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Pleiotropic actions of ticagrelor versus clopidogrel – Do molecular differences translate into superior clinical efficacy after myocardial infarction?

Antiplatelet therapy encompassing P2Y12 adenosine diphosphate (ADP) receptor antagonists is a cornerstone of secondary prevention in patients after myocardial infarction (MI). The past decade has seen a dramatic evolution of P2Y12-targeting therapeutics, from the first-generation thienopyridine ticlopidine to the safer and more efficacious agents available now [1]. Yet even these differ significantly in their pharmacology and net cardiovascular outcome, so the questions remains which agent is most appropriate for an individual patient, and whether P2Y12 antagonists can be switched when patients present with acute coronary syndrome (ACS) [2].

Clopidogrel is a pro-drug activated by a two-step biotransformation after oral intake, and inhibits P2Y12 receptors irreversibly for the lifespan of the platelet. The limiting features of clopidogrel are its dependence on cytochrome P450 iso-enzymes for hepatic metabolism [3], wide inter-individual variation in response, substantial drug interactions and a slow onset of action. Ticagrelor inhibits P2Y12 reversibly at a site distinct from ADP, requires no biotransformation and forms an active metabolite. Accordingly, ticagrelor provides a more rapid, greater and more consistent platelet inhibition than clopidogrel [4], and was superior in terms of preventing MI, stroke, and cardiovascular death in the PLATO (Platelet Inhibition and Patient Outcomes) study of patients with ACS [5]. Preclinical studies identified pleiotropic actions unique to ticagrelor that can be attributed to inhibition of the equilibrative nucleoside transporter (ENT) type-1 (ENT-1) [6,7]. ENT-1 is located mainly on erythrocytes, but has also been described in other cells of the cardiovascular system, and mediates adenosine uptake and delivery to intracellular degradation machinery. ENT-1 inhibition will conceivably preserve extracellular adenosine levels and augment cardioprotective signaling through adenosine receptors (reviewed in [8]). P2Y12-independent anti-inflammatory actions of ticagrelor [9,10] may therefore be partially ascribed to its ability to elevate adenosine.

P2Y12 antagonism is without doubt a proven approach to reduce mortality and cardiovascular events of MI survivors, but as with all pharmacological approaches that modify the hemostatic system, adverse bleeding might offset the benefits of using ADP antagonists. The important question is if the more potent antiplatelet action and possible pleiotropic benefits of ticagrelor come at the cost of increased bleeding, which is itself associated with higher mortality in MI survivors. The PLATO trial clearly showed a greater benefit with ticagrelor compared to clopidogrel, with no difference in adverse bleeding. But do the rigorous selection criteria in such trials adequately reflect the so-called real-world patient population?

In the current issue of the *International Journal of Cardiology Heart & Vasculature*, Alfredsson and colleagues [11] addressed this question. In a cohort of patients representing the typical elderly, multimorbid survivor of ST-elevation MI, the authors identify increased bleeding complications with the aggressive ticagrelor-based antiplatelet regimen compared to the conservative clopidogrel-based approach, with no discernible benefit in terms of adverse cardiovascular events. This contrasts directly the PLATO findings, highlighting the need for caution when extrapolating data from well-controlled clinical trials to the real-world population at large. A recent propensity score analysis of contemporary European ACS registries suggests that, compared to clopidogrel, ticagrelor does show a favourable outcome/safety profile [12]. Yet in the Swedish register study presented here [11], the pleiotropic actions of tiagrelor, whether due to inhibition of ENT-1 and/or modulation of other targets, do not seem to translate into a better risk-safety profile compared to clopidogrel. This effectively reiterates findings from a just-published US population-based cohort study of patients with ACS, where ticagrelor was not associated with a statistically significant reduction in major adverse coronary events (MACE) compared to clopidogrel, but with a heightened risk of adverse bleeding [13].

The authors of both studies critically considered inherent study limitations in their conclusions, particularly sample size, and differences between patients receiving aggressive versus conservative antiplatelet treatment. In the Swedish study [11], patients in the clopidogrel group were older (mean age 69 versus 65 years), more often women (32% versus 24%), were more often discharged with an oral anticoagulant (11% vs <1%) and exhibited a higher comorbidity burden. Yet even after appropriate propensity score matching and adjustment, bleeding complications and TIMI major/minor bleeding were still significantly higher in the ticagrelor cohort, and this increased risk was relevant for both younger patients and those over 75 years. MACE were numerically lower in the group treated with ticagrelor, but this difference not significant after

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adjustment. This is another clear example of how mechanistic insight gained at the bench may be lost in translation to the clinical setting.

In the end, it is the individual bleeding risk and requirement for stringent platelet inhibition that will decide which antiplatelet approach is best for each patient. In this context, two aspects arising from the non-competitive and reversible pharmacology of ticagrelor should be kept in mind. First, while the rate of offset is faster for ticagrelor compared to clopidogrel, full platelet reactivity does not actually return for up to 5 days after the last dose, resulting in a sustained bleeding risk after discontinuation [1]. Second, in situations where platelet function needs to be urgently restored, ticagrelor dissociating from P2Y12 binding in patients may inhibit donor P2Y12, and render platelet transfusion ineffective [14]. Finally, ticagrelor was also associated with more dyspnea and ventricular pauses than clopidogrel in PLATO, and may moreover lead to QTc prolongation [15]. Thus in some patients the putative benefit of ticagrelor may not be worth taking the proven risk.

Disclosure

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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