

What is the Sweet Spot for Platelet Reactivity in Japanese Patients?

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Despite a dramatic decline, atherosclerotic cardiovascular disease (ASCVD) remains the leading cause of mortality and morbidity worldwide, with various treatment strategies being considered. Based on the pathogenetic mechanism of atherosclerosis, the current three main treatment targets can be summarized as lipids, inflammation, and thrombosis. Clinical trials of intensive lipid-lowering therapy with statins, ezetimibe, and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors have confirmed the soundness of the concept “lower is better”, and the evidence obtained has been adopted in various guidelines¹⁻³. However, patients treated with lipid-lowering drugs still develop major ASCVD events, even after achieving the target low density lipoprotein cholesterol level, prompting the need to develop alternative therapies. By demonstrating the feasibility and efficacy of treatment with an interleukin-1b neutralizing monoclonal antibody (canakinumab), Ridker *et al.* recently opened the door to strategies targeting inflammation⁴. Thus, the potential for using anti-inflammatory therapy to treat ASCVD is emerging.

Antiplatelet therapy is important in thrombotic scenarios, especially for patients with acute coronary syndrome. Research on antiplatelet drugs has generally focused on two different approaches. One is development of new potent antiplatelet drugs to improve the outcomes of ASCVD by enhancing antiplatelet activity. The TRITON-TIMI 38 and PLATO trials successfully demonstrated the superiority of more potent novel antiplatelet drugs over clopidogrel in the setting of acute coronary syndrome^{5, 6}. The other approach involves point-of-care measurement of antiplatelet activity. Since many studies have demonstrated wide variability of antiplatelet activity between individuals, it would seem reasonable to titrate antiplatelet therapy

based on measurement of antiplatelet activity, but clinical implementation has been difficult. The VerifyNow system has overcome this problem and has promoted clinical investigation of the relationship between platelet reactivity and the outcomes of percutaneous coronary intervention (PCI). In the large-scale ADPAT DES study, platelet reactivity measured by VerifyNow was clearly associated with the risk of stent thrombosis and mortality after PCI⁷. In addition, sub-analysis of ADPT-DES showed that controlling platelet reactivity is important to prevent adverse events in patients with peripheral artery disease and stroke^{8, 9}. These findings strongly suggest that the antiplatelet activity of antiplatelet therapy influences the occurrence of ischemic events, but it is not clear whether this is applicable in Japanese patients. Clopidogrel is a prodrug that is metabolized to its active form by CYP2C19. There are well-known ethnic differences in the prevalence of loss-of-function abnormalities of CYP2C19, and the high prevalence of CYP2C19 polymorphism in Japanese patients undergoing PCI may have a crucial influence on clopidogrel treatment. In fact, the prevalence of high platelet reactivity was higher in this study than in previous reports, indicating ethnic differences of CYP2C19 polymorphism¹⁰. Even so, the reported incidence of ischemic events, including stent thrombosis, is generally lower among Japanese patients than in western countries. This paradox is difficult to explain and the apparent relationship between high platelet reactivity and a low frequency of ischemic events has long been questioned. In their paper, Nishikawa *et al.* addressed the causal influence of platelet reactivity on the outcomes of PCI in Japanese patients and attempted to identify optimal cutoff points for platelet reactivity in the Japanese population. They demonstrated that platelet reactivity was an independent determinant of adverse events after PCI. Accordingly, their study confirmed observations from the

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ADPT-DES study about the causative relationship of platelet reactivity with stent thrombosis. However, they found a low specificity of platelet reactivity for the risk of serious adverse events (31.9%). As the authors stated, optimization of the stent deployment by imaging guide (done for >90% of stents in Japan) may be a more important determinant of the outcome of PCI. The ADPT-DES sub-study also demonstrated that use of intravascular ultrasound was independently associated with a lower frequency of stent thrombosis. Another important finding was that the cutoff point of 221 for platelet reactivity with the VerifyNow test was within the range reported in previous papers (208-230). Based on previous findings, the so-called East Asian paradox can be stated as follows: "East Asians have a low potential risk of ischemic events and a high risk of bleeding". This suggests that the optimal cutoff value for platelet reactivity may be higher in Japanese patients. However, it seems the optimal antiplatelet effect for preventing ischemic events based on VerifyNow is likely to be universal and consistent. Nevertheless, the finding that the prognostic value of platelet reactivity alone is relatively limited in Japanese patients may reflect their lower incidence of adverse events. Another important finding was that the cutoff points for major / minor / minimal TIMI bleeding were not captured by the VerifyNow assay. Although it has been reported that lower platelet reactivity is associated with bleeding episodes, this result was also not consistent with the East Asian paradox (higher cutoff value for bleeding complications). Multivariate Cox hazard analysis revealed that an age ≥ 75 years and an estimated glomerular filtration rate < 15 mL/min/1.73 m² were two independent predictors of all bleeding. This suggests that the risk factors for bleeding need to be considered more carefully. The optimal level of platelet reactivity may change over time as the risk of ischemia and bleeding changes. In addition, adequate activity of antiplatelet therapy may vary between different clinical scenarios. While "one size fits all" may be convenient, the reality is different. A personalized approach seems to be the best way to prevent ASCVD. This study has provided deep insight into the importance of platelet reactivity in Japanese ASCVD patients. Performing a larger investigation of platelet reactivity using potent antiplatelet agents would further enhance our understanding of antiplatelet therapy. Nishikawa et al. have initiated and promoted discussion about this important, but difficult, issue in Japanese patients, which represents one step towards the future.

Conflict of Interest

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