

**Inhibitory Effects of Ticagrelor Compared With Clopidogrel on Platelet Function in Patients With Acute Coronary Syndromes: The PLATO (PLATElet inhibition and patient Outcomes) PLATELET Substudy**

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# Inhibitory Effects of Ticagrelor Compared With Clopidogrel on Platelet Function in Patients With Acute Coronary Syndromes

The PLATO (PLATElet inhibition and patient Outcomes) PLATELET Substudy

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- Objectives** The PLATO (PLATElet inhibition and patient Outcomes) PLATELET substudy aimed to compare the antiplatelet effects of clopidogrel and ticagrelor in patients with acute coronary syndromes.
- Background** The PLATO study demonstrated superiority of ticagrelor over clopidogrel in the prevention of ischemic events in patients with acute coronary syndromes.
- Methods** Patients were randomized to receive either clopidogrel (300- to 600-mg loading dose [LD], 75 mg/day) or ticagrelor (180-mg LD, 90 mg twice daily). The effects of maintenance therapy were studied in 69 patients pre- and 2 to 4 h post-dose after at least 28 days. The LD effect was studied in 24 clopidogrel-naive patients. Light transmittance aggregometry (adenosine diphosphate 5 to 20  $\mu$ M), VerifyNow P2Y12, and VASP phosphorylation assays were performed.
- Results** During maintenance therapy, ticagrelor achieved greater suppression of platelet reactivity compared with clopidogrel. The mean maximum light transmittance aggregometry responses (adenosine diphosphate 20  $\mu$ M) post-maintenance dose were  $44 \pm 15\%$  for clopidogrel and  $28 \pm 10\%$  for ticagrelor ( $p < 0.001$ ). High platelet reactivity was seen more frequently in the clopidogrel group. Proton pump inhibitor use was associated with higher platelet reactivity with clopidogrel but not ticagrelor. The ticagrelor LD also achieved greater inhibition of platelet aggregation compared with the clopidogrel LD.
- Conclusions** Ticagrelor achieves greater antiplatelet effect than clopidogrel in patients with acute coronary syndromes, both in the first hours of treatment and during maintenance therapy. (J Am Coll Cardiol 2010;56:0000-0) © 2010 by the American College of Cardiology Foundation

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Novartis, Mediceur, Accumetrics, Arena Pharmaceutical, AstraZeneca, and Evolve; and has received research grants from GlaxoSmithKline, Otsuka, Eli Lilly Co., Daiichi-Sankyo Inc., The Medicines Co., Portola, Accumetrics, Schering-Plough, AstraZeneca, Eisai, and Johnson & Johnson. Dr. Emanuelsson is an AstraZeneca employee. Dr. Cannon has received research grant/support from Accumetrics, AstraZeneca, Bristol-Myers Squibb/Sanofi Partnership, GlaxoSmithKline, Intekrin Therapeutics, Merck, Novartis, and Takeda; is on the advisory board of Bristol-Myers Squibb/Sanofi Partnership; and is a clinical advisor with equity in Automedics Medical Systems. Dr. Becker has received research support from and is on the scientific advisory board of AstraZeneca. Dr. Wallentin has received institutional grants from AstraZeneca, Boehringer-Ingelheim, Bristol-Myers Squibb, Schering-Plough, Lilly, and GlaxoSmithKline. All other authors have reported that they have no relationships to disclose.

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Abbreviations  
and Acronyms

**ACS** = acute coronary syndromes  
**ADP** = adenosine diphosphate  
**IPA** = inhibition of platelet aggregation  
**LD** = loading dose  
**LTA** = light transmittance aggregometry  
**PRI** = platelet reactivity index  
**VASP** = vasodilator-stimulated phosphoprotein

Ticagrelor, an oral, reversibly binding platelet P2Y<sub>12</sub> receptor inhibitor, yields greater inhibition of platelet aggregation (IPA) than clopidogrel (1,2). The inhibitory effects of clopidogrel are predominantly determined by platelet exposure to its active metabolite, which varies widely among individuals as a consequence of drugs such as proton pump inhibitors and genetic and other factors (3). The inhibitory effects of ticagrelor predominantly reflect the plasma levels of ticagrelor; consequently its onset of action is faster and its

**Table 1** Demographic Characteristics, Recorded at Randomization, and Comedication at the Time of Blood Sampling After >28 Days of Study Drug

	Clopidogrel (n = 32)	Ticagrelor (n = 37)	p Value
Age, yrs	63	61	0.41
Female sex	5 (16)	8 (22)	0.55
Median body weight, kg	84 (58–112)	76 (42–119)	0.29
Body mass index, kg/m <sup>2</sup>	28 (23–36)	27 (12–42)	0.66
Body mass index, kg/m <sup>2</sup>	628	628	
Race			
White	29 (91)	33 (89)	1.00
Black	2 (6)	1 (3)	0.59
Asian	0 (0)	2 (5)	0.49
Oriental	1 (3)	0 (0)	0.46
Other	0 (0)	1 (3)	1.00
Diagnosis			
STEMI	12 (38)	14 (38)	1.00
NSTEMI	20 (63)	20 (54)	0.62
Unstable angina	0 (0)	3 (8)	0.24
Cardiovascular risk factors			
Habitual smoker	7 (22)	14 (38)	0.19
Diabetes mellitus	8 (25)	5 (14)	0.35
Duration of treatment with study medication, days	160 ± 129	201 ± 134	0.21
Concomitant medications			
Aspirin	31 (97)	35 (95)	1.00
Mean aspirin dose (mg)	108	98	
Aspirin 75–81 mg/day	27 (84)	31 (84)	
Aspirin 150–162.5 mg/day	0 (0)	1 (3)	
Aspirin 300–325 mg/day	4 (13)	3 (8)	
Beta-blockers	29 (91)	28 (76)	0.12
ACE inhibitors	26 (81)	32 (87)	0.74
Calcium channel blocker	6 (19)	4 (11)	0.49
Statins	31 (97)	36 (97)	1.00
Proton pump inhibitors	13 (41)	12 (32)	0.46
Nitrates	22 (69)	27 (73)	0.79

Values are mean, n (%), median (range), or mean ± SD. p values determined by the Fisher exact test for proportions or unpaired t test for continuous variables.

ACE = angiotensin-converting enzyme; STEMI = ST-segment elevation myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction.

**Table 2** Demographic Characteristics and Comedication at Time of Loading Dose Administration

	Clopidogrel (n = 12)	Ticagrelor (n = 12)	p Value
Age, yrs	66	65	0.86
Female sex	1 (8)	1 (8)	1.00
Median body weight, kg	84 (63–112)	72 (67–117)	0.44
Body mass index, kg/m <sup>2</sup>	27 (21–35)	25 (18–42)	0.55
Body mass index, kg/m <sup>2</sup>	27	26	
Race			
White	11 (92)	11 (92)	1.00
Black	0 (0)	1 (8)	1.00
Asian	0 (0)	0 (0)	1.00
Oriental	1 (8)	0 (0)	0.47
Other	0 (0)	0 (0)	1.00
Diagnosis			
STEMI	5 (42)	5 (42)	1.00
NSTEMI	7 (58)	6 (50)	1.00
Unstable angina	0 (0)	1 (8)	1.00
Cardiovascular risk factors			
Habitual smoker	2 (17)	5 (42)	0.37
Diabetes mellitus	2 (17)	2 (17)	1.00
Concomitant medications			
Aspirin	11 (92)	12 (100)	0.47
Mean aspirin dose, mg	293	306	
Beta-blockers	3 (25)	2 (17)	1.00
ACE inhibitors	5 (42)	2 (17)	0.37
Calcium channel blocker	2 (17)	0 (0)	0.47
Statins	2 (17)	3 (25)	0.59
Proton pump inhibitors	3 (25)	2 (17)	1.00
Nitrates	3 (25)	5 (42)	0.66

Values are mean, n (%), or median (range). p values determined by the Fisher exact test. Abbreviations as in Table 1.

inhibitory effects more pronounced and predictable than those of clopidogrel (1,2).

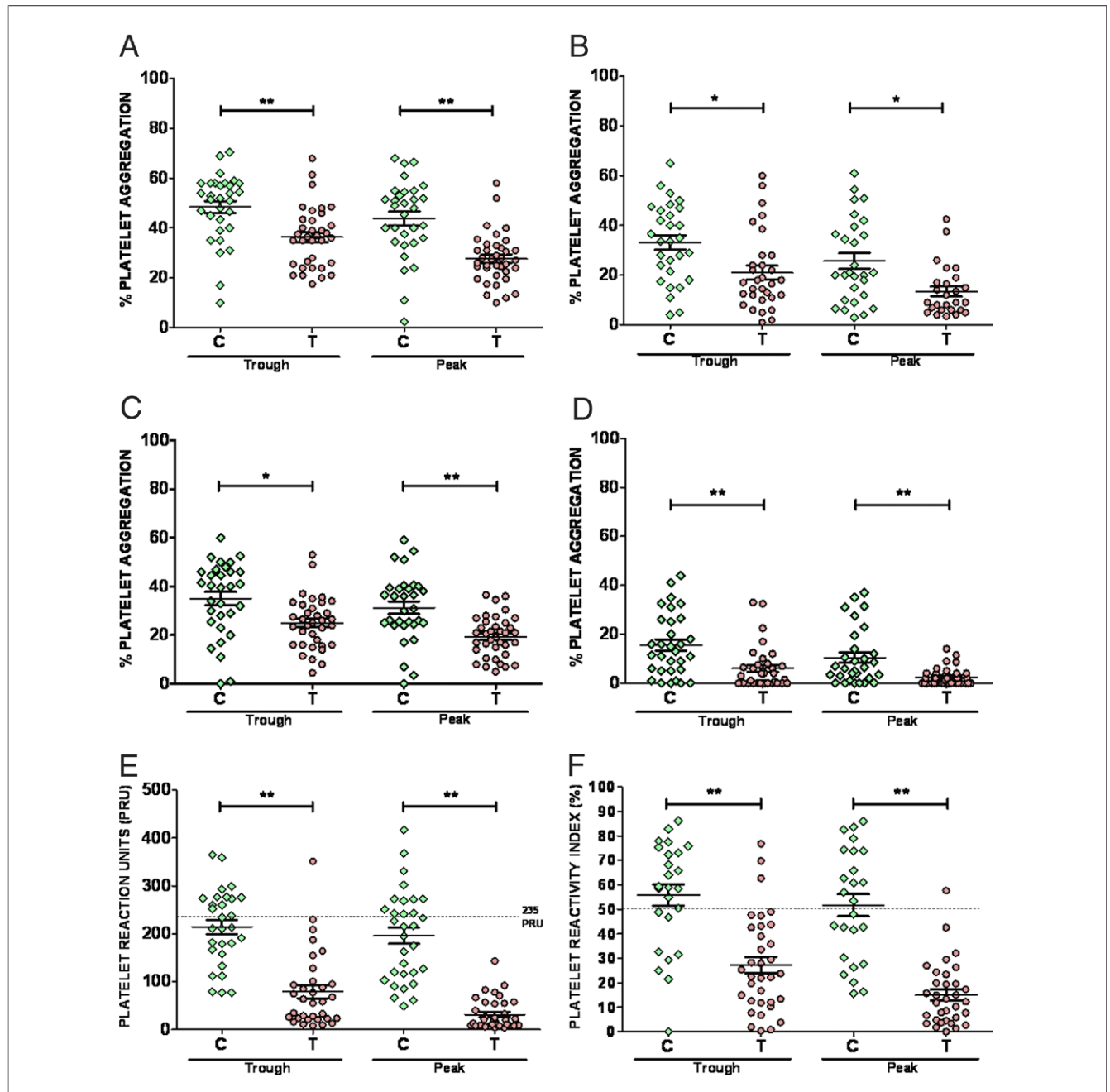
In the PLATO (PLATElet inhibition and patient Outcomes) study, ticagrelor reduced the incidence of the primary end point of cardiovascular death, myocardial infarction, and stroke compared with clopidogrel (4). The PLATO PLATELET substudy was conducted to further characterize the effects of ticagrelor compared with clopidogrel in patients with acute coronary syndromes (ACS).

## Methods

**Study design.** The inclusion criteria for this substudy were the same as for the main PLATO study (4). Two cohorts of patients were studied: patients who had received study medication for at least 28 days and patients who had not received treatment with clopidogrel within the past 14 days and had not yet received study medication. Venous blood samples were collected by venipuncture into citrated tubes at time points indicated in the Results section. Further details of the study design and other supplementary information are provided in the Online Appendix.

**Platelet aggregation studies.** Light transmittance aggregometry (LTA) was performed at all time points using adenosine diphosphate (ADP) (5 and 20  $\mu$ M) as agonist (1). The maximum percentage LTA response and final response after 6 min were recorded. The proportions of patients in each group with responses associated with increased risk of ischemic events were determined according

to the following thresholds: maximum response to ADP 20  $\mu$ M >50% (5) and final response to ADP 5  $\mu$ M >14% (6). **VerifyNow P2Y12 assay.** Venous blood was collected into a 2-ml citrate Vacutainer and analyzed using the VerifyNow P2Y12 system (Accumetrics Inc., San Diego, California) according to the manufacturer's instructions. Platelet reaction units and the thrombin receptor activat-



**Figure 1** Responses to Maintenance Doses of Clopidogrel and Ticagrelor

Effects of clopidogrel (C) 75 mg/day (n = 32) or ticagrelor (T) 90 mg twice daily (n = 37) on individual platelet function responses pre- (trough) and 2 to 4 h post- (peak) maintenance dose assessed by light transmittance aggregometry (LTA) showing maximum LTA response (adenosine diphosphate [ADP] 20  $\mu$ M) (A), final LTA response (ADP 20  $\mu$ M) (B), maximum LTA response (ADP 5  $\mu$ M) (C), final LTA response (ADP 5  $\mu$ M) (D), VerifyNow P2Y12 (E), and vasodilator-stimulated phosphoprotein assay (F). \*p < 0.01; \*\*p < 0.001.

ing peptide-induced response were recorded. The proportion of patients in each treatment group with responses  $>235$  platelet reaction units was determined because this threshold has been previously associated with increased ischemic risk (7).

**Vasodilator-stimulated phosphoprotein (VASP) assay.** Aliquots of whole blood were processed using a VASP phosphorylation assay kit, and the platelet reactivity index (PRI) was determined according to the manufacturer's instructions (BioCytex, Marseille, France). The proportions of patients in each treatment group with PRI  $>50\%$  were determined because this threshold has been associated with increased ischemic risk (8).

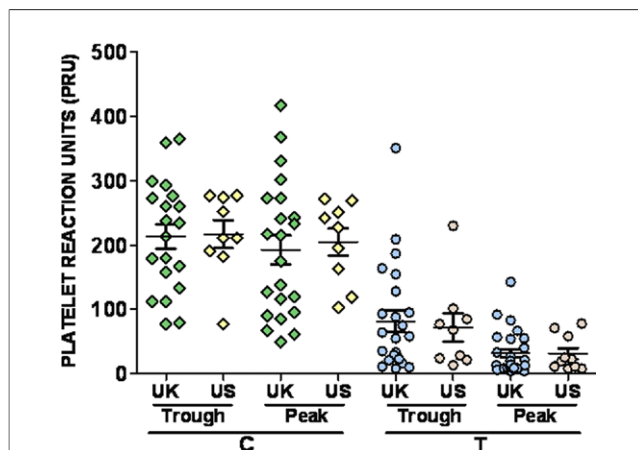
**Statistical analysis.** Data were analyzed using SPSS (version 15.0, SPSS Inc., Chicago, Illinois) and expressed as mean and SD. Clopidogrel and ticagrelor group continuous data were compared using either an unpaired  $t$  test for parametric data or the Mann-Whitney test for data with significantly different variances determined by the Levene test. Categorical variables were compared using the Fisher exact test. Statistical significance was attached to  $p$  values  $<0.01$  to allow for multiple group comparisons.

## Results

**Study population.** Sixty-nine patients were studied after at least 28 days of maintenance treatment with either clopidogrel 75 mg/day ( $n = 32$ ) or ticagrelor 90 mg twice daily ( $n = 37$ ). Twenty-four clopidogrel-naive patients were enrolled and received either a clopidogrel LD of 300 mg ( $n = 7$ ) or 600 mg ( $n = 5$ ) or a ticagrelor LD of 180 mg ( $n = 12$ ). Demographic characteristics and comedication were well matched in both cohorts (Tables 1 and 2).

**Effects of clopidogrel and ticagrelor maintenance regimens.** LTA responses were lower in the ticagrelor group compared with the clopidogrel group, both before the next maintenance dose (trough) and 2 to 4 h post-dose (peak) (Figs. 1A to 1D). VerifyNow P2Y<sub>12</sub> measurements were also lower in the ticagrelor group compared with the clopidogrel group at both trough and peak, and there was remarkable consistency of response in the ticagrelor group at peak (Fig. 1E). PRI levels were lower at both peak and trough in the ticagrelor group compared with the clopidogrel group (Fig. 1F). Comparison of the ticagrelor and clopidogrel groups according to geographic location in the United Kingdom or United States showed similar patterns of responses (Fig. 2).

**Effects of clopidogrel and ticagrelor LDs.** Clopidogrel achieved overall moderate inhibition of platelet aggregation induced by ADP 20  $\mu\text{M}$ , with marked interindividual variation, whereas ticagrelor achieved marked inhibition by 1 h post-dose in all except 1 patient (for whom a 2-h sample was not obtained); in the latter patient, who presented with an inferior ST-segment elevation myocardial infarction, onset of effect was delayed until 4 to 8 h post-dose (Figs. 3A and 3B). Platelet



**Figure 2** VerifyNow Responses According to Geographic Location

Effects of clopidogrel (C) 75 mg/day or ticagrelor (T) 90 mg twice daily on individual platelet function responses at trough and peak assessed by VerifyNow P2Y<sub>12</sub> according to geographic location in United Kingdom (C:  $n = 23$ ; T:  $n = 26$ ) or U.S. (C:  $n = 9$ ; T:  $n = 11$ ). All  $p = \text{NS}$ .

aggregation induced by ADP 5  $\mu\text{M}$  was more sensitive to inhibition by clopidogrel (Figs. 3C and 3D).

VerifyNow assay showed greater inhibitory effects of ticagrelor at 4 h compared with clopidogrel, whereas the VASP data at 4 h only showed a nonsignificant trend ( $p = 0.028$ ) (Figs. 3E and 3F).

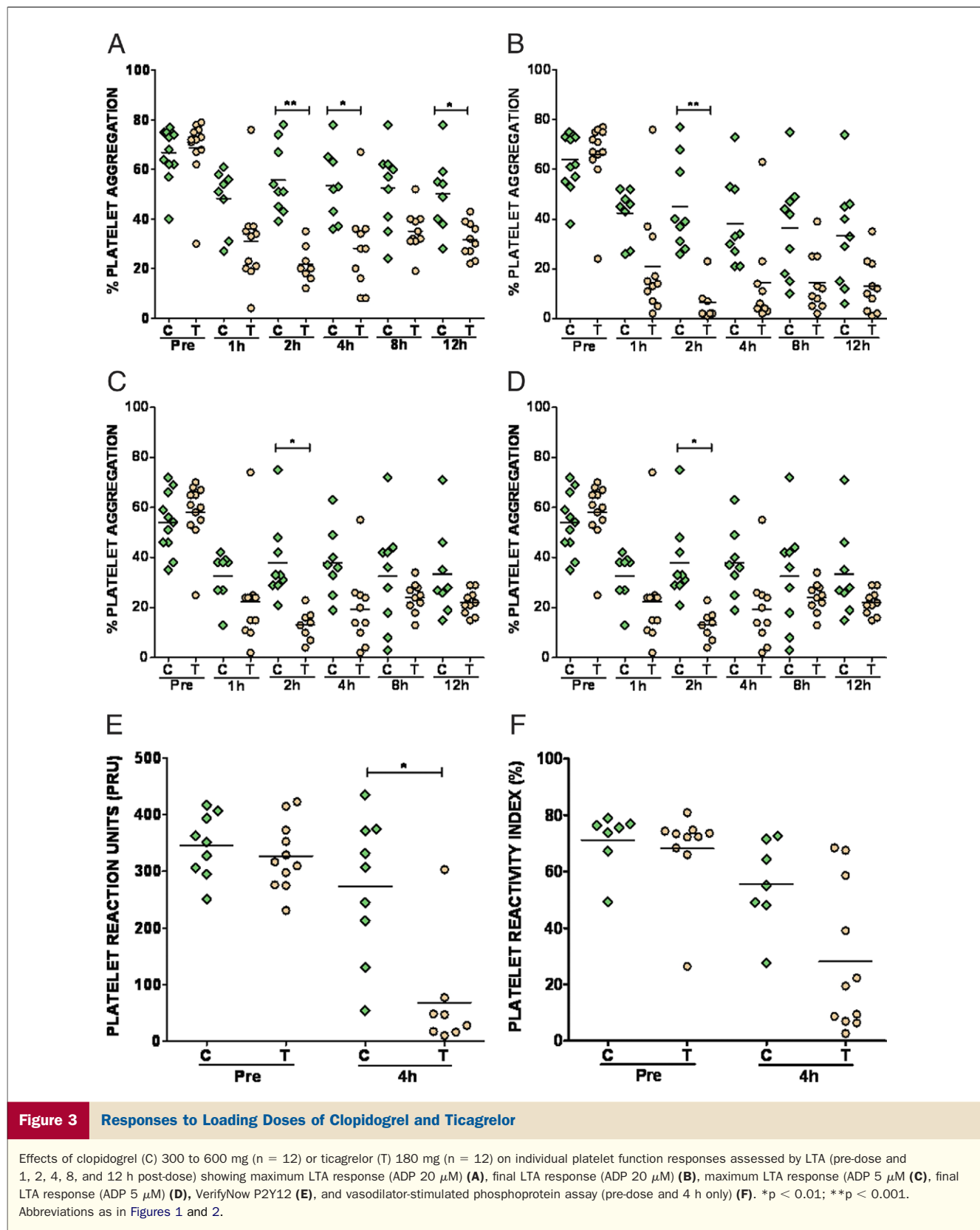
**Response to study therapy according to thresholds of ischemic risk.** During maintenance treatment, all measures showed almost no poor responders in the ticagrelor group, whereas this was fairly common in the clopidogrel group both at trough and peak (Table 3).

**Proton pump inhibitors and platelet reactivity.** During maintenance therapy, patients treated with both clopidogrel and a proton pump inhibitor had greater platelet aggregation values than clopidogrel-treated patients not receiving a proton pump inhibitor (Table 4). There was no difference in platelet reactivity between ticagrelor-treated patients receiving or not receiving this comedication.

**IPA.** IPA was determined for the 24 clopidogrel-naive patients using LTA results with ADP 20  $\mu\text{M}$  (Figs. 4A and 4B).

## Discussion

This PLATO substudy is the largest assessment to date of platelet reactivity in the maintenance phase of treatment of ACS patients with ticagrelor and incorporated additional methods of assessing P2Y<sub>12</sub> inhibition compared with our previous assessment with LTA alone (1). All the platelet function measurements show greater levels of inhibition with ticagrelor compared with clopidogrel, and the discrimination between the 2 treatment groups with the VerifyNow P2Y<sub>12</sub> system is striking.



The PLATO PLATELET substudy also demonstrates that ticagrelor has a more rapid onset of action than clopidogrel when administered to patients with ACS,

reinforcing data from previous studies (1,2). The majority of patients treated with ticagrelor in this acute setting showed marked IPA at 1 h post-LD compared with a

**Table 3** Proportions of Platelet Function Responses Greater Than Risk Thresholds for Ischemic Events

No. Above Threshold/Total n (%)	Clopidogrel	Ticagrelor	p Value
Maximum LTA response to ADP 20 $\mu$ M >50%			
Pre-MD	18/31 (58)	3/35 (9)	<0.0001
2–4 h post-MD	13/31 (42)	1/37 (3)	0.0001
1 h post-LD	5/8 (63)	1/11 (9)	0.04
2 h post-LD	6/9 (67)	1/8 (13)	0.05
4 h post-LD	5/8 (63)	1/10 (10)	0.04
8 h post-LD	6/9 (67)	1/10 (10)	0.02
12 h post-LD	4/8 (50)	0/10 (0)	0.02
Final LTA response to ADP 5 $\mu$ M >14%			
Pre-MD	15/31 (48)	4/34 (12)	0.02
2–4 h post-MD	7/31 (23)	0/36 (0)	0.01
1 h post-LD	5/8 (63)	2/11 (18)	0.07
2 h post-LD	4/9 (44)	0/8 (0)	0.08
4 h post-LD	2/8 (25)	1/10 (10)	0.56
8 h post-LD	4/9 (44)	1/10 (10)	0.14
12 h post-LD	4/9 (44)	1/9 (11)	0.29
VerifyNow P2Y12 >235 PRUs			
Pre-MD	13/29 (45)	1/34 (3)	0.0001
2–4 h post-MD	12/31 (39)	0/36 (0)	<0.0001
4 h post-LD	6/9 (67)	1/8 (13)	0.05
VASP PRI >50%			
Pre-MD	17/25 (68)	3/34 (9)	<0.0001
2–4 h post MD	13/25 (52)	1/33 (3)	<0.0001
4 h post-LD	4/7 (57)	3/11 (27)	0.33

p values derived by the Fisher exact test.

ADP = adenosine diphosphate; LD = loading dose; LTA = light transmittance aggregometry; MD = maintenance dose; PRI = platelet reactivity index; PRUs = platelet reaction units; VASP = vasodilator-stimulated phosphoprotein.

relatively slow onset of action of the clopidogrel LD, mirroring recent findings in patients with stable coronary artery disease (2).

Our analysis of the proportions of patients with platelet reactivity above thresholds associated with increased risk of ischemic events showed that there were fewer patients with high platelet reactivity in the ticagrelor group compared

with the clopidogrel group, during both maintenance treatment and after LD administration. A PRU level >235 was previously been shown to be associated with an increased risk of stent thrombosis (7), and only 1 of the ticagrelor-treated patients had a level greater than this at trough during maintenance treatment, with all the ticagrelor-treated patients having levels less than this at peak, compared with 45% and 39% of the clopidogrel-treated patients at trough and peak, respectively (both  $p < 0.001$ ). Similarly, a PRI value greater than approximately 50% in clopidogrel-treated PCI patients has been associated with an increased risk of stent thrombosis (8), and only 1 patient (3%) in the ticagrelor group had a PRI level >50% at peak compared with 13 patients (52%) in the clopidogrel group ( $p < 0.001$ ). Consistent with other studies, we found that platelet reactivity was higher in clopidogrel-treated patients receiving proton pump inhibitors compared with those not receiving proton pump inhibitors. Numerous confounding variables may influence platelet reactivity differentially in the 2 nonrandomized groups other than an interaction between proton pump inhibitors and clopidogrel. However, the finding that there was no apparent effect of proton pump inhibitors on the response to ticagrelor provides reassurance about the appropriateness of coprescribing ticagrelor and proton pump inhibitors.

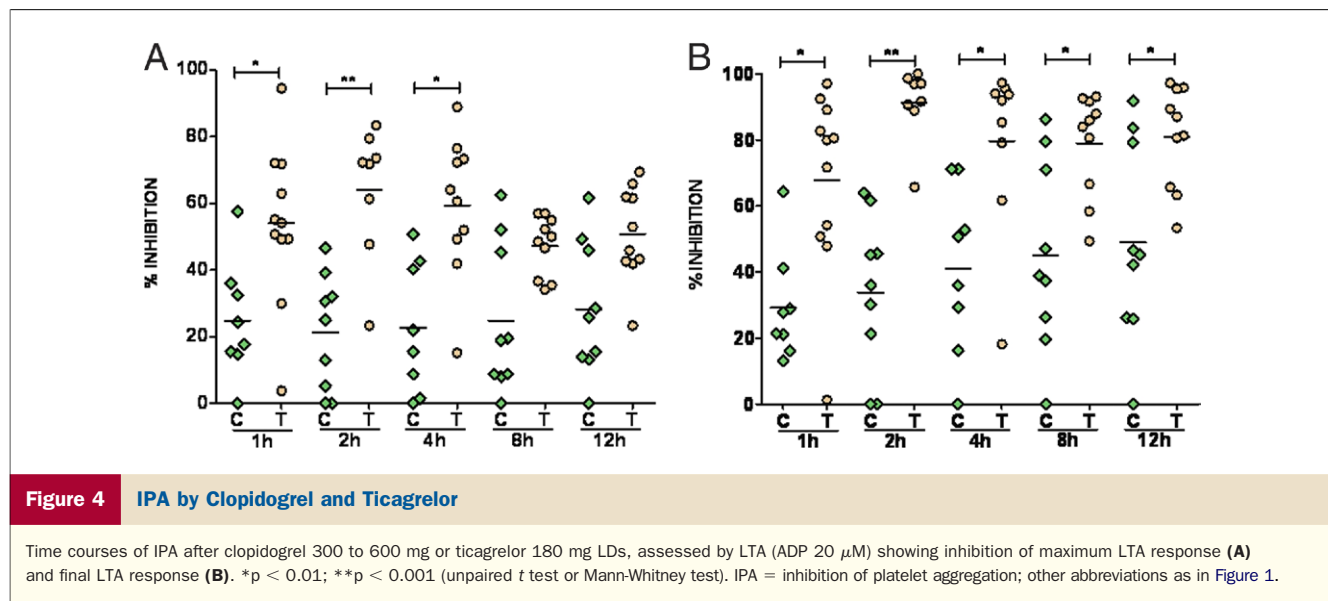
**Study limitations.** There were insufficient numbers of clopidogrel-naïve patients receiving the standard and double LD of clopidogrel to compare each separately with the ticagrelor LD. There were insufficient numbers in the maintenance phase to analyze completely the effects of potential drug interactions on response to clopidogrel. Pharmacokinetic samples were not collected simultaneously to the samples for platelet function analysis to allow assessment of relationships between the two. This substudy was not powered to assess the relationship between pharmacodynamic data and clinical outcomes.

**Table 4** Platelet Function Responses During Maintenance Therapy According to Treatment With Proton Pump Inhibitors

	Clopidogrel		p Value	Ticagrelor		p Value
	PPI (n = 13)	No PPI (n = 19)		PPI (n = 12)	No PPI (n = 25)	
Maximum LTA response to ADP 20 $\mu$ M, %						
Pre-MD	56 $\pm$ 10	45 $\pm$ 15	0.04	37 $\pm$ 14	35 $\pm$ 14	0.59
27–4 h post-MD	55 $\pm$ 15	39 $\pm$ 15	0.007	29 $\pm$ 12	27 $\pm$ 9	0.68
Final LTA response to ADP 5 $\mu$ M, %						
Pre-MD	25 $\pm$ 21	13 $\pm$ 11	0.054	9 $\pm$ 9	5 $\pm$ 8	0.21
2–4 h post-MD	23 $\pm$ 22	7 $\pm$ 8	0.013	3 $\pm$ 3	2 $\pm$ 4	0.73
VerifyNow P2Y12, PRUs						
Pre-MD	262 $\pm$ 76	181 $\pm$ 64	0.005	92 $\pm$ 116	74 $\pm$ 61	0.56
2–4 h post-MD	247 $\pm$ 99	151 $\pm$ 70	0.005	32 $\pm$ 29	31 $\pm$ 34	0.98
VASP PRI, %						
Pre-MD	59 $\pm$ 18	53 $\pm$ 25	0.47	31 $\pm$ 19	25 $\pm$ 20	0.43
2–4 h post-MD	58 $\pm$ 20	47 $\pm$ 24	0.23	18 $\pm$ 11	13 $\pm$ 13	0.32

p values derived by unpaired Student t test.

PPI = proton pump inhibitor; other abbreviations as in Table 3.



## Conclusions

Ticagrelor demonstrates a greater platelet inhibitory effect than clopidogrel in ACS patients both during maintenance therapy and in the first hours of treatment. These effects likely explain a substantial portion of the superior efficacy of ticagrelor compared with clopidogrel.

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**Key Words:** clopidogrel ■ coronary artery disease ■ P2Y<sub>12</sub> receptor ■ platelet ■ platelet inhibitor.

## APPENDIX

For further details of the study design and other supplementary information, please see online version of this article.

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