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Platelet inhibition with ticagrelor versus clopidogrel in Hispanic patients with stable coronary artery disease with or without diabetes mellitus

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ABSTRACT

Background/purpose: Diabetes mellitus (DM) disproportionately affects Hispanic patients. DM patients have enhanced platelet reactivity and reduced sensitivity to clopidogrel. Ticagrelor demonstrated a more rapid onset and greater magnitude of platelet inhibition than clopidogrel in Hispanic patients with stable coronary artery disease (CAD). This subgroup analysis examined the onset and level of platelet inhibition of ticagrelor and clopidogrel in Hispanic patients with DM.

Methods/materials: This was a subgroup analysis of a randomized, open-label, crossover study in which 40 Hispanic patients with stable CAD received ticagrelor 180 mg loading dose (LD)/90 mg twice-daily maintenance dose (MD) then clopidogrel 600 mg LD/75 mg once-daily MD, or vice versa. The primary end point was on-treatment platelet reactivity at 2 hours post-LD using the VerifyNow™ P2Y12 test.

Results: 21 patients had DM and 19 were non-diabetic. At 2 hours post-LD, mean platelet reactivity in the diabetic group was 34.5 PRU with ticagrelor versus 219.3 PRU with clopidogrel ($P < 0.001$), and in the non-diabetic group was 33.7 PRU with ticagrelor versus 181.0 PRU with clopidogrel ($P < 0.001$). In both diabetic and non-diabetic subgroups, mean platelet reactivity declined to a significantly greater extent with ticagrelor than clopidogrel at all time points evaluated (0.5, 2, and 8 hours post LD and after 7–9 days of MD). Patients were significantly more likely to have high on-treatment platelet reactivity (≥208 PRU) during treatment with clopidogrel compared with ticagrelor, regardless of diabetic status.

Conclusions: Among Hispanic patients with stable CAD, ticagrelor achieves a faster onset and greater magnitude of platelet inhibition compared with clopidogrel, irrespective of diabetic status.

1. Introduction

The prevalence of diabetes mellitus (DM) is expected to continue increasing, with some estimates suggesting that one third of the US adult population will be affected by diabetes by 2050 [1]. However, the burden of diabetes is not evenly spread across the US population, with a disproportionately high prevalence among ethnic minorities, including Hispanics [2,3], and those at the lowest income and educational levels [4]. Diabetes is the fifth leading cause of death among Hispanic Americans and, compared with non-Hispanic white adults, the risk of developing DM is 66% higher among Hispanic/Latino adults [3].

Patients with DM have high platelet reactivity [5–7], which contributes to a high incidence of coronary artery disease (CAD) in these individuals. Studies show that patients with diabetes have a more than three-fold higher risk of developing fatal CAD compared with non-diabetic individuals, which may be associated with the clustering of cardiovascular risk factors in patients with diabetes [8]. This highlights the importance of effective primary and secondary preventive therapies in diabetic patients to minimize the risk. However, diabetes may also affect response to treatment. For example, diabetic patients show a reduced responsiveness to the $P2Y_{12}$ inhibitor clopidogrel compared with non-diabetic patients [5], and this reduced responsiveness is linked to worse cardiovascular outcomes [9].

Ticagrelor is an orally administered, direct-acting, reversibly binding $P2Y_{12}$ receptor antagonist that inhibits adenosine diphosphate (ADP)-induced platelet aggregation [10,11]. Ticagrelor differs from clopidogrel in that it is not a prodrug and does not require conversion by hepatic metabolism to be active [10,12]. Another key difference between the two agents is that ticagrelor has also been shown to inhibit cellular uptake of adenosine via inhibition of the equilibrative nucleoside transporter 1 (ENT1), whereas clopidogrel has not [13].

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Ticagrelor is approved for use, in combination with low-dose aspirin (75–100 mg/day), to prevent atherothrombotic events in patients with acute coronary syndrome (ACS) [14], based on its efficacy and safety over 12 months of follow-up in the large-scale, randomized, phase III PLATelet inhibition and patients Outcomes (PLATO) trial [15]. A substudy of the PLATO trial found that ticagrelor reduced the incidence of ischemic events compared with clopidogrel in patients with DM in a manner consistent with the results of the overall PLATO cohort. [16] These data suggest that ticagrelor may be a suitable alternative to clopidogrel for patients with diabetes.

We have previously conducted a multicenter, open-label, randomized, multiple-dose, crossover study in Hispanic patients with documented CAD, and found that platelet reactivity was more strongly inhibited by ticagrelor than clopidogrel [17]. The inclusion of a high proportion of diabetic patients in this study provided the opportunity to study the effects of ticagrelor or clopidogrel in Hispanic patients with and without diabetes. Therefore, the objectives of the current substudy were to compare on-treatment platelet reactivity during treatment with ticagrelor versus clopidogrel in Hispanic CAD patients with and without DM, and to assess the safety profile of ticagrelor in this patient group.

2. Materials and methods

This was a subgroup analysis of a randomized, open-label, crossover study conducted at 6 US centers between April 2012 and May 2013 (clinicaltrials.gov identifier, NCT01523366). The complete methods have been published previously [17]. Briefly, the study included adults aged ≥18 years, who self-identified as Hispanic, had documented stable CAD based on having stable angina pectoris, or a history of MI, or revascularization, and were receiving aspirin 75–100 mg/day. The diabetic status of each patient was assessed at randomization. Patients with DM were eligible for enrolment if they had a glycosylated hemoglobin (HbA1c) level of <10%. Patients at increased risk of bleeding were excluded from the study, as were patients who had any indication for oral anticoagulant or dual antiplatelet therapy, and those taking strong cytochrome P450 (CYP) 3A4 inhibitors or inducers. Other exclusion criteria have been described in detail previously [17].

The study was approved by the Institutional Review Boards at all sites, and conducted in accordance with the provisions of the Declaration of Helsinki and AstraZeneca policy on bioethics. All patients provided written informed consent prior to study entry.

Patients were randomized 1:1 to receive open-label treatment in two possible sequences: clopidogrel first and ticagrelor second, or vice versa, each for 7–9 days, separated by a 10- to 14-day washout period (Fig. 1). During each active treatment period, patients received a single loading dose (LD) followed by maintenance dosing (MD) for 7–9 days, in addition to their usual daily aspirin dose of 75–100 mg. Clopidogrel doses were 600 mg for LD and 75 mg once daily for MD; ticagrelor doses were 180 mg for LD and 90 mg twice daily for MD.

Each patient made eight visits to the study center during the 11-week study. Screening was conducted at visit 1 and randomization at visit 2, then three visits occurred during each treatment period, and one follow-up visit at 7–10 days after the final treatment visit.

Blood samples were taken for analysis of platelet reactivity at baseline prior to LD, and at 0.5, 2, and 8 hours after the LD. In addition, samples were taken just prior to, and 2 and 8 hours after the last morning dose of both agents, as well as 12 hours after the last evening dose of ticagrelor and 24 hours after the last morning dose of clopidogrel. During the ticagrelor treatment period, blood samples were drawn at the same time as the platelet reactivity samples, to measure plasma concentrations of ticagrelor and its active metabolite AR-C124910XX.

Platelet reactivity was assessed using the VerifyNow® P2Y12 test (Accumetrics, San Diego, CA), a validated measure of ADP-induced platelet aggregation [18,19]. In this assay, $P2Y_{12}$-mediated reactivity is expressed in $P2Y_{12}$ reaction units (PRU), with higher values reflecting greater reactivity. Study personnel were blinded to the PRU results.

The primary end point of the substudy was the inhibition of platelet reactivity with ticagrelor versus clopidogrel 2 hours after LD, by DM status. Secondary end points included the PRU at other time points by DM status, and the safety of ticagrelor in Hispanic patients with versus without diabetes. Safety and tolerability were assessed by the incidence and severity of adverse events, and by assessment of clinical laboratory parameters, physical examination, 12-lead electrocardiograph (ECG) and vital signs.

2.1. Statistical analysis

A pretrial estimate showed that a sample size of 12 patients would provide 90% power to detect a difference of 100 PRUs in the primary end point between ticagrelor and clopidogrel, assuming a standard deviation (SD) of 93 PRU, a correlation of 0.5 between paired observations and a 2-sided alpha level of 0.05. However, it was planned that 34 patients would be enrolled to ensure 28 evaluable patients, which would provide >99% power to detect the anticipated primary outcome effect. This sample size would also provide sufficient power to evaluate $P2Y_{12}$ inhibition at secondary time points, within the subgroups of patients with versus without diabetes, and provide a larger sample size for analysis of potential adverse events.

Categorical variables were reported as counts and percentages, and continuous variables as mean ± SD. The primary end point, PRU analysis, was undertaken using a mixed-effect model with terms for treatment period, treatment sequence and a random effect for patient within sequence. Mean on-treatment reactivity was estimated using least squares means and 2-sided 95% confidence intervals (CIs). Data were analyzed in each group of patients with versus without diabetes

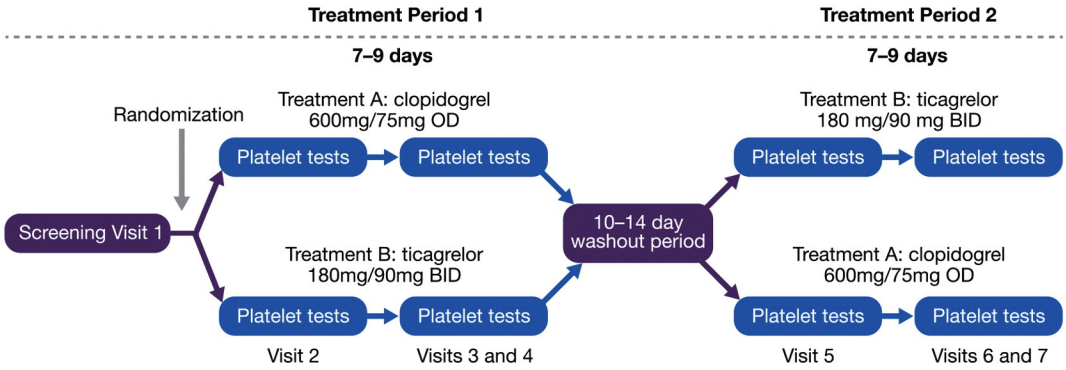

Fig. 1. Study design. Taken from *J Thromb Thrombolysis* 2015;39:8–14 [17](with permission). BID, twice daily; QD, once daily.