JACC: ASIA VOL. 2, NO. 6, 2022

EDITORIAL COMMENT

Third Generation $P2Y_{12}$ Inhibition for East Asian ACS Patients

Are We Really Different?*

Yann Shan Keh, MD,[a] Derek P. Chew, MD, MSc,[b] Jack Wei Chieh Tan, MBBS[a]

Over the past decade, ticagrelor and prasugrel have emerged as the preferred $P2Y_{12}$ inhibitors in the setting of acute coronary syndrome (ACS). This has been largely driven by randomized data supporting the use of more potent $P2Y_{12}$ inhibitors in ACS patients.[1,2] However, the lower rates of MACE with prasugrel and ticagrelor are often counterpoised by increase bleeding rates.

The overall efficacy of ticagrelor and prasugrel in patients of East Asian ethnicity remains a substantial point of debate. The TICAKOREA (TICAgrelor Versus Clopidogrel in Asian/KOREan Patients with ACS Intended for Invasive Management) study was a small randomized control trial (n = 800) comparing 12 months of standard dose ticagrelor (180-mg loading dose and 90-mg twice-daily maintenance dose) to standard dose clopidogrel in ACS patients receiving early invasive management.[3] In this study, ticagrelor was associated with higher rates of bleeding compared with clopidogrel (11.7% [45 of 400] vs 5.3% [21 of 400]; number needed to harm: 16, HR: 2.26; 95% CI: 1.34-3.79; $P = 0.002$), with no differences in MACE between the groups.[3] By contrast, the ticagrelor arm of the PLATO (Platelet Inhibition and Patient Outcomes) trial had a significantly lower composite endpoint of vascular death, myocardial infarction, or stroke, but higher noncoronary artery bypass grafting-related major bleeding, compared with clopidogrel.[1]

In East Asia, the findings of the TICAKOREA and PHILO (Ticagrelor vs. clopidogrel in Japanese, Korean and Taiwanese patients with acute coronary syndrome) randomized trials are very similar, both pointing toward higher rates of bleeding and lower efficacy with standard dose ticagrelor compared with clopidogrel.[3,4] Conversely, data from Japan suggests that dose-adjusted prasugrel (20-mg loading and 3.75-mg maintenance dose) had lower major adverse cardiac events and comparable bleeding rates compared with clopidogrel.[5,6] This data might give dose-adjusted prasugrel the current edge over standard dose ticagrelor as a preferred regimen in the East Asian cohort.

In this issue of *JACC: Asia*, Choi et al[7] reported a prespecified analysis of the TICOKOREA trial, investigating the effect of diabetes mellitus (DM) on the outcomes of the Korean ACS patients who were randomized to either ticagrelor or clopidogrel. In this analysis, 216 patients (27.0%) had DM, whereas 584 (73%) patients were nondiabetic. The TICAKOREA defined their primary safety endpoints as a composite of PLATO major or minor bleeding, which differed from the PLATO trial that used major bleeding as its primary safety endpoint. The rates of clinically significant bleeding at 12 months were numerically higher with ticagrelor in both the DM (13.8% vs 8.0 %) and the non-DM groups (10.2% vs 4.3%). On the other hand, the rates of MACE at 12 months were also higher with ticagrelor compared with clopidogrel in both DM (10.8% vs 6.0%) and non-DM (8.5% vs 5.7%) patients. Due to its small sample size, this trial was underpowered to detect differences in both its primary safety and efficacy endpoints. Hence, we feel these findings should be considered exploratory and highlight the need for larger dedicated randomized trials to address the question of whether ethnicity plays a role in antithrombotic choice.

*Editorials published in *JACC: Asia* reflect the views of the authors and do not necessarily represent the views of *JACC: Asia* or the American College of Cardiology.

From the [a]Department of Cardiology, National Heart Centre, Singapore; and the [b]College of Medicine and Public Health, Flinders University, Adelaide, Australia.

Yibin Wang, PhD, served as Guest Editor-in-Chief for this paper.

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

ISSN 2772-3747 https://doi.org/10.1016/j.jacasi.2022.09.006

JACC: ASIA, VOL. 2, NO. 6, 2022
NOVEMBER 2022:675–676

We would also like to highlight that the data for ticagrelor in East Asian patients may not be representative of all Asian patients. In the PLATO Asian substudy, the benefits of ticagrelor over clopidogrel were seen both the Asian and non-Asian cohorts. (n = 1,106; no significant interaction for the primary efficacy endpoint [P = 0.974], net clinical benefit [P = 0.521], or PLATO major bleeding [P = 0.938]).[8]

A number of solutions have been proposed to help mitigate the higher bleeding rates with ticagrelor, namely reducing the duration of DAPT therapy or dose reduction. Two randomized trials [TICO (Ticagrelor Monotherapy After 3 Months in the Patients Treated With New Generation Sirolimus Stent for ACS) and TWILIGHT (Ticagrelor Monotherapy After 3 Months in the Patients Treated With New Generation Sirolimus Stent for ACS)], have aptly demonstrated that a shorter duration (1-3 months) of DAPT followed by ticagrelor monotherapy has successfully reduced the risk of major bleeding with no apparent effects on MACE rates.[9,10]

The totality of evidence appears to continue to support potent $P2Y_{12}$ inhibitors as the standard of care in ACS patients without robust evidence that the balance of ischemic benefit and bleeding risk differs substantially in East Asian populations. Perhaps the solution to reducing bleeding events lies in dose adjustment and early $P2Y_{12}$ monotherapy, which should ideally be tailored to the individual patient.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr Tan has received honoraria from AstraZeneca, Bayer, Amgen, Medtronic, Abbott Vascular, Biosensors, Alvimedica, Boehringer Ingelheim, and Pfizer; has received research and educational grants from Medtronic, Biosensors, Biotronik, Philips, Amgen, AZ, Roche, Otsuka, Terumo, and Abbott Vascular; and has received consulting fees from Elixir and CSL Behring. Dr Keh has received a modest education grant from AstraZeneca. Dr Chew has reported that he has no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr Jack Wei Chieh Tan, Department of Cardiology, National Heart Centre, 5 Hospital Drive, Singapore 169609. E-mail: jack.tan.w.c@singhealth.com.sg.

REFERENCES

1. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2009;361(11):1045–1057.

2. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2007;357(20):2001–2015.

3. 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(23):1865–1877.

4. Goto S, Huang CH, Park SJ, Emanuelsson H, Kimura T. Ticagrelor vs. clopidogrel in Japanese, Korean and Taiwanese patients with acute coronary syndrome—randomized, double-blind, phase III PHILO study. *Circ J*. 2015;79(11):2452–2460.

5. Saito S, Isshiki T, Kimura T, et al. Efficacy and safety of adjusted-dose prasugrel compared with clopidogrel in Japanese patients with acute coronary syndrome: the PRASFIT-ACS study. *Circ J*. 2014;78(7):1684–1692.

6. Mori H, Mizukami T, Maeda A, et al. A Japanese dose of prasugrel versus a standard dose of clopidogrel in patients with acute myocardial infarction from the K-ACTIVE Registry. *J Clin Med*. 2022;11(7):2016. https://doi.org/10.3390/jcm11072016

7. Choi Y, Kang D-Y, Lee JB, et al. Ticagrelor versus clopidogrel in East Asian patients with acute coronary syndrome and diabetes mellitus. *JACC: Asia*. 2022;2(6):666–674.

8. Kang HJ, Clare RM, Gao R, et al. Ticagrelor versus clopidogrel in Asian patients with acute coronary syndrome: a retrospective analysis from the Platelet Inhibition and Patient Outcomes (PLATO) Trial. *Am Heart J*. 2015;169(6):899–905.e1.

9. Mehran R, Baber U, Sharma SK, et al. Ticagrelor with or without aspirin in high-risk patients after PCI. *N Engl J Med*. 2019;381(21):2032–2042.

10. 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(23):2407–2416.

KEY WORDS acute coronary syndrome, antiplatelet therapy, diabetes mellitus, East Asian