JACC: ASIA VOL. 4, NO. 3, 2024

EDITORIAL COMMENT

Beyond Complexity

Addressing the Prognostic Landscape of High Platelet Reactivity*

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Percutaneous coronary intervention (PCI) has undergone significant evolution over the past 4 decades and currently stands as a globally recognized safe and effective therapeutic option for patients diagnosed with coronary artery disease (CAD). The advent of drug-eluting stents (DES), coupled with advancements in implantation techniques and supplementary pharmacologic therapies, has expanded the application of PCI to patients with heightened comorbidities or more intricate lesions.[1] Consequently, specific patient groups and lesion subtypes pose distinctive challenges for interventional cardiologists, persistently linked to technical complexities, periprocedural complications, and elevated restenosis rates. Ongoing trends suggest that approximately 30% of PCI procedures are now classified as complex, considering both lesion and procedural factors.[2]

Accumulated evidence indicates that complex PCI is associated with unfavorable clinical outcomes.[2,3] However, the optimal treatment strategies for patients undergoing complex PCI remain contentious because of lack of evidence. Notably, there is a dearth of data regarding the potential benefits of adjusting medical treatment, including antiplatelet therapy, for this high-risk population.

The continued advancement of stent technologies with improved drug release kinetics, novel stent materials or platforms, and 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 duration of dual antiplatelet therapy (DAPT).[4] The current landscape of PCI treatment strategies is marked by a prevailing trend toward short DAPT and de-escalation.[5] Nevertheless, in the face of this trend, identifying patients at elevated risk for ischemic events takes on a contrasting but crucial role. Furthermore, the complexity of the procedure was considered as an important parameter in determining the appropriate duration of DAPT.[6] Despite these considerations, the relationship between platelet reactivity and procedural complexity remains unclear. In this issue of *JACC: Asia*, Jin et al[7] present a valuable study assessing the prognostic implications of platelet reactivity, as evaluated by the VerifyNow P2Y12 platelet function test (PFT), in relation to the procedural complexity of PCI. This investigation offers significant insights into the impact of platelet reactivity on clinical outcomes based on the complexity of the procedure.

The investigation revealed that complex PCI with DES significantly was associated with the higher 3-year rates of major adverse cardiac and cerebrovascular events (MACCE) (adjusted HR: 1.21; 95% CI: 1.01-1.44; $P = 0.035$) and all-cause death (adjusted HR: 1.45; 95% CI: 1.15-1.83; $P = 0.002$) compared with noncomplex PCI with DES. In addition, the fourth quartile group of $P2Y_{12}$ reaction unit (PRU), according to the VerifyNow $P2Y_{12}$ PFT, showed the highest risk of MACCE in the complex PCI group (adjusted HR for the fourth vs first group: 1.58; 95% CI: 1.08-2.51; $P = 0.045$), whereas the incidence of MACCE increased according to the quartile category of PRU in the noncomplex PCI group. Irrespective of procedural complexity, the high platelet reactivity (HPR)

*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.

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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.2023.11.009

phenotype defined as on-treatment platelet reactivity ≥252 PRU was significantly associated with MACCE ($P_{interaction}$ = 0.731) and all-cause mortality ($P_{interaction}$ = 0.978). These findings suggested that potent $P2Y_{12}$ inhibition might be necessary to overcome ischemic risk related to factors in the thrombogenic milieu such as HPR phenotype in patients with complex cases who have had PCI.

Although benefiting from the strengths of a 3-year follow-up observation involving more than 10,000 East Asian individuals, this study, as noted by the authors, is not without its limitations. No data on compliance with antiplatelet therapy were collected during follow-up. A single measurement of platelet reactivity may not be representative, as platelet reactivity can fluctuate over time, based on the type and phase of the disease. In addition, generally, patients undergoing complex PCI exhibit more extensive atherosclerosis and higher comorbidity rate compared with those undergoing noncomplex PCI. Although multivariate analysis was conducted, using propensity score-based methods could have further enhanced the reliability of the analysis.

Despite the routine application of PFT or genetic testing in PCI-treated patients not being advocated, the expert consensus acknowledges that a highly selective and discretionary use of PFT to inform potential escalation of $P2Y_{12}$-inhibiting therapy is a reasonable consideration.[8] This is particularly relevant in specific clinical scenarios in which achieving adequate platelet inhibition is paramount, such as in left main coronary artery stenting, last patent vessel PCI, complex lesions, 2-stent bifurcation treatment, cases of patients who have histories of stent thrombosis, and in patients not at excessive risk for bleeding. The findings of the current analysis further align with the expert opinion, supporting the notion that modifying antiplatelet therapy based on PFT in patients undergoing complex PCI may be necessary to mitigate the heightened risk of adverse cardiac events.

Although the prevailing trend in PCI treatment leans toward shorter DAPT and de-escalation, the importance of singling out patients with high ischemic risk cannot be overstated. The present research underscores the importance of discerning high-risk patients through biomarkers and revitalizes the significance of a tailored approach to treatment. The findings are poised to contribute to redefining clinical directions, particularly by accurately identifying high-risk patients amid the emphasis on reduced-dose regimens or de-escalation strategy in the East Asian population who are characterized with lower thrombogenicity and higher bleeding traits.[9] The groundwork for the theoretical rationale supporting the use of potent $P2Y_{12}$ inhibitors or dose escalation in antiplatelet therapy, guided by HPR assessment, is now in place. Future randomized trials are imperative to substantiate the advantages of adapting antithrombotic therapy for minimizing ischemic risk in personalized approaches for patients undergoing complex PCI.

FUNDING SOURCES 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 clinical outcomes, complex percutaneous coronary intervention, platelet reactivity