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Editorial

What is the meaning of P2Y12 reaction units in patients with essential thrombocythemia?

In this issue of the Journal, Yoshida et al. presented a report regarding the platelet reactivity assessed with P2Y12 reaction units (PRU) in patients with acute coronary syndrome with essential thrombocythemia (ET) [1]. There are several previous publications regarding cases of acute myocardial infarction concomitant with ET [2–4]. Some suggest higher risk of thrombus formation in patients with ET [5–7]. In general, increased platelet cell count correlates with higher thrombogenicity mostly due to increased probability for adhesion and cohesion of platelets [8]. The same is true that the risk of bleeding increases in patients with reduced platelet count unless the sizes of individual platelet cells become bigger than normal [9]. It is important to note that even platelet activation under blood flow conditions is regulated by platelet cell counts [10]. The mechano-biological relationship between platelet membrane glycoprotein (GP) Ibα with von Willebrand factor (VWF) under high shear blood conditions and platelet activation is still to be elucidated. We have to realize the complexity of platelet function and its modification by antiplatelet therapy in ET patients even considering just one parameter of increased platelet count.

Prediction of antiplatelet effects with $P2Y_{12}$ inhibitor within ET patients with the use of platelet function testing is even more difficult because of increased platelet count and functional abnormality of platelets in ET patients. There are a few differences in platelet function in ET patients and those without ET. The fact that the known stimulus for increased platelet cell count of thrombopoietin is also known as one of the potent platelet stimulating agents [11]. Most probably, platelet cells in ET patients should be sensitive to other stimuli such as VWF, ADP, and so on.

In the report published by Yoshida et al., they suggested that evaluating platelet reaction units (PRU) with the point of care device (Verify Now, Accumetrics, San Diego, CA, USA) is helpful for predicting the effects of dual antiplatelet therapy (DAPT) in patients after percutaneous coronary intervention (PCI) with ET. However, it is impossible to generalize the results with one case for the general patient population with ET. The "Verify Now" they used to measure PRU is one of the new measures for assessing the effect of antiplatelet therapy [12]. In general, "Verify Now" measures ADP-induced platelet aggregation just like the old measure of ADP-induced platelet aggregation measured by light transmittance [13]. One critical difference from traditional ADP-induced platelet aggregation is that another important platelet ADP receptor of $P2Y_1$-induced activation cascade was blocked by addition of prostaglandin E (PGE)-1 in "Verify Now" [14]. There are numerous contradicting publications whether PRU measures are meaningful for "personalized" dose adjustment of $P2Y_{12}$ inhibitors such as clopidogrel or not [12,15,16]. One of the largest hypothesis-testing clinical trials demonstrated that neither efficacy nor safety was improved by dose adjustment of clopidogrel using "Verify Now" [17,18]. Thus, the clinical relevance of PRU measured by "Verify Now" in patients treated by $P2Y_{12}$ ADP antagonists is still to be elucidated even in patients without ET [19].

A platelet is a small cell, but the exact functional regulation mechanism in this cell is yet to be clarified [8]. Unlike the concepts used for developing "Verify Now," some reports suggest a relevant role of both $P2Y_1$ and $P2Y_{12}$ for increasing intra-cellular calcium ion concentrations [20]. PRU may reflect $P2Y_{12}$ inhibition more closely than ADP-induced platelet aggregation, but this hypothesis is still to be elucidated. Although "Verify Now" is widely used for assessing the efficacy of $P2Y_{12}$ inhibitors, we have to be aware that all the results might just be an interesting artifact and not relevant to clinical outcomes.

A previous publication suggests that platelet cells in patients with ET are resistant to stimulation by catecholamines [21]. Platelet cells express α_2-receptor for stimulation by catecholamines. Platelet cells become more sensitive to other stimulation when α_2-receptors are stimulated by small amounts of catecholamine [22]. Increased number of platelets with heterogeneous characteristics of sensitivity or resistance to ADP stimulation in ET might result either in apparently "resistant" or "sensitive" to any stimulations in mass of platelet cells as shown in Fig. 1. "Verify Now" assesses platelet function as a "mass of platelet cells" and not as individual ones. Reaction as a "mass of cells" may not be the same as "individual platelets". One typical example is that the intracellular calcium ion concentrations of individual platelet cells go up and down over time [20], while it looks like an increased monophasic response in a "mass of platelet cells" [23]. Platelet cells in vivo are hugely heterogeneous in size, number of expressing proteins, and reaction to various stimuli in individual cells [10]. A greater inter-platelet heterogeneity in patients with ET might be the reason to show apparently different behavior against ADP receptor stimulation as shown in Fig. 1.

Finally, the use of "point of care devices" to individualize antithrombotic therapies remains challenging. Even though some trials suggest correlation of PRU and thrombotic event rates, no study has demonstrated the benefit of personalized adjustment of the dose of $P2Y_{12}$ ADP receptor inhibitors by PRU. All results using "Verify Now" might just be an interesting artifact. If we really want

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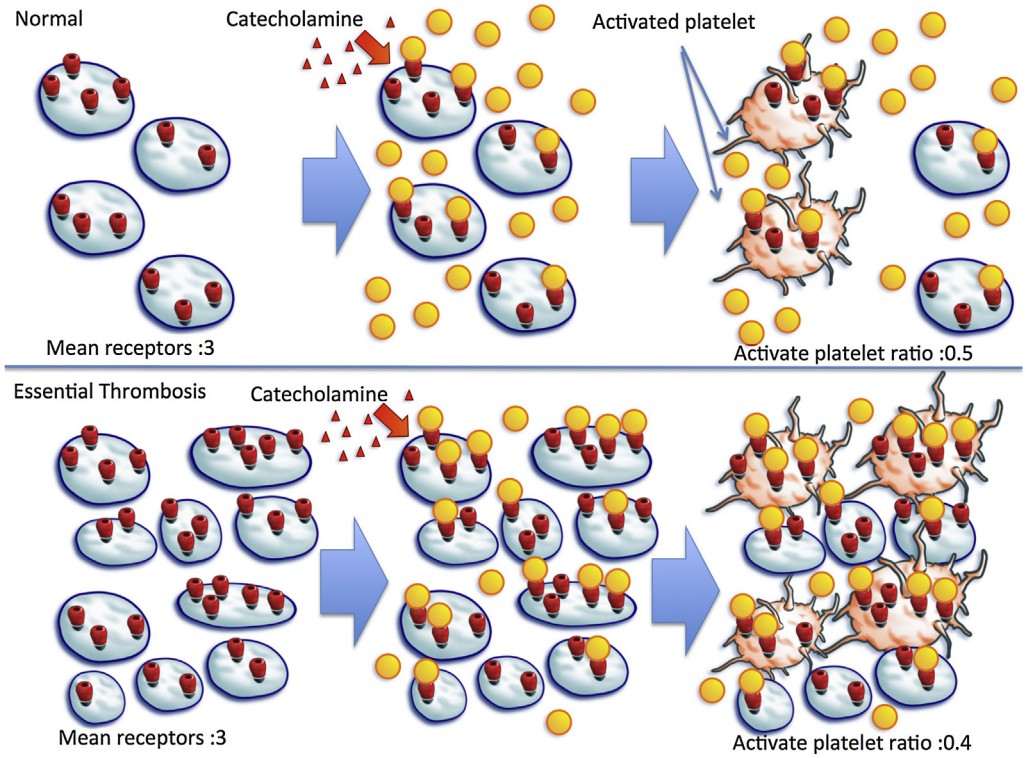

Fig. 1. Why the speculation based upon the results of "VerifyNow" for the mechanism of platelet activation and/or its inhibition by drug intervention is problematic? Increased number of platelet cells in ET may influence the apparent response of platelets in "mass". We have to be careful for assessing the effects of antiplatelet agents with the use of point of care devices just measuring the reaction of "mass of cells".

to establish the logic for "personalized medicine" for the use of $P2Y_{12}$ ADP receptor inhibitors, quantitative understanding of the relationship between the dose taken as drugs, the actual $P2Y_{12}$ ADP receptor blockage (e.g. number of receptors blocked/number of available receptors) [8], and the quantification of the heterogeneity between actual $P2Y_{12}$ ADP receptor blockage and cell response (such as number of GPIIb/IIIa proteins changed to activated form, number of dense granules released, number of fibrinogen molecules released from activated platelet, etc.) is necessary. An evidence-based approach emphasizing the importance of randomized control trials (RCTs) might still have some role for personalized medicine by selecting a small high-risk population who needs new therapies [24]. For the rare case such as ET, a "bottom up" approach with constructive logic from exact understanding of the detailed mechanism of platelet cells is essentially important.

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