Arteriosclerosis, Thrombosis, and Vascular Biology

EDITORIAL

Ticagrelor and Endothelial Function: An Effect That Persists Far From the Acute Phase and in Monotherapy

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Ticagrelor is an oral reversible inhibitor of the P2Y12 platelet receptor. From the first randomized clinical trial, which presented this drug to the cardiovascular panorama, it was clear that ticagrelor has something different compared with other P2Y12 inhibitors. In the PLATO trial (Study of Platelet Inhibition and Patient Outcomes), ticagrelor was superior to clopidogrel in the reduction of major cardiac and cerebrovascular adverse events.[1] Surprisingly, the reduction of the composite primary end point was not only driven by a reduction in myocardial infarction (which was similar to the other newer P2Y12 inhibitor prasugrel), but also in cardiovascular mortality. This finding cannot be explained only by a stronger platelet inhibition as compared with clopidogrel. Indeed, prasugrel shows a similar platelet inhibition as compared with ticagrelor but did not affect cardiovascular mortality in any trials. Therefore, investigators looked for pleiotropic effects of ticagrelor, different from the one mediated by P2Y12 inhibition. Although with conflicting results, many studies reported that ticagrelor increased adenosine plasma level in patients with acute coronary syndrome (ACS) by inhibiting adenosine uptake by red blood cells[2] and improved endothelial function, which is significantly impaired in patients with ACS or in other conditions characterized by acute/chronic inflammation.

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In the NATHAN-NEVER trial (Comparison Between Ticagrelor and Clopidogrel Effect on Endothelial, Platelet and Inflammation Parameters in Patients With Stable Coronary Artery Disease and Chronic Obstructive Pulmonary Disease Undergoing Percutaneous Coronary Intervention), ticagrelor administration as compared with clopidogrel (during dual antiplatelet regimen with aspirin) improved endothelial function in patients with stable coronary artery disease and chronic obstructive pulmonary disease treated with percutaneous coronary intervention by lowering circulating level of EGF (endothelial growth factor), increasing eNOS activity in a dose-dependent manner,[3] and reducing the rate of apoptosis and levels of reactive oxygen species in peripheral blood mononuclear cell.[4] This effect seemed to be related to a reduction of systemic and chronic inflammation and oxidative stress, being ticagrelor also a regulator of the HES1 and SIRT1 genes.[5]

In contrast, the HI-TECH trial (Hunting for the Off-Target Properties of Ticagrelor on Endothelial Function in Humans), focused on stable patients after ACS and showed that ticagrelor did not improved endothelial function in terms of reactive hyperemia index, flow-mediated dilatation, systemic adenosine plasma level or vascular biomarkers compared with prasugrel and clopidogrel.[6]

The study of Tam et al[7] ranks midway between the results of these 2 studies.[3–6] It uses the same population evaluated by the HI-TECH trial[6] (Stable Patients After ACS) investigating the mechanisms underlying the complicated network that forms the basis of the endothelial response. However, the main difference in the study design is related to the innovative use of monotherapy with ticagrelor. In line with recent trials as GLOBAL LEADERS (Clinical Study Comparing Two Forms of Anti-Platelet Therapy After Stent Implantation) and TWILIGHT (Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention),[8,9] both proposing the use of ticagrelor monotherapy after ACS or high risk-percutaneous coronary intervention, respectively (of course after a brief period of DAPT with aspirin), Tam et al[7] chose to propose low-dose ticagrelor

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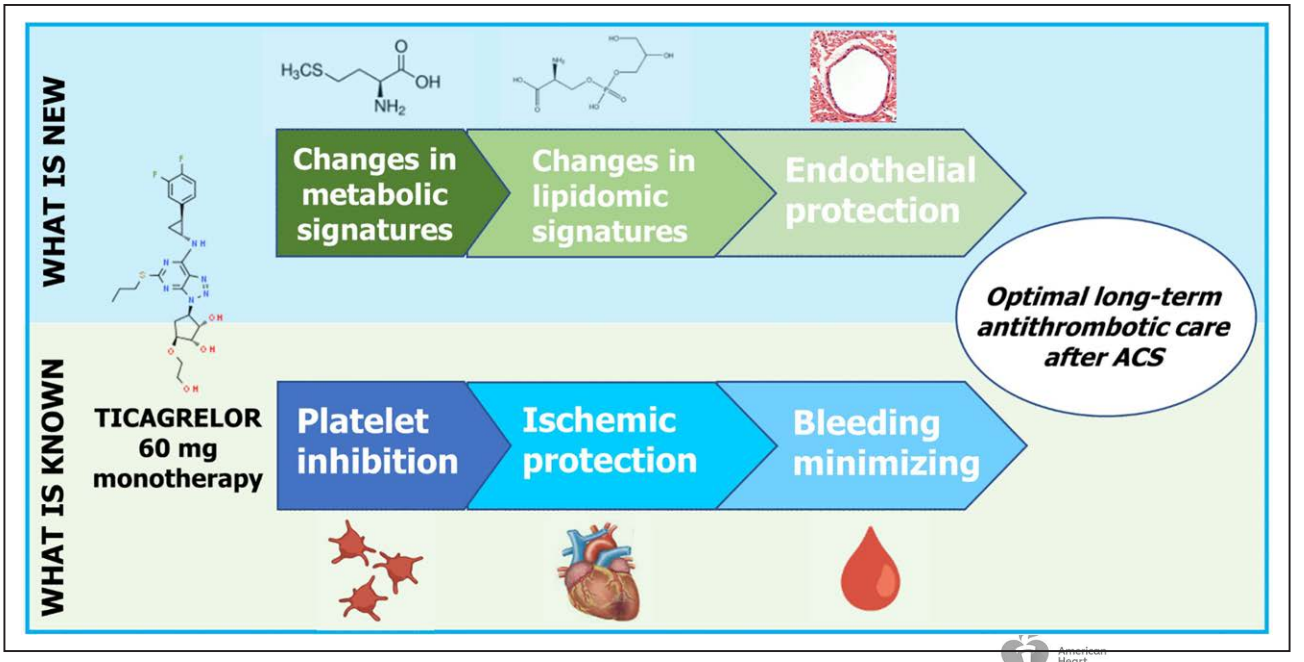

Figure. Ticagrelor 60 mg bid monotherapy between platelet inhibition and endothelial protection.
ACS indicates acute coronary syndrome.

(60 mg bid) in monotherapy in patients with previous MI (occurring 18 months or more before randomization) and so in a stable state. This is an intriguing never tested mix, because in the GLOBAL LEADERS and TWILIGHT trials[8,9] ticagrelor was given at 90 mg bid, whereas the 60 mg bid dose was tested in the PEGASUS TIMI 54 (Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared With Placebo on a Background of Aspirin) and THEMIS (Cardiovascular Effects of Ticagrelor Versus Placebo in Patients With Type 2 Diabetes) trials,[10,11] but in association with aspirin. As with the NATHAN-NEVER trial before,[3–5] Tam et al showed that ticagrelor improved endothelial function, this time in terms of increased flow-mediated dilatation (Figure).

The study offers an interesting and important food for thought: ticagrelor, even at low dose if used for at least 12 weeks in stable disease (and once again compared with aspirin and not to other P2Y12 inhibitors), is able to improve a surrogate end point of endothelial function (ie, flow-mediated dilatation; Figure). The major novelty of the present study is the identification of the mechanisms behind this finding. It is not related to plasma adenosine or EGF increase in stable phase. Tam et al found that ticagrelor modifies the metabolic pathways of amino acids (cysteine, methionine, phenylalanine, tyrosine, and tryptophan) and phospholipids (glycerophosphoethanolamines and glycerophosphoserines). This was independent of its effect on platelets.

From a clinical standpoint, the study of Tam et al has an important implication. In the continuous effort to balance ischemic and bleeding risks in the antithrombotic treatment of patients with ACS, there has been a move from an aspirin-based to P2Y12 inhibitor-based monotherapy (Figure). Although beyond the aim of the study, Tam et al tested what could be the future best treatment for long-term care of patients with ACS. The present study cannot demonstrate the safety of ticagrelor 60 mg bid monotherapy because the treatment window was short and the number of patients low. Future studies are clearly needed to assess this. Importantly, this study adds another brick in the wall because it shows that ticagrelor, in addition to the known platelet inhibition, shows also in the chronic phase endothelial protection by several pathways. Clinical implications of ticagrelor actions on these pathways are still under investigation and may complete the puzzle of the optimal long-term antithrombotic care of patients with ACS.

ARTICLE INFORMATION

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Disclosures

None.

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