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EDITORIAL COMMENT

# Ticagrelor Antibiotic Effect

## Ready for Exploring Clinical Implementation?*

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Ticagrelor is an extensively used thienopyridine antiplatelet drug that reversibly inhibits platelet adenosine diphosphate $P2Y_{12}$ receptor. $P2Y_{12}$ receptors are located on the surface of platelets and can be activated by aggregation agonist adenosine diphosphate. Ticagrelor binds directly to $P2Y_{12}$ receptors on platelet membranes, thereby blocking adenosine diphosphate attachment and preventing the induction of platelet aggregation. It is frequently used in combination with aspirin but can also be prescribed as single antiplatelet agent. Surface $P2Y_{12}$ receptors are also present in endothelial cells and vascular smooth muscle cells. Interestingly, these receptors are present as well in cells related with our immune response against infections, such as leukocytes, macrophages, and dendritic cells. $EP2Y_{12}$ receptors have been shown to play a pivotal role in amplifying the release of proinflammatory chemokines from the granules within platelets, perpetuating the inflammatory response related to tumor necrosis factor-α and interleukin-6, and causing platelet-mediated inflammation.

In 2014, a post hoc analysis of the PLATO (A Comparison of Ticagrelor and Clopidogrel in Patients With Acute Coronary Syndrome) trial revealed that patients in the ticagrelor arm had a lower risk of infection-related death than those in clopidogrel arm.[1] Since then, several animal studies[2] and retrospective clinical data[3,4] have shown a protective effect of ticagrelor against infection, particularly in the case of Gram-positive bacteria. The only prospective clinical information of this potential antibacterial effect comes from the XANTHIPPE (Targeting Platelet-Leukocyte Aggregates in Pneumonia With Ticagrelor) trial.[5] XANTHIPPE was a double-blind clinical trial that randomized patients hospitalized for pneumonia to receive placebo or ticagrelor in doses similar to the ones used to achieve antiplatelet effect (180-mg loading dose, followed by 90 mg twice a day) for up to 7 days or until discharge from the hospital. Despite the small sample size, with only 60 patients included, ticagrelor was found to be associated with improved lung function.

Most experimental studies focused on ticagrelor bactericidal activity have been performed with much higher doses than the ones that are reached when the drug is used in clinical practice to obtain an antiplatelet effect. However, in this issue of *JACC: Basic to Translational Science*, Oury et al[6] describe a positive effect of ticagrelor to prevent *Staphylococcus aureus* endocarditis in mice with low doses, equivalent to the ones we use in patients with acute coronary syndromes. Their study adds to the scarce experimental evidence of ticagrelor antibiotic activity against Gram-positive bacteria in these conventional antiplatelet dosages.[2] The fact that this effect was seen at doses similar to the ones used in clinical practice is very relevant, because it confirms the presence of antivirulence activity against *S aureus* in patients that are currently receiving the drug, as suggested by retrospective clinical studies[3,4] and XANTHIPPE randomized clinical trial.[5] Moreover, in the study by Oury et al,[6] clopidogrel, also an antiplatelet $P2Y_{12}$ receptor inhibitor, did not provide this antibacterial protection.

Although clinical observations and data in mice clearly support ticagrelor antibacterial activity, its underlying mechanisms remain unclear. The fact that

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this effect is not seen with other platelet adenosine diphosphate $P2Y_{12}$ receptor inhibitors (clopidogrel, prasugrel and its active metabolite) suggests that antiplatelet action is not the key factor. The data provided by Oury et al[6] offer some possible explanations for the underlying antibacterial mechanism, including inhibition of toxin production and bacterial adherence. Moreover, ticagrelor pleiotropic effects have been suggested and include a potential anti-inflammatory effect, inhibitory effect of ticagrelor on alfa-toxin mediated platelet clearance, erythrocyte adenosine reabsorption inhibition, stimulation of adenosine triphosphate secretion from erythrocytes, and atherosclerotic plaque stabilization. In addition, previous studies have shown antibiofilm activity and synergistic effects with antibiotics, such as rifampicin, ciprofloxacin, and vancomycin, for the in vitro inhibition of methicillin-resistant *S aureus*.[2] Whether these effects are only caused by ticagrelor or also to its major metabolites (M5 AR-C133913, M7, M8 AR-C124910) is unclear.

Because ticagrelor was given prior to infection in the in vivo model used by Oury et al,[6] their data open the door to the use of ticagrelor in infective endocarditis prevention. Antibiotic prophylaxis is currently recommended to prevent infective endocarditis development in high-risk patients. However, the data regarding the effect of the current protocols used is scarce. In fact, a recent Cochrane database systematic review regarding antibiotic prophylaxis following dental procedures concluded that there is no clear evidence about whether antibiotic prophylaxis is effective or ineffective against infective endocarditis in at-risk people that undergo invasive dental procedures. We do know that the use of antibiotics faces the challenge of a low efficacy because of the steadily increasing infection rate by resistant bacteria strains, and the widespread use of antibiotics contributes to the development of this resistance. The truth is that it is unclear whether the potential harms and costs of antibiotic administration outweigh any beneficial effect. Ticagrelor could have a role in endocarditis prophylaxis, although this prophylaxis is recommended before invasive interventions where ticagrelor antiplatelet effect might be problematic and might increase bleeding risk. Ticagrelor antiplatelet effect could also be a problem for its potential use in the prevention of S aureus prosthetic joint infection. However, recent data have shown the efficacy of antiplatelet drugs for thromboprophylaxis after fractures treated operatively, suggesting scenarios where both antiplatelet and antibacterial effects might be desirable. Ticagrelor is frequently used after coronary artery stenting, but infection of coronary stents is extremely rare. However, patients that undergo transcatheter aortic valve replacement (TAVR) also need antiplatelet treatment, and TAVR infection is not so uncommon. In fact, the rates of early infective endocarditis occurring during the first 12 months seem to be higher after TAVR than after surgical aortic valve replacement and can reach 3%.

The data presented by Oury et al[6] are extremely interesting, but a word of caution is also needed. First, their study only supports the potential effect of ticagrelor in the prevention of *S aureus* endocarditis, because the investigators did not study ticagrelor as a treatment. In addition, on initiation of infective endocarditis, survival was similar in control, in ticagrelor-, and in clopidogrel-treated mice. Moreover, the in vivo demonstration of ticagrelor antibacterial activity at antiplatelet dosages was obtained in the mouse, which differs from humans in terms of ticagrelor pharmacokinetics. Finally, although previous evidence seems to support that ticagrelor in vitro have bactericidal activity is relevant in clinical practice, this has not been shown in all settings. In particular, infectious complications after coronary artery bypass grafting in patients preoperatively treated with ticagrelor or clopidogrel seem to be similar, even after propensity score matching.

The findings presented by Oury et al[6] add to the growing evidence regarding a potential use of ticagrelor to prevent and/or treat Gram-positive bacterial infections. The fact that its antimicrobial effect has been proved in common virulent bacteria, such as *S aureus* and Clostridioides difficile, implies that ticagrelor might be further developed as a new antimicrobial agent. More research initiatives are needed, including the design of randomized clinical trials aimed at studying the effect of ticagrelor as adjuvant therapy or in preventive strategies. As ticagrelor is an approved drug, its use as an antibiotic falls into a drug repurposing approach, which could shorten the development process. In fact, the information regarding ticagrelor pharmacokinetic and safety profiles are readily available. The recent experience with sodium-glucose co-transporter-2 inhibitors, first approved as oral antidiabetics and currently included in heart failure guidelines, is a good example of fast repurposing. Finally, as ticagrelor antibiotic effect does not seem to be related with its antiplatelet action, future investigation of potential new ticagrelor-derived antibiotics, devoid of antiplatelet activity, would be welcome, because much higher doses could potentially be used without increasing bleeding risk.

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