

# **Antithrombotic Therapy in East Asian with ACS/PCI: Updated Evidence for the East-Asian Paradox**

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## Platelet Focus: What is the "East Asian Paradox"?

The combination of clopidogrel and aspirin has been the mainstay treatment to prevent ischemic events in a wide spectrum of patients with high-risk coronary artery disease. Multiple lines of evidence have demonstrated that clopidogrel therapy is associated with wide interindividual variability in pharmacodynamic response. Patients who are poor responders or who have high on-clopidogrel platelet reactivity (HPR) to adenosine diphosphate (ADP) are at an increased risk of post-PCI ischemic event occurrence. A consensus paper suggested cutoffs for HPR determined by various platelet function tests to be used for personalized antiplatelet therapy.<sup>1</sup>

The CYP2C19 loss-of-function allele is significantly associated with the level of platelet reactivity and the prevalence of HPR during clopidogrel treatment. There are multiple CYP2C19 alleles associated with loss-of-function (\*2-\*8), and interethnic differences in loss-of-function allele carriage exist (Table).

**Table.** Frequencies of CYP2C19\*2 and \*3 Minor Alleles and Genetically-Predicted Phenotype Across Races

| *2 Allele frequency | *3 Allele frequency | % Intermediate metabolizer | % Poor metabolizer |
|---------------------|---------------------|----------------------------|--------------------|
|                     |                     |                            |                    |



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# "East Asian Paradox" First Description



Jeong YH, Tantry US, Gurbel P. What is the "east Asian Paradox"  
Cardiosource Interventional News 2012; 1: 38-39

Young-Hoon Jeong, MD, PhD

# CONSENSUS STATEMENTS

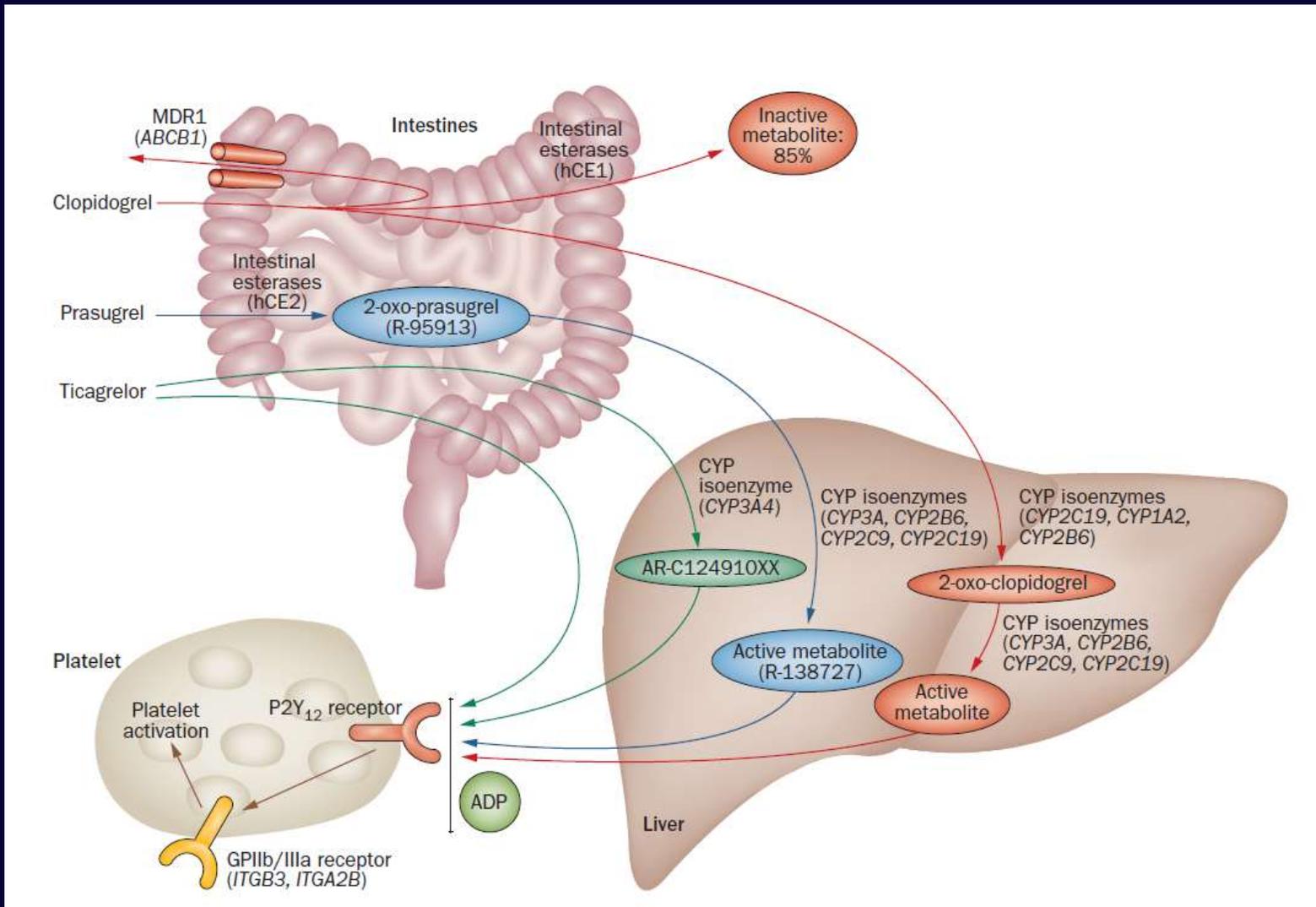
EXPERT CONSENSUS DOCUMENT

## **World Heart Federation expert consensus statement on antiplatelet therapy in East Asian patients with ACS or undergoing PCI**

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*Glenn N. Levine, Young-Hoon Jeong, Shinya Goto, Jeffrey L. Anderson, Yong Huo, Jessica L. Mega, Kathryn Taubert and Sidney C. Smith Jr*

# Clopidogrel Metabolism and Efficacy



- East Asians have a higher prevalence of CYP2C19 loss-of-function alleles
- 30% in whites, 60% in East Asians (mostly \*2 or \*3 alleles)
- Higher level of platelet reactivity (less inhibition) with clopidogrel Rx in East Asians

Ahmad T, et al. Nat Rev Cardiol 2011  
Levine GN et al. Nat Rev Cardiol 2014

# Frequency of *CYP2C19* Loss-of-function Allele and Phenotype Prevalence Across the Ethnicity

*CYP2C19* LOF allele: \*2, \*3, \*4, \*5, \*6, \*7 and \*8

|                  | *2 frequency | *3 frequency | % Intermediate Metabolizer | % Poor Metabolizer |
|------------------|--------------|--------------|----------------------------|--------------------|
| Caucasian        | 0.14         | 0.0          | 24%                        | 2%                 |
| African American | 0.18         | 0.008        | 30%                        | 3.5%               |
| Asian            | 0.27         | 0.09         | 46%                        | 10.0%              |

Intermediate metabolizer (IM): \*1/\*2, \*1/\*3

Poor metabolizer (PM): \*2/\*2, \*2/\*3, \*3/\*3

Beitelshees AL, et al. *Clin Pharmacol Ther.* 2011;89:455-9.

Slide courtesy of Dr. Young-Hung Jeong

# Prasugrel and Ticagrelor

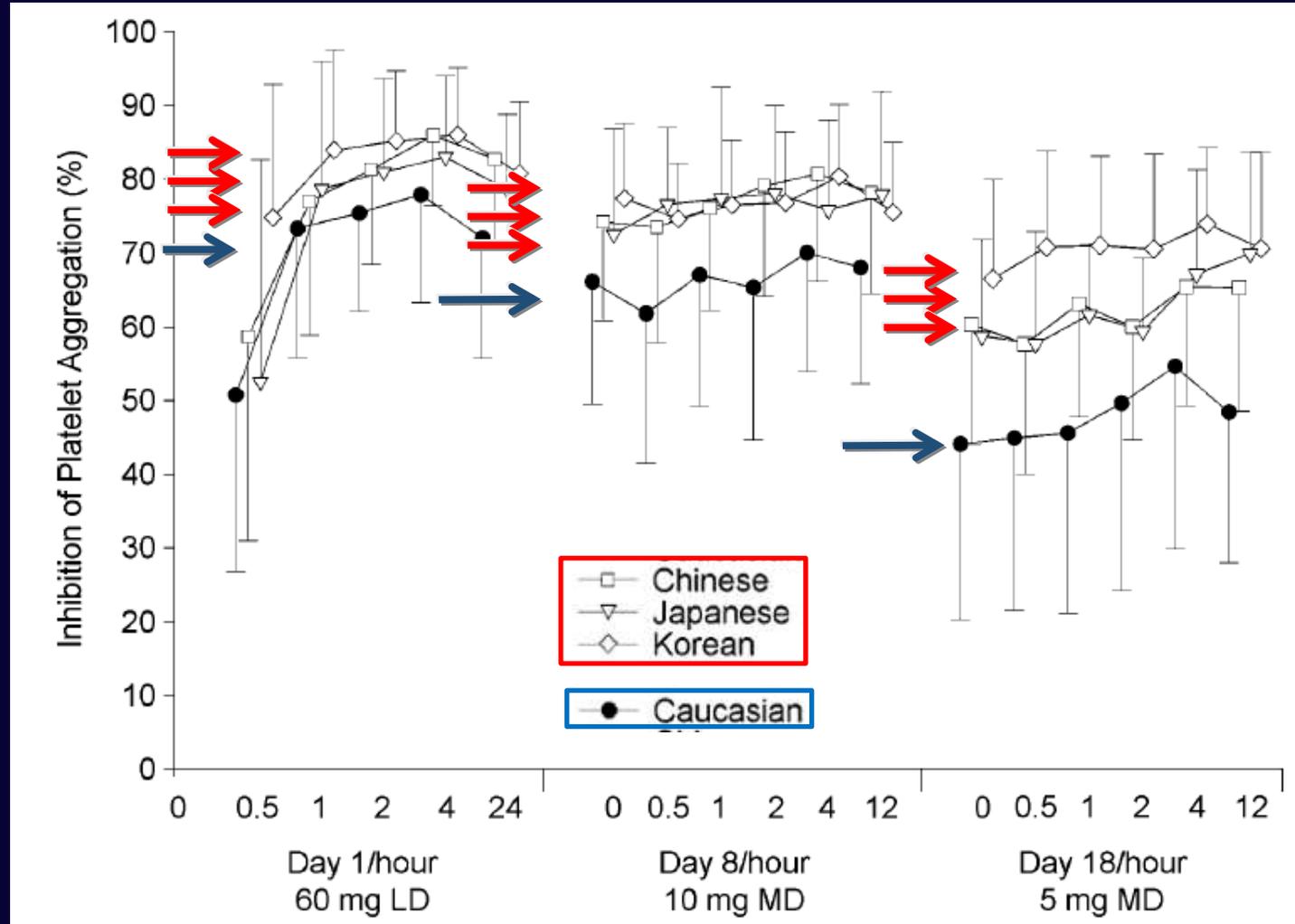
## Prasugrel

- Platelet inhibition with the prasugrel active metabolite is 30-47% higher in East Asian patients
- Inhibition of platelet inhibition is comparable with 10 mg daily in white patients and 5 mg daily in East Asian patients

## Ticagrelor

- Exposure of the same doses of ticagrelor is  $\approx$ 20-40% higher in East Asian patients than white patients
- Platelet inhibition with the same doses of ticagrelor is  $\approx$ 40% higher in East Asian patients than white patients

# Prasugrel Pharmacodynamics in East Asians vs. Caucasians

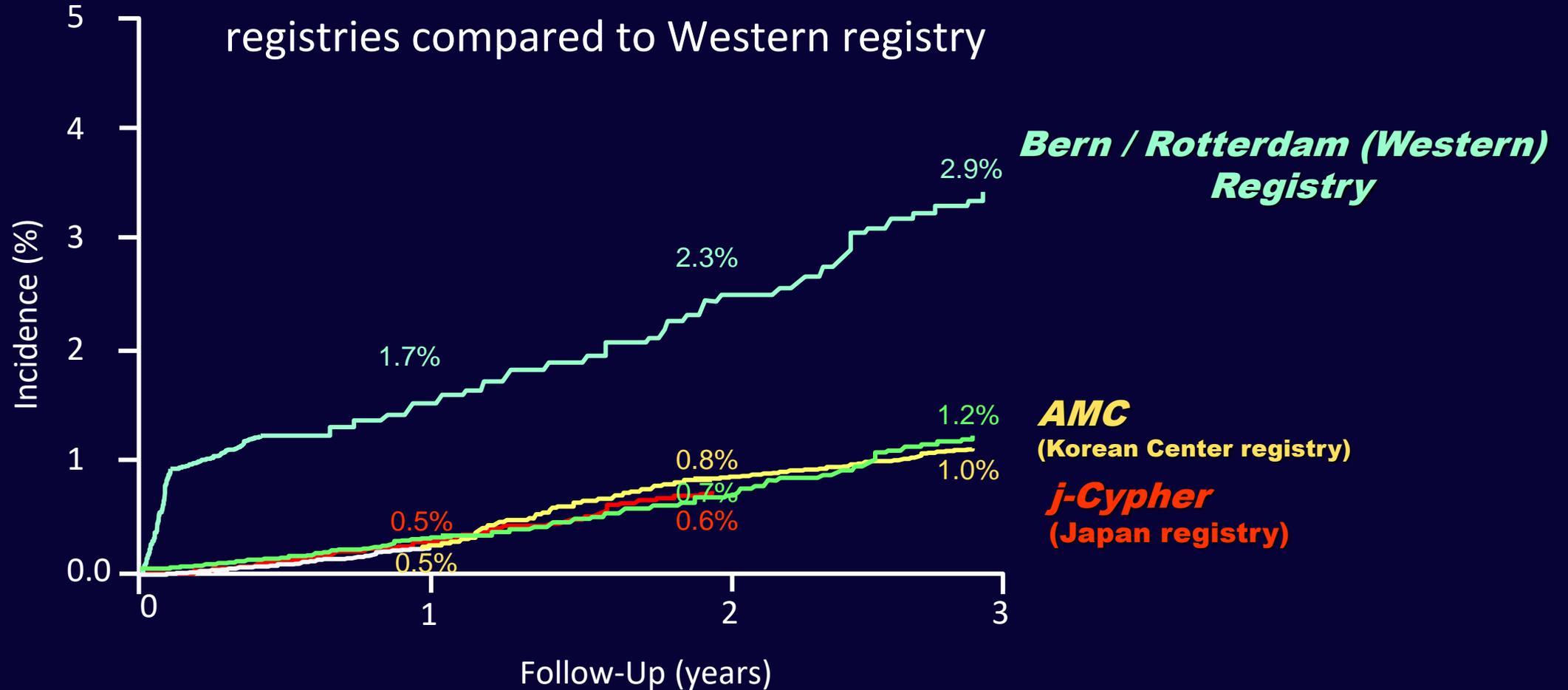


# The Paradox

Although East Asian patients have a higher prevalence of high on-treatment platelet reactivity (less platelet inhibition) during clopidogrel treatment than white patients, the incidence of adverse ischaemic outcomes or stent thrombosis after PCI is similar or lower than that in white patients.

# Racial difference of Stent Thrombosis in 1<sup>st</sup> Generation DES

Lower incidence of stent thrombosis in East Asian registries compared to Western registry



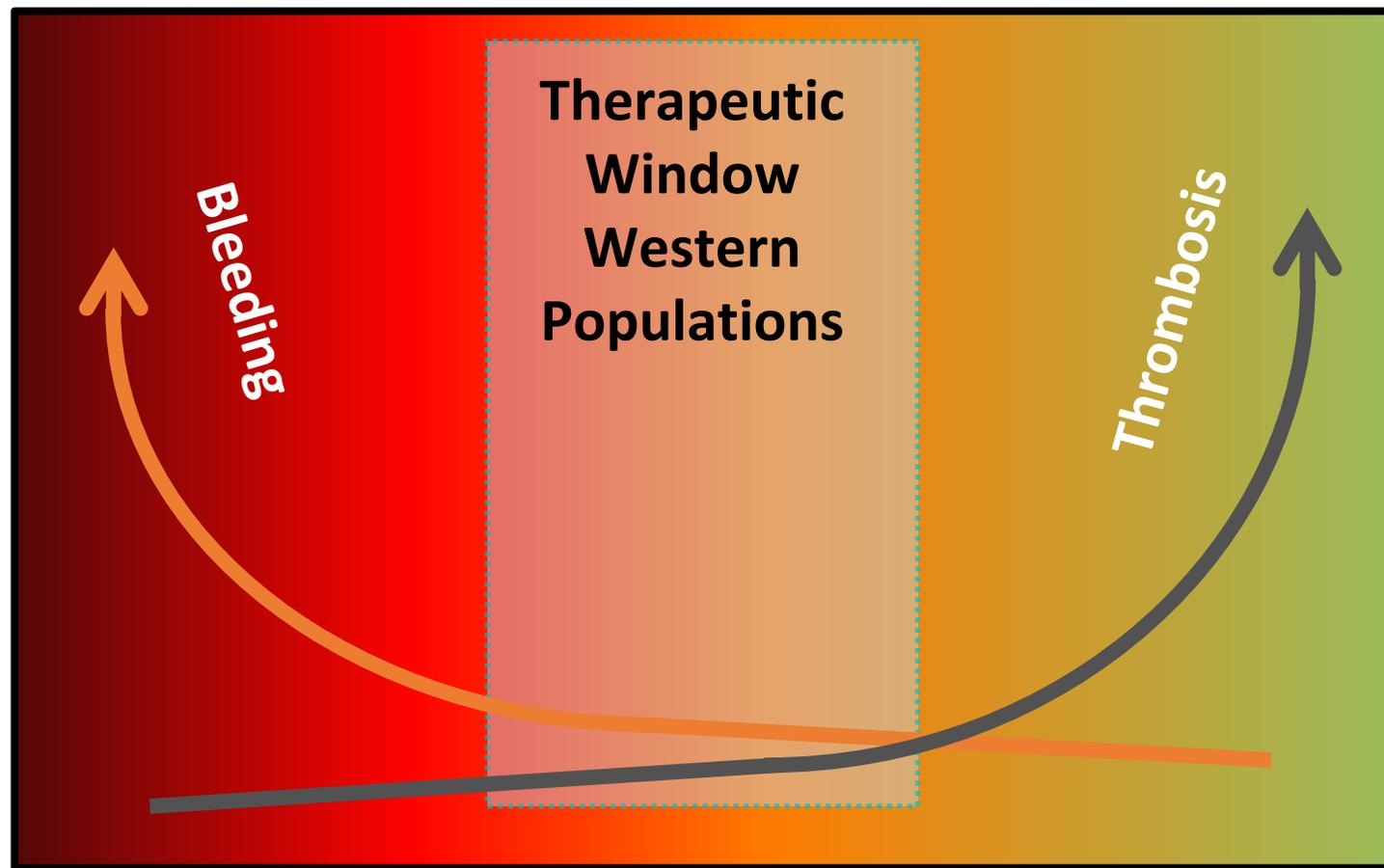
# East Asian Paradox: Bleeding

- East Asians are at greater risk of warfarin-associated intracranial haemorrhage than white individuals (despite similar INR)
- Some studies also report a greater bleeding risk on the same doses of DAPT in East Asians

# East Asian Paradox

- **Hemostatic and Thrombotic Differences**
  - Differences in levels of haemostatic factors
    - Factor V Leiden and prothrombin
    - Fibrinogen
    - D-dimer
    - Factor VIII
  - Differences in endothelial function and activation
    - Intercellular adhesion molecule 1
    - E-selectin
- **Pharmacokinetic and pharmacodynamic considerations**
  - Smaller body size and lower BMI of East Asians
  - Differences in drug metabolism
  - Relatively lower renal clearance of East Asians

# Clinical Events

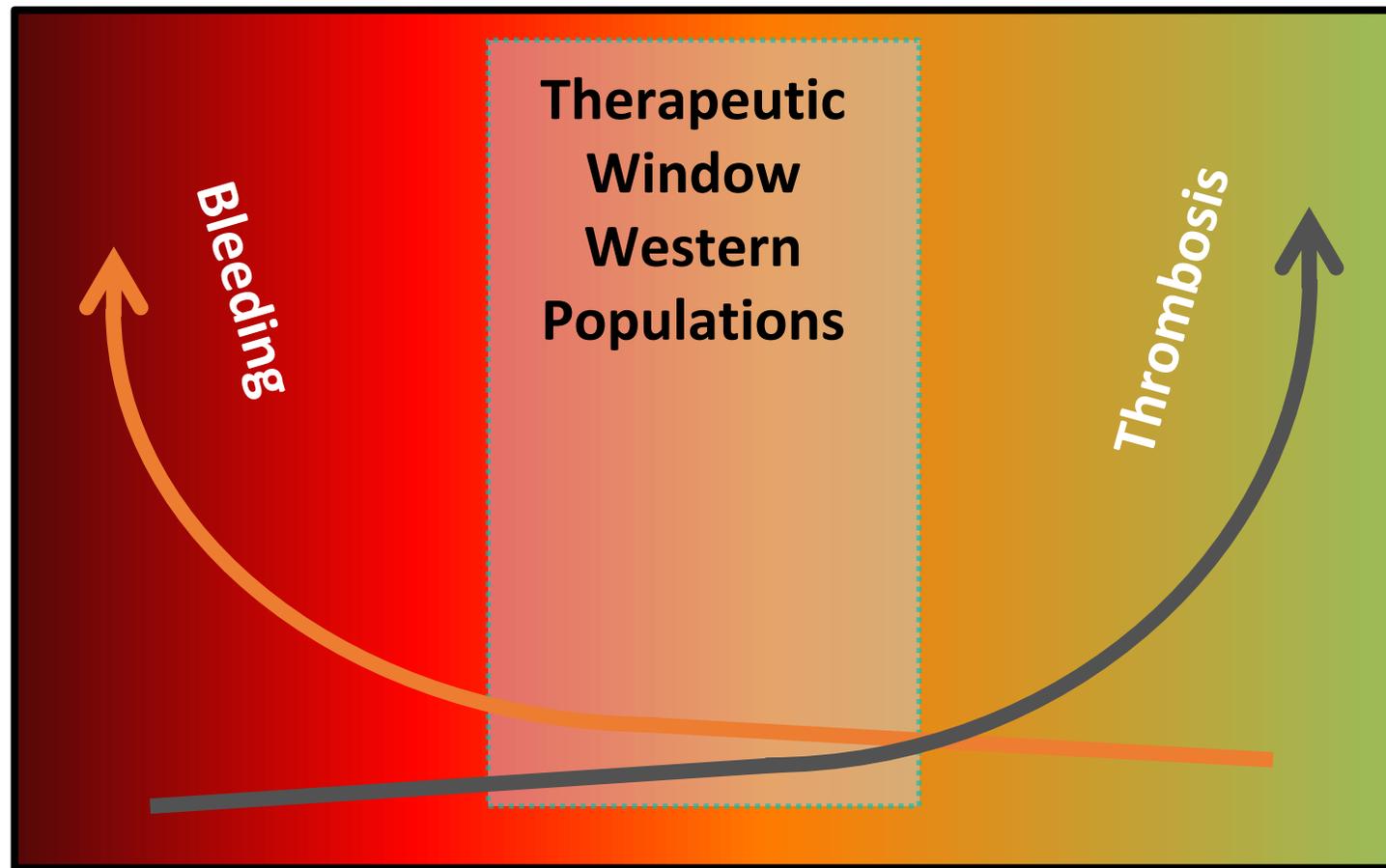


**LPR**

**HPR**

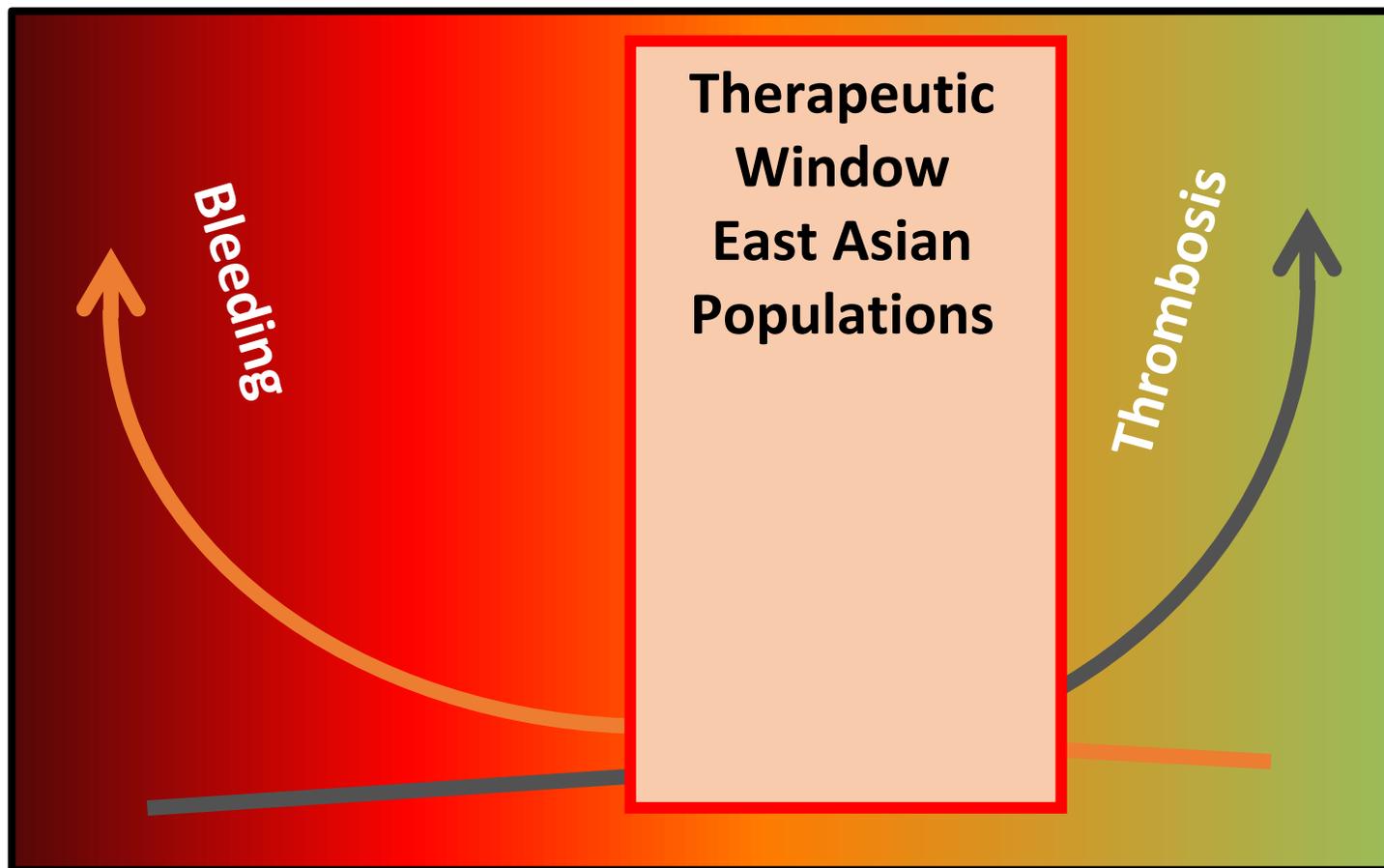
|           |       |        |         |         |
|-----------|-------|--------|---------|---------|
| MEA       | 0U    | 20U    | 50U     | 200 U   |
| LTA       | 0%    | 35%    | 60%     | 100%    |
| VASP      | 0%    | 20%    | 50%     | 100%    |
| VerifyNow | 0 PRU | 85 PRU | 235 PRU | 550 PRU |

# Clinical Events



|           |       | LPR    | LPR     | HPR     | HPR     |         |
|-----------|-------|--------|---------|---------|---------|---------|
| MEA       | 0U    | 20U    | 30U     | 50U     | 60U     | 200 U   |
| LTA       | 0%    | 35%    | 45%     | 60%     | 70%     | 100%    |
| VASP      | 0%    | 20%    | 30%     | 50%     | 60%     | 100%    |
| VerifyNow | 0 PRU | 85 PRU | 230 PRU | 235 PRU | 275 PRU | 550 PRU |

# Clinical Events

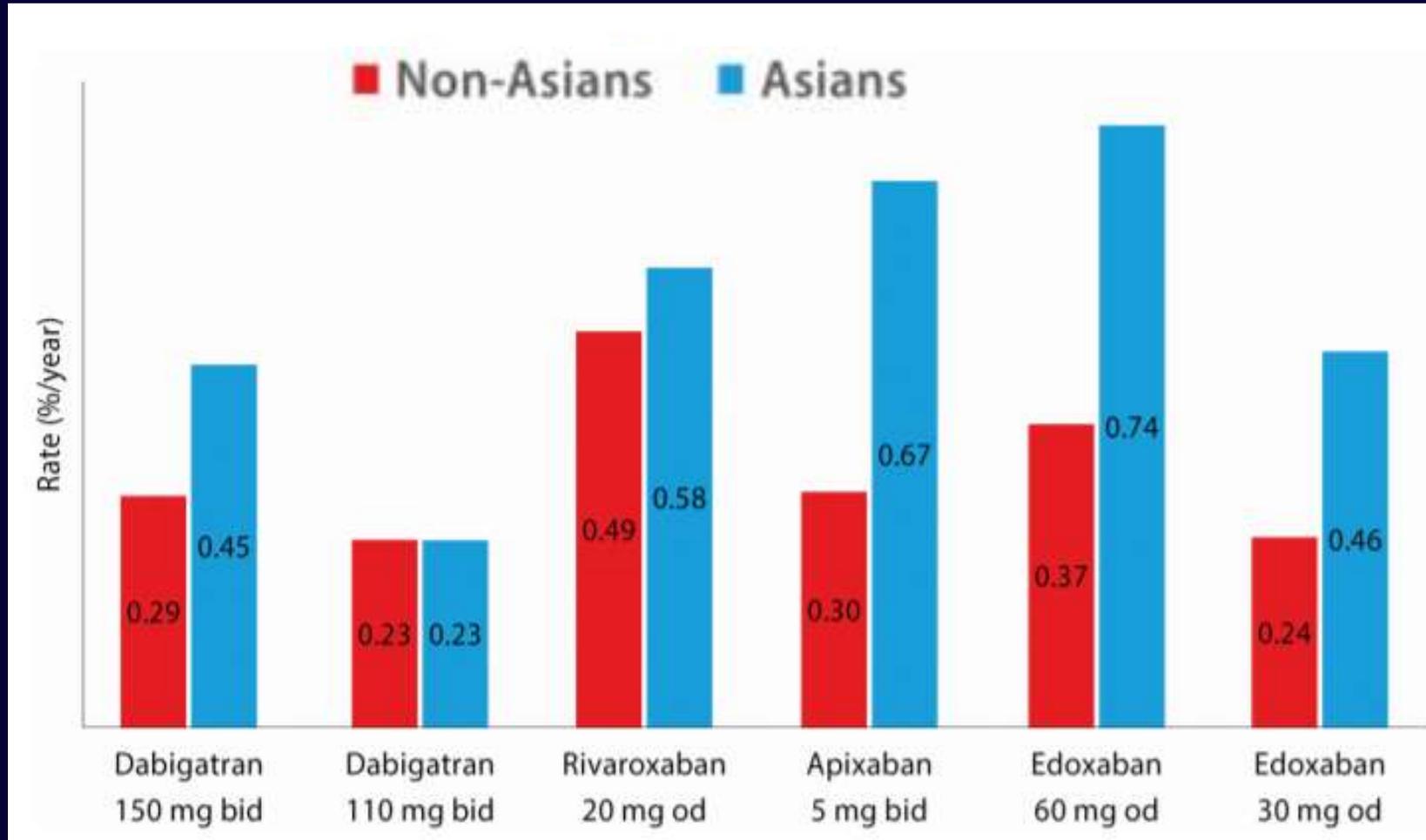


|           |       | LPR    | LPR     | HPR     | HPR     |         |
|-----------|-------|--------|---------|---------|---------|---------|
| MEA       | 0U    | 20U    | 30U     | 50U     | 60U     | 200 U   |
| LTA       | 0%    | 35%    | 45%     | 60%     | 70%     | 100%    |
| VASP      | 0%    | 20%    | 30%     | 50%     | 60%     | 100%    |
| VerifyNow | 0 PRU | 85 PRU | 230 PRU | 235 PRU | 275 PRU | 550 PRU |

## Different response to antithrombotic agents: Active metabolite concentration in East Asians vs. Caucasians

| P2Y <sub>12</sub> receptor inhibitors |              | DOACs              |            |
|---------------------------------------|--------------|--------------------|------------|
| <i>Clopidogrel</i>                    | ↓            | <i>Dabigatran</i>  | ↑ (20-30%) |
| <i>Prasugrel</i>                      | ↑ ↑ (30-47%) | <i>Rivaroxaban</i> | ↑ (20-30%) |
| <i>Ticagrelor</i>                     | ↑ ↑ (40-48%) | <i>Apixaban</i>    | ↔          |
|                                       |              | <i>Edoxaban</i>    | ↓ (20-25%) |

# Annual risk of ICH during DOAC treatment in Asians versus non-Asians from randomized clinical trials

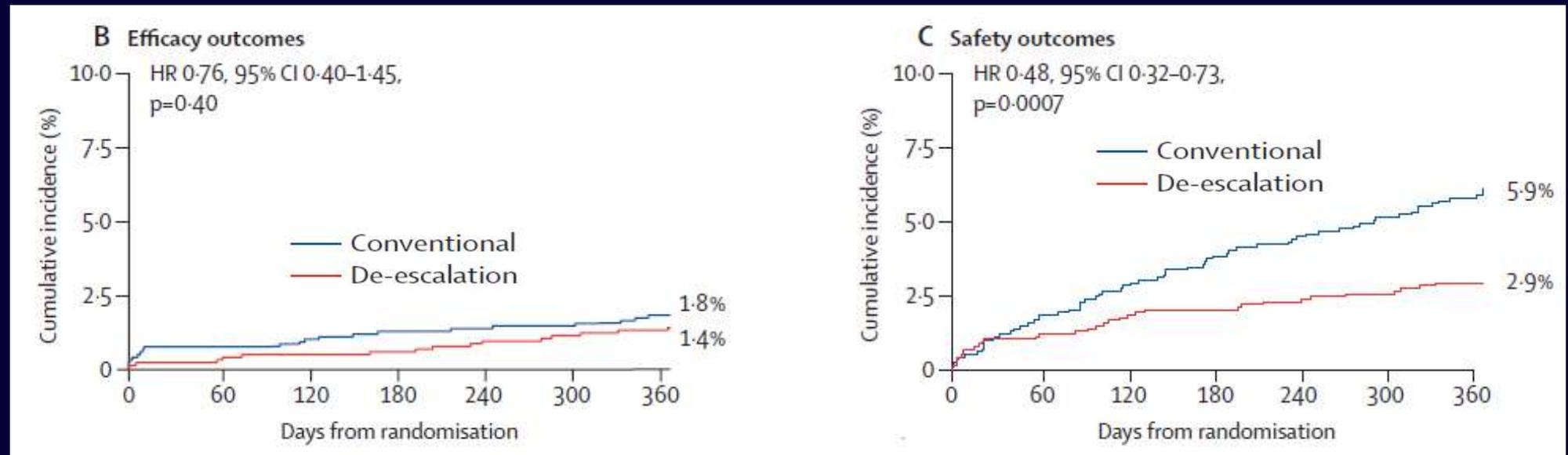
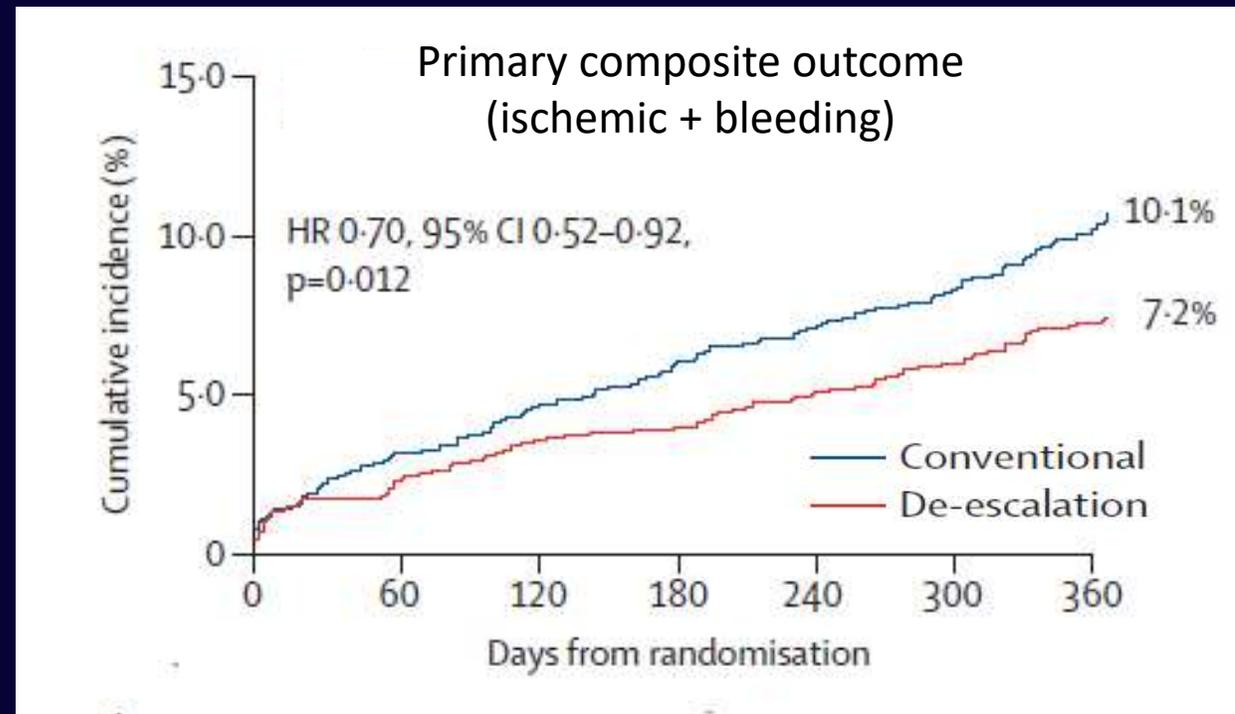


Bang OY et al. J Stroke 2016

Figure reproduced from Kim HK et al. Thrombosis and Haemostasis 2020

# HOST-REDUCE- POLYTECH-ACS

- De-escalation (to prasugrel 5 mg) vs standard dosing (prasugrel 10 mg) in 3429 South Korean patients with ACS undergoing PCI



# The East Asian Paradox: An Updated Position Statement on the Challenges to the Current Antithrombotic Strategy in Patients with Cardiovascular Disease

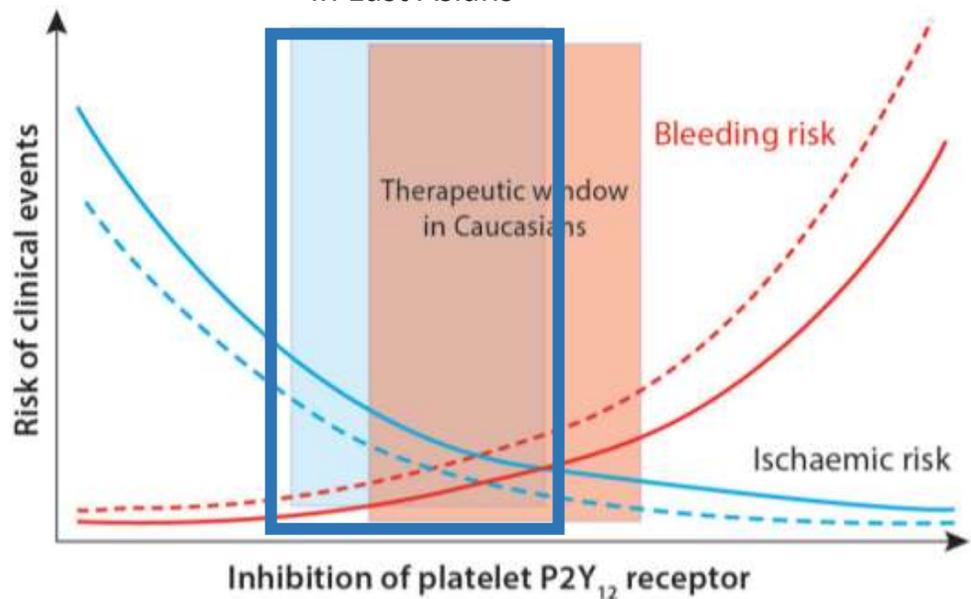
Hyun Kuk Kim<sup>1</sup> Udaya S. Tantry<sup>2</sup> Sidney C. Smith Jr.<sup>3</sup> Myung Ho Jeong<sup>4</sup> Seung-Jung Park<sup>5</sup>  
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# Different therapeutic window of antithrombotic effect in East Asians vs. Caucasians

## P2Y<sub>12</sub> receptor inhibitors

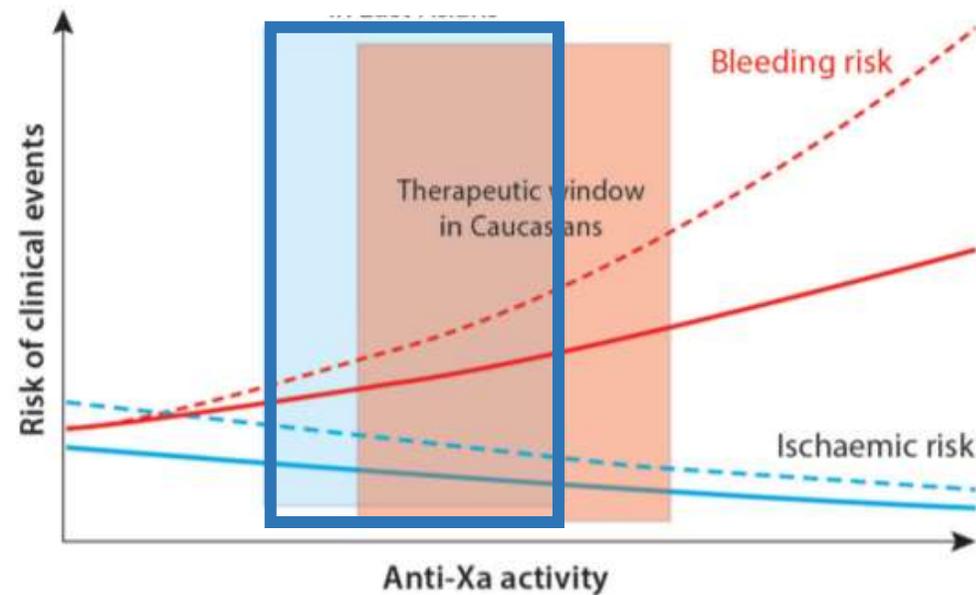


Therapeutic Window  
In East Asians



## DOACs

Therapeutic Window  
In East Asians



Future direction

# Conclusions and Take-Home Messages

- East Asians have lower atherothrombotic risk but higher bleeding risks than non-East Asians, particularly if dosing is not tailored
- “The East Asian Paradox” first described a decade ago and in relationship to clopidogrel therapy, continues to be expanded and validated, now including more potent P2Y12 inhibitors and DOAC
- Data, trial results, dosing, and recommendations based upon US and European populations, studies, and guideline recommendations should not necessarily be directly extrapolated to East Asian populations
- Tailored or “personalized” therapy in East Asians, particularly dosing, continues to be advisable

# Thank You

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ありがとうございました

Arigatōgozaimashita

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