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Letters

TO THE EDITOR

Pleiotropic Effects of Ticagrelor Beyond its Potent Antiplatelet Effects Contributing to Additional Clinical Benefits

We read with interest the report in which Ariotti et al. (1) investigated whether ticagrelor improves endothelium-dependent dilation. This is an excellent randomized, crossover trial.

However, these results were inconsistent with previous studies. In comparison to our previous study (2), the enrolled patients were not at relatively high risk because the prevalence of diabetes was only 20%. Sample size calculation was based on the reactive hyperemia index which targeted disease-free participants. Consequently, absolute number needed for confirming vascular benefits of ticagrelor by the reactive hyperemia index should be higher. In this trial, because changes of flow-mediated dilation improved significantly in the ticagrelor group compared with the clopidogrel group, the pleiotropic effects of ticagrelor should be further investigated.

More importantly, the authors enrolled the stabilized patients after acute coronary syndrome. Sixty-nine percent of patients had been prescribed ticagrelor before randomization. In our study (2), improvement of vascular function accessed by flow-mediated dilation was observed during the periods of administrating ticagrelor with partial maintenance of beneficial effects even after crossover. Because there were no washout periods, retained effects of ticagrelor could not be excluded. How long-term uses of ticagrelor could impact the vascular functions or biomarkers was not investigated until now.

In addition, targeting vascular biomarkers should focus on the pathways of adenosine. In our study (2), we already confirmed that circulating adhesion molecules and C-reactive protein did not show significant differences between ticagrelor and prasugrel; however, interleukin-6 and tumor necrosis factor-α decreased significantly only after ticagrelor administration, presumably via stimulating adenosine 2A and 2B receptors.

In this trial, adenosine level was not increased even in the ticagrelor group. To measure the adenosine plasma level, it is known that the role of stop solution is critical to prevent adenosine degradation and uptake right after the blood collection. For instance, the treatment time of stop solution to blood, the ratio of blood and stop solution, and the volume of blood are critical parameters influencing the plasma adenosine concentration (μmol/l). Detailed description about materials and methods of adenosine measurement would help in understanding the results.

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Please note: The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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REPLY: Pleiotropic Effects of Ticagrelor Beyond Its Potent Antiplatelet Effects Contributing to Additional Clinical Benefits

We appreciate the comments of Dr. Jeong and colleagues on the HI-TECH (Hunting for the Off-Target Properties of Ticagrelor on Endothelial Function and Other Circulating Biomarkers in Humans) trial (1).

Our study was not meant to focus on patients with diabetes because there is no evidence or biological premises suggesting that the off-target effects of ticagrelor might be enhanced in this population. Yet, randomization was stratified based on diabetes, and our pre-specified subgroups analyses did not show that diabetes is a treatment modifier with respect to our primary endpoint measure or adenosine levels. Our sample size calculation was based on published information on test-retest reliability of pulse amplitude tonometry measures of vascular endothelial function (2). Our assumptions in terms of expected endothelial function values and reproducibility were met, and actual study power, based on the final number of patients who completed all study measures, was in excess of 90% for a 10% relative difference between ticagrelor versus prasugrel and clopidogrel. Hence, claiming that the null findings of our study were justified by lack of power is an artificial argument. Flow-mediated dilatation was restricted to a subset of patients and did not prove to be significantly better either in ticagrelor sequences as compared with both the clopidogrel and prasugrel ones. As detailed in the paper, there was no signal of a true carryover effect of ticagrelor during other $P2Y_{12}$ inhibitor sequences, and the selected $P2Y_{12}$ inhibitor before inclusion had no measurable impact on study results (1). As previously detailed (3), all precautions were taken in order to properly measure circulating adenosine, including an AstraZeneca supervised and certified central core lab for the analyses and the use of pre-filled syringes containing a stop-solution for blood sampling.

We did not measure interleukin-6 or tumor necrosis factor-alpha. We did measure, however, C-reactive protein, which is highly correlated to interleukin-6, and which was unaffected by the $P2Y_{12}$ inhibitor sequences.

Dr. Jeong and colleagues claim that our results were inconsistent with previous studies, but are actually referring only to their own study: a previous large and multicenter trial that assessed a large set of vascular and inflammatory biomarkers, including interleukin-6 and tumor necrosis factor-alpha, and failed to observe any difference between ticagrelor and clopidogrel (4).

We remain open to follow the lessons provided by Albert Einstein, who noted that if the facts do not fit the theory, the latter and not the former should be changed.

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TO THE EDITOR

Superficial Femoral Artery Recanalization via Transradial Access or a Combined Radial-Pedal Access Strategy

We read with interest the paper by Ruzsa et al. (1), which corroborates the feasibility of transradial access and a combined radial-pedal access strategy in superficial femoral artery (SFA) recanalization, as we previously described (2-5). We have the following technical comments.

First, the investigators did not specify how many of the 22 patients undergoing a radial-pedal access strategy had unfavorable femoral access features. As we previously published, we reserve the combined radial-pedal access strategy for patients with both complex SFA disease and no reasonable transfemoral option, that is, patients with features that make crossover femoral recanalization and/or antegrade crossing unfavorable: 1) complex aortoiliac anatomy; 2) ostial SFA occlusion without a stump; or 3) severely diseased and calcified distal reconstitution (2,3). In the latter cases, retrograde access is readily required, and controlled antegrade-retrograde tracking is frequently needed, which may justify the tibiopedal