JACC: ASIA VOL. 3, NO. 1, 2023

EDITORIAL COMMENT

De-Escalation Therapy After PCI in ACS Patients With Chronic Kidney Disease*

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Dual antiplatelet therapy (DAPT) with a $P2Y_{12}$ blocker on top of aspirin is recommended for up to 1 year in patients with acute coronary syndrome (ACS) receiving percutaneous coronary intervention (PCI).[1] However, prolonged DAPT was also reported to be associated with higher risk for bleeding events, and marginally higher mortality risk.[2,3] Therefore, achieving the optimal balance between ischemia and bleeding is indispensable for better clinical outcomes after PCI in ACS. Short duration of DAPT is one of the strategies to reduce bleeding events especially those with high bleeding risks (HBR).[4] HBR patients are recommended to discontinue $P2Y_{12}$ blocker 3 months after stent implantation even in ACS.[1] DAPT de-escalation (switch from potent drugs like prasugrel or ticagrelor to clopidogrel) in ACS patients may be considered as an alternative treatment regimen. The benefit of switching DAPT from aspirin plus a newer $P2Y_{12}$ blocker to aspirin plus clopidogrel 1 month after ACS was evaluated in TOPIC (Timing of Platelet Inhibition After Acute Coronary Syndrome) randomized study.[5] A switched DAPT was superior to an unchanged DAPT strategy to prevent bleeding complications without an increase in ischemic events following ACS. A prasugrel-based dose de-escalation strategy from 1 month after PCI was evaluated in HOST-REDUCE-POLYTECH-ACS (Prasugrel-Based De-Escalation of Dual Antiplatelet Therapy After Percutaneous Coronary Intervention in Patients With Acute Coronary Syndrome) trial.[6] Pharmacodynamic data have shown that the extent of platelet inhibition achieved by reduced-dose prasugrel (5 mg) was weaker than that of the conventional dose of prasugrel (10 mg), but was stronger than that of 75-mg clopidogrel.[7-9] Therefore, 5-mg prasugrel plus 100-mg aspirin was adopted as the de-escalation strategy and was compared with conventional DAPT with 10-mg prasugrel plus 100-mg aspirin. Dose de-escalation strategy from 1 month after PCI reduced the risk of net clinical outcomes up to 1 year, mainly driven by a reduction in bleeding without increasing ischemic events.[6] In the meta-analysis, de-escalation was the most effective strategy as compared with other established uses of DAPT for ACS treatment, resulting in fewer bleeding events without increasing ischemic events.[10] Therefore, de-escalation of $P2Y_{12}$ blocker treatment (switch from prasugrel or ticagrelor to clopidogrel) is a Class IIb recommendation as an alternative DAPT strategy, especially for ACS patients deemed unsuitable for potent platelet inhibition in the 2020 European Society of Cardiology guideline.[1]

Chronic kidney disease (CKD) is reported to be 1 of the high-risk features of stent-driven recurrent ischemic events.[1] CKD is also included as 1 of the risk factors of bleeding events in Academic Research Consortium High Bleeding risk (ARC-HBR) criteria.[11] Therefore, antiplatelet therapy after PCI for the optimal balance of both ischemia and bleeding is still a matter of debate in patients with CKD, especially in ACS.

In this issue of *JACC: Asia*, Yun et al[12] conducted a post hoc analysis of the HOST-REDUCE-POLYTECH-ACS study. Clinical outcomes were compared between the prasugrel dose de-escalation group and the conventional prasugrel dose group according to estimated glomerular filtration rate (eGFR) (high eGFR ≥90 mL/min; intermediate eGFR ≥60 and <90 mL/min; low eGFR <60 mL/min). Prasugrel dose de-escalation was associated with numerically lower rates of net adverse clinical events regardless of

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

ISSN 2772-3747 https://doi.org/10.1016/j.jacasi.2022.10.010

renal function (P for interaction = 0.508). Bleeding occurred less frequently in the de-escalation group than in the conventional group in each eGFR group (high eGFR group 2.1% vs 4.3%; $P = 0.084$, intermediate eGFR group 2.9% vs 5.8%; $P = 0.018$, low eGFR group 4.6% vs 11.1%; $P = 0.024$). The reduction of bleeding was consistent without interaction between the antiplatelet therapy strategy and renal function. However, the magnitude of effect was largest in those with a low eGFR. Regarding the ischemic outcome, the event rates were not significantly different between the de-escalation and conventional groups in all eGFR groups. These findings support the benefit of prasugrel dose de-escalation strategy relative to conventional strategy especially for those with low eGFR in east Asian patients with ACS receiving PCI.

Attention should be paid to the study population of the current post-hoc analysis of the HOST-REDUCE-POLYTECH-ACS study. Although patients with available eGFR were categorized into 3 groups (high eGFR ≥90 mL/min; intermediate eGFR ≥60 and <90 mL/min; low eGFR <60 mL/min), severe CKD patients with eGFR <30 mL/min were rarely included in this study. The risks for ischemic and bleeding events are higher in patients with severe CKD than in those with moderate or mild CKD. Indeed, moderate CKD (eGFR 30-59 mL/min) is included as a minor criterion for ARC-HBR, whereas severe CKD (eGFR <30 mL/min) is included as a major criterion.[4] Therefore, further evidences are warranted regarding the optimal antiplatelet therapy after PCI in patients with severely decreased renal function or dialysis. The dose of prasugrel is also one of the issues to be discussed. Low-dose prasugrel (3.75 mg) is a standard and approved dose in Japan, considering the East Asian paradox with a lower risk of ischemic and a higher risk of bleeding complication in East Asian patients. In the PRASFIT-ACS (Prasugrel Compared With Clopidogrel for Japanese Patients With ACS Undergoing PCI) trial, low-dose prasugrel as compared with a global dose of clopidogrel was associated with a lower incidence of ischemic events without increasing bleeding events in Japanese ACS patients.[13] Therefore, 3.75-mg prasugrel could be 1 of the options in the prasugrel dose de-escalation strategy in East Asian patients.

$P2Y_{12}$ blocker monotherapy is now emerging as 1 of the novel strategies of antiplatelet therapy to reduce bleeding events in ACS. The NEO-MINDSET (Percutaneous Coronary Intervention Followed by Monotherapy Instead of Dual Antiplatelet Therapy in the Setting of Acute Coronary Syndromes) trial is now ongoing that randomizes 3,400 patients with ACS within 96 hours of hospital stay either to the $P2Y_{12}$ monotherapy or DAPT (NEOMINDSET; NCT04360720). The STOPDAPT-3 trial (Short and Optimal Duration of Dual Antiplatelet Therapy-3 Study) that randomizes 6,000 patients with HBR and/or ACS before PCI either to the prasugrel monotherapy or to the conventional DAPT is also being conducted in Japan (STOPDAPT-3; NCT04609111). These trials could provide novel strategies reducing bleeding events without increasing ischemic events in ACS after PCI.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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KEY WORDS acute coronary syndrome, chronic kidney disease, prasugrel