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The optimal threshold of high post-treatment platelet reactivity could be defined by a point-of-care VerifyNow P2Y12 assay

We read with great interest the study by Price *et al.*,[1] which verifies that high post-treatment platelet reactivity (HPPR) measured with a point-of-care VerifyNow assay (Accumetrics Inc., San Diego, CA, USA) is associated with post-discharge events after percutaneous coronary intervention (PCI) with drug-eluting stent (DES), including stent thrombosis. To the best of our knowledge, this is the first study to identify a threshold of HPPR of VerifyNow based on the clinical outcomes.

Recently, a number of studies have demonstrated that clopidogrel non-responsiveness proven in the laboratory testing, i.e. HPPR, has been associated with an increased risk for cardiovascular events.[2] Light transmittance aggregometry (LTA) is the gold standard test to determine the clopidogrel responsiveness. However, the abundant demands of LTA make it difficult to utilize in daily practice. VerifyNow was developed as a point-of-care test and showed a significant correlation with ADP-induced LTA ($r = 0.64 - 0.73$).[3]

In previous studies using LTA, platelet aggregation of >50% induced by 5 μM ADP[4] or of >70% induced by 10 μM ADP[5] has been suggested an absolute threshold of HPPR for predicting the ischaemic outcomes. In the study of Price *et al.*, the optimal cut-off for the combined endpoint was a post-treatment reactivity of ≥235 PRU (P2Y12 reactivity unit) (area under curve [AUC] 0.711, 95% confidence interval [CI] 0.529–0.893, $P = 0.03$). Because this study did not show the association between the HPPRs by a point-of-care test and ADP-induced LTA, we estimated the relation using our data. Three hundred consecutive patients undergoing PCI with DES implantation at our hospital were enrolled between October 2007 and March 2008. We performed 5 μM ADP-induced LTA and VerifyNow using the same blood sampling via the arterial sheath. LTA was performed in all patients according to standard protocols.[6] Both PRU ($r = 0.641$, $P < 0.001$) and percentage platelet inhibition ($r = 0.679$, $P < 0.001$) measured by VerifyNow had significant correlations with the results of 5 μM ADP-induced platelet aggregation. By the receiver-operating characteristics curve analysis, the optimal cut-off for predicting HPPR on LTA (5 μM ADP-induced platelet aggregation >50%) was PRU ≥ 239 (AUC 0.794, 95% CI 0.736–0.851, $P < 0.001$). The PRU value ≥ 239 showed a sensitivity of 83.6% and a specificity of 68.3%, and was similar to the threshold of high reactivity value (PRU ≥ 235), suggested by Price *et al.*[1] The percentage platelet inhibition of ≤20 was the optimal cut-off for predicting HPPR on LTA (AUC 0.841, 95% CI 0.790–0.891, $P < 0.001$), which showed a sensitivity of 76.2% and a specificity of 83.6%.

A VerifyNow assay has been used widely in the daily practice instead of LTA. However, its usefulness for predicting adverse cardiovascular events has been still undetermined. On the basis of our data analysis, we could ascertain that high platelet reactivity on VerifyNow (PRU ≥ 235 suggested by Price *et al.*) is significantly correlated with HPPR on ADP-induced LTA. It might suggest a substitutability of VerifyNow in terms of assessment of clopidogrel responsiveness and practical implication for risk stratification.

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'A threshold of platelet reactivity for ischaemic events?' and 'The optimal threshold of high post-treatment platelet reactivity could be defined by a point-of care VerifyNow P2Y12 assay': reply

We thank Dr Bonello and colleagues and Jeong and colleagues for their interest in our paper.[1] We agree with Dr Bonello and colleagues that the clopidogrel regimen around the time of platelet function measurement is crucial, since this impacts both the level of platelet reactivity and possibly acute clinical outcomes. As we note in the methods section of our paper, patients on chronic clopidogrel therapy in our study were not re-loaded, and those who were clopidogrel-naïve received a 600 mg loading dose. There was no significant difference in ADP-induced platelet reactivity between these two groups (mean 183 + 94 PRU vs. 186 + 73 PRU), nor was there a difference between these groups in the rate of patients having high platelet reactivity (28 vs. 35%, $P = 0.15$). While it does not specifically apply to our study, the author's concern about the effect of additional clopidogrel loading doses on platelet function testing around the time of PCI is a valid one, because the measured platelet reactivity after an additional loading dose in patients already on clopidogrel therapy may not reflect steady-state platelet reactivity on standard maintenance treatment after discharge. Another issue raised by Dr Bonello and colleagues is the interference by glycoprotein IIb/IIIa inhibition with the particular point-of-care platelet function assay used in our study. These issues highlight the challenge of using point-of-care platelet function testing to stratify long-term patient risk in the 'real world' of clinical practice where patients receive heterogeneous clopidogrel therapy and frequent glycoprotein inhibition around the time of percutaneous coronary intervention.

We chose to report absolute post-treatment platelet reactivity (HPPR) rather than the percentage of receptor inhibition for several reasons. Baseline reactivity prior to clopidogrel exposure was not available in all patients, so that the percentage change in ADP-induced platelet reactivity after exposure could not be determined. Although the current VerifyNow P2Y12 assay that is commercially available reports a '%' inhibition by comparing the ratio of ADP-induced reactivity with iso-TRAP-induced reactivity, this was not available because the assay device used in a portion of our study did not contain the iso-TRAP channel required for this calculation (but did have the same ADP-channel). However, from a pathophysiological standpoint, we believe that post-treatment reactivity is a better measure of risk. Indeed, the 'response' to clopidogrel as measured by percent inhibition may overestimate the risk of stent thrombosis in non-responders and underestimate the risk of stent thrombosis in responders. This is because patients with low pre-treatment reactivity who demonstrate only a small percentage change post-treatment will be categorized as 'non-responders' despite persistent low reactivity. Conversely, patients with very high pre-treatment reactivity who have a large percentage inhibition may be categorized as 'responders' but continue to have high post-treatment reactivity.[2]

Dr Jeong and colleagues provide important data regarding the relationship between platelet reactivity measured by the VerifyNow device and light transmittance aggregometry (LTA). They demonstrate that our 'optimal' cut-off for high HPPR with the VerifyNow P2Y12 assay that we identified using the receiver–operator characteristic curve analysis is consistent with previous, operational definitions of HPPR proposed by investigators using LTA. Despite the growing body of data that support the clinical significance of inter-individual response variability, the clinical implication of any definition of HPPR, including our own, must be verified in much larger, prospective studies. Moreover, the appropriate management of patients with HPPR is unknown. The Gauging Responsiveness with A VerifyNow assay- Impact on Thrombosis And Safety (GRAVITAS) trial (Clinicaltrials.gov identifier NCT00645918)—a randomized, placebo-controlled study which is examining whether an increased clopidogrel maintenance dose in patients with HPPR reduces thrombotic events in patients undergoing drug-eluting stent implantation—may help answer this question.

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