

Review Article



“East Asian Paradox” Revisited: Precision Medicine for Antithrombotic Strategies Tailored to Atherothrombotic Cardiovascular Risks

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OPEN ACCESS

Received: Mar 23, 2024

Revised: Apr 9, 2024

Accepted: Apr 11, 2024

Published online: Apr 17, 2024

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ABSTRACT

Following percutaneous coronary intervention (PCI) in patients with coronary artery disease (CAD), patients may face a prolonged elevated risk of atherothrombotic events. This enduring vulnerability underscores the need for refined secondary prevention strategies, grounded in a deepening understanding of the pathobiology involved. The shift in CAD pathophysiology research from focusing on ‘vulnerable plaques’ to embracing the concept of the ‘vulnerable patient’, emphasizing the essential role of medical therapy in secondary prevention. Despite the current guideline-directed medical therapy, a consistent proportion of post-PCI patients experience recurrent atherothrombotic events due to unaddressed ‘residual atherothrombotic cardiovascular (CV) risks’. Contemporary clinical research highlights the pivotal role of lipid phenotype, systemic inflammation, glycemia, platelets, coagulation, and fibrinolytic activity, advocating for a more personalized, targeted therapeutic approach. Balance between clinical efficacy and safety during antithrombotic agents may be different according to ‘residual atherothrombotic CV risks’. Blacks generally exhibits the highest level of atherothrombotic CV risks, followed by Hispanics and Caucasians with comparable levels, and finally the lowest level is observed in East Asians, which will be a major factor supporting the ‘East Asian Paradox’. In this review, we discuss available evidence regarding the racial differences in atherothrombotic CV risks and its impact on clinical post-PCI outcomes to determine precision medicine for antithrombotic strategies.

Keywords: Coronary artery disease; Thrombosis; Cardiovascular risk; Race;
Antithrombotic agent

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This study was supported by the Science Research Program through the CAU Thrombosis and Biomarker Center funded by the Chung-Ang University Gwangmyeong Hospital. The content is solely the responsibility of the authors and does not necessarily represent the official views of any funding agencies.

Conflict of Interest

Dr. Jeong YH has received honoraria for lectures from Daiichi Sankyo, Sanofi-Aventis, Han-mi Pharmaceuticals, and Daewoong Pharmaceuticals and research grants or support from Samjin Pharmaceuticals, Hanmi Pharmaceuticals, Yuhan Pharmaceuticals, Biotronik Korea, and U and I Corporation.

Dr. Gorog DA has received institutional grants from Bayer Plc, AstraZeneca, Werfen, Medtronic, and AlphaMD and honoraria for lectures from AstraZeneca and Boehringer Ingelheim. Dr. Gurbel PA reports grants and personal fees from Bayer HealthCare LLC, Otitopic Inc, Amgen, Janssen, US WorldMeds LLC; grants from Instrumentation Laboratory, Hikari Dx, Haemonetics, medicure, Idorsia pharmaceuticals, and personal fees from Up-To-Date. He has a patent, Detection of restenosis risk in patients issued and a patent, Assessment of cardiac health and thrombotic risk in a patient. The other author reports no conflicts of interest.

Author Contributions

Conceptualization: Jeong YH; Supervision: Tantry US, Navarese E, Gorog DA, Gurbel PA; Visualization: Jeong YH, Omar M; Writing - original draft: Jeong YH; Writing - review & editing: Tantry US, Navarese E, Gorog DA, Gurbel PA.

INTRODUCTION

Multiple lines of epidemiological evidence suggest that the prevalence of atherosclerotic cardiovascular disease (ASCVD) and its related mortality rate vary across the races.^{1,5} Despite having comparable levels of traditional cardiovascular (CV) risk factors, East Asian populations (such as South Korea, Japan, and China) have lower rates of coronary artery disease (CAD) and myocardial infarction (MI) compared to Western populations.³ In 2012, Jeong et al.⁶ firstly proposed the concept of 'East Asian Paradox' to explain the unique association between clinical prognosis and antiplatelet potency following percutaneous coronary intervention (PCI).

Caucasian populations experience higher morbidity and mortality rates from arterial atherothrombotic events (ATEs) compared to East Asians.^{1,2} In addition, clinical evidence showed that the incidence of venous thromboembolic events (VTEs) varies according to race, with Blacks experiencing up to about 5-fold greater incidence than individuals from Asian ancestry populations, and an intermediate risk in Caucasians and Hispanics.⁴ With the extension of life expectancy and the global spread of infectious diseases, exposure to clinical triggers that enhance thrombogenic milieu (such as coronavirus disease 2019 [COVID-19] and active malignancy) has recently increased.^{5,7} A meta-analysis, encompassing 102 trials with a total of 64,503 participants, predominantly involving hospitalized Western patients with COVID-19, reported VTEs at a rate of 14.7%, and ATEs at a rate of 7.8%, respectively.⁸ However, surveillance studies conducted in Japan have shown a low prevalence of documented thrombotic events associated with COVID-19 infection (~2.0%).^{9,10}

Further research is needed to clarify the mechanisms behind the racial disparities observed in different clinical contexts of ASCVD. This review explores the difference and prognostic implication of 'residual atherothrombotic CV risks' across races, and the adaptation of antithrombotic strategies within the framework of precision medicine.

CONCEPT OF ATHEROTHROMBOTIC CV RISKS

Prior studies have underscored notable variations in conventional CV risk factors (e.g., hypertension, chronic kidney disease, diabetes mellitus, and smoking) among different racial groups.¹¹ They have also identified a different correlation between risk scores and actual clinical events across races. Several genetic and epigenetic factors have been suggested to explain a low incidence rate of ASCVD in East Asian population.¹²

1. Lifestyle and environmental factors: Although the traditional East Asian diet is high in sodium, it is also rich in vegetables, fish, and soy products, which may confer a protective effect against heart disease. Lower rate of obesity, high level of physical activity, and other healthy lifestyle practice common in these populations may play a role in offsetting the negative impacts of high sodium consumption.
2. Genetic factors: Gene-environment interactions exist for almost every polygenic disease (e.g., CAD). CAD is known to be highly heritable with more than 160 susceptibility loci described. CAD susceptibility in East Asians may involve unique genetic loci and variations that differ from those commonly identified in other populations.
3. Methodological differences: Differences in study designs, methods of measuring CV risk factors, and definitions of CV events might contribute to this observed paradox.

The differences in the incidence and prognosis of ASCVD across the racial groups may be understood by leveraging the detailed understanding provided by current biomarkers and imaging criteria. The processes of arterial and venous atherothrombosis, finely regulated by 'Virchow's triad', involve a complex interplay among blood components (vulnerable blood), the vessel wall (vulnerable vessel), and hemodynamic variables (stasis or turbulence).¹³

Traditionally, acute coronary syndrome (ACS) was understood to primarily result from the rupture of thin-capped atherosclerotic plaques with large lipid or necrotic cores, leading to the exposure of prothrombotic materials and the further propagation of pro-thrombotic mediators.¹⁴ However, a consistent body of evidence has prompted a reassessment of this perspective, revealing a much more intricate picture of the processes involved in ACS. While evidence for inter-racial differences in vessel vulnerability and hemodynamic profiles is scarce, increasing evidence suggests significant racial differences in 'atherothrombotic CV risks'. Hemostasis, crucial for preventing excessive bleeding when blood vessels are damaged, involves cellular elements such as platelets and plasma factors related to inflammation, procoagulation, anticoagulation, and fibrinolysis. In addition, these 'atherothrombotic CV risks' are closely linked to the progression of atherosclerosis and clinical outcomes in ASCVD.^{1,2}

Low-density lipoprotein cholesterol (LDL-C) is widely recognized as a key factor in the development of atherosclerosis and the occurrence of clinical events, constituting a significant part of 'residual atherothrombotic CV risks' (**Fig. 1**).^{15,17} Despite a decline in total cholesterol levels through lifestyle changes and LDL-C-targeting pharmacological strategies, ASCVD events still frequently occur, even in individuals with controlled LDL-C levels.¹⁸ Recent efforts have concentrated on addressing another CV risks, such as elevated lipoprotein (a) [LP (a)], hypertriglyceridemia, systemic inflammation, glycemic phenotype, and thrombosis profiles including platelets, coagulation and fibrinolytic activity. Large-scale

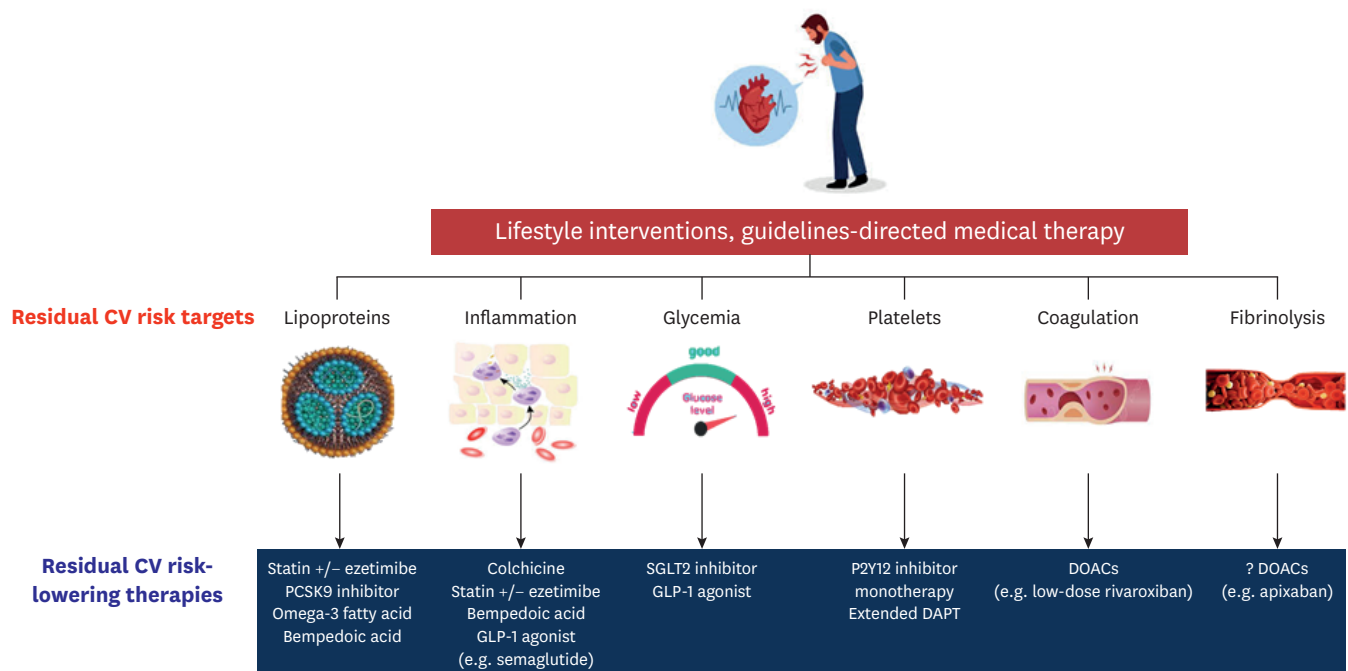


Fig. 1. Framework for residual atherothrombotic CV risks during guideline-directed medical therapy. This figure was modified from the original version.¹⁷ CV = cardiovascular; PCSK9 = proprotein convertase subtilisin/kexin type 9; GLP-1 = glucagon-like peptide 1; SGLT2 = sodium-glucose cotransporter 2; DAPT = dual antiplatelet therapy; DOAC = direct oral anticoagulant.

phase 3 CV outcome trials have shown that targeting these residual CV risk pathways can significantly lower clinical event risk in ASCVD patients on statin therapy.^{15,17}

Atherosclerosis is increasingly recognized not only as a disorder of lipid accumulation but also as a chronic inflammatory state.² This perspective underscores inflammation's significant role in the initiation, progression, and destabilization of atherosclerotic plaques, highlighting the complex interaction between lipid metabolism and inflammatory processes. Various inflammatory pathways critically influence atherosclerosis progression, plaque destabilization, and responses to MI.¹⁷ Additionally, the coagulation cascade, especially Factor Xa and thrombin's roles via proteinase-activated receptors (PARs), significantly impacts endothelial cell function, inflammatory cell recruitment, and vascular smooth muscle cell activities, leading to plaque instability and thrombus formation.¹⁹ This thrombo-inflammatory axis underscores the interconnected nature of thrombotic and inflammatory processes in atherosclerosis development and ASCVD exacerbation, emphasizing its critical importance in the disease's pathophysiology.

RACIAL DIFFERENCES IN ATHEROTHROMBOTIC CV RISKS

Incidence of VTE, encompassing deep venous thrombosis and pulmonary embolism, varies by race, and its occurrence is influenced by a complex mix of genetic and environmental risk factors (**Fig. 2**).⁴ The racial differences in VTE incidence may involve genetic variants, such as factor V Leiden and the prothrombin gene polymorphism, primarily found in Caucasian population, accounting for a significant portion of VTE risk. Additionally, heritable abnormalities in coagulation factors and inflammation play crucial roles, with Blacks experiencing the highest levels of inflammation and East Asians the lowest.^{20,21} Consequently, African ancestries exhibit the highest atherothrombotic risk, while East Asian populations show the lowest risk.

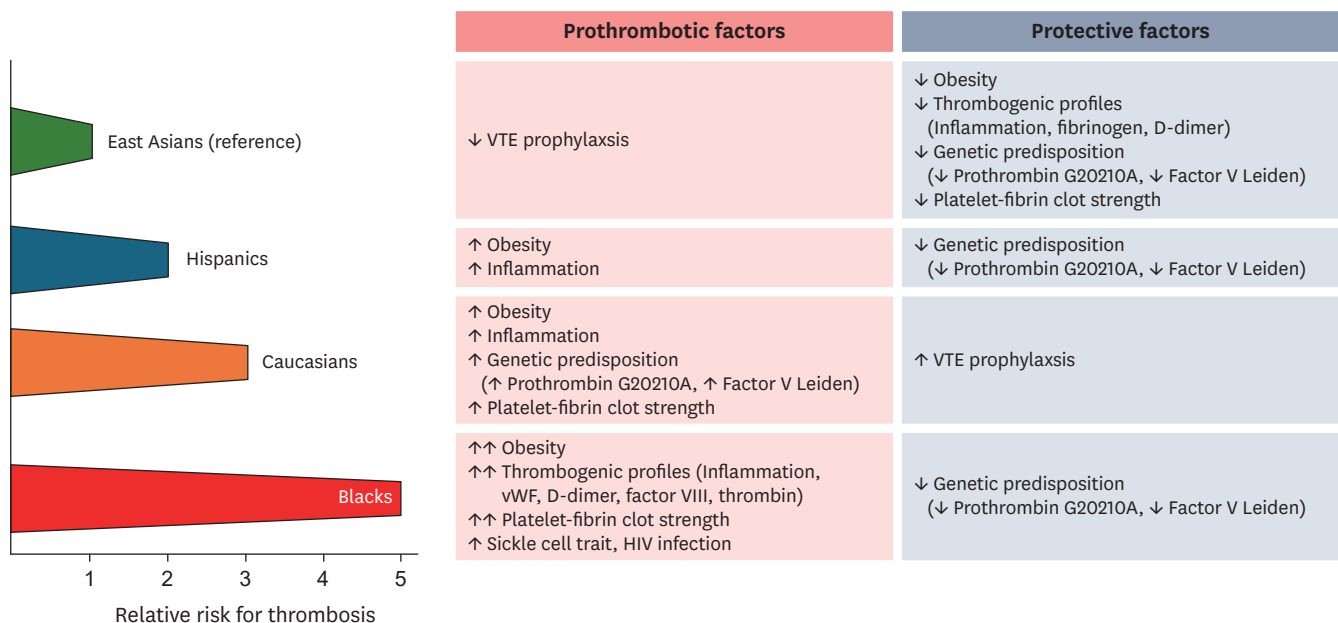


Fig. 2. Risk of venous thromboembolism across races and postulated mechanisms. This figure was modified from the original version.^{1,2} VTE = venous thromboembolism; vWF = von Willebrand factor; HIV = human immunodeficiency virus.

Biomarkers or surrogates reflective of atherothrombotic risks may provide important clues to explain racial differences in incidence and prognosis of ASCVD including VTE and ATE together.^{1,2} During guideline-directed medical therapy (GDMT), East Asians have a lower biomarker level of residual atherothrombotic CV risks compared to Caucasians, which may substantially explain the lower morbidity and mortality rates associated with ASCVD in East Asians compared to Western populations (Table 1).^{2,22,23}

- 1) Lipid profile: There are marked differences in the prevalence of dyslipidemia subtypes among racial classes, which show lower prevalence for any dyslipidemia subtype in Black Americans, higher rates of low high-density lipoprotein-cholesterol and high triglyceride in Hispanics and higher rate of high triglyceride in East Asians.²⁴ Elevated LP (a) level is associated with the risk of ASCVD in all racial groups. Blacks have the highest LP (a) level, followed by South Asians, Caucasians, Hispanics and East Asians.²⁵
- 2) Inflammation: Significant racial differences exist in inflammatory activity, with African Americans showing the highest and East Asians the lowest levels.^{26,27} Compared with other races, Korean healthy population (n = 268,803) had low high-sensitivity C-reactive protein (hs-CRP) level, but there was a linear relationship between hs-CRP levels and the risk of ASCVD as well as all-cause mortality ($P < 0.001$).²⁸ A meta-analysis including 221,287 individuals found that geometric mean levels of hs-CRP varied significantly among racial groups, even after adjusting for age and body mass index: 2.60 mg/L (95% confidence interval [CI], 2.27–2.96) in Blacks; 2.51 mg/L (95% CI, 1.18–2.86) in Hispanics; 2.03 mg/L (95% CI, 1.77–2.3) in Caucasians; and 1.01 mg/L (95% CI, 0.88–1.18) in East Asians.²⁹ Persistent residual inflammatory risk during GDMT (maintained hs-CRP ≥ 2 mg/L by serial measurements) was significantly associated with the higher rate of recurrent atherothrombotic events following PCI.^{22,30} In PCI cohorts, Korean patients had a lower prevalence of this phenotype compared with American individuals (18.3% vs. 36.5%).

Table 1. Racial differences in atherothrombotic CV risks^{2,24,25}

Factors	Racial difference	Component
Lipid profile		
High LDL-cholesterol	Hispanics = Caucasians > East Asians > Blacks	Atherosclerosis
Low HDL-cholesterol	Hispanics > Caucasians $\geq$ East Asians > Blacks	Atherosclerosis
High triglyceride	East Asians > Hispanics > Caucasians > Blacks	Atherosclerosis
Lipoprotein (a) level	Blacks > Caucasians > Hispanics > East Asians	Atherosclerosis
Inflammation		
CRP level	Blacks > Hispanics > Caucasians > East Asians	Inflammation
Platelet		
Platelet count	Blacks > Hispanics > Caucasians	Hemostasis
Regulation of Gq pathway after PAR-4 stimulation	Blacks > Caucasians	Platelet activation
Response to clopidogrel	Caucasians = Hispanics > Blacks > East Asians	Antiplatelet effect
Response to ticagrelor	East Asians > Caucasians = Hispanics > Blacks	Antiplatelet effect
Coagulation		
Factor V Leiden mutation	Caucasians (~5%) > Blacks (~1.5%) > Hispanics = Asians	Coagulant activity
Prothrombin G20210A mutation	Caucasians (2–5%) > Blacks = Hispanics = Asians	Coagulant activity
Von Willebrand factor level	Blacks > Caucasians = Hispanics $\geq$ East Asians	Endothelial adhesion factor
Fibrinogen, factor VII and VIII, and thrombin levels	Blacks $\geq$ Caucasians = Hispanics $\geq$ East Asians	Coagulant activity
D-dimer level	Blacks > Caucasians = Hispanics > East Asians	Prothrombotic and hypofibrinolytic state
Anticlotting activity		
Effect of activated protein C	Asians = Hispanics $\geq$ Blacks > Caucasians	Anti-coagulant activity
PAI-1 level	Caucasians > Hispanics > East Asians $\geq$ Blacks	Anti-fibrinolytic activity

This table was modified from the original version.²

CV = cardiovascular; LDL = low-density lipoprotein; HDL = high-density lipoprotein; CRP = C-reactive protein; PAR = proteinase-activated receptor; PAI-1 = plasminogen activator inhibitor-1.

- 3) Platelet count and function: Platelet counts and functions are significantly associated with the risks of ASCVD and related mortality. Significant differences exist in platelet count and function among different racial groups. Blacks were found to have significantly higher platelet counts compared to Caucasians, with Hispanic Americans displaying intermediate levels, even adjusted with age and sex.³¹ Platelet gene polymorphisms might contribute to the observed variability in platelet reactivity, which appears to differ by race. For instance, platelet aggregation triggered by the PAR-4 receptor agonist was markedly higher in Blacks than in Caucasians.³² Moreover, Blacks had a higher incidence of high on-treatment platelet reactivity (HPR) and showed diminished responsiveness to aspirin and P2Y₁₂ inhibitors relative to Caucasians,³³ potentially explaining the poorer clinical outcomes observed following coronary stenting.³⁴
- 4) Coagulation: Significant differences in coagulation exist among different racial groups. Factor V Leiden and prothrombin G20210A are the most common single nucleotide polymorphisms associated with inherited thrombophilia.⁴ Factor V Leiden hinders the normal binding of activated protein C to Factor V, leading to a state of increased coagulation. This allele is found in approximately 5% of Caucasians, about 1.5% of African Americans, and is almost not existent in Asians. The Prothrombin G20210A mutation occurs in 2–5% of Caucasians, but is rare in other racial groups. Additionally, African Americans tend to have higher levels of von Willebrand factor, factor VIII, thrombin generation, and D-dimer compared to other groups. In contrast, East Asians exhibit the lowest levels of fibrinogen, factor VIII, and D-dimer when compared to individuals from other ethnic groups.^{35,36} The levels of fibrinogen and D-dimer are closely related to the increased risk of atherothrombotic events in patients with ACS or COVID-19 infection.^{37,38}
- 5) Anticoagulant and fibrinolytic activity: There is a limited evidence to compare fibrinolytic activity among different racial groups. There are several studies that have identified lower levels of circulating proteins C and S in Blacks.³⁹ In a registry study, plasminogen activator inhibitor-1 value varied significantly among the races, with the order being Caucasians > Hispanics > Blacks ($P < 0.0001$).⁴⁰

RACIAL DIFFERENCES IN GLOBAL HEMOSTASIS PROCESS

Hemostasis is a meticulously regulated process that encompasses approximately 80 biochemical reactions, involving both cellular elements and plasma proteins. Furthermore, routine coagulation tests and specific biomarkers predominantly concentrate on specific pathways, overlooking the interplay between cellular elements and plasma proteins. Global hemostatic assays are capable of reflecting the interactions among these factors, providing a more accurate process of intrinsic hemostatic capacity.⁴¹

The absence of reliable laboratory tests for measuring the clot formation-lysis process may result in an underestimation of its impact on clinical prognosis. To address this issue, several candidate assays for global hemostasis process are currently available, which utilize native whole blood (e.g., thromboelastography [TEG], rotational thromboelastometry [ROTEM], or global thrombosis test [GTT]) or plasma.⁴¹ The TEG assay employs citrated whole blood to assess clot formation under a low-shear rate, while the GTT utilizes a non-anticoagulated blood sample under a high-shear rate.

The TEG assay is an ex vivo whole blood test that measures the dynamic viscoelastic properties of a clot, covering stages from initial plasmatic thrombin generation, through

platelet-fibrin-dependent clot formation and strengthening, to clot lysis.^{23,42,43} Platelet-fibrin clot strength (PFCS: maximal amplitude [MA] measured by TEG) is considered to be an indicator for the absolute strength of the final hemostatic plug, which reflects the dynamic properties of fibrin, platelet number, and their functional status. In addition, the percentage of the clot that has lysed 30 minutes after the MA (LY₃₀ by TEG) indicates the level of fibrinolytic activity. A Korean PCI registry compared TEG indices and their prognostic implications between acute myocardial infarction (AMI) and non-AMI patients (n = 2,705).⁴² Index AMI presentation was associated with the levels of PFCS (per 1-mm increase: odds ratio [OR], 1.024; 95% CI, 1.013–1.036; *P* < 0.001) and LY₃₀ (per 1% increase: OR, 0.934; 95% CI, 0.893–0.978; *P* = 0.004). The combined phenotype of ‘MA ≥ 68 mm’ and ‘LY₃₀ < 0.2%’ was a major predictor of post-PCI atherothrombotic events in the AMI group (adjusted hazard ratio [HR], 1.744; 95% CI, 1.1352–6.79; *P* = 0.011), but not in the non-AMI group (adjusted HR, 1.031; 95% CI, 0.499–2.129; *P* = 0.935). In another subanalysis, ‘MA ≥ 68 mm’ showed the similar prognostic implication compared with HPR (> 208 P2Y12 reaction unit [PRU] measured by VerifyNow assay), which showed an additive effect for clinical outcomes.⁴³

Meanwhile, the GTT assay is an automated, point-of-care method that assesses thrombus formation and lysis using a non-anticoagulated blood sample.⁴¹ This technique relies solely on a high-shear rate as the thrombogenic stimulus, without the addition of any platelet agonists or pro-coagulants. The blood sample is exposed to high shear, prompting the formation of an occlusive thrombus (measured as ‘occlusion time’ [OT]). This process, along with the spontaneous resumption of flow, is detected by a photosensor (measured as ‘lysis time’ [LT]). LT value was highly predictive of recurrent major adverse CV events (MACEs) (LT ≥ 2,500 seconds: HR, 9.1; 95% CI, 5.29–15.75; *P* < 0.001), driven by CV death (HR, 18.5; 95% CI, 7.69–44.31; *P* < 0.001) and MI (HR, 6.2; 95% CI, 2.64–14.73; *P* < 0.001) despite primary PCI and dual antiplatelet therapy (DAPT) in patients with ST-segment elevation MI (STEMI).⁴⁴

Racial difference in TEG indices

Several studies have compared the TEG indices across the races. In patients with known or suspected CAD on clopidogrel therapy (n = 924), African American patients showed greater level of PFCS than European Americans (67.8 ± 7 vs. 66.4 ± 6 mm, *P* = 0.005).⁴⁵ In age- and sex-matched East Asian vs. Caucasian patients with stable CAD (n = 249 each), TEG measurement demonstrated lower clot strength (MA: 61.8 ± 7.9 vs. 65.4 ± 5.0 mm, *P* < 0.001) and greater clot lysis (LY₃₀: 1.6 ± 7.5% vs. 0.5 ± 3.7%, *P* = 0.042).²³ ‘High PFCS’ (MA ≥ 68 mm) was significantly associated with 3-year MACE rate (OR, 6.27; 95% CI, 2.41–16.30; *P* < 0.001), which incidence was lower in East Asians than Caucasians (OR, 0.50; 95% CI, 0.27–0.93; *P* = 0.028). Taken together, Blacks exhibit the highest and the East Asians exhibit the lowest thrombogenic tendency, which may explain in part the racial disparity in clinical outcomes among CAD patients (Table 2).

Table 2. Global hemostasis assay according to the races^{23,45,46}

Factors	Interpretation	Racial difference
Thromboelastography		
Platelet-fibrin clot strength (MA)	Global thrombotic potential	Blacks > Caucasians > East Asians
Clot lysis (LY ₃₀)	Endogenous fibrinolysis activity	East Asians ≥ Caucasians
Global thrombosis test		
Occlusion time	Inverse indicator of thrombosis formation	East Asians > Caucasians
Lysis time	Inverse indicator of endogenous fibrinolysis	East Asians ≥ Caucasians

MA = maximal amplitude; LY₃₀ = the percentage of the clot that has lysed 30 minutes after the maximal amplitude.

Racial difference in GTT indices

A collaborative AMI cohort ($n = 515$) showed that East Asian showed longer OT (646 [interquartile range {IQR}, 470–818] vs. 436 seconds [IQR, 320–580], $P < 0.001$) without definite difference in LT (1,735 [IQR, 1,238–2,669] vs. 1,542 [IQR, 1,171–2,160], $P = 0.052$) compared with Caucasians.⁴⁶ LT value ($> 2,731$ seconds) was a strong independent predictor of MACE after adjustment for risk factors (adjusted HR, 3.70; 95% CI, 1.43–9.57; $P = 0.007$), predominantly in Caucasian patients and more so in STEMI patients.

RACIAL DIFFERENCES IN BLEEDING RISK AND PHARMACOKINETICS

East Asians have a higher tendency towards major bleeding compared to Caucasians.^{1,2} The prevalence of *Helicobacter pylori* infection, related with chronic inflammatory process, is higher in East Asians (50–70%) compared to Caucasians (30–50%). Similarly, intracranial atherosclerosis and poststroke hemorrhagic transformation are more common among East Asians than Caucasians (30–50% and 15–30%, respectively). These inherited conditions can contribute to the increased rates of gastrointestinal (GI) bleeding and intracranial hemorrhage (ICH) during antithrombotic therapy among East Asian population.

Following the introduction of a specific antithrombotic agent, East Asian patients may experience a diminished reduction in ischemic events and an increased risk of bleeding, which could influence the optimal potency and duration of DAPT. This observation can be partly explained by variations in the concentrations of active metabolites between different racial groups during P2Y₁₂ inhibitors (**Table 3**).⁴⁷ East Asians exhibit 30% to 47% higher levels of prasugrel's active metabolites compared to Caucasians. Similarly, the exposure to ticagrelor and its major active metabolite (AR-C124910XX) is increased by approximately 40% and 48%, respectively, in East Asians as opposed to Caucasians. Furthermore, each direct oral anticoagulant (DOAC) demonstrates variable pharmacokinetic profiles based on ethnicity.¹ The active metabolites of dabigatran and rivaroxaban are approximately 20% to 30% higher in Japanese individuals compared to Caucasians. Apixaban exhibits similar plasma concentrations in both Japanese and Caucasian populations. Conversely, during edoxaban therapy, the trough concentration and anti-factor Xa activity are 20% to 25% lower in Asians. Similar to antiplatelet therapy, Asian patients experience a higher incidence of major bleeding events and ICH, even at relatively low concentrations of DOACs, compared to non-Asians.⁴⁸

A recent meta-analysis, which included 2 randomized controlled trials (RCTs) from East Asian participants ($n = 17,003$) and 9 RCTs from Western participants ($n = 117,467$), compared the clinical effects of low-dose aspirin for primary prevention.⁴⁹ The treatment with aspirin demonstrated a similar effect in reducing the MACE rate (relative risk [RR] for East Asians,

Table 3. Pharmacokinetic profile: concentration of active metabolites of antithrombotic regimens in East Asians vs. Caucasians

P2Y ₁₂ receptor inhibitors		Direct oral anticoagulants	
Clopidogrel	↓↓	Dabigatran	↑ (20–30%)
Prasugrel	↑↑ (30–47%)	Rivaroxaban	↑ (20–30%)
Ticagrelor	↑↑ (40–48%)	Apixaban	=
		Edoxaban	↓ (20–25%)

This table was modified from the original version.^{1,2}

0.87; 95% CI, 0.71–1.05; RR for Westerners, 0.90; 95% CI, 0.85–0.95) with no significant interaction between the populations ($P_{\text{interaction}} = 0.721$). In contrast, the risk of major bleeding during aspirin vs. control treatment was significantly higher in East Asian population (RR, 2.48; 95% CI, 1.86–3.30) compared with Western population (RR, 1.45; 95% CI, 1.26–1.66) ($P_{\text{interaction}} = 0.001$), which was mostly driven by a higher frequency of GI bleeding in East Asians (RR, 3.29; 95% CI, 2.26–4.80) vs. Westerners (RR, 1.56; 95% CI, 1.29–1.88) ($P_{\text{interaction}} < 0.001$). In terms of clinical evidence for secondary stroke prevention, aspirin treatment resulted in approximately 0.2%/year incidence of hemorrhagic stroke in Western trials, whereas in East Asian population, this rate was about 1.0%/year during aspirin therapy.⁵⁰

In CAD patients treated with PCI, the duration and potency of DAPT should be determined by weighing clinical efficacy against the bleeding risk. The distinct balance between ischemic benefit and bleeding risk in East Asian patients may influence the optimal DAPT strategy. A meta-analysis that included PCI-treated patients (7 RCTs, $n = 16,518$) suggested differing levels of ischemic and bleeding rates between aspirin monotherapy and DAPT.⁵¹ Ischemic events were more frequent in Western patients (1.8% vs. 0.8%, $P < 0.001$), while major bleeding events were more common in East Asians (0.6% vs. 0.3%, $P < 0.001$). Additionally, the proportion of patients with a higher likelihood of bleeding than experiencing ischemia during DAPT was significantly greater in East Asian compared to Western patients (32.3% vs. 0.4%, $P < 0.001$).

“EAST ASIAN PARADOX”: TAILORED ANTITHROMBOTIC STRATEGY ACCORDING TO ATHEROTHROMBOTIC CV RISKS

The concept of the “East Asian Paradox” was initially described to illustrate the racial differences in therapeutic window of platelet reactivity during clopidogrel therapy, which may be related with different response to clopidogrel and a low risk of ischemic event following PCI in East Asian patients.^{6,52} Following, the distinctive trait of East Asian populations regarding the ischemia-bleeding trade-off has been noted with newer antithrombotic treatments, including potent P2Y₁₂ inhibitors and DOACs. An updated consensus document has evolved this concept towards crafting a precision medicine of antithrombotic strategy according to ‘atherothrombotic CV risks’ in East Asians.¹ This observation can be explained by varying pharmacodynamic profiles of antithrombotic agents (**Table 3**), the limited efficacy in reducing ischemic events, and an increased risk of serious bleeding in East Asian population receiving antithrombotic treatment.

Therapeutic range of antiplatelet effect

Among high-risk ASCVD patients (e.g., PCI cohort), East Asians have demonstrated the best clinical outcomes, followed by Hispanics and Caucasians with similar levels, with Blacks experiencing the worst outcomes. A pooled database of 10 RCTs ($n = 22,638$) evaluated the race-based differences in ischemic endpoints (death, MI and ischemia-driven revascularization) among PCI-treated patients.³⁴ The 5-year MACE rates were found to be 18.8% in Caucasians, 23.9% in Blacks, 21.5% in Hispanics, and 11.2% in Asians. A multivariate analysis indicated a significant independent association between Black race and MACE risk (HR, 1.28; 95% CI, 1.05–1.57; $P = 0.01$).

The criteria for platelet reactivity in ischemic and bleeding events are established to weigh ischemic and bleeding risks among CAD patients during antiplatelet therapy.⁵³ Therefore, the cutoffs for HPR and low platelet reactivity (LPR) may vary dynamically based on the disease entity and its phase, the PCI complexity, intrinsic bleeding risk, and ethnicity. Western consensus document proposed the cutoffs based on clinical outcomes from Caucasian patients, indicating a HPR of 208 PRU and a LPR of 85 PRU measured by VerifyNow assay.^{53,54}

Clinical evidence indicates that East Asian patients have higher HPR cutoffs, ranging from 252.5 to 289 PRU, compared to those established for Caucasian patients.¹ The PTRG-DES (Platelet Function and genoType-Related Long-term progGosis in DES-treated Patients) consortium is a coalition composed of multi-center, real-world registries including CAD patients treated with drug-eluting stent in South Korea (n = 13,160) enrolled between July 2003 and August 2018.⁵⁵ In multivariable analysis that included the results from VerifyNow assay, 'PRU $\geq$ 252' was identified as the optimal cutoff, which was strongly related to atherothrombotic events (HR, 1.39; 95% CI, 1.11–1.74; $P = 0.003$) and all-cause death (HR, 1.42; 95% CI, 1.04–1.94; $P = 0.026$) at 5 years after PCI.⁵⁶ Moreover, the LPR thresholds in East Asians were found to be higher than those for Caucasians, ranging from 110 to 139 PRU during DAPT with thienopyridine treatment.^{57–59}

East Asian population, when compared to Caucasian population, exhibits a greater resistance to atherothrombotic events at similar levels of platelet reactivity but are more prone to bleeding (Fig. 3). Therefore, it has been proposed that a specific therapeutic target for antiplatelet effect may be adopted for a better clinical outcome.

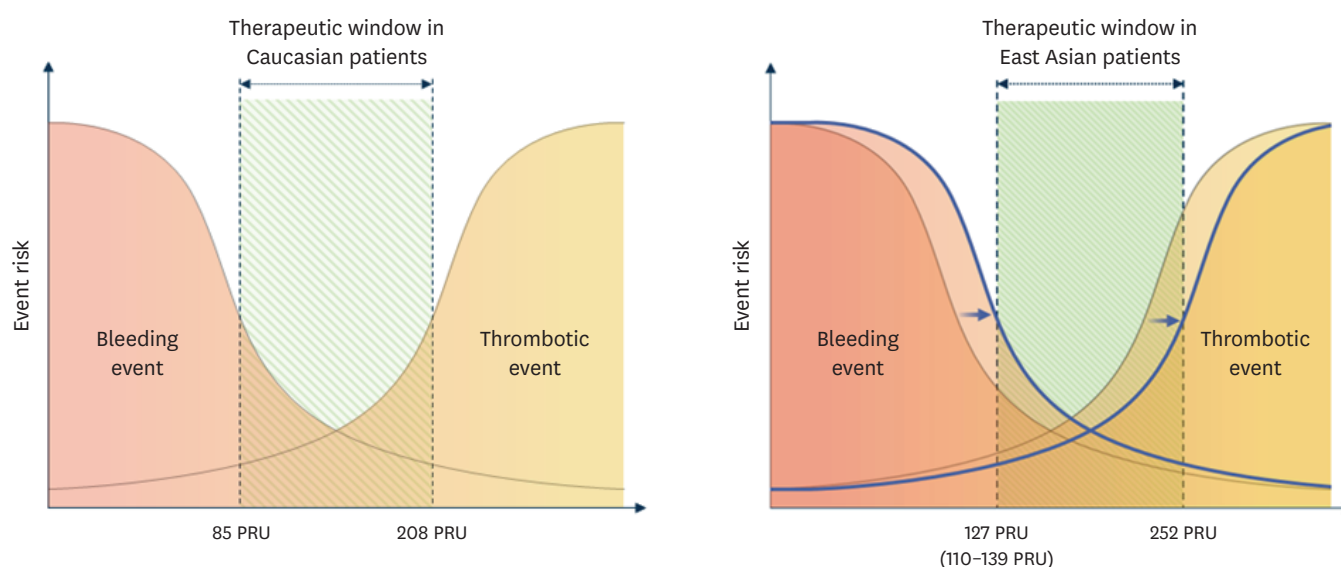


Fig. 3. Postulated therapeutic range of platelet reactivity during thienopyridine: Caucasian vs. East Asian patients.^{53–59} Left and right borders of therapeutic window indicate the cutoffs of LPR and HPR. The Caucasian criteria of LPR and HPR were derived from the expert consensus⁵³ and the ADAPT-DES (Platelet reactivity and clinical outcomes after coronary artery implantation of drug-eluting stents) trial.⁵⁴ The HPR criteria of East Asians was derived from the PTRG-DES (Platelet Function and genoType-Related Long-term progGosis in DES-treated Patients) consortium,^{55,56} and the LPR criteria was suggested from the evidence from multiple clinical registries.^{57–59}

PRU = P2Y12 reaction unit measured by VerifyNow P2Y12 assay; LPR = low platelet reactivity; HPR = high platelet reactivity.

De-escalation or abbreviation of DAPT

For ACS patients undergoing PCI, conventional DAPT strategy includes aspirin and a potent P2Y₁₂ inhibitor (either prasugrel or ticagrelor) for 12 months. While effective in reducing ischemic risk, this regimen also significantly increases the risk of bleeding. Strategies to mitigate this bleeding risk include the de-escalation of DAPT intensity, by switching from a potent P2Y₁₂ inhibitor at conventional dose of clopidogrel or a reduced dose of prasugrel, or shortening the duration of DAPT. An expert consensus statement recommended that these strategies may reduce bleeding rate without an increase in ischemic events in patients with a high-bleeding risk, particularly in those without high-ischemic risk.⁶⁰ Considering the unique balance between efficacy and safety in East Asian patients, the optimal potency and duration of DAPT for achieving a better clinical outcome may be different for East Asians compared to Western subjects.

East Asian population shows increased levels of pharmacokinetic and pharmacodynamic profiles when receiving a potent P2Y₁₂ inhibitor (**Table 3**). A standard-dose of prasugrel or ticagrelor in East Asians achieved much potent antiplatelet effect and showed a high prevalence of LPR (50–85%),^{58,59,61} which was significantly associated with the increased bleeding rate. A meta-analysis including 23 RCTs demonstrated the different balance between ischemic and bleeding events during the reduction of DAPT intensity or duration compared with conventional DAPT (**Fig. 4**).⁶² In Caucasians, reduced DAPT intensity

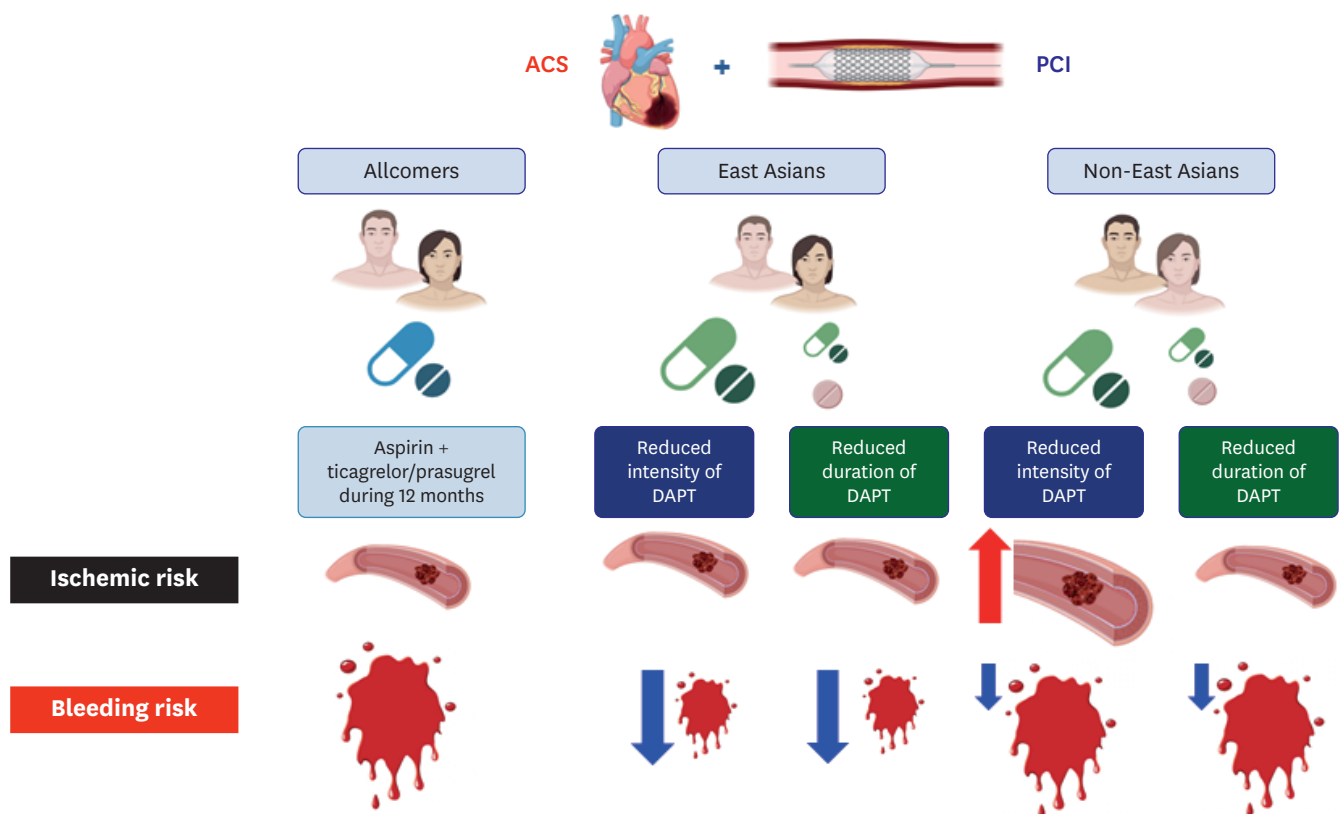


Fig. 4. Clinical benefit of de-escalation or abbreviation DAPT strategy between East Asian vs. Western patients presented with ACS. Following PCI in patients presented with ACS, guideline-DAPT comprises aspirin plus standard-dose of ticagrelor/prasugrel for 12 months. Reduction of DAPT intensity or duration in East Asian patients significantly reduced the risk of bleeding without safety concerns. In non-East Asians, reduction of DAPT intensity could increase an ischemic risk, while abbreviated DAPT strategy had no overall benefit. This figure was modified from the original version.⁶² DAPT = dual antiplatelet therapy; ACS = acute coronary syndrome; PCI = percutaneous coronary intervention.

increased MACE (OR, 1.20; 95% CI, 1.09–1.31; $P < 0.0001$) without impacting bleeding; while in East Asians, it reduced major bleeding (OR, 0.71; 95% CI, 0.53–0.95; $P = 0.02$) without affecting MACE. Abbreviation of DAPT duration did not impact MACE, or major bleeding in Caucasians, while this strategy reduced major bleeding (OR, 0.60; 95% CI, 0.40–0.91; $P = 0.02$) without impacting MACE in East Asians. Taken together, de-escalation of DAPT intensity, or shortening DAPT duration can be a default strategy in East Asian patients presenting with ACS during a standard-dose of potent P2Y₁₂ inhibitor, particularly after the acute phase (~1 month post-PCI).

Adjunctive anticoagulant treatment

In patients with atrial fibrillation (AF), DOACs are preferred over warfarin. However, Asian patients on identical DOAC doses have shown a relatively higher risk of ICH compared to non-Asian patients.⁴⁸ Moreover, DOACs exhibit different pharmacokinetic profiles in East Asians vs. Caucasians (**Table 2**). Similar to the effects of P2Y₁₂ inhibitors, Asian patients exhibit an increased risk of major bleeding and ICH at relatively lower DOAC concentrations compared to non-Asian counterparts.⁵⁰

The number of AF patients for high-risk CAD is on the rise. In these cases, a combination therapy that includes both a DOAC and antiplatelet mono-therapy becomes popular. Western guidelines recommend a full-dose of DOAC in AF patients undergoing PCI, whereas East Asian patients have been treated with a reduced-potency of anticoagulants.¹ In the AFIRE (Atrial Fibrillation and Ischemic Events With Rivaroxaban in Patients With Stable Coronary Artery Disease) trial, 54% of the patients were treated with 15-mg rivaroxaban and 46% with 10-mg rivaroxaban additive to aspirin in Japanese AF patients.⁶³ Subanalysis of the COMPASS (Cardiovascular Outcomes for People Using Anticoagulation Strategies) trial demonstrated that Asian compared with non-Asian patients with chronic CAD and/or peripheral artery disease had higher rates of ICH (0.63% vs. 0.29%, $P = 0.01$) and minor bleeding (13.61% vs. 6.49%, $P < 0.001$) during antithrombotic treatment.⁶⁴ The combination of vascular-dose rivaroxaban (2.5 mg twice a day) and aspirin vs. aspirin alone produced similar effects for MACE (Asians: HR, 0.64; 95% CI, 0.45–0.90; non-Asians: HR, 0.78; 95% CI, 0.67–0.90; $P_{interaction} = 0.29$) and major bleeding (Asians: HR, 2.24; 95% CI, 1.40–3.58; non-Asians: HR, 1.60; 95% CI, 1.30–1.97; $P = 0.20$) but higher rate of ICH (Asians: HR, 3.50; 95% CI, 0.98–12.56; non-Asians: HR, 0.81; 95% CI, 0.43–1.53; $P = 0.04$) in Asian patients. Therefore, there's a clinical need to develop the most beneficial strategy of DOAC and antiplatelet combination in terms of both dose and treatment duration for high-risk ASCVD patients.

Infection- and cancer-associated thrombosis

Infection (e.g., COVID-19) and cancer (e.g., brain, kidney, and pancreas) predispose patients to thromboembolic events (both VTE and ATE), owing to excessive inflammation, endothelial cell activation and injury, platelet activation and hypercoagulability.⁶⁵ Patients with COVID-19 and active malignancy exhibit a prothrombotic state, marked by elevated levels of thrombosis biomarkers linked to the severity and prognosis of the disease. Incidence rates of COVID- and cancer-associated coagulopathy/thrombosis vary across the racial groups, with a higher incidence in Black patients and lower incidence in East Asians.^{66–68} Blacks have worse clinical outcomes related with COVID-19 infection than Caucasians and Asians, a disparity potentially attributed to social, environmental, and epigenetic factors.

While early in the pandemic, fibrinogen and D-dimer levels were identified as biomarkers for COVID-19-associated coagulopathy, a range of new biomarkers indicating thrombotic

risk in COVID-19 patients has since been discovered.⁶⁵ Activity of thrombosis-inflammation cascade and predisposition to coagulopathy varies between the races, with African Americans trending toward a more prothrombotic state. In addition, race-based differences in circulating inflammatory markers, which may contribute to cancer-associated thrombosis risk, have also been noted.⁶⁹

D-dimer is extensively used as a biomarker for assessing the severity and outcomes of COVID-19 and active malignancy, with recommendations for increased antithrombotic therapy in cases of high D-dimer levels.⁶⁶ Nevertheless, D-dimer's utility in monitoring the combined coagulopathy is limited. Global hemostasis tests (e.g., TEG or ROTEM) measure the whole blood capability to make and sustain clot formation including the dynamics of coagulation, platelet function and fibrinolysis. Accumulating clinical evidence has demonstrated a hypercoagulable and hypofibrinolytic state in patients with COVID-19 infection or active malignancy.⁶⁷ In severe COVID-19 infections, the predictive capacity for VTE events was most pronounced in cases of fibrinolysis shutdown via TEG assay, identified by an LY₃₀ value of less than 0.8%, which demonstrated greater predictive value than either D-dimer or fibrinogen level.⁷⁰

Compared with Caucasians and Blacks, East Asian patients have shown decreased level of PFCS and enhanced fibrinolytic activity.²³ These unique profiles observed in East Asian population may in part explain a low incidence of thromboembolic events associated with COVID-19 and active malignancy. The variations in mortality observed in these patients may also be partially attributed to under-recognized inter-ethnic disparities in intrinsic thrombogenicity.⁶⁷ Early viscoelastic analysis of blood clots could be a key step in tailoring antithrombotic treatments to individual needs. This approach to personalized antithrombotic therapy may overcome the racial disparities regarding clinical outcomes following COVID-19 infection or active malignancy.

CONCLUSIONS

It is a widespread practice for countries to adopt Western guidelines for CV treatment, which are primarily based on the results from clinical trials involving predominantly Caucasian patients. Nonetheless, recent research has underscored racial disparities in 'residual atherothrombotic CV risks' during GDMT, revealing that Blacks tend to have the highest thrombogenic state, while East Asians exhibit the lowest thrombogenic environment.^{1,2} The aggregates of these CV risks play critical role in determining clinical outcomes across the entire spectrum of ASCVD (**Fig. 5**).⁷ Tailoring antithrombotic treatment based on individual residual CV risks could be a promising approach to optimize the balance between clinical efficacy and safety.

The 'East Asian Paradox' concept emerged from the challenges associated with DAPT in patients with high-risk CAD.^{1,6,52} In today's context, a customized antithrombotic approach that includes antiplatelet and/or anticoagulant therapies may be advisable for East Asian patients across the varied range of ASCVD. Furthermore, the use of global hemostasis assays or a comprehensive set of biomarkers that encompass 'residual atherothrombotic CV risks' could play a pivotal role in guiding precision medicine for antithrombotic treatment in the foreseeable future.⁷¹

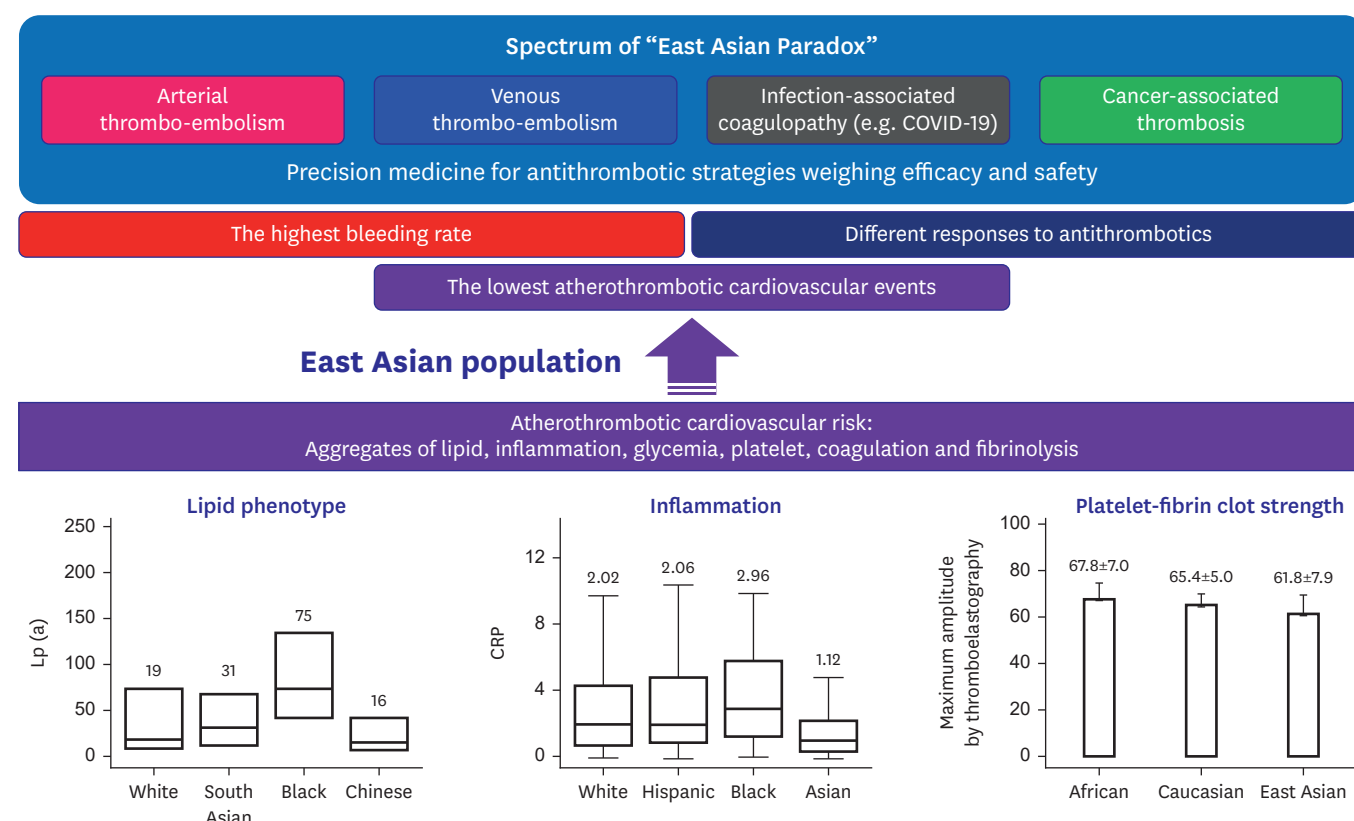


Fig. 5. Conceptual mechanism of "East Asian Paradox" and precision medicine for antithrombotic strategy in East Asian population. Accumulating evidence demonstrates that East Asian population has the lowest aggregates of atherothrombotic cardiovascular risks including lipoprotein (a) [Lp (a)], platelet-fibrin clot strength (maximum amplitude measured by thromboelastography), and inflammation (CRP), which may be associated with the lowest risk of atherothrombotic events across diverse clinical scenarios. This population also has the lowest risk of serious bleeding (mainly related with increased risk of gastrointestinal bleeding and intracranial hemorrhage), and different pharmacokinetic and pharmacodynamics profiles of antithrombotic regimens compared with other races. These observations may suggest that precision medicine for antithrombotic strategy will become possible by considering various biologic and physiologic factors together. This figure was modified from the original version.⁷

COVID-19 = coronavirus disease 2019; Lp (a) = lipoprotein (a); CRP = C-reactive protein.

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