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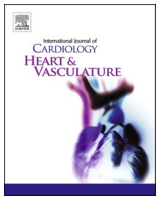

Cangrelor to optimise platelet inhibition in STEMI patients pre-treated with ticagrelor: A Sisyphean task?

In Greek mythology, Sisyphus was condemned by Hades to roll a boulder up a hill in Tartarus. However, each time the boulder neared the top, it was enchanted to roll back down to the bottom of the hill, condemning Sisyphus to repeating this labour for eternity. As a result, the term 'Sisyphean' is now used to refer to a task that is arduous but ultimately futile [1].

In the current edition of *International Journal of Cardiology Heart and Vasculature*, Gargiulo and colleagues present a pharmacodynamic analysis of patients presenting with ST-elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PPCI) who were treated with intravenous cangrelor following earlier pre-treatment with the potent $P2Y_{12}$ inhibitor ticagrelor [2]. These data are from the '*PharmacOdynaMic effects of cangrelor in PatiEnts wIth acute or chronIc coronary syndrome undergoing percutaneous coronary intervention*' (POMPEII) study, a registry enrolling patients undergoing treatment with PCI who received cangrelor. A previous analysis by the same authors had focused on the pharmacodynamic effects of cangrelor in the setting of elective complex PCI [3]. In that study, the authors had reported that cangrelor resulted in rapid platelet inhibition. However, they had expressed caution with respect to a potential rebound effect at the end of the cangrelor infusion, before the effects of the oral $P2Y_{12}$ inhibitor had been achieved. It was also noted by the authors that the patients who demonstrated high residual platelet reactivity (HRPR) after cangrelor cessation had received clopidogrel as the switching drug, with no patients in the ticagrelor-switched group demonstrating HRPR [3].

Ticagrelor may be particularly suitable for use in conjunction with cangrelor. The exact mechanism of action of cangrelor, a nucleotide mimetic, is not entirely clear, although it is thought to act via competitive binding at the ADP binding site of the $P2Y_{12}$ receptor [4]. This mechanism of action would fit with the results of pharmacodynamic studies, which have suggested that there is an interaction when a thienopyridine is administered during a cangrelor infusion, with cangrelor inhibiting the active metabolites of clopidogrel and prasugrel from binding to the $P2Y_{12}$ receptor [5]. Ticagrelor, a cyclopentyltriazolopyrimidine, is an allosteric antagonist of the $P2Y_{12}$ receptor, binding at a separate site from the ADP binding site and resulting in a conformational change in the receptor.

The 13 STEMI patients included in this analysis were pre-treated with ticagrelor within 1 h of undergoing PPCI in addition to receiving cangrelor. In addition to treatment with ticagrelor, all patients received aspirin and unfractionated heparin. Cangrelor was administered as a 30 μg/kg bolus followed by a 4 μg/kg/min infusion for 2 h. The authors report that the patients included in this analysis demonstrated low levels of maximal platelet aggregation after 30 minutes of cangrelor, a finding that was maintained at 1 h and at 2–4 h after stopping the 2-hour cangrelor infusion, with no patients demonstrating high residual platelet reactivity. The authors used several different pharmacodynamic assays to assess levels of platelet inhibition (light transmittance aggregometry with 20- and 5-uM adenosine diphosphate stimuli, the VerifyNow P2Y12-test and the multiplate electrode aggregometry ADP test).

While the authors are to be congratulated for attempting to better understand the potential role cangrelor might play in the treatment of patients presenting with STEMI undergoing PCI, this study is not without limitations. The first is the absence of a control group. Without this, it is not possible to determine how much of the observed platelet inhibition is due to the effect of cangrelor and how much is due to the effects of ticagrelor pretreatment. The second important limitation is the small size of the study, with only 13 patients included. Thirdly, it is important for us to remember that the patients enrolled in the POMPEII registry were treated with cangrelor at the discretion of the operator. Therefore, it is unclear how representative these patients are of the wider STEMI population. Finally, it is a pharmacodynamic study and therefore does not inform us regarding clinical outcomes.

The concept that rapid inhibition of platelet activity via $P2Y_{12}$ inhibition will result in improved outcomes in patients presenting with acute coronary syndrome (ACS) appears logically sound and may be intuitively attractive to physicians. The *Platelet Inhibition With Cangrelor and Crushed Ticagrelor in STEMI Patients Undergoing Primary Percutaneous Coronary Intervention* [CANTIC] study previously reported that cangrelor results in rapid platelet inhibition in the setting of STEMI [6]. In the CANTIC study, patients were randomized to treatment with either cangrelor or a matching placebo. All patients were also treated with a 180-mg loading dose of crushed ticagrelor tablets at the time of the cangrelor/placebo bolus. The CANTIC authors also reported that after discontinuation of the cangrelor/placebo infusion, there were no differences in levels of platelet reactivity between the two groups, suggesting that there was no drug–drug interaction with concomitant administration of cangrelor and ticagrelor [6].

It is also recognised that the pharmacodynamics of ticagrelor can vary depending on the mode of administration (integral, crushed and dissolved tablets). The MOJITO study reported that in the context of STEMI, crushed ticagrelor tablet administration provided earlier platelet inhibition compared with standard integral ticagrelor tablets. This

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difference was apparent only at 1 h after administration, with comparable platelet inhibition in the two groups at 2,4 and 8 h. However, clinical trials in patients with STEMI undergoing PPCI, including ATLANTIC (pre-hospital vs in-hospital loading with ticagrelor) and COMPARE-CRUSH (integral vs crushed prasugrel tablets), have failed to demonstrate that more rapid platelet inhibition translates into clear clinical benefits [7–8]. It may be relevant to note that while the COMPARE-CRUSH randomized trial demonstrated that pre-hospital crushed prasugrel resulted in improved platelet inhibition at the time of coronary angiography in comparison to integral tablets in patients with STEMI undergoing PPCI, this did not result in improved clinical outcomes [8]. Similarly, currently available randomized and observational data have failed to strongly support the concept of pre-treatment in patients presenting with STEMI [9–10].

Available data from the large randomized clinical trials of cangrelor (the Cangrelor versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition [CHAMPION] series of trials) suffer from the shared limitation that cangrelor was compared to, or investigated in the setting of, treatment with clopidogrel rather than prasugrel or ticagrelor, which are the preferred $P2Y_{12}$ inhibitors in patients with ACS undergoing PCI as per current guidelines [9,11–13]. With respect to STEMI populations, it is also relevant to note that in the CHAMPION-PHOENIX trial, less than half of the enrolled patients presented with ACS and less than one-fifth with STEMI [11].

Consequently, current European guidelines do not provide strong recommendations for pre-treatment with a $P2Y_{12}$ inhibitor or for cangrelor in patients presenting with STEMI [9]. For patients with STEMI undergoing PPCI, pretreatment with a $P2Y_{12}$ inhibitor received a Class IIb, level of evidence (LoE) B recommendation in the latest European Society for Cardiology ACS guidelines [9]. In the same guideline, cangrelor received a Class IIb, LoE A recommendation for $P2Y_{12}$ inhibitor naïve ACS patients undergoing PCI [9]. Given that the treatment regimen received by the patients in this analysis does not fully represent guideline recommended care, it is unclear how applicable the findings from the study by Gargiulo et al. are to current clinical practice [2,9].

Overall, while these data provide further support to the concept that cangrelor is capable of achieving rapid platelet inhibition in the setting of STEMI it remains unclear whether this would ultimately translate into a meaningful benefit in terms of clinical outcomes in comparison to potent oral $P2Y_{12}$ inhibition alone [2,6]. However, the only way this can be definitively determined is through dedicated randomized controlled trials in this population, powered for clinical outcomes and comparing a strategy using cangrelor and an oral potent $P2Y_{12}$ inhibitor to a strategy consisting of oral $P2Y_{12}$ inhibition alone. If well designed, adequately sized clinical trials were conducted and demonstrated a clinical benefit with cangrelor, this would result in changes to our treatment paradigm. Until we have such supporting data, patients with STEMI undergoing PCI should continue to be managed as per current guideline recommendations, with parenteral anticoagulation, a loading dose of aspirin, and a loading dose of an oral $P2Y_{12}$ inhibitor at the time of PCI [9]. Based on currently available data, trying to achieve better clinical outcomes by improving upon the rapid platelet inhibition already achieved with oral loading doses of potent $P2Y_{12}$ inhibitors in patients with STEMI may represent a Sisyphean task.

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