

EDITORIAL COMMENT

Ethnicity, P2Y₁₂ Inhibitor Potency, and Bleeding

Revisiting the “East Asian Paradox”

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Bleeding complications along with residual thrombotic risk remain a principal concern of dual antiplatelet therapy (DAPT) after acute coronary syndrome (ACS), and the balance between ischemic protection and bleeding harm is not uniform across ethnic groups. The landmark PLATO (Platelet Inhibition and Patient Outcomes) trial established ticagrelor as superior to clopidogrel for ischemic prevention in ACS, albeit with more bleeding.¹ However, the predominance of White participants has long prompted questions about how well the PLATO results translate to Asian populations.^{2,3}

In this issue of *JACC: Asia*, a multiethnic database analysis from Singapore provides updated comprehensive real-world evidence regarding this issue.⁴ In approximately 15,000 ACS patients undergoing revascularization, ticagrelor use was associated with significantly higher rates of clinically relevant bleeding (adjusted HR: 1.20; 95% CI: 1.02-1.40; $P = 0.022$) and Bleeding Academic Research Consortium type 3 bleeding (adjusted HR: 1.33; 95% CI: 1.04-1.69; $P = 0.023$) compared with clopidogrel.⁴ This excess risk emerged within the first month after discharge and persisted during the first year. A key contribution of this analysis is ethnicity-specific evaluation of bleeding risk. Although the higher

bleeding risk with ticagrelor was a uniform finding, the magnitude of risk varied across ethnicities. The largest subgroup, Chinese patients (~60%), had elevated bleeding odds with ticagrelor that were similar to those observed in Malay patients (South-east Asians; ~15%). By contrast, Indians (South Asians; ~15%) had comparatively lower bleeding odds compared with Chinese (adjusted OR: 0.71; 95% CI: 0.61-0.86; $P = 0.001$), although heterogeneity within this latter category makes firm conclusions difficult. The persistent high bleeding signal among Chinese patients is concordant with prior reports of an “East Asian paradox,”^{2,3} whereas the reduced bleeding risk in Indian patients argues against treating “Asian” populations as a single category in net clinical benefit calculations. In addition, age ≥ 65 years and higher comorbidity burden were independently associated with high bleeding risk (HBR). Even among ACS populations, antiplatelet intensity, including potency and duration, should reflect the HBR phenotype and ethnic background.

These results align with, and further refine, the “East Asian paradox,” whereby East Asian patients have lower ischemic event rates but higher bleeding risk during antithrombotic therapy.²⁻⁴ The Singapore study’s observations mirror a randomized clinical trial for Korean ACS patients, which revealed higher major bleeding on ticagrelor than on clopidogrel with no mortality benefit.⁵ Proposed mechanisms include a less thrombogenic milieu (eg, lower baseline inflammation and coagulation activity), distinctive pharmacodynamic profiles of P2Y₁₂ inhibitors, and a heightened bleeding propensity (eg, lower body weight, unique vascular and anatomopathologic characteristics) in East Asian patients compared with other ethnicities.^{2,3} These factors amplify bleeding risk under intensified antiplatelet therapy without a proportional reduction in ischemic events among East Asians.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors’ institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the [Author Center](#).

TABLE 1 East Asians vs South Asians: Cardiovascular Risk, Biomarkers, and Clinical Implications		
	East Asians	South Asians
Baseline ASCVD burden	Generally lower ASCVD burden and better clinical outcomes than Westerners	Higher and earlier ASCVD burden than Europeans; not fully explained by traditional risk factors
Metabolic profile	Lower BMI on average; diabetes prevalence rising but regional variation	More diabetes, central adiposity, insulin resistance at younger ages
Lipid profile	LDL-C similar or lower than Western comparators Higher HDL-C Higher triglyceride Lower Lp(a): Chinese < Malays < Indians	"Atherogenic dyslipidemia" High ApoB at a given LDL-C Lower HDL-C Lower triglyceride More small, dense LDL at similar LDL-C Elevated and prognostically important Lp(a)
Coagulation-inflammation	Lower inflammation Lower fibrinogen Normal fibrinolysis	"Prothrombotic biology" Higher inflammation Higher fibrinogen Impaired fibrinolysis (↑ PAI-1)
Antiplatelets	Clopidogrel: lower response due to higher prevalence of CYP2C19 LoF allele (~65%) Ticagrelor/prasugrel: enhanced pharmacodynamic profile than Westerners	Clopidogrel: substantial prevalence of CYP2C19 LoF allele (UK British-South Asian cohort: 57%) Ticagrelor/prasugrel: limited data
Ischemic outcomes in ACS	Lower ischemic event rates than Westerners at a given platelet reactivity ("East Asian paradox")	Greater ischemic risk rates than Europeans; need to ensure adequate platelet inhibition and aggressive risk control
Bleeding on antithrombotic agents	Higher bleeding propensity on potent P2Y ₁₂ inhibitor; benefit/risk often favors de-escalation/short DAPT Higher ICH risk during warfarin DOACs mitigate but do not eliminate gap	No clear excess vs Whites reported; evidence thinner Lower bleeding than East Asians when matched for clinical factors
Clinical considerations	Emphasize bleeding risk mitigation Early de-escalation or abbreviated DAPT when appropriate	Aggressive atherosclerosis risk reduction: tight glucose and BP control, and Lp(a) testing Adequate platelet inhibition with conventional DAPT therapy
Evidence gaps	Stronger clinical evidence base	Sparse, heterogeneous data South Asian-specific clinical studies are needed

ACS = acute coronary syndrome; ApoB = apolipoprotein B; ASCVD = atherosclerotic cardiovascular disease; BMI = body mass index; BP = blood pressure; CYP = cytochrome P450; DAPT = dual antiplatelet therapy; DOAC = direct oral anticoagulant; HDL-C = high-density lipoprotein cholesterol; ICH = intracranial hemorrhage; LDL-C = low-density lipoprotein-cholesterol; LoF = loss-of-function; Lp(a) = lipoprotein(a); PAI-1 = plasminogen activator inhibitor-1.

South Asian populations, particularly of Indian ancestry, have distinct risk profiles that challenge a one-size-fits-all approach to antithrombotic therapy (Table 1).²⁻⁸ South Asians have greater visceral and hepatic fat (central obesity), with earlier insulin resistance and type 2 diabetes despite lower body mass index than other groups.⁶ They exhibit a distinctive atherogenic dyslipidemia at relatively modest low-density lipoprotein cholesterol concentrations, with a higher prevalence of elevated apolipoprotein B and lipoprotein(a), both more strongly associated with atherosclerotic cardiovascular disease (ASCVD) than in many other groups. In addition, they demonstrate a proinflammatory and prothrombotic profile, characterized by higher inflammation activity and impaired fibrinolysis, which likely increases atherothrombotic risk. Reflecting distinctive pathophysiology, South Asians have earlier onset ASCVD and roughly double the burden seen in Europeans, with potentially higher long-term CVD-specific mortality even when short-term outcomes are similar.⁷ For example, in the SABRE (Southall and Brent Revisited) study, South Asians had substantially higher rates of myocardial infarction and cardiovascular mortality than Europeans,

despite lower smoking prevalence and greater statin use.⁸

Contrary to the ASCVD prevalence and prognosis, robust clinical evidence comparing bleeding risk in South Asians with that in other ethnic groups remains limited at present. The Singapore multiethnic analysis demonstrated significant interethnic differences in bleeding risk, with Chinese patients displaying relatively high susceptibility and Indian patients showing attenuation.⁴ These findings likely reflect differences in underlying biochemical characteristics (eg, thrombogenicity phenotype) and pharmacodynamic profiles during antithrombotic therapy.^{2,3} East Asian patients, including Chinese, have a high prevalence of cytochrome P450 2C19 loss-of-function alleles, which reduce clopidogrel activation and enhance the relative antiplatelet effect when switching to potent P2Y₁₂ inhibitors (eg, ticagrelor). In addition, smaller body size, lower baseline hemoglobin, and greater age-related vascular fragility in these groups contribute to a higher bleeding propensity compared with other ethnicities. Dietary factors, chronic low-grade inflammation, and a higher prevalence of hypertension may further modulate bleeding risk. Conversely,

the attenuated bleeding risk observed in Indian patients within the same geographic and health care context underscores the need for ethnicity-specific risk stratification when selecting the intensity and duration of antithrombotic therapy.

Among ACS patients undergoing percutaneous coronary intervention, the conventional DAPT strategy consists of aspirin plus a potent P2Y₁₂ inhibitor (prasugrel or ticagrelor) for 12 months. Although effective at reducing ischemic events, this approach also increases bleeding risk, especially in HBR patients (eg, many East Asian patients with multiple comorbidities). Given the distinct efficacy-safety balance in East Asians, the optimal potency and duration of DAPT may differ from that in other ethnic groups.^{2,3,9} The Singapore multiethnic analysis has important clinical implications for optimizing DAPT selection in ACS patients across diverse Asian ethnicities. Because Chinese and Malay patients (East Asian and Southeast Asian groups) exhibit bleeding profiles consistent with the classic “East Asian paradox,”^{2,3} early de-escalation or abbreviated strategy from conventional DAPT therapy is supported.^{10,11} For Indian (South Asian) patients, the enhanced thrombogenic phenotype and relatively lower bleeding susceptibility may permit closer adherence to conventional DAPT therapy including a potent P2Y₁₂ inhibitor; however, current evidence is insufficient to endorse prolonged potent DAPT without further validation. The 2025 position statement for East Asians reports a high prevalence of the HBR phenotype—up to two-thirds—when Asian-specific HBR criteria (eg, low body weight) are applied.¹² Accordingly, de-escalating DAPT intensity

or abbreviating DAPT duration may be a reasonable default for East Asian ACS patients initially treated with standard-dose potent P2Y₁₂ inhibitors, particularly beyond the acute phase (1-3 months after the index event).

Taken together, the Singapore multiethnic analysis not only corroborates the “East Asian paradox”²⁻⁴ but also extends its relevance to South Asia, highlighting meaningful interethnic differences in bleeding risk. Coupled with clinical evidence of a high ASCVD burden and poor outcomes in South Asians, potent antithrombotic regimens tend to yield greater ischemic benefit relative to bleeding harm in this population. ACS care ought to adopt ethnicity-specific, risk-stratified antithrombotic approaches that optimize the ischemia-bleeding trade-off, maximizing ischemic protection and limiting bleeding.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

This work was supported by the Science Research Program funded by the Sinai Center for Thrombosis Research and Drug Development. Dr Jeong has received honoraria for lectures from Daiichi-Sankyo, Sanofi, Han-mi Pharmaceuticals, and Daewoong Pharmaceuticals; and has received research grants or support from Samjin Pharmaceuticals, Hanmi Pharmaceuticals, Yuhan Pharmaceuticals, Biotronik Korea, and U&I Corporation. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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KEY WORDS antiplatelet, bleeding, East Asia, South Asia