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Adenosine and Ticagrelor Plasma Levels in Patients With and Without Ticagrelor-Related Dyspnea

Ortega-Paz et al: Adenosine and Ticagrelor in Drug-Related Dyspnea

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Dyspnea is a common side effect of ticagrelor, leading to drug discontinuation in roughly one in every 20 treated patients.[1, 2] Studies have suggested that ticagrelor inhibits the sodium-independent equilibrative nucleoside transporter–1, which may increase adenosine plasma levels and explain drug-related dyspnea.[3] However, the identification of a pattern of periodic breathing associated to increased chemosensitivity to hypercapnia in patients with ticagrelor-related dyspnea[4] has reinforced the hypothesis that this side effect may result from direct inhibition of $P2Y_{12}$ receptors on neurons leading to purinergic stimulation of the chemoreflex system.[3, 4] Simultaneous measurements of adenosine and ticagrelor plasma levels in patients with and without dyspnea while on treatment with ticagrelor may help unraveling the mechanism of this common and clinically relevant side effect.

Patients on dual antiplatelet therapy who suffered at least 30 days earlier from an acute coronary syndrome and remained free of ischemic recurrences qualified for inclusion. Across the five recruiting centers, consenting patients were exposed to ticagrelor, clopidogrel and prasugrel following a three-period balanced Latin square crossover design with four weeks per treatment period as part of the HI-TECH trial (URL: https://www.clinicaltrials.gov. Unique identifier: NCT02587260).[5] The occurrence of dyspnea was prospectively assessed in 28 patients by means of the Medical Research Council dyspnea scale and Baseline and Transitional Dyspnea Index. Systemic plasma adenosine levels (Q&Q Labs AB, Sweden), ticagrelor, ticagrelor active metabolite (AR-C124910XX) (Bioanalytical Covance Laboratory, USA) and platelet reactivity (VerifyNow system, Accriva diagnostics, USA) were assessed. Post-randomization blood sampling was performed one to two hour(s) following the loading dose of the first assigned oral $P2Y_{12}$ inhibitor (ticagrelor at 180 mg or prasugrel at 60 mg or clopidogrel at 600 mg). Blood sampling was repeated 30±5 days after, before and one to two hour(s) after the witnessed intake of the

maintenance dose of the same $P2Y_{12}$ inhibitor (90 mg twice daily for ticagrelor, 10 mg/day for prasugrel or 5 mg/day if age >75 years or weight <60 Kg, and 75 mg/day for clopidogrel). One to seven days thereafter, patients received the loading dose of the second randomized $P2Y_{12}$ inhibitor followed by an identical assessment algorithm until the completion of the randomized sequence.[5] All the corresponding institutional review committees approved the study protocol, and all subjects gave informed consent.

Three (10.7%) patients suffered from rest dyspnea of new-onset few hours after ticagrelor administration (**Figure 1A)**. Their baseline characteristics did not differ as compared to patients without dyspnea. Timing, intensity, and consequence of ticagrelor-related dyspnea are shown in **Figure 1B**.

Plasma adenosine did not differ in patients with or without ticagrelor-related dyspnea after loading (6.5 μM [3.1–12.8] vs. 6.6 μM [4.0–11.4]; p=1.000), before (3.6 μM [3.2–8.5] vs. 7.4 μM [5.5–10.5]; p=0.398), or after maintenance doses (6.7 μM [3.4–17.5] vs. 8.2 μM [4.7–11.5]; p=1.000) (**Figure 1C**). Plasma adenosine was also similar at all time points in patients with or without ticagrelor-related dyspnea as compared to values measured during prasugrel or clopidogrel sequence.

Platelet reactivity units did not differ in patients with as compared to those without ticagrelor-related dyspnea after loading (8 [5–9] vs. 8 [5–34]; p=0.724) or before (34 [21–46] vs. 33 [21–46]; p=0.935) and after (9 [7–32] vs. 8 [4–58]; p=0.821) maintenance doses (**Figure 1C**).

In contrast, ticagrelor plasma levels were two to three-fold higher in patients with as compared to those without ticagrelor-related dyspnea both after loading (1950 ng/mL [1170–3670] vs. 793 ng/mL [679–1260]; p=0.041) and after maintenance doses (1230 ng/mL [844–2330] vs. 493 ng/mL [267–629]; p=0.025) (**Figure 1C**). Ticagrelor active metabolite was numerically but not statistically higher in patients with as compared to those without

ticagrelor-related dyspnea, after loading (223.0 ng/mL [140.0–505.0] vs. 186.0 ng/mL [88.4–246.0]; p=0.393) or maintenance doses (222.0 ng/mL [132.0–353.0] vs. 115.0 ng/mL [83.8–182.0]; p=0.108).

These findings further question the role of systemic adenosine as a mediator of ticagrelor-related dyspnea. We did not find any difference in the adenosine levels after loading and before or after ticagrelor maintenance doses in patients with or without dyspnea. Conversely, our data support the relevance of persistently higher plasma concentration of ticagrelor in patients experiencing this side effect. Our study provides additional evidence that a direct $P2Y_{12}$ inhibitory effect on the central nervous system may explain the occurrence of ticagrelor-related dyspnea. We cannot rule out however that higher adenosine tissue levels or greater sensitivity towards adenosine may still account, at least partially, for the occurrence of ticagrelor-related dyspnea.

Lower ticagrelor loading and maintenance regimens or new controlled release formulations have potential to mitigate the occurrence of ticagrelor-related dyspnea without compromising the degree of $P2Y_{12}$ receptor inhibition, as shown in the PEGASUS-TIMI 54 trial, in which ticagrelor 60 mg b.i.d. resulted in lower dyspnea rates as compared to the 90 mg b.i.d. regimen.[1]

Data Sharing

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

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Disclosures

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Alexios Karagiannis is affiliated with CTU Bern, University of Bern, which has a staff policy of not accepting honoraria or consultancy fees. However, CTU Bern is involved in design, conduct, or analysis of clinical studies funded by not-for-profit and for-profit organizations. In particular, pharmaceutical and medical device companies provide direct funding to some of these studies. For an up-to-date list of CTU Bern's conflicts of interest see http://www.ctu.unibe.ch/research/declaration_of_interest/index_eng.html

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The other authors report nothing to disclose.

Appendix

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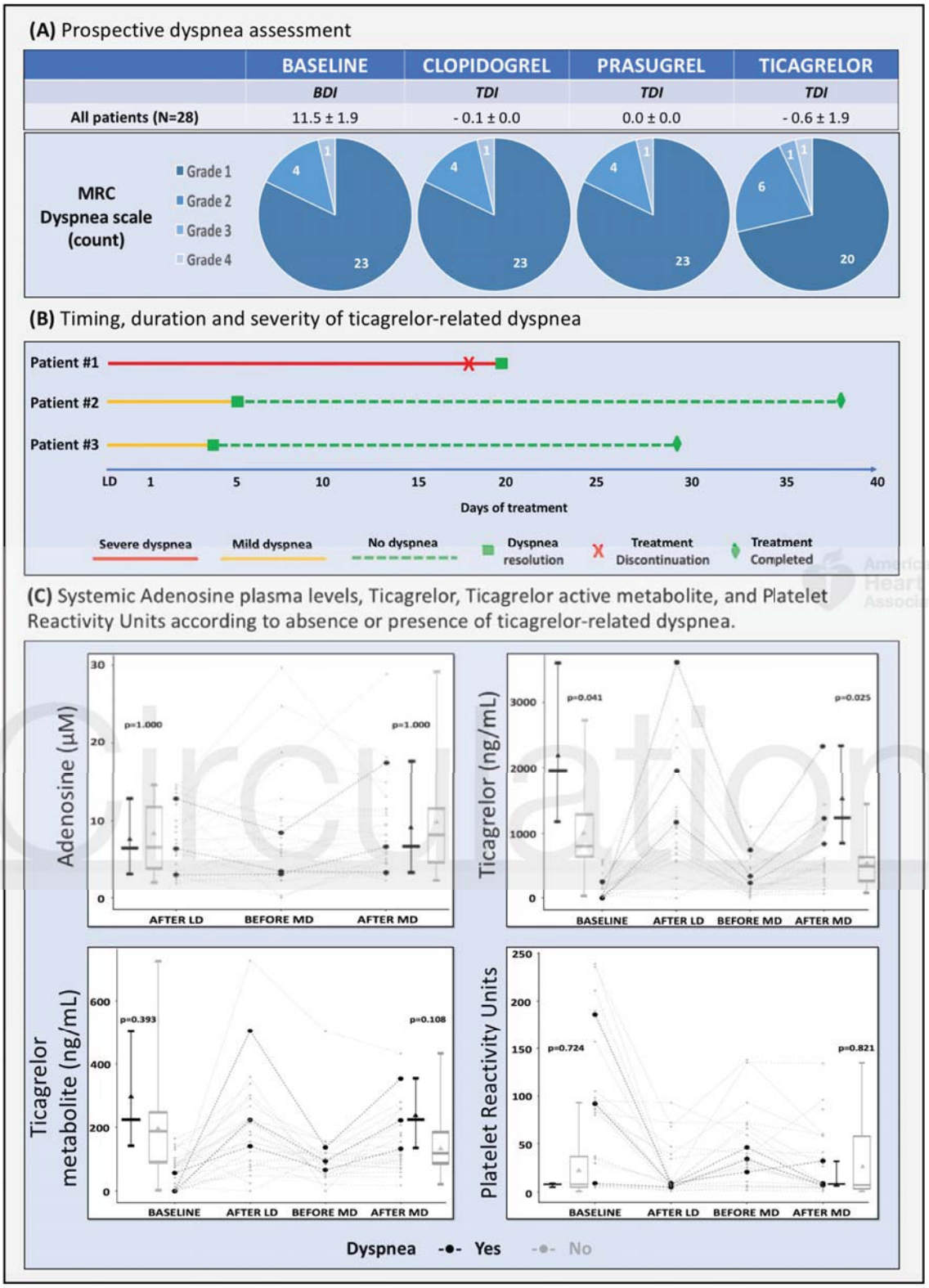
Figure Legend

Figure 1. Dyspnea assessment and ticagrelor-related dyspnea cases in HI-TECH trial.

Panel (A) The occurrence of dyspnea was prospectively assessed by means of the Baseline Dyspnea Index (BDI)/Transitional Dyspnea Index (TDI). A negative value in the TDI indicates an increase in dyspnea symptoms. Additionally, dyspnea was simultaneously assessed by the Medical Research Council dyspnea scale (MRC), with grade 1 corresponding to the absence of dyspnea and grade 4 to severe dyspnea. According to both scales, three patients developed dyspnea during ticagrelor treatment, of whom one fulfilled severe criteria. *Panel (B)* Three patients developed ticagrelor-related dyspnea few hours after loading dose administration. In the single patient developing severe symptoms, with no further improvement despite treatment persistence, drug discontinuation was subsequently required. *Panel (C)* Black dots and black dotted lines identify the patients who suffered from dyspnea whereas grey dots and grey dotted lines those who did not. Ticagrelor plasma levels were two to three times higher in patients with as compared to those without ticagrelor-related dyspnea. The box and whisker plots denote summary non-parametric statistics after loading (LD) and after maintenance (MD) doses based on the presence or absence of ticagrelor-related dyspnea. The boxes identify the median and interquartile range values, and whiskers the minimum and maximum value. In the dyspnea group, the lines represent the median value and the whiskers the minimum and maximum value. The triangles (▲) represent the mean value and AR-C124910XX denotes ticagrelor active metabolite.



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Appendix

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