Immunity to thrombotic events is achievable if we stop the guessing game: Is this the major hidden message from GRAVITAS?

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The GRAVITAS (Gauging Responsiveness With A VerifyNow assay-Impact on Thrombosis And Safety) trial (1) was the first large prospective study designed to answer the fundamental question: “Does adjustment of antiplatelet therapy in post-DES (drug-eluting stent) patients with high platelet reactivity (HPR) to adenosine diphosphate (ADP) reduce the occurrence of thrombotic events?”. The P2Y12 receptor plays a critical role in amplifying platelet activation in response to numerous agonists and the ADP-P2Y12 interaction is central to the genesis of thrombosis (2). Therefore, it is rational to quantify the intensity of ADP-P2Y12 interaction in the individual patient as a modifiable risk factor for post-PCI (percutaneous coronary intervention) ischaemic event occurrence and reduce its intensity as a strategy to obviate platelet-mediated ischaemic event occurrence.

Mostly non-emergent patients were enrolled in GRAVITAS and the VerifyNow P2Y12 assay was used to identify HPR (>230 P2Y12 reaction units [PRU]) (1). The strategy to combat it was a 600 mg extra loading dose given the day after stenting followed by 150 mg (high-dose) vs. 75 mg clopidogrel maintenance therapy. The major findings of GRAVITAS were: i) high-dose clopidogrel was ineffective in reducing the six-month composite ischaemic event occurrence (cardiovascular death, non-fatality myocardial infarction, and stent thrombosis); both groups had a remarkably low event rate (2.3%); ii) high-dose clopidogrel was associated with a 40% prevalence of HPR at 30-days that essentially persisted for six months; and iii) in the secondary comparison, the group without HPR treated with standard-dose clopidogrel had the numerically lowest thrombotic event rate (1.4%).

Some possible reasons why GRAVITAS ended up being a “negative” trial have been postulated: mainly non-emergent and not “high-risk” patients were enrolled, resulting in much lower event rates than predicted, the pharmacodynamic effect of high-dose was overestimated – a large number of patients had persistent HPR, and the chosen PRU cut-point was too high. The results of GRAVITAS may have been “positive” had a highly effective combatant against HPR such as prasugrel or ticagrelor (3–5) been used and the PRU cut-point been lower. However, the new P2Y12 inhibitors that provide clearly more uniform and potent antiplatelet effects than high-dose clopidogrel were not available at the time GRAVITAS began.

A vasodilator-stimulated phosphoprotein derived platelet reactivity index (VASP-PRI) 50% has been associated with the onset of post-PCI ischaemic event occurrence (6). In order to estimate the corresponding PRU value (by VerifyNow P2Y12 assay) that matched a PRI >50% (VASPY assay), we conducted a receiver-operating characteristic (ROC) curve analysis using platelet function data collected from stable coronary artery disease patients who were on dual antiplatelet therapy (n=1,165 data points) (4–6). In this analysis, a PRI >50% correlated with a PRU >167 (sensitivity 89%, specificity 80% and concordance rate 85%, p<0.001) (Fig. 1, left panel). This PRU level is identical to the lowest PRU value measured at 12–24 hours post-stenting that was associated with ischemic event occurrence in GRAVITAS during treatment with 75 mg maintenance therapy: ∼170 PRU was associated with a 100% negative predictive value (1). Moreover, a poorer correlation was observed between PRI >50% and PRU >230 (sensitivity 74%, specificity 87%, and concordance rate 80%) (Fig. 1, right panel).

In the end, GRAVITAS still does not provide an answer to the interventionist’s main question. However, in a very important secondary analysis from GRAVITAS of patients treated with standard maintenance dose clopidogrel in both non-HPR and HPR groups, patients with platelet reactivity <170 PRU cut-point were immune to post-PCI event occurrence. The concept that we can not just reduce but prevent the arguably most critical event – thrombosis is a major hidden message within the data from GRAVITAS. However, more work needs to be done to determine if bleeding risk significantly increases as PRU falls from 230 to 170. These data support the “threshold hypothesis”, which tells us that thrombotic events may be significantly reduced (or eliminated) by achieving platelet reactivity below a specific level (2). Further reduction may only enhance the risk for bleeding without further attenuating thrombotic risk. More work to validate the “threshold hypothesis” with proper patient selection, a stronger P2Y12 antagonist strategy and a revised optimal VerifyNow P2Y12 cut-off value are needed. We should now use the valuable information gained from GRAVITAS and other studies to move forward in designing future studies to prove once and for all that personalisation of antiplatelet therapy is the optimal way to enhance outcomes in PCI patients. Most importantly, the GRAVITAS data provide hope that immunity to post-PCI thrombosis is achievable if we stop the guessing game.
Figure 1: ROC curve analysis and distribution of platelet measurements. Left panel: PRU value corresponding to VASP-PRI > 50%. Right panel: VASP-PRI > 50% (black arrow) was compared with PRU > 230 (blue arrow) versus 167 (red arrow). ROC, receiver-operating characteristics; VN, VerifyNow P2Y12 assay; PRU, P2Y12 reaction unit; VASP, vasodilator-stimulated phosphoprotein; PRI, platelet reactivity index; AUC, area under curve; CI, confidence interval.

Conflict of interest
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References
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