SCIENTIFIC EDITORIAL

Pleiotropic effects of ticagrelor: Myth or reality?

Effets pleiotropes du ticagrelor : mythe ou réalité ?

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Background

In the PLATO study, ticagrelor, a direct-acting and reversible P2Y\textsubscript{12} adenosine diphosphate receptor blocker, slightly but significantly reduced the incidence of cardiovascular and total mortality compared with clopidogrel [1]. The accuracy of the PLATO mortality data has been questioned by some authors [2]. In an adjusted indirect meta-analysis comparing prasugrel with ticagrelor for acute coronary syndromes (ACS), prasugrel and ticagrelor appeared similarly superior to clopidogrel, without any significant difference between them in terms of risk of death and overall major adverse events. Ticagrelor was associated with a significantly lower risk of any major bleeding, while prasugrel caused more bleeding [3]. So, most of these allegations have been rebutted by the PLATO investigators [4].

KEYWORDS
Antiplatelet; Acute coronary syndrome; Adenosine plasma; P2Y\textsubscript{12} adenosine diphosphate receptor blocker

Abbreviations: ACS, acute coronary syndrome; APC, adenosine plasma concentration; ENT\textsubscript{1}, type 1 equilibrative nucleoside transporter; EPC, endothelial progenitor cell; RHI, reactive hyperaemia index.

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Alternative interpretations may exist [5]. In a review, Cattaneo et al. carried out a critical evaluation of recent publications that described an additional mode of action for ticagrelor [6]. The effect is mediated by inhibition of the adenosine transporter ENT1 (type 1 equilibrative nucleoside transporter), which provides protection for adenosine from intracellular metabolism, thus increasing its concentration and biological activity. Most of the studies described were performed using in vitro models, healthy volunteers and animal models [6]. In a recent study, Nanhwan et al. [7] demonstrated that ticagrelor reduces myocardial infarct size; the protective effect of ticagrelor was dependent on adenosine receptor activation, with downstream upregulation of endothelial nitric oxide synthase and cyclooxygenase-2 activity.

In this editorial, we summarize our investigations into the effect of ticagrelor on adenosine plasma concentration (APC), and the consequential effect on endothelial function and endothelial cell migration, in the setting of ACS.

Effect of ticagrelor on APC during ACS

In a prospectively randomized trial, 60 patients with an ACS received ticagrelor or clopidogrel. Six hours after administration of the P2Y12-receptor antagonist loading dose, patients who received ticagrelor had a significantly higher APC than patients who received clopidogrel (P < 0.01) (Fig. 1) [8]. The mechanism of action seems to be inhibition of adenosine uptake by red blood cells, as described in the review by Cattaneo et al. [6].

Is ticagrelor responsible for so-called ‘’pleiotropic’’ properties, such as improvement of endothelial function, in ACS patients?

In a second study, we sought to determine whether the increase in APC achieved with ticagrelor improved endothelial dysfunction in patients with primary ACS [9]. Sixty patients were prospectively randomized to receive ticagrelor or clopidogrel. Endothelial function was assessed by digital peripheral artery tonometry, and was evaluated using the reactive hyperaemia index (RHI). Endothelial dysfunction was suspected if the RHI was < 1.67 [10].

Treatment with ticagrelor improved peripheral arterial function compared with clopidogrel

Under basal conditions, all the patients had microvascular dysfunction (RHI < 1.67; mean, 1.37 ± 0.12). The APC and RHI did not differ between the two groups of patients. At day 30, the APC increased significantly only in the ticagrelor group. The APC was more than two-fold higher in patients taking ticagrelor than in patients taking clopidogrel. After 30 days, the mean RHI increased slightly (mean, +15%) in the clopidogrel group and greatly (+100%) in the ticagrelor group. We found a correlation between the increase in the APC and the increase in RHI in the ticagrelor group (Fig. 2). So, endothelial function responded more effectively to ticagrelor than to clopidogrel within 30 days. Ticagrelor induced an increase in APC that correlated with the increase in RHI; clopidogrel improved endothelial function, but this was not related to the increase in APC. Consequently, the underlying mechanism of action seems to be the increase in APC. Finally, our study demonstrated a correlation between the increase in APC and the improvement in RHI, but whether this increase in APC has a direct effect on endothelial function remains to be established.
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Effect of ticagrelor on endothelial progenitor cell migration

Endothelial progenitor cells (EPCs) originating from the bone marrow play a critical role in vascular homeostasis. EPCs participate in the regeneration of the damaged endothelium and reduce neointimal hyperplasia after vascular injury. A low concentration of EPCs (CD34+ EPCs expressing KDR or CD133) correlates with cardiovascular risk factors and poor short- and long-term clinical outcomes in stable coronary artery disease and ACS [11]. Cattaneo et al. [6] suggested that ticagrelor might participate in EPC migration, but no clinical data were available to support this hypothesis.

In a third study [12], we randomly compared the effect of ticagrelor and clopidogrel on EPC concentration in 106 ACS patients undergoing percutaneous coronary intervention. We observed that the use of ticagrelor compared with clopidogrel was associated with a significant increase in the EPC concentration during the first month after an ACS (Table 1). The favourable effect on EPC concentration was independent of the vasodilator-stimulated phosphoprotein index, suggesting a specific platelet-independent effect of ticagrelor (data not shown).

A number of substances have been shown to influence the bone marrow production of EPCs through various pathways, including cytokines, growth factor synthesis and cell–cell interactions. Adenosine may be one of these substances, but this has not been established.

Table 1  Comparison of the change in concentration of CD34+133+ and CD34+KDR+ progenitor cells, assessed as the number of progenitor cells at 1 month between the ticagrelor and clopidogrel patient groups.

<table>
<thead>
<tr>
<th>Progenitor cells</th>
<th>Ticagrelor group</th>
<th>Clopidogrel group</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD34+133+</td>
<td>0.23 (−0.33; 0.79)</td>
<td>0.00 (−0.5; 0.34)</td>
<td>0.036</td>
</tr>
<tr>
<td>CD34+KDR+</td>
<td>0.01 (−0.04; 0.05)</td>
<td>−0.01 (−0.06; 0.03)</td>
<td>0.019</td>
</tr>
</tbody>
</table>

Data are expressed as median (25th percentile; 75th percentile).

Figure 2. Correlation between increase in APC (ΔAPC) and increase in the RHI (ΔRHI).

Conclusion

The clinical benefit of ticagrelor compared with clopidogrel in patients with an ACS suggested an off-target property [5]. A number of observations led to the hypothesis that ticagrelor has pleiotropic properties, and suggested some novel non-platelet-directed mechanisms of action [6,7]. This editorial constitutes a critical evaluation of recent publications in the setting of ACS patients. Ticagrelor was associated with a significant increase in APC in these clinical studies [9,12]. The mechanism of action seems to be inhibition of adenosine reuptake by red blood cells [8]. This effect of ticagrelor on APC may be responsible for the so-called “pleiotropic” properties, particularly at sites of ischaemia and tissue injury, where adenosine is formed. Ticagrelor exerts an additional mode of action — endothelial regeneration [12] — leading to improvement in endothelial function through an increase in APC [9]. Because low APC concentration and endothelial dysfunction have been associated with a higher rate of adverse events during follow-up, our studies have led to the hypothesis that adenosine-mediated effects of ticagrelor may explain the PLATO mortality data [1]. Our studies were not powered to explore a link between adenosine and specific side-effects such as bradycardia and dyspnoea, which can also be triggered by APC.

Disclosure of interest

The authors have not supplied their declaration of competing interest.

References


