Optimal Antiplatelet Therapy in Asians

Kyung Woo Park, MD, PhD

Seoul National University Hospital, Seoul, Korea

I have no potential conflict of interest to disclose

What is the purpose of prescribing antiplatelet agents?

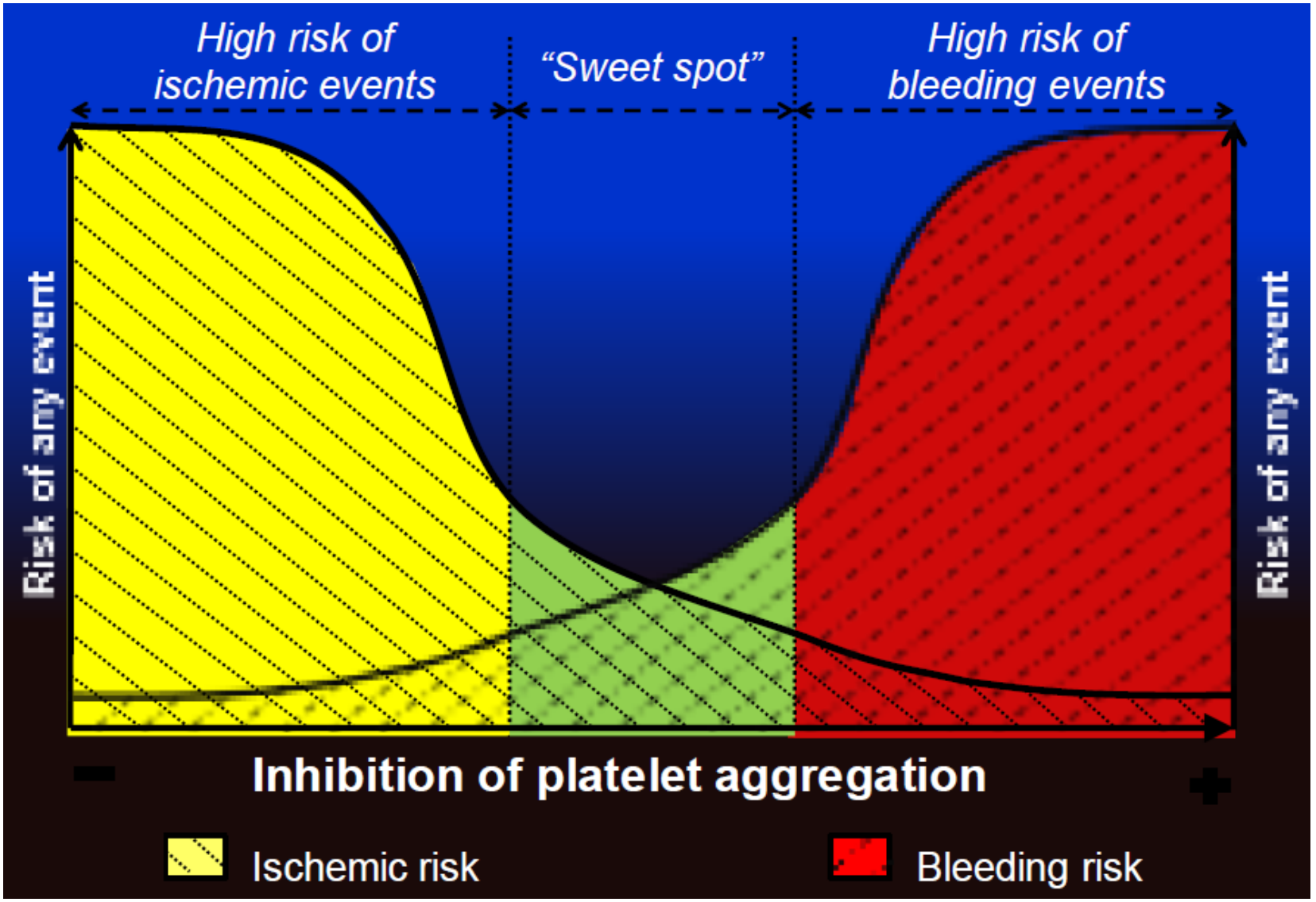
→ To inhibit platelet reactivity

What major effects do we expect?

1. Prevent ischemic events

2. Cause bleeding

The Balancing Act



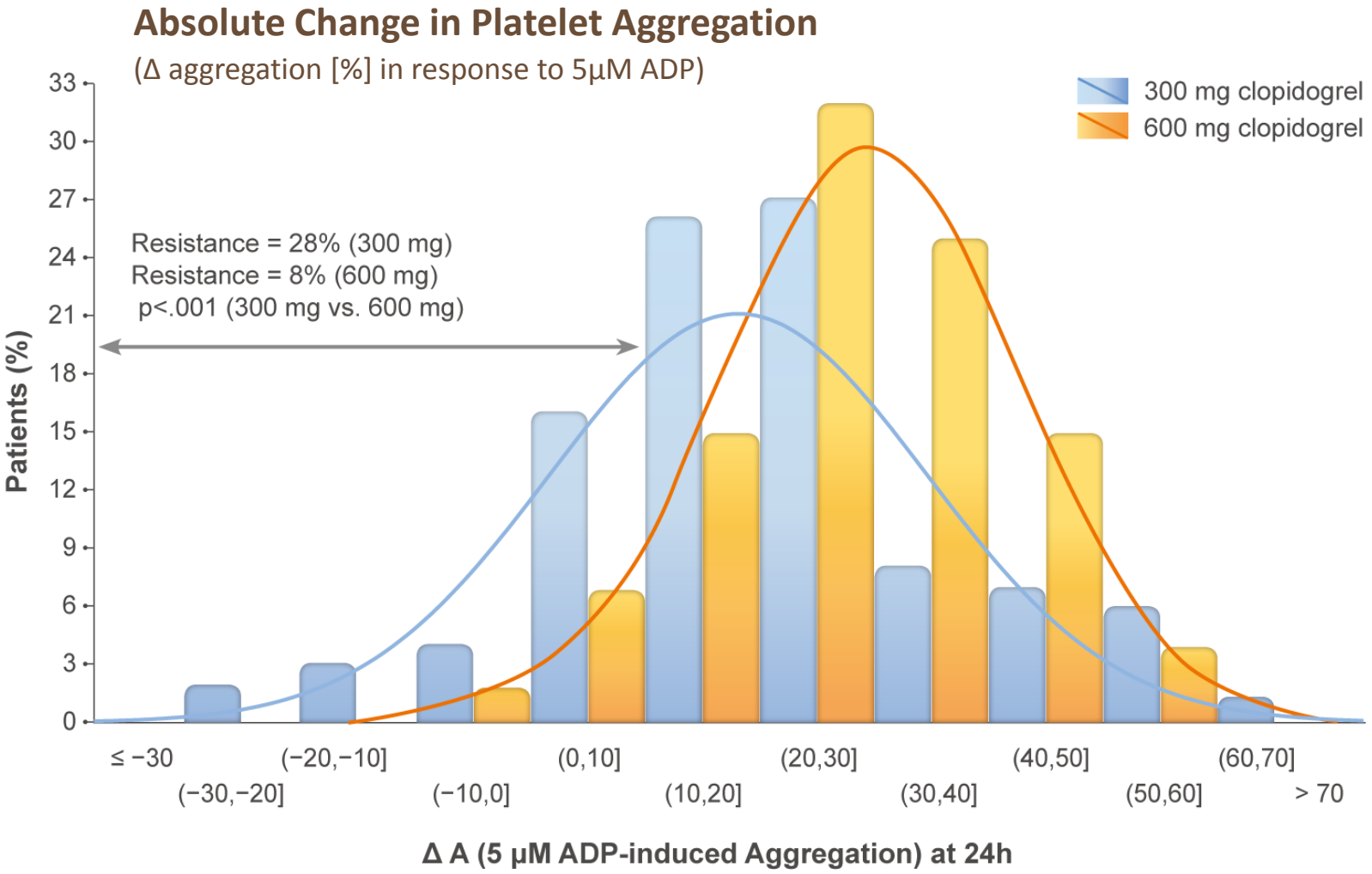
What choices do we have?

1. Clopidogrel
2. Prasugrel
3. Ticagrelor

Why might there be differences in antiplatelet therapy between Westerners and Asians?

1. Because the genetics of drug metabolism may be different
2. Because BMI and volume of distribution may be different
3. Because the sweet spot between ischemia & bleeding may be different

Clopidogrel Response



Note : The loading dose of clopidogrel approved by KFDA is 300 mg.

Gurbel PA et al. *J Am Coll Cardiol*. 2005;45:1392-96)

Does ethnicity matter?

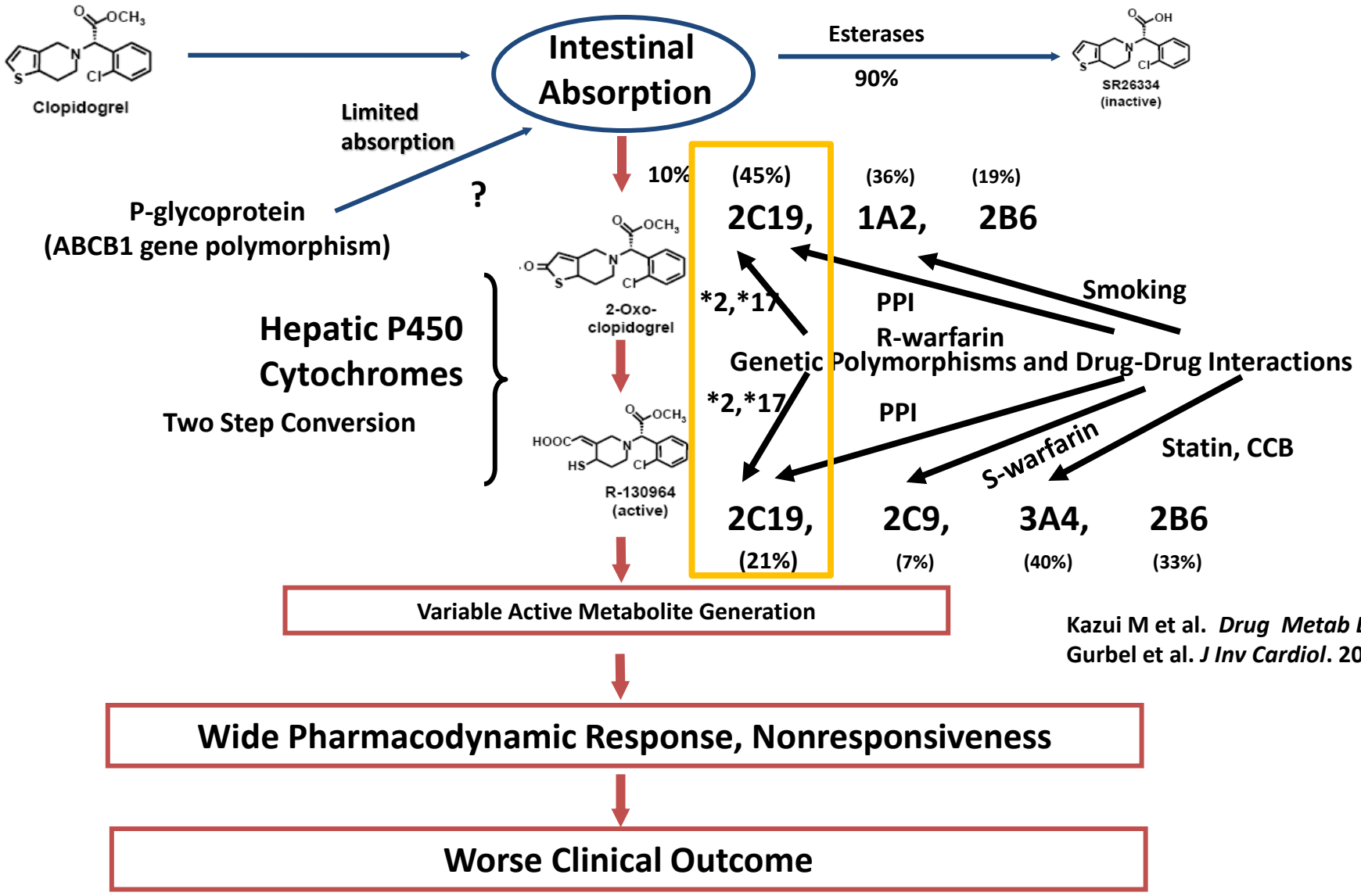
Characteristic	Mean Residual Platelet Reactivity (PRU)		P Value
	Characteristic present	Characteristic absent	
Age > 75 yrs	214 ±77	201±79	0.161
Men	200±77	220±82	0.041
Non-Caucasian ethnicity	229±79	202±78	0.047
Diabetes mellitus	220±73	196±80	0.005
⋮	⋮	⋮	⋮

- 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)

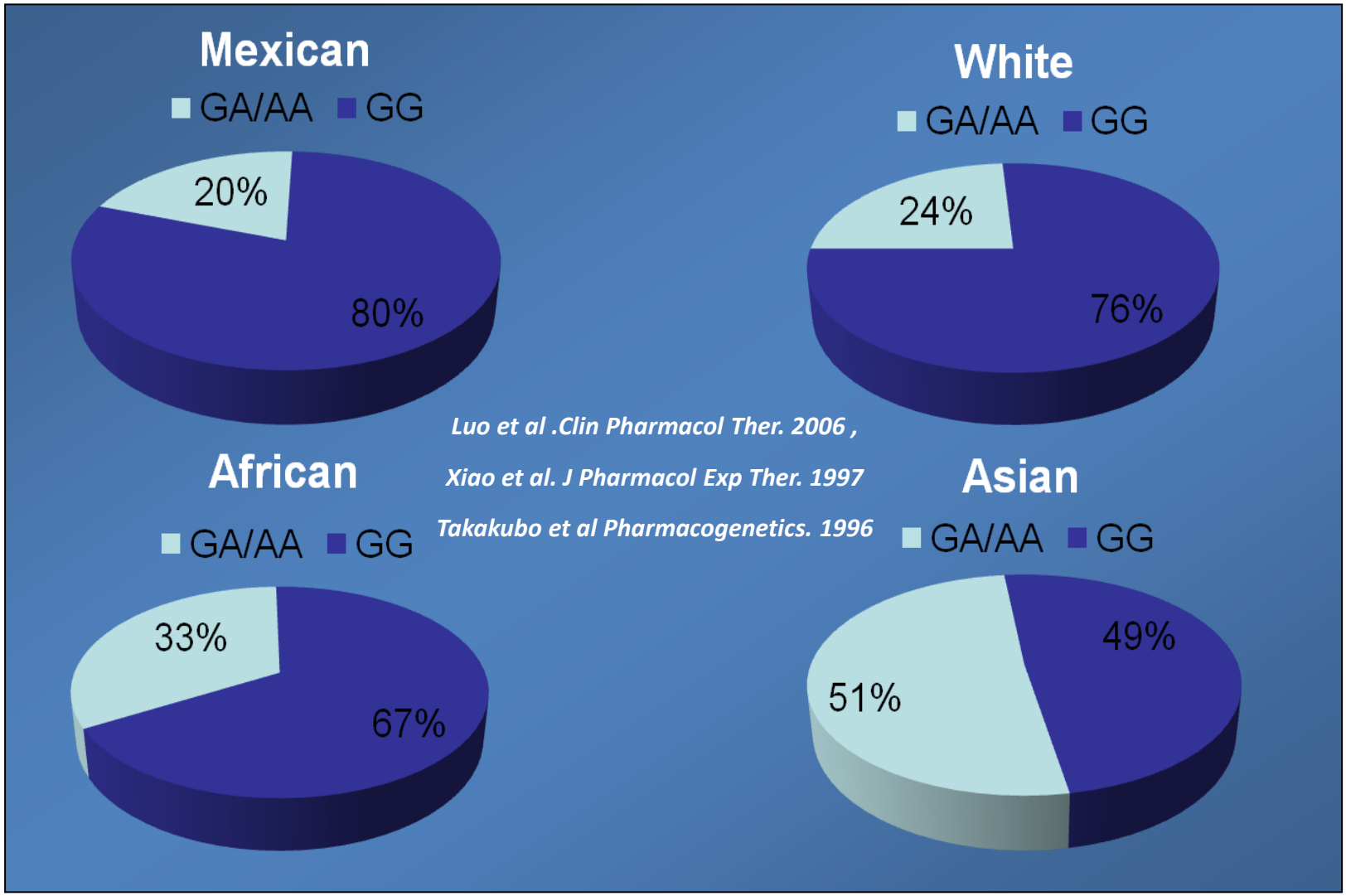
Price MJ et al, Circulation 2009

Clopidogrel Activation and Metabolism



Kazui M et al. *Drug Metab Dispos*. 20
Gurbel et al. *J Inv Cardiol*. 2009

Different CYP2C19 *2 Allele Frequency



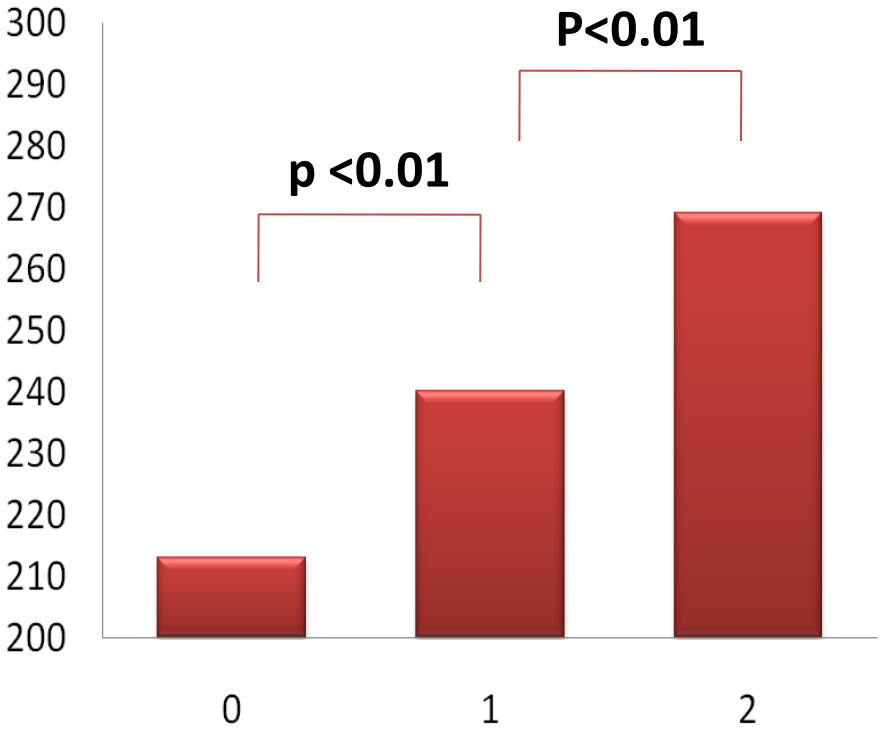
Luo et al .Clin Pharmacol Ther. 2006 ,

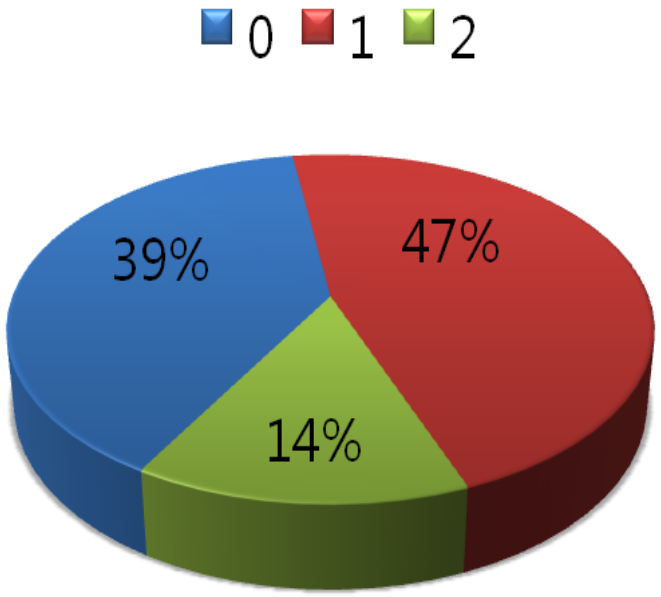
Xiao et al. J Pharmacol Exp Ther. 1997

Takakubo et al Pharmacogenetics. 1996

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

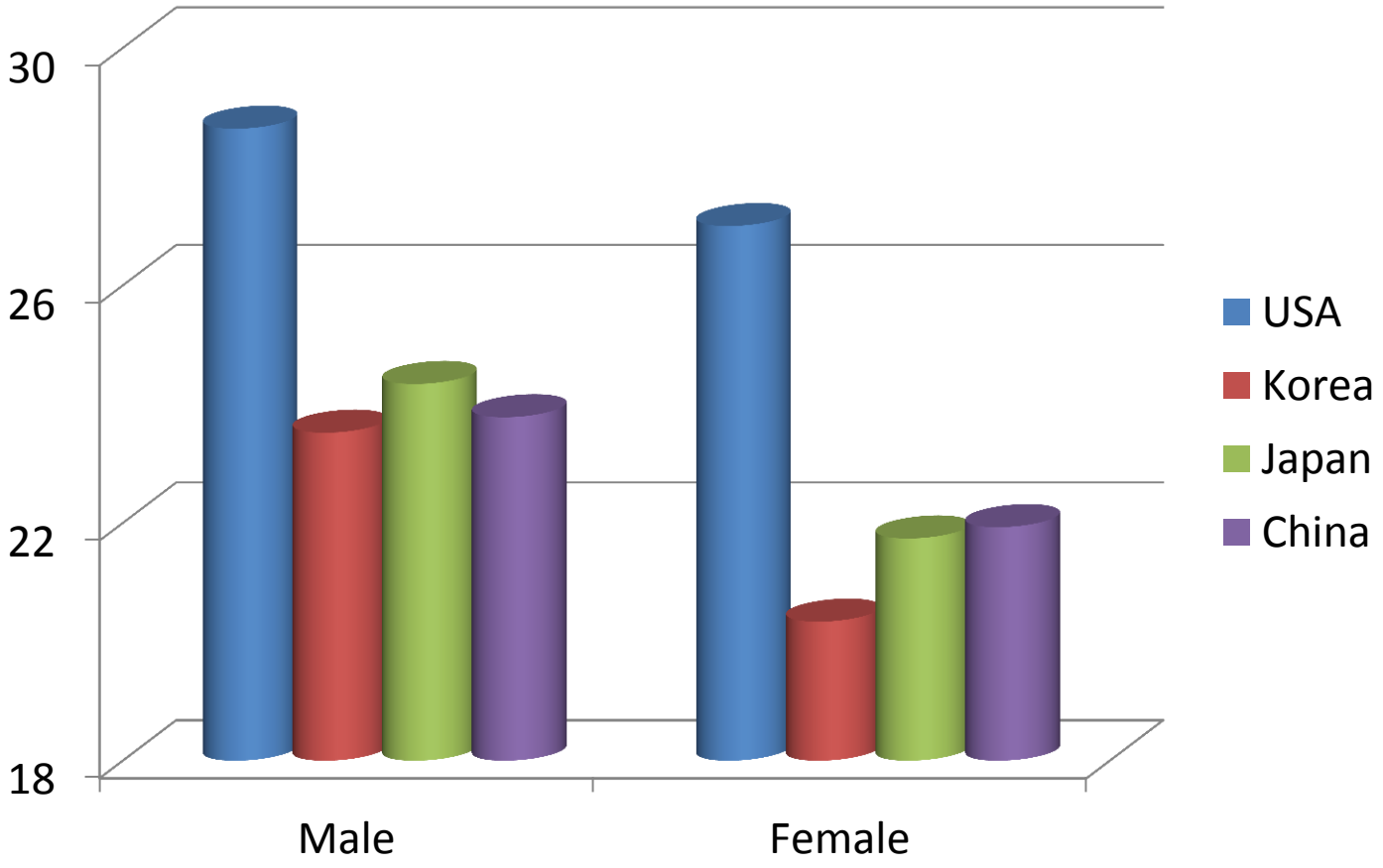
Park KW, Kim HS et al. Int J Cardiol 2013

BMI and VOD Issue

VS.

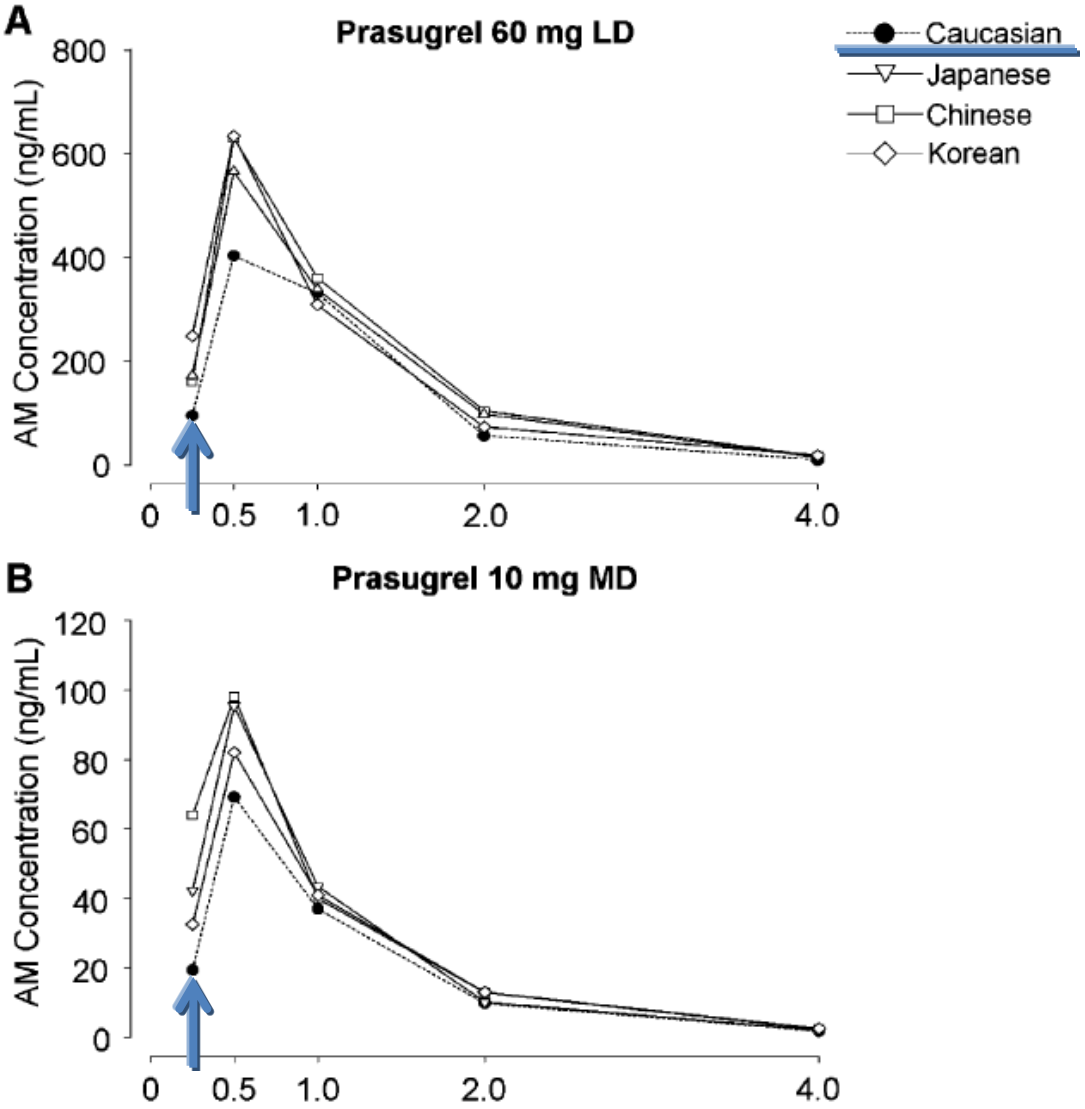
Mean BMI according to Country

- WHO data (from the London School of Hygiene and Tropical Medicine)



Prasugrel Pharmacokinetics

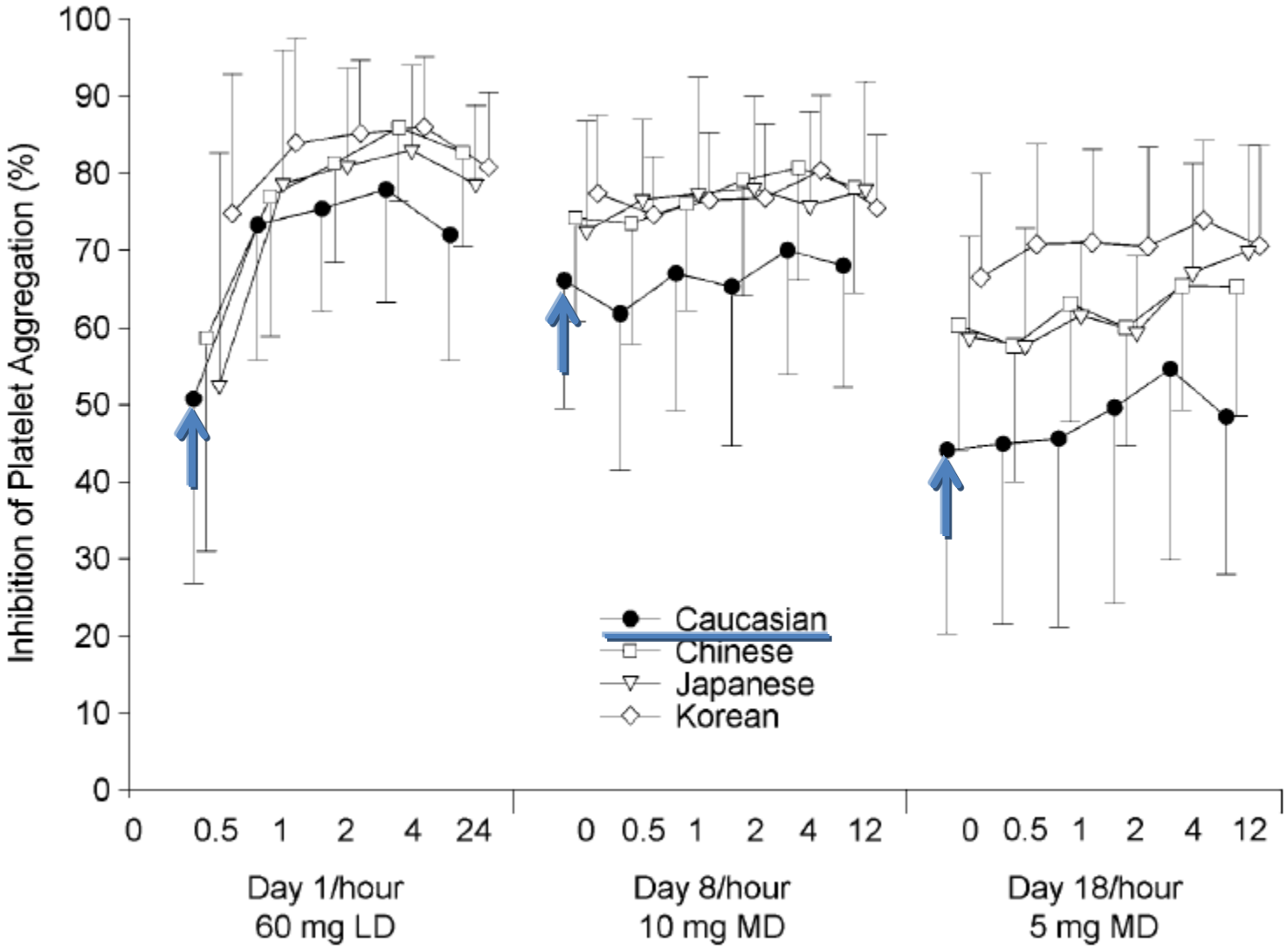
East Asians vs. Caucasians



Small DS et al. Eur J Clin Pharmacol 2010;66:127–135.

Prasugrel Pharmacodynamics

East Asians vs. Caucasians

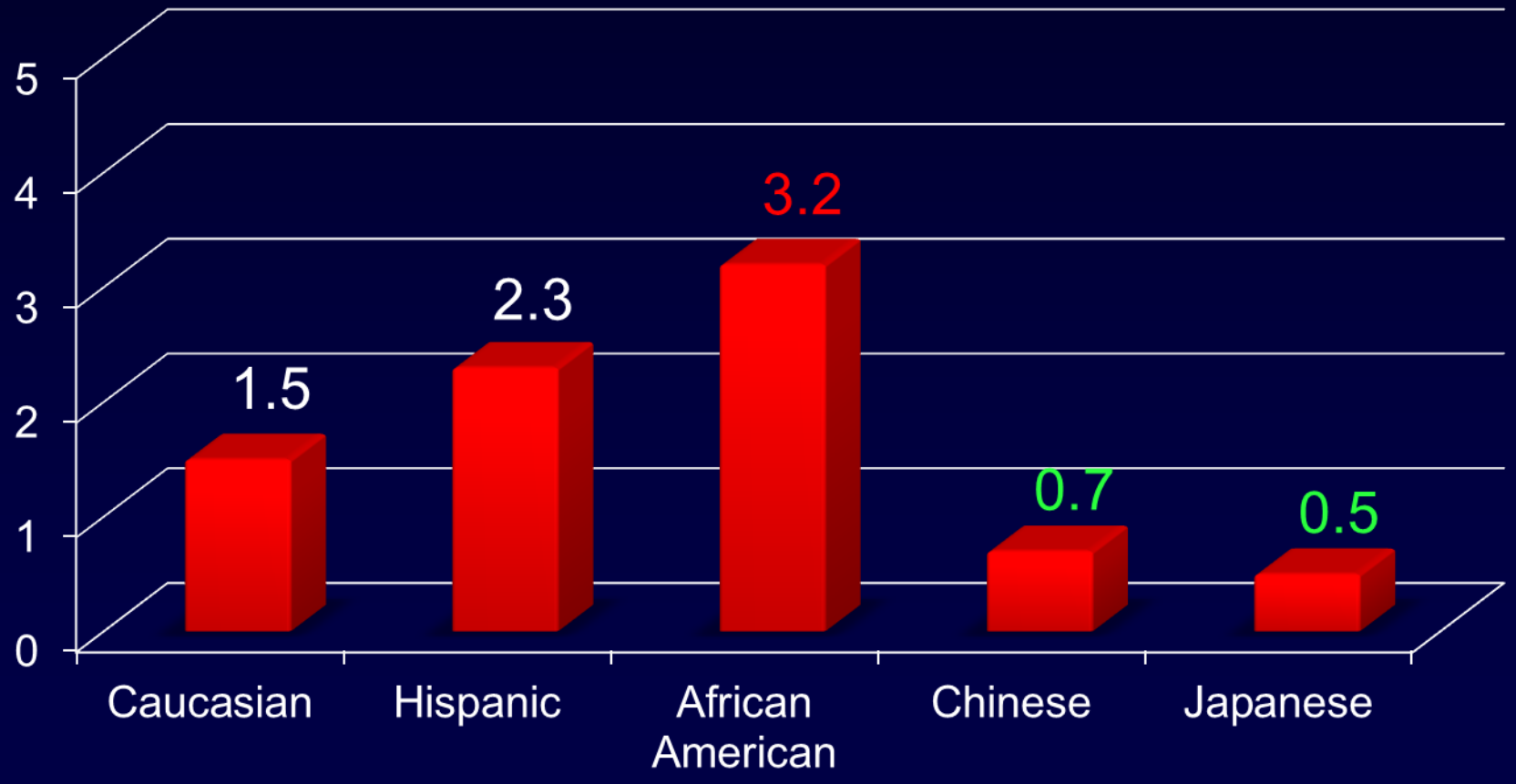


Small DS et al. Eur J Clin Pharmacol 2010;66:127–135.

What about the “Sweet Spot” between ischemia & bleeding?

Ethnic Difference in CRP level

A cross-sectional analysis of 3154 women, without known CVD and hormone therapy (SWAN study)



Kelley-Hedgepeth et al. *Clin Chem*. 2008;54:1027-37.

Hemostatic & Endothelial Markers

MESA study (US citizen: men cohort)

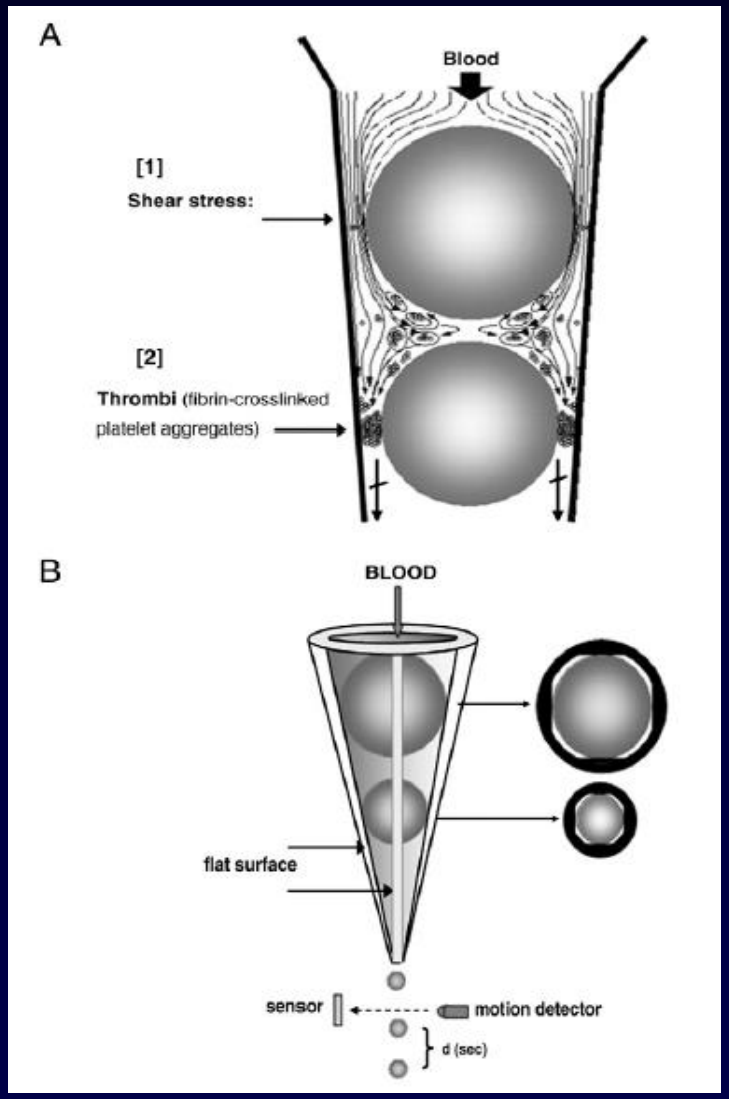
	Caucasian (n = 2599)	Hispanic (n = 1864)	Black (n = 1481)	Chinese (n = 803)
Fibrinogen (mg/dL)	329	344	334	317
Factor VIII (%)	153	150	172	153
D-dimer (ug/mL)	0.20	0.20	0.23	0.15
PAI-1 (ng/mL)	20.4	20.1	14.2	18.4
vWF (%)	136	140	152	144
ICAM-1 (ng/mL)	285	282	252	233
E-selectin (ng/mL)	57.0	56.9	61.8	50.8

* Adjusted for age, education, individual income, and site.

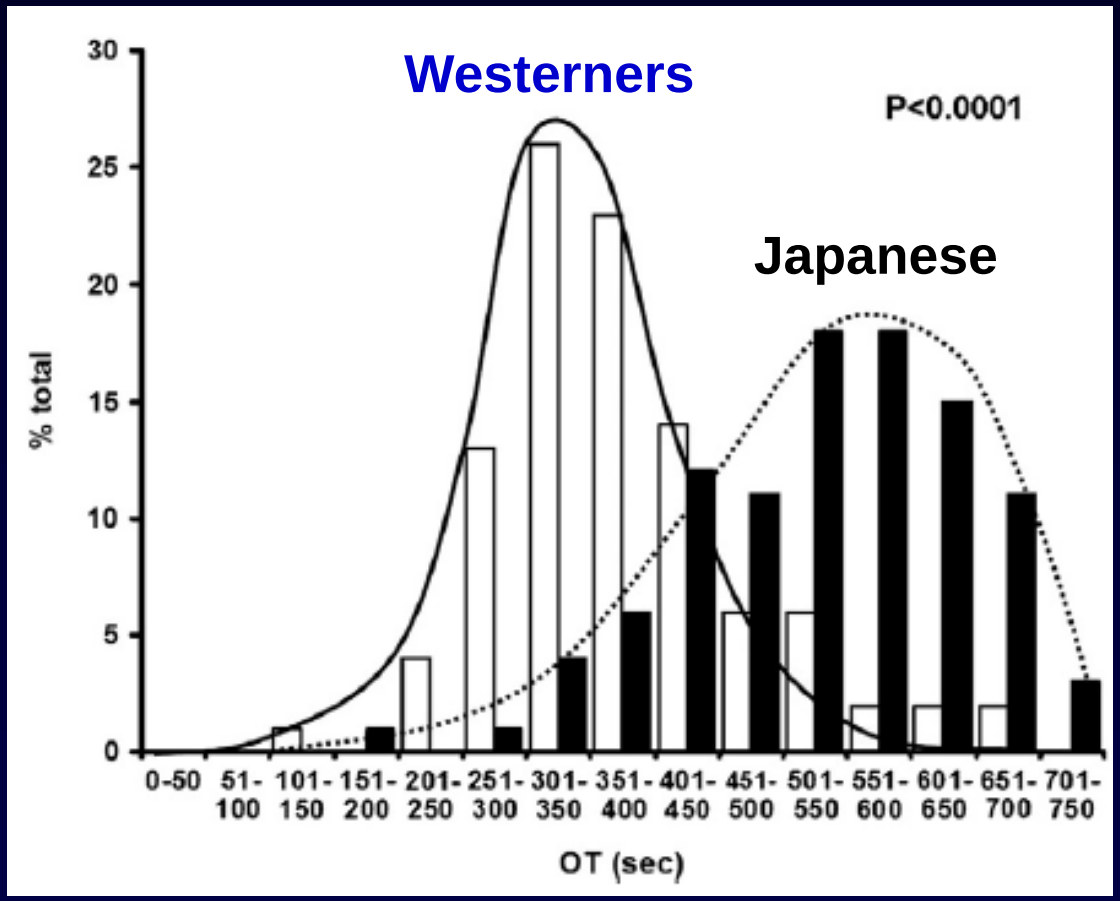
Lutsey et al. *J Thromb Haemost* 2006; 4: 2629–35.

Comparison of Platelet-Fibrin Clot Strength: Japanese vs. Western Volunteers

Global Thrombosis Test



Occlusion Time (sec) in healthy subjects



Gorog DA, et al. Int J Cardiol. 2011;152:43-8.

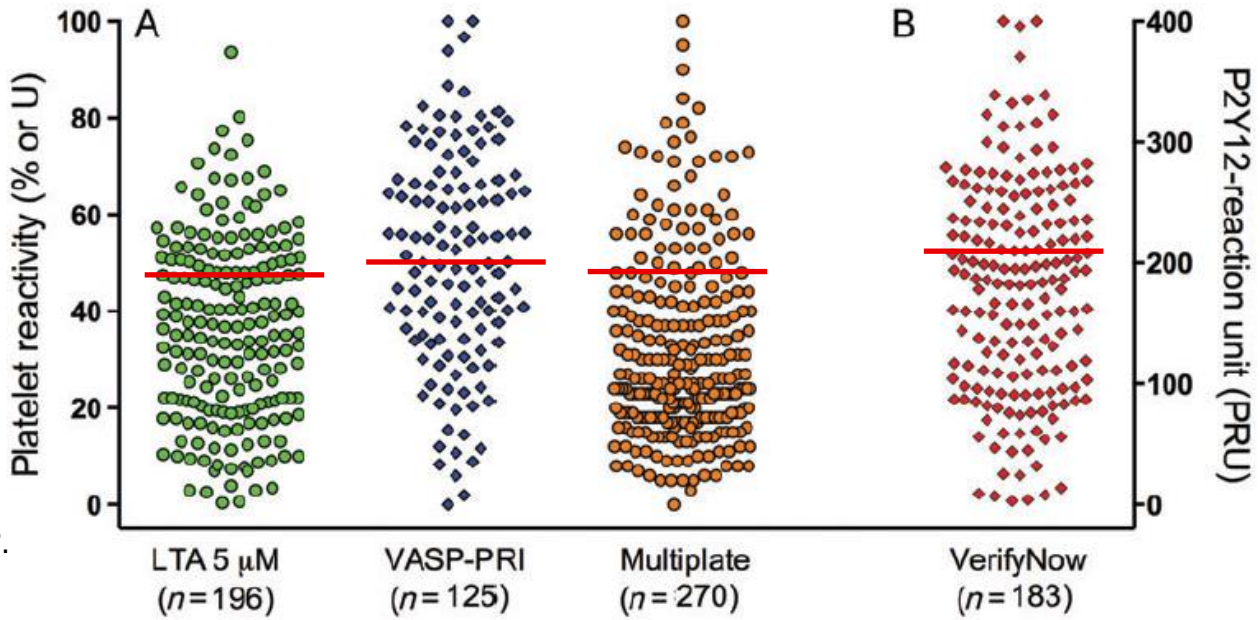
HPR Prevalence After 600 mg CLPD LD

Westerners

HPR (Western):

20~30%

Aradi D, et al. *Eur Heart J 2013*.

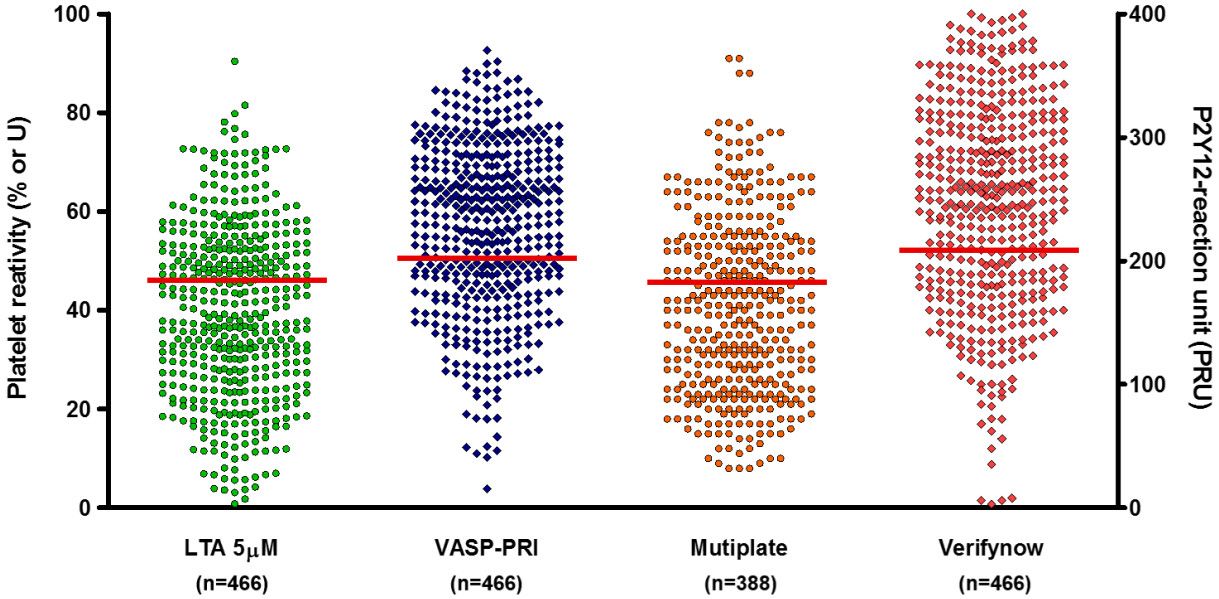


East Asians

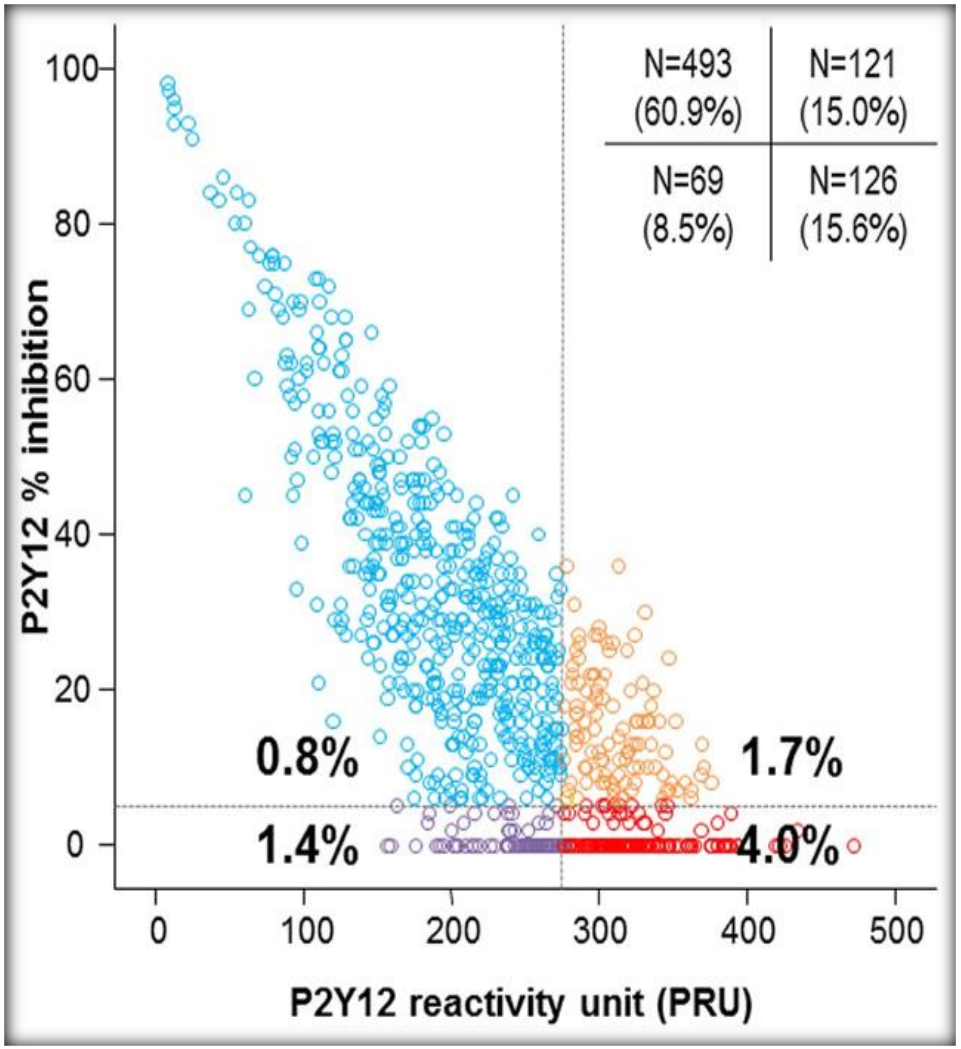
HPR (Western):

45~60%

Jeong YH, et al. *Am Heart J 2013*.



P2Y12 reactivity unit versus P2Y12 % inhibition



PRU : Platelet Reactivity
PRU% : Response

A : PRU<275 and PRU%>5 (493/60.9%)
low platelet activity & high response

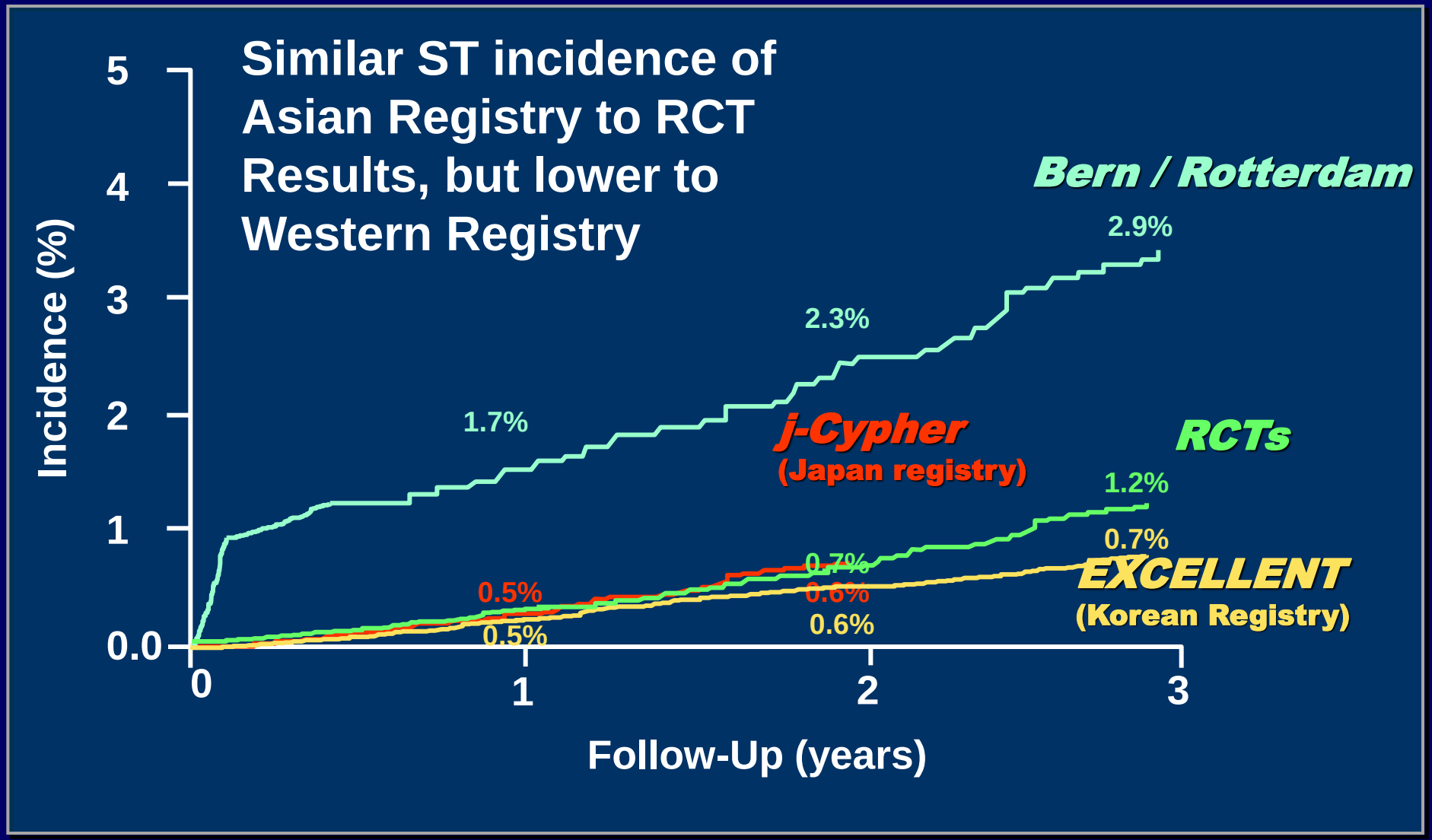
B : PRU≥275 and PRU%>5 (121/15.0%)
high platelet activity & high response

C : PRU<275 and PRU%≤5 (69/8.5%)
low platelet activity & low response

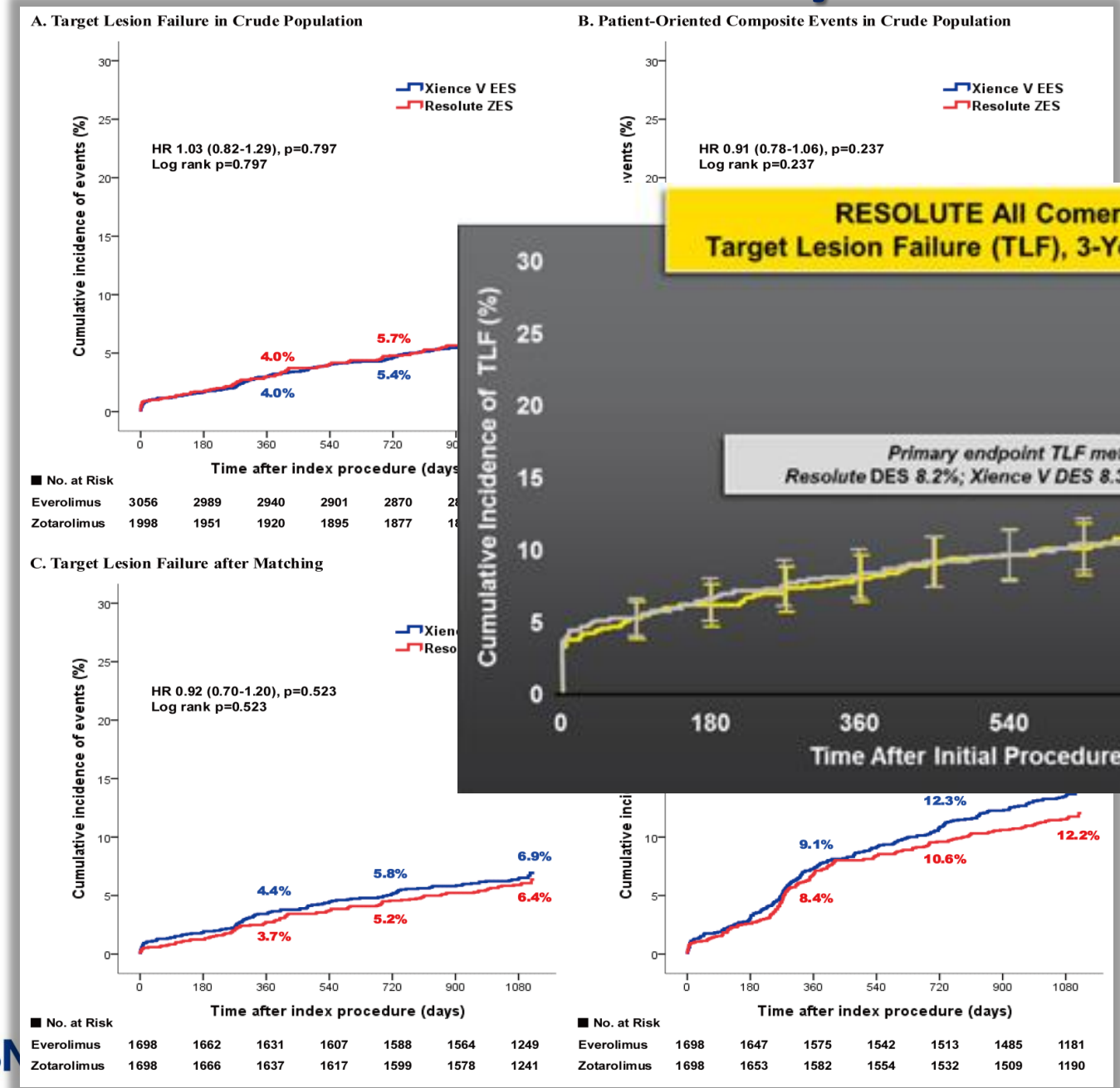
D : PRU≥275 and PRU%≤ 5 (126/15.6%)
High platelet activity & low response

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

Racial difference of Stent Thrombosis in 1st generation DES

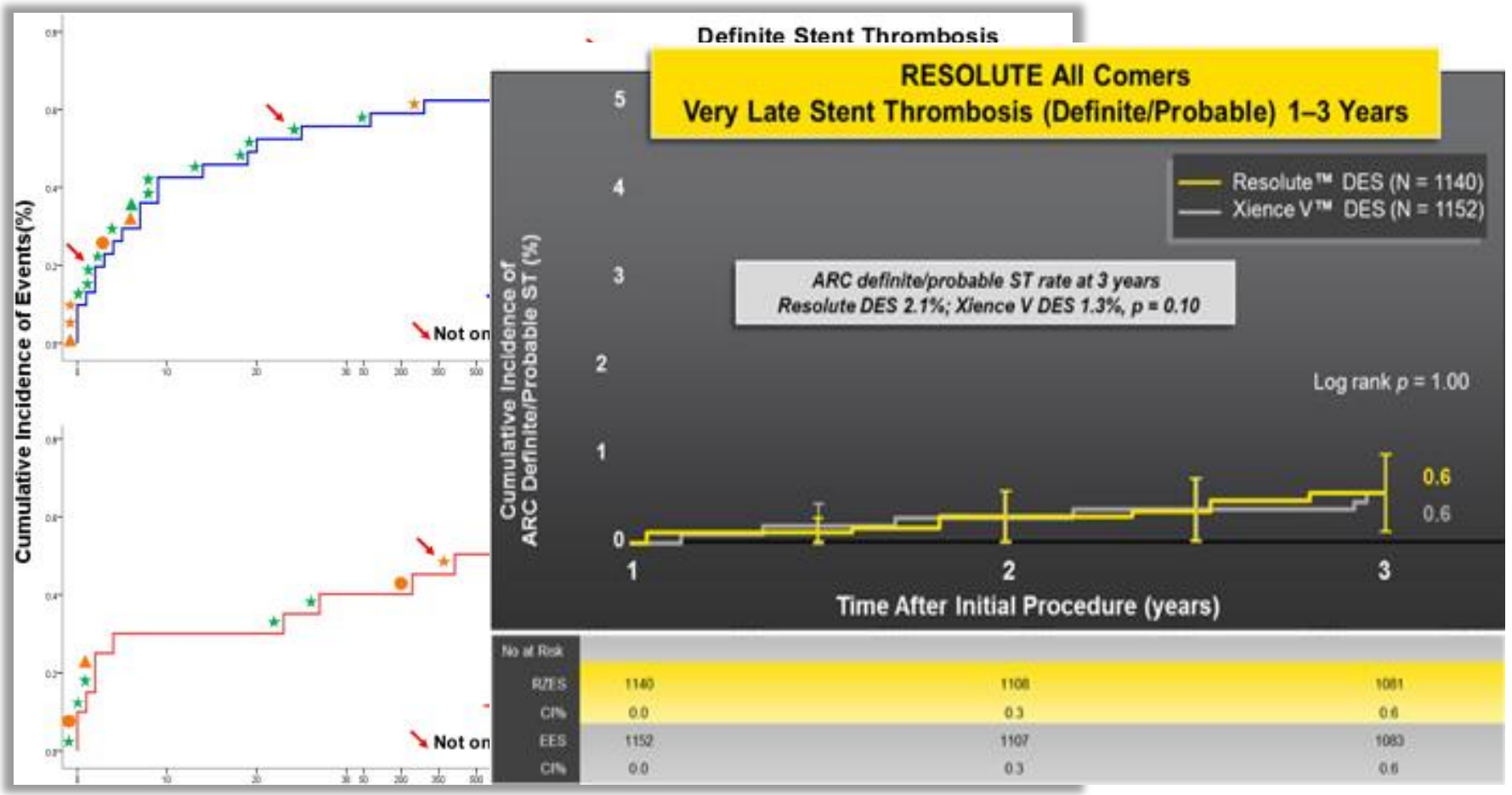


RESOLUTE vs. Xience V 3yr Outcomes: TLF



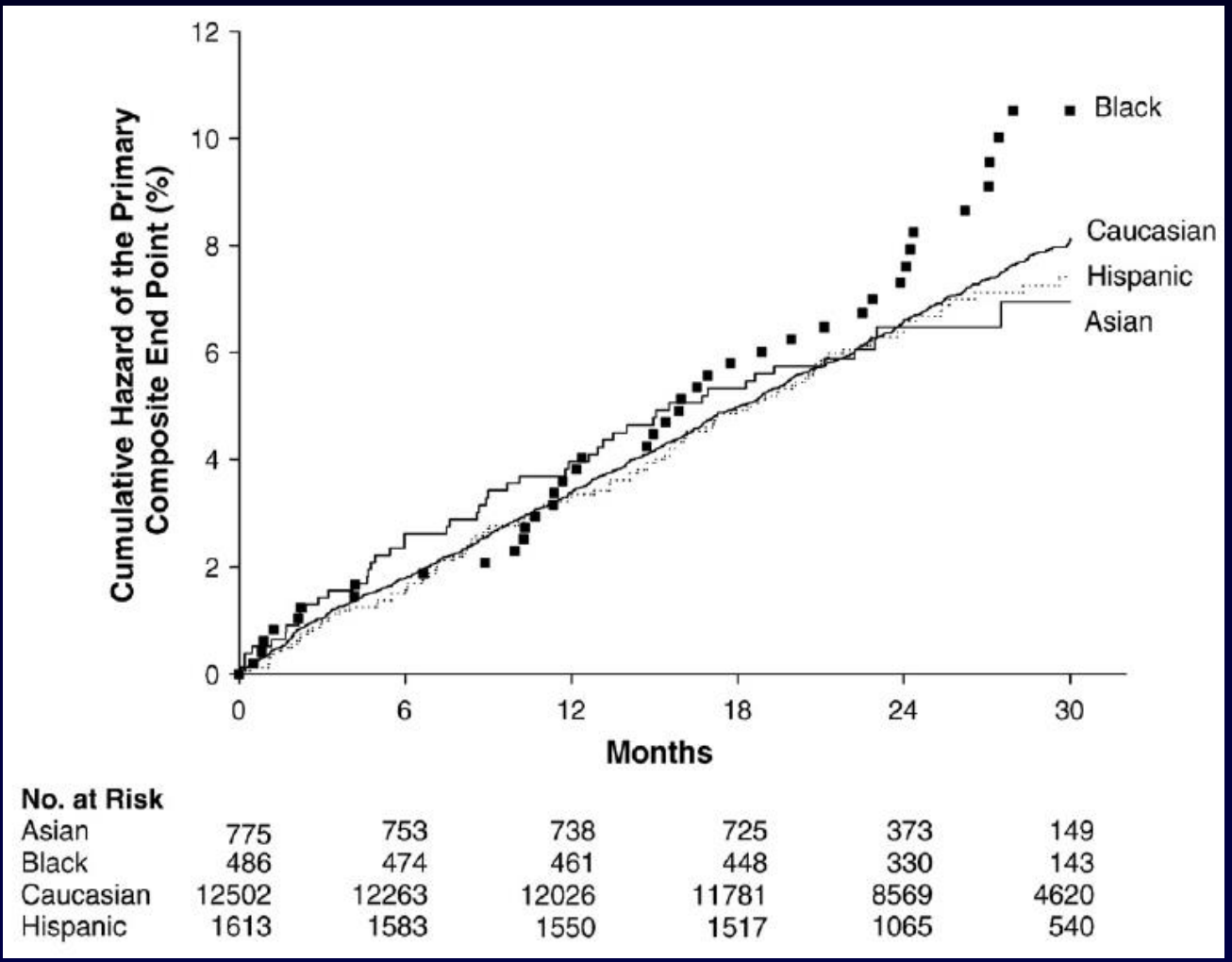
Park KW, Kim HS et al. JACC 2013
Park KW, Kim HS et al. AJC 2014

RESOLUTE vs. Xience V 3yr Outcomes: ST



Park KW, Kim HS et al. JACC 2013
Park KW, Kim HS et al. AJC 2014

Racial Difference in CV death/MI/stroke among Pts on Antiplatelet Therapy

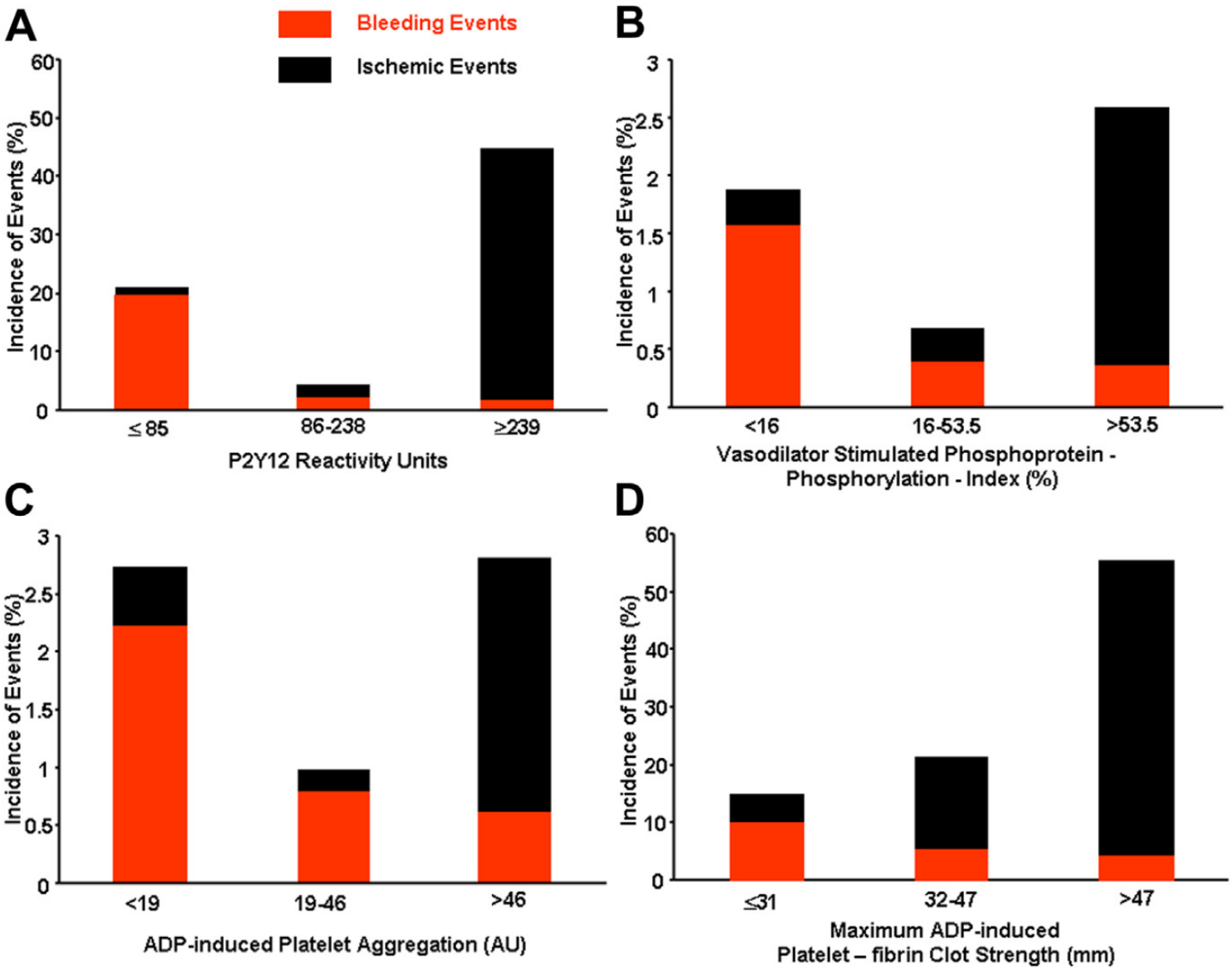


	Efficacy	Bleeding
Black	1.32 (0.87-1.99)	3.06 (1.59-5.89)
Caucasian	1.07 (0.80-1.43)	1.39 (0.87-2.22)
Hispanic	1.04 (0.74-1.46)	1.00 (Reference)
Asian	1.00 (Reference)	2.21 (1.17-4.19)

Mak KH et al. CHARISMA study. *Am Heart J* 2009;157:658.

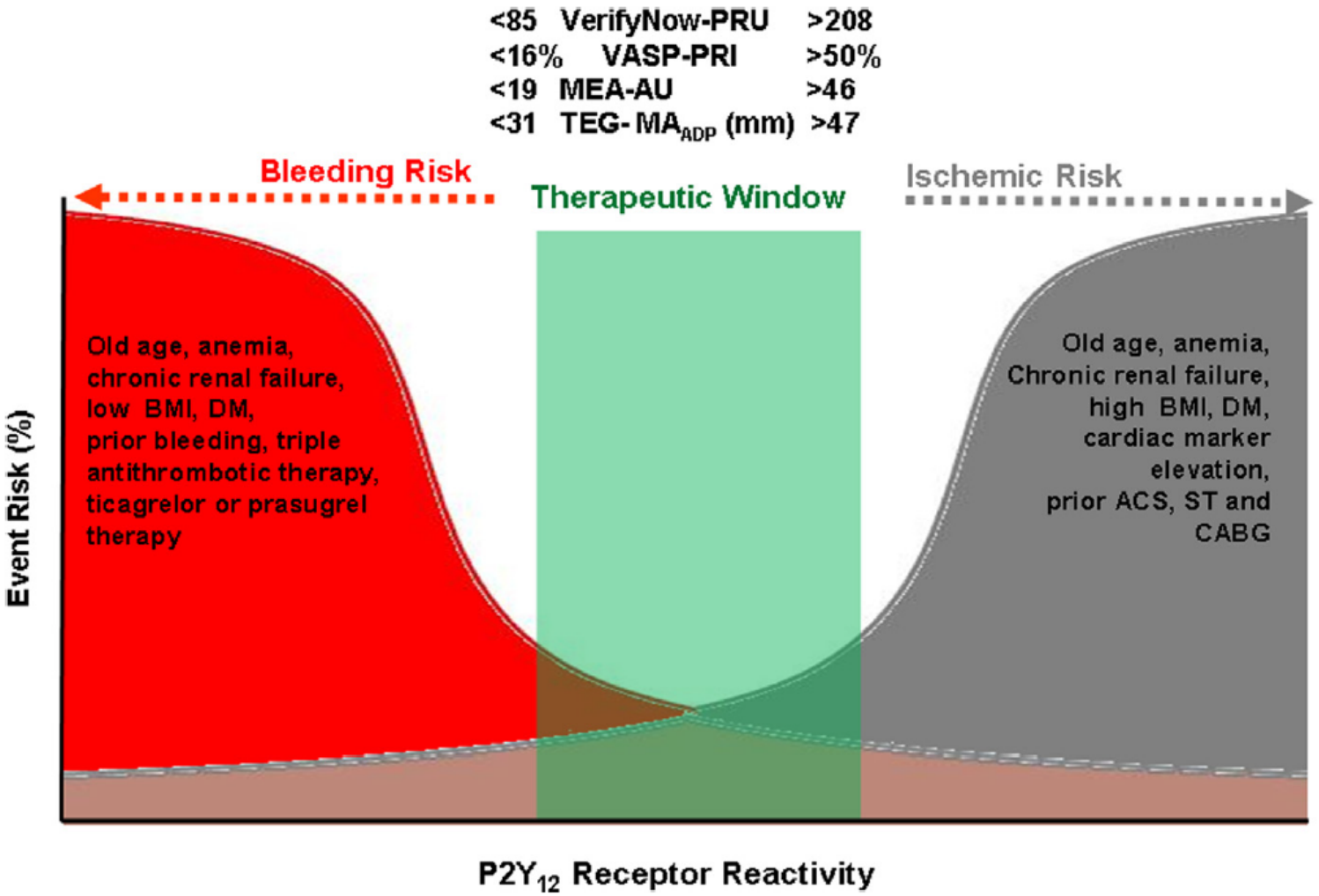
Is the current dose of Prasugrel or Ticagrelor optimal in Asians?

Therapeutic Window Concept



SNUH

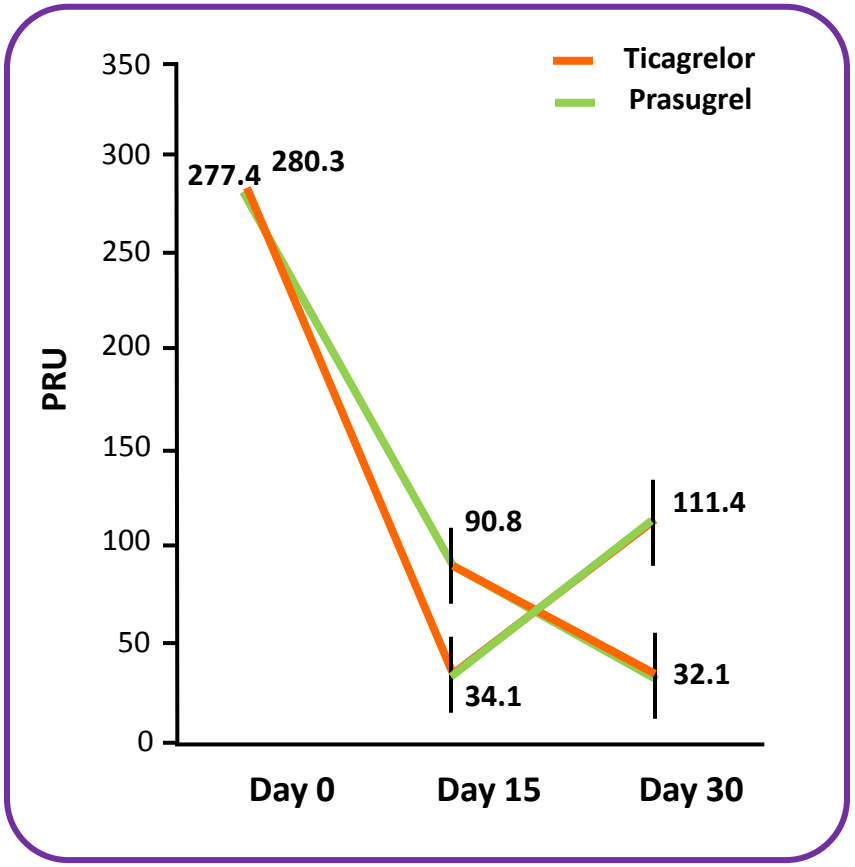
“Sweet Spot”


<85 VerifyNow-PRU >208
<16% VASP-PRI >50%
<19 MEA-AU >46
<31 TEG-MA$_{ADP}$ (mm) >47
Bleeding Risk
Therapeutic Window
Ischemic Risk
Old age, anemia, chronic renal failure, low BMI, DM, prior bleeding, triple antithrombotic therapy, ticagrelor or prasugrel therapy
Old age, anemia, Chronic renal failure, high BMI, DM, cardiac marker elevation, prior ACS, ST and CABG
Event Risk (%)
P2Y$_{12}$ Receptor Reactivity

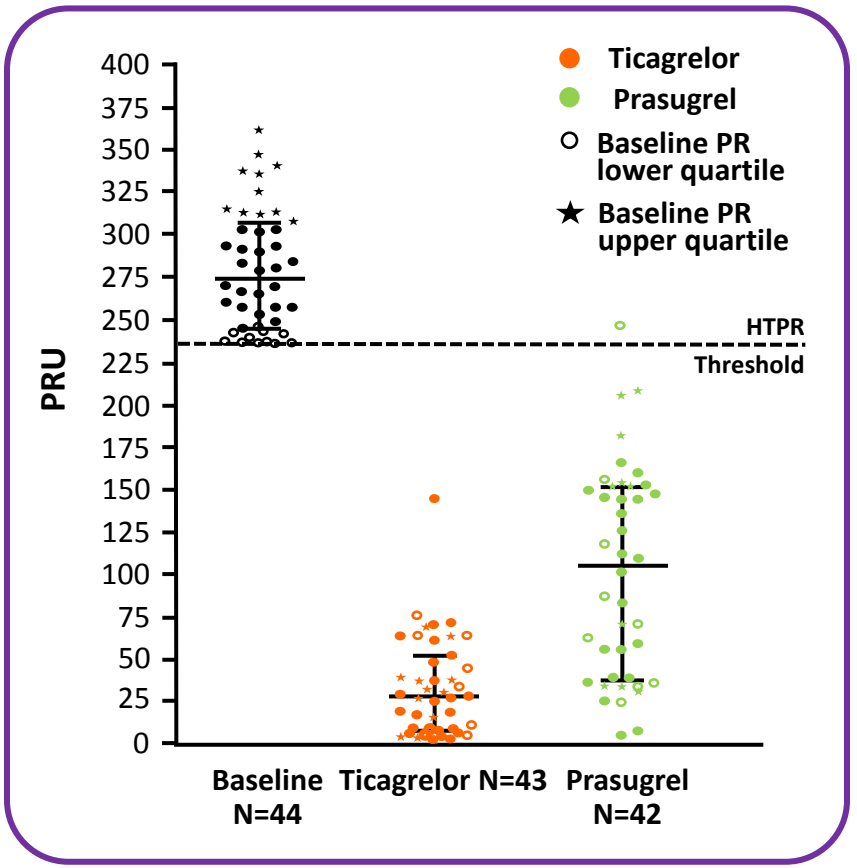
Both Agents May Be Too Strong

- Prasugrel: 10mg qd, 5mg qd
- Ticagrelor: 90mg bid

Platelet Reactivity (in PRU) by Treatment sequence



Individual PR values according to treatment

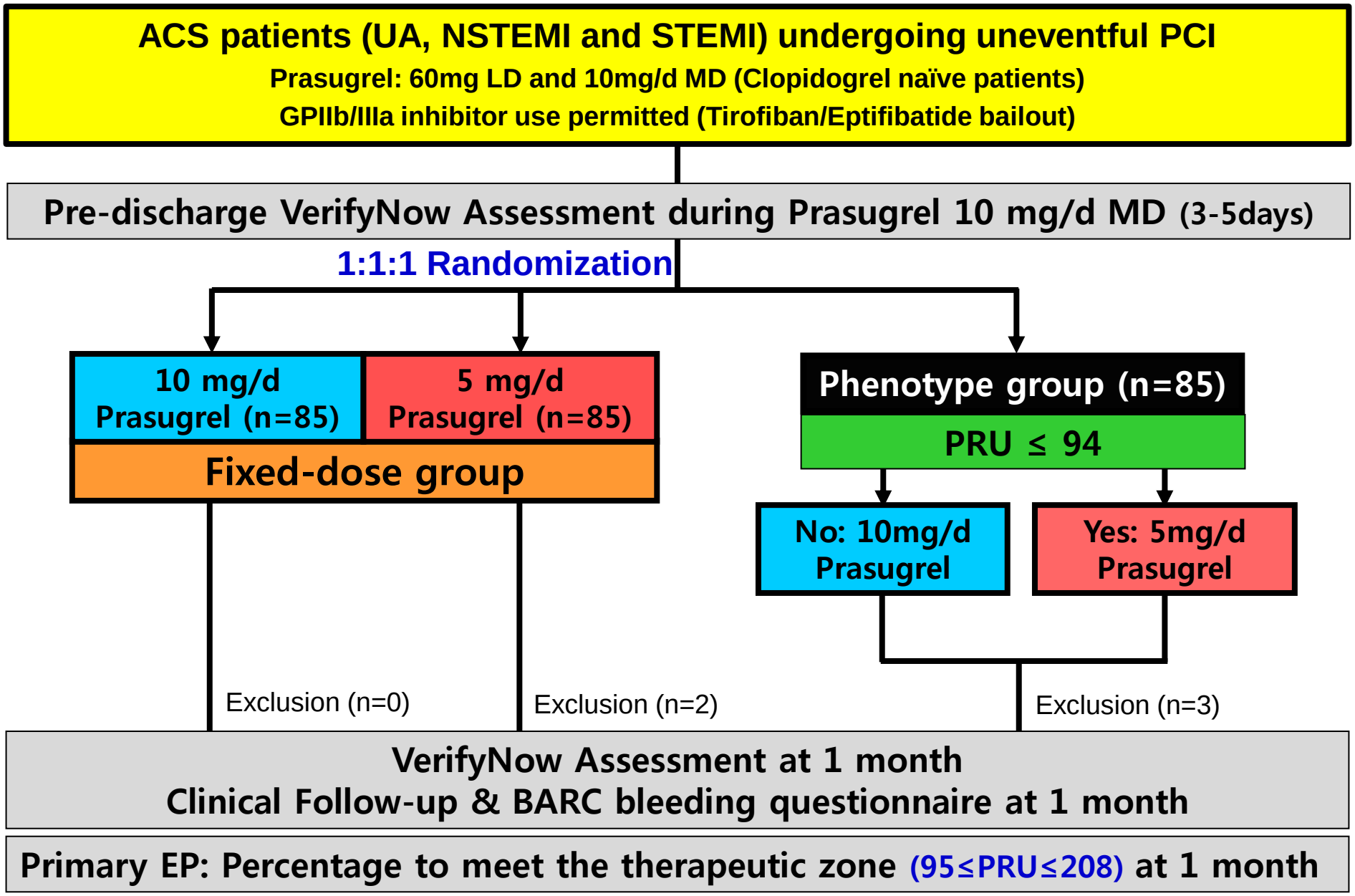


Platelet reactivity is significantly lower in patients receiving ticagrelor compared with prasugrel. Least squares estimates and 95% confidence intervals are presented. PRU platelet reactivity unit(s).

What is the Optimal Maintenance Dose of Prasugrel or Ticagrelor in Asians?

A-MATCH Trial

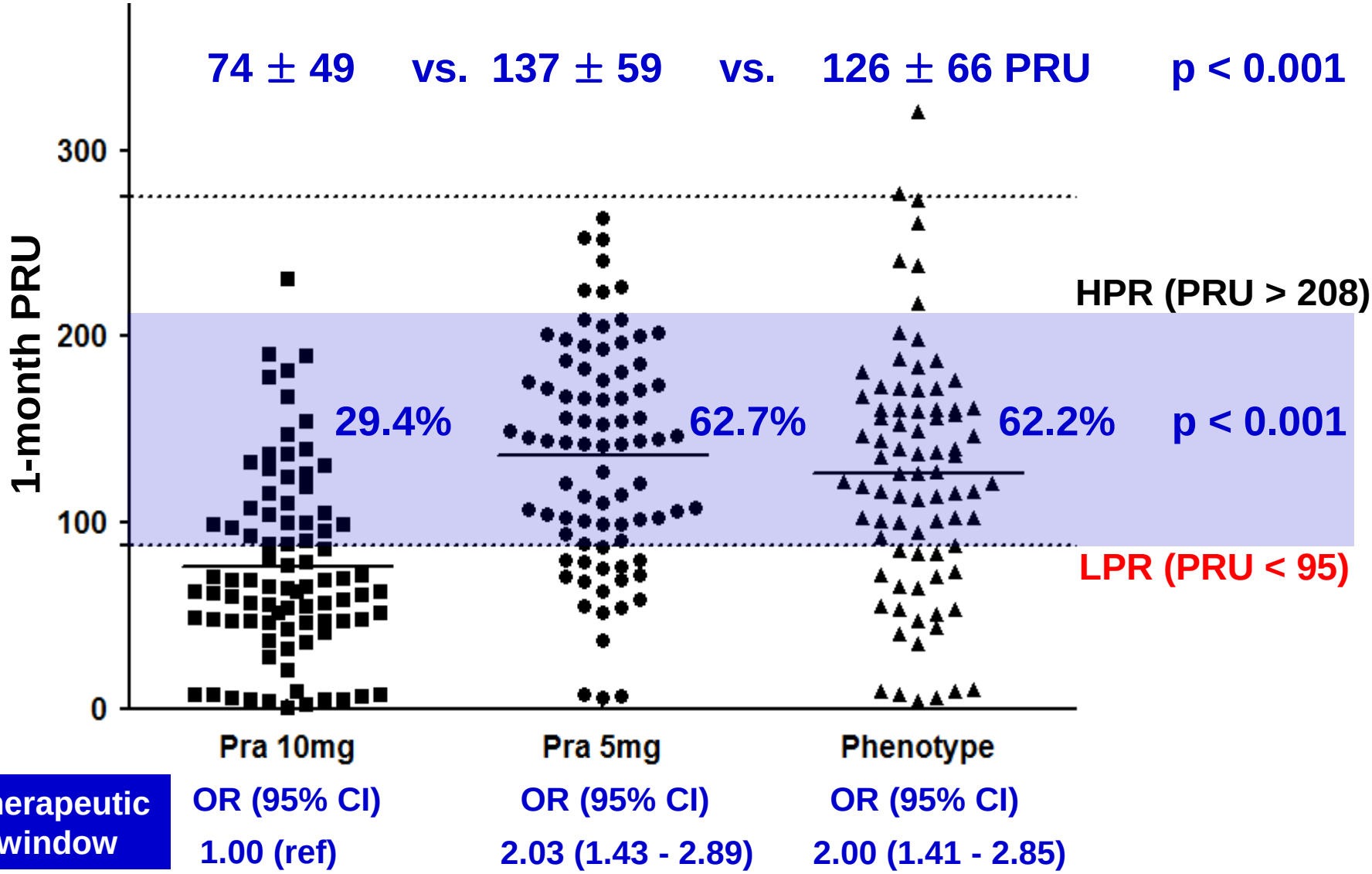
The first RCT to use **"de-escalation strategy"** and the concept of LPR in antiplatelet therapy



Primary End Point

Jeong YH, et al. ESC 2015

Therapeutic window of platelet reactivity in Westerners



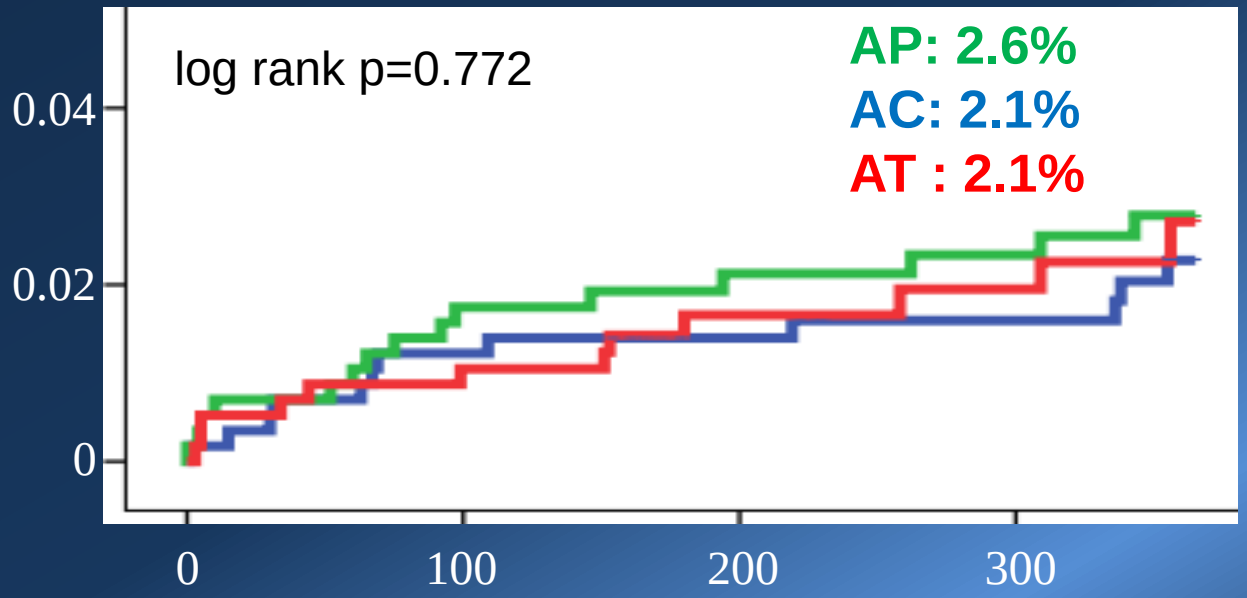
C vs. T vs. P in AMI patients: Study Population

- Patients form the KAMIR ***(2011.11 – 2015.11)***
  - N=13,643
- Patients treated with PCI or medical therapy
  - N=13,373
- Patients treated with initial DAPT
  - N=10,901
- Patients with successful follow-up
  - N=9,355
    - Aspirin+Clopodigrel (AC), n=6,455 (68.9%)
    - Aspirin+Prasugrel (AP), n=1,100 (11.8%)
      : available since 2012/7
    - Aspirin+Ticagrelor (AT), n=1,810 (19.3%)
      : available since 2013/3

'Adjusted' 1-year outcome by DAPTs

Propensity Score Matching for "MACE"

- Clopidogrel vs. Prasugrel vs. Ticagrelor
  - Factors included for calculation of the propensity score
    - (Identical with prev. slide)
  - Matched population of 572 pairs (1:1:1 matching) in each group

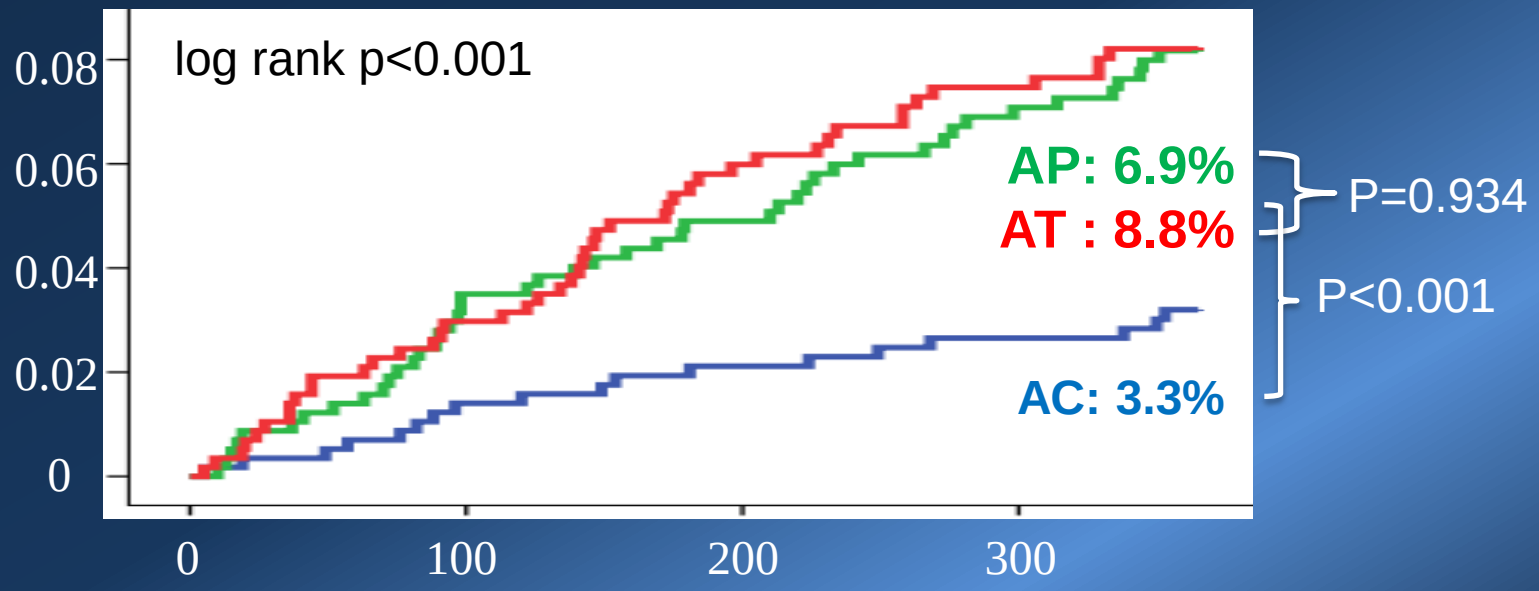


Unpublished Data from SNUH

'Adjusted' 1-year outcome by DAPTs

Propensity Score Matching for "Bleeding events"

- Clopidogrel vs. Prasugrel vs. Ticagrelor
  - Factors included for calculation of the propensity score
    - (Identical with prev. slide)
  - Matched population of 572 pairs (1:1:1 matching) in each group



Unpublished Data from SNUH

What is the Optimal Maintenance Dose of Prasugrel or Ticagrelor in Asians?

*PRAS*ugrel Compared to Clopidogrel *F*or Japanese Pat*I*en*T*s with *ACS* Undergoing PCI (PRASFIT-ACS)

S Saito, T Isshiki, H Ogawa,
T Kimura, H Yokoi, and M Nakamura

On behalf of PRASFIT-ACS Study Investigators

Study funded by Daiichi Sankyo Company, Limited
JapicCTI-No: **JapicCTI-101339**

Study Design

PRASFIT ACS

ACS (STEMI, NSTEMI, UA) patients undergoing PCI

N=1,363

Randomized

Prasugrel	**Clopidogrel**
20 mg LD/ 3.75 mg MD	**300 mg LD/ 75 mg MD**

Treatment duration: 24 to 48 weeks
(Combination with aspirin)

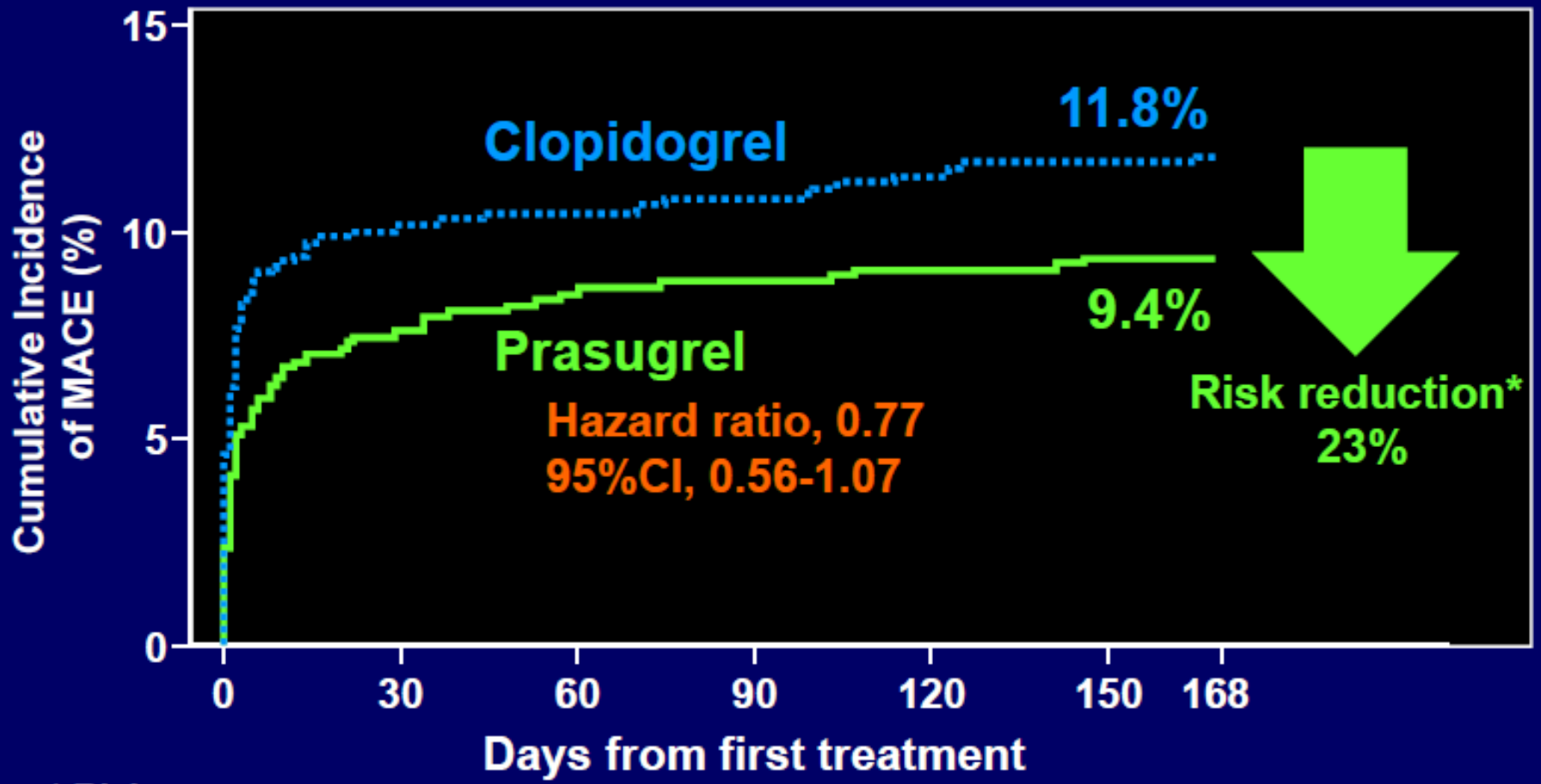
LD: Loading Dose
MD: Maintenance Dose

Primary Efficacy Endpoint: **Major Adverse Cardiovascular Events (MACE)**
Cardiovascular(CV) death, Nonfatal MI and Nonfatal ischemic stroke
for during the 24 week follow-up period

Safety Endpoints:
Non-CABG TIMI major, TIMI minor or clinically relevant bleeding

Primary Efficacy Endpoint (MACE at 24 weeks)

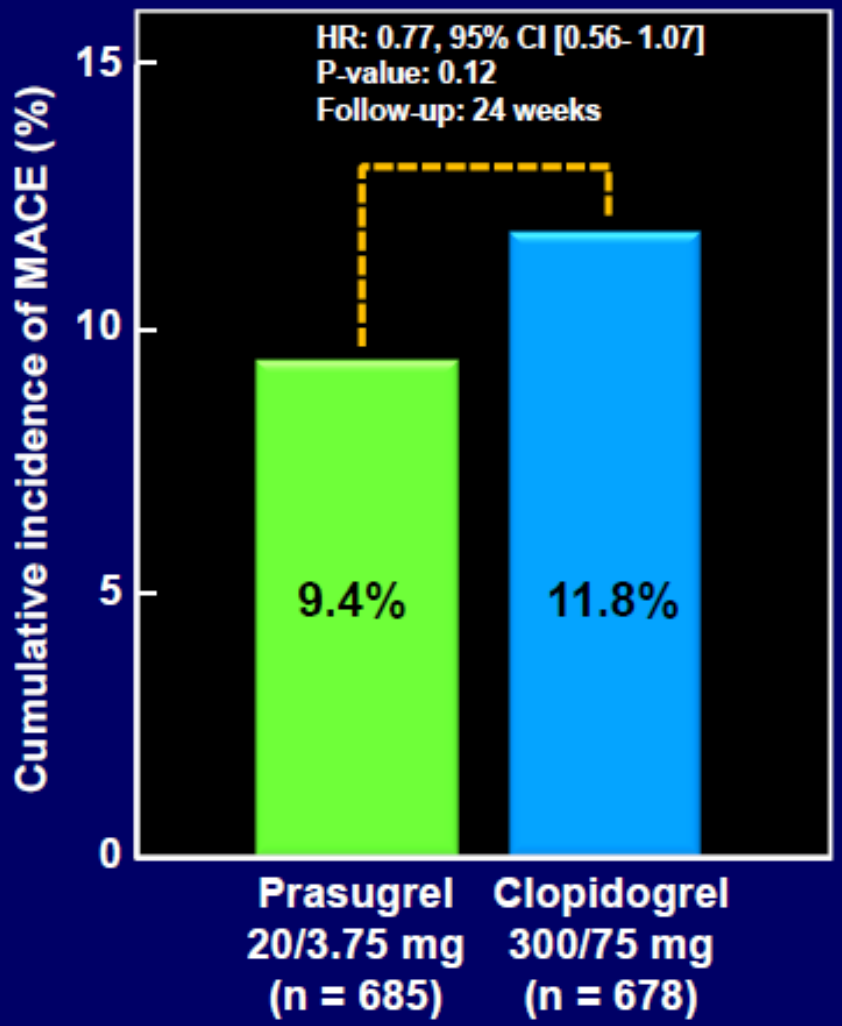
PRASFIT ACS

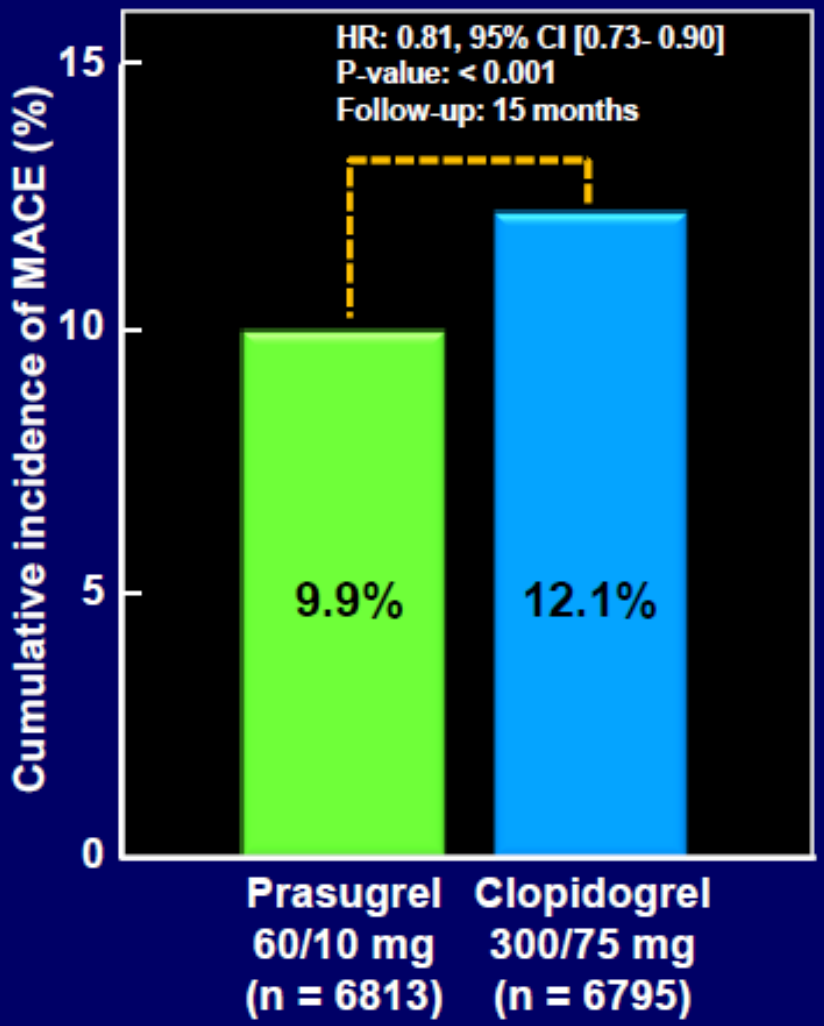


No. at Risk:							
Prasugrel	685	624	617	615	613	611	609
Clopidogrel	678	604	599	597	592	588	584

Based on Full Analysis Set
*Risk reduction: 1-HR (Hazard ratio)

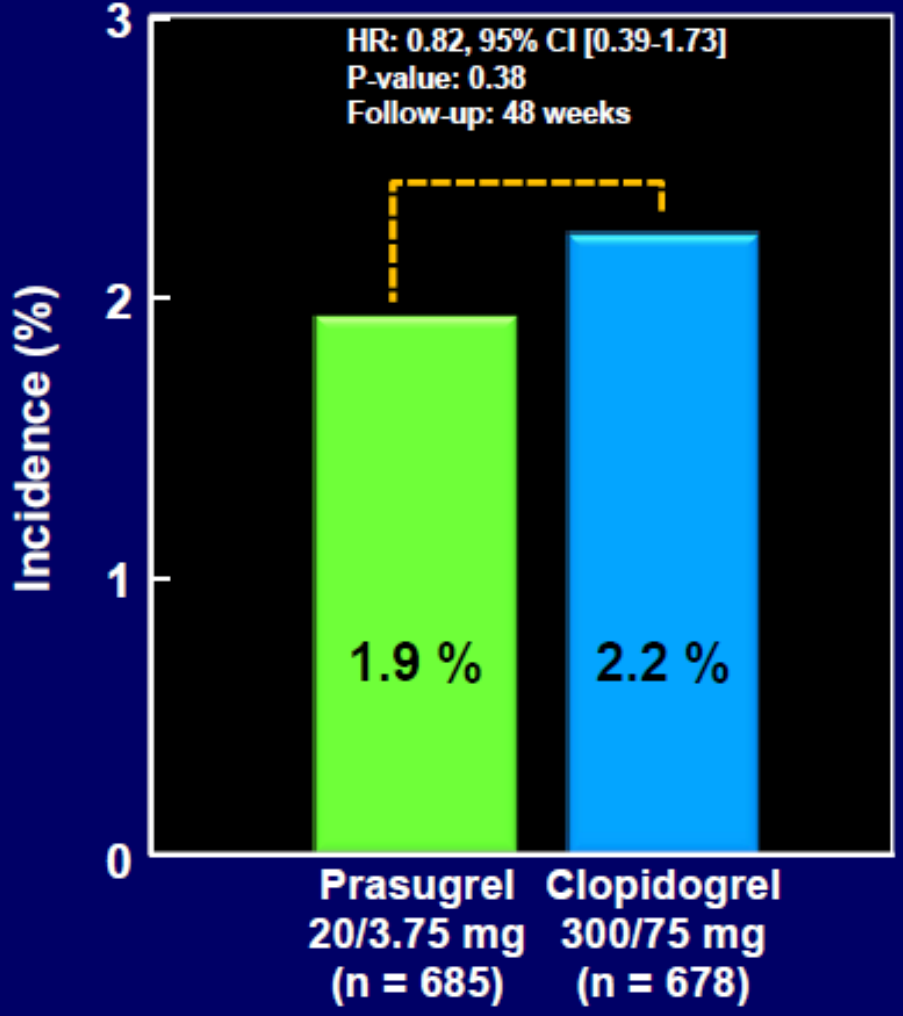
Primary Endpoint of PRASFIT-ACS and TRITON-TIMI 38

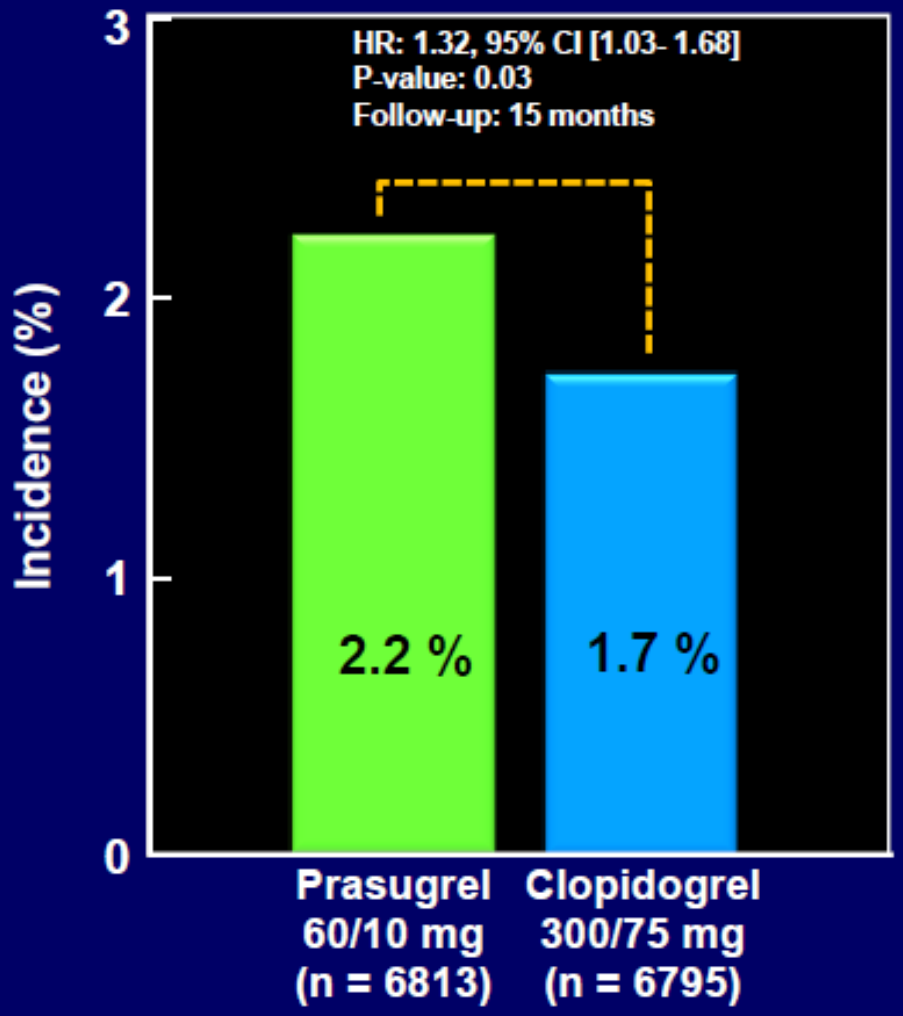




[11] Wiviott S et al. *NEJM* 2007;357:2001-2015

Non-CABG TIMI-Major Bleeding Events of PRASFIT-ACS and TRITON-TIMI 38



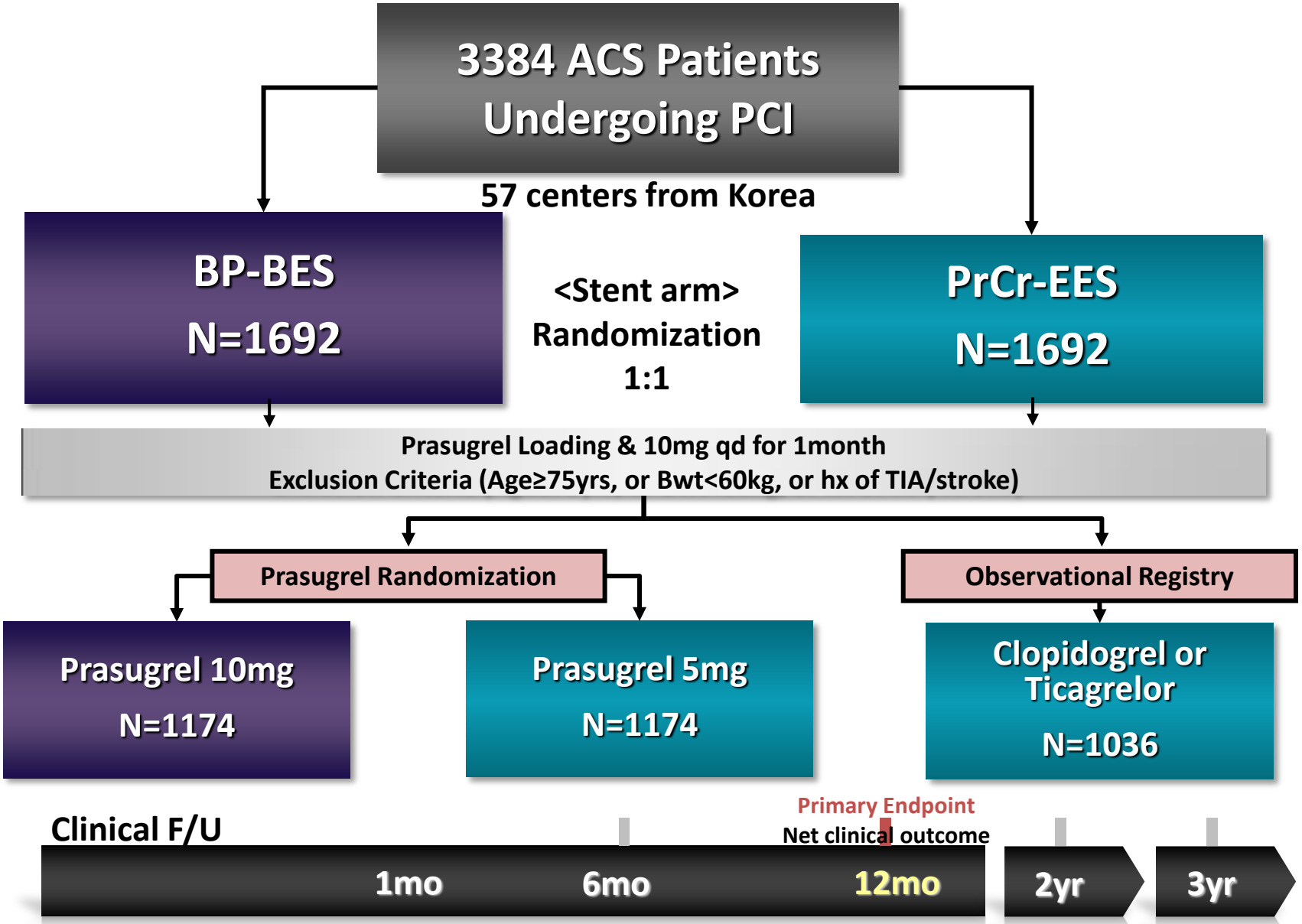


Based on Safety Analysis Set
Incidence: (n / n) x 100%

[11] Wiviott S et al. *NEJM* 2007;357:2001-2015

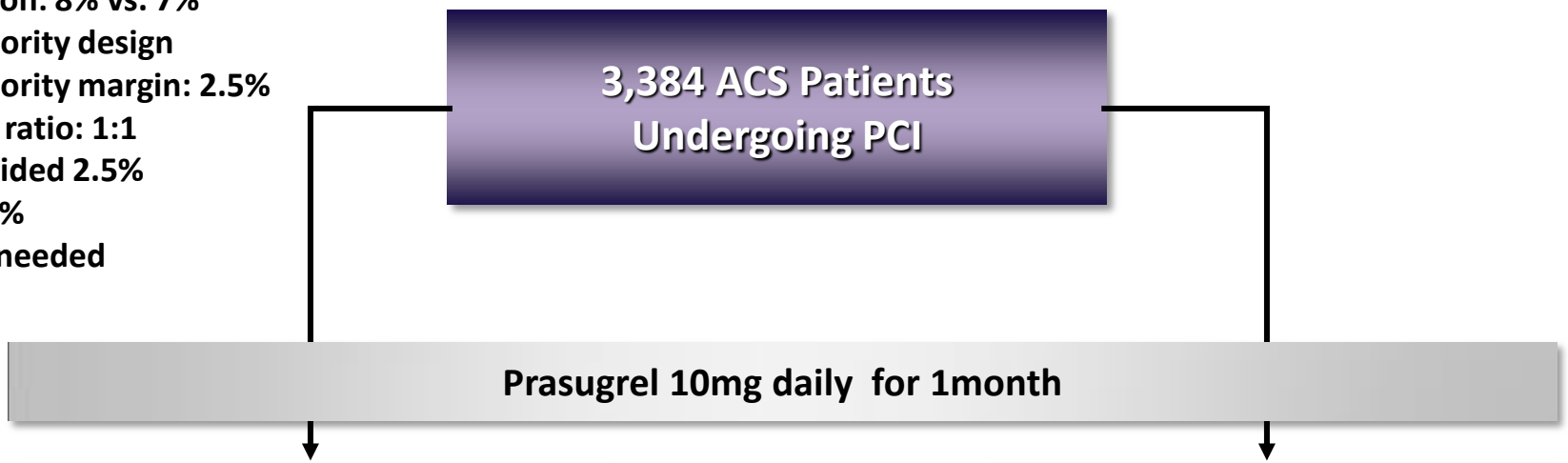
HOST III-REDUCE POLYTECH Trial

Prospective, open label, randomized multi-center trial



Prasugrel arm comparison

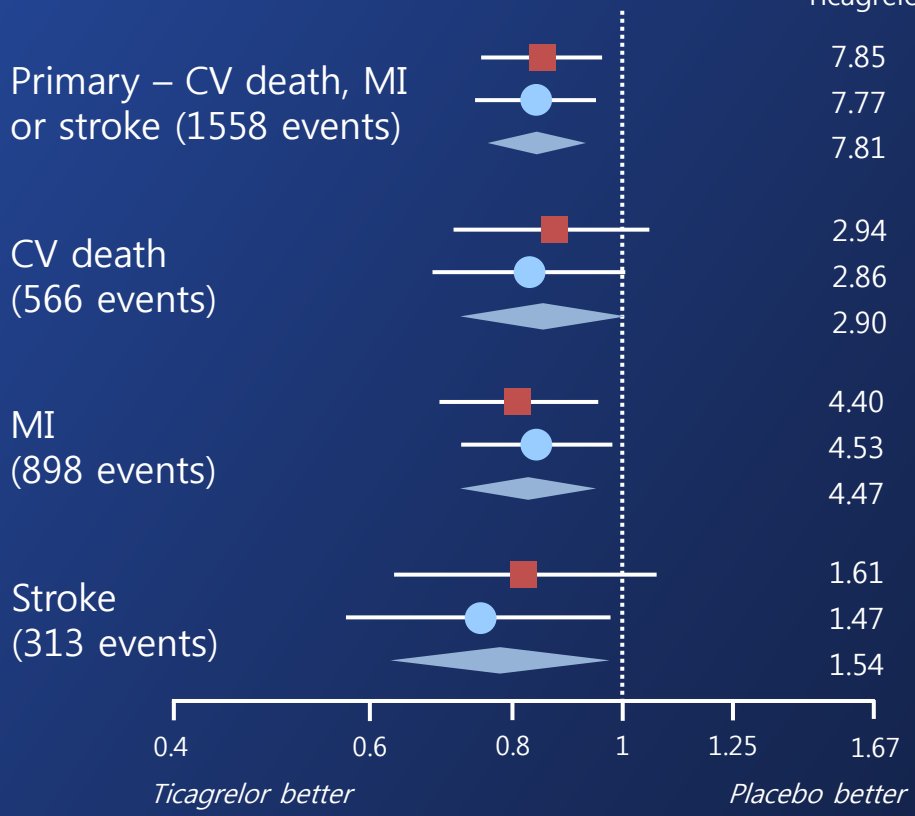
Assumption: 8% vs. 7%
Noninferiority design
Noninferiority margin: 2.5%
Sampling ratio: 1:1
Alpha:1-sided 2.5%
Power 75%
2348 pts needed



Composite of
Any death, MI, ST,
repeat revascularization,
stroke, bleeding (BARC≥2)

What about Ticagrelor?

PEGASUS-TIMI 54: Efficacy Endpoints



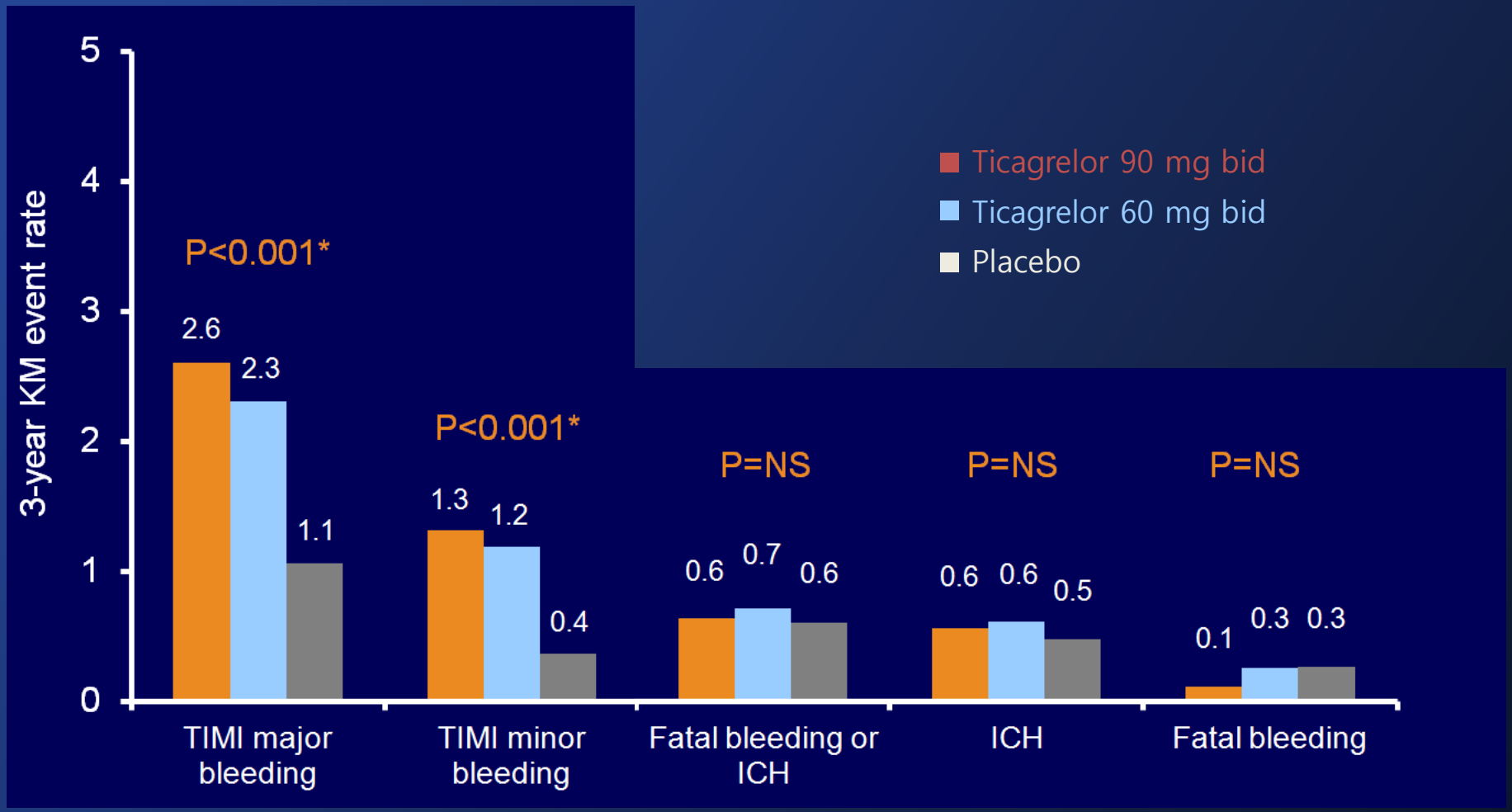
Endpoint	3-year KM event rates (%) Ticagrelor	Placebo	HR (95% CI)	P value
Primary – CV death, MI or stroke (1558 events)	7.85	9.04	0.85 (0.75–0.96)	0.008
	7.77	9.04	0.84 (0.74–0.95)	0.004
	7.81	9.04	0.84 (0.76–0.94)	0.001
CV death (566 events)	2.94	3.39	0.87 (0.71–1.06)	0.15
	2.86	3.39	0.83 (0.68–1.01)	0.07
	2.90	3.39	0.85 (0.71–1.00)	0.06
MI (898 events)	4.40	5.25	0.81 (0.69–0.95)	0.01*
	4.53	5.25	0.84 (0.72–0.98)	0.03*
	4.47	5.25	0.83 (0.72–0.95)	0.005*
Stroke (313 events)	1.61	1.94	0.82 (0.63–1.07)	0.14*
	1.47	1.94	0.75 (0.57–0.98)	0.03*
	1.54	1.94	0.78 (0.62–0.98)	0.03*

Ticagrelor 90 mg bid
Ticagrelor 60 mg bid
Ticagrelor pooled

*Indicates nominal P value; P<0.026 indicates statistical significance

Bonaca MP *et al. N Engl J Med* 2015;372:1791–1800

PEGASUS-TIMI 54: Bleeding

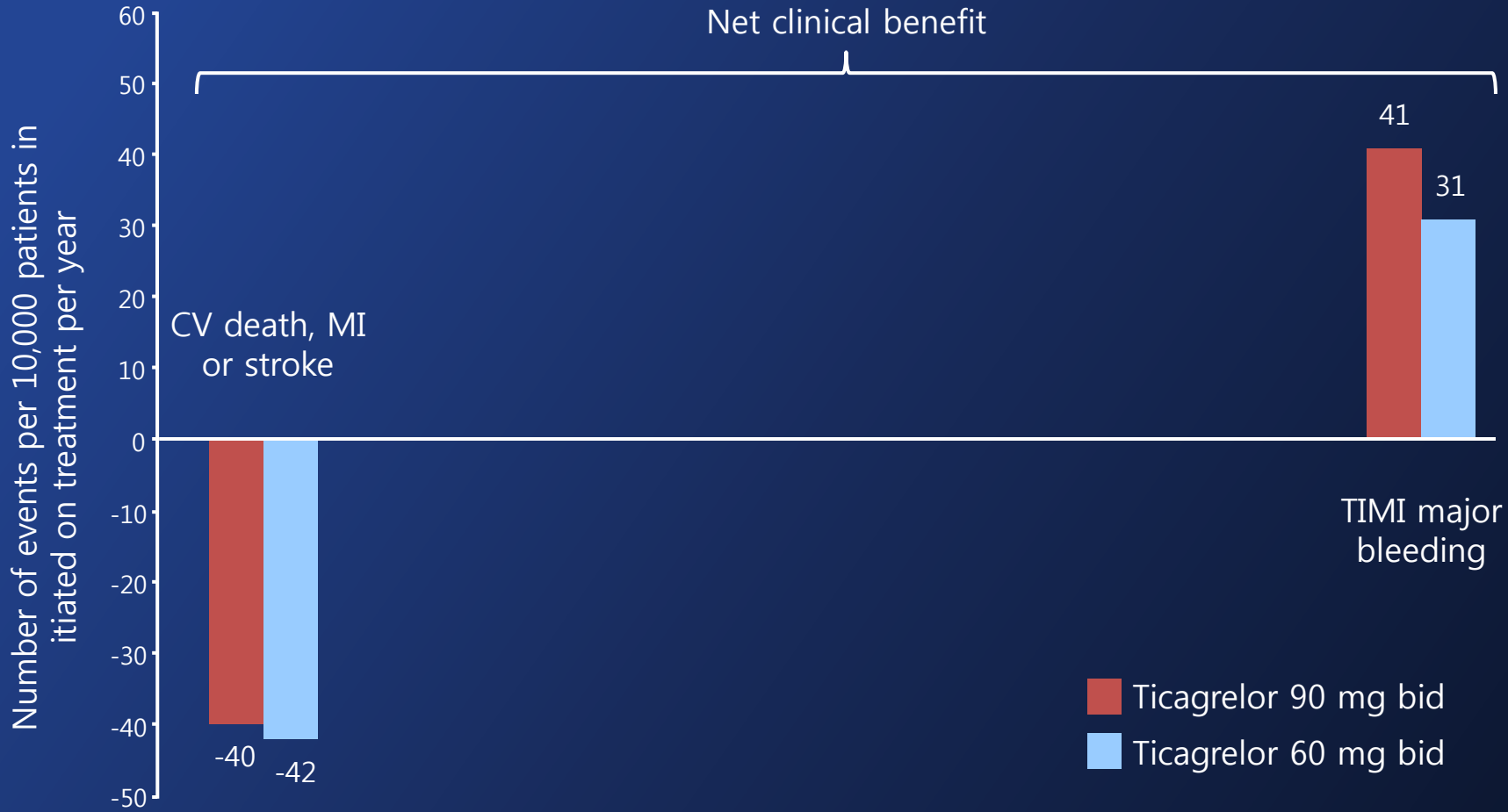


*Indicates nominal P value
Rates are presented as 3-year Kaplan-Meier estimates

Bonaca MP *et al. N Engl J Med* 2015;372:1791–1800

PEGASUS-TIMI 54: Estimates of First Efficacy and Bleeding Events 'Prevented' and 'Caused'

Annualized from 3-year Kaplan-Meier event rates in the intention-to-treat population



Net clinical benefit is defined as the comparison of first occurrence of CV death, MI or stroke with first occurrence of TIMI major bleeding; irreversible events are defined as CV death, MI, stroke, fatal bleeding and ICH

Note these are estimated events based on calculations made from the observed ARRs in the PEGASUS-TIMI 54 study and therefore should be viewed as estimates of events 'prevente d' and 'caused' rather than specific indicators of efficacy. Also note that these analyses are based on Kaplan-Meier time to first event curves, and therefore the sum of the events for C V death, MI and stroke individually do not equal that for the composite of CV death/MI/stroke

Bonaca MP *et al. N Engl J Med* 2015;372:1791–1800, Supplementary Appendix
Data on file: ATLAS approval ID 773,116.011

PEGASUS-TIMI 54: Numbers Needed to Treat and Numbers Needed to Harm (ITT Population)

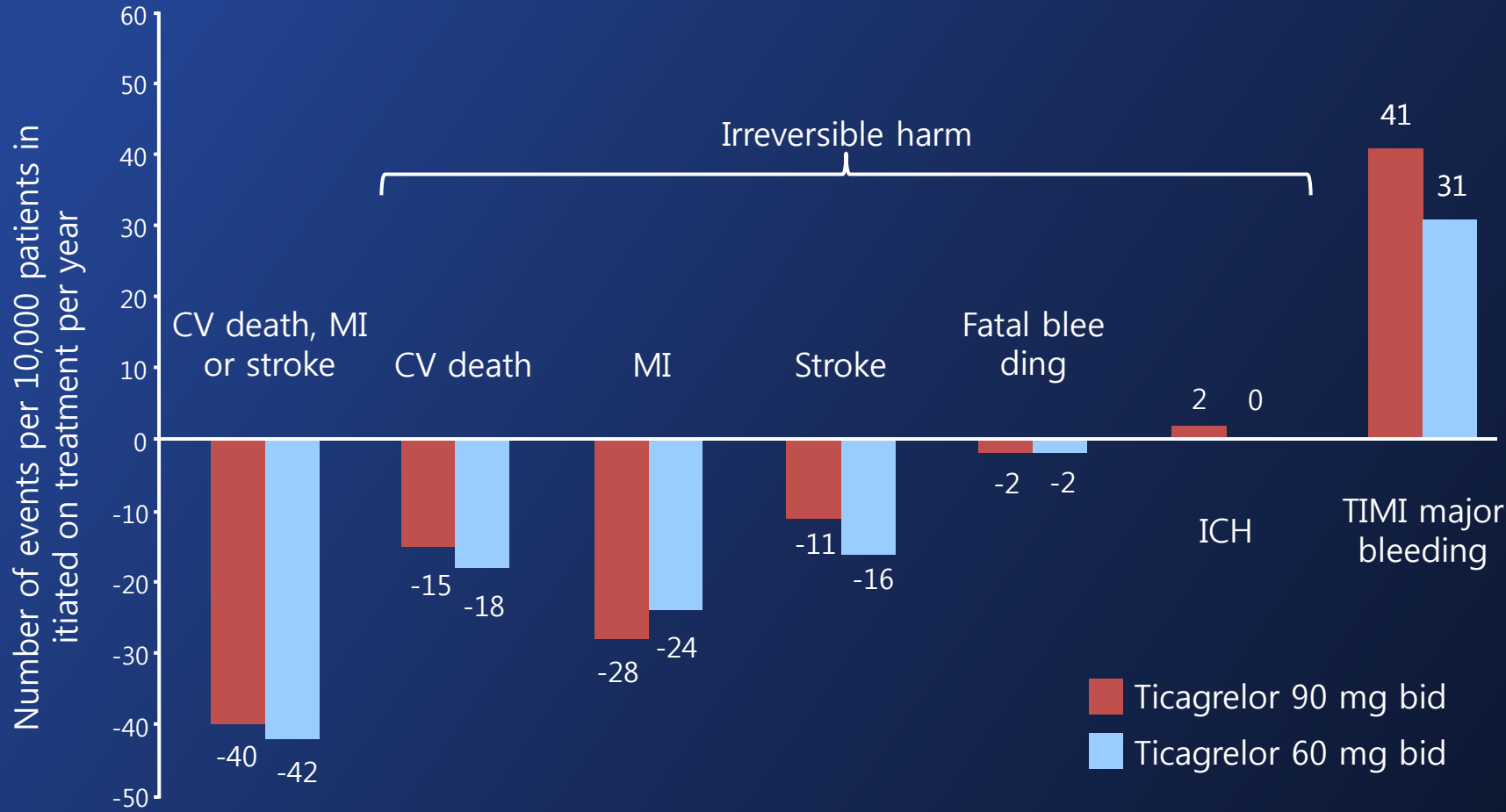
	Ticagrelor 90 mg bid		Ticagrelor 60 mg bid	
Efficacy endpoint	**Estimated risk difference**	**NNT**	**Estimated risk difference**	**NNT**
Primary endpoint: CV death, MI or stroke	1.19%	**85**	1.27%	79
CV death	0.45%	221	0.53%	189
MI	0.85%	119	0.72%	139
Stroke	0.33%	304	0.47%	213
Safety endpoint	**Estimated risk difference**	**NNH**	**Estimated risk difference**	**NNH**
Primary safety endpoint: TIMI major bleeding	1.22%	**82**	0.94%	107
ICH	0.08%	1309	-0.01%	-8005
Fatal bleeding	-0.06%	-1753	-0.05%	-2182

Estimated risk difference is the difference in 3-year Kaplan-Meier percent between ticagrelor and placebo based on intention-to-treat analyses
NNH, number needed to harm; NNT, number needed to treat

Data on file: ATLAS approval ID 961,101.011

PEGASUS-TIMI 54: Estimates of First Efficacy and Bleeding Events 'Prevented' and 'Caused'

Annualized from 3-year Kaplan-Meier event rates in the intention-to-treat population



Net clinical benefit is defined as the comparison of first occurrence of CV death, MI or stroke with first occurrence of TIMI major bleeding; irreversible events are defined as CV death, MI, stroke, fatal bleeding and ICH

Note these are estimated events based on calculations made from the observed ARRs in the PEGASUS-TIMI 54 study and therefore should be viewed as estimates of events 'prevente d' and 'caused' rather than specific indicators of efficacy. Also note that these analyses are based on Kaplan-Meier time to first event curves, and therefore the sum of the events for C V death, MI and stroke individually do not equal that for the composite of CV death/MI/stroke

Bonaca MP *et al. N Engl J Med* 2015;372:1791–1800, Supplementary Appendix
Data on file: ATLAS approval ID 773,116.011

PEGASUS-TIMI 54: Analyses of Net Clinical Benefit (ITT Population)

	Ticagrelor 90 mg bid versus placebo			Ticagrelor 60 mg bid versus placebo		
Characteristic	**RRR**	**HR (95%CI)**	***P* value**	**RRR**	**HR (95%CI)**	***P* value**
Net clinical benefit: CV death, MI, stroke, or TIMI major bleeding	0%	1.00 (0.90–1.12)	0.9563	5%	0.95 (0.85–1.06)	0.3412
Irreversible harm: CV death, MI, stroke, ICH and fatal bleeding	12%	0.88 (0.78–0.99)	0.0372	14%	0.86 (0.77–0.97)	0.0160

Rates are annualized from 3-year Kaplan-Meier event rates in the intention-to-treat population
RRR, relative risk reduction

Data on file: ATLAS approval ID 773,116.011

Summary

I believe that antiplatelet therapy should be different for East Asians because :

1. Our genetic background is different

2. BMI and volume of distribution is different

3. The balancing point between ischemia and bleeding may also be different.

Dose reduction may be a plausible option for Asian patients but we need more dedicated data in our patients.

Thank you for your attention!