Why does ticagrelor induce dyspnea?

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Summary
In studies that compared the reversible P2Y12 inhibitor ticagrelor with the irreversible inhibitor clopidogrel, dyspnea was observed more frequently among ticagrelor-treated patients than among clopidogrel-treated patients. Because dyspnea was not associated with acidosis, pulmonary or cardiac dysfunction, alterations in the mechanisms and pathways of the sensation of dyspnea may be involved in its pathogenesis. It has been hypothesised that the sensation of dyspnea in ticagrelor-treated patients is triggered by adenosine, because ticagrelor inhibits its clearance, thereby increasing its concentration in the circulation. However, dipyridamole, a much stronger inhibitor of adenosine clearance than ticagrelor, usually does not cause dyspnea. We hypothesise that inhibition of P2Y12 on sensory neurons increases the sensation of dyspnea, particularly when reversible inhibitors are used. We base our hypothesis on the following considerations: 1) cangrelor and eliogrel, which, like ticagrelor, are reversible P2Y12 inhibitors, also increase the incidence of dyspnea; 2) it is biologically plausible that inhibition of P2Y12 on sensory neurons increases the sensation of dyspnea; 3) inhibition of P2Y12 on platelets (which do not have a nucleus) by clopidogrel is permanent, despite the once daily administration and the short plasma half-life of the inhibitor; 4) in contrast, inhibition of P2Y12 on neurons by clopidogrel may be temporary and transient, because neurons have a nucleus and can therefore rapidly replace the inhibited receptors with newly synthesised ones; 5) inhibition of P2Y12 on neurons by reversible inhibitors is permanent, because the plasma drug concentration is maintained high by repeated dosing, in order to ensure permanent inhibition of platelet P2Y12.

Keywords
ADP receptors, arterial thrombosis, nervous system

Introduction
P2Y12 is one of the two platelet receptors for adenosine diphosphate (ADP), which play a very important role in platelet function and thrombus formation (1). Although it was initially considered to have a much more selective tissue distribution than the other platelet ADP receptor, P2Y1, it was later shown to be expressed in many cell lines, including endothelial cells, smooth muscle cells, neurons and glial cells (1). Drugs that target P2Y12 reduce the incidence of arterial thrombosis, as documented by the results of several randomised clinical trials (1, 2).

Compared to the thienopyridine drug clopidogrel, which irreversibly inhibits P2Y12, ticagrelor, a direct, reversibly binding P2Y12 antagonist, causes greater and more consistent inhibition of platelet function, and decreases the incidence of major adverse cardiovascular events (MACE) and total mortality in patients with acute coronary syndromes (ACS) (1, 2).

Dyspnea is a relatively frequent adverse event of ticagrelor therapy (3–8). In all the studies in which ticagrelor and clopidogrel were compared, the frequency of ticagrelor-associated dyspnea was higher, compared to that associated with clopidogrel (Table 1). In phase 2 studies, ticagrelor was associated with a dose-dependent incidence of dyspnea of 10 to 20%, compared to 0–6.4% with clopidogrel (4, 5). In the ONSET/OFFSET study, which evaluated the onset and offset of the antiplatelet effects of ticagrelor compared with clopidogrel and placebo in patients with stable coronary artery disease (CAD) (6), dyspnea occurred in 38.6%, 9.3% and 4% with ticagrelor, clopidogrel and placebo groups and was judged by the investigator to be likely or possibly due to the study drug in 24.6%, 3.7% and 0% (7). The frequency of dyspnea was 13% with ticagrelor and 4% with clopidogrel in the RESPOND study, which, using a cross-over design, tested the ability of ticagrelor to inhibit P2Y12-dependent platelet function in patients who were non-responders to clopidogrel (8). Finally, the PLATO study, a multicenter, double-blind, randomised trial, comparing ticagrelor and clopidogrel for the prevention of MACE in patients with ACS, reported 13.8% dyspnea associated with ticagrelor versus 7.8% associated with clopidogrel (3).

Ticagrelor-associated dyspnea was reported to be mild to moderate in nature, disappearing after drug withdrawal and rarely determining drug discontinuation of affected patients (3–5, 7–9).

Causes of dyspnea
Dyspnea has many causes, including pulmonary, cardiac and metabolic diseases (14). In-depth studies of pulmonary and car-

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Hypothese: ticagrelor-induced dyspnoea is mediated by inhibition of the P2Y_{12} receptors

The hypothesis that the pathogenesis of dyspnoea during ticagrelor treatment is mediated by the main mechanism of action of the drug, i.e. inhibition of the P2Y_{12} receptor (expressed by cells different from platelets), has never been considered or suggested, probably based on the assumption that clopidogrel, which is also an inhibitor of P2Y_{12}, is not associated with this adverse effect. Indeed the incidence of dyspnoea was not different in clopidogrel-treated patients and aspirin-treated patients in the CAPRIE study (14). However, after the first demonstration that treatment with ticagrelor is associated with a high incidence of dyspnoea (4), all the following studies that compared ticagrelor with clopidogrel did show that dyspnoea is an, albeit rarer and milder, adverse effect also of clopidogrel treatment (Table 1). Because pulmonary, cardiac and metabolic diseases that are associated with dyspnoea may be common among patients with ACS, the critical point is to identify those cases of dyspnoea that are not attributable to these conditions. In the PLATO and ONSET/OFFSET studies, dyspnoea was considered “unexplained” (i.e. not attributed to suspected aetiologies) or “likely or possibly due to the study drug” in 27.3% (366/1339) (9) and 63.3% (14/22) (6) of ticagrelor-treated patients, and in 20.1% (160/798) (9) and 40% (2/5) (6) of clopidogrel-treated patients. Similarly, Serebruany et al. showed that, among 3,719 patients who underwent coronary stenting, 157 (4.2%) developed dyspnoea while on treatment with clopidogrel, which was attributable to underlying pulmonary or cardiac diseases in most instances, but remained unexplained in 17/157 (10.8%) (14). Moreover, 13 patients in the PLATO study (9) and 10 patients in the Disperse-2 study (5) had to discontinue clopidogrel treatment, due to the severity of dyspnoea. In conclusion, we think that, based on the available published evidence, it is likely that clopidogrel may cause dyspnoea in a small proportion of treated patients. Therefore, although we acknowledge that dyspnoea does not appear to be a relevant clinical problem associated with clopidogrel treatment, the published reports do not oppose our hypothesis that inhibition of P2Y_{12} may increase the sensation of dyspnoea. Based on this hypothesis, one may argue that the lower incidence of clopidogrel-associated dyspnoea, compared to ticagrelor, could be due to the fact that clopidogrel does not adequately inhibit P2Y_{12} in about 30% of patients (1, 2). However, this hypothesis is not completely supported by the observation that in the TICAR-TIMI 38 trial (19) the frequency of dyspnoea among patients treated with prasugrel, which, like ticagrelor, adequately inhibits P2Y_{12} in the vast majority of treated patients (2), was only about 1.10-fold higher than that observed among clopidogrel-treated patients (4.9% vs. 4.5%) (20). Based on these data, it appears reasonable to conclude that the more efficient inhibition of P2Y_{12} by ticagrelor may only partially account for the much higher incidence of dyspnoea observed in ticagrelor-treated patients, compared to clopidogrel treated patients (1.64– to 4.17-fold higher, Table 1).

Certainly more enlightening, albeit often overlooked in the literature, are the data from recent clinical trials, which demonstrate that, similarly to ticagrelor, two other P2Y_{12} inhibitors, cangrelor (10) and elinogrel (11), are associated with an incidence of dyspnoea that is 2.5– to 3.3-fold higher compared to clopidogrel (Table 1). Although it cannot be formally ruled out, it is unlikely that three drugs with different molecular structures (elinogrel, in particular, belongs to a different structural family of non-nucleotide antagonists), which were developed to inhibit P2Y_{12}, all share the same side effect of inhibiting adenosine uptake. At any rate, no reports have demonstrated that either cangrelor or elinogrel does so. We consider more probable that these three drugs (and, perhaps, albeit to a lesser extent, clopidogrel) increase the incidence of dyspnoea through their main mechanism of action, i.e. inhibition of the
P2Y₁₂ receptor. The characteristic that unites ticagrelor, cangrelor and elinogrel is that they are reversible inhibitors of P2Y₁₂, at variance with clopidogrel, which inhibits the receptor irreversibly.

Based on these considerations, we hypothesise that drugs inhibiting P2Y₁₂ increase the incidence of dyspnea, particularly if they reversibly inhibit the receptor. In the following paragraphs we will attempt to demonstrate that this hypothesis is biologically plausible.

Is it biologically plausible that drugs inhibiting the P2Y₁₂ receptor increase the incidence of dyspnea?

As previously mentioned, dyspnea can be induced via central mechanisms, chemoreceptors or stimulation of afferent vagal C-fibers (16). P2Y₁₂ was shown to be expressed in neuronal tissues and to inhibit neuronal signaling, through the inhibition of cyclic adenosine monophosphate (cAMP) generation (21, 22). Therefore, it can be predicted that inhibitors of P2Y₁₂ will increase neural signalling. Indeed, Kubista et al. showed that cangrelor antagonises the inhibition of neuronal Ca²⁺ channels by adenine nucleotides, which is mediated by P2Y₁₂, and paralleled by inhibition of cAMP accumulation (23). The importance of cAMP in the activation of afferent C-fibers is highlighted by the effect of prostaglandin E₂ (PGE₂), which potentiated hyperthermia-induced hypersensitivity of vagal pulmonary C-fibers through its interaction with Gs-coupled EP2 and EP4 receptors (24).

Moreover, inhalation of PGE₂ aerosol significantly increased the dyspneic sensation during exercise in healthy human subjects, without inducing changes in airway resistance or lung volume (25). Since P2Y₁₂ is negatively coupled to adenylyl cyclase, its inhibition should enhance the effects of PGE₂, as much as it enhances the antiplatelet effects of prostacyclin, which is also mediated by increased cAMP levels (26).

In conclusion, experimental evidence indicates that it is biologically plausible that inhibition of P2Y₁₂ increases the conductivity of vagal C-fibers and, hence, the sensation of dyspnea.

Is it biologically plausible that reversible P2Y₁₂ inhibitors cause dyspnea more commonly than the irreversible inhibitor clopidogrel?

Adequate and constant blood levels of reversible inhibitors must be maintained in order to achieve an adequate and constant degree of inhibition of the platelet P2Y₁₂ receptors. The dose and frequency of their administration depend on their pharmacodynamic and pharmacokinetic properties. Ticagrelor and elinogrel, whose half-lives are about 8–12 hours (27, 28), are given twice daily, (3, 29) while cangrelor, which is a parenteral drug with a very short half-life (<10 minutes) (28), is administered by continuous intravenous infusion. Maintaining adequate blood levels of the drug will not only inhibit the P2Y₁₂ receptors that are expressed on platelets, but

<table>
<thead>
<tr>
<th>Study drug (reversible inhibitor)</th>
<th>Patients (total n)</th>
<th>Dose</th>
<th>Duration of treatment</th>
<th>A Percent of dyspnea in study drug group</th>
<th>B Percent of dyspnea in clopidogrel group</th>
<th>A/B</th>
<th>Study (reference)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ticagrelor*</td>
<td>Patients with atherosclerosis (200)</td>
<td>50 mg b.i.d.</td>
<td>28 d</td>
<td>10</td>
<td>0</td>
<td>∞</td>
<td>DISPERSE (4)</td>
</tr>
<tr>
<td></td>
<td>Ticagrelor</td>
<td>NSTE-ACS (990)</td>
<td>90 mg b.i.d.</td>
<td>12 wk</td>
<td>10.5</td>
<td>6.4</td>
<td>∞</td>
</tr>
<tr>
<td></td>
<td>Ticagrelor#</td>
<td>Stable CAD (123)</td>
<td>90 mg b.i.d.</td>
<td>6 wk</td>
<td>38.6</td>
<td>9.3</td>
<td>4.15</td>
</tr>
<tr>
<td>Ticapagrelor§</td>
<td>Stable CAD (98)</td>
<td>90 mg b.i.d.</td>
<td>14 d</td>
<td>13</td>
<td>4</td>
<td>3.25</td>
<td>RESPOND (8)</td>
</tr>
<tr>
<td>Ticagrelor§</td>
<td>ACS (18,624)</td>
<td>90 mg b.i.d.</td>
<td>12 mo</td>
<td>13.8</td>
<td>7.8</td>
<td>1.77</td>
<td>PLATO (3)</td>
</tr>
<tr>
<td>Cangrelor§</td>
<td>ACS (8,877)</td>
<td>4 μg/Kg/min IV</td>
<td>2–4 h</td>
<td>1</td>
<td>0.4</td>
<td>2.5</td>
<td>CHAMPION-PCI (10)</td>
</tr>
<tr>
<td>Elinogrel§</td>
<td>Nonurgent PCI (626)</td>
<td>100 mg b.i.d.</td>
<td>120 d</td>
<td>12.4</td>
<td>3.8</td>
<td>3.26</td>
<td>INNOVATE-PCI (11)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>150 mg b.i.d.</td>
<td>120 d</td>
<td>12.1</td>
<td>3.8</td>
<td>3.18</td>
<td></td>
</tr>
</tbody>
</table>

Clopidogrel was given at the maintenance dose of 75 mg q.d. Variable loading doses of reversible P2Y₁₂ inhibitors and clopidogrel were administered to patients in all studies, with the exception of DISPERSE. *The formulation of ticagrelor that was used in this study was different from that used in the other studies listed in this table: 100 mg of this formulation are equivalent to 90 mg of the other formulation. ‡In this study, ticagrelor was compared also to placebo. The frequency of dyspnea in placebo-treated patients was 8.3%. The drug-attributable frequency of dyspnea, according to the judgment of the investigators, was 24.6%, 3.7% and 0% for ticagrelor, clopidogrel and placebo. §Cangrelor was tested also in two additional randomised clinical trials, CHAMPION-PLATFORM (12) and BRIDGE (13), in which it was compared to placebo. The frequency of dyspnea in cangrelor-treated patients was 1.4 and 1.9, compared to 0.5 and 1.0 in placebo treated patients: therefore, the frequency of dyspnea in cangrelor-treated patients was 2.8-fold and 1.9-fold higher than in placebo-treated patients. CAD: coronary artery disease; ACS: acute coronary syndrome; NSTE: non ST elevation; b.i.d.: twice daily; q.d.: once daily.
also those that are expressed on other cells, like, for instance, neurons. Therefore, ticagrelor, elinogrel and cangrelor, at the dose regimens that have been used, could constantly inhibit P2Y12 receptors on sensory neurons, thereby increasing the dyspnea sensation.

Clopidogrel is a pro-drug that needs to be metabolised in vivo by hepatic cytochrome-P450 isoenzymes to its active metabolite (AM), which forms a disulfide bond with cysteine residues on P2Y12, thereby irreversibly inhibiting the receptor (2). Since platelets are anucleated cells, they cannot replace the inhibited receptors with newly synthesised ones and will remain inhibited for their entire lifespan. In contrast, in all other cells expressing the receptor, inhibition of P2Y12 by clopidogrel-AM during its very short appearance in the circulation (30), would only be temporary and transient, because cells will rapidly replace the inhibited receptors with newly synthesised ones. In particular, in vitro experiments demonstrated that newly synthesised proteins can be detected within few minutes since the start of observation, both in the somata and dendrites of neurons (31). Therefore, P2Y12 on sensory neurons could very transiently be inhibited by clopidogrel-AM, accounting for the very low frequency of dyspnea that is associated with its administration.

In conclusion, differences between the pharmacological properties of reversible P2Y12 inhibitors and clopidogrel, in association with differences in biology of anucleated platelets and nucleated P2Y12 bearing neurons, could account for the higher incidence of dyspnea observed during treatment with reversible inhibitors, compared to clopidogrel. More in general, considering that the presence of P2Y12 on nucleated cells is more widespread than initially believed, this model could account for differences in the pharmacological responses to thienopyridines compared to reversible P2Y12 inhibitors (Fig. 1), not only in terms of incidence of untoward side effects, but also in terms of clinical efficacy.

Why is ticagrelor-induced dyspnea transient?

A remaining issue to be explained concerns the transient nature of dyspnea in most patients, despite continuous administration of ticagrelor. This could be explained by the fact that the intensity of the sensation of dyspnea is determined by a mismatch between the new afferent/efferent information and a sort of “memory” in the cortical centers of “normal” afferent input and “normal” respir-

![Figure 1: Differences in the pharmacokinetics (PK) and pharmacodynamics (PD) of thienopyridines, which irreversibly inhibit the P2Y12 receptors, and reversible inhibitors of P2Y12. The continuous inhibition of P2Y12 on nucleated cells by reversible inhibitors of the receptor, as opposed to its transient inhibition by thienopyridines may account for differences in the pharmacological responses to the drugs, not only in terms of incidence of untoward side effects, but also in terms of clinical efficacy. The hypothesis that we raise in this manuscript is that continuous inhibition of P2Y12 on sensory neurons (which are nucleated cells) by reversible P2Y12 inhibitors accounts for the higher incidence of dyspnea in patients treated with reversible inhibitors, compared to clopidogrel (see text for details). Values in the graph are not based on real data and should be considered illustrative. Values of PK of thienopyridines are inspired by the data shown in [35]; PD data of thienopyridines account for a theoretical decrease of inhibition of the platelet P2Y12 receptors of about 10% at 24 hours post dosing, due to the appearance of about 10% (6), newly formed, non-inhibited platelets in the circulation. PD data of reversible P2Y12 inhibitors are inspired to the PD data of ticagrelor, reported in the ONSET-OFFSET study (6). Arrows at the top of the graphs indicate the times of administration of the drugs.](image-url)
atory system response, in terms of effort required to achieve a given airflow or ventilation (16). After some days of treatment with ticagrelor, the new afferent/efferent information, determined by the hyperactivity of sensory neurons, will be retained as a new “memory” by the cortical centers, which will be unable to recognise them as new or pathological.

Conclusion

In conclusion, we think that inhibition of P2Y\textsubscript{12}, on C fibers of sensory neurons is responsible for the observed incidence of dyspnea in patients treated with antiplatelet drugs that target P2Y\textsubscript{12}. The much higher incidence of dyspnea that has been observed in patients treated with ticagrelor or other drugs that reversibly bind to the receptor, than in patients treated with the irreversible inhibitor clopidogrel, is likely explained by differences in pharmacokinetic properties of these drugs. In contrast, differences in the inhibitory efficiency of the drugs seem to play a marginal role. In fact, the incidence of dyspnea in patients treated with clopidogrel is only slightly lower than in patients treated with prasugrel, which is a more efficient, irreversible P2Y\textsubscript{12} inhibitor than clopidogrel.

We are aware that we are purporting a hypothesis that is difficult to test for at least two reasons: i) the definition of the precise physical stimulus that causes dyspnea is problematic (32); ii) dyspnea is a sensation that can only be properly assessed in collaborating human beings (16) (these difficulties likely explain why previous pathogenic hypotheses that have been published [33] have not been successfully tested yet). Due to these difficulties, and considering that C fibers can react to various stimuli, which may be thermal, mechanical or chemical in nature (34), we are planning to test our hypothesis in preliminary experiments, in which the effects of different P2Y\textsubscript{12} inhibiting drugs on surrogates end-points, such as thermal and tactile sensations, will be measured.

Conflicts of interest

None declared.

This article reflects the view of its author(s) and is not representative of the view of the Editorial Board or the Publishers.

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