Pharmacodynamic Effects of Switching From Prasugrel to Ticagrelor
Results of the Prospective, Randomized SWAP-3 Study

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ABSTRACT

OBJECTIVES The study sought to assess the pharmacodynamic (PD) effects of switching to ticagrelor patients who were treated with prasugrel after undergoing percutaneous coronary intervention in the setting of an acute coronary syndrome.

BACKGROUND In clinical practice, there is a frequent need to switch between P2Y12 receptor inhibitors. However, concerns on drug interactions have emerged when switching therapies. To date, the PD effects of switching from prasugrel to ticagrelor have yet to be investigated.

METHODS This was a prospective, randomized, open-label, 3-arm, parallel-design study conducted in patients (n = 82) on maintenance dual antiplatelet therapy with aspirin (81 mg QD) and prasugrel (10 mg QD). Patients were randomized to continue prasugrel 10 mg QD or switch to ticagrelor 90 mg bid, with or without a 180 mg loading dose (LD), for 1 week. PD assessments included P2Y12 reaction units (PRU) by VerifyNow, platelet reactivity index by vasodilator-stimulated phosphoprotein (VASP), and platelet aggregation by light transmittance aggregometry (LTA) at a total of 6 time points: baseline, 2 h, 4 h, 24 h, 48 h, and 1 week after randomization.

RESULTS After switching to ticagrelor, PRU levels decreased as early as 2 h after drug administration. Mean PRU levels remained low during the study time course, without evidence of drug interactions. The primary endpoint of noninferiority of ticagrelor (2 arms combined) versus prasugrel measured by PRU at 1 week was met (least squares mean difference: -18; 95% confidence interval: -41 to 5). There was no increase in rates of high on-treatment platelet reactivity (PRU >208), which were overall very low throughout the study time course. Similar levels of platelet reactivity were observed irrespective of the use of a ticagrelor LD. Parallel findings were observed with VASP and LTA.

CONCLUSIONS Switching from prasugrel to ticagrelor leads to transiently higher levels of platelet inhibition, irrespective of the use of a LD, without evidence of drug interactions. (Pharmacodynamic Evaluation of Switching From Prasugrel to Ticagrelor [SWAP3]; NCT02016170) (J Am Coll Cardiol Intv 2016; :- - - -) © 2016 by the American College of Cardiology Foundation.

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Dual antiplatelet therapy (DAPT) consisting of aspirin and a P2Y→ receptor antagonist is the cornerstone of treatment for secondary prevention of thrombotic events, particularly in patients with acute coronary syndrome (ACS) undergoing percutaneous coronary intervention (PCI) (1). Although clopidogrel is the most widely used P2Y→ receptor antagonist, prasugrel and ticagrelor have more favorable pharmacodynamic (PD) profiles that result in reduced rates of high on-treatment platelet reactivity (HPR), a well-established marker associated with risk of thrombotic recurrences (1,2-4). Moreover, compared with clopidogrel, prasugrel and ticagrelor are associated with greater net clinical benefit in ACS patients undergoing PCI leading to an increase in their use in daily practice (1,5,6).

Switching antiplatelet therapies is a common occurrence in clinical practice (7). In fact, the current availability of different oral P2Y→ receptor antagonists allows for multiple treatment options and has indeed raised the question on the optimal approach for switching among these therapies if needed or desired. To date, most studies have been designed to specifically assess the PD effects associated with switching from clopidogrel to either prasugrel or ticagrelor (7). However, there are limited studies on other switching options that occur in clinical practice, such as those between the new-generation P2Y→ receptor inhibitors. In a recent study, switching from ticagrelor to prasugrel was associated with an increase in platelet reactivity and HPR rates, which was suggestive of a drug interaction (8). Transitioning therapy with the use of a loading dose (LD) of prasugrel rather than with just a maintenance dose (MD) regimen mitigated such increase in platelet reactivity. Indeed, these observations have led to question the PD profiles occurring when switching from prasugrel to ticagrelor as well as the optimal dosing regimen for clinicians to consider when this is required.

**METHODS**

**STUDY DESIGN AND POPULATION.** The SWAP (Switching AntiPlatelet)-3 study was a prospective, randomized, single-center, open-label, 3-arm, parallel-design study aimed to assess the PD response of switching from prasugrel to ticagrelor (NCT02016170). Patients were considered eligible for the study if they met all of the following inclusion criteria: 1) between 18 and 74 years of age; 2) underwent PCI in the setting of an ACS; 3) on maintenance DAPT with aspirin 81 mg QD and prasugrel 10 mg QD for at least 14 days per standard of care; and 4) provided written informed consent. In the absence of prior investigations on the safety of switching from prasugrel to ticagrelor, the rationale for waiting 14 days prior to randomization was to assure that patients had been stabilized following their acute coronary event without ischemic or bleeding complications. Patients were excluded in the presence of contraindications or warnings for the use of prasugrel or ticagrelor (see Online Appendix for details). The study complied with the Declaration of Helsinki, and was approved by the Western Institutional Review Board, and all patients gave their written informed consent.

Patients meeting study entry criteria were randomized in a 1:1:1 fashion to 1 of the following 3 treatment arms: maintain prasugrel 10 mg QD MD; switch to ticagrelor with a 180 mg LD; or switch to ticagrelor 90 mg bid MD without LD. Randomized treatment was maintained for 1 week. Aspirin 81 mg QD was maintained throughout the study. Compliance with treatment was assessed by pill count and patient interview. After study completion patients resumed a DAPT regimen at the discretion of the treating cardiologist. PD testing was performed at 6 time points. A flow diagram of the study is presented in Figure 1.

**BLOOD SAMPLING AND PD TESTING.** Blood sampling for PD testing was performed at 6 time points: baseline (prior to randomization) and 2 h, 4 h, 24 h, 48 h, and 1 week (7 ± 2 days) after administration of the randomized treatment. In order to ensure measurement of trough levels of platelet reactivity, baseline blood samples were collected 24 h after last MD of prasugrel; the 24- and 48-h samples were collected before administration of the scheduled morning dose of study drug, and the 1-week blood sample was collected 24 and 12 h after last MD of prasugrel and ticagrelor, respectively. PD testing was conducted by laboratory personnel blinded to treatment assignment using 3 assays. In brief, PD assessments included: 1) P2Y→ reaction units (PRU) by VerifyNow P2Y12 point-of-care testing (VN-P2Y12) (Accriva, San Diego, California); 2) platelet reactivity index (PRI) by whole blood vasodilator-stimulated phosphoprotein (VASP) (Biocytex Inc, Marseille, France); and 3) maximal platelet aggregation (MPA) following 5 and 20 μM ADP stimuli by light transmittance aggregometry (LTA) (Chrono-Log Corp., Havertown, Pennsylvania) (8,9). In line with expert consensus,
HPR was defined by a PRU >208 as assessed by VN-P2Y12, a PRI >50% as assessed by VASP, or MPA >59% as assessed by LTA following 20 µM ADP stimuli (4). Because LTA results with 5 µM ADP were consistent with 20 µM ADP, these are reported in the Appendix (Online Figures 1A and B).

SAMPLE SIZE CALCULATION AND STUDY ENDPOINTS. The primary hypothesis of our study was that after 1 week of randomized treatment PRU levels would be noninferior in patients switched from prasugrel to ticagrelor (2 arms combined) compared with patients remaining on prasugrel. Noninferiority was assessed using a 95% confidence interval (CI) of the difference in mean PRU between prasugrel and ticagrelor (2 arms combined). Under the assumption of 0 difference in mean PRU between ticagrelor 90 mg bid MD and prasugrel 10 mg QD MD and a common standard deviation of 60 PRU, a sample size of 24 patients per group allowed for the 95% CI to stay within ±45 PRU with a 90% power and alpha of 0.05. Considering the 3 arms of treatment and a 20% to 25% rate of invalid results due to hemolysis or technical problems, we estimated that up to 90 patients would potentially need to be randomized in order to ensure complete available data for analysis. The sample size of this study was established according to results of previous PD investigations (3,9). In line with a previously reported switching investigation, 45 PRU was arbitrarily chosen for the noninferiority margin for the upper 95% CI limit of the difference (8). Other endpoints included: 1) comparisons of platelet reactivity between prasugrel and combined ticagrelor assessed at each time point; 2) comparisons of platelet reactivity between prasugrel and each ticagrelor treatment regimen; 3) comparisons between the 2 ticagrelor treatment regimens; and 4) comparisons of rates of HPR among groups.

STATISTICAL ANALYSIS. Conformity to the normal distribution was evaluated for continuous variables with the Kolmogorov-Smirnov test. For baseline characteristics, continuous variables are expressed as mean ± SD or median (interquartile range). One-way analysis of variance or Kruskal-Wallis test was used to compare continuous variables. Chi-square test was used to compare categorical variables among groups. An analysis of covariance method with a general linear model, with treatment as the main effect and baseline values of platelet reactivity as a covariate, was used to evaluate the primary endpoint as well as all between-group comparisons at each time point. Least squares mean (LSM) differences in PRU between the combined ticagrelor groups and the prasugrel group and the corresponding 2-sided 95% CI for the difference were obtained based on the analysis of covariance model. A repeated measures analysis of variance was used to evaluate within groups comparisons. The Bonferroni approach was used to correct for multiple comparisons. A 2-tailed p value of <0.05 was considered to indicate a statistically significant difference for all the analyses performed. Results are reported as LSM and 95% CI for the previous detailed analyses. Statistical analysis was performed using SPSS version 22.0 software (SPSS Inc., Chicago, Illinois).
The primary population was defined as patients who received the randomized treatment and had a valid primary endpoint value (PRU at 1 week), and was used for analysis of all PD endpoints. The treated population comprised all patients who received any dose of study medication and was considered for analysis of safety and adverse events.

RESULTS

PATIENT POPULATION. Between March 2014 and October 2015, a total of 150 patients on maintenance DAPT with aspirin and prasugrel were identified. Of these, 83 patients meeting study entry criteria agreed to participate and provided their written informed consent. One patient was excluded after providing informed consent because of inadequate venous access. Thus a total of 82 patients were randomized: prasugrel 10 mg MD (n = 27), ticagrelor 180 mg LD followed by 90 mg bid MD (n = 27), or ticagrelor 90 mg bid MD without LD (n = 28). The randomized cohort was exposed to at least 1 dose of study medication and represented the safety population. No bleeding (major or minor) or ischemic complications were observed in the safety population during the overall study time course. One patient treated with ticagrelor experienced chest pain, which did not require any intervention. Dyspnea occurred in 17 (30.9%) and 0 patients randomized to ticagrelor and prasugrel, respectively (p < 0.001). In most patients, dyspnea was mild in intensity and resolved within 24 to 48 h. Overall, 3 patients were withdrawn from the study: 2 in the ticagrelor 180 mg LD group (angioedema, n = 1; medication noncompliance, n = 1) and 1 in the ticagrelor 90 mg bid MD without LD group (dyspnea, n = 1). Thus, a total of 79 patients (prasugrel, n = 27; ticagrelor with LD, n = 25; ticagrelor without LD, n = 27) completed the study and met criteria to be included in the primary population. Patient disposition is summarized in Figure 2. Demographics and baseline characteristics of the primary population are summarized in Table 1; there were no significant differences among the 3 treatment groups.

PHARMACODYNAMIC FINDINGS. At baseline, while on maintenance prasugrel therapy, there were no significant differences among groups in levels of on-treatment platelet reactivity with all assays: PRU...
(p = 0.195), PRI (p = 0.283), and MPA (p = 0.444) (Figures 3A, 3B, and 3C). At 1 week, PRIU levels with ticagrelor (combined groups) compared with prasugrel were within the 45 PRIU noninferiority margin, meeting the pre-specified primary endpoint (LSM difference: -18; 95% CI: -41 to 5; primary endpoint) (Figure 4). Similar results were observed with PRIU (LSM difference: -11; 95% CI: -18 to -4) and MPA (LSM difference: -1; 95% CI: -7 to 4) (Figures 5A and 5B). After switching to ticagrelor, there was a marked decrease in PRIU, PRI, and MPA levels as early as 2 h after drug administration which persisted up to 48 h (Figures 4, 5A, and 5B); a significant reduction in platelet reactivity compared with prasugrel was observed both with and without the use of an LD of ticagrelor (p < 0.001) (Figures 3A, 3B, and 3C). In patients switched to ticagrelor there was an increase in platelet reactivity from 48 h to 1 week (p < 0.010 with all assays for the combined ticagrelor group). At 1 week, levels of PRIU were nonsignificantly higher with prasugrel (p = 0.142) (Figure 3A), while the differences in PRIU were statistically significant (p = 0.005) (Figure 3B) compared with ticagrelor groups. At 1 week, similar levels of platelet reactivity were shown with MPA (p = 0.568) (Figure 3C). There were no differences between the ticagrelor 180 mg LD group and ticagrelor 90 mg bid MD without LD group at any time point (p > 0.1 for all time points).

HPR rates varied according to the assay used (Table 2). In particular, at baseline, HPR rates reflecting trough levels of platelet reactivity induced by maintenance prasugrel therapy were 1.3%, 26.6%, and 6.3% as assessed by PRIU, PRI, and MPA. After randomization, there were no patients with HPR as defined by PRIU at all study time points with the exception of 2 patients at 1 week, who both received ticagrelor. Rates of HPR as assessed by PRIU were overall higher; following randomization, HPR rates decreased with both prasugrel and ticagrelor, although these were more markedly reduced with ticagrelor, leading to significant differences between groups at 4, 24, and 48 h, but not at 1 week. HPR rates assessed by MPA were similar to those defined by PRIU.

**DISCUSSION**

The SWAP-3 study is the first prospective, randomized study to assess the PD effects of switching from prasugrel to ticagrelor. In particular, we demonstrated that transitioning to ticagrelor patients who were on standard of care maintenance treatment with prasugrel, on a background of aspirin, following PCI in the setting of an ACS, was associated with a

**Table 2**

<table>
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<th>Medications</th>
<th>Baseline*</th>
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<th>24 h</th>
<th>48 h</th>
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<td>4 (14.8)</td>
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<td>MPA Baseline*</td>
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<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>3 (11.1)</td>
</tr>
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</table>

*Baseline was measured while on prasugrel maintenance therapy before randomization. High on-treatment platelet reactivity rates at baseline, 24 h, 48 h, and 1 week reflect trough levels of platelet aggregation. p = 0.05, p = 0.015, p = 0.001 (across-grouns comparisons).

<table>
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<th>48 h</th>
<th>1 week</th>
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<td>2 (7.4)</td>
<td>3 (11.5)</td>
</tr>
<tr>
<td>Ticagrelor 90 mg</td>
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<td>0 (0)</td>
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<td>2 (7.4)</td>
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<table>
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<th>PRI Baseline*</th>
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<th>48 h</th>
<th>1 week</th>
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<td>Ticagrelor 180 mg</td>
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*Baseline was measured while on prasugrel maintenance therapy before randomization. High on-treatment platelet reactivity rates at baseline, 24 h, 48 h, and 1 week reflect trough levels of platelet aggregation. p = 0.05, p = 0.015, p = 0.001 (across-grouns comparisons).
reduction in levels of platelet reactivity. These PD findings were observed as early as 2 h after switching therapy, without any signs of drug interactions during the entire study time course. Accordingly, there was no increase in HPR rates, which were overall very low throughout the study time course. In particular, switching from prasugrel to ticagrelor significantly decreased HPR rates in the first 48 h, with no patient experiencing HPR. Although HPR rates were higher with PRI compared with PRU and LTA, this is in line with PRI measurements.
with previous investigations (10). Of note, these findings were observed when switching to ticagrelor by means of a standard 90 mg bid MD regimen without any differences in PD assessments when a 180 mg LD was used. Importantly, our PD observations were consistent using 3 assays, which included the VN assay, chosen for the primary endpoint, VASP and LTA, which corroborates the validity of our study conclusions. Similar to other PD investigations, dyspnea occurred in approximately one-third of patients who switched to ticagrelor (11,12); however, this was mostly mild and transient and led to discontinuation of study drug only in 1 patient. Overall, these results provide important PD insights to clinicians who may choose to switch patients from prasugrel to ticagrelor treatment, which can be performed without any concerns for drug interactions by simply transitioning to a standard 90 mg bid dosing regimen, without the need for a LD.

Overall, the availability of 3 oral P2Y₁₂ receptor inhibitors makes switching amongst these therapies common in clinical practice (7). In a recent study, a reduction in platelet reactivity and HPR rates was shown 30 days after switching to ticagrelor patients with HPR while on prasugrel (13). However, to date, the early PD profiles of transitioning patients from prasugrel to ticagrelor, as well as the differential effects of switching with or without a LD, had not been explored. In clinical practice, several reasons may prompt a switch from prasugrel to ticagrelor. These include both patient and physician preference as a result of drug access (e.g., depending on health care system or medical insurance) and ticagrelor’s mortality benefit during the first year after an ACS (6).

The recent demonstration of ischemic benefits, albeit at the expense of increased bleeding, associated with prolonging ticagrelor therapy beyond 1 year post-ACS may also be a reason to switch from prasugrel to ticagrelor (14). Moreover, data from real-world clinical practice show that some patients may be treated with prasugrel, despite having a contraindication, and may be candidates for ticagrelor therapy. These include ACS patients who get pretreated with prasugrel prior to defining coronary anatomy but do not undergo PCI or those who have a prior cerebrovascular event (15,16).

The need to define how to transition from prasugrel to ticagrelor treatment is underscored by prior studies demonstrating drug interactions and inadequate platelet inhibition when switching between different classes of P2Y₁₂ receptor inhibitors (i.e., thienopyridines and nonthienopyridines) (7,8,17,18). The potential clinical implications of an increase in platelet reactivity and HPR rates are noteworthy, as this may expose patients to an increased risk of a thrombotic complication, particularly patients who
recently suffered an ACS or underwent recent stent implantation (4,19). A drug interaction was demonstrated when transitioning from an intravenous P2Y12 receptor inhibitor (i.e., cangrelor) to oral thienopyridines (i.e., clopidogrel and prasugrel)(17,18). Most recently, a drug interaction was suggested when switching from ticagrelor to prasugrel(8). In particular, this latter study prompted the design of this investigation assessing the PD effects of switching from prasugrel to ticagrelor.

The rationale for drug interactions when switching between certain P2Y12 receptor inhibitors is attributed to their different pharmacological properties (1,7). The active metabolites of thienopyridines have a short half-life and bind irreversibly to the ADP-binding site of the P2Y12 receptor, making this nonfunctional for the entire life of the platelet (1,7). Ticagrelor and its major metabolite (AR-C124910XX) have a longer half-life and reversibly bind the P2Y12 receptor at a location distinct from the ADP-binding site; this leads to an inactive state of the receptor through allosteric modulation for the life span of the drug (1,7). In a previous study, when ticagrelor-treated patients were switched to prasugrel, platelet reactivity and HPR rates increased after 24 h and even more so at 48 h (8). In contrast, in the present investigation, there were no signals of a drug interaction when switching from prasugrel to ticagrelor. This may be attributed to...
Switching From Prasugrel to Ticagrelor

WHAT IS KNOWN? Switching among oral P2Y12 receptor antagonists frequently occurs in real-world clinical practice. Switching from ticagrelor to prasugrel is associated with a drug interaction leading to increased platelet reactivity.

WHAT IS NEW? Switching patients from prasugrel to ticagrelor is associated with transiently higher levels of platelet inhibition and no drug interactions. Switching can be performed using a standard 90 mg bid MD dose regimen, without the need for a LD.

WHAT IS NEXT? Prospective clinical studies are needed to define the safety of this strategy on bleeding and thrombotic outcomes.

multiple factors. First, standard MD regimens of prasugrel do not yield complete P2Y12 receptor blockade (20). Therefore, this allows for binding of ticagrelor to unoccupied receptors. This may explain why we observed that platelet reactivity was promptly reduced after transitioning from prasugrel to ticagrelor therapy. The finding that there were no additive platelet inhibitory effects associated with the use of a LD regimen of ticagrelor is indicative that receptor occupancy while on prasugrel therapy, although not complete, is indeed substantial (as reflected by the high levels of platelet inhibition), thus not allowing for further platelet blockade beyond that achieved when switching using just a MD regimen. This is in contrast to investigations on clopidogrel-treated patients, who have modest P2Y12 receptor occupancy, in whom more potent and immediate platelet blockade is achieved when switching to prasugrel with the use of a LD compared with a MD regimen (9). Similar considerations can be made when switching from clopidogrel to ticagrelor, which implies a transition between the same classes of agents (i.e., thienopyridine to a cyclopentyltriazolopyrimidine) used in the present investigation (21). Second, even if binding to the P2Y12 receptor cannot occur at the time of drug administration due to receptor occupancy by another agent, ticagrelor and its major metabolite have a half-life of ~10 to 12 h. Therefore, even in patients who have been on treatment with an irreversible binding agent such as prasugrel, the half-life of ticagrelor and its metabolite allows them to bind with the P2Y12 receptor of newly generated platelets entering systemic circulation. Ultimately, we cannot exclude that the distinct binding site of ticagrelor on the P2Y12 receptor could have a role on our PD observations. It is important to note that after switching to ticagrelor there was an increase in platelet reactivity from 48 h to 1 week, although these values were never higher than those observed with maintenance prasugrel therapy. However, these findings are likely reflective of recovery of residual prasugrel-mediated platelet inhibitory effects (22).

STUDY LIMITATIONS. It may be argued that switching patients from prasugrel to ticagrelor was associated with enhanced platelet inhibition and that low platelet reactivity has been associated with bleeding complications (4,19). However, significant reductions in platelet reactivity were limited to the first 48 h after switching, and we did not observe any major bleeding complications. Nevertheless, our study was not powered to make any safety conclusions. Because of our study design, some residual effect of prasugrel may have still been present up to 7 days (22). Indeed, prolonging the study would have allowed for complete recovery from prasugrel exposure and thus provided information on the comparative PD efficacy between the 2 agents. However, this was not the intent of our study design. In fact, the PD measurements at 7 days were assessed to rule out any drug interaction beyond the first 24 to 48 h and should not be considered to compare the PD efficacy between prasugrel and ticagrelor, which was the objective of other reported investigations (11,23). Ultimately, we studied the PD effect of switching to ticagrelor patients who were on a MD regimen of prasugrel. Thus we cannot extrapolate our findings to patients who had just received a prasugrel LD, although our observations would not suggest that this would be associated with a drug interaction.

CONCLUSIONS

In patients on maintenance treatment with prasugrel, on a background of aspirin, switching to ticagrelor therapy led to transiently higher levels of platelet inhibition. These PD findings were observed in the early hours after switching therapy, without any signs of drug interactions, with similar results irrespective of the use of a LD regimen. Overall, these findings provide important PD insights to clinicians who choose to switch patients from prasugrel to ticagrelor therapy, which can be performed without any concerns about drug interactions by transitioning to a standard 90 mg bid MD dose regimen, without the need for a LD.

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Switching From Prasugrel to Ticagrelor

REFERENCES


KEY WORDS platelet reactivity, prasugrel, switching, ticagrelor

APPENDIX For an expanded Methods section and supplemental figure, please see the online version of this article.