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Original Investigation

Platelet Reactivity After Receiving Clopidogrel Compared With Ticagrelor in Patients With Kidney Failure Treated With Hemodialysis: A Randomized Crossover Study

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Background: Patients with kidney failure treated with maintenance hemodialysis (HD) are poor responders to clopidogrel. More beneficial platelet-inhibiting strategies in HD patients therefore are required.

Study Design: Single-center, prospective, randomized, crossover study.

Setting & Participants: 25 HD patients in Seoul, Korea.

Intervention: Patients were randomly assigned to receive clopidogrel (300 mg loading, 75 mg once daily for maintenance dose) or ticagrelor (180 mg loading, 90 mg twice daily for maintenance dose) for 14 days, and after a 14-day washout period, crossover treatment for another 14 days. All patients received aspirin (100 mg/d).

Outcomes & Measurements: Platelet function was evaluated predosing and at 1, 5, and 48 hours and 14 days after the first loading dose. During the offset phase, platelet function was assessed at 1 hour and 2, 4, and 14 days after the last dose by light transmittance aggregometry and the VerifyNow P2Y12 assay, and patients were genotyped for the *CYP2C19*2* allele. Maximal extent of aggregation, inhibition of platelet aggregation (IPA), P2Y12 reaction units (PRUs), and percentage of inhibition were evaluated. We performed per-protocol analysis, excluding patients who did not complete the protocol.

Results: 9 patients did not complete the protocol (7 patients due to adverse events; 2, nonadherence). Higher IPA occurred with ticagrelor than with clopidogrel at 1, 5, and 48 hours and 14 days after loading. By 5 hours after loading, a greater proportion of patients in the ticagrelor group than in the clopidogrel group achieved IPA $>$ 50% (75% vs 12%, respectively; $P < 0.05$) and IPA $>$ 70% (44% vs 0%, respectively; $P < 0.05$). Rates (slope) of onset and offset of the antiplatelet effect were faster in patients receiving ticagrelor than for those receiving clopidogrel ($P < 0.05$). Regardless of *CYP2C19*2* allele, the ticagrelor group had significantly lower PRUs at all times than the clopidogrel group.

Limitations: Single-center study with a small number of patients, not a double-blind study, and not intention-to-treat analysis.

Conclusions: Ticagrelor may result in more rapid and greater platelet inhibition than clopidogrel in patients with kidney failure receiving HD.

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INDEX WORDS: Platelet inhibition; platelet reactivity; high on-treatment platelet reactivity (HTPR); platelet aggregation assay; ticagrelor; clopidogrel; antiplatelet therapy; thrombosis; kidney failure; hemodialysis (HD); end-stage renal disease (ESRD).

Being a strong risk factor for cardiovascular morbidity and mortality, chronic kidney disease (CKD) also confers an increased risk of stent thrombosis even when dual-antiplatelet therapy (clopidogrel and aspirin) is administered.[1-3] Recently, we demonstrated that patients with severe CKD or kidney failure on hemodialysis (HD) therapy exhibited higher platelet reactivity when treated with clopidogrel than did those with normal kidney function.[4,5] Furthermore, a substantial percentage of HD patients exhibited nonresponsiveness (resistance) to clopidogrel in a previous study.[4] Cumulative evidence has demonstrated that high on-treatment platelet reactivity (HTPR) is associated with increased risk of cardiovascular death and recurrent ischemic events, including myocardial infarction and stent thrombosis.[6,7]

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Adjunctive cilostazol treatment can overcome HTPR in patients with kidney failure undergoing HD.[4] However, in a multicenter randomized controlled trial (RCT) in patients with normal kidney function, triple therapy (aspirin, clopidogrel, and cilostazol) did not reduce adverse cardiovascular outcomes.[8] Further studies with other antiplatelet agents are required to establish their clinical benefits.

Ticagrelor, the first reversibly binding P2Y12 receptor antagonist, has a faster onset and stronger antiplatelet effect than clopidogrel.[9,10] In the PLATO (Platelet Inhibition and Patient Outcomes) trial, treatment with ticagrelor rather than clopidogrel reduced ischemic adverse events and mortality in acute coronary syndrome, regardless of kidney function.[11,12] These clinical benefits could be related to ticagrelor's significant inhibition of platelet reactivity.[13,14] However, the PLATO study, similar to other RCTs, excluded dialysis patients. Especially in HD patients, CKD is associated with complex thrombotic and hemostatic characteristics, such as bleeding and thrombosis.[15] RCTs often exclude patients at high risk for complications or death. Therefore, little is known about the effects of antiplatelet agents in this growing high-risk population. We hypothesized that antiplatelet agents with rapid pharmacokinetics and greater platelet inhibition would be more beneficial in patients with kidney failure than those with slower pharmacokinetics and less platelet inhibition. However, the onset and offset antiplatelet effects of ticagrelor in patients with kidney failure receiving maintenance HD with HTPR have not been investigated. We designed the present study to determine the antiplatelet effects, as well as onset and offset effects, of ticagrelor compared to clopidogrel in patients with kidney failure undergoing maintenance HD.

METHODS

Study Design and Participants

This clinical trial, the PIANO-3 CKD (Platelet Inhibition According to Novel Drug in Patients With CKD) study, was a single-center, prospective, randomized, crossover platelet reactivity study of patients with kidney failure with HTPR. Based on a previous study that demonstrated that patients receiving clopidogrel whose posttreatment platelet reactivity was >235 P2Y12 reaction units (PRUs) had significantly higher rates of cardiovascular death,[16] we defined a value ≥235 PRUs by the VerifyNow P2Y12 assay (Accumetrics) as HTPR for clopidogrel treatment. From January 2013 through August 2013, a total of 27 patients with kidney failure undergoing regular (≥6 months) maintenance HD and ongoing (≥2 months) treatment with clopidogrel were screened for inclusion. Two patients were excluded because their platelet reactivity was <235 PRUs, and a total of 25 patients were enrolled. All patients had been treated with clopidogrel with or without aspirin because of moderate coronary stenosis by coronary angiography or because they were at high risk (Framingham heart risk score ≥ 20%) for coronary artery disease.

Exclusion criteria were as follows: known allergies to aspirin, clopidogrel, or ticagrelor; concomitant use of other antithrombotic drugs (oral anticoagulants and dipyridamole); previous coronary intervention, thrombocytopenia (platelet count < 100,000/μL); hematocrit < 25%; uncontrolled hyperglycemia (hemoglobin A_{1c} > 10%); liver disease (bilirubin > 2 mg/dL); symptomatic severe pulmonary disease; active bleeding or bleeding diathesis; gastrointestinal bleeding within the past 6 months; hemodynamic instability; acute coronary or cerebrovascular event within the past 3 months; pregnancy; any malignancy; concomitant use of a cytochrome P450 inhibitor or nonsteroidal anti-inflammatory drug; or recent treatment (<30 days) with a glycoprotein IIb/IIIa antagonist.

Total duration of the study was 10 weeks (Fig 1). After a screening period (visit 1), patients with HTPR were randomly assigned at a 1:1 ratio by an independent investigator to the clopidogrel or ticagrelor groups using computerized random-number generation. After randomization, an initial loading dose of clopidogrel (300 mg) or ticagrelor (180 mg) was given and maintenance doses (clopidogrel, 75 mg, once daily with aspirin, 100 mg, or ticagrelor, 90 mg, twice daily with aspirin, 100 mg) were provided for 14 days. A visit at 14 ± 2 days was performed for platelet reactivity assessment and safety evaluation, with a 14-day drug-offset (washout) period. After this washout phase, crossover treatment assignments were followed for another 14 days. Treatment adherence was measured by the amount of medication returned at subsequent visits. Bleeding was defined according to PLATO criteria.[11] Heart rate, respiratory rate, and arterial oxygen saturation were measured at every visit. All HD characteristics were kept constant during the study period.

The study complied with the Declaration of Helsinki and was approved by the Institutional Review Board of Kyung Hee University Hospital (KMC IRB 1237-02). Written consent was obtained from all patients.

Blood Sampling and Genotyping Assays

Samples for platelet function analyses were taken at predosing (0 hour) and after the first dose of the study drug on visit 2 (1 and 5 hours after the first loading dose), then during the onset and maintenance period (48 hours and 14 days after the first loading dose), within 1 hour of the start of the offset (washout) period, and throughout the 14-day offset period (2, 4, and 14 days after the last dose). Blood samples were collected from an antecubital vein with a loose tourniquet through a 21-gauge needle before starting HD (predosing and at 1 and 48 hours and 14 days after loading) except for the sample taken 5 hours after the start of the onset period, which occurred after an HD session. Samples were processed within 1 hour after blood draw by operators blinded to the patients' treatment assignments.

Genotyping was performed for the single-nucleotide polymorphism *CYP2C19*2* (an A instead of a G at nucleotide 681 of the complementary DNA for *CYP2C19*) as described previously.[17]

Platelet Function Measurements

Light transmittance aggregometry and the VerifyNow P2Y12 assay were used to measure platelet aggregation as a measure of platelet function. Platelet aggregation induced by 5 and 20 μmol/L of adenosine diphosphate (ADP) in platelet-rich plasma was assessed using the turbidimetric method in a 2-channel aggregometer (Chrono-log 490; Chrono-log Corp) as described previously.[4] Final extent of aggregation, measured at 7 minutes after agonist addition, and the maximal extent of aggregation (Agg_{max}) were expressed as percent change in light transmittance from baseline, with platelet-poor plasma as a reference. Inhibition of platelet aggregation (IPA) was defined as the percent decrease in aggregation values obtained at baseline and after treatment, as follows: IPA (%) = (intensity of aggregation at baseline) − (intensity of aggregation after treatment)/(intensity of aggregation at baseline). The VerifyNow P2Y12 assay also was used to