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EDITORIAL

Platelet reactivity when switching from cangrelor to oral P2Y$_{12}$ receptor inhibitors: insights from a real-world registry

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Dual antiplatelet therapy with aspirin and a P2Y$_{12}$ receptor inhibitor (P2Y$_{12}$-i) is the standard of care for patients undergoing percutaneous coronary intervention (PCI)[1]. However, in high-risk settings, such as patients with acute coronary syndrome (ACS), the onset of action of an oral P2Y$_{12}$-i, including the more potent prasugrel and ticagrelor, can be delayed, leaving a gap in platelet inhibition up to 4-6 hours after PCI. Cangrelor, the only currently available intravenous P2Y$_{12}$-i, is characterised by high antiplatelet potency and fast onset and offset of action, making it a viable option in patients undergoing PCI who require immediate and potent platelet inhibition[2]. In clinical trials, cangrelor has been shown to reduce thrombotic events in patients undergoing PCI when used in addition to clopidogrel[3]. However, in real-world practice, prasugrel and ticagrelor are more commonly used among cangrelor-treated patients. Although most pharmacodynamic (PD) studies have shown that cangrelor is able to provide additional platelet inhibition when used along with prasugrel and ticagrelor in various clinical settings[4-6], one study has suggested high residual platelet reactivity (HRPR) in patients with ST-segment elevation myocardial infarction (STEMI) receiving cangrelor[7]. In addition, switching from cangrelor to an oral P2Y$_{12}$-i poses some concerns about drug-drug interactions, which have been extensively explored in PD studies but poorly explored in real-world practice[8].

In this issue of EuroIntervention, Gargiulo and colleagues present data from the ongoing POMPEII Registry, an investigator-initiated prospective registry evaluating the pharmacodynamic effects of cangrelor in patients undergoing PCI[9]. Patients received ticagrelor, prasugrel and clopidogrel as loading and maintenance doses according to guidelines, but the type of oral P2Y$_{12}$-i as well as the timing of loading dose administration when transitioning from cangrelor were left to the operator's discretion. The study involved 150 patients undergoing PCI, with 86 (57%) presenting with ACS, including 56 patients with STEMI, of whom 24 received pretreatment with ticagrelor.

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Platelet reactivity was assessed at different timepoints by light transmittance aggregometry (LTA) and Multiplate (Roche Diagnostics) with adenosine diphosphate stimuli, as well as with VerifyNow (Werfen) to report P2Y$_{12}$ reaction units. The primary endpoint was the percentage of inhibition of platelet aggregation (%IPA) at 30 minutes after bolus administration, as assessed by LTA. The authors found that %IPA at 30 minutes was 57.6%, and 3.2% of patients showed HRPR, which was assessed to be lower by Multiplate and VerifyNow (1.6%). At 3 hours (1 hour after stopping infusion), platelet reactivity increased significantly, leading to a %IPA of 43.9% at this timepoint and 37.1% of patients with HRPR. Platelet reactivity then decreased again at 4-6 hours, with a %IPA of 55.7% and 15.3% of patients with HRPR. Notably, the presence of HRPR appeared to be related to the drug administered for switching to the oral route. Up to 68% and 30% of patients receiving clopidogrel had HRPR at 30 minutes and 4 to 6 hours, respectively, while only 10% and 3% of patients transitioning to ticagrelor had HRPR at these timepoints. Interestingly, up to 75% of patients pretreated with ticagrelor had HRPR at baseline, but platelet reactivity was significantly inhibited by the administration of cangrelor and progressively reduced over time even after termination of cangrelor infusion. Specifically, maximal platelet reactivity assessed by LTA went from 67.5±22% at baseline to 34.7±16.4% at 30 minutes and further reduced to 27.6±19.3% at 4 to 6 hours.

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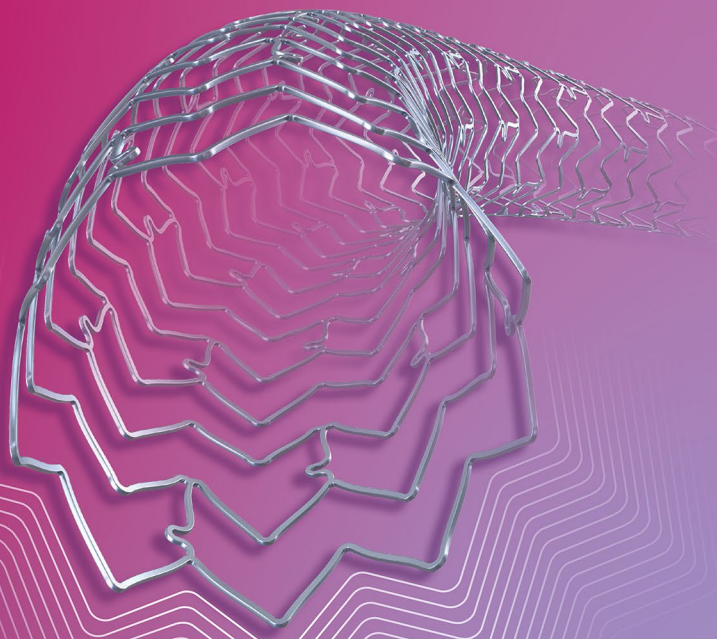

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Overall, the authors should be congratulated for the granularity of their analysis, which provides valuable insights into cangrelor's periprocedural effects in a real-world setting. However, some factors should be considered when interpreting the results of the present study. First, this was an observational study conducted at a single centre, which may limit the applicability of the results to other cohorts. Only a minority of patients received prasugrel, which is currently favoured in ACS patients over ticagrelor according to guidelines[1]. Second, there was no assessment of the CYP2C19 genotype involved in clopidogrel metabolism, therefore raising the question of whether the HRPR observed in patients transitioning to oral clopidogrel could have been in part due to the unwanted selection of carriers of loss-of-function alleles. Third, in the absence of a control group, the value of this study in assessing drug-drug interactions after stopping cangrelor infusion is limited. An increase in platelet reactivity after stopping infusion is expected because of the higher potency of cangrelor. Finally, the present results should be compared with the previous data for cangrelor reported in the FABOLUS-FASTER trial, which randomised $P2Y_{12}$-i-naïve patients who presented with STEMI undergoing PCI to receive either cangrelor, tirofiban or prasugrel[7]. The trial found that cangrelor was associated with high rates of HRPR, which are lower in the current study[7]. Differences in study results may stem from differences in laboratory processing or study design or enrolled population. FABOLUS-FASTER was a randomised trial specifically enrolling STEMI patients at 3 centres across Italy and Switzerland, while in the present analysis of the POMPEII Registry, only 25.4% of the patients presented with STEMI, thus limiting the generalisability of the results in this population. Indeed, both these studies used %IPA as the primary endpoint, aiming at very high levels of inhibition. However, an intravenous antiplatelet agent does not necessarily need to aim at the highest possible %IPA, but at a sweet spot of inhibition to balance thrombotic protection and bleeding risk[10]. The highest level of %IPA with glycoprotein IIb/IIIa inhibitors is clinically associated with increased bleeding. In addition, HRPR rates, a well-known surrogate for ischaemic events, were very low at 30 minutes in this study, and would probably have been even lower at 1 hour, a timepoint that was not tested. Notably, propensity score-matched data focusing on clinical outcomes are reassuring in terms of the periprocedural clinical efficacy and safety of cangrelor in STEMI patients[11].

In conclusion, the present study confirms that concomitant use of cangrelor and oral $P2Y_{12}$-i may lead to drug-drug interactions, which could translate into non-negligible rates of HRPR, especially in patients switched to clopidogrel, although it is still uncertain how these interactions may affect patient outcomes. In addition, although the present data reassure on the efficacy of cangrelor in STEMI patients, including those already on ticagrelor, larger studies are warranted to better elucidate the clinical outcomes of patients transitioning from cangrelor to potent oral $P2Y_{12}$-i, especially in high-risk clinical settings.

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Conflict of interest statement

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