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COMMENT & RESPONSE

Are Antiplatelet Agents Beneficial in Prevention of Infective Endocarditis?

To the Editor Recently, Lancellotti et al[1] suggested that ticagrelor protected the participants of the Platelet Inhibition and Patient Outcomes study from infectious adverse events[2] via an unforeseen antimicrobial activity. Ticagrelor was found bactericidal in vitro against gram-positive pathogens, including *Staphylococcus aureus*, but not gram-negative bacteria. Moreover, ticagrelor interfered with *S aureus* biofilm formation in vitro and in a mouse model of patch infection. However, in vitro bactericidal concentrations of ticagrelor were 10-fold to 40-fold greater than reachable in vivo serum levels. The authors speculated that platelets could have delivered the drug at the infected site. While this could be measured, it is in contradiction with the ticagrelor antiplatelet activity, which should curb platelet deposition at inflamed sites.

Here, we suggest a few alternative mechanisms that could explain ticagrelor-induced modulation of *S aureus* infectivity. First, platelet inhibitors interfering with the glycoprotein IIb/IIIa activation, such as aspirin, can modulate *S aureus* global regulatory networks that determine the expression of virulence factors.[3] Salicylic acid altered the expression of the *S aureus* alternative σ factor B, which in turn alters the expression of global regulator genes accessory gene regulator (*agr*) and staphylococcal accessory regulator (*sar*). *agr* is a quorum-sensing regulator that decreases the expression of adhesins (including fibrinogen-binding and fibronectin-binding proteins) and increases the expression of toxins (including hemolysins) at high bacterial densities. *agr* also indirectly promotes biofilm formation. *sar* is a reciprocal DNA-binding regulator stimulating adhesin expression and inhibiting *agr*. Thus, σ factor B alteration simultaneously alters *S aureus* expression of surface adhesins and secretes toxins, decreasing the ability of *S aureus* to colonize damaged tissues and form necrotic abscesses and biofilm.

Second, *S aureus* binds to fibrinogen. Staphylococcal-bound fibrinogen undergoes a conformational change that induces binding of fibrinogen to platelet receptor glycoprotein IIb/IIIa, resulting in platelet activation. Activated platelets bind to endothelial-attached von Willebrand factor and trigger local coagulation, which provides a sheath protecting staphylococci from attack by phagocytes. Not to say that alteration of expression of membrane-bound muropeptide resistance factor, a positively charged protein that can impair the activity of membrane-active daptomycin, could explain the interesting ticagrelor-daptomycin synergism.

All in all, the potential pleiotropic mechanisms behind ticagrelor-mediated protection against infection further highlight the importance of the work by Lancellotti et al.[1] It reinforces other recent studies showing that platelet inhibitors can protect infection-related mortality[4] as well as experimental endocarditis in rodents.[5] This is one more argument to seriously consider platelet inhibition as a potent strategy to prevent infection in selected at-risk patients.

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1. Lancellotti P, Musumeci L, Jacques N, et al. Antibacterial activity of ticagrelor in conventional antiplatelet dosages against antibiotic-resistant gram-positive bacteria. *JAMA Cardiol*. 2019;4(6):596-599. doi:10.1001/jamacardio.2019.1189

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In Reply Heying et al proposed some mechanisms that could underlie the in vivo bactericidal activity of the antiplatelet drug ticagrelor against gram-positive bacteria.[1] They speculate that these mechanisms would be common to those already observed in the presence of other platelet inhibitors, in particular in the context of *Staphylococcus aureus* bloodstream infection or experimental endocarditis. On the one hand, salicylic acid alters the expression of adhesins or toxins by *S aureus*, thereby potentially decreasing its ability to colonize damaged tissues, and acetylsalicylic conferred some protection to patients against *S aureus* bloodstream infection. On the other hand, by interfering with *S aureus*–triggered glycoprotein IIb/IIIa activation, platelet inhibitors targeting this platelet pathway might also prevent local fibrin generation that hampers bacteria eradication by immune cells. In view of the paucity of treatments against septicaemiae or infective endocarditis, more research is needed to determine whether antiplatelet agents could prove beneficial to patients with cardiovascular

disease at risk of such bacterial infection. However, whether the in vivo bactericidal effect of ticagrelor is related to its antiplatelet activity and/or to its ability to inhibit platelet-leucocyte interactions[2] or whether it directly targets bacteria survival mechanisms is currently unknown.

Our hypothesis that platelets could serve as ticagrelor carriers and produce local bactericidal concentration is based both on the reversibility of ticagrelor binding to platelet P2Y12[3] and on experimental studies showing that platelets are recruited to sites of bacterial infection similarly as immune cells. Platelets indeed express receptors for chemokines, such as CCR1, CCR3, CCR4, and CXCR4, which recognize the 4 classes of chemokines (C, CC, CXC, and CX3C) generated at sites of infection, as well as pattern recognition receptors, which detect various bacterial pathogen-associated molecular patterns.[4] To the best of our knowledge, no studies have ever investigated whether ticagrelor inhibits platelet chemotaxis or whether it interferes with direct or indirect platelet binding to bacteria. Platelet receptors that have been involved in platelet-bacteria interactions include glycoprotein IIb/IIIa, glycoprotein Ibα, and the Fcγ receptor IIa receptor for immunoglobulin G. Moreover, it has been reported that platelets exert antistaphylococcal responses by releasing microbicidal proteins or kinocidins, a process that is inhibited by the direct P2Y12 inhibitor cangrelor but not by the antagonism of the thromboxane A_2 and cyclooxygenase 1 pathway.[5] This implies that targeting platelet P2Y12 might not always be beneficial. Furthermore, currently available antiplatelet agents may have different or opposite effects on bacterial infection.

Thus, as indicated by Heying et al, the pleiotropic properties of ticagrelor are likely to be responsible for its in vivo bactericidal activity. The use of appropriate animal models is required to compare platelet inhibitors targeting P2Y12 or those targeting distinct platelet pathways in bacterial infection. Models with human-like pharmacokinetics should be preferred to guarantee data transferability to humans.

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Substantial Differences Between Cohorts of Patients Hospitalized With Heart Failure in Canada and the United States

To the Editor Samsky et al[1] compared the trends in readmissions for patients hospitalized with heart failure in Canada and the United States, but substantial differences between the cohorts from the 2 countries call into question the validity of their conclusion. The cohort from the United States included patients who were younger than 65 years and enrolled in Medicare owing to disability or end-stage renal disease—a distinct group of younger patients who accounted for about 10% of the cohort. The Canadian cohort also included patients who were younger than 65 years but who, unlike their counterparts in the United States, were in general healthier than the older patients and accounted for about 15% of the cohort. The readmission rate for the younger group from Canada was more than 3% lower than that of the older patients in the cohort (15.6% vs 18.7%), while the readmission rate for the younger patients in the United States was about 2.5% higher than that of the older patients in the cohort (22.1% vs 19.6%). Although the authors conducted a sensitivity analysis restricted to patients 65 years and older, it was limited to the association of length of stay with 30-day readmissions. No sensitivity analysis results were reported on trends of readmission, which is the focus of the article.

The article reports a large difference in in-hospital mortality between the patients in Canada (9.9%) and the United States (3.8%), although eFigure 1B in the Supplement[1] surprisingly indicates an even lower in-hospital mortality (less than 1%) for patients in the United States. Lack of mortality information in the postdischarge 30-day period creates additional concern about rate comparisons between the countries—a concern that cannot be alleviated by the finding of 0.9% postdischarge 30-day mortality from a study cited by the authors[2] that was based on Medicare Advantage patients admitted for all causes. The postdischarge 30-day mortality rate for Medicare fee-for-service patients with heart failure is known to be much higher, at approximately 8%.[3]

Lastly, the rationale for restricting data to the period from 2006 to 2015 for segmented regression analysis is unclear. Although 2005 data did not comprise a complete year, they did span 3 full fiscal quarters, which were the units of segmented regression analysis. The Figure[1] outlining quarterly trends over the years did not present data points after 2013, and it is not clear whether quarterly data from 2014 and 2015 were included for the segmented regression analysis, which would have implications for the results.