The "East Asian Paradox": update on the challenges to the current antithrombotic strategy

Hyun Kuk Kim[1], Udaya S. Tantry[2], Sidney C. Smith Jr.[3], Myung Ho Jeong[4], Seung-Jung Park[5], Moo Hyun Kim[6], Do-Sun Lim[7], Eun-Seok Shin[8], Duk-Woo Park[5], Yong Huo[9], Shao-Liang Chen[10], Zheng Bo[9], Shinya Goto[11], Takeshi Kimura[12], Satoshi Yasuda[13], Wen-Jone Chen[14], Mark Chan[15], Daniel Aradi[16], Tobias Geisler[17], Diana A. Gorog[18], Dirk Sibbing[19], Gregory Y. H. Lip[20], Dominick J. Angiolillo[21], Paul A Gurbel[2], Young-Hoon Jeong[22]

[1]Department of Cardiology, Chosun University Hospital, Gwangju, South Korea;
[2]Sinai Center for Thrombosis Research, Sinai Hospital of Baltimore, Baltimore, MD, USA;
[3]Division of Cardiology, University of North Carolina, Chapel Hill, NC, USA;
[4]Department of Cardiology, Chonnam National University Hospital, Gwangju, South Korea;
[5]The Heart Institute, Asan Medical Center, University of Ulsan, Seoul, South Korea;
[6]Department of Cardiology, Dong-A University Hospital, Busan, South Korea;
[7]Department of Cardiology, Cardiovascular Center, Korea University Anam Hospital, Seoul, South Korea;
[8]Division of Cardiology, Ulsan Hospital, Ulsan, South Korea;
[9]Department of Cardiology, Peking University First Hospital, Beijing, China;
[10]Cardiovascular Department, Nanjing First Hospital, Nanjing Medical University, Nanjing, China;
[11]Department of Medicine (Cardiology), Tokai University School of Medicine, Kanagawa, Japan;
[12]Department of Cardiovascular Medicine, Kyoto University Graduate School of Medicine, Kyoto, Japan;
[13]National Cerebral and Cardiovascular Center, Suita, Osaka, Japan;
[14]Cardiology Division, Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan;
[15]Department of Cardiology, National University Heart Centre Singapore, NUHS, Singapore, Singapore;
[16]Heart Centre Balatonfüred and Heart and Vascular Centre, Semmelweis University, Budapest, Hungary;
[17]Department of Cardiology and Cardiovascular Medicine, University Hospital of Tübingen, Tübingen, Germany;
[18]National Heart and Lung Institute, Imperial College, London, United Kingdom; Postgraduate Medical School, University of Hertfordshire, Hertfordshire, United Kingdom;
[19]Department of Cardiology, LMU München, Munich, Germany; DZHK (German Centre for Cardiovascular Research), partner site Munich Heart Alliance, Munich, Germany;
[20]Liverpool Centre for Cardiovascular Science, University of Liverpool and Liverpool Heart & Chest Hospital, Liverpool, United Kingdom;
[21]Division of Cardiology, University of Florida College of Medicine, Jacksonville, Florida, USA;
[22]Department of Internal Medicine, Gyeongsang National University School of Medicine and Cardiovascular Center, Gyeongsang National University Changwon Hospital, Changwon, South Korea.

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Correspondence to;

Prof. Young-Hoon Jeong

Cardiovascular Center, Gyeongsang National University Changwon Hospital

11 Samjeongja-ro, Seongsan-gu, Changwon, Gyeongsangnam-do, 51472 South Korea.

E-mail: goodoctor@naver.com

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Standfirst

East Asian patients have reduced anti-ischemic benefits and increased bleeding risk during treatment with antithrombotic therapies compared with Caucasian patients. As potent $P2Y_{12}$ receptor inhibitors and direct oral anticoagulants (DOACs) 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 document, we propose an updated strategy of antithrombotic treatment in these patients.

Historical perspective

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 events and a higher tendency of serious bleeding during antithrombotic treatment compared to Caucasians (**FIG. 1**)[1]. Clinical experiences and the unique risk-benefit trade-off of the 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 Asians -**"East Asian Paradox"**[1,2]. East Asians show attenuated response to clopidogrel compared to Caucasians, which can be in part explained by the different frequencies of the cytochrome P450 *2C19 loss-of-function allele* carriage (~65% in East Asians vs. ~30% in Caucasians)[1,2]. However, there was no increased risk of atherothrombotic events with clopidogrel treatment among East Asians vs. Caucasians[3]. On the basis of this observation, a different therapeutic window of platelet inhibition to minimize ischemic and bleeding complications in East Asian vs. Caucasian patients undergoing percutaneous coronary intervention (PCI) was proposed (**FIG. 1**)[3,LINK1].

Subsequently, expert consensus statements on antiplatelet therapy in East Asian patients were proposed in 2014[3] and 2018[LINK1], respectively. Although various 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 antithrombotic strategy to minimize complications in East Asians.

Potential underlying mechanisms of the "East Asian Paradox" (FIG. 1)

Underlying mechanisms of this phenomenon are 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 inter-ethnic disparity.

***Low ischemic risk*:** East Asians have shown a lower incidence of ischemic heart disease and a decreased risk of post-PCI atherothrombotic complications compared to Caucasians[1,3]. Virchow's triad describes major factors that contribute to thrombosis: hypercoagulability, shear stress, and endothelial dysfunction. Of these, differences in intrinsic hypercoagulability may be a crucial factor to explain the East Asian Paradox (e.g. lower coagulation and inflammation levels in East Asians vs. Caucasians)[1,2].

***High bleeding risk*:** East Asians have a greater propensity for major bleeding compared with Caucasians[4]. *Helicobacter pylori* infection, intracranial atherosclerosis (ICAS) and post-stroke haemorrhagic transformation are more prevalent among Asians, which may be associated with increased risk of gastrointestinal bleeding and intracranial haemorrhage (ICH) on antithrombotic agents[LINK1].

***Different response to antithrombotic agents*:** East Asians vs. Caucasians have shown different response to antithrombotic regimen. Most antithrombotic agents have enhanced pharmacokinetic and pharmacodynamic profiles in East Asian vs. Caucasian subjects, except for clopidogrel and edoxaban[1,3,5].

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,

therapeutic range of antithrombotic agents may be different between East Asians and Caucasians. These observations argue against East Asians following recommendations on standard antithrombotic regimens provided by guidelines in North American and Europe.

Optimal potency and duration of DAPT in East Asians

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

Based on the experiences with clopidogrel[2], East Asian consensus documents highlighted the potential risk of bleeding during standard-dose prasugrel or ticagrelor in East Asians[3,LINK1]. Subsequently, clinical evidence from registries[LINK1] and randomized trials[6] mostly supported the experts' initial recommendation[3,LINK1], with markedly increased bleeding and limited benefit in reducing ischemic events during prasugrel/ticagrelor vs. clopidogrel treatment. A recent meta-analysis (n=38,255) suggested that optimal DAPT duration can be shorter in PCI-treated East Asians[7]. Short- vs. long-term DAPT strategy significantly increased ischemic event only in non-East Asians (by 24%, $P<0.01$), while bleeding events were decreased by short-term DAPT in both ethnicities.

There is growing concern regarding patients at "high bleeding risk" [LINK1]. This concept would be more important in East Asians and numerous clinical trials are ongoing to find the best strategy for achieving the maximal net clinical benefit in East Asian countries[1, LINK1].

1. Short-term DAPT by early discontinuation of aspirin or $P2Y_{12}$ inhibitor: The TICO trial[LINK2] showed clinical benefit of ticagrelor monotherapy (following 3-month DAPT) vs. 12-month DAPT, where the difference was mainly driven by a reduced risk of major bleeding (0.2% vs. 1.6%, hazard ratio 0.13, P= 0.001).

2. A reduced-dose of potent $P2Y_{12}$ inhibitors (e.g., HOST-REDUCE-POLYTECH[LINK3]): Based on clinical trials in Japanese population, 20 mg loading followed by 3.75-mg prasugrel was used to treat Japanese ACS patients[3]. 3. Switching from potent $P2Y_{12}$ inhibitor to clopidogrel after the acute phase (e.g., TALOS-AMI[LINK4])

4. Chosing $P2Y_{12}$ inhibitor according to genetic or platelet function test (e.g., TAILOR-PCI[LINK5])

5. Selecting the groups according to risk scoring: The KAMIR-NIH DAPT score[8] was developed to guide the selection of $P2Y_{12}$ inhibitor by evaluating combined ischemic and bleeding events. The high-risk group (≥3 points: 17.8% of the cohort) showed an overall benefit from potent $P2Y_{12}$ inhibitor vs. clopidogrel from the net benefit of 1-year ischemic (8.6% vs. 17.1%, P< 0.001) and bleeding events (10.1% vs. 6.8%, P=0.073). (Would be fair to add the validation study for DAPT (doi: 10.1161/CIRCULATIONAHA.117.028924). Indeed, DAPT score still valide in East Asian, but the thrombotic events are much smaller.)

Use of direct oral anticoagulants in East Asians

Warfarin administration was associated with a substantially higher risk of ICH in Asian patients compared with Caucasian patients, impelling adoption of lower INR target (e.g., 1.6-2.5) in many

Asians patients by their responsible physicians[1]. The evidence for such a lower target INR range is not compelling [ref], and attention to improve quality of anticoagulation control (as reflected by high Time in Therapeutic Range, TTR) is crucial (ideally >70%), especially since Asian patients often have poor TTR (It is of note that TTR is influenced by target INR. TTR in East Asian country become better if INR 1.6-2.6 as target for elder patients (doi: 10.1253/circj.CJ-15-0621).). DOACs are the preferred oral anticoagulants over warfarin in patients with atrial fibrillation (AF), but ICH risk in Asian patients on DOAC is still higher than in non-Asians[1,9]. Additionally, increase of PCI-treated patients with AF and various antithrombotic combination (DOAC+antiplatelet) raise attention of care.

Each DOAC shows variable pharmacokinetic profile according to ethnicity[1,LINK1]. The active metabolites of dabigatran and rivaroxaban were about 20~30% higher in Japanese vs. Caucasians. Meanwhile, trough concentration and anti-factor Xa activity during edoxaban were 20~25% lower in Asians[5]. Similar to antiplatelet treatment, Asian patients sustain more major bleeding and ICH with relatively low DOAC concentration compared with non-Asians (**FIG. 1**)[5].

East Asian doctors widely prescribed reduced-doses of DOACs, and their clinical outcomes appeared favorable compared with warfarin[1,9]. In Taiwan's nationwide cohort study, ~90% of rivaroxaban and dabigatran, and the two-thirds of apixaban and edoxaban were prescribed with lower doses[9]. Overall, DOACs were associated with a comparable risk of ischemic events and significantly lower risk of major bleeding than warfarin. In addition, reduced-dose DOAC and/or antiplatelet therapy has been commonly prescribed in PCI-treated Asian patients with AF: the AFIRE trial used 54% of 15-mg rivaroxaban and 46% of 10-mg rivaroxaban for Japanese patients[10]. There are no randomized trials to evaluate the best combination strategy in East Asian patients with AF undergoing PCI.

Conclusions

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 $P2Y_{12}$ inhibitors and DOACs. 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 the “race-tailored antithrombotic strategies” and implement them in routine practice to minimize bleeding risk in this population.

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RELATED LINK

1. 2018 update of expert consensus statement on antiplatelet therapy in East Asian patients with ACS or undergoing PCI: https://www.sciencedirect.com/science/article/pii/S2095927318306 029?via%3Dihub

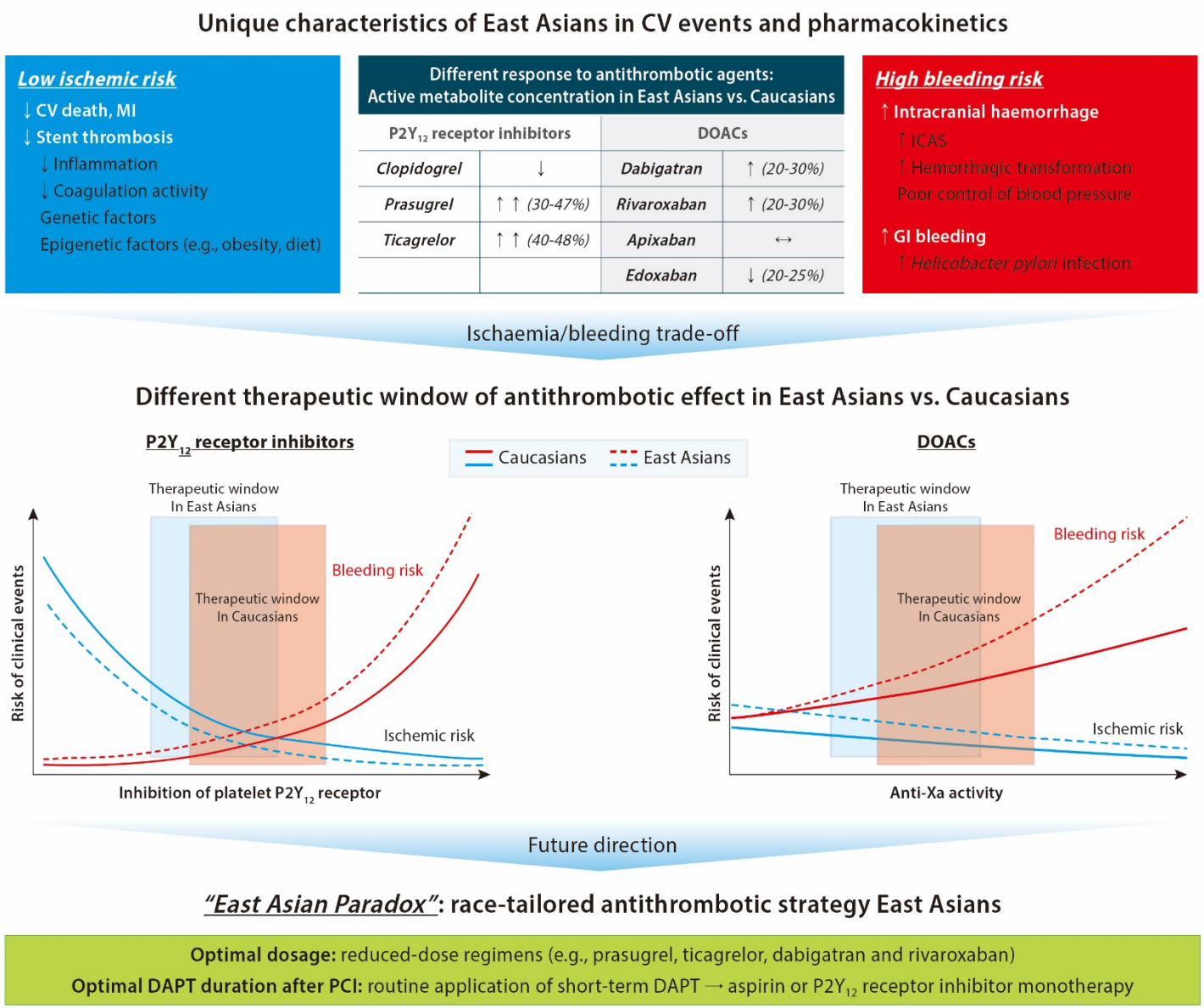
2. Harmonizing Optimal Strategy for Treatment of Coronary Artery Diseases Trial - Comparison of REDUCTION of PrasugrEl Dose & POLYmer TECHnology in ACS Patients (HOST REDUCE POLYTECH): https:// clinicaltrials.gov/ct2/show/NCT02193971

3. Tailored Antiplatelet Therapy Following PCI (TAILOR-PCI): https://clinicaltrials.gov/ct2/show/ NCT01742117

4. Ticagrelor Monotherapy After 3 Months in the Patients Treated With New Generation Sirolimus Stent for Acute Coronary Syndrome (TICO): https://clinicaltrials.gov/ct2/show/ NCT02494895

5. TicAgrelor Versus CLOpidogrel in Stabilized Patients With Acute Myocardial Infarction (TALOS-AMI): https://clinicaltrials.gov/ct2/show/results/NCT02018055

Fig. 1. Unique features of East Asian patients during antithrombotic treatment and future direction[1,3,5,LINK3]



The figures show 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[LINK1]: multifactorial mechanisms including low levels of inflammation and coagulation activity. These patients also have increased tendency for gastrointestinal (GI) and intracranial bleeding[LINK1]: possible roles of intracranial atherosclerosis (ICAS) or Helicobacter pylori infection. The active metabolite level of $P2Y_{12}$ receptor inhibitors or direct oral anticoagulants (DOACs) also differ between East Asians vs. Caucasians[LINK1]. Complex interactions between these observations can make the different therapeutic window of antithrombotic treatment among East Asian vs. Caucasian patients[3,5]. In this point, we need to adapt the race-tailored antithrombotic strategy 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.