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2018 update of expert consensus statement on antiplatelet therapy in East Asian patients with ACS or undergoing PCI

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ABSTRACT

East Asians are the most populous race in the world and their health status is an important global issue. Compared with Caucasian populations, East Asian patients have a different benefit/risk ratio when using antithrombotic treatment. Despite this observation, treatment strategies in East Asian patients are mostly based on the American and European guidelines. Despite a lower platelet inhibitory response to clopidogrel, East Asian patients show a similar or even a lower rate of ischemic event occurrence and higher bleeding risk compared with Caucasian patients. For potent $P2Y_{12}$ inhibitors (ticagrelor and prasugrel), East Asian patients have shown less favorable net clinical benefits compared with Caucasian patients, which may be related to differences in pharmacokinetic/pharmacodynamic profiles and therapeutic zone of antiplatelet effect. This updated consensus mainly focuses on state-of-the-art and current controversies in the East Asian population. In addition, when East Asian patients are administered potent $P2Y_{12}$ receptor inhibitors, the strategies and ongoing trials to overcome the related hurdles are discussed.

1. Introduction

In 2014, the World Heart Federation (WHF), in collaboration with East Asian experts, published the first version of a consensus statement on antiplatelet therapy in East Asian patients with acute coronary syndrome (ACS) or undergoing percutaneous coronary intervention (PCI) [1]. Consequently, more attention has been paid to the differences in the clinical efficacy and safety of antiplatelet therapy between East Asians and Caucasians.

An increasing body of evidence suggests that East Asian patients have different risk profiles for both thrombophilia and bleeding compared with Caucasian patients (Fig. 1) [1,2]. During antithrombotic treatment, East Asian patients have shown a lower risk of atherothrombotic morbidity/mortality (especially, in coronary artery disease (CAD)) and a higher tendency of bleeding. There are recognized concerns in this ethnic group about increased incidence of gastrointestinal (GI) bleeding and hemorrhagic stroke, even in the absence of hypertension. Therefore, the linkage of known cardiovascular (CV) risk factors or scores to CV disease

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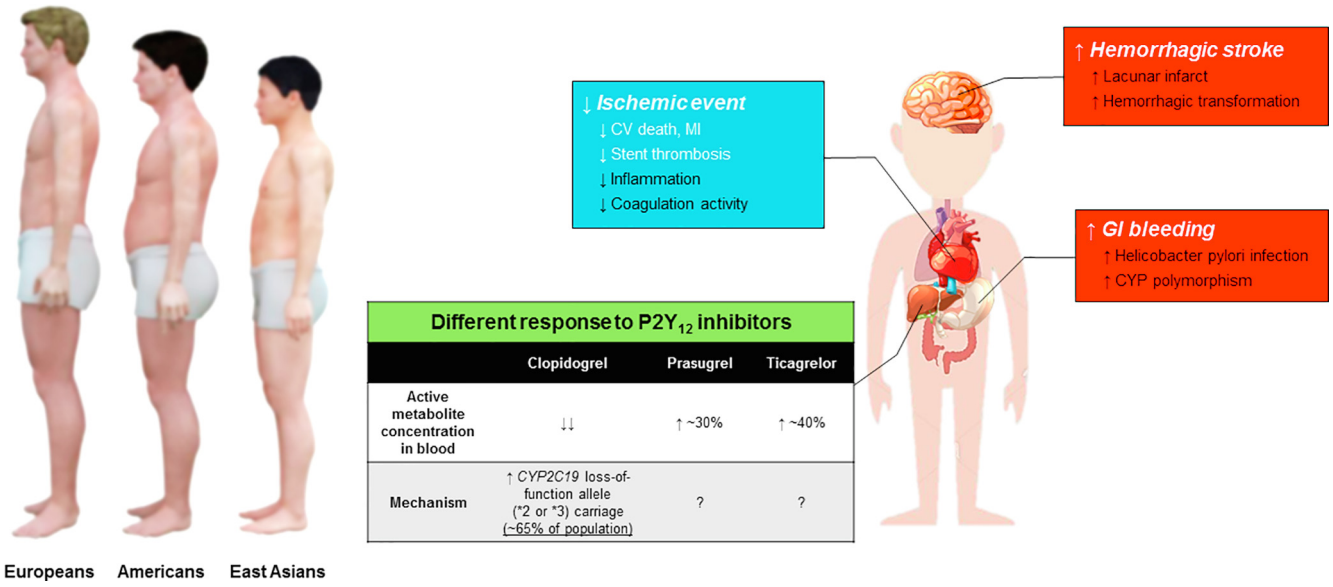

Fig. 1. Unique characteristics of East Asian population in terms with ischemic & bleeding tendency. Abbreviations: CV, cardiovascular; CYP, cytochrome P450; GI, gastrointestinal, MI, myocardial infarction.

occurrence appears weaker in East Asians than in Caucasian subjects [3–5]. Likewise, East Asian patients have a similar or lower rate of ischemic events after PCI compared with Caucasian patients despite a lower response to clopidogrel in East Asians [6–8]. This phenomenon was first noted in 2011 by Jeong and co-investigators who developed the concept of "East Asian Paradox" [2,9], suggesting a different therapeutic targeting of antiplatelet effect in East Asian patients.

The quantity of studies specific to East Asian patients has been increasing since the first consensus statement was published in 2014. Several issues unaddressed in the previous consensus statement have arisen. With trials on research in East Asian patients emerging, data collection and analysis on antiplatelet therapy in this population are needed. This 2018 updated consensus mainly focuses on the following state-of-the-art and ongoing controversies in East Asian population: (1) comparison of clopidogrel with potent $P2Y_{12}$ receptor inhibitors; (2) appropriate dose of potent $P2Y_{12}$ receptor inhibitors; (3) switching between $P2Y_{12}$ receptor inhibitors; (4) clinical application of genotype- or phenotype-guided strategy; (5) GI protective regimen in combination with $P2Y_{12}$ receptor inhibitors; (6) optimal duration of dual antiplatelet therapy (DAPT).

2. $P2Y_{12}$ inhibitors in East Asians

2.1. Clinical outcomes during aspirin plus clopidogrel treatment

After clopidogrel was approved for medical use in 1998, DAPT consisting of aspirin and clopidogrel has been the standard-of-care for patients with ACS or those undergoing PCI. The efficacy and safety profiles of this "standard DAPT" was tested for East Asians more than a decade ago [10]: COMMIT enrolled 45,852 patients of suspected myocardial infarction (MI), in which the clopidogrel (75 mg daily) vs. placebo arm reduced the risk of 4-week death, reinfarction, or stroke by 9% (9.2% vs. 10.1%; $P = 0.002$) without increase of major bleeding (0.58% vs. 0.55%; $P = 0.59$).

There are no direct comparison studies to compare the clinical efficacy and safety of this DAPT regimen in PCI-treated patients between East Asian vs. Caucasian populations. However, there are accumulating clinical evidences to show different clinical use and risk–benefit profile across the races. Low-dose aspirin (~40 mg daily) suppresses most thromboxane A_2 formation and platelet aggregation [11]. There are no experimental results to show an interethnic difference in responsiveness to aspirin. Aspirin dosage of 75 mg daily reduces the risk of GI bleeding by about 40% compared with 300 mg daily and by about 30% compared with 150 mg daily [12]. In clinical practice, a lower dose of aspirin is frequently used for patients in Japan and other parts of Asia compared with non-Asian regions [13]. However, the risk of 2-year CV death was the lowest in East Asians than in other ethnic groups (1.8% in East Asians vs. 4.5% in Caucasians) in the global REACH registry ($n = 45,191$).

The CHARISMA randomized study [14] showed that the Asian population vs. other races had the lowest prevalence of CV mortality and a higher tendency for moderate GUSTO (Global Utilization of Streptokinase and Tissue-plasminogen activator for Occluded coronary arteries) bleeding. Another analysis of the NCDR (National Cardiovascular Data Registry CathPCI Registry) database (423,965 American citizens) also demonstrated favorable clinical outcomes in Asians following PCI [15]. Despite the similar adoption of drug-eluting stent (DES), Asian patients showed a lower prevalence of death and MI compared with Caucasians (adjusted hazard ratio (HR), 0.890; 95% confidence interval (CI), 0.822 to 0.963; $P = 0.004$). After implantation of the first-generation DES, East Asian registries have shown a lower incidence of stent thrombosis (~0.2% per year) compared with those from Western registries (~0.6% per year) [6–8]. There has been an emerging concern about the safety of bioresorbable vascular scaffold (BRS) after implantation. Recent Korean experience provided the low risk of scaffold thrombosis in ACS patients: 9 scaffold thrombosis (0.32%) from 2833 BRSs [9]. Taken together, numerous clinical studies consistently have shown lower atherothrombotic events following ACS or PCI in East Asians compared with Caucasians during clopidogrel treatment.

2.2. Clinical outcomes during potent $P2Y_{12}$ inhibitors treatment

In the previous studies, potent $P2Y_{12}$ receptor inhibitors (ticagrelor and prasugrel) showed more rapid platelet inhibition and more CV benefits in ACS patients compared with clopidogrel [1], but the cohorts of these studies were mainly from non-Asian pop-

ulation. With the emergence of studies focusing on East Asian patients, these results presented have been relatively inconsistent, in some of which potent $P2Y_{12}$ receptor inhibitors showed no more clinical efficacy and increased risk of bleeding compared with clopidogrel.

2.2.1. Ticagrelor

The PLATO [16] and PHILO randomized trials [17] did not show efficacy superiority of ticagrelor over clopidogrel in East Asian patients. Wu et al. [18] made a meta-analysis on these two trials that compared ticagrelor with clopidogrel in East Asian patients with ACS. Compared with clopidogrel, ticagrelor had no difference in ischemic events (HR, 1.08; $P = 0.726$). In addition, ticagrelor provoked significant increases in major bleeding (HR, 1.48; $P = 0.043$) and non-coronary artery bypass graft (CABG) major bleeding (HR, 1.62; $P = 0.045$). It concluded that ticagrelor and clopidogrel has similar efficacies and ticagrelor displays an increased risk of major bleeding in East Asia patients with ACS.

The GEMINI-ACS-1 randomized study was carried out to assess the safety of a dual pathway antithrombotic therapy approach combining low-dose rivaroxaban vs. aspirin with a $P2Y_{12}$ inhibitor [19]. ACS patients ($n = 3037$) were randomly assigned to receive aspirin or rivaroxaban: 1,704 patients (56%) were in the ticagrelor and 1,333 (44%) in the clopidogrel strata. Higher frequency of thrombolysis in Myocardial Infarction (TIMI) non-CABG clinically significant bleeding was found in the ticagrelor stratum compared with the clopidogrel stratum (HR, 1.929; $P = 0.0006$). Notably, patients from Asia and Pacific region (about 80% from Japan and Korea) showed the highest risk of clinically significant bleeding compared with other regions (HR, 3.236; $P = 0.0135$ compared with Central Europe), suggesting special attention should be paid to Asian population. A recent study including Korean ACS patients reported that questionnaire-based prevalence of bleeding and dyspnea at 1 month during standard-dose ticagrelor treatment were as high as 40.6% and 42.2%, respectively [20].

In addition to the analysis from randomized clinical trials, several registries have suggested the controversial results in clinical efficacy and safety of ticagrelor for East Asian patients with ACS (Table 1). In the KAMIR-NIH registry [21] (the Korean prospective observational cohort; $n = 9355$), no significant difference in ischemic events at 12 months was observed between the ticagrelor vs. clopidogrel group (2.1% vs. 2.1%, $P = 0.447$) after propensity score matching (572 pairs). However, the incidence of BARC major bleeding (type 2, 3 or 5) was higher in ticagrelor than in clopidogrel (8.0% vs. 3.1%, $P < 0.001$). Taiwan Health Insurance Research Database [22] (27,339 AMI patients) was retrospectively analyzed and showed the different result: the ischemic event rate was 22% lower in the ticagrelor group than in the clopidogrel group (10.6% vs. 16.2%; HR, 0.779; 95% CI: 0.684 to 0.887) with the similar risk of major bleeding between the groups (3.2% vs. 4.1%; HR, 0.731; 95% CI: 0.522 to 1.026). There would be concerns regarding reliability in terms with the quality of the registry data.

Based on the East Asian data from the latest analysis and registries, ticagrelor may not show definite advantages in reducing CV events over clopidogrel, but may increase the risk of bleeding and dyspnea. Moreover, the recent registry data showed that clopidogrel was more often prescribed to patients with more CV complications and higher risk of bleeding compared with ticagrelor [21–24]. In real-world clinical practice, the difference in baseline characteristics of the cohorts may potentially raise the risk of bleeding in the clopidogrel-treated patients compare with the ticagrelor-treated patients.

2.2.2. Prasugrel

Prasugrel has been studied in large-scale clinical trials [25,26]. As very limited East Asians were included in these trials, it is difficult to draw reliable conclusions regarding whether standard-dose prasugrel will provide superior benefits over clopidogrel in East Asians.

The KAMIR-NIH registry [21] did not show any clinical benefit of prasugrel over clopidogrel in ACS patients. After propensity score matching (572 pairs), there was no significant difference in ischemic events at 12 months (2.6% vs. 2.1%; $P = 0.534$) with increased risk of major bleeding (BARC type 2, 3 or 5) between the prasugrel vs. clopidogrel group (8.0% vs. 3.1%; $P < 0.001$) (Table 1).

Recommendations:

- Clopidogrel in combination with aspirin is a reasonable DAPT choice for elective PCI or ACS (during the chronic phase) in East Asian population.
- Use of standard-dose potent $P2Y_{12}$ inhibitors needs attention to the increased risk of bleeding when used in East Asian ACS population (e.g., prior stroke, old age, low body weight, and recurrent episodes of nuisance bleeding).

3. Reduced-dose strategy of potent $P2Y_{12}$ inhibitors in East Asians

Standard-dose potent $P2Y_{12}$ receptor inhibitors vs. clopidogrel have been found to be associated with a higher risk of significant bleeding in East Asian patients, raising concern over potential bleeding complications in this population. This may be partly due to a lower atherothrombotic events and a higher tendency for bleeding in East Asian individuals over Caucasian individuals, which may be partly associated with the different therapeutic window of antiplatelet effect ("East Asian Paradox") [1,2,9]. In addition, the recent pharmacokinetic and pharmacodynamic studies showed the higher exposure of the major active metabolites and enhanced platelet inhibition by potent $P2Y_{12}$ receptor inhibitors in East Asian individuals compared with Caucasian individuals [2]. Thus, the optimal dose of potent $P2Y_{12}$ receptor inhibitors applying to this population needs further investigations.

A subgroup analysis enrolling East Asian ACS patients from prospective, randomized clinical trials provided important insight for this issue [10,18,26–29]. Compared with standard-dose clopidogrel, moderate-intensity antiplatelet regimens (doubling clopidogrel, adjunctive cilostazol to DAPT and low-dose prasugrel of 3.75 mg daily) showed an overall trend toward better clinical outcome, whereas high-intensity antiplatelet regimens (standard-dose prasugrel of 10 mg daily and standard-dose ticagrelor of 90 mg twice daily) showed a trend for worse clinical outcomes (Fig. 2).

3.1. Ticagrelor

The presence of ticagrelor and its major active metabolite (AR-C124910XX) was greater in East Asian individuals than in Caucasian individuals [30–32]. After multiple doses of ticagrelor (100 mg twice daily), the presence of ticagrelor and AR-C124910XX was 40% and 48% higher in Japanese volunteers than in Caucasian volunteers, which remained 20% and 24% greater even after adjusting for body weight [31]. After ticagrelor administration (100 mg twice daily for 9 days), the peak level of platelet inhibition (final extent) in Japanese volunteers was higher than that in Caucasian volunteers (99% vs. 85%).

The recent studies have shown the pharmacokinetic and pharmacodynamic profiles of reduced-dose ticagrelor in healthy volunteers and CAD patients. In the sub-study of the PEGASUS-TIMI 54 study ($n = 180$) [33], post-dose plasma level of ticagrelor was 38%

Table 1
Registry data regarding clinical effects of P2Y12 inhibitors in East Asian patients.[a]

Study	P2Y12 inhibitors	East Asian No./ Total No. (%)	Disease entity	Efficacy endpoint			Safety endpoint		
				Definition	Events	HR (95% CI), *P* value	Definition	Events	HR (95% CI) *P* value
KAMIR-NIH [21]	Prasugrel vs. ticagrelor vs. clopidogrel (1 year follow-up)	9,355/9,355 (100%)	AMI	Cardiac death, MI, stroke or stent thrombosis (post-discharge)	2.6% vs. 2.1% vs. 2.1%	(Prasugrel vs. clopidogrel)1.27 (0.60–2.72), *P* = 0.534 (ticagrelor vs. clopidogrel) 1.35 (0.62–2.93), *P* = 0.447	BARC 2,3 or 5	8.0% vs. 8.0% vs. 3.1%	(Prasugrel vs. clopidogrel) 2.62 (1.52–4.51), *P* < 0.001 (ticagrelor vs. clopidogrel) 2.65 (1.53–4.56), *P* < 0.001
Taiwan Database [22]	Ticagrelor vs. clopidogrel (mean 8 mo.)	27,339/27,339 (100%)	AMI	Death, MI or stroke	10.6% vs. 16.2%	0.779 (0.684–0.887)	Major bleeding requiring hospitalization	3.2% vs. 4.1%	0.731 (0.522–1.026)
BleeMACS [24]	Prasugrel vs. ticagrelor vs. clopidogrel (1 year follow-up)	2,332/12,336 (18.9%)	ACS	Death or re-infarction	0% vs. 0% vs. 4.3%	*P* = 0.03	Serious bleeding	1.5% vs. 0% vs. 2.6%	*P* = 0.59

[a] ACS, acute coronary syndrome; AMI, acute myocardial infarction; BARC, bleeding academic research consortium; BleeMACS, bleeding complications in a multicenter international registry of patients discharged after an Acute Coronary Syndrome; CI, confidence interval; HR, hazard ratio; KAMIR-NIH, Korea Acute Myocardial Infarction Registry-National Institutes of Health.

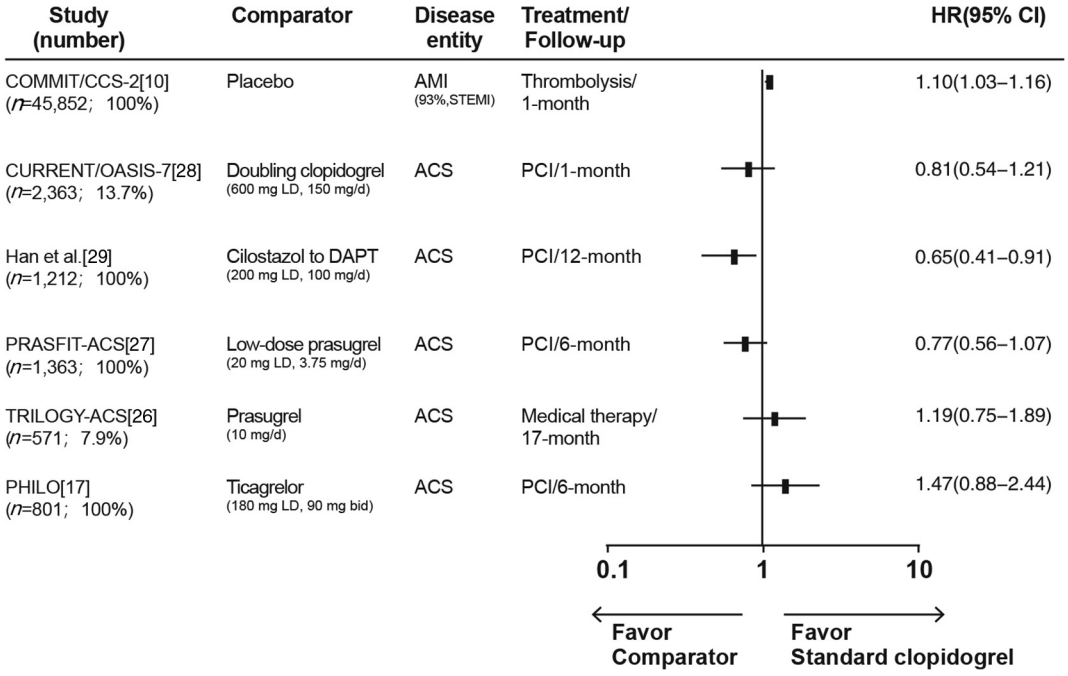

Fig. 2. Subgroup analysis of East Asians from randomized clinical trials including ACS patients: risk of primary ischemic endpoint during comparator treatment vs. standard-dose clopidogrel. Abbreviations: ACS, acute coronary syndrome; AMI, acute myocardial infarction; CI, confidence interval; COMMIT/CCS-2, Clopidogrel and Metoprolol in Myocardial Infarction Trial/Second Chinese Cardiac Study; CURRENT/OASIS-7, Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent EveNTs/Optimal Antiplatelet Strategy for InterventionS-7; HR, hazard ratio; DAPT, dual antiplatelet therapy; LD, loading dose; PCI, percutaneous coronary intervention; PHILO, Study to Assess Safety and Efficacy of Ticagrelor Versus Clopidogrel in Asian/Japanese Patients With Non-ST or ST Elevation Acute Coronary Syndromes; PRASFIT-ACS, PRASugrel compared with clopidogrel For Japanese patIenTs with ACS undergoing PCI; STEMI, ST-segment elevation myocardial infarction; TRILOGY-ACS, TaRgeted platelet Inhibition to cLarify the Optimal strateGy to medicallY manage Acute Coronary Syndromes.

lower with 60 mg than with 90 mg, but levels of platelet reactivity in both doses did not differ (29 ± 39 vs. 20 ± 19 $P2Y_{12}$ reaction unit [PRU] measured by VerifyNow test; *P* = 0.73). In a double-blind study including Japanese patients with stable CAD (*n* = 139) [34], the plasma concentrations of ticagrelor and AR-C124910XX on day 28 were about half with 45 mg vs. 90 mg twice daily. At the end of the study, the level of platelet inhibition (final extent) was only 10.0% lower (95% CI, −19.5% to −0.5%) for 45 mg vs. 90 mg ticagrelor.

Once-daily regimen with 90 mg ticagrelor might deserve consideration in clinical practice. However, the antiplatelet effect of this regimen was considerably variable over time compared with

other antiplatelet treatments, which may diminish any pleiotropic effects depending on its plasma concentration (reversibly binding) [35,36]. In PCI-treated patients, half-dose ticagrelor (45 mg twice daily) showed the lowest level of platelet reactivity (65.5 ± 58.8 PRU) compared with ticagrelor of 90 mg once daily (98.6 ± 73.4 PRU) and clopidogrel of 75 mg daily (221.2 ± 50.1 PRU) [37]. A crossover study including Chinese patients with stable CAD evaluated the antiplatelet effect of very low-dose of ticagrelor (22.5 mg twice daily) vs. standard-dose of clopidogrel (75 mg daily) for 7 days [38]. The level of platelet reactivity in the ticagrelor group was significantly lower than that in the clopidogrel group (87.0 ± 51.4 vs. 163.8 ± 58.7 PRU, $P < 0.01$), while the prevalence of high platelet reactivity (HPR; defined as PRU $\geq$ 208) was 0% with ticagrelor and 16.7% with clopidogrel. These findings support the hypothesis that 90 mg twice daily ticagrelor in East Asians would achieve more than the optimal antiplatelet effect and that the platelet inhibition achieved by low-dose ticagrelor would be more optimal in East Asians [2,9].

The clinical efficacy and safety of reduced-dose ticagrelor remains still uncertain in East Asian patients with ACS. In the PEGASUS-TIMI 54 trial [39], 21,162 patients who had had a MI 1 to 3 years earlier were enrolled to investigate the efficacy and safety of ticagrelor at a dose of 90 and 60 mg twice daily compared with placebo on a background of low-dose aspirin. The study showed that the rate of the composite primary efficacy endpoint (CV death, MI, or stroke) at 3 years was 7.85% in the 90 mg group, 7.77% in the 60 mg group, and 9.04% in the placebo group (HR for 90 mg ticagrelor vs. placebo, 0.85; $P = 0.008$; HR for 60 mg ticagrelor vs. placebo, 0.84; $P = 0.004$). Rates of TIMI major bleeding were higher with ticagrelor (2.60% and 2.30% with 90 and 60 mg, respectively) than with placebo (1.06%) ($P < 0.001$ for each dose vs. placebo); the rates of intracranial hemorrhage or fatal bleeding in the three groups were 0.63%, 0.71%, and 0.60%, respectively. There was no interaction with ethnicity with respect to the primary efficacy and the primary safety endpoint for both ticagrelor doses. In conclusion, 60 and 90 mg of ticagrelor presented similar efficacy, while 90 mg of ticagrelor had slightly higher risk of bleeding. Based on these results, the Food and Drug Administration (FDA) approved the use of 60 mg ticagrelor for the high-risk patients in post-MI 1 to 3 years. This study enrolled 11.2% ($n = 2,369$) of Asian population (East Asians: about three quarters of the Asian cohort) [40]. Compared with placebo, 60 mg ticagrelor did not provide the net clinical benefit (7.11% vs. 6.86% for ischemic endpoint; 3.74% vs. 1.44% for TIMI major bleeding). In East Asian patients presented with ACS ($n = 65$), low-dose ticagrelor (60 mg twice daily) showed the comparable level of antiplatelet effect at 30 days compared with standard-dose ticagrelor (90 mg twice daily) (77 ± 41 vs. 59 ± 38 PRU) [41]. At 8 h after loading, the incidence of high on-treatment platelet reactivity (>208 PRU) was rare with low-dose ticagrelor ($n = 2$; 9.1%) and absent with standard-dose ticagrelor.

Further studies are required to evaluate the clinical impact of inter-ethnic difference in ticagrelor pharmacodynamics. Whether reduced-dose ticagrelor can provide acceptable efficacy and safety compared with standard-dose ticagrelor or clopidogrel needs further investigation in ACS patients.

3.2. Prasugrel

Prasugrel was studied at the dose of 10 mg daily for clinical usage in a phase III study [25], and 10 mg was later recommended as the maintenance dose in its drug instructions in USA and Europe. However, it may be not applicable to East Asian patients. After prasugrel administration, the level of the active metabolite was 19%–41% higher in East Asian subjects than in Caucasian subjects [42]. This pharmacokinetic profile in East Asians has been translated into the pharmacodynamic profile.

In the PRASFIT-ACS randomized study including Japanese patients ($n = 1,363$) [27], the investigators selected low-dose prasugrel strategy (20 mg loading-dose (LD), 3.75 mg daily maintenance-dose (MD)) based on a phase II pharmacodynamic study [43]. Results showed a slightly stronger platelet inhibition compared with that of standard-dose clopidogrel (300 mg LD, 75 mg daily MD). The PRASFIT-ELECTIVE trial [44] showed that the incidence of the primary TRITON endpoint and TIMI major/minor/clinically relevant bleeding was numerically lower with prasugrel (20 mg LD, 3.75 mg daily MD) than with clopidogrel (300 mg LD, 75 mg daily MD) (4.1% vs. 6.7% for primary endpoint; 5.4% vs. 6.2% for TIMI bleeding).

To further determine the appropriate dose of prasugrel in East Asian patients undergoing elective PCI, a dose-finding phase II study was carried out [45]. A total of 422 Japanese patients were randomly assigned to receive clopidogrel or prasugrel in two strata (the standard group: <75 years of age and body weight >50 kg and the high-risk group: $\geq$75 years of age and/or body weight $\leq$50 kg). The rates of TIMI major and minor bleeding were similar among three treatment arms in the standard group and the high-risk group. In the standard group, all of the prasugrel arms showed lower PRU than the clopidogrel arm, but the prasugrel arms failed to show the advantage on the primary ischemic endpoint (20/3.75 mg of prasugrel: 4%; 20/5 mg of prasugrel: 13%; 300/75 mg of clopidogrel: 4%). In the high-risk group, 20/2.5 mg of prasugrel arm showed a similar platelet inhibition with 300/75 mg of clopidogrel, while the primary ischemic endpoint was numerically lower in this prasugrel arm. The A-MATCH trial [46] ($n = 250$) evaluated the clinical safety of fixed low-dose treatment (5 mg prasugrel) and phenotype-guided treatment (switched by 5 mg prasugrel only for patients with low platelet reactivity [LPR], defined as $\leq$94 PRU) vs. standard-dose prasugrel of 10 mg allocated before discharge in Korean ACS patients. After 1-month treatment, the matching prevalence of the therapeutic zone of platelet reactivity (95 $\leq$ PRU $\leq$ 208) was almost twice in the de-escalation stratum than in the standard-dose stratum (62.7% vs. 62.2% vs. 29.4%, $P < 0.001$). The prevalence of LPR was lower in the fixed low-dose and phenotype-guided strata compared with the standard-dose stratum (22.9% vs. 30.5% vs. 64.7%, $P < 0.001$), which could reduce the risk of BARC bleeding episodes at 1 month (24.1% vs. 23.2% vs. 35.3%).

Although the prasugrel MD may be recommended as 3.75–5 mg based on the small-scale East Asian studies discussed above, further data from randomized studies are needed to confirm this suggestion. Further large-scale, long-term, randomized trials should be conducted to determine an appropriate dose of prasugrel for East Asian patients.

Recommendation:

- After considering the risk-benefit profile, a reduced-dose strategy of potent $P2Y_{12}$ receptor inhibitors (especially, prasugrel) may be a considerable choice in East Asian population with ACS.

4. Switching strategy between $P2Y_{12}$ inhibitors

In clinical practice, it is common to switch $P2Y_{12}$ inhibitor, and switching may be related with a variety of factors. The availability of different oral $P2Y_{12}$ inhibitors has enabled physicians to contemplate switching among therapies because of specific clinical sce-

narios [47–50]. Because the low response to clopidogrel and increased bleeding risk on potent $P2Y_{12}$ inhibitors in East Asian patients, switching between different $P2Y_{12}$ receptor inhibitors becomes problem of concern [47].

4.1. Prevalence and reasons of switching

In-hospital switching between a potent $P2Y_{12}$ receptor inhibitor and clopidogrel is frequent in ACS patients, ranging from 5.0% to 13.6% [50], and it can be even higher in patients after hospital discharge [51]. The prevalence of switching appeared higher in East Asian patients. For example, ACS Chinese patients (n = 404) discontinued ticagrelor in 158 (39.1%) within 12 months, while 119 (29.5%) switched to clopidogrel [52].

Increased bleeding tendency and requirement for oral anticoagulation may be the important clinical scenarios necessitating switching to clopidogrel. Furthermore, a considerable proportion of patients on ticagrelor may develop dyspnea or bleeding [51,53], which may warrant consideration for its discontinuation due to intolerance. The incremental cost of potent $P2Y_{12}$ receptor inhibitors compared to generic clopidogrel may necessitate substitution in the certain patients. The availability of new drugs is another reason for drug discontinuation in East Asian countries. The Chinese data showed the common reasons for discontinuation of ticagrelor within 12 months: unavailable drug (34.8%), economic reason (17.7%), bleeding (18.4%), and dyspnea (5.1%) [52].

4.2. How to switch and its clinical impact

Recently, the expert consensus group developed recommendations on when and how to switch between $P2Y_{12}$ inhibitors [50]. Robust clinical outcome data for switching strategies (escalation, de-escalation and change) are lacking, but strategies can be guided by the different pharmacological profiles of these agents. For example, the CAPITAL OPTI-CROSS study evaluated switching strategies from ticagrelor to clopidogrel in ACS patients [54]. Compared with a bolus arm (clopidogrel 600 mg bolus followed by 75 mg daily, n = 30), a no-bolus arm (clopidogrel 75 mg daily, n = 30) showed the largest difference of platelet reactivity at 48 h post-switching (165.1 ± 70.5 vs. 114 ± 73.1 PRU; P = 0.0076) and this difference became insignificant at 72 h (184.1 ± 67.7 vs. 165.8 ± 71.0 PRU; P = 0.19).

The TOPIC study [55] (n = 645) suggested the clinical benefit of the switched stratum (switching from potent $P2Y_{12}$ inhibitor to clopidogrel at 1 month post-ACS) compared with the unchanged stratum (potent $P2Y_{12}$ inhibitor maintenance) during 1 year. Compared with the unchanged stratum, the switched stratum reduced the risk of the primary endpoint (CV death, urgent revascularization, stroke, and bleeding episodes as defined by ≥BARC type 2) (13.4% vs. 26.3%; P < 0.01). No significant differences were reported on ischemic endpoints, while serious bleeding occurred less frequently in the switched vs. unchanged stratum (4.0% vs. 14.9%; P < 0.01). The data from Chinese registries also demonstrated the acceptable efficacy of the de-escalation strategy between $P2Y_{12}$ inhibitors. Among 158 patients who discontinued ticagrelor early (119 switched to clopidogrel) in the TIFU study, ischemic events occurred in 1.3% during 1 year, compared with 2.2% in the continued group (n = 223) [52]. In PCI-treated Chinese patients (n = 417) [47], poor adherence was observed in patients from clopidogrel to ticagrelor (64.8%) or treated only by ticagrelor (50.9%), but excellent adherence in patients from ticagrelor to clopidogrel (100%) at 6 month follow-up. In addition, patients switching from ticagrelor to clopidogrel had a relatively lower bleeding risk (any TIMI criteria) in comparison with subjects with continued ticagrelor treatment and those switching from clopidogrel to ticagrelor (29.5% vs. 50.0% vs. 46.6%; adjusted P = 0.02).

Although switching from potent $P2Y_{12}$ receptor inhibitors to clopidogrel is frequent in the real-world setting, an optimal switching strategy has not yet been decided. The feasibility of switching from clopidogrel to a potent $P2Y_{12}$ receptor inhibitor needs more supportive evidences, especially on adverse events like bleeding or dyspnea. Further studies are needed to explore the optimal timing and dosage of antiplatelet drugs when switching is inevitable.

Recommendation:

- When discontinuation of potent $P2Y_{12}$ receptor inhibitors (ticagrelor and prasugrel) is required due to intolerance (bleeding or dyspnea), switching to clopidogrel following clopidogrel bolus may be a considerable option for East Asian patients with ACS.

5. Genotype- or phenotype-guided antiplatelet approach in East Asians

5.1. Impacts of genotype and phenotype on clinical outcomes

Clopidogrel is an inactive prodrug converted to the pharmacologically active metabolite in liver by two steps. The cytochrome P450 (*CYP*) *2C19* involves the two metabolism steps of clopidogrel, and the correlation between its polymorphism and clinical outcome is the most investigated [56,57]. There are inter-ethnic differences in the prevalence of *CYP2C19* polymorphism [58]. The wild-type *CYP2C19* allele is **1*, carried by 85% of Europeans and 60% of East Asians. The frequency of the *CYP2C19*2 loss-of-function* (*LOF*) allele is ∼15% and ∼30% in Caucasians and East Asians, respectively. The *CYP2C19*3 LOF* allele is only observed in East Asians (∼10%). The prevalence of intermediate metabolizers (IMs; *1/*2 and *1/*3) among East Asians is about twice as frequent as compared to that for Europeans (∼50% vs. ∼25%). The prevalence of poor metabolizers (PMs; *2/*2, *2/*3, and *3/*3) in East Asians is much more frequent than that in Europeans (10% vs. 2%). Therefore, clopidogrel responsiveness in East Asians is decreased compared with Caucasians.

For East Asian population, the initial report suggested the close relationship between *CYP2C19 LOF* allele and CV event [59]. In patients who survived an AMI (n = 266), CV event occurrence increased according to the number of the *CYP2C19 LOF* allele. In DES-treated patients from a Korean multicenter genetic registry (n = 2,146) [60], the composite of CV death, MI and stent thrombosis was significantly higher in carriers of the *CYP2C19*2* allele than non-carriers (2.0% vs. 0.8%, P = 0.02). Another Korean multicenter genetic registry (n = 2,188) suggested the different impact of *CYP2C19 LOF* allele on adverse CV events according to the disease entity [61]. Compared with extensive metabolizers, the *CYP2C19* poor metabolizer was significantly associated with higher risk of major CV events in 532 patients with AMI (HR, 2.88; 95% CI, 1.27 to 6.53; P = 0.011). However, this finding was not seen in patients with stable angina (n = 1,656). A systematic meta-analysis (n = 36,076) suggested a different association between *CYP2C19 LOF* allele and major CV outcomes according to the ethnic population [62]. The association between presence of ≥1 *CYP2C19 LOF* allele and major CV outcomes differed significantly (P < 0.001) between studies of Caucasian patients not undergoing PCI (HR, 0.99; 95% CI, 0.84 to 1.17; n = 7,043), Caucasians undergoing PCI (HR, 1.20; 95% CI, 1.10 to 1.31; n = 19,016), and Asians undergoing PCI (HR, 1.91; 95% CI, 1.61 to 2.27; n = 10,017). In a recent Chinese multicenter genetic cohort including ACS patients undergoing PCI

(n = 5,820) [63], the composite endpoint of CV death, MI and stroke was observed in only 1.4%. The carriage of *CYP2C19 LOF* allele(s) was not associated with the risk of CV events (P > 0.05). While, in a study which enrolled 1016 Chinese ACS patients undergoing DES implantation, the *CYP2C19 LOF* allele was associated with HPR and an increased risk of adverse CV events at 1-year follow-up during clopidogrel treatment [64]. Generally, the influence of *CYP2C19 LOF* allele carriage on adverse CV outcomes during clopidogrel treatment was more prominent in patients with high-risk profile (e.g., ACS, complex PCI) [65]. Therefore, the impact of *CYP2C19 LOF* allele on atherothrombotic events during clopidogrel treatment might be relatively low in East Asians, but the clinical evidence of these observations still remains unclear.

During antiplatelet treatment, the therapeutic window of platelet reactivity may vary according to the atherothrombotic and bleeding risks [66]. Multiple clinical studies have shown a higher therapeutic window of platelet reactivity in East Asians (“East Asian Paradox”) (Fig. 3), which may be partly related with the unique characteristics of this ethnic group (low thrombogenecity and higher bleeding tendency) Table 2 [67–75]. As the use of potent $P2Y_{12}$ receptor inhibitors is increasing in East Asian populations, the prevalence of HPR has decreased and the increase in prevalence of LPR raises concern regarding potential bleeding risk.

5.2. Genotype-guided strategy

In high-risk patients undergoing PCI, the antiplatelet strategies overcoming the hurdle of *CYP2C19 LOF* allele carriage has been under investigation. When increasing the dose of clopidogrel to 225 mg daily for *CYP2C19*2* heterozygotes (*1/*2), the level of platelet reactivity could be compensated as the same level as non-carriers on 75 mg daily. By contrast, increasing the dose of clopidogrel (up to 300 mg daily) for *CYP2C19*2* homozygotes did not achieve comparable efficacy in Caucasians [76]. In the ACCEL-DOUBLE study (PCI-treated Koreans) [77], prevalence of HPR during double-dose clopidogrel of 150 mg daily was 8.7%, 21.7%, and 50.0% in carriers of 0, 1, and 2 *CYP2C19 LOF* alleles, respectively (P < 0.001). Carriage of *CYP2C19 LOF* allele increased the risk of HPR (odds ratio (OR), 5.525; 95% CI, 1.333 to 23.256; P = 0.018).

Another Korean study evaluated the benefit of genotyping-guided de-escalation strategy in MI patients who initially treated with prasugrel (n = 50) [78]. Among EM + IM patients, patients were switched with clopidogrel of 75 mg daily. The prevalence of matching the therapeutic window (85 < PRU ≤ 275) increased from 48% to 76% (P = 0.007), primarily driven by a decrease of LPR (52% to 16%, P < 0.001). In the post hoc analysis of the PRASFIT-ACS study [79], although among IM + PM patients, PRU was significantly lower in the prasugrel group than in the clopidogrel group, the difference of major adverse CV events was not statistically significant (HR, 0.78; 95% CI, 0.45 to 1.35), and overall bleeding events were higher in the prasugrel group than the clopidogrel group (50.2% vs. 31.9%; HR, 1.80; 95% CI, 1.35 to 2.39). A Chinese study randomized IM + PM ACS patients (n = 181) into the ticagrelor group (180 mg LD, 90 mg twice daily MD) or the clopidogrel group (600 mg LD, 75 mg daily MD). After 6 months, the incidence of a composite of death, stroke, MI and stent thrombosis occurred in 4.4% among the ticagrelor group compared with 20.0% among the clopidogrel group (P < 0.001) [80].

In summary, although the *CYP2C19* gene polymorphism may affect the antiplatelet effect and adverse CV outcomes during clopidogrel treatment in East Asian patients with high-risk profile, routine genetic testing is not recommended, as tailoring of antiplatelet therapy based on genetic testing has not been shown to result in a better clinical outcome in the large-scale clinical studies. But it could be considered in selected high-risk patients treated with clopidogrel, including those with a history of stent thrombosis, AMI, as well as complex PCI.

5.3. Phenotype-guided strategy

Although on-treatment platelet reactivity has been identified as an independent predictor of subsequent ischemic events, tailoring of antiplatelet therapy based on platelet function testing has not been associated with improved outcomes after PCI in randomized clinical trials [81–84].

In East Asian populations, use of potent $P2Y_{12}$ receptor inhibitors increased the concern of bleeding risk [1,2]. Even in East Asian patients presenting with STEMI, standard-dose of prasugrel (60 mg LD and 10 mg daily MD) and ticagrelor (180 mg LD and 90 mg twice daily MD) showed a much enhanced level of antiplatelet effect [85]. At 48 h post-loading, almost all patients (about 95%) met the criteria of LPR (PRU < 85) by both regimens, which suggests that a high number of East Asian patients may have very low level of platelet reactivity and questions the safety of potent $P2Y_{12}$ inhibitor.

Several pharmacodynamic studies have shown a laboratory benefit of phenotyping-guided antiplatelet therapy in East Asians. The antiplatelet effect of 90 mg ticagrelor twice daily, 10 mg prasugrel daily and 5 mg prasugrel daily were evaluated in Korean ACS patients. After 2 to 4 weeks, the 5 mg prasugrel group had the highest proportion of matching the therapeutic window (85 < PRU ≤ 275), followed by the 10 mg prasugrel and ticagrelor groups (90.0% vs. 46.2% vs. 12.5%, respectively; P < 0.001) [86]. The majority of patients in the ticagrelor group showed the low level of platelet reactivity (PRU < 85: 87.5%). A Korean study evaluated the laboratory impact of phenotype- or genotype-guided

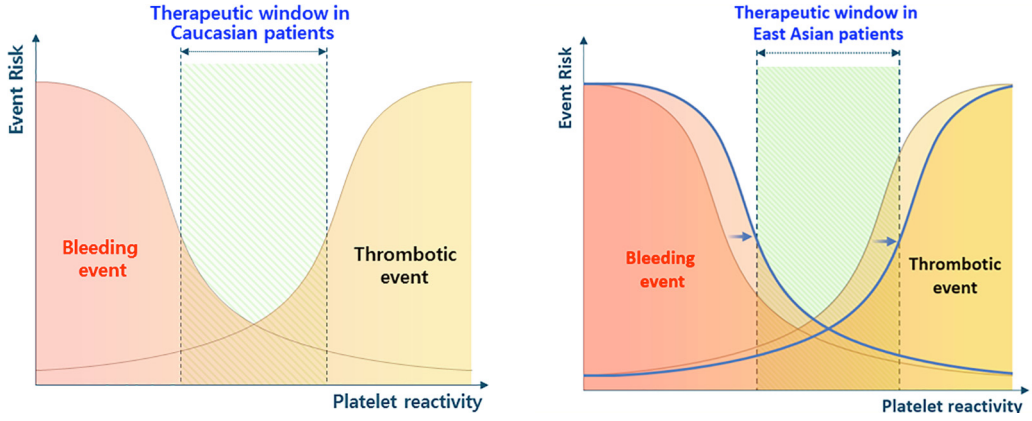

Fig. 3. Presented therapeutic window of platelet reactivity during P2Y12 ADP inhibitor: Caucasian vs. East Asian patients.

Table 2
The cutoffs of HPR in East Asian patients evaluated by the receiver-operating characteristic curve analysis (total $n = 9,091$).[a]

Study	Cohort	Follow-up duration (month)	Primary endpoint	Cutoff
ACCEL-LOADING-ACS study (RCT) [67]	NSTE-ACS ($n = 218$); emergent PCI	1	CV death, nonfatal MI, and TVR	PRU $\geq$ 289*
Zhang et al. (Registry) [68]	NSTE-ACS ($n = 228$); emergent PCI	1	CV death, nonfatal MI, stent thrombosis and TVR	PRU > 272*
Ko et al. (Registry) [69]	all comers ($n = 222$); PCI	1	death, nonfatal MI, stroke and TVR	PRU $\geq$ 275*
PRASFIT-ACS study (RCT) [70]	ACS ($n = 660$); emergent PCI	6	CV death, nonfatal MI and nonfatal ischemic stroke	PRU $\geq$ 262*
CILON-T study (RCT) [71]	All comers ($n = 960$); DES implantation	6	Cardiac death, nonfatal MI, ischemic stroke, and TLR	PRU $\geq$ 252.5*
Ahn et al. (Registry) [72]	All comers ($n = 1,226$); stenting	12	CV death, nonfatal MI and stent thrombosis	Non-AMI: no cutoff* AMI: PRU $\geq$ 272*
CROSS-VERIFY cohort (Registry) [73]	All comers ($n = 809$); elective PCI	12	Cardiac death and nonfatal MI	PRU $\geq$ 275*
Jin et al. (Registry) [74]	STEMI ($n = 181$); primary PCI	12	CV death, nonfatal MI, and ischemic stroke	PRU $\geq$ 282*
GENIUS study (Registry) [75]	All comers ($n = 4,587$); PCI	12	CV death, nonfatal MI	PRU $\geq$ 266*

[a] ACCEL-LOADING-ACS, ACCELerated Inhibition of Platelet Aggregation, Inflammation and Myonecrosis by Adjunctive Cilostazol LOADING in Patients With Acute Coronary Syndrome; ACS, acute coronary syndrome; AMI, acute myocardial infarction; CAD, coronary artery disease; CILON-T, Influence of CILostazol-based triple antiplatelet therapy ON ischemic complication after drug-eluting stenT implantation; CROSS-VERIFY, Measuring Clopidogrel Resistance to Assure Safety After Percutaneous Coronary Intervention Using VerifyNow; CV, cardiovascular; DES, drug-eluting stent; HPR, high platelet reactivity; MI, myocardial infarction; NSTE-ACS, non-ST-elevation elevation acute coronary syndrome; PCI, percutaneous coronary intervention; PRASFIT-ACS, PRASugrel compared with clopidogrel For Japanese patIenTs with Acute Coronary Syndrome undergoing percutaneous coronary intervention; PRU, $P2Y_{12}$ reaction units; RCT, randomized controlled trial; STEMI, ST-segment elevation myocardial infarction; TLR, target lesion revascularization; TVR, target vessel revascularization.

treatment in NSTE-ACS patients initially treated with clopidogrel [87]. In the genotype-guided group, carriers of *CYP2C19 LOF* allele (s) were switched to ticagrelor of 90 mg twice daily. The level of platelet reactivity was decreased from 242 ± 83 PRU to 109 ± 90 PRU ($P < 0.001$), but 16.2% of the patients still met the criteria of HPR at 1 month. In the phenotype-guided group, patients with HPR ($\geq$230 PRU) were switched to ticagrelor of 90 mg twice daily. The level of platelet reactivity was decreased from 216 ± 74 to 109 ± 90 PRU ($P = 0.001$), and only 3.3% of the patients met the criteria of HPR at 1 month. In the A-MATCH trial [46], the prevalence of LPR (<95 PRU) at 1 month was almost twice in the conventional group (prasugrel of 10 mg daily) compared with the phenotype group (prasugrel of 5 mg daily in cases of LPR before discharge) (30.5% vs. 64.7%, $P < 0.001$), which was related with the reduced risk of BARC bleeding by about 30% (23.2% vs. 35.3%).

Although the level of platelet reactivity during $P2Y_{12}$ receptor inhibitor may affect adverse CV outcomes in East Asian patients, the linkage between platelet reactivity and CV outcomes appeared different between Caucasian and East Asian populations [1,2]. For phenotype-tailored treatment, developments in reliable therapeutic window of platelet reactivity and estimated antiplatelet effect of each drug for East Asians are needed from the large-scale clinical data. However, phenotype-guided strategy could be considered in selected high-risk patients for ischemic or bleeding events (e.g., anemia, old age, chronic kidney disease, and prior bleeding) [88].

Recommendation:

- Routine genetic or platelet function testing is not recommended to guide antiplatelet therapy, but can be considered in high-risk East Asian patients for ischemic or bleeding events.

6. Prevention of GI bleeding

GI track is the most common site of non-access site-related bleeding after PCI (30%–40%). GI bleeding was associated with increased risk of the composite of death, MI, or stroke (adjusted HR, 3.75; 95% CI, 1.99 to 7.07; $P < 0.001$) [89].

Compared with Caucasian patients, East Asians have shown a greater tendency for GI bleeding even during low potency of antiplatelet therapy (e.g., low-dose aspirin for primary prevention) [90,91], which may be associated with a higher prevalence of Helicobacter pylori infection and genetic differences related with CYP polymorphism. Therefore, routine use of GI protective agent is considered in East Asians with high-risk profile for GI bleeding (e.g., old age, nonsteroidal anti-inflammatory drug, triple antithrombotic therapy, current smoking, history of GI bleeding and acute phase of ACS) [92,93]. Among the antiulcer drugs, proton pump inhibitors (PPIs) are the preferred agents in patients receiving DAPT [92]. A recent meta-analysis showed that PPIs were superior to histamine H_2 receptor antagonists (H_2RAs) for prevention of GI erosion/ulcer (OR, 0.28; 95% CI, 0.16 to 0.50) and bleeding (OR, 0.28; 95% CI, 0.14 to 0.59) in patients receiving low-dose aspirin [93]. In a randomized trial from Hong-Kong ($n = 311$), the esomeprazole group (20 mg daily) reduced the risk of a composite of upper GI bleeding, perforation, or obstruction from ulcer/erosion compared with famotidine (40 mg daily) in ACS patients receiving DAPT (HR, 0.095; 95% CI, 0.005 to 0.504; $P = 0.0052$), in which this effect appeared maintained up to 6 months [94]. In a Hong-Kong cohort study [95] including patients on DAPT with aspirin plus clopidogrel, upper GI bleeding occurred in 4.0% during 6-month follow-up. After adjustment, the risk was marginally reduced by H_2RA (OR, 0.43; 95% CI, 0.18 to 0.91; $P = 0.04$) and significantly reduced by PPI (OR, 0.04; 95% CI, 0.002 to 0.21; $P = 0.002$), as compared to control. Therefore, use of H_2RAs may be a reasonable option in patients at low risk for GI bleeding [92].

PPIs and clopidogrel share common metabolic pathways mediated by *CYP2C19* and *CYP3A4*. Theoretically, concurrent use of PPI and clopidogrel can competitively inhibit the conversion of clopidogrel to its active metabolite, leading to reduced platelet inhibition. This interaction depends on the potency of each PPI, from stronger inhibitors such as lansoprazole (Ki: 0.4–1.5 μmol/L), omeprazole (Ki: 2–6 μmol/L), and esomeprazole (Ki: 8 μmol/L) down to weaker ones such as rabeprazole (Ki: 17–21 μmol/L) and pantoprazole (Ki: 14–69 μmol/L) [96]. Due to the differences in pharmacogenetic profile, there are no convincing evidences of pharmacodynamic interaction between ticagrelor/prasugrel and

PPIs [97]. Because ticagrelor or prasugrel vs. clopidogrel has a potential to increase the risk of GI bleeding in ACS patients, the use of PPIs is more recommended in ticagrelor- or prasugrel-treated patients who are at an increased risk of GI hemorrhage.

In several clinical studies mainly including Caucasian patients [98,99], the combination of PPI and clopidogrel did not affect its clinical efficacy. In East Asian patients, the clinical relevance of clopidogrel-PPI interaction on CV events risk has been investigated, but the results remain controversial. A Korean registry including PCI-treated patients evaluated the clinical impact of PPI, in which these patients were classified into DAPT (aspirin + clopidogrel; $n = 2,209$) and TAT (DAPT + cilostazol; $n = 697$) according to discharge medication. For any treatment stratum, there were no significant differences in the risk of ischemic events between PPI and non-PPI users [100]. From a Japanese registry including stented patients treated with clopidogrel, 500 pairs with or without PPI were matched after propensity score analysis. No significant difference was observed in the composite of all-cause death or MI between the group without vs. with PPI (4.2% vs. 4.4%, $P = 0.91$). In contrast, a significant difference was found between the group without and with PPI in regard to the incidence of GI bleeding (2.4% vs. 0.8%; $P = 0.026$) [101]. However, the Taiwan Health Insurance database showed the different result [102]. From PCI-treated patients receiving clopidogrel ($n = 3,278$; PPI-users, $n = 572$; non PPI-users, $n = 2,706$), concomitant PPI use was associated with an increased risk of hospitalization (HR, 1.23; 95% CI, 1.07 to 1.41; $P = 0.003$) and mortality (HR, 1.65; 95% CI, 1.35 to 2.01; $P < 0.001$).

There are multiple clinical studies showing the adverse events related with prolonged use of PPI (e.g., infection, kidney injury, dementia, hypomagnesemia, fracture, and increased risk of stroke or cardiac disease) [97,103]. For example, the Taiwan Health Insurance Research Database suggested the potential of increased MI risk in chronic PPI users [103]. From 126,367 pairs between 2000 and 2009 (PPI users and non-users) after propensity score matching, PPI use was associated with a 1.58-fold greater risk of MI during 4-month follow-up (adjusted HR, 1.58; 95% CI, 1.11 to 2.25).

In summary, there is still insufficient evidence to support the statement that the concomitant use of PPIs and antiplatelet treatment, especially clopidogrel, will increase the risk of CV events in East Asian population. In view of the pharmacokinetic and pharmacodynamic evidence, PPIs with weaker inhibition of *CYP2C19* are preferred in combination with clopidogrel compared with those with stronger inhibition such as omeprazole and esomeprazole. The threshold for concomitant PPI use in patients on DAPT should be lower in East Asian patients than in other ethnic groups. Even in patients at low risk for GI bleeding, an antiulcer drug may be considered during antiplatelet therapy for East Asian patients.

Recommendations:

- When receiving DAPT in East Asian patients, PPIs should be used in patients with a history of GI bleeding or in those with increased risk of GI bleeding (shock state or heart failure, the acute phase following ACS, Helicobacter pylori infection, the current smoker, aspirin >100 mg daily, and the concomitant use of anticoagulant, steroid and nonsteroidal anti-inflammatory drug).
- Even in patients at low risk for GI bleeding, an antiulcer drug (PPIs or H_2 receptor antagonists) may be considered during antiplatelet therapy for East Asian patients.

7. Duration of DAPT in East Asians

Duration of DAPT must be determined depending on the benefit/risk ratio between ischemic and bleeding events [104,105]. If the cohorts have a higher risk of atherothrombotic event following PCI (e.g., ACS), prolonged DAPT use would decrease the recurrence of CV events without the significant increase of bleeding events. With the usage of "newer generation" DES (e.g., everolimus- or zotarolimus-eluting, polymer-free stent) having a lower risk of stent thrombosis than that of "first-generation" DES (e.g., sirolimus- and paclitaxel-eluting), shorter-duration of DAPT may be more favorable following PCI. Therefore, duration of DAPT may be influenced by the disease activity, stent type and lesion/PCI complexity.

The "DAPT score", derived from the DAPT trial, suggested a useful method for how to determine DAPT duration after 1-year DAPT without significant bleeding or ischemic events in stented patients [106]. In cases of a high DAPT score (≥ 2), the benefit/risk ratio with prolonged DAPT may be favorable since prolonged DAPT reduces net (ischemic + bleeding) events compared with non-prolonged DAPT. Conversely, in those with a low DAPT score (<2), the benefit/risk ratio with prolonged DAPT is not favorable (increased bleeding without a reduction in ischemic events). Factors that contribute to a high DAPT score were diabetes mellitus, current cigarette use, MI at presentation, prior PCI or prior MI, congestive heart failure or left ventricular ejection fraction <30%, vein graft PCI, paclitaxel-eluting stent, and stent diameter <3 mm; older age contributes to a low (less favorable) DAPT score.

Because the benefit/risk ratio with prolonged DAPT can be different between East Asian and Caucasian populations following PCI, the optimal duration of DAPT might be reconsidered based on the data of East Asian patients. Currently, six large-scale randomized clinical trials are available from East Asian patients treated with DES (Table 3). Overall, prolonged DAPT use (12–24 months) decreased numerically the prevalence of ischemic events with a numerical increase of serious bleeding episodes than short-term DAPT use (3–12 months) [107–112]. However, net (ischemic + bleeding) events appeared neutral across the treatments. Four clinical trials evaluated the clinical efficacy and safety of 3–6 month DAPT compared with 12-month DAPT after newer-generation DES implantation [109–112]. These trials did not show any significant differences of major ischemic and bleeding events between 12-month vs. short-term DAPT strategy. Even in ACS patients, the benefit of 12-month DAPT as compared with 3–6 month DAPT was not definite. Another a real-world study showed that PCI-treated patients insisted on 6–12 month DAPT treatment had a lower adverse cardiac event rate (cardiovascular death, MI and revascularization) than those with a short-term DAPT treatment (HR, 0.172; 95% CI, 0.039 to 0.763; $P = 0.021$) [113].

From these East Asian trials, the risk of atherothrombotic events following DES implantation appeared low compared with the Western clinical trials. The clinical outcomes from the DES-LATE [107] ($n = 5,045$: 100% from Korea) and DAPT [114] ($n = 9,961$: about 90% from North America) trials gave important insight regarding the benefit of prolonged DAPT (>30 vs. ~12 months) between the races. The cohorts in DES-LATE had more complex lesion and PCI procedure than those in DAPT. In the DES-LATE trial, the composite of 18-month CV death, MI, or stroke after randomization occurred in about 2.0% and 2.0% for the dual-therapy and aspirin-only group, respectively (HR, 1.00). In the DAPT trial, the composite of death, MI or stroke during the same period was observed in 4.3% for the

Table 3
Randomized clinical trials evaluating optimal DAPT duration for East Asian patients with coronary artery disease.[a]

Study/country	No. of patients	Clinical features of patients	Type of Stent	DAPT duration (month)	Ischemic events			Bleeding events		
					Definition	Events	HR (95% CI) *P* value	Criteria	Events	HR (95% CI) *P* value
DES-LATE/ Korea [107]	5,045	DES-treated patients free of clinical events at least 12 months	SES, PES, ZES, EES and other DESs	12 vs. 36	Cardiac death, MI, or stroke	2.4% vs. 2.6%	0.94 (0.66–1.35) *P* = 0.75	TIMI major bleeding	1.1% vs. 1.4%	0.71 (0.42–1.20) *P* = 0.20
NIPPON/Japan [108]	3,773	All comers treated with DES	BES	6 vs. 18	Death, MI, or stroke	1.6% vs. 0.8%	NA	REPLACE-2 major bleeding	0.7% vs. 0.7%	*P* = 0.84
EXCELLENT/ Korea [109]	1,443	All comers treated with DES	SES and EES	6 vs. 12	Cardiac death, MI or TVR	4.8% vs. 4.3%	1.14 (0.70–1.86) *P* = 0.60	TIMI major bleeding	0.3% vs. 0.6%	0.50 (0.09–2.73) *P* = 0.42
IVUS-XPL/ Korea [110]	1,400	All comers treated with DES	EES	6 vs. 12	Cardiac death, MI, or TLR	5.2% vs. 3.8%	1.40 (0.84–2.35) *P* = 0.193	TIMI major bleeding	0.7% vs. 1.0%	0.71 (0.23–2.2) *P* = 0.563
I-LOVE-IT 2/ China [111]	1,829	All comers treated with DES	Biodegradable polymer SES	6 vs. 12	Cardiac death, target vessel MI, or TLR	6.8% vs. 5.9%	Difference: −0.87% (-3.11%-1.37%) *P* = 0.0065 for non-inferiority	BARC type ≥ 3	1.2% vs. 0.7%	*P* = 0.21
RESET/Korea [112]	2,117	All comers treated with DES	3-Mo. group: Endeavor ZES 12-Mo. group: SES, EES, and Resolute ZES	3 vs. 12	Death, MI, or stent thrombosis	0.8% vs. 1.3%	Difference: −0.5% (-1.5%-0.5%) *P* = 0.48	TIMI major or minor bleeding	0.5% vs. 1.0%	Difference: −0.5% (-1.2%-0.2%) *P* = 0.20

[a] BARC, bleeding academic research consortium; BES, biolimus-eluting stent; CI, confidence interval; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; DES-LATE, Optimal Duration of Clopidogrel Therapy With DES to Reduce Late Coronary Arterial Thrombotic Event; EES, everolimus-eluting stent; EXCELLENT, Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting; HR, hazard ratio; I-LOVE-IT 2, Evaluate Safety and Effectiveness of the Tivoli DES and the Firebird DES for Treatment of Coronary Revascularization; IVUS-XPL, Impact of Intravascular Ultrasound Guidance on Outcomes of XIENCE PRIME Stents in Long Lesions; MI, myocardial infarction; NA, not applicable; NIPPON, Nobori Dual Antiplatelet Therapy as Appropriate Duration; PES, paclitaxel-eluting stent; REPLACE-2, Randomized Evaluation in PCILinking Angiomax to Reduced Clinical Events 2; RESET, REal Safety and Efficacy of 3-month dual antiplatelet Therapy following Endeavor zotarolimus-eluting stent implantation; SES, sirolimus-eluting stent; TIMI: Thrombolysis in Myocardial Infarction; TLR, target lesion revascularization; TVR, target vesselrevascularization; ZES, zotarolimus-eluting stent.

dual-therapy group and 5.9% for the aspirin-only group, respectively (HR, 0.71). These findings support that the benefit/risk ratio of prolonged DAPT duration may be related to the cohort's risk of atherothrombotic events post-PCI. In a recent meta-analysis including 7 RCTs (8,605 East Asians, 7,913 non-East Asians) [115], a composite of ischemic events occurred more frequently in non-East Asians (0.8% vs. 1.8%, $P < 0.001$), while major bleeding events occurred more frequently in East Asians (0.6% vs. 0.3%, $P = 0.001$). In Cox proportional hazards model, prolonged DAPT significantly increased the risk of major bleeding in East Asians (HR, 2.843; 95% CI, 1.474 to 5.152; $P = 0.002$), but not in non-East Asians (HR, 1.375; 95% CI, 0.523-3.616; $P = 0.523$). East Asians had a higher median probability risk ratio of bleeding to ischemia (0.66 vs. 0.15), and the proportion of patients with higher probability of bleeding than ischemia was significantly higher in East Asians (32.3% vs. 0.4%, $P < 0.001$).

Because East Asian patients have the different profile of ischemic and bleeding events compared with Caucasian population, the benefit/risk ratio related with DAPT duration can be different between the populations. The benefit of prolonged DAPT might be relatively lower in East Asian subjects compared with Caucasian subjects. Large-scale clinical study would be required to determine the optimal duration of DAPT in East Asian population. Because the DAPT and PRECISE-DAPT scores originated from the Caucasian patients does not work in East Asian patients, there are unmet needs to develop the East Asian scoring system for balancing their unique risk/benefit ratio.

Recommendations:

- After DES implantation, 6-month DAPT is recommended in East Asian patients with stable CAD.
- After coronary stenting in ACS patients, 12-month DAPT is reasonable for East Asian population. In high-risk patients (e.g., prior MI, diabetes mellitus, chronic kidney disease, multi-vessel disease, complex intervention or BVS implantation), prolonged use of DAPT over 12 months can be useful to prevent recurrent ischemic events.
- Shortened duration of DAPT can be considered for patients with high bleeding risk or intolerant to long-term DAPT treatment.

8. Ongoing clinical trials and concept in East Asians

During antiplatelet therapy, "one-size-fits-all-races" may not be the optimal treatment strategy. The development of the smart treatment strategies to maximize net clinical benefit that depend on the disease state appears critical for the vulnerable East Asian population. In ACS patients, the benefit of potent $P2Y_{12}$ inhibitor vs. clopidogrel in reducing ischemic risk was more remarkable during the early phase, but the risk of bleeding become more prominent during the chronic phase.

Multiple clinical trials from East Asian countries are ongoing to evaluate the efficacy and safety of "de-escalation antiplatelet strategy". These dedicated large-scale clinical trials and comparative analysis can give important insight into the optimal antiplatelet strategy for East Asian population. First, reduced-dose strategy of potent $P2Y_{12}$ receptor inhibitor could be considered after the acute phase in ACS patients [46]. The HOST-REDUCE POLYTECH trial is currently exploring the optimal maintenance dose of prasugrel beyond 1 month after PCI for ACS in East Asian population (n = 2,348) [116]. After PCI-treated ACS patients take the standard-dose of prasugrel (10 mg daily) for 1 month, patients will be randomized 1:1 to either the conventional dose of prasugrel (10 mg daily) or the reduced-dose of prasugrel (5 mg daily). The primary endpoint is a composite of all-cause mortality, MI, stent thrombosis, repeat revascularization, stroke, or bleeding (BARC type $\geq$2) at 12 months after index PCI. Second, a switching strategy from potent $P2Y_{12}$ receptor inhibitor to clopidogrel could be another approach during the stabilized phase in ACS patients [57]. The TALOS-AMI trial is comparing clinical efficacy and safety of clopidogrel vs. ticagrelor in Korean patients with stabilized MI (n = 3,288) (https://clinicaltrials.gov/ct2/show/NCT02018055?term=TALOS-AMI&rank=1). Finally, another de-escalation strategy would include discontinuation of aspirin after the acute phase in ACS patients [117]. In the GLOBAL LEADERS trial (n = 15,968) [117], 3.81% in the experimental group (75–100 mg aspirin daily plus 90 mg ticagrelor twice daily for 1 month, followed by 23 months of ticagrelor monotherapy) had died or had Q-wave MI at 2 years, compared with 4.37% in the standard group (HR, 0.87; 95% CI, 0.75 to 1.01; P = 0.073). The TWILIGHT (mostly Caucasians) and TICO (Koreans) trials are evaluating the clinical outcomes of DAPT with aspirin plus ticagrelor vs. ticagrelor monotherapy from 3 months after PCI in ACS patients (https://clinicaltrials.gov/ct2/show/NCT02270242?term=TWILIGHT&rank=2; https://clinicaltrials.gov/ct2/show/NCT02494895?term=TICO&rank=2).

Another strategy of low-intensity novel oral anticoagulants (NOAC) can be applied for patients with stable atherosclerotic vascular disease. In the COMPASS trial [118], low-dose rivaroxaban (vascular dose, 2.5 mg twice daily) plus aspirin could reduce the composite of CV death, MI or stroke compared with aspirin alone (100 mg once daily) (4.1% vs. 5.4%; HR, 0.76; 95% CI, 0.66 to 0.86; P < 0.001), but major bleeding events occurred in more patients in the former vs. latter group (3.1% vs. 1.9%; HR, 1.70; 95% CI, 1.40 to 2.05; P < 0.001). However, there was no significant difference in intracranial or fatal bleeding between these two groups. Based on this trial, FDA has recently updated the labeling that rivaroxaban is indicated to reduce the risk of major cardiovascular events in patients with chronic CAD or peripheral artery disease. About 10% of the cohort in COMPASS were from Asian ethnicity (of whom approximately 80% were East Asians) [119]; a regimen of 2.5 mg of rivaroxaban twice daily increased major bleeding by 1.18% in whites and 2.13% in Asians, with the similar benefit of reducing ischemic events. Like $P2Y_{12}$ inhibitor, optimal dose of NOAC in East Asians still remains controversial [57]. More clinical evidences from East Asians would be required to establish the consensus.

9. Conclusions

The East Asian population may present a different profile (higher bleeding potential and lower ischemic event risk) compared with Caucasian population. Emerging evidences from East Asian patients have suggested that potent $P2Y_{12}$ receptor inhibitors exhibit greater antiplatelet effect and consequently higher bleeding risk in this population compared with Caucasian patients. Reduced dose of ticagrelor and prasugrel may provide more acceptable clinical efficacy and safety comparing with standard-dose treatment, but there are no reliable large-scale prospective studies to confirm the clinical benefit of this antiplatelet strategy in East Asian population with ACS. Switch of antiplatelet drugs from potent $P2Y_{12}$ receptor inhibitors to clopidogrel is common in real world practice because of their higher bleeding risk and combined adverse effects, but the methodology of switching such as genotype- or phenotype-guided approach is not well established. Because of a high risk of GI bleeding during DAPT in East Asian population, the adjunctive use of PPI (avoid omeprazole and esomeprazole when combined use with clopidogrel) in addition to antiplatelet agents is recommended in high-risk patients for GI bleeding. Management of DAPT or single antiplatelet therapy for patients with indication for oral anticoagulant can be another important issue for East Asian patients.

Moreover, there are very limited comparative data assessing the pharmacokinetic and pharmacodynamic profiles of antithrombotic therapies between in East Asian vs. Caucasian subjects. Dedicated investigations and development of regional consensus/guideline (s) for East Asian patients are needed instead of blind application of Western recommendations for antithrombotic therapy in the East Asian population. Therefore, the concept of "ethnic-tailored antithrombotic strategy" should be strongly considered to maximize net clinical benefit across the races in the era of precision medicine.

Conflict of interest

Young-Hoon Jeong received honoraria for lectures from AstraZeneca, Sanofi-Aventis, Daiichi Sankyo/Lilly, Haemonetics, Otsuka, Han-mi Pharmaceuticals and Yuhan Pharmaceuticals; and financial support from AstraZeneca, Korean Society of Interventional Cardiology, Han-mi Pharmaceuticals, Yuhan Pharmaceuticals, Otsuka and Haemonetics. Shinya Goto Received research grant from Ono, Bristol Myersquibb and Pfeizer. He also received honoralia from Bayer and AstraZenneca. Paul A. Gurbel received consultant fees/receiving honoraria from Daiichi Sankyo, Bayer, AstraZeneca, Merck, Boehringer, New Haven Pharmaceuticals, Janssen, and CSL and receiving financial support from the National Institutes of Health, Daiichi Sankyo, CSL, AstraZeneca, Harvard Clinical Research Institute, Haemonetics, New Haven Pharmaceuticals, Duke Clinical Research Institute, Sinnowa, and Coramed. DrGurbel has patents in the field of platelet function testing.

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