The East Asian Paradox: An Updated Position Statement on the Challenges to the Current Antithrombotic Strategy in Patients with Cardiovascular Disease

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Abstract

East Asian patients have reduced anti-ischemic benefits and increased bleeding risk during antithrombotic therapies compared with Caucasian patients. As potent $P2Y_{12}$ receptor inhibitors (e.g., ticagrelor and prasugrel) and direct oral anticoagulants are commonly used in current daily practice, the unique risk–benefit trade-off in East Asians has been a topic of emerging interest. In this article, we propose updated evidence and future directions of antithrombotic treatment in East Asian patients.

Keywords

- race
- antiplatelet therapy
- direct oral anticoagulants
- ischemic risk
- bleeding risk

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Introduction

In excess of 1.5 billion people, East Asians are among the most populous ethnic groups. An increasing body of evidence demonstrates that East Asian population has a lower risk of atherothrombotic event and a higher tendency of serious bleeding during antithrombotic treatment compared with Caucasians (►**Fig. 1**).[1–4] Clinical experiences and the unique risk–benefit trade-off of East Asian population have urged clinicians to prescribe different antithrombotic regimens and reduced doses of antithrombotic agents in patients with cardiovascular disease (CVD).

In 2012, Jeong et al proposed a comprehensive concept to explain this phenomenon in East Asian patients with coronary artery disease (CAD)—"*East Asian Paradox*".[5] East Asians show attenuated response to clopidogrel compared with Caucasians, which is in part explained by the different frequencies of the cytochrome P450 *2C19* (*CYP2C19*) *loss-of-function allele* carriage (~65% in East Asians vs. ~30% in Caucasians) (►**Table 1**).[1,3,6] Contrary to the prediction, East Asian registry showed a lower risk of stent thrombosis after implantation of first-generation drug-eluting stent compared with Western registry.[7,8]

Multiple lines of evidence have supported the concept of a "therapeutic window of platelet reactivity" in CAD patients undergoing percutaneous coronary intervention (PCI) during dual antiplatelet therapy (DAPT).[9,10] High platelet reactivity (HPR) is associated with ischemic event occurrence and low platelet reactivity (LPR) is associated with bleeding. Western consensus documents proposed the cutoffs of HPR and LPR, based on the data of clinical outcomes from Caucasian patients.[9,10] For example, the consensus suggested a HPR of

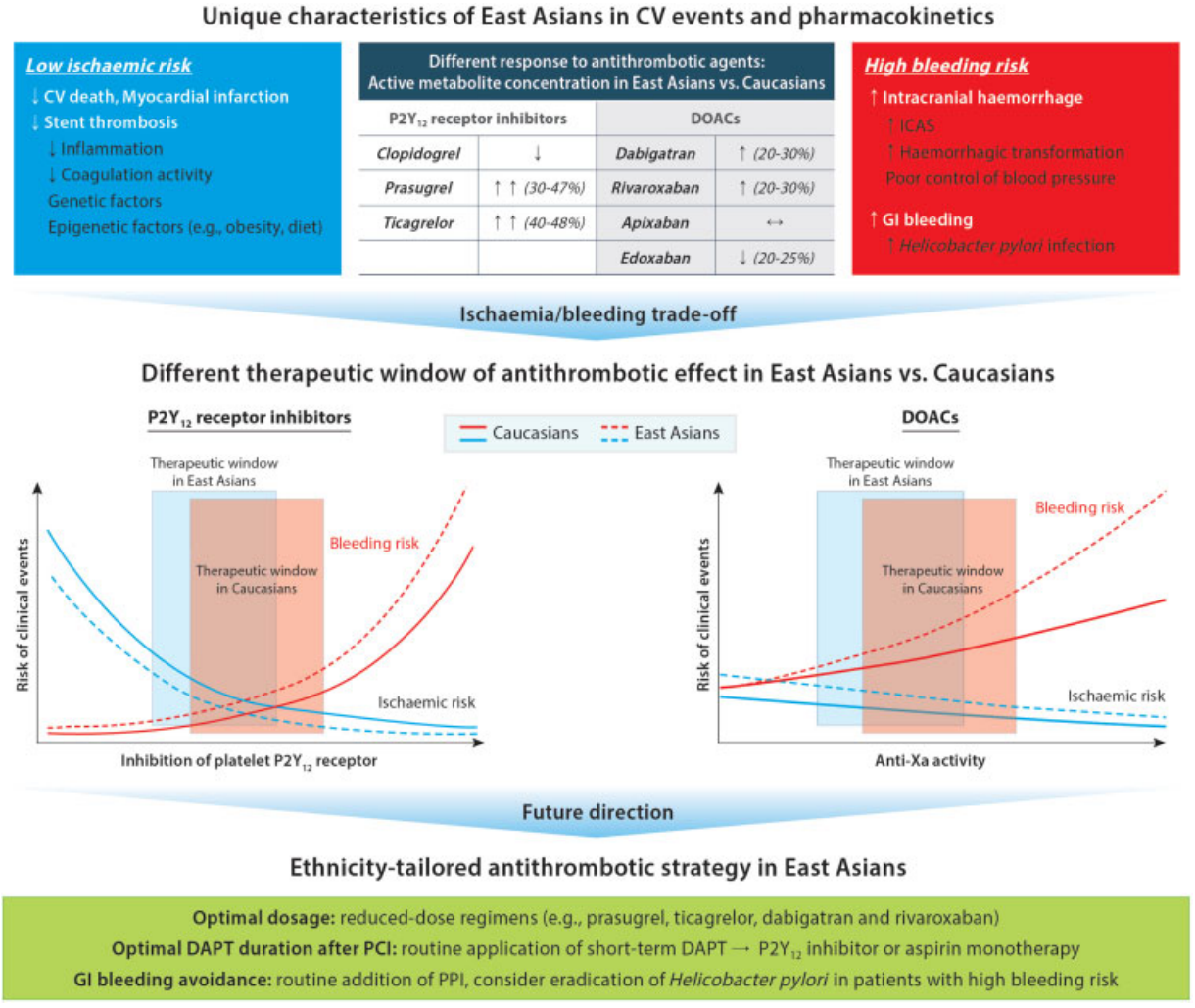

Fig. 1 Unique features of East Asian patients during antithrombotic treatment and future direction. The figure shows potential underlying mechanisms of the unique risk–benefit trade-off in East Asian population during antithrombotic treatment. East Asians have shown low risk of atherothrombotic events including cardiovascular (CV) morality: potential role of inflammation and coagulation activity. These patients also have increased tendency for gastrointestinal (GI) and intracranial bleeding events: different prevalence of intracranial atherosclerosis (ICAS) or *Helicobacter pylori* infection. The active metabolite levels of $P2Y_{12}$ receptor inhibitors or direct oral anticoagulants (DOACs) also differ between East Asians and Caucasians. Complex interactions between these findings can make a different therapeutic window of antithrombotic treatment among East Asian versus Caucasian patients. Given this aspect, the ethnicity-tailored antithrombotic strategy would be mandatory to minimize serious complications in East Asian patients. Routine application of short-term dual antiplatelet therapy (DAPT) and addition of proton pump inhibitor (PPI) after percutaneous coronary intervention (PCI) can be typical examples. (Adapted from Levine et al[2], Huo et al[4], and Chao et al[30].)

Table 1 Frequencies of *CYP2C19*2* and **3* alleles, and genetically predicted phenotype across the races[6]

	**2* Allele frequency	**3* Allele frequency	% Intermediate metabolizer	% Poor metabolizer
European	0.14	0.0	24	2
East Asian	0.27	0.09	46	10
African	0.14	0.0	24	2
African American	0.18	0.008	30	3.5

Note: Estimates based on HapMap and PharmGKB data (http://www.pharmgkb.org). Intermediate and poor metabolizers indicate the carriers of one and two CYP2C19 loss-of-function allele(s), respectively.

208 P2Y12 reaction unit (PRU) and a LPR of 85 PRU, measured by the point-of-care VerifyNow P2Y12 assay. Clinical evidence from East Asian patients suggested higher cutoffs of HPR than those from Caucasian patients (252.5–289 PRU) (►**Table 2**).[11–20] In addition, the cutoffs of LPR during DAPT in East Asians also appeared higher compared with Caucasians (126–139 PRU).[21,22] Compared with Caucasian patients, East Asians appear more resistant to atherothrombotic events at the same level of platelet reactivity and more vulnerable to bleeding. On the basis of clinical evidence, a different therapeutic window of platelet inhibition to minimize ischemic and bleeding complications in East Asian versus Caucasian patients undergoing PCI was proposed (►**Fig. 1**).[1–4]

Subsequently, the expert consensus statements on antiplatelet therapy in East Asian patients were proposed in 2014[2] and 2018.[4] Although various biomedical investigations focusing on East Asians have been ongoing, several clinical issues remain unsolved. As various $P2Y_{12}$ inhibitors and direct oral anticoagulants (DOACs) are more widely used in recent years, there is an urgency to define the optimal

Table 2 The cutoffs of HPR (VerifyNow P2Y12 assay) in East Asian patients treated with PCI (total $n = 11{,}515$)

Study	Cohort	Follow-up duration (mo)	Primary endpoint	Cutoff
ACCEL-LOADING-ACS study (RCT)[11]	NSTE-ACS ($n = 218$); emergent PCI	1	CV death, nonfatal MI, TVR	PRU $\geq$ 289[a]
Zhang et al (registry)[12]	NSTE-ACS ($n = 228$); emergent PCI	1	CV death, nonfatal MI, stent thrombosis, TVR	PRU $>$ 272[a]
Ko et al (registry)[13]	All comers ($n = 222$); PCI	1	Death, nonfatal MI, stroke, TVR	PRU $\geq$ 275[a]
PRASFIT-ACS study (RCT)[14]	ACS ($n = 660$); emergent PCI	6	CV death, nonfatal MI, nonfatal ischemic stroke	PRU $\geq$ 262[a]
CILON-T study (RCT)[15]	All comers ($n = 960$); DES implantation	6	Cardiac death, nonfatal MI, ischemic stroke, TLR	PRU $\geq$ 252.5[a]
Ahn et al (registry)[16]	All comers ($n = 1{,}226$); stenting	12	CV death, nonfatal MI, stent thrombosis	Non-AMI: no cutoff[a] AMI: PRU $\geq$ 272[a]
CROSS-VERIFY cohort (registry)[17]	All comers ($n = 809$); elective PCI	12	Cardiac death, nonfatal MI	PRU $\geq$ 275[a]
Jin et al (registry)[18]	STEMI ($n = 181$); primary PCI	12	CV death, nonfatal MI, ischemic stroke	PRU $\geq$ 282[a]
GENIUS study (registry)[19]	All comers ($n = 4{,}587$); PCI	12	CV death, nonfatal MI	PRU $\geq$ 266[a]
Asan-Verify cohort (registry)[20]	All comers ($n = 2{,}424$); PCI	22 (median)	Death, nonfatal MI, stroke, stent thrombosis	Stable CAD: no cutoff[b] ACS: PRU $\geq$ 235[b]

Abbreviations: ACS, acute coronary syndrome; ACCEL-LOADING-ACS, Accelerated Inhibition of Platelet Aggregation, Inflammation and Myonecrosis by Adjunctive Cilostazol Loading in Patients With 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; GENIUS, Genotyping Influences Outcomes of Coronary Artery Stenting; HPR, high platelet reactivity; 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, P2Y12 reaction units; RCT, randomized controlled trial; STEMI, ST-segment elevation myocardial infarction; TLR, target lesion revascularization; TVR, target vessel revascularization.
[a]Indicates the cutoffs of HPR evaluated by the receiver-operating characteristic curve analysis.
[b]Indicates the cutoff of HPR using predefined criteria from Western patients.

antithrombotic strategy to meet the best clinical benefit in East Asians.

Potential Mechanisms of the East Asian Paradox

Although there are numerous pieces of second-hand experimental and clinical evidence to show the unique ischemia/bleeding ratio in East Asian population, there are not many grounds for direct comparison between the races. A recent large-scale meta-analysis ($n = 16{,}518$; seven randomized clinical trials comparing DAPT duration in PCI-treated patients) suggested the differences in ischemic and bleeding events.[23] 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 addition, the proportion of patients with higher probability of bleeding than ischemia was significantly higher in East Asians (32.3 vs. 0.4%, $p < 0.001$).

Underlying mechanisms of this phenomenon must be complex and multifactorial. The unique demographics (e.g., low body weight), comorbidities, and disease patterns of East Asians can influence clinical outcomes. The polygenic nature of inherited thrombophilia and the complex interaction between genetic and epigenetic factors are also important components to explain this interethnic disparity. Virchow's triad describes major biological factors that contribute to thrombosis: hypercoagulability, shear stress, and endothelial dysfunction.[1,3] The comparison of these factors through biomarkers or surrogates may give important hints to explain the difference in incidence of CVD among races (►**Fig. 1**).

Low Ischemic Risk

East Asians have shown a lower incidence of ischemic heart disease and a decreased risk of post-PCI atherothrombotic complications compared with Caucasians.[2,4,5,7,24] Difference in hypercoagulability may be a crucial factor to account for the "East Asian Paradox" (e.g., low coagulation and inflammation in East Asians).[1,3,25] Most common single-point mutations related with inherited thrombophilia are factor V Leiden and prothrombin G20210A, which have been related with the prevalence of CAD.[26] Factor V Leiden allele is present in approximately 5% of the Caucasian individuals and is virtually absent in Asians. Prothrombin G20210A mutation is present in 2 to 4% of Caucasians, whereas this mutation is rare in other groups. In the general population, Japanese and Chinese subjects showed lower C-reactive protein levels compared with Caucasians (0.52- and 0.36-fold).[25]

High Bleeding Risk

East Asians have a greater propensity for major bleeding compared with Caucasians.[2,4,27] Compared with Caucasians, *Helicobacter pylori* infection (50–70% in East Asians vs. 30–50% in Caucasians),[28] intracranial atherosclerosis (30–50% in East Asians vs. 15–30% in Caucasians), and poststroke hemorrhagic transformation[29] are more prevalent among East Asians, which may be associated with risk of gastrointestinal bleeding and intracranial hemorrhage (ICH) during antithrombotic therapy.[4] In clinical evidence of secondary stroke prevention, aspirin treatment caused approximately 0.2% per year of hemorrhagic stroke in Western trials, whereas approximately 1.0% per year of hemorrhagic stroke occurred during aspirin therapy in East Asian population.[29]

Different Responses to Antithrombotic Agents

East Asians and Caucasians have shown different responses to antithrombotic regimens. Most antithrombotic agents have enhanced pharmacokinetic and pharmacodynamic profiles in East Asian versus Caucasian subjects, except for clopidogrel and edoxaban.[2–4,30]

Achieving optimal balance between ischemic and bleeding risks in CVD patients is fundamental to determine whether one specific dose of antithrombotic agent can be administered as standard treatment. Considering the different thresholds between ischemic and bleeding risks, the therapeutic range of antithrombotic agents may be different between East Asians and Caucasians. These observations argue against East Asians following the current recommendations on standard antithrombotic regimens provided by guidelines from North America and Europe.

Optimal Potency and Duration of DAPT in East Asians

The potency of $P2Y_{12}$ inhibitors and duration of DAPT can be determined by weighing clinical efficacy and hazard. After introduction of a specific antiplatelet agent, reduced benefit in ischemic events and increased risk of bleeding in East Asian patients may affect the optimal potency and DAPT duration (►**Fig. 1**). In addition, different concentrations of the active metabolites during $P2Y_{12}$ inhibitor treatment were observed between these races. For example, the active metabolite levels of prasugrel are 30 to 47% higher in East Asians than in Caucasians, and the exposures of ticagrelor (~40%) and its major active metabolite (AR-C124910XX) (~48%) are greater in East Asians versus Caucasians.[2,3]

Based on the experiences with clopidogrel,[1,5] the global experts highlighted the potential risk of bleeding during standard-dose prasugrel or ticagrelor in East Asians.[2,4] Subsequently, clinical evidence from registries[31,32] and randomized trials[33] mostly supported the experts' initial recommendation, with markedly increased bleeding and limited benefit in reducing ischemic events during prasugrel/ticagrelor versus clopidogrel treatment among patients with acute coronary syndrome (ACS). In addition, DAPT duration also needs to be determined depending on the benefit/risk ratio between ischemic and bleeding events.[4] A recent meta-analysis including 13 randomized trials ($n = 38{,}255$) suggested that optimal DAPT duration may be shorter in East Asians.[34] After PCI, short- versus long-term DAPT strategy significantly increased ischemic event only in non-East Asians (odds ratio [OR]: 1.24; 95% confidence interval [CI]: 1.09–1.42), while bleeding events were decreased by short-term DAPT in both ethnicities.

There are growing concerns regarding patients at "high bleeding risk"[35] and de-escalation strategy of antiplatelet treatment.[9,10] These concepts would be more important in

East Asians and multiple clinical trials are ongoing to find the best strategy for achieving the desirable clinical benefit in East Asian countries.

Short-Term DAPT by Early Discontinuation of Aspirin

Compared with 12-month DAPT, $P2Y_{12}$ inhibitor monotherapy (mostly clopidogrel) following 1- to 3-month DAPT reduced the risk of clinically serious bleeding (by 42–74%) in East Asians undergoing PCI.[36,37] The TICO (Ticagrelor With or Without Aspirin in Acute Coronary Syndrome After PCI) trial ($n = 3{,}056$) showed clinical benefit of ticagrelor monotherapy following 3-month DAPT versus 12-month DAPT in ACS patients,[38] where the difference was mainly driven by a reduced risk of major bleeding (1.7 vs. 3.0%; hazard ratio [HR]: 0.56; 95% CI: 0.34–0.91, $p = 0.02$).

A Reduced Dose of Potent $P2Y_{12}$ Inhibitors

Based on clinical trials in the Japanese population,[39] 20-mg loading followed by 3.75-mg prasugrel maintenance is widely used for Japanese patients with ACS. The REDUCE-POLYTECH-ACS (Harmonizing Optimal Strategy for Treatment of Coronary Artery Diseases Trial—Comparison of REDUCtion of PrasugrEl Dose and POLYmer TECHnology in ACS Patients) trial randomized ACS patients into either the conventional dose of prasugrel (10 mg daily) or the reduced dose of prasugrel (5 mg daily) after 10-mg prasugrel during 1 month.[40] De-escalation strategy of prasugrel reduced bleeding events (HR: 0.48; 95% CI: 0.32–0.73, $p = 0.0007$) without increasing ischemic risks (HR: 0.76; 95% CI: 0.40–1.45; $p = 0.40$). However, there are no clinical trials to evaluate a reduced-dose ticagrelor strategy in East Asian patients.

Switching from Potent $P2Y_{12}$ Inhibitor to Clopidogrel after the Acute Phase

The TALOS-AMI (TicAgrelor Versus CLOpidogrel in Stabilized Patients With Acute Myocardial Infarction) trial finished the enrollment, which compares clinical efficacy and safety of clopidogrel versus ticagrelor in Korean patients with stabilized myocardial infarction (MI) (after 1 month following PCI) (https://clinicaltrials.gov/ ct2/show/NCT02018055? term =TALOS-AMI&rank = 1).

Choosing $P2Y_{12}$ Inhibitor According to Genetic or Platelet Function Test

The TAILOR-PCI (Tailored Antiplatelet Therapy Following PCI) trial (1,849 patients with the *CYP2C19* *2 or *3 *allele*) showed that genotype-guided therapy (mostly treated with ticagrelor) reduced ischemic events compared with clopidogrel-based therapy (adjusted HR: 0.66; 95% CI: 0.43–1.02, $p = 0.056$).[41] The ischemic benefit was only prominent during early 90 days post-PCI (absolute risk reduction 2.1%; 95% CI: 1.0–3.4%, $p = 0.001$). However, this benefit was relatively low in East Asians versus Caucasians (38.3 and 47.3% of the total cohort, respectively) (absolute risk reduction: 1.5 vs. 2.6%).

Selecting the Groups According to Risk Scoring

The KAMIR-NIH DAPT (Korean Myocardial Infarction Registry—National Institute of Health Dual Antiplatelet Therapy) score was developed to guide selection of $P2Y_{12}$ inhibitor by evaluating combined ischemic and bleeding events from East Asian patients presented with MI.[42] The high-risk group ($\geq$3 points: 17.8% of the total cohort) showed an overall benefit from potent $P2Y_{12}$ inhibitor versus clopidogrel in reducing 1-year ischemic events (8.6 vs. 17.1%, $p < 0.001$) without significant increase in bleeding events (10.1 vs. 6.8%, $p = 0.073$).

Use of Oral Anticoagulants in East Asians

Patients with atherosclerotic CVD (ASCVD) have a higher thrombin concentration compared with those without ASCVD.[43,44] In addition, patients with polyvascular disease (e.g., CAD + peripheral artery disease [PAD]) had a greater level of platelet–fibrin clot strength than subjects with single vascular disease.[45] Clinical trials with adjunctive DOACs have shown clinical benefit in reducing the risk of ischemic events in high-risk ASCVD patients (e.g., multivessel CAD, PAD, heart failure, diabetes mellitus, chronic kidney disease, and recurrent MI).[43,44,46] In the COMPASS (Rivaroxaban for the Prevention of Major Cardiovascular Events in Coronary or Peripheral Artery Disease) trial including stable ASCVD patients ($n = 27{,}395$),[46] the vascular-dose rivaroxaban (2.5 mg twice daily) + aspirin strategy reduced the risk of ischemic events (4.1 vs. 5.4%; HR: 0.76: 95% CI: 0.66–0.86, $p < 0.001$) at the expense of increased risk of major bleeding (3.1 vs. 1.9%; HR: 1.70: 95% CI: 1.40–2.05, $p < 0.001$) compared with aspirin monotherapy. The subanalysis of PAD patients (lower extremity or carotid artery disease) showed prominent clinical benefit of the vascular-dose rivaroxaban plus aspirin regimen, which lowered the incidence of major adverse limb events by 43%, major vascular amputation by 67%, and peripheral vascular intervention by 24% compared with aspirin monotherapy.[47,48] However, dual-pathway inhibition with rivaroxaban and aspirin versus aspirin monotherapy increased the risk of major bleeding in Asian patients (3.9 vs. 1.8%) more than in white patients (3.4 vs. 2.2%) (relative risk [RR] increase by 80%)[49]; adjunctive use of low-intensity DOAC in addition to antiplatelet therapy also has brought the issue of increasing clinically serious bleeding in East Asian patients.

In patients with atrial fibrillation (AF), warfarin administration is associated with a substantially higher risk of ICH in East Asian patients compared with Caucasian patients,[50,51] resulting in many clinicians adopting a lower international normalized ratio (INR) target range (e.g., INR: 1.6–2.6). However, the evidence for such a lower target INR does not support this approach; in a systematic review and evidence appraisal, lower INR targets reduce bleeding but increase thromboembolism in AF, with similar trends in East Asian and Western studies.[52] Rather than actual INRs per se, bleeding and thromboembolic risks on warfarin can be more dependent on quality-of-anticoagulation control, as reflected by time in therapeutic range (TTR); the latter generally tends to be low in East Asians.[53]

There are conflicting data regarding the optimal target INR in East Asian patients with AF. In the recent meta-analysis for AF patients,[52] a low level of INR target ranges

(1.5–2.0) was associated with higher rates of thromboembolism (7.1 vs. 4.4%; RR: 1.50; 95% CI: 1.29–1.74), lower rates of major bleeding (2.2% vs. 4.4%; RR: 0.54; 95% CI: 0.44–0.67), and similar mortality (4.8% vs. 5.2%; RR: 1.00; 95% CI: 0.85–1.19), whereby data were dominated by East Asian studies. A recent Korean experience suggested that mean INR 1.6 to 2.6 was better than mean INR 2.0 to 3.0 for the prevention of both thromboembolism and major bleeding in patients with nonvalvular AF, but did not focus on TTR to substantiate this conclusion.[51]

Overall, DOACs in AF patients were associated with a comparable risk of ischemic events and significantly lower risk of major bleeding than warfarin. Therefore, DOACs are the preferred oral anticoagulants over warfarin in AF patients, but ICH risk in Asian patients on the same dose of DOAC (or their associated drug levels) still appeared to be relatively higher compared with non-Asian patients (►**Fig. 2**).[30,54] In addition, there is an increasing percentage of AF patients undergoing PCI, where combination therapy of DOAC and antiplatelet therapy is required.

Each DOAC shows variable pharmacokinetic profiles according to ethnicity (►**Fig. 1**).[3,30] The active metabolites of dabigatran and rivaroxaban were approximately 20 to 30% higher in Japanese versus Caucasians.[55,56] Apixaban shows a similar plasma concentration among Japanese and Caucasians.[57] Meanwhile, the trough concentration and antifactor Xa activity during edoxaban therapy were 20 to 25% lower in Asians.[30] Similar to antiplatelet treatment, Asian patients sustain more major bleeding events and ICH with relatively low DOAC concentrations compared with non-Asians (►**Fig. 1**).[30]

East Asian physicians widely prescribed reduced doses of DOACs, and their clinical outcomes appeared broadly favorable compared with warfarin (especially where TTR is often suboptimal) in the observational cohorts.[58,59] Nonetheless, there are no data to inform whether appropriate dose adjustment in accordance with the label or guidelines was performed. In a Taiwanese nationwide cohort study, approximately 90% of rivaroxaban and dabigatran, and two-thirds of apixaban and edoxaban were prescribed with lower doses.[59] Overall, these DOAC regimens were associated with a comparable ischemic risk and significantly lower bleeding risk than warfarin. A Korean nationwide cohort analysis ($n = 53{,}649$) suggested that underdosing (31.2% of the total cohort) was not associated with worse clinical outcomes compared with label-adherent use (60.4% of the total cohort).[60]

Western guidelines recommend the full dose of DOAC even in AF patients undergoing PCI.[61] However, PCI-treated Asian patients with AF were mostly prescribed with reduced-dose DOACs. For example, the AFIRE (Atrial Fibrillation and Ischemic Events With Rivaroxaban in Patients With Stable Coronary Artery Disease) trial used 54% of 15-mg rivaroxaban and 46% of 10-mg rivaroxaban for Japanese patients.[62] There are no randomized trials to evaluate the best combination strategy including DOAC and antiplatelet therapy in East Asian patients with AF undergoing PCI.

Emerging Issue: Ethnic Differences in Thromboinflammation Syndrome

Similar to prevalence of CAD, the incidence of venous thromboembolism (VTE) varies by race, with African Americans having over approximately fivefold greater incidence than Asian-ancestry populations, and an intermediate risk for Caucasian and Hispanic populations (►**Fig. 3**).[63] Known racial differences in CV risk factors associated with atherothrombotic events cannot account for this gradient of risk, nor do known ethnic variations in environmental risk factors. This difference has been consistently observed, even in individuals of different ethnicities living within the same geographical location.[25,64] Difference in hypercoagulability

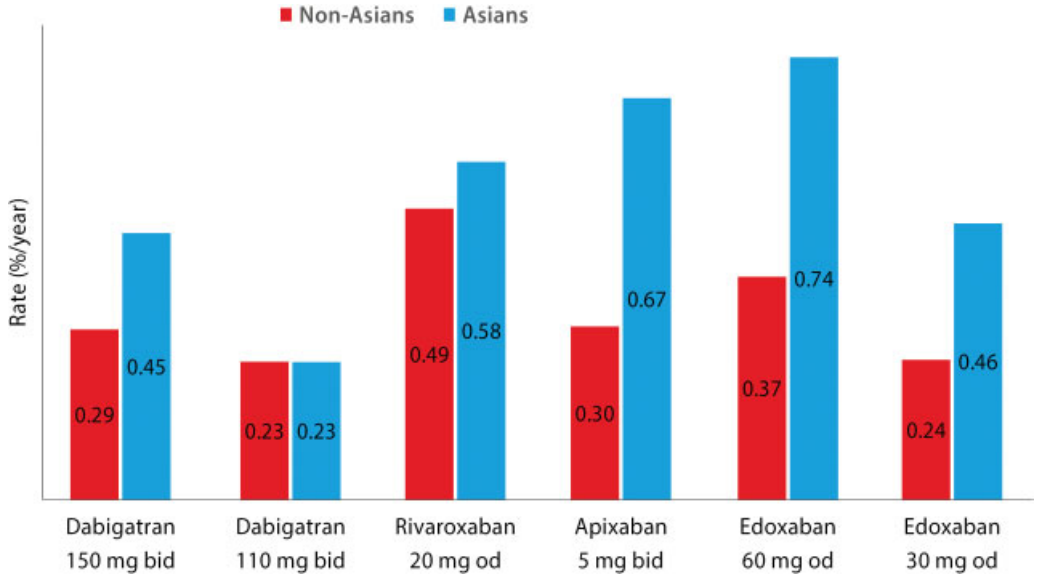

Fig. 2 Annual risk of ICH during DOAC treatment in Asians versus non-Asians from randomized clinical trials.[54] bid, bis in die (twice a day); DOAC, direct oral anticoagulant; ICH, intracranial hemorrhage; od, omni die (once a day).

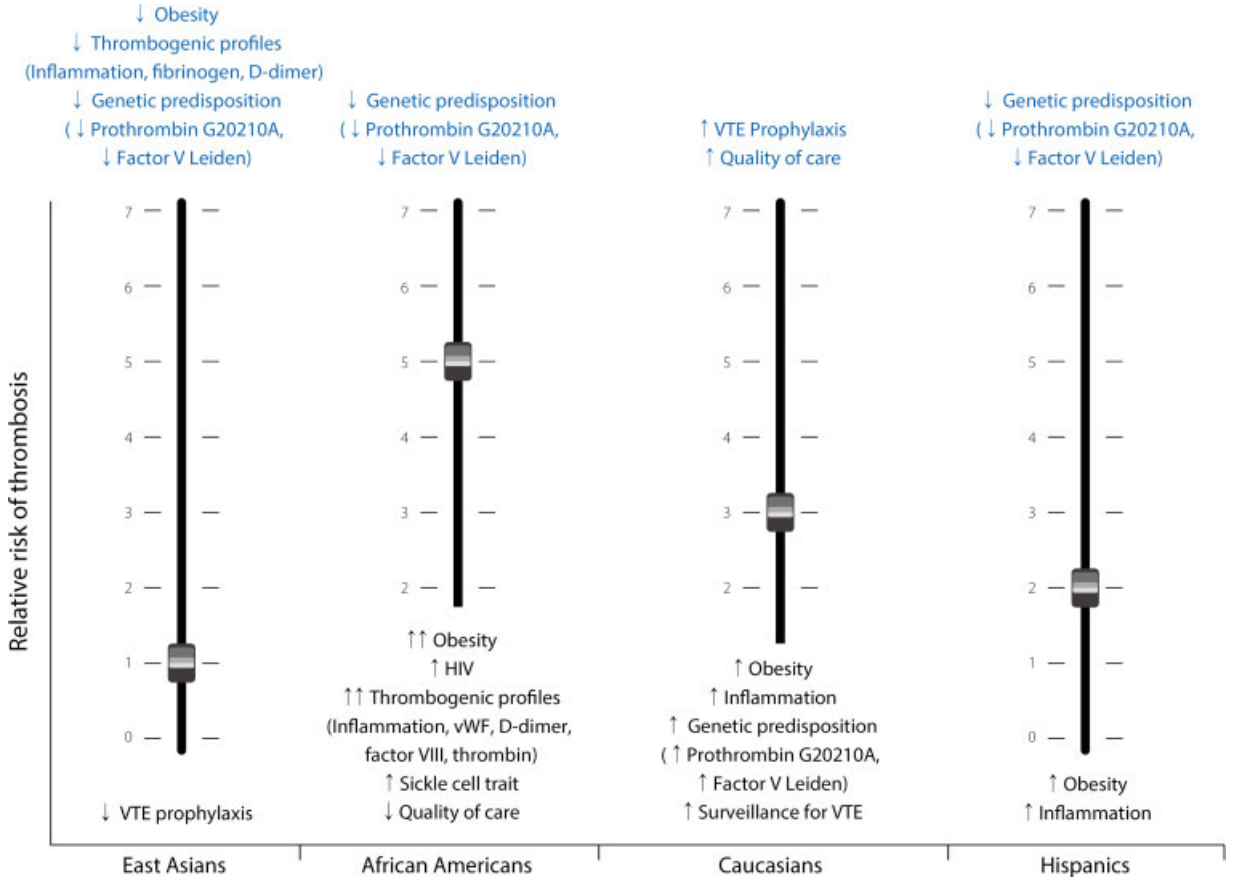

Fig. 3 Suggested mechanisms for racial differences in VTE.[63–70] HIV, human immunodeficiency virus; VTE, venous thromboembolism; vWF, von Willebrand factor.

may be an important biological factor to explain the ethnic disparity in prevalence of CVD including atherothrombotic events from arterial and venous vascular beds.

Although more researches are needed in this field to reach a reliable conclusion, researchers and clinicians are beginning to indicate the importance of differences in hypercoagulability including inflammation and coagulation status.[63] Numerous studies have suggested the different levels of inflammation between the races. Overall, African Americans exhibit the highest inflammatory levels, whereas East Asians appear to have the lowest inflammatory status.[65–67] For example, the Women's Health Study demonstrated that African American women have significantly a higher median C-reactive protein level (2.96 mg/L) compared with Caucasians (2.02 mg/L), Hispanics (2.06 mg/L), and East Asians (1.12 mg/L).[67] The differences in the levels of hemostatic factors (e.g., fibrinogen, D-dimer, factor VIII) and plasma endothelial activation markers (e.g., von Willebrand factor, E-selectin) may be another contributing factor to this ethnic disparity. The MESA (Multi-ethnic Study of Atherosclerosis) study evaluated these components in healthy individuals living in the United States.[68] African Americans generally had the most thrombogenic and dysfunctional endothelial profiles, followed by Hispanics and Caucasians with similar levels, and finally East Asians. Most of the inherited mechanisms of thrombosis that have been studied are present primarily in Caucasian populations, such as factor V Leiden, resulting in resistance to protein C, and prothrombin G20210A.[26,63] However, African Americans have an increased risk of atherothrombosis as compared with Caucasians.[63,69] African Americans show a trend toward having higher baseline levels of coagulation factor VIII, von Willebrand factor, thrombin generation, and D-dimer.[63,70] Obesity is an important risk factor of CVD occurrence, which is most popular in the African American population. This phenotype presents a vicious cycle related with the progression of atherothrombosis, due to oxidative stress, chronic thromboinflammatory cascade, and platelet activation.[63] In addition, there are significant differences in numbers and functions of platelets. African American women tend to have a higher platelet count than Caucasians and Latinos. In addition, several studies demonstrated differences in the protease-activated receptor-4 pathway, with African Americans being less responsive to inhibitors of cyclooxygenase and $P2Y_{12}$ receptor.[71,72] These findings suggest that African Americans may not respond well to DAPT compared with other races, and this may be related with their worse clinical outcomes after coronary stenting.[69,73]

Global hemostatic assays (e.g., thromboelastography [TEG]) that reflect the interaction between cellular elements and plasma proteins better represent hemostatic capacity and may assist us in differentiating the mechanism(s) associated with clot generation and associated clinical outcomes.[74] In patients with known or suspected CAD ($n = 1,172$), black patients

showed greater level of TEG-measured platelet–fibrin clot strength than white patients (67.8 ± 7 vs. 66.4 ± 6 mm, $p = 0.005$).[75] From the cohorts with stable CAD, East Asians showed a lower platelet–fibrin clot strength compared with Caucasians (61.8 ± 7.9 vs. 65.4 ± 5.0 mm, $p < 0.001$).[76] A high platelet–fibrin clot strength (≥68 mm) was significantly associated with ischemic events (OR: 6.27; 95% CI: 2.41–16.30, $p < 0.001$) and East Asians versus Caucasians had a lower prevalence of high clot strength (OR: 0.50; 95% CI: 0.27–0.93, $p = 0.028$). Taken together, African Americans have been shown to have the highest thrombogenic profile, whereas East Asians have the lowest thrombogenic tendency, which may be associated with the ethnic disparity in ASCVD occurrence and related mortality from arterial and venous vascular beds.[1,3]

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) disease (COVID-19) predispose patients to thrombotic disease, resulting in the formation of clinical arterial and venous blood clots (COVID-19 coagulopathy: large-vessel stroke, VTE such as deep vein thrombosis and pulmonary thromboembolism).[77,78] As COVID-19 spreads all over the world, African population living in the United States or European countries has been disproportionately affected and their CV mortality appeared highest compared with other races.[70,79] Their vulnerability has not been fully understood by the differences in health care resources and infrastructure. Severe systemic inflammation results in enhanced activation of the hemostasis and coagulation system (thromboinflammatory syndrome). Coagulation–inflammation status and predisposition to the development of coagulopathies vary between races and ethnicities, with African Americans trending toward a more prothrombotic state.[63,64,70] Patients with severe manifestations of COVID-19 have elevated levels of D-dimer, fibrin-degradation products, and fibrinogen, as well as low levels of antithrombin. Many patients also have elevated concentrations of factor VIII and von Willebrand factor.[77,78,80] Baseline differences in coagulation factors in conjunction with activation of the immune system and platelets may contribute to the disproportionate impact of COVID-19 disease in African American patients.[70] The low level of thromboinflammatory cascade in East Asian population may partly explain their better outcomes following COVID-19 infection, but this hypothesis needs more supportive clinical and experimental evidence.[63,70,81]

Conclusion

Clinical safety and efficacy of a specific antithrombotic treatment are closely associated with intrinsic ischemic and bleeding risk. More pieces of evidence are accumulating to show differences in thrombogenicity across the races. Because most clinical data have demonstrated that East Asian population has low hypercoagulability (e.g., low levels of coagulation and inflammation),[1,3,9] their optimal potency and achieved risk–benefit ratio during antithrombotic treatment would be relatively different compared with the Western population.

The "East Asian Paradox" concept was first described with the racial difference in the therapeutic window of on-clopidogrel platelet reactivity. The tendency of low ischemic risk and a higher bleeding risk were also observed during newer antithrombotic treatments such as potent $P2Y_{12}$ inhibitor and DOAC therapies. This position statement would like to update the concept of "East Asian Paradox" into development of a unique antithrombotic strategy for East Asian population, on the basis of the observations of different pharmacodynamic profiles of antithrombotic agents, and low benefit in reducing ischemic events and high risk in increasing bleeding events during antithrombotic treatment.

Although updated experts' consensus has suggested how to approach this issue during antiplatelet treatment,[2,4] there is still lack of detailed recommendations. Several large-scale East Asian studies are ongoing, and recent global clinical trials gradually reflect the unique risk–benefit trade-off in East Asians. The time has come to recognize and develop the "ethnicity-tailored antithrombotic strategies" for East Asians, based on the reliable clinical and experimental evidence.

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Conflict of Interest
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