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

OPTIMA Trial:
P2Y12 Dose Adjustment for East-Asian ACS Patients

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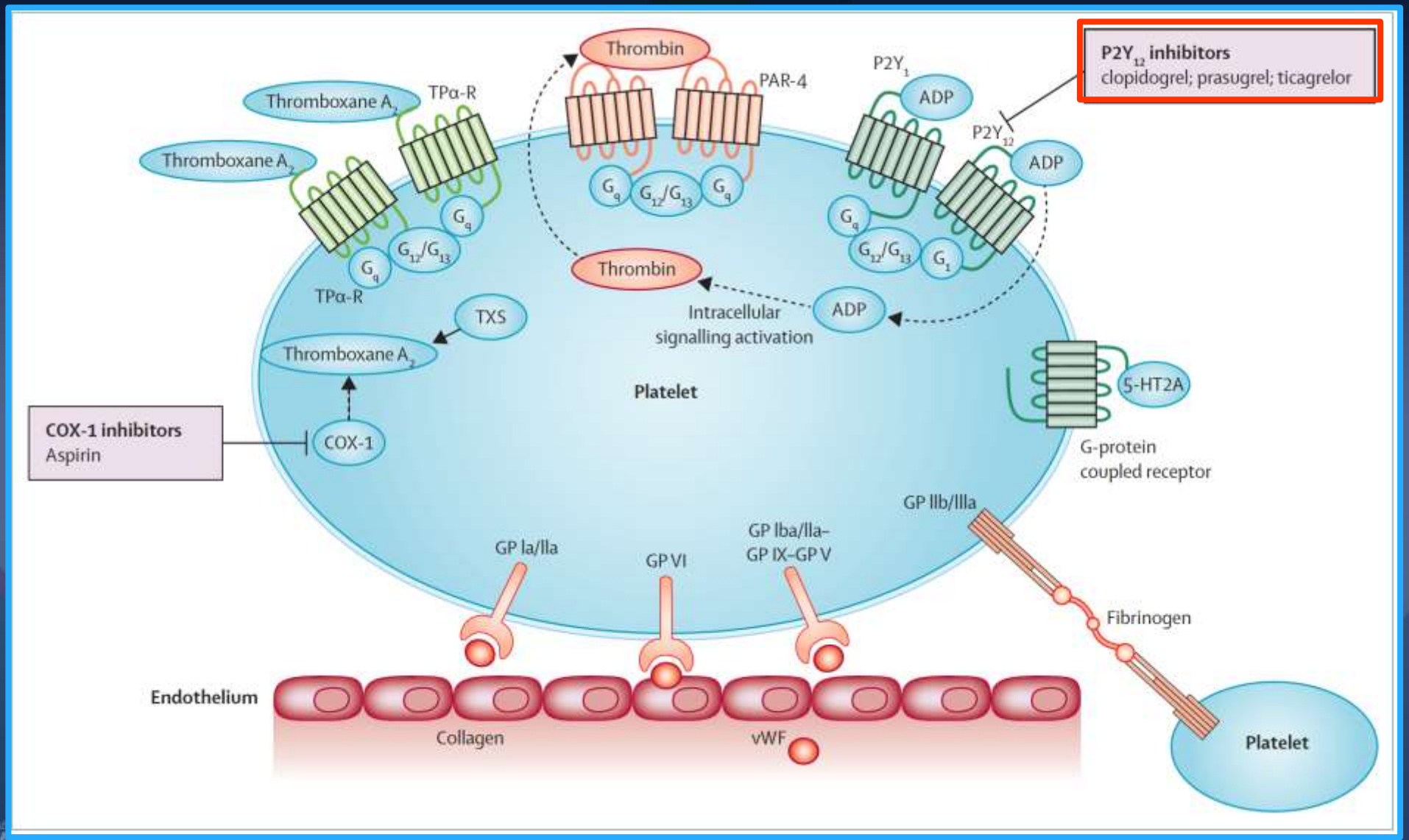
OPTIMA Trial – Disclosure Information

- The OPTIMA Trial was funded by AstraZeneca.
- The VerifyNow P2Y12 assay was provided by an investigator-initiated grant from Accumetrics.

Contemporary P2Y12 Inhibitors



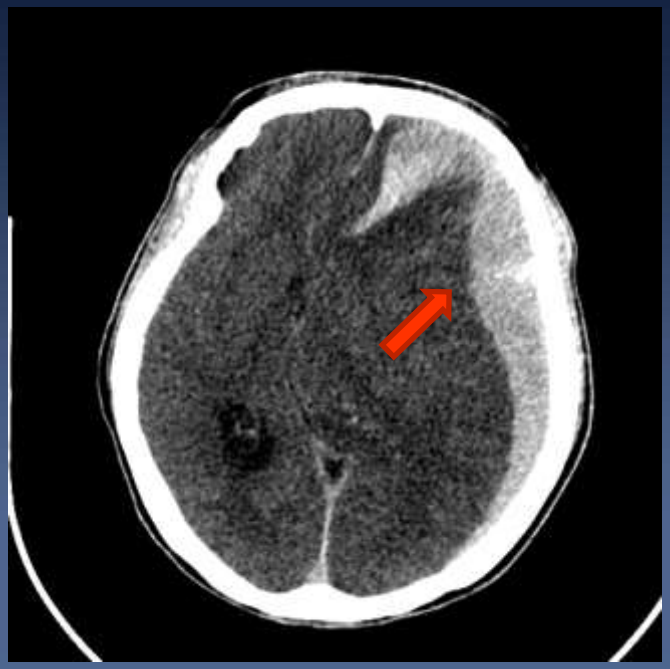
BACKGROUND

- Due to greater and consistent platelet inhibition and clinical benefit of potent P2Y12 inhibitors (ticagrelor or prasugrel), 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 therapies compared with Western patients (the so-called **'East Asian paradox'**)

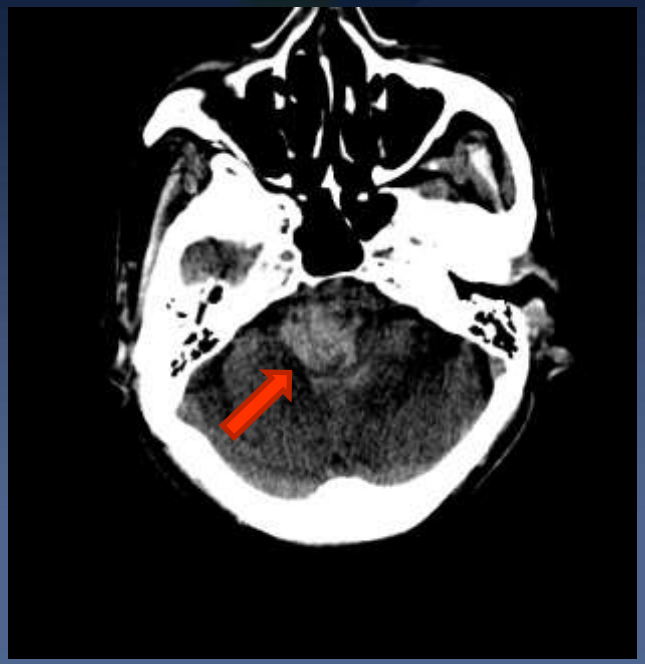
BACKGROUND

- Prior trial (i.e., the PHILO trial) suggested that East Asian patients with ACS who received standard-dose ticagrelor had a higher rate of major/minor bleeding events and nonsignificantly more major cardiovascular events compared with clopidogrel.
- It is suggested that 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).

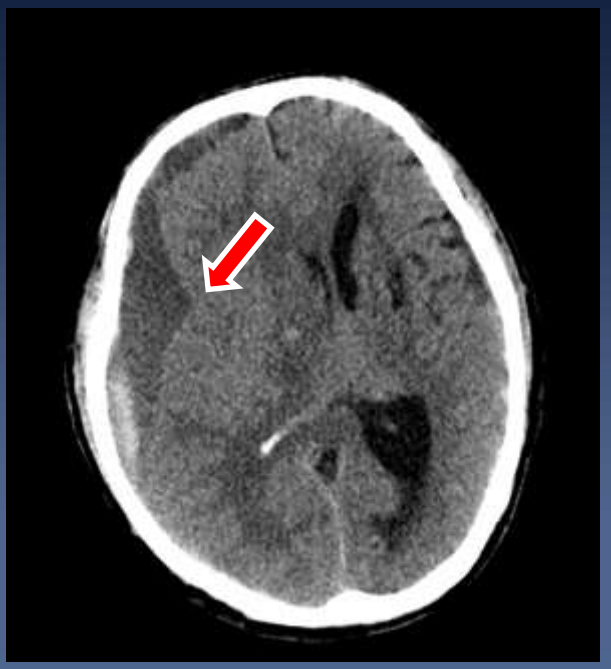
Fatal Case Series



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

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”

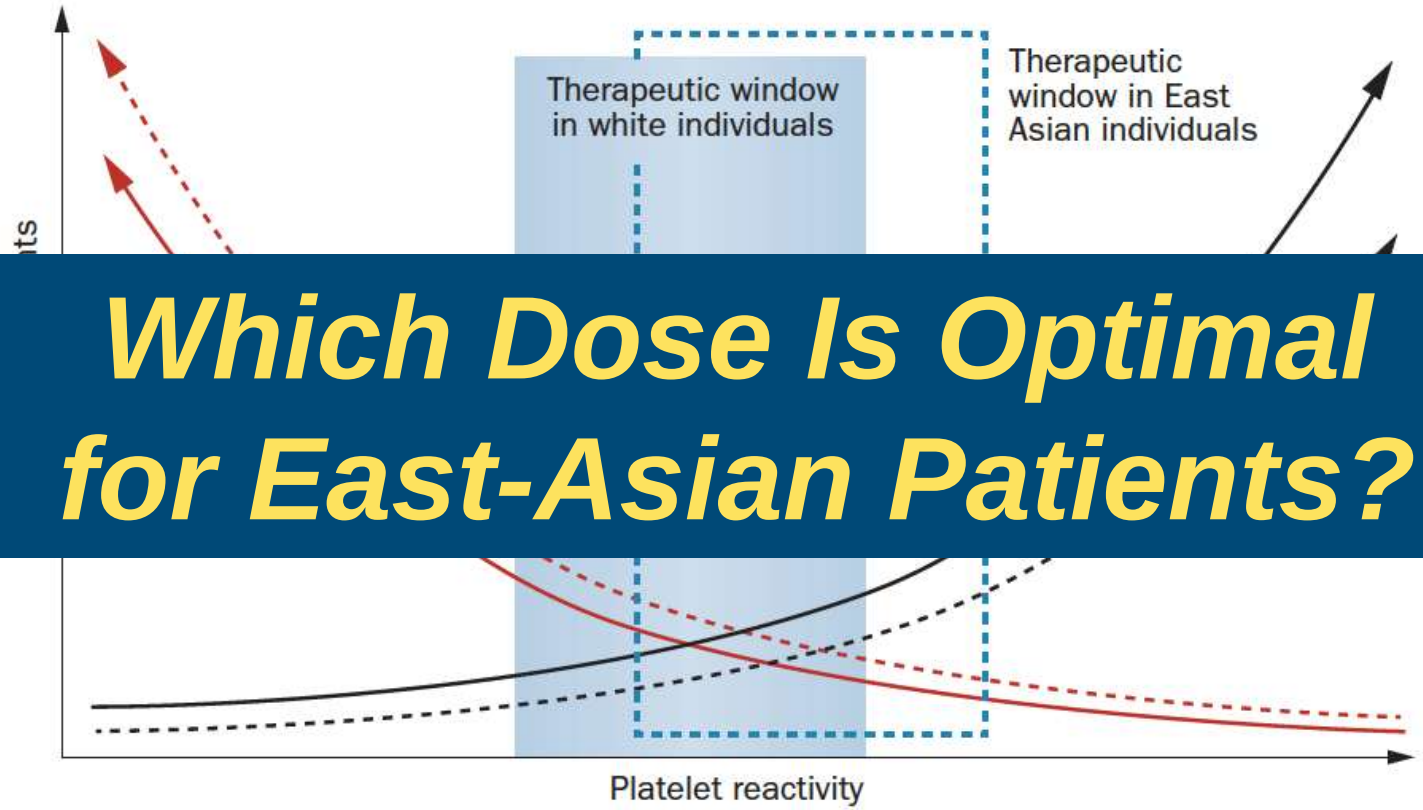


Figure 2 | Postulated differences in the optimal ‘therapeutic window’ of platelet reactivity between white and East Asian populations.

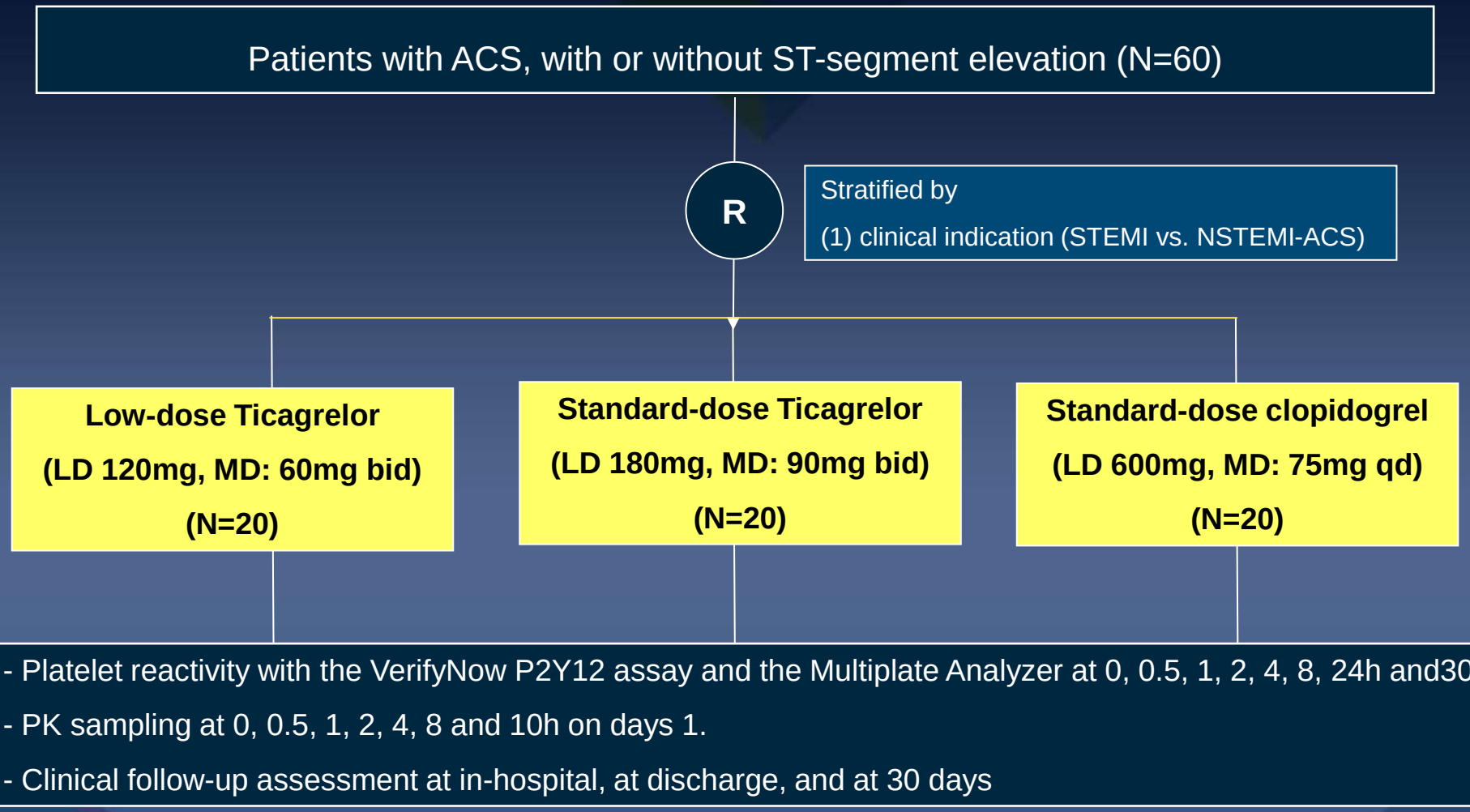
Which Dose Is Optimal for East-Asian Patients?

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

OBJECTIVE

- To explore the potential applicability of low-dose ticagrelor and to define the most appropriate dosing in East Asian patients with ACS, we conducted the OPTIMA trial to compare the pharmacodynamic and pharmacokinetic effects of low-dose ticagrelor with those of standard-dose ticagrelor and clopidogrel.

OPTIMA Trial Design



Enrollment Criteria

Inclusion Criteria

- Eligible patients were ≥18 years of age who were P2Y12 antagonist-naïve and who presented with ACS (either unstable angina or acute MI).

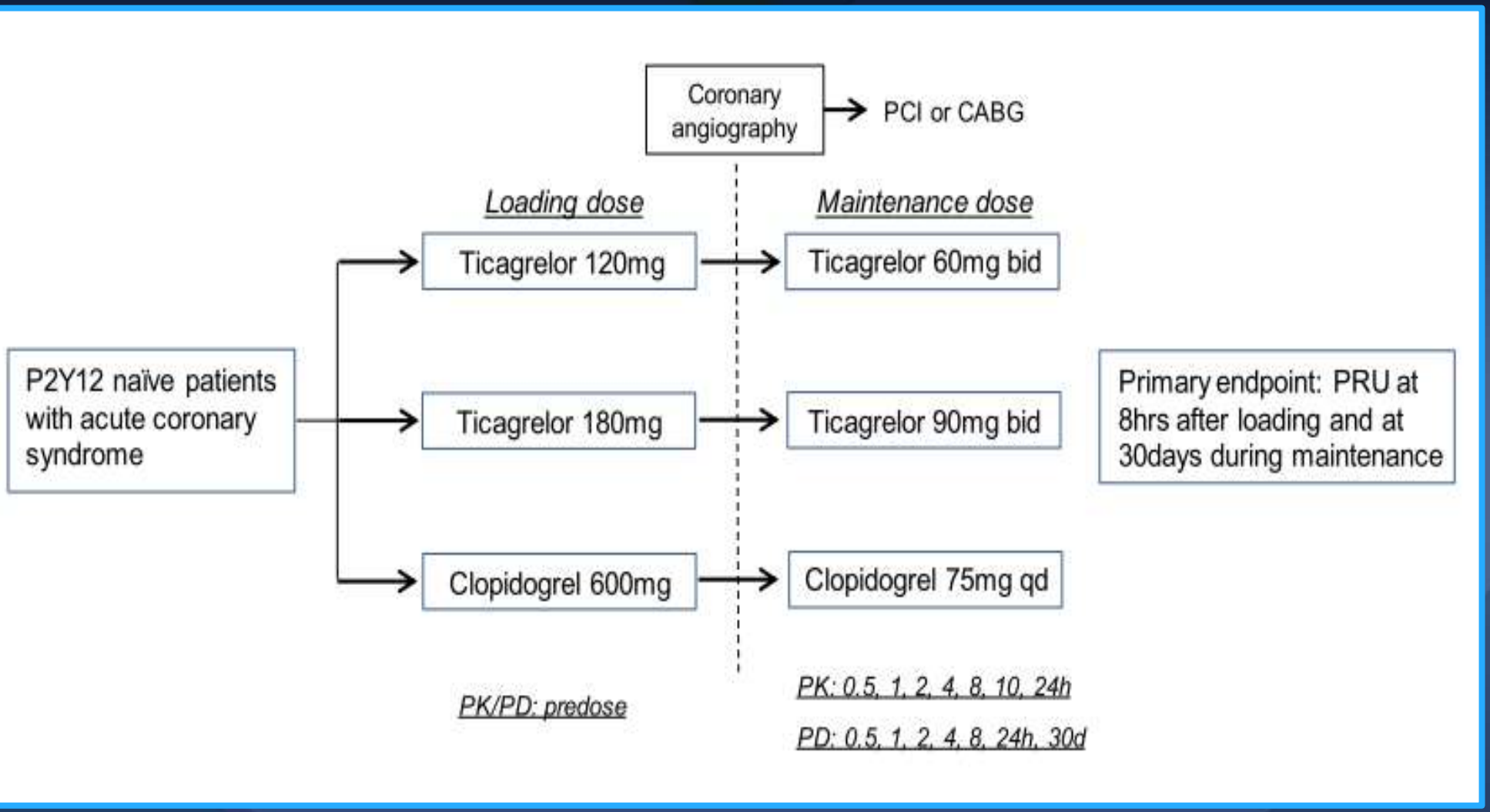
Exclusion Criteria

- Any contraindication or hypersensitivity to P2Y12 inhibitors.
- A need for oral anticoagulation therapy.
- Fibrinolytic therapy within 24 h before randomization.
- Use of glycoprotein IIb/IIIa inhibitors.
- A history of major hemorrhage or major surgery within 30 days.
- Cardiogenic shock or severe LV dysfunction (EF <30%).
- An increased risk of bradycardia.
- Concomitant use with a cytochrome P-450 3A inhibitor.

Randomization and Masking

- Patients were randomly assigned (1:1:1) to low-dose ticagrelor, standard-dose ticagrelor, or standard-dose clopidogrel based on a computer-generated randomization schedule.
- Investigators and patients were masked to the treatment assignment of low-dose and standard-dose ticagrelor, but the use of clopidogrel was open-labelled.
- Ticagrelor 60 mg and 90 mg were identical in appearance and were packaged in identical containers.
- Study drug (ie, ticagrelor or clopidogrel) should be maintained at least 30 days after randomization.

PD and PK Measurement



Primary and Secondary Endpoints

Primary End point

• On-treatment PRU value 8 h after the LD and at 30 days during the MD by the VerifyNow P2Y12 assay.

Secondary End points

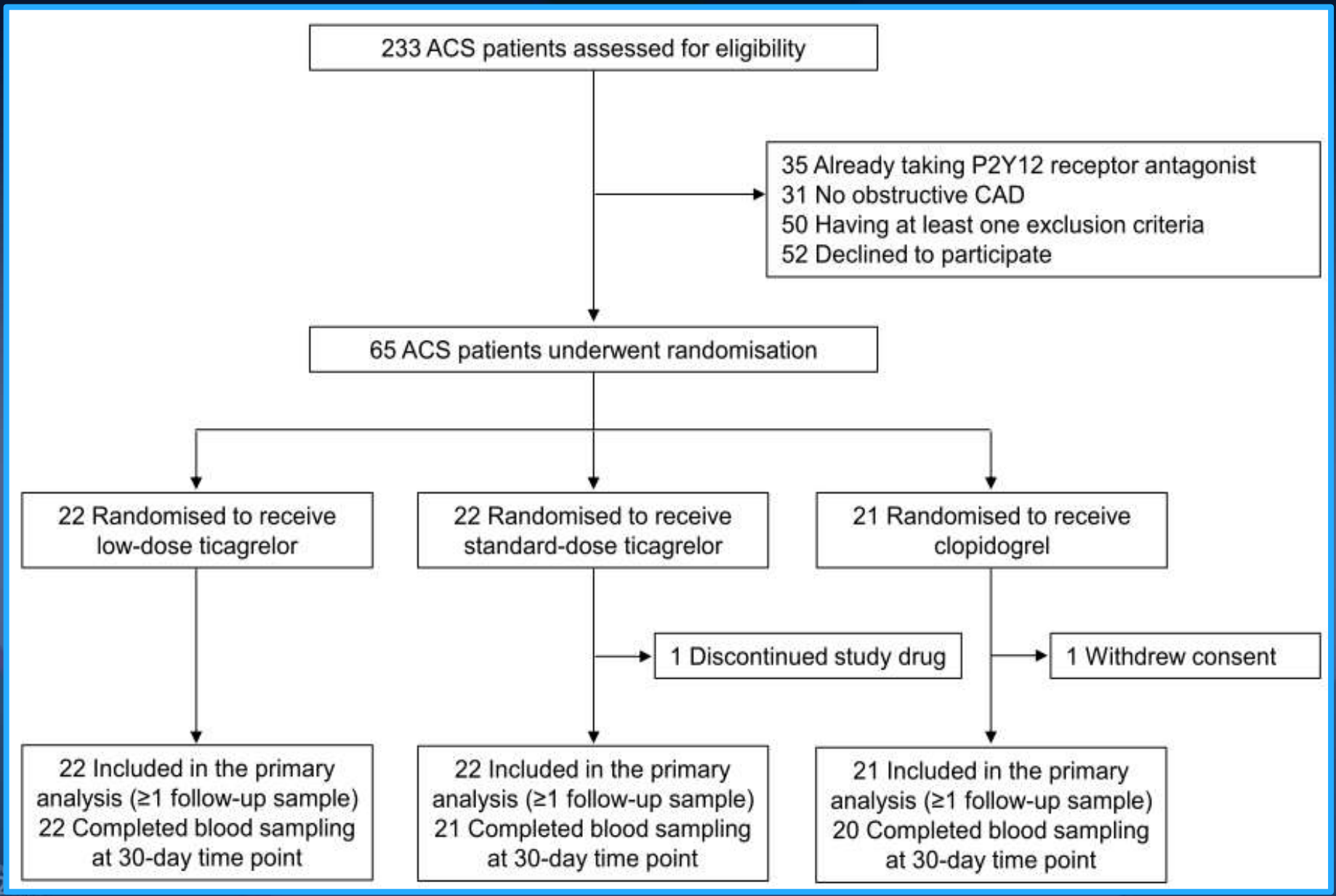
• Platelet % inhibition after the LD and MD.
• The incidence of high on-treatment platelet reactivity (HTPR) using thresholds of 230 PRU and 208 PRU.
• The pharmacokinetic profiles of ticagrelor and AR-C124910XX.
• Clinical outcomes at in-hospital, at discharge, and at 30 days:
- death, MI, stent thrombosis, stroke, or bleeding.

Statistical Analysis

- The main hypothesis of this trial was that low-dose ticagrelor would be superior to clopidogrel for inhibition of platelet reactivity after the LD and during the MD.
- To detect an absolute mean difference of a 60 PRU level (SD 65) 8 h after the LD and at 30 days during the MD of low-dose ticagrelor vs. clopidogrel, which was assumed based on prior research, we estimated that 19 patients in each-group were needed to demonstrate superiority of low-dose ticagrelor over clopidogrel with 80% power and 2-sided α value of 0.05.
- Considering an attrition rate of 5%, a total sample size of 60 patients (20 patients in each group) was planned for this trial.
- Analyses were performed on an ITT principle.

RESULTS

Patient Flow Diagram



Baseline Characteristics

	Overall (N=65)	Low-dose ticagrelor (N=22)	Standard-dose ticagrelor (N=22)	Clopidogrel (N=21)	p value
Age, y	64.0 (55.0–70.0)	63.5 (55.0–70.0)	65.5 (59.0–68.0)	62.0 (54.0–73.0)	>0.99
Male sex	53 (81.5)	20 (90.9)	19 (86.4)	14 (66.7)	0.10
Weight, kg	68.0 (60.8–78.0)	66.0 (61.0–72.6)	64.9 (60.7–78.0)	70.5 (61.0–80.0)	0.72
BMI kg/m^2	24.5 (22.8–26.9)	23.5 (21.9–25.5)	24.8 (23.7–26.4)	25.5 (23.1–28.4)	0.06
Body surface area	1.8 (1.6–1.9)	1.8 (1.7– 1.9)	1.7 (1.6– 1.9)	1.8 (1.6– 1.9)	0.76
Hypertension	38 (58.5)	11 (50.0)	14 (63.6)	13 (61.9)	0.61
Diabetes mellitus	16 (24.6)	2 (9.1)	5 (22.7)	9 (42.9)	0.04
Dyslipidemia	44 (67.7)	12 (54.5)	17 (77.3)	15 (71.4)	0.25
Current smoker	25 (38.5)	10 (45.5)	7 (31.8)	8 (38.1)	0.65

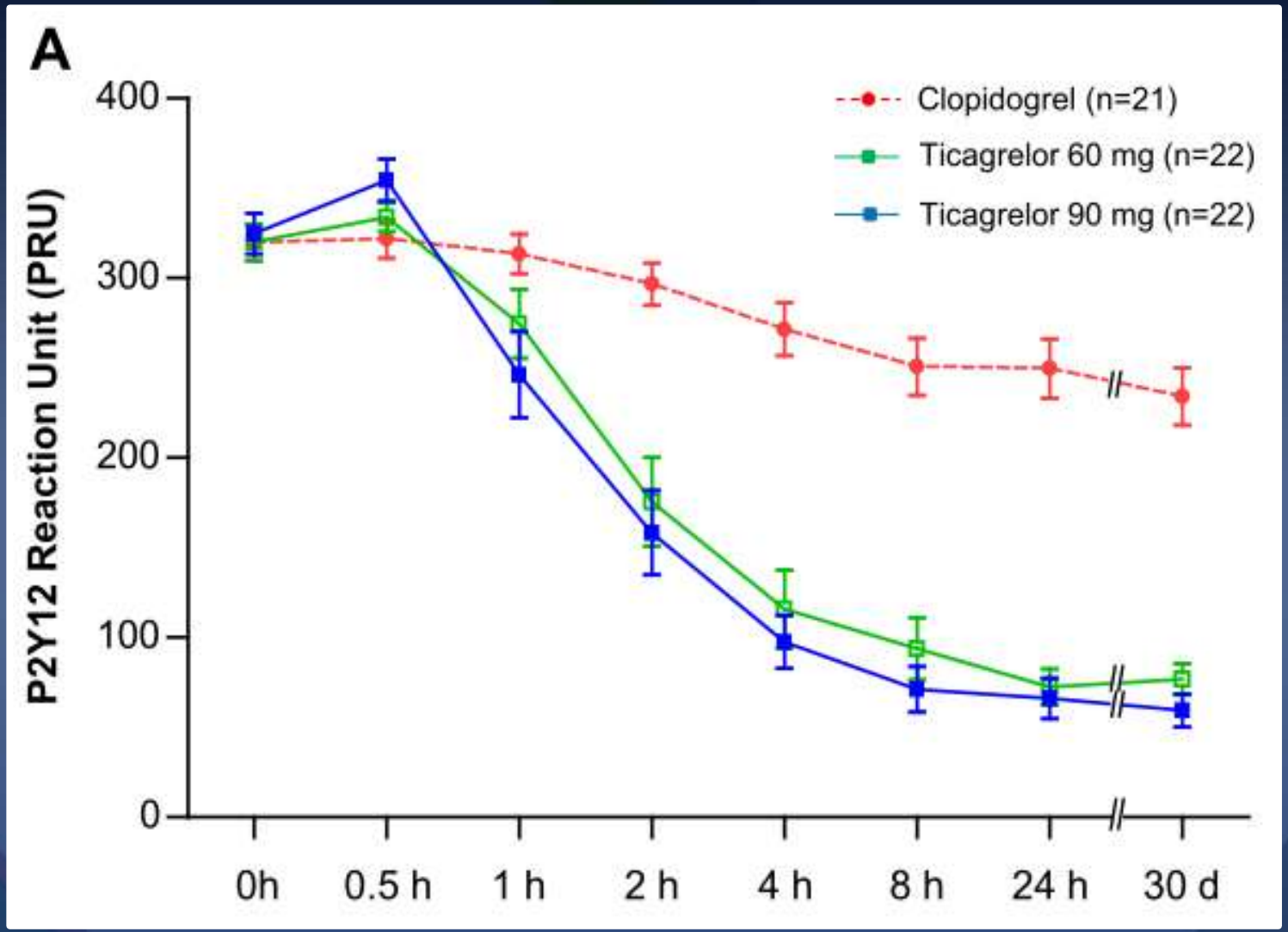
Baseline Characteristics

	Overall (N=65)	Low-dose ticagrelor (N=22)	Standard-dose ticagrelor (N=22)	Clopidogrel (N=21)	p value
Prior CABG	1 (1.5)	0	1 (4.5)	0	0.37
History of MI	1 (1.5)	0	0	1 (4.8)	0.35
Prior PCI	7 (10.8)	1 (4.5)	3 (13.6)	3 (14.3)	0.51
Chronic lung disease	2 (3.1)	2 (9.1)	0	0	0.13
Hemoglobin, g/dL	14.4 (13.5–15.5)	14.9 (14.0–15.6)	14.1 (13.2–15.2)	14.1 (13.6–15.4)	0.15
Hematocrit, %	42.5 (40.3–45.8)	44.5 (41.3–46.8)	42.4 (37.9–44.1)	42.2 (40.3–45.6)	0.19
Platelets, ×1000/mm^3	228 (196–269)	235 (208–281)	218 (181–262)	223 (212–258)	0.30
Creatinine	0.9 (0.8–1.0)	0.9 (0.8– 1.0)	0.9 (0.8– 1.0)	0.9 (0.9– 1.0)	0.55
Cr Clearance, mL/min	91.0 (78.0–96.0)	94.5 (85.0–97.0)	91.0 (77.0–94.0)	85.0 (73.0–96.0)	0.20

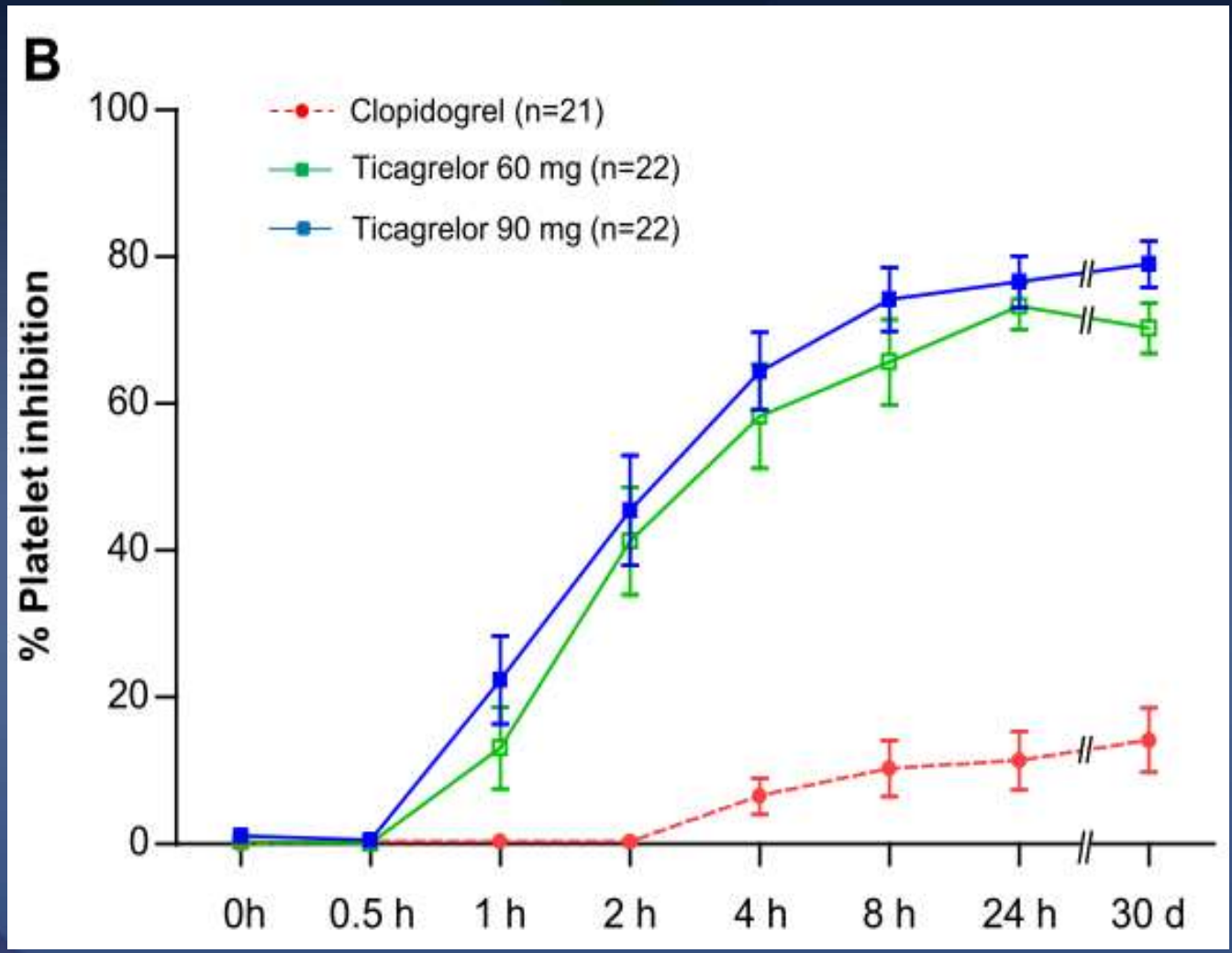
Baseline Characteristics

	Overall (N=65)	Low-dose ticagrelor (N=22)	Standard-dose ticagrelor (N=22)	Clopidogrel (N=21)	p value
Final diagnosis					0.45
Unstable angina	47 (72.3)	14 (63.6)	16 (72.7)	17 (81.0)	
NSTEMI	18 (27.7)	8 (36.4)	6 (27.3)	4 (19.0)	
Final Tx for ACS					0.22
PCI	58 (89.2)	18 (81.8)	19 (86.4)	21 (100.0)	
CABG	3 (4.6)	1 (4.5)	2 (9.1)	0	
Medication	4 (6.2)	3 (13.6)	1 (4.5)	0	
LVEF	60.0 (58.0–63·.0)	60.0 (55.0–62.0)	60.0 (60.0–65.0)	60.0 (58.5–63.5)	0.74

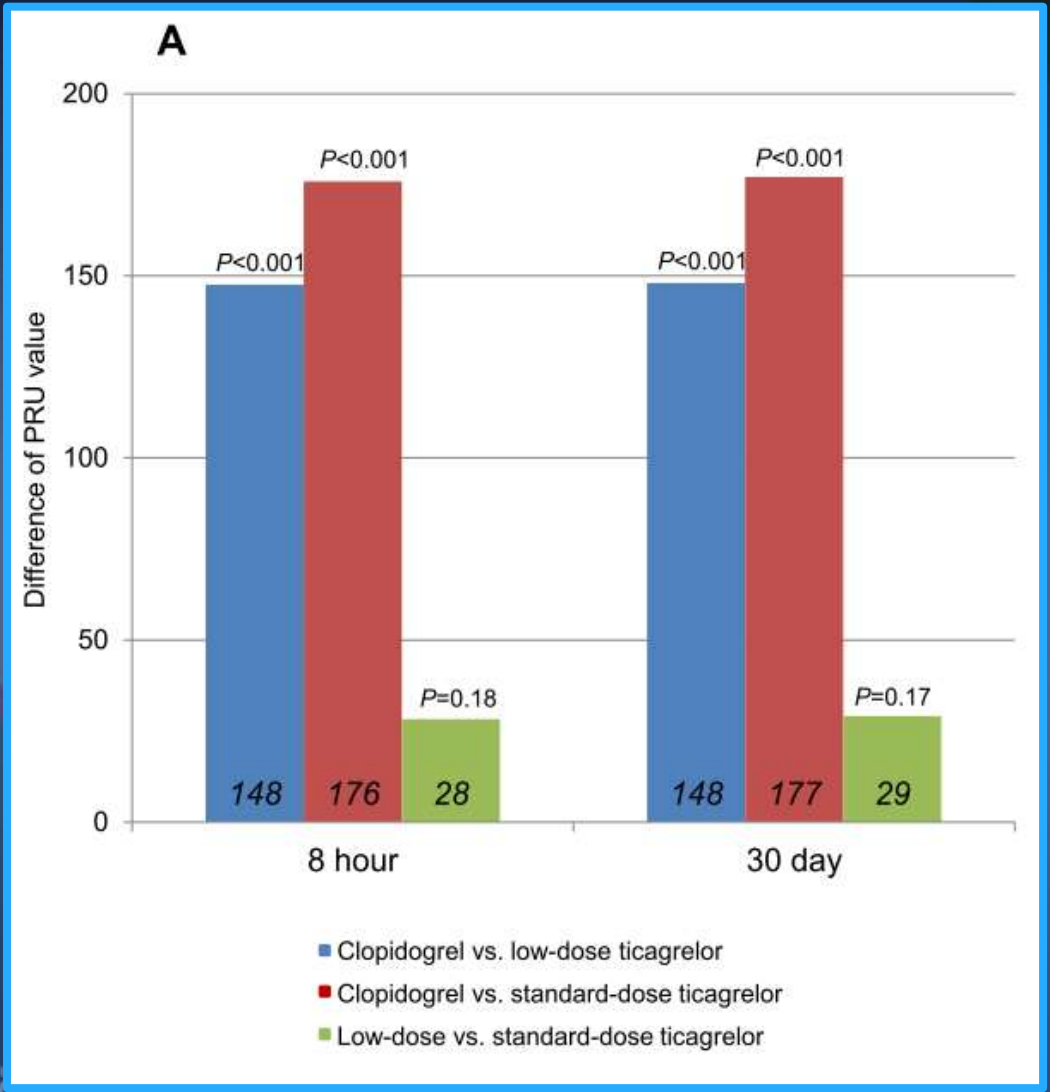
Primary Endpoint: PRU

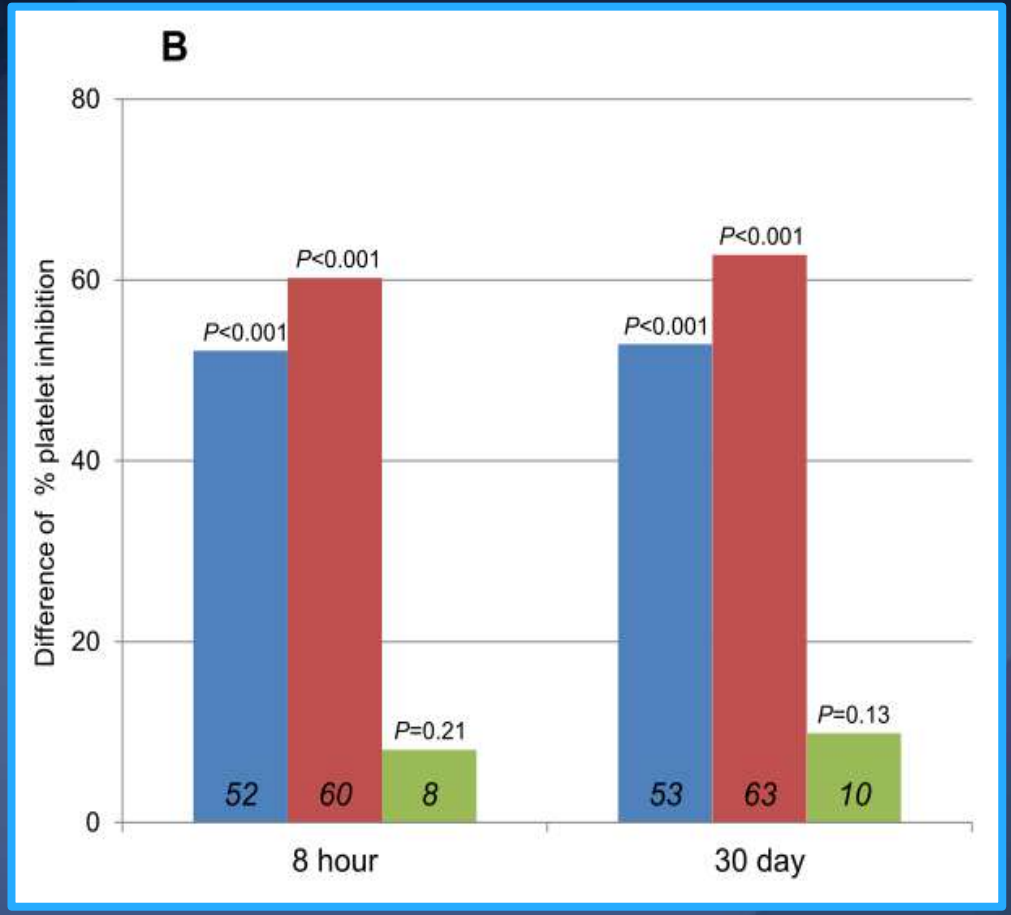


% Inhibition


B
Clopidogrel (n=21)
Ticagrelor 60 mg (n=22)
Ticagrelor 90 mg (n=22)
% Platelet inhibition
100
80
60
40
20
0
0h
0.5 h
1 h
2 h
4 h
8 h
24 h
30 d

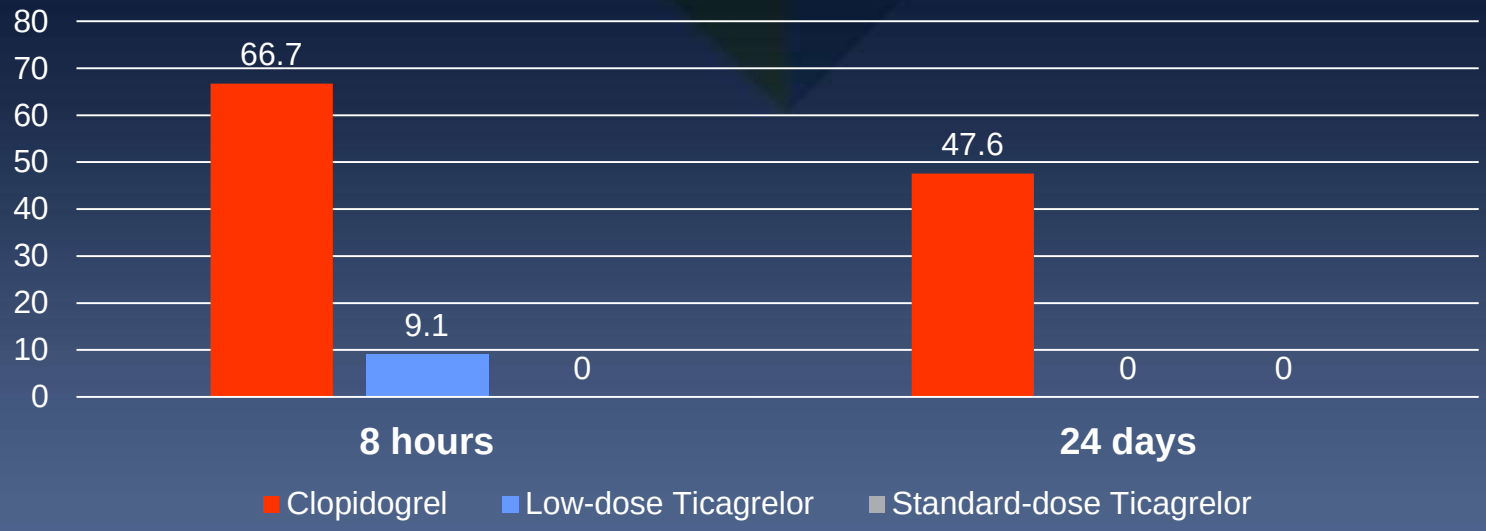
Difference of PRU and % Inhibition



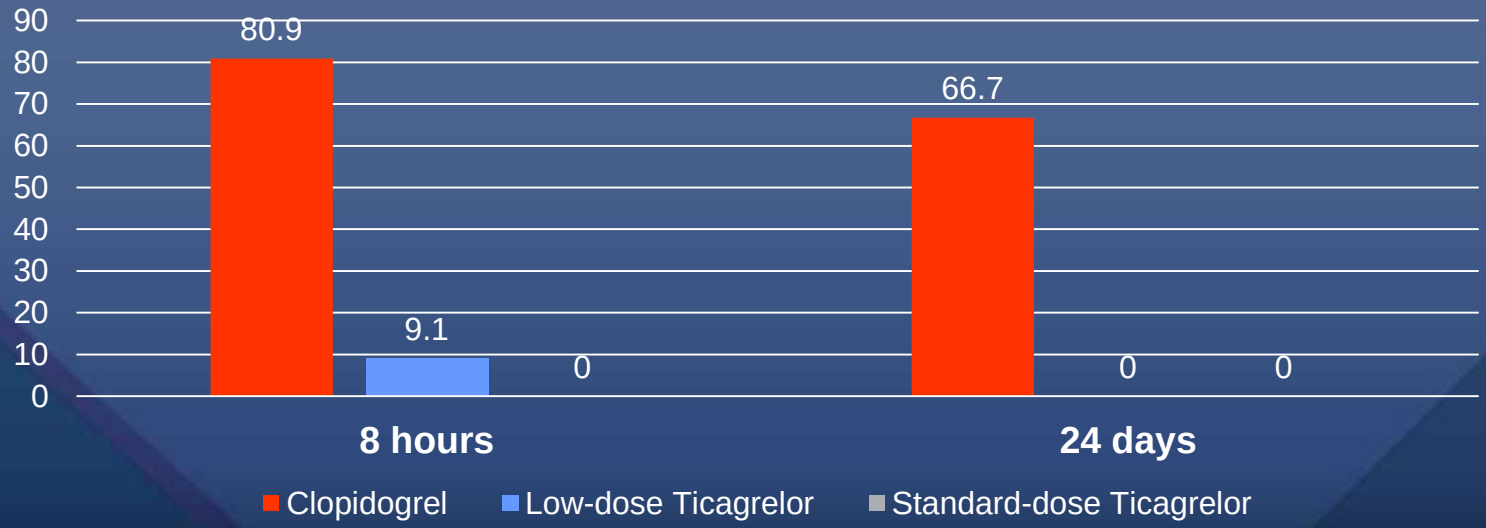


HTPR Incidence

Threshold of 230 PRU

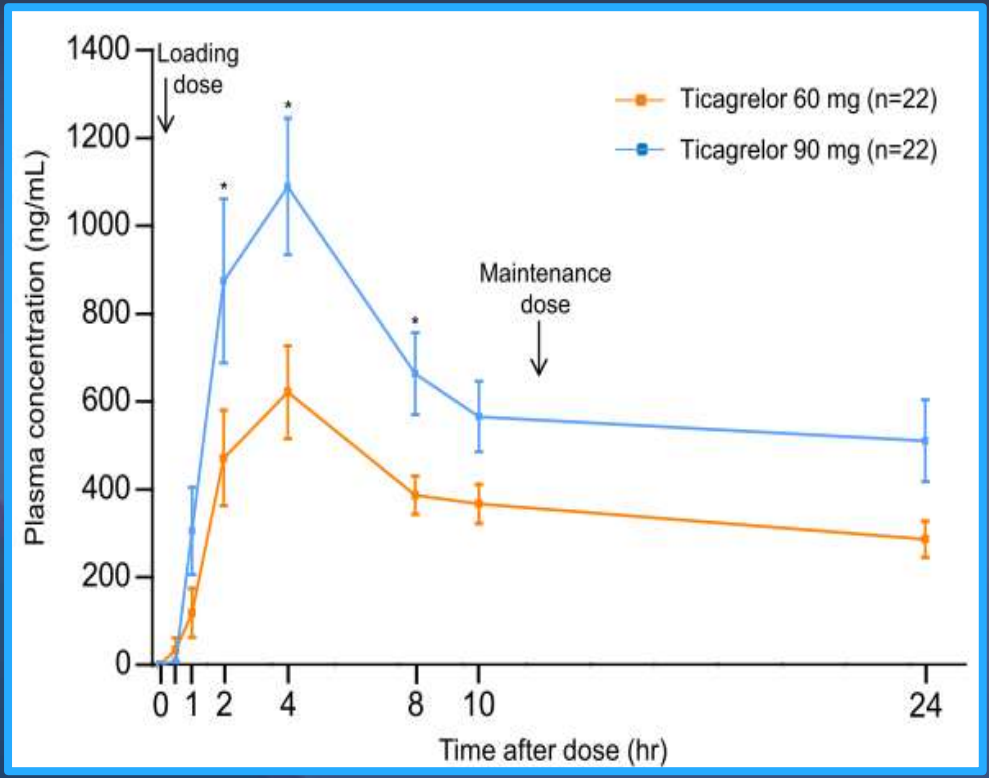


Threshold of 208 PRU

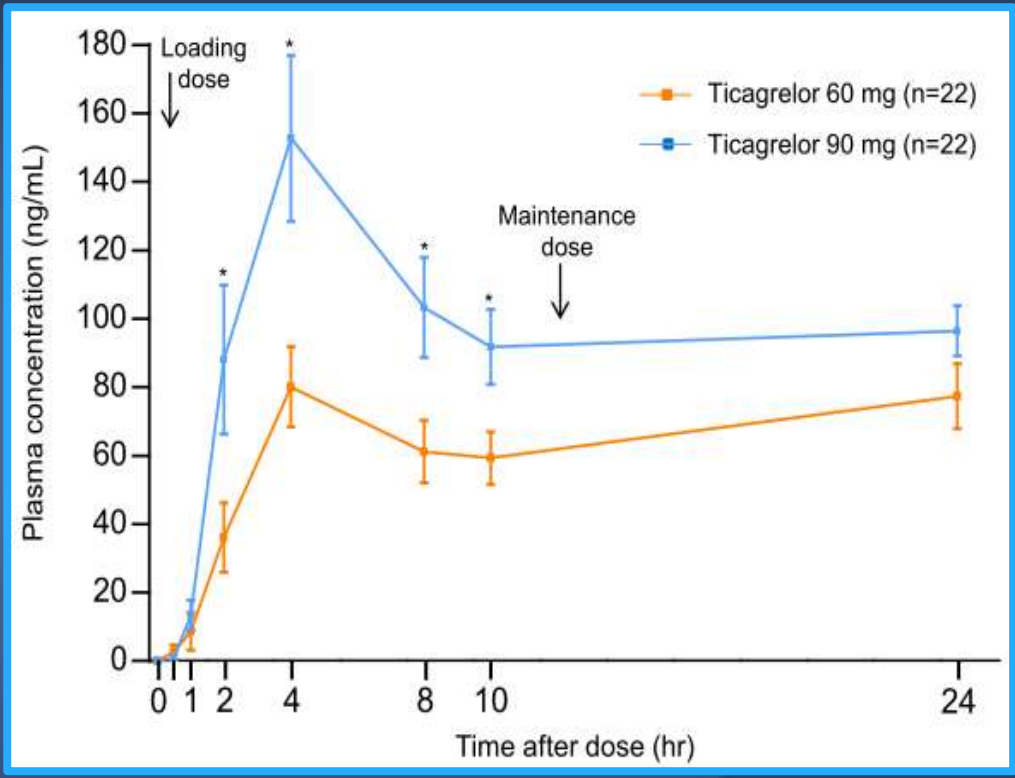


Pharmacokinetics

Mean plasma concentrations of Ticagrelor



Mean plasma concentrations of AR-C124910XX



Clinical Outcomes at 30-Days

	Low-dose ticagrelor (N=22)	Standard-dose ticagrelor (N=22)	Clopidogrel (N=21)
Death	0	0	0
MI			
Periprocedural MI	2 (9.1%)	3 (13.6%)	2 (9.5%)
Q-wave MI	0	0	0
Stroke	0	0	0
PLATO-major bleeding	1 (4.5%)	2 (9.1%)	0
PLATO-minimal bleeding	12 (54.5%)	13 (59.1%)	13 (61.9%)

Conclusion

- The OPTIMA trial is the first RCT to compare the PD/PK of low-dose ticagrelor (120 mg loading and 60 mg bid) with those of clopidogrel and standard-dose ticagrelor in patients presenting with ACS.
- The plasma concentrations of ticagrelor and its metabolite were approximately 1.5-fold higher with standard-dose ticagrelor than with low-dose ticagrelor.
- Nevertheless, low-dose and standard-dose ticagrelor achieved a similar magnitude of platelet inhibition, which both showed faster and higher levels of peak and trough platelet inhibition than clopidogrel.

Clinical Implication

- Low-dose ticagrelor 60 mg is as effective for adequate platelet inhibition in East Asian patients with ACS as standard-dose ticagrelor, but is remarkably more effective than clopidogrel.

- Finally, an adequately powered clinical trial is required to confirm that adjusted-dose ticagrelor offers better safety and similar efficacy for East Asian patients presented with ACS compared to standard-dose ticagrelor.

Study Limitations

- There were some imbalances in baseline characteristics, presumably due to the relatively small sample size or by chance.
- Owing to the limited sample size and short follow-up period, we could not assess the relationship between platelet function results and clinical outcomes.
- The inclusion of patients with STEMI was difficult in reality due to the strict time-line of multiple blood samplings and prompt testing for platelet function. Thus, the platelet inhibition of low-dose ticagrelor in STEMI is still unknown.

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Letters

Effect of Low-Dose Versus Standard-Dose Ticagrelor and Clopidogrel on Platelet Inhibition in Acute Coronary Syndromes

Because of different risk profiles and genetic backgrounds, East Asian populations are regarded as more susceptible to bleeding events but relatively resistant to atherothrombosis compared with Western populations (the so-called "East Asian paradox") (1). Thus, we sought to determine whether the relative safety and efficacy margin with the more potent $P2Y_{12}$ antagonist (i.e., ticagrelor or prasugrel) is identical between Asian and Western patients with acute coronary syndrome (ACS). To explore the potential applicability of a reduced dose of ticagrelor in East Asian patients with ACS, we compared the effect of low-dose ticagrelor (120-mg loading dose, 60 mg twice daily) versus standard-dose ticagrelor (180-mg loading dose, 90 mg twice daily) and clopidogrel (600-mg loading dose, 75 mg once daily) on platelet inhibition.

AR-C124910XX were assessed at pre-dose and at 0.5, 1, 2, 4, 8, 10, and 24 h post-dose.

The primary outcome was the $P2Y_{12}$ reaction unit (PRU) value at 8 h after the loading dose and at 30 days during the maintenance dose. The mixed-effect model was used to compare pharmacodynamic assessments at each time point with the baseline PRU, body mass index, and presence of diabetes mellitus as covariates. To detect an absolute mean difference of 60 ± 65 PRU 8 h after loading and at 30 days during maintenance of low-dose ticagrelor versus clopidogrel, which was assumed based on prior research (2,3), we estimated that 60 patients in total (20 in each group) were required to reach statistical significance with a power of 80%, a 2-sided α value of 0.05, and an attrition rate of 5%.

Between January 2016 and February 2017, 65 patients with ACS (72% unstable angina, 28% acute MI) were randomized. Baseline characteristics did not significantly differ among groups. As a primary endpoint, both ticagrelor therapies showed significantly lower mean PRU values than clopidogrel therapy at 8 h after loading (94 ± 81 PRU vs. 71 ± 55 PRU vs. 251 ± 71 PRU for low-dose ticagrelor vs. standard-dose ticagrelor vs. clopidogrel, respectively; $p < 0.001$) and at 30 days (77 ± 41 PRU vs. 59 ± 38 PRU vs. 234 ± 71 PRU, respectively; $p < 0.001$) (Figure 1). There was no statistical difference in PRU values be-

J Am Coll Cardiol. 2018 Apr 10;71(14):1594-1595. doi: 10.1016/j.jacc.2018.02.010.