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Adenosine-Mediated Effects of Ticagrelor

Evidence and Potential Clinical Relevance

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This review constitutes a critical evaluation of recent publications that have described an additional mode of action of the $P2Y_{12}$ receptor antagonist ticagrelor. 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, particularly at sites of ischemia and tissue injury where it is formed. Understanding the mode of action of ticagrelor is of particular interest given that its clinical profile, both in terms of efficacy and adverse events, differs from that of thienopyridine $P2Y_{12}$ antagonists. (J Am Coll Cardiol 2014;63:2503–9) © 2014 by the American College of Cardiology Foundation

Ticagrelor is a direct-acting, reversibly binding $P2Y_{12}$ antagonist that provides rapid onset of antiplatelet effects after oral administration. $P2Y_{12}$, 1 of the 2 purinergic receptors for adenosine diphosphate (ADP) expressed by platelets, is essential for normal ADP-induced platelet aggregation. $P2Y_{12}$ signaling amplifies platelet responses to agonists that cause ADP release from delta granules, stabilizes platelet aggregates, and opposes the antiplatelet effects of natural platelet inhibitors such as prostacyclin that induce production of the inhibitory cyclic adenosine monophosphate (cAMP) by activating adenylyl cyclase (1).

The essential role of $P2Y_{12}$ in hemostasis and thrombosis is demonstrated by observations that patients with inherited $P2Y_{12}$ defects have a bleeding diathesis and that the administration of antagonists reduces the incidence of major adverse cardiovascular events in patients at risk (1). The most widely used $P2Y_{12}$ antagonist is the thienopyridine prodrug clopidogrel, which, through hepatic conversion to its active metabolite, irreversibly inhibits $P2Y_{12}$. Compared with clopidogrel, ticagrelor provides higher and much less variable $P2Y_{12}$ inhibition. This is also true for the third-generation thienopyridine prasugrel (1), albeit ticagrelor has been shown to provide slightly greater platelet inhibition (2). In the PLATO (Platelet Inhibition and Patient Outcomes) study, ticagrelor was superior to clopidogrel in preventing cardiovascular death, myocardial infarction, or stroke (9.8% vs. 11.7%, a 16% reduction) in patients with acute coronary syndrome (ACS); two-thirds of these patients had undergone percutaneous coronary intervention (PCI) (3). Prasugrel was also superior to clopidogrel in preventing the same composite endpoint in patients with ACS who underwent PCI in the TRITON (Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel) trial (4). Although the 2 trials had quite different designs, they showed that more rapid, higher, and more consistent $P2Y_{12}$ inhibition than afforded by clopidogrel was associated with better clinical outcome. PLATO and TRITON did display some differences. In PLATO, ticagrelor slightly but significantly reduced the incidence of cardiovascular (4.0% vs. 5.1%) and total (4.5% vs. 5.9%) mortality compared with clopidogrel, whereas no significant reduction in cardiovascular (2.1% vs. 2.4%) or total (3.0% vs. 3.2%) mortality was observed with prasugrel versus clopidogrel in TRITON (3,4). In addition, a greater incidence of dyspnea and ventricular pauses was observed with ticagrelor (3). Although the accuracy of the PLATO mortality data has been questioned by some authors (5), their allegations have been rebutted by the PLATO investigators (6). Thus, although alternative interpretations exist (7), the PLATO data on mortality suggest that ticagrelor may have unique and clinically relevant effects, as also demonstrated by the observed increased incidence of dyspnea and ventricular pauses (3). These effects of ticagrelor may be accounted for by its reversible binding to $P2Y_{12}$, its systemic presence at pharmacologically active concentrations over 24 h of the day (8), and/or by additional $P2Y_{12}$-independent effects (9).

Here, we will review the experimental and clinical evidence that ticagrelor increases the half-life and plasma concentration of adenosine, and critically evaluate whether

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Abbreviations and Acronyms

ACS = acute coronary syndrome(s)

ADP = adenosine diphosphate

cAMP = cyclic adenosine monophosphate

CNT = concentrative nucleoside transporter

ENT1 = equilibrative nucleoside transporter

PCI = percutaneous coronary intervention

this additional effect of ticagrelor may explain the drug's clinical profile.

Ticagrelor Inhibits Cellular Uptake of Adenosine

Adenosine is a purine nucleoside produced primarily through the metabolism of ADP or adenosine triphosphate by the nucleotidases CD39 and CD73; its plasma levels increase after cellular stresses such as injury, ischemia/reperfusion, or inflammation (10). Adenosine is rapidly taken up by cells through sodium-independent equilibrative nucleoside transporters (ENT 1/2) and sodium-dependent concentrative nucleoside transporters (CNT 2/3) (11). Intracellular adenosine is metabolized to inosine by adenosine deaminase or transformed into adenine nucleotides by adenosine kinase (10,12). Because of its rapid cellular uptake and metabolism, extracellular adenosine has a half-life of a few seconds (13), which can be prolonged by inhibition of its transport into cells (Fig. 1).

Several studies provide evidence that ticagrelor inhibits cellular uptake of adenosine (11,14,15). Ticagrelor inhibited adenosine uptake by washed human erythrocytes and by human, dog, and rat cell lines. Considering that the experiments were performed under sodium-free conditions and with cell lines that express ENT1 but not ENT2, it was assumed that ticagrelor inhibits sodium-independent ENT1 (14). The identity of the target transporter was recently confirmed with cells transfected with human transporters (ENT1, ENT2, CNT2, and CNT3). In these experiments, ticagrelor significantly inhibited adenosine uptake only in cells that expressed ENT1 (11). Compared with dipyridamole, an established ENT1 inhibitor (16), ticagrelor displayed a lower affinity for the transporter (K_i 41 vs. 2.6 nmol/l). Other $P2Y_{12}$ antagonists, (cangrelor, elinogrel, and the active metabolites of clopidogrel and prasugrel) did not display any significant activity versus any of the transporters. The main metabolites of ticagrelor (AR-C124910XX, present in blood, and AR-C133913XX, present in urine) showed weak ENT1 inhibition and low affinity (K_i: 330 and 23,000 nmol/l, respectively). Finally, the main metabolite of cangrelor displayed very weak inhibition of adenosine uptake (11). The 16-fold higher affinity of dipyridamole for ENT1 relative to ticagrelor is in line with the potency data obtained in the aforementioned in vitro experiments (14). The affinity of ticagrelor for $P2Y_{12}$ (K_i 2 nmol/l or pK_i 8.7) (17) is thus approximately 20-fold higher than for ENT1. Ticagrelor 1 μmol/l, but not the active metabolite of prasugrel, significantly conserved adenosine in human whole blood in vitro. Because the mean maximal plasma exposure after 90 mg of ticagrelor is 1.5 μmol/l (15), these in vitro data indicate a potential for clinical relevance. Importantly, it has been demonstrated that ticagrelor does not display relevant direct activity on adenosine receptors (11,18) and is not metabolized to adenosine (19).

Biological Effects of Adenosine

Adenosine exerts its biological effects by interacting with 4 G-protein–coupled receptors: A_1R and A_3R are coupled to G_i, the inhibitory G protein, which inhibits adenylyl cyclase and thus decreases intracellular cAMP, whereas $A_{2A}R$ and $A_{2B}R$ are coupled to the stimulatory G protein, G_s, which stimulates adenylyl cyclase, increasing intracellular cAMP. Of the 2 A_2R subtypes, A_{2A} is the high- and A_{2B} the low-affinity receptor (12,20).

Effects of adenosine on blood vessels. $A_{2A}R$ is the main adenosine receptor responsible for coronary vasodilation, which is mediated by both nitric oxide-dependent and -independent pathways (21). $A_{2B}R$ also mediates coronary vasodilation, whereas both A_1R and A_3R negatively modulate coronary vasodilation induced by $A_{2A}R$ and/or $A_{2B}R$ activation (22–24). Adenosine also induces endothelial progenitor cell migration via A_{2A} and A_3 (25).

Effects of adenosine on platelets. Adenosine is a potent inhibitor of platelet aggregation in platelet-rich plasma but not in whole blood as a consequence of its rapid uptake by erythrocytes. This discrepancy is abolished by the addition of dipyridamole to whole blood samples (26). Adenosine inhibits platelet activation mainly via $A_{2A}R$ but also via $A_{2B}R$ (27). The gene that encodes for A_{2B} is up-regulated after injury and systemic inflammation in vivo; as a consequence, the contribution of A_{2B} to adenosine-mediated platelet inhibition appears to increase under stress conditions (28).

Effects of adenosine on inflammatory responses. Adenosine modulates the inflammatory responses to a variety of stressful conditions. Low concentrations of adenosine, which activate A_1R and A_3R, promote neutrophil chemotaxis and phagocytosis, whereas high concentrations of adenosine, which activate $A_{2B}R$, inhibit neutrophil trafficking, granule release, and the production of reactive oxygen species and inflammatory mediators (29). The genetic deficiency of $A_{2B}R$ increased mortality in mice with sepsis and reduced levels of inflammatory markers (30). Thus, elevation of endogenous adenosine concentrations may reduce the inflammatory responses. Indeed, dipyridamole elevated adenosine concentrations and augmented the anti-inflammatory response during experimental human endotoxemia and was associated with a faster decline in proinflammatory cytokines (31).

Effects of adenosine on the heart. Adenosine exerts cardiac electrophysiological effects through activation of A_1R. It has a negative chronotropic effect through suppression of the automaticity of cardiac pacemakers and a negative dromotropic effect through inhibition of AV nodal conduction (32). These effects of adenosine constitute the rationale for its use as a diagnostic and therapeutic agent (e.g., treatment of supraventricular tachycardia) (33).

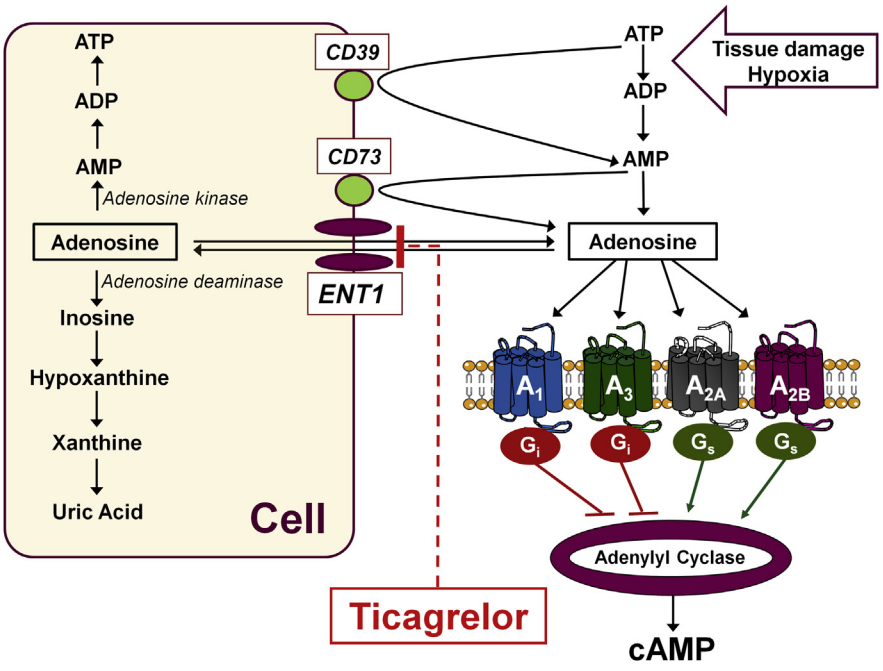

Figure 1 **Formation of Adenosine and its Intracellular Uptake and Metabolism, Which Are Reduced by Ticagrelor Through Inhibition of ENT1**

Adenosine is formed locally at sites of hypoxia and tissue damage through degradation of released adenosine triphosphate (ATP) and adenosine diphosphate (ADP) by CD39 and CD73 and is rapidly internalized by cells through equilibrative nucleoside transporter 1 (ENT1). Because adenosine degradation is primarily restricted to the intracellular space, inhibition of cellular uptake of adenosine via ENT1 effectively prolongs the half-life of adenosine, thereby increasing its extracellular concentration. As a consequence, ENT1 inhibition by ticagrelor results in enhanced responses to adenosine, mediated by interaction with the adenosine receptor subtypes A_1R, $A_{2A}R$, $A_{2B}R$, and A_3R, which are coupled to G_s or G_i proteins. AMP = adenosine monophosphate; cAMP = cyclic adenosine monophosphate.

Effects of adenosine on ischemia/reperfusion injury. Timely coronary reperfusion improves outcomes in patients with ACS, although reperfusion itself may contribute to the extent of irreversible myocardial injury (reperfusion injury). Adenosine reduced ischemia/reperfusion injury in humans (34,35) and in animal models (10). A recent meta-analysis of 7 randomized clinical trials indicated that intracoronary adenosine administration increased post-PCI ST-segment resolution and reduced residual ST-segment elevation and the incidence of major adverse cardiovascular events, although the latter did not reach statistical significance (36). Additionally, infarct size in post-PCI patients was reduced by high-dose intracoronary adenosine (37) or continuous intravenous adenosine infusion (38); however, another study failed to show any beneficial effect of adenosine in patients undergoing PCI, likely because of the very low risk of the enrolled patients (39). As an alternative to infusion of exogenous adenosine, inhibition of ENT1 might exert cardioprotective effects by increasing the concentration of endogenous adenosine. Indeed, ENT1 knockout mice had a reduced infarct size after ischemia/reperfusion (40), and dipyridamole reduced infarct size in rabbits (41) and improved heart function after PCI in patients (42).

Effects of adenosine on sensory nerves. Adenosine stimulates pulmonary vagal C fibers through A_1R and $A_{2A}R$, which mediates the sensation of dyspnea (43).

Effects of adenosine on the kidney. Coordination between kidney blood flow and glomerular filtration rate with tubular reabsorption is maintained by the tubuloglomerular feedback system and metabolic products; adenosine triphosphate and adenosine (through A_1R) mediate tubuloglomerular feedback via afferent arteriolar vasoconstriction. Tubuloglomerular feedback responsiveness was significantly attenuated in the absence of ENT1 in mice (44), and dipyridamole decreased diuresis in patients, in part in relation to a fall in glomerular filtration rate (45).

Ticagrelor Increases the Biological Effects of Exogenous Adenosine

Ticagrelor increases the effects of exogenous adenosine on blood vessels. Ticagrelor, like dipyridamole, dose-dependently increased local blood flow in the coronary artery of dogs after infusion of adenosine (14). Similar results were obtained in healthy volunteers, who had 180 mg of ticagrelor significantly enhance the coronary blood flow velocity increases induced by adenosine infusion (46). There

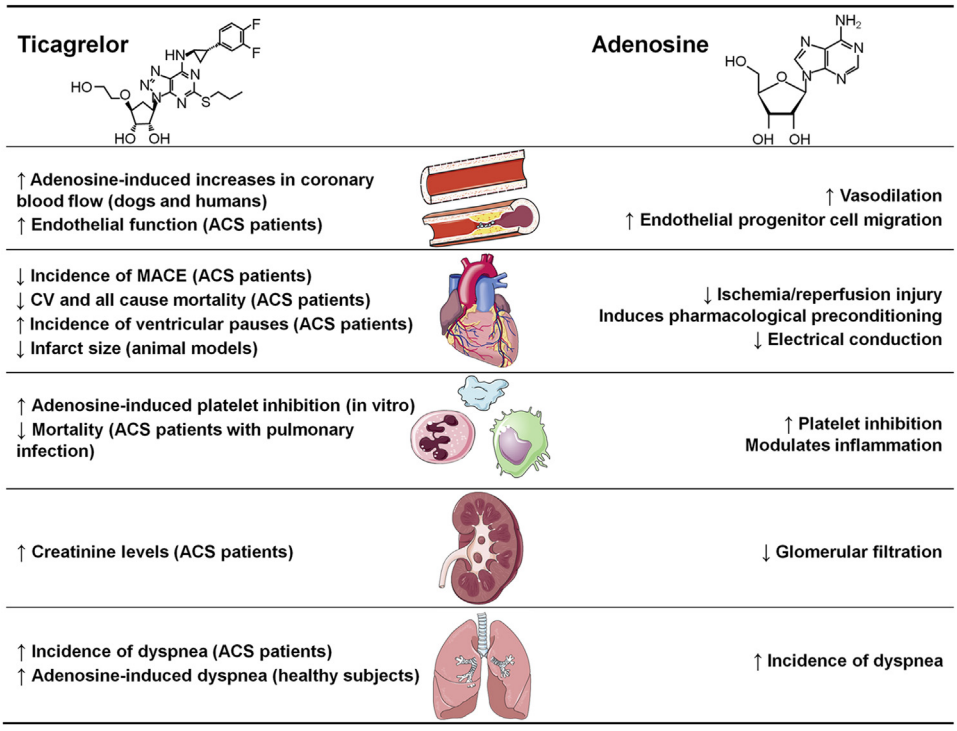

Figure 2 Selection of Effects Mediated by Ticagrelor and Adenosine

There are similarities between the biological effects of adenosine **(right)** and the pharmacological effects of ticagrelor **(left)**, which suggests that at least some of the latter may be mediated by the drug-induced inhibition of equilibrative nucleoside transporter type 1, which causes an increase in plasma concentration of adenosine. ACS = acute coronary syndrome(s); CV = cardiovascular; MACE = major adverse cardiovascular effect(s).

was a significant correlation between coronary blood flow velocity and the plasma concentration of ticagrelor but not for its metabolite AR-C124910XX, which has low affinity for ENT1 (11). These data were confirmed in patients with non–ST-elevation myocardial infarction undergoing PCI: ticagrelor (90 mg bid), but not prasugrel (10 mg o.d.), significantly enhanced the increases in coronary blood flow velocity induced by adenosine infusion (47).

Ticagrelor increases the inhibitory effect of exogenous adenosine on platelet aggregation. In vitro, ticagrelor unmasked the inhibitory effect of exogenous adenosine on platelet aggregation in whole blood from healthy volunteers and patients with inherited severe $P2Y_{12}$ deficiency (15). The effect of ticagrelor on platelet aggregation was greater than that of dipyridamole, despite the fact that dipyridamole inhibited adenosine clearance more efficiently than ticagrelor. This may be explained by the fact that ticagrelor, by opposing the $P2Y_{12}$-mediated inhibition of adenylyl cyclase, enhanced the antiplatelet effect of adenosine, which, by interacting with $A_{2A}R$, activates adenylyl cyclase and increases cAMP (1,15).

Ticagrelor increases the sensation of dyspnea caused by exogenous adenosine. Ticagrelor (180 mg) significantly enhanced the sensation of dyspnea, measured by the Borg scale, after adenosine infusion in healthy volunteers (46). The increase in sensation of dyspnea was attenuated by intravenous administration of theophylline.

Effects of Ticagrelor on Plasma Levels of Endogenous Adenosine and on its Biological Effects

Studies in animal models suggest that ticagrelor enhances the biological effects of endogenous adenosine. A study of coronary blood flow after local ischemia by temporary coronary artery occlusion in dogs showed that ticagrelor, like dipyridamole, dose-dependently increased local blood flow, likely mediated by endogenous adenosine (14).

In a canine model of electrolytic injury–induced thrombus formation, ticagrelor, initiated 5 min before reperfusion by tissue plasminogen activator, reduced infarct size by approximately 60%. Clopidogrel had no protective effect under the same experimental conditions. Because both $P2Y_{12}$ antagonists were dosed to completely inhibit $P2Y_{12}$ but only ticagrelor reduced infarct size, these data indicate a $P2Y_{12}$-independent cardioprotective effect of ticagrelor (48). A subsequent reperfusion study in rats confirmed that ticagrelor reduced infarct size, whereas clopidogrel had no effect, and provided evidence that the effect of ticagrelor

Table 1 Antiplatelet Agents and Dyspnea

Drug	Inhibition of $P2Y_{12}$	Inhibition of Cellular Uptake of Adenosine	Increased Sensation of Dyspnea
Ticagrelor	Yes (reversible)	Yes (+)	Yes (++)
Cangrelor	Yes (reversible)	No*	Yes (++)
Elinogrel	Yes (reversible)	No	Yes (++)
Clopidogrel	Yes (irreversible)	No	Yes (+/−)†
Dipyridamole‡	No	Yes (++)	No

*The main metabolite of cangrelor showed weak inhibition of adenosine uptake but no affinity versus the equilibrative nucleoside transporter type 1 (11). †Clopidogrel increased the incidence of dyspnea in clinical trials, albeit to a lesser degree than the reversible $P2Y_{12}$ antagonists. In the PLATO (Platelet Inhibition and Patient Outcomes) (58) and ONSET/OFFSET (A Study of the Onset and Offset of Antiplatelet Effects Comparing Ticagrelor, Clopidogrel, and Placebo With Aspirin) (59) studies, dyspnea was considered unexplained or likely or possibly caused by the study drug in 20.1% (160 of 798) and 40% (2 of 5) of clopidogrel-treated patients, respectively. Moreover, 13 patients in the PLATO study (58) discontinued clopidogrel treatment because of the severity of dyspnea. Finally, in a study by Serebruany et al. (60), 4.2% (157 of 3,719) of patients who underwent percutaneous coronary intervention developed dyspnea, which was attributable to underlying diseases in most instances but remained unexplained in 10.8% (17 of 157). ‡Dipyridamole induces dyspnea after intravenous infusion at high doses, as in dipyridamole-thallium imaging for the evaluation of coronary artery disease, but not when given orally at therapeutic doses.

was mediated by endogenous adenosine, because it was completely reversed by an adenosine receptor antagonist (49). Although the results of these studies suggest that under the experimental conditions that were tested, the cardioprotective effect of ticagrelor is mediated by the induced increase in adenosine and not by its inhibitory effect on $P2Y_{12}$, previous studies demonstrated that other antiplatelet agents that do not affect ENT1 were cardioprotective (50,51).

In light of these data, the important question to address is whether or not ticagrelor, when administered to humans at clinically approved doses, increases the levels of adenosine and enhances the biological effects of adenosine. Indeed, a recent study in patients with ACS revealed that adenosine plasma concentrations were significantly higher in blood samples taken 6 h after ticagrelor (180 mg) compared with clopidogrel (600 mg) (18). Moreover, serum from ticagrelor-treated patients, but not from clopidogrel-treated patients, inhibited in vitro uptake of exogenous adenosine by erythrocytes (18). These results confirm that the concentration of ticagrelor attained in vivo after oral administration is sufficient to inhibit cellular uptake of adenosine, thereby prolonging its half-life and increasing its concentration.

The effect of ticagrelor on in vivo adenosine concentrations may convey unique properties of the drug not shared by other $P2Y_{12}$ antagonists. Although it is a matter of conjecture, a number of reported clinical effects of ticagrelor, including its increased serum creatinine levels, improved endothelial function (52), and protection from the consequences of pulmonary infection (53), are compatible with an enhanced effect of adenosine (Fig. 2).

However, on the basis of 2 considerations, the increase in endogenous adenosine is unlikely to be the main cause of the increased incidence of the sensation of dyspnea in ticagrelor-treated patients, although it might contribute partially. First, dipyridamole, a stronger ENT1 inhibitor than ticagrelor, has not been reported to increase the sensation of dyspnea when administered orally at doses able to enhance the effect of exogenous adenosine (54). Second, $P2Y_{12}$ antagonists that do not significantly inhibit ENT1 increase the sensation of dyspnea (8,11). This is particularly evident for cangrelor and elinogrel, which, like ticagrelor but unlike thienopyridines, reversibly bind $P2Y_{12}$ (Table 1), and mechanisms responsible have been hypothesized (8,55). Furthermore, it is unlikely that the ticagrelor-mediated increase in adenosine accounts for the observed increased incidence in ventricular pauses, because these were of sinoatrial origin (56), whereas adenosine primarily affects atrioventricular conductivity (32), although it may also modulate the hyperpolarization-activated current (I_f), as shown in rabbit sinoatrial myocytes (57).

Conclusions

Several studies consistently showed that ticagrelor inhibits the cellular uptake of adenosine, in addition to antagonizing the $P2Y_{12}$ receptor. This effect of ticagrelor is sufficient to increase the circulating levels of adenosine in patients. To what extent the adenosine-mediated mode of action contributes to the clinical profile of ticagrelor is not yet documented. Further studies are required to better elucidate the extent to which enhanced adenosine responses contribute to the clinical profile of ticagrelor.

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