



UNIVERSITÀ  
DEGLI STUDI  
FIRENZE

## FLORE

# Repository istituzionale dell'Università degli Studi di Firenze

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

Questa è la Versione finale referata (Post print/Accepted manuscript) della seguente pubblicazione:

*Original Citation:*

Ticagrelor recommended over clopidogrel, only in clinical trials or also in a real-world practice? / Lombardi, Niccolò; Crescioli, Giada; Mugelli, Alessandro; Vannacci, Alfredo. - In: EXPERT REVIEW OF CARDIOVASCULAR THERAPY. - ISSN 1477-9072. - ELETTRONICO. - 14:(2016), pp. 1-2. [10.1080/14779072.2016.1222902]

*Availability:*

This version is available at: 2158/1052477 since: 2022-05-04T11:51:02Z

*Published version:*

DOI: 10.1080/14779072.2016.1222902

*Terms of use:*

Open Access

La pubblicazione è resa disponibile sotto le norme e i termini della licenza di deposito, secondo quanto stabilito dalla Policy per l'accesso aperto dell'Università degli Studi di Firenze (<https://www.sba.unifi.it/upload/policy-oa-2016-1.pdf>)

*Publisher copyright claim:*

(Article begins on next page)



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

Niccolò Lombardi, Giada Crescioli, Alessandro Mugelli & Alfredo Vannacci

To cite this article: Niccolò Lombardi, Giada Crescioli, Alessandro Mugelli & Alfredo Vannacci (2016): Ticagrelor recommended over clopidogrel, only in clinical trials or also in a real-world practice?, Expert Review of Cardiovascular Therapy, DOI: [10.1080/14779072.2016.1222902](https://doi.org/10.1080/14779072.2016.1222902)

To link to this article: <http://dx.doi.org/10.1080/14779072.2016.1222902>



Accepted author version posted online: 10 Aug 2016.  
Published online: 22 Aug 2016.



Submit your article to this journal [↗](#)



Article views: 3



View related articles [↗](#)



View Crossmark data [↗](#)

LETTER TO THE EDITOR

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

Niccolò Lombardi<sup>a,b</sup>, Giada Crescioli<sup>a,b</sup>, Alessandro Mugelli<sup>a,b</sup> and Alfredo Vannacci<sup>a,b</sup>

<sup>a</sup>Department of Neurosciences, Psychology, Drug Research and Child Health, Section of Pharmacology and Toxicology, Centre for Molecular Medicine (CIMMBA), University of Florence, Florence, Italy; <sup>b</sup>Tuscan Regional Centre of Pharmacovigilance, Florence, Italy

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<sub>12</sub> 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 confirmation 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

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.

## Funding

This paper was not funded.

## Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties. The authors would like to thank Ersilia Lucenteforte ScD, PhD for academic supervision.

## References

- Pappas C, Lekakis J, Alexopoulos D. Ticagrelor recommended over clopidogrel in STEMI patients. *Expert Rev Cardiovasc Ther.* 2016;1–3. [Epub ahead of print].
- Harding SA, Van Gaal WJ, Schrale R, et al. Practical experience with ticagrelor: an Australian and New Zealand perspective. *Curr Med Res Opin.* 2015;31(8):1469–1477.
- Kolansky DM. Acute coronary syndromes: morbidity, mortality, and pharmaco-economic burden. *Am J Manag Care.* 2009;15(2 Suppl): S36–S41.
- Steg PG, James S, Harrington RA, et al. Ticagrelor versus clopidogrel in patients with ST-elevation acute coronary syndromes intended for reperfusion with primary percutaneous coronary intervention: a Platelet Inhibition and Patient Outcomes (PLATO) trial subgroup analysis. *Circulation.* 2010;122(21):2131–2141.
- Parodi G, Storey RF. Dyspnoea management in acute coronary syndrome patients treated with ticagrelor. *Eur Heart J Acute Cardiovasc Care.* 2015;4(6):555–560.
- Unverdorben M, Parodi G, Pistolesi M, et al. Dyspnea related to reversibly-binding P2Y12 inhibitors: a review of the pathophysiology, clinical presentation and diagnostics. *Int J Cardiol.* 2016;202:167–173.
- Sanchez-Galian MJ, Flores-Blanco PJ, Lopez-Cuenca A, et al. Ticagrelor related dyspnea in patients with acute coronary syndromes: incidence and implication on ticagrelor withdrawn. *Int J Cardiol.* 2015;187:517–518.
- Gaubert M, Laine M, Richard T, et al. Effect of ticagrelor-related dyspnea on compliance with therapy in acute coronary syndrome patients. *Int J Cardiol.* 2014;173(1):120–121.
- Husted S, Emanuelsson H, Heptinstall S, et al. Pharmacodynamics, pharmacokinetics, and safety of the oral reversible P2Y12 antagonist AZD6140 with aspirin in patients with atherosclerosis: a double-blind comparison to clopidogrel with aspirin. *Eur Heart J.* 2006;27(9):1038–1047.
- Storey RF, Bliden KP, Patil SB, et al. Incidence of dyspnea and assessment of cardiac and pulmonary function in patients with stable coronary artery disease receiving ticagrelor, clopidogrel, or placebo in the ONSET/OFFSET study. *J Am Coll Cardiol.* 2010;56(3):185–193.
- Storey RF, Becker RC, Harrington RA, 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(23):2945–2953.
- Lombardi N, Lenti MC, Matucci R, et al. Ticagrelor-related dyspnea: an underestimated and poorly managed event? *Int J Cardiol.* 2015;179:238–239.
- Subiakto I, Asrar ul Haq M, Van Gaal WJ. Bleeding risk and incidence in real world percutaneous coronary intervention patients with ticagrelor. *Heart Lung Circ.* 2015;24(4):404–406.
- Sánchez-Galian MJ, Flores-Blanco PJ, López-Cuenca A, et al. Ticagrelor related dyspnea in patients with acute coronary syndromes: incidence and implication on ticagrelor withdrawn. *Int J Cardiol.* 2015;187:517–518.
- Granger CB, Berger PB. Understanding the adverse effects of ticagrelor in practice. *JAMA Cardiol.* 2016;1:4.
- McKee M, Britton A, Black N, et al. Methods in health services research. Interpreting the evidence: choosing between randomised and non-randomised studies. *BMJ.* 1999;319(7205):312–315.
- Pocock SJ, Elbourne DR. Randomized trials or observational tribulations? *N Engl J Med.* 2000;342(25):1907–1909.