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EDITORIAL COMMENT

Shortening Dual Antiplatelet Therapy Duration in High-Risk Patients Undergoing Percutaneous Coronary Intervention*

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Following percutaneous coronary intervention (PCI), a 6- to 12-month course of dual antiplatelet therapy (DAPT) with aspirin and a $P2Y_{12}$ receptor inhibitor is typically prescribed to mitigate the risk of thrombotic complications at the level of stented or nonstented coronary segments.[1-3] Bleeding, however, is a major downside of DAPT and challenges the selection of antiplatelet strategies for PCI.[4] Patients at high bleeding risk (HBR) may benefit from changing or adjusting either the components or the duration of DAPT.[5] Shortening DAPT by discontinuation of aspirin or the $P2Y_{12}$ receptor inhibitor at 1 to 6 months, for example, is a viable option to reduce bleeding and is supported by current guidelines for coronary revascularization.[1-3] Yet, short DAPT may be associated with an increased incidence of major adverse cardiac events (MACE) among patients at high thrombotic risk, such as those undergoing complex PCI.[6] The interplay between high-risk characteristics of bleeding and thrombosis (**Figure 1**) is a daily clinical dilemma.

Hitting the sweet spot of antiplatelet therapy is especially challenging among East Asian patients who have reduced anti-ischemic benefits and increased bleeding as a consequence of the so-called East Asian paradox.[7] Acknowledging the unique trade-off of DAPT in East Asians, several dedicated trials have been conducted in this population (**Figure 1**), including trials comparing $P2Y_{12}$ inhibitors in patients with acute coronary syndromes (ACS) (eg, low-dose prasugrel vs clopidogrel in PRASFIT-ACS, or ticagrelor vs clopidogrel in PHILO and TICAKOREA) and trials of DAPT duration.[4] In the single-arm STOPDAPT study, using a historical comparator, the authors concluded that 3-month DAPT followed by aspirin monotherapy was at least as safe as a prolonged DAPT regimen.[8] In addition, in the SMART-CHOICE trial, 3-month DAPT followed by $P2Y_{12}$ inhibitor monotherapy was noninferior to standard DAPT on ischemic events, and reduced the risk of bleeding.[4] In the STOPDAPT-2 trial, 1-month DAPT followed by clopidogrel monotherapy was noninferior and even superior to 12-month DAPT in patients undergoing elective PCI.[9] However, a strategy of DAPT for 1 to 2 months followed by clopidogrel monotherapy failed to show noninferiority to standard DAPT in patients with ACS from the STOPDAPT-2 ACS trial, mainly owing to a higher risk of myocardial infarction.[10] This result was in contrast with that of TICO, a trial where ticagrelor monotherapy after 3 months of DAPT reduced the risk of combined ischemic and bleeding events.[4] In aggregate, although these studies have provided important insights on the optimal DAPT strategy for East Asian patients, the specific relationship of short DAPT with clinical outcomes in patients stratified by HBR and PCI complexity remains uncertain.

In this issue of *JACC: Asia*, Yamamoto et al[11] report a comparison of 1-month DAPT followed by clopidogrel monotherapy vs 12-month DAPT with aspirin and clopidogrel in patients with or without HBR and with or without complex PCI from a pooled cohort of the STOPDAPT-2 and STOPDAPT-2 ACS trials. A number of HBR criteria defined by the Academic Research Consortium[12] and accepted criteria of PCI

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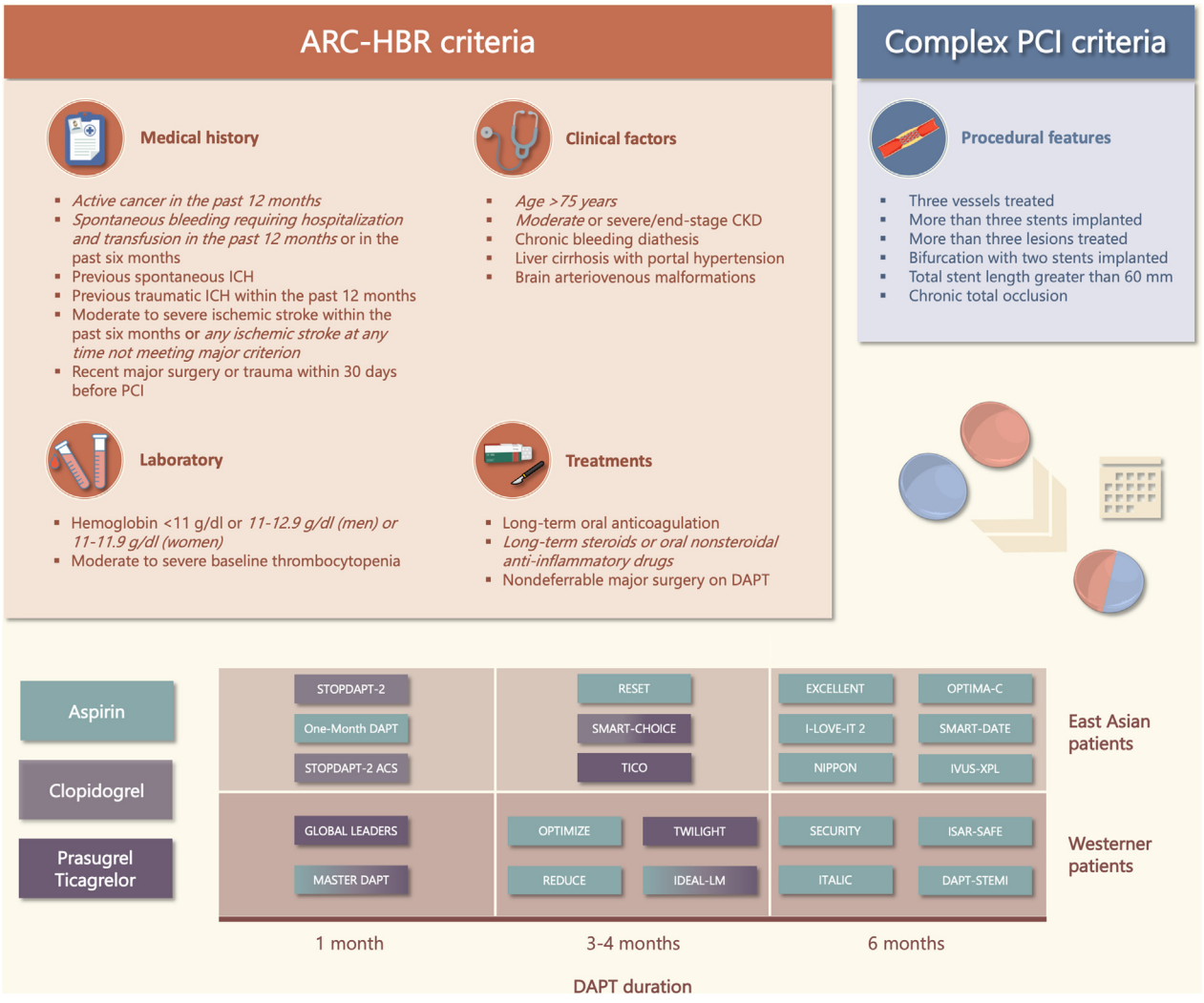
FIGURE 1 HBR Criteria and DAPT Duration in East Asians and Westerners



At the top of the figure, risk stratification criteria for bleeding and complexity of percutaneous coronary intervention are listed; bleeding criteria can be major **(roman font)** or minor **(italic font)**. The bottom part of the figure illustrates randomized controlled trials of shortening DAPT duration at different time points (per division in **columns**) in East Asian or Western populations (per division in **rows**). ARC-HBR = Academic Research Consortium high bleeding risk; CKD = chronic kidney disease; DAPT = dual antiplatelet therapy; ICH = intracranial hemorrhage; PCI = percutaneous coronary intervention.

complexity[6] were applied to 5,997 patients, approximately one-third of whom finally presented with HBR, and approximately one-sixth of whom underwent a complex PCI. The main finding of the study is that HBR status did not modify the treatment effect of 1-month DAPT in the pooled analysis of the parental trials (ie, similar net benefit and thrombotic outcomes, less bleeding) as it relates to the risk of combined ischemic and bleeding events (P = 0.95 for interaction), MACE (P = 0.90 for interaction), and bleeding (P = 0.36 for interaction). Similarly, there were no statistical interactions between PCI complexity and the effect of short DAPT on the same end points (P for interaction = 0.48, 0.53, and 0.90, respectively). Not surprisingly, the absolute benefit of short DAPT in reducing major bleeding was larger in HBR patients.

The authors should be congratulated for an interesting analysis that advances our understanding on personalized DAPT duration after PCI in East Asian patients. Beyond limitations that are common to any post hoc analysis, several considerations contribute

to critical appraisal of the results of this study and putting them into perspective. Regarding the study design and internal validity, it must be noted that stratifying patients by HBR or PCI complexity implies losing the benefit of randomization if such randomization was not stratified by the same variables in the parent trials. Also, the use of combined ischemic and bleeding outcomes as the primary end point is a challenge to the interpretation of the results: net benefit end points summarize the overall treatment effect with the use of a single quantitative measure and are used to increase the number of events for more efficient sample size determination. However, with ischemia and bleeding directed in opposite directions from DAPT, net adverse cardiac events tend to skew toward the null. Furthermore, ischemic and bleeding complications may display different degrees of severity, an issue that cannot be taken into account when the weight of each event equally contributes to a composite end point. Because HBR features and PCI complexity often coexist, another caveat is that the 2 analyses based on such criteria were performed separately, and no data have been made available on their combination. Regarding the study analyses, it is worth also noting that—with the exception of clinical presentation and the parent study (ie, STOPDAPT-2 vs STOPDAPT-2 ACS)—there was no statistical adjustment to account for factors unduly distributed between subgroups.

Regarding generalizability of the findings, it is notable that most patients who received clopidogrel had an ACS (69%), for which Western countries typically consider prasugrel or ticagrelor as first-line $P2Y_{12}$ inhibitors. The analysis by HBR excluded patients on long-term oral anticoagulation and did not consider some criteria included in the Academic Research Consortium HBR consensus, which may have resulted in a lower-risk population than that commonly observed even among East Asians.[13] Similarly, the analysis by PCI complexity considered procedural but not clinical characteristics of high thrombotic risk, and the timing of randomization (ie, before hospital discharge) led to the exclusion of patients experiencing in-hospital MACE. All these factors may have also resulted in some degree of patient selection. Finally, the STOPDAPT-2 and STOPDAPT-2 ACS trials were conducted in Japan, where the use of intracoronary imaging is much higher than commonly reported in other countries; also, the effects of short DAPT in Japanese patients may be different compared with Western patients.[7]

Despite these limitations, the study by Yamamoto et al[11] is important as it raises awareness on the role of HBR and PCI complexity in risk stratification, and suggests that HBR should be prioritized regardless of PCI complexity to guide decision making on DAPT duration. This is consistent with a previous pooled analysis of 14,963 patients from 8 randomized trials of DAPT duration, where the benefit of prolonged vs short DAPT was neutralized in HBR patients regardless of PCI complexity.[14] Yet, more studies are needed to clarify a number of remaining questions on tailored strategies for East Asian patients: the ongoing OPTIMIZE-APT trial (NCT05418556) is investigating 1-month DAPT followed by clopidogrel monotherapy and 3-month DAPT followed by ticagrelor monotherapy in the chronic and acute setting, respectively, and the STOPDAPT-3 trial (NCT04609111) is comparing 1-month prasugrel monotherapy started at the time of PCI (ie, with no DAPT) followed by clopidogrel monotherapy vs 1-month DAPT followed by aspirin monotherapy. On top of current evidence, the results of these and other upcoming trials are expected to inform clinical practice and recommendations on short DAPT after PCI in patients from East Asia.

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