Joint Meeting of Coronary Revascularization
December 13~14, 2013 | Busan, Korea

Platelet Function Testing:
Which Test, and How to Apply?
- Current Limitations and Future Perspectives -

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Disclosures

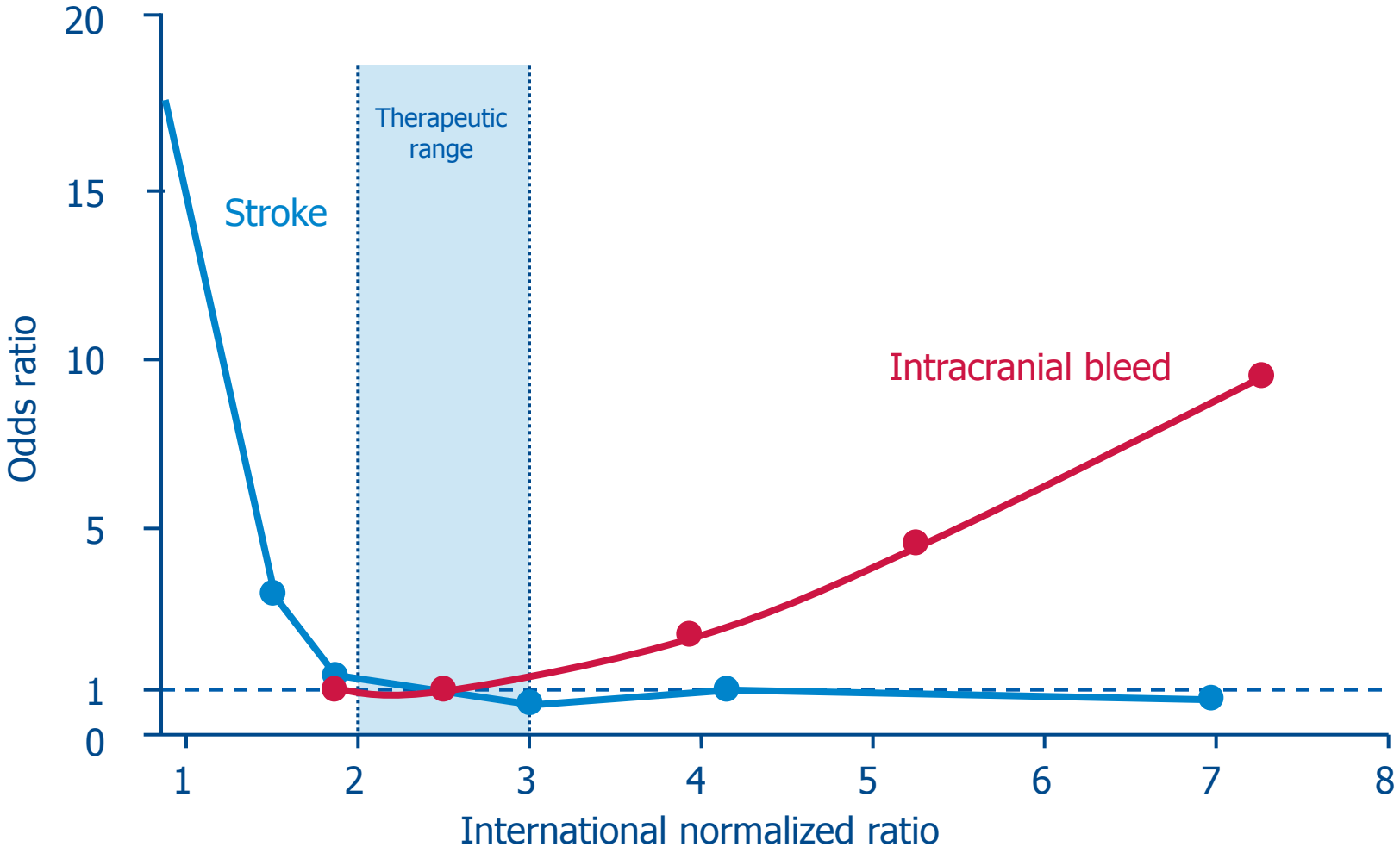
Research Grants/Support

- *Otsuka*
- *Accumetrics*
- *Boehringer-Ingelheim*
- *Haemonetics*
- *Dong-A Pharmaceutical*
- *Han-Mi Pharmaceutical*

Honoraria/Consulting

- *Otsuka*
- *Sanofi-Aventis*
- *Daiichi Sankyo Inc*
- *Astrazeneca*
- *Nanosphere*
- *Haemonetics*
- *Han-Dok Pharmaceutical*

“Warfarin” has a narrow therapeutic window

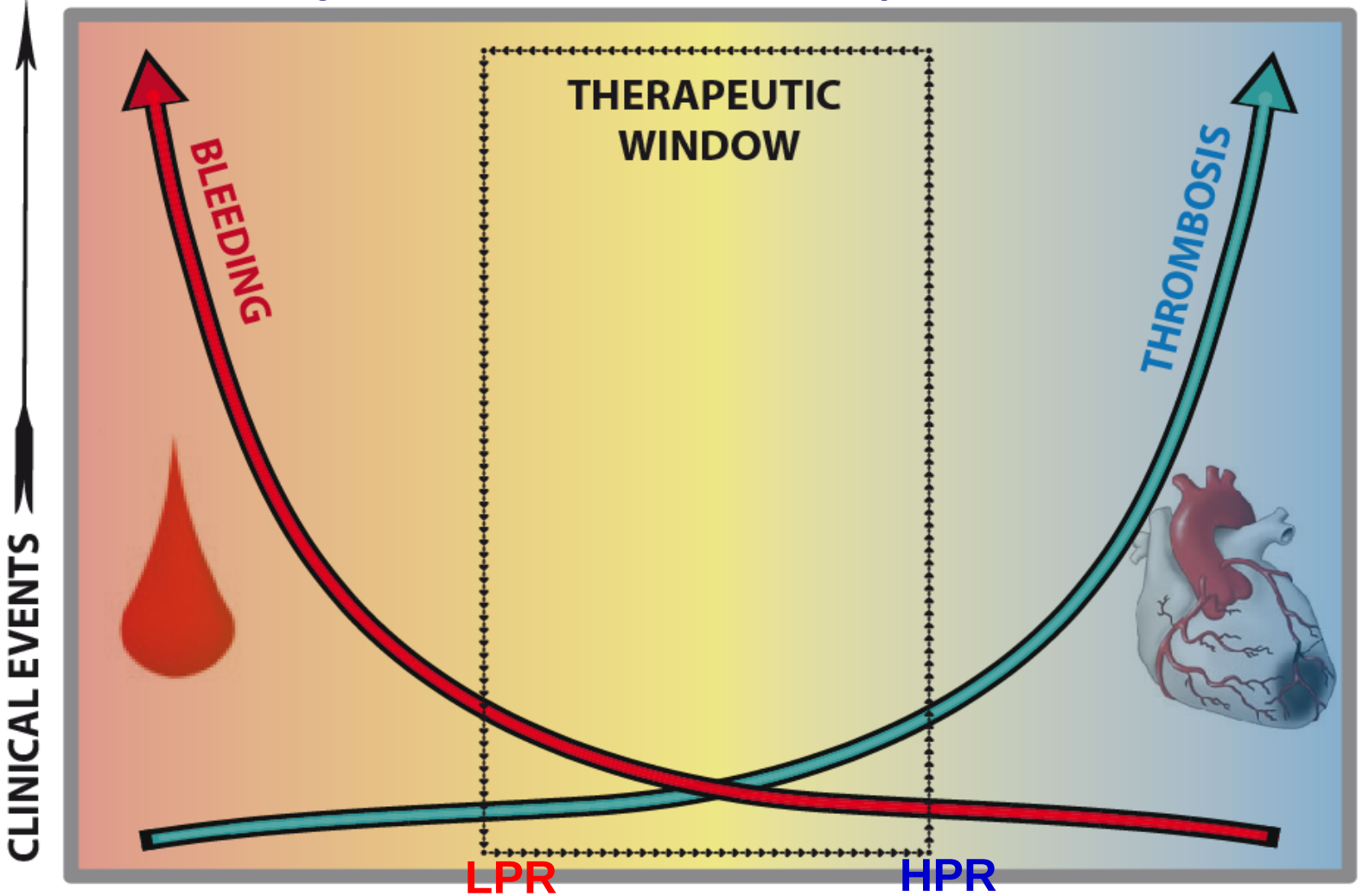


VKAs = vitamin K antagonists

ACCF/AHA/HRS focused update guidelines: Fuster V et al. Circulation 2011;123:e269-e367; Wann LS et al. Circulation 2011;123:104–23 & Circulation 2011;123:1144–50

Therapeutic Window of $P2Y_{12}$ Inhibitor

Tantry US, Aradi D… Jeong YH, et al. Consensus for Therapeutic Window. JACC 2013:E-pub.



MEA:	0U.....	20U.....	50U.....	200U	
LTA:	0%.....	35%	60%	100%	(20μM ADP)
VASP:	0%.....	20%	50%.....	100%	
VerifyNow:	0	85	235	550 PRU	

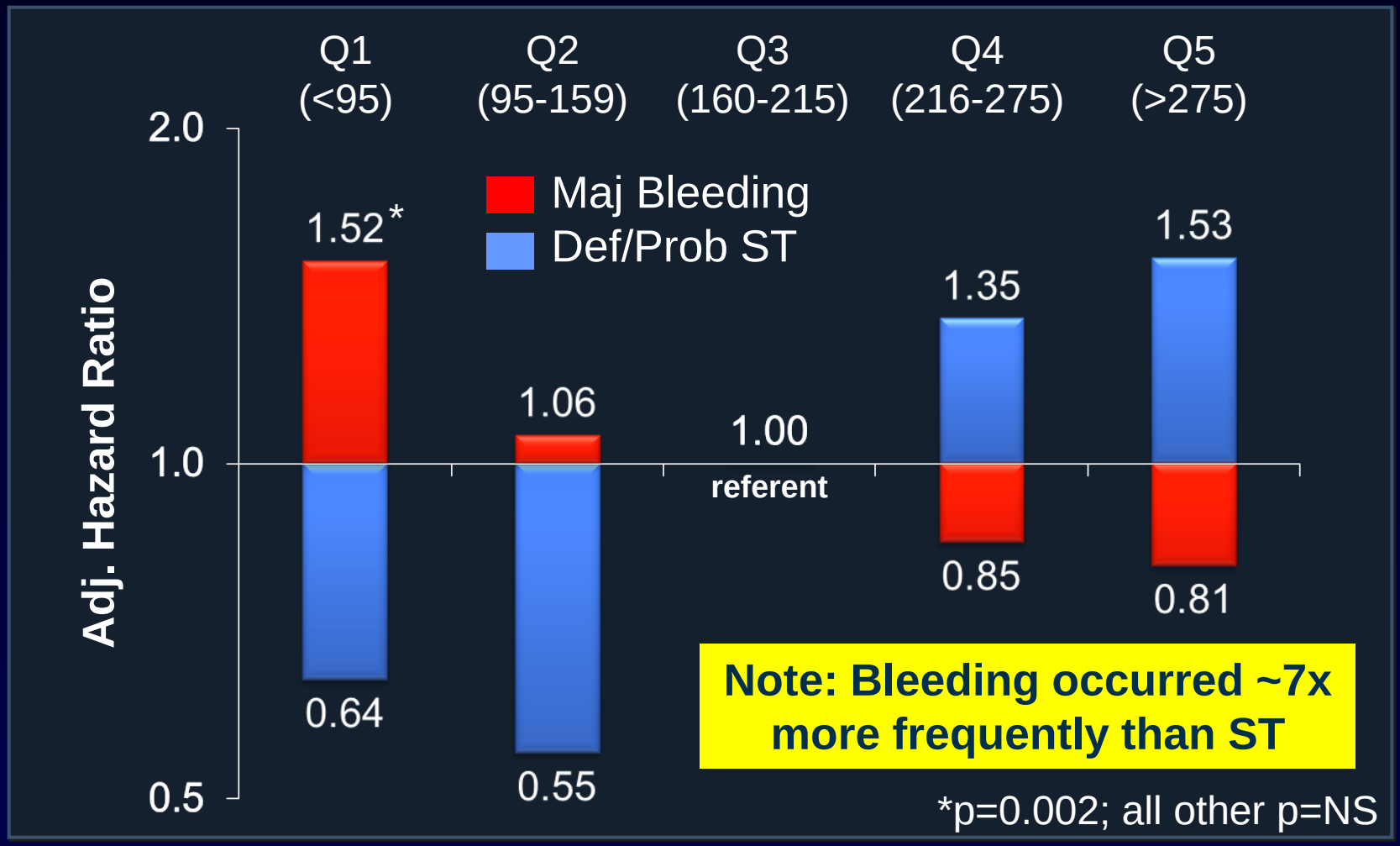
Relationship btw Platelet Function and Bleeding

Study	Patient number and $P2Y_{12}$ inhibitor	Platelet function test	Bleeding Criteria	Outcome
Cuisset et al.[16]	NSTE-ACS (n=597), clopidogrel	LTA, VASP-P assay	Non-CABG-related TIMI major or minor bleeding	<40% aggregation associated with higher risk of 30-day bleeding
Sibbing et al.[17]	PCI (n=2533), clopidogrel	Multiplatelet analyzer	Procedure-related TIMI major bleeding	<19 U associated with 3.5x bleeding
Gurbel et al.[18]	PCI (n=225), clopidogrel	TEG platelet mapping assay		≤31 mm MAADP associated with post-PCI bleeding
Bonello et al.[19]	PCI-treated ACS (n=301), prasugrel	VASP-P Assay	Non-CABG-related TIMI major or minor bleeding	VASP-PRI £ 16% associated with major bleedings
Mokhtar et al.[20]	PCI-treated ACS (n=346), clopidogrel	VASP-P Assay	Non-CABG-related TIMI major or minor bleeding	LPR independent predictor of bleedings
Patti et al.[21]	PCI (n=310), clopidogrel	VerifyNow $P2Y_{12}$ assay	TIMI major bleeding	≤189 PRU associated with bleeding
Tsukahara et al.[22]	PCI (n=184), clopidogrel	LTA	REPLACE 2 bleeding	First quartile ADP-induced aggregation associated with bleeding
Parodi et al.[23]	PCI (n=298), prasugrel	LTA	Entry site bleeding	LPR associated with bleeding
ARCTIC[7]	PCI (n=2440), Clopidogrel or prasugrel	VeruifyNow $P2Y_{12}$ Assay	STEEPLE major bleeding	No association between bleeding and platelet reactivity
POPULAR[24]	PCI (n=1,069), clopidogrel	LTA, VerifyNow $P2Y_{12}$ assay, Plateletworks, IMPACT-R, PFA100, Innovance PFA	TIMI bleeding	No relation between bleeding and platelet reactivity measured by any assay
GRAVITAS[5]	DES implantation (n=2214), clopidogrel	VerifyNow $P2Y_{12}$ assay	GUSTO bleeding	No association between bleeding and platelet reactivity

AUC: area under the curve, DES: drug-eluting stent, MA: maximum amplitude, LTA: light transmittance aggregometry, NSTE-ACS: non-ST-segment elevation acute coronary syndrome, PCI: percutaneous coronary intervention, ROC: receiver operating characteristic, TIMI: thrombolysis in myocardial infarction

PCI Cohorts. Tantry US, et al. *JACC* 2013;E-pub.

ADAPT-DES Registry at 1 Year:
MV Analysis of ST and Major Bleeding by PRU

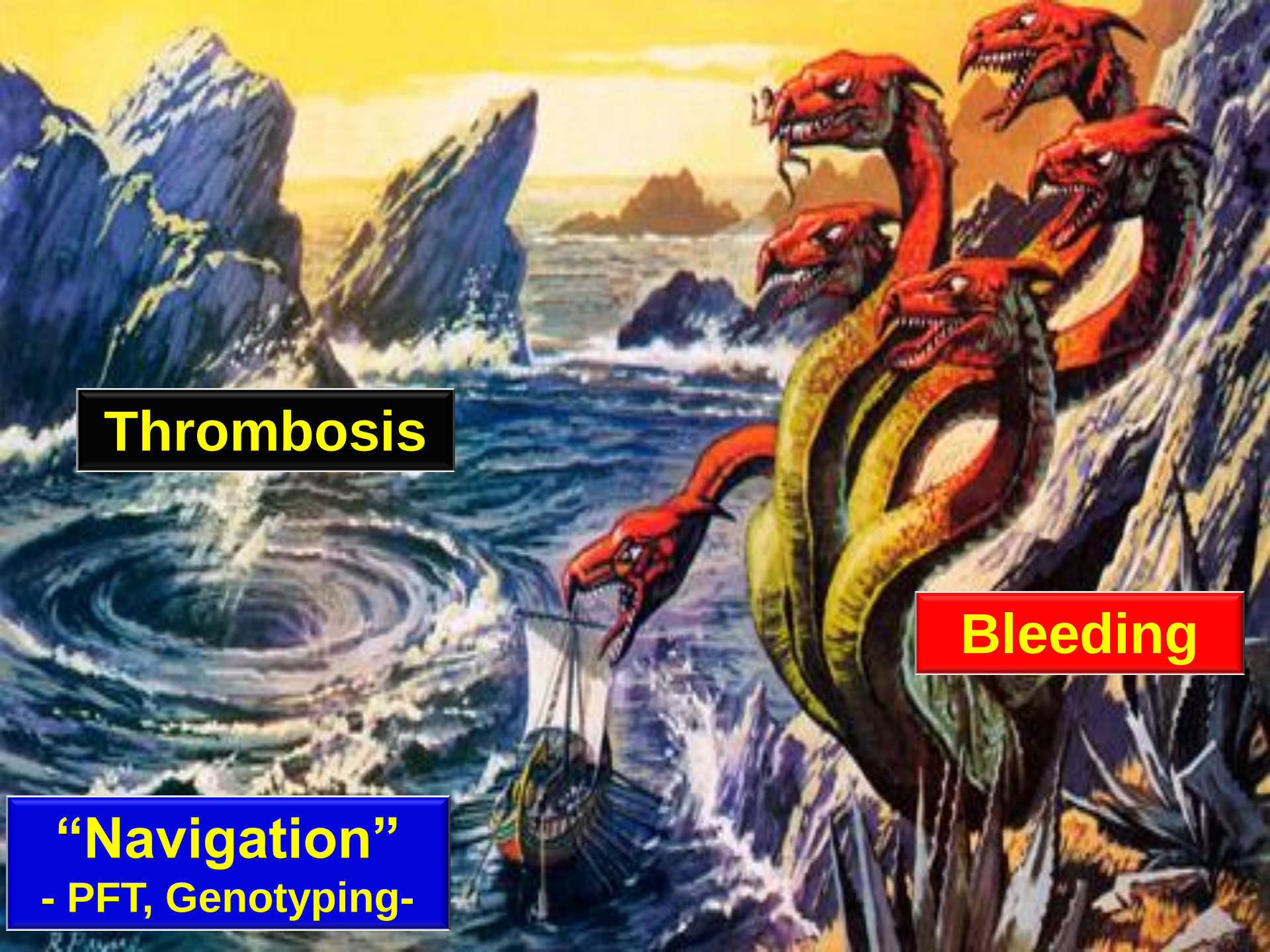


Stone GW, et al. *Lancet* 2013;382:614-23.

ADAPT-DES Registry at 1 Year:
MV Analysis of Mortality by PRU Quintiles

	Event	No event	Unadjusted HR (95% CI)	p value
Definite ST				
Number of events	53	8530		
Deaths	5 (9·6%)	156 (1·9%)	5·47 (2·25–13·31)	<0·0001
MI without ST				
Number of events	224	8359		
Deaths	21 (9·7%)	140 (1·7%)	5·78 (3·65–9·14)	<0·0001
Bleeding				
Number of events	531	8052		
Deaths	45 (8·6%)	116 (1·5%)	5·97 (4·23–8·42)	<0·0001

Stone GW, et al. *Lancet* 2013;382:614-23.


Thrombosis
Bleeding
“Navigation”
- PFT, Genotyping-

Platelet Function Testing:

Which Test?

Available methods for PFT

Laboratory-based methods
(Platelet-oriented method)

LTA

Methods allowing near-patient testing
(Whole blood test: promising in clinics)

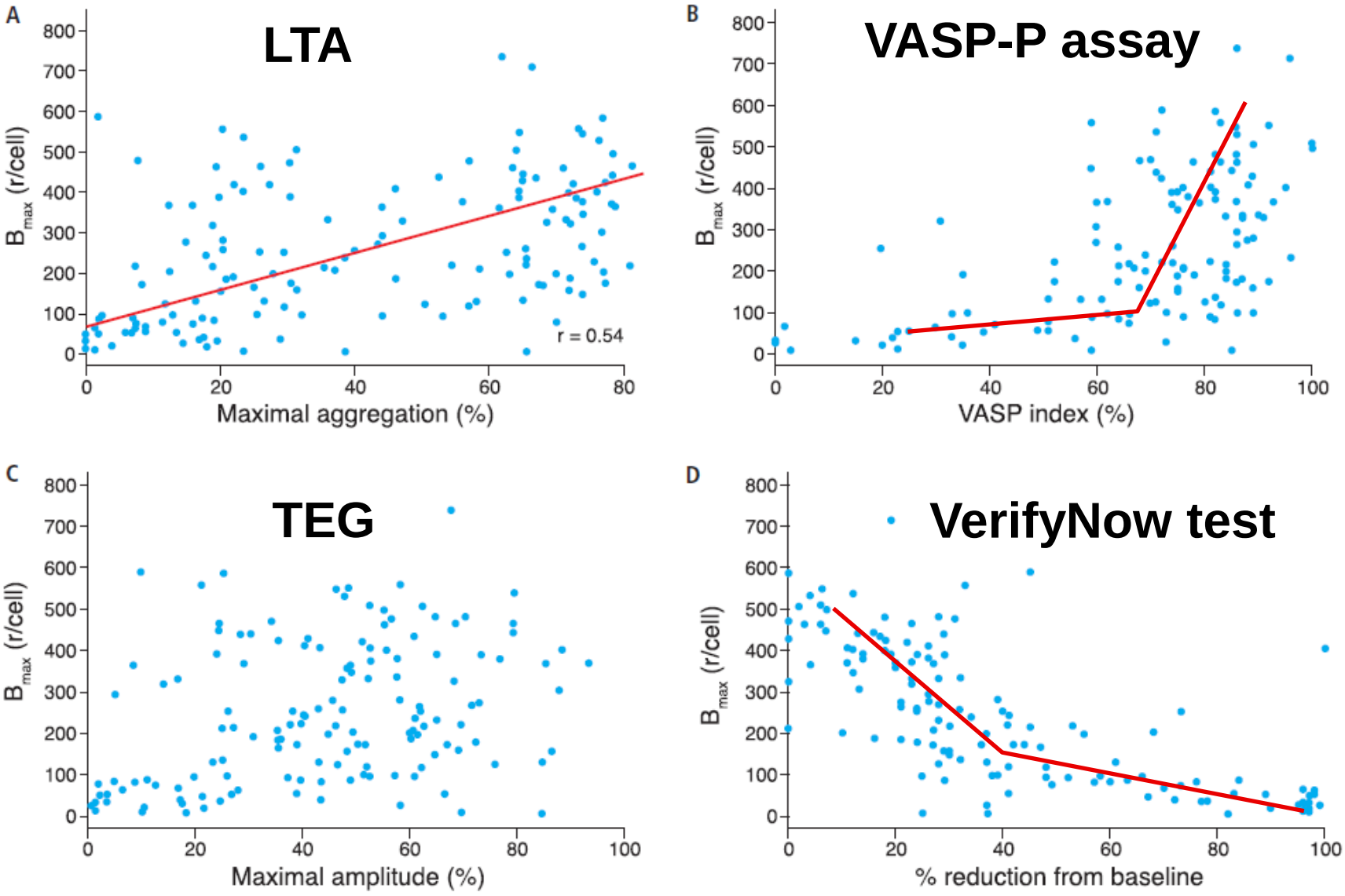
TEG

What is "ideal platelet function test"?

- **Biology: platelet receptor occupancy**
- **Laboratory: validated and POC system**

  ? Whole blood vs. Platelet-oriented
- **Practice: prediction for clinical events (ischemia and bleeding)**

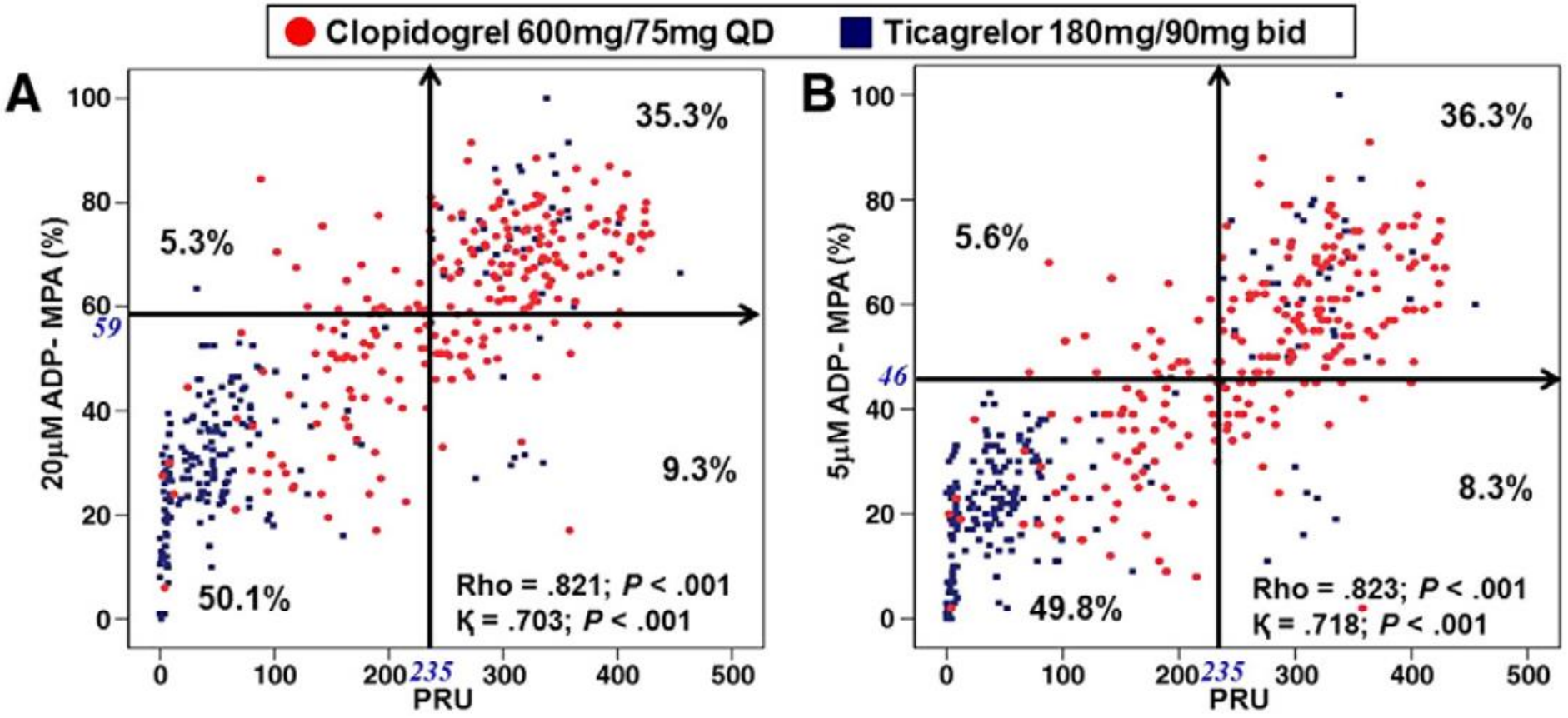
Relationship btw R Occupancy and *ex vivo* Tests



Sollier et al. *Thromb Haemost* 2010; 104: 571–81.

VerifyNow Test During Clopidogrel & Ticagrelor

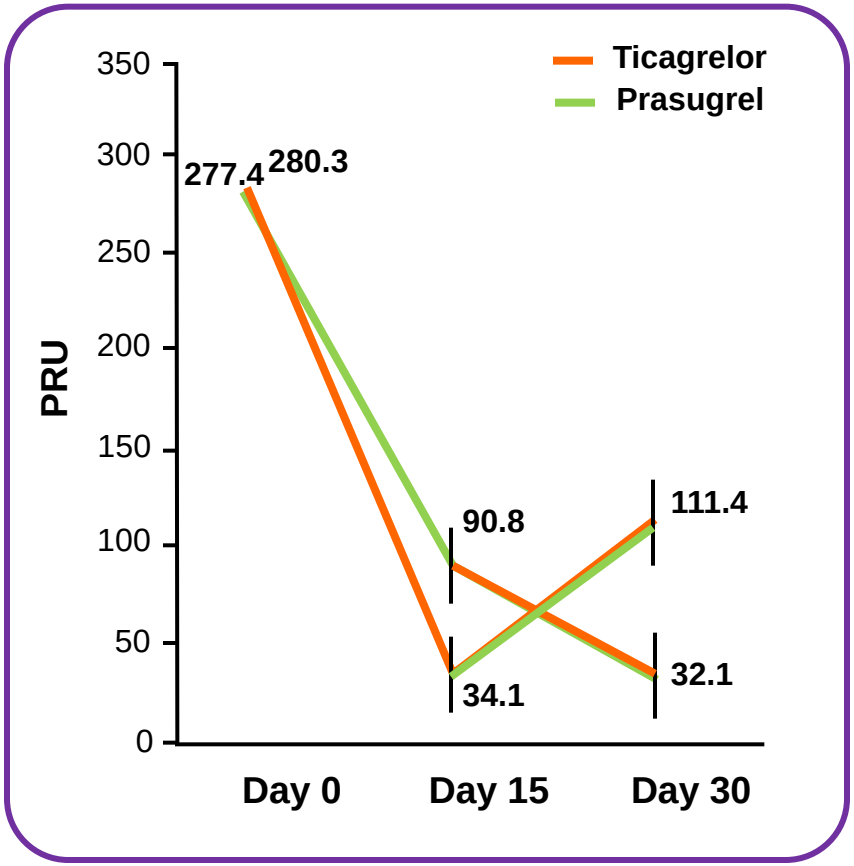
ONSET/OFFSET and RESPOND Substudy (n = 760 pairs)



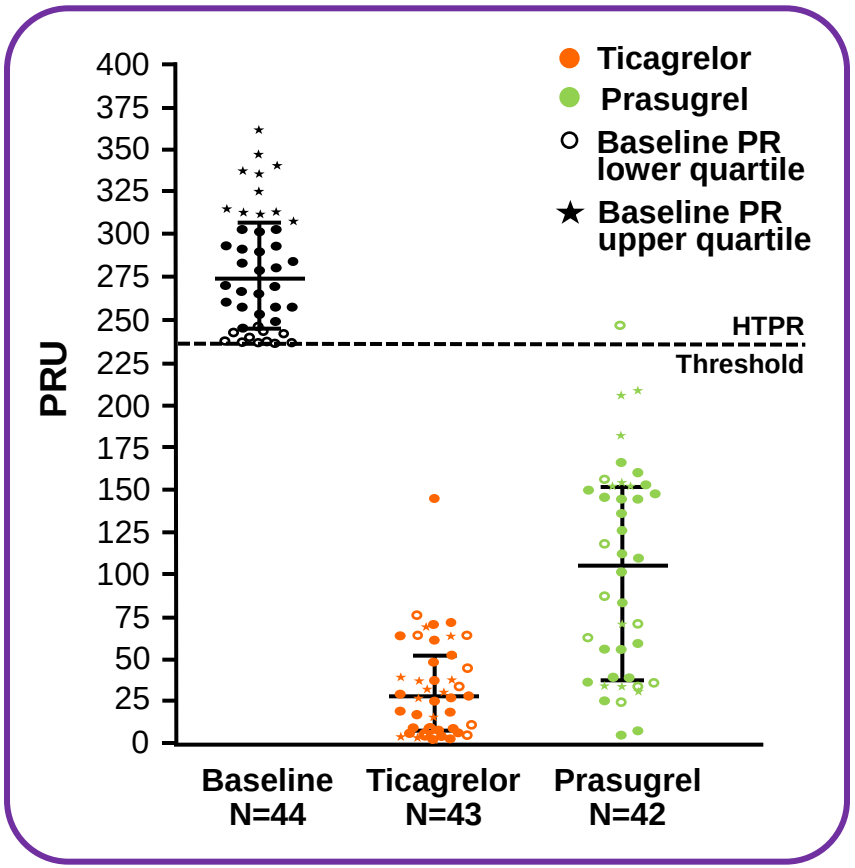
Jeong YH, et al. *Am Heart J* 2012;164:35-42.

Ticagrelor vs. prasugrel produces a significantly higher platelet inhibition

Platelet Reactivity
(in PRU) by Treatment sequence



Individual PR values
according to treatment

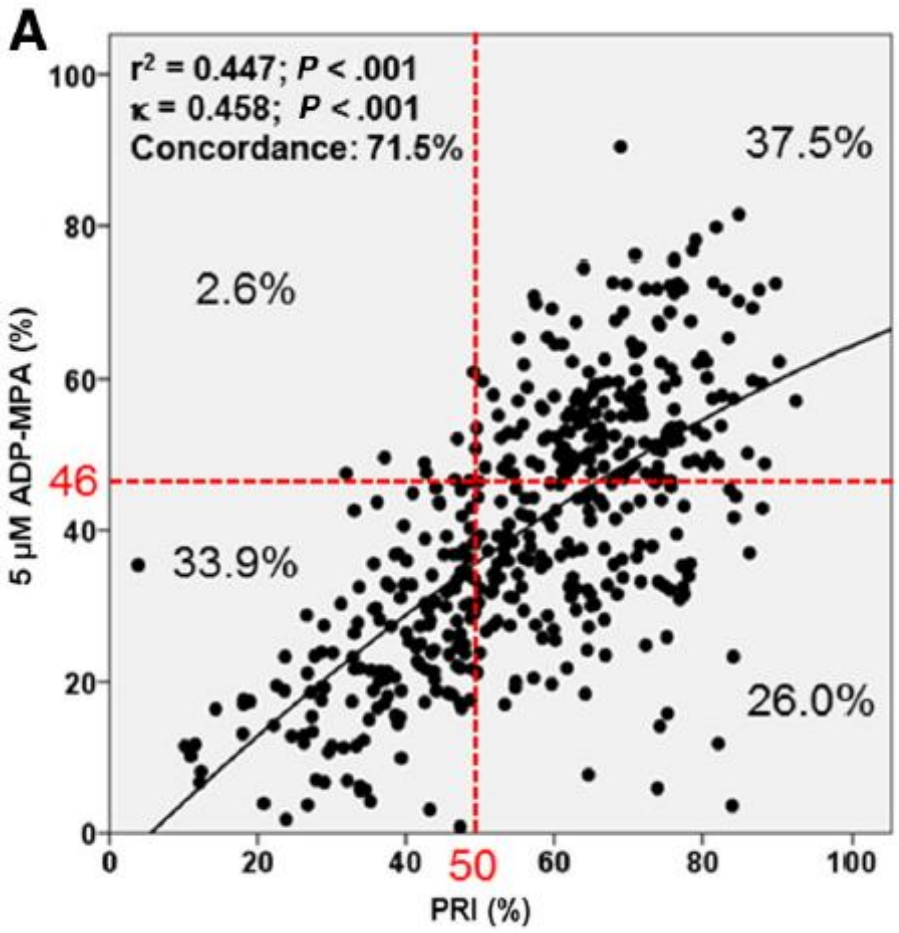


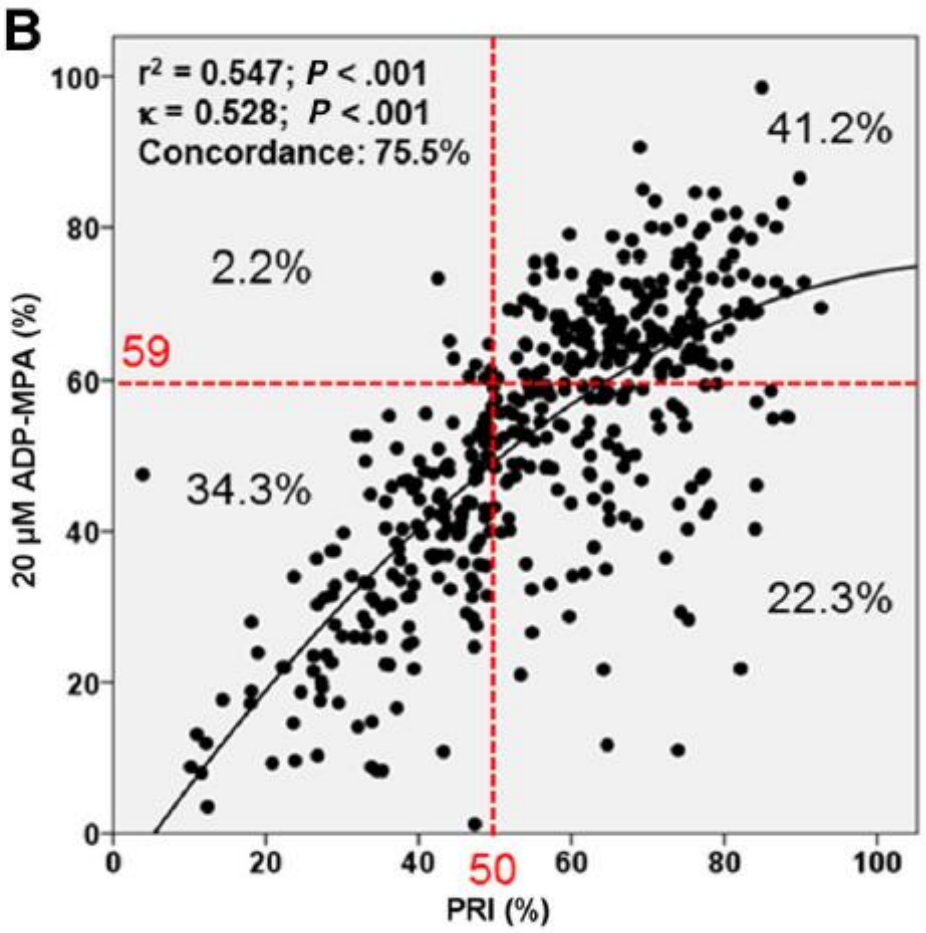
Platelet reactivity is significantly lower in patients receiving ticagrelor compared with prasugrel. Least squares estimates and 95% confidence intervals are presented.
PRU platelet reactivity unit(s).

Alexopoulos et al. *J Am Coll Cardiol* 2012;60(3):193-9.

VASP-P Assay During Dual Antiplatelet Therapy

CAD Patients Treated with Elective PCI (n = 466)



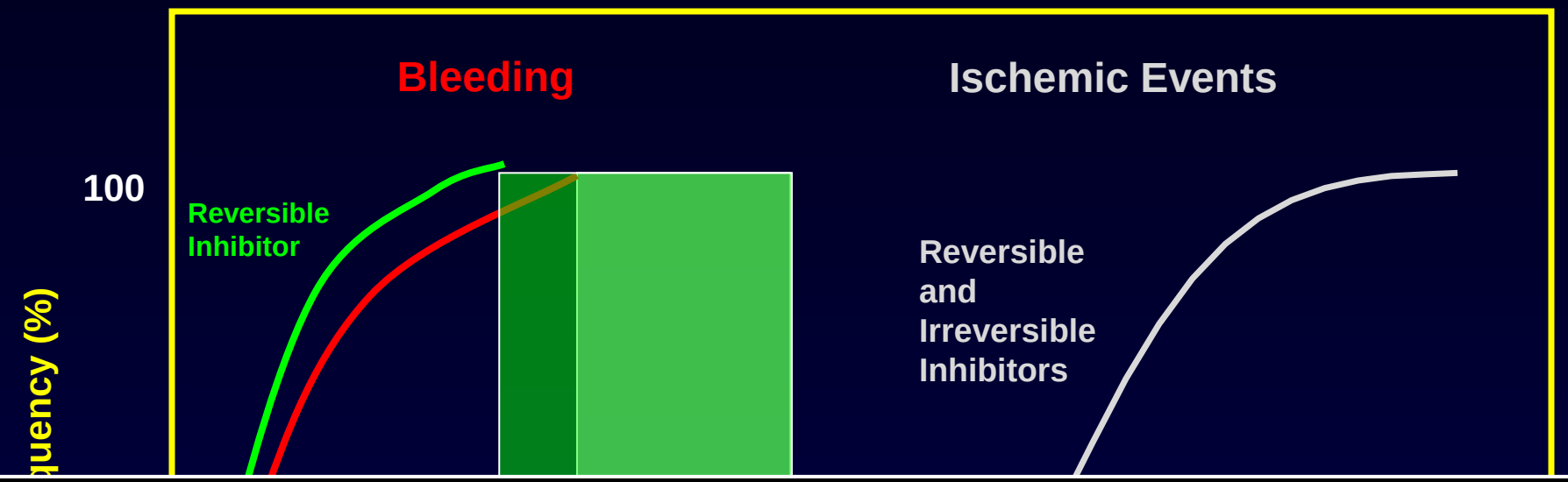


Kim IS Jeong YH, et al. *Am Heart J* 2013;166:95-103.

Platelet Function Testing:

Reversible vs. Irreversible Inhibitor

Theoretical Construct for $P2Y_{12}$ Reactivity Therapeutic Window



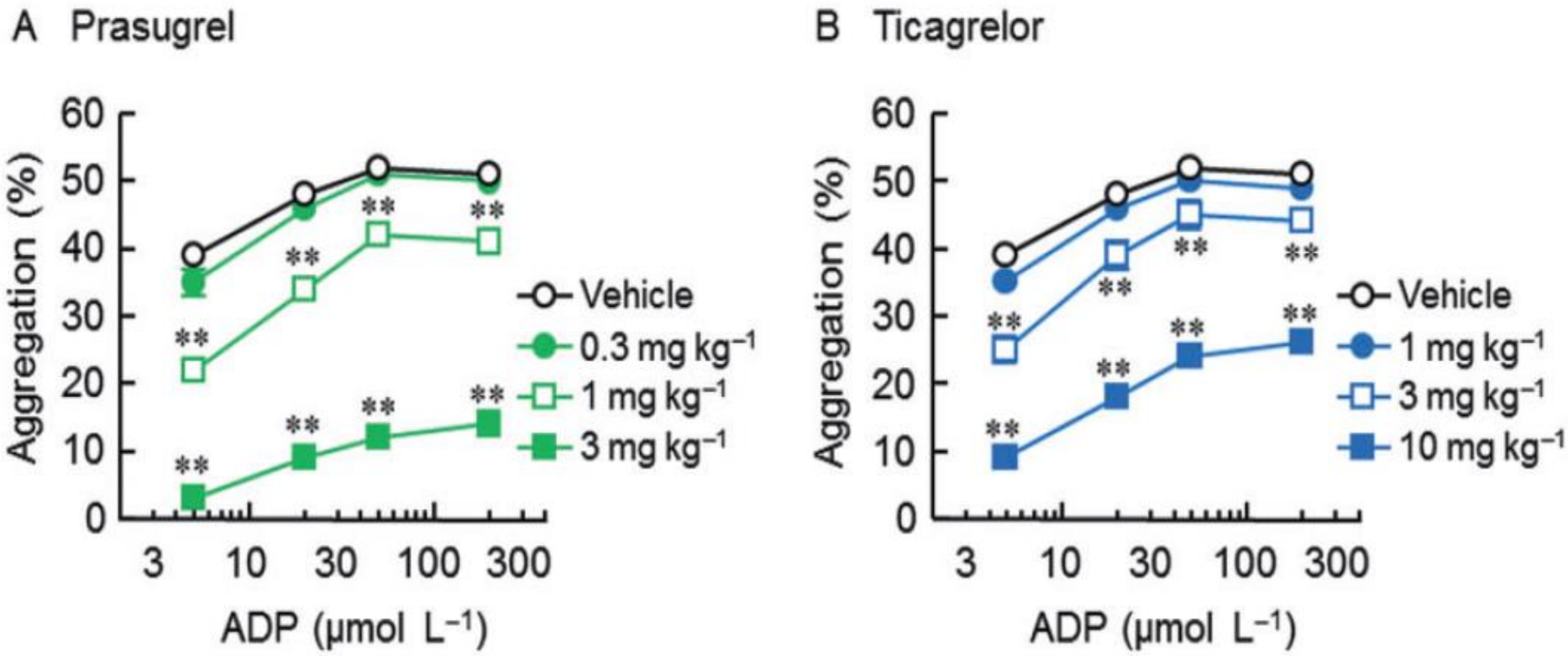
Do you believe that

"Ticagrelor, more potent $P2Y_{12}$ inhibitor, is safer than Prasugrel?"

Adapted from Gurbel PA et al. *J Am Coll Cardiol*. 2008;51:B86

PK and PD of Prasugrel vs. Ticagrelor in Rats

Concentration-response curve for ADP-induced PA (4h after dosing)



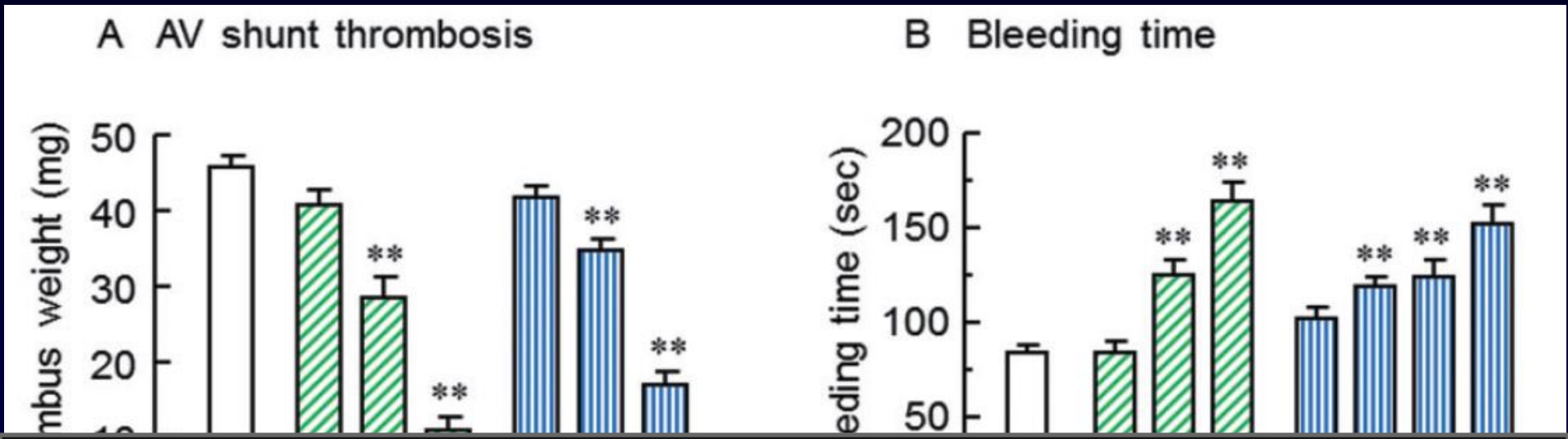
ED50 value (20 μM ADP): Prasugrel, 1.9 mg/kg vs. Ticagrelor, 8.0 mg/kg

Sugidachi A et al. *BJP*. 2013;169:82-89.

PK and PD of Prasugrel vs. Ticagrelor in Rats

AV shunt thrombosis model (4h after dosing)

21-G needle into the tail (4h after dosing)



"Potency" Prasugrel vs. Ticagrelor = 4 : 1

Inhibition of Platelet Aggregation

= Inhibition of Thrombus Formation

= Prolongation of Bleeding Time

Clinical Outcome (PCI Cohort)

TRITON-PCI vs. PLATO-Invasive (PCI/CABG: 82.1%)

TRITON-PCI (14.5 mo F/U)	Prasugrel (n=6422)	Clopidogrel (n = 6422)	HR (95% CI)	P value
CV death/MI/Stroke	10%	12%	0.81 (0.72-0.90)	0.0001
CV death	2%	2%	0.84 (0.66-1.08)	0.17
Non-fatal MI	7%	10%	0.76 (0.67-0.86)	<0.0001
TIMI major bleed	2.4%	1.8%	1.27 (0.99-1.63)	0.06

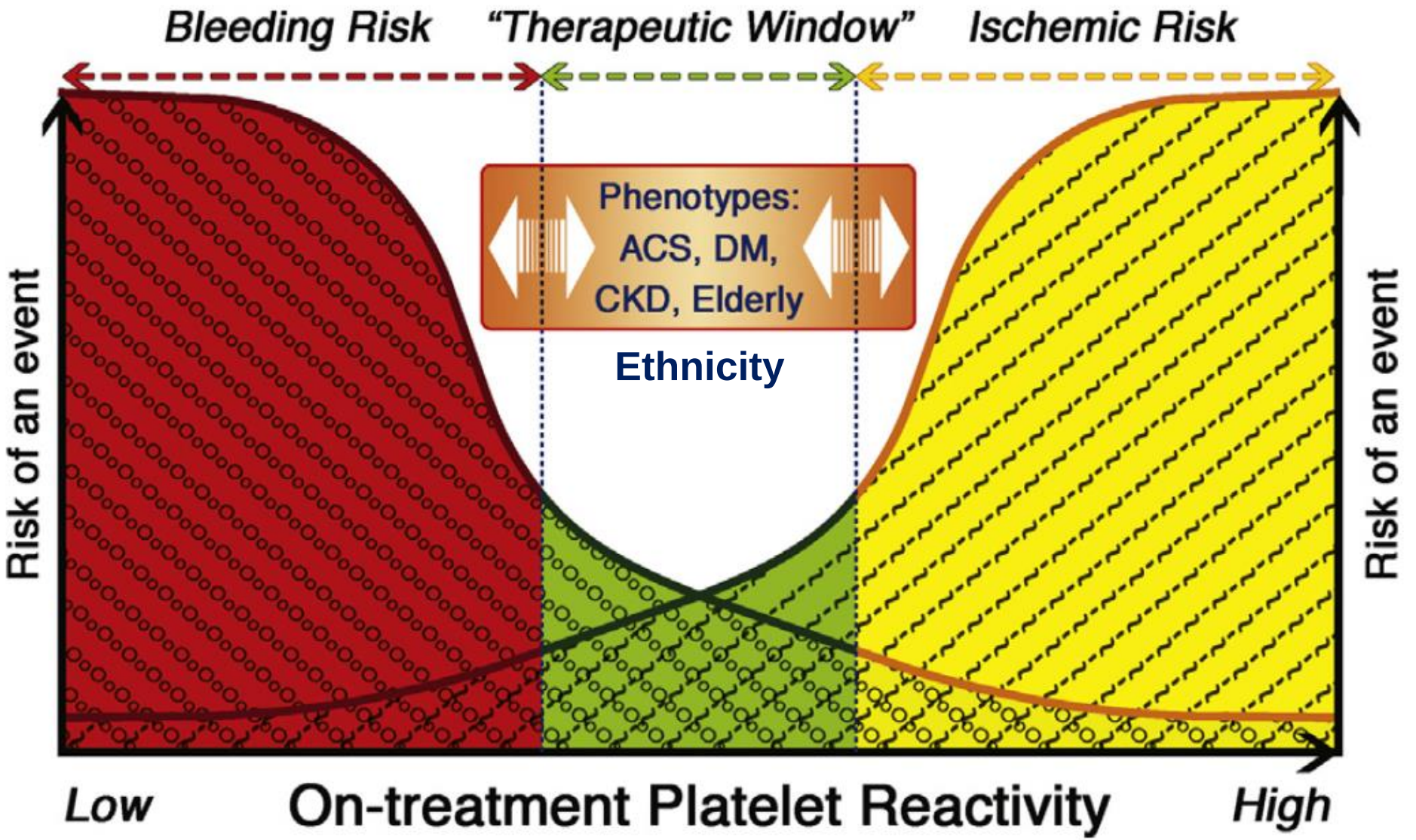
PLATO-Invasive (9 mo F/U)	Ticagrelor (n=6732)	Clopidogrel (n = 6676)	HR (95% CI)	P value
CV death/MI/Stroke	9.0%	10.7%	0.84 (0.75-0.94)	0.0025
CV death	3.4%	4.3%	0.82 (0.68-0.98)	0.0250
Non-fatal MI	5.3%	6.6%	0.80 (0.69-0.92)	0.0023
TIMI major bleed				
Non-CABG	2.8%	2.2%	1.23 (0.98-1.55)	0.0814
CABG	5.3%	5.9%	0.90 (0.78-1.05)	0.1914

Wiviott et al. *Lancet* 2008;371:1353-63.: Cannon et al. *Lancet* 2010;375:283-93.

Platelet Function Testing:

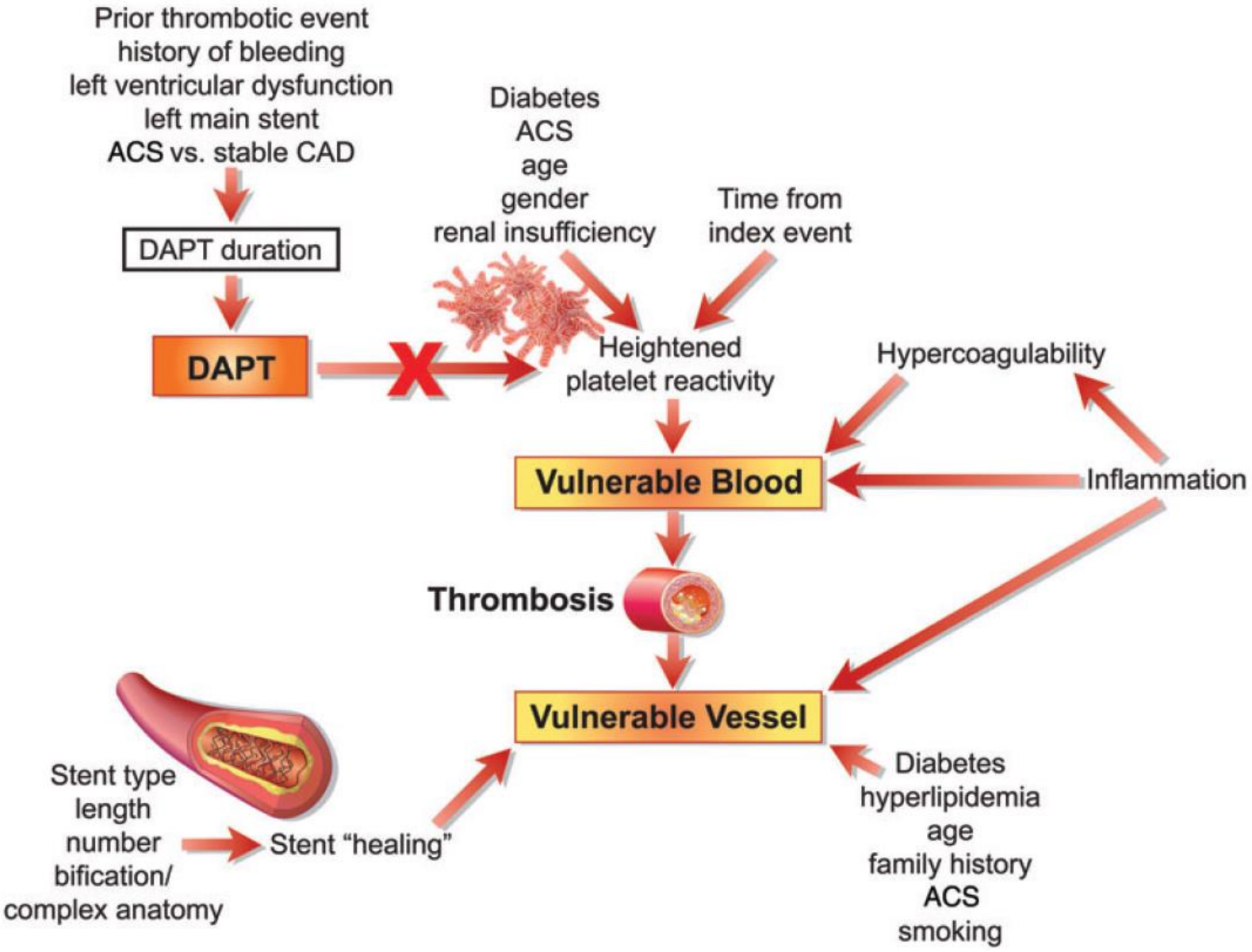
How to Apply?

Impact of Platelet Reactivity on Balance Between Efficacy and Safety



Angiolillo DJ et al. *JACC* 2013;62:S21-31.

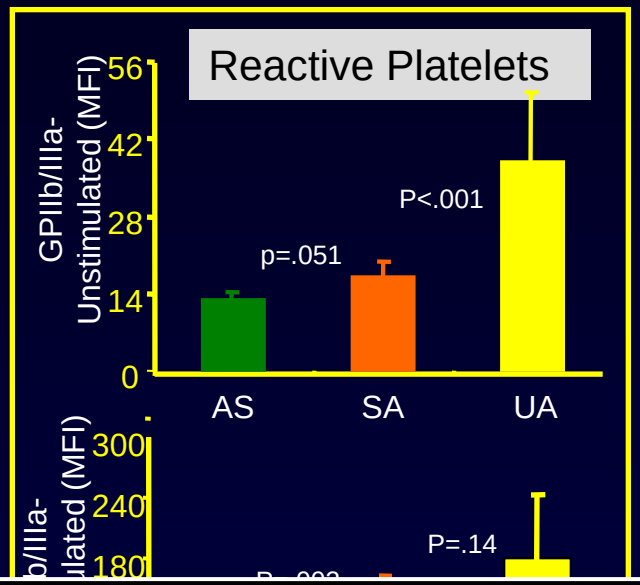
Factors Influencing Thrombotic Events

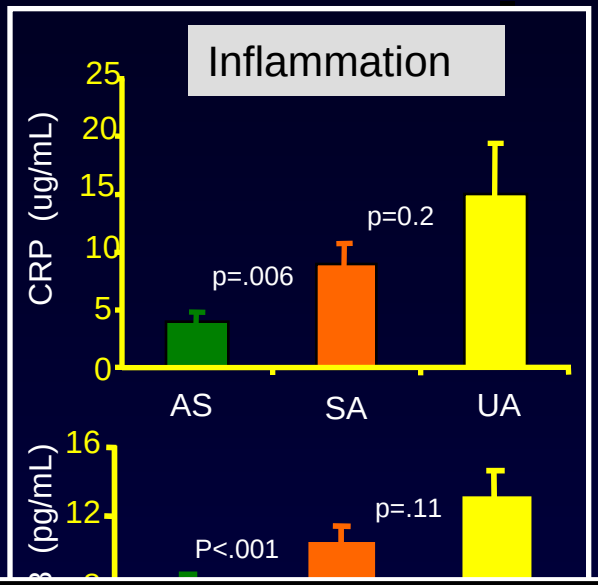


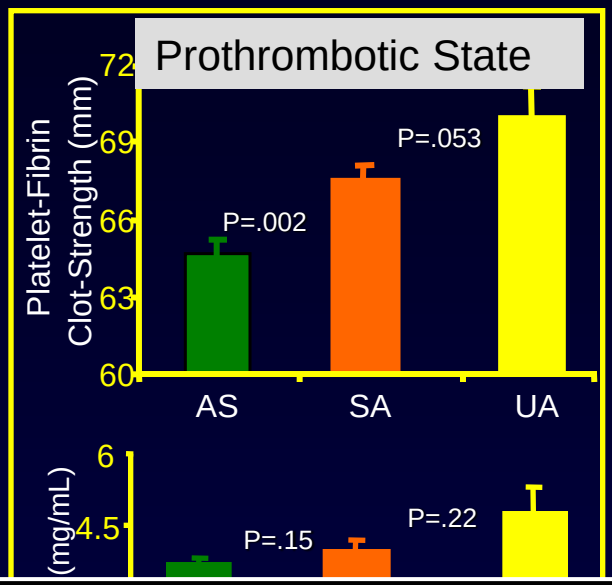
Gurbel P, et al. *Eur Heart J* 2013;E-pub.

Relation: Platelet Physiology, Inflammation and Disease Activity

AS = Asymptomatic Patients, SA= Stable Angina, UA= Unstable Angina







"The level of thrombogenecity"

(vulnerable or sticky blood) and "vulnerable vessel"

can be different according to the disease activity.

Stable CAD < NSTE-ACS < STEMI

Level of IPA: Stable CAD < NSTE-ACS < STEMI

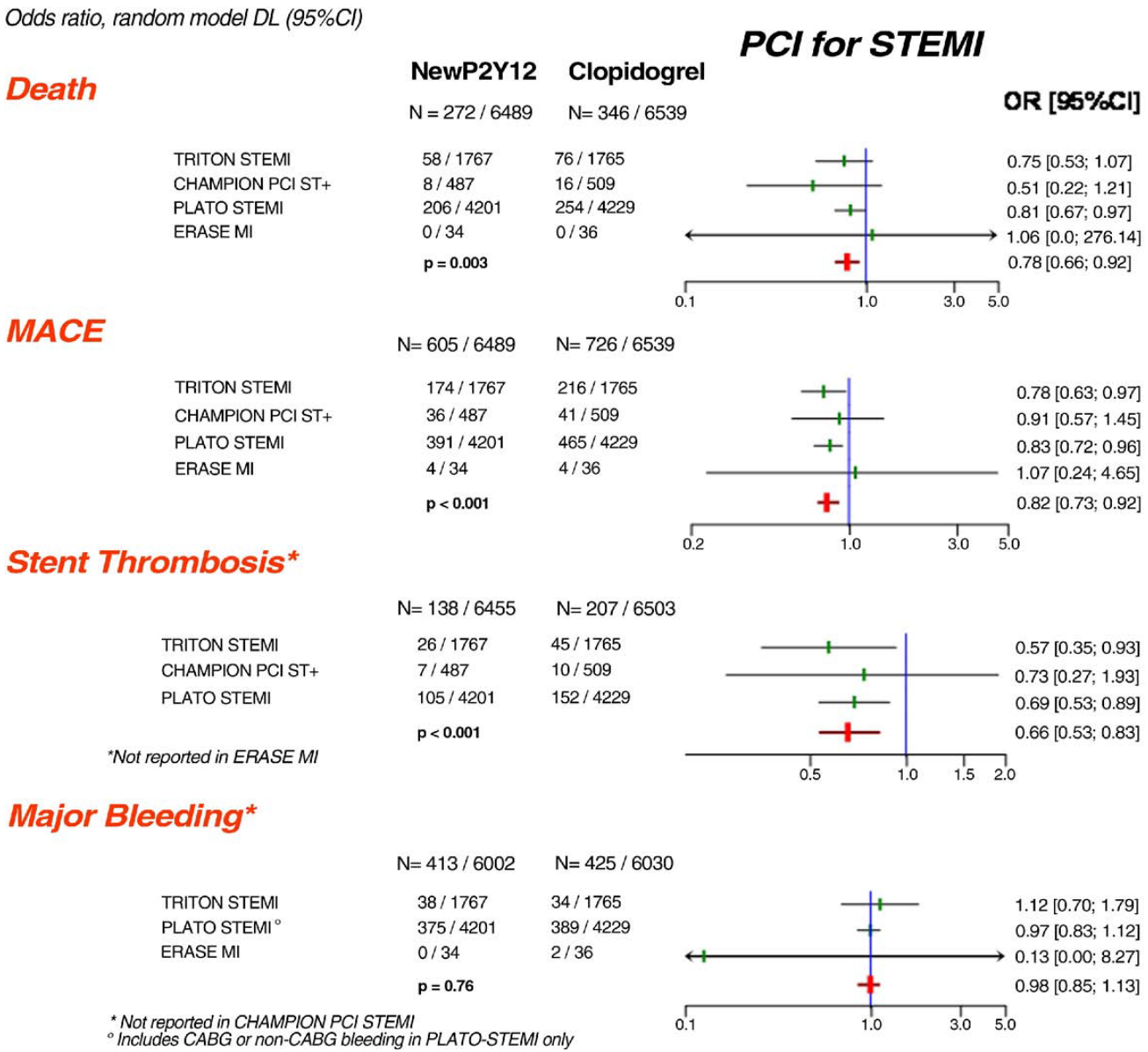
Efficacy and Safety of Prasugrel vs. Clopidogrel - *CYP2C19* LOF Allele Carriage -

TRITON TIMI-38: NSTE-ACS cohort

	LoF allele	Prasugrel	Clopidogrel	Relative risk (95% CI)
CV death, MI and Stroke	No	9.6%	9.8%	0.98 (0.80–1.20)
	Yes	8.5%	15.0%	0.57 (0.39–0.83)
TIMI major or minor bleeds	No	4.7%	3.4%	1.38 (1.00–1.93)
	Yes	5.5%	3.5%	1.60 (0.8–3.1)

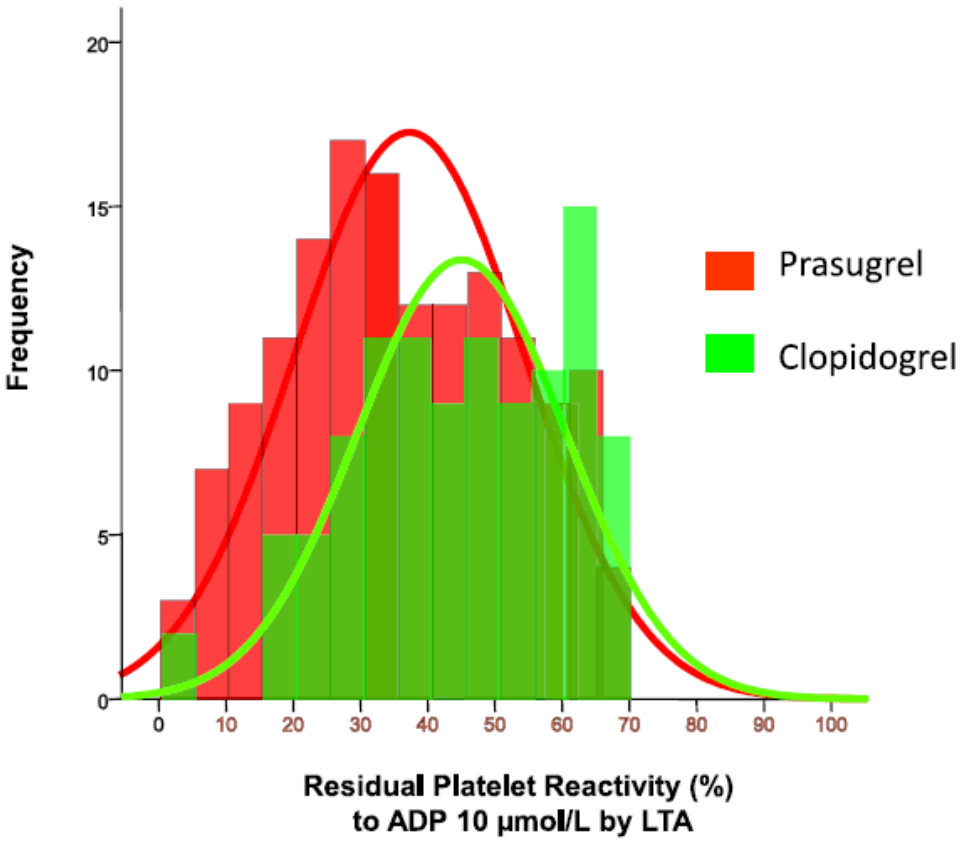
Sorich MJ, et al. *J Thromb Haemost* 2010; 8: 1678–84.

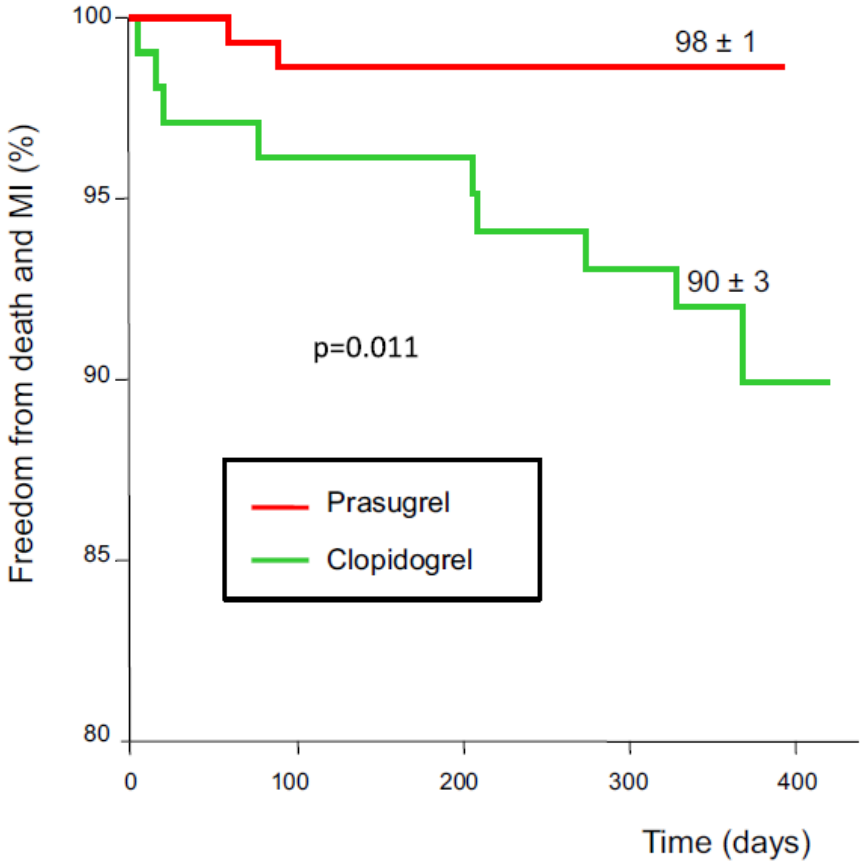
New $P2Y_{12}$ Inhibitors vs. Clopidogrel in PCI



Bellemain-Appaix, et al. J Am Coll Cardiol. 2010;56:1542-51.

Prasugrel vs. Clopidogrel Therapy after EES Stenting in Unprotected LMCAD



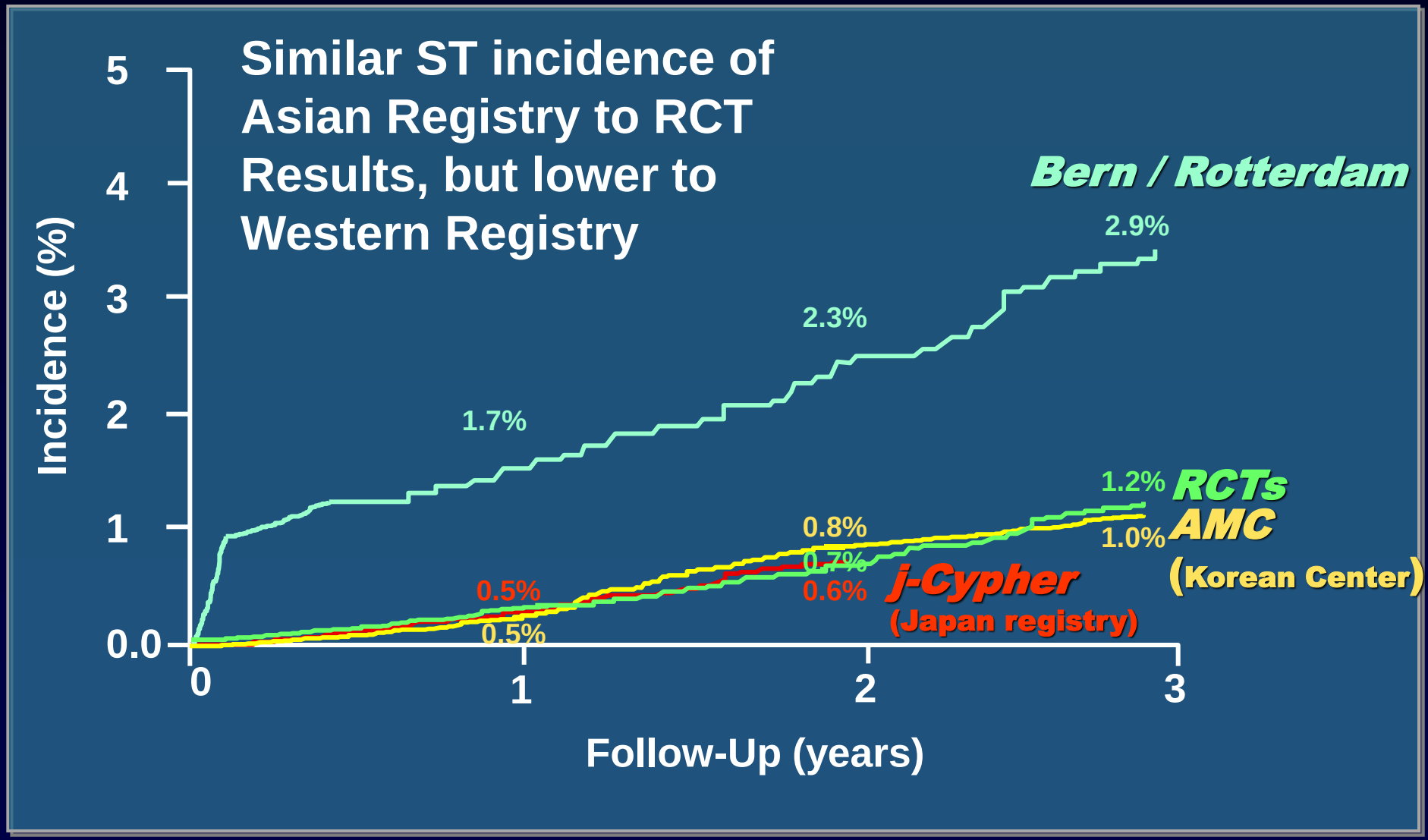


Lesion or PCI complexity ("vulnerable vessel") in stable CAD: "Different level of platelet inhibition"

Migliorini A, et al. *Am J Cardiol.* 2013;112:1843-8.

Racial Difference of Stent Thrombosis Risk

East Asians vs. Westerners after 1st DES



Relationship between VerifyNow and Post-PCI Outcome

Korea: ROC curve analysis for HPR (total n = 3,844)

Study	Cohort	EP	Cutoff
ACCEL-LOADING-ACS (Randomized)[1]	NSTE-ACS (n=218); emergent PCI	1-mo MACE	**PRU ≥ 289** **% inhibition ≤ 12%**
Zhang et al. (Registry)[2]	NSTE-ACS (n=228); emergent PCI	1-mo MACE	**PRU > 272**
Ko et al. (Registry)[3]	All comer (n=222); PCI	1-mo MACE	**PRU ≥ 275**
CILON-T (Randomized)[4]	All comer (n=960); DES implantation	6-mo MACE	**PRU ≥ 252.5**
Ahn et al.	All comer (n=1226);	12-mo	**Non-AMI: no cutoff**

Different cutoff of HPR between races

PRU: Western (208~235) vs. Korean (253~289)

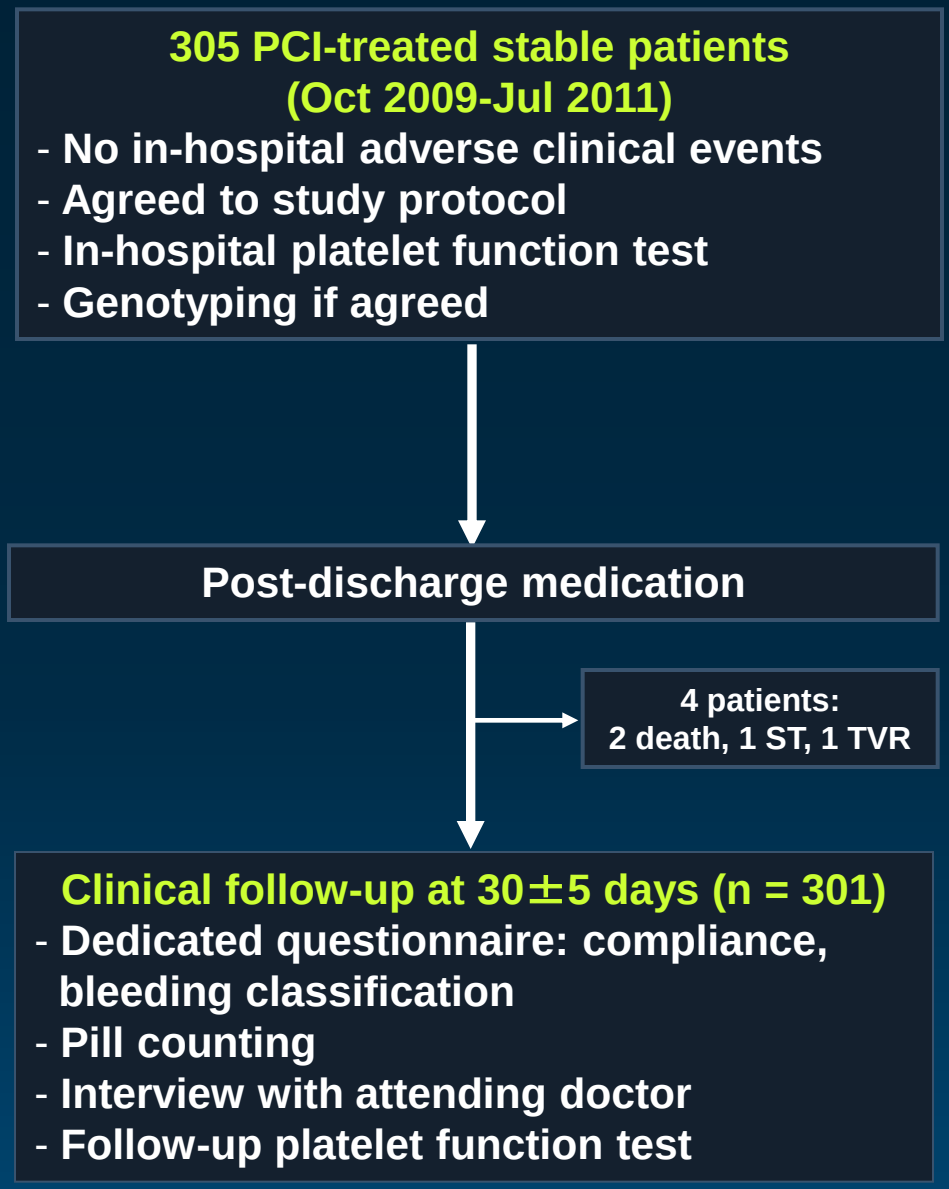
"Influence of different thrombogenecity"

al. Int J Cardiol 2013;167:1877.

ACCEL-BLEED trial

Design

- **NAME:** the ACCEL-BLEED (*A C*orrelation between on-*C*lopidogr*EL* platelet reactivity and *BLEED*ing events in PCI-treated patients) study
- **DESIGN:** Prospective, non-randomized, single-center clinical observation (Gyeongsang National University Hospital)
- **OBJECTIVE:** To examine the relationship between the platelet reactivity and bleeding episodes

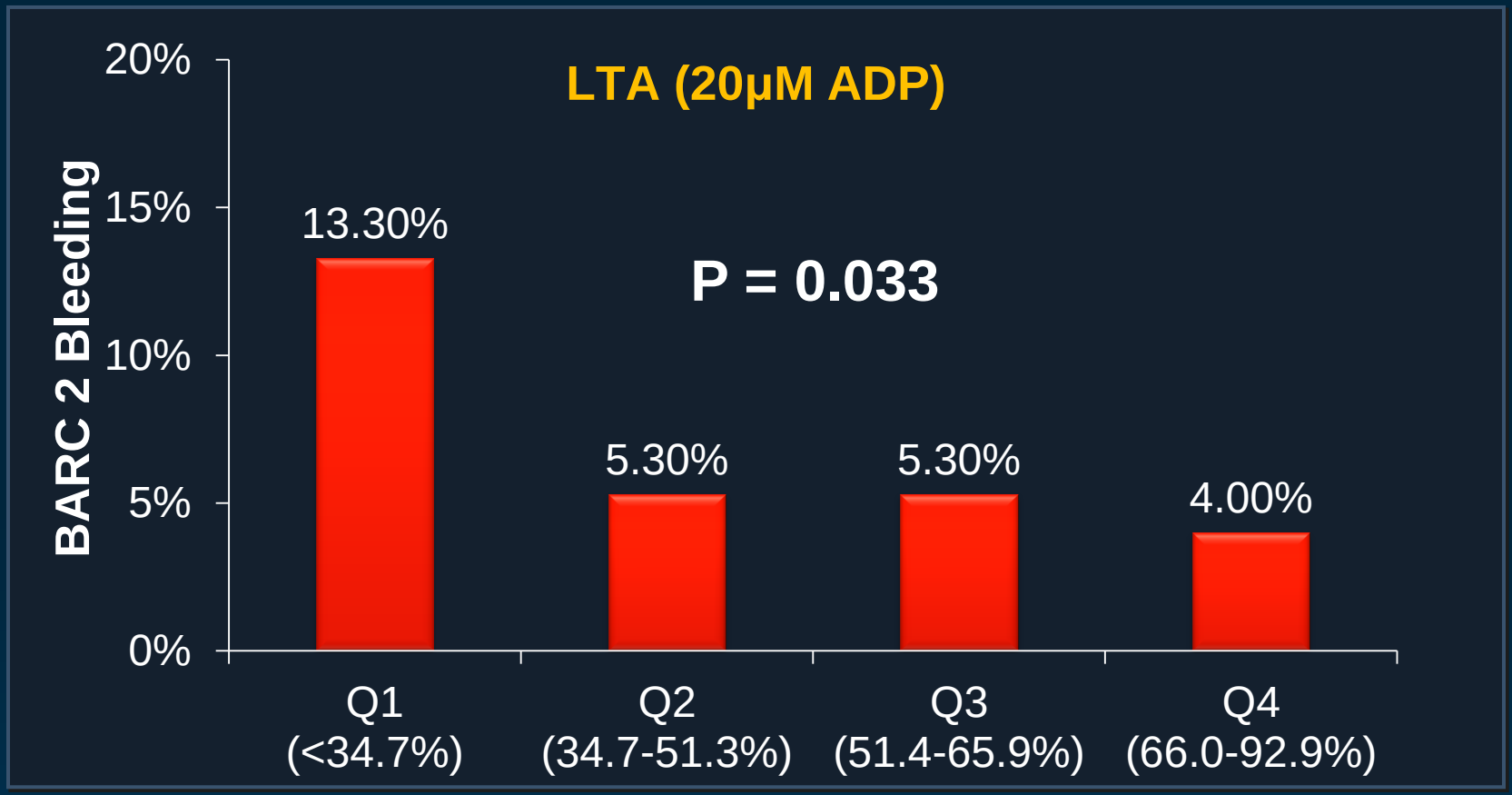


Jeong YH. Featured Clinical Trial. TCT 2011.

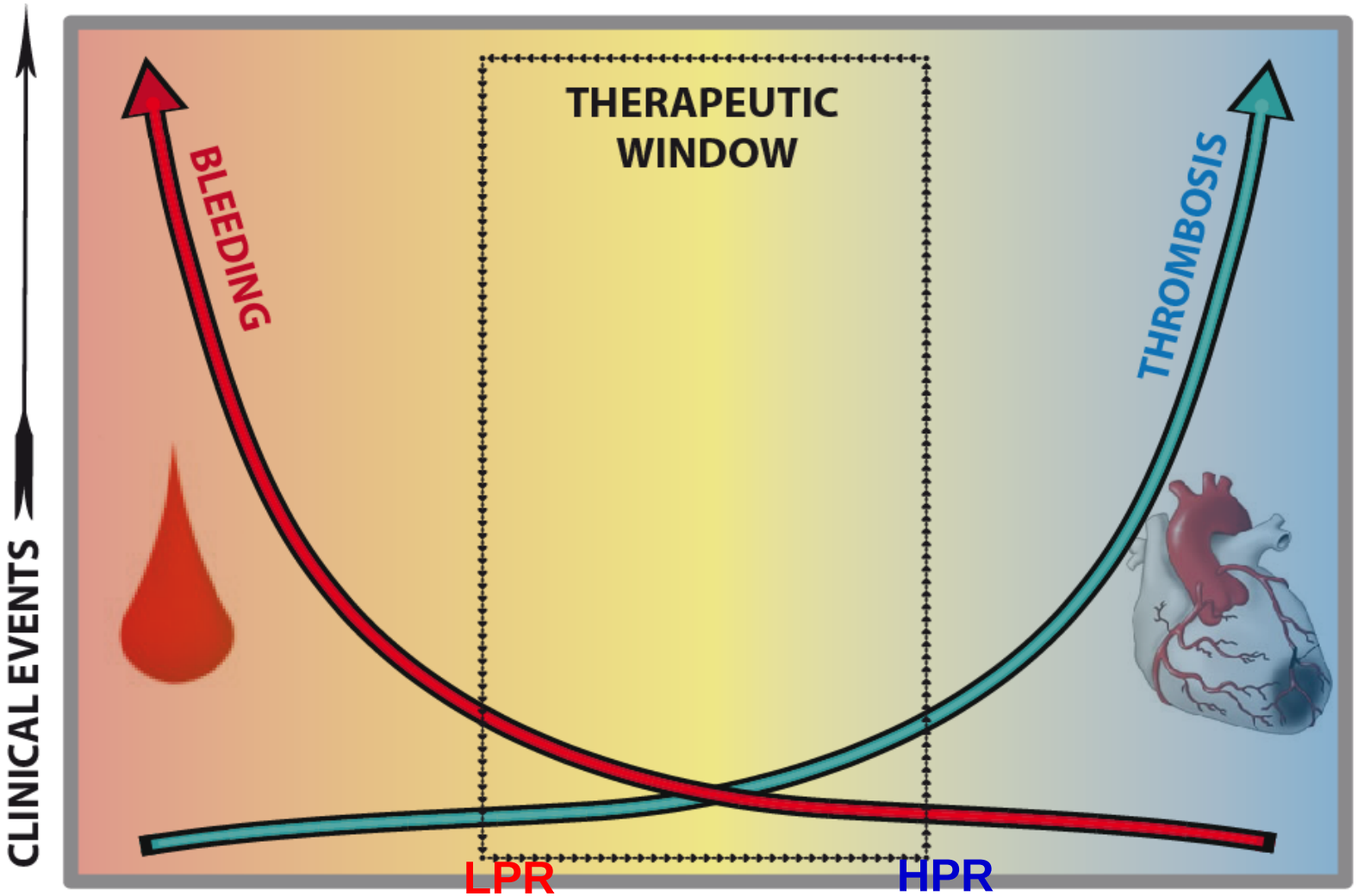
Incidence of Bleeding Events

Post-discharge
1-month F/U
(n = 301)

BleedScore™	
Superficial (BARC 1)	67 (22.3%)
Internal (BARC 2)	21 (7.0%)
Alarming	0 (0%)



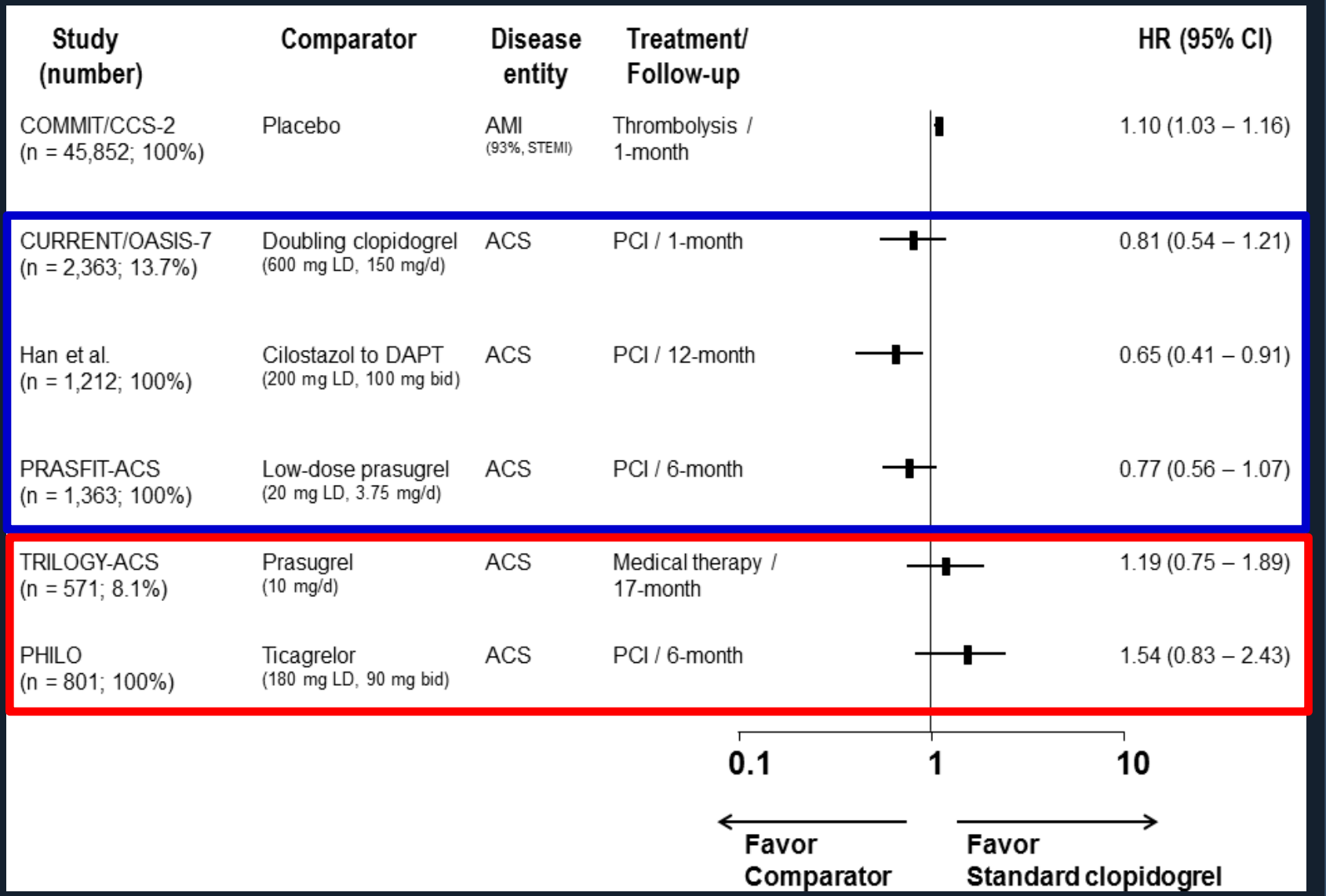
“East Asian Paradox”; Different Therapeutic Zone



MEA:	0U	30U	60U	200U	
LTA:	0%	35%	70%	100%	(20μM ADP)
VASP:	0%	35%	70%	100%	
VerifyNow:	0	130	275	550 PRU	

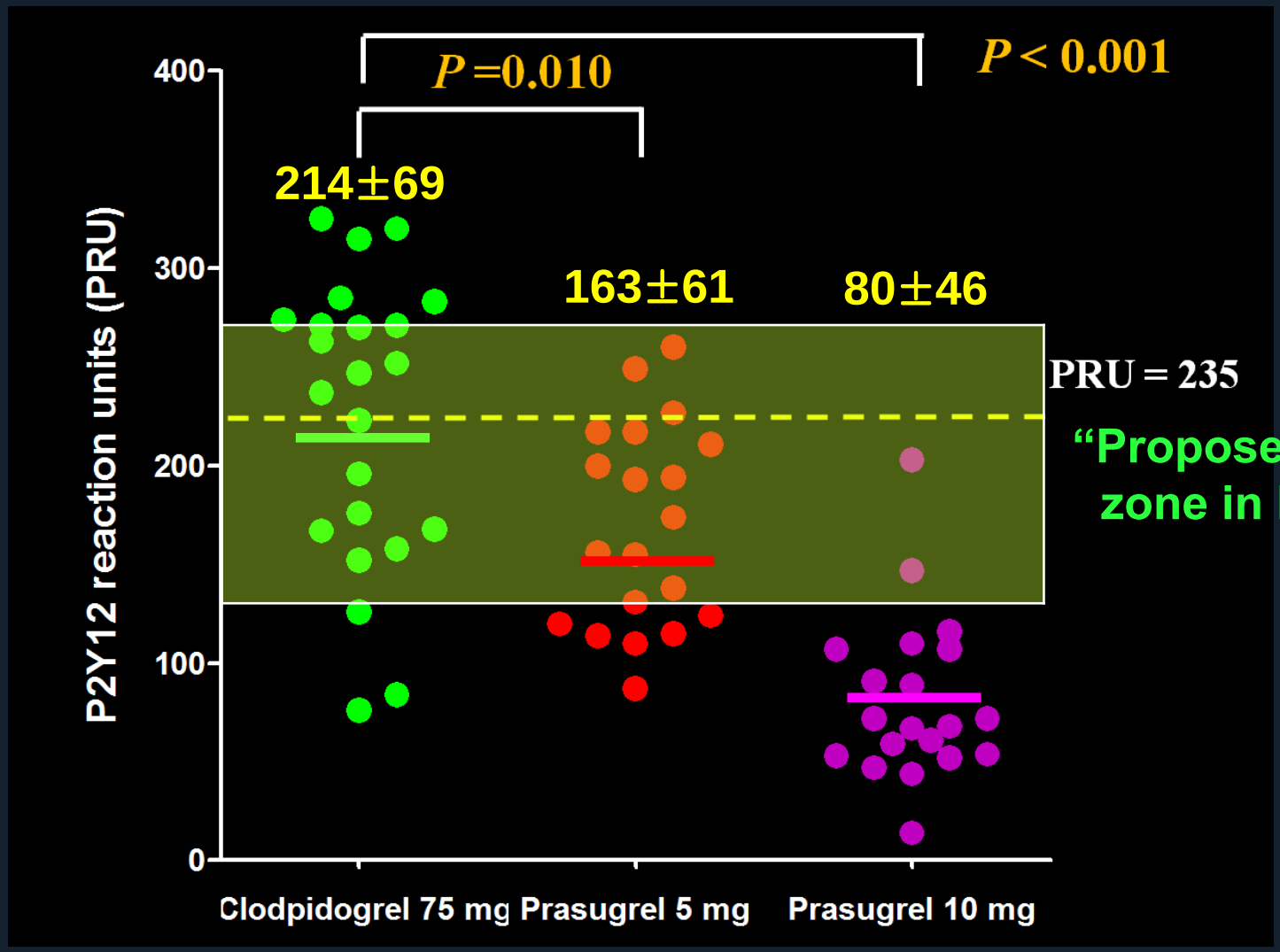
RCTs: Comparator vs. Standard-dose Clopidogrel

East Asian ACS Patients



Jeong YH. *Curr Cardiol Report* 2014;In press.

PD Date on Prasugrel (5 vs. 10 mg/d) vs. Clopidogrel (75 mg/d) in Korean Patients



Jin HY, et al. Korean Heart Autumn Symposium 2012