"East-Asian Paradox" De-Escalation Strategy of Ticagrelor

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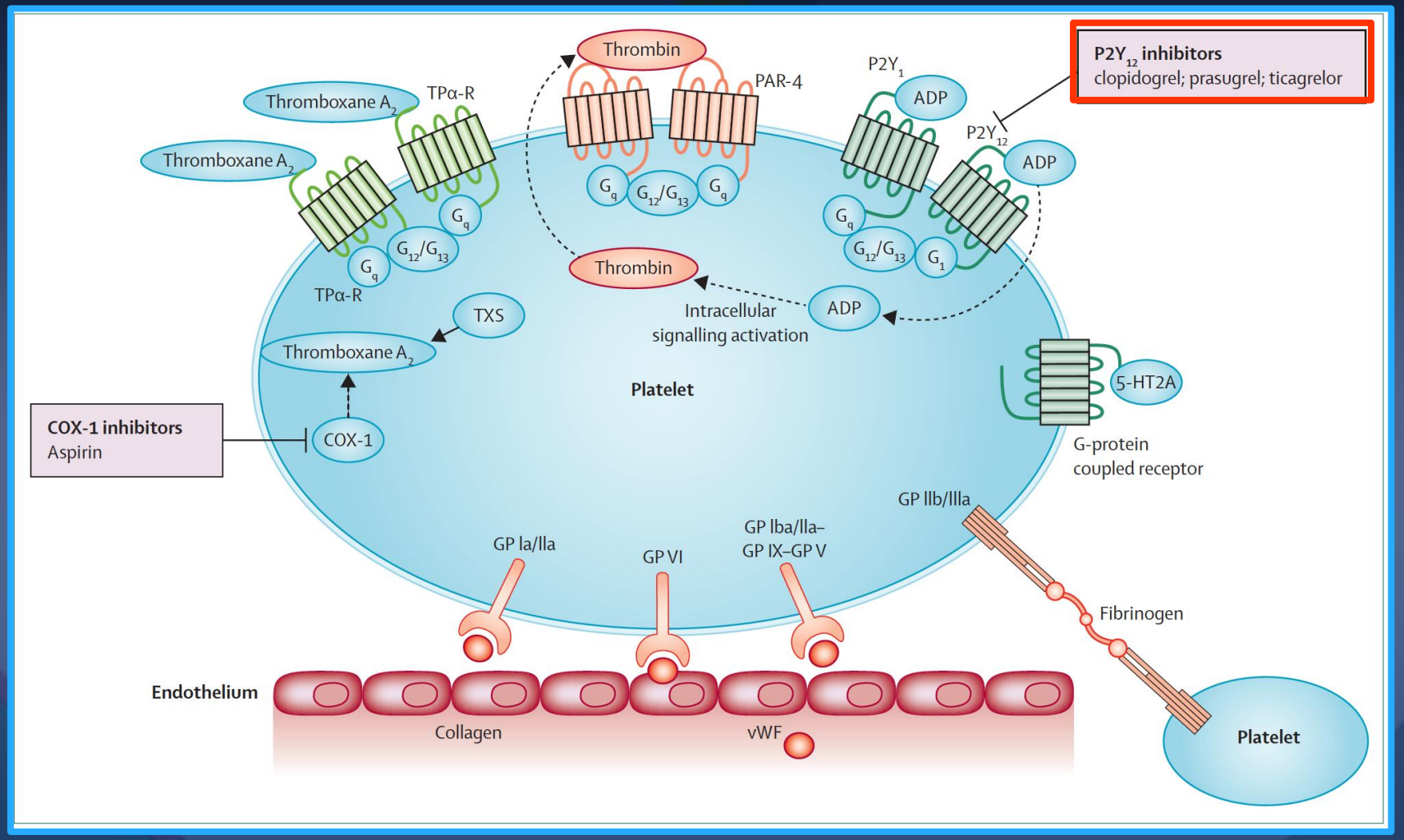
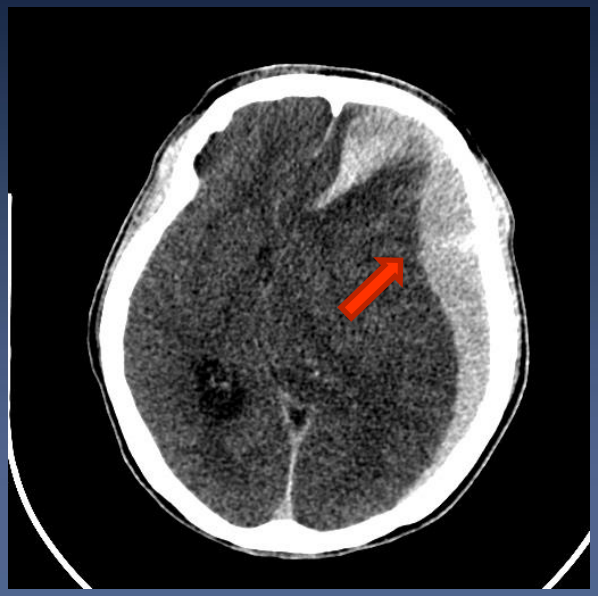
Disclosure Statement of Financial Interest

- Research funding from Chong Kun Dang pharmaceutical Corp, AstraZeneca, Accumetrics, Daiichi Sankyo.

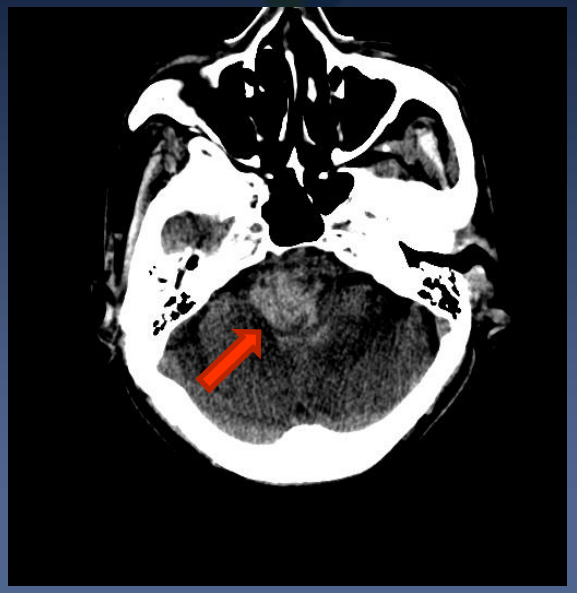
Contemporary P2Y12 Inhibitors



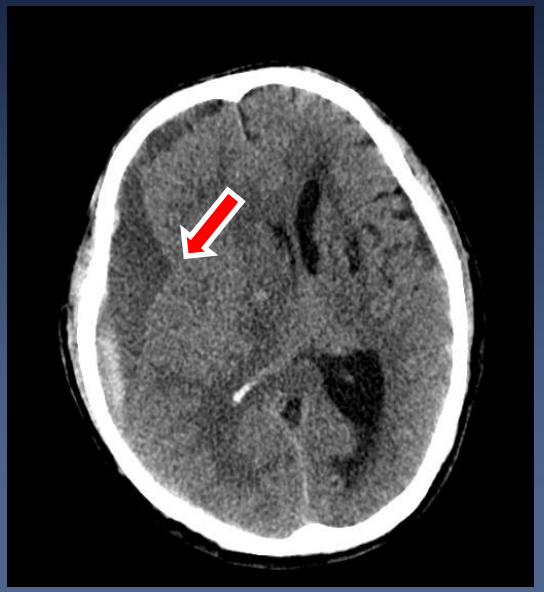
Fatal Case Series



74/F, ACS, PCI
Extensive subdural hemorrhage
after ticagrelor use
➔ Expired



74/M, ACS, PCI
Acute ICH, pons
after ticagrelor use
➔ Expired



70/M, ACS, PCI
Multiple SDH
after ticagrelor use
➔ Vegetative state

Current P2Y12 Guidelines in ACS/PCI

- Current European and US guidelines recommend that use of ticagrelor or prasugrel in preference to clopidogrel is reasonable for ACS patients with or without PCI.
- However, several studies suggested that East Asian patients had differential ischemic and bleeding propensity in response to antithrombotic treatment compared with Western patients (the so-called **'East Asian paradox'**)

Optimal Antiplatelet Therapy: Ethnic Difference

“East-Asian Paradox”

EXPERT CONSENSUS DOCUMENT

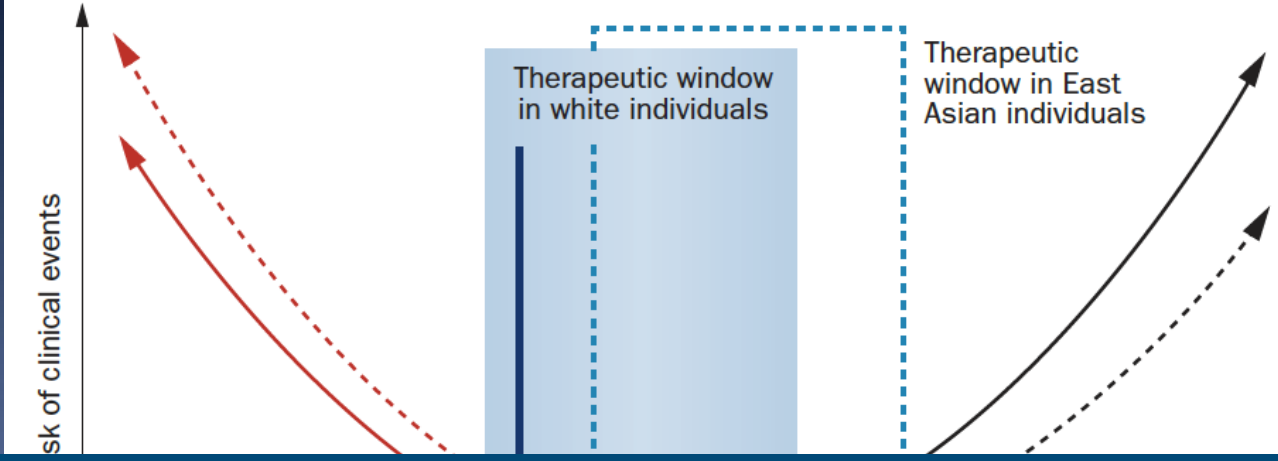
World Heart Federation expert consensus statement on antiplatelet therapy in East Asian patients with ACS or undergoing PCI

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

Abstract | Guideline recommendations on the use of dual antiplatelet therapy (DAPT) in patients with acute coronary syndromes and in those undergoing percutaneous coronary intervention (PCI) have been formulated by both the ACC/AHA and the ESC. These recommendations are based primarily on large, phase III, randomized, controlled trials of the $P2Y_{12}$ inhibitors clopidogrel, prasugrel, and ticagrelor. However, few East Asian patients have been included in the trials to assess the use of these agents, particularly the newer agents prasugrel and ticagrelor. Additionally, an increasing body of data suggests that East Asian patients have differing risk profiles for both thrombophilia and bleeding compared with white patients, and that a different ‘therapeutic window’ of on-treatment platelet reactivity might be appropriate in East Asian patients. Furthermore, a phenomenon referred to as the ‘East Asian paradox’ has been described, in which East Asian patients have a similar or even a lower rate of ischaemic events after PCI compared with white patients, despite a higher level of platelet reactivity during DAPT. Recognizing these concerns, the World Heart Federation has undertaken this evidence-based review and produced this expert consensus statement to determine the antiplatelet treatment strategies that are most appropriate for East Asian patients.

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

East-Asian Paradox



Which Dose Is Optimal for East-Asian Patients?

— Bleeding risk in white individuals
- - - Bleeding risk in East Asian individuals
— Ischaemic risk in white individuals
- - - Ischaemic risk in East Asian individuals

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. 11, 597–606 (2014);

Clinical Phenotype of "East-Asian Paradox" What It Is?

The 'East Asian paradox' describes a phenomenon in which, despite a higher level of platelet reactivity in response to antiplatelet therapy, East Asian patients have **a similar or even lower rate of ischemic events** and **a higher rate of bleeding events** after ACS or PCI compared with white patients.

Always "Under-Report of Events" critics from many, many reviewers for our submitted papers

Plausible Mechanisms of "East-Asian Paradox"

- 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)
- A relatively small body size and lower renal clearance in Asian patients
- Thus, the relative tradeoff "sweet spot" between ischemia & bleeding may be different

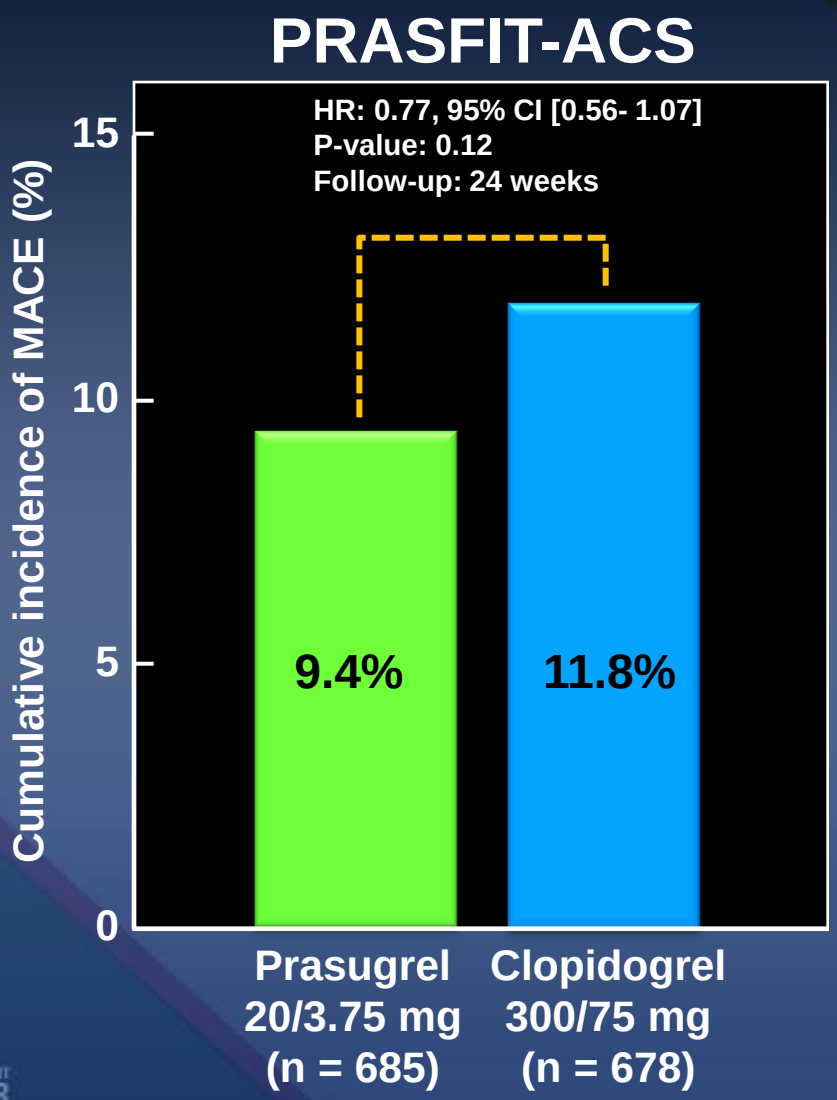
Clinical Evidences and Experiences of P2Y12 Inhibitors in East Asian Patients

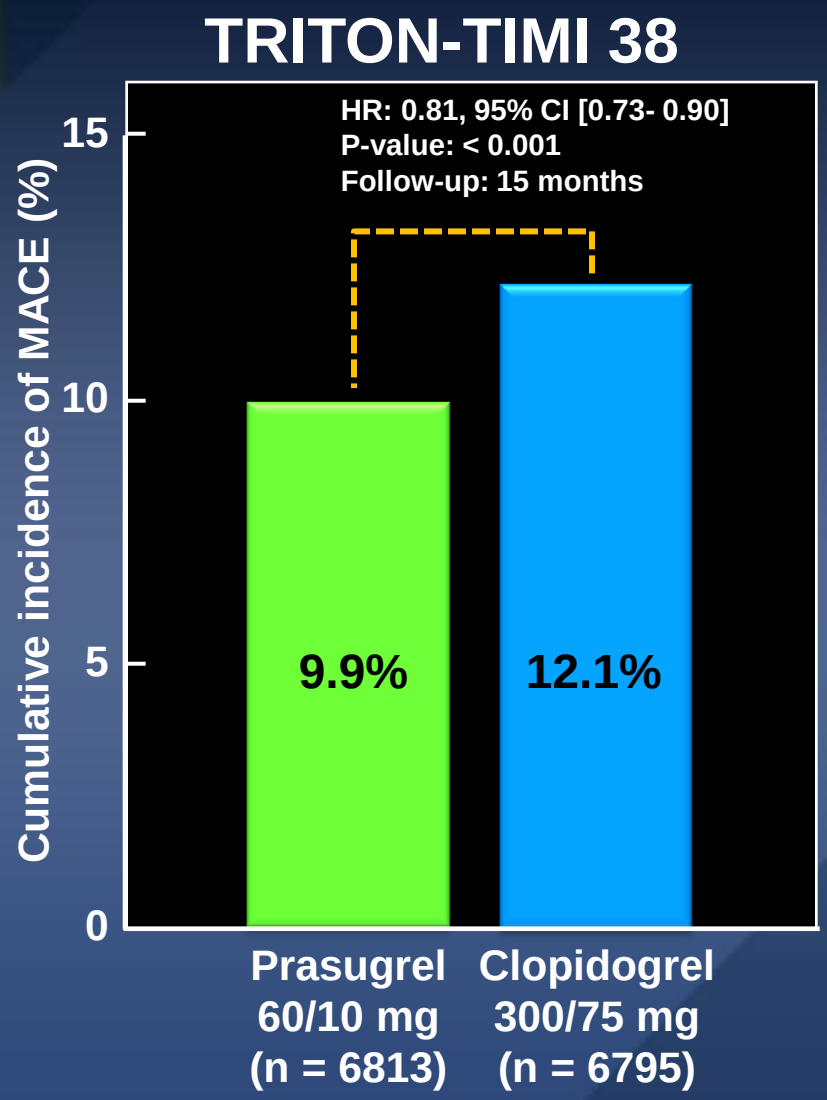
This Hypothesis Was Realized in the Japanese Drug-Approval Trials

1. PRASFIT-ACS trials suggested the efficacy and safety profile of 20 mg loading and 3.75 mg maintenance dose of prasugrel (around 1/3 of US dose)
2. PHILO trial suggested ticagrelor (180 mg loading dose plus 90 mg twice daily maintenance dose) may be harmful for especially Japanese patients.

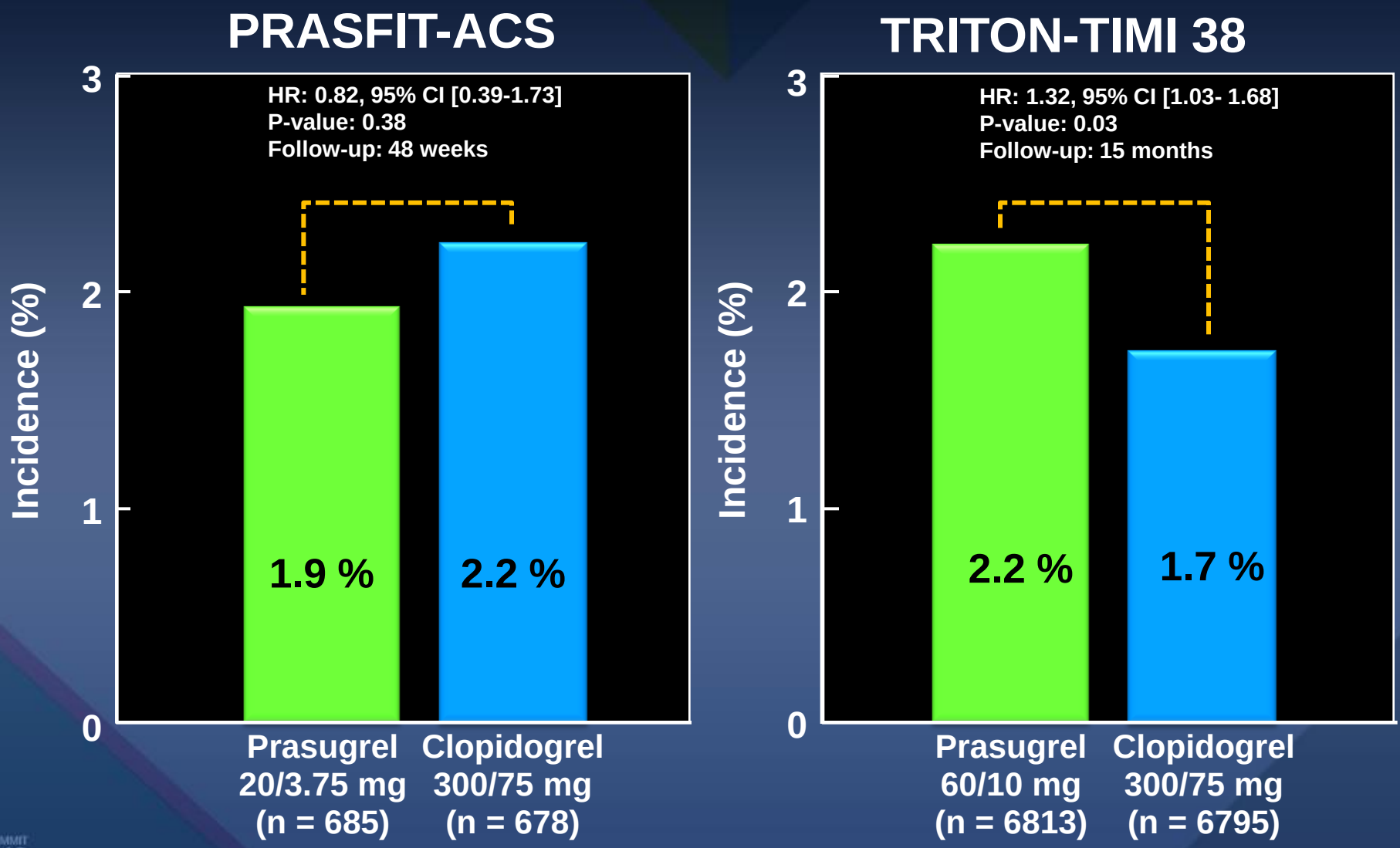
Saito S. et al. Circ J 2014;78:1684-92
Goto S. et al. Circ J 2015;79:2452-60

Primary Endpoint of PRASFIT-ACS and TRITON-TIMI 38





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



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

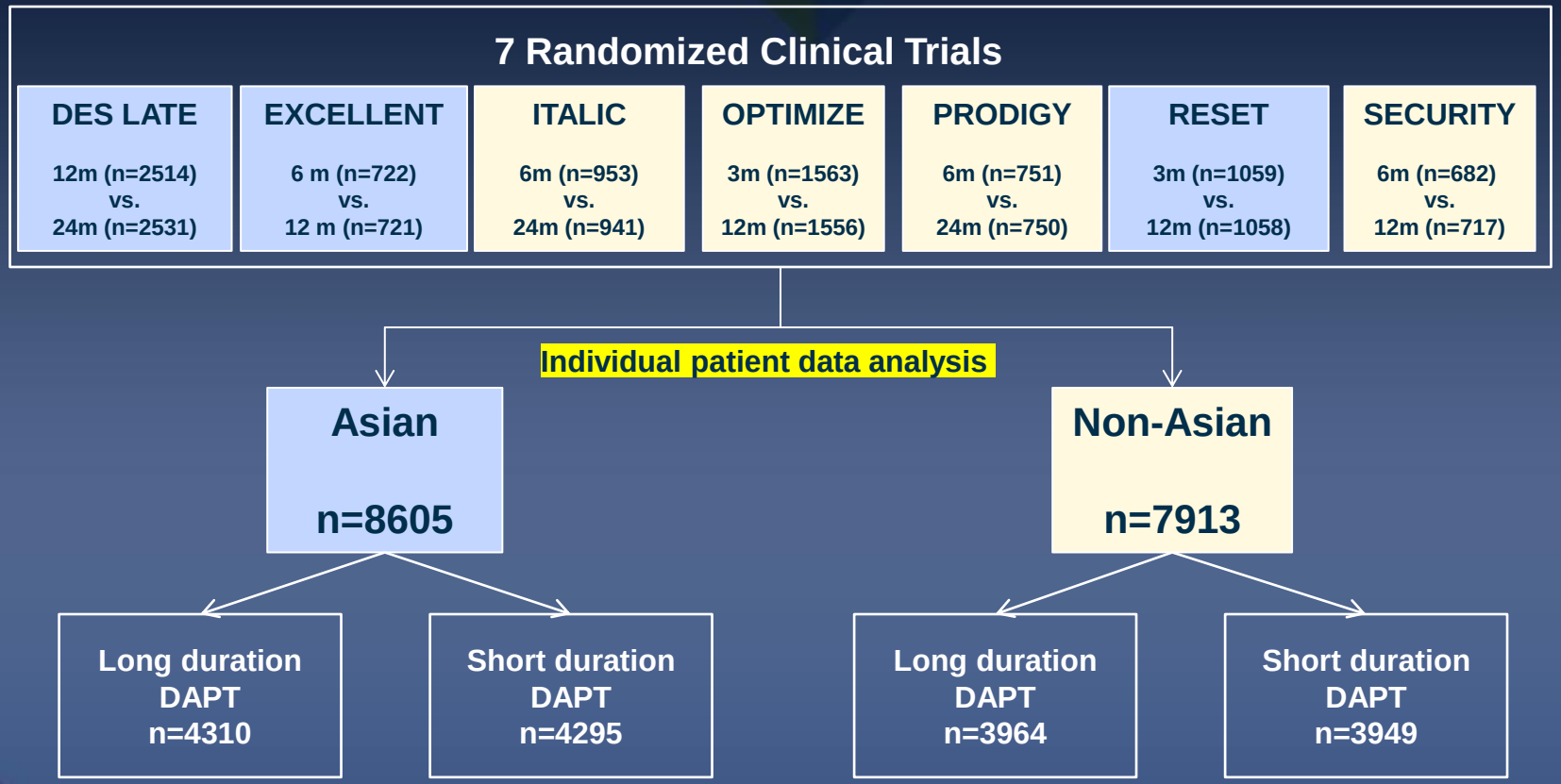
PHILO trial with ticagrelor

- PHILO was designed to explore the consistency of the eff ects of ticagrelor in PLATO patients with patients from Ea st Asian countries.

	Ticagrelor	Clopidogrel	OR (95%CI)	P-value
	N=401	N=400		
Composite end point	43	28	1.60(0.97-2.62)	0.08
Death	10	7	1.44(0.54-4.25)	0.63
Stroke	9	6	1.51(0.54-4.25)	0.60
MI	24	15	1.63(0.85-3.15)	0.19
Bleeding*	92	56	1.83(1.27-2.63)	0.001
Net clinical Benefit**	76	51	1.6(1.09-2.35)	0.02

MI (excluding silent), * PLATO defined, ** PLATO defined as CV death, MI, stroke, or CABG related or non CABG related major bleeding.

Patient Level Meta-Analysis (7 RCTs)

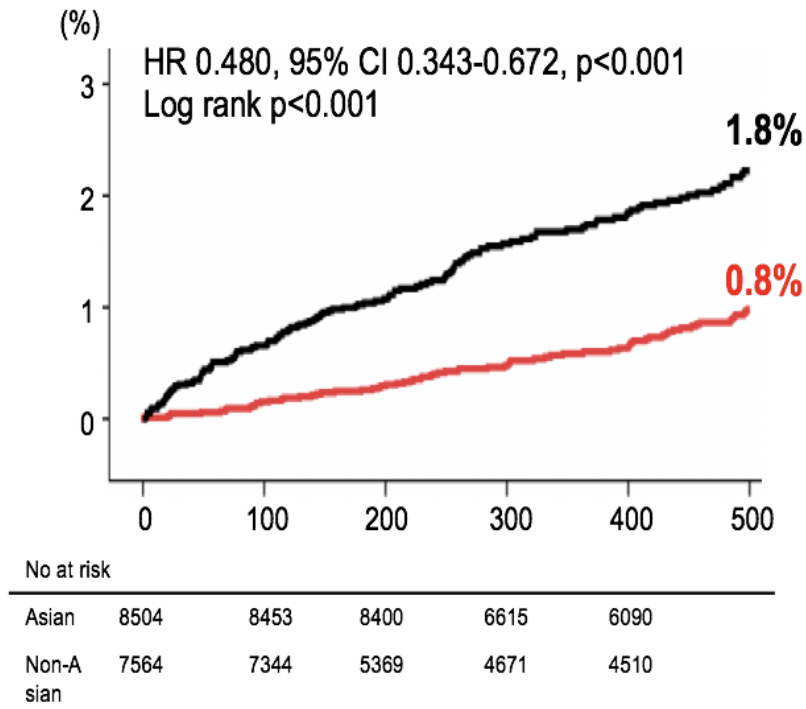


Courtesy by Dr. Park KW. submitted

Disparity in ischemia and bleeding risk (according to ethnicity)

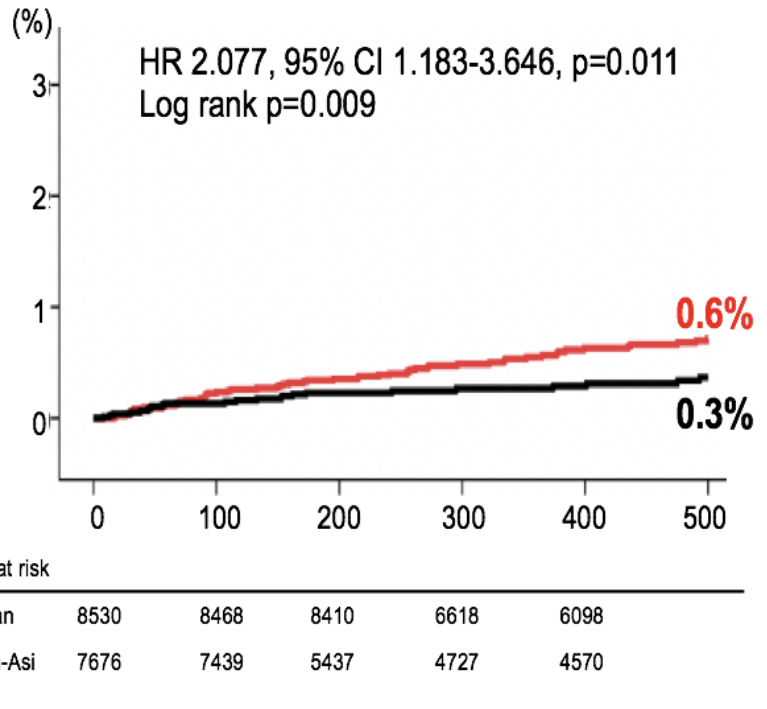
Asian
Non-Asians

A. Ischemic outcomes



No at risk					
Asian	8504	8453	8400	6615	6090
Non-Asian	7564	7344	5369	4671	4510

B. Bleeding outcomes



No at risk					
Asian	8530	8468	8410	6618	6098
Non-Asian	7676	7439	5437	4727	4570

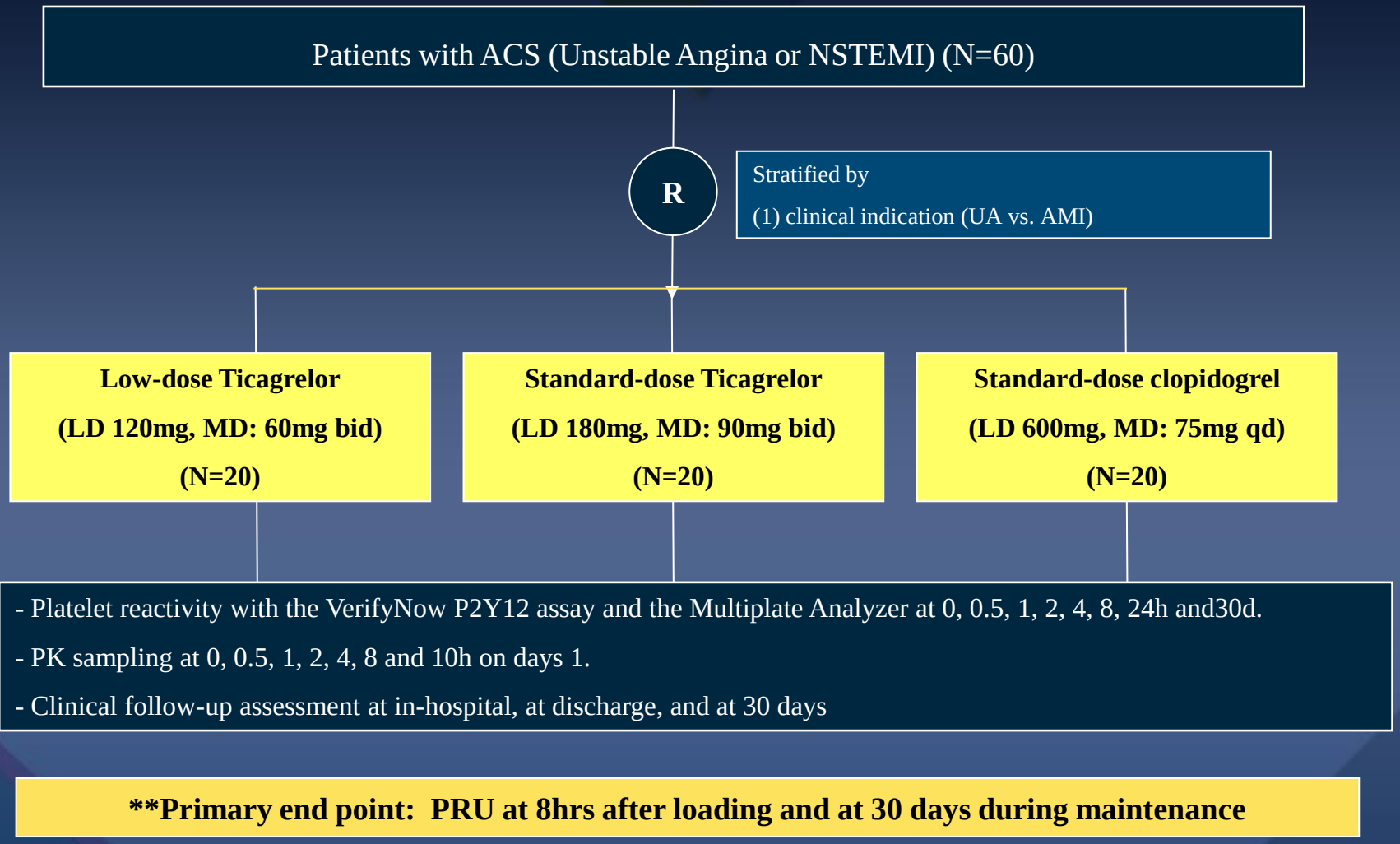
Courtesy by Dr. Park KW. submitted

A Randomized Double-Blind Trial Evaluating Platelet Inhibition with Low-Dose Ticagrelor versus Standard-Dose Ticagrelor and Clopidogrel in Acute Coronary Syndromes:

The OPTIMA Trial

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

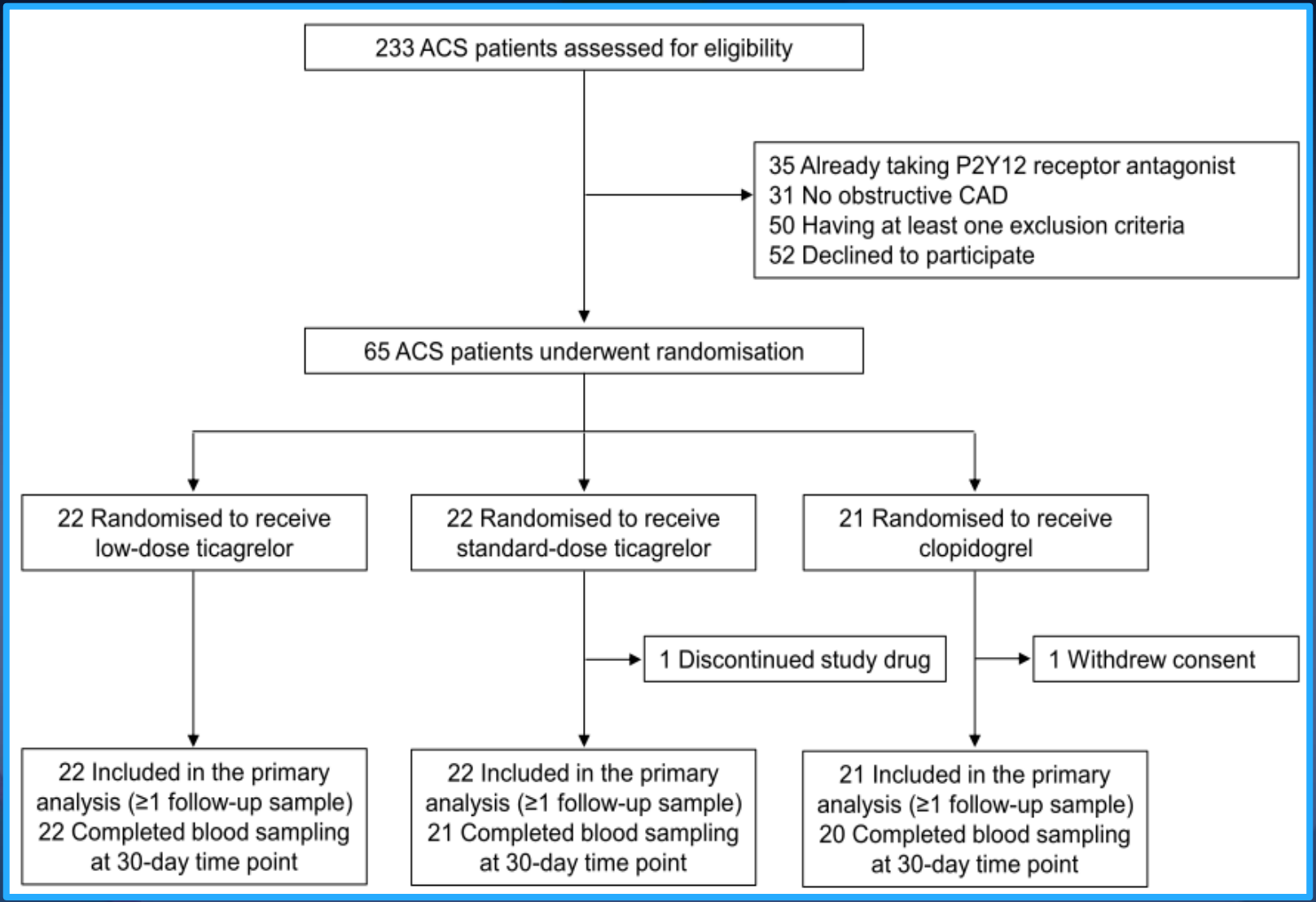
Trial Design



****Primary end point: PRU at 8hrs after loading and at 30 days during maintenance**

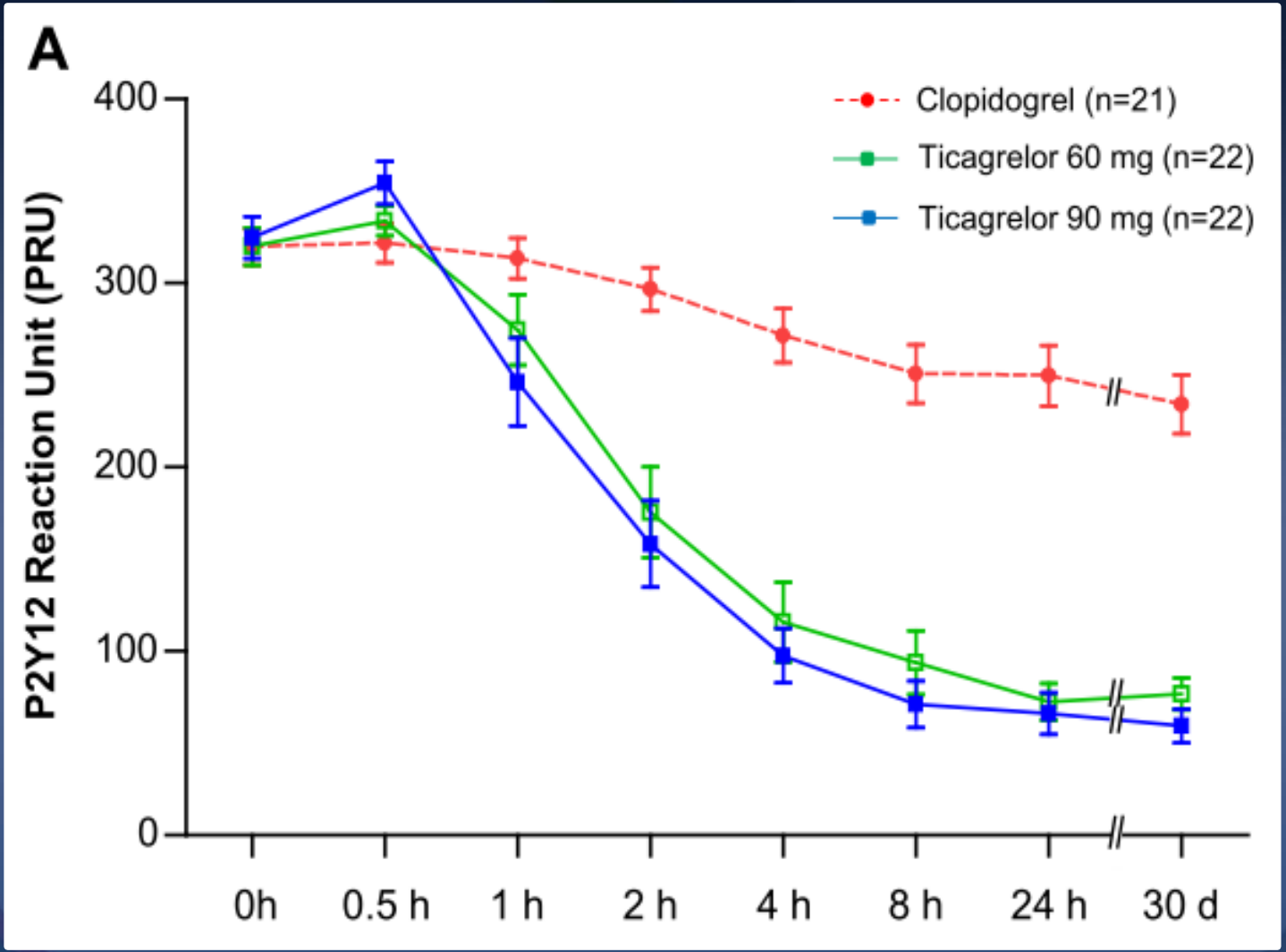
Park DW et al. J Am Coll Cardiol. 2018;71:1594-1595.

Patient Flow Diagram



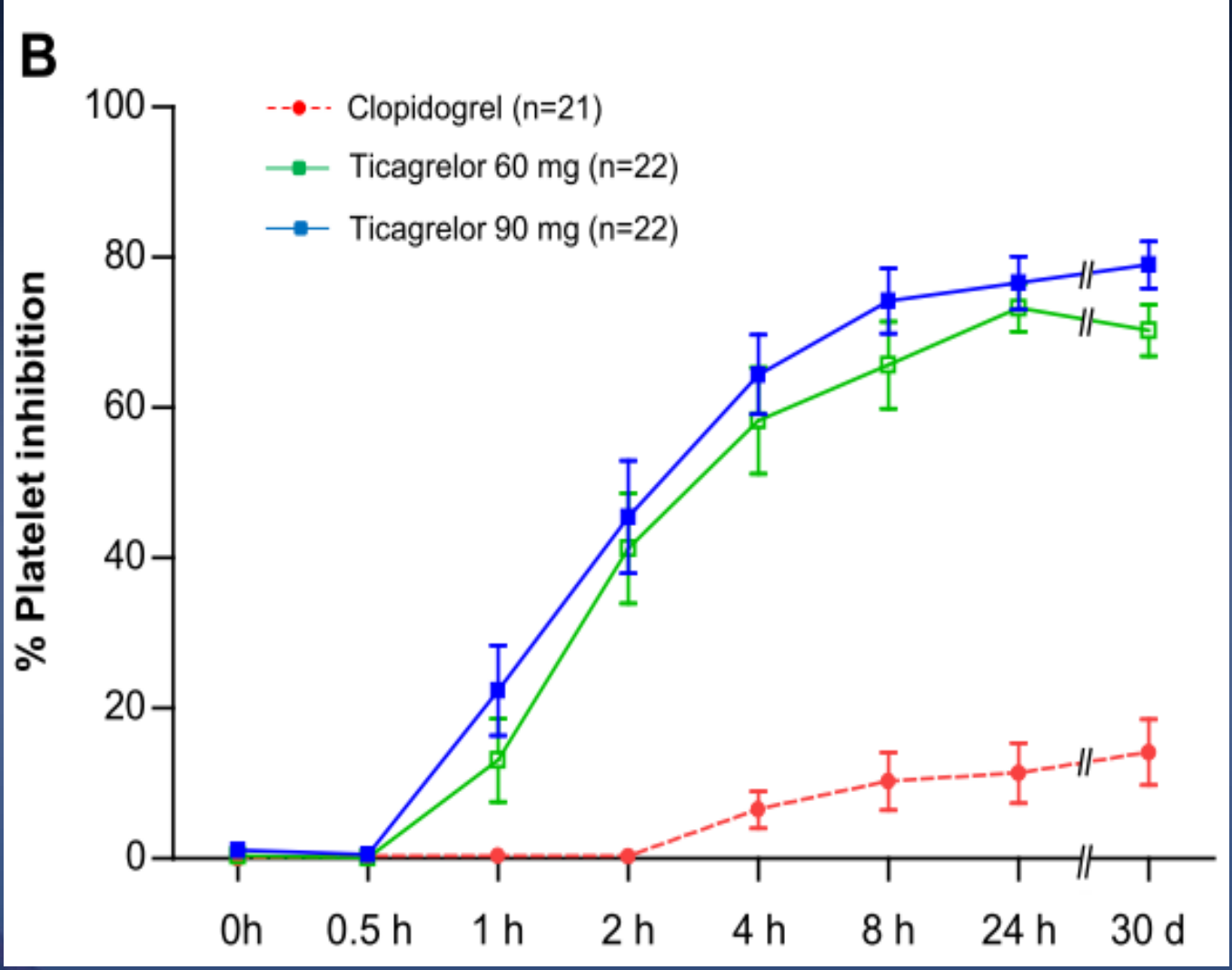
Park DW et al. J Am Coll Cardiol. 2018;71:1594-1595.

Primary Endpoint: P2Y12 - PRU



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

P2Y12 - % Inhibition



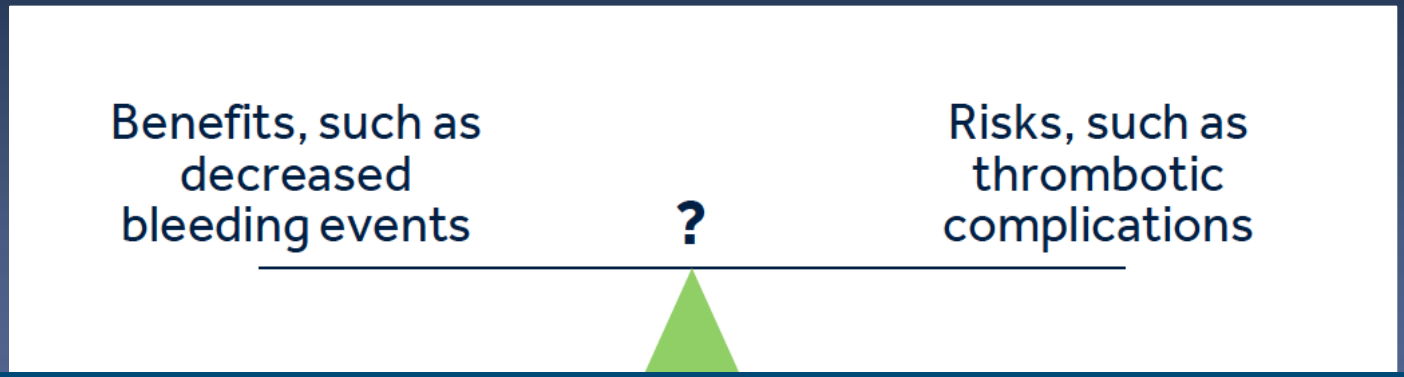
Park DW et al. J Am Coll Cardiol. 2018;71:1594-1595.

Clinical Implication of the OPTIMA

- Low-dose ticagrelor 60 mg is as effective for adequate platelet inhibition in East Asia with ACS as standard-dose ticagrelor, but is remarkably more effective than clopidogrel.
- A reduced dose of ticagrelor might be more appropriate in East Asian patients due to their differential bleeding and ischemic risk profiles (i.e., low BMI, more vulnerable to bleeding, genetic polymorphism).
- However, an adequately powered RCT is required to confirm that adjusted-dose ticagrelor offers better safety and similar efficacy for East Asian patients with ACS.

“East-Asian Paradox”

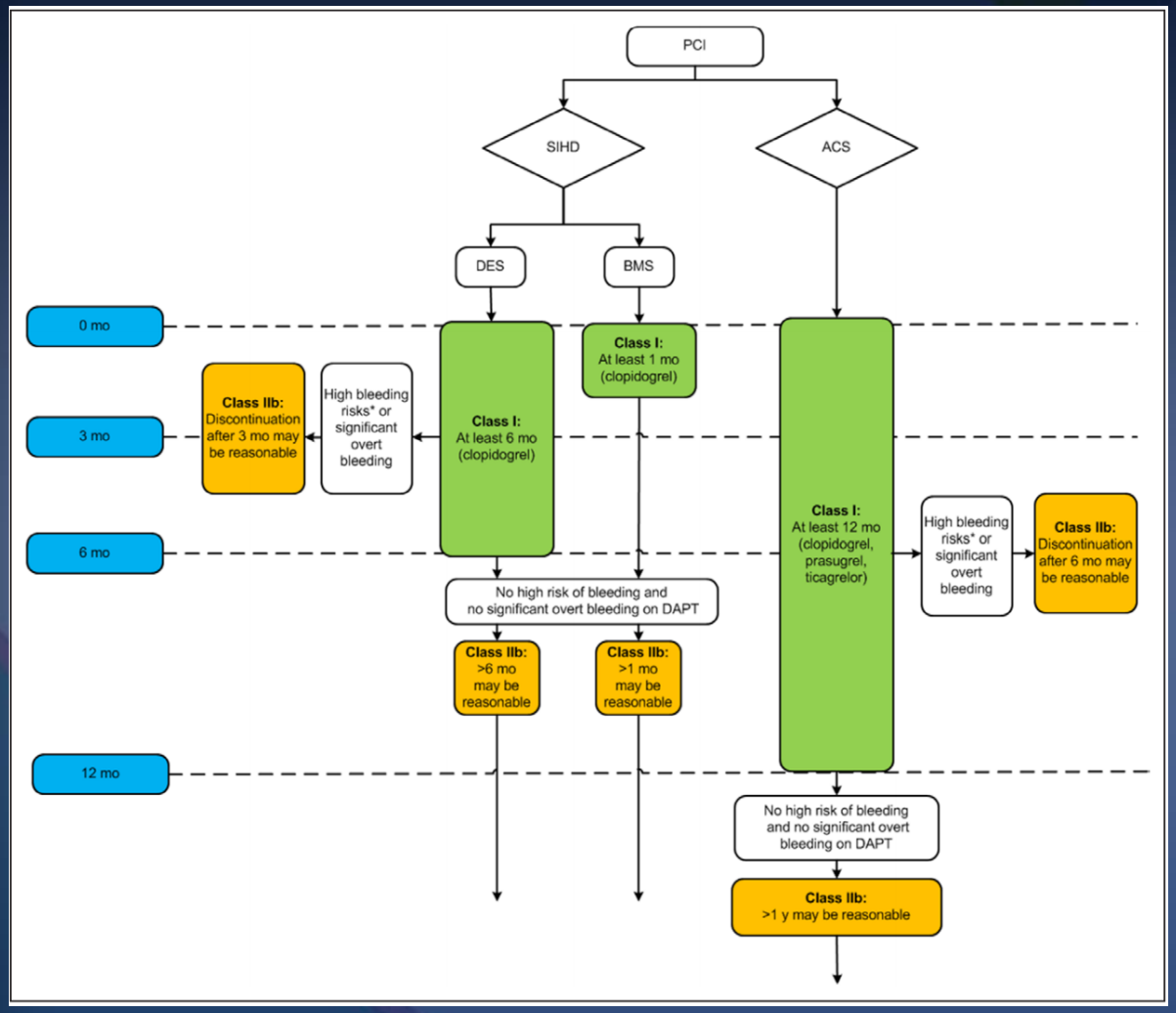
How To Do ?



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

All Hypothesis Should Be Confirmed via a Large-Sized RCTs

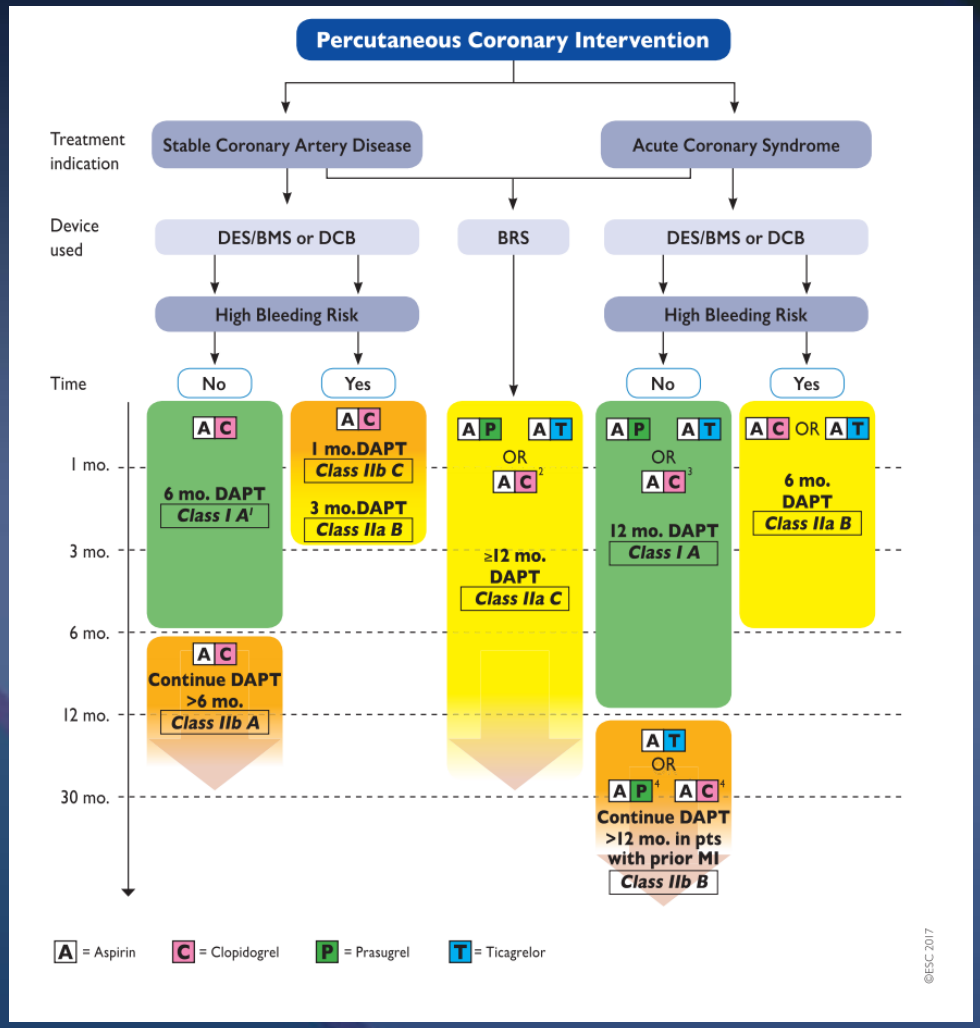
Antithrombotic Strategy after PCI



SIHD: 6 months
ACS : 12 months

2016 ACC/AHA Guideline

Antithrombotic Strategy after PCI



SIHD: 6 months

ACS : 12 months

2017 ESC Guideline

Current Hot Issue in PCI

New drugs	New DES	Subjects
Ticagrelor	Ultra-thin strut DES	High Bleeding risk
Prasugrel	BRS	Complex High risk
DOACs		

What is the OPTIMAL DAPT?

Complex High-Risk PCI

High-risk Patient

Previous NSTEMI or STEMI
Recurrent ischemic event on DAPT
History of Stent thrombosis
Chronic inflammatory disease
Diabetes
Chronic renal dysfunction

High-risk PCI

>3 Stents
Total stent length >60 mm
Complex PCI
: CTO, Complex Bifurcation, Multivessel PCI
PCI with BRS

Continue Long-term DAPT

Lancet 2017;390:810-20.

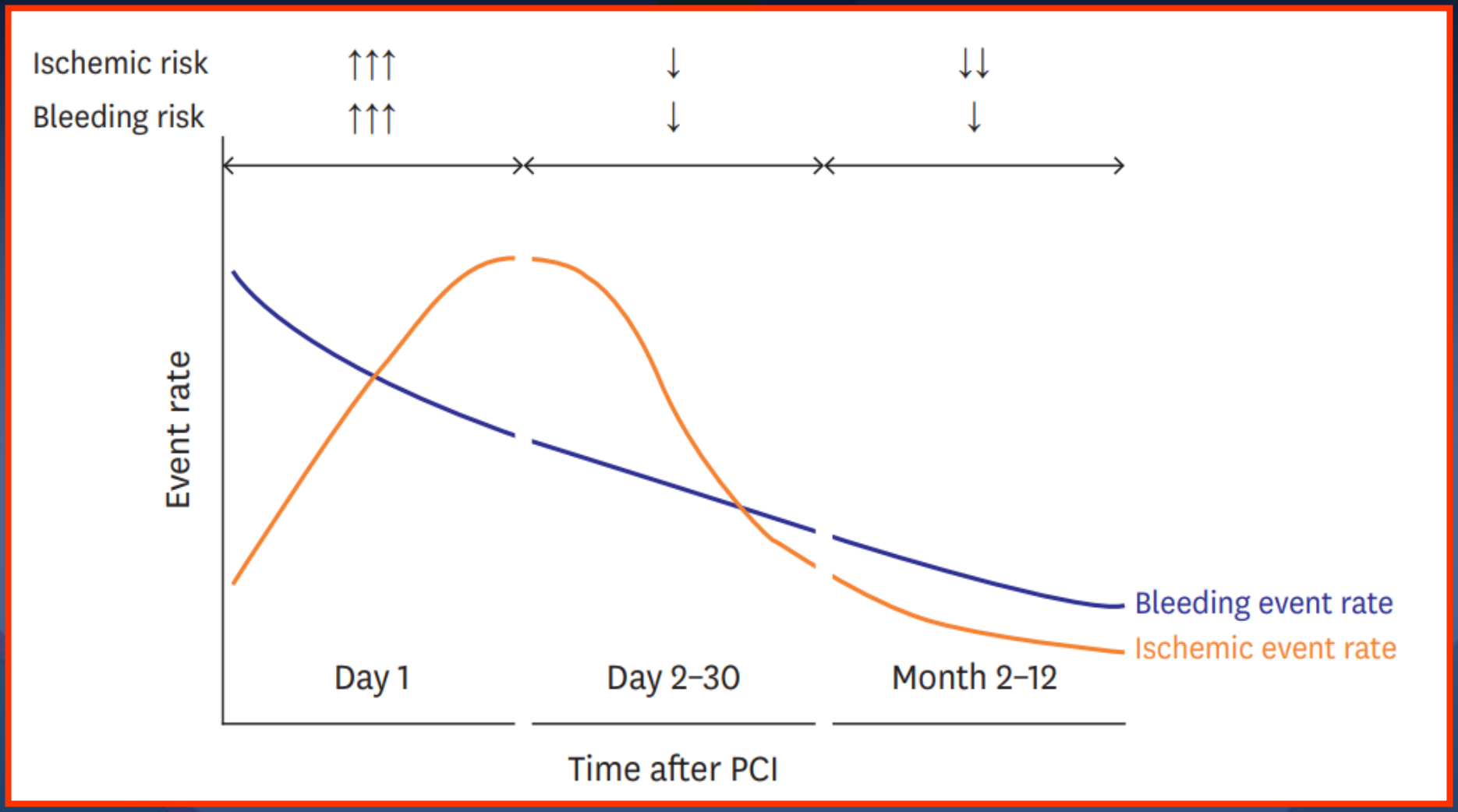
Complex High-Risk PCI

Prolonged (i.e. >6 months) DAPT duration[d] may be considered in patients who under-went complex PCI.[247]	IIb	B

"Optimal *DAPT duration* of *complex high-risk PCI* is still unknown"

2017 ESC Guideline

Timing of ischemic versus bleeding event after PCI

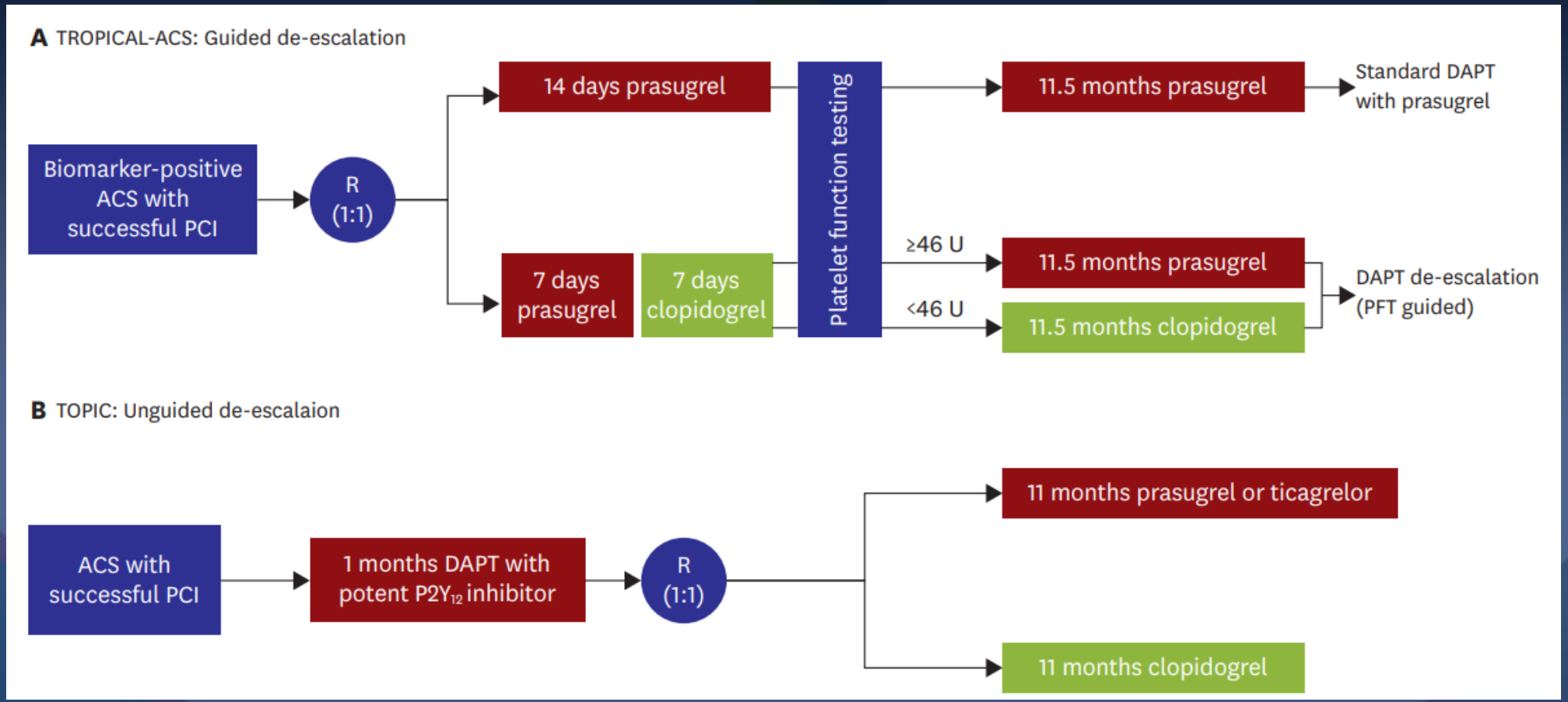


Korean Circ J. 2018;48(10):863-872.

Current evidence

- Complex High-risk PCI: more DAPT (duration or potency)
- Early Ischemic risk and Late bleeding risk
- The best DAPT may be *Escalation and De-escalation* strategy in Complex High-Risk PCI

Ongoing Clinical trials: De-escalation



Korean Circ J. 2018;48(10):863-872.

2018.11.29. Kick-off Meeting

TAILored Versus COnventional AntithRombotic StratEgy IntenDed for Complex HIgh-Risk PCI TAILORED-CHIP trial

Duk-Woo Park, MD.

Heart institute, Asan Medical Center

What is TAILORED-CHIP trial?

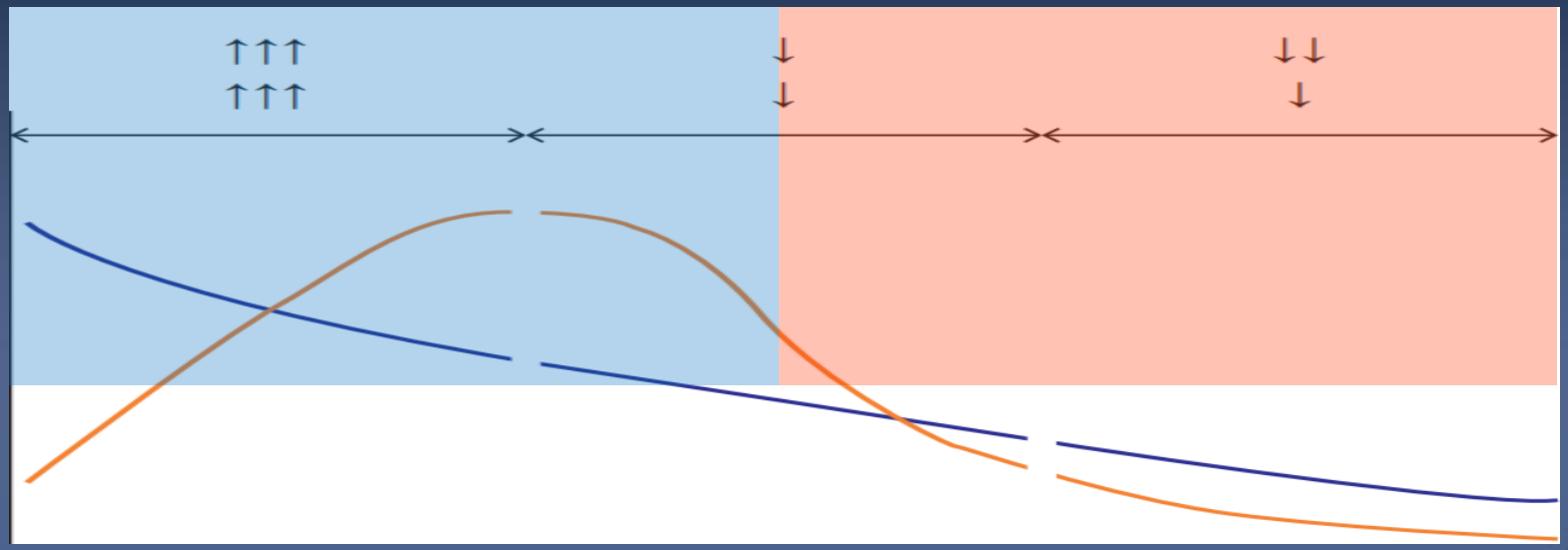
To evaluate the **efficacy** and **safety** of **tailored antithrombotic therapy** with *early (< 6-month post-PCI) escalation and late (> 6-month post-PCI) de-escalation strategy* in patients **undergoing complex high-risk PCI** as compared with conventional DAPT (clopidogrel plus aspirin for 12 months).

Trial Hypothesis

Complex High-risk PCI

Ischemic

Bleeding

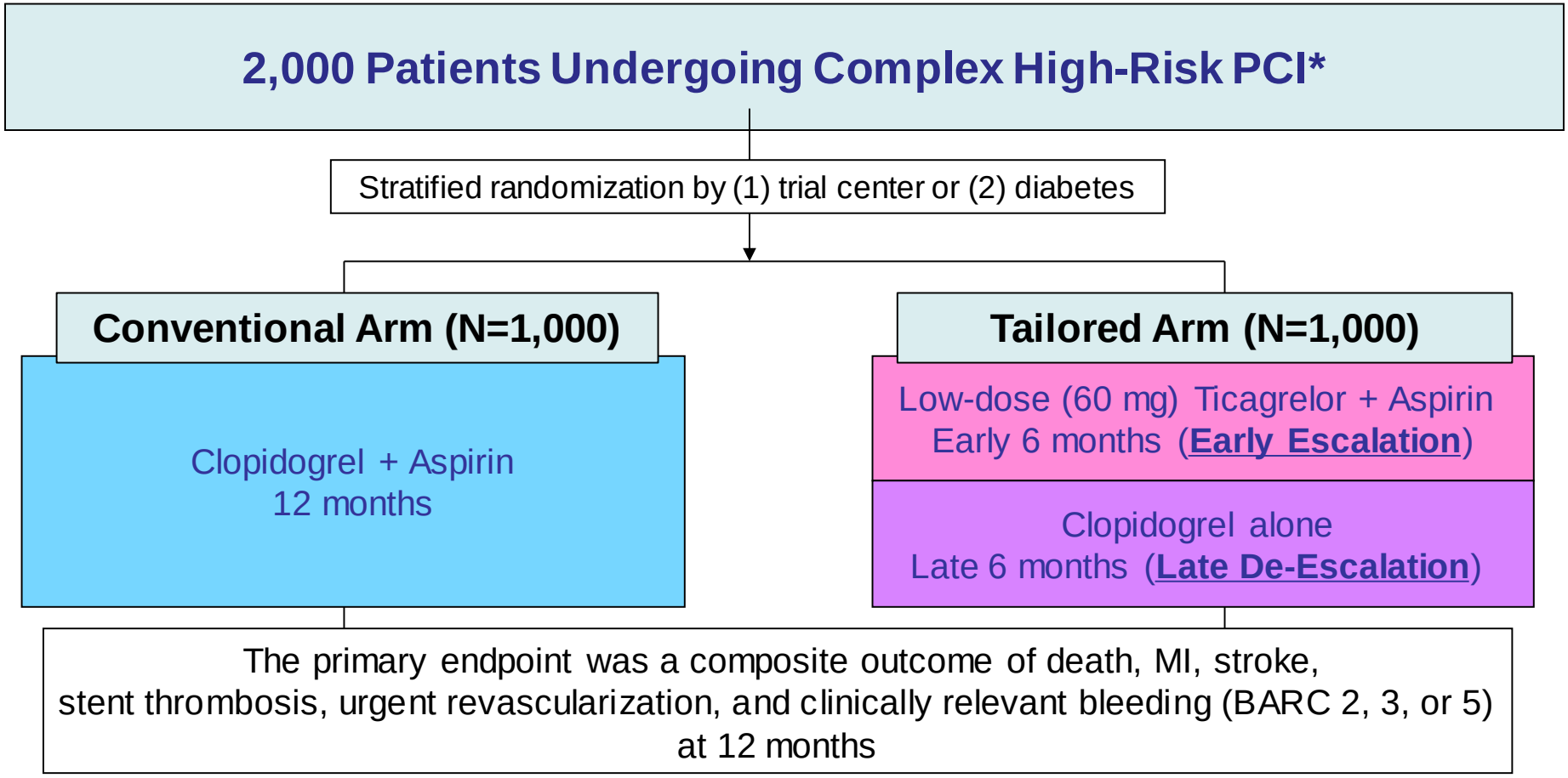


More Potent DAPT
For Ischemic Risk
"Ticagrelor + ASA"

Less Potent DAPT
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 requiring two-stent technique, severe calcification, diffuse long lesion (lesion length ≥ 30mm), multivessel PCI (≥ 2 vessels requiring stent implantation), ≥3 requiring stents implantation, ≥3 lesions will be treated, predicted total stent length for revascularization >60mm, diabetes, CKD (Cr-clearance <60ml/min) or severe LV dysfunction (EF <40%).

Study endpoints

Primary

A net clinical outcome of all-cause death, MI, stroke, stent thrombosis, urgent revascularization and clinical relevant bleeding (BARC 2,3, or 5) at 12 months post-PCI

Study endpoints

Secondary

- Each component of primary outcome
- Composite of death (all or CV), MI, stroke, stent thrombosis or urgent revascularization
- Composite of death (all or CV), MI, or stroke
- Composite of death (all or CV) or MI
- Any revascularization
- BARC 3 or 5 bleeding
- Major or minor bleeding according to definition from TIMI
- Major or minor bleeding to definition from ISTH

Inclusion criteria

- Men or women aged ≥18 years
- Patients scheduled PCI with contemporary DES.
- Patients must have at least one of any features of complex high-risk anatomic, procedural and clinical-related factors.
  - ✓ Clinical factors; ***diabetes, chronic kidney disease*** (CrCl <60 mL/min), severe LV dysfunction (***LVEF<40%***)
  - ✓ Lesion- or procedure-related factors; ***left main*** lesion, bifurcation lesion requiring ***two stent technique***, ***CTO*** lesion, severe ***calcification***, ***diffuse long*** lesion (lesion length ≥ at least 30mm), multi-vessel PCI (***≥ 2 vessels requiring stent implantation***), ***≥3 requiring stent*** implantation, ***≥3 lesions*** will be treated, or predicted ***total stent length > 60 mm***

Exclusion criteria

- ***Enzyme-positive ACS (NSTEMI or STEMI)***
- Contraindication to aspirin or P2Y12 inhibitors (ticagrelor or clopidogrel)
- Cardiogenic shock at index admission
- Patients treated with only BMS or balloon angioplasty during index procedure
- ***Need for chronic oral anticoagulation*** (warfarin or NOAC)
- ***Active bleeding or extreme-risk for major bleeding*** (e.g. active PUD, GI pathology with high risk for bleeding, malignancy with high risk for bleeding)

Study Status

- AMC : ①IRB 승인완료
  ②MFDS 승인완료
  ③ Brilinta 60 mg 입고

- 공동연구기관: 국내 22개 센터
  → 22개 기관 IRB 초기 심의 진행 중

Study Institution

Site	Institution	PI	Site	Institution	PI
1	서울아산병원	박승정	13	가톨릭대학교 대전성모병원	허성호
2	가톨릭대학교 서울성모병원	고윤석	14	동아대학교병원	김무현
3	분당서울대학교병원	서정원	15	차의과대학교 분당차병원	김원장
4	전남대학교병원	안영근	16	가톨릭대학교 여의도성모병원	박철수
5	영남대학교병원	김웅	17	을지대학교 을지병원	최재웅
6	고려대학교 구로병원	나승운	18	가톨릭대학교 성빈센트병원	이수남
7	순천향대학교 천안병원	이세환	19	성가롤로병원	조장현
8	강원대학교병원	이봉기	20	가천대학교길병원	안태훈
9	원주세브란스기독병원	윤정한	21	순천향대학교 부천병원	서존
10	한림대학교 성심병원	박경하	22	충북대학교병원	배장환
11	대구가톨릭대학교병원	이진배	23	인제대학교 부산백병원	장재식
12	전북대학교병원	체제건			

Summary-I

- The “East Asian paradox” describes a phenomenon of differential ischemic and bleeding response to antithrombotic therapies.
- Despite a higher level of platelet reactivity to antithrombotic therapy, East Asian patients have a higher risk of bleeding events, but a similar or even lower risk of ischemic events as compared with White patients.

Summary-II

- No definitive data are available to support the clinical superiority of the more potent P2Y12 inhibitors (prasugrel and ticagrelor) over clopidogrel as an adjunct to aspirin for DAPT in East Asian patients with ACS or those undergoing PCI.
- Further studies are required to assess the efficacy and safety of potent P2Y12 inhibitors (ticagrelor or prasugrel) for ACS or PCI among East Asian patients.
- The optimal antiplatelet therapy for east Asian population should be a balancing act between risk of ischemia and risk of bleeding.