The Secrets Behind Bleeding in PCI Patients

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Disclosure

Research Grants/Support

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- Haemonetics
- ITC
- Han-Mi Pharmaceutical
- KSIC
- GNUH

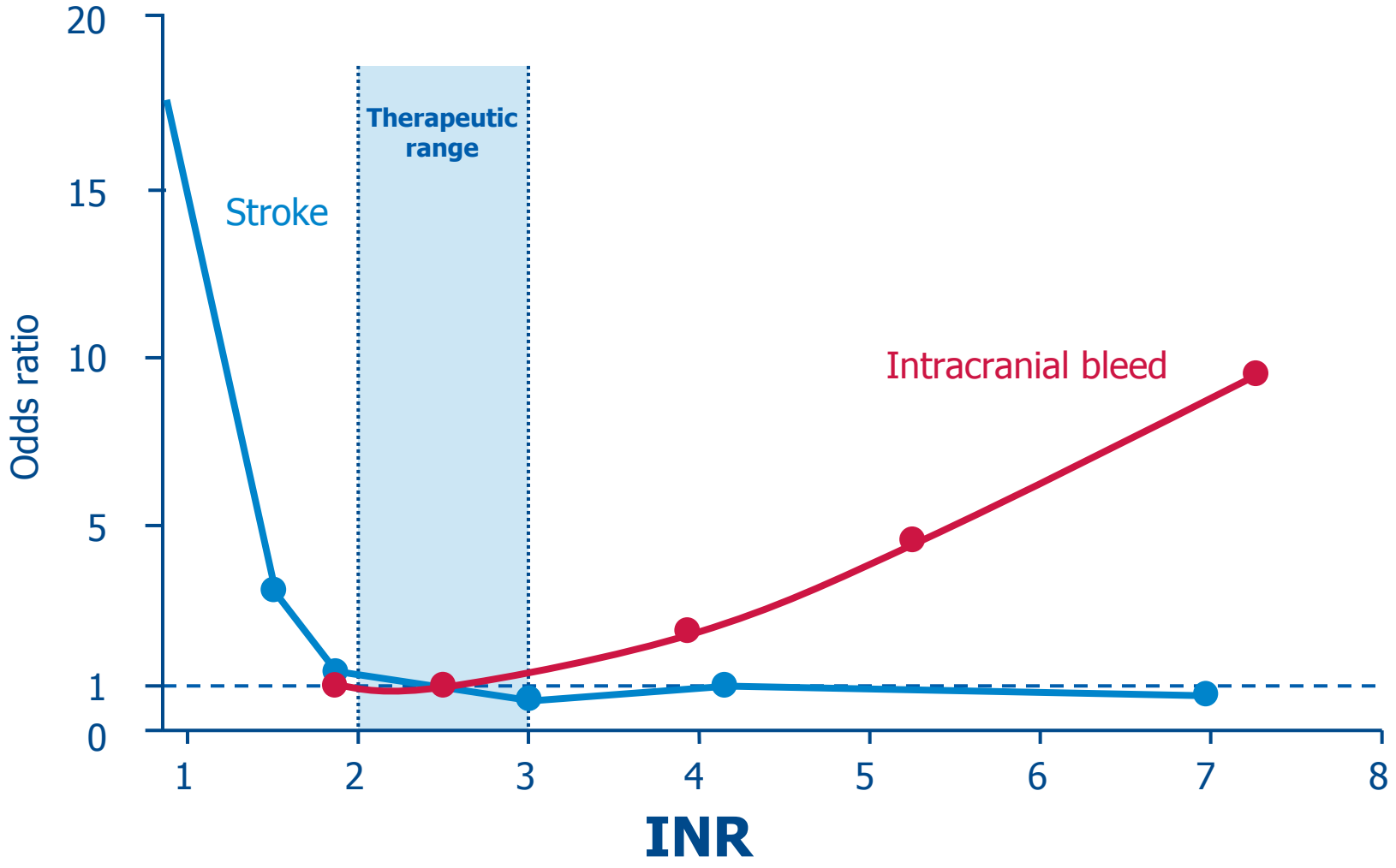
Honoraria/Consulting

- Astrazeneca
- Daiichi Sankyo Inc
- Sanofi-Aventis
- Otsuka
- Haemonetics
- Han-Mi Pharmaceutical

Q1. Is Platelet Reactivity Related With Bleeding ?

- **Yes**
- **No**

Warfarin: Narrow Therapeutic Window



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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

Current Platelet Function Testing

Chrono-log impedance aggregometry

VerifyNow™

Plateletworks™

Multiplate®

PFA-100®

Born aggregation

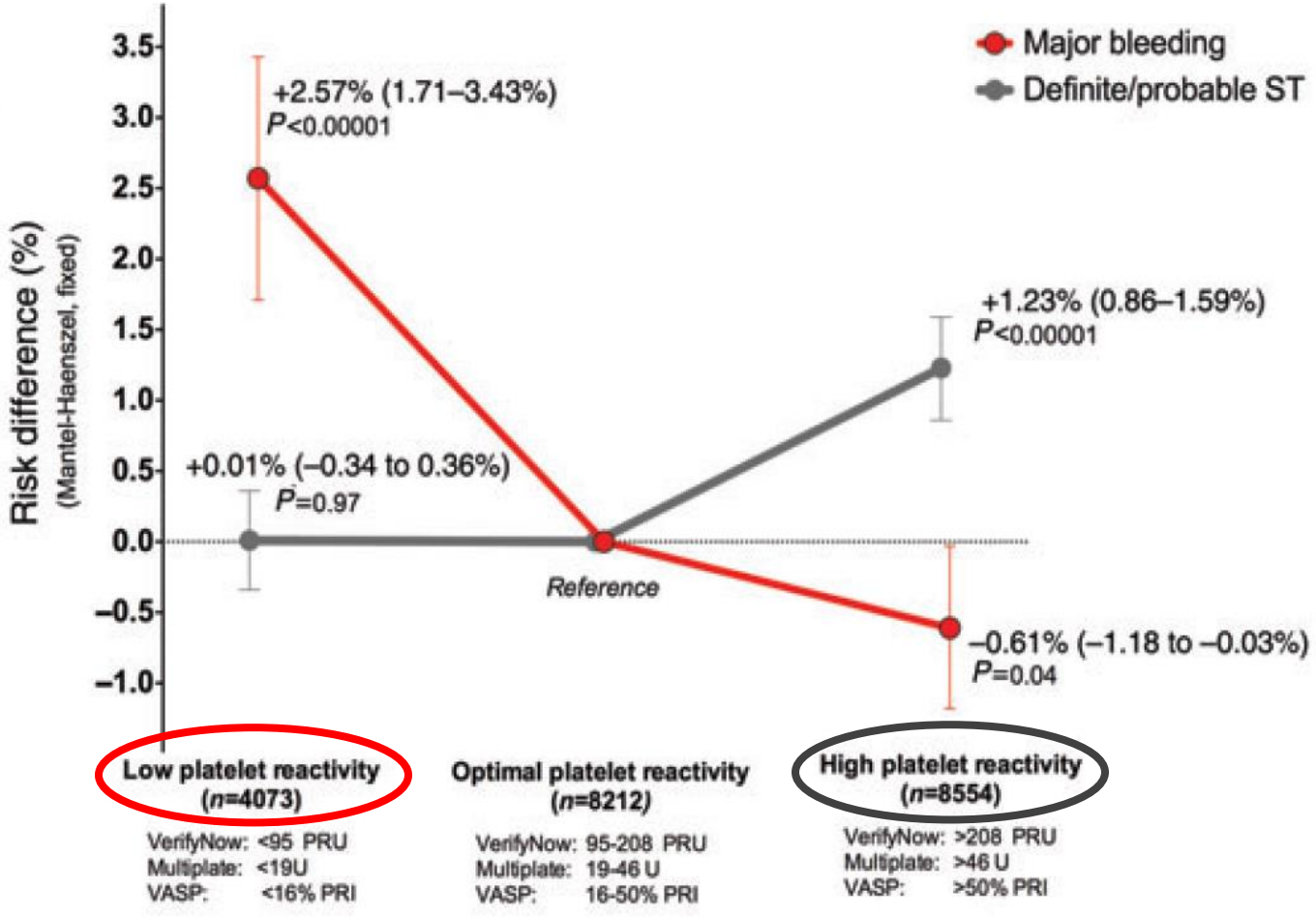
Flow cytometry

The majority of currently available assays:

- Evaluate platelet function in the presence of an anticoagulant
  - Completely ignore the influence of coagulation on thrombus formation and its relation to clinical event occurrence
- Largely measure platelet function in isolation, ignoring the contribution of platelet-fibrin interaction characteristics

Therapeutic Window Between HPR & LPR

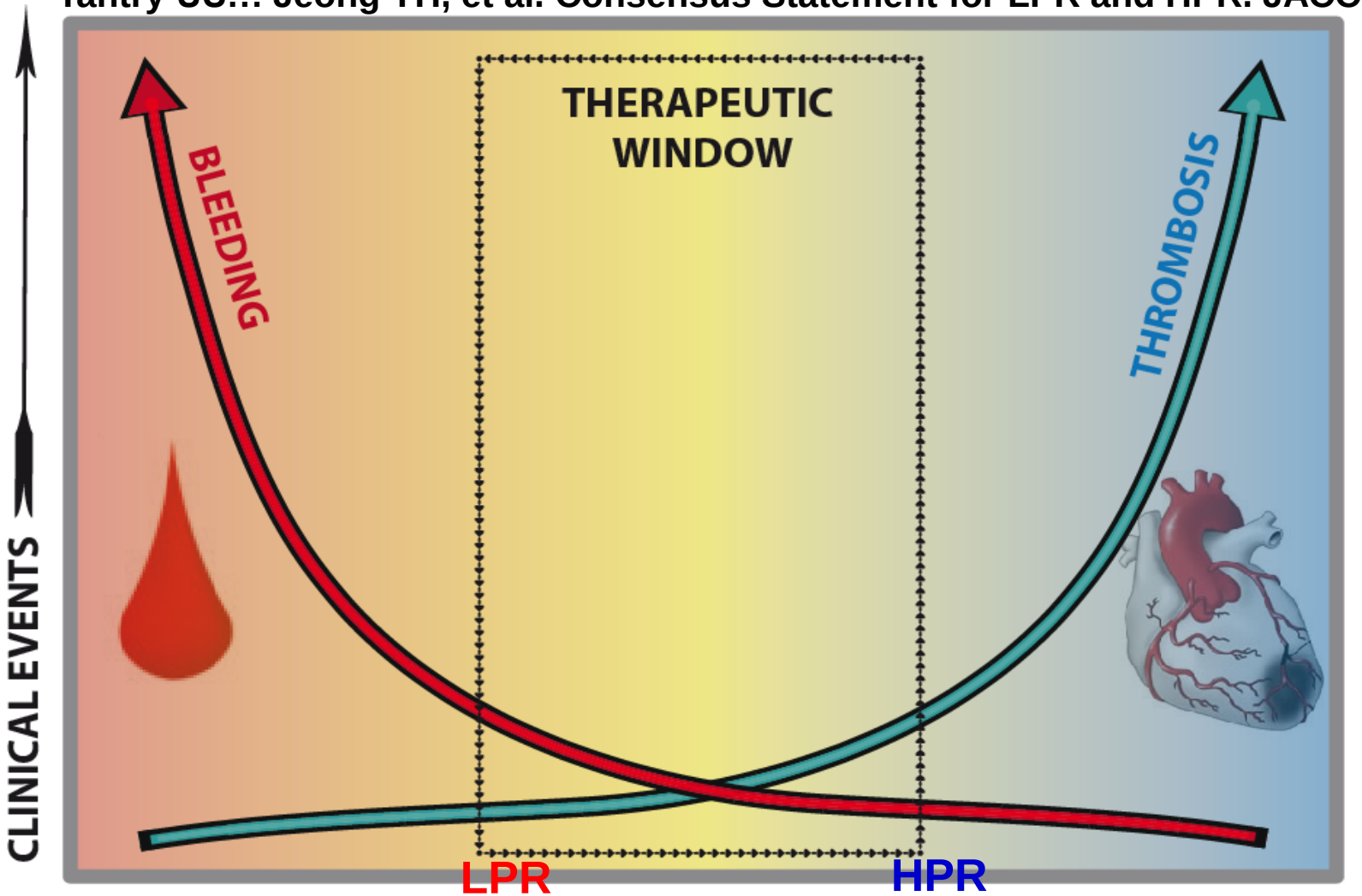
Collaborative meta-analysis (n = 20,839): 17 clinical trials including Western population only



Aradi D, et al. *Eur Heart J* 2015.: Tantry US, et al. JACC 2013.

Therapeutic Window of PLT Reactivity

Tantry US… Jeong YH, et al. Consensus Statement for LPR and HPR. JACC 2013.



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

Q2. Prevalence of Bleeding on 1-mo DAPT (ASP+CLPD) ?

- < 5%
- 5-10%
- 10-20%
- 20-30%

Previous Studies Underestimate The Risk of Bleeding

- **Prevalence of bleeding**
  - < 5% during 30 days
- **Reasons**
  - Retrospective data collection
  - Focusing on major bleeding only
  - Different and non-standardized definitions
  - Initially excluded high-risk patients for bleeding

Bleeding Academic Research Consortium (BARC) Definition

Type 1 (nuisance)	- bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a healthcare professional - may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a healthcare professional
Type 2 (Superficial)	any overt, actionable sign of hemorrhage (eg, more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4, or 5 but does meet at least one of the following criteria (1) requiring nonsurgical, medical intervention by a healthcare professional (2) leading to hospitalization or increased level of care (3) prompting evaluation
Type 3a (TIMI minor)	- Overt bleeding plus hemoglobin drop of 3 to 5 g/dL - Any transfusion with overt bleeding
Type 3b (TIMI major)	- Overt bleeding plus hemoglobin drop 5 g/dL - Cardiac tamponade - Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid) - Bleeding requiring intravenous vasoactive agents

Prospective & Dedicated Studies Reports More Bleedings

PCI-treated patients on DAPT (ASP + CLPD): post-discharge

TRIUMPH registry (n = 3,560)

Cohort	AMI (USA)
BARC 1 bleeding	24.3% (1 mo.)
BARC 1 bleeding	37.5% (12 mo.)

Amin AP, et al. *JACC* 2013;61:2130-8.

ACCEL-BLEEDING registry (n = 301)

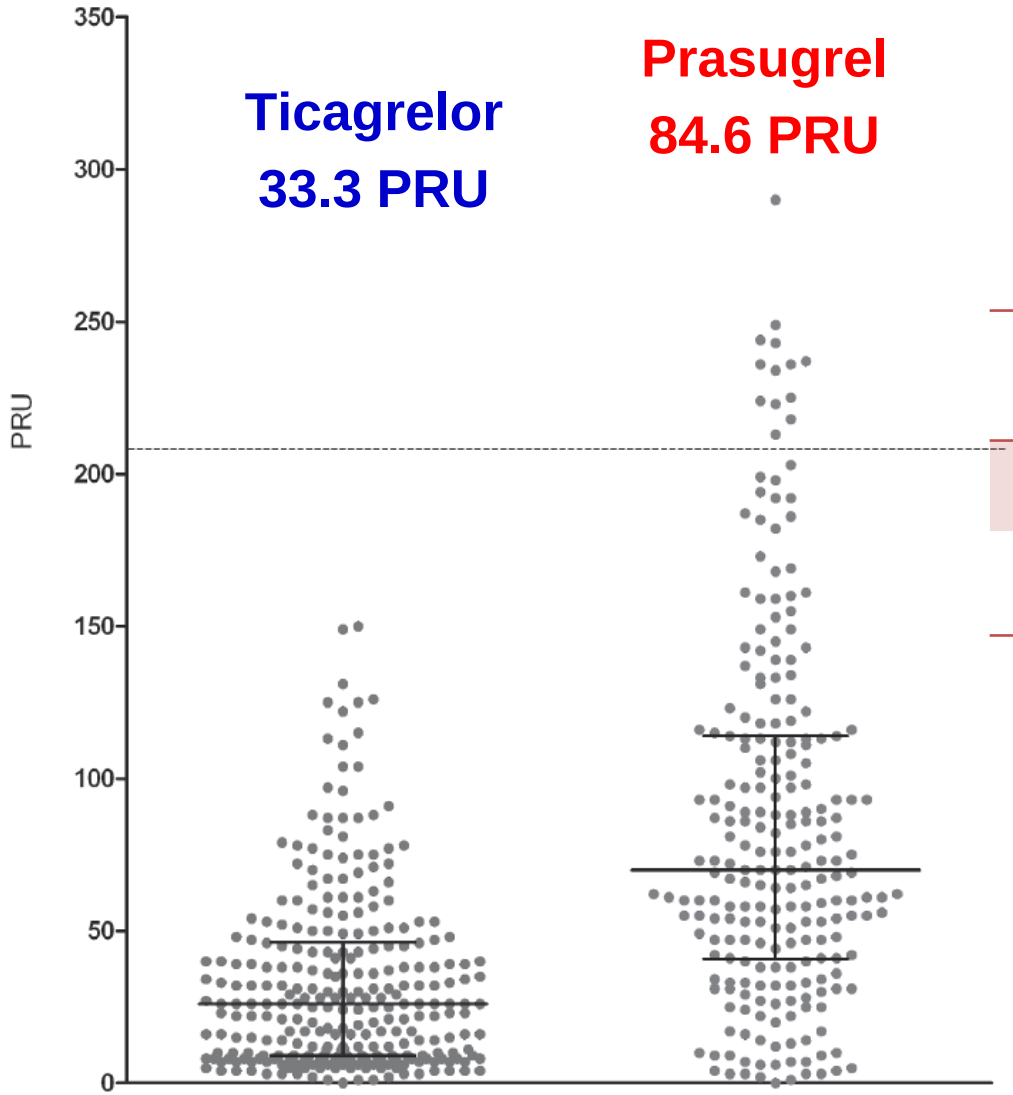
Cohort	All-comer (Korea)
BARC 1 bleeding	24.6% (1 mo.)
BARC 2 bleeding	7.0% (1 mo.)

Kwon TJ, Jeong YH, et al. *T&H* 2016;on-line.

Q3. Cutoff of Bleeding During *Ticagrelor* vs. *Thienopyridine* ?

- **Higher**
- **Similar**
- **Lower**

Ticagrelor vs. Prasugrel: 1-mo Maintenance Tx



	TICA	PRAS	p
BARC 1	36.7%	28.2%	0.047
BARC 2	2.1%	2.9%	0.8

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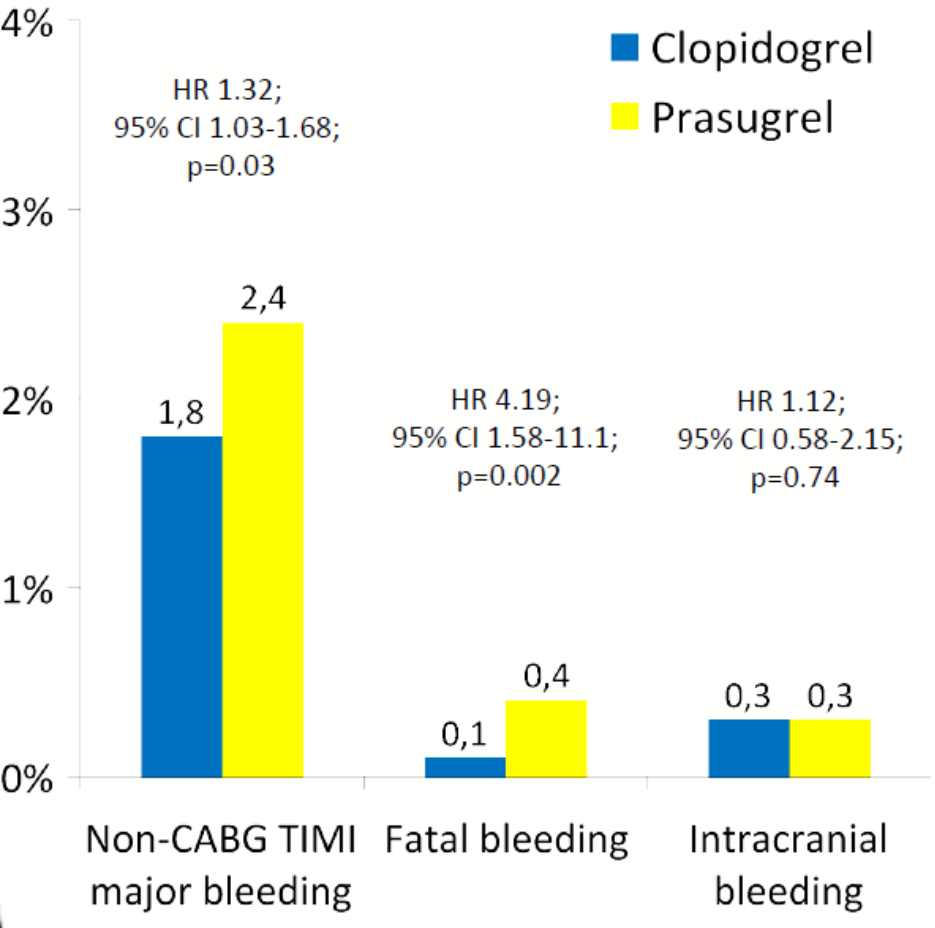
Alexopoulos D, et al. *Thromb Haemost* 2014;12.

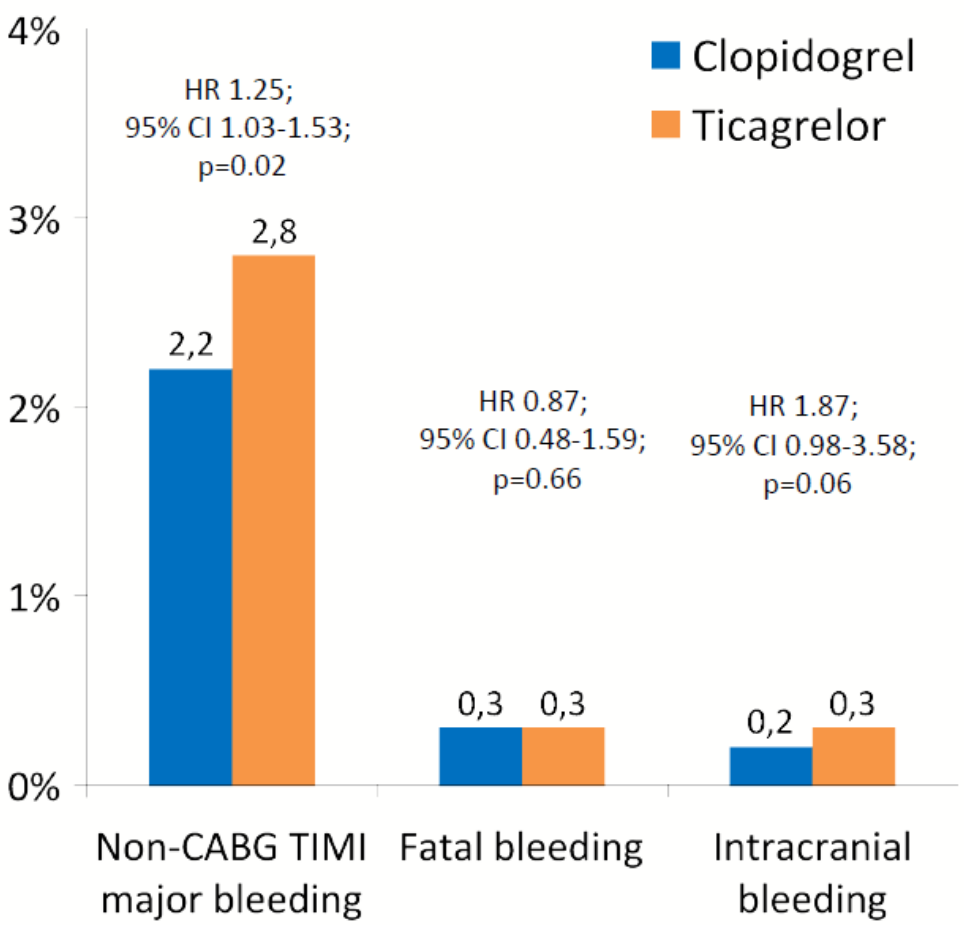
Bleeding on Prasugrel vs. Ticagrelor in ACS Pts

TRITON-TIMI 38



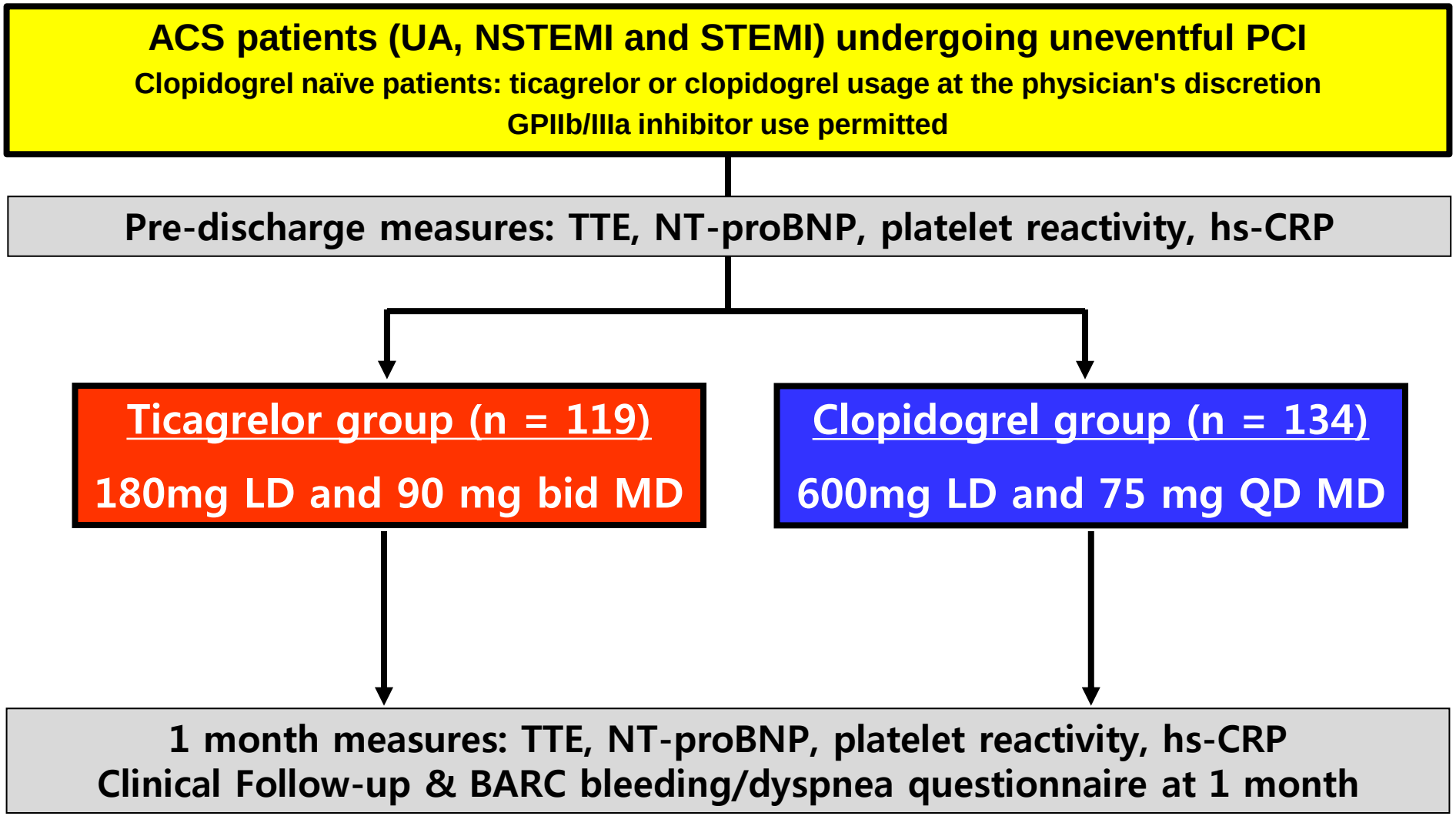
Wiviott et al. N Engl J Med 2007;357:2001-15.

PLATO



Wallentin et al. N Engl J Med 2009;361:1045-57.

GNUH Registry



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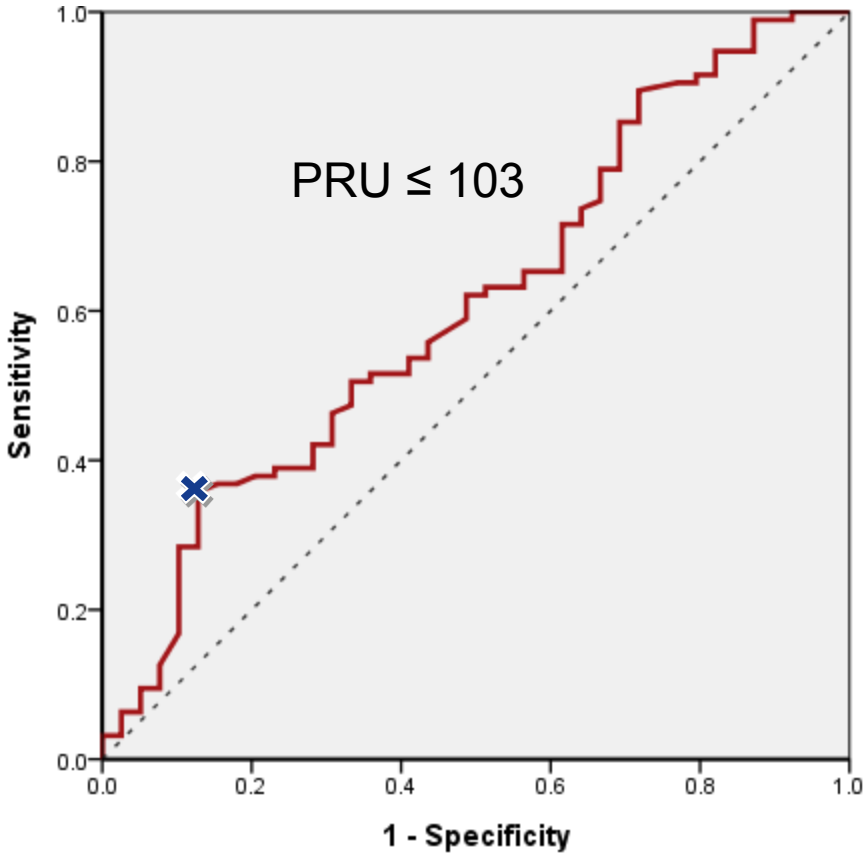
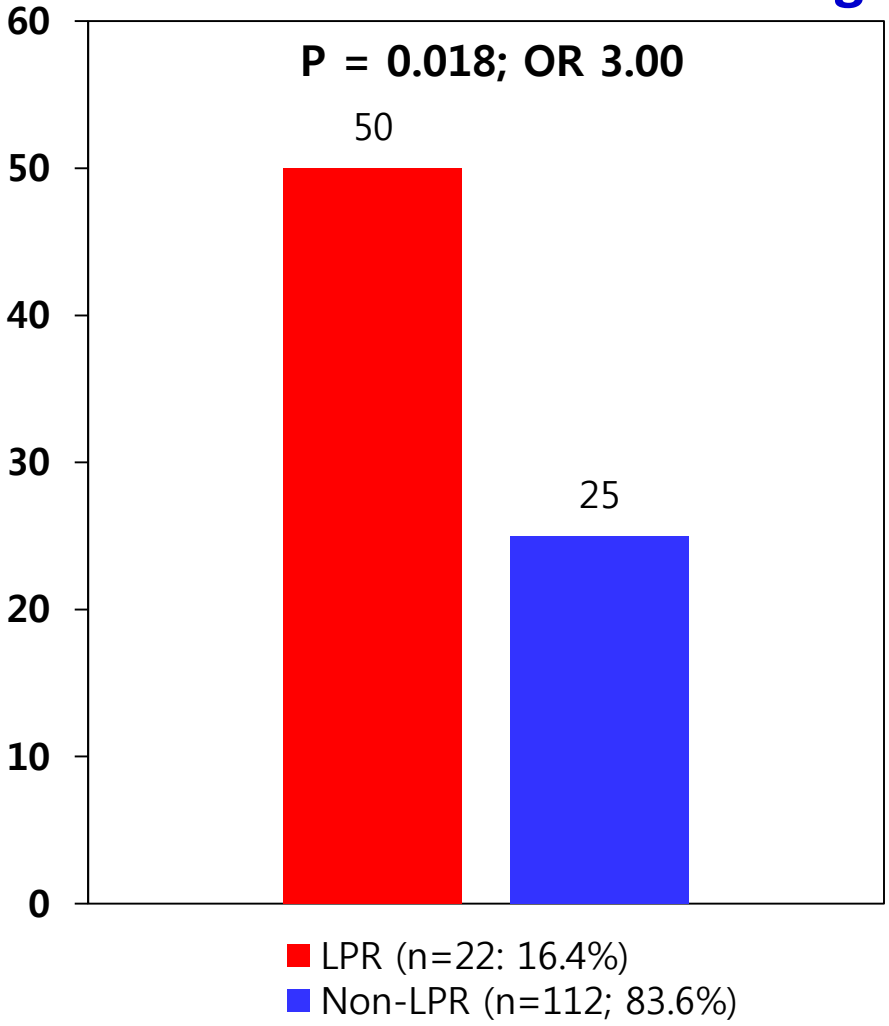
Kang MG, et al. *Unpublished data*.

Clopidogrel: LPR Cutoff for BARC Bleeding



AUC: 0.610
95% CI: 0.505 - 0.715
Sensitivity: 64.2%, Specificity: 87.2%
P = 0.046

Prevalence of BARC bleeding



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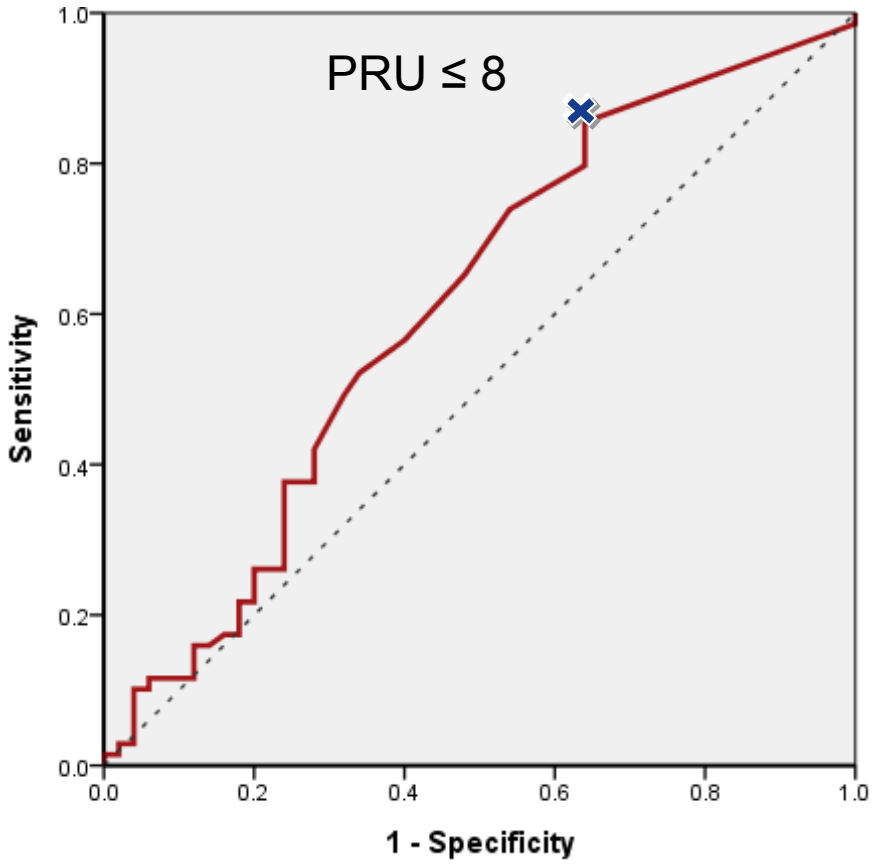
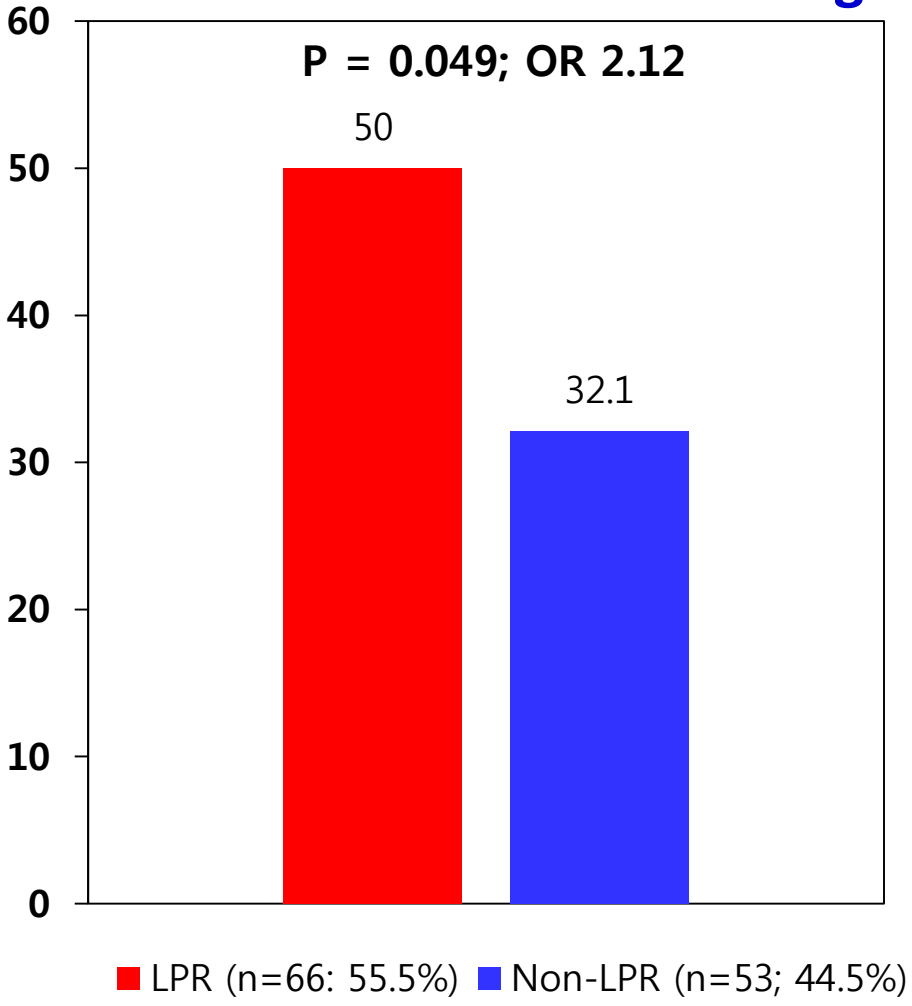
Ticagrelor: LPR Cutoff for BARC Bleeding



AUC: 0.609
95% CI: 0.504 - 0.714
Sensitivity: 85.5%, Specificity: 64.0%,
P = 0.042

Prevalence of BARC bleeding



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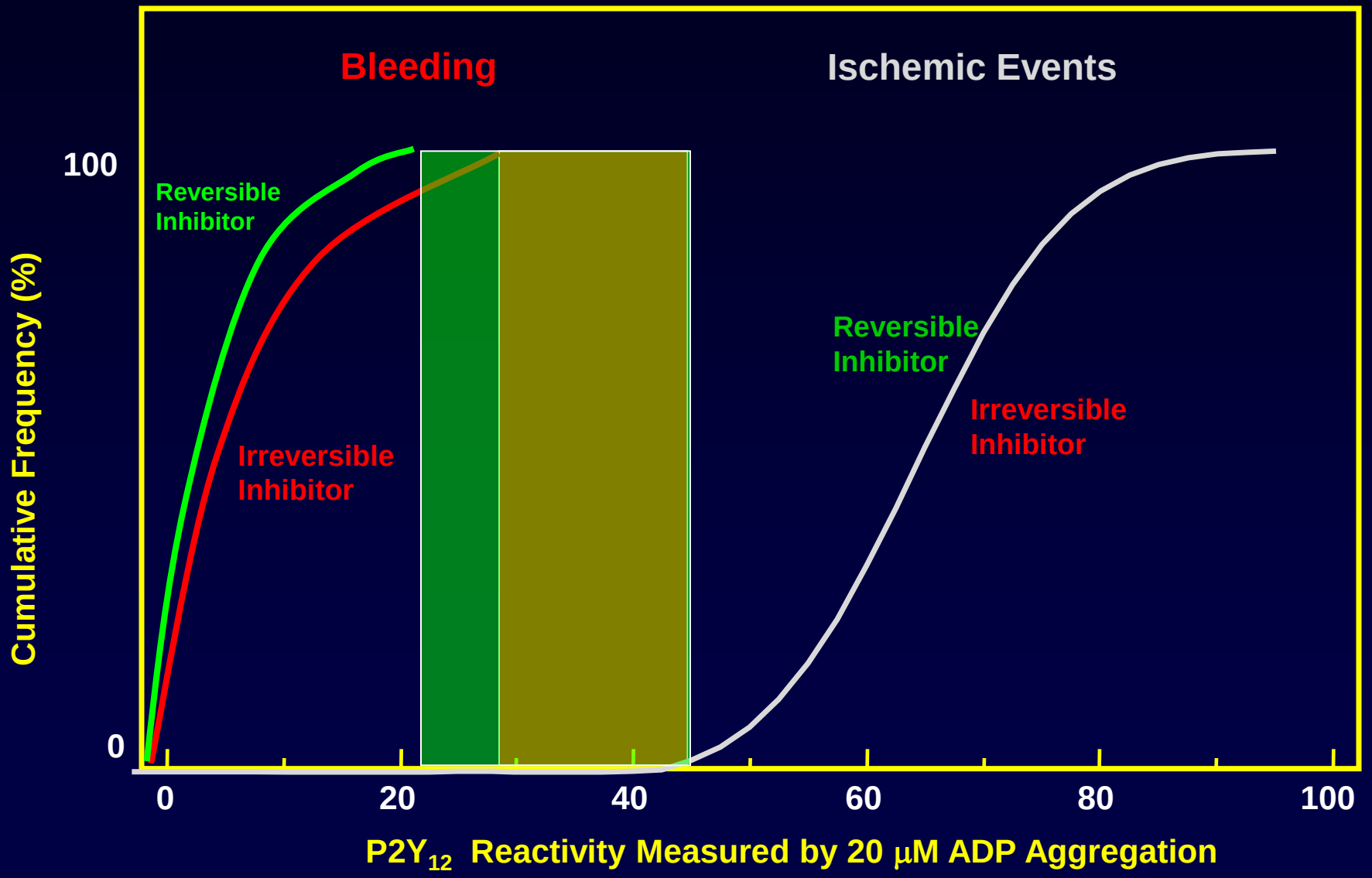
Ticagrelor: Wider Therapeutic Window



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

Q4. Risk of Bleeding in *ACS* vs. *Non-ACS* on DAPT ?

- **Higher**
- **Similar**
- **Lower**

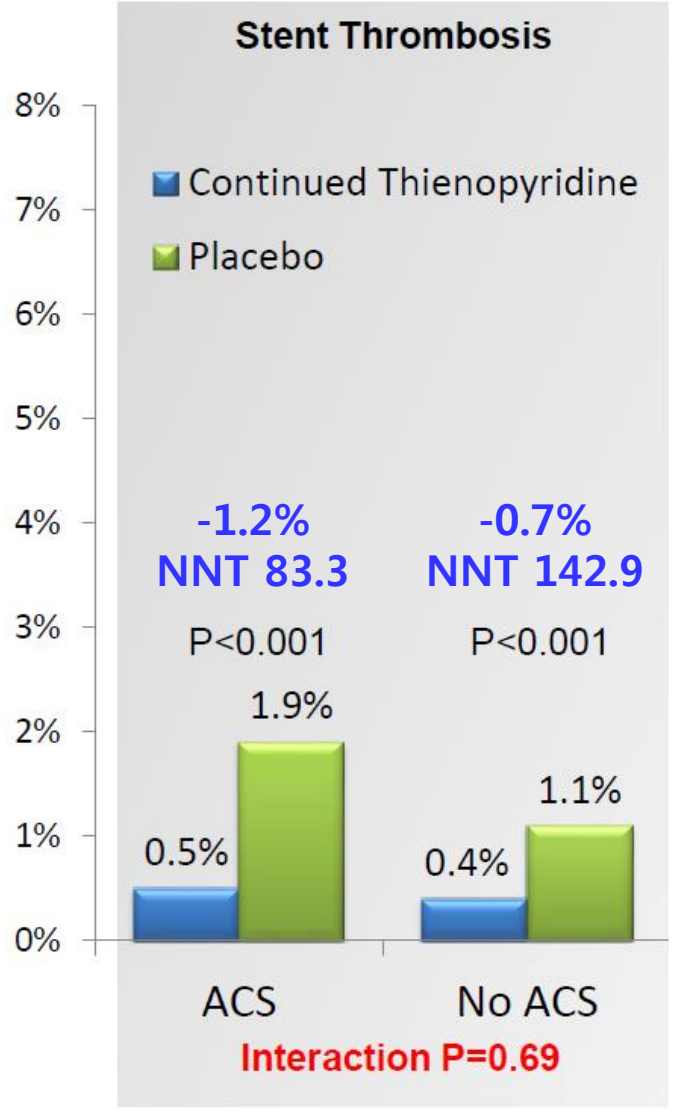
PRU Criteria: 1–year Event Rate in SAP vs. ACS

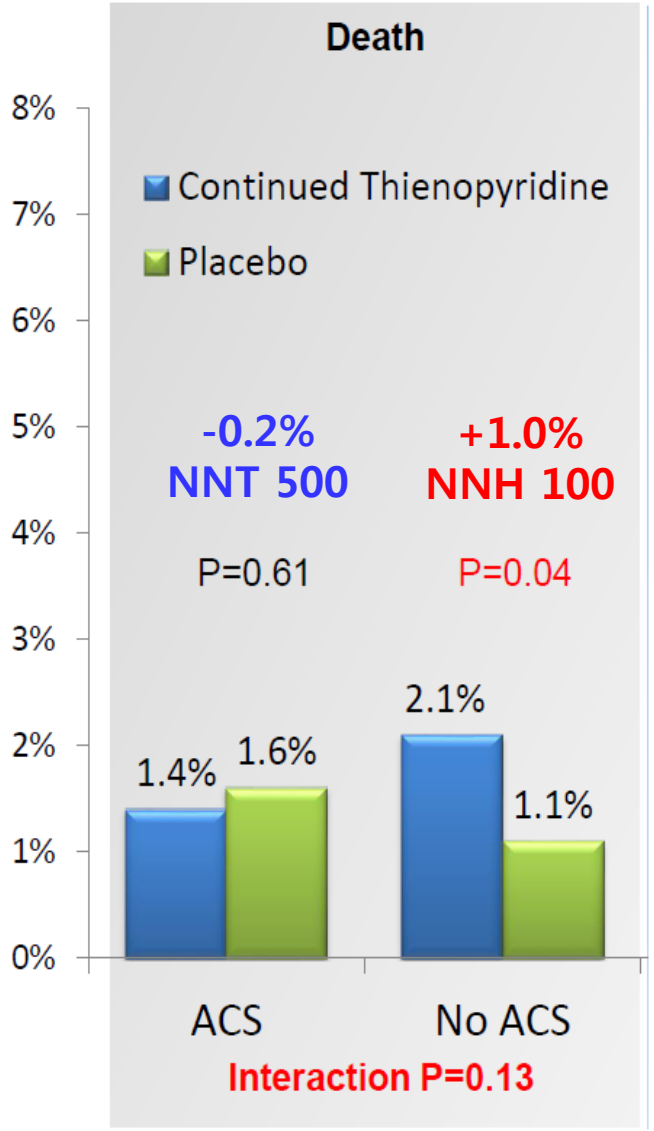
ADAPT-DES registry

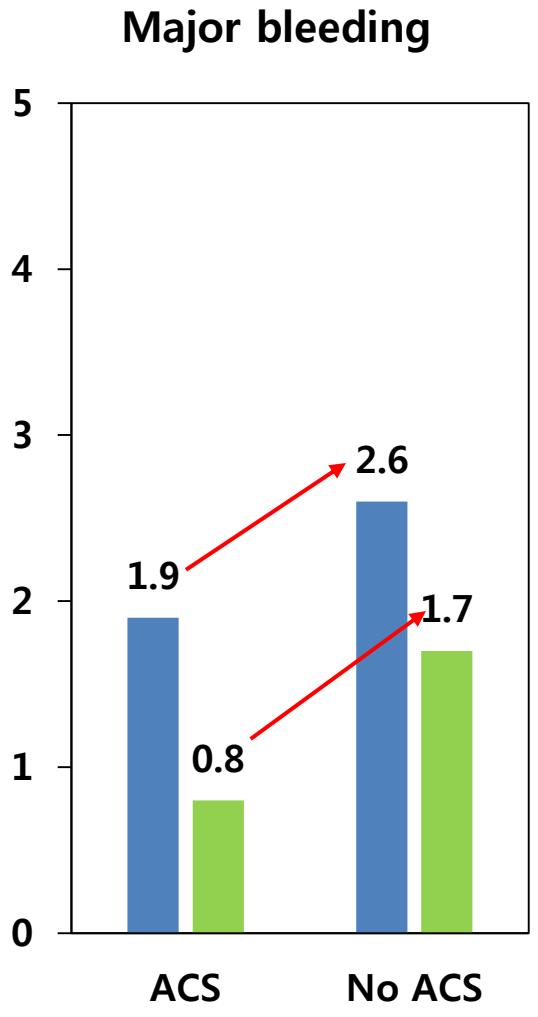
	PRU > 208	PRU ≤ 208	p-value
ACS	**N = 1,979**	**N = 2,369**	
ST, definite or probable	**1.8%**	**0.6%**	**0.0002**
MI	**4.3%**	**3.0%**	**0.003**
Death	2.5%	1.6%	0.05
Clinically relevant bleeding	4.6%	5.1%	0.44
Stable AP	**N = 1,631**	**N = 2,470**	
ST, definite or probable	0.6%	0.4%	0.34
MI	1.2%	0.8%	0.25
Death	2.3%	1.3%	0.02
Clinically relevant bleeding	**6.6%**	**8.1%**	**0.07**

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

Treatment Effect According to ACS Status
Primary Endpoints at 12-30 Months
All Randomized Subjects (N=11648)



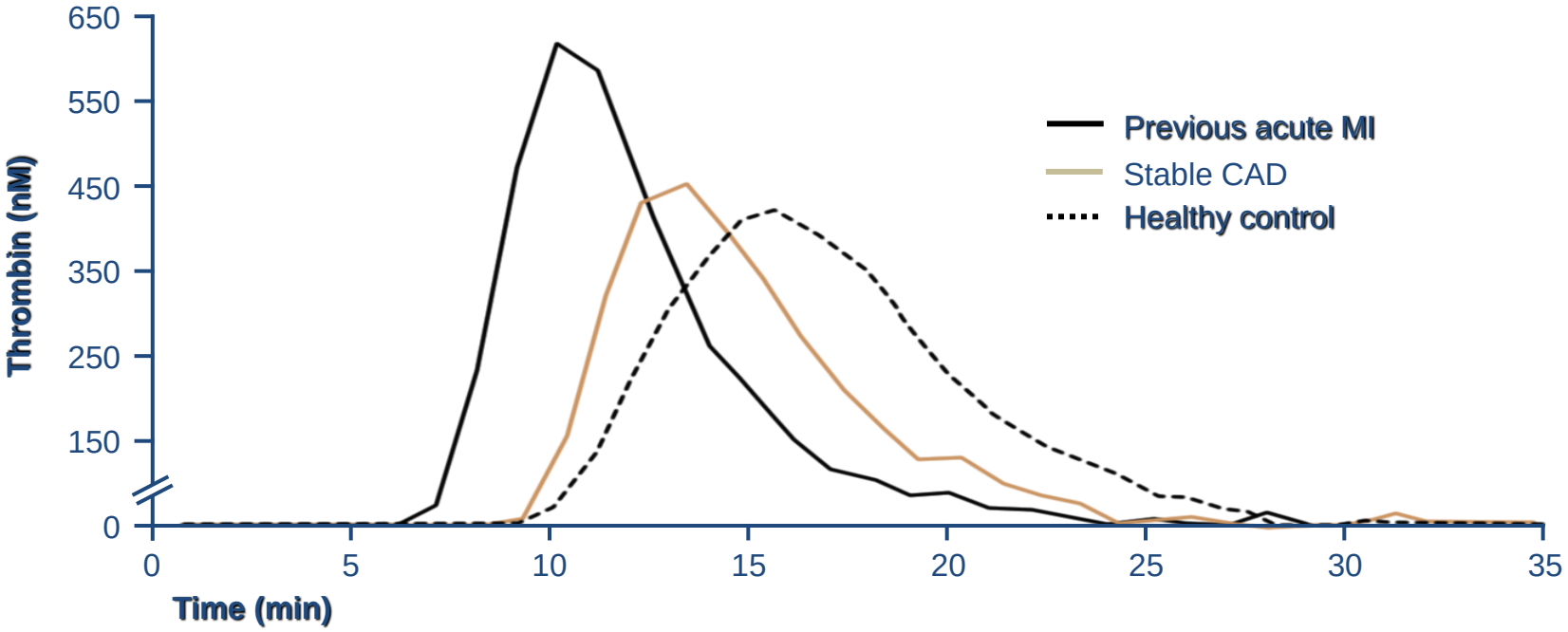




Thrombin Generation Across Disease

Faster & greater thrombin response in ACS persists “long-term”

- Study in AMI patients (n=60), stable CAD (n=35) or healthy controls (n=15)
- Thrombin generation assessed by fluorogenic assay, 3–11 months (mean 6 months) after initial diagnosis



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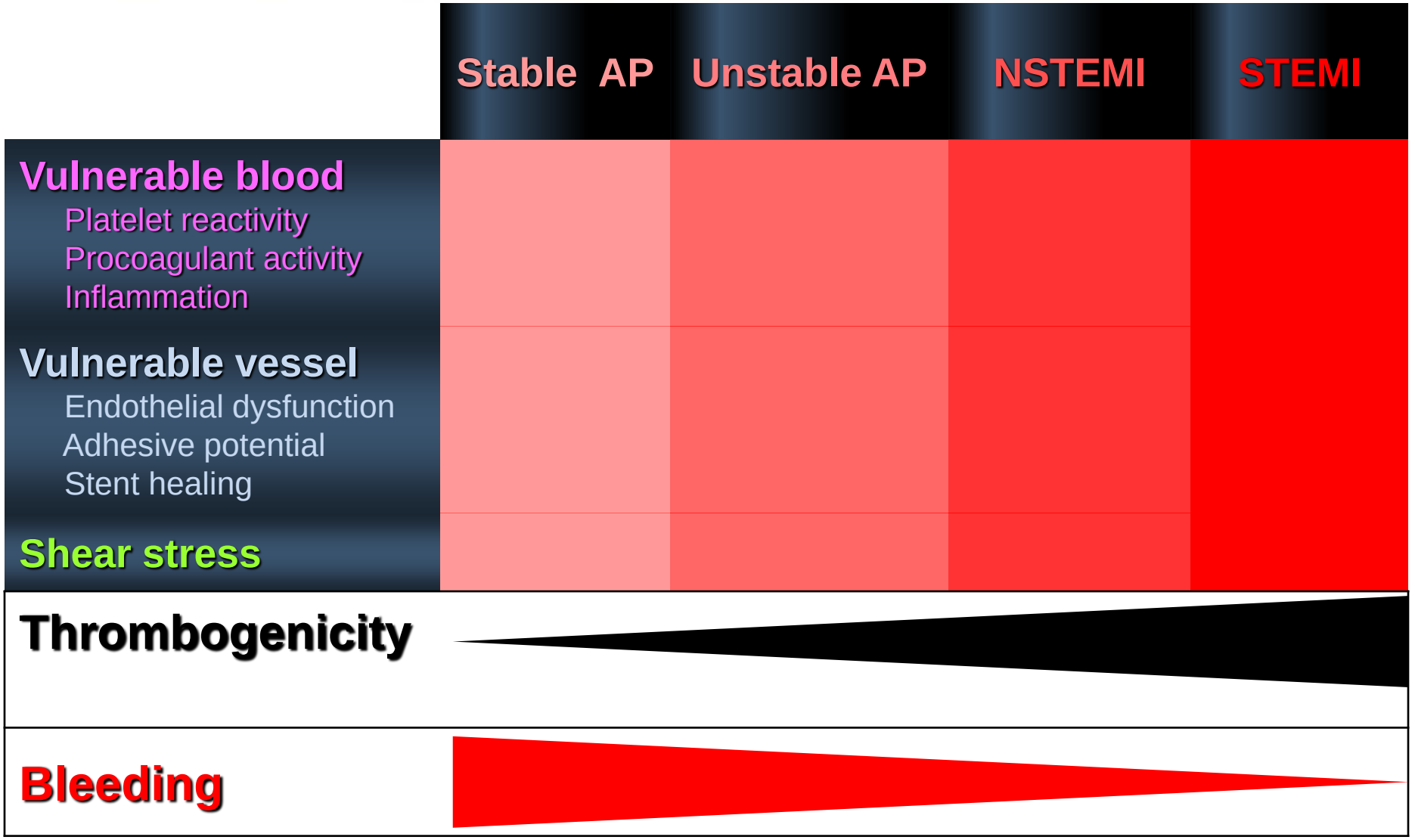
Orbe et al. Thromb Haemost 2008;99:382–7.

Disease Activity Determines Thrombogenicity



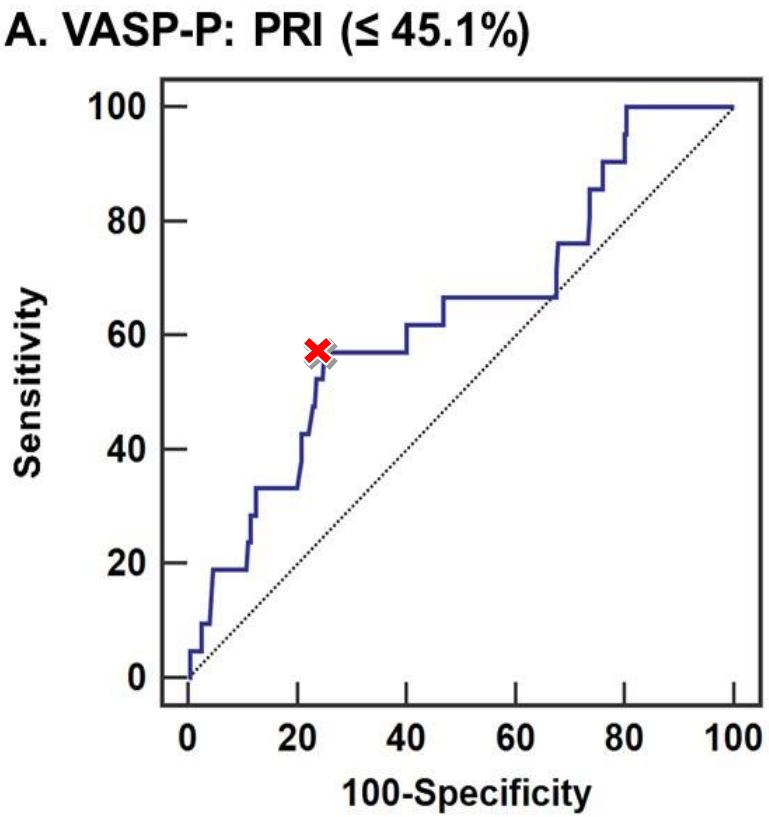
Gurbel P, et al. *Eur Heart J* 2014;35:951-4.

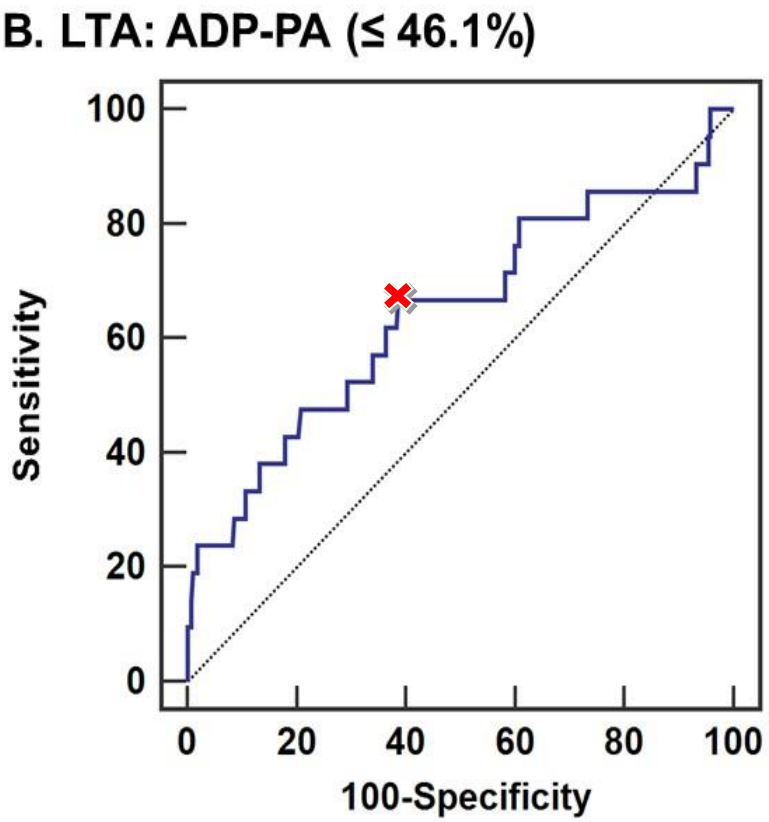
Q5. Cutoff of Bleeding in *East Asians* vs. *Caucasians* ?

- **Higher**
- **Similar**
- **Lower**

The Cutoffs of Bleeding in East Asians

ACCEL-BLEEDING: PCI-treated Pts on DAPT (n = 301)





Caucasians **VASP ≤ 16%** **ADP-LTA ≤ 31%**

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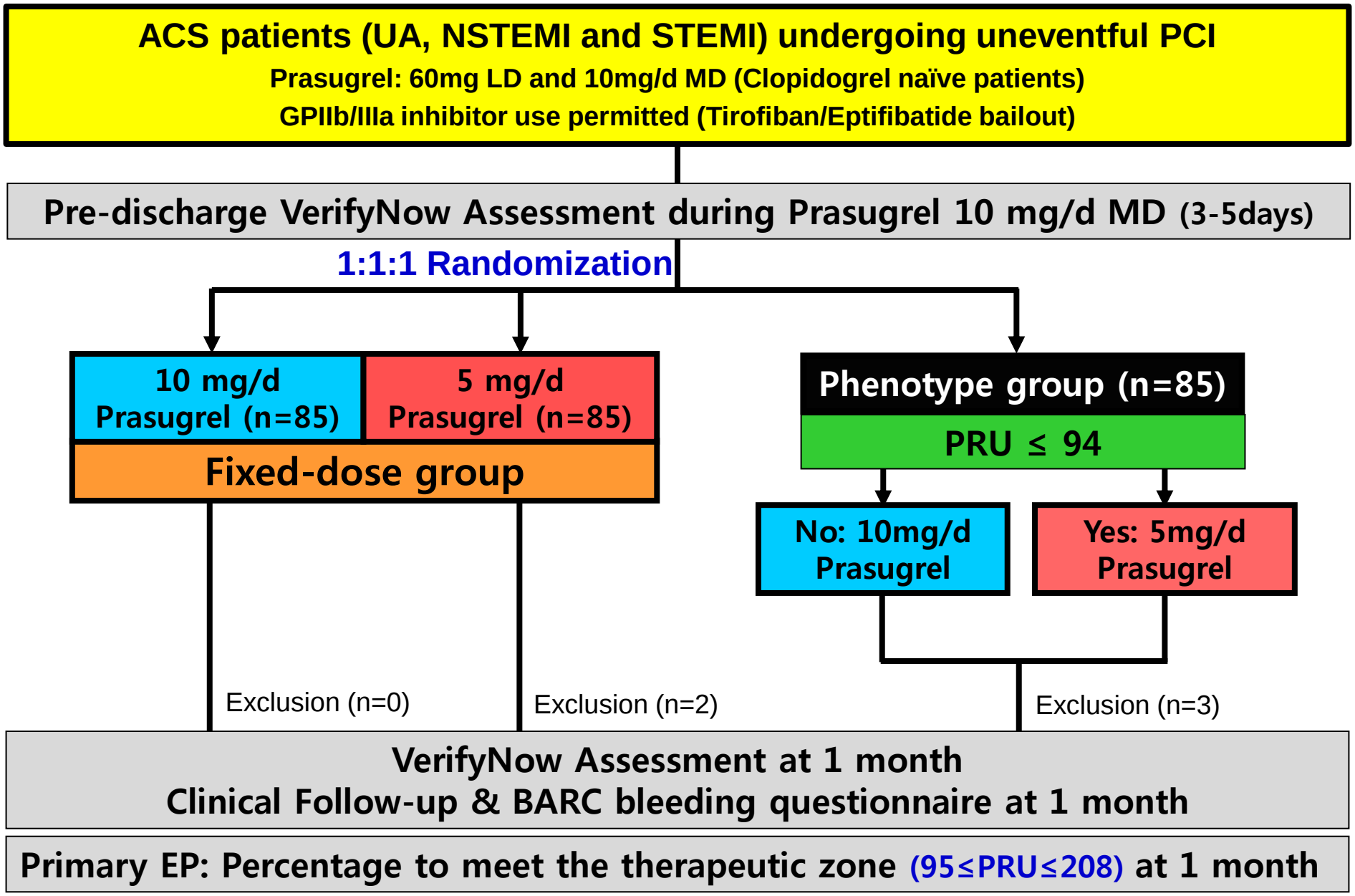
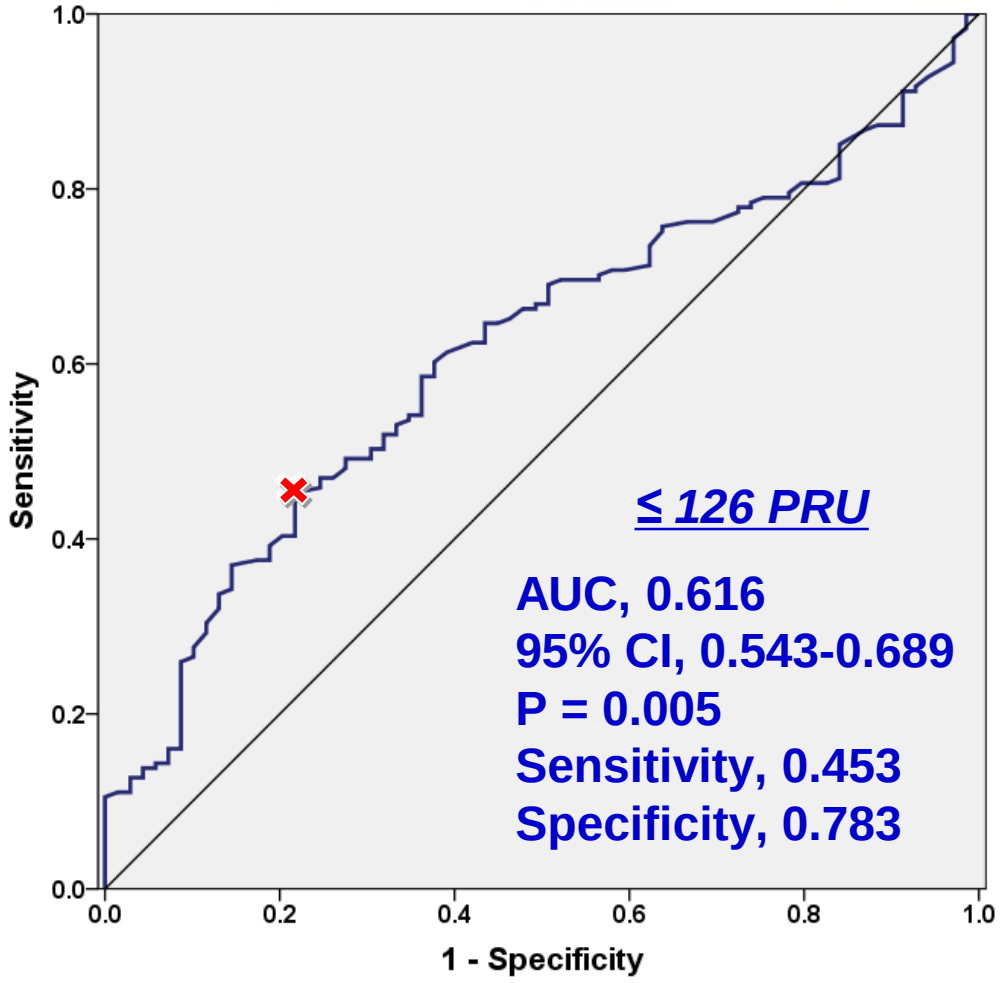
Kwon TJ, Jeong YH, et al. *T&H* 2016;on-line.: Tantry US, et al. JACC 2013.

A-MATCH Trial

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



The Cutoffs of BARC Bleeding



Caucasians **PRU ≤ 85**

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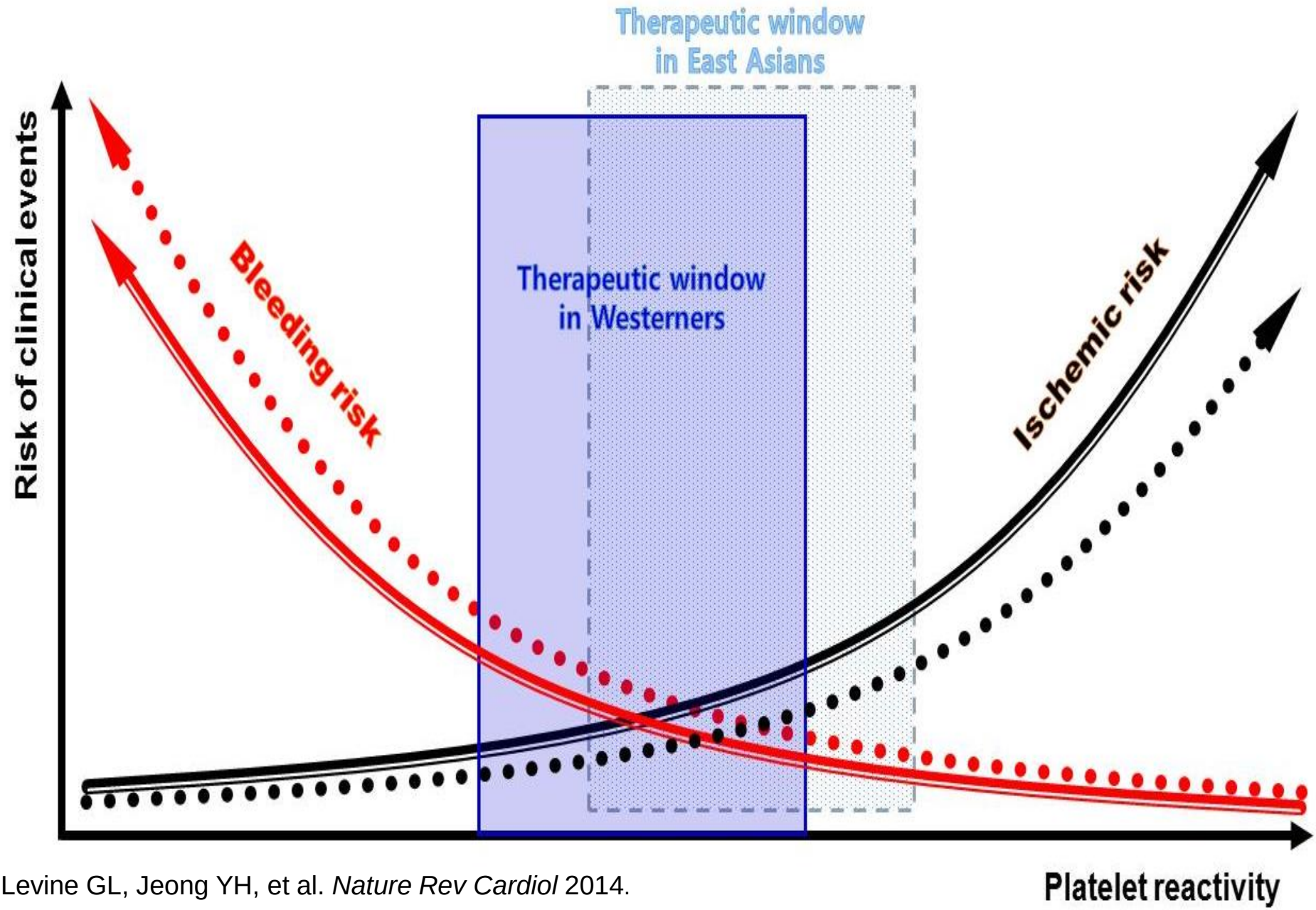
Tantry US, et al. JACC 2013.

Optimal Intensity of $P2Y_{12}$ Inhibitor



Levine GL, Jeong YH, et al. *Nature Rev Cardiol* 2014.

Q6. Clinical Impact of Minor or Nuisance Bleeding ?

- **Drug discontinuation**
- **Anxiety or depression**
- **Rehospitalization**
- **↑ MACE**

Prevalence of Premature DAPT Discontinuation

PCI-treated patients on DAPT: post-discharge

Italian registry (n = 396)

Cohort	ACS (Italy)
BARC 1 or 2 bleeding	15.3%
No bleeding	4.0%
P value	**0.03**

Armero S, et al. *Am J Cardiol* 2011.

ACCEL-BLEEDING registry (n = 301)

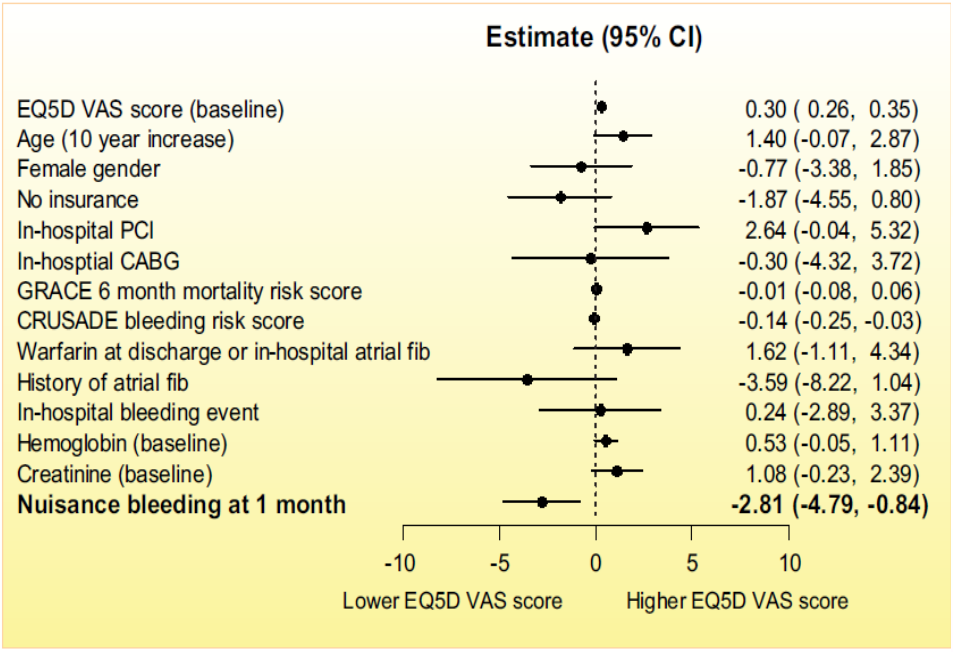
Cohort	All-comer (Korea)
BARC 1 or 2 bleeding	11.4%
BARC 2 bleeding	4.7%
P value	**0.035**

Kwon TJ, Jeong YH, et al. *T&H* 2016;on-line.

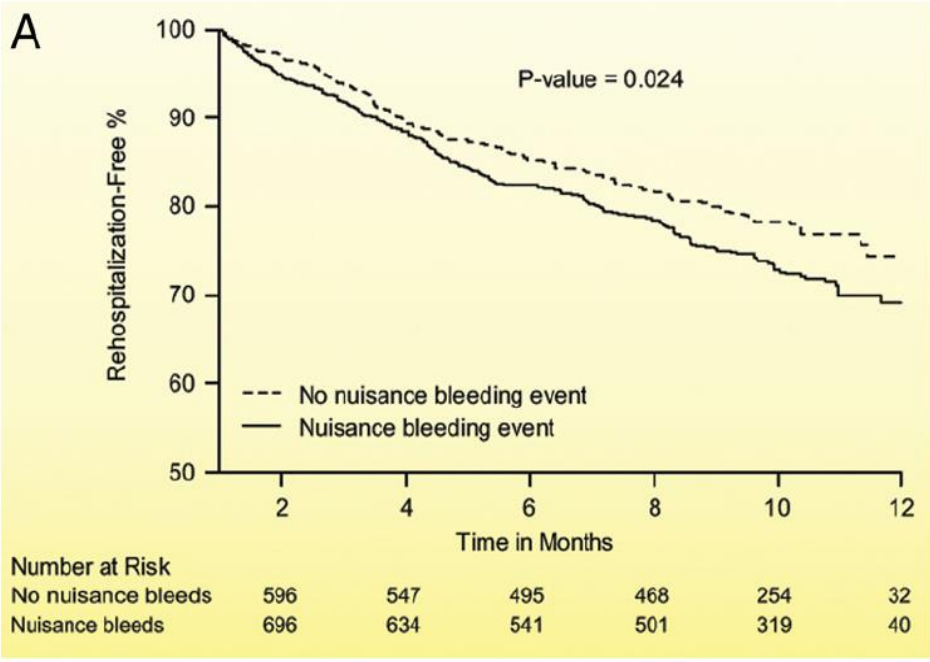
Clinical Impact of Nuisance Bleeding

TRIUMPH registry (n = 3,560)
PCI-treated patients on DAPT: post-discharge

Quality of Life (EQ5D VAS)



Rehospitalization



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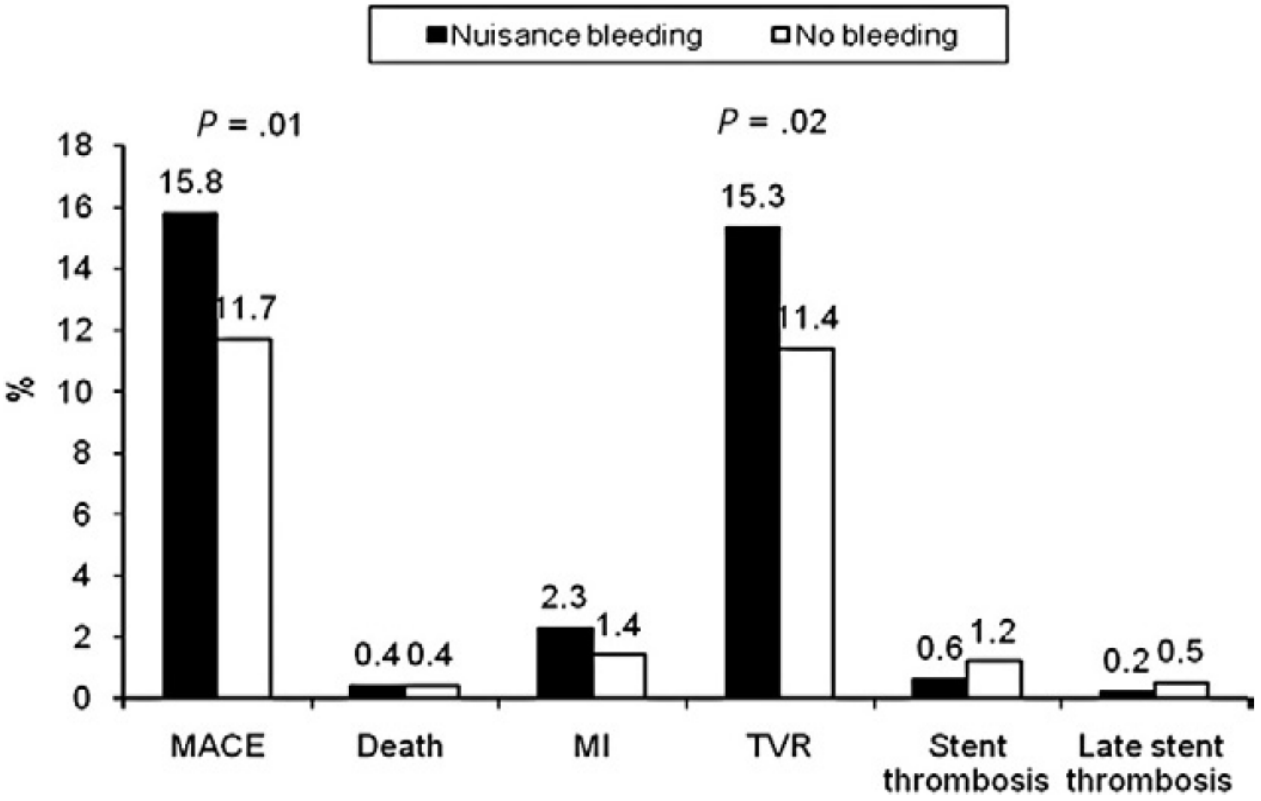
Amin AP, et al. *JACC* 2013;61:2130-8.

Clinical Impact of Nuisance Bleeding on MACE

Washington Hospital Experience (n = 2,948): DES Pts

- 2-yr clinical outcome: nuisance bleed (n= 812) vs. no bleed (n = 1999)



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Ben-Dor I, et al. *Am Heart J* 2010;159:871-5.

Q7. Impact of *Major bleeding* vs. *MI* on Mortality ?

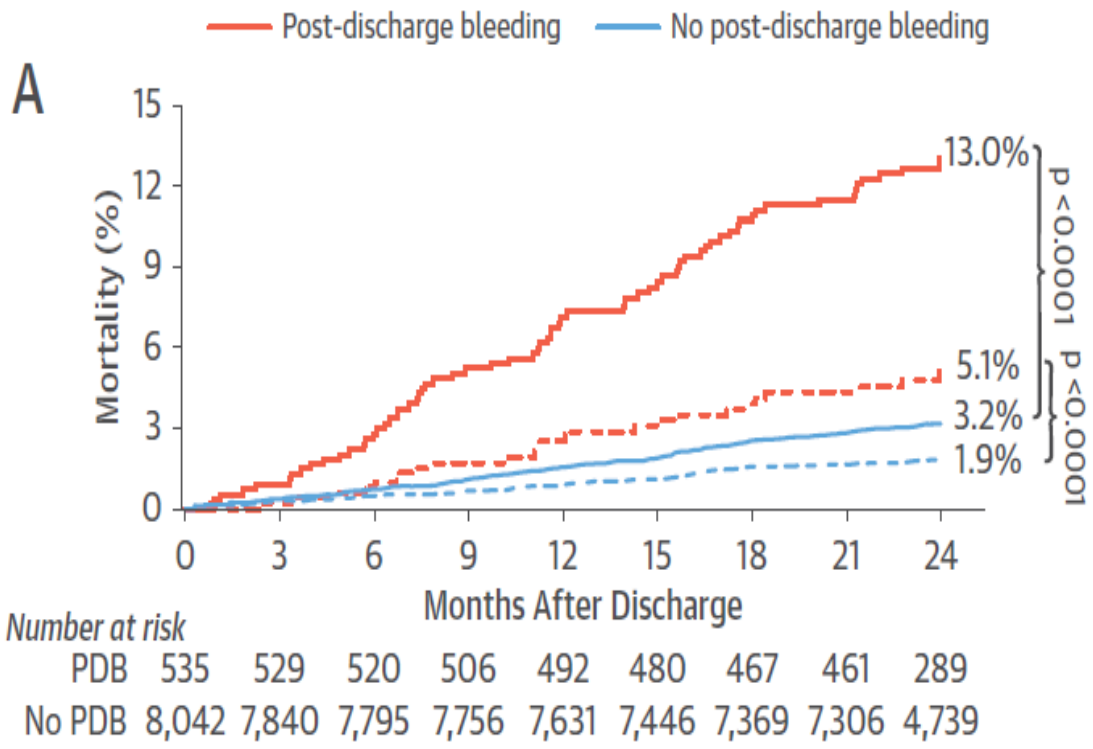
- **Higher**
- **Similar**
- **Lower**

Impact of Post-discharge Bleeding After PCI

ADAPT-DES registry (n = 8,582): DES Pts

- PD bleeding (n= 535; 6.2%) vs. no PD bleeding (n = 8,047)

Mortality according to PDB



Predictors of mortality

Variable*	Adjusted HR (95% CI)	p Value
PDB†	5.03 (3.29-7.66)	<0.0001
With transfusion	4.71 (2.76-8.03)	<0.0001
Without transfusion	5.27 (3.32-8.35)	<0.0001
Post-discharge MI†	1.92 (1.18-3.12)	0.009
Current smoker	1.69 (1.25-2.29)	0.001
Age (per yr increase)	1.04 (1.02-1.05)	<0.0001
Male	1.45 (1.11-1.90)	0.007
Diabetes mellitus	1.48 (1.17-1.88)	0.001
Previous MI	1.42 (1.12-1.81)	0.004
STEMI or non-STEMI presentation	1.41 (1.10-1.83)	0.008
VerifyNow $P2Y_{12}$ reactivity units >208	1.22 (0.96-1.54)	0.10
IVUS use	0.83 (0.65-1.06)	0.13
Creatinine clearance (per ml/min increase)‡	0.99 (0.99-1.00)	0.0007
Baseline white blood cells (per 10^3/ml increase)	1.03 (1.01-1.04)	<0.0001
Baseline hemoglobin (per g/dl increase)	1.18 (1.09-1.28)	<0.0001

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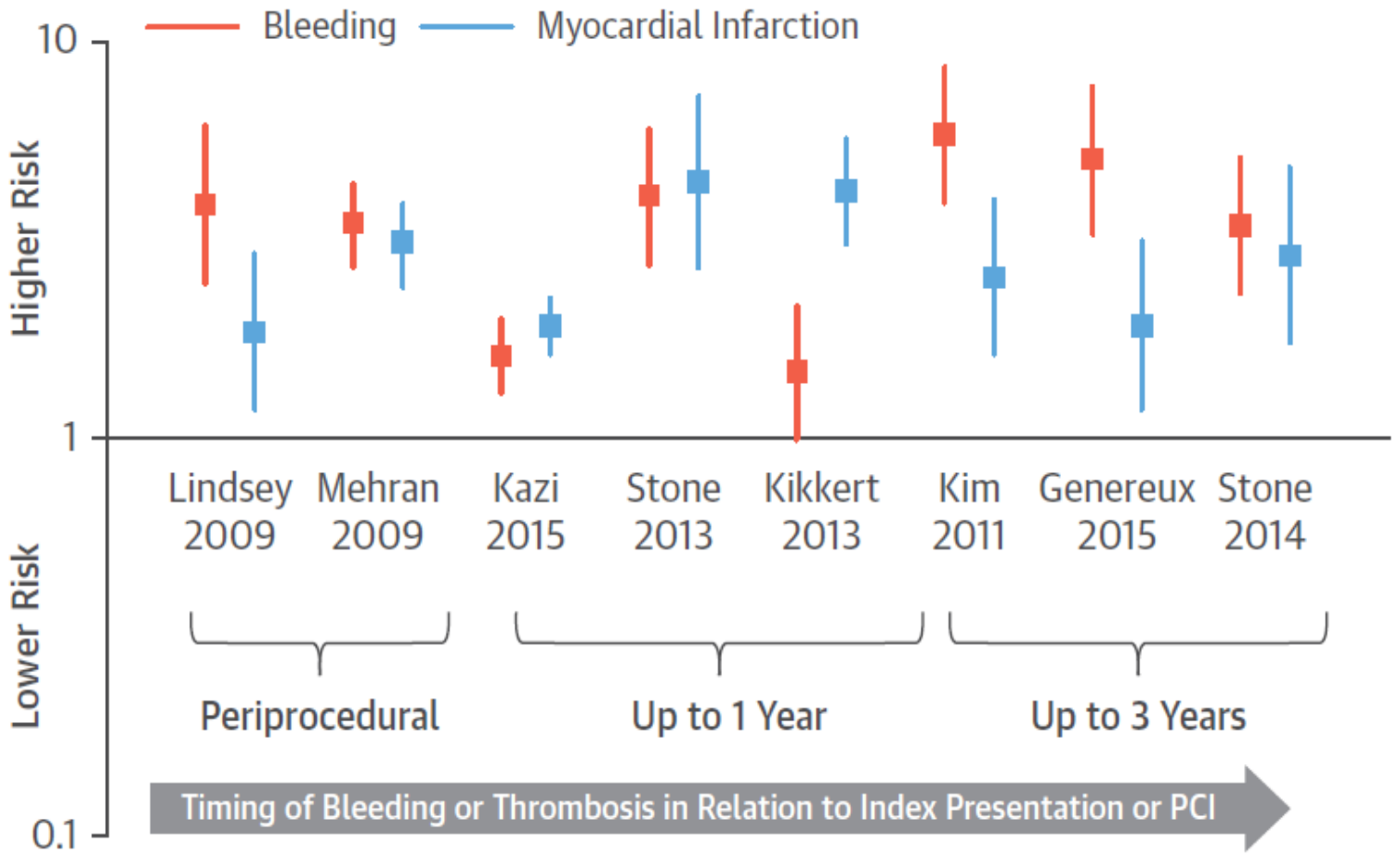
Genereux P, et al. *JACC* 2015;66:1036-45.

Impact of Bleeding and MI on Mortality Risk



Sharma SK, et al. *JACC* 2015;66:1046-9.

Summary

1. Bleeding during DAPT:
   Common clinical phenomenon

2. Risk of bleeding during DAPT:
   Disease entity (ACS), Race (East Asians), APT type (TICA)

3. Impact of major bleeding on mortality:
   Possibly higher than impact of MI on mortality

4. Unmet Needs to develop bleeding avoidance strategy in the era of potent $P2Y_{12}$ inhibitor


Thanks for
your attention