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A pharmacodynamic comparison of a personalized strategy for anti-platelet therapy versus ticagrelor in achieving a therapeutic window☆

Nikita Malhotra [a,1], Joseph Abunassar [a,1], George A. Wells [b], Ruth McPherson [c], Angel Fu [a], Benjamin Hibbert [a], Marino Labinaz [a], Michel Le May [a], Alexander Dick [a], Chris Glover [a], Michael Froeschl [a], Jean-François Marquis [a], Luan Tran [a], Jordan Bernick [a], Aun-Yeong Chong [a], Derek Y.F. So [a,*,2], on behalf of the CArdiovascular Percutaneous Intervention TriAL (CAPITAL) investigators

[a] Division of Cardiology, University of Ottawa Heart Institute, Ottawa, ON, Canada
[b] Cardiovascular Methods Centre, University of Ottawa Heart Institute, Ottawa, Ontario, Canada
[c] Canadian Cardiovascular Genetics Centre, University of Ottawa Heart Institute, Ottawa, Ontario, Canada

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ABSTRACT

Background: A therapeutic window in antiplatelet treatment has been associated with concurrent lowering of bleeding and ischemic risks. Prasugrel and ticagrelor provide potent platelet inhibition, but may increase bleeding. No study has evaluated a personalized therapy with selective use of novel P2Y12 inhibitory agents compared to empiric ticagrelor use. The objective of this study was to compare a personalized anti-platelet therapy strategy to empiric ticagrelor in achieving a therapeutic window.

Methods: Using the CAPITAL registry, we performed a retrospective analysis to evaluate a personalized anti-platelet therapy (PAT) strategy, using a pharmacogenetic approach, and compared it to empiric ticagrelor. In the PAT group, carriers of *CYP2C19*2* received prasugrel and non-carriers received clopidogrel. The primary outcome was the proportion of patients within a validated therapeutic window, after a steady state treatment (≥48 h) of antiplatelet therapy, as measured by a P2Y12 reaction unit (PRU) >85 and <208.

Results: Of 199 patients with platelet function measurements, 150 received PAT, while 49 received ticagrelor. Significantly more patients on PAT achieved the primary outcome (50.0% vs. 4.1%, $p < 0.0001$). This was predominantly driven by an increase in low on-treatment reactivity with ticagrelor (95.9% vs. 37.3%, $p < 0.0001$). Multivariable analysis demonstrated PAT to be the strongest predictor of achieving PRU values within the therapeutic window (odds ratio 20.27; 95% CI: 4.33–94.82, $p = 0.0001$).

Conclusion: Patients treated with PAT were more likely to achieve a therapeutic window compared to a strategy of ticagrelor. Future prospective evaluation of novel PAT strategies will be required to prove clinical utility.

1. Introduction

Dual anti-platelet therapy, with aspirin and a P2Y12 receptor blocker, is the mainstay pharmacologic therapy after acute coronary syndromes (ACS) and percutaneous coronary intervention (PCI) [1]. A large number of observational studies, involving more than 20,000 patients have demonstrated that high on-treatment platelet reactivity (HPR), characterized by insufficient inhibition of platelet P2Y12 receptor during clopidogrel treatment, is a strong independent risk factor for post-PCI thrombotic events [2]. Conversely, excessive inhibition of the P2Y12 receptor or low on-treatment platelet reactivity (LPR) has been correlated to bleeding complications [3–6].

Novel P2Y12 agents, ticagrelor and prasugrel, have been shown to be superior compared to clopidogrel in reducing ischemic outcomes [7,8]. Accordingly, these agents are endorsed as front line therapy in ACS guidelines [1]. The efficacy of these agents is attributed primarily to more potent P2Y12 inhibition and reduction in HPR. However, increased P2Y12 inhibition may predispose these patients to bleeding [9]. Both prasugrel and ticagrelor cause increased non-coronary artery bypass graft (CABG) major bleeding compared to clopidogrel [7,8]. Hence, the balance between risk reduction of ischemic and bleeding risks may be paramount.

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

* Corresponding author at: University of Ottawa Heart Institute, 40 Ruskin Street, Ottawa, Ontario K1Y 4W7, Canada.
E-mail address: dso@ottawaheart.ca (D.Y.F. So).

[1] Equally contributing authors.
[2] Communicating author.

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The theory of a "ceiling effect" in the reduction of ischemic events, coupled with the lower rates of stent thrombosis observed in recent clinical trials [10,11], shifts the focus towards finding strategies that could avoid excessive bleeding while maintaining the benefit of reduced ischemic events. Recently, a consensus statement supported the concept of a therapeutic window based upon validated HPR and LPR values [12]. Patients receiving P2Y12 inhibitory drugs, who achieved a therapeutic window, have concurrent reduction in ischemic and bleeding risks compared to those falling outside of the window [3,4,12]. The consensus group further endorsed ongoing evaluation of novel strategies to optimize the likelihood of achieving a therapeutic window with P2Y12 inhibitors.

Accordingly, the objective of the present study was to evaluate the pharmacodynamic effects of a personalized anti-platelet therapy (PAT) strategy with selective use of more potent second generation P2Y12 inhibitors and compare this to a strategy of universal ticagrelor use. The *CYP2C19*2* allele has been associated with increased ischemic complications among patients with ACS undergoing PCI. Utilization of a pharmacogenetic strategy, with selective use of novel P2Y12 receptor inhibitors for carriers of the *CYP2C19*2* allele, has been shown to decrease HPR compared to clopidogrel [13]. Although the concept of using platelet reactivity to personalize anti-platelet therapy has been evaluated [14], to date, no study has evaluated a PAT strategy using a pharmacogenetic approach and compared it to a strategy of empiric ticagrelor use in achieving a therapeutic window.

2. Methods

2.1. Study design and study group

The study was conducted in accordance with the Declaration of Helsinki and approved by the local human research ethics board. Informed consent was obtained from each patient. We performed a retrospective cohort study, using the CAPITAL-PCI registry [15,16], which consists of patients undergoing PCI for stable CAD or ACS. Patients were included if platelet function measurements were available immediately post-PCI before the initiation of the final P2Y12 strategy, and at a steady state of treatment, as defined by ≥48 h after the initiation of the P2Y12 strategy. The rationale for a ≥48 hour measurement is supported by previous pharmacodynamic studies in stable and ACS patients which document that measurement of platelet function ≥24 h after initial dosing is indicative of long-term platelet inhibition values for ticagrelor, prasugrel and clopidogrel [17,18]. Patients were excluded if they had: a history of stroke or transient ischemic attack (TIA), body weight < 60 kg, platelet < 100,000 per μL, known bleeding diathesis, hematocrit < 30% or >52%, liver dysfunction, or renal insufficiency (defined as a creatinine clearance <30 mL/min). All patients in the PAT group had been pre-treated with a 600 mg bolus of clopidogrel, consistent with the practice pattern at our institution. Patients receiving PAT underwent point-of-care rapid genotyping after PCI, and had selective treatment with prasugrel 10 mg daily if found to be carriers of *CYP2C19*2*. Non-carriers were treated with 75 mg clopidogrel once daily. Patients in the ticagrelor group were treated with a 180 mg bolus followed by 90 mg twice daily.

2.2. Platelet function measurements and endpoints

Platelet function measurements were determined using the VerifyNow P2Y12 assay (Accumetrics, USA) and reported in P2Y12 reaction units (PRU). Upper and lower limits of the therapeutic window were defined based on an extensive review of the literature and according to the recent consensus statement by the Working Group on On-treatment Platelet Reactivity [12], which was based on validated cutoffs for HPR and LPR. Patients with PRU >208 or <85 were considered outside of the therapeutic window and at-risk for ischemic or bleeding complications respectively. The primary endpoint was the proportion of patients in each group achieving the therapeutic window at a steady state (first PRU measurement at ≥48 h after initiation of the post-PCI P2Y12 inhibitor strategy). Secondary endpoints included the proportion of patients with HPR and LPR in the two strategies.

2.3. Statistical analysis

Based on our previous study [13], we approximated that 40% of patients treated with a pharmacogenetic approach would achieve the therapeutic window. From pharmacodynamic data from Alexopoulos et al, we had assumed that 5% of ticagrelor treated ACS patients would achieve a therapeutic window [18]. Using these assumptions, we calculated that 28 patients would be required per group to achieve a power of 90%, using an alpha of 0.05. A Fisher's exact test was used for comparisons of categorical variables and presented as frequencies or percentages. For comparisons of continuous variables, a Student *t*-test or Mann–Whitney *U* test was used and expressed as mean ± SD or median [interquartile range] as appropriate. PRU values between baseline and at steady states were compared using a paired *t*-test, and multiple groups were compared using ANOVA. Multivariable analysis using logistic regression was conducted to account for known factors affecting ability for achieving the therapeutic window. Covariates in the model included: ACS, diabetes, BMI, statin and proton pump inhibitor use. All p-values were two-tailed with a significance level of 0.05. Analyses were performed using SAS (version 9.2).

2.4. Systematic review of current PRU cutoffs for bleeding and ischemia

We performed a comprehensive computerized literature search of SCOPUS and PubMed till June 2014 for English language studies using permutations of: therapeutic window, platelet function, P2Y12 inhibitor, P2Y12 reaction unit, platelet reactivity, high platelet reactivity, low platelet reactivity, clinical outcomes, bleeding outcomes and ischemic outcomes. Additional studies were identified using references of identified studies, as well as citing articles. We included studies evaluating clinical outcomes, in patients undergoing PCI, to platelet function PRU cut-offs using the VerifyNow P2Y12 Assay. Data was extracted by two independent authors and disagreement resolved by consensus.

3. Results

Within the CAPITAL registry, 199 patients meeting the inclusion criteria were identified. Of these, 150 received a PAT strategy, while 49 received empiric ticagrelor (Fig. 1). The age of patients in the study ranged from age 35–75, with a median age of 59 and interquartile range (51-66). Baseline demographics (Table 1) were similar between groups except more patients in PAT had hypercholesterolemia (68.7% vs. 38.8%, p = 0.0003). Of note, all patients receiving a ticagrelor strategy had undergone PCI for ACS compared to 61.3% in the PAT strategy group. In the PAT group, 41 patients (27.3%) were carriers of at least one CYP2C19*2 allele and received prasugrel post-PCI.

For the primary outcome, significantly more patients with PAT achieved PRU values within a therapeutic window (50.0% vs. 4.1%, p < 0.0001, Fig. 2). Mean PRU (± standard deviation) at steady state was 115.8 ± 78.0 in the PAT group as compared to 26.3 ± 29.8 in ticagrelor treated patients (p < 0.0001). Of note, 95.9% in the ticagrelor group, compared with 50.0% on PAT were out of the therapeutic window, p < 0.0001 (Table 2a). This was predominantly driven by the high incidence of LPR in ticagrelor, with 47 of 49 (95.9%) patients having a PRU <85 (p < 0.0001). Conversely, 19 of 150 patients (12.7%) receiving a PAT strategy had a PRU > 208 compared to none with ticagrelor (p = 0.0046). Of patients achieving PRU values within the therapeutic window, 97.4% were on PAT and 2.6% were on ticagrelor (p < 0.0001). After adjusting for covariates, the odds ratio for PAT to achieving the therapeutic window was ratio 20.27; (95% CI: 4.33–94.82, p = 0.0001). To ascertain that achieving a therapeutic window in the PAT group was not confounded