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Letters

Effects of Ticagrelor, Prasugrel, or Clopidogrel at Steady State on Endothelial Function

Ticagrelor is a nonthienopyridine direct and reversible $P2Y_{12}$ platelet receptor antagonist, and unlike prasugrel or clopidogrel inhibits, at least partially, the sodium-independent equilibrative nucleoside transporter 1 (1). This ticagrelor-mediated off-target effect has potential to improve endothelial function (1,2), but the evidence is limited (3,4).

The HI-TECH (Hunting for the off-target propertIes of Ticagrelor on Endothelial function and other Circulating biomarkers in Humans) study (NCT02587260) is a randomized, open-label, multicenter crossover study (5). Eligible patients suffered at least 30 days earlier from an acute coronary syndrome (ACS), were free from ischemic or bleeding complications and reported regular intake of a dual antiplatelet therapy regimen. Each patient was exposed to each of the 3 oral $P2Y_{12}$ inhibitors following a 3-period balanced Latin square crossover design with 4 weeks per treatment period.

Primary endpoint measurements were performed 30 ± 5 days after the witnessed intake each $P2Y_{12}$ inhibitor (90 mg twice a day for ticagrelor, 10 mg/day for prasugrel [or 5 mg/day if >75 years of age or weight <60 kg], and 75 mg/day for clopidogrel).

Assessment of endothelial function was obtained using pulse amplitude tonometry, which records digital pulse wave amplitude using fingertip plethysmography (EndoPAT, Itamar Medical, Caesarea, Israel) and quantifies the endothelium-mediated changes in vascular tone, elicited by a 5-min occlusion of the brachial artery. A post-occlusion to pre-occlusion ratio is calculated by the EndoPAT software and expressed as reactive hyperemia index (RHI). Assessment of platelet $P2Y_{12}$ inhibitor functional assay was performed with VerifyNow system (Accriva Diagnostics, San Diego, California).

The primary endpoint was defined as RHI at treatment steady state, assessed 1 to 2 h after MD (maintenance dose) intake of the 3 $P2Y_{12}$ inhibitors, and consisted of 2 main comparisons: ticagrelor versus prasugrel difference in RHI and ticagrelor versus clopidogrel difference in RHI. With 36 patients completing all sequences (i.e., 6 patients/sequence) the study provided 90% power to detect a 10% RHI relative change in the ticagrelor group (RHI after ticagrelor MD administration) with a 2-sided alpha level at 5%. A total of 54 patients were allocated to 1 of the 6 randomization sequences in 5 centers. Of these, 50 (92.6%) patients completed the randomized $P2Y_{12}$ inhibitor sequence and the primary endpoint measure was available for 47 (87.0%) patients.

Mean time from index ACS to baseline visit was 233 ± 189 days, ranging from 38 to 1,023 days. RHI after MD assessment (primary endpoint) did not differ after ticagrelor ($n = 51$; 1.970 ± 0.535) as compared with prasugrel ($n = 50$; 2.007 ± 0.64; difference: −0.048; 95% confidence interval: −0.212 to 0.115; $p = 0.557$) or clopidogrel ($n = 49$; 2.072 ± 0.646; difference: −0.034; 95% confidence interval: −0.200 to 0.132; $p = 0.685$) (**Figure 1**). $P2Y_{12}$ platelet reactivity units were lower after ticagrelor as compared to clopidogrel as compared with prasugrel after MD (**Figure 1**). Sequence of $P2Y_{12}$ did not impact treatment effects ($p = 0.492$).

Several lines of research have suggested that ticagrelor may exert an adenosine-mediated $P2Y_{12}$-independent mechanism of action. Ours is the third randomized trial to assess the off-target effects of ticagrelor on vascular function (3,4), yet it is the first extending the comparison of ticagrelor to both prasugrel and clopidogrel and the first multicenter trial being executed in a chronic setting (i.e., focusing on stabilized post-ACS patients).

In prior investigations, the duration of treatment with ticagrelor was either 4 or 5 weeks, and therefore comparable to the 4-week duration of each $P2Y_{12}$ inhibitor in our study. We recruited patients after a mean time from index ACS of 233 ± 189 days, ranging from 38 to 1,023 days. In both prior studies, patients were recruited at index admission for ACS without prior exposure to dual antiplatelet therapy. Our findings do not prove that ticagrelor exerts measurable off-target effects on endothelial function in stabilized post-ACS patients.

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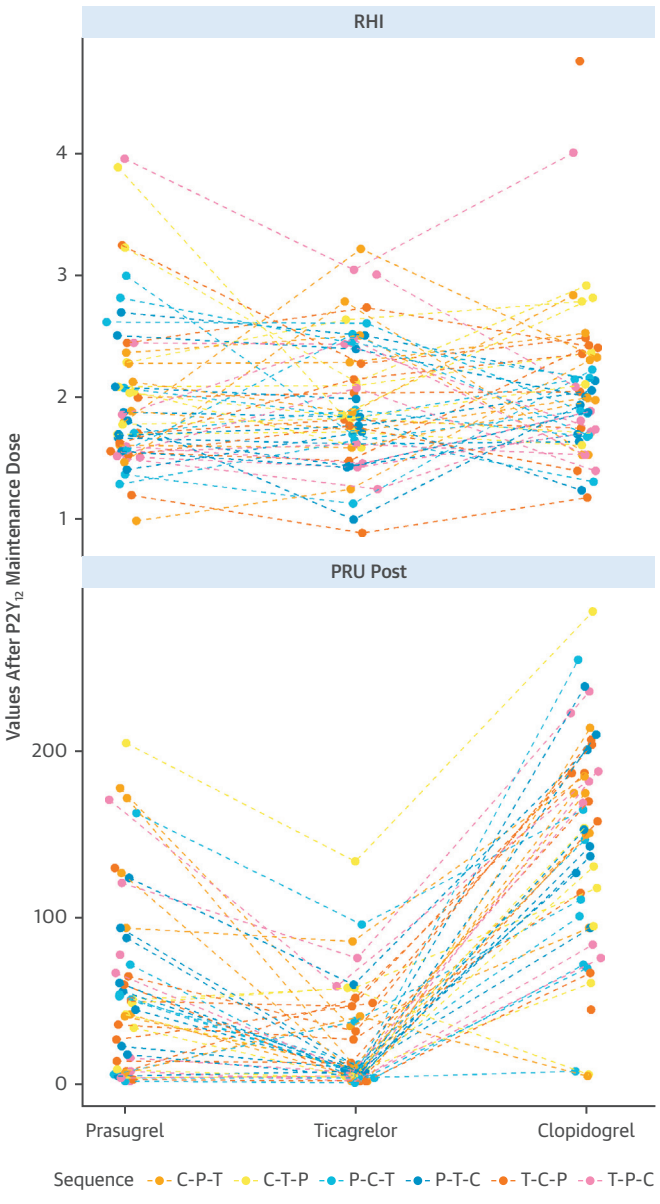
FIGURE 1 Reactive Hyperemia and Platelet Reactivity at Steady State



C = clopidogrel; P = prasugrel; PRU = platelet reactivity units; RHI = reactive hyperemia index; T = ticagrelor.

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Clarifying the Proper Definitions for Type 2 Myocardial Infarction

We read with interest the paper by Nestelberger et al. (1) and would like to take this opportunity to comment on it. It would appear that Nestelberger et al. (1) have misunderstood the criteria for type 2 myocardial infarction that were defined in the documents of the Universal Definition of Myocardial Infarction in 2007 and 2012, respectively (2,3). These criteria have remained unchanged in these 2 documents, although the text of the 2007 version was slightly modified and, in addition, a figure was inserted in the 2012 version to improve readability and perception of the latter document. Nevertheless, it seems that Nestelberger et al. (1) have misinterpreted the text inasmuch as they state that the criteria for the presence of coronary artery disease were changed between the 2 documents. This was, indeed, not the case (2,3). Thus, Nestelberger et al. (1) incorrectly used the 2007 and 2012 Universal Definition of Myocardial Infarction criteria as a starting point for a comparison of type 2 myocardial infarction patients with and without coronary artery disease (1). This mistaken interpretation seriously damages their conclusions.

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REPLY: Clarifying the Proper Definitions for Type 2 Myocardial Infarction

As the conclusions from our large multicenter diagnostic study are data-driven, they are not affected by preferences in the interpretation of the 2007 second universal definition (1,2). Our findings clearly show that in the absence of overt ischemic heart disease, patients presenting to the emergency department with symptoms related to supply demand mismatch and associated cardiomyocyte injury as, for example, in patients with paroxysmal supraventricular tachycardia who have a much lower risk of cardiovascular death as compared to patients with type 1 myocardial infarction or patients with