Antithrombotic Therapy After Acute Coronary Syndromes or Percutaneous Coronary Interventions in East Asian Populations

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ABSTRACT

Because guidelines and recommendations in response to multiple randomized clinical trials (RCTs) of new therapies undergo rapid changes, antithrombotic therapies for patients after acute coronary syndrome, or percutaneous coronary intervention, are becoming more complex in daily clinical practice. The proportion of Asian populations enrolled in landmark RCTs is substantially low, which limits the direct application of trial findings into clinical practice in Asian countries. Moreover, compared with Caucasian patients, East Asian patients are considered to have a different ischemia/bleeding propensity in response to antithrombotic therapy, known as the "East Asian paradox" (i.e., more bleeding events but fewer thromboembolic events). Coincident with consecutive RCTs in Western populations to optimize antithrombotic strategies, several such studies have now been conducted in East Asian cohorts. Herein, we provide a comprehensive summary of the key RCTs in this regard and propose future directions and perspectives for optimal antithrombotic therapies in East Asian patients. (JACC: Asia 2022;2:1-18) © 2022 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Antithrombotic drugs, which include anti-platelet and anticoagulant therapeutics, are the most commonly prescribed worldwide to prevent and treat a variety of cardiovascular disorders, including coronary artery disease (CAD). Over the last few decades, numerous randomized clinical trials (RCTs) have been performed to evaluate the efficacy and safety of antithrombotic drugs and to assess different strategies in patients with acute coronary syndrome (ACS) or who had received percutaneous coronary intervention (PCI).1 Because of the rapidly changing clinical guidelines and practical recommendations following from the multiple RCTs of novel therapies or strategies, the management of antithrombotic agents for patients after ACS or PCI is becoming increasingly complex.2

East Asia is the eastern subregion of the Asian continent, where the modern states include China (including Hong Kong and Macau), Japan, Mongolia, North and South Koreas, and Taiwan, and is distinguished from other Asian ethnics such as South Asians, Indians, and Middle and West Asians.3 East Asian people comprise approximately 1.7 billion people, making up about 20.5% of the global population. A growing body of evidence now suggests that East Asians have a different risk-benefit profile for

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antithrombotic therapy compared with Western populations, the so-called “East Asian paradox.” With regard to dual antithrombotic therapy (DAPT) of aspirin and clopidogrel, a patient-level meta-analysis suggested that the ischemia/bleeding trade-off may be different between East Asian and non-East Asian patients. In addition, potent P2Y12 inhibitors including prasugrel and ticagrelor have been shown to have unique optimal therapeutic zones and different safety or efficacy profiles in East Asian patients. We herein further review the ethnic differences in the antithrombotic management of East Asian patients with ACS or undergoing PCI, principally on the basis of RCT findings, and discuss the still unmet need to establish a tailored antithrombotic strategy for East Asian patients.

**BLEEDING AND ISCHEMIC RISK IN EAST ASIAN POPULATIONS**

**BLEEDING AND ISCHEMIC PROPENSITY IN EAST-ASIAN COHORTS IN COMPARISON TO OTHER REGIONS.** Cumulative data have now indicated that there are significant race- or ethnic-based differences in thrombogenicity, platelet inhibition by P2Y12 inhibitors, the propensity for bleeding, and ischemic events. Traditionally, East Asians are identified to be more likely to experience bleeding complications, but less likely to experience thromboembolic complications in response to anticoagulation or antiplatelet therapies. Accordingly, it has been an ongoing issue over the last decade as to whether differences in the clinical efficacy and safety of antithrombotic therapy after ACS or PCI exist between East Asian patients and other ethnic groups. Secondary analysis of the CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance) trial with patients receiving aspirin and clopidogrel in multiple geographic regions has revealed that Asian populations had the lowest incidence of cardiovascular mortality, but a higher rate of bleeding events compared with other ethnic cohorts. Another prior study of the National Cardiovascular Data Registry database in the United States comprising 423,965 cases has also shown that patients of Asian ethnicity had more favorable clinical outcomes following PCI, including a lower rate of death and myocardial infarction (MI), compared with black or Hispanic patients. In the PCI era of the first-generation drug-eluting stent (DES), a lower rate of stent thrombosis (~0.4% per year) in East Asian cohorts has been observed compared with Western cohorts (~1.0% per year). A recent individual-patient level meta-analysis pooling 7 RCTs comprising a total of 16,518 patients has shown a differential bleeding or ischemic propensity in East Asian populations compared with non-East Asian patients. East Asian patients showed a higher median probability risk ratio of bleeding to ischemia (0.66 vs 0.15), and the proportion of patients with higher probability of bleeding than ischemia was significantly higher in East Asian patients (32.3% vs 4.8%, P < 0.001). Collectively, this evidence indicates that the optimal ischemia/bleeding trade-off for antiplatelet therapies is substantially different between East Asian and non-East Asian patients undergoing PCI.

**EAST-ASIAN PARADOX.** Since 2 landmark trials (ie, the CURE [Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events] and the PCI-CURE trial) of clopidogrel in early 2000, clopidogrel has become an essential P2Y12 inhibitor as a part of DAPT after ACS or PCI. Clopidogrel is a thienopyridine prodrug and its conversion to its active metabolite, R-130964, requires a 2-step cytochrome P450 (CYP)-dependent process in the liver. Because the metabolism of prodrugs can differ between individuals, mainly related to CYP2C19 polymorphisms, substantial interindividual variabilities and interethnic differences in the response to clopidogrel have been reported. East Asian patients have been found in particular to have a less profound response to clopidogrel than Caucasian patients, which is primarily attributed to a higher frequency of the CYP2C19 loss-of-function alleles in East Asian patients (~55% vs ~30%).

With such theoretical concerns, several pharmacodynamic studies have shown that the on-treatment platelet reactivity after clopidogrel was substantially higher in East Asian patients than in Western patients (40%-63.5% vs 20%-35%). In addition, as compared with non-Asian patients, different cutoff points for high on-treatment platelet reactivity in East Asian patients have been suggested. However, contrary to theoretical predictions (ie, a less robust response to clopidogrel), it has been repeatedly reported that East Asian patients have a higher rate of bleeding complications but have a similar or even lower rate of ischemic events at the same level of platelet reactivity compared with Caucasian patients. This unique phenomenon is now commonly known as the East Asian paradox, which relates to a decoupling of clinical events with the level of platelet reactivity in response to antithrombotic therapy in East Asian patients (Figure 1).
Intricate and multifactorial mechanisms may be responsible for this phenomenon. Although ethnic differences such as a lower body mass index, traditional cardiovascular risk factors, comorbidities, atherosclerotic disease patterns, and regional/environmental characteristics can influence the clinical outcomes, these factors may not completely account for ethnic differences in the response to antithrombotic therapy. It has been suggested that inter-ethnic differences in “intrinsic thrombogenicity” provide an underlying explanation for this phenomenon. Multiple lines of experimental and clinical data have revealed inter-racial differences in coagulation, fibrinolysis, and inflammation, which are the main determinants of thrombogenicity. Consistently, East Asian patients have been identified to have a lower level of intrinsic thrombogenicity than other populations. Remarkable differences in genetic polymorphisms (ie, factor V Leiden [G1691A] and prothrombin [G20210A] gene mutations), plasma hemostatic factors (ie, fibrinogen, D-dimer, and factor VIII), and endothelial activation markers (ie, von Willebrand factor, intercellular adhesion molecule 1, and E-selectin) might partly contribute to this disparity. From a clinical viewpoint, East Asian patients are also known to be more susceptible to gastrointestinal bleeding and intracranial hemorrhage compared with Caucasians. A higher prevalence of Helicobacter pylori infection, intracranial atherosclerosis, and post-stroke hemorrhagic transformation among East Asian patients may partly explain such clinical phenotypes during antithrombotic therapy. Hence, the East Asian population who are characterized with lower thrombogenicity and higher bleeding trait may have a dissimilar therapeutic window of platelet inhibition with response to antiplatelet drugs compared with other ethnic groups.

DURATION OF DAPT

After DES was introduced in early 2000, first-generation regimens appeared to be associated with a higher risk of cardiac mortality or MI, mainly because of an increased risk of late and very late stent thrombosis, compared with bare metal stents. It was found that the majority of these late thrombotic events occurred after DAPT had been discontinued. To reduce the risk of such late-occurring adverse events from the use of DES and develop more optimal DAPT protocols, multiple RCTs have been conducted worldwide. Several such trials have also been conducted in East Asian populations and are summarized in Table 1 and Figure 2. The representative REAL-LATE (Correlation of Clopidogrel Therapy Discontinuation in Real-World Patients Treated with Drug-Eluting Stent Implantation and Late Coronary Arterial Thrombotic Events)/ZEST-LATE (Evaluation of the Long-Term Safety after Zotarolimus-Eluting Stent, Sirolimus-Eluting Stent, or Paclitaxel-Eluting Stent Implantation for Coronary Lesions-Late Coronary Arterial Thrombotic Events) trial, which was the first RCT to evaluate the optimal duration of DAPT after DES, reported that an extended use of DAPT for

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![Image](98x478 to 410x651)
| Trial, Year, Country | Population | Design | Endpoints and Follow-Up | Results |
|----------------------|------------|--------|-------------------------|---------|
| REAL-LATE/ZEUS-LATE, 2010, South Korea | 2,701 patients treated with DES and free of MACCE and major bleeding for at least 12 mo | Open label, 1:1 randomized, Clopidogrel + aspirin vs aspirin alone | Primary endpoint: a composite of MI, or death from cardiac causes at 2 y | Clopidogrel + aspirin vs aspirin alone |
| RESET, 2012, South Korea | 2,117 patients treated with DES | Open label, 1:1 randomized, 3-mo DAPT vs 12-mo DAPT with aspirin and clopidogrel | Primary endpoint: cardiovascular death, MI, stent thrombosis, target-vessel revascularization, or TIMI bleeding at 1 y | 3-mo DAPT vs 12-mo DAPT |
| I-LOVE-IT 2, 2016, China | 1,829 patients treated with multiple DES | Open label, 1:1 randomized, 6-mo DAPT vs 12-mo DAPT with aspirin and clopidogrel | Primary endpoint: a composite of cardiovascular death, MI, or target lesion revascularization at 1 y | Aspirin alone vs clopidogrel + aspirin |
| IVUS-XPL, 2016, South Korea | 1,400 patients treated with DES | 2 x 2 factorial design, Open label, 1:1 randomized, 6-mo DAPT vs 12-mo DAPT with aspirin and clopidogrel | Primary endpoint: a composite of cardiovascular death, MI, or stroke at 1 y | 6-mo DAPT vs 12-mo DAPT |
| NIPPON, 2017, Japan | 3,773 ACS patients treated with DES | Open label, 1:1 randomized, 6-mo DAPT vs 18-mo DAPT | Net adverse clinical and cerebrovascular events: a composite of all-cause mortality, MI, stroke, and major bleeding from 6 to 18 mo after stenting | 18-mo DAPT vs 6-mo DAPT |
| SMART-DATE, 2018, South Korea | 2,712 ACS patients treated with DES | Open label, 1:1 randomized, 6-mo DAPT vs 12-mo DAPT | Primary endpoint: a composite of all-cause death, MI, or stroke at 18 mo | 6-mo DAPT vs 12-mo DAPT |
| SMART-CHOICE, 2019, South Korea | 2,993 patients treated with DES | Open label, 1:1 randomized, 3-mo DAPT followed by P2Y12 inhibitor monotherapy vs 12-mo DAPT | Primary endpoint: a composite of all-cause death, MI, or stroke at 1 y | 3-mo DAPT followed by P2Y12 inhibitor monotherapy vs 12-mo DAPT |
| STOP-DAPT-2, 2019, Japan | 3,045 patients treated with DES | Open label, 1:1 randomized, 1-mo DAPT followed by clopidogrel monotherapy vs 12-mo DAPT with aspirin and clopidogrel | Primary endpoint: a composite of cardiovascular death, MI, stroke, definite stent thrombosis, or TIMI major or minor bleeding at 1 y | 1-mo DAPT followed by clopidogrel monotherapy alone vs 12-mo DAPT with aspirin and clopidogrel |
more than 12 months was not significantly more effective than aspirin monotherapy in reducing the risk of MI or death from cardiac causes. Subsequent RCTs in East Asian populations treated with first-generation DES showed similar results.

The continued advancement of stent technologies with improved drug release kinetics, novel stent materials or platforms, and more biocompatible or biodegradable polymers has resulted in better clinical outcomes after second-generation DES implantation with a significant reduction in restenosis and thrombotic complications, allowing a shorter DAPT duration. Accordingly, additional RCTs have been performed in recent years to determine the minimum safe duration of DAPT after the implantation of the newer stents under various clinical conditions. Most of these trials have shown that a short-duration (3 to 6 months) was generally as effective as an extended duration of DAPT. A large body of such evidence was derived from East Asian countries including South Korea and Japan. Compared with Europe or North America, intravascular imaging (eg, intravascular ultrasound or optical coherence tomography) is used widely in East Asia, particularly in South Korea and Japan, which might contribute to favorable clinical outcomes despite the shorter-duration DAPT strategy. In addition, it was further revealed that even a 1-month DAPT strategy (vs 12-month DAPT) followed by clopidogrel monotherapy after elective PCI for mostly stable CAD patients has shown an equivalent efficacy to 12-month DAPT with respect to the primary net composite endpoint. However, the recent STOP-DAPT-2 ACS trial including only ACS presentation comprising 56% patients with ST-segment elevated myocardial infarction, which also compared 1 month of DAPT followed by clopidogrel monotherapy compared with standard DAPT post-PCI with DES, showed that a 1-month DAPT strategy did not meet criteria for noninferiority for the net composite of ischemic/bleeding events. Although major bleeding was significantly reduced with this approach, there appeared to be a significant increase in adverse ischemic events, and there was a clear signal in relation to overall mortality.

During the chronic maintenance period in patients undergoing PCI with DES, the optimal choice of antiplatelet monotherapy (aspirin or clopidogrel) is still uncertain. The recent HOST-EXAM (Harmonizing Optimal Strategy for Treatment of CAD-Extended Antiplatelet Monotherapy) trial randomized 5,438 patients receiving DAPT after coronary stenting, comparing 1-month DAPT followed by clopidogrel monotherapy vs 12-month DAPT with aspirin and clopidogrel. The primary endpoint was a composite of cardiovascular death, MI, stroke, definite stent thrombosis, or TIMI major or minor bleeding at 1 year. The trial showed that 1-month DAPT followed by clopidogrel monotherapy was non-inferior to 12-month DAPT with aspirin and clopidogrel (HR: 0.73; 95% CI: 0.59 to 0.90). However, there was a significant increase in adverse ischemic events, and there was a clear signal in relation to overall mortality.
Korean patients in whom DAPT had been maintained without clinical events for 6 to 18 months after PCI with DES (mostly second-generation) to monotherapy of either clopidogrel or aspirin. The 24-month incidence of a primary net composite of all-cause death, MI, stroke, readmission due to ACS, and BARC (Bleeding Academic Research Consortium) bleeding of type 3 or greater was significantly lower for the clopidogrel monotherapy than with the aspirin monotherapy (5.7% vs 7.7%; HR: 0.73; 95% CI: 0.59-0.90). The incidences of the secondary composite thrombotic endpoint and the cumulative incidence of any bleeding events were also consistently lower in the clopidogrel monotherapy.

In summary, a reasonable duration of DAPT and long-term antiplatelet regimens, given the current evidence favoring a short-duration DAPT and the high bleeding tendency in East Asian patients, would be 3 to 6 months even in patients with ACS. Moreover, a much shorter DAPT (ie, 1 month) could be considered...
as high bleeding risk (HBR) for patients with stable CAD in East Asia. In addition, taking into account the total body of evidence, P2Y₁₂ monotherapy with aspirin omission after a short period of DAPT would be an effective and safe strategy for lowering the risk of bleeding while preserving the ischemic benefit in East-Asian patients. For the long-term maintenance of an antiplatelet monotherapy after the intended duration of DAPT, clopidogrel is superior to aspirin in preventing future adverse clinical events, including both thrombotic issues and bleeding, in East Asian patients undergoing PCI with contemporary DES.

**POTENT P2Y₁₂ INHIBITORS**

**PIVOTAL LANDMARK RCTs OF POTENT P2Y₁₂ INHIBITORS.**

Large-scale, phase III, double-blind RCTs (TRITON-TIMI 38 [Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel-Thrombolysis In Myocardial Infarction 38] and PLATO [Platelet Inhibition and Patient Outcomes]) have shown that the use of potent P2Y₁₂ inhibitors such as prasugrel or ticagrelor as compared with clopidogrel was significantly associated with a lower risk of ischemic events but an increased risk of major bleeding events in patients with ACS.

However, the risk-benefit ratios are favorable, with a number needed to treat to prevent a primary outcome of 46 and 53, respectively, and the number needed to harm of 167 for both drugs. Consequently, U.S. and European guidelines recommend prasugrel or ticagrelor over clopidogrel for preferred antithrombotic agents for patients after an ACS. However, because the Asian subgroup of the TRITON-TIMI and PLATO trials represented only a small proportion (<10%) of the enrolled patients, a direct extrapolation of the trial findings into clinical practice for many Asian countries might be problematic. Hence, to determine the relative safety and effectiveness of potent P2Y₁₂ inhibitors in East Asian populations, various race-specific experimental studies and clinical trials have now been conducted, as outlined below.

**TICAGRELOR.**

**Pharmacokinetic/pharmacodynamic research.** An experimental study of healthy volunteers found that the level of ticagrelor and its major active metabolite (ARC124910XX) was approximately 33% to 55% higher in Japanese patients than in Caucasian patients. Similarly, a pharmacokinetic study of ACS patients reported that Asians showed 39% higher bioavailability of ticagrelor compared with Caucasians. Given that there was marked interethnic differences in intrinsic thrombogenicity, pharmacokinetic and pharmacodynamic profiles of potent P2Y₁₂ inhibitors between Asians and Caucasians, a reduced dose of ticagrelor might be more applicable in East Asian patients with ACS. In this concept, the OPTIMA (Optimal anti-Platelet Therapy In Management of Asian Patients With Acute Coronary Syndromes) trial enrolled Korean patients with ACS who were P2Y₁₂ antagonist-naïve within the past 6 months; patients were randomly assigned (1:1:1) to low-dose ticagrelor (120-mg loading dose, 60 mg twice daily), standard-dose ticagrelor (180-mg loading dose, 90 mg twice daily), or standard-dose clopidogrel (600-mg loading dose, 75 mg once daily) on top of aspirin. There was no statistical difference in P2Y₁₂ reaction unit (PRU) values between low- (60-mg) and standard-dose (90-mg) ticagrelor at any time point, whereas both ticagrelor therapies showed significantly lower mean PRU values than clopidogrel therapy. The OPTIMA trial suggests that 60 mg or even a lower dose of ticagrelor may be a potential therapeutic option for East Asian patients with ACS. Along with the key findings in the large-scaled PEGASUS-TIMI 54 (Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis In Myocardial Infarction 54) trial that a 60-mg dose of ticagrelor might offer a more attractive risk-benefit profile than a 90-mg dose, the key findings of the OPTIMA trial also suggested that low-dose ticagrelor of 60 mg might provide better safety and similar efficacy compared with standard-dose ticagrelor of 90 mg in East Asian patients with ACS. Further dose-finding studies would reveal the best-balanced dose of ticagrelor in East Asian patients, which may not be the same as the global dose; this proposed concept should be confirmed or refuted through larger, adequately powered clinical RCTs.

**Clinical evidence from RCTs.** The design features and primary results of RCTs to assess the efficacy and safety of potent P2Y₁₂ inhibitors among East Asian patients are summarized in Table 2. The PHILO (Study to Assess Safety and Efficacy of Ticagrelor Versus Clopidogrel in Asian/Japanese Patients With Non-ST or ST Elevation ACS) trial enrolled 801 Japanese, Taiwanese, and Korean patients with ACS undergoing PCI to compare the 1-year clinical outcomes of standard-dose ticagrelor (180/90 mg twice) vs clopidogrel (300/75 mg/d). The primary efficacy endpoints of death from vascular causes, MI, or stroke (9.0% vs 6.0%), and PLATO-defined major (10.3% vs 6.8%) and minor (15.2% vs 9.2%) bleeding events, had a higher incidence in the ticagrelor group than in the clopidogrel group. Similar results were observed in the TICAKOREA (Ticagrelor Versus Clopidogrel in Asian/Korean Patients With ACS Intended for
Invasive Management) trial, which evaluated the safety and effectiveness of standard-dose ticagrelor vs clopidogrel among 800 ACS Korean patients. The primary safety outcome of clinically significant bleeding (PLATO major or minor bleeding) at 12 months was significantly higher in the ticagrelor group than in the clopidogrel group (11.7% vs 5.3%, respectively). In addition, the incidences of major and fatal bleeding were also higher in the ticagrelor group. The 12-month incidence of cardiovascular death, MI, or stroke tended to be higher in the ticagrelor group than in the clopidogrel group (9.2% vs 5.8%, respectively). Overall, these trials are underpowered, but do suggest a common theme of more bleeding without benefits on ischemic events in East Asian patients receiving ticagrelor-based DAPT. The surprising trend of more ischemic cardiovascular events in both PHILO and TICAKOREA should be further reviewed. However, it remains uncertain whether the response to antiplatelet therapy in East Asian patients is different enough to justify a different dosing strategy to that used globally, and more compelling clinical evidence from an ample number of RCTs involving East Asian populations is needed.

More recently, in light of the widespread use of potent P2Y₁₂ inhibitors and the feasibility of adopting
a short DAPT duration, clinically important questions have been raised about whether aspirin use should be mandatory. Accordingly, a strategy of omitting aspirin and maintaining potent P2Y12 inhibitors after short-period DAPT has been explored in multiple consecutive RCTs. The results of 3 large trials of this nature with ticagrelor are now available, 2 from Europe and North America, and 1 from Korea. The GLOBAL LEADERS (Clinical Study Comparing Two Forms of Antiplatelet Therapy After Stent Implantation) trial tested that a 1-month short DAPT of ticagrelor plus aspirin followed by 23-months of ticagrelor plus aspirin followed by 23-months of ticagrelor monotherapy would be superior to aspirin and maintaining potent P2Y12 inhibitors after short DAPT period among patients who were at high risk for bleeding or ischemic events and had undergone PCI. This trial showed that ticagrelor-based monotherapy (3-month DAPT and then ticagrelor alone) was associated with a lower risk of clinically relevant bleeding (BARC 2, 3, or 5) without an increase in risk of death, MI, or stroke, compared with ticagrelor plus aspirin. Similarly, the TICO (Ticagrelor Monotherapy After 3 Months in the Patients Treated With New Generation Sirolimus-Eluting Stent for ACS) trial conducted in Korean multicenters with 3,056 ACS patients revealed favorable clinical outcomes of ticagrelor monotherapy after 3 months of DAPT, compared with a ticagrelor-based 12 month DAPT (Table 2). The primary composite of net adverse clinical events (ie, major bleeding and major adverse cardiac and cerebrovascular events) at 1 year was significantly lower in the ticagrelor monotherapy group. This difference was mainly driven by major bleeding events as there were no differences in the major adverse cardiac events. However, defining the primary trial endpoint in testing antithrombotics with a net clinical benefit that combines the opposite directional endpoints of bleeding and ischemic events is still problematic and summarizing these opposite endpoints with a unidimensional variable can be clinically misleading. If novel antithrombotic drugs or strategies result in improved efficacy at the expense of increased bleeding, this will tend to skew the net clinical benefit toward a null value. Furthermore, as the sample size in an RCT might not be sufficient to detect clinically relevant differences in ischemic events with a relatively low incidence, adopting a net primary endpoint that includes more frequent bleeding events can always achieve positive primary trial results with less potent antithrombotic strategy (a so-called “less is more” antithrombotic strategy). In addition, bleeding risks can be magnified by including more events in the bleeding definition or by including minor and nuisance bleeding. Hence, there is an ongoing debate regarding how to best categorize clinically relevant bleeding events and define the fair net benefit to balance the risk and benefit in a single quantitative measure. This will require further deliberation.

**PRASUGREL. Pharmacokinetic/pharmacodynamic research.** Several pharmacokinetic and pharmacodynamics studies have found that after the administration of prasugrel, the presence of the active metabolite was greater in East Asian subjects than in Caucasian patients. In a study involving healthy volunteers, East Asian subjects on a prasugrel dose of 5 mg daily showed a similar level of platelet inhibition to Caucasian subjects receiving twice that amount. In another study testing reduced dosages of prasugrel in Japanese patients with CAD undergoing PCI, the degree of platelet inhibition was higher using prasugrel 10/2.5 mg, 15/3.75 mg, and 20/5 mg than with clopidogrel (12.3%, 20.9%, 29.8% vs 8.4%, respectively). In addition, the A-MATCH (Fixed-dose vs. Phenotype-Based Prasugrel Dose to Match Therapeutic Zone in Asians With Acute Coronary Syndrome) trial compared the pharmacodynamic profiles in 255 Korean ACS patients who were randomly assigned to the fixed-dose prasugrel (10-mg vs 5-mg group) or platelet function test-guided group (1:1 fashion). After 1 month, the primary endpoint of the percentage of patients within the therapeutic window (95% CR: PRU ≤ 208) was significantly lower in the 10-mg prasugrel group compared with the 5-mg prasugrel and platelet function test-guided groups (35.3% vs 67.5% vs 65.9%, respectively). Overall, these findings indicated that a reduced dose of prasugrel may provide a more optimal therapeutic window and a lower tendency toward bleeding episodes in East Asian patients presenting with ACS.

**Clinical evidence from RCTs.** A low dose of prasugrel has been tested in several RCTs in Western and Asian populations. In the elderly or lower-weight European patients presenting with ACS, a reduced-dose prasugrel (5 mg daily) compared with the standard-dose ticagrelor (90 mg twice a day) was associated with maintained anti-ischemic efficacy while protecting these patients against the excess risk for bleeding.

In Asia, based on a pharmacodynamic study, the
PRASFIT-ACS (Prasugrel Compared to Clopidogrel for Japanese Patients with ACS Undergoing PCI) trial evaluated the efficacy and safety of a low-dose prasugrel strategy (20/3.75 mg) in comparison with standard-dose clopidogrel (300/75 mg) in 1,363 Japanese ACS patients undergoing PCI (Table 2).6,64 Prasugrel (20/3.75 mg) was associated with a low incidence of ischemic events, similar to the results of the TRITON-TIMI 38 RCT, and with a low risk of clinically serious bleeding in Japanese ACS patients. The PRASFIT-ELECTIVE (Prasugrel For Japanese Patients With CAD Undergoing Elective PCI) trial investigating reduced-dose prasugrel (20/3.75 mg) in 742 Japanese patients undergoing elective PCI also found favorable efficacy and safety outcomes of this regimen.65 On the basis of these trials, the updated 2020 Japanese guideline recommends a reduced dose of prasugrel (15/3.75 mg) as the standard regimen for ACS or PCI patients.66 Recently, the HOST-REDUCE-POLYTECH-ACS (Host-comparison of Reduction of Prasugrel Dose or Polymer Technology in ACS Patients) trial conducted in Korea tested prasugrel-based de-escalation of DAPT after PCI in 2,338 patients with ACS.69 The primary net adverse clinical events (comprising all-cause death, MI, stent thrombosis, repeat revascularization, stroke, and BARC 2 or higher bleeding) at 1 year was significantly lower in the de-escalation group (5 mg) than in the conventional group (10 mg), which was mainly driven by a reduction in bleeding events without an increase in ischemic events. In summary, based upon the cumulative evidence from RCTs conducted in Asian countries, a reduced dose (5 mg) of prasugrel may be a feasible standard or alternative strategy during initial or chronic maintenance therapy in East Asian populations after considering the risk-benefit profile.

**HIGH-RISK PATIENTS**

**PCI PATIENTS INDICATED FOR ORAL ANTICOAGULATION.** Life-long oral anticoagulation (OAC) is required for most patients with mechanical heart valves and high-risk atrial fibrillation, of whom up to 15% have concomitant CAD indicated for PCI.70 Traditionally, triple therapy with a combination of warfarin and DAPT has been used to prevent cardiac thromboembolic and coronary ischemic events in such cases. However, classical triple therapies significantly increase the risk of bleeding complications.71,72 Furthermore, concerns of bleeding complications from warfarin therapy remain, especially in the Asian population, because the risk of warfarin-related bleeding such as intracranial hemorrhage is higher in the Asian population compared with non-Asians.10

Recently, a series of RCTs evaluating triple vs double therapies with the use of direct oral anticoagulant (DOAC) have shown more favorable risk-benefit profiles of double therapy (clopidogrel plus DOAC) in terms of reducing bleeding complications with no significant increase in thrombotic events.73 It is noteworthy in these DOAC RCTs that the patients were randomized within 3 to 14 days following PCI, without prespecified antithrombotic therapy during the periprocedural period, during which triple therapy was probably given. Based on this cumulative evidence, the current U.S. and European guidelines have recommended early cessation (≤1 week) of aspirin and continuation of double therapy with DOAC and a P2Y12 inhibitor74,75; this recommendation is now widely applied in the clinic in many Asian countries. Because of the lack of head-to-head comparisons among different DOACs, there are no definitive recommendations for a specific selection of these drugs for double therapy. With respect to a specific P2Y12 inhibitor, it is plausible that clopidogrel may be the safest use with a DOAC because of the lowest bleeding risk among the P2Y12 inhibitors in accumulative evidence from extensive research.

Few RCTs to date have been conducted to determine the optimal timing of the cessation of antiplatelet agents in PCI patients receiving chronic OAC therapy. To resolve this unmet issue, 2 RCTs have been recently performed in Japan. Unfortunately, however, the OAC-ALONE (Optimizing Antithrombotic Care in Patients With Atrial Fibrillation and Coronary Stent) trial was underpowered and inconclusive because patient enrollment was prematurely terminated.76 In the AFIRE (Atrial Fibrillation and Ischemic Events With Rivaroxaban in Patients With Stable CAD) trial, a total of 2,236 patients who had undergone PCI or coronary bypass grafting more than 1 year earlier, or who had angiographically confirmed CAD, were randomized to receive DOAC (rivaroxaban 10 to 15 mg) monotherapy or rivaroxaban plus a single antiplatelet agent (either aspirin or a P2Y12 inhibitor).77 This trial was prematurely stopped because of increased mortality in the double-therapy group. Rivaroxaban monotherapy was found to be associated with a 28% reduction in the primary efficacy endpoint comprising stroke, systemic embolism, MI, unstable angina requiring revascularization, or death from any cause, and a 41% reduction in the primary safety endpoint of major bleeding.

In summary, among patients undergoing PCI that has been indicated for chronic OAC therapy, triple therapy may be warranted in the periprocedural period after PCI, followed by a double therapy of OAC (DOAC is preferable over warfarin) and a P2Y12
inhibitor. Although there remains uncertainty regarding the optimal timing for the cessation of combined antiplatelet drugs, current U.S. and European guidelines recommend life-long OAC alone without antiplatelet agents beyond 1 year, which was also supported by a recent Japanese RCT.42,44,47 Given the growing evidence for the efficacy of a shorter DAPT such as 3 to 6 months, OAC monotherapy beyond 3-6 months can be a viable option for patients with HBR. Further larger RCTs are required to establish the optimal antithrombotic regimen for East Asian patients with such complex clinical conditions.

**HBR PATIENTS.** Precise identification and proper management of patients at HBR with ACS or undergoing PCI are of major importance. Unfortunately, because patients considered HBR were either excluded from or underrepresented in prior RCTs, clinical evidence on such HBR patients is still lacking. In addition, defining the optimal management of HBR patients with ACS or undergoing PCI is the challenge because of a paucity of relevant clinical data and various or heterogeneous definitions of HBR among studies. The Academic Research Consortium for High Bleeding Risk criteria defining HBR in patients undergoing PCI, which takes into account the available evidence for HBR patients with PCI, were recently proposed through a collaboration among leading research organizations, regulatory authorities, and physician-scientists from the United States, Europe, and Asia.78 A Japanese working group has since developed a Japanese version of these HBR criteria to take account the unique characteristics of their population.79 The patient features that are not included in the Academic Research Consortium for High Bleeding Risk criteria such as lower body weight, frailty, chronic kidney disease involving dialysis, heart failure, and peripheral vascular disease were included in this Japanese version. As a sizable proportion of East Asian patients can be categorized as HBR, these new criteria may help to minimize the bleeding risk in daily clinical practice.79

HBR patients have been frequently treated using bare metal stents. Several RCTs have compared the safety and efficacy of different stent platforms (DES vs bare metal stent or different DESs) with short DAPT durations in patients undergoing PCI perceived to be at increased bleeding risk.80,81 Recently, the MASTER-DAPT (Management of High Bleeding Risk Patients Post Bioresorbable Polymer Coated Stent Implantation With an Abbreviated Versus Prolonged DAPT Regimen) study targeting HBR patients with implantation of a biodegradable-polymer sirolimus-eluting stent treated with DES showed that 1 month of DAPT was noninferior to the continuation therapy for at least 2 additional months for the occurrence of net and major adverse cardiac or cerebral events, with a lower incidence of major or clinically relevant nonmajor bleeding.82 However, because most of these trials to date have mainly been targeted at Western populations, further ethnic-specific studies are required to optimize the abbreviated DAPT duration, specific type of coronary stent, and antithrombotic strategy in East Asian patients with HBR features.

**HIGH ISCHEMIC RISK-COMPLEX HIGHER-RISK AND INDICATED-PROCEDURE PATIENTS.** Nowadays, as the elderly population is rapidly increasing and medical management for cardiovascular disease is much improving, there is a trend toward performing PCI in high-risk patients with increasingly complex lesions and procedures. Furthermore, the evolution of PCI over the last 40 years has facilitated treatment of increasingly complex and high-risk patients. Even with DAPT, the risk of adverse clinical events and ischemic complications remains unacceptably high among patients with enhanced thrombotic risk due to various clinical factors (eg, diabetes mellitus, chronic renal insufficiency, poor hemodynamic status, or left ventricular dysfunction) or angiographic factors (eg, complex CAD such as left main, multivessel, complex bifurcation, diffuse long, chronic total occlusion, and severe calcified lesions).83

To address the clinical imperatives of lowering the risk of bleeding while preserving an ischemic benefit, several therapeutic strategies to decouple thrombotic and hemorrhagic risks have been tested.59-61,65 In addition, based on extensive RCT data, the scales have now tipped toward an intensive approach to reducing thrombotic complications with an aggressive use of antiplatelet and anticoagulant agents during the initial phase of ACS or high-risk PCI. However, this benefit dissipates with time after the ACS event or when using high-risk procedures and thus subsequent management requires individualized approaches, with the benefits weighed more against the risk of bleeding events than initial thrombotic events.2 In this context, alternative DAPT regimens (ie, early escalation, late de-escalation) may be reasonable in this complex, high-risk patient subset to achieve a balance between timely sufficient platelet inhibition and an acceptable bleeding risk. Using this clinical concept, the ongoing comparison of TAILORED CHIP (Tailored Versus Conventional Antithrombotic Strategy Intended for Complex High-risk CHIP; NCT03465644) trial in Korea will yield further
insights into an optimal late de-escalation strategy, particularly for East-Asian patients (Figure 3). This trial is planned to enroll 2,000 patients with complex high-risk indicated procedure/clinical factors in Korea and designed to evaluate the efficacy and safety of tailored antithrombotic therapy of early (<6-month post-PCI) intensified (low-dose ticagrelor [120 mg loading, then 60 mg twice daily

FIGURE 3 Escalation and De-Escalation Strategies: Rationale, Proposed Strategy and Related Ongoing Trials in East Asian Populations

| Rationale | Proposed strategy | Related ongoing trial |
|-----------|------------------|-----------------------|
| PCI Day 30 | **DAPT de-escalation**<br>• P2Y12-guided<br>• Genotype-guided<br>• Non-guided | **TAILORED-CHIP Trial Design** |
| Risk | **DAPT escalation with potent P2Y12 inhibitors**<br>Aspirin or P2Y12 inhibitor monotherapy | **BARC** = Bleeding Academic Research Consortium; **CHIP** = complex high-risk PCI; **CKD** = chronic kidney disease; **EF** = ejection fraction; **LV** = left ventricle; **PFT** = platelet function test; other abbreviations as in Figures 1 and 2. |

In the early phase following percutaneous coronary intervention (PCI), intensive antithrombotic therapy is generally beneficial; however, this benefit dissipates with additional time. Hence, escalation and de-escalation antithrombotic strategies after PCI have been proposed. The left figure was adapted from Rodriguez and Har- rington. BARC = Bleeding Academic Research Consortium; CHIP = complex high-risk PCI; CKD = chronic kidney disease; EF = ejection fraction; LV = left ventricle; PFT = platelet function test; other abbreviations as in Figures 1 and 2.

TABLE 3 Developed Risk Scores for Decision-Making for DAPT in East Asian Patients

| Year of publication | Clinical use | Development data set | External validation set | Study population | Ischemic outcome | Bleeding outcome | Follow-up, y | Score system | Variable number | Variables | Range and cutoff values |
|---------------------|-------------|----------------------|------------------------|------------------|-----------------|-----------------|-------------|--------------|----------------|----------|------------------------|
| 2019                | Determination of the adequate duration of DAPT | Grand DES (Korean nationwide multicenter pooled registry of drug-eluting stents) registry (n = 13,172) | HOST-ASSURE (n = 3,755) and NIPPON trials (n = 3,773) | Stable or ACS undergoing PCI | A composite of MI or definite or probable ST | TIMI major bleeding | 3           | Net ischemia/bleeding risk | 7               | Previous MI or PCI, presentation with acute MI, stent diameter <3 mm, total stent length of ≥30 mm, older age, CKD, or creatinine clearance <60 mL/m² and anemia | -6 to 6 A higher ischemic risk ≥ 1 |
| 2018                | Predictive for both ischemic and bleeding outcomes | CREDO-Kyoto registry cohort 2 (n = 4,778) | RESET and NEXT trial (n = 4,669) | Stable or ACS undergoing PCI | A composite of MI, definite or probable ST or ischemic stroke | GUSTO moderate or severe bleeding | 5           | Ischemia and bleeding risks | 8               | Thrombotic event: severe chronic kidney disease, AF, PVD, and anemia and 1 point for age ≥75 y, HF, DM, and CTO. Bleeding: thrombocytopenia, severe chronic kidney disease, PVD, and HF and 1 point for prior MI, malignancy, and AF | A higher bleeding risk ≤ -1 |
| 2021                | Guidance of the selection of potent P2Y12 inhibitors in acute MI patients | KAMIR-NIH (n = 10,687) | JAMIR dataset (n = 3,412) and SMART-DATE dataset (n = 2,712) | Acute MI | A composite of cardiac death, MI, and ST | BARC 2, 3, and 5 bleeding | 1           | Net ischemic/bleeding risk | 11              | cardiological shock, LVEF <30%, anemia at presentation, acute pulmonary edema or decompensated HF, STEMI, MI, previous MI, multivessel disease, angiographic complete revascularization, Cr >2.0 mg/dL, and oral anticoagulants | A high bleeding risk score ≥3 |

**AF** = atrial fibrillation; **CKD** = chronic kidney disease; **CREDO-Kyoto** = coronary revascularization demonstrating outcome study in Kyoto; **CTO** = chronic total occlusion; **DM** = diabetes mellitus; **GUSTO** = global use of strategies to open occluded coronary arteries; **HF** = heart failure; **KAMIR-NIH** = Korean Myocardial Infarction Registry - National Institute of Health; **LVEF** = left ventricular ejection fraction; **PVD** = peripheral vascular disease; **STEMI** = ST-elevation myocardial infarction; other abbreviations as in Tables 1 and 2.
maintenance] and aspirin) and late (>6-month post-PCI) de-escalated (clopidogrel alone) strategy vs conventional therapy (clopidogrel plus aspirin for 12 months).

INDIVIDUALIZING DECISION-MAKING AND STRATEGIES

RISK SCORE ASSESSMENT IN EAST ASIAN PATIENTS.
In the contemporary clinical practice, all patients are not equally at risk of bleeding, ischemic, or thromboembolic events. Therefore, an individualized or personalized antithrombotic strategy is frequently recommended after considering the risk of both bleeding and ischemic events based on patients’ unique clinical or anatomic characteristics. Thus, risk prediction models could assist clinical decision-making for individuals in real-world practice. Within the last decade, several risk score systems such as the DAPT score, the PARIS (Patterns of Non-adherence to Antiplatelet Regimen in Stented Patients) score, and the PRECIS-DAPT (Predicting Bleeding Complications in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy) score were developed and have been used in daily clinical practice.1 However, most of these tools were derived from Western studies and given the different ischemic and bleeding propensities and PCI characteristics between different ethnic groups, risk prediction models applicable to East-Asians have been required. Accordingly, ischemic and bleeding risk scores derived from East Asian cohorts have recently been developed including the Asian DAPT score, the CREDO-Kyoto (Coronary Revascularization Demonstrating Outcome Study in Kyoto) risk score, and the KAMIR-NIH DAPT (Korean Myocardial Infarction Registry-National Institute of Health DAPT) score.84-86 Detailed information on these tools for East Asian populations are summarized in Table 3.

The Asian DAPT score was developed to determine the DAPT duration, based on 13,172 patients registered in the Korean nationwide prospective registry, and was validated in 7,529 patients enrolled in 2 RCTs from South Korea and Japan.84 CREDO-Kyoto thrombotic and bleeding risk scores were developed to discriminate ischemic and bleeding risks in the Japanese population.85 Although the Asian DAPT score and CREDO-Kyoto scores have shown modest accuracy in stratifying thrombotic and bleeding risks, these risk-prediction models may be useful also for tailoring the DAPT duration after PCI in East Asian patients. Recently, the KAMIR-NIH DAPT score was developed to guide the selection of potent P2Y12 inhibitors in acute MI patients.86

| TABLE 4 | Pragmatic Antithrombotic Strategies for East Asian Patients According to Bleeding and Ischemic Risk |
|----------|-------------------------------------------------------------------------------------------------------------------------------|
| **Clinical Situations** | **Default Approach** | **High Bleeding Risk** |
| | **DAPT Duration** | **Antiplatelet Agents** | **DAPT Duration** | **Antiplatelet Agents** | **After DAPT Duration** |
| Stable angina | 3-6 mo | Aspirin + clopidogrel | 1-3 mo | Aspirin + clopidogrel | Clopidogrel |
| Acute coronary syndrome | 6-12 mo | Aspirin + prasugrel 3.75 or 5mg (or reduced-dose ticagrelor) | 3-6 mo | Aspirin + clopidogrel | Clopidogrel |
| Requiring oral anticoagulation | 1 wk | Aspirin + clopidogrel + DOAC and then, clopidogrel + DOAC up to 12 mo | Until discharge (1 to 2 d) | Aspirin + clopidogrel + DOAC and then, clopidogrel + DOAC up to 3-6 mo | DOAC alone after double therapy |
| CHIP (or high ischemic risk) | 6-12 mo | Aspirin + (reduced-dose) potent P2Y12 inhibitors | Continue DAPT or potent P2Y12 inhibitors monotherapy |

*For patients at risk of high ischemic/thrombotic events, triple therapy with DAPT and DOAC would be indicated up to 1 month. CHIP = complex higher-risk and indicated procedure/patients; DOAC = direct oral anticoagulant; other abbreviations as in Table 1.

| TABLE 5 | Specific Considerations for East Asian Patients According to Bleeding and Ischemic Risk |
|----------|---------------------------------------------------------------------------------------|
| **Issue** | **Suggestion** |
| Risk scoring models | To determine DAPT duration or P2Y12 inhibitors, risk scores to stratify the bleeding and thrombosis risks developed from East Asian cohorts may be considered. |
| PFT/genotype guidance | Routine use of genetic or PFT is not recommended to tailor antiplatelet strategies; however, they may be considered in high-risk East Asian patients for thrombotic or bleeding complications. |
| Routine use of PPIs | GI protective agents (eg, PPIs or H2 receptor antagonists) may be routinely considered in East Asian patients, and PPIs should be prescribed in patients with a history of GI bleeding or in those with increased risk of GI bleeding. |

*GI = gastrointestinal; PFT = platelet function testing; PPI = proton pump inhibitor; other abbreviations as in Table 1.*
this tool with different East Asian cohorts yielded a modest discriminant function and further validation studies with other cohorts will thus be required to verify this new system.

**PLATELET FUNCTION TESTING AND GENOTYPING.** Until recently, most RCTs testing tailored antithrombotic strategies in accordance with platelet function testing or genetic testing have failed to show the clinical superiority of a laboratory-guided strategy over conventional therapy. However, the recent TAILOR-PCI (Tailored Antiplatelet Therapy Following PCI) trial of 1,849 patients with the CYP2C19 *2 or *3 allele has suggested that genotype-guided therapy (mostly involving ticagrelor treatment) reduces the incidence of ischemic events compared with clopidogrel-based therapy (adjusted HR: 0.66; 95% CI: 0.43-1.02; \(P = 0.06\)). 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 clinical benefit was relatively lower in East Asian than Caucasian patients (absolute risk reduction: 1.5% vs 2.6%, respectively). Race-based pharmacogenetic screening recommendations can result in considerable practice variation and stereotyping in the absence of compelling clinical evidence and thereby reinforce pre-existing beliefs about race as a biological construct. Nevertheless, a recent meta-analysis has revealed that the guided selection of antiplatelet therapies improved both composite and individual efficacy outcomes with a favorable safety profile, driven by a reduction in minor bleeding and supporting the use of platelet function or genetic testing for antithrombotic decision-making after PCI. Therefore, this approach should be refuted or supported through further RCTs adopting an ethnic-based approach.

**FUTURE PERSPECTIVES AND DIRECTION**

Diverse studies involving experimental or clinical data have confirmed the unique thrombotic and bleeding risk profiles of East Asian patients and differences in the optimal therapeutic window for antiplatelet treatment. Although this better understanding today has improved the clinical outcomes for East Asian patients, there is still much to be accomplished. Considering these clinically important differences in thrombogenicity and bleeding propensity, the results of major antithrombotic therapy trials from Western populations and clinical guidelines cannot be directly extrapolated to East Asian populations. Hence, focused investigations and the development of representative consensus/guidelines for East Asian populations are required. In addition, refined risk prediction tools, generally applicable to East Asian patients, should be developed to improve real-world clinical practice in those countries.
Moreover, further large-scale studies among all East Asian countries are required to identify the optimal antithrombotic therapy for the modern era of coronary interventions. As precision medicine, taking into account individual variabilities in genes and in the environment has been evolving and future antithrombotic therapies could be more personalized with a combination of individualized clinical risk assessment, incorporating perhaps both in vitro tests of the thrombotic status as well as a treatment plan based on individual risk.

**Active clinical trials evaluating diverse strategies or investigational agents may improve the risk-benefit balance in current antithrombotic strategies.**

Considering the higher bleeding risk and different therapeutic window in the East Asian population compared with Western populations, we propose pragmatic antithrombotic strategies for East Asian patients according to their bleeding and ischemic risk (Tables 4 and 5). This recommendation would be helpful to facilitate optimal decision-making and clinical judgements in the daily clinical practice. A tailored antithrombotic regimen with appropriate dosages to balance the ischemic and bleeding risks should be considered for each individual patient’s clinical situation.

**CONCLUSIONS**

Throughout considerable and extensive research efforts, the unique ischemic and bleeding propensity of East Asian patients, the so-called East-Asian paradox, has become well-established and ethnically tailored antithrombotic strategies have emerged (Central Illustration). Based on the cumulative evidence from multiple RCTs, a short DAPT duration such as a 3- to 6-month timeframe after ACS or PCI, would be feasible and a shorter DAPT (ie, 1 month) can be a viable option for select East Asian patients with HBR characteristics. Several RCTs have consistently shown that use of the potent P2Y12 inhibitors such as prasugrel and ticagrelor at standard doses requires more caution in East Asian patients due to a higher risk of bleeding complications. Recent RCTs from East Asian countries further indicate that reduced-dose strategies with these agents would be appropriate, and further investigations are needed. In addition, modified strategies with potent P2Y12 inhibitors such as escalation or de-escalation protocols represent substantial new approaches, and ongoing trials will provide further insights and evidence. In daily clinical practice, physicians should comprehensively assess the individual ischemic and bleeding risk and tailor the antithrombotic strategy. Lastly, understanding the differences and unique feature of the East Asian population, and tailoring the antithrombotic regimens accordingly, will provide maximum clinical benefits for patients with ACS or those receiving PCI.

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References

1. Cao D, Chandraramani R, Chiariello M, Claessen BE, Mehran R. Evolution of antithrombotic therapy in patients undergoing percutaneous coronary intervention: a 40-year journey. Eur Heart J. 2021;42:339–351.

2. Rodriguez F, Harrington RA. Management of antithrombotic therapy after acute coronary syndromes. N Engl J Med. 2021;384:452–460.

3. East Asia. Wikipedia. Accessed October 19, 2021. https://en.wikipedia.org/wiki/East_A sia

4. Kim HK, Tantry US, Smith SC Jr, et al. The East Asian paradox: an updated position statement on the challenges to the current antithrombotic strategy in patients with cardiovascular disease. Thromb Haemost. 2021;121:422–432.

5. Kang J, Park KW, Palmenini T, et al. Racial differences in ischaemia/bleeding risk trade-off during anti-platelet therapy: individual patient level landmark meta-analysis from seven RCTs. Thromb Haemost. 2019;119:149–162.

6. Saito S, Ishiki T, Kimura T, et al. Efficacy and safety of adjusted-dose prasugrel compared with clopidogrel in Japanese patients with acute coronary syndrome: the PRASIT-ACS study. Circ J. 2014;78:1684–1692.

7. Goto S, Huang CH, Park SJ, Emanuelsson H, Kimura T. Ticagrelor vs clopidogrel in Korean patients with acute coronary syndromes–randomized, double-blind, phase III PHILO study. Circ J. 2015;79:2452–2460.

8. Park DW, Kwon O, Jang JS, et al. Clinically significant bleeding with ticagrelor versus clopidogrel in Korean patients with acute coronary syndromes intended for invasive management: a randomized clinical trial. Circulation. 2019;140:1865–1877.

9. Lev EI, Biden KP, Jeong YH, et al. Influence of race and sex on thrombogenicity in a large cohort of coronary artery disease patients. J Am Heart Assoc. 2014;3:e001167.

10. Shen AU, Yao JF, Brar SS, Jorgensen MB, Chen W. Racial/ethnic differences in the risk of intracranial hemorrhage among patients with atrial fibrillation. J Am Coll Cardiol. 2007;50:309–315.

11. Shinohara Y. Regional differences in incidence and management of stroke—is there any difference between Western and Japanese guidelines on antithrombotic therapy? Cerebrovasc Dis. 2006;21(suppl 1):17–24.

12. Mak KH, Bhatt DL, Shao M, et al. Ethnic variation in adverse cardiovascular outcomes and bleeding complications in the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) study. Am Heart J. 2009;157:658–665.

13. Kumar RS, Douglas PS, Peterson ED, et al. Effect of race and ethnicity on outcomes with drug-eluting and bare metal stents: results in 423,965 patients in the linked National Cardiovascular Data Registry and Centers for Medicare & Medicaid Services payer databases. Circulation. 2013;127:1395–1403.

14. Park DW, Yun SC, Lee SW, et al. Stent thrombosis, clinical events, and influence of prolonged clopidogrel use after placement of drug-eluting stent data from an observational cohort study of drug-eluting versus bare-metal stents. J Am Coll Cardiol Intv. 2008;1:494–503.

15. Kimura T, Morimoto T, Nakagawa Y, et al. Antipla telet therapy and stent thrombosis after sirolimus-eluting stent implantation. Circulation. 2009;119:987–995.

16. Daemen J, Wenausser P, Tuschida K, et al. Early and late coronary stent thrombosis of sirolimus-eluting and paclitaxel-eluting stents in routine clinical practice: data from a large two-institutional cohort study. Lancet. 2007;369:667–678.

17. Yusuf S, Zhao F, Mehta SR, et al. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med. 2001;345:494–502.

18. Mehta SR, Yusuf S, Peters RJ, et al. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. Lancet. 2001;358:527–533.

19. Scott SA, Sanghiuk I, Stein CM, et al. Clinical Pharmacogenetics Implementation Consortium guidelines for CYP2C19 genotype and clopidogrel therapy: 2013 update. Clin Pharmacol Ther. 2013;94:317–323.

20. Gan XD, Wei BZ, Fang D, et al. Efficacy and safety analysis of new P2Y12 inhibitors versus clopidogrel in patients with percutaneous coronary intervention: a meta-analysis. Curr Med Res Opin. 2015;31:2313–2322.

21. Levine GN, Jeong YH, Goto S, et al. Expert consensus document: World Heart Federation expert consensus statement on antiplatelet therapy in East Asian patients with ACS or undergoing PCI. Nat Rev Cardiol. 2014;11:597–606.

22. Kim IS, Jeong YH, Tantry US, et al. Relation between the vasodilator-stimulated phosphoprotein phosphorylation assay and light transmittance aggregometry in East Asian patients after high-dose clopidogrel loading. Am Heart J. 2013;166:95–103.

23. Aradi D, Storey RF, Komosci A, et al. Expert position paper on the role of platelet function testing in patients undergoing percutaneous coronary intervention. Eur Heart J. 2014;35:209–215.

24. Tantry US, Bonello L, Aradi D, et al. Consensus and update on the definition of on-treatment platelet reactivity to adenosine diphosphate associated with ischemia and bleeding. J Am Coll Cardiol. 2013;62:2261–2273.

25. Ko YG, Suh JW, Kim BH, et al. Comparison of 2 point-of-care platelet function tests, VerifyNow Assay and Multiple Electrode Platelet Aggregometry, for predicting early clinical outcomes in patients undergoing percutaneous coronary intervention. Am Heart J. 2011;161:383–390.

26. Jeong YH. “East asian paradox”: challenge for the current antiplatelet strategy of “one-guideline-fits-all races” in acute coronary syndrome. Curr Cardiol Rep. 2014;16:485.

27. Kwon TJ, Tantry US, Park P, et al. Influence of platelet reactivity on BARC classification in East Asian patients undergoing percutaneous coronary intervention. Results of the ACCEL-BLEED study. Thromb Haemost. 2016;115:979–992.

28. Kim HK, Tantry US, Park HW, et al. Ethnic difference of thrombogenicity in patients with cardiovascular disease: a pandora box to explain prognostic differences. Korean Circ J. 2021;51:202–221.

29. Luts ey PL, Cushman M, Steffen LM, et al. Plasma hemostatic factors and endothelial markers in four racial/ethnic groups: the MESA study. J Thromb Haemost. 2006;4:2629–2635.

30. Ye Z, Liu EH, Higgins JP, et al. Seven haemostatic gene polymorphisms in coronary disease: meta-analysis of 66,155 cases and 91,307 controls. Lancet. 2006;367:651–658.

31. Huo Y, Jeong Y-H, Gong Y, et al. 2018 update of expert consensus statement on antiplatelet therapy in East Asian patients with ACS or undergoing PCI. Science Bulletin. 2019;64:166–179.

32. Nordmann AJ, Briel M, Bucher HC. Mortality in randomized controlled trials comparing drug-eluting vs. bare metal stents in coronary artery disease: a meta-analysis. Eur Heart J. 2006;27:2784–2814.

33. Camenzind E, Steg PG, Wijns W. Stent thrombosis late after implantation of first-generation drug-eluting stents: a cause for concern. Circulation. 2007;115:1440–1455. discussion 1455S.

34. Ellis SG, Colombo A, Grube E, et al. Incidence, timing, and correlates of stent thrombosis with the polymeric paclitaxel drug-eluting stent: a TAXUS II, IV, V, and VI meta-analysis of 3,445 patients followed up for 3 years. J Am Coll Cardiol. 2007;49:1034–1051.

35. Giustino G, Baber U, Sartori S, et al. Duration of dual antiplatelet therapy after drug-eluting stent implantation: a systematic review and meta-analysis of randomized controlled trials. J Am Coll Cardiol. 2015;65:1298–1310.

36. Park SJ, Park DW, Kim YH, et al. Duration of dual antiplatelet therapy after implantation of drug-eluting stents. N Engl J Med. 2010;362:1374–1382.

37. Lee CW, Ahn JM, Park DW, et al. Optimal duration of dual antiplatelet therapy after drug-eluting stent implantation: a randomized controlled trial. Circulation. 2014;129:304–312.

38. Gwon HC, Hahn JY, Park KW, et al. Six-month versus 12-month dual antiplatelet therapy after implantation of drug-eluting stents: the EFFICACY of Xience/Prusam versus Cypher to Reduce Late Loss After Stenting (EXCELLENT) randomized, multicenter study. Circulation. 2012;125:505–513.

39. Kim BK, Hong MK, Shin DH, et al. A new strategy for discontinuation of dual antiplatelet therapy: the RESET Trial (Real Safety and Efficacy of 3-month dual antiplatelet Therapy following
2020;15:1–18

Endeavor zotarolimus-eluting stent implantation. J Am Coll Cardiol. 2012;60:1340–1348.

Hong S-J, Shin D-H, Kim J-S, et al. 6-month versus 12-month dual-antiplatelet therapy following long everolimus-eluting stent implantation. J Am Coll Cardiol Intv. 2016;9:1438–1446.

Nakamura M, Iijima R, Ako J, et al. Dual antiplatelet therapy for 6 versus 18 months after biodegradable polymer drug-eluting stent implantation. J Am Coll Cardiol Intv. 2016;9:1189–1198.

Hahn JY, Song YB, Oh JH, et al. 6-month versus 12-month or longer dual antiplatelet therapy after percutaneous coronary intervention in patients with acute coronary syndrome (SMART-DATE): a randomised, open-label, non-inferiority trial. Lancet. 2018;391:1274–1284.

Hahn JY, Song YB, Oh JH, et al. Effect of P2Y12 inhibitor monotherapy vs dual antiplatelet therapy on cardiovascular events in patients undergoing percutaneous coronary intervention: the SMART-CHOICE randomized clinical trial. JAMA. 2019;321:2428–2437.

Watanabe H, Domel T, Morimoto T, et al. SMART-CHOICE randomized clinical trial. JAMA. 2019;321:2428–2437.

Watanabe H, Domel T, Morimoto T, et al. Effect of 1-month dual antiplatelet therapy followed by clopidogrel vs 12-month dual antiplatelet therapy on cardiovascular and bleeding events in patients receiving PCI: the STOPDAPT-2 randomized clinical trial. JAMA. 2019;321:2414–2427.

Watanabe H. STOPDAPT-2 ACS: one-month dual antiplatelet therapy followed by clopidogrel monotherapy in acute coronary syndrome. Paper presented at: European Society of Cardiology Congress 2021 the digital experience; August 31, 2021; London, United Kingdom.

Palmerini T, Benedetto U, Bianchi-Zoccai G, et al. Long-term safety of drug-eluting and bare-metal stents: evidence from a comprehensive network meta-analysis. J Am Coll Cardiol. 2015;65:2496–2507.

Koskinas KC, Nakamura M, Raber L, et al. Current use of intraprocedural imaging in interventional practice – results of a European Association of Percutaneous Cardiovascular Interventions (EAPCI) and Japanese Association of Cardiovascular Interventions and Therapeutics (CVIT) Clinical Practice Survey. Circ. J. 2018;82:1360–1368.

Koo BK, Kang J, Park KW, et al. Aspirin versus clopidogrel for chronic maintenance monotherapy after percutaneous coronary intervention (HOST-EXAM): an investigator-initiated, prospective, randomised, open-label, multicentre trial. Lancet. 2021;397(10293):2487–2496.

Wixvott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2007;357:2001–2015.

Wallentin L, Becker RC, Busija J, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2009;361:1045–1057.

Camareo TG, de la Torre Hernandez JM. Antithrombotic treatment after coronary intervention: agreement and controversy. Eur Heart J. 2020;129:623–628.

Levine GN, Bates ER, Bititl JA, et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. J Am Coll Cardiol. 2016;68:1082–1115.

Valgimigli M, Bueno H, Byrne RA, et al. ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: the task force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2018;39:213–260.

Teng R, Butler K. Pharmacokinetics, pharmacodynamics, and tolerability of single and multiple doses of ticagrelor in Japanese and Caucasian volunteers. Int J Clin Pharmacol Ther. 2014;52:478–491.

Li J, Tang W, Storey RF, Husted S, Teng R. Population pharmacokinetics of ticagrelor in patients with acute coronary syndromes. Int J Clin Pharmacol Ther. 2016;54:666–674.

Park DW, Lee PH, Jang S, et al. Effect of low-dose versus standard-dose ticagrelor and clopidogrel on platelet inhibition in acute coronary syndromes. J Am Coll Cardiol. 2018;71:1594–1595.

Bonaca MP, Bhatt DL, Cohen M, et al. Long-term use of ticagrelor in patients with prior myocardial infarction. N Engl J Med. 2015;371:1791–1800.

Goto S. Global trial or local one? Circulation. 2019;140:1878–1880.

van Rieckx P, Valgimigli M, Juni P, et al. Ticagrelor plus aspirin for 1 month, followed by ticagrelor monotherapy for 23 months vs aspirin plus clopidogrel or ticagrelor for 12 months, followed by aspirin monotherapy for 12 months after implantation of a drug-eluting stent: a multicentre, open-label, randomised superiority trial. Lancet. 2018;392:940–949.

Mohran R, Baber U, Sharma SK, et al. Ticagrelor with or without aspirin in high-risk patients after PCI. N Engl J Med. 2019;381:2032–2042.

Kim BK, Hong SJ, Cho YH, et al. Effect of ticagrelor monotherapy vs ticagrelor with aspirin on major bleeding and cardiovascular events in patients with acute coronary syndrome: the TICO randomized clinical trial. JAMA. 2020;323:2407–2416.

Steeg PG, Bhatt DL. Is there really a benefit to net clinical benefit in testing antithrombics? Circulation. 2018;137:1429–1431.

Small DS, Kothare P, Yuen E, et al. The pharmacokinetics and pharmacodynamics of prasugrel in healthy Chinese, Japanese, and Korean subjects compared with healthy Caucasian subjects. Eur J Clin Pharmacol. 2010;66:127–135.

Yokoi H, Kimura T, Isshiki T, Ogawa H, Ikeda Y. Pharmacodynamic assessment of a novel P2Y12 receptor antagonist in Japanese patients with coronary artery disease undergoing elective percutaneous coronary intervention. Thromb Res. 2012;129:623–628.

Jeong YH, Oh JH, Yoon HJ, et al. Pharmacodynamic profile and prevalence of bleeding episode in East Asian patients with acute coronary syndromes treated with prasugrel standard-dose versus de-escalation strategy: a randomized A-MATCH trial. Thromb Res. 2021;121(10):1376–1386.

Menichelli M, Neumann FJ, Ndrepepa G, et al. Age- and weight-adapted dose of prasugrel versus standard dose of ticagrelor in patients with acute coronary syndromes: results from a randomized trial. Ann Intern Med. 2020;173:436–444.

Isshiki T, Kimura M, Ogawa H, et al. Prasugrel, a third-generation P2Y12 receptor antagonist, in patients with coronary artery disease undergoing elective percutaneous coronary intervention. Circ. J. 2014;78:2926–2934.

Nakamura M, Kimura K, Kimura T, et al. JCS 2020 guideline focused update on antithrombotic therapy in patients with coronary artery disease. Circ. J. 2020;84:831–865.

Kim HS, Kang J, Hwang D, et al. Prasugrel-based de-escalation of dual antiplatelet therapy after percutaneous coronary intervention in patients with acute coronary syndrome (HOST-REDUCE-POLYTECH-ACS): an open-label, multicentre, non-inferiority randomised trial. Lancet. 2020;396:1079–1089.

Angiolillo DJ, Goodman SG, Bhatt DL, et al. Antithrombotic therapy in patients with atrial fibrillation treated with oral anticoagulation undergoing percutaneous coronary intervention: a North American perspective – 2018 update. Circulation. 2018;138:527–536.

Hansen ML, Sorensen R, Clausen MT, et al. Risk of bleeding with single, dual, or triple therapy with warfarin, aspirin, and clopidogrel in patients with atrial fibrillation. Arch Intern Med. 2010;170:1433–1441.

Choi HJ, Ahn JM, Kang SH, et al. Prevalence, management, and long-term (6-year) outcomes of atrial fibrillation among patients receiving drug-eluting coronary stents. J Am Coll Cardiol Intv. 2017;10:1075–1085.

Eyelten C, Postula M, Jakubík D, et al. Non-vitamin K oral anticoagulants (NOAC) versus vitamin K antagonists (VKA) for atrial fibrillation with elective or urgent percutaneous coronary intervention: a meta-analysis with a particular focus on combination type. J Clin Med. 2020;9(4):1120.

Angiolillo DJ, Bhatt DL, Cannon CP, et al. Antithrombotic therapy in patients with atrial fibrillation treated with oral anticoagulation undergoing percutaneous coronary intervention: a North American perspective: 2021 update. Circulation. 2021;143:583–596.

Hindricks G, Potpara T, Dagens N, et al. 2020 ESC guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2021;42:373–498.

Matsumura-Nakano Y, Shizuta S, Komasa A, et al. Open-label randomized trial comparing oral anticoagulation with and without single antiplatelet therapy in patients with atrial fibrillation and stable coronary artery disease beyond 1 year.
after coronary stent implantation. Circulation. 2019;139:604-616.

77. Yasuda S, Kalkits K, Akas M, et al. Antithrombotic therapy for atrial fibrillation with stable coronary disease. N Engl J Med. 2019;381:1103-1113.

78. Urban P, Mehran R, Colleran R, et al. Defining high bleeding risk in patients undergoing percutaneous coronary intervention. Circulation. 2019;140:240-261.

79. Natsuaki M, Morimoto T, Shiomi H, et al. Application of the academic research consortium high bleeding risk criteria in an all-comers registry of percutaneous coronary intervention. Circ Cardiovasc Interv. 2019;12: e008307.

80. Ariotti S, Adamo M, Costa F, et al. Is bare-metal stent implantation still justifiable in high bleeding risk patients undergoing percutaneous coronary intervention?: a pre-specified analysis from the ZEUS trial. J Am Coll Cardiol Intv. 2016;9: 426-436.

81. Wischocker S, Latib A, Kedhi E, et al. Polymer-based or polymer-free stents in patients at high bleeding risk. N Engl J Med. 2020;382:1208-1218.

82. Valgimigli M, Frigoli E, Heg D, et al. Dual antiplatelet therapy after PCI in patients at high bleeding risk. N Engl J Med. 2021;385(18):1643-1655.

83. Kirtane AJ, Doshi D, Leon MB, et al. Treatment of higher-risk patients with an indication for revascularization: evolution within the field of contemporary percutaneous coronary intervention. Circulation. 2016;134:422-431.

84. Kang J, Park KW, Ki YJ, et al. Development and validation of an ischemic and bleeding risk evaluation tool in East Asian patients receiving percutaneous coronary intervention. Thromb Haemost. 2019;119:1182-1193.

85. Natsuaki M, Morimoto T, Yamaji K, et al. Prediction of thrombotic and bleeding events after percutaneous coronary intervention: CREDO-Kyoto thrombotic and bleeding risk scores. J Am Heart Assoc. 2018;7(11): e008708.

86. Lee SH, Kim HK, Jeong MH, et al. Practical guidance for P2Y12 inhibitors in acute myocardial infarction undergoing percutaneous coronary intervention. Eur Heart J Cardiovasc Pharmacother. 2021;7:112-124.

87. Price MJ, Berger PB, Teirstein PS, et al. Standard vs high-dose clopidogrel based on platelet function testing after percutaneous coronary intervention: the GRAVITAS randomized trial. JAMA. 2011;305:1097-1105.

88. Trenk D, Stone GW, Gawaz M, et al. A randomized trial of prasugrel versus clopidogrel in patients with high platelet reactivity coronary intervention with implantation of drug-eluting stents: results of the TRIGGER-PCI (Testing Platelet Reactivity In Patients Undergoing Elective Stent Placement On Clopidogrel to Guide Alternative Therapy With Prasugrel) study. J Am Coll Cardiol. 2012;59:2159-2164.

89. Collet JP, Cuisset T, Range G, et al. Bedside monitoring to adjust antiplatelet therapy for coronary stenting. N Engl J Med. 2012;367:2100-2109.

90. Cayla G, Cuisset T, Silvain J, et al. Platelet function monitoring to adjust antiplatelet therapy in elderly patients stented for an acute coronary syndrome (ANTARCTIC): an open-label, blinded-endpoint, randomised controlled superiority trial. Lancet. 2016;388:2015-2022.

91. Pereira NL, Farkouh ME, So D, et al. Effect of genotype-guided oral P2Y12 inhibitor selection vs conventional clopidogrel therapy on ischemic outcomes after percutaneous coronary intervention: the TAILOR-PCI randomized clinical trial. JAMA. 2020;324:761-771.

92. Goodman CW, Brett AS. Race and pharmacogenomics-personalized medicine or misguided practice? JAMA. 2021;325:625-626.

93. Galli M, Benenati S, Capodanno D, et al. Guided versus standard antiplatelet therapy in patients undergoing percutaneous coronary intervention: a systematic review and meta-analysis. Lancet. 2021;397:1470-1483.

94. Gorog DA, Geisler T. Platelet inhibition in acute coronary syndrome and percutaneous coronary intervention: insights from the past and present. Thromb Haemost. 2020;120:565-578.

95. Claassen DM, Ten Berg JM. Genotype-guided treatment of oral P2Y12 inhibitors: where do we stand? Pharmacogenomics. 2020;21:83-86.

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