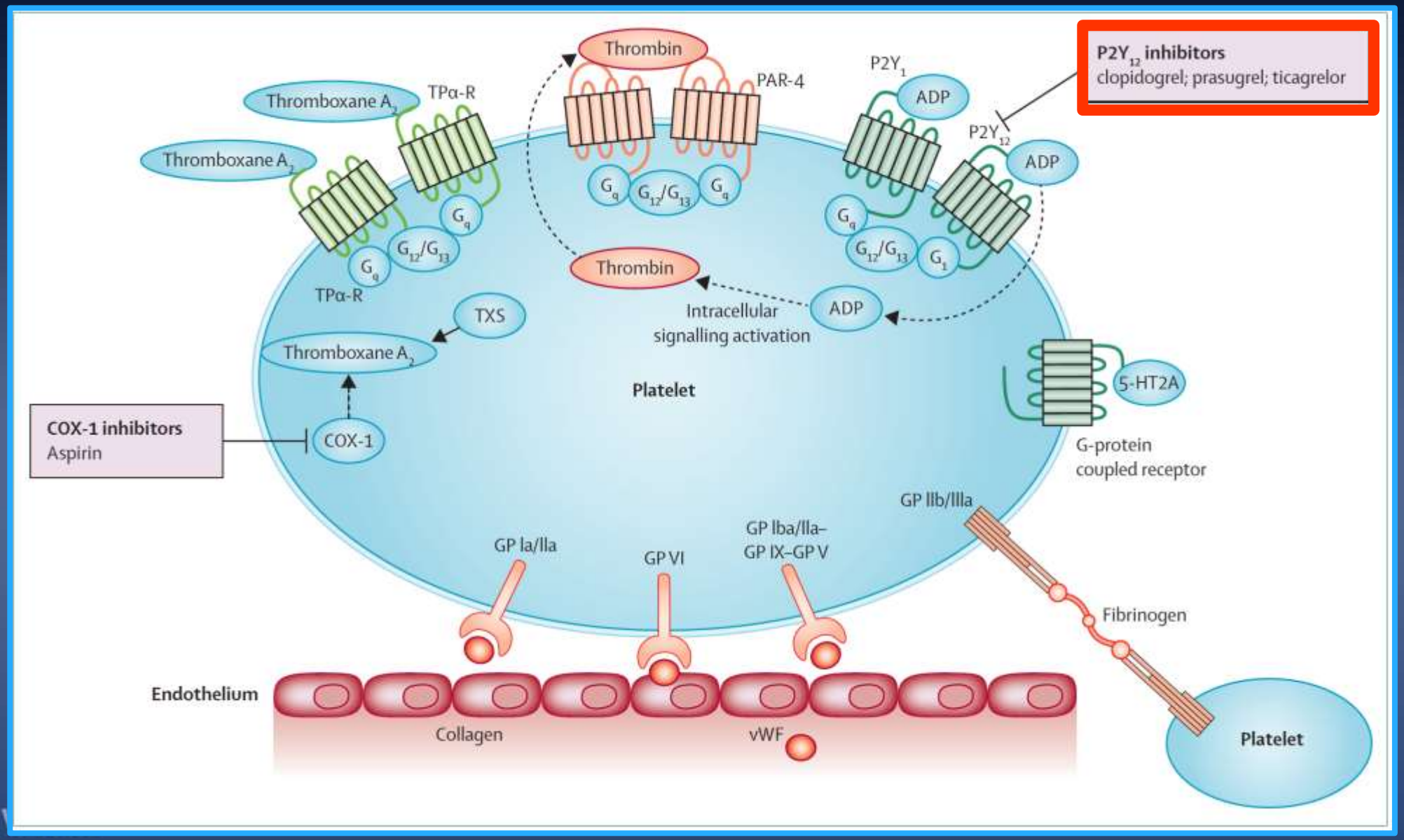
East-Asian Paradox for Antithrombotics: Theory, Evidence, and Next Strategy

Duk-Woo Park, MD
Professor, Heart Institute, Asan Medical Center,
University of Ulsan College of Medicine, Seoul, Korea

Disclosure

Institutional grant/research funding to CardioVascular Research Foundation (CVRF, Korea) and/or Asan Medical Center from Daiichi-Sankyo, Abbott, Boston Scientific, Medtronics, Edwards, Biosensor, ChongKunDang Pharm and Daewoong Pharm,

Contemporary P2Y12 Inhibitors in ACS or PCI



Current P2Y12 Guidelines in ACS/PCI

- Current European and US guidelines recommend that use of potent P2Y12 inhibitors (i.e., ticagrelor or prasugrel) in preference to clopidogrel is reasonable for ACS patients with or without PCI.

- However, this recommendations is not unconditionally applicable for East Asians, given several studies suggested that “East Asian” population had **differential ischemic and bleeding propensity** compared to Western population (**‘East-Asian Paradox’**)

M. Valgimigli, et al. Eur Heart J, 2018;39:213-260
G.N. Levine, et al. J Am Coll Cardiol, 2016;68:1082-1115

“East Asian Paradox” :Challenge for Antithrombotic Strategy

“One Guideline Does Not Fit All Races”

East-Asian Paradox for Antithrombotics

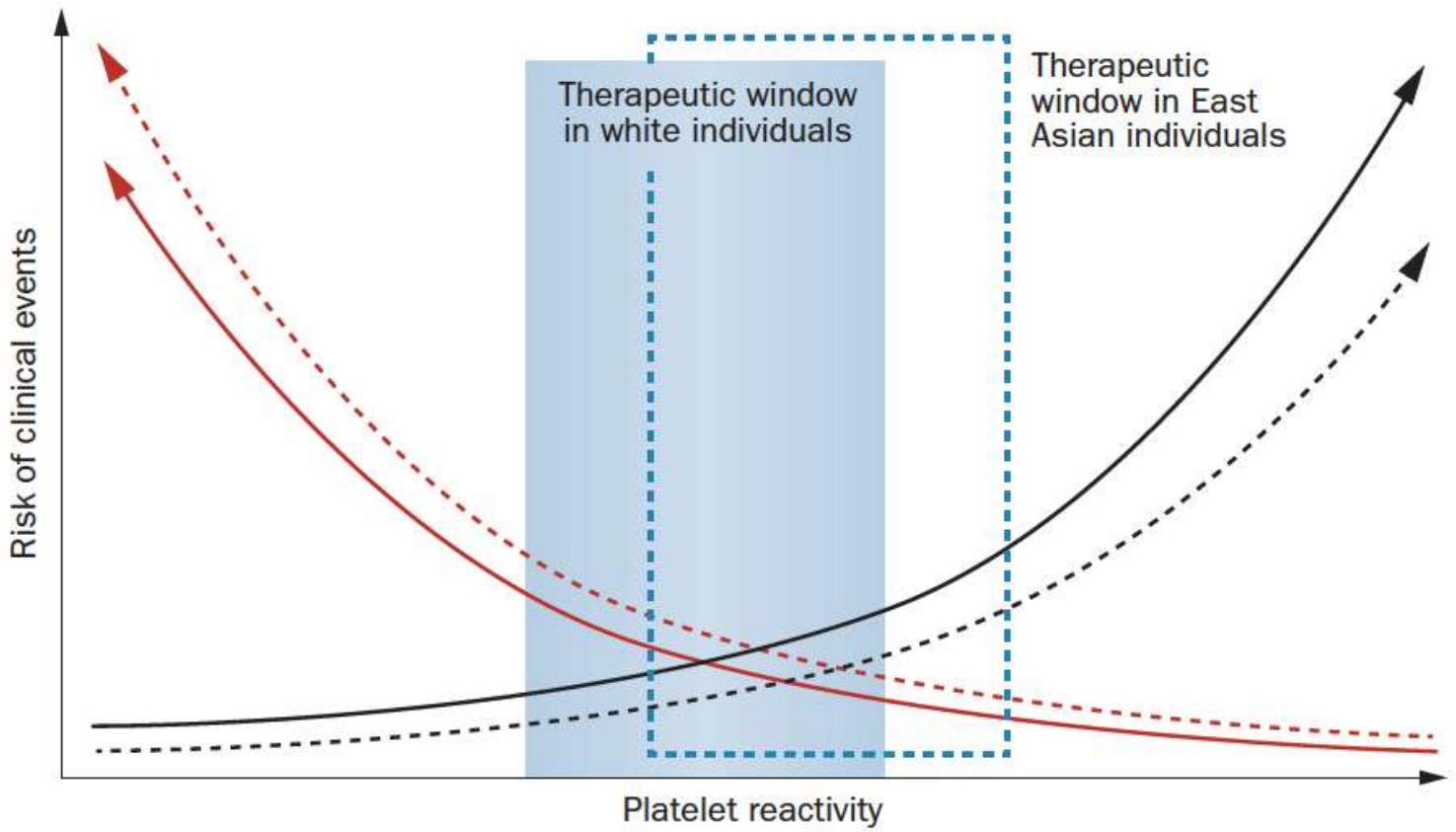


Figure 2 | Postulated differences in the optimal 'therapeutic window' of platelet reactivity between white and East Asian populations.

Levine, G. N. et al. Nat. Rev. Cardiol. 2014;11:597–606

Unique Features of East Asian Population Regarding Ischemic & Bleeding Tendency

Europeans Americans East Asians

↓ *Ischemic event*
- ↓ CV death, MI
- ↓ Stent thrombosis
- ↓ Inflammation
- ↓ Coagulation activity

↑ *Hemorrhagic stroke*
- ↑ Lacunar infarct
- ↑ Hemorrhagic transformation

↑ *GI bleeding*
- ↑ Helicobacter pylori infection
- ↑ CYP polymorphism

Different response to $P2Y_{12}$ inhibitors

	Clopidogrel	Prasugrel	Ticagrelor
Active metabolite concentration in blood	↓↓	↑ ~30%	↑ ~40%
Mechanism	↑ *CYP2C19* loss-of-function allele (*2 or *3) carriage (~65% of population)	?	?

Y. Huo et al. / Science Bulletin 2019;64:166–179

Decoupling Pharmacogenetics, PK/PD and Clinical Presentation

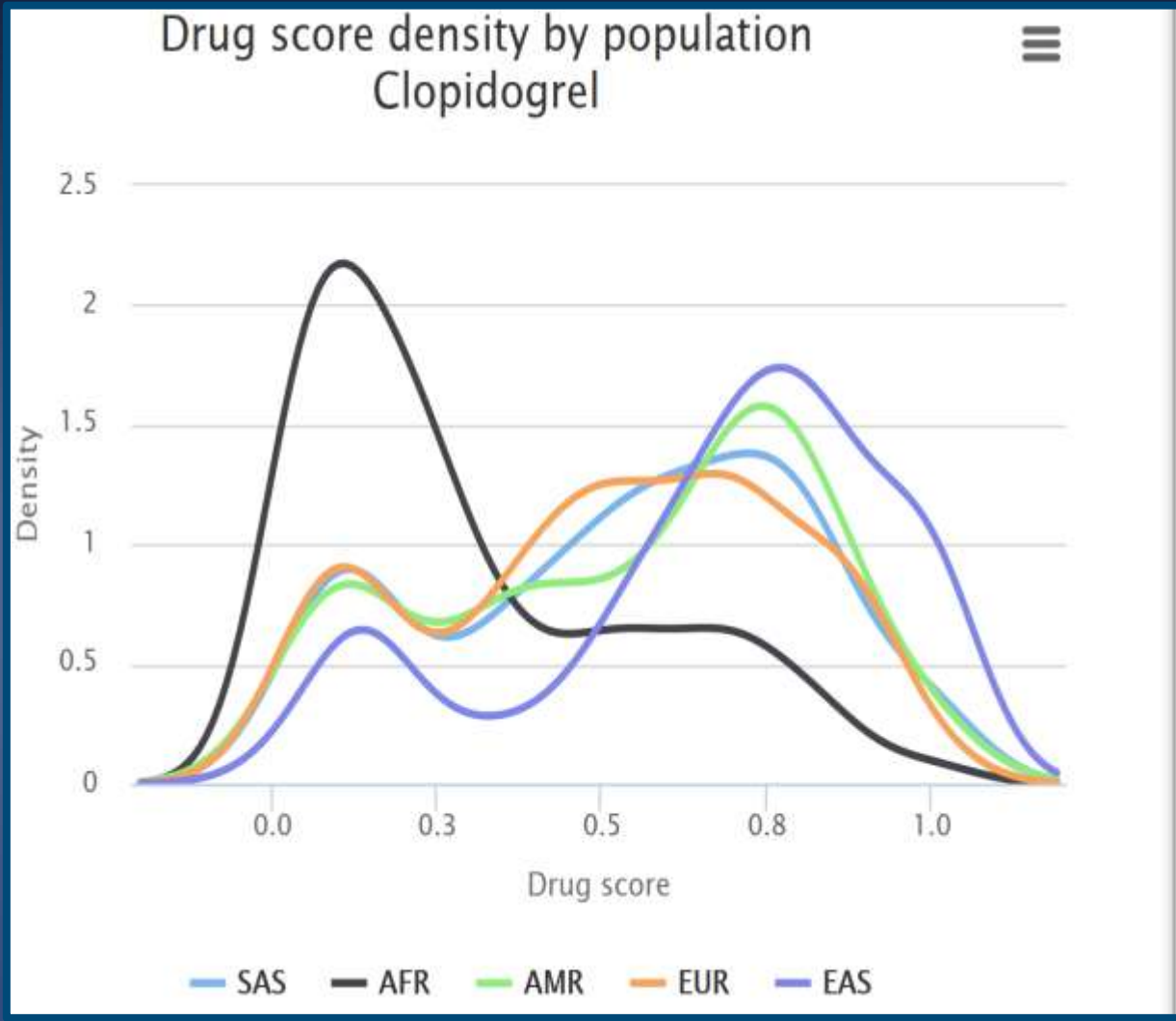
- Asian population has a high prevalence of the CYP2C19 loss-of-function (LOF) genotype compared with white population (70% vs. 35%).
- PD/PK studies showed that CYP2C19 LOF alleles attenuate response to clopidogrel.
- Despite a high prevalence of CYP2C19 LOF allele, several studies reported similar or relatively low ischemic events in ACS or PCI among East Asians compared with Western population.

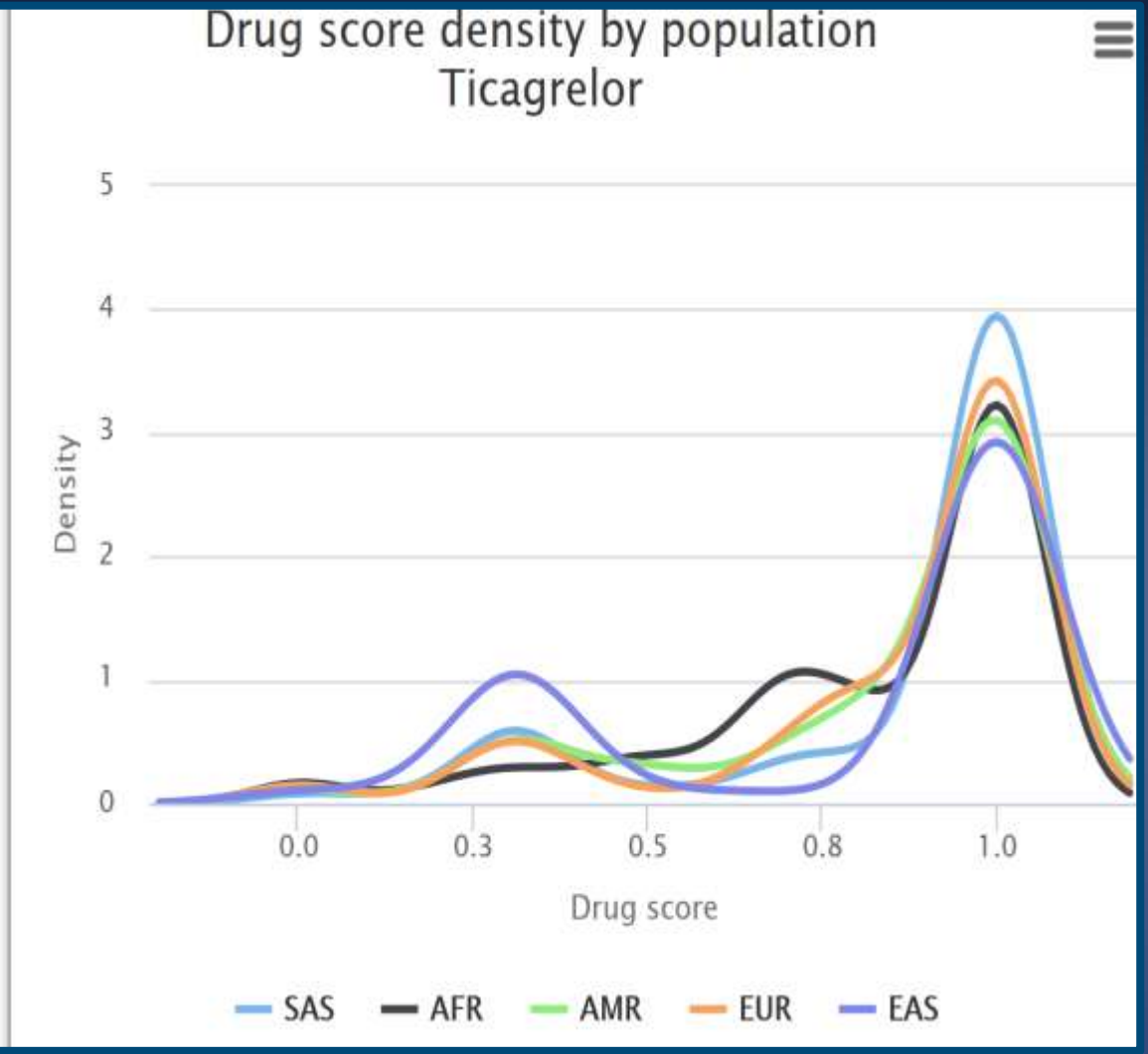
Jeong YH et al. . Circ Cardiovasc Interv. 2011;4:585-594.

Proposed Mechanisms of "East-Asian Paradox" for Antithrombotic Therapy

- A small body size and lower BMI in East Asians
- A relative lower renal clearance in East Asians
- A genetic differences in metabolic or pharmacodynamic features:
  - genetic polymorphisms (ie, CYP2C19 LOF alleles, factor V Leiden [G1691A] and prothrombin [G20210A] gene mutations),
  - plasma hemostatic factors (ie, fibrinogen, d-dimer, and factor VIII),
  - endothelial activation markers (ie, von Willebrand factor, intercellular adhesion molecule 1, and E-selectin)

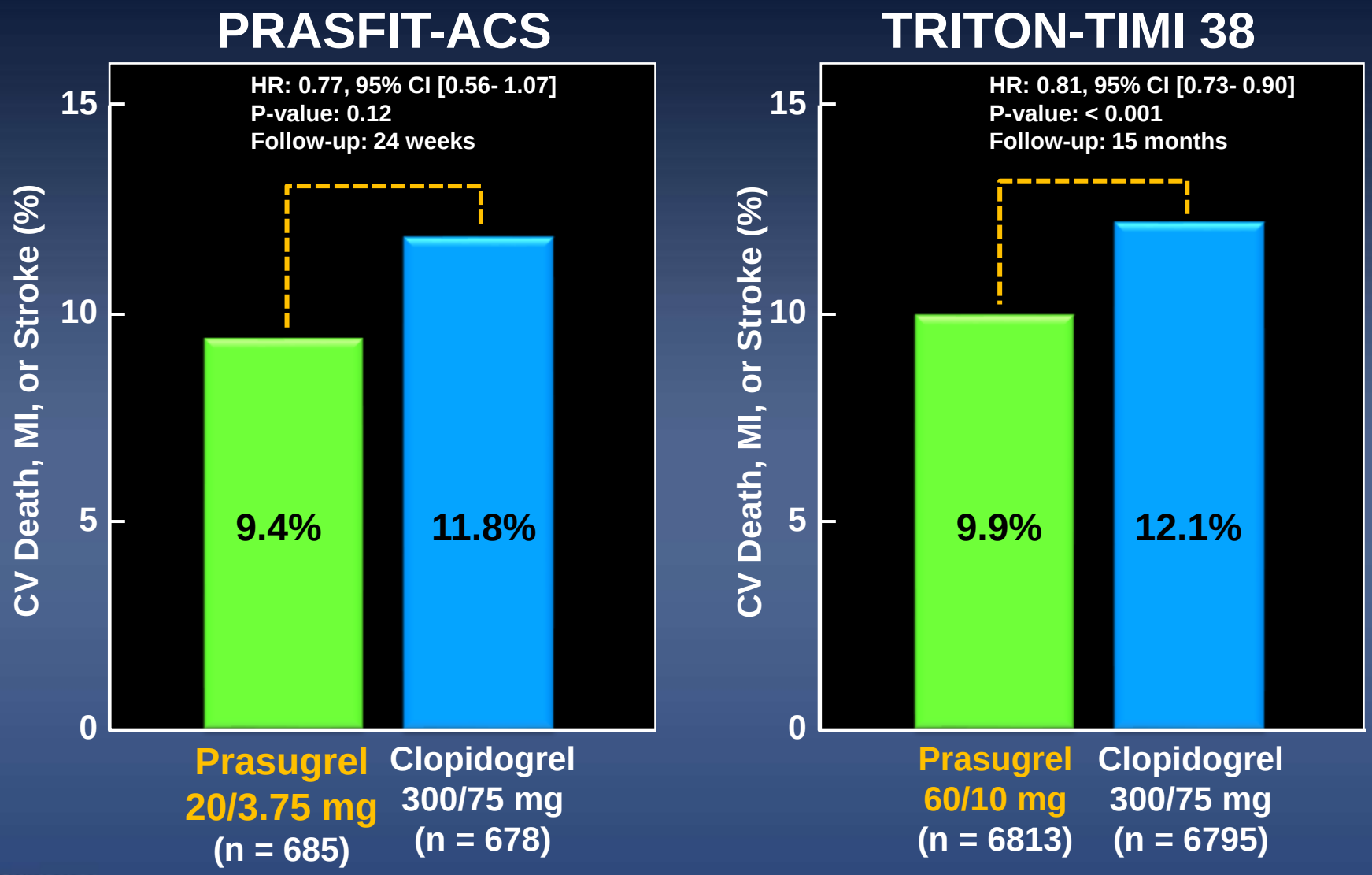
Pharmacogenomics for East-Asian Paradox:
Differential Inter-Ethnic Pharmacogenomic Variants





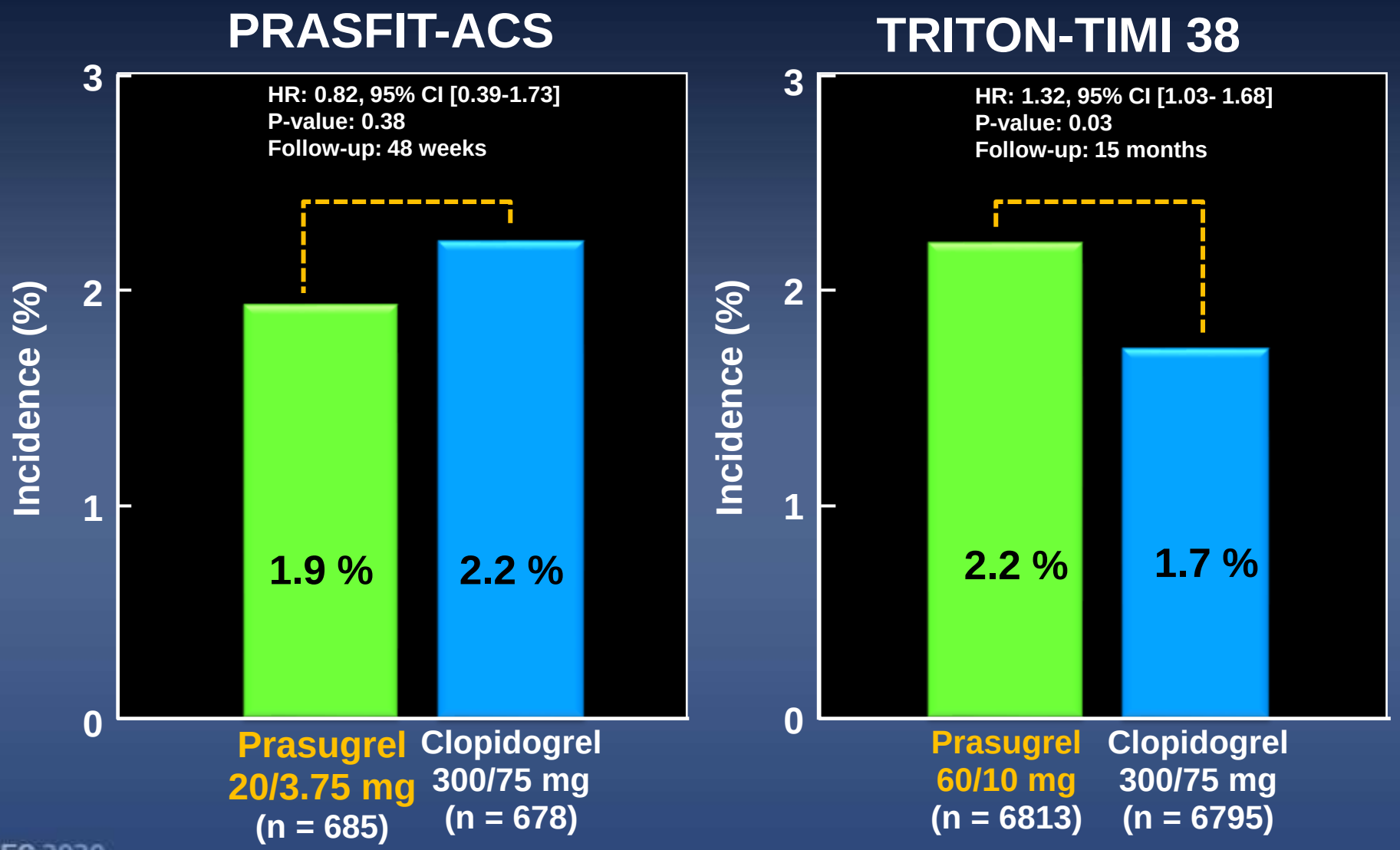
Clinical Evidences of Contemporary P2Y12 Inhibitors in East Asian Patients

Primary Efficacy Endpoint of PRASFIT-ACS and TRITON-TIMI 38



Saito S. et al. Circ J 2014;78:1684-92

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



Saito S. et al. Circ J 2014;78:1684-92

PHILO Trial with Ticagrelor in Japan/Asia

Bleeding Events

	Ticagrelor 90 mg b.i.d.	Clopidogrel 75 mg o.d.	HR for ticagrelor (95% CI)
Major bleeding (PLATO-defined)	40 (10.3)	26 (6.8)	1.54 (0.94–2.53)
CABG-related	8 (2.1)	5 (1.3)	1.57 (0.51–4.81)
Non-CABG-related	32 (8.3)	22 (5.8)	1.45 (0.84–2.50)
Coronary procedural	14 (3.6)	11 (2.9)	1.25 (0.57–2.77)
Non-coronary procedural	2 (0.5)	3 (0.8)	0.66 (0.11–3.93)
Minor bleeding (PLATO-defined)	59 (15.2)	35 (9.2)	1.75 (1.15–2.67)
CABG-related	0	1 (0.3)	
Non-CABG-related	59 (15.2)	34 (8.9)	1.81 (1.18–2.76)
Coronary procedural	31 (8.0)	22 (5.8)	1.43 (0.82–2.48)
Non-coronary procedural	10 (2.6)	4 (1.1)	2.51 (0.79–8.01)
Composite of major and minor bleeding	92 (23.8)	56 (14.7)	1.72 (1.23–2.40)
CABG-related	8 (2.1)	5 (1.3)	1.57 (0.51–4.81)
Non-CABG-related			
Coronary procedural			
Non-coronary procedural			

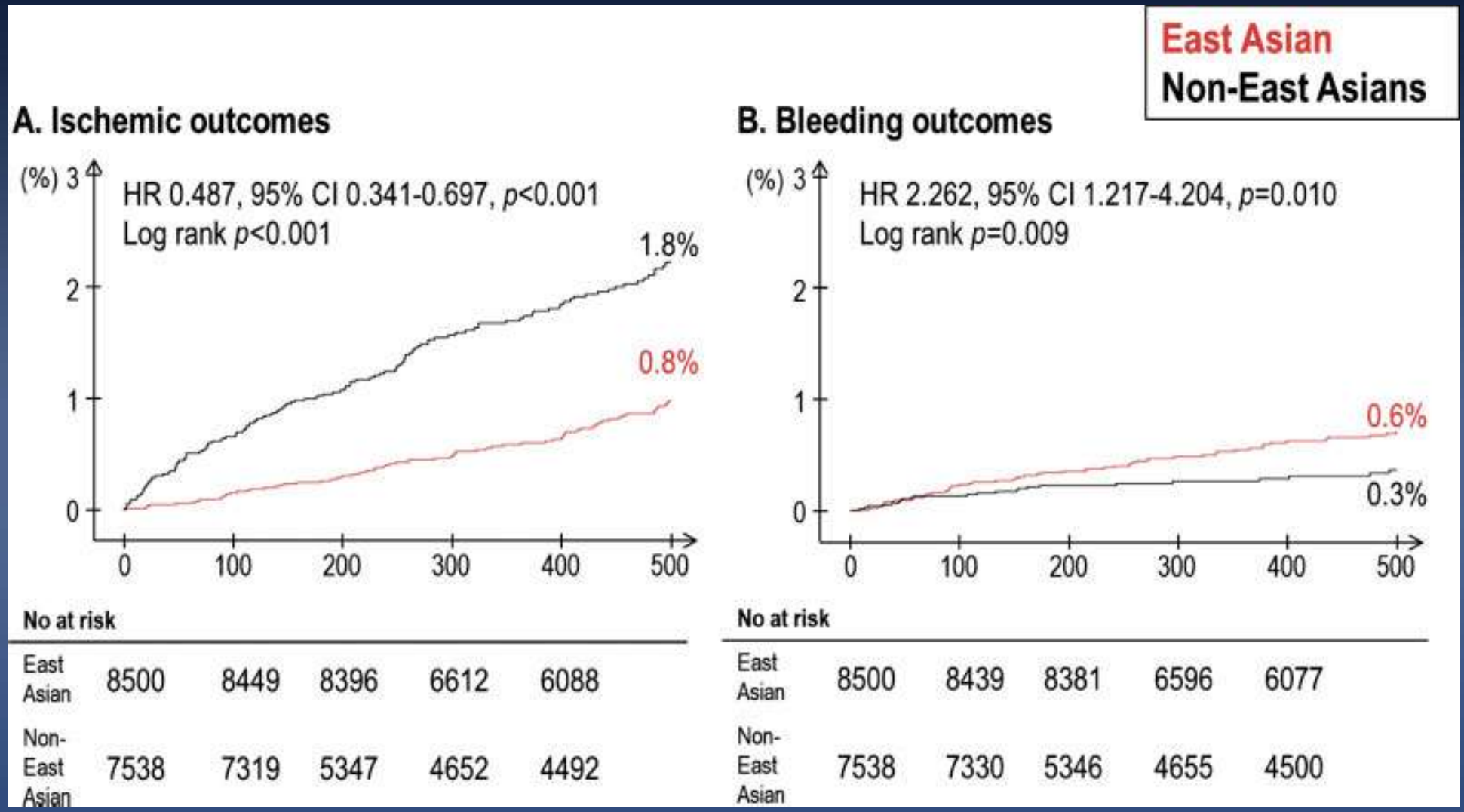
Ischemic Events

	Ticagrelor 90 mg b.i.d. (n=401)	Clopidogrel 75 mg o.d. (n=400)	HR (95% CI)
Primary			
Composite of CV death/MI (excluding silent MI)/stroke	36 (9.0)	25 (6.3)	1.47 (0.88–2.44)
Post-hoc			
Composite of CV death/spontaneous MI/stroke	18 (4.5)	13 (3.3)	1.39 (0.68–2.85)
Secondary			
Composite of all-cause mortality/MI (excluding silent MI)/stroke	37 (9.2)	25 (6.3)	1.51 (0.91–2.50)
Composite of CV death/total MI/stroke/RI (including SRI)/TIA/Other ATE	38 (9.5)	32 (8.0)	1.20 (0.75–1.93)
MI (excluding silent MI)	24 (6.0)	15 (3.8)	1.63 (0.85–3.11)
Peri-procedural MI	18	12	–
Spontaneous MI	6	3	–
CV death	9 (2.2)	7 (1.8)	1.28 (0.48–3.45)
Stroke	9 (2.2)	6 (1.5)	1.50 (0.54–4.23)
All-cause mortality	10 (2.5)	7 (1.8)	1.42 (0.54–3.74)

Goto S. et al. Circ J 2015;79:2452-60

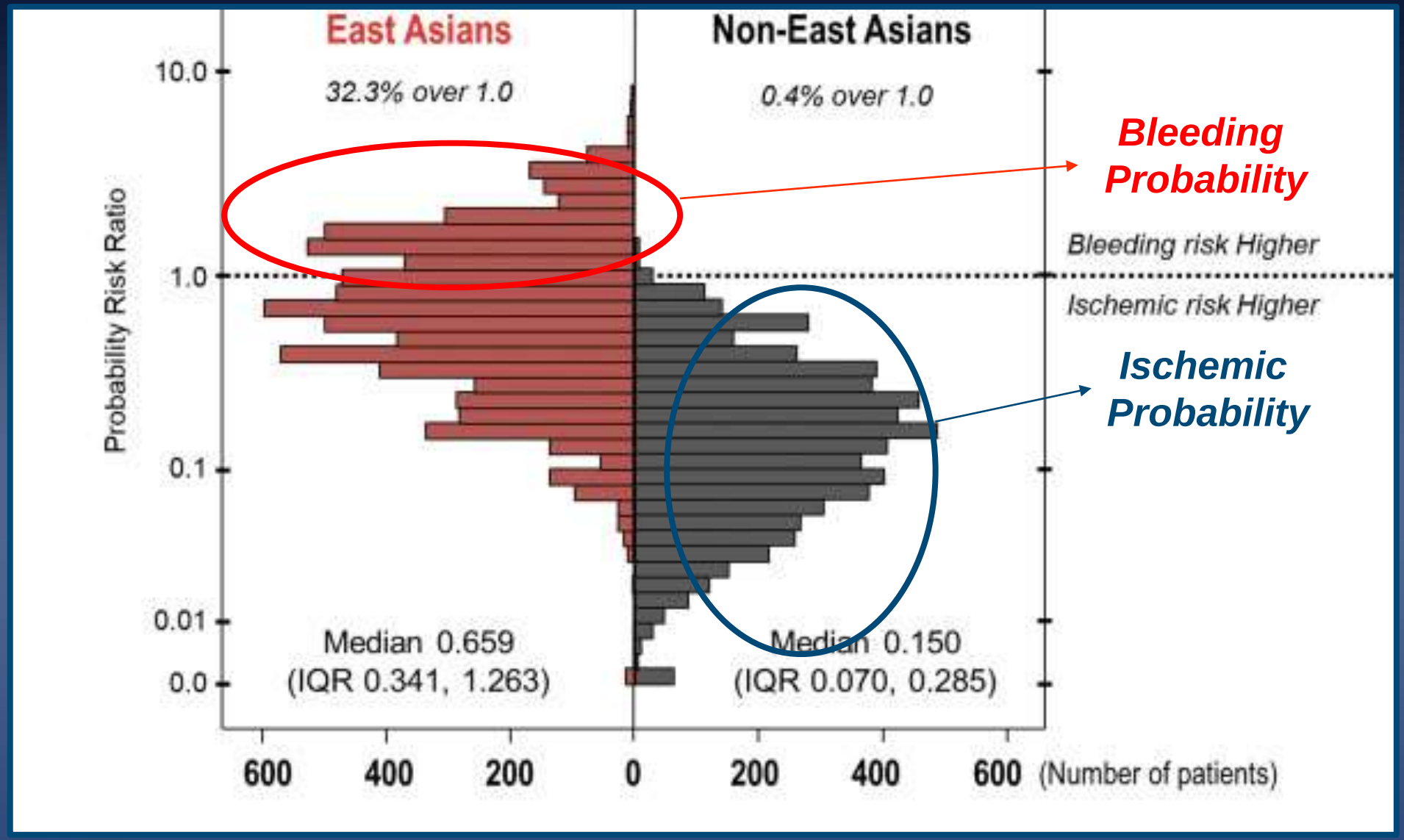
IPD Meta-Analysis (7 RCTs)

DESLATE, EXCELLENT, ITALIC, OPTIMIZE, PRODIGY, RESET, SECURITY



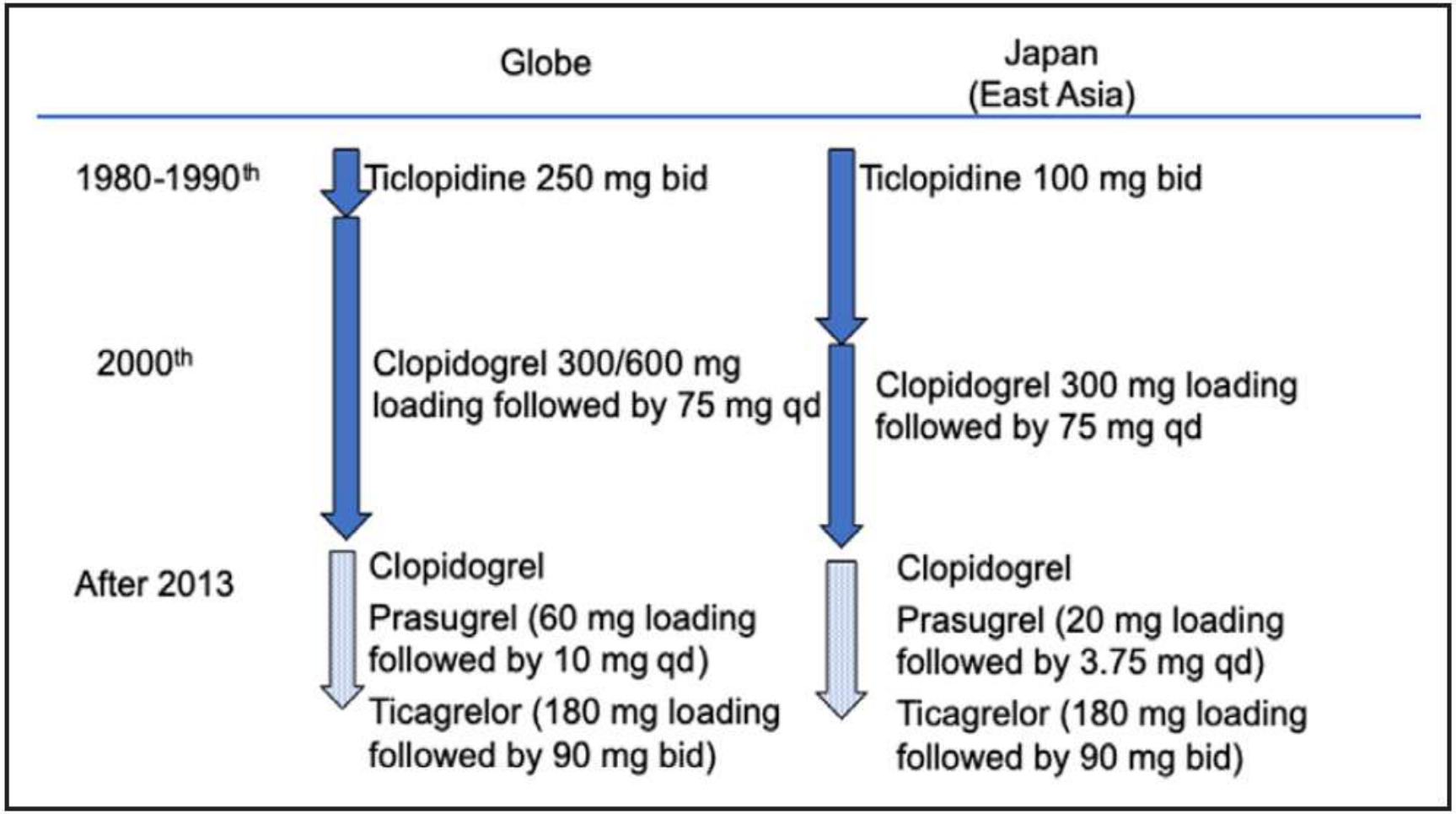
Kang JH et al. Thromb Haemost 2019;119:149–162

Differential Bleeding and Ischemic Tendency



Kang JH et al. Thromb Haemost 2019;119:149–162

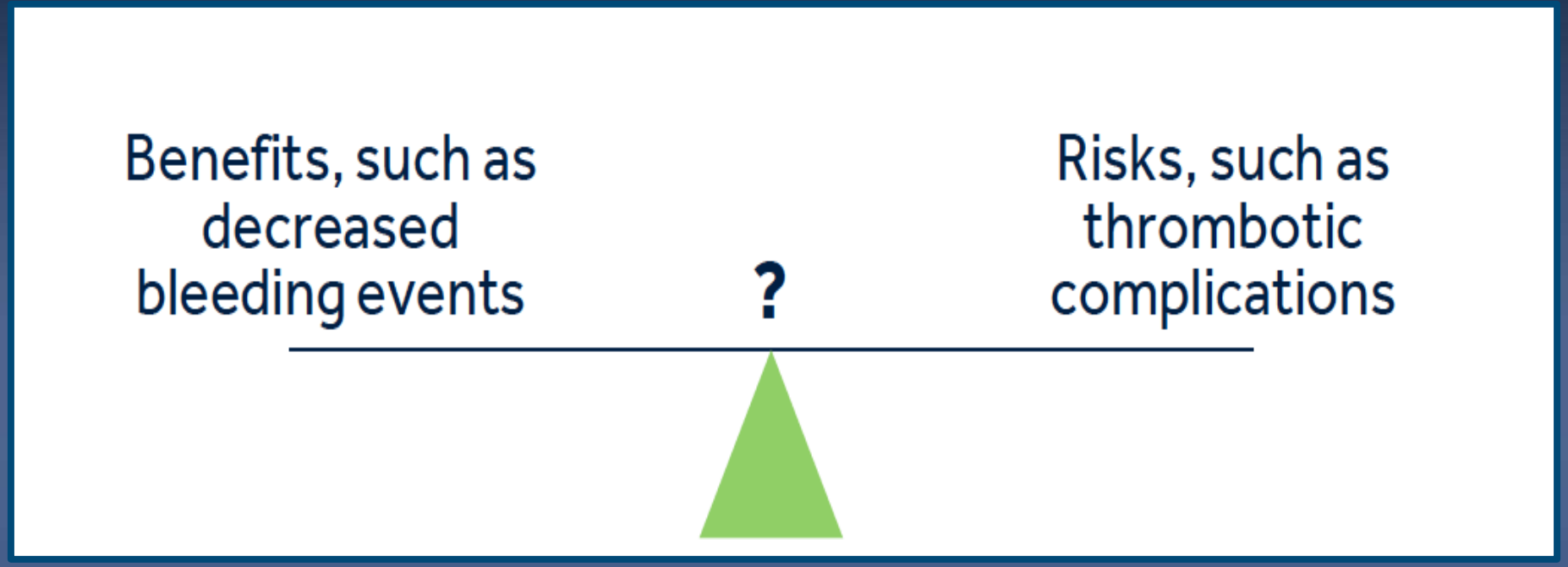
Global Trial or Local One?
:Global doses vs. Local doses in East Asian



Shinya Goto. Circulation. 2019;140:1878–1880

“East-Asian Paradox” How To Do?

Different Dosing and Strategy Is Required for East-Asian Population.

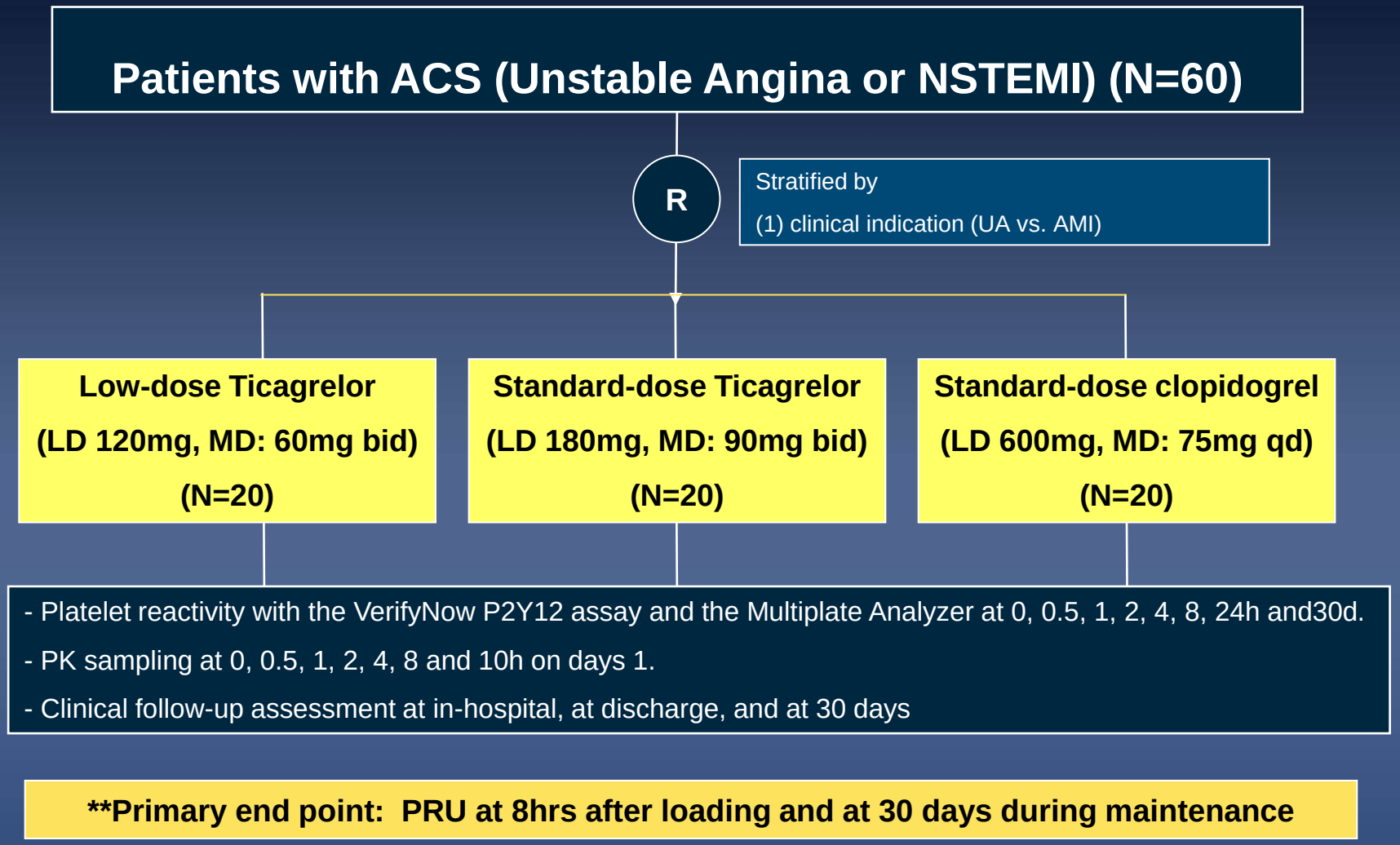


All Hypothesis Should Be Confirmed Through RCTs

RCT to Guide Antithrombotics In "East-Asian Paradox"

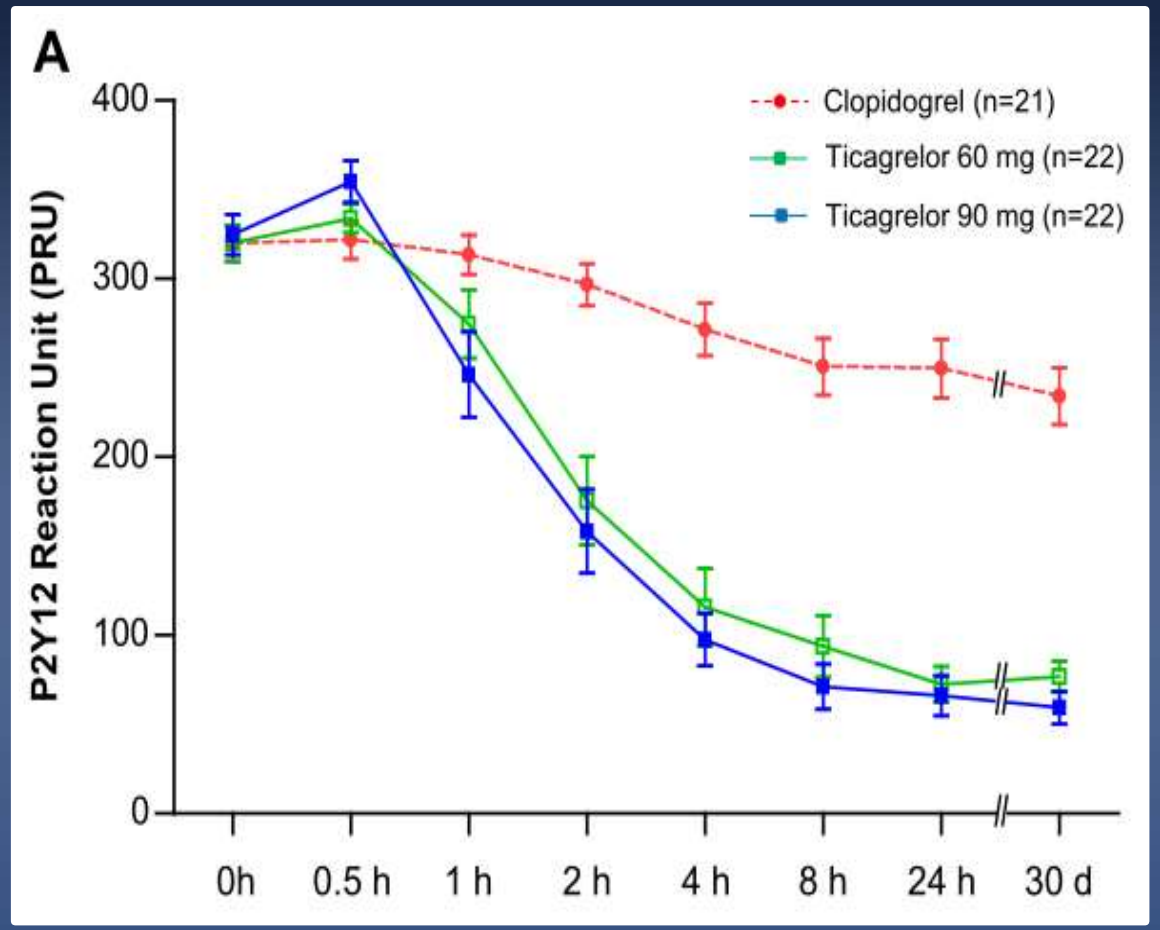
- OPTIMA Trial: PK/PD Trial
- TICAKOREA Trial: Pragmatic Trial
- TICO Trial: P2Y12 Monotherapy in East Asians
- TAILORED-CHIP Trial: New Concept Trial

OPTIMA Trial:
Double-Blinded, RCT for Pharmacodynamics

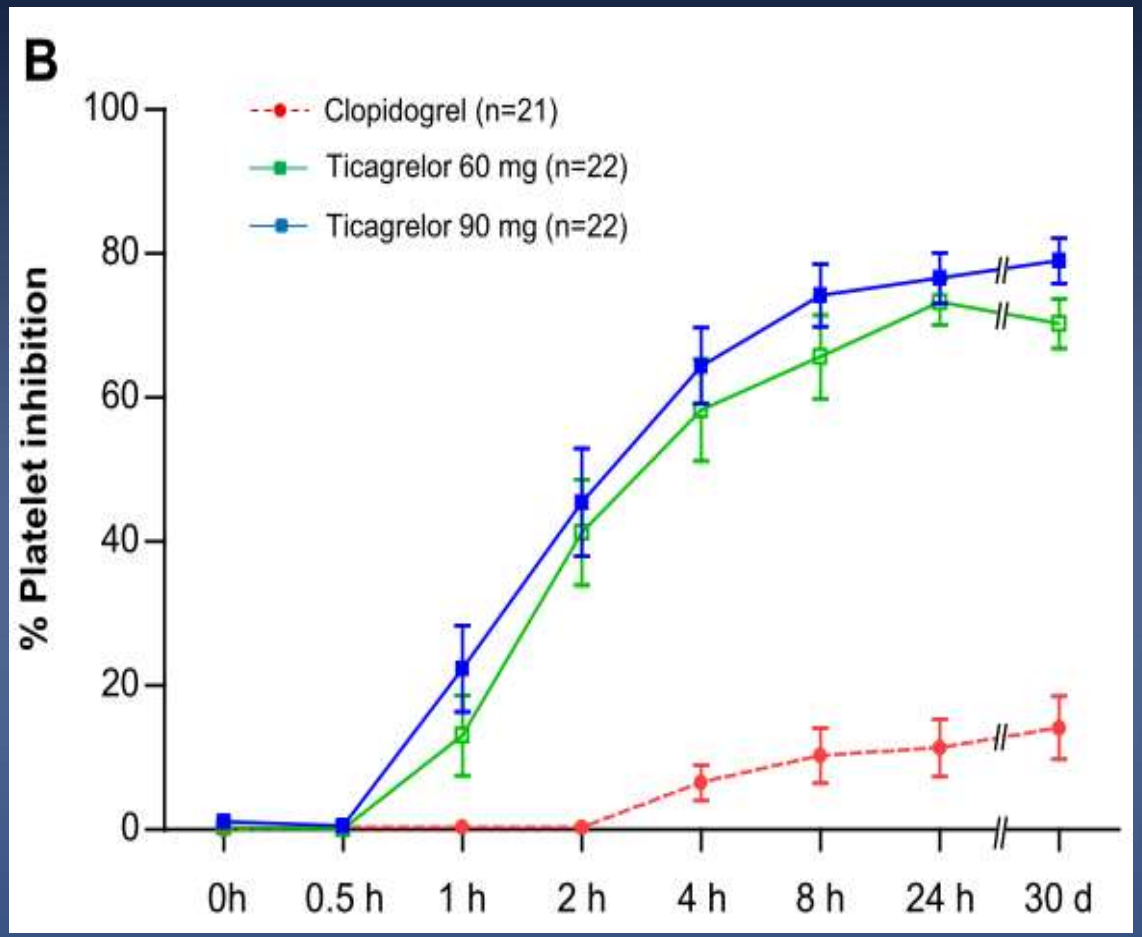


DW Park et al. J Am Coll Cardiol. 2018;71:1594-1595.

Primary Endpoint: P2Y12 - PRU



P2Y12 - % Inhibition

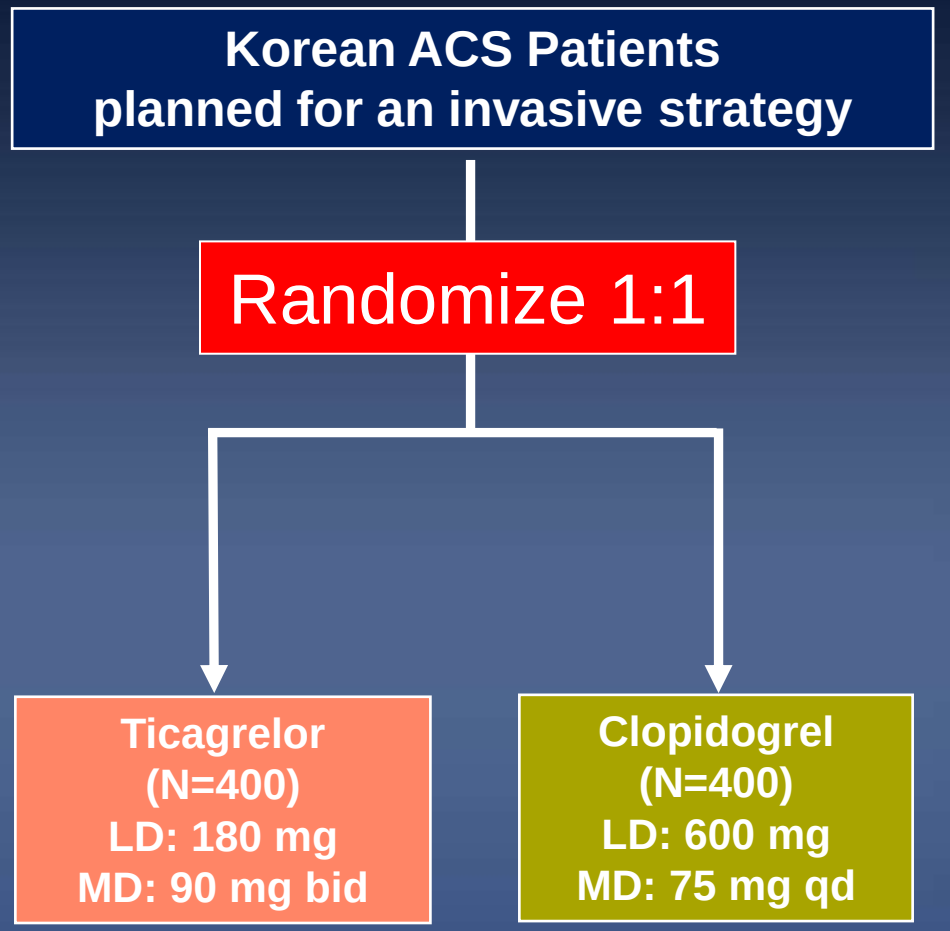


DW Park et al. J Am Coll Cardiol. 2018;71:1594-1595.

TICAKOREA

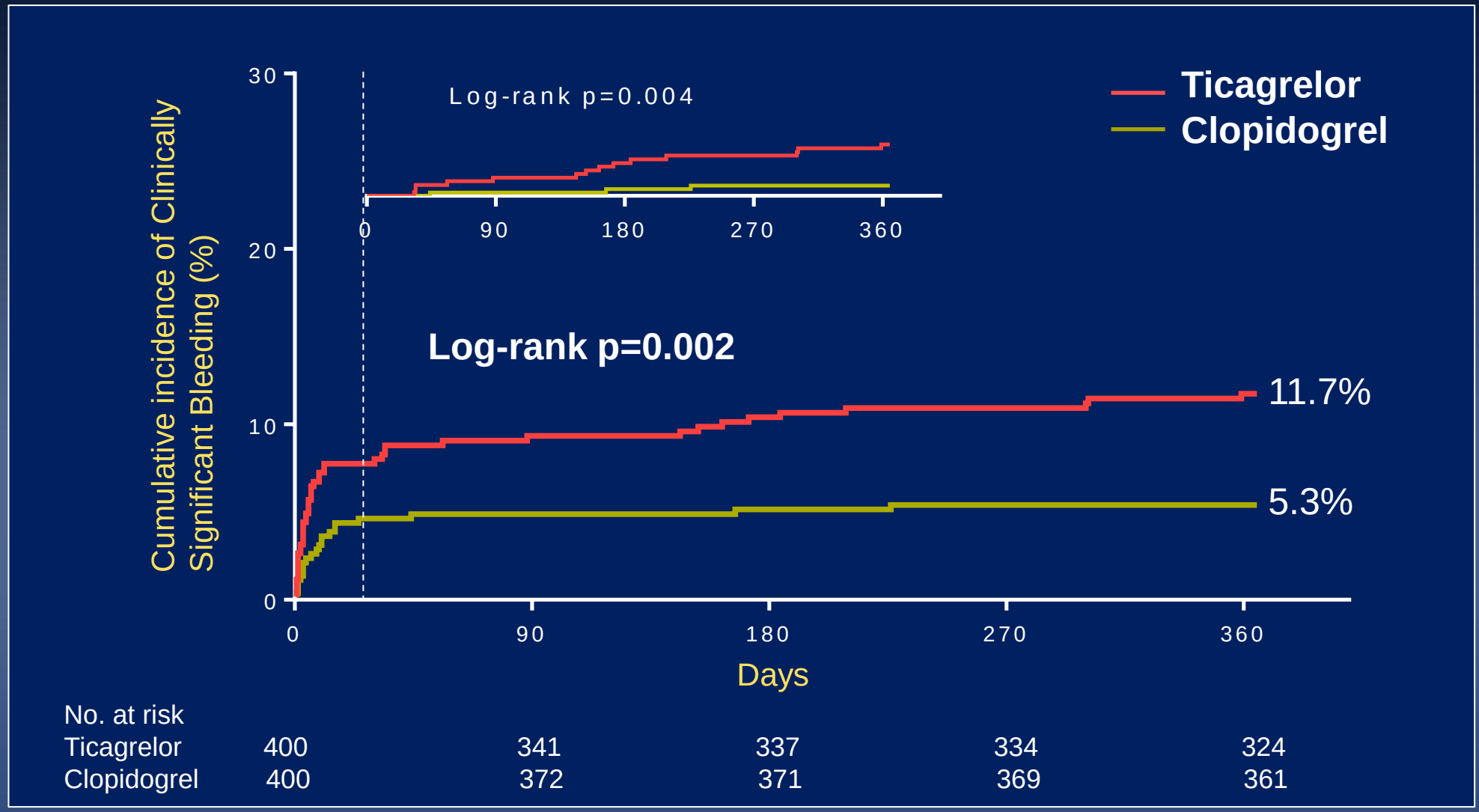
Design

- **DESIGN:** Prospective, open-label, multi-center, investigator-initiated, practical RCT
- **OBJECTIVE:** To compare the safety and effectiveness of standard-dose ticagrelor vs. clopidogrel on top of low-dose aspirin in Korean patients with ACS who were planned for an invasive strategy
- **PRINCIPAL INVESTIGATOR**
  Duk-Woo Park, MD / Seung-Jung Park, MD
  Asan Medical Center, Seoul, South Korea



DW Park et al. Circulation. 2019;140:1865-1877

Primary Safety Endpoint



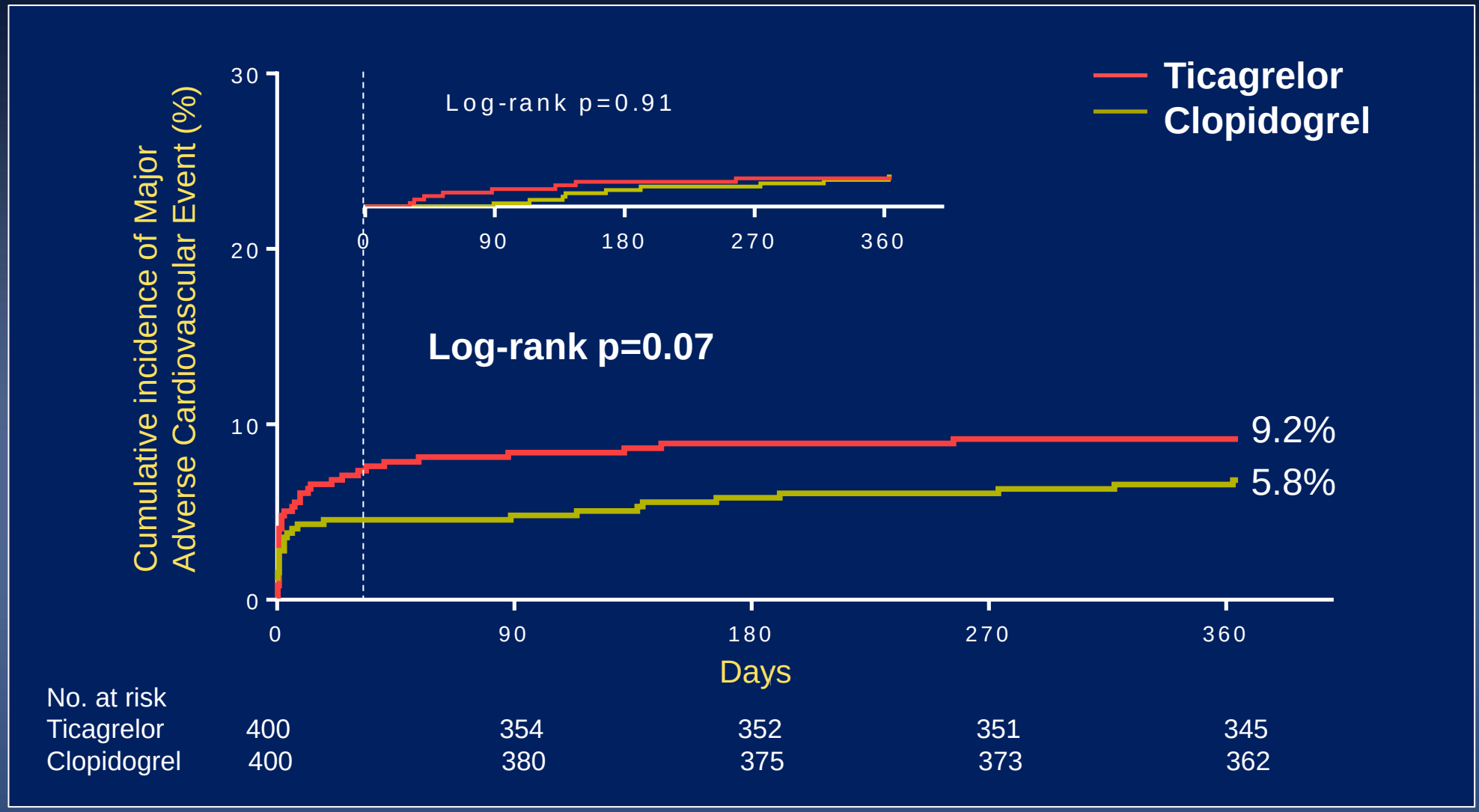
DW Park et al. Circulation. 2019;140:1865-1877

Primary Safety Endpoint and Its Components

Endpoint number (%)	Ticagrelor (N=400)	Clopidogrel (N=400)	HR for Ticagrelor (95% CI)	P value
Clinically significant bleeding (PLATO major or minor bleeding)	**45 (11.7)**	**21 (5.3)**	**2.26 (1.34–3.79)**	**0.002**
Procedure-related	11 (2.8)	7 (1.8)	1.59 (0.62–4.11)	0.34
CABG-related	11 (2.8)	4 (1.0)	2.85 (0.91–8.94)	0.07
Non-procedure or CABG-related	23 (6.0)	10 (2.5)	2.39 (1.14–5.02)	0.02
PLATO major bleeding	**29 (7.5)**	**16 (4.1)**	**1.89 (1.03–3.48)**	**0.04**
Procedure-related	4 (1.0)	5 (1.3)	0.81 (0.22–3.01)	0.75
CABG-related	11 (2.8)	4 (1.0)	2.85 (0.91–8.94)	0.07
Non-procedure or CABG-related	14 (3.7)	7 (1.8)	2.07 (0.84–5.13)	0.12
PLATO minor bleeding	**20 (5.2)**	**5 (1.3)**	**4.16 (1.56–11.1)**	**0.002**
Procedure-related	8 (2.0)	2 (0.5)	4.05 (0.86–19.07)	0.06
CABG-related	0 (0.0)	0 (0.0)	NA	NA
Non-procedure or CABG-related	12 (3.2)	3 (0.8)	4.17 (1.18–14.79)	0.02
Fatal bleeding	**4 (1.0)***	**0 (0.0)**	**NA**	**0.04**

DW Park et al. Circulation. 2019;140:1865-1877

Secondary Efficacy Endpoint



DW Park et al. Circulation. 2019;140:1865-1877

Ticagrelor With Or Without Aspirin In Acute Coronary Syndrome After PCI : Randomized Evaluation Of Ticagrelor Monotherapy After 3-month Dual-antiplatelet Therapy In Acute Coronary Syndrome The TICO trial

ACC.20 Late-Breaking Clinical Trial

Yangsoo Jang, MD. PhD
On the behalf of the TICO trial investigators

YONSEI UNIVERSITY COLLEGE OF MEDICINE
SEVERANCE CARDIOVASCULAR HOSPITAL

JAMA | Original Investigation

Effect of Ticagrelor Monotherapy vs Ticagrelor With Aspirin on Major Bleeding and Cardiovascular Events in Patients With Acute Coronary Syndrome
The TICO Randomized Clinical Trial

Byeong-Keuk Kim, MD; Sung-Jin Hong, MD; Yun-Hyeong Cho, MD; Kyeong Ho Yun, MD; Yong Hoon Kim, MD; Yongsung Suh, MD; Jae Young Cho, MD; Ae-Young Her, MD; Sungsoo Cho, MD; Dong Woon Jeon, MD; Sang-Yong Yoo, MD; Deok-Kyu Cho, MD; Bum-Kee Hong, MD; Hyuckmoon Kwon, MD; Chul-Min Ahn, MD; Dong-Ho Shin, MD; Chung-Mo Nam, PhD; Jung-Sun Kim, MD; Young-Guk Ko, MD; Donghoon Choi, MD; Myeong-Ki Hong, MD; Yangsoo Jang, MD; for the TICO Investigators

IMPORTANCE Discontinuing aspirin after short-term dual antiplatelet therapy (DAPT) was evaluated as a bleeding reduction strategy. However, the strategy of ticagrelor monotherapy has not been exclusively evaluated in patients with acute coronary syndromes (ACS).

OBJECTIVE To determine whether switching to ticagrelor monotherapy after 3 months of DAPT reduces net adverse clinical events compared with ticagrelor-based 12-month DAPT in patients with ACS treated with drug-eluting stents.

DESIGN, SETTING, AND PARTICIPANTS A randomized multicenter trial was conducted in 3056 patients with ACS treated with drug-eluting stents between August 2015 and October 2018 at 38 centers in South Korea. Follow-up was completed in October 2019.

INTERVENTIONS Patients were randomized to receive ticagrelor monotherapy (90 mg twice daily) after 3-month DAPT (n = 1527) or ticagrelor-based 12-month DAPT (n = 1529).

MAIN OUTCOMES AND MEASURES The primary outcome was a 1-year net adverse clinical event, defined as a composite of major bleeding and adverse cardiac and cerebrovascular events (death, myocardial infarction, stent thrombosis, stroke, or target-vessel revascularization). Prespecified secondary outcomes included major bleeding and major adverse cardiac and cerebrovascular events.

RESULTS Among 3056 patients who were randomized (mean age, 61 years; 628 women [20%]; 36% ST-elevation myocardial infarction), 2978 patients (97.4%) completed the trial. The primary outcome occurred in 59 patients (3.9%) receiving ticagrelor monotherapy after 3-month DAPT and in 89 patients (5.9%) receiving ticagrelor-based 12-month DAPT (absolute difference, −1.98% [95% CI, −3.50% to −0.45%]; hazard ratio [HR], 0.66 [95% CI, 0.48 to 0.92]; $P = .01$). Of 10 prespecified secondary outcomes, 8 showed no significant difference. Major bleeding occurred in 1.7% of patients with ticagrelor monotherapy after 3-month DAPT and in 3.0% of patients with ticagrelor-based 12-month DAPT (HR, 0.56 [95% CI, 0.34 to 0.91]; $P = .02$). The incidence of major adverse cardiac and cerebrovascular events was not significantly different between the ticagrelor monotherapy after 3-month DAPT group (2.3%) vs the ticagrelor-based 12-month DAPT group (3.4%) (HR, 0.69 [95% CI, 0.45 to 1.06]; $P = .09$).

CONCLUSIONS AND RELEVANCE Among patients with acute coronary syndromes treated with drug-eluting stents, ticagrelor monotherapy after 3 months of dual antiplatelet therapy, compared with ticagrelor-based 12-month dual antiplatelet therapy, resulted in a modest but statistically significant reduction in a composite outcome of major bleeding and cardiovascular events at 1 year. The study population and lower than expected event rates should be considered in interpreting the trial.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT02494895

Visual Abstract
Supplemental content
CME Quiz at jamacmelookup.com

Author Affiliations: Author affiliations are listed at the end of this article.
Group Information: The TICO Investigators appear at the end of the article.
Corresponding Author: Yangsoo Jang, MD, PhD, Division of Cardiology, Severance Cardiovascular Hospital, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, 03722, Seoul, South Korea (jangys1212@yuhs.ac).

JAMA. 2020;323(23):2407-2416. doi:10.1001/jama.2020.7580

Schematic study design of the TICO trial

HYPOTHESIS.
The switching to ticagrelor monotherapy after 3-M DAPT is superior over the ticagrelor-based 12-M DAPT in the occurrence of net adverse clinical events among ACS patients with DESs

ACS patients undergoing BP-SES (n=3,056)

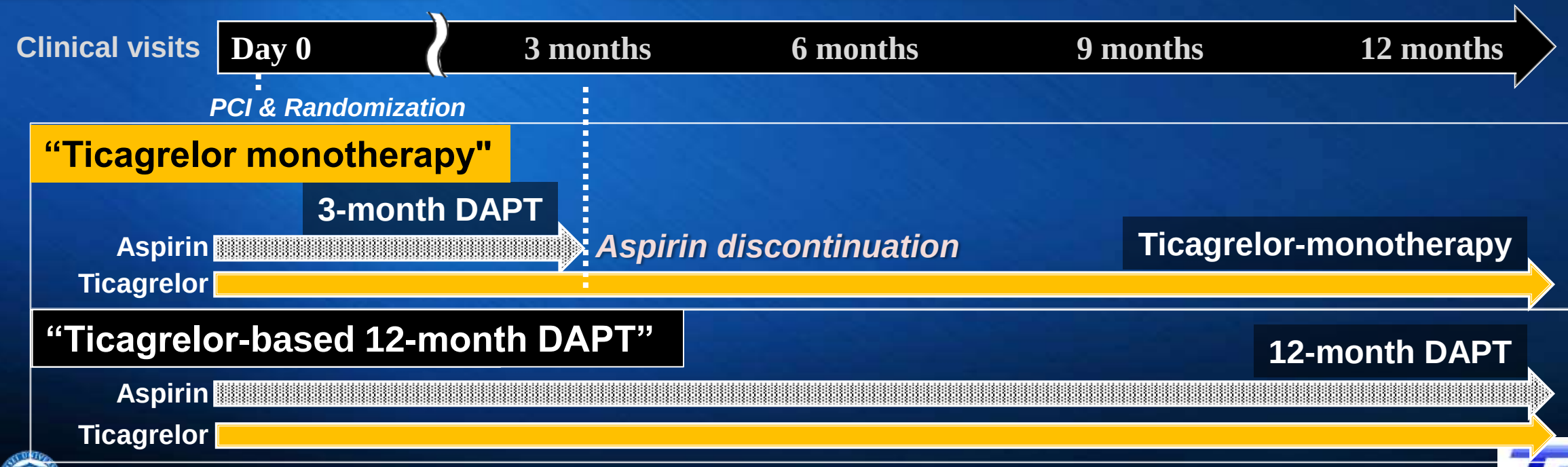
1:1 Randomization

Stratified by DM and STEMI

Ticagrelor monotherapy after 3-month DAPT

Ticagrelor-based 12-month DAPT

Primary endpoint;
Net clinical adverse events @ 12M
: TIMI-major bleeding + MACCE (All death, MI, ST, stroke, and TVR)



YONSEI UNIVERSITY COLLEGE OF MEDICINE
SEVERANCE CARDIOVASCULAR HOSPITAL

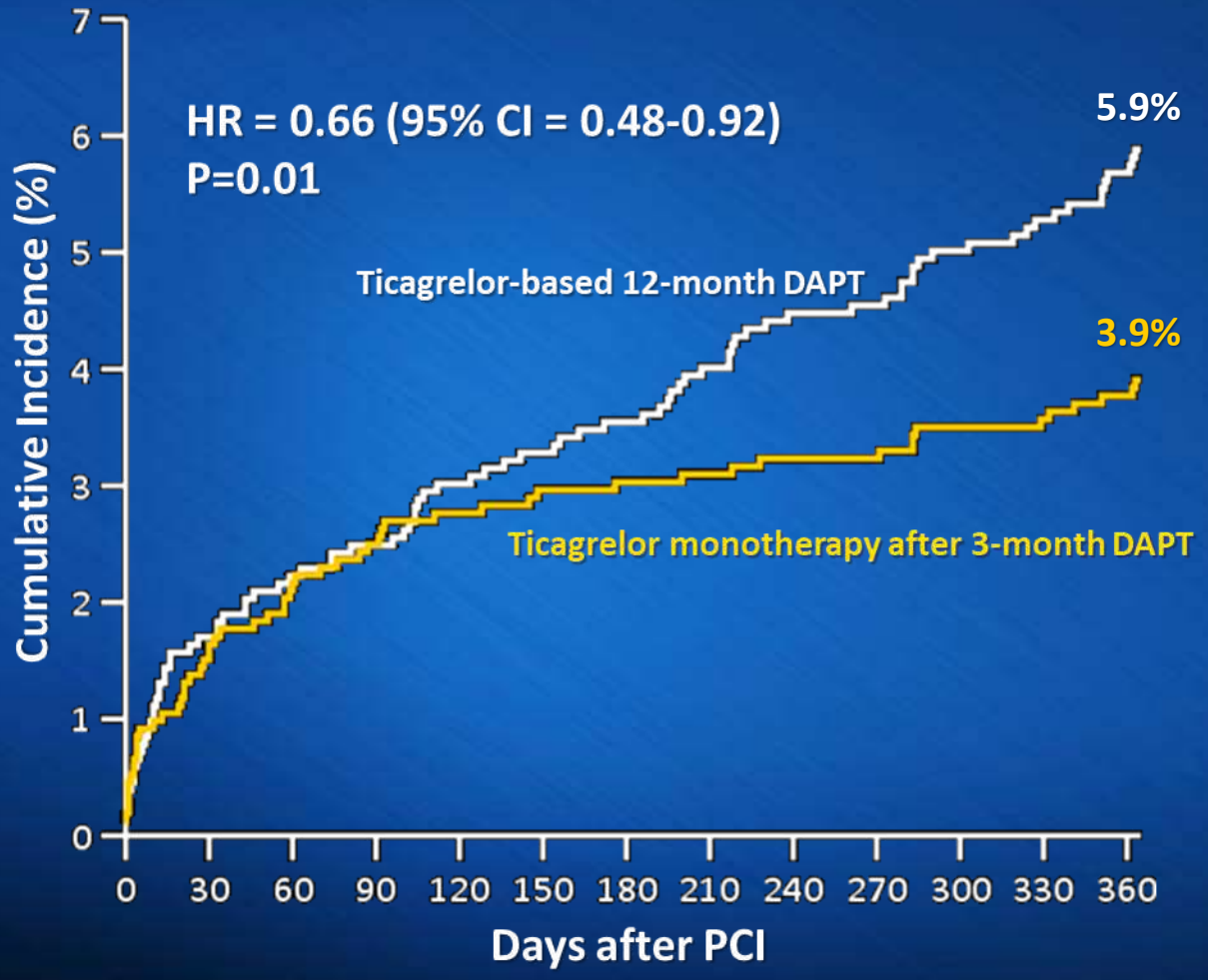
Kim C,...& Kim BK. Am Heart J. 2019 ;212:45-52

Clinicaltrials.gov Identifier: NCT02494895

TICO

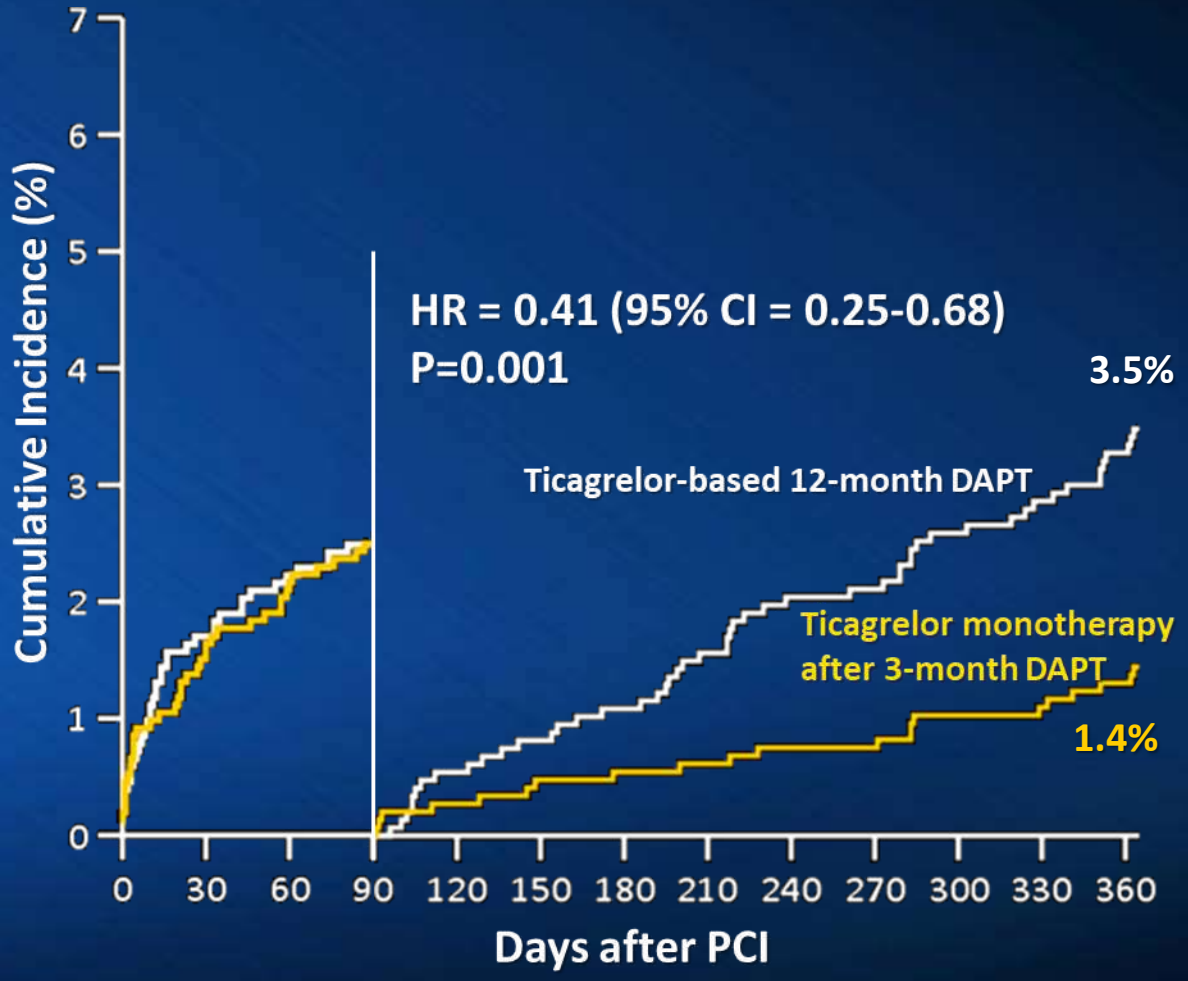
Primary outcome, NACE at 12 months

12-month Clinical Outcome



Conventional	1529	1481	1455	1430	1407
Monotherapy	1527	1471	1452	1437	1424

3-month Land-mark Analyses

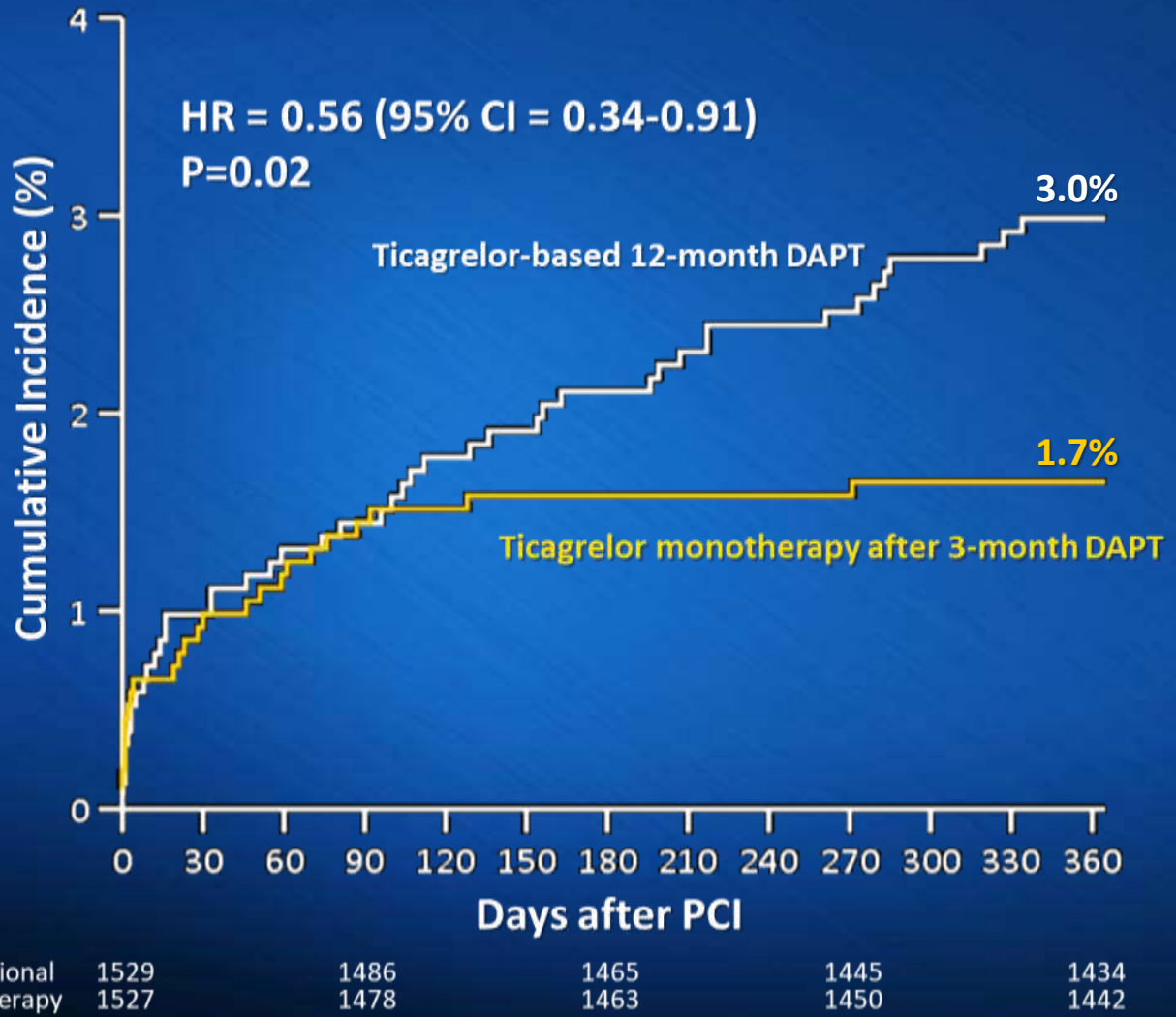


YONSEI UNIVERSITY COLLEGE OF MEDICINE
SEVERANCE CARDIOVASCULAR HOSPITAL

TICO

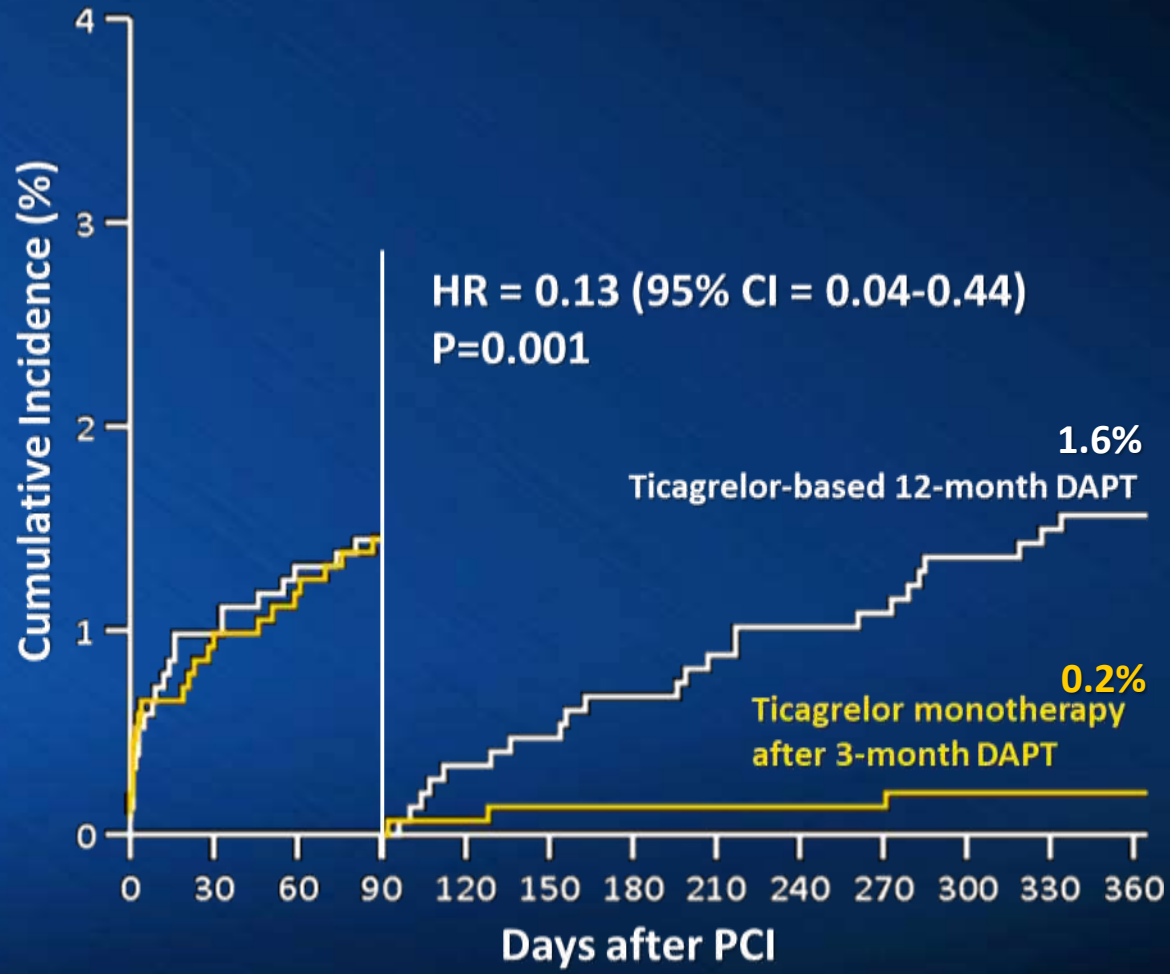
Major Bleeding

12-month Clinical Outcome



Conventional	1529	1486	1465	1445	1434
Monotherapy	1527	1478	1463	1450	1442

3-month Land-mark Analyses

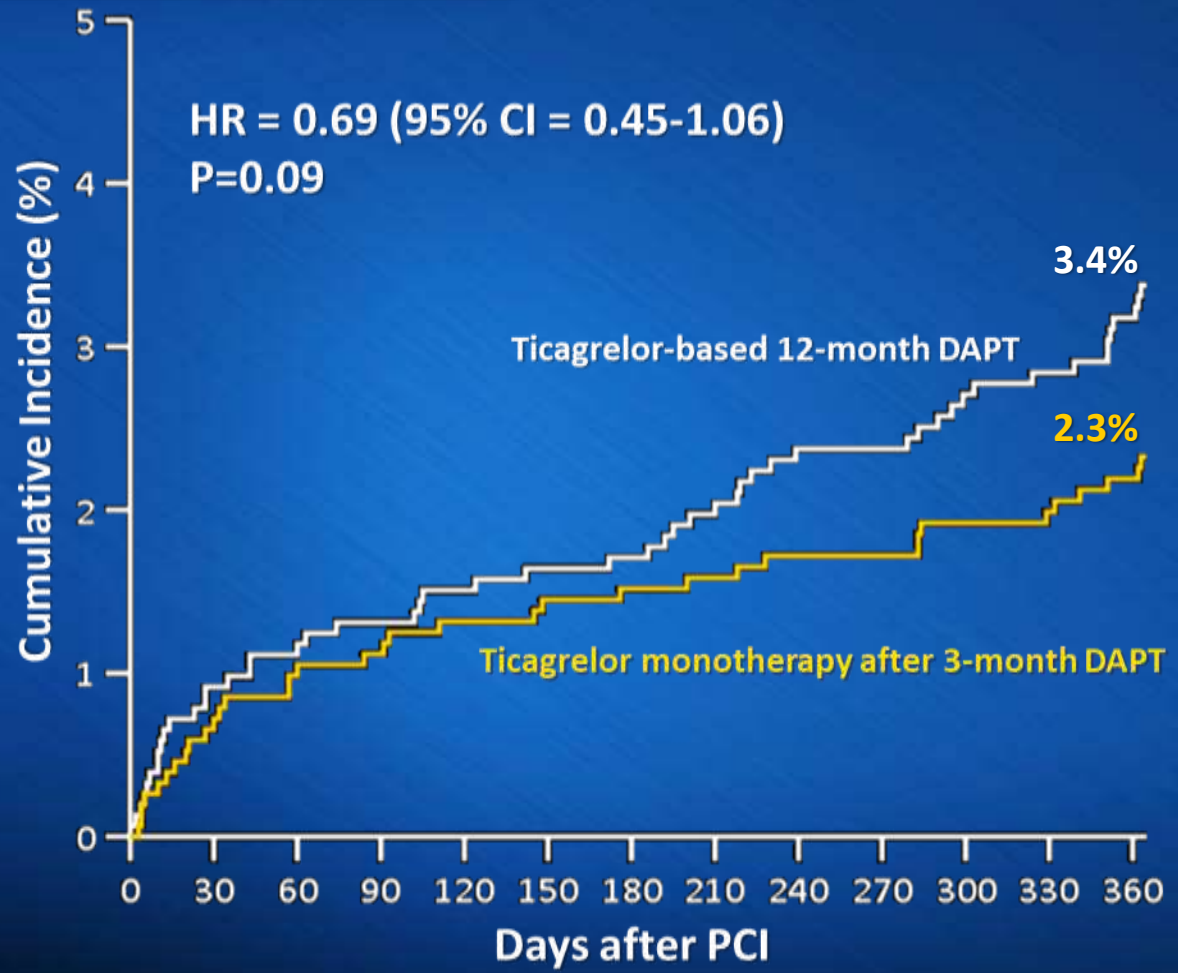


YONSEI UNIVERSITY COLLEGE OF MEDICINE
SEVERANCE CARDIOVASCULAR HOSPITAL

TICO

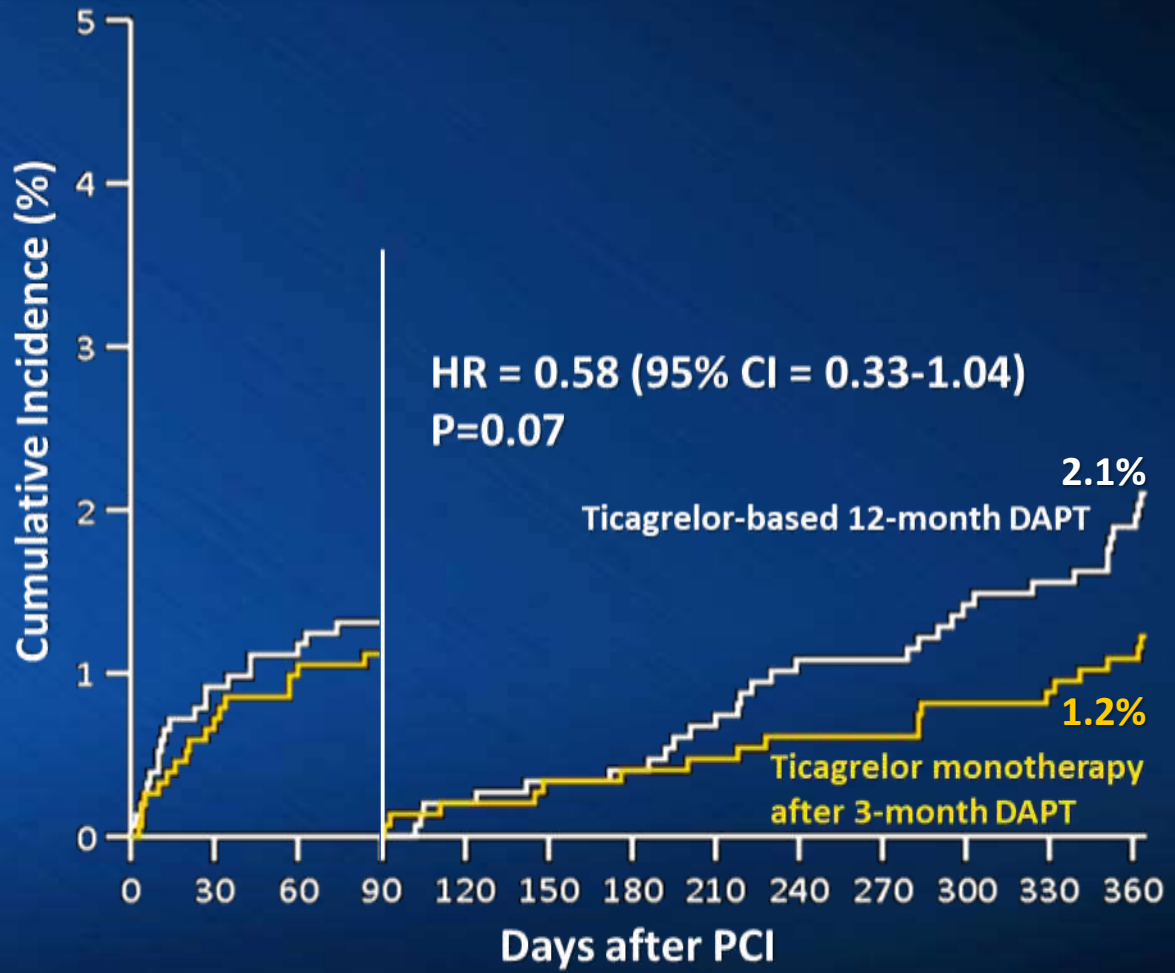
Major Adverse Cardiac and Cerebrovascular Event

12-month Clinical Outcome



Conventional	1529	1498	1482	1462	1444
Monotherapy	1527	1492	1475	1460	1448

3-month Land-mark Analyses



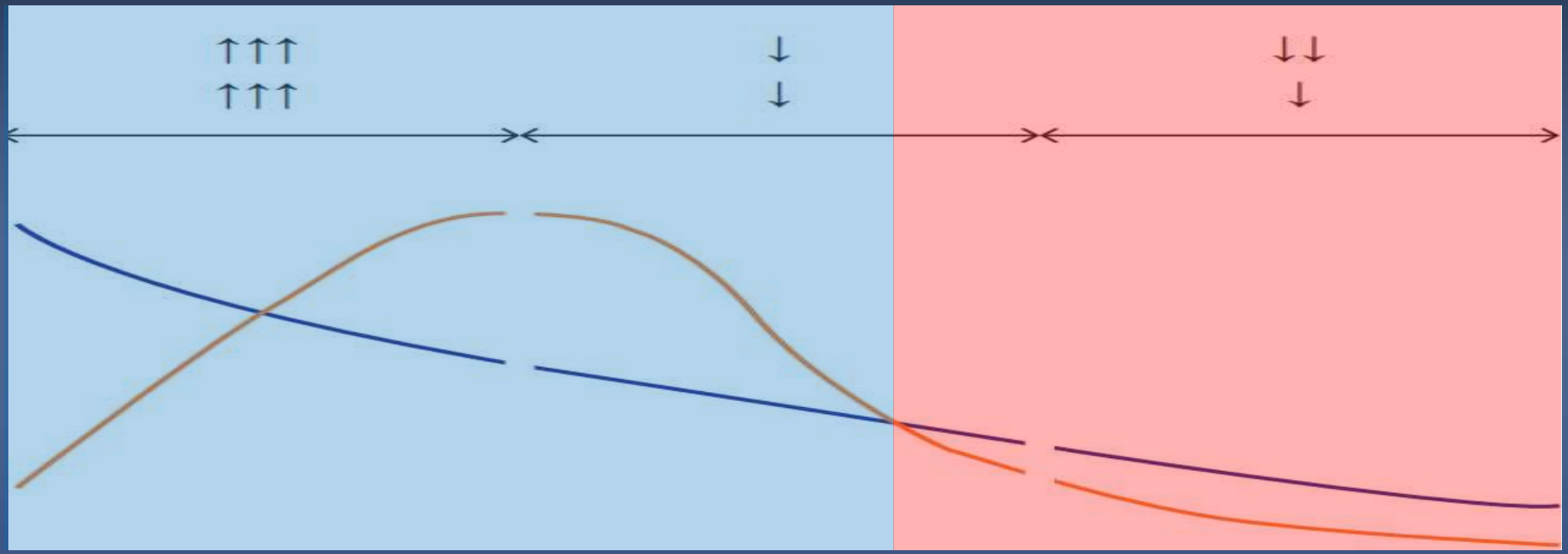
YONSEI UNIVERSITY COLLEGE OF MEDICINE
SEVERANCE CARDIOVASCULAR HOSPITAL

TICO

TAILORED-CHIP Trial: Rationale

Complex High-Risk PCI (CHIP Patients)

"Ischemic vs. Bleeding Balancing Over Time in High-Risk PCI"

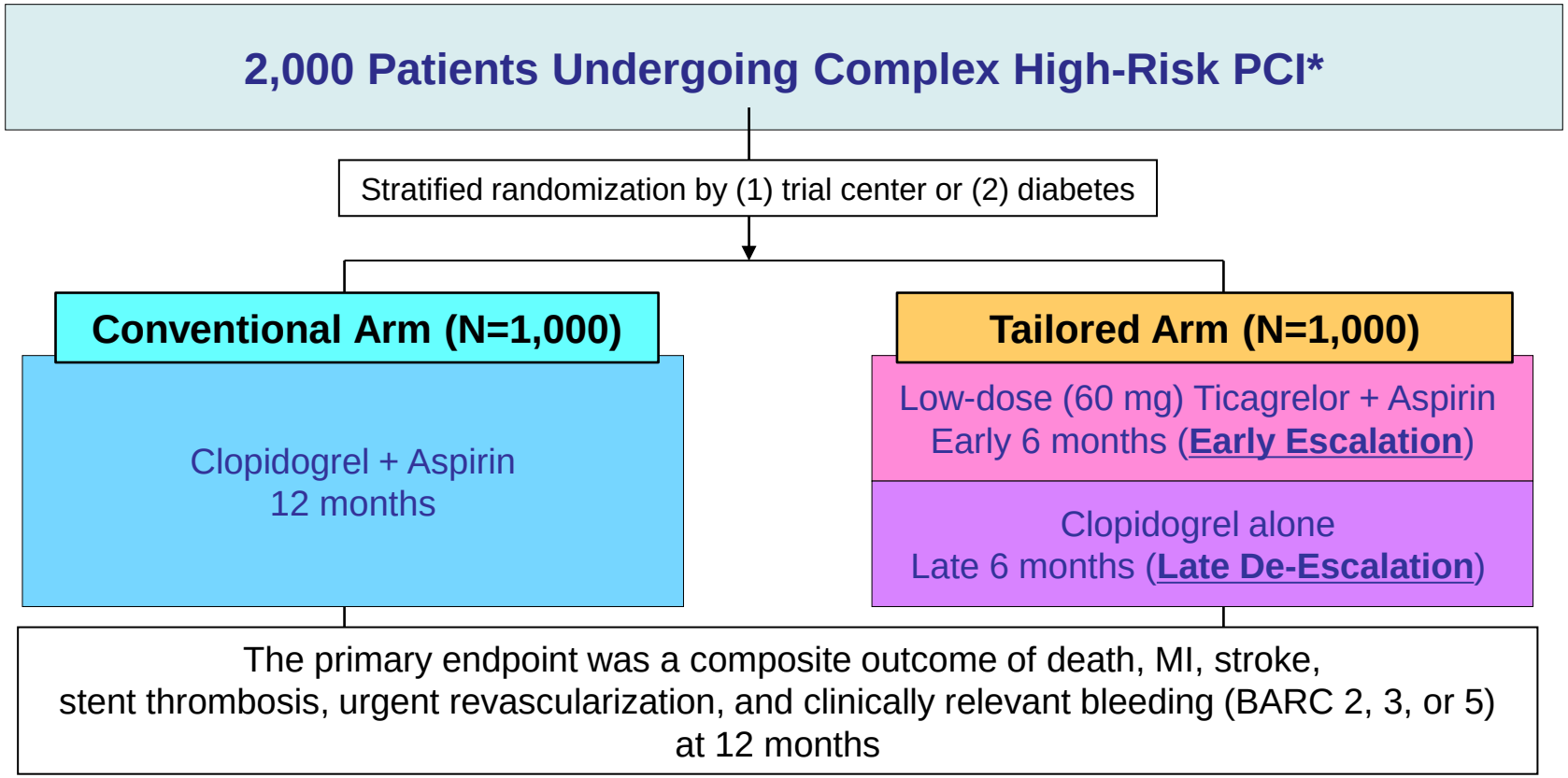


More Potent Strategy
For Ischemic Risk
"Low-Dose Ticagrelor + ASA"

Less Potent Strategy
For Bleeding Risk
"Clopidogrel Only"

TAILored versus C***O***nventional Antith***R***ombotic Strat***E***gy
Inten***D***ed for **C**omplex **HI**gh-Risk **P**CI

TAILORED-CHIP Trial



***Complex High-Risk PCI**

: Left main PCI, chronic total occlusion, bifurcation with 2 stents implanted, severe calcification, diffuse long lesion (lesion length ≥ 30mm), multivessel PCI (≥ 2 vessels stented), ≥3 stents implanted, ≥3 lesions treated, total stent length >60mm, diabetes, CKD (Cr-clearance <60ml/min) or severe LV dysfunction (EF <40%).

Summary

- The “East Asian paradox” describes a differential ischemic and bleeding tendency to antithrombotic agents in East Asian population as compared with Western population.
- The optimal antithrombotic therapy for East Asian population should be a balancing act between less ischemic and more bleeding risks.
- Further dose-finding studies may reveal the best balanced dose of more potent P2Y12 inhibitors (ticagrelor or prasugrel) in East Asian patients, which may not be the same as the global dose (“race-tailored antithrombotic strategies”).