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Letter to the Editor

# Ticagrelor safety profile in real-life setting of acute coronary syndrome patients

*Dear Editor,*

We read with great interest the paper by Chen et al,[1] the first of its kind that investigated the efficacy and safety of ticagrelor versus clopidogrel in patients with acute coronary syndrome (ACS) in Asia (including Taiwan) in a real-life clinical setting. In their analysis, the authors reported that a higher number of patients treated with ticagrelor experienced dyspnea as compared with those patients treated with clopidogrel in both overall (25.0% vs. 14.6%, $p < 0.001$) and propensity-matched (21.0% vs. 11.6%, $p = 0.01$) cohorts. Furthermore, they affirmed that the incidence of dyspnea-related discontinuation of $P2Y_{12}$ antagonist treatment tended to be higher in the ticagrelor group by propensity score matching. In particular, their study showed that when compared with clopidogrel treatment, ticagrelor causes a fourfold increase in the incidence of dyspnea and required discontinuation of a $P2Y_{12}$ antagonist. During our intensive pharmacovigilance activities in emergency departments (EDs), we encountered several cases of dyspnea associated with ticagrelor treatment. In particular, we observed a case of severe paroxysmal nocturnal dyspnea developed in a post-stenting 90-year-old man associated with the first use of ticagrelor.[2] We then conducted a retrospective cohort study in the EDs of the Florence (Italy) metropolitan area to define the occurrence rate of dyspnea leading to ED admission in ACS for patients treated with ticagrelor. Among community-dwelling patients who were prescribed ticagrelor from 2012−2014, the overall dyspnea occurrence was about 2% (1.86%, 20/1073 patients). All cases of outpatient dyspnea were severe and caused an ED admission. The median time between the first prescription of ticagrelor and the onset of dyspnea was 47 days (interquartile range: 10−185).[3] Although the clinical data showed that ticagrelor treatment is generally well-tolerated and discontinuation rates are comparable to those observed for clopidogrel,[4,5] the Chen et al[1] observational study fits perfectly within this context, since few postmarketing studies (i.e., conducted in the real-world setting) evaluated ticagrelor's safety profile.[6−8] Consistent with the results of Chen et al[1] and based on our pharmacovigilance experience, what we observed for dyspnea might happen for other adverse drug reactions (ADRs) related to ticagrelor use. While randomized controlled trials (RCTs) are preferable when evidence of treatment efficacy must be provided, circumstances become more complex when the risk of ADRs needs to be assessed.[9] The lack of ADR data from RCTs is well-known; generally, RCTs often do not include a large population sample or do not have adequate follow-up to identify rare ADRs, and safety data quality is generally poor. Considering the relevant differences between data derived from RCTs and observational studies, as we observed in the case of dyspnea from the platelet inhibition and patient outcomes trial[10] and the study by Chen et al[1], we strongly agree with the authors' observations when they affirmed that the discretion of a physician in a real-world setting should derive from both observational and clinical evidence. In conclusion, we also believe that further and larger observational studies are needed to identify the real-world safety profile of ticagrelor in ACS patients, in order to guarantee the clinician's best therapeutic choice.

## References

1. Chen IC, Lee CH, Fang CC, Chao TH, Cheng CL, Chen Y, et al. Efficacy 44 and safety of ticagrelor versus clopidogrel in acute coronary syndrome in Taiwan: a multicenter retrospective pilot study. *J Chin Med Assoc* 2016;**79**:521−30.
2. Lombardi N, Lenti MC, Matucci R, Mugelli A, Vannacci A. Ticagrelor-related dyspnea: an underestimated and poorly managed event? *Int J Cardiol* 2015;**179**:238−9.
3. Lucenteforte E, Lombardi N, Barchielli A, Torrini M, Mugelli A, Vannacci A. Ticagrelor-related dyspnea in patients with acute coronary syndrome: a three year cohort study. *Drug Saf* 2015;**38**:935−1048.
4. Parodi G, Storey RF. Dyspnoea management in acute coronary syndrome patients treated with ticagrelor. *Eur Heart J Acute Cardiovasc Care* 2015;**4**:555−60.
5. Unverdorben M, Parodi G, Pistolesi M, Storey RF. Dyspnea related to reversibly-binding P2Y12 inhibitors: a review of the pathophysiology, clinical presentation and diagnostics. *Int J Cardiol* 2016;**202**:167−73.

Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

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6. Harding SA, Van Gaal WJ, Schrale R, Gunasekara A, Amerena J, Mussap CJ, et al. Practical experience with ticagrelor: an Australian and New Zealand perspective. *Curr Med Res Opin* 2015;**31**:1469−77.
7. Sanchez-Galian MJ, Flores-Blanco PJ, Lopez-Cuenca A, Gomez-Molina M, Guerrero-Perez E, Cambronero-Sanchez F, et al. Ticagrelor related dyspnea in patients with acute coronary syndromes: incidence and implication on ticagrelor withdrawn. *Int J Cardiol* 2015;**187**:517−8.
8. Gaubert M, Laine M, Richard T, Fournier N, Gramond C, Bessereau J, et al. Effect of ticagrelor related dyspnea on compliance with therapy in acute coronary syndrome patients. *Int J Cardiol* 2014;**173**:120−1.
9. Lombardi N, Crescioli G, Mugelli A, Vannacci A. Ticagrelor recommended over clopidogrel, only in clinical trials or also in a real-world practice? *Expert Rev Cardiovasc Ther* 2016;**14**:1103−4.
10. Storey RF, Becker RC, Harrington RA, Husted S, James SK, Cools F, et al. Characterization of dyspnoea in PLATO study patients treated with ticagrelor or clopidogrel and its association with clinical outcomes. *Eur Heart J* 2011;**32**:2945−53.

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