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Effects of Ticagrelor, Prasugrel, or Clopidogrel on Endothelial Function and Other Vascular Biomarkers

A Randomized Crossover Study

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ABSTRACT

OBJECTIVES The study sought to assess whether treatment with ticagrelor, as compared with prasugrel and clopidogrel, improves endothelium-dependent dilation throughout the course of the treatment and other vascular biomarkers, including systemic adenosine plasma levels.

BACKGROUND The in vivo off-target effects of ticagrelor in post-acute coronary syndrome (ACS) patients remain poorly characterized.

METHODS Fifty-four stable post-ACS patients were sequentially exposed to each of the 3 oral $P2Y_{12}$ inhibitors following a 3-period balanced Latin square crossover design with 4 weeks per treatment in 5 European centers. The primary endpoint was the assessment of endothelial function with pulse amplitude tonometry and expressed as reactive hyperemia index at treatment steady state. Secondary endpoints included reactive hyperemia index after loading or before maintenance regimen, systemic adenosine plasma levels, a wide set of vascular biomarkers, and ticagrelor or AR-C124910XX plasma levels throughout each ticagrelor period. In 9 patients, the evaluation of endothelial function was performed simultaneously by pulse amplitude tonometry and flow-mediated dilation.

RESULTS Reactive hyperemia index did not differ after ticagrelor (1.970 ± 0.535) as compared with prasugrel (2.007 ± 0.640; $p = 0.557$) or clopidogrel (2.072 ± 0.646; $p = 0.685$), nor did systemic adenosine plasma levels or vascular biomarkers at any time points. $P2Y_{12}$ platelet reactivity units were lower after ticagrelor as compared with clopidogrel at all time points and after maintenance dose as compared with prasugrel. Flow-mediated dilatation did not differ after the maintenance dose of ticagrelor as compared with clopidogrel and prasugrel.

CONCLUSIONS Ticagrelor did not improve endothelial function or increased systemic adenosine plasma levels as compared with prasugrel and clopidogrel in stabilized patients who suffered from an ACS. (Hunting for the Off-Target Properties of Ticagrelor on Endothelial Function in Humans [HI-TECH]; NCT02587260). (J Am Coll Cardiol Intv 2018;■:■–■) © 2018 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome

ANOVA = analysis of variance

ENT1 = equilibrative nucleoside transporter 1

FMD = flow-mediated dilation

LD = loading dose

MD = maintenance dose

RHI = reactive hyperemia index

Ticagrelor, prasugrel, and clopidogrel inhibit platelet aggregation by inhibiting the adenosine diphosphate $P2Y_{12}$ receptor, and in combination with aspirin have become a class I guideline-recommended treatment in patients with acute coronary syndromes (ACS) or percutaneous coronary intervention (1).

Prasugrel and clopidogrel are thienopyridines, require conversion to an active metabolite, and mediate an irreversible inhibition of the target receptor. Ticagrelor is a nonthienopyridine direct and reversible $P2Y_{12}$ platelet receptor antagonist and, unlike prasugrel or clopidogrel, concentration-dependently inhibits the sodium-independent equilibrative nucleoside transporter 1 (ENT1) (2). This ticagrelor-mediated off-target effect has potential to increase adenosine levels, which may carry important clinical implications (2,3).

Increased adenosine levels in patients taking ticagrelor may explain some drug-specific side effects such as dyspnea and bradycardia or ventricular pauses (3). In addition, the ticagrelor-mediated increase of adenosine levels might improve endothelial function (4), a possible barometer of the total atherosclerotic risk burden (5) and this effect may contribute to explain the reduced risk of mortality observed with ticagrelor as compared with clopidogrel in the PLATO (Platelet Inhibition and Patient Outcomes) study.

There is limited and inconsistent evidence (6–8) that ticagrelor can increase adenosine plasma levels and subsequently improve endothelial function as compared with prasugrel and clopidogrel. We aimed to assess the effects of ticagrelor compared with other oral $P2Y_{12}$ inhibitors on the endothelial function, systemic adenosine plasma levels, and circulating vascular biomarkers at currently approved regimens in post-ACS patients.

METHODS

STUDY DESIGN, PROCEDURES, AND PATIENTS. The HI-TECH (Hunting for the off-target propertIes of Ticagrelor on Endothelial function and other Circulating biomarkers in Humans) trial (NCT02587260) is a randomized, open-label, crossover study conducted at 5 centers in Switzerland, the Netherlands, Spain, and Italy. Detailed inclusion and exclusion criteria were previously reported (9) and are itemized in the Online Appendix. Eligible patients were those who suffered at least 30 days earlier from an ACS, were free from ischemic or bleeding complications, and reported regular intake of dual antiplatelet therapy regimen consisting of aspirin (80 to 160 mg daily) and a clinically indicated $P2Y_{12}$ inhibitor, including ticagrelor, prasugrel or clopidogrel. After a baseline pre-randomization assessment, each patient was sequentially exposed to each of the 3 oral $P2Y_{12}$ inhibitors following a 3-period balanced Latin square crossover design with 4 weeks per treatment period. Patients were allocated in a 1:1:1:1:1:1 ratio to 1 of 6 possible treatment sequences (**Figure 1**). Allocation of study treatment was performed via an Internet-based interactive randomization system and achieved with a computer-generated random sequence with random block size, stratified according to the clinical site and the presence of diabetes mellitus.

Post-randomization measurements were performed 1 to 2 h following the loading dose (LD) of the first assigned oral $P2Y_{12}$ inhibitor (ticagrelor at 180 mg [T1] or prasugrel at 60 mg [P1] or clopidogrel at 600 mg [C1]). Patients were then requested to come back to each recruiting site 30 ± 5 days thereafter. All measurements were then repeated before (T2, P2, or C2) and 1 to 2 h after (T3, P3, or C3) the witnessed intake of the maintenance dose (MD) of the same $P2Y_{12}$ inhibitor (90 mg twice a day for ticagrelor; 10 mg/day for prasugrel, or 5 mg/day if >75 years of age or weight <60 kg; and 75 mg/day for clopidogrel). One to 7 days thereafter, patients returned to the referral hospital to receive the LD of the second randomized $P2Y_{12}$ inhibitor followed by an identical assessment algorithm until the completion of the randomized sequence (Online Appendix). No washout time was allowed before or in-between the randomized treatment sequences. Patients were requested to fast for at least 2 h before each hospital visit; caffeine-containing beverages were not permitted for 12 h before each study visit.

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