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Response to Ticagrelor in Clopidogrel Nonresponders and Responders and Effect of Switching Therapies

The RESPOND Study

Paul A. Gurbel, MD; Kevin P. Bliden, BS; Kathleen Butler, MD; Mark J. Antonino, BS; Cheryl Wei, PhD; Renli Teng, PhD; Lars Rasmussen, MD; Robert F. Storey, MD; Tonny Nielsen, MD; John W. Eikelboom, MBBS; Georges Sabe-Affaki, MD; Steen Husted, MD; Dean J. Kereiakes, MD; David Henderson, MD; Dharmendra V. Patel, MD; Udaya S. Tantry, PhD

Background—The antiplatelet effects of the Platelet Inhibition and Patient Outcomes (PLATO) trial dose of ticagrelor in patients nonresponsive to clopidogrel and after they switch agents are unknown.

Methods and Results—Patients with stable coronary artery disease on aspirin therapy received a 300-mg clopidogrel load; nonresponders were identified by light transmittance aggregometry. In a 2-way crossover design, nonresponders (n=41) and responders (n=57) randomly received clopidogrel (600 mg/75 mg once daily) or ticagrelor (180 mg/90 mg twice daily) for 14 days during period 1. In period 2, all nonresponders switched treatment; half of the responders continued the same treatment, whereas the others switched treatment. Inhibition of platelet aggregation was higher in nonresponders treated with ticagrelor compared with clopidogrel ($P<0.05$). Treatment with ticagrelor among nonresponders resulted in a $>10\%$, $>30\%$, and $>50\%$ decrease in platelet aggregation from baseline in 100%, 75%, and 13% of patients, respectively. Platelet aggregation fell from $59\pm 9\%$ to $35\pm 11\%$ in patients switched from clopidogrel to ticagrelor and increased from $36\pm 14\%$ to $56\pm 9\%$ in patients switched from ticagrelor to clopidogrel ($P<0.0001$ for both). Platelet reactivity was below the cut points previously associated with ischemic risk measured by light transmittance aggregometry, VerifyNow P2Y₁₂ assay, and vasodilator-stimulated phosphoprotein phosphorylation in 98% to 100% of patients after ticagrelor therapy versus 44% to 76% of patients after clopidogrel therapy.

Conclusions—Ticagrelor therapy overcomes nonresponsiveness to clopidogrel, and its antiplatelet effect is the same in responders and nonresponders. Nearly all clopidogrel nonresponders and responders treated with ticagrelor will have platelet reactivity below the cut points associated with ischemic risk.

Clinical Trial Registration—<http://www.clinicaltrials.gov>. Unique Identifier: NCT00642811.

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Key Words: antiplatelet agents ■ clopidogrel ■ platelet aggregation inhibitors ■ ticagrelor

Inhibition of P2Y₁₂ receptors by thienopyridines combined with aspirin therapy improved the outcome of patients with acute coronary syndromes and patients treated with stents compared with aspirin monotherapy.¹⁻³ However, the antiplatelet effect of the most widely used thienopyridine, clopidogrel, is irreversible and variable.⁴ Patients treated with percutaneous coronary intervention who have high platelet reactivity (HPR) during clopidogrel and aspirin therapy or who are nonresponsive to clopidogrel have higher rates of ischemic events than responders.⁵⁻⁷ The latter observations are the rationale for new P2Y₁₂ receptor inhibitors.

Editorial see p 1169
Clinical Perspective on p 1199

Ticagrelor (formerly AZD6140), an oral, direct-acting, reversible, P2Y₁₂ receptor antagonist, was associated with less ischemic event occurrence than clopidogrel in patients with acute coronary syndromes in the Platelet Inhibition and Patient Outcomes (PLATO) trial. This beneficial effect may be related to more uniform and greater platelet inhibition.⁸ However, the antiplatelet effect of ticagrelor in patients who are nonresponsive to clopidogrel is unknown. In addition, the

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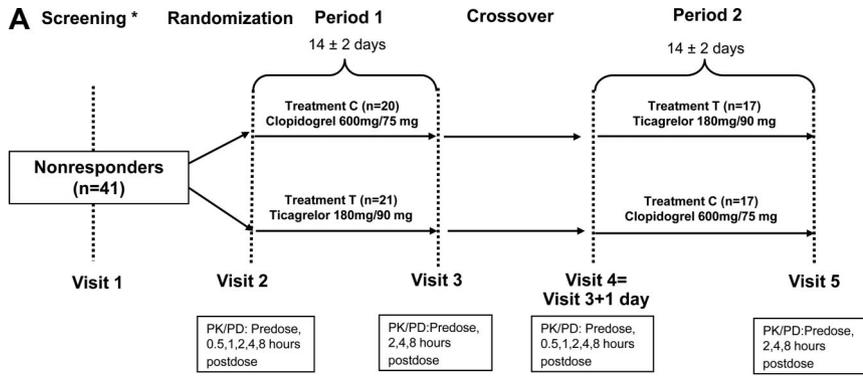
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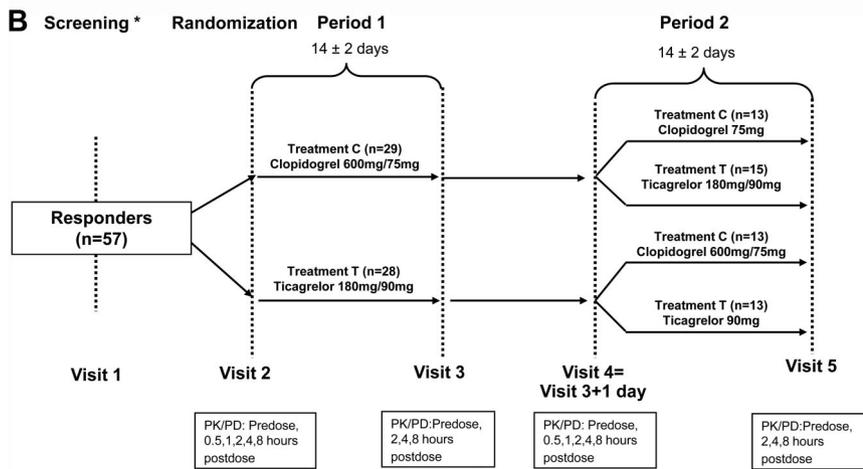
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*patients were dosed with study drug >14 days after screening



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Figure 1. Study flow diagram demonstrating treatment in A, nonresponders and B, responders. PK/PD indicates pharmacokinetic/pharmacodynamic.

antiplatelet effect of switching from ticagrelor to clopidogrel therapy and vice versa is also unknown. Therefore, the aim of the present study was 2-fold: (1) to investigate the antiplatelet effect of ticagrelor dosed according to the PLATO trial in clopidogrel nonresponders and (2) to study platelet function during switching from clopidogrel to ticagrelor therapy and vice versa.

Methods

This study was a randomized, double-blind, double-dummy crossover investigation comparing the antiplatelet effects of ticagrelor with clopidogrel in patients with stable coronary artery disease identified as nonresponders or responders to a prior dose of clopidogrel. There were 10 study sites in North America and Europe. The methods and equipment were standardized across participating centers. The investigational review boards approved the study, and patients provided written informed consent.

Patients

Patients aged ≥18 years with documented stable coronary artery disease who were on aspirin therapy (75 to 100 mg once daily) were enrolled. Exclusion criteria were as follows: a history of acute coronary syndrome within 12 months of screening, a history of bleeding diathesis or severe pulmonary disease, pregnancy, current smoking (>1 pack per day), concomitant therapy with moderate or strong cytochrome P450 3A inhibitors or strong cytochrome P450 3A inducers within 14 days of the study, concomitant antithrombotic treatment other than aspirin within 14 days of the study, platelet count <100 000 mm³ or hemoglobin <10 g/dL, diabetic patients with hemoglobin A_{1c} ≥10%, history of drug addiction or alcohol

abuse in the past 2 years, nonsteroidal antiinflammatory drug use, and creatinine clearance <30 mL/min.

Definitions

To assess clopidogrel responsiveness, patients received a single 300-mg clopidogrel load. Responsiveness was based on 20 μmol/L ADP-induced platelet aggregation determined before the dose and at 6 to 8 hours after the dose.^{9,10} Patients were defined as nonresponders when the absolute change in platelet aggregation (maximum extent) was ≤10%, whereas patients with an absolute change of >10% were categorized as clopidogrel responders. Response status was confirmed 2 to 4 weeks before the first dose of study drug was received. Inhibition of platelet aggregation (IPA) was defined as follows:

$$\frac{(\text{Predose Aggregation} - \text{Postdose Aggregation})}{\text{Predose Aggregation}} \times 100\%$$

Study Design

The study design is shown in Figure 1A and 1B. Nonresponders and responders were randomly treated with either a 600-mg clopidogrel load followed by 14 ± 2 days of 75-mg daily maintenance therapy or a 180-mg ticagrelor load followed by 14 ± 2 days of 90-mg twice daily maintenance therapy (period 1). The last dose of study drug in period 1 was administered in the morning. All treatments were administered in a double-blind, double-dummy design, with matching placebo ticagrelor tablets and clopidogrel capsules administered (ie, all patients received both tablets and capsules daily). Randomization schedules for responder and nonresponder treatment regimens were independently generated in blocks (Global Randomization System, AstraZeneca).

In period 2, all nonresponders switched treatment, whereas half of the responders continued the same treatment, and the other half of the responders switched to the other treatment. Patients received treatments again for 14 ± 2 days. Patients who switched drugs received the other drug (patients treated with ticagrelor in period 1 received a 600-mg clopidogrel load followed by 75-mg daily maintenance therapy; patients treated with clopidogrel in period 1 received a 180-mg ticagrelor load followed by 90-mg twice daily maintenance therapy). Patients continuing on the same treatments in both study periods did not receive loading doses of study drug during period 2. In addition to study drug, all patients received concomitant aspirin therapy (75 to 100 mg once daily).

Blood Sampling

Blood samples were collected from the antecubital vein into 3 Vacutainer tubes (Becton-Dickinson, Franklin Lakes, NJ) containing 3.2% trisodium citrate for light transmittance aggregometry and flow cytometry measurements (Figure 1A and 1B). In addition, blood was collected in 1 tube containing 3.2% sodium citrate (Greiner Bio-One Vacuette, North America, Inc, Monroe, NC) for VerifyNow measurements. After the first 3 mL of free-flowing blood was discarded, the tubes were filled to capacity and gently inverted 3 to 5 times to ensure complete mixing of the anticoagulant.

Platelet Function Measurements

Light Transmittance Aggregometry

Platelet aggregation (5 and 20 $\mu\text{mol/L}$ ADP and 2 $\mu\text{g/mL}$ collagen) in platelet-rich plasma was assessed with the use of a Chronolog Optical Aggregometer (model 490–4D) as described previously.⁹ Maximum aggregation was determined and expressed as the maximum percent change in light transmittance from baseline, with platelet-poor plasma used as a reference.

VerifyNow P2Y₁₂ Assay

The VerifyNow P2Y₁₂ assay, a turbidimetric-based optical detection system, was used according to the manufacturer's instructions. An optical signal, reported as P2Y₁₂ reaction units (PRU), was recorded.¹¹

Vasodilator-Stimulated Phosphoprotein Phosphorylation

Vasodilator-stimulated phosphoprotein (VASP) phosphorylation, a measure of P2Y₁₂ receptor reactivity, was determined by flow cytometry with the use of the Platelet VASP-FCM kit (Biocytex Inc, Marseille, France) and recorded as the platelet reactivity index (PRI), as described previously.¹²

Glycoprotein IIb/IIIa and P-Selectin Expression

Nonstimulated and ADP-stimulated expression levels of glycoprotein IIb/IIIa and P-selectin were determined by whole blood flow cytometry with a multicolor analysis method as described previously.⁹ The differences in mean fluorescence intensity and percent positive cells between stimulated and nonstimulated cells were determined for activated glycoprotein IIb/IIIa and P-selectin expression, respectively.

Primary Analysis

The primary outcome variable was the estimation of the proportion of clopidogrel nonresponders who responded to ticagrelor after steady state dosing based on the platelet aggregation measurements taken 4 hours after the last dose. A patient was defined as a responder by the same definition used at screening. The proportion of patients who responded (P_{resp}) was determined by the following equation:

$$P_{\text{resp}} = 100\% \times (N_{\text{resp}}/N_{\text{total}})$$

where N_{resp} was the number of patients whose platelet aggregation (20 $\mu\text{mol/L}$ ADP, maximum extent) was $>10\%$, and N_{total} was the total number of dosed patients.

Table 1. Patient Demographics, Medical History, Concomitant Medications, and Baseline Laboratory Data

	Total Group (n=98)	Nonresponders (n=41)	Responders (n=57)	P
Demographics				
Age, y	65 \pm 8	66 \pm 7	64 \pm 9	0.24
Male, n (%)	76 (78)	28 (68)	48 (84)	0.07
BMI, kg/m ²	31 \pm 7	30 \pm 10	29 \pm 5	0.60
Ethnicity, n (%)				
White	87 (89)	38 (93)	49 (86)	0.30
Black	8 (8)	3 (7)	5 (9)	0.79
Other	3 (3)	0 (0)	3 (5)	0.14
Medical history, n (%)				
Smoking (current)	17 (17)	2 (5)	15 (26)	0.007
Family history of CAD	61 (62)	24 (59)	37 (65)	0.52
Hypertension	79 (81)	33 (81)	46 (81)	0.98
Hyperlipidemia	92 (94)	38 (93)	54 (95)	0.69
Diabetes mellitus	25 (26)	9 (22)	16 (28)	0.50
HbA _{1c} >6.0%	20 (21)	6 (15)	14 (25)	0.23
HbA _{1c} \leq 6.0%	2 (2)	1 (2)	1 (2)	0.84
Prior MI	56 (57)	22 (54)	34 (60)	0.57
Prior CABG	36 (37)	18 (44)	18 (32)	0.22
Prior PCI	47 (48)	21 (51)	36 (63)	0.24
Baseline medications n, (%)				
Statins	88 (90)	35 (85)	53 (93)	0.23
ACE inhibitors	20 (20)	10 (24)	10 (18)	0.41
β -Blockers	69 (70)	29 (71)	40 (70)	0.96
Diuretics	34 (35)	15 (37)	19 (33)	0.74
Organic nitrates	15 (15)	8 (20)	7 (12)	0.34
PPI	21 (22)	10 (24)	11 (19)	0.55
Calcium channel blockers	24 (25)	8 (20)	16 (28)	0.34
Baseline laboratory data				
WBC, $\times 1000/\text{mm}^3$	6.9 \pm 2.0	6.8 \pm 1.9	6.9 \pm 2.0	0.81
Platelets, $\times 1000/\text{mm}^3$	221 \pm 58	225 \pm 60	218 \pm 57	0.56
Hematocrit, %	42 \pm 4	42 \pm 4	42 \pm 4	1.0
Creatinine, $\mu\text{mol/L}$	90 \pm 21	93 \pm 26	88 \pm 18	0.27
LDL, mg/dL	97 \pm 35	105 \pm 28	91 \pm 40	0.06
HDL, mg/dL	48 \pm 12	48 \pm 12	48 \pm 12	1.0
Uric acid, $\mu\text{mol/L}$	372 \pm 88	363 \pm 89	378 \pm 87	0.41

BMI indicates body mass index; CAD, coronary artery disease; Hb, hemoglobin; MI, myocardial infarction; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; ACE, angiotensin-converting enzyme; PPI, proton pump inhibitor; WBC, white blood cells; LDL, low-density lipoprotein; and HDL, high-density lipoprotein.

Other Analyses

Other analyses included the following: (1) comparison of IPA, PRU, and PRI during clopidogrel versus ticagrelor therapy in responders and nonresponders measured at the same time points; (2) comparison of the effect of ticagrelor versus clopidogrel therapy on platelet receptor expression, and IPA stimulated by 2 $\mu\text{g/L}$ collagen and 5 $\mu\text{mol/L}$ ADP; (3) comparison of the effect of clopidogrel versus ticagrelor in reducing platelet reactivity below cut points associated with ischemic risk; and (4) comparison of the antiplatelet effects of ticagrelor and clopidogrel in responders versus nonresponders.

Table 2. Proportion of Patients Who Responded to Ticagrelor vs Clopidogrel Based on the Primary Analysis (20 $\mu\text{mol/L}$ ADP, Maximum Extent Platelet Aggregation, Responsiveness at 4 Hours After Last Maintenance Dose) in the Nonresponder Cohort

Platelet Aggregation (20 $\mu\text{mol/L}$ ADP, Maximum Extent)	Ticagrelor		Clopidogrel		Ticagrelor vs Clopidogrel		McNemar Test <i>P</i>
	Patients, %	95% CI	Patients, %	95% CI	Difference, %	95% CI	
Decrease from baseline >10%	100	89–100	75	57–89	25	8–41	0.005
Decrease from baseline >30%	75	57–89	13	4–29	62	42–79	<0.001
Decrease from baseline >50%	13	4–29	0	0–11	13	1–23	0.046

Decrease from baseline=pretreatment aggregation (%) minus posttreatment aggregation (%). CI indicates confidence interval.

Other Assessments

The safety and tolerability of clopidogrel and ticagrelor were assessed. Bleeding events were classified according to PLATO trial definitions.⁸ Compliance was measured at visits 3 and 5 by the number of medication tablets returned by the patient.

Statistical Methods

Sample Size

On the basis of a previous study, we expected that ticagrelor therapy will result in an absolute increase in IPA of 25% compared with clopidogrel therapy.¹³ With the assumption of SD of 12 and an intrapatient correlation of 0.5, a sample size of ≈ 26 patients will be required to achieve at least 95% power to find this difference with an $\alpha=5\%$ on the basis of a 2-sided *t* test.¹⁴ Twenty-six patients will also yield 86% power to detect a difference of 50% in the proportions of subjects responding to antiplatelet therapy with the use of a 2-sided 0.05 level McNemar test if it is assumed that the proportion of discordant pairs is 80%. When the proportion of discordant pairs is 90%, the same difference in proportions can be detected with 80% power. If a potential dropout rate of 20% is considered, the study will enroll 32 patients into the nonresponder cohort of the study and 48 patients into the responder cohort of the study. In the case of the responder cohort, with the same sample size, type I error, testing assumptions, and an assumed variability of 14%, an absolute difference of 19% in 20 $\mu\text{mol/L}$ ADP final extent IPA can be detected with at least 91% power.¹⁴

Primary and Secondary Analyses

An intention-to-treat analysis model was used. The primary analysis was conducted with the McNemar test, and each patient was treated as a matching pair for clopidogrel and ticagrelor treatment. The proportion (with 95% confidence intervals) of patients who re-

sponded to treatment was determined, and the differences between the treatments were recorded. To analyze the pharmacodynamic parameters with repeated assessments, a repeated-measures mixed effect model was applied. The mixed effect model was used to compare the pharmacodynamic assessments between responders and nonresponders for ticagrelor and clopidogrel. The mixed effect model included fixed factors of treatment, cohort, cohort and treatment interaction, center, period, and treatment sequence and a random effect of patient within sequence. Treatment level means were estimated by least squares means and 2-sided 95% confidence intervals. The primary contrast (least squares mean difference between ticagrelor and clopidogrel) was also estimated with the use of least squares means and 2-sided 95% confidence intervals.

The McNemar test was used to assess the potential clinical efficacy of ticagrelor compared with clopidogrel. We used the following previously defined cut points of on-treatment HPR associated with long-term ischemic event occurrence: >59% 20 $\mu\text{mol/L}$ ADP-induced maximal platelet aggregation,⁷ ≥ 235 PRU based on the VerifyNow P2Y₁₂ assay,¹¹ and >50% PRI based on the VASP phosphorylation assay.¹² We determined the frequency of patients with HPR during both treatments on the basis of measurements taken at 4 hours after the last dose. Statistical analysis was performed by QDS, King of Prussia, Pa, with the use of SAS (version 8.2, SAS Institute Inc, Cary, NC). All statistical tests were 2-sided with a statistical significance level of 5% (ie, $\alpha=0.05$).

Results

Patients

Between May 19, 2008, and March 25, 2009, 144 patients satisfying the inclusion and exclusion criteria were screened for clopidogrel responsiveness. Patients were excluded from

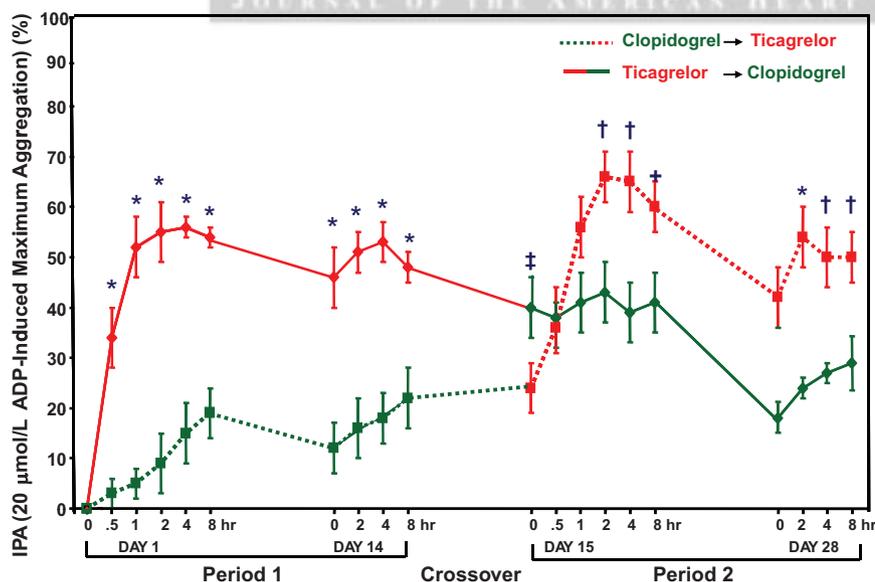


Figure 2. Inhibition of platelet aggregation in response to ADP (20 $\mu\text{mol/L}$, maximum extent) in clopidogrel-nonresponsive patients. * $P<0.0001$, † $P<0.001$, ‡ $P<0.05$.

randomization after screening when a sufficient number of responders and nonresponders were identified on the basis of sample size calculation. Two patients voluntarily discontinued, and 1 patient had an adverse event before randomization. After 57 serial responders and 41 nonresponders were identified and randomized to treatment, no further patients were enrolled. Thirty-four nonresponders (83%) and 54 responders (95%) completed the study. In the nonresponder cohort, 5 patients discontinued because of an adverse event (3 during ticagrelor and 2 during clopidogrel treatment), 1 for noncompliance, and 1 for non-treatment-related reasons. In the responder cohort, 3 patients discontinued: 1 because of an adverse event and 2 for non-treatment-related reasons. Patients were aged 45 to 85 years and were predominantly white men. Demographics and concomitant medications were similar between groups except for a higher percentage of smokers in the responder cohort (Table 1). For nonresponders, the overall mean percent compliance at visits 3 and 5 was 79% and 89%, and for responders it was 79% and 91%, respectively.

Nonresponder Cohort

Primary Analysis

In the nonresponder cohort, the proportion of patients who responded to ticagrelor was higher than those who responded to clopidogrel ($P=0.005$; Table 2). In addition, the proportion of patients with an absolute change in platelet aggregation (20 $\mu\text{mol/L}$ ADP, maximum extent) $>30\%$ and $>50\%$ was also greater after ticagrelor therapy ($P<0.05$ for both) (Table 2). Platelet aggregation fell from $59\pm 9\%$ to $35\pm 11\%$ after patients switched from clopidogrel to ticagrelor treatment and increased from $36\pm 14\%$ to $56\pm 9\%$ in patients after they switched from ticagrelor to clopidogrel treatment ($P<0.0001$ for both). As analyzed by the repeated-measures mixed effect model, there was no center heterogeneity ($P=0.0998$) or treatment by time interaction ($P=0.2429$).

Inhibition of Platelet Aggregation

IPA (20 $\mu\text{mol/L}$ ADP, maximum extent) was higher at all times after the ticagrelor loading and maintenance doses and was maximal within 1 to 2 hours ($P\leq 0.05$; Figure 2). The highest IPA occurred after patients switched from clopidogrel therapy and loading with ticagrelor (Figure 2). At day 28 after patients switched from clopidogrel to ticagrelor, IPA was similar to the IPA in patients treated with ticagrelor in period 1. After patients switched from ticagrelor to clopidogrel therapy, an early carryover effect of increased IPA was present. However, at 14 days after switching of treatment, IPA was similar to the IPA at the end of period 1 during treatment with clopidogrel. IPA based on 5 $\mu\text{mol/L}$ ADP-induced and 2 $\mu\text{g/mL}$ collagen-induced aggregation was higher at steady state in nonresponders treated with ticagrelor versus clopidogrel (Table 3).

VerifyNow P2Y₁₂ Assay

The VerifyNow P2Y₁₂ assay findings were consistent with platelet aggregation (Figure 3). For nonresponders, PRU was significantly lower during ticagrelor therapy compared with clopidogrel therapy at all time points, except the initial crossover period up to 1 hour ($P\leq 0.05$). An early carryover

Table 3. Comparison of Difference in Response at Steady State (Day 14; 0, 2, 4, and 8 Hours) With Ticagrelor and Clopidogrel in Nonresponders

Time, h	Ticagrelor Least Squares Mean (95% CI)	Clopidogrel Least Squares Mean (95% CI)	Difference of Least Squares Means (Point Estimate, 95% CI)
% IPA (5 $\mu\text{mol/L}$ ADP-induced, maximum extent)			
0	57 (49–64)	22 (15–30)	34 (28–40)
2	65 (57–72)	30 (23–38)	34 (28–40)
4	64 (56–71)	30 (22–38)	34 (28–40)
8	62 (54–69)	34 (27–42)	27 (22–33)
% IPA (2 $\mu\text{g/mL}$ collagen-induced, maximum extent)			
0	48 (35–61)	26 (12–39)	22 (19–35)
2	66 (53–79)	38 (24–51)	29 (16–42)
4	60 (47–73)	42 (29–56)	18 (5–31)
8	63 (50–77)	41 (27–54)	23 (10–36)
P-selectin expression, % positive cells (stimulated minus nonstimulated)			
0	12 (7–17)	27 (22–32)	-16 (-22 to -10)
2	9 (3–14)	26 (21–31)	-18 (-24 to -12)
4	7 (2–12)	22 (17–27)	-15 (-21 to -9)
8	9 (4–14)	24 (19–30)	-15 (-21 to -9)
Activated glycoprotein IIb/IIIa receptor expression, MFI (stimulated minus nonstimulated)			
0	18 (9–26)	40 (31–49)	-22 (-33 to -12)
2	12 (3–21)	34 (25–43)	-22 (-33 to -11)
4	14 (5–23)	31 (22–40)	-17 (-27 to -6)
8	15 (7–25)	24 (15–33)	-8 (-19 to 3)

MFI indicates mean fluorescence intensity.

effect of lower PRUs was present after patients switched from ticagrelor to clopidogrel therapy.

VASP Phosphorylation

During treatment periods 1 and 2, PRI was lower in ticagrelor-treated patients, and a carryover effect was observed when patients were crossed over to clopidogrel therapy (Figure 4).

Platelet Receptors

P-selectin and activated glycoprotein IIb/IIIa expression levels were lower at steady state in nonresponders treated with ticagrelor compared with clopidogrel (Table 3).

Responder Cohort

Platelet Aggregation

Platelet aggregation (20 $\mu\text{mol/L}$ ADP, maximum extent) was lower after ticagrelor compared with clopidogrel therapy in

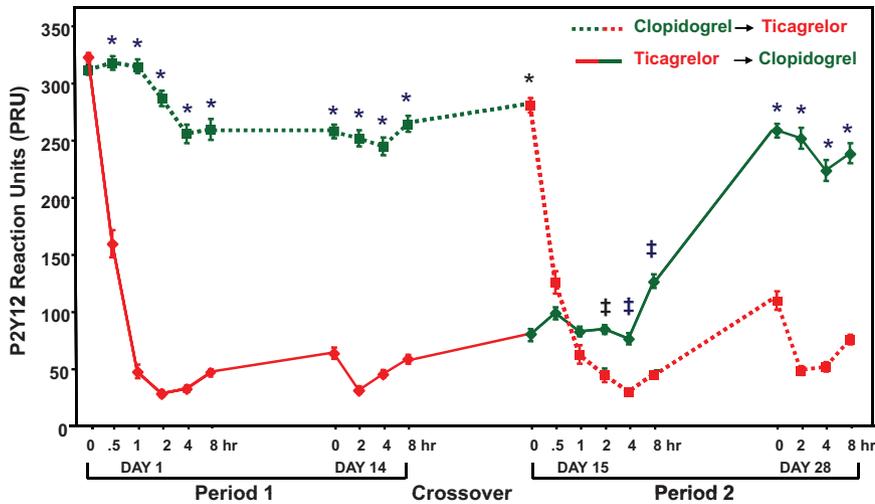


Figure 3. P2Y12 reaction units in clopidogrel-nonresponsive patients. * $P < 0.0001$, † $P < 0.05$.

period 1 ($26 \pm 9\%$ versus $49 \pm 16\%$, $P < 0.0001$ at day 1, 4 hours; $25 \pm 11\%$ versus $47 \pm 15\%$, $P < 0.0001$ at day 14, 4 hours) and after crossing over in period 2 ($24 \pm 9\%$ versus $37 \pm 10\%$, $P < 0.001$ at day 1, 4 hours; $32 \pm 8\%$ versus $45 \pm 8\%$, $P < 0.001$ at day 14, 4 hours). In patients who continued on the same therapy, platelet aggregation was significantly lower at all the time points after steady state was reached in patients treated with ticagrelor ($P < 0.05$).

Inhibition of Platelet Aggregation

IPA was higher at all time points after loading and maintenance ticagrelor therapy ($P < 0.05$) except at period 2, day 15, 0 hours (Figure 5A). After patients switched from clopidogrel to ticagrelor, IPA was maximal within 1 hour after loading. Similar to the nonresponder group, loading with ticagrelor after patients switched from clopidogrel provided the greatest IPA. IPA at day 28 in patients switched from clopidogrel to ticagrelor was similar to IPA in patients treated with ticagrelor in period 1. In patients continued on the same therapy, IPA was higher with ticagrelor after steady state was reached ($P < 0.05$; Figure 5B). IPA ($5 \mu\text{mol/L}$ ADP-induced and $2 \mu\text{g/mL}$ collagen-induced platelet aggregation, maximal extent) was also higher at steady state in patients treated with ticagrelor ($P < 0.001$; data not shown).

VerifyNow P2Y₁₂ Assay

Results of the VerifyNow assay provided findings consistent with platelet aggregation data. PRU levels were significantly lower during ticagrelor therapy compared with clopidogrel therapy at all time points except the initial crossover period up to 1 hour (Figure 6A; $P \leq 0.05$); in patients who were continued on the same therapy, PRU levels were also significantly lower with ticagrelor after the initial steady state was reached ($P < 0.05$; Figure 6B).

VASP Phosphorylation

For all comparisons at steady state, PRI was lower during ticagrelor treatment compared with clopidogrel treatment (Figure 7A and 7B). After treatments were switched, PRI was significantly lower during ticagrelor treatment compared with clopidogrel at all time points except on day 15 in patients who crossed over because of residual ticagrelor effect (Figure 7A). PRI in the noncrossover group was lower during steady state ticagrelor therapy at nearly all time points compared with clopidogrel therapy (Figure 7B).

Flow Cytometry Analysis

P-selectin and activated glycoprotein IIb/IIIa expression levels were consistently lower at steady state in responders

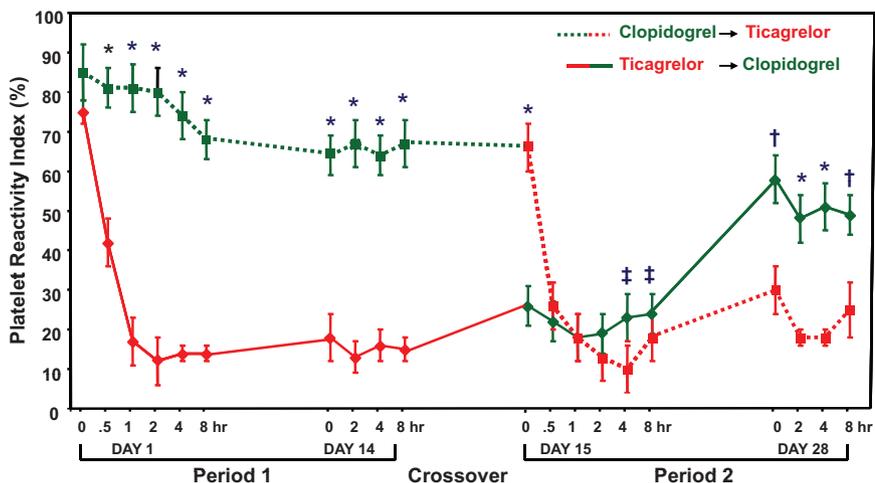


Figure 4. Platelet reactivity index measured by VASP phosphorylation in clopidogrel-nonresponsive patients. * $P < 0.0001$, † $P < 0.001$, ‡ $P < 0.05$.

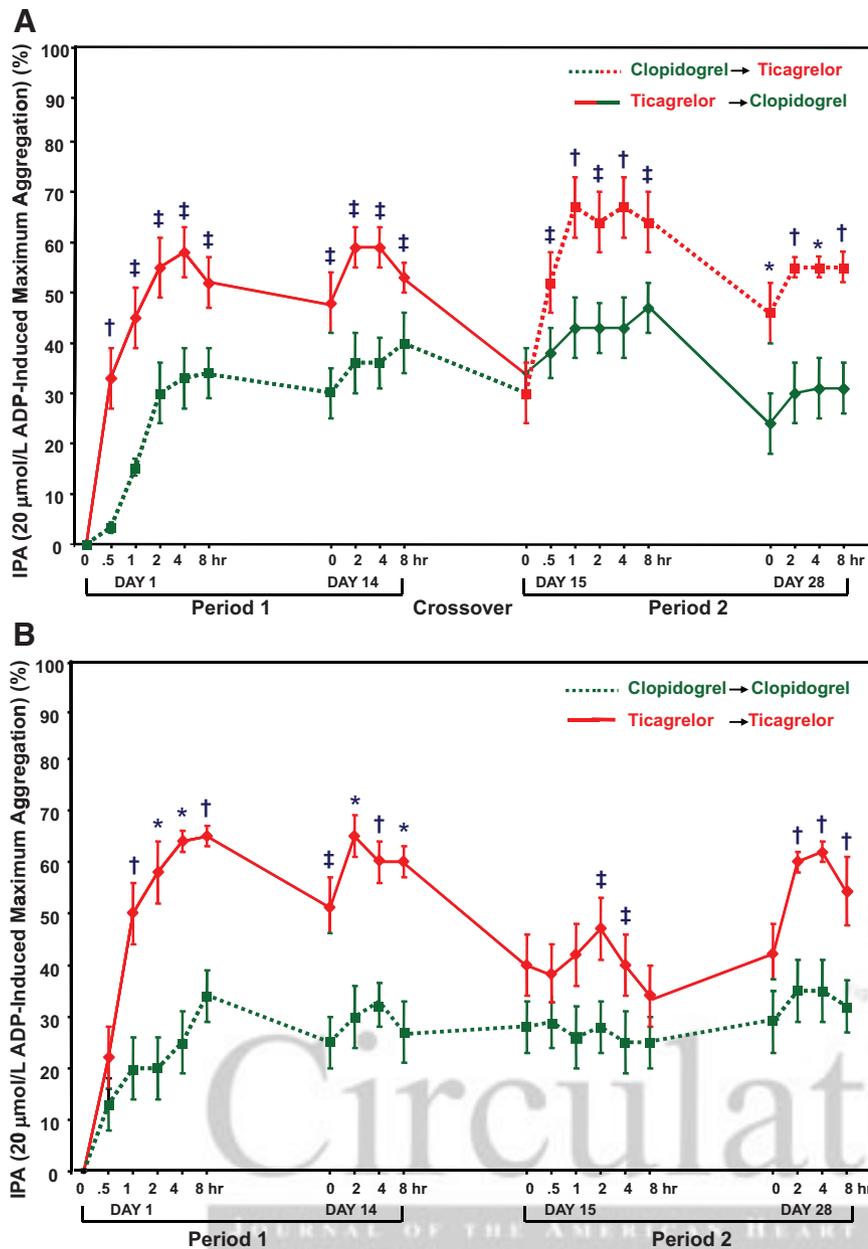


Figure 5. A, Inhibition of platelet aggregation in response to ADP (20 μmol/L, maximum extent) in clopidogrel-responsive patients before and after crossover. * $P < 0.0001$, † $P < 0.001$, ‡ $P < 0.05$. B, IPA in response to ADP (20 μmol/L, maximum extent) in clopidogrel-responsive patients maintained on constant therapy. * $P < 0.0001$, † $P < 0.001$, ‡ $P < 0.05$.

treated with ticagrelor compared with clopidogrel ($P < 0.001$; data not shown).

Platelet Function in Relation to HPR Cutoff Values

The prevalence of patients with on-treatment HPR measured at 4 hours after the last maintenance dose in both responder and nonresponder groups treated with ticagrelor and clopidogrel is shown in Table 4. Overall, 98% to 100% of patients had platelet reactivity below the cut point as measured by platelet aggregation, the VerifyNow P2Y₁₂ assay, and VASP phosphorylation after ticagrelor therapy compared with 44% to 70% of patients after clopidogrel treatment. Ticagrelor was equally effective at overcoming HPR in both responders and nonresponders to clopidogrel therapy. Overall, the highest rate of HPR was identified by the VASP-PRI >50% cutoff.

Effect of Ticagrelor Versus Clopidogrel on IPA, VerifyNow, and VASP Phosphorylation: Responders Versus Nonresponders

Clopidogrel nonresponders exhibited less platelet inhibition and higher platelet reactivity while on clopidogrel maintenance therapy (Table 5). In contrast, the effect of ticagrelor did not differ between clopidogrel responders and nonresponders except as measured by VerifyNow. However, platelet reactivity measured by VerifyNow during ticagrelor therapy was low in both groups.

Safety

Four patients (2 patients were nonresponders, and 2 patients were responders) experienced the 5 serious adverse events, and all events occurred during or after ticagrelor therapy. The events were myocardial infarction, hypotension, atrial fibril-

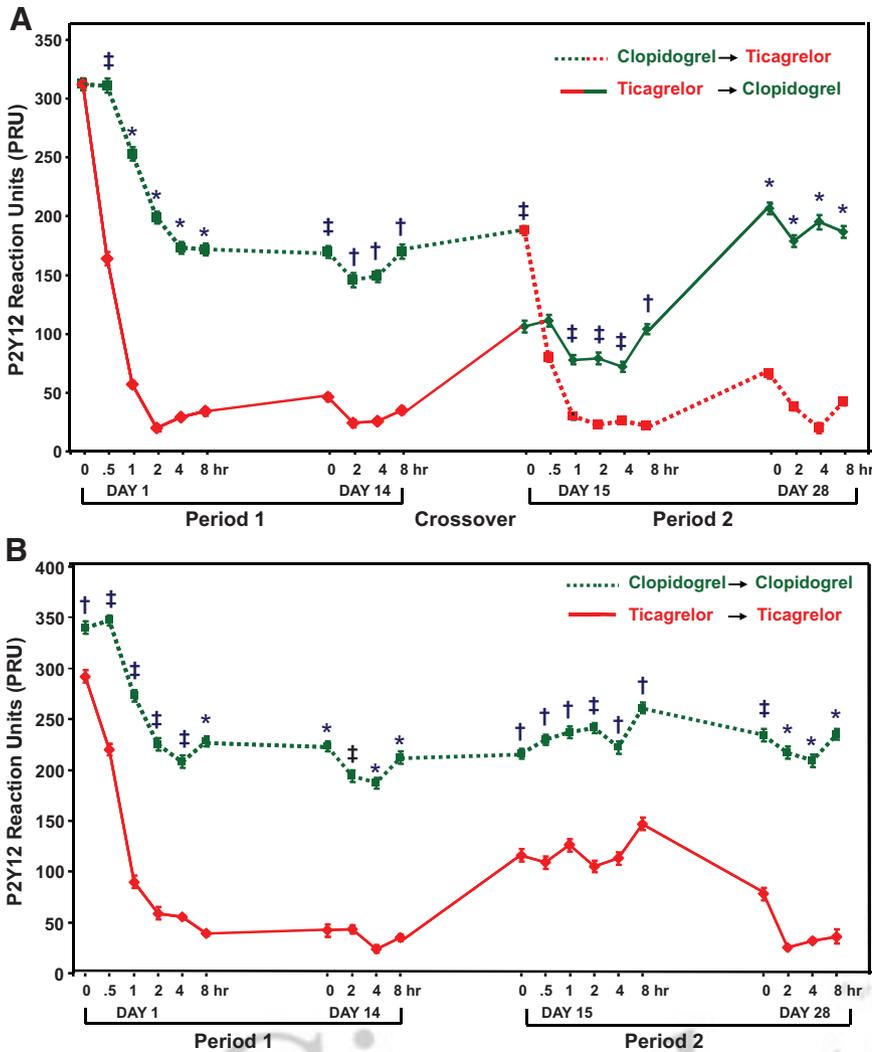


Figure 6. A, P2Y12 reaction units in clopidogrel-responsive patients before and after crossover. * $P < 0.0001$, † $P < 0.001$, ‡ $P < 0.05$. B, P2Y12 reaction units in clopidogrel-responsive patients maintained on constant therapy. * $P < 0.0001$, † $P < 0.001$, ‡ $P < 0.05$.

lation, and bradycardia during therapy. One death occurred on day 30 of follow-up after ticagrelor treatment and was not related to study treatment. One major and 3 minor bleeding events occurred during ticagrelor treatment, and no bleeding events occurred during clopidogrel treatment. Dyspnea was reported in 13 and 4 patients receiving ticagrelor and clopidogrel, respectively. Two nonresponder patients had dyspnea during switching of treatment. Most dyspnea episodes occurred early in the study, resolved without intervention, and did not result in discontinuation.

Discussion

The present study demonstrated that (1) ticagrelor therapy was associated with greater platelet inhibition compared with clopidogrel treatment in both clopidogrel responders and nonresponders; (2) the antiplatelet effect of ticagrelor was largely not influenced by clopidogrel response status; ticagrelor therapy overcame clopidogrel nonresponsiveness; (3) during switching of therapies, ticagrelor produced a rapid enhancement in platelet inhibition in both clopidogrel responders and nonresponders, whereas changing to clopidogrel therapy was associated with a reduction in platelet inhibition; and (4) ticagrelor was extremely effective in

reducing the prevalence of HPR using previously defined cutoffs; nearly all patients during ticagrelor therapy, irrespective of clopidogrel response status, had platelet reactivity below the cutoffs associated with ischemic risk determined by all assays.

Various limitations of clopidogrel therapy include variable and irreversible platelet inhibition, a comparatively slow onset of action, and an overall modest level of platelet inhibition, with a considerable proportion of patients exhibiting a limited response.⁴ Several strategies have been examined to improve responses to clopidogrel, including increasing dosages or adding other agents.^{4,12,15–17} Before the present study, there were no investigations designed to examine the effect of ticagrelor in clopidogrel nonresponders and the effect of changing therapy from clopidogrel to ticagrelor and vice versa. One prior study has shown that treatment with a direct-acting, reversible P2Y₁₂ inhibitor, elinogrel, can overcome clopidogrel nonresponsiveness.¹⁸ The data from the Response to Ticagrelor in Clopidogrel Nonresponders and Responders and Effect of Switching Therapies (RESPOND) study are consistent with this finding and also with phase II studies of ticagrelor treatment that demonstrated greater and faster platelet inhibition compared with clopidogrel.^{13,19,20}

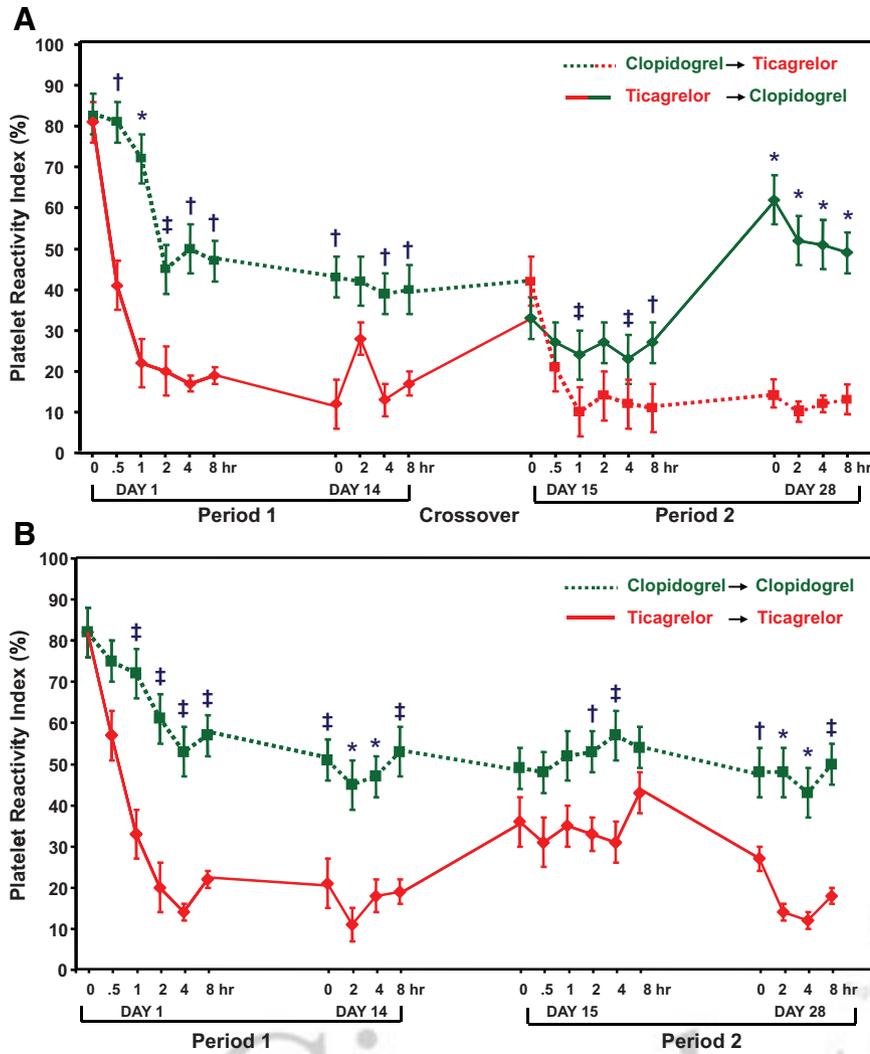


Figure 7. A, Platelet reactivity index measured by VASP phosphorylation in clopidogrel-responsive patients before and after crossover. * $P < 0.0001$, † $P < 0.001$, ‡ $P < 0.05$. B, Platelet reactivity index measured by VASP phosphorylation in clopidogrel-responsive patients maintained on constant therapy. * $P < 0.0001$, † $P < 0.001$, ‡ $P < 0.05$.



These pharmacodynamic properties may be related to the direct antiplatelet effect of ticagrelor compared with the requirement for active metabolite generation in the case of clopidogrel.¹³ In addition, we found that switching from clopidogrel to ticagrelor not only overcame clopidogrel nonresponsiveness (mean increase in IPA of $\approx 40\%$ in nonresponders) but also provided additional platelet inhibition in clopidogrel responders ($\approx 20\%$ increase in IPA).

The definition of nonresponders was based on a previous report in patients undergoing percutaneous coronary intervention. In that study, a 300-mg clopidogrel load was administered, and nonresponsiveness was estimated at $\approx 30\%$ at 24 hours after dosing.⁹ The present findings demonstrating an $\approx 28\%$ prevalence of nonresponsiveness are consistent with a previous investigation in which the prevalence of nonresponsiveness was 32% to a 300 mg-load as measured by the absolute change in platelet aggregation $\leq 10\%$ from baseline with the use of 20 $\mu\text{mol/L}$ ADP stimulation.¹⁰ Moreover, patients determined to be nonresponders at screening consistently had less clopidogrel-induced platelet inhibition by all assays after randomization. These data demonstrate that screening with a 300-mg clopidogrel load indeed discriminates patients who will have a reduced antiplatelet effect

measured by all assays after high-dose loading and during clopidogrel maintenance therapy.

The higher and more consistent IPA and lower platelet reactivity upon switching to ticagrelor demonstrate that the latter may be a reasonable strategy for clopidogrel nonresponders. The speed of the effect may improve treatment compared with previous strategies of repeated clopidogrel loading.¹¹ Our results also demonstrate that patients can switch directly from clopidogrel to ticagrelor without any reduction in antiplatelet effects. In contrast, responders who switched from ticagrelor to clopidogrel had a decrease in IPA $\approx 25\%$.

Results from the VASP analyses showed minor differences compared with the light transmittance aggregometry measurements. Flow cytometric assessment of VASP phosphorylation and the VerifyNow P2Y₁₂ assay have the advantage of measuring P2Y₁₂ function directly, whereas ADP-induced IPA is influenced by P2Y₁ receptor in addition to P2Y₁₂ being activated and contributing to platelet aggregation.²¹ Our findings demonstrating the near elimination of HPR during ticagrelor therapy using previously published cut points support the findings of the PLATO trial.^{4,8}

In the Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation–Thrombolysis in

Table 4. On-Treatment HPR Cut Points Associated With Ischemic Risk: Relation to Ticagrelor and Clopidogrel Therapy

	Ticagrelor		Clopidogrel		McNemar Test, Ticagrelor vs Clopidogrel		
	Patients, % (n/N)	95% CI	Patients, % (n/N)	95% CI	Difference, %	95% CI	P
Platelet aggregation (20 μ mol/L ADP, maximum extent) \leq 59%							
Nonresponder group	94 (31/33)	86–100	61 (20/33)	44–77	31	12–51	0.002
Responder group	100 (52/52)	94–100	76 (41/54)	65–87	21	4–39	0.01
Total group	98 (83/85)	94–100	70 (61/87)	60–80	27	14–40	<0.0001
VerifyNow P2Y ₁₂ -PRU \leq 235							
Nonresponder group	100 (32/32)	91–100	53 (17/32)	36–70	45	22–69	0.0002
Responder group	100 (51/51)	94–100	66 (35/53)	53–79	17	0–33	0.05
Total group	100 (83/83)	96–100	61 (52/85)	51–72	33	18–48	<0.0001
VASP-PRI \leq 50%							
Nonresponder group	100 (34/34)	92–100	29 (10/34)	14–45	71	42–99	<0.0001
Responder group	98 (52/53)	94–100	53 (28/53)	39–66	38	15–62	0.002
Total group	99 (86/87)	97–100	44 (35/87)	33–54	57	38–76	<0.0001

CI indicates confidence interval; PRU, P2Y₁₂ reaction units.

Myocardial Infarction 44 (PRINCIPLE-TIMI 44) study, the antiplatelet effect of clopidogrel was compared with prasugrel, a third-generation thienopyridine.²² IPA after a 60-mg prasugrel load and a 10-mg prasugrel maintenance dose was greater than the IPA after a 600-mg clopidogrel load and a 150-mg maintenance dose. After patients were switched from clopidogrel to prasugrel during the maintenance phase, there was increased platelet inhibition. However, in this study, there was no categorization of patients with respect to clopidogrel response status. Therefore, it is not possible to compare the antiplatelet effects of prasugrel versus ticagrelor in clopidogrel nonresponders. There have been no studies to determine the antiplatelet effect of prasugrel in clopidogrel nonresponders or that compare the antiplatelet effects of prasugrel with ticagrelor.

In the pharmacodynamic substudy of the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Plate-

let Inhibition With Prasugrel (TRITON)-TIMI 38 trial, antiplatelet effects of prasugrel were compared with standard-dose clopidogrel.²³ In the TRITON substudy, \approx 15% of patients exhibited HPR as determined by 20 μ mol/L ADP-induced aggregation during maintenance prasugrel therapy compared with 2% during ticagrelor therapy in our study. Similarly, a greater antiplatelet effect was demonstrated during ticagrelor therapy by the presence of 1% of patients above the VASP phosphorylation cutoff for risk compared with 24% of patients treated with prasugrel in the TRITON substudy. The frequency of patients above the cut point during clopidogrel treatment in the TRITON substudy is consistent with our findings (43% versus 39%).²³ These results suggest that ticagrelor may be more effective than prasugrel in achieving optimal platelet reactivity. However, platelet reactivity may be influenced by the clinical disease state, with higher platelet reactivity observed in patients with

Table 5. Antiplatelet Effect of Clopidogrel and Ticagrelor: Responders vs Nonresponders

	Responder Least Squares Mean (95% CI)	Nonresponder Least Squares Mean (95% CI)	Responder vs Nonresponder	
			Difference (95% CI)	P
IPA (20 mmol/L ADP, maximum extent)				
Ticagrelor	57 (51–63)	50 (43–57)	7 (–2 to 16)	0.114
Clopidogrel	34 (28–40)	21 (14–28)	13 (4 to 21)	0.004
VerifyNow-PRU				
Ticagrelor	39 (15–64)	59 (31–86)	–20 (–55 to –16)	0.270
Clopidogrel	182 (157–206)	245 (218–273)	–64 (–99 to –29)	0.0004
VASP-PRI				
Ticagrelor	15 (9–21)	20 (14–27)	–5 (–13 to –3)	0.240
Clopidogrel	47 (42–53)	61 (54–67)	–13 (–21 to –5)	0.003

CI indicates confidence interval. For the responder cohort, both period 1 and 2 day-14, 4-hour data were used. For the crossover treatment groups, both period 1 and 2 day-14, 4-hour data were used. For stay-on-treatment groups, only period 1 day-14, 4-hour data were used.

acute coronary syndromes. The observation may, at least in part, explain the differences in HPR after prasugrel treatment in the TRITON substudy compared with ticagrelor treatment in the present study. A randomized comparison of prasugrel with ticagrelor will be necessary before any definitive conclusion can be made.

Limitations

The definition of clopidogrel nonresponsiveness remains controversial and is dependent on the time, dose, and method of assessment. However, in the present study, patients meeting the definition of clopidogrel nonresponsiveness at screening clearly had significantly lower IPA and higher PRI and PRU during clopidogrel therapy. The study is underpowered to look at safety end points. The RESPOND study population differs from the PLATO study that enrolled patients with unstable coronary artery disease.

Conclusion

In conclusion, this is the first study to demonstrate that ticagrelor therapy overcomes nonresponsiveness to and HPR during clopidogrel therapy. The antiplatelet effect of ticagrelor is essentially uniform and high in clopidogrel responders and nonresponders. In addition, platelet inhibition in patients responsive to clopidogrel was significantly enhanced by switching to ticagrelor therapy. The extremely low prevalence of HPR in patients treated with ticagrelor provides a mechanism for the clinical benefit of ticagrelor therapy, as demonstrated in the PLATO trial.

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CLINICAL PERSPECTIVE

The Response to Ticagrelor in Clopidogrel Nonresponders and Responders and Effect of Switching Therapies (RESPOND) study is the first to demonstrate that ticagrelor therapy overcomes nonresponsiveness to and high platelet reactivity during clopidogrel therapy. The antiplatelet effect of ticagrelor is essentially uniform and high in both clopidogrel responders and nonresponders. Moreover, platelet inhibition in patients responsive and nonresponsive to clopidogrel is enhanced by switching to ticagrelor therapy. These data suggest that ticagrelor may be an important therapeutic alternative in patients who have experienced thrombotic events during clopidogrel therapy. The extremely low prevalence of high platelet reactivity associated with ticagrelor therapy as defined by cut points associated with ischemic event occurrence with the use of 3 different methods in the RESPOND study provides a mechanism for the clinical benefit demonstrated in the Platelet Inhibition and Patient Outcomes (PLATO) trial. All of these findings support the particular utility of ticagrelor in clinical settings associated with high platelet reactivity, such as acute coronary syndromes, percutaneous coronary intervention, and stent thrombosis.

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