Pharmacology

Ticagrelor Versus Clopidogrel in Black Patients With Stable Coronary Artery Disease

Prospective, Randomized, Open-Label, Multiple-Dose, Crossover Pilot Study

Ron Waksman, MD; Juan Maya, MD, MS; Dominick J. Angiolillo, MD, PhD; Glenn F. Carlson, MD; Renli Teng, PhD; Richard J. Caplan, PhD; Keith C. Ferdinand, MD

Background—The burden of coronary artery disease (CAD) is high in blacks, highlighting the need for clinical research of antiplatelet agents in this population. We sought to evaluate platelet reactivity during loading and maintenance dosing of ticagrelor versus clopidogrel, and the pharmacokinetic profile of ticagrelor and its metabolite AR-C124910XX, in black patients with stable CAD taking low-dose aspirin (acetylsalicylic acid).

Methods and Results—In a multicenter, randomized, open-label, crossover study, 34 blacks with stable CAD receiving acetylsalicylic acid 75 to 100 mg/d were randomized to clopidogrel (600 mg, then 75 mg QD for 7–9 days) or ticagrelor (180 mg, then 90 mg BID for 7–9 days). After washout 10 to 14 days, patients switched regimens. The primary end point was platelet reactivity 2 hours post loading dose (P2Y\textsubscript{12} reactivity units [PRU] measured by the VerifyNow assay). Least-squares mean PRU at 2 hours post loading dose was lower with ticagrelor (27.6) versus clopidogrel (211.2); least-squares mean difference was –183.6 (95% confidence interval, –213.9 to –153.3; P<0.001). At all time points, the least-squares mean PRU was significantly lower, and the percent reduction in PRU from baseline was statistically greater, with ticagrelor versus clopidogrel. At 2 hours post dose, the prevalence of high on-treatment platelet reactivity (≥208 PRU) was lower with ticagrelor (0%) than with clopidogrel (57.1%). Pharmacokinetic profiles of ticagrelor and AR-C124910XX were consistent with previous reports in stable CAD populations.

Conclusions—In black patients with stable CAD receiving low-dose acetylsalicylic acid, ticagrelor provided a faster onset and greater degree of platelet inhibition than clopidogrel.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT01523392.

Key Words: African Americans ■ clopidogrel ■ coronary artery disease ■ platelet function tests ■ ticagrelor
WHAT IS KNOWN

- In the study of Platelet Inhibition and Patient Outcomes (PLATO), the pivotal phase III study, the P2Y₁₂ receptor antagonist ticagrelor significantly reduced the rate of myocardial infarction, stroke, or death from vascular causes without an increase in overall major bleeding compared with clopidogrel in patients with acute coronary syndrome (ACS).
- Ticagrelor has been shown to produce a greater and more consistent inhibition of platelet reactivity than clopidogrel in patients with coronary artery disease.
- A higher proportion of black patients taking clopidogrel show higher on-treatment platelet reactivity than white patients, which is clinically relevant in view of the high burden of coronary artery disease in this patient population.

WHAT THE STUDY ADDS

- This study broadens the currently limited clinical evidence base for the efficacy of antiplatelet therapy in black populations by demonstrating that ticagrelor inhibits platelet aggregation more rapidly and to a greater extent than clopidogrel in black patients with coronary artery disease.
- These findings suggest that the clinical benefits seen in previous studies with ticagrelor over clopidogrel may extend to black patients with acute coronary syndrome or stable coronary artery disease, highlighting the need for further evaluation in this area.

Methods

Patients and Study Design

This was a multicenter, randomized, open-label, multiple-dose, crossover, pilot study conducted at 8 centers in the United States between March 2012 and September 2013 (NCT01523392).

Patients were eligible to participate if they were aged ≥18 years and black by self-reporting, had documented stable CAD (defined as stable angina pectoris and objective evidence of CAD, a previous MI, or previous revascularization with percutaneous coronary intervention or coronary artery bypass grafting), and were taking ASA 75 to 100 mg/d. Women were required to be postmenopausal or surgically sterile. Patients who were taking clopidogrel or prasugrel were required to discontinue these agents at least 14 days before randomization. Patients were not eligible if they had experienced ACS or undergone percutaneous coronary intervention in the preceding 12 months; they were scheduled for revascularization during the study period; they had any indication for oral anticoagulant or dual antiplatelet therapy during the study; they were taking strong CYP3A4 inhibitors, inducers, or substrates with a narrow therapeutic window; or had diabetes mellitus with glycosylated hemoglobin ≥10%. Other key exclusion criteria were current smoking, contraindications to study drugs, conditions that placed them at increased risk of bleeding or bradycardia, moderate or severe hepatic impairment, renal disease requiring dialysis, or other chronic unstable condition. All patients provided written informed consent before participation. The study was conducted after Ethics Committee approval, and in accordance with the Declaration of Helsinki, ICH/Good Clinical Practice and applicable regulatory requirements, and the AstraZeneca policy on Bioethics.

Patients were randomized 1:1 to receive treatment A (clopidogrel: 600-mg loading dose followed by a 75-mg once-daily [QD] maintenance dose for 7, 8, or 9 days) followed by treatment B (ticagrelor: 180-mg loading dose followed by a 90-mg twice-daily [BID] maintenance dose for 7, 8, or 9 days), or treatment B followed by treatment A (Figure 1). Each period of active treatment was separated by a washout of 10 to 14 days. All patients received ASA of 75 to 100 mg/d, maintained at a constant dose, and self-administered at approximately the same time of day throughout the study.

Study visits were scheduled on days 1, 7, and 8 of each treatment period, during which patients underwent a physical examination. Venous blood samples for platelet function testing were taken before the first dose of medication, and at 0.5, 2, and 8 hours after the loading dose on day 1; predose and at 2 and 8 hours post dose on day 7; and at the end of the dosing interval on day 8 (12 hours after the last evening dose of ticagrelor and 24 hours after the last morning dose of clopidogrel). These samples were analyzed using the VerifyNow P2Y₁₂ assay (Accumetrics; San Diego, CA) to determine the P2Y₁₂ reaction units (PRU) at each time point. In this assay, higher PRU values reflect greater P₂Y₁₂-mediated reactivity.© During ticagrelor treatment, additional blood samples were taken at the same time as the platelet function samples for pharmacokinetic analysis of plasma concentrations of ticagrelor and its major metabolite AR-C124910XX, and analyzed using validated bioanalytical methods by Covance Clinical Laboratories on behalf of AstraZeneca (lower limits of quantification 1 ng/mL for ticagrelor and 2.5 mg/mL for AR-C124910XX). Safety data were reviewed by the Patient Safety Physician and Medical Science Director at AstraZeneca. Individual investigators determined treatment-related adverse events (AEs).

Study End Points and Statistical Analyses

The primary end point was platelet reactivity at 2 hours after the loading dose of ticagrelor and clopidogrel on day 1. Secondary end points were platelet reactivity at other measured time points on days 1, 7, and 8. Platelet reactivity data are presented as the absolute PRU at each time point. An additional secondary analysis examined the percentage reduction from baseline (pretreatment) in PRU, which was calculated as follows: (1−[PRU after study drug/PRU at baseline])×100%. Analyses were performed using SAS version 9.1 (SAS Institute, Inc, Cary, NC).
It was estimated that a sample size of 12 patients would be needed for a paired t test to have 90% power to demonstrate a difference of 100 PRU between ticagrelor and clopidogrel using a 2-sided $\alpha$ of 0.05, assuming a SD of 93 PRU (the largest variability for ticagrelor or clopidogrel observed within the first 24 hours in A Study of the Onset and Offset of Antiplatelet Effects Comparing Ticagrelor, Clopidogrel, and Placebo With Aspirin [ONSET/OFFSET] study). However, to evaluate P2Y12 receptor inhibition at secondary time points and collect safety data, it was planned that 34 patients would be enrolled to ensure that 28 patients were evaluable, providing >99% power to detect the anticipated primary outcome effect. The primary end point analysis was conducted using the pharmacodynamic analysis set, consisting of all patients who had pharmacodynamic data available with no protocol deviations. The primary end point was analyzed using a mixed-effects model with fixed effects for period (1/2), treatment sequence (AB/BA), treatment (A/B), and a random effect for patient within sequence. Treatment level means were estimated using least-squares (LS) means and 2-sided 95% confidence intervals. Tests were evaluated with a 2-sided $\alpha$ level of 0.05. Residual plots were used to assess the distribution assumptions underlying the analysis, and if the assumptions were violated, a Wilcoxon signed-rank test was used. Data for PRU at other time points were analyzed with similar mixed-effects models. An exploratory analysis was undertaken to evaluate the percentage of patients with HPR (defined as $\geq 208$ PRU) in the ticagrelor versus clopidogrel groups at all time points, using Fisher exact test.

The safety of the 2 treatments was assessed by monitoring the incidence and severity of AEs, physical examination findings, and vital signs in the safety analysis set (all patients who received $\geq 1$ dose of study medication). In addition, 12-lead ECG, clinical chemistry, hematology, and urinalysis were conducted at screening. Safety was evaluated using descriptive statistics.

**Results**

**Patient Baseline Characteristics**

Of the 50 patients screened, 34 were enrolled; 30 of these patients completed 14 days of treatment and 31 completed follow-up (Figure 1 in the Data Supplement). Three patients discontinued the study during ticagrelor treatment and did not cross over to clopidogrel. One of these patients experienced an acute MI during the washout period after completion of ticagrelor treatment; the remaining 2 patients withdrew consent on days 7 and 11, respectively. In addition, 1 patient developed hemorrhoidal bleeding that led to discontinuation of ticagrelor but crossed over to and completed treatment with clopidogrel.

Demographics and baseline characteristics are shown in Table 1 for randomized patients. The mean age was 62.3 years; 12 patients (35.3%) were $\geq 65$ years old, and 23 patients (67.6%) were men. The majority of patients (64.7%) were obese (body mass index, $>30$ kg/m²). Fifteen patients (44.1%) had a history of MI, and 22 (64.7%) had undergone previous percutaneous coronary intervention. All patients had dyslipidemia and hypertension, and 17 (50%) had type 2 diabetes mellitus.

**Platelet Reactivity**

Baseline platelet reactivity (mean PRU±SD) was 279.5±54.7 before clopidogrel treatment and 273.0±49.5 before ticagrelor treatment. The primary end point of LS mean PRU at 2 hours post loading dose was lower with ticagrelor than clopidogrel (27.6 versus 211.2), with a statistically significant LS mean difference in PRU between the 2 treatment groups (ticagrelor minus clopidogrel) of $-183.6$ (95% confidence interval, $-213.9$ to $-153.3$; $P<0.001$; Table 2). Individual patient PRU profiles showed that the effect on PRU at 2 hours post loading dose was consistent across the entire range of doses used in the study.

**Table 1. Patient Demographics and Baseline Characteristics**

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Patients, n=34</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blacks, n (%)</td>
<td>34 (100.0)</td>
</tr>
<tr>
<td>Age ≥65, n (%)</td>
<td>12 (35.3)</td>
</tr>
<tr>
<td>Median age, y (range)</td>
<td>62.5 (50–75)</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>23 (67.6)</td>
</tr>
<tr>
<td>Median weight, kg (range)</td>
<td>91 (49–177)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>34 (100.0)</td>
</tr>
<tr>
<td>Dyslipidemia, n (%)*</td>
<td>34 (100.0)</td>
</tr>
<tr>
<td>Type 2 diabetes mellitus,n (%)</td>
<td>17 (50.0)</td>
</tr>
<tr>
<td>Peripheral artery disease,n (%)</td>
<td>2 (5.9)</td>
</tr>
<tr>
<td>Cardiovascular disease history</td>
<td>6 (17.6)</td>
</tr>
<tr>
<td>Stable angina pectoris, n (%)</td>
<td>15 (44.1)</td>
</tr>
<tr>
<td>Previous MI, n (%)</td>
<td>4.8 (1.1–25.6)</td>
</tr>
<tr>
<td>Median time since last MI, y (range)</td>
<td>22 (64.7)</td>
</tr>
<tr>
<td>Previous PCI, n (%)</td>
<td>16 (47.1)</td>
</tr>
<tr>
<td>Previous CABG, n (%)</td>
<td></td>
</tr>
</tbody>
</table>

*Including hypercholesterolemia.
dose was more marked and more consistent after ticagrelor than after clopidogrel (Figure 2). At all other time points, the LS mean in PRU was significantly lower with ticagrelor versus clopidogrel ($P<0.001$; Table 2). The unadjusted mean PRU at 2 hours post loading dose was lower with ticagrelor (26.6±SD 28.4) versus clopidogrel (211.1±SD 76.4).

The percent reduction in PRU from baseline at all time points was statistically greater with ticagrelor versus clopidogrel (Figure 3). At 2 hours post loading dose, the LS mean difference for this end point between ticagrelor (90%) and clopidogrel (24.1%) was 65.9 (95% confidence interval, 56.5 to 75.3; $P<0.001$).

In the exploratory analysis of HPR, platelet reactivity was at or above the threshold of 208 PRU at baseline in 96.3% of patients before clopidogrel treatment and 96.6% of patients before ticagrelor treatment. At 0.5 hours after the loading dose, 92.9% of clopidogrel-treated patients met the threshold for HPR, compared with 34.5% of ticagrelor-treated patients ($P<0.00001$). At 2 hours after the first dose of clopidogrel, 57.1% of patients had HPR, compared with 0% of patients 2 hours after ticagrelor ($P<0.000001$). At other measured time points, thereafter, no patients had HPR after ticagrelor dosing, compared with 17.9% to 44.4% of patients after clopidogrel dosing (Figure 4).

### Pharmacokinetic Analysis

Mean plasma levels of ticagrelor and AR-C124910XX were the highest at the measured time point of 2 hours after the loading dose (Table 3). The mean plasma levels of ticagrelor and AR-C124910XX over time (Figure II in the Data Supplement) were consistent with those observed in previous studies of ticagrelor in white patients with stable atherosclerosis and in a mainly (90%) white population of patients with stable CAD.

### Safety

Seven patients experienced a total of 12 AEs, with a higher incidence observed during ticagrelor (6 patients, 17.6%) than clopidogrel (2 patients, 6.5%) treatment (Table 4). All AEs were mild or moderate, with no severe AE occurring in either group. The one serious AE reported, a moderate-intensity acute MI, was not considered to be treatment related, as the last dose of ticagrelor was taken 14 days before the event. Three patients experienced bleeding events: 2 during ticagrelor treatment (hemorrhoidal hemorrhage after 6 days of dosing, leading to ticagrelor discontinuation; and epistaxis occurring 5 days after dosing) and 1 (vaginal hemorrhage) occurring after the end of clopidogrel treatment. No other notable safety findings occurred in terms of AEs, vital signs,
Discussion

This pilot study in black patients with stable CAD receiving low-dose ASA daily provided 3 important findings. Firstly, ticagrelor inhibited platelet aggregation with a faster onset and to a greater extent compared with clopidogrel in this population. Secondly, plasma concentrations of ticagrelor and ARC124910XX in black patients with CAD were consistent with those observed in previous studies of ticagrelor. Thirdly, there were no unexpected safety findings in black patients during ticagrelor treatment.

According to 2012 estimates, >43 million people in the United States are blacks. However, relative to white individuals, blacks are over-represented in heart disease statistics, and recent reductions in overall rates of heart disease and related morbidity have disproportionately favored other racial groups. For example, the average age-adjusted rate of first MI or fatal CAD is higher in black men and women than in white men and women, although the rate of heart disease has been generally declining in the adult US population during the past decades, there has been a nonsignificant increase among black adults. The reasons for these racial disparities are multifactorial and may include a higher prevalence of cardiovascular risk factors among blacks, as well as socioeconomic factors affecting access to health care.

The statistical imbalance of cardiovascular health between the blacks and other populations highlights the importance of investigating the clinical efficacy of new treatments in this patient group. Unfortunately, for many reasons that include historical mistreatment, blacks may be reluctant to participate in clinical research, and racial disparities in clinical trials have led to incomplete knowledge with regard to this study question in different ethnic groups. However, US Food and Drug Administration—and National Medical Association—led initiatives aimed at increasing their participation, and strengthening the evidence base for effective medicines.

Although the PLATO trial included 229 black patients, this accounted for 1.2% of the total trial population, and it was therefore important to increase the evidence base for ticagrelor among black patients in other studies. Our study demonstrated that in black patients with stable CAD on low-dose daily ASA, ticagrelor provided a greater degree of platelet inhibition than clopidogrel, with a faster onset. Importantly, no patients had HPR (≥208 PRU) from 2 hours after receiving ticagrelor to the end of the study period, whereas HPR was observed in 17.9% to 57.1% of patients taking clopidogrel. Our findings are consistent with data from the PLATO PLATELET substudy, in which platelet activity above a threshold of ≥235 PRU after the loading dose was observed in only 1 patient during ticagrelor maintenance dosing, compared with 67% of patients 2 to 4 hours after the clopidogrel loading dose and 39% during clopidogrel maintenance dosing. In addition,
ticagrelor was generally well tolerated in our study in black patients, with no new or unexpected safety concerns observed. As expected with antiplatelet agents, the most common events were related to bleeding (epistaxis and hemorrhage). Taken together, these findings suggest that benefits observed with ticagrelor over clopidogrel in the PLATO trial could potentially extend to black patients with ACS, although further investigation is needed to confirm this.

Further characterization of the potential genetic basis of HPR in black patients would also provide important data for clinical practice in antiplatelet therapy. Previous studies have demonstrated that there is a higher prevalence of HPR during clopidogrel treatment in black compared with white patients,1,4–6 which may be explained by the high frequency of CYP2C19*2 alleles (43% in this population versus 29% in white patients).1,3 Such loss-of-function mutations reduce clopidogrel’s antiplatelet effects but do not influence the antiplatelet activity of ticagrelor.35 However, CYP genotype may not be the only determinant of HPR. A recent study showed that the Native American Ogala Sioux tribe have similar PRU variability after clopidogrel and ASA treatment, despite a low frequency of CYP2C19*2 alleles.33 Other recently noted genetic influences on antiplatelet activity include the rs12041331 A-allele in the Native American Ogala Sioux tribe.33 This allele, present in approximately two thirds of Africans, is associated with a significantly reduced response to dual antiplatelet therapy with ASA and clopidogrel.34

**Table 3. Plasma Concentrations of Ticagrelor and Its Active Metabolite AR-C124910XX**

<table>
<thead>
<tr>
<th>Plasma Concentration, ng/mL</th>
<th>0.5 h Post LD</th>
<th>2 h Post LD</th>
<th>8 h Post LD</th>
<th>2 h Post MD</th>
<th>8 h Post MD</th>
<th>End of MD Dosing Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ticagrelor</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Geometric mean±SD</td>
<td>108.6±7.3</td>
<td>1001.0±1.9</td>
<td>271.8±4.9</td>
<td>412.0±5.9</td>
<td>221.0±5.0</td>
<td>289.0±2.1</td>
</tr>
<tr>
<td>Arithmetic mean±SD</td>
<td>302.4±336.2</td>
<td>1174.0±631.5</td>
<td>416.2±225.0</td>
<td>706.6±444.8</td>
<td>376.0±297.6</td>
<td>361.4±240.7</td>
</tr>
<tr>
<td>AR-C124910XX</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Geometric mean±SD</td>
<td>5.9±4.9</td>
<td>193.9±2.6</td>
<td>89.6±3.7</td>
<td>149.2±4.4</td>
<td>97.9±3.9</td>
<td>128.3±1.8</td>
</tr>
<tr>
<td>Arithmetic mean±SD</td>
<td>20.1±40.8</td>
<td>256.4±165.1</td>
<td>128.7±74.5</td>
<td>231.5±173.8</td>
<td>144.1±88.8</td>
<td>147.9±77.1</td>
</tr>
</tbody>
</table>

LD indicates loading dose; and MD, maintenance dose.

**Study Limitations**

Although relatively small, our study was adequately powered to detect a significant difference in antiplatelet activity between clopidogrel and ticagrelor, although larger patient numbers would provide additional insight. The open-label nature of the study may have contributed to bias, although the use of an objective assessment parameter (PRU) would have mitigated this effect. Similarly, the crossover design meant that patients acted as their own controls to minimize variation. There is no agreed threshold of PRU for consistent use in clinical trials, and various thresholds have been included in different studies.14,35 We selected a threshold of 208 PRU, which was shown to be associated with an increased risk of cardiovascular events in the Gauging Responsiveness with A VerifyNow P2Y12 assay: Impact on Thrombosis and Safety (GRAVITAS) study35 and is consistent with expert consensus.32 We did not attempt to classify patients as clopidogrel responders or nonresponders, and so, we could not assess whether ticagrelor’s effect on platelet reactivity differed between those groups since A Study of the Antiplatelet Effects Comparing Ticagrelor With Clopidogrel Responder and Non-Responders (RESPOND) study36 has previously shown that the antiplatelet effect of ticagrelor is essentially uniform and high in both clopidogrel responders and nonresponders. No pharmacokinetic analysis of clopidogrel was undertaken to determine whether plasma levels of this agent were affected by race. In addition, we did not test CYP2C19 genotype to evaluate the frequency of HPR-associated alleles in this patient group. It should also be noted that our study was undertaken in black patients with stable CAD, and results may not be generalizable to black patients with other cardiovascular conditions, such as ACS.

**Conclusions**

In conclusion, ticagrelor provided greater platelet inhibition than clopidogrel in this pilot study in black patients with stable CAD who were receiving low-dose ASA therapy. Furthermore, the pharmacokinetic profile of ticagrelor observed in this study was consistent with that reported in previous studies.

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Disclosures

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References


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Patient flow through the study by treatment period.
Supplemental Figure 2. Plasma Concentrations of (A) Ticagrelor and (B) AR-C124910XX Following Ticagrelor Dosing

Geometric mean plasma concentrations of ticagrelor and its major active metabolite AR-C124910XX following ticagrelor dosing (log-transformed data). SD = standard deviation.