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LETTER TO THE EDITOR

Ticagrelor recommended over clopidogrel, only in clinical trials or also in a *real-world* practice?

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Dear Editor,

We read with interest the review entitled 'Ticagrelor recommended over clopidogrel in ST-segment elevation myocardial infarction (STEMI) patients' by Pappas et al. [1]. This is an expert evaluation of the pharmacological characteristics of ticagrelor vs. clopidogrel in acute coronary syndrome (ACS) patients. Ticagrelor is an oral drug that acts by inhibiting the platelet $P2Y_{12}$ receptors in a reversible manner [2] and is recommended, 90 mg twice a day, for acute (in-hospital) and post-discharge therapy [3]. Based on the results from the phase 3 trial that led to ticagrelor's approval, the PLATelet inhibition and patient Outcomes (PLATO) study, the drug shows a clear benefit over clopidogrel in preventing cardiovascular events and death in patients with ACS [4]. Regarding the efficacy profile of ticagrelor vs. clopidogrel in a clinical setting, the authors state that ticagrelor represents the new standard of care for the management of patients with STEMI intended for primary percutaneous coronary intervention (PCI).

We agree with the authors' statement [1] that a clinician deciding whether to use ticagrelor or clopidogrel should carefully consider the contraindications, special warnings, and precautions for these drugs. Clinical data show that ticagrelor treatment is generally well tolerated, and discontinuation rates are comparable to those observed for clopidogrel [5,6]. Nevertheless, few post-marketing studies, i.e., conducted in the *real-world* setting, evaluated ticagrelor's safety profile [2,7,8]. An important example is ticagrelor-related dyspnea. In several clinical studies [5], dyspnea incidence in ticagrelor-treated subjects varied between 10%, in the Dose conflrmation Study assessing antiPlatelet Effects of AZD6140 vs. clopidogRel in non–STsegment Elevation myocardial infarction (DISPERSE) study (200 patients with atherosclerosis treated for 4 weeks with 100 or 200 mg/day) [9], and 38.6%, in The ONSET and OFFSet of the Antiplatelet Effects of Ticagrelor (ONSET/OFFSET) study (123 subjects with stable coronary artery disease) [10]. In the PLATO trial, 13.8% of ticagrelor-treated patients reported dyspnea compared with 7.8% of the clopidogrel-treated ones ($p < 0.001$) [11].

During our activities of intensive pharmacovigilance monitoring in emergency departments (EDs) in Florence (Italy), we encountered several cases of dyspnea, in particular one of them developed in a poststenting ACS 90-year-old man and was associated with the first administration of ticagrelor (90 mg/day plus acetylsalicylic acid 100 mg/day) [12]. In this case, ticagrelor-related dyspnea, often described in clinical studies as mild and moderate [11], was severe, caused an ED admission, and replaced with a well-tolerated clopidogrel therapy. Furthermore, several studies have addressed the safety of ticagrelor with regard to dyspnea and other adverse drug reactions (ADRs). In a single-center study of 100 patients treated with aspirin and ticagrelor 90 mg twice daily following PCI for ACS, ticagrelor was discontinued in nine patients (9%) because of dyspnea within the first 30 days of treatment [13]. Sanchez-Galian et al. conducted a retrospective study on a university hospital registry and identified 113 consecutive patients treated with ticagrelor after ACS [14]. Within the first week of treatment, 15 patients (14%) had dyspnea judged by the investigator to be related to ticagrelor. Gaubert et al. conducted a multicenter, observational prospective study and observed that the rate of ticagrelor withdrawal due to dyspnea was 17% (27 out of 164 patients) [8].

Based on our pharmacovigilance experience, what we observed for dyspnea might happen for other potential ADRs related to ticagrelor use (e.g. bleeding) [15]. Although randomized controlled trials (RCTs) are preferable when evidences of treatment efficacy must be provided, the situation becomes more complex when the risk of adverse effects needs to be assessed. The lack of adverse events data from RCTs is well known; RCTs often do not include large population sample or do not have adequate follow-up to identify rare adverse effects (or adverse effects that happen months/years after the intervention), and the quality of safety data may be poor. Thus, generalizability for RCT results is limited because patients at high risk of adverse effects, medically frail, or with multiple comorbidity are often excluded [16,17]. In some trials, there is a run-in period where those who cannot tolerate the study medication or show adherence to whatever they are assigned to (possibly including placebo) are not randomized. In order to overcome these limitations, data from observational studies should be taken in consideration for the safety profile evaluation of a particular intervention. In our opinion, in order to limit uncertainty and take decisions based on valid evidences, it is necessary to combine the results from both observational and clinical studies when

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answering clinical questions on safety and effectiveness of treatments.

In conclusion, we believe that further and larger post-marketing studies are needed to identify the *real-world* safety profile of ticagrelor vs. clopidogrel in ACS patients. This should clarify which is the best treatment option for clinicians.

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