More transparency for a therapeutic window in platelet P2Y_{12} inhibition?

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This editorial refers to ‘Bleeding and stent thrombosis on P2Y\textsubscript{12}-inhibitors: collaborative analysis on the role of platelet reactivity for risk stratification after percutaneous coronary intervention’\textsuperscript{†}, by D. Aradi et al., on page 1762.

Ever since the first evidence of aspirin’s benefits in prevention of arterial thrombotic events at the expense of increased risk of bleeding, clinicians have had to contend with carefully balancing thrombotic and haemorrhagic risks in individual patients in order to tailor treatment for optimization of risk. The development of platelet P2Y\textsubscript{12} receptor antagonists, used in conjunction with aspirin, has been pivotal in the widespread adoption of percutaneous coronary intervention (PCI) as a dominant treatment strategy for stable angina and acute coronary syndromes. This dual antiplatelet therapy has transformed clinical outcomes by dramatically cutting the risks of stent thrombosis, myocardial infarction, ischaemic stroke, and cardiovascular death. However, as expected, this has come at the expense of greater risks of spontaneous and procedure-related bleeding, although strategies exist to attenuate these risks, such as use of proton pump inhibitors, restricted use of glycoprotein IIb/IIIa antagonists, cautious anticoagulant dosing, preferential use of radial artery access for PCI, and following guidelines for discontinuation of antiplatelet therapy prior to surgery. Clopidogrel replaced ticlopidine as a safer thienopyridine for P2Y\textsubscript{12} inhibition, but does not have universal efficacy due to poor efficiency of active metabolite formation in some individuals, only partly due to genetic factors, and this predisposes these individuals to higher risk of thrombotic events, particularly stent thrombosis.\textsuperscript{1,2} At the other extreme are individuals who have a high response to clopidogrel and are better protected from stent thrombosis at the expense of increased risk of bleeding\textsuperscript{3} and protracted time to recovery of normal platelet reactivity after cessation of therapy.\textsuperscript{4} Poor response to clopidogrel has been addressed by developing, first, a more efficiently metabolized thienopyridine, prasugrel, and, secondly, an oral, reversibly binding, non-prodrug P2Y\textsubscript{12} receptor antagonist, ticagrelor.\textsuperscript{5} These more effective P2Y\textsubscript{12} receptor antagonists have replaced clopidogrel as recommended first-line therapy for the majority of patients with acute myocardial infarction,\textsuperscript{6,7} but are not yet recommended for patients undergoing PCI for stable coronary artery disease who have a lower risk of thrombotic events.\textsuperscript{8}

The platelet P2Y\textsubscript{12} receptor plays a critical role in overall platelet reactivity since it mediates powerful amplification of platelet activation in response to a wide range of platelet agonists and thereby controls the extent of platelet responses that underpin, first, platelet plug formation and, secondly, occlusive thrombus formation (Figure 1). Increasing platelet P2Y\textsubscript{12} receptor blockade, therefore, progressively inhibits a wide range of platelet responses.\textsuperscript{9} Several standardized platelet function assays are now available that can assess differing levels of P2Y\textsubscript{12}-mediated platelet reactivity, with most evidence linking the assay results to clinical outcomes for the VerifyNow P2Y12 assay, Multiplate ADPtest, and the vasodilator-stimulated phosphoprotein (VASP) phosphorylation assay. Daniel Aradi and co-workers have now performed intriguing analyses of numerous studies assessing the prognostic value of these assays in thienopyridine-treated patients undergoing PCI.\textsuperscript{10} Their findings confirm and reinforce those of individual studies that have indicated a threshold of platelet reactivity above which the risk of stent thrombosis is much greater. In addition, they find that the risk of bleeding is significantly greater at lower levels of platelet reactivity determined by these assays. This now consolidates the concept of a therapeutic window of platelet P2Y\textsubscript{12} inhibition that optimizes the combined risks of stent thrombosis and bleeding (Figure 2).

So do the analyses of Aradi et al. herald a new era of platelet function testing for guiding the extent of P2Y\textsubscript{12} inhibition in PCI patients? Certainly this is an attractive concept for minimizing the risk of stent thrombosis. Despite the failure of large studies to support a role for platelet reactivity assays in clopidogrel-treated PCI patients,\textsuperscript{11–13} design limitations of these studies mean that they do not refute the over-riding concept that more effective P2Y\textsubscript{12} inhibition leads to lower stent thrombosis rates.\textsuperscript{10} On the other hand, barring delayed absorption in morphine-treated ST-elevation myocardial infarction patients, the responses to ticagrelor and prasugrel are much...
more consistent than those of clopidogrel and may negate the need for platelet function testing to assess stent thrombosis risk in patients receiving these newer agents. Consequently, the burning question is whether it should be recommended that all clopidogrel-treated patients should have platelet function testing at the time of PCI and, if so, can this ever be a cost-effective strategy. The analyses of Aradi et al. provide a caveat to such an approach—adjusting treatment to minimize the risk of stent thrombosis might lead to unnecessarily increased risk of bleeding if such treatment adjustment leads to very low P2Y₁₂-mediated platelet reactivity. Repeat testing may be needed to guide therapy within the putative therapeutic window with the potential frustration that variability in the assay results may undermine such an approach. Translating observations within populations to individualization of therapy is not a simple process! More work is clearly needed before targeting a therapeutic window of P2Y₁₂ inhibition can be recommended.

One important point to bear in mind is that the platelet reactivity assays described in the paper by Aradi et al. do not measure all aspects...
of platelet reactivity, only platelet reactivity to ADP, and are specifically estimating the level of P2Y12 receptor blockade. Consequently, these assays do not take into account the effects of aspirin on platelet reactivity to some other platelet agonists such as collagen (Figure 1). Thus, a therapeutic window of P2Y12 inhibition established in aspirin-treated patients is unlikely to be applicable to patients who are treated with P2Y12 inhibitor monotherapy since aspirin has additional effects on platelet reactivity and haemostasis, even at the highest levels of P2Y12 inhibition. Further studies would be required to determine whether a therapeutic window exists for P2Y12 inhibitor monotherapy, and these studies potentially could find that a lower limit for optimal platelet reactivity no longer exists for the assays of P2Y12-mediated platelet reactivity, in the absence of concomitant aspirin therapy.

A further question is whether the therapeutic window varies between individuals according to their thrombotic and bleeding risks. This is highly likely to be the case. For example, inappropriate low platelet reactivity for a low thrombotic risk patient may represent optimal platelet reactivity for a high thrombotic risk patient without high bleeding risk. In the PLATO PLATELET substudy, the overwhelming majority of ticagrelor-treated patients had a post-doce VerifyNow PRU value of <95,14 identified in the paper of Aradi et al. as ‘low platelet reactivity’,10 and yet ticagrelor in the PLATO study was shown to reduce ischaemic events and cardiovascular mortality, with no increase in fatal bleeding despite more spontaneous bleeding, compared with a clopidogrel strategy that placed more patients in the therapeutic window identified by Aradi et al. The PEGASUS study produced similar clinical outcome findings when ticagrelor was compared with placebo in aspirin-treated patients with previous myocardial infarction.15 Therefore, it is unclear whether ticagrelor breaks the mould, constructed from studies of thienopyridine-treated patients, regarding the link between the level of P2Y12 inhibition and clinical outcomes or whether patients with acute coronary syndromes require a greater level of P2Y12 inhibition compared with PCI patients with stable coronary artery disease in order to lower cardiovascular mortality risk optimally. More spontaneous bleeding may be the price to pay for attaining this goal. On the other hand, dropping aspirin in the context of consistent and high-level platelet P2Y12 inhibition may achieve a better balance of risks, particularly following a period of stent endothelialization, and future studies will address this hypothesis.

In conclusion, the important findings of Aradi et al. should stimulate further work in this area to optimize the application of oral antiplatelet therapy for PCI patients in order to achieve the best balance of thrombotic and bleeding risks in individual patients and so further improve clinical outcomes following PCI. Meanwhile, it is clear that high platelet reactivity in clopidogrel-treated patients is an important risk factor for stent thrombosis, while the optimal level of P2Y12 inhibition for cardiovascular mortality reduction remains uncertain and is likely to be influenced by concomitant antithrombotic therapy.

Conflicts of interest: R.F.S. reports grants, consultancy fees, and honoraria from AstraZeneca; grants and consultancy fees from Merck; consultancy fees, honoraria, and non-financial support from Accutomecs; consultancy fees from Aspen, PlaqueTec, The Medicines Company, ThermoFisher Scientific, Correvio, Daiichi Sankyo, Eli Lilly, Roche, Regeneron, and Sanofi Aventis; and travel support from Medtronic. In addition, he is listed by AstraZeneca as an inventor in a patent pending based on the results of the PEGASUS study, but has no financial interest in this.

References


