



Pharmacodynamic Effects of Ticagrelor Dosing Regimens in Patients on Maintenance Ticagrelor Therapy

Results From a Prospective, Randomized, Double-Blind Investigation

Jung Rae Cho, MD, Fabiana Rollini, MD, Francesco Franchi, MD, Christopher DeGroat, MD, Mona Bhatti, MD, Elizabeth C. Dunn, RN, Elisabetta Ferrante, PhD, Ana Muniz-Lozano, MD, Siva Suryadevara, MD, Martin M. Zenni, MD, Luis A. Guzman, MD, Theodore A. Bass, MD, Dominick J. Angiolillo, MD, PhD

ABSTRACT

OBJECTIVES The aim of this study was to assess the impact of ticagrelor dosing regimens on pharmacodynamic (PD) profiles in patients on maintenance ticagrelor therapy.

BACKGROUND Many patients on maintenance P2Y₁₂-inhibiting therapies may require coronary revascularization procedures, raising a common clinical question with regard to the dosing regimen of the P2Y₁₂-inhibiting agent to be used. To date, investigations assessing dosing regimens of P2Y₁₂ receptor inhibitors in patients on maintenance therapy have been only assessed with thienopyridines, but not with ticagrelor.

METHODS This was a prospective, randomized, double-blind, placebo-controlled study assessing the PD effects of 2 dosing regimens of ticagrelor in patients on standard aspirin and ticagrelor maintenance therapy. A total of 60 patients were randomized to either 90 mg (maintenance dose [MD] group) or 180 mg (loading dose [LD] group) dose of ticagrelor. PD assessments were conducted at 3 time points (baseline, 1 h and 4 h). PD assessments were defined according to the platelet reactivity index (PRI) (vasodilator-stimulated phosphoprotein phosphorylation assay), P2Y₁₂ reaction unit (VerifyNow P2Y₁₂ assay) and adenosine diphosphate-induced platelet aggregation by light transmittance aggregometry.

RESULTS There were no differences in baseline levels of platelet reactivity with all assays. Intergroup comparisons by means of repeated-measures analysis adjusted for baseline PRI values showed that the LD group had significantly lower PRI levels compared with the MD group during the overall study time course ($p = 0.031$). Consistent findings were found for P2Y₁₂ reaction unit ($p = 0.026$) and light transmittance aggregometry ($p = 0.004$). Intragroup comparisons showed that a more prompt and sustained platelet inhibitory effect was achieved more consistently with an LD regimen compared with a MD regimen.

CONCLUSIONS In patients on maintenance ticagrelor therapy, a 180-mg LD regimen of ticagrelor is associated with more potent and prompt platelet inhibition compared with a 90-mg MD. (Impact of Ticagrelor Re-Load Pharmacodynamic Profiles; [NCT01731041](#)). (J Am Coll Cardiol Intv 2015;8:1075-83) © 2015 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome

ADP = adenosine diphosphate

ANCOVA = analysis of covariance

ANOVA = analysis of variance

DAPT = dual antiplatelet therapy

LD = loading dose

LTA = light transmittance aggregometry

MD = maintenance dose

PCI = percutaneous coronary intervention

PD = pharmacodynamic

PRI = platelet reactivity index

PRU = P2Y₁₂ reaction units

VASP = whole-blood vasodilator-stimulated phosphoprotein

Dual antiplatelet therapy (DAPT) with aspirin and a P2Y₁₂ receptor inhibitor is the recommended therapy for secondary prevention of ischemic events in patients with acute coronary syndrome (ACS) and those patients undergoing percutaneous coronary interventions (PCIs) (1-3). Ticagrelor represents a new class of oral non-thienopyridine P2Y₁₂ receptor inhibitor, called a cyclopentyltriazolo-pyrimidine. Compared with clopidogrel, ticagrelor has reversible binding properties and more prompt and potent pharmacodynamic (PD) effects as well as less variability in interindividual response (4-7). In a large-scale clinical trial of ACS patients, ticagrelor was associated with a significant reduction in ischemic events, including cardiovascular mortality, compared with clopidogrel at 12 months (8). Such benefit was observed irrespective of management strategy (invasive or noninvasive) and occurred without any differences in overall major

bleeding complications, although noncoronary artery bypass graft bleeding events were increased with ticagrelor. Despite such benefit, recurrent atherothrombotic events still occur in ticagrelor-treated patients who may also require PCI (8,9). Moreover, many patients receiving maintenance ticagrelor therapy may need revascularization because of coronary atherosclerotic disease progression or for staged PCI (10,11).

Numerous investigations have been conducted to define the dosing regimen associated with more favorable PD effects in patients on maintenance P2Y₁₂-inhibiting therapy using thienopyridines (12-17). In particular, reloading patients on maintenance clopidogrel therapy is associated with additional platelet inhibition (12-14). This was also demonstrated among prasugrel-treated patients, suggesting that a sizable number of P2Y₁₂ receptors remain uninhibited during maintenance therapy even with a more potent agent (15,16). However, there are substantial differences in the pharmacological properties between ticagrelor and thienopyridines (4-7), and whether PD profiles vary according to the dosing regimen administered in patients on maintenance ticagrelor therapy remains unexplored. Therefore, we conducted a study to assess the PD effects of different ticagrelor dosing regimens in patients on ticagrelor maintenance therapy.

METHODS

STUDY POPULATION AND RESEARCH DESIGN.

This was a prospective, randomized, double-blind,

placebo-controlled PD study conducted in patients on maintenance ticagrelor therapy (NCT01731041). All patients had experienced an ACS and a guideline-based indication to be on DAPT with aspirin and ticagrelor (1-3). Patients were screened at the Division of Cardiology of the University of Florida College of Medicine - Jacksonville. All patients were eligible for the study if they were between 18 and 80 years of age and if they were receiving treatment with low-dose aspirin (<100 mg/day) and ticagrelor (90 mg/bid) for at least 14 days as part of their standard treatment regimen. Exclusion criteria included history of intracranial bleeding, severe hepatic impairment (hepatic enzymes >2.5 times the upper limit of normal), active bleeding or propensity to bleed, recent (<14 days) antiplatelet treatment with a glycoprotein IIb/IIIa antagonist, platelet count <80 × 10⁶/ml, hemodynamic instability, glomerular filtration rate <30 ml/min, on treatment with any oral anticoagulant, patients with sick sinus syndrome or second- or third-degree atrioventricular block without pacemaker protection, drugs interfering with CYP3A4 metabolism (ketoconazole, itraconazole, voriconazole, clarithromycin, nefazodone, ritonavir, saquinavir, nelfinavir, indinavir, atazanavir, and telithromizycin), hemoglobin <10 g/dl, and pregnant and lactating females.

Using a computer-based randomization system, patients were randomized in a 1:1 fashion to 1 of 2 treatment groups: 1) 90-mg dose of ticagrelor (maintenance dose [MD] group); 2) 180 mg of ticagrelor (loading dose [LD] group). Patients randomized to the MD group received 1 ticagrelor 90-mg tablet and 1 matching placebo tablet. Patients randomized to the LD group received 2 ticagrelor 90 mg tablets. Ticagrelor 90-mg tablets and matching placebo were provided by AstraZeneca (Wilmington, Delaware). Investigators, laboratory personnel, and patients were blinded to treatment assignments. PD assessments were performed at 3 time points using 3 different assays as described in the following. After completing the study, patients resumed their standard ticagrelor 90 mg twice-daily dosing regimen at their scheduled times. Adverse events, including bleeding, bradyarrhythmias, and dyspnea, were recorded (8). Patients received a follow-up phone call the following day to confirm that no adverse events had occurred.

BLOOD SAMPLING AND PLATELET FUNCTION ASSAYS.

Blood samples were collected at 3 time points at baseline (while on maintenance ticagrelor therapy) and at 1 h and 4 h after randomized treatment. Baseline blood samples were collected 12 ± 2 h after

the last MD of ticagrelor to assess trough levels of platelet reactivity (18). At each time point, PD assessments were conducted using 3 different platelet function assays: whole-blood vasodilator-stimulated phosphoprotein (VASP), VerifyNow system (VN-P2Y12), and light transmittance aggregometry (LTA) (7,15,18). In brief, VASP phosphorylation was measured by quantitative flow cytometry using commercially available labeled monoclonal antibodies according to standard protocols (Biocytex Inc., Marseille, France) and quantified by the platelet reactivity index (PRI). The VN-P2Y12 assay (Accriva, San Diego, California) measures platelet-induced aggregation as an increase in light transmittance and reports results in P2Y₁₂ reaction units (PRUs). LTA was conducted using platelet-rich plasma by the turbidimetric method in a 2-channel aggregometer (Chrono-Log 490 Model, Chrono-Log Corp., Havertown, Pennsylvania) after 20 μ M adenosine diphosphate (ADP) stimuli and the percentage of aggregation recorded at 6 min.

SAMPLE SIZE CALCULATION AND STUDY ENDPOINTS.

The primary endpoint of the study was the comparison in the PRI determined by VASP between baseline and 4 h after dosing in each arm of treatment. Assuming an absolute 10% difference in VASP-PRI between baseline and 4 h with a common SD of 14%, 28 patients need to be enrolled in each arm to obtain a 95% power and a 2-sided alpha of 0.05. Considering a possible dropout rate of ~5% to 10%, we estimated that a total of 60 patients needed to be randomized to ensure that complete data would be available for analysis. A cutoff of 10% absolute change in PRI was chosen because this has been associated with a 44% relative reduction of thrombotic events in patients undergoing PCI (19). Additional analysis assessing intergroup and intragroup PD differences using the VN-P2Y12 and LTA were also conducted.

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 \pm SD or median (interquartile range) where appropriate, and categorical variables are expressed as frequencies and percentages. The Student *t* test or Mann-Whitney *U* test was used to compare continuous variables where appropriate. The chi-square or Fisher exact test (if expected value in any cell was <5) were used to compare categorical variables between the 2 groups. The comparison of platelet reactivity at baseline was performed with a univariate analysis of variance with a general linear model. An analysis of

covariance (ANCOVA) method with a general linear model, using the baseline value of platelet reactivity as a covariate, was used to evaluate all other between-group comparisons. A mixed between-within subjects ANCOVA was conducted with a general linear model to assess the impact of the 2 different treatments on platelet reactivity across time points using baseline platelet reactivity levels as covariate. A repeated-measures analysis of variance (ANOVA) model was used to evaluate intragroup comparisons. A 2-tailed *p* value <0.05 was considered to indicate a statistically significant difference for all the analyses performed. Results are reported as least-square mean \pm SE for these detailed analyses. Statistical analysis was performed using SPSS version 22.0 software (SPSS Inc., Chicago, Illinois).

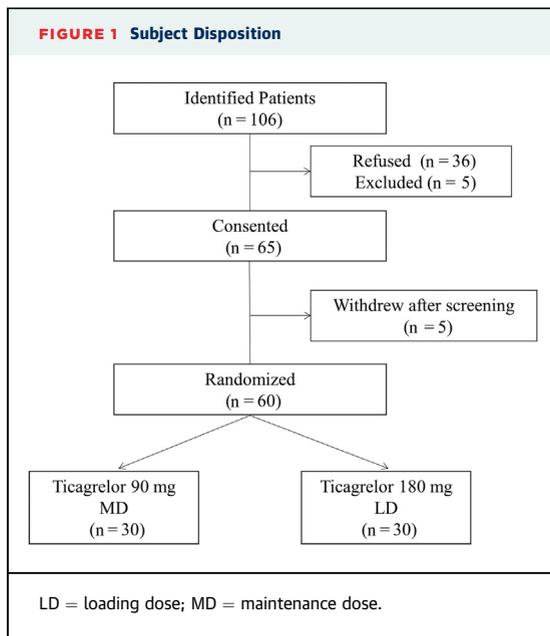
RESULTS

PATIENT POPULATION. Between January 2013 and April 2014, a total of 106 patients with a previous ACS on maintenance ticagrelor therapy were identified. Of these, 65 patients provided written consent to participate in the study; 5 patients withdrew after screening. Therefore, a total of 60 patients on maintenance ticagrelor 90 mg bid therapy were included. These patients were randomized to either a 90 mg (*n* = 30; MD group) or 180 mg (*n* = 30; LD group) dose of ticagrelor. Patient disposition is summarized in Figure 1. Baseline characteristics of the study population are summarized in Table 1. There were no differences in baseline characteristics between groups. No adverse events were reported.

PHARMACODYNAMIC FINDINGS.

Whole-Blood Vasodilator-Stimulated Phosphoprotein-Platelet Reactivity Index. There were no significant differences between groups in baseline platelet reactivity as assessed by VASP-PRI (*p* = 0.350). Repeated-measures analysis adjusted for baseline PRI values showed that the LD group had significantly lower PRI levels compared with the MD group (ANCOVA, *p* = 0.031) (Online Figure 1). PRI levels at 1 h were not significantly different between groups (*p* = 0.117), whereas the PRI levels at 4 h were significantly lower in the LD group compared with the MD group (*p* = 0.012) (Online Figure 1).

Intragroup comparisons in the MD group showed a nonsignificant reduction in PRI over time (ANOVA, *p* = 0.206) (Figure 2A); there were no intragroup differences between time points (baseline vs 1 h, *p* = 0.931; baseline vs. 4 h, *p* = 0.318; 1 h vs. 4 h,



$p > 0.999$) (Figure 2A). Intragroup comparisons in the LD group showed a significant decrease in PRI levels over time (ANOVA, $p < 0.001$) (Figure 2B). PRI values at 1 h ($p = 0.011$) and 4 h ($p = 0.001$) were markedly reduced compared with PRI levels at baseline, whereas there were no significant differences between 1 and 4 h ($p = 0.666$) (Figure 2B).

VerifyNow P2Y₁₂ assay. P2Y₁₂ reaction units. There were no significant differences in baseline PRU between groups ($p = 0.448$). In the intergroup comparison adjusted for baseline value, PRU values were significantly reduced in the LD group compared with the MD group during the overall time course (ANCOVA, $p = 0.026$) (Online Figure 2). At 1 h, PRU levels were nonsignificantly lower in the LD group compared with the MD group ($p = 0.128$), but were significantly reduced at 4 h ($p = 0.006$) (Online Figure 2).

Intragroup comparison in the MD group showed that PRU levels significantly decreased over time (ANOVA, $p = 0.019$) (Figure 3A). PRU values were significantly reduced compared with baseline only at 4 h ($p = 0.033$), but not at 1 h ($p = 0.113$) (Figure 3A). Intragroup comparisons in the LD group showed that PRU levels significantly decreased over time (ANOVA, $p < 0.001$) (Figure 3B), with a significant decrease already at 1 h ($p = 0.001$), which was sustained at 4 h ($p < 0.001$), without significant changes between 1 and 4 h ($p = 0.317$) (Figure 3B).

Light transmittance aggregometry. There were no significant differences in baseline ADP-induced platelet aggregation between groups ($p = 0.213$). The adjusted

TABLE 1 Baseline Characteristics

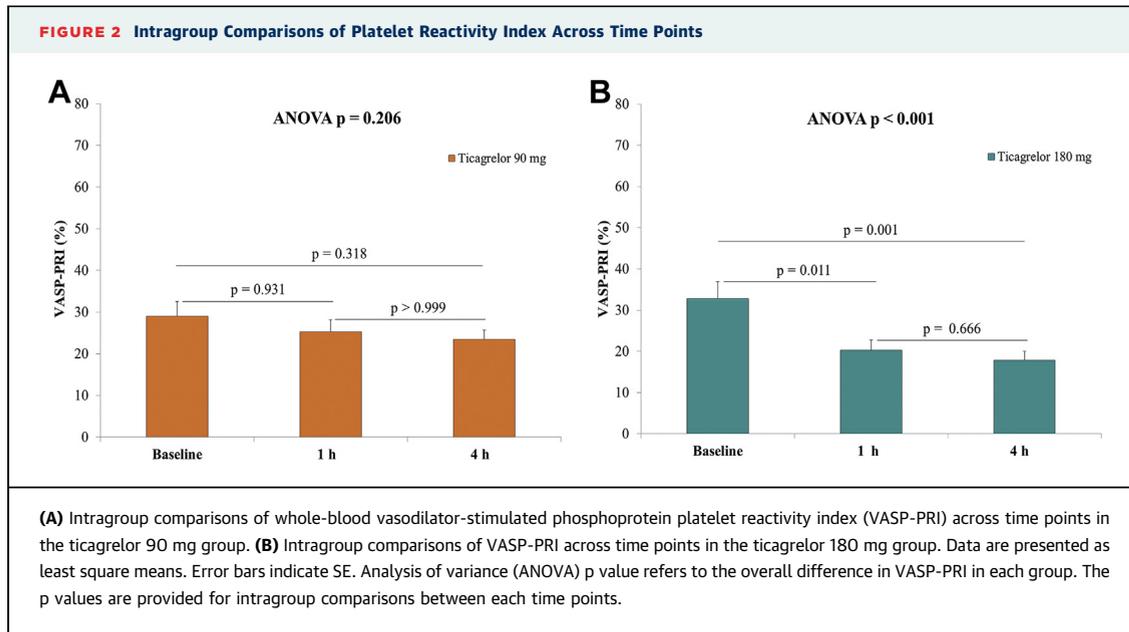
	Ticagrelor 90 mg (n = 30)	Ticagrelor 180 mg (n = 30)	p Value
Age, yrs	57.97 ± 7.92	55.80 ± 7.41	0.277
Male	22 (73.3)	22 (73.3)	>0.999
BMI, kg/m ²	29.33 ± 4.02	29.02 ± 5.50	0.803
Race			0.599
Caucasian	20 (66.7)	21 (70)	
African American	9 (30)	9 (30)	
Hispanic	1 (3.3)	0	
Hypertension	26 (86.7)	28 (93.3)	0.671
Dyslipidemia	26 (86.7)	29 (96.7)	0.353
Smoking	6 (20)	6 (20)	>0.999
Diabetes mellitus	8 (26.7)	5 (16.7)	0.532
Medications*			
Beta-blocker	28 (93.3)	27 (90.0)	>0.999
ACEI/ARB	21 (70)	24 (80)	0.552
Statins	30 (100)	30 (100)	>0.999
PPI	6 (20)	3 (10)	0.472
CCB	2 (6.7)	2 (6.7)	>0.999
Nitrate	8 (26.7)	8 (26.7)	>0.999
LVEF, %	56 ± 12	55 ± 12	0.571
Creatinine clearance, ml/min	110 ± 27	108.3 ± 29	0.742
Hematocrit	38.7 ± 3.7	39 ± 4.3	0.823
Platelet count, 1,000/mm ³	249.2 ± 104	233.9 ± 69.2	0.505
PCI†	27 (90)	28 (93)	>0.999
Maintenance therapy duration, days‡	20.5 (17.0-25.2)	26.5 (18.7-33.7)	0.053

Values are mean ± SD, n (%), or median (interquartile range). *All patients on aspirin 81 mg/day and ticagrelor 90 mg twice daily. †Most (91.7%) patients treated with PCI at time of acute coronary syndrome presentation; 8.3% of patients medically managed after undergoing invasive evaluation. ‡Time frame between first ticagrelor dose after the acute event and first study blood draw.

ACEI/ARB = angiotensin-converting enzyme inhibitors/angiotensin receptor blocker; BMI = body mass index; CCB = calcium channel blocker; LVEF = left ventricular ejection fraction; PCI = percutaneous coronary intervention; PPI = proton pump inhibitor.

intergroup comparison showed a significant reduction of ADP-induced platelet aggregation in the LD group compared with the MD group during the overall time course (ANCOVA, $p = 0.004$) (Online Figure 3). Intergroup comparisons showed a nonsignificant reduction in ADP-induced platelet aggregation in the LD group compared with the MD group at 1 h ($p = 0.155$), which reached statistical significance at 4 h ($p < 0.001$) (Online Figure 3).

Intragroup comparison in the MD group showed that ADP-induced platelet aggregation significantly decreased over time (ANOVA, $p < 0.001$) (Figure 4A). ADP-induced platelet aggregation was significantly reduced compared with baseline at 1 h ($p < 0.001$) and 4 h ($p = 0.001$) (Figure 4A). Intragroup comparisons in the LD group showed that ADP-induced platelet aggregation significantly decreased over



time (ANOVA, $p < 0.001$) (Figure 4B), with a significant decrease at 1 h ($p = 0.011$) which was sustained at 4 h ($p = 0.001$) (Figure 4B).

DISCUSSION

The need for coronary revascularization despite being compliant with P2Y₁₂-inhibiting therapy may occur for a variety of reasons, including treatment failure

with the occurrence of an acute ischemic event, the need for a staged PCI, or progression of coronary atherosclerotic disease (9-11). This therefore raises a clinical question with regard to the dosing regimen of a P2Y₁₂-inhibiting agent to be used in a patient on maintenance DAPT therapy. To date, investigations assessing dosing regimens of P2Y₁₂ receptor inhibitors in patients on maintenance therapy have been limited to thienopyridines but not the nonthienopyridine

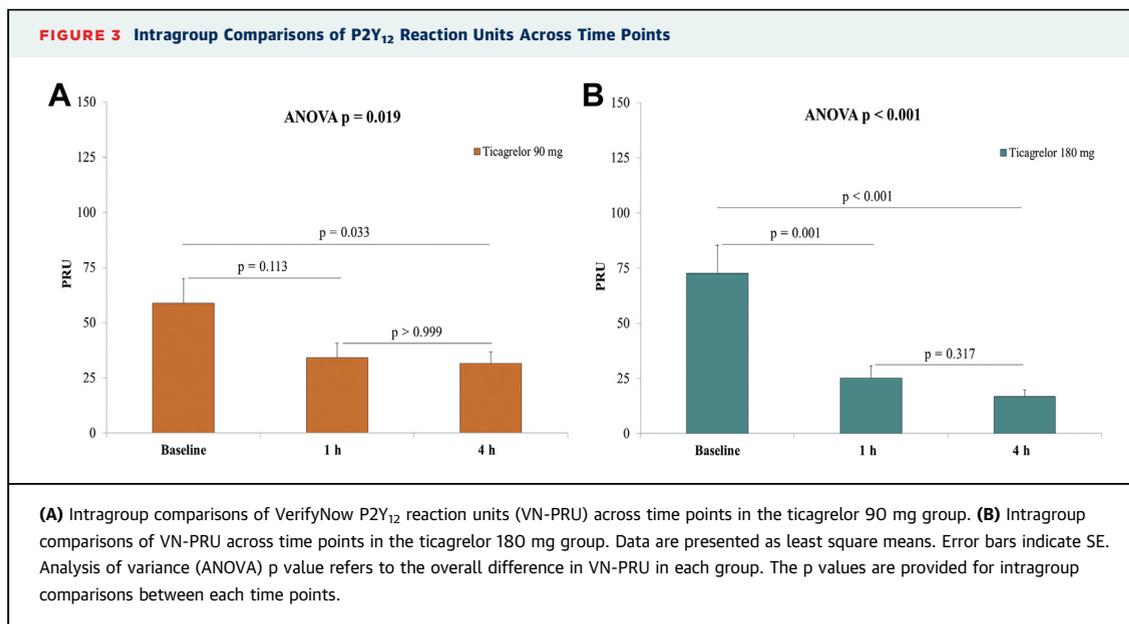
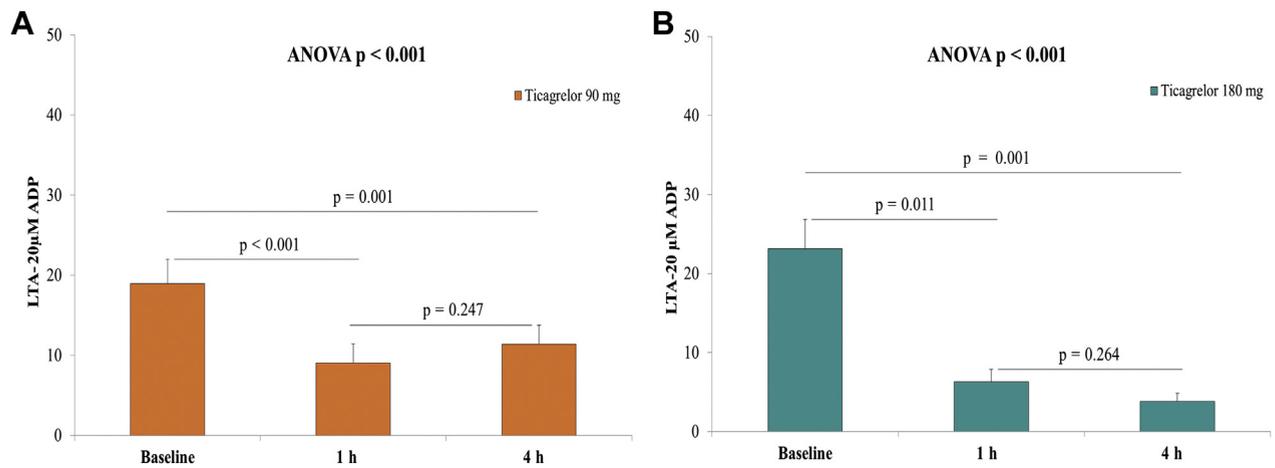


FIGURE 4 Intragroup Comparisons of ADP-Induced Platelet Aggregation Across Time Points

(A) Intragroup comparisons of ADP 20 μ M-induced platelet aggregation measured by light transmission aggregometry (LTA) across time points in the ticagrelor 90 mg group. (B) Intragroup comparisons of ADP 20 μ M-induced platelet aggregation measured by LTA across time points in the ticagrelor 180 mg group. Data are presented as least square means. Error bars indicate SE. Analysis of variance (ANOVA) p value refers to the overall difference in platelet aggregation in each group. The p values are provided for intragroup comparisons between each time points.

ticagrelor (12-17). We therefore conducted a study to address the impact of 2 different ticagrelor dosing regimens in patients on a standard 90-mg bid maintenance therapy. Our PD investigation showed that compared with a 90-mg dose, a 180-mg reloading dose of ticagrelor is associated with enhanced platelet inhibition in patients on maintenance therapy. Furthermore, enhanced platelet inhibitory effects were achieved promptly with this regimen. Importantly, consistent findings were observed using 3 different PD assays.

Currently, practice guidelines provide limited recommendations with regard to the management of patients already on maintenance P2Y₁₂ receptor-inhibiting therapy undergoing PCI or presenting with an ACS (1-3). Various studies have been conducted to assess the impact of different dosing regimens of P2Y₁₂ receptor inhibitors, either reloading with the same agent or switching therapy, in patients on maintenance therapy (20). A \geq 600-mg LD of clopidogrel has been shown to reduce residual platelet reactivity in patients on long-term clopidogrel therapy, as well as decrease peri-PCI ischemic complications, particularly in ACS patients (12-14). The fact that clopidogrel therapy is associated with only modest P2Y₁₂ receptor occupancy explains why switching to either prasugrel or ticagrelor leads to further platelet blockade (21-26). Importantly, although randomized studies specifically designed to

assess the clinical impact of switching from clopidogrel to a novel P2Y₁₂ receptor inhibitor are lacking, nearly one-half the patients randomized to ticagrelor in the landmark PLATO (Study of Platelet Inhibition and Patient Outcomes) trial were pre-treated with clopidogrel, showing consistent findings with the overall trial results (27). Moreover, many registries have supported the efficacy and safety of switching from clopidogrel to prasugrel (28-31).

The PD impact of administering escalating prasugrel dosing regimens in patients on standard maintenance therapy has been recently reported, demonstrating that a 60-mg LD of prasugrel induces more prompt and potent reduction in platelet reactivity, with better response profiles, compared with lower dosing regimens (15,16). These study findings also suggest that maintenance therapy with a potent P2Y₁₂-inhibiting agent such as prasugrel still leaves a considerable number of P2Y₁₂ receptors uninhibited. This is in line with in vitro and ex vivo PD investigations using cangrelor in which residual P2Y₁₂-mediated signaling in patients on maintenance prasugrel therapy is virtually abolished (32,33). However, ticagrelor has several pharmacological differences compared with thienopyridines. In particular, ticagrelor is direct acting with reversible binding and has a plasma half-life of 6 to 13 h requiring twice-daily administration to maintain steady-state levels of platelet inhibition (4-7). In contrast to the

thienopyridines, which require LD regimens that are several fold higher than their MD (e.g., 4- to 8-fold higher for clopidogrel and 6-fold higher for prasugrel), the LD of ticagrelor is the same as the total daily MD. Therefore, although the enhanced PD differences observed with LD regimens of thienopyridines may be intuitive, this is less obvious for ticagrelor and provides further support for the rationale of our investigation.

CLINICAL IMPLICATIONS. Although our study was not designed to assess clinical outcomes, there are potential clinical implications of this investigation. In fact, achieving enhanced platelet inhibition in the peri-PCI period reduces ischemic events, in particular when optimizing blockade of the P2Y₁₂ receptor signaling pathway (34,35). This is supported by large-scale clinical trial data showing a significant reduction in myocardial infarction and stent thrombosis in the peri- and post-PCI period associated with the potent P2Y₁₂ receptor inhibitor cangrelor (36-38). Our study findings clearly demonstrate more prompt and potent P2Y₁₂ inhibition when a 180-mg reloading dose of ticagrelor is administered to patients on maintenance therapy. In turn, this also indicates that uninhibited P2Y₁₂ receptors persist on the platelet membrane of patients while on maintenance therapy. This observation is also supported by ex vivo PD investigations conducted in ticagrelor-treated patients in which residual P2Y₁₂-mediated signaling is markedly reduced by cangrelor (39). Importantly, uninhibited P2Y₁₂ receptors may represent a pathway for circulating ADP, released during an acute ischemic event or during a revascularization procedure, to activate platelets and lead to a periprocedural ischemic complication. Therefore, administration of a 180-mg LD of ticagrelor may be a more optimal strategy than using a 90-mg dose in patients on maintenance therapy requiring PCI or presenting with an acute coronary event. It may be argued that in another study, there were no PD differences between a 90-mg and a 180-mg dose in clopidogrel-treated patients (40). However, this study was conducted in patients with optimal response to clopidogrel, which may have limited the ability to see a treatment effect and was in contrast with a more detailed PD investigation that demonstrated enhanced platelet inhibitory effects of a 180-mg LD irrespective of clopidogrel responsiveness (25).

STUDY LIMITATIONS. This investigation was powered to assess intragroup comparisons but not intergroup comparisons. Therefore, the latter results

should be considered as exploratory. In addition, our study was conducted in patients who were clinically stable after experiencing an ACS and not in patients undergoing PCI who may therefore share different PD profiles. Moreover, our study was not powered to assess safety or efficacy, which would require larger clinical studies. Hence, the lack of adverse events, including bleeding complications (e.g., arterial access site complications), in this study should be interpreted with caution.

CONCLUSIONS

In patients on maintenance ticagrelor therapy, a 180-mg LD of ticagrelor is associated with more prompt and potent PD effects compared with a 90-mg dosing regimen. Although the clinical implications of our PD study findings remain to be demonstrated, achieving enhanced P2Y₁₂ receptor blockade in the peri-PCI period is well established to reduce ischemic events, suggesting the use of a 180-mg reloading dose of ticagrelor in patients on maintenance therapy when undergoing PCI. Clinical outcomes studies are warranted to support these PD findings.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Dominick J. Angiolillo, University of Florida College of Medicine-Jacksonville, 655 West 8th Street, Jacksonville, Florida 32209. E-mail: dominick.angiolillo@jax.ufl.edu.

PERSPECTIVES

WHAT IS KNOWN? Ticagrelor is a new-generation P2Y₁₂ receptor inhibitor associated with better clinical outcomes compared with clopidogrel. However, many patients on maintenance P2Y₁₂-inhibiting therapies, including ticagrelor, may need to undergo coronary revascularization procedures, raising a common clinical question with regard to the dosing regimen to be used.

WHAT IS NEW? Our study findings demonstrate that in patients on standard maintenance ticagrelor therapy, a 180-mg reloading dose achieves more prompt and potent P2Y₁₂ inhibition compared with a 90-mg dosing regimen as assessed by multiple pharmacodynamic assessments.

WHAT IS NEXT? Because enhanced platelet inhibition in the periprocedure period reduces ischemic events, larger studies are needed to support the clinical impact of these pharmacodynamic findings.

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APPENDIX For supplemental figures, please see the online version of this article.