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# Ticagrelor-related late-onset dyspnea as cause of emergency department visit: a 3-year outpatient study

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**Introduction** The aim of the current study was to define the rate of emergency department visits for late-onset dyspnea in acute coronary syndrome patients treated with ticagrelor.

**Methods** We conducted a population-based study on about 850 000 residents of Florence metropolitan area, by using data from healthcare records.

**Results** Between 2012 and 2014, 1073 subjects in Florence metropolitan area had at least one prescription of ticagrelor. Two-hundred and thirty-four patients were diagnosed with 'respiratory system or other chest symptoms' or 'other diseases of lung', and among them we identified 20 subjects with ticagrelor-related late-onset dyspnea. These, and the 979 nonevent subjects (receiving ticagrelor but not developing dyspnea), contributed to 413 person-years overall. The dyspnea rate was 4.84 per 100 person-years (95% confidence interval: 3.12–7.51).

**Conclusion** Late-onset dyspnea rate is notably lower than early-onset one; nevertheless prescribing clinicians should

be aware that about one in 20 outpatients with a stabilized ticagrelor treatment might develop a dyspnea leading to an emergency department visit, and they should consider ticagrelor replacement only in patients who cannot tolerate dyspnea.

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**Keywords:** acute coronary syndrome, adverse drug reaction, dyspnea, emergency department, rate, ticagrelor

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## Introduction

Acute coronary syndromes (ACS), which include unstable angina, non-ST-elevation myocardial infarction and ST-elevation myocardial infarction are life-threatening disorders, and a source of high morbidity and mortality.<sup>1,2</sup>

Dual antiplatelet therapy with low-dose aspirin (acetylsalicylic acid) and P2Y<sub>12</sub> receptor antagonists (i.e. clopidogrel, prasugrel, or ticagrelor) is standard postdischarge therapy after ACS for secondary prevention of vascular events.<sup>3,4</sup>

Ticagrelor is an oral drug that acts by inhibiting P2Y<sub>12</sub> receptors in a reversible manner,<sup>5</sup> and is recommended, with a dose of 90 mg twice a day, for acute (in-hospital) and postdischarge therapy.<sup>6,7</sup>

Ticagrelor treatment is generally well tolerated and discontinuation rates are comparable with those observed for clopidogrel.<sup>6,8</sup> Nevertheless, an increased risk of mild-to-moderate dyspnea was observed in premarketing studies.<sup>9–11</sup>

The onset of dyspnea in ticagrelor-treated patients is usually early, with the syndrome mainly developing shortly after the first days of drug administration<sup>6,12–14</sup>; nevertheless, cases of late-onset dyspnea were

described,<sup>15</sup> developing in outpatients weeks or months after hospital discharge.

Although some postmarketing studies evaluated the occurrence of ticagrelor-related dyspnea,<sup>7,15–24</sup> none of them evaluated the actual rate of late-onset dyspnea as a cause of emergency department (ED) visit. Thus, in the current study, we aimed at evaluating the rate of ED visits for dyspnea in ticagrelor-treated ACS outpatients in Florence (Italy) local health unit.

## Methods

The study was conducted on about 850 000 residents of the metropolitan area of Florence, Tuscany (Italy), by using 2012–2014 healthcare data records obtained from the administrative archives of the Local Health Authority. The administrative databases contained demographic information of subjects assisted by the national healthcare system (NHS), information on ticagrelor prescriptions reimbursed by the NHS (coded by the Anatomical Therapeutic Chemical – classification), and information recorded in ED medical charts (coded by the International Classification Disease, 9th version, Clinical Modification – ICD9CM) of all general hospitals of Florence metropolitan area.

Subjects with one or more prescription of ticagrelor were identified and the first prescription of the drug was defined as the index date. Patients were followed until the end of prescription duration or until the end of the study (i.e. 31 December 2014). The end of prescription duration was defined as the day of the last prescription and 33 days (mean duration of one box of pills in our sample).

Patients with ED visit diagnoses of ‘respiratory system or other chest symptoms’ (ICD9CM code equal to 786) or ‘other diseases of lung’ (ICD9CM code equal to 518) were selected. A Medical Doctor expert in Intensive Care (M.T.) and a Pharmacologist expert in Clinical Pharmacy (N.L.) independently reviewed ED medical records of the identified patients and defined dyspnea events. All diagnoses were made by exclusion. Based on ED diagnosis, all cases of dyspnea related to cardiovascular, respiratory, metabolic, or psychiatric comorbidities were excluded.<sup>6</sup> Inclusion of the remaining cases was confirmed and clinical discordances were resolved by a third clinician expert in Medical Toxicology and Pharmacovigilance (A.V.). Event date was defined as the day of hospital discharge or ED visit. Nondyspnea subjects with less than 30 days of observation were excluded.

According to previous studies,<sup>6,7,12–24</sup> we defined early-onset dyspnea as the occurrence of respiratory symptoms within the first 24 h from ticagrelor administration. Consistently, all dyspnea events occurring after the first 24 h were defined as late-onset.

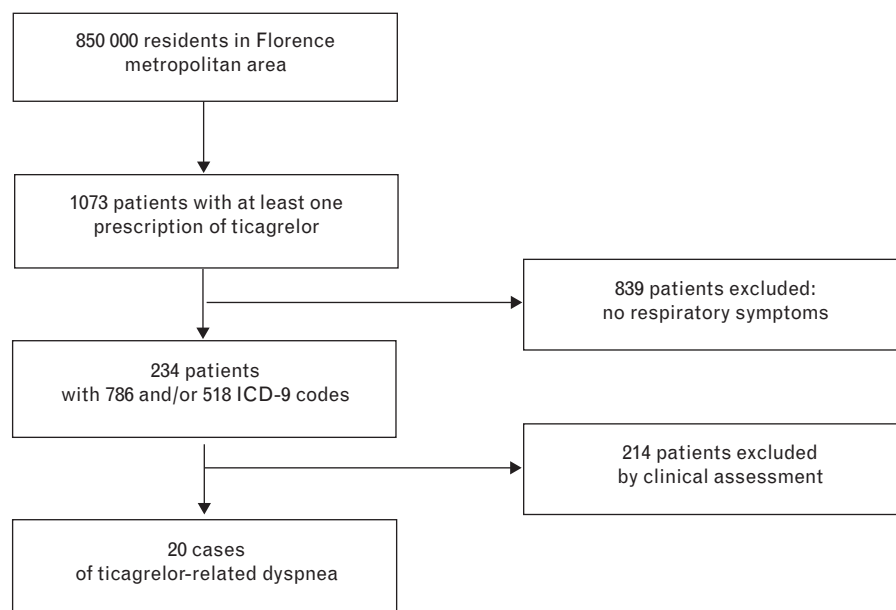
Incidence rates were calculated by dividing the number of events by the person-time. Confidence intervals (95% CI) were calculated using the quadratic approximation to the Poisson log likelihood for the log-rate parameter. Differences between medians were tested using the nonparametric equality-of-medians Person Chi-square test.

The study was conducted within the framework of the *Monitoraggio Epidemiologico di Reazioni ed Eventi Avversi da Farmaci in Pronto Soccorso* that obtained ethics approval by the Local Health Authority of Florence (Italy).

## Results

Between 2012 and 2014, 1073 subjects in Florence metropolitan area had at least one prescription of ticagrelor. The first prescription date was 30 April 2012, showing that the cohort was fully composed of new-users (drug authorization in Italy was 3 December 2010 and no prescription was present between 1 January 2012 and 29 April 2012); therefore, no wash-out period was needed. Two-hundred and thirty-four patients had diagnosis of ‘respiratory system or other chest symptoms’ (ICD9CM code 786,  $n = 185$ ) or ‘other diseases of lung’ (ICD9CM code 518,  $n = 49$ ); among them, 20 subjects with ticagrelor-related dyspnea were identified (14 coded as 786 and 6 coded as 518) (Fig. 1 and Table 1). The majority of cases of ticagrelor-related dyspnea ED visits occurred in the 1st year after the initiation, and 10 of them

Fig. 1



Flowchart of the study cohort.

**Table 1** Characteristics of ticagrelor-related dyspnea emergency department visits

Case	Age	Sex	Onset (days)	Paroxysmal/persistent	Exercise-related	Pulmonary disease	Daily dose (mg)
1	77	F	67	Paroxysmal	Yes	No	180
2	69	M	216	Paroxysmal	No	No	180
3	63	M	2	Paroxysmal (nocturnal)	No	No	180
4	80	M	354	Persistent	No	No	180
5	79	F	13	Paroxysmal	No	COPD	180
6	48	M	15	Persistent	No	No	180
7	76	M	449	Persistent	Yes	No	180
8	60	M	25	Paroxysmal	No	No	180
9	72	M	96	Persistent	No	COPD	180
10	77	M	26	Paroxysmal (nocturnal)	No	No	180
11	79	F	1	Paroxysmal (nocturnal)	No	No	180
12	84	F	437	Paroxysmal	No	No	180
13	89	M	8	Persistent	No	No	180
14	62	F	154	Persistent	No	No	180
15	84	M	255	Paroxysmal	Yes	COPD	180
16	50	M	146	Paroxysmal	Yes	No	180
17	78	M	27	Paroxysmal (nocturnal)	Yes	No	180
18	70	M	8	Paroxysmal	No	No	180
19	59	M	4	Paroxysmal (nocturnal)	No	No	180
20	78	F	97	Paroxysmal	No	No	180

COPD, chronic obstructive pulmonary disease.

(50%) occurred within the 1st month of ticagrelor administration. Moreover, seven patients stopped treatment after ED visit for dyspnea. For these patients no prescriptions of ticagrelor after dyspnea event were recorded in administrative databases. For them, ED clinicians reported an improvement of ticagrelor-related dyspnea after discontinuation, evidence which could be useful in causality assessment (*positive dechallenge*).<sup>25</sup> Almost all cases were paroxysmal and five of them had a nocturnal onset. In five patients, dyspnea episodes were related to exercise. On arrival at ED, only three patients (15%) reported a previous respiratory problem (chronic obstructive pulmonary disease, COPD) in their ED medical history. For these patients, ED physicians had expressly reported a diagnosis of dyspnea as an adverse event related to ticagrelor exposure. Doctors also reported that COPD was in good therapeutic control and that these patients were not affected by other comorbidities. The number of ED visits for ‘respiratory system or other chest symptoms’ or ‘other diseases of lung’ in the Florence metropolitan area during the period of time under study was 33,371, 23% of which resulted in hospitalization; the ED visit code was confirmed after hospital discharge in 37% of cases, showing that chosen ICD codes are suitable to identify ‘aspecific’ dyspnea ED visits that need better definition during hospital stay. Seventy-four subjects

receiving ticagrelor but not developing dyspnea were excluded because they had less than 33 days of observation (mean duration of one box of pills in our sample) (Table 2). The 20 events and the 979 nonevents contributed overall to 413 person-years. The median of observational days was 47 (interquartile range: 10–185) for dyspnea subjects and 113 (49–226) for nondyspnea ones; the difference was not statistically significant ( $P$  value = 0.180). The dyspnea incidence rate was 4.84 per 100 persons-year (95% CI: 3.12–7.51). The rate was higher in women and for subjects older than 70 years. Women were older than men: the median age being 73 (65–79) years for women and 68 (58–76) years for men,  $P$  value less than 0.0001. Age differences were also observed among dyspnea subjects: the median was 78.5 (77–79) for women and 71 (60–78) for men ( $P$  value = 0.051). As five out of six female subjects with dyspnea were older than 77 years, the interaction between age and sex could not be further explored.

## Discussion

The current study is the first study conducted in Italy in an outpatient sample of subjects exposed to ticagrelor and resulted in a 4.84% rate per 100 person-years of ticagrelor-associated late-onset dyspnea leading to ED visit.

**Table 2** Incidence rates and 95% confidence intervals for dyspnea leading to emergency department visit among 999 ticagrelor-treated subjects

	No. events of dyspnea	Persons-year	Dyspnea rate per 100 person-years	(95% CI)	$P$ value <sup>a</sup>
Overall	20	413.05	4.84	(3.12–7.51)	
Sex					
Female	6	90.09	6.66	(2.99–14.82)	0.474
Male	14	322.96	4.33	(2.57–7.32)	
Age (years)					
<70	7	216.75	3.23	(1.54–6.77)	0.148
≥70	13	196.30	6.62	(3.85–11.41)	

CI, confidence interval. <sup>a</sup> $P$  value from heterogeneity Chi-squared test.

**Table 3** Characteristics of published postmarketing studies evaluating ticagrelor-related dyspnea rate

Reference	Country	Design	Patients exposed to ticagrelor	Dyspnea rate (%)	Setting of dyspnea occurrence
Gaubert <i>et al.</i> <sup>16</sup>	France	Multicenter observational prospective study	164	22.6	In-hospital
Subiakto <i>et al.</i> <sup>17</sup>	Australia	Single-center observational prospective study	100	9 <sup>a</sup>	In-hospital and out-hospital
Sanchez-Galian <i>et al.</i> <sup>18</sup>	Spain	Retrospective analysis of a hospital prospective registry	111	14	In-hospital
Molife <i>et al.</i> <sup>19</sup>	United States	Retrospective observational study	2964	10.5	In-hospital and out-hospital
Simeone <i>et al.</i> <sup>20</sup>	United States	Retrospective observational study	2991	16.4	In-hospital and out-hospital
Lee <i>et al.</i> <sup>21</sup>	New Zealand	Retrospective observational study	133	14 <sup>b</sup>	Out-hospital
Wang <i>et al.</i> <sup>22</sup>	China	Single-center observational prospective study	417	3	In-hospital
Chen <i>et al.</i> <sup>7</sup>	China	Multicenter retrospective study	324	25	In-hospital and out-hospital
Alexopoulos <i>et al.</i> <sup>15</sup>	Greece	Prospective multicenter cohort study	738	19	In-hospital and out-hospital
Bergmeijer <i>et al.</i> <sup>24</sup>	Oland	Single-center observational retrospective study	301	11.6	Out-hospital
Harding <i>et al.</i> <sup>23</sup>	New Zealand	Prospective single-center cohort study	243	37.4	In-hospital and out-hospital

<sup>a</sup> Percentage of patients who stopped ticagrelor for dyspnea. <sup>b</sup> Percentage of patients who discontinued ticagrelor for dyspnea.

Dyspnea is common in patients with ACS,<sup>6</sup> as well as in patients treated with ticagrelor<sup>1</sup> and can have a variety of clinical causes. Early-onset dyspnea related to ticagrelor is typically not caused by heart dysfunctions, usually occurs within the 1st days of treatment and it was traditionally attributed to drug's adenosine-mediated actions, as ticagrelor has a chemical structure similar to that of adenosine.<sup>26</sup> However, given that dyspnea is an adverse event also observed for other antiplatelet reversible agents (i.e. elinogrel), with a different chemical structure compared with adenosine molecule, alternative hypotheses were formulated.<sup>27</sup> In particular, it was recently suggested that dyspnea could be related to the reversible mechanism of action of these agents. In fact, their reversible platelet inhibition causes premature cell aging, apoptosis, impaired turnover due to sequestration of overloaded and exhausted platelets in the pulmonary circulation, leading to the development of an autoimmune transfusion-related acute lung injury like reaction and dyspnea.<sup>27</sup>

Patients with ACS can present shortness of breath due to several reasons, and all possible concomitant conditions should be investigated before making the decision for drug suspension or switching to another P2Y<sub>12</sub> inhibitor.

A systematic review of 12 randomized controlled trials aimed at estimating the efficacy and safety of ticagrelor for ACS patients<sup>28</sup> found that the pooled rate of early-onset dyspnea was higher in the ticagrelor group than in the clopidogrel group (odds ratio: 1.90; 95% CI: 1.73–2.08).

In recent years, several postmarketing studies have been published (Table 3).<sup>7,15–24</sup> Four were conducted in Europe, two in the United States, New Zealand and China, respectively, and one in Australia. They included from 100 to 2991 patients and reported a dyspnea rate between 3 and 37.5%. Six studies identified dyspnea events in and

out of the hospital, three in the hospital, and two out of the hospital.

Observational studies were generally conducted on newly prescribed in-hospital patients,<sup>16–18</sup> including all dyspnea events with early onset that represent the majority of ticagrelor-related dyspnea events. Such studies are therefore able to evaluate only early-onset dyspnea cases or both early-onset and late-onset cases together. The current study was instead aimed at defining for the first time the rate of late-onset dyspnea in out-hospital treated subjects, to investigate only dyspnea events with late onset leading to ED visit. The rate of late-onset dyspnea seems to be higher in women and in subjects older than 70 years. However, five out of six women with dyspnea were older than 77, thus, we could not explore the interaction between age and sex. Due to the fact that all recruited subjects received the recommended dose (90 mg twice a day), it was not possible to investigate the dose–response relationship, even if it has been observed that early-onset dyspnea may be directly associated with high doses of ticagrelor,<sup>11</sup> nor we can exclude a specific individual susceptibility to this adverse drug reaction. Moreover, five patients out of 20 showed an exercise-related dyspnea. It is known that drug-induced dyspnea usually occurs at rest, and is typically not related to exertion, not limiting exercise capacity.<sup>6</sup> On the other hand, this does not seem a sufficient condition to rule out the association, as the exact mechanism of ticagrelor-related dyspnea has not been definitively studied.<sup>29</sup> Finally, we observed only two patients admitted with dyspnea who experienced the adverse event after 449 and 437 days of ticagrelor treatment, respectively. In ACS patients, the international guidelines<sup>30,31</sup> recommended a dual antiplatelet therapy (DAPT) for 12 months (standard therapy). These two subjects were probably patients at low bleeding risk, for whom guidelines allow the extension of DAPT beyond 12 months.

The current study has several limitations. First, we have no information on concomitant use of other drugs, thus we cannot investigate their role on the occurrence of dyspnea as well as the role of interaction between other medications and ticagrelor. Although all cases were validated by expert clinicians one by one, we cannot completely exclude a potential selection bias due to the fact that dyspnea could be incorrectly diagnosed, being actually a symptom and not a disease. Moreover, we have no population data on the incidence of dyspnea among subjects not receiving ticagrelor (*control group*); furthermore, the attribution of the cause of dyspnea from a retrospective analysis performed on ED medical charts may have led to an underestimation of the real rate of this complication during ticagrelor exposure. However, the exclusion of 74 patients without a follow-up period of at least 33 days (mean duration of one box of pills in our sample) may have led to an overestimation of the rate, reasonably balancing such a potential bias. Moreover, except for sex and age, we have not adjusted for other confounding variables; thus, we cannot exclude residual confounding bias. Finally, another important limit of our study is the low number of patients identified in the primary cohort. Although we covered all subjects exposed to ticagrelor during the study period, a set of 1073 patients could represent a sample too small to reach a final conclusion regarding the safety of ticagrelor in outpatients.

## Conclusion

The rate of ED visits for ticagrelor-related late-onset dyspnea in the whole sample of Florence metropolitan area patients exposed to the drug at its introduction on the market at the end of 2014 was 4.84 per 100 person-year. The late-onset dyspnea rate is notably lower than the early-onset rate; nevertheless, the prescribing clinician should be aware that about 1 in 20 outpatients with a stabilized ticagrelor treatment might develop a dyspnea leading to an ED visit.

Although larger postmarketing studies are still needed to identify the *real-world* safety profile of ticagrelor in ACS patients,<sup>32,33</sup> to correctly obtain definitive data on the rate of ED visit for ticagrelor-related dyspnea, and to identify the individual characteristics influencing its rate, the current study clearly indicates that clinicians should not underestimate the risk of severe dyspnea also in patients with stabilized treatment, in particular women over 70. Anyway, given the benefits provided by the drug in this subset of patients, we believe that prescribers should consider ticagrelor replacement only in patients who cannot tolerate dyspnea.<sup>26</sup>

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Author contributions: N.L. and E.L. were involved in the conception, design, analysis, and interpretation of the data, and in the drafting of the submitted article. M.T., D.B. and A.B. were involved in the collection of clinical and administrative data. A.M. and A.V. were involved in the critical revision of the submitted article for intellectual content. All authors approved the final version of the submitted article; and all authors agree to be accountable for all aspects of the present work.

## Conflicts of interest

*There are no conflicts of interest.*

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