

World Heart Federation Expert Consensus Statement on Antiplatelet Therapy in East Asian Patients with ACS or Undergoing PCI

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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 P2Y₁₂ 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.

INTRODUCTION

At the 65th World Health Assembly in May 2012, all 194 WHO member states endorsed a target to reduce premature deaths caused by noncommunicable diseases by 25% by 2025 [1]. Cardiovascular diseases are the leading cause of death and disability among the noncommunicable diseases [2]. Therefore, effective treatment of patients with atherosclerotic coronary artery disease—both those with acute coronary syndrome (ACS) and those undergoing percutaneous coronary intervention (PCI)—is an important strategy to reduce the rate of premature death from cardiovascular disease as well as global mortality associated with noncommunicable diseases.

Compelling evidence supports the use of dual antiplatelet therapy (DAPT) in patients with ACS and also those with stable ischaemic heart disease undergoing PCI. In these clinical settings, the use of a P2Y₁₂ inhibitor combined with aspirin is recommended in the ACC/AHA and ESC guidelines [3–7]. These recommendations are based primarily on large, phase III, randomized, controlled trials of these agents. In addition, patients who are poor responders or who have a high on-treatment platelet reactivity to ADP during DAPT are at increased risk of ischaemic events after PCI [8]. Multiple lines of evidence have suggested that low on-treatment platelet reactivity to ADP is associated with an increased risk of bleeding [8].

Therefore, a ‘therapeutic window’ concept of platelet reactivity has been proposed for P2Y₁₂-inhibitor therapy. However, the relationship between platelet reactivity and ischaemic or bleeding events might differ according to intrinsic thrombogenicity or disease activity [9].

As with most cardiovascular drugs, P2Y₁₂ inhibitors have shown marked interethnic differences in pharmacokinetic and pharmacodynamic profiles [9]. Although East Asian ethnic groups are among the most populous (more than 1.5 billion people), very few East Asian patients have been included in the trials to assess the use of P2Y₁₂ inhibitors, particularly the newer agents prasugrel and ticagrelor. Recognizing concerns about an increased incidence of haemorrhagic stroke and potential bleeding that might occur among East Asian patients receiving antithrombotic therapy [10,11], even in the absence of hypertension [12], the World Heart Federation has undertaken an evidence-based review and produced this expert consensus statement to determine the antiplatelet treatment strategies that are most appropriate for East Asian patients. This consensus statement (members of the expert panel are listed in Box 1) provides observations and recommendations addressing the regional clinical practice trends in East Asia and highlights the need for future research. The concepts discussed should contribute to the global strategy to reduce

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Competing interests of expert panel members who were not part of the executive writing group: Y.C. has served on an advisory board or speakers' bureau for Sanofi. P.S. has received honoraria from AstraZeneca, Daiichi Sankyo, and Sanofi. He served on an advisory board or speakers' bureau for AstraZeneca, Daiichi Sankyo, and Sanofi. He served as an investigator on a study or trial sponsored by AstraZeneca, Daiichi Sankyo, and Sanofi. J.C., J.G., Y.Han, B.H., and S.Z. declare no competing interests.

the rate of premature death from noncommunicable diseases by 25% by 2025 [1].

CURRENT P2Y₁₂ INHIBITORS

Clopidogrel replaced ticlopidine 2 decades ago as a part of DAPT for the prevention of stent thrombosis, and has subsequently been used in the majority of patients undergoing coronary stent implantation. Clopidogrel is established as a beneficial therapy in patients with ACS [13], and is recommended as part of the treatment of these patients [7]. Clopidogrel is a thienopyridine prodrug, and its conversion to its active metabolite R-130964 requires a two-step process in the liver (Figure 1) [8]. Through biotransformation, R-130964 irreversibly inhibits platelet aggregation. Although numerous epigenetic factors influence generation of the active metabolite and platelet-reactivity phenotype [14–16], variation in the cytochrome P450 (CYP) allele, especially CYP2C19, has been shown to have the greatest influence [8]. The clinical importance of these factors has been the subject of much research and debate.

Prasugrel, is another thienopyridine that irreversibly inhibits platelet aggregation. Prasugrel requires a single, CYP-dependent oxidation step to its active metabolite (Figure 1). Compared with clopidogrel, administration of prasugrel results in faster and greater platelet inhibition, owing to rapid and efficient generation of the active metabolite, with less patient-to-patient variation [8,17,18].

Ticagrelor is a nonthienopyridine, direct-acting, oral antagonist that binds reversibly to the P2Y₁₂ receptor (Figure 1). The major metabolite of ticagrelor (AR-C124910XX), formed by metabolism via CYP3A4, is as potent as the parent compound ticagrelor. Compared with

clopidogrel, ticagrelor results in faster and greater platelet inhibition, with less patient-to-patient variation (similar to prasugrel) [8,19].

CLINICAL EVIDENCE FOR DAPT

Clopidogrel

Several major studies of platelet P2Y₁₂-receptor inhibitors involving patients with ACS and those undergoing PCI form the evidence base for the US and European guideline recommendations [3–7]. In the CURE trial [20], 12,562 patients with non-ST-segment elevation ACS were treated with clopidogrel (300 mg loading dose, 75 mg daily maintenance dose) plus aspirin (81–325 mg daily) or aspirin alone. At 12 months, clopidogrel plus aspirin was associated with a 20% relative reduction compared with aspirin alone (9.3% vs 11.4%; $P = 0.00009$) in the primary composite end point of cardiovascular death, nonfatal myocardial infarction (MI), and nonfatal stroke [20]. In PCI-CURE [21], a prospective subgroup analysis of 2,658 patients from the CURE study who underwent PCI with a bare-metal stent, a 31% relative reduction in the composite end point was reported with clopidogrel plus aspirin compared with aspirin alone (8.8% vs 12.6%; $P = 0.002$). In the CREDO trial [22], which involved 2,116 patients undergoing elective PCI, the benefits of a preprocedural loading dose of clopidogrel, and of continuing clopidogrel for 12 months after PCI with a bare-metal stent, both in addition to aspirin therapy, were investigated. Treatment with clopidogrel in addition to aspirin for 12 months after PCI was associated with a 26.9% relative reduction in the composite end point of death, MI, and stroke compared with aspirin alone (8.5% vs 11.5%; $P = 0.02$) [22]. A subgroup analysis of the

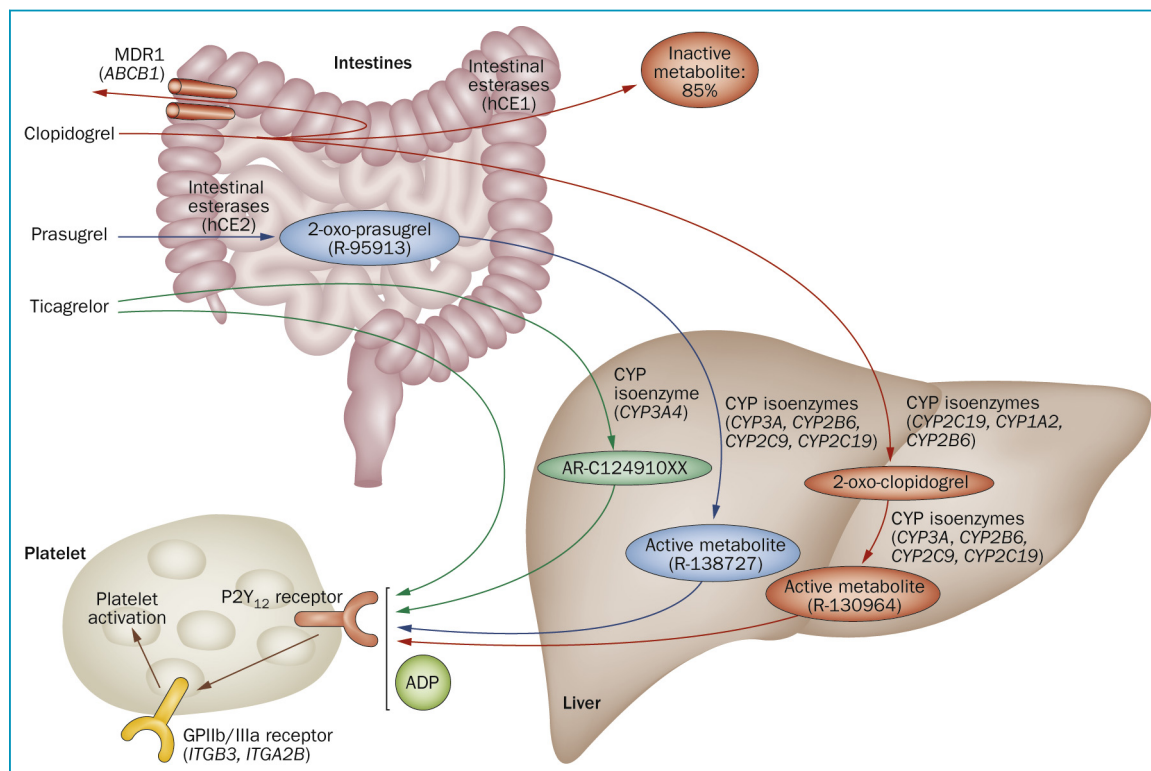


FIGURE 1. Metabolic pathway of P2Y₁₂-receptor inhibitors. The antiplatelet effect of P2Y₁₂-receptor inhibitors might be modified by genetic variation in proteins involved in the absorption, metabolism, and target receptor. Bioavailability of the prodrug clopidogrel is determined by intestinal absorption, which might be limited by the efflux pump MDR1 (encoded by *ABCB1*). Subsequently, the majority of the prodrug is inactivated by ubiquitous esterases, but the remainder is activated in a two-step process by CYP isoenzymes in the liver. Genetic variation in the activity of CYP2C19 is particularly important in determining clopidogrel response. The bioactive metabolite irreversibly binds to P2Y₁₂ receptors on platelets, and subsequently prevents ADP-induced stimulation of GPIIb/IIIa (encoded by *ITGB3* and *ITGA2B*) and platelet activation. The prodrug prasugrel is hydrolysed to a thiolactone derivative in the intestine and is then oxidized to its active metabolite by CYP isoenzymes in the liver, but seems to be little affected by genetic variation in these enzymes. Ticagrelor is a direct-acting, reversible, P2Y₁₂-receptor inhibitor, and seems to be little affected by genetic variation in the CYP isoenzymes. CYP, cytochrome P450; GP, glycoprotein; hCE, human carboxylesterase; MDR1, multidrug resistance protein 1. Permission obtained from NPG © Ahmad, T. *et al. Nat. Rev. Cardiol.* 8, 560–571 (2011).

timing of the preprocedural loading dose suggested that clopidogrel 300 mg should be given ≥ 6 h, and ideally ≥ 15 h, before PCI [23]. In the COMMIT trial [24] of Chinese patients with suspected acute MI, short-term (in-hospital for up to 4 weeks) treatment with clopidogrel resulted in a 9% reduction in the composite ischaemic end point ($P = 0.002$), and a 7% reduction in all-cause mortality ($P = 0.03$). The results of these studies provided the basis for establishing the evidence-based guidelines for the early use of a P2Y₁₂-receptor antagonist in patients with ACS or those undergoing PCI with a bare-metal stent.

Prasugrel

Subsequent to these early studies with clopidogrel, two newer P2Y₁₂-receptor inhibitors have been studied in large

trials to compare their efficacy with that of clopidogrel. In TRITON-TIMI 38 [25], prasugrel was compared with clopidogrel in 13,608 patients with moderate-to-high-risk ACS who were referred for PCI. Prasugrel was associated with a 19% relative reduction in the primary combined end point of cardiovascular death, nonfatal MI, and nonfatal stroke compared with clopidogrel (9.9% vs 12.1%; $P < 0.001$) [25]. The benefits were largely associated with a reduction in nonfatal MI, with no significant difference in cardiovascular death or nonfatal stroke. The rate of stent thrombosis was significantly reduced with prasugrel compared with clopidogrel (1.1% vs 2.4%; $P < 0.001$) [25]. However, prasugrel was associated with a significant increase in the rate of TIMI (Thrombolysis In Myocardial Infarction) major haemorrhage and fatal bleeding [25]. A *post-hoc* analysis suggested that patients with a history of stroke or transient ischaemic attack (TIA), those aged ≥ 75 years, or with a body mass < 60

kg had an increased rate of bleeding. Patients with a history of stroke or TIA experienced net harm, whereas those aged ≥ 75 years or with a mass < 60 kg derived no net benefit [25]. Importantly, an unacceptable 2.5% rate of intracranial haemorrhage occurred in those with a history of stroke or TIA treated with prasugrel and, for this reason, prasugrel is contraindicated in these patients. By contrast, a subsequent subgroup analysis suggested that patients with a history of ST-segment elevation MI or diabetes mellitus derived greater relative benefit from prasugrel than clopidogrel therapy [26].

The second major phase III study in which prasugrel was compared with clopidogrel was the TRILOGY ACS trial [27]. This trial included a population of 9,326 patients with ACS who were being medically managed. The daily dose of prasugrel was reduced to 5 mg (instead of 10 mg) for patients aged ≥ 75 years and those with a body mass < 60 kg. No significant difference in the primary combined end point of cardiovascular death, MI, and stroke was reported between treatment with prasugrel or clopidogrel [27]. None of the safety end points was significantly different between the two study groups.

Ticagrelor

In the Platelet Inhibition and Patient Outcomes (PLATO) trial [28], 18,624 patients hospitalized with ACS were randomly allocated to treatment with ticagrelor or clopidogrel, with all patients also receiving aspirin. Overall, 60.6% of patients underwent stent implantation. At 12 months, ticagrelor was associated with a 16% relative reduction (9.8% vs 11.7%; $P = 0.0003$) in the combined primary efficacy end point of cardiovascular death, MI, and stroke [28]. Importantly, reductions in all-cause mortality (4.5% vs 5.9%; $P < 0.001$) and definite stent thrombosis (1.3% vs 1.9%; $P = 0.009$) were observed with ticagrelor therapy [28]. In the PLATO substudy [29] of 5,216 patients with ACS who were prespecified by the enrolling physician before randomization to be noninvasively managed, the primary end point of cardiovascular death, MI, and stroke was lower among those treated with ticagrelor than among those treated with clopidogrel (12.0% vs 14.3%; $P = 0.04$). In the overall study population, no significant difference existed between ticagrelor and clopidogrel in the overall rate of PLATO major bleeding in patients undergoing CABG surgery, although ticagrelor was associated with a modestly increased rate of PLATO major bleeding not associated with coronary artery bypass graft (CABG) surgery (4.5% vs 3.8%; $P = 0.03$) [28]. No increased risk of overall or intracranial bleeding existed with ticagrelor therapy in those with a history of stroke or TIA [30]. Subsequent analysis of the trial, spurred by the finding of no benefit in the North American cohort of patients, revealed that the benefits of ticagrelor over clopidogrel for reduction in ischaemic events are observed only when the daily aspirin dose is ≤ 100 mg [31], which is now reflected in a recommendation on package labelling [32].

US AND EUROPEAN GUIDELINES

ACC/AHA and ESC recommendations regarding DAPT and P2Y₁₂ inhibitors for patients with ACS [3,5,33] and those undergoing PCI [4,34] are generally similar. Importantly, as discussed above, these guideline recommendations are based to a large extent on phase III randomized trials in which few, if any, East Asian patients (or those of East Asian descent) were enrolled. Neither ACC/AHA nor ESC guidelines make any specific recommendations according to ethnicity.

P2Y₁₂ INHIBITORS IN EAST ASIAN PATIENTS

Pharmacokinetics and pharmacodynamics

Although the degree of antiplatelet effect with clopidogrel treatment is dependent on multiple clinical and pharmacogenetic variables, the *CYP2C19* loss-of-function alleles (*2–*8) are a main determinant of degree of platelet inhibition (Figure 1) [35]. Compared with white individuals, East Asian individuals have a higher prevalence of a *CYP2C19* loss-of-function allele [35]. Approximately 30% of white individuals are carriers of a *CYP2C19* loss-of-function allele (mostly the *2 allele), whereas about 65% of East Asian individuals carry a *CYP2C19* loss-of-function allele (mostly the *2 or *3 alleles) [9,35]. This finding has been correlated with a higher level of platelet reactivity during clopidogrel treatment in East Asian patients than in white patients [9].

By contrast, the degree of platelet inhibition with prasugrel and ticagrelor is higher in East Asian patients than in white patients, but the underlying mechanisms for this finding remain unknown. In individual studies, the level of the prasugrel active metabolite was 30–47% higher in East Asian patients than in white patients after loading and maintenance doses [36–40]. After adjusting for body mass, active metabolite exposure was still 19% higher in East Asian patients than in white patients [40], and this finding was more prominent (45–56% higher) in patients with a low body mass (< 60 kg) [38]. The higher exposure of the prasugrel active metabolite in East Asian individuals than in white patients translates into the pharmacodynamic profile [36–42]. In a single-centre study of healthy volunteers, the level of inhibition of platelet aggregation induced by 20 $\mu\text{mol/l}$ ADP in East Asian individuals taking 5 mg of prasugrel daily did not differ from that in white individuals taking 10 mg of prasugrel daily (mean value at 4 h last-dose: 68.9% vs 70.1%) [40]. In Japanese patients undergoing PCI, 15 mg loading and 3.75 mg maintenance doses of prasugrel achieved a faster, higher, and more-consistent antiplatelet effect than 300 mg loading and 75 mg maintenance doses of clopidogrel [41]. Likewise, the exposure of ticagrelor and its major active metabolite (AR-C124910XX) was higher in East Asian individuals than in white individuals after loading and maintenance doses [43–45]. After a 200 mg loading dose of ticagrelor, Japanese volunteers had a higher exposure of ticagrelor and AR-C124910XX compared with white individuals (ratio of

TABLE 1. Major studies of P2Y₁₂ inhibitors in patients with ACS or undergoing PCI

Study	Study design	Number (%) of East Asian patients	Findings in East Asian subgroup
Clopidogrel vs placebo in ACS or PCI			
CURE [20]	Clopidogrel vs placebo in patients with NSTEMI-ACS	0	NA
CURE-PCI [21]	Clopidogrel vs placebo in patients with NSTEMI-ACS undergoing PCI	0	NA
CREDO [22]	Clopidogrel vs placebo in patients undergoing bare-metal stenting	0	NA
COMMIT/CCS-2 [24]	Clopidogrel vs placebo in patients with suspected MI (primarily STEMI)	45,852 Chinese patients (100%)	HR 0.91, 95% CI 0.86–0.97, <i>P</i> = 0.002 for clopidogrel
CLARITY [75]	Clopidogrel vs placebo in patients with STEMI undergoing lytic therapy	0	NA
PCI-CLARITY [76]	Clopidogrel vs placebo in patients with STEMI undergoing lytic therapy treated with PCI	0	NA
Dual antiplatelet therapy in coronary stenting			
ISAR [77]	Aspirin plus ticlopidine vs anticoagulant therapy	0	NA
STARS [78]	Aspirin alone vs aspirin plus ticlopidine vs aspirin plus warfarin	0	NA
Standard-dose vs double-dose clopidogrel in PCI for ACS			
CURRENT-OASIS 7 [79]	Double-dose (1 week) vs standard-dose clopidogrel in patients with ACS treated with PCI	2,363 East Asian patients (13.7%)	HR 0.81, 95% CI 0.54–1.21 for double-dose clopidogrel
Clopidogrel vs prasugrel or ticagrelor in ACS			
TRITON-TIMI 38 [25]	Prasugrel vs clopidogrel in patients with ACS undergoing PCI	<1%	NA
TRILOGY-ACS [27]	Prasugrel vs clopidogrel in medically-managed patients with NSTEMI-ACS	571 East Asian patients (8.1%)	HR 1.19, 95% CI 0.75–1.89 for prasugrel
PLATO [28,80]	Ticagrelor vs clopidogrel in patients with ACS	1,096 Asian patients (5.9%), of whom 644 were East Asian	HR 0.87, 95% CI 0.62–1.21 for ticagrelor, in all Asian patients
Therapy guided by platelet-function testing			
GRAVITAS [81]	Standard vs double-dose clopidogrel based on platelet-function testing after PCI	0	NA
ARCTIC [82]	Antiplatelet treatment adjusted on the basis of platelet-function testing in patients undergoing stenting	0	NA

ACS, acute coronary syndrome; MI, myocardial infarction; NA, not available; NSTEMI, non-ST-segment elevation; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

geometric means 1.18, 90% CI 0.76–1.84 for ticagrelor; and 1.28, 90% CI 1.01–1.62 for AR-C124910XX [44]. After multiple doses of ticagrelor (100 mg twice daily), the exposure of ticagrelor and AR-C124910XX was 40% (90% CI 1.11–1.78) and 48% (90% CI 1.27–1.71) higher in Japanese volunteers than in white volunteers, which remained 20% and 24% higher in these groups after adjusting for body mass [44]. During ticagrelor treatment

(90 mg twice daily) in patients with ACS, the systemic exposure in East Asian patients was approximately 40% higher than in white patients [45]. The higher exposure of ticagrelor and its major active metabolite in East Asian individuals compared with white individuals correlates with the level of platelet inhibition, especially during maintenance treatment [44]. After ticagrelor administration (100 mg twice daily for 9 days), the maximal level of

inhibition of platelet aggregation (final extent) in Japanese volunteers was significantly higher than that in white volunteers (99% vs 85%) [44].

Trial evidence for ACS or PCI

Other than from the COMMIT trial [24], into which investigators enrolled only Chinese patients, only minimal data are available from the major ACS and PCI studies on clopidogrel therapy (in addition to standard contemporaneous therapy) in East Asian patients (Table 1). Investigators in early trials, such as CURE [13], CREDO [46], and CLARITY-TIMI 28 [47], did not enrol participants in Asia. Most of the Asian patients included in CHARISMA [10] were from Hong Kong, Malaysia, Singapore, and Taiwan, but only a regional analysis was conducted.

Only limited data exist on the comparison between the newer P2Y₁₂ inhibitors (prasugrel and ticagrelor) and clopidogrel in East Asian patients with ACS or undergoing PCI (Table 1). Investigators in TRITON-TIMI 38 [25], in which prasugrel was compared with clopidogrel, enrolled <1% of patients from East Asia. In the PLATO trial [28], in which ticagrelor was compared with clopidogrel, only 644 patients were enrolled from East Asian countries (China, including Hong Kong; South Korea; and Taiwan; but not Japan), but a subgroup analysis of only these patients has not been reported. A comparison of outcomes in all Asian ($n = 1,106$) versus non-Asian ($n = 17,515$) patients has been reported in abstract form, and found no significant differences between the two groups in the primary composite outcome (cardiovascular death, MI, and stroke), major bleeding, or net clinical benefit [48].

The relative efficacy and safety of the newer P2Y₁₂ inhibitors compared with clopidogrel has been specifically examined in East Asian patients in only three modestly sized trials, one of which (the PRASFIT-ACS study [49]) has been published in a peer-reviewed journal. The results of two other trials cannot be considered to provide the same level of evidence.

In the phase III, double-blind, randomized PRASFIT-ACS trial [49], the clinical efficacy and safety of low-dose prasugrel (20 mg loading and 3.75 mg daily maintenance) was compared with clopidogrel (300 mg loading and 75 mg daily maintenance) in 1,363 Japanese patients with ACS who were undergoing PCI. The incidence of the primary composite end point (cardiovascular death, nonfatal MI, and ischaemic stroke) was numerically lower with prasugrel than with clopidogrel, but this difference was not significant (9.4% vs 11.8%; HR 0.77, 95% CI 0.56–1.07, $P = 0.12$) [49]. TIMI major bleeding not associated with CABG surgery occurred in 1.9% of patients receiving prasugrel and 2.2% of those receiving clopidogrel (HR 0.82, 95% CI 0.39–1.73, $P = 0.38$) [49]. The incidence of TIMI major, minor, or clinically relevant bleeding was 9.6% in both groups [49].

The results of PRASFIT-ELECTIVE study [50] were presented in 2013, but have not been peer-reviewed or published. In this phase III study involving 742 Japanese

patients with coronary artery disease (stable angina, previous MI, or silent myocardial ischaemia) and undergoing elective PCI, the incidence of the composite primary end point (cardiovascular death, nonfatal MI, and ischaemic stroke) was 4.1% with low-dose prasugrel and 6.7% with clopidogrel [50]. The incidence of TIMI major, minor, or clinically relevant bleeding was 5.4% in the prasugrel group and 6.2% in the clopidogrel group [50]. The incidence of TIMI major bleeding was 0% with prasugrel and 2.2% with clopidogrel [50].

In the PHILO trial [45], guideline-recommended ticagrelor therapy (180 mg loading and 90 mg twice daily maintenance doses) was compared with clopidogrel therapy (300 mg loading and 75 mg daily maintenance doses) in 801 East Asian (predominantly Japanese) patients with ACS who were scheduled to undergo PCI. The study results are currently available online, but have not been formally presented, peer-reviewed, or published. The incidence of the composite primary end point (cardiovascular death, MI, and stroke) was 10.2% per year with ticagrelor and 8.1% per year with clopidogrel (HR 1.47, 95% CI 0.88–2.44) [45]. The incidence of the primary safety end point (PLATO major bleeding) was 10.3% per year for ticagrelor and 6.8% per year for clopidogrel (HR 1.54, 95% CI 0.94–2.53) [45].

The 'East Asian paradox'

Important differences in thrombogenicity, platelet P2Y₁₂-receptor inhibition, and propensity for bleeding complications exist between white and East Asian patients. In the past decade, evidence from numerous clinical studies has demonstrated a strong association between high on-treatment platelet reactivity to ADP and ischaemic events after PCI, particularly stent thrombosis [8]. The prevalence of high on-treatment platelet reactivity (assessed using criteria derived from a Western population), is higher among East Asian than among white patients [9]. As discussed above, this observation might be primarily caused by a higher frequency of the *CYP2C19* loss-of-function alleles in East Asian than in white individuals (~65% vs ~30%) [35,51–53]. In addition, multiple clinical studies from South Korea have suggested that different cut-off points for high on-treatment platelet reactivity might be appropriate in East Asian patients compared with white patients [8,54–57]. On the basis of receiver-operating characteristic curve analysis, East Asian patients show a higher level of platelet reactivity than white patients (253–275 versus 208–240 P2Y₁₂ reaction units, measured using the VerifyNow® P2Y₁₂ assay [Accumetrics, USA]) [9,55–57].

Although East Asian patients have a higher prevalence of high on-treatment platelet reactivity during clopidogrel treatment than white patients [9,51], the incidence of adverse ischaemic outcomes or stent thrombosis after PCI is similar or lower than that in white patients [58–61]. Analysis of data from the US National Cardiovascular Data Registry showed that Asian patients undergoing coronary stent implantation had a lower adjusted risk for the

composite end point of death, MI, and repeat revascularization than white patients (HR 0.89, 95% CI 0.82–0.96, *P* value not given) [58]. In this analysis, the individual end point of death was slightly lower in Asian patients than in white patients, and the incidence of MI was similar in each group. The incidence of stent thrombosis reported in South Korean and Japanese registries (~0.2% per year) is lower than that in Western registries (~0.6% per year) after first-generation drug-eluting stent implantation [59–61]. This finding of a higher prevalence of high on-treatment platelet reactivity, but a thrombotic event rate after PCI that is similar or lower in East Asian patients than in white patients, has been called the ‘East Asian paradox’ [9].

Multiple factors are likely to be associated with the differences in thrombogenicity between East Asian and white individuals, and might explain the variation in propensity for thrombosis. Differences in genetic polymorphisms between ethnicities might partially account for the underlying mechanism [62]. For example, factor V Leiden (G1691A) and prothrombin (G20210A) gene mutations are more common in white than in Asian individuals [62]. Differences in levels of haemostatic factors (such as fibrinogen, d-dimer, and factor VIII) and plasma endothelial activation markers (such as von Willebrand factor, intercellular adhesion molecule 1, and E-selectin) might be additional factors contributing to the ethnic disparity. Investigators in MESA [63] evaluated these factors in individuals from the USA. African-American individuals generally had the highest thrombogenic and dysfunctional endothelial profile, followed by Hispanic and white individuals, and finally East Asian individuals [63]. In addition, multiple studies have suggested different levels of inflammatory markers between ethnicities [64]. East Asian individuals seem to have lower levels of inflammatory markers (such as C-reactive protein) than white individuals [64]. In a study in which thrombus formation and endogenous fibrinolytic capacity were measured using the Global Thrombosis Test (Thromboquest Ltd, UK), healthy Japanese individuals had a longer occlusion time than white British individuals (545 s vs 364 s; *P* < 0.0001), suggesting a lower level of thrombogenicity in East Asian versus white individuals [65].

Differences in the propensity for bleeding between East Asian and white populations have also been described [10–12]. In an analysis of individuals from the USA with atrial fibrillation, Asian patients were at greater risk of warfarin-associated intracranial haemorrhage than white individuals, despite similar international normalized ratios between the two groups [11]. In contrast to the risk of ischaemic events after PCI, the risk of serious bleeding in East Asian individuals seems to be greater than in white individuals. In a study of Japanese patients undergoing elective implantation of a drug-eluting stent and treated with aspirin plus a thienopyridine (200 mg daily of ticlopidine or 75 mg daily of clopidogrel), a notable 6.5% incidence of major bleeding was observed during the 16 months of DAPT [66]. Major bleeding occurred more

frequently in high-responders than in other groups (15.0% vs 4.2%; *P* = 0.02) [66]. The ACCEL-BLEED trial [67] was designed to examine the relationship between platelet reactivity and bleeding episodes in South Korean patients treated with PCI. This study showed that East Asian patients might be more likely to have mild bleeding than white patients at the same level of on-treatment platelet reactivity, further supporting the hypothesis that the relationship between platelet reactivity and bleeding episodes might vary with ethnicity.

Taken together, these data suggest that clinically important differences in thrombogenicity and propensity for bleeding complications might exist between white patients, on whom most study data and guidelines are based, and East Asian patients. The findings also suggest that the optimal ‘therapeutic window’ of platelet reactivity might differ between white and East Asian patients (Figure 2). Considering these apparent differences in thrombogenicity and response to P2Y₁₂-receptor inhibitors, extrapolation of major trials of DAPT, as well as guidelines based on these trials, might not be applicable to East Asian patients.

SELECTED NATIONAL GUIDELINE RECOMMENDATIONS

China

Between September 2004 and May 2006, <20% of patients with ACS in China were estimated to have received 12 months of DAPT [68]. In a large, multinational, Asian registry of patients with ACS, of whom most were Chinese, 51.4% of those with a final diagnosis of ACS were classified as having ST-segment elevation MI [69]. Chinese cardiologists largely follow the ACC/AHA guidelines when treating patients with ACS, and the Chinese recommendations

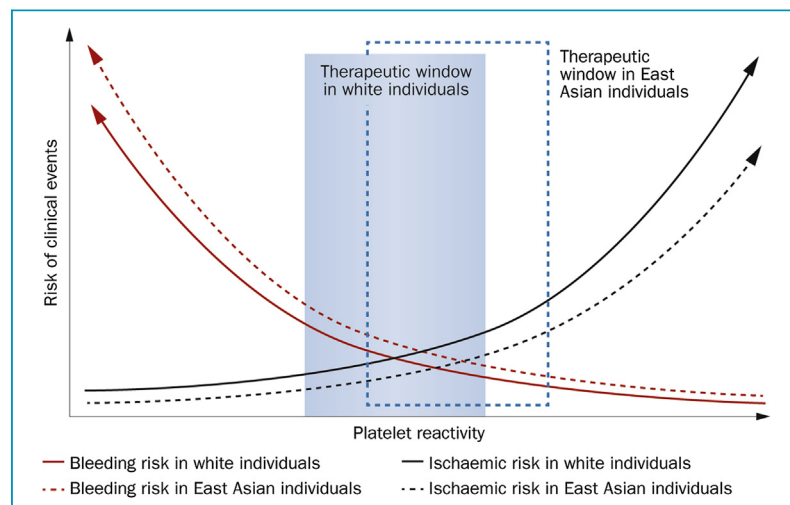


FIGURE 2. Postulated differences in the optimal ‘therapeutic window’ of platelet reactivity between white and East Asian populations. Permission obtained from NPG © Levine, G. N. *et al.* *Nat. Rev. Cardiol.* doi:10.1038/nrcardio.2014.104.

for antiplatelet therapy in patients with ACS [70,71] are generally similar to those of the ACC/AHA.

Japan

In contrast to Western countries, the incidence of ST-segment elevation MI in Japan is greater than that of non-ST-segment elevation MI [72]. Clopidogrel was approved in Japan in 2006, but only for stroke prevention. Before October 2007, clopidogrel was not used in Japanese patients with ACS. Instead, ticlopidine was widely used. However, on the basis of a study in Japanese patients with ACS in which clopidogrel was shown to have a better safety profile than ticlopidine [73], clopidogrel has subsequently been adopted for the treatment of these patients. Japanese doctors have reduced the dose of ticlopidine (100 mg twice daily instead of the usual 250 mg twice daily) to decrease bleeding complications, and this strategy has been extrapolated to clopidogrel therapy. Therefore, both 75 mg and 25 mg tablets of clopidogrel are available for Japanese patients. In Japanese patients treated with clopidogrel, the dose of clopidogrel is often reduced from 75 mg daily during the first 3 months of treatment, to 50 mg daily from 3 months to 1 year, most commonly in patients with stable coronary artery disease who have undergone PCI. After 1 year of treatment with clopidogrel, the dose is often further

reduced to 25 mg. As of February 2014, both 5.00 mg and 3.75 mg doses of prasugrel are approved for patients with either ACS or stable coronary artery disease who are undergoing PCI, on the basis of several phase III trials conducted in Japan [49,50]. Ticagrelor is not currently approved in Japan.

South Korea

The South Korean guidelines [74] for antiplatelet therapy in patients with ACS mostly parallel recommendations in the ACC/AHA and ESC guidelines on antiplatelet therapy. Interestingly, cilostazol is recommended as an adjunct to DAPT with aspirin and clopidogrel in selected patients, because many pharmacodynamic and clinical studies have demonstrated its clinical efficacy and safety in South Korean patients with ACS [74]. In South Korea, prasugrel and ticagrelor are now available and reimbursed for the treatment of patients with ACS. Although clopidogrel has been used as the first-line antiplatelet treatment, the use of prasugrel and ticagrelor is becoming increasingly common. However, many South Korean physicians have suggested that the recommended doses of prasugrel and ticagrelor might be too high for South Korean patients and have expressed concerns about an increased risk of bleeding. Furthermore, many physicians in South Korea have

Box 2 Summary of data on antiplatelet therapy in East Asian patients

Observations

- No significant differences exist in recommendations for aspirin use in East Asian patients with ACS or undergoing PCI from those in the current ACC/AHA and ESC guidelines [3–7]
- The current database of randomized clinical trials that support the use of P2Y₁₂-receptor inhibitors for patients with ACS or those undergoing PCI contains only a small number of East Asian patients, with the exception of the COMMIT [24], PRASFIT-ACS [49], PRASFIT-ELECTIVE [50], and PHILO [45] studies
- No definitive data are available to support the clinical superiority of the more potent P2Y₁₂-receptor inhibitors prasugrel and ticagrelor over clopidogrel as an adjunct to aspirin for DAPT in East Asian patients with ACS or those undergoing PCI
- In the COMMIT trial [24], the benefit of clopidogrel added to aspirin was demonstrated for DAPT in Chinese patients with acute myocardial infarction, predominantly STEMI, not undergoing PCI. The primary composite end point of death, reinfarction, and stroke was significantly reduced by the addition of clopidogrel to aspirin therapy, without a significant increase in bleeding
- The PRASFIT-ACS study [49] of Japanese patients with ACS undergoing PCI showed a trend in favour of prasugrel, but no significant difference between treatment with clopidogrel (300 mg loading and 75 mg daily maintenance doses) and low-dose prasugrel (20 mg loading and 3.75 mg daily maintenance doses) in the primary composite end point of cardiovascular death, nonfatal myocardial infarction, or ischaemic stroke, and no difference in bleeding
- The 'East Asian paradox' describes a phenomenon in which, despite a higher level of platelet reactivity during treatment with aspirin and clopidogrel, East Asian patients have a similar or even lower rate of ischaemic events after PCI compared with white patients
- Unlike in Western countries, the reported prevalence of STEMI in East Asian countries is higher than that of non-STEMI. This finding might have important implications for treatment strategies

Conclusions

- The use of clopidogrel and aspirin is a reasonable first choice of DAPT for East Asian patients with ACS or undergoing PCI
- Routine platelet-function testing is not recommended in the management of East Asian patients receiving DAPT
- A need exists to include East Asian patients in trials to assess the efficacy and safety of DAPT for ACS or PCI, and particularly the potential benefit of potent P2Y₁₂-receptor inhibitors, such as prasugrel and ticagrelor
- These observations and conclusions should be taken into consideration during the development of regional and national guidelines for East Asian patients with ACS or undergoing PCI

ACS, acute coronary syndrome; DAPT, dual antiplatelet therapy; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

adopted a selective and limited approach using genotyping and platelet-function testing.

CONCLUSIONS

A summary of observations and conclusions that can be made from the available study data is given in [Box 2](#). At present, few randomized data on the efficacy and safety of P2Y₁₂-receptor inhibitors for the treatment of East Asian patients with ACS or undergoing PCI, other than those from the COMMIT trial [24], have been published. No data specific to East Asian patients are available to demonstrate the superiority of prasugrel or ticagrelor over clopidogrel, which will be an important area for future research. The 'East Asian paradox' describes a phenomenon in which, despite a higher level of platelet reactivity during clopidogrel treatment, East Asian patients have a similar or lower rate of ischaemic events after PCI compared with white patients. These observations and conclusions should be taken into consideration during the development of regional and national guidelines for East Asian patients with ACS or undergoing PCI.

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