High on-treatment platelet reactivity (HPR): What does it mean, and does it matter?

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In this issue of *Thrombosis and Haemostasis*, Saucedo et al. (1) demonstrate that the prevalence of high on-treatment platelet reactivity was decreased after changing clopidogrel to prasugrel. It is perhaps appealing that the patients with adverse "high on-treatment platelet reactivity (HPR)" with clopidogrel was reduced when switched to prasugrel. From a scientific point of view, the meaning of "HPR" is still unclear. This uncertainty is derived from an arguably confusing clinical development history of the thienopyridine-type antiplatelet agents (ticlopidine, clopidogrel, and prasugrel). Indeed, the use of these agents was greatly expanded based on the clinical experience, rather than on their mechanistic understanding.

A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE) was published in 1996 (2). However, the precise mechanism of antiplatelet action exerted by clopidogrel was clarified only after cloning the target ADP receptor of P2Y₁₂ in 2001 (3). Moreover, the extent of P2Y₁₂ ADP receptor blockade by active metabolite of clopidogrel in an individual patient, which should be a real bio-marker for this drug, has been measured in a very limited number of studies only (4).

Nonetheless, some uncertainty remains about how much percentage of P2Y₁₂ receptor should be blocked to achieve appropriate antithrombotic effects in individual patients. Obviously, the goal is not to achieve 100% inhibition of P2Y₁₂ because P2Y₁₂ deficiency manifests as a bleeding disorder (5).

Where do we go from here?

One approach is to suggest that "HPR" can be defined by more complex platelet function testing. Nonetheless, the percentage of P2Y₁₂ blockade in patients with "HPR" is yet to be understood.

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Invited Editorial Focus

**Figure 1: Exertion of anti-P2Y₁₂ effects by thienopyridine(s).** Thienopyridine(s) including ticlopidine, clopidogrel, and prasugrel are pro-drug(s). Active metabolite(s) are generated by the effects of enzyme(s) located in the liver. Since the active metabolite(s) are very reactive, they can easily bind with P2Y₁₂ receptors in liver circulation (A, C). The rest of active metabolite(s) diffuses to plasma (B). Since the active metabolite(s) is irreversibly bound to P2Y₁₂, the extent of P2Y₁₂ on platelets circulating in the liver is equal to that circulating in the peripheral circulation (D).

Figure 1A: Microcirculation around liver. Inactive clopidogrel

Figure 1B: Peripheral Blood. Diffusion to peripheral blood

Figure 1C: Platelet in Liver Circulation. P2Y₁₂ ADP Receptors

Figure 1D: Platelet in Peripheral Blood

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“Evidence-based” or “Personalised”

Patients with “HRP” might exist, yet what could be done for those patients also remains undetermined. In attempting to identify the specific patients with “HRP”, that is insufficient P2Y12 receptor blockage, one could recommend to measure P2Y12 receptor occupancy by the drugs. More complicated platelet function testing, for example, platelet aggregation, VerifyNow, VASP-P, without measuring P2Y12 receptor occupancy, might provide information that platelets from those patients with “HRP” are more sensitive to other stimulations (9). Those patients might be at higher risk of thrombotic events (10), but there is insufficient clinical evidence to conclude whether or not their thrombotic risk would be reduced by additional P2Y12 antagonism.

Antiplatelet therapy is widely used based on clinical evidence. Yet, even the clinical evidence with new antiplatelet drugs has stirred some debate and discussion (11-17). In the field of “evidence-based medicine”, physicians are more concerned about the results that have occurred in the “patient population”. However, the “patient population” might not be homogenous. Some of the patients recruited in CAPRIE trials might be low-responders to clopidogrel while the other are hyper-responders. If the “patient population” is homogenous, the result of each clinical trial can be fully generalised.

Thus, one could argue a potential role for HPR since it is important to select specific patient(s) at high risk of thrombosis for risk-stratified “personalised” antiplatelet intervention(s). Until more data become available, it remains unclear whether the selection of “high on-treatment platelet reactivity” by platelet function tests will be useful or not. Things can only get better once the knowledge gaps are addressed (18).

Conflicts of interest

S. Goto has received honoraria from Sanofi-Aventis and AstraZeneca. A. Tomiya declares no conflicts of interest.

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