Use of the VerifyNow point of care assay to assess the pharmacodynamic effects of loading and maintenance dose regimens of prasugrel and ticagrelor

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Abstract
Prasugrel and ticagrelor are potent oral platelet P2Y12 inhibitors and are recommended over clopidogrel in patients with acute coronary syndrome (ACS). Oral platelet P2Y12 inhibitors are characterized by varying degrees of pharmacodynamic response profiles as assessed by a variety of commercially available assays. Because of its ease of use, rapid turnaround times and ability to provide results specific to P2Y12 inhibitory effects, VerifyNow has emerged as one of the most commonly utilized platelet function assays. However, reference ranges with VerifyNow have been reported mainly for clopidogrel and there has not yet been any study specifically conducted to provide the expected on treatment reference ranges following administration of prasugrel and ticagrelor. This was a prospective single center investigation conducted in 120 patients with ACS who were treated with prasugrel or ticagrelor as per standard of care. Patients who underwent percutaneous coronary interventions (PCI) were treated with a loading dose of prasugrel (60 mg) or ticagrelor (180 mg), and patients who were on maintenance therapy were taking prasugrel (10 mg qd or 5 mg qd) or ticagrelor (90 mg bid). Platelet function testing was performed using the VerifyNow™ PRUTest™. The overall range of PRUTest values was lower than that observed in studies of patients treated with clopidogrel. The use of a maintenance dose regimen had a wider range of PRUTest values compared to the use of a loading dose for both prasugrel (1–179 vs. 2–128) and ticagrelor (1–196 vs. 1–177). The average PRUTest values in patients on prasugrel and ticagrelor maintenance dosing were 20% and 9% higher those observed in patients treated with a loading dose. PRUTest results following loading dose administration were very similar between drugs, but were 20% higher with prasugrel compared with ticagrelor during maintenance dosing. This study establishes expected PRUTest ranges for patients taking loading and maintenance doses of prasugrel and ticagrelor.

Clinical Trial Registration http://www.clinicaltrials.gov Unique Identifier: NCT04492423, registered July 2020 retrospectively registered.

Keywords Platelet function · Prasugrel · Ticagrelor

Introduction
Dual antiplatelet therapy (DAPT) with aspirin and a P2Y12 inhibitor is the standard of care for the prevention of recurrent atherothrombotic events in patients with an acute coronary syndrome (ACS) [1]. Clopidogrel, prasugrel and ticagrelor are P2Y12 inhibitors approved for clinical use in ACS patients [2]. However, clopidogrel-induced antiplatelet effects are subject to broad variability in individual response with a considerable number of patients persisting with high on-treatment platelet reactivity (HPR) [3]. Importantly, HPR is an established marker of thrombotic risk particularly among patients undergoing percutaneous coronary interventions (PCI) [4]. Ticagrelor and prasugrel are newer generation potent P2Y12 inhibitors, both are characterized by more robust and less variable antiplatelet effects compared with clopidogrel [2]. Moreover, outcome studies conducted in patients with ACS have shown a greater reduction in recurrent atherothrombotic events with prasugrel and ticagrelor...
ticagrelor compared with clopidogrel, albeit at the expense of increased bleeding [5]. Accordingly, guidelines recommend the use of prasugrel and ticagrelor over clopidogrel in patients with ACS, particularly in the absence of high bleeding risk [6]. The clinical implications associated with different levels of platelet reactivity induced by platelet P2Y₁₂ inhibitors has fueled the interest of developing assays able to detect their effect [4, 7]. Although several assays are commercially available, many of these may be labor intensive and require technical laboratory expertise [4, 7]. Hence, an assay which is easy to use and provides prompt and reliable results is key towards their acceptance and routine implementation in clinical practice [4].

VerifyNow uses a whole blood sample to measure platelet reactivity by assessing the rate and extent of changes in light transmittance caused by platelets aggregating in the presence of agonists that are specific to define the effects of a given antiplatelet agent [7, 8]. In light of its ease of use, rapid turnaround times and ability to provide results specific to P2Y₁₂ inhibitory effects, VerifyNow has emerged as one of the most commonly utilized platelet function assays in clinical trials as well as in real-world practice [4, 7]. However, despite its broad utilization in patients treated with all commercially available P2Y₁₂ inhibitors, reference ranges with VerifyNow have been reported mainly for clopidogrel and there has not yet been any study specifically conducted to provide the expected on treatment reference ranges following administration of prasugrel and ticagrelor [9]. The ever-growing use of these agents underscores the importance of defining these ranges to help guide practitioners in the management of their patients treated with prasugrel or ticagrelor if testing with VerifyNow is performed. The primary aim of this study was to determine the range of expected values of platelet reactivity measured by VerifyNow in patients with ACS following acute and chronic administration of prasugrel or ticagrelor.

Methods

Study design and participants

This was a prospective single center investigation conducted in male and female adult (> 18 years of age) patients with an ACS (n = 120) treated with prasugrel or ticagrelor as per standard of care (Clinicaltrials.gov identifier: NCT04492423). The study was performed at the University of Florida Health-Jacksonville (Jacksonville, FL, USA), and approved by Western Institutional Review Board (WIRB). Patients with ACS included those with a non-ST elevation ACS (NSTE-ACS), including unstable angina and non-ST elevation myocardial infarction, and ST elevation myocardial infarction (STEMI). Written informed consent was obtained from all individual participants included in the study prior to their enrollment. Assessments included patients undergoing PCI and treated with a loading dose of prasugrel (60 mg) or ticagrelor (180 mg) as well as patients who were on maintenance therapy with prasugrel (10 mg qd or 5 mg qd) or ticagrelor (90 mg bid). Loading and maintenance doses were administered as uncrushed integral tablets. All patients were on a background of aspirin therapy (325 mg loading dose in patients undergoing PCI followed by 81 mg qd). Key exclusion criteria were inability to provide written informed consent, subjects treated with an investigational antiplatelet agent, use of a glycoprotein IIb/IIIa inhibitor within past 2 weeks, treatment with any therapy containing dipyridamole within past 2 weeks, and women who were pregnant or of child bearing potential. The study complied with the Declaration of Helsinki, was approved by the Western Institutional Review Board and all patients gave their written informed consent.

Blood sampling

Peripheral venous blood samples were drawn through a short venous catheter inserted into an arm vein and collected in citrated tubes as appropriate for assessments. The first 2–4 mL of blood were discarded to avoid spontaneous platelet activation. For all enrolled patients undergoing PCI, duplicate samples were collected and assayed between 2 and 6 h post loading or maintenance dose administration. Blood samples were drawn in conjunction with routine testing performed as part of standard patient care. All blood samples were assayed in duplicate between 10 min and 1 h following sample collection. A complete blood count measurement was performed for each enrolled subject from a sample collected at the time of blood draw or within 1 week.

Platelet function testing

Platelet Function Testing was performed using VerifyNow PRUTest (Accriva Diagnostics, wholly owned by Instrumentation Laboratory, San Diego, USA). Platelet activation induced by adenosine diphosphate (ADP) is mediated by two receptors located on platelets, P2Y₁ and P2Y₁₂ [10]. As depicted in Fig. 1, both receptors are activated by ADP and lead to the final common pathway that mediates platelet aggregation, i.e., activation of glycoprotein IIb/IIIa receptors. VerifyNow is a turbidimetric based optical detection system, which measures platelet-induced aggregation. The VerifyNow PRUTest is designed to measure platelet aggregation mediated by P2Y₁₂ receptor blockade. The VerifyNow PRUTest is based upon the ability of activated platelets to bind fibrinogen. Fibrinogen-coated microparticles aggregate in whole blood in proportion to the number of expressed platelet GP IIb/IIIa receptors. Results are reported.
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as P2Y12 Reaction Units (PRU) based on the rate and extent of aggregation, which reflects the amount of P2Y12 receptor-mediated aggregation specific to platelets. A PRU result is calculated based upon the rate and extent of platelet aggregation recorded in the channel containing the platelet agonist, ADP. P2Y12 receptor mediated platelet aggregation and PRUTest results from VerifyNow are not influenced by non-specific platelet aggregation mediated through P2Y1.

To accomplish the goal of having a test with reduced non-specific aggregation, the VerifyNow PRUTest uses prostaglandin E1 (PGE1) in addition to ADP to make the test more sensitive and specific for the effects of ADP mediated by the P2Y12 receptor. A PRU > 208 identifies patients with HPR, an established marker of increased thrombotic risk [4].

Statistical analysis

Results were analyzed per Clinical and Laboratory Standards Institute (CLSI) Guideline (“Defining, Establishing and Verifying Reference Intervals in the Clinical Laboratory”) [11]. The per treatment evaluable population consisted of subjects who were enrolled and had no pre-specified protocol deviations. Data from the patients not meeting study entry criteria after blood sample collection were excluded from the analysis. Continuous variables are expressed as mean, standard deviation, 25th and central 95th percentile reference limits (RL), 90% confidence intervals (CI), and range. Categorical variables are expressed as number (N), standard deviation (SD), correlation coefficient (Pearson’s r) and percentage (%) of total for the ticagrelor and prasugrel populations. There was no imputation for missing data. The study was not designed for statistical comparisons between the different cohorts and accordingly descriptive reporting of data are provided.

Results

Baseline characteristics

A total of 130 male and female adult patients receiving aspirin plus prasugrel or ticagrelor were enrolled. A total of 10 patients were excluded from analysis due to protocol deviations which included lack of baseline complete blood count (n = 5), study procedure violation (n = 4) and incorrect P2Y12 inhibitor (n = 1). Therefore, a total of 120 patients were eligible for analysis. The mean age for all participating patients was 59.8 (9.7), with a range of 34 to 70 years. Prasugrel was used in 63 (53%) of patients; 28 (44%) of these received a loading dose of 60 mg in the catheterization laboratory; the remaining 35 (56%) were on either a 5 mg (n = 4) or 10 mg (n = 31) qd maintenance dose at the time of enrollment. Ticagrelor was used in 57 (47%) of patients; 32 (56%) of these received a loading dose of 180 mg in the catheterization laboratory; the remaining 25 (44%) were on a 90 mg bid maintenance dose at the time of enrollment. A detailed description of baseline demographics is provided in Table 1.

VerifyNow testing

The average time from prasugrel loading dose to PRUTest blood draw was 4 h 46 min, range 3 h 48 min to 8 h 38 min, median 4 h 21 min. The average time from last prasugrel maintenance dose to PRUTest blood draw for these patients was 3 h 9 min, range 2 h 1 min to 5 h 47 min, median 3 h 6 min. The average time from ticagrelor loading dose to PRUTest blood draw was 4 h 48 min, range 1 to 7 h and 10 min, median 4 h 8 min. The average time from last ticagrelor maintenance dose to PRUTest blood draw for these patients was 3 h 53 min, range 2 h 10 min to 5 h 20 min, median 3 h 40 min.

The range of PRUTest values for patients on prasugrel was 1–196 with an average of 52.3, with Pearson’s correlation coefficient of duplicate measurements of 0.96–0.97 (Table 2). Box–Whisker distribution plots of individual patient data of prasugrel treated patients are illustrated in Fig. 2. Ranges of PRUTest values were 1–177 with an average of 45.6 for patients treated with a loading dose and 1–196 with an average of 57.8 for those on maintenance dosing. The range of PRUTest values for patients on ticagrelor was 1–179 with an average of 42.2 (Table 3),
with Pearson’s correlation coefficient of duplicate measurements of 0.94–0.99. Box–Whisker distribution plots of individual patient data of ticagrelor treated patients are illustrated in Fig. 3. Specifically, ranges of PRUTest values were 2–128 with an average of 43.7 for patients treated with a loading dose and 1–179 with an average of 40.3 for those on maintenance dosing (Table 3).

A total of 2 patients (prasugrel, n = 1; ticagrelor, n = 1) had HPR status. The prasugrel treated patient was confirmed to be compliant with a 10 mg maintenance dose regimen and had a PRUTest value of 257 with the last dose taken was 2 h and 19 min prior to the study blood draw. The ticagrelor treated patient received a 180 mg loading dose and had a PRUTest value of 322 at 5 h and 26 min following drug administration. These patients were included in the per treatment evaluable group for statistical evaluation.

### Discussion

The use of platelet P2Y$_{12}$ inhibiting therapy, in adjunct to aspirin, is the cornerstone of treatment for patients with an ACS [1]. Clopidogrel, prasugrel and ticagrelor are P2Y$_{12}$ inhibitors approved for clinical use in ACS patients [2]. However, in the absence of contraindications, guidelines recommend the use of prasugrel and ticagrelor over clopidogrel in light of their superior clinical outcomes [1]. In particular, both prasugrel and ticagrelor are associated with a greater reduction in recurrent ischemic events, albeit at the expense

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**Table 1** Baseline and demographic data

| Parameter                  | Prasugrel | Ticagrelor | All  |
|----------------------------|-----------|------------|------|
| Evaluable subjects         | 63        | 57         | 120  |
| Male—N (%)                 | 41        | 37         | 78   |
| Female—N (%)               | 22        | 20         | 42   |
| Mean age (SD)—N (%)       | 59.7 (9.5)| 59.9 (10.1)| 59.8 (9.7)|
| Age ≥ 65                   | 17        | 22         | 39   |
| Ethnicity—N (%)            | 63 (100)  | 57 (100)   | 120 (100)|
| White                      | 49 (77.8) | 35 (61.4)  | 84 (70.0)|
| Asian                      | 0 (0)     | 0 (0)      | 0 (0) |
| Hispanic or Latino         | 2 (3.2)   | 3 (5.3)    | 5 (4.2)|
| Black or African American  | 12 (19.0) | 19 (33.3)  | 31 (25.8)|
| Other                      | 0 (0)     | 0 (0)      | 0 (0) |
| Smoking—N (%)              | 12 (19.0) | 8 (14.0)   | 20 (16.7)|
| Diabetes mellitus—N (%)    | 22 (34.9) | 18 (31.6)  | 40 (33.3)|
| Hyperlipidemia—N (%)       | 35 (55.6) | 33 (57.9)  | 68 (56.7)|
| Hypertension—N (%)         | 51 (81.0) | 40 (70.2)  | 91 (75.8)|
| Prior MI p—N (%)           | 33 (52.4) | 33 (57.9)  | 66 (55.0)|
| Prior CABG—N (%)           | 10 (15.9) | 8 (14.0)   | 18 (15.0)|
| Prior PCI—N (%)            | 39 (61.9) | 39 (68.4)  | 78 (65.0)|
| PAD—N (%)                  | 2 (3.2)   | 4 (7.0)    | 6 (5.0)|
| Prior CVA—N (%)            | 0 (0)     | 8 (14.0)   | 8 (6.7)|
| Mean BMI kg/M$^2$ (SD)     | 32.3 (8.6)| 30.0 (5.9) | 31.2 (7.4)|
| Mean hematocrit, % (SD)    | 40.3 (4.2)| 38.2 (5.7) | 39.3 (5.1)|
| Mean platelets × 10$^3$ (SD)| 227 (56.4)| 237 (67.7) | 232 (62)|
| Mean hemoglobin, g/dL (SD) | 13.4 (1.4)| 12.7 (2.2) | 13.1 (1.9)|

**Table 2** Prasugrel PRUTest data

| Parameter                  | All         | 5 to 10 mg | 60 mg |
|----------------------------|-------------|------------|-------|
| N                          | 63          | 35         | 28    |
| Average                    | 52.3        | 57.8       | 45.6  |
| SD                         | 44.70       | 44.3       | 45.0  |
| 5th Percentile             | 5           | 5.7        | 4.4   |
| 25th Percentile            | 8.88        | 20.9       | 7.1   |
| 95th Percentile            | 142.38      | 135.8      | 126.9 |
| Range                      | 1–196       | 1–196      | 1–177 |
| Pearson’s r                | 0.96        | 0.97       | 0.96  |

**Table 3** Ticagrelor PRUTest data

| Parameter                  | All         | 90 mg   | 180 mg |
|----------------------------|-------------|---------|--------|
| N                          | 57          | 25      | 32     |
| Average                    | 42.2        | 40.3    | 43.7   |
| SD                         | 54.2        | 42.4    | 62.8   |
| 5th Percentile             | 4.625       | 4.2     | 5.3    |
| 25th Percentile            | 7.5         | 10.5    | 7.0    |
| 95th Percentile            | 117.1       | 111.2   | 114.5  |
| Range                      | 1–179       | 1–179   | 2–128  |
| Pearson’s r                | 0.98        | 0.99    | 0.94   |

**Fig. 2** Distribution of on treatment PRUTest values among prasugrel treated patients. Box Whisker plot of the minimum, median, maximum, interquartile range and outliers of PRUTest values in prasugrel treated patients
of increased bleeding, but with a net benefit profile which still favors their use over clopidogrel [5, 6]. These findings are attributed to the more potent platelet inhibitory effects of prasugrel and ticagrelor over clopidogrel [2]. Clopidogrel in fact is well known to be associated with broad variability in platelet inhibitory effects with a considerable number of patients persisting with HPR, an established marker of thrombotic risk [3, 4]. Studies associating HPR with adverse outcomes have been mostly conducted among clopidogrel treated patients [4]. Although a number of assays have been used to support this association, most data are derived from the use of the VerifyNow [4]. This is due to its ease of use, rapid turnaround times and ability to provide results specific to P2Y₁₂ inhibitory effects [4, 7]. However, reference ranges with the VerifyNow have been reported mainly for clopidogrel and, despite its broad utilization in patients treated with all commercially available P2Y₁₂ inhibitors, there has not yet been any study specifically conducted to provide the expected on treatment reference ranges following administration of prasugrel and ticagrelor. For these reasons, it is important to determine the degree at which these newer generation P2Y₁₂ inhibitors impact platelet function and therefore PRUTest values. This cannot be established without the benefit of a carefully conducted study, using proven methods in the intended population for P2Y₁₂ inhibitor therapy.

Our findings demonstrate the following: (a) the overall range of PRUTest values is lower than that observed in studies of patients treated with clopidogrel [9, 12–14]; (b) in both patients treated with prasugrel and those treated with ticagrelor, the use of a maintenance dose regimen had a wider range of PRUTest values compared to the use of a loading dose (1–179 vs. 2–128 for prasugrel and 1–196 vs. 1–177 for ticagrelor); (c) the average PRUTest values in patients on prasugrel and ticagrelor maintenance dosing were 20% and 9% higher than those observed in patients treated with a loading dose; (d) PRUTest results following loading dose administration were very similar between drugs, but were 20% higher with prasugrel compared with ticagrelor during maintenance dosing.

Overall, the results of our investigation provide important insights on anticipated ranges of PRUTest values among patients treated with the newer generation P2Y₁₂ inhibitors prasugrel and ticagrelor both following loading dose and maintenance dose administration [15, 16]. The PRUTest values are in line with the greater potency of these agents compared with clopidogrel [15, 16]. Indeed, the presence of a variability in platelet inhibitory effects is consistent with orally administered drugs which were not developed to cause complete suppression of P2Y₁₂ mediated signaling like that achieved with intravenous therapy (i.e., cangrelor) [17–20]. Nevertheless, they do support the concept that patients treated with these agents have enhanced platelet inhibition which fall well below previously defined thresholds of HPR associated with increased thrombotic risk [4]. In fact, only 1 patient per group was identified to have HPR status. The mechanisms associated with this HPR are unknown, but most likely to be associated with impaired drug absorption or metabolism. Pharmacokineti...
administration of prasugrel and ticagrelor and not to make comparative assessments on the pharmacodynamic effects of these two agents which would have required a larger sample size. Similarly, the limited sample size of this study did not allow for subgroup analysis. Although opioids, commonly used in STEMI, have shown to affect absorption of oral P2Y12 inhibitors, their impact on our study results is unknown as information on ACS type and opioid use was not collected [26, 27]. Similarly, hematologic parameters other than hematocrit, platelet count, and hemoglobin were not collected. Moreover, the current study had as objective evaluating on treatment reference ranges following administration of prasugrel and ticagrelor in patients with ACS for whom these agents are recommended [1]. Therefore, our findings cannot be extrapolated to a stable clinical setting where these agents, albeit not recommended for use, are not infrequently used. Ultimately, our study was limited to the investigation of prasugrel and ticagrelor in patients with an ACS and the on treatment reference ranges following administration of other P2Y12 inhibitors (i.e., clopidogrel, cangrelor, selatogrel) in this clinical setting were not tested.

Conclusions

The PRUTest values of ticagrelor and prasugrel in this study reflect the greater potency of these agents compared with clopidogrel. The variability in platelet inhibitory effects, as reflected in PRUTest results, is consistent with orally administered drugs which were not developed for complete suppression of P2Y12 medicated signaling. The use the VerifyNow PRUTest assay is well standardized, and makes it a reproducible point of care assay that allows for measuring platelet reactivity and assessing interindividual variability in response to oral P2Y12 Receptor inhibitors, including prasugrel and ticagrelor, convenient in the acute/in-patient care or outpatient/office settings.

Disclosure

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