Comparison of Platelet Reactivity in Black Versus White Patients With Acute Coronary Syndromes After Treatment With Ticagrelor

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Ticagrelor, a potent platelet inhibitor, has primarily been studied in white patients. Platelet reactivity among black patients with acute coronary syndrome (ACS) on ticagrelor, however, is unknown. Our objective was to compare platelet reactivity in black versus white patients with ACS treated with ticagrelor. We conducted a prospective, pharmacodynamic study of 29 black patients with ACS treated with ticagrelor. Platelet reactivity was assessed at 1, 4, and 8 hours after a loading dose of ticagrelor 180 mg and at 30 days on a maintenance dose of ticagrelor 90 mg twice daily. Assays included light transmission aggregometry, VerifyNow P2Y12, and vasodilator-stimulated phosphoprotein. We provided comparison with a historical white cohort. Platelet reactivity among blacks with ACS on ticagrelor was similar to that in whites, except that blacks had lower values at 4 hours, 8 hours, and on maintenance therapy for light transmission aggregometry with 20 μmol/L adenosine diphosphate. Among blacks, high-on-treatment platelet reactivity for all 3 assays was uncommon at 1 hour and nonexistent at 4 hours, 8 hours, and while on maintenance therapy. Blacks preloaded with clopidogrel (n = 17) had significantly lower results of VerifyNow (64 ± 65 vs 198 ± 86, p <0.001) and vasodilator-stimulated phosphoprotein (12.8 ± 21.6 vs 58.9 ± 19.9, p <0.001) at 1 hour compared with those with no clopidogrel preload. In conclusion, among patients with ACS receiving ticagrelor, levels of platelet reactivity in blacks are similar to that in whites. This suggests that the cardiovascular benefits of ticagrelor observed in the platelet inhibition and patient outcomes (PLATO) trial are likely to be observed in blacks and whites. **(Am J Cardiol 2017;119:1135−1140)**

Platelet reactivity has been previously studied in patients with acute coronary syndrome (ACS) receiving ticagrelor, but this consisted of an almost exclusively white population.[1] Although platelet reactivity has been studied in black patients with stable coronary artery disease,[2] little is known about platelet reactivity in black patients with ACS receiving ticagrelor. We, therefore, sought to describe platelet reactivity on ticagrelor, as measured by a variety of platelet function assays, in a population of patients with ACS that is exclusively black. We also sought to compare platelet reactivity in this population to historical controls that consisted of white patients with an ACS receiving ticagrelor.

Methods

This is a prospective, single-center, open-label pharmacodynamic study of on-treatment platelet reactivity among consecutive black patients with ACS receiving ticagrelor. Determination of black race was based on patient self-report; it was required, however, for potential subjects to identify all 4 grandparents as black as well. ACS was defined as elevation in troponin above the upper limit of normal in addition to at least 1 of the following: symptoms consistent with ACS or ST-segment elevation or depression of at least 1 mm in at least 2 contiguous electrocardiographic leads. All patients received a loading dose of ticagrelor 180 mg before PCI and a maintenance dose of 90 mg twice daily thereafter, in addition to aspirin 81 mg daily. Patients who had received a loading dose of clopidogrel during their current admission were included in the study.

Patients unable to take ticagrelor and aspirin for at least 30 days were excluded. This included patients with an increased risk of bleeding as defined by the following criteria: requirement for oral anticoagulation or nonsteroidal antiinflammatory drugs; recent (<30 days) gastrointestinal bleeding or major trauma; any history of intracranial,

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See page 1139 for disclosure information.

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intraocular, retroperitoneal, or spinal bleeding; sustained uncontrolled hypertension; history of bleeding diathesis; and platelet count less than 100,000/mm^3 or hemoglobin <10 g/dl. Patients receiving glycoprotein IIb/IIIa inhibitors ≤8 hours before platelet reactivity testing were also excluded, as were patients who had received fibrinolytics within 48 hours. Finally, patients with severe renal impairment (creatinine clearance <30 ml/min or on dialysis) or moderate-to-severe hepatic failure were excluded. Written informed consent was obtained before enrollment and platelet reactivity testing. The Institutional Review Board at Washington Hospital Center (Washington, DC) approved this study.

All patients underwent platelet reactivity testing with 3 assays simultaneously: light transmission aggregometry (LTA; Chrono-Log, Havertown, Pennsylvania), vasodilator-stimulated phosphoprotein (VASP) phosphorylation analysis (FACSCalibur flow cytometer; BD Biosciences, San Jose, California), and the VerifyNow P2Y12 assay (Accriva Diagnostics, San Diego, California). The objective was to assess on-treatment platelet reactivity, measured at 1, 4, and 8 hours after a loading dose of ticagrelor 180 mg, and at 30 days while on a maintenance dose of ticagrelor 90 mg twice daily. Testing at 30 days was performed 2 to 4 hours following the maintenance dose (i.e., peak level). Whole blood samples were drawn through an 18 gauge (or larger) needle into 3.2% sodium citrate tubes. Platelet reactivity was assessed within 2 hours of blood sampling.

LTA was performed at 37°C using platelet-rich plasma, obtained by centrifugation of citrated whole blood for 30 seconds at 4,400 g, and platelet-poor plasma, obtained by centrifugation for 120 seconds at 4,400 g using a platelet function centrifuge (BIO/DATA Corp, Horsham, Pennsylvania). LTA results were not adjusted for baseline platelet count, as this has been shown to be unnecessary.[3,4] Aggregation parameters were measured with both 5 and 20 μmol/L of adenosine diphosphate (ADP) as agonists; these on-treatment platelet reactivity values are reported as percentages of maximal platelet aggregation (MPA).[5]

VASP phosphorylation analysis was performed using the PLT VASP/P2Y12 assay (BioCytex, Marseille, France). First, whole blood was incubated with ADP with or without prostaglandin E1. A monoclonal antibody to label the VASP protein in its phosphorylated state was then added. This antibody was stained with a fluorescein reagent, which can be detected as mean fluorescence intensity (MFI) by flow cytometry. The ratio of $(MFI^{PGE1} - MFI^{ADP} + {}^{PGE1})/MFI^{PGE1}$ was then calculated to estimate the ratio of activated versus nonactivated platelets. This value is reported as the platelet reactivity index (PRI).[6]

The VerifyNow P2Y12 assay was performed by the addition of whole blood to dedicated cartridges containing fibrinogen-coated beads, 20 μmol/L of ADP (as the agonist), and 22 nmol/L of prostaglandin E1 (to reduce the nonspecific contribution of P2Y1 receptors). This point-of-care system utilizes turbidimetric optical detection to measure changes in light transmittance that result from clumping of the fibrinogen-coated beads, with these changes reported as P2Y12 reaction units (PRU).[7,8]

A dedicated data coordinating center at the Medstar Cardiovascular Research Network performed all data management and analyses. Prespecified clinical and laboratory data during hospitalization were obtained from hospital charts reviewed by independent research personnel blinded to the objectives of the study. High on-treatment platelet reactivity (HPR) was defined according to the following criteria: MPA >60% for LTA with 20 μmol/L ADP; PRI >50% for VASP phosphorylation; and PRU >208 for VerifyNow P2Y12.[9]

There were 2 cohorts of patients receiving ticagrelor that were compared in this study: (1) black patients with ACS (the cohort first reported here) and (2) white patients with ACS from the platelet inhibition and patient outcomes (PLATO) PLATELET substudy.[1] Although study design and drug dosing for both cohorts were similar, the schedule for platelet reactivity testing varied. We, therefore, chose to conduct comparisons only at time points that matched exactly to minimize variation. More specifically, platelet reactivity levels of black patients with ACS in the present study cohort were compared with white patients with ACS at 4 hours after a loading dose and 2 hours after a maintenance dose. Among patients in the present study cohort, those who received a clopidogrel loading dose (before a ticagrelor loading dose) were also compared with those who did not receive clopidogrel. The aforementioned PLATO PLATELET substudy included 33 white patients, 1 black patient, 2 Asian patients, and 1 patient categorized as other. We used only the white patients from the PLATO substudy for this analysis.

Continuous variables are presented as mean ± SD, and categorical variables are presented as percentages. Comparison of categorical variables between groups was performed using the chi-squared analysis or Fisher's exact test. Comparison of continuous variables was performed with unpaired *t* test analysis using Mann-Whitney correction. Comparisons were considered significant if $p < 0.05$. Statistical analysis was performed with Graphpad PRISM software 6.0 (San Diego, California).

Results

In our study, 30 patients received ticagrelor as part of the protocol. One patient, however, received a glycoprotein IIb/IIIa inhibitor during the procedure and was excluded. Twenty-nine patients are therefore reported in Table 1, which compares baseline characteristics of the black and white populations. Blacks had a greater incidence of diabetes mellitus (48% vs 14%, $p = 0.002$) and were slightly older, more likely to be women (48% vs 22%, $p = 0.03$) and more likely to present with non−ST-segment elevation myocardial infarction (90% vs 54%, $p = 0.002$). Conversely, whites were more likely to present with ST-segment elevation myocardial infarction (STEMI; 38% vs 3%, $p < 0.001$). Blacks were at high cardiovascular risk in general; 76% of the patients had hypertension, 52% dyslipidemia, 48% current smokers, and 31% history of PCI.

During the study period, 1 patient experienced a periprocedural myocardial infarction secondary to guide catheter-induced coronary dissection complicated by cardiac arrest. They underwent a short round of cardiopulmonary resuscitation and emergent PCI with stenting. Despite a prolonged hospitalization, they completed the