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RESEARCH LETTER

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

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Dyspnea is a common side effect of ticagrelor, and can lead to drug discontinuation in roughly 1 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 with 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 in 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 5 recruiting centers, consenting patients were exposed to ticagrelor, clopidogrel, and prasugrel following a 3-period balanced Latin square crossover design with 4 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. Postrandomization blood sampling was performed 1 to 2 hours after the loading dose of the first assigned oral $P2Y_{12}$ inhibitor (ticagrelor at 180 mg, prasugrel at 60 mg, or clopidogrel at 600 mg). Blood sampling was repeated 30±5 days after, before, and 1 to 2 hours after the witnessed intake of the maintenance dose of the same $P2Y_{12}$ inhibitor (90 mg twice daily for ticagrelor, 10 mg/d for prasugrel or 5 mg/d if age >75 years or weight <60 kg, and 75 mg/d for clopidogrel). One to 7 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 a few hours after ticagrelor administration (Figure [A]). Their baseline characteristics did not differ as compared to patients without dyspnea. Timing, intensity, and consequence of ticagrelor-related dyspnea are shown in the Figure (B).

Plasma adenosine did not differ in patients with or without ticagrelor-related dyspnea after loading (6.5 nM [3.1–12.8] versus 6.6 nM [4.0–11.4]; P=1.000), before (3.6 nM [3.2–8.5] versus 7.4 nM [5.5–10.5]; P=0.398), or after maintenance doses (6.7 nM [3.4–17.5] versus 8.2 µmol/L [4.7–11.5]; P=1.000) (Figure [C]). Plasma adenosine was also similar at all time points in patients with or

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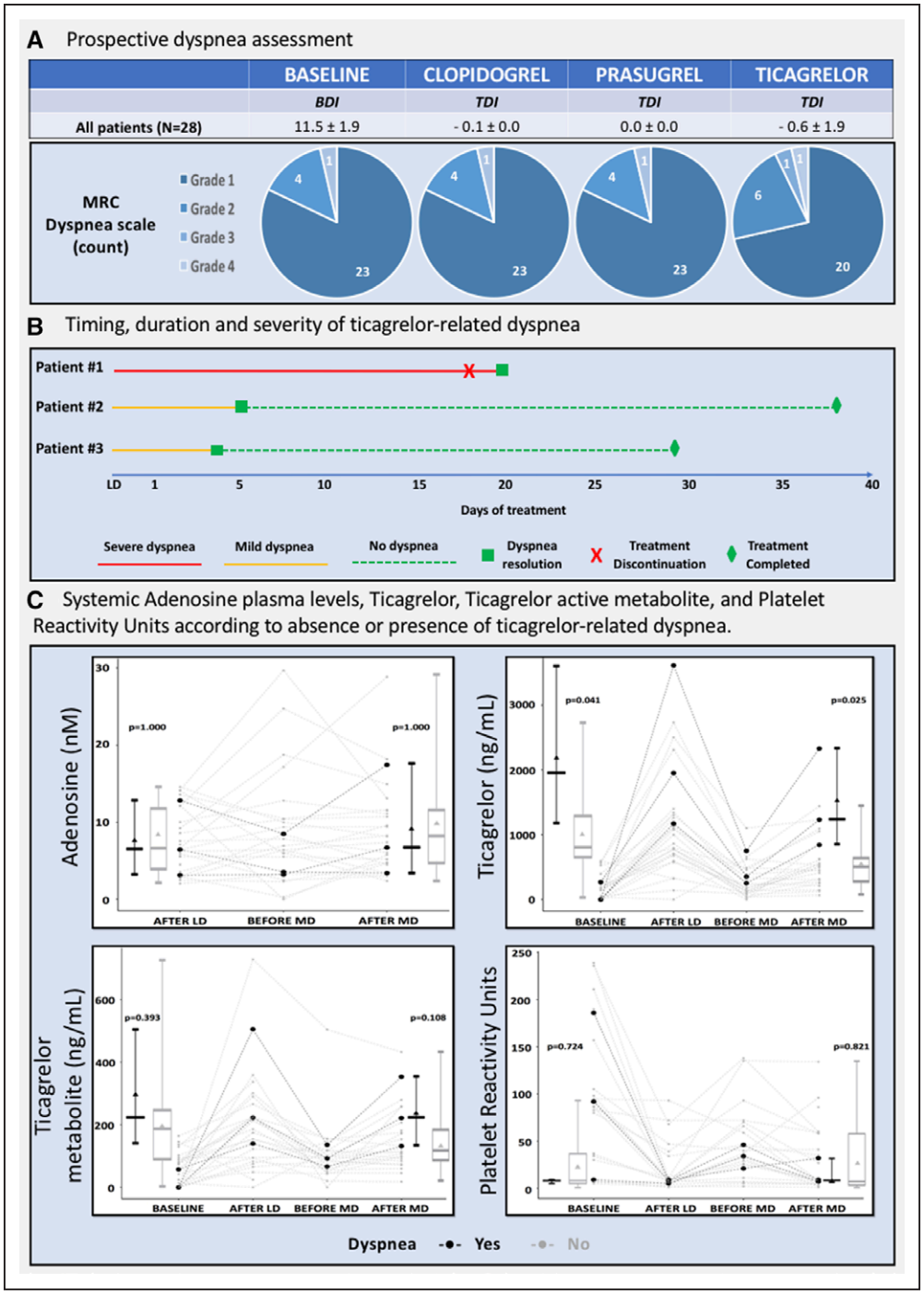

Figure. Dyspnea assessment and ticagrelor-related dyspnea cases in HI-TECH trial.
A, The occurrence of dyspnea was prospectively assessed by means of the Baseline Dyspnea Index (BDI)/Transitional Dyspnea Index (TDI). A negative value in the TDI indicates an increase in dyspnea symptoms. Additionally, 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, 3 patients developed dyspnea during ticagrelor treatment, 1 of whom fulfilled severe criteria. **B**, Three patients developed ticagrelor-related dyspnea a 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. **C,** Black dots and black dotted lines identify the patients who suffered from dyspnea, whereas gray dots and gray dotted lines identify those who did not. Ticagrelor plasma levels were 2 to 3 times higher in patients with, as compared to those without, ticagrelor-related dyspnea. The box and whisker plots denote summary nonparametric 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.

without ticagrelor-related dyspnea as compared to values measured during the 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] versus 8 [5–34]; *P*=0.724)

or before (34 [21–46] versus 33 [21–46]; *P*=0.935) and after (9 [7–32] versus 8 [4–58]; *P*=0.821) maintenance doses (Figure [C]).

In contrast, ticagrelor plasma levels were 2- to 3-fold higher in patients with as compared to those without ticagrelor-related dyspnea, both after loading (1950 ng/mL [1170–3670] versus 793 ng/mL [679–1260]; *P*=0.041) and after maintenance doses (1230 ng/mL [844–2330] versus 493 ng/mL [267–629]; *P*=0.025) (Figure [C]). 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] versus 186.0 ng/mL [88.4–246.0]; *P*=0.393) or maintenance doses (222.0 ng/mL [132.0–353.0] versus 115.0 ng/mL [83.8–182.0]; *P*=0.108).

These findings help in further questioning 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 toward 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 BID resulted in lower dyspnea rates as compared to the 90 mg BID regimen.[1]

ARTICLE INFORMATION

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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APPENDIX

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