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Creative scientific dispute — different points of view on the protocol and execution of the ISAR-REACT 5 trial

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ABSTRACT

Discordant interpretations of the results of clinical trials often drive scientific disputes.

Our position concerning the protocol and performance of the ISAR-REACT 5 trial have been termed as false and groundless in the recently published article. We deeply disagree with this judgement and still maintain all our opinions expressed in the previous publications, without any exceptions. As demonstrated in multiple studies, prasugrel has excellent effectiveness and predictability. In our previous publications, it was not the drug itself that we put under criticism, but rather the quality of the trial assessing the drug. As a consequence of this critical approach, we stated that taking into account the serious limitations of the ISAR-REACT 5 trial, its results should be taken with cautiousness.

To summarize, we remain open to further creative scientific dispute enriching both readers and authors.

Key words: Prasugrel, ticagrelor, antiaggregation drugs, acute coronary syndrome, clinical trials

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Introduction

Creative scientific dispute presenting results of clinical trials from different points of view is a valuable tool for enriching the knowledge of the adversaries and the readers.

One of the articles published in the latest issue of „Folia Cardiologica”, titled „Modern therapy of acute coronary syndromes based on prasugrel — available to Polish patients” [1], undermines the arguments adduced in our two earlier publications critical of the methodology of the ISAR-REACT 5 trial [2, 3]. As authors of the former two publications, we feel obliged to refer to these objections.

We are deeply convinced that criticism can be of a stimulative value only when not left unresponded.

Critical analysis and dispute

The majority of our remarks concerning the protocol of the ISAR-REACT 5 trial [4] and its performance [5] were termed by our opponent as false and groundless. We deeply disagree with this judgement and still maintain all our opinions expressed in the previous publications [2, 3], without any exceptions.

The long-anticipated results of the ISAR-REACT 5 trial comparing ticagrelor with prasugrel turned out to be a surprise, pointing to superiority of prasugrel over ticagrelor and contradicting the trial's initial assumptions [4, 5]. In our opinion this contradiction whatsoever does not enhance the validity of the results of the trial.

Our dispute adversary, truthfully notices our criticism of the open character of the trial, underestimation of non-compliance to recommended therapy and the form of follow-up based on telephone calls. Further, she states that these features in fact underlie the strength of the trial, rendering it closer to everyday clinical reality rather than concentrating on a highly selected population of a clinical trial [1]. We disagree with this opinion — none of the mentioned factors (open character of the trial, compliance underestimation, indirect contact with the patient) are relevant regarding the trial's inclusion and exclusion criteria and as such, they remain irrelevant with respect to patient selection. In our opinion, the situation is exactly opposite. The assumption of nearly absolute compliance (according to the authors of the ISAR-REACT 5 trial amounting 99.1% and 99.6% in the prasugrel and ticagrelor arm, respectively) seems quite risky and in fact it moves the results away from reality, rather than renders them closer to it [2, 3].

Our opponent's [1] astonishment derived from our remarks concerning the ITT-type of analysis (intention-to-treat – population receiving the originally assigned treatment) and inclusion of patients who eventually did not receive the medication as originally allocated, is quite incomprehensible as we clearly stated an opposite fact, namely, that such method is commonly accepted in this type of clinical trials. However, in this specific case, taking into account the exceptionally high rate of study drug discontinuation (ticagrelor arm: 653 of 2012 patients (32%), prasugrel arm: 609 of 2006 patients (30.4%)), a significant bias might have occurred [5]. Therefore, it is not the methodology that we subject to criticism, but only the possible consequences of including into the analysis a surprisingly high number of patients who in fact were not treated with the originally assigned drug [2, 3]. Of note, among the 4018 patients randomized for the trial, the study drugs were discontinued in 820 (20.4%) of them within first few days after randomization, even before discharge from hospital [5].

According to our opponent, it is quite unlikely that the difference in the rate of the primary endpoint (death, myocardial infarction or stroke) within a year following randomization between the ticagrelor (9.8%) and prasugrel (6.8%) arm is insignificant [1]. In order to clarify, we would like to clearly state that in our both publications a detailed statistical analysis of the primary endpoint in the ISAR-REACT 5 trial was presented [2, 3]. However, we also included information, which due to space constraints was published in the supplemental contents outside the main text, telling that the on-treatment analysis did not show significant differences between the study arms regarding the primary endpoint occurrence between discharge from hospital and either therapy discontinuation or follow-up completion [5]. We also highlighted that taking into account the fact that 1262 patients of those included in the analysis had had the study drug discontinued, while 37 patients were lost to follow-up, the absolute difference between both study groups in the primary endpoint occurrence amounted barely 47 cases and can hardly be considered significant [2, 3].

Our adversary also disagrees with our objections concerning the ISAR-STAR 5 trial, resulting from the comparison of its results with the outcomes reported for the TRITON-TIMI38 trial. She also finds our position stating that the differences in the primary endpoint rates between these both trials (6.9% for ISAR-REACT 5 versus 9.9% for TRITON-TIMI 38) seem unexpected and hard to explain, to be surprising [1]. In response to these remarks – stating that such differences in outcomes between the both trials exist is simply acknowledging a fact rather than raising an objection against the ISAR-REACT 5 trial [5, 6]. Regarding the other remark, we admit that we were and still are startled with this difference, and we

seem to be not the only ones, as the outcomes of the ISAR-STAR 5 trial were an unexpected finding even for the authors of the trial [5]. We admit, we cannot explain the magnitude of the difference and we remain open for any explanatory suggestions for this fact. Interestingly, the major difference in the occurrence of the primary endpoint between the prasugrel arms of the ISAR-REACT 5 and TRITON-TIMI38 trials was not accompanied by analogous difference between the ticagrelor arms of these trials [5].

The Orville Wright quote: “If we all worked on the assumption that what is accepted as true is really true, there would be little hope of advance.” used by our opponent as a comment, although otherwise arousing appreciation, in our opinion, in this specific setting is misguided and wrongful. We are deeply convinced that none of our two criticized papers [2, 3], neither our previous publications regarding antiaggregation therapy [7–74], legitimate assumptions that our intention is inhibition of progress through creation of opinion stagnation, instead of quest for the truth aimed at advance.

The closing critical remark addressed at our publications argues against our objections regarding the lack of identification of causes for patient exclusion from the safety analysis, pointing that such causes were reported in the original publication of the ISAR-REACT 5 trial [1]. Unfortunately, we cannot support this point of view, as the original report reveals that in 172 and 184 patients respectively randomized to ticagrelor and prasugrel, the initial diagnosis of acute coronary syndrome was not confirmed. According to the trial protocol, the consequence of this fact in case of prasugrel should be desisting from drug administration, in conjunction with exclusion of these patients from the safety analysis (modified intention to treat). The numbers reported in the original publication were 23 and 233 respectively and they do not correspond to the numbers of patients with unconfirmed diagnosis of acute coronary syndrome, while no explanation for the real numbers of exclusions in both groups were presented [5].

Following the critical review of our position, our opponent highlights the excellent results of acute coronary syndrome treatment based on prasugrel, in an attempt to convince the readers about the advantages of this P2Y₁₂ receptor inhibitor [1]. In this aspect, we fully support her point of view, however in the global context of the paper, the initial reference to ticagrelor in the summary paragraph may surprise. The author indicates that ticagrelor is likely to produce intermittent dyspnea, occasionally leading to drug discontinuation [1], however she omits the crucial fact that ticagrelor is the only antiplatelet agent with proven reduction in cardiovascular mortality and all-cause mortality [75].

Juxtaposition of the final portion of the paper with its earlier part, critical of our publications, brings to

mind an attempt of defending prasugrel. In this aspect, this action resembles convincing ones who are already convinced as prasugrel needs no defense. The effectiveness and predictability of prasugrel has been demonstrated in numerous publications, also those coming from our research team [11, 17, 25, 26, 35, 38, 39, 46, 60, 62, 69], and undeniably prasugrel holds a strong position in multiple guidelines.

We would like to clearly stress that the critical remarks presented in our publications strictly apply to the quality of the drug-assessing study, not the drug itself. That is why we concluded that concerning the serious shortcomings of the ISAR-REACT 5 trial, its results should be taken with cautiousness [2, 3].

Concluding, we remain open to further creative scientific dispute enriching both readers and authors.

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