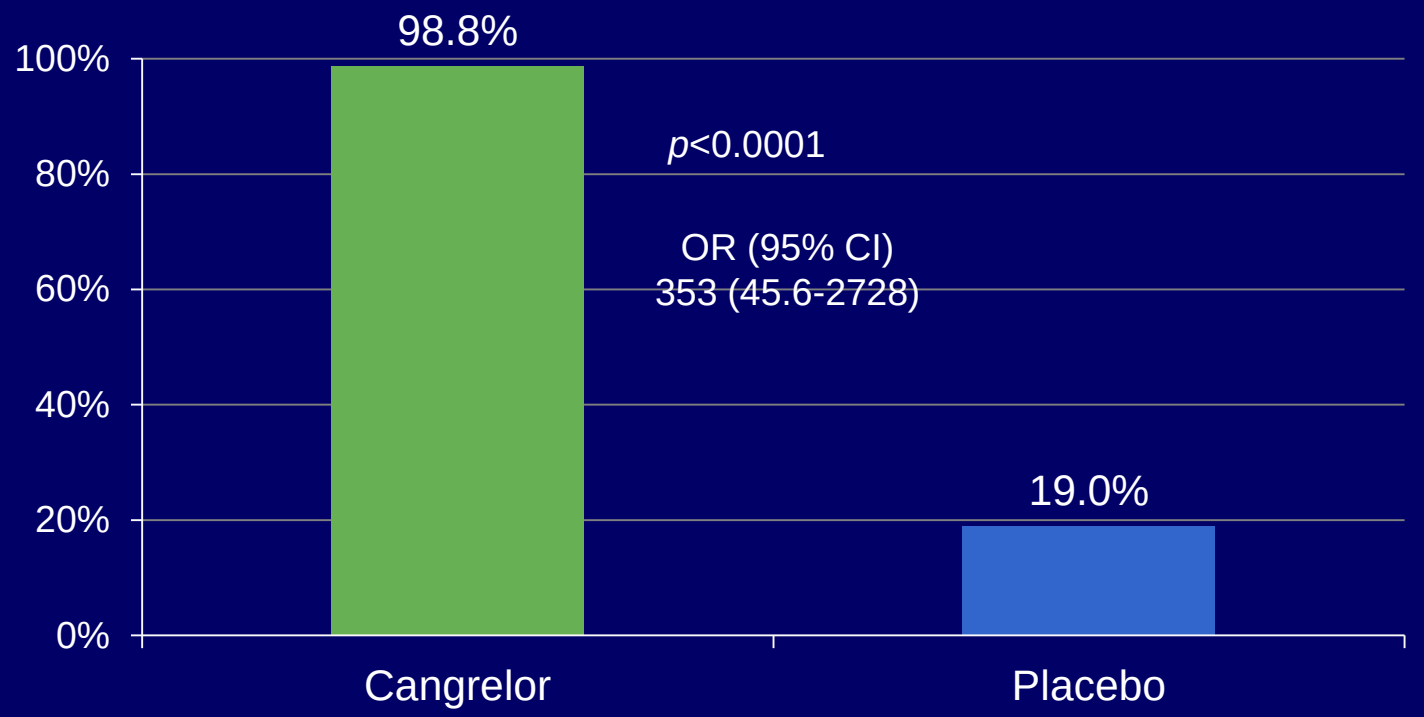

- Patients with an ACS or treated with a coronary stent (BMS or DES) on a thienopyridine (ticlopidine, clopidogrel or prasugrel) awaiting CABG.
- After thienopyridine discontinuation (<72 hours), patients were administered cangrelor/placebo for at least 48 hours and up to 7 days, which was discontinued 1-6 hours prior to CABG.
- Objective: demonstrate that cangrelor would maintain levels of platelet reactivity <240 P2Y12 Reaction Units (PRU) throughout the pre-operative period as measured by the VerifyNow™ P2Y12 test.

# Patient distribution

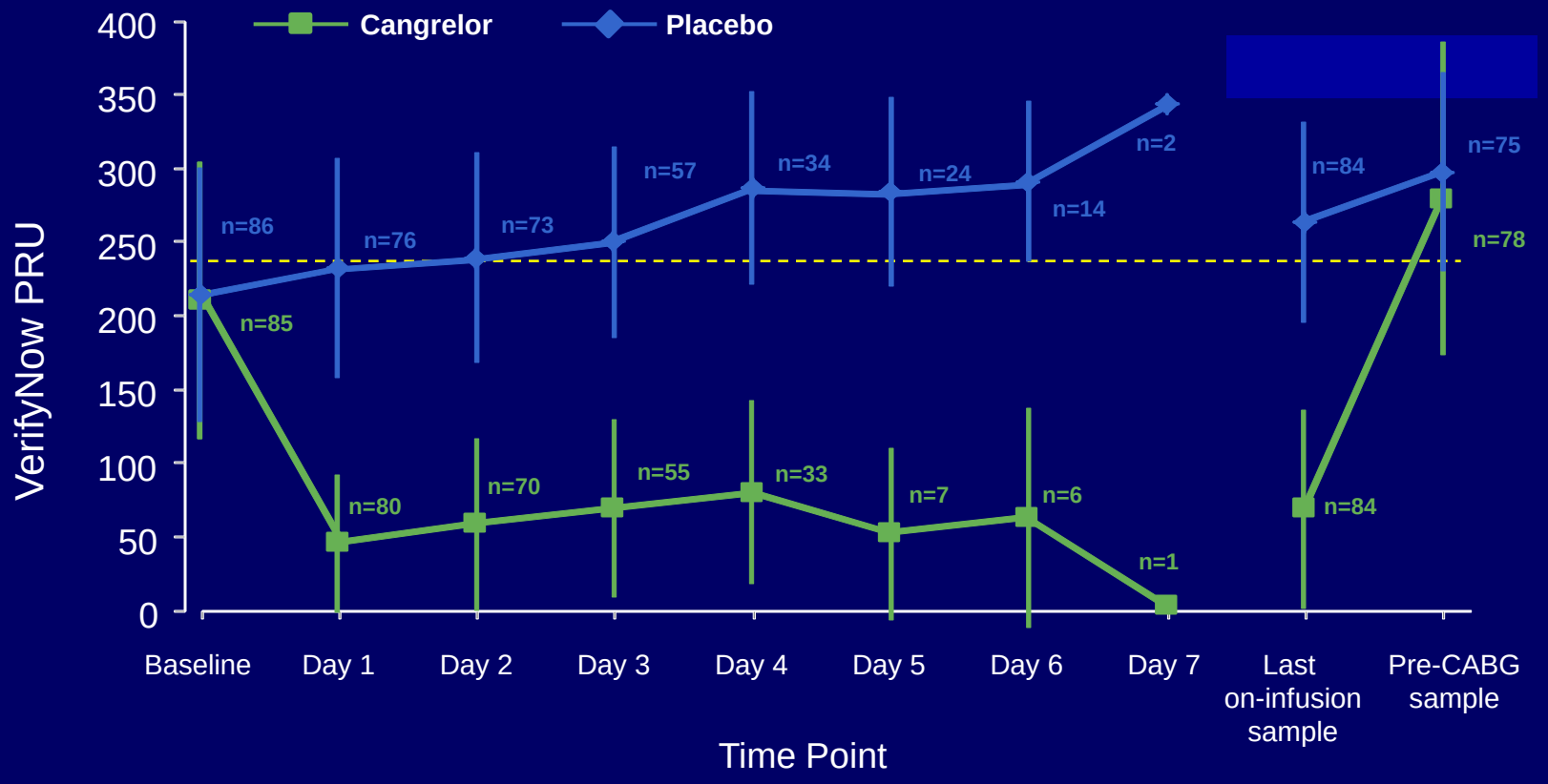


# Primary endpoint

- Percent of patients with PRU<240 for all on-treatment samples:



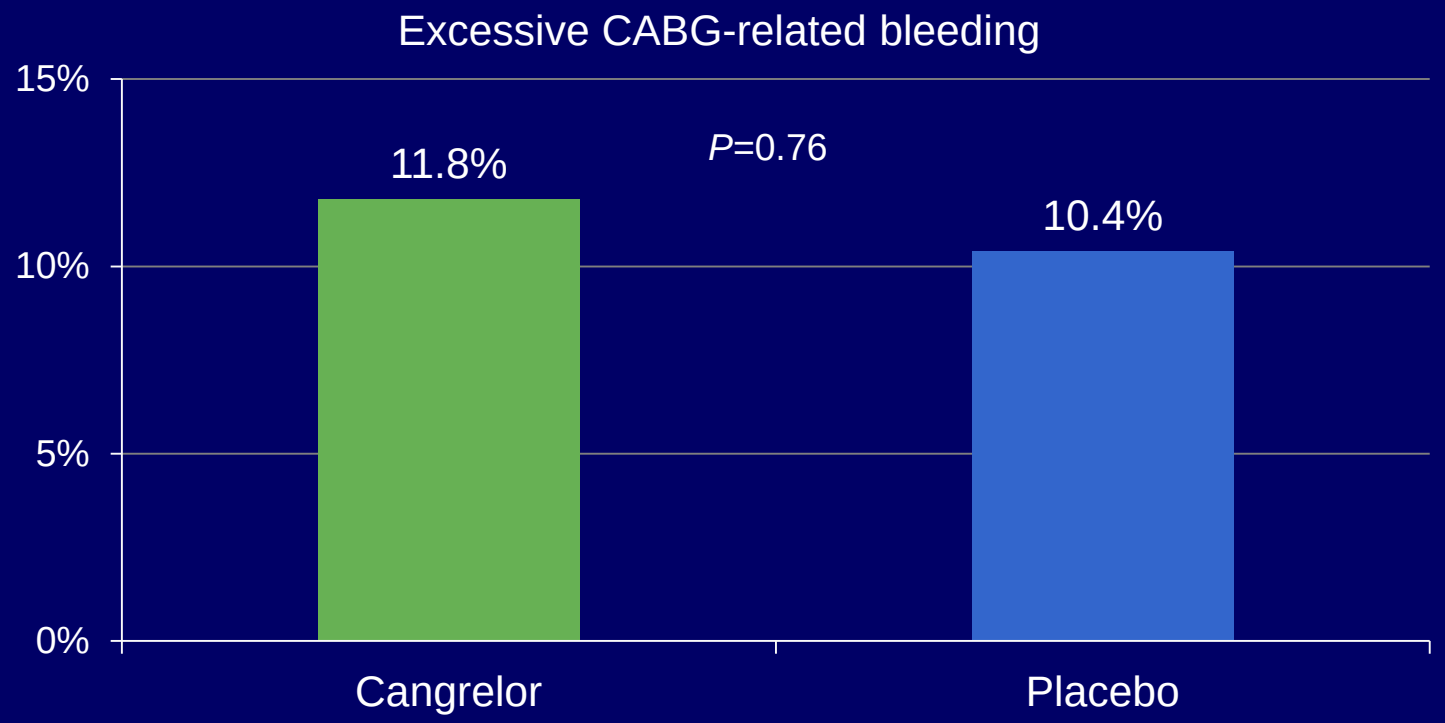
# Platelet reactivity by day




N indicates number of patients with valid samples in the intention to treat population; PRU= P2Y12 reaction units; Data expressed as mean±SD

# Bleeding endpoint

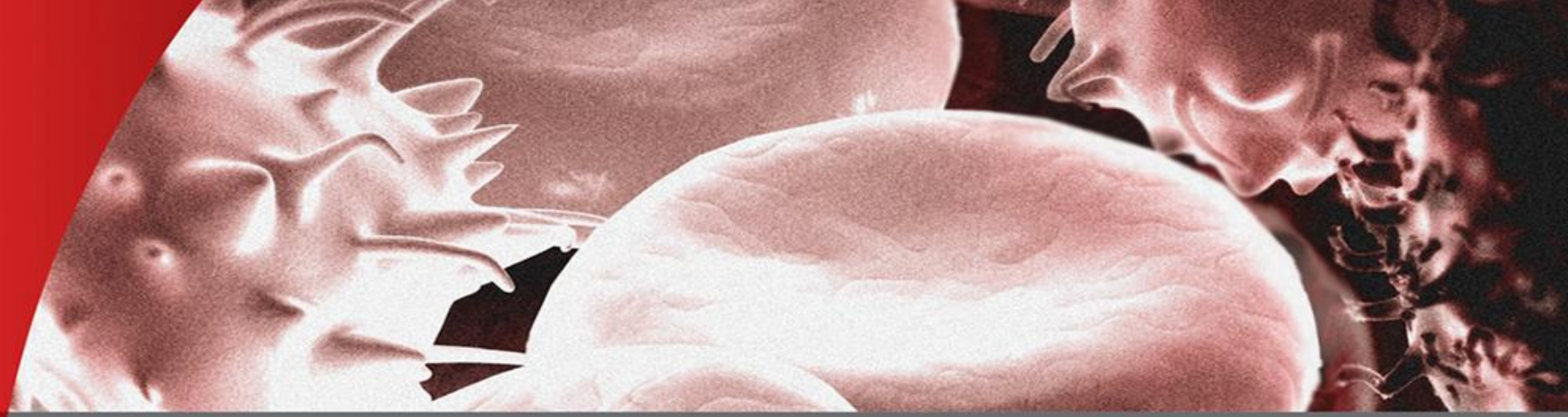
- Excessive CABG-related bleeding (primary safety endpoint)*




*Excessive CABG-related bleeding is defined as the occurrence of one or more of the following 3 components during the CABG procedure or post-operative hospitalization: Surgical re-exploration, 24 hour CT output > 1.5 liters, Incidence of PRBC transfusion > 4 units.

# Properties of Elinogrel

- The only reversible and competitive $P2Y_{12}$ receptor antagonist
- Direct-acting: no metabolic activation required
- Available for intravenous and oral administration, enabling acute and chronic use
- Immediate and near maximal platelet inhibition achieved with IV
- Duration of action
  - Half-life: 12 hours
- No major CYP metabolism – low potential for drug-drug interactions (including PPIs)
- Balanced clearance: 50% renal; 50% hepatic (10% metabolized to pharmacologically inactive metabolite)



# A Randomized, Double-Blind, Active Controlled Trial to Evaluate Intravenous and Oral PRT060128 (elinogrel), a Selective and Reversible $P2Y_{12}$ Receptor Inhibitor, vs. Clopidogrel, as a Novel Antiplatelet Therapy in Patients Undergoing Non-urgent Percutaneous Coronary Interventions (INNOVATE-PCI)

INNOVATE-PCI

August 30, 2010

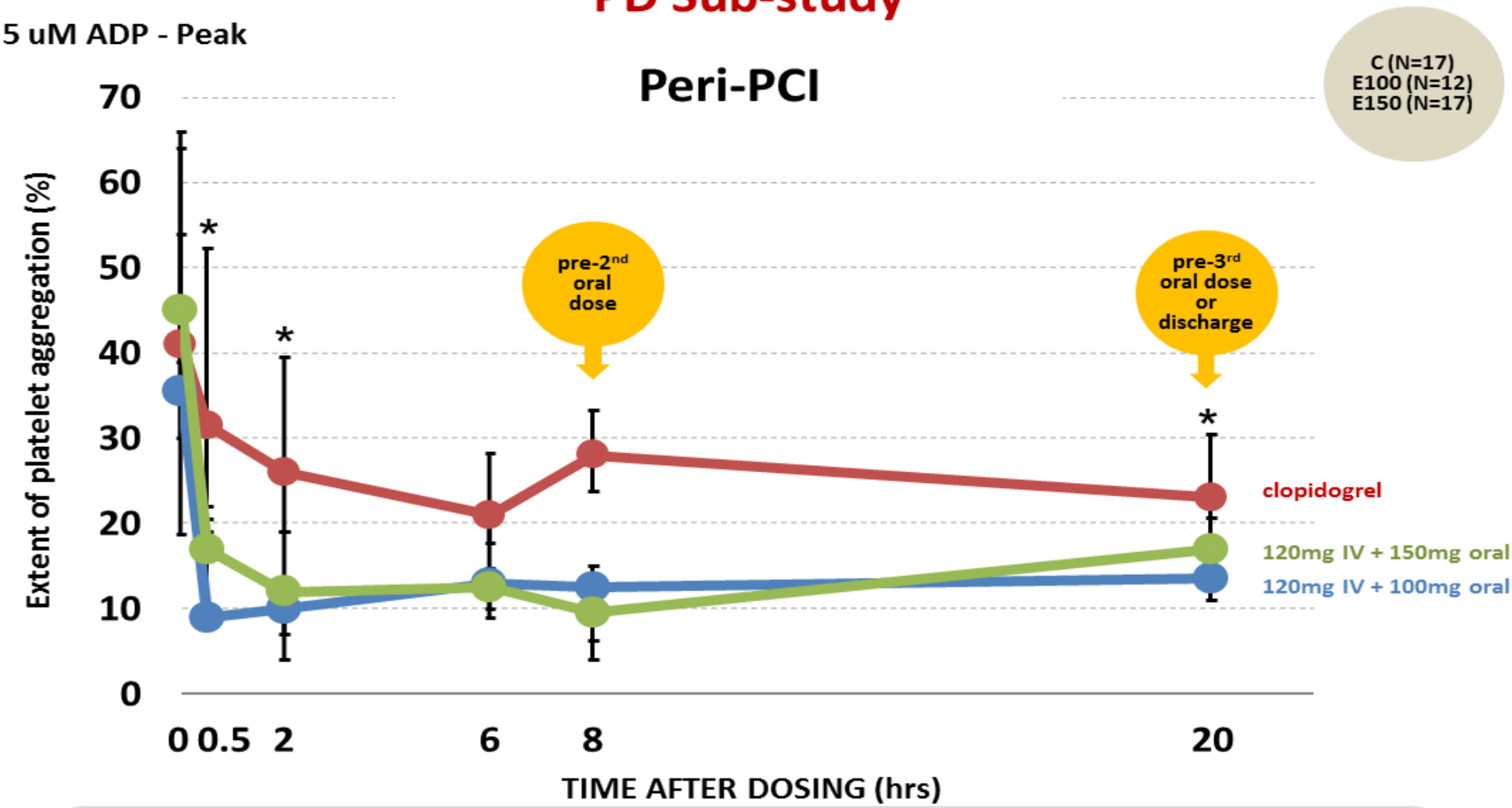
# Treatment Schema

| | ACUTE PHASE Peri-PCI | | CHRONIC PHASE Post-PCI | |
|---|---|---|---|---|
| ARM 1: clopidogrel | 300-600mg Loading Dose | PCI | 75 mg QD | n=200 |
| ARM 2: elinogrel | 80 mg IV Bolus+ 50mg PO | PCI | 50 mg BID | n=200 |
| ARM 3: elinogrel | 80mg IV Bolus + 100mg PO | PCI | 100 mg BID | n=200 |
| ARM 4: elinogrel | 80mg IV Bolus + 150mg PO | PCI | 150 mg BID | n=200 |

# Pharmacodynamic Effect of Elinogrel vs. Clopidogrel

## PD Sub-study

5 uM ADP - Peak



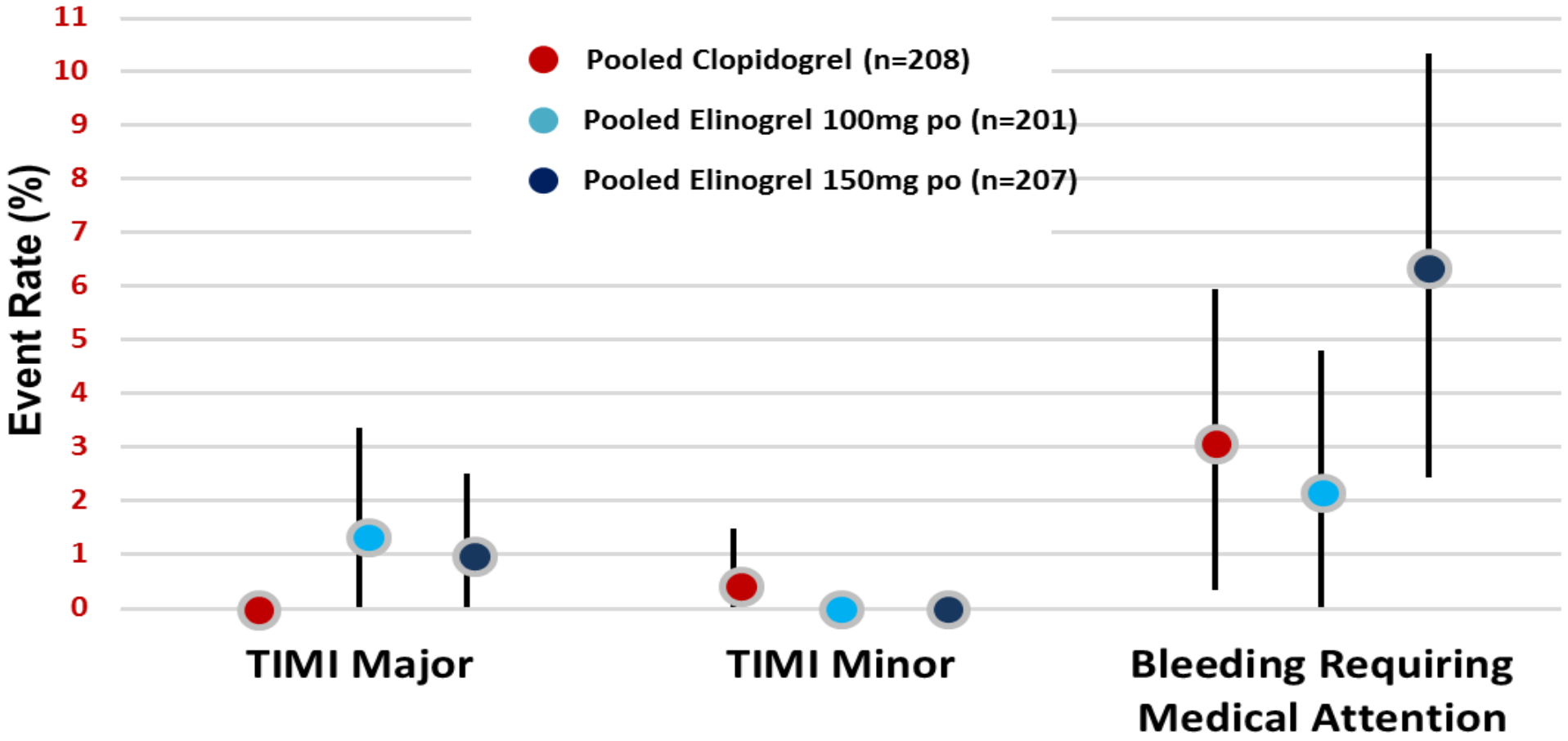

**74% of pts represented above were on maintenance clopidogrel**

* p<0.025 for both elinogrel vs. clopidogrel comparisons

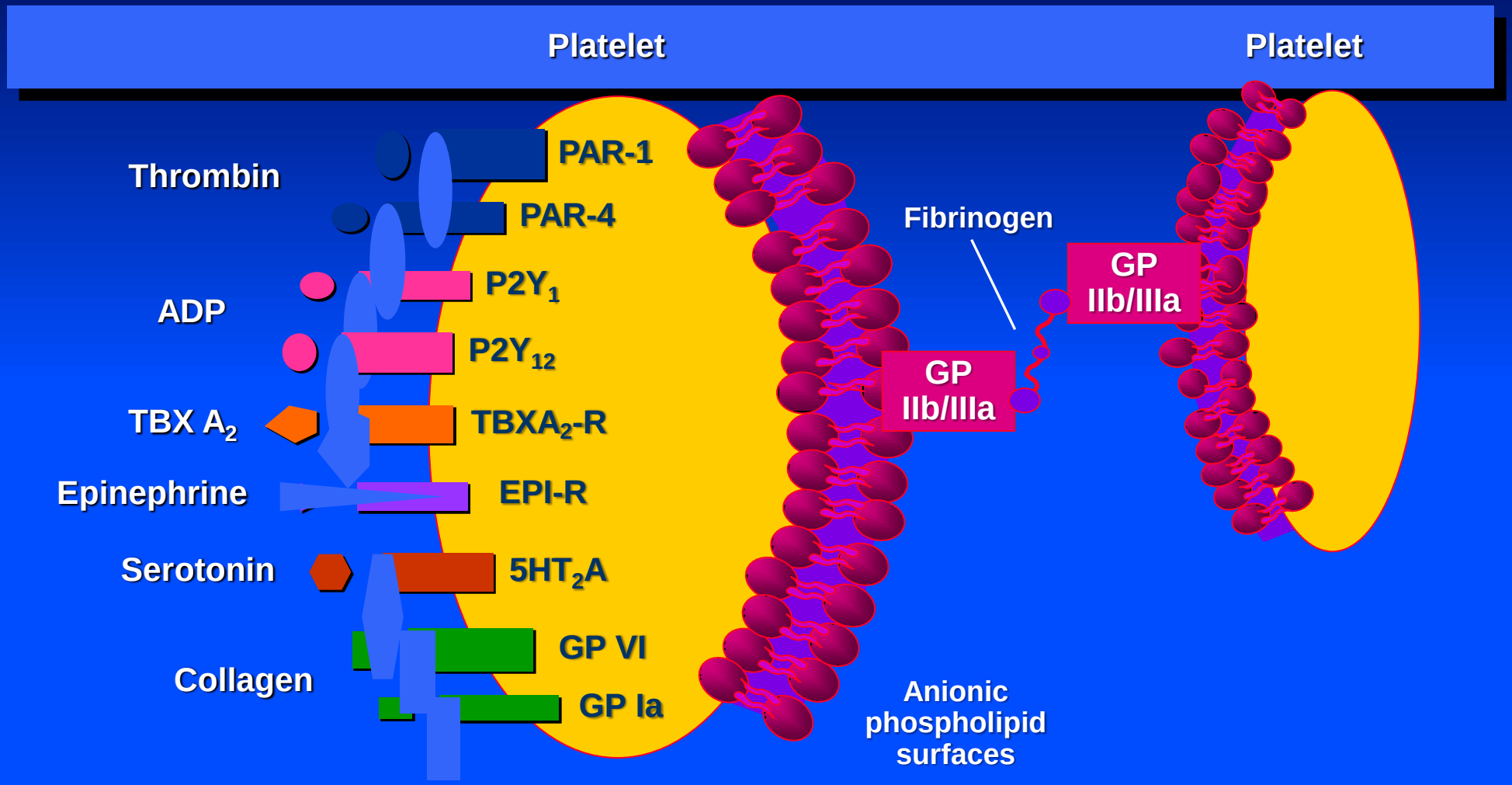
Median, quartiles

# Bleeding at 24h-120d – TIMI Scale

## Rates and 95% confidence intervals



# Platelet Receptors



# TRACER

***Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome***

**NSTEACS**
**N = 10,000**

**SCH 530348**
**40 mg bolus, 2.5 mg daily**
**n=5000**

**Placebo**
**(and usual therapy)**
**n=5000**

**• >1-Year Cardiovascular Death, MI, Stroke, Recurrent Ischemia with Rehosp, Urgent Coronary Revas (2334 events) •**

www.clinicaltrials.gov

TRA·CER
Thrombin Receptor Antagonist for Clinical Events Reduction

# TRA 2P—TIMI 50

## *Thrombin Receptor Antagonist for 2º Prevention*

**Hx MI, CVA, PVD**
**N ~ 25,000**

**SCH 530348**
**2.5 mg daily**
**N ~ 12,500**

**Placebo**
**(and usual therapy)**
**N ~ 12,500**

**• 1-Year Cardiovascular Death, MI, Stroke, or Urgent Coronary Revascularization (2279 events) •**

www.clinicaltrials.gov

TRA 2°P TIMI 50

# TRA•2P TIMI-50

"The DSMB has communicated to us that based on all of the data (safety and efficacy) available to them from both trials, they recommend that subjects with a history of stroke not receive vorapaxar. They have observed an increase in intracranial hemorrhage in patients with a history of stroke that is not outweighed by their considerations of potential benefit."

"In contrast, on the basis of their risk/benefit assessment in patients without a history of stroke, the DSMB recommended to us that it is important that the trial continue to completion in the more than 20,000 subjects who qualified for the trial with myocardial infarction or peripheral arterial disease who have not had a stroke. On the basis of their recommendation, we and Merck remain committed to completing this important scientific investigation with a potential for a reduction in death and ischemic events in these patients."

Eugene Braunwald, MD
Commenting on TRA 2P-TIMI 50
January 2011

# Conclusion and take home message

1. *Clopidogrel is still the thienopyridine of choice for most conventional indications [medical tx, stable angina elective PCI, alternative to aspirin…]*

2. *There is still a need for new agents because of various shortcomings of clopidogrel, including wide variability of response and susceptibility to genetics risk.*

3. *There is also an unmet need in thrombosis especially for patients with DM, previous ST, AMI, large thrombus burden.*

# Conclusion and take home message

***4.*** ***Newer agents are definitely more potent and can improve outcome in high risk patients. However, the risk of bleeding increases, which has to be kept in mind.***

***5.*** ***New reversible agents are under development and may help patients undergoing surgergy.***

***6.*** ***Always balance the risk of thrombosis and bleeding and choose the most appropriate therapy for your patients.***

# *Thank you*

# *for your attention!!*