Randomized Assessment of Ticagrelor Versus Prasugrel Antiplatelet Effects in Patients With Diabetes

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OBJECTIVE—It has been postulated that prasugrel might be the preferred treatment option in diabetes mellitus (DM) patients with acute coronary syndrome (ACS) undergoing percutaneous coronary intervention (PCI). We aimed to compare the pharmacodynamic action of ticagrelor versus prasugrel.

RESEARCH DESIGN AND METHODS—In a prospective, single-center, single-blind, crossover study, 30 consecutive ACS patients with DM who had been pretreated with clopidogrel were randomized to either 90 mg ticagrelor twice daily or 10 mg prasugrel once daily with a 15-day treatment period. Platelet reactivity (PR) was assessed with the VerifyNow P2Y12 function assay, measured in P2Y12 reaction units (PRU).

RESULTS—PR was significantly lower after ticagrelor (45.2 PRU [95% CI 27.4–63.1]) compared with prasugrel (80.8 PRU [63.0–98.7]), with a least squares mean difference of –35.6 PRU (−55.2 to −15.9, $P = 0.001$). High PR rate was 0% for ticagrelor and 3.3% for prasugrel ($P = 1.0$).

CONCLUSIONS—In DM patients with ACS who had been pretreated with clopidogrel and who undergo PCI, ticagrelor achieves a significantly higher platelet inhibition than prasugrel. Both antiplatelet agents effectively treat high PR. The relevance of these findings to the clinical efficacy and safety of ticagrelor and prasugrel in DM patients needs further elucidation.

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Patients with diabetes mellitus (DM) suffering from acute coronary syndrome (ACS) and/or undergoing percutaneous coronary intervention (PCI) have an increased platelet reactivity (PR) and prothrombotic potential, a lower response to clopidogrel, and a higher risk of cardiovascular complications and recurrent atherothrombotic events than non-DM patients (1–8).

Prasugrel and ticagrelor are newer and more potent than clopidogrel antiplatelet agents, which have been introduced recently into our armamentarium while treating ACS patients undergoing PCI (9,10). In the Prasugrel Optimizing Antiplatelet Therapy in Diabetes Mellitus (OPTIMUS-3) study, in patients with DM and coronary artery disease (CAD), prasugrel provided a higher inhibitory platelet activity than high-dose clopidogrel (11). A prespecified, subgroup analysis of the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction 38 (TRITON-TIMI 38) showed that prasugrel significantly reduced the incidence of the composite of cardiovascular death, myocardial infarction, and stroke compared with clopidogrel (12.2 and 17.0%, respectively, HR 0.70; $P < 0.001$) among DM patients, although without significant DM status-by-treatment interaction (12). Of note, no benefit on mortality was observed with prasugrel over clopidogrel. Furthermore, in the subgroup analyses of the Platelet Inhibition and Patient Outcomes (PLATO) trial, the reduction in the primary composite end point, all-cause mortality, and stent thrombosis with no increase in major bleeding in DM patients by ticagrelor was consistent with the overall cohort (3,13). While interpreting the above subanalyses, it has been proposed that prasugrel may be the preferred treatment option in DM patients (14), although a word of caution has been raised by others for comparison between PLATO and TRITON regarding early ischemic events in such patients (3).

There are no direct clinical outcome comparisons of ticagrelor versus prasugrel. In a pharmacodynamic comparison of ticagrelor versus prasugrel in ACS patients undergoing PCI and exhibiting high PR (HPR) while on clopidogrel, ticagrelor reduced PR to a lower level than prasugrel (15). In ST segment elevation myocardial infarction patients undergoing primary PCI, both ticagrelor and prasugrel appeared similarly effective in reducing PR during the first 24 h, with lower PR achieved with ticagrelor than prasugrel at day 5 (16). In the current study, we aimed to compare the pharmacodynamic action of ticagrelor versus prasugrel in DM patients with ACS undergoing PCI who had been pretreated with clopidogrel.

RESEARCH DESIGN AND METHODS

Study protocol

In consecutive type 2 DM patients with ACS undergoing PCI with drug eluting stent implantation, we performed a prospective, randomized, single-center, single-blind, investigator-initiated, crossover study to compare platelet inhibition by 90 mg ticagrelor twice daily versus 10 mg prasugrel once daily. At the time of PCI, clopidogrel-naive patients and those on 75 mg clopidogrel for <7 days without initial loading dose received 600 mg clopidogrel. Patients on clopidogrel <7 days but with 300-mg loading or those on clopidogrel for >7 days did not receive any additional loading. Patients were excluded if they had periprocedural IIb/IIIa inhibitor administration, a history of stroke/transient ischemic attack, age

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≥75 years, body weight <60 kg, active bleeding, bleeding diathesis, chronic oral anticoagulation treatment, PCI or coronary artery bypass grafting during the previous 3 months, hemodynamic instability, platelet count <100,000/μL, hematocrit <30%, HbA_{1c} >10%, creatinine clearance <30 mL/min, severe hepatic dysfunction, use of strong CYP3A inhibitors or inducers, increased risk of bradycardia, or severe chronic obstructive pulmonary disease. All patients received an intra-arterial dose of 70 IU/kg heparin. After PCI, all patients received aspirin 100 mg/day indefinitely. All patients were on DM treatment for at least 1 month, which was kept constant during the study period.

After a baseline blood sampling while on clopidogrel and at least 24 h post-PCI, patients were randomized (day 0) in a 1:1 ratio using computerized random-number generation by an independent investigator to 90 mg ticagrelor twice daily or 10 mg prasugrel once daily, until day 15 post-randomization. At day 15 ± 2, a visit was performed for PR measurement and safety evaluation, with the blood sample being obtained 2–4 h after the last study drug dose, followed by crossover directly to the alternate therapy for an additional 15 days without an intervening washout period. Compliance to antiplatelet therapy was assessed by interview and tablet counting. At day 30 ± 2, patients returned for the clinical and laboratory assessment as they did on day 15. Physicians and operators who performed platelet function testing were blinded as to the actual drug used, while an independent physician monitored bleeding and adverse event data. The study complied with the Declaration of Helsinki and was approved by the institutional review board of our institution. All patients gave their informed written consent. A flowchart diagram of the study is shown in Fig. 1.

Platelet function assay

Peripheral venous blood samples were drawn in a fasting state with a loose tourniquet through a short venous catheter inserted into a forearm vein. The first 2–4 mL of blood was discarded to avoid spontaneous platelet activation, and blood was collected in 3.2% citrate (1.8-mL draw plastic Vacuette tubes; Greiner, Monroe, NC). Platelet function testing was performed with the VerifyNow (Accumetrics Inc., San Diego, CA) point-of-care P2Y12 function assay as previously described (17). The results are reported in P2Y12 reaction units (PRU), BASE, and percent inhibition. The percent inhibition is calculated as: ([BASE − PRU]/BASE) × 100. A value ≥230 PRU was considered as an indication of HPR based on a previous investigation, linking the cutoff point to post-PCI ischemic risk (18).

End points

End points were prespecified in the study protocol and statistical analysis plan. The primary end point was PR assessed at the end of the two (precrossover and postcrossover) study periods. The HPR rate during the same periods was a secondary end point. Bleeding (per the Bleeding Academic Research Consortium [BARC] definition) and major adverse cardiac events (cardiovascular death, myocardial infarction, and stroke) were evaluated during the pre- and postcrossover period.

Sample size calculation

Based on previously published data and on diabetic subgroup analysis (15), we hypothesized that 90 mg ticagrelor twice daily would be superior to 10 mg prasugrel once daily, resulting in an absolute PR

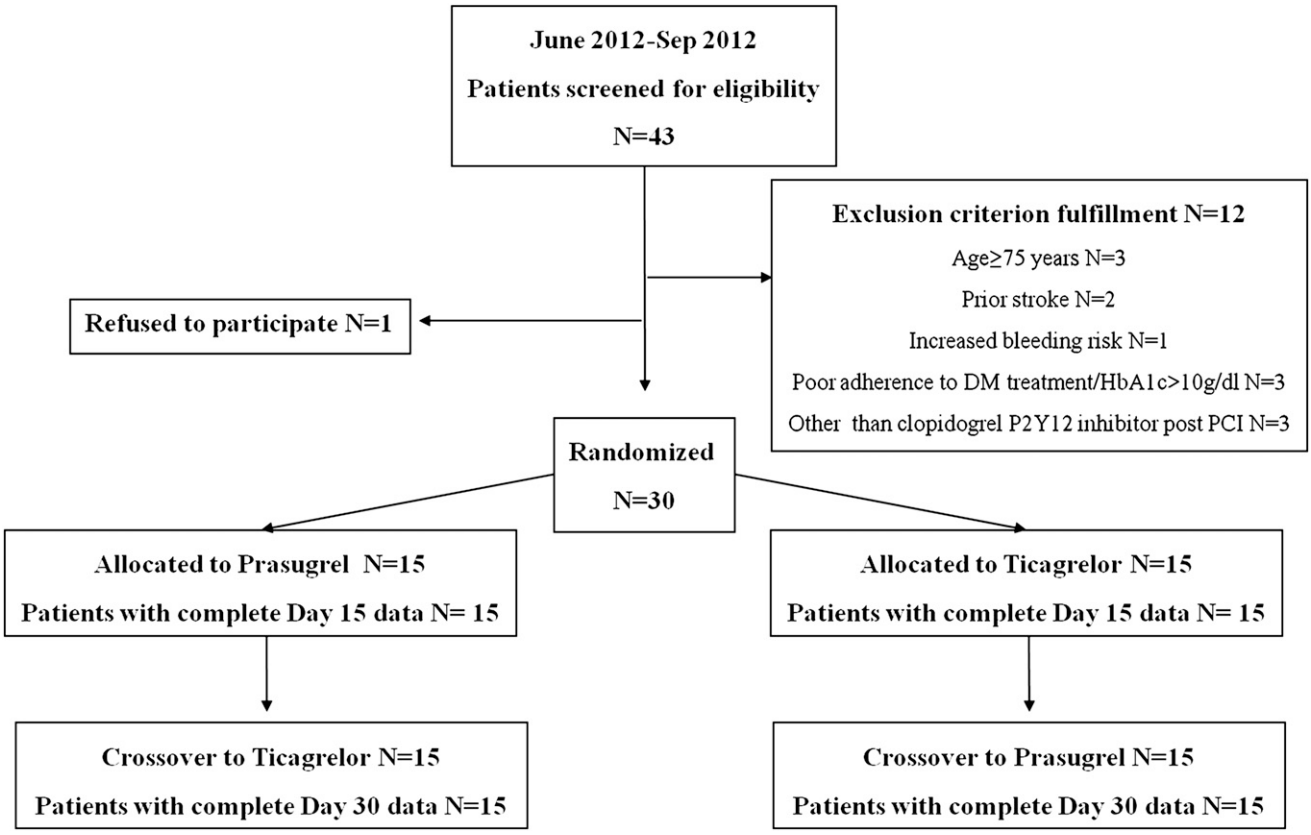

Figure 1—*Study flowchart.*

Table 1—*Demographic characteristics of randomized patients*

	Ticagrelor→prasugrel (*n* = 15)	Prasugrel→ticagrelor (*n* = 15)	*P* value
Male sex	14 (93.3)	14 (93.3)	1.0
Age (years)	65.4 ± 7.7	60.9 ± 8.0	0.1
BMI (kg/m^2)	29.5 ± 3.9	28.9 ± 4.6	0.7
Dyslipidemia	8 (53.3)	7 (46.7)	1.0
Hypertension	10 (66.7)	11 (73.3)	1.0
Time from diagnosis of DM (months)	96 (60–180)	84 (48–180)	0.6
Smoking	6 (40.0)	5 (33.3)	1.0
Family history of CAD	4 (26.7)	2 (13.3)	0.7
Prior myocardial infarction	4 (26.7)	3 (20.0)	1.0
Prior CABG	1 (6.7)	0 (0)	1.0
Prior PCI	3 (20.0)	4 (26.7)	1.0
Peripheral arterial disease	1 (6.7)	0 (0)	1.0
Diagnosis at admission			0.6
ST elevation myocardial infarction	3 (20.0)	4 (26.7)	
Non-ST elevation myocardial infarction	7 (46.7)	4 (26.7)	
Unstable angina	5 (33.3)	7 (46.7)	
Bivalirudin	3 (20.0)	8 (53.3)	0.1
Time from onset of ischemic symptom to balloon (h)	66 (30–92)	66 (26–85)	1.0
Treatment with clopidogrel pre-PCI			
Clopidogrel naive	2 (13.3)	2 (13.3)	1.0
Clopidogrel <7 days without initial LD	1 (6.7)	0 (0)	1.0
Clopidogrel ≥7 days	5 (33.3)	3 (20.0)	0.7
Clopidogrel <7 days with initial 300 mg LD	7 (46.7)	10 (66.7)	0.5
Discharge medication			
Statin	15 (100)	15 (100)	NA
Proton pump inhibitor	9 (60.0)	11 (73.3)	0.7
β-Blocker	14 (93.3)	14 (93.3)	1.0
Nitrate	4 (26.7)	6 (40.0)	0.7
Calcium channel blocker	3 (20.0)	1 (6.7)	0.6
ACE inhibitor	9 (60.0)	8 (53.3)	1.0
Angiotensin II blocker	4 (26.7)	4 (26.7)	1.0
Aspirin	15 (100)	15 (100)	NA
Diuretic	4 (26.7)	3 (20.0)	1.0
Oral hypoglycemic agents	13 (86.7)	14 (93.3)	1.0
Insulin	4 (26.7)	1 (6.7)	0.3
Laboratory evaluation			
Hematocrit (%)	39.7 ± 3.1	40.1 ± 5.5	0.8
Platelets (×1,000/mm^3)	246.1 ± 81.4	244.6 ± 63.8	0.9
HbA_{1c} % (mmol/mol)	7.4 ± 0.7 (57.1 ± 8.3)	7.7 ± 1.0 (60.4 ± 11.1)	0.4
Creatinine clearance (mL/min)	96.4 ± 31.8	84.0 ± 33.1	0.3
PR at day 0			
PRU	214.0 ± 62.4	184.1 ± 70.2	0.2
BASE	228.0 ± 38.1	231.9 ± 58.1	0.8
Inhibition (%)	0 (0–23)	23 (0–35)	0.1

Data are expressed as means ± SD, medians (Q1−Q3), or *n* (%). CABG, coronary artery bypass grafting; LD, loading dose.

difference of 40 PRU (with the assumption that the within-patient standard deviation of the response variable is 50). Choosing a power of 80% and a two-sided α-level of 0.05, at least 27 patients in total were required to reach statistical significance based on the above assumptions.

Statistical analysis

Categorical data are presented as frequencies and group percentages, normally distributed continuous data as means ± SD, and skewed continuous data as medians and range. The Kolmogorov-Smirnov test was used to test the normality of the samples. The two-sample Student *t* test, Mann-Whitney *U* test, and Fisher exact test were used for comparison of normal continuous, skewed continuous, and categorical data, respectively. The primary study end point was analyzed via a mixed linear model, adjusting for period, treatment sequence (carryover), and treatment effect (fixed factors), with patient indicator as a random intercept and PR at baseline as a covariate. Platelet inhibition (%) at the end of treatment periods was analyzed with a similar model with period, treatment sequence (carryover), and treatment effect as fixed factors, patient indicator as random intercept, and percent inhibition at baseline as a covariate. Least squares (LS) estimates of the mean difference are presented, with 95% CIs. Separate ANCOVAs were conducted for the pre- and postcrossover period, with treatment as a fixed effect and PR (PRU) or inhibition (%) at baseline as a covariate. The secondary study end point was analyzed with a Prescott test. All tests were two-tailed, and statistical significance was considered for *P* values <0.05. Analyses were performed using SPSS for Windows (version 16.0; SPSS Inc., Chicago, IL).

RESULTS—Between June 2012 and September 2012, all 30 randomized patients completed both treatment periods and served as their own control. There was no difference in patient demographic and clinical characteristics between groups (Table 1). The primary end point was significantly lower for ticagrelor (45.2 PRU [95% CI 27.4–63.1]) compared with prasugrel (80.8 PRU [63.0–98.7]) with LS mean difference of −35.6 PRU (−55.2 to −15.9, *P* = 0.001) (Table 2). Data for the precrossover and postcrossover periods are shown in Fig. 2. No period or carryover effect was found. Similar results were found for percent inhibition (Table 3). The secondary end point of the HPR rate was 0% for ticagrelor and 3.3% for prasugrel (1 of 30, *P* = 1.0). Individual PR values according to treatment are depicted in Fig. 3.

No major bleedings or major adverse cardiovascular events occurred in either treatment group. In total, six patients (20%) reported a BARC-1 bleeding event (four and two while under ticagrelor and prasugrel, respectively). Mild to moderate dyspnea not leading to study drug

Table 2—*PR (in PRU) at the end of treatment periods*

End point	*N*	Ticagrelor LS estimates (95% CI)	*n*	Prasugrel LS estimates (95% CI)	*n*	LS mean difference (95% CI)	*P* value
PR day 15 (precrossover)	30	55.1 (29.7–80.3)	15	66.0 (40.8–91.2)	15	−10.9 (−46.9 to 25.2)	0.5
PR day 30 (postcrossover)	30	37.8 (10.9–64.6)	15	93.2 (66.4–120.1)	15	−55.4 (−93.9 to −16.9)	0.006
Combined data (pre- and postcrossover)	60	45.2 (27.4–63.1)	30	80.8 (63.0–98.7)	30	−35.6 (−55.2 to −15.9)	0.001

discontinuation occurred in seven patients (23.3%) while receiving ticagrelor.

CONCLUSIONS—In this first direct pharmacodynamic comparison of ticagrelor versus prasugrel in an exclusively DM population, we have demonstrated that ticagrelor provides stronger platelet inhibition than prasugrel. However, both agents effectively treat HPR. These results are in the same line of evidence with studies in mixed (DM and non-DM) patient populations (15,16).

In the OPTIMUS-3 study, in DM patients with CAD, prasugrel resulted in a higher inhibitory platelet activity than high-dose clopidogrel (11). In prasugrel-treated patients, PR was 120 PRU at 7 days (24 h after the last maintenance dose), and the HPR rate was 2.9%. In DM patients also undergoing PCI for ACS and treated by clopidogrel, switching to 10 mg prasugrel daily resulted in a reduction of PR and HPR at 1 month (19). Our findings concerning prasugrel are in agreement with these results. To our knowledge, there has been no previous pharmacodynamic study with ticagrelor exclusively in DM patients. In diabetic rats, the ADP-induced platelet aggregation was strongly reduced by ticagrelor (20). The consistent, very low PR levels achieved with ticagrelor in our DM patients are similar to those described in stable CAD and in ACS patients undergoing PCI and exhibiting HPR while on clopidogrel and receiving this agent (15,21).

In the TRITON-TIMI 38 trial, the primary end point's absolute reduction with prasugrel compared with clopidogrel was 4.8%, while in the PLATO trial, the primary end point's absolute reduction with ticagrelor compared with clopidogrel was 2.1%. This has led to the suggestion that prasugrel treatment may a be a more appropriate choice when treating DM patients (14). Our results point in the opposite direction, since ticagrelor appears to be a stronger antiplatelet agent than prasugrel in DM patients, in consistency with pharmacodynamic results from direct comparisons of the two agents in mixed populations (15,16). Prasugrel might be, indeed, more suitable than ticagrelor for DM patients. This hypothesis, however, should be clinically tested with a direct comparison of the two agents in a DM population. If this scenario proves to be valid, our study suggests that differences other than PR reduction will be sought between the two agents. The possibility that, despite very high levels of platelet inhibition achieved by ticagrelor, this treatment may not be sufficient for adequate protection against ischemic events in patients with DM has been raised previously, along with the possible requirement of other therapy, beyond the antiplatelet, antithrombin, or long-term anticoagulation one (3). Of note, in the diabetic cohort of the Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes (TRILOGY ACS) trial, prasugrel did not significantly reduce the frequency of the primary end point, as compared with clopidogrel, a finding consistent with the overall trial results (22).

Only one method of platelet function testing was used, and in a recent study, altering antiplatelet therapy on the basis of results from VerifyNow did not change clinical outcomes (23). However, the Verify Now assay is most likely the best validated platelet function test and has been found to correlate well with light transmittance aggregometry, which is considered to be the "gold standard" method. Active metabolites were not measured and pharmacokinetic correlations cannot be made. Since the majority of ACS patients in our area still receive clopidogrel at first medical contact, switching thereafter to the newer agent most commonly in the PCI hospital, we did not study clopidogrel-naive patients for recruitment purposes. This practice, however, is commonly followed (19). Our study was a pharmacodynamic one, and no conclusions on the clinical outcome of DM patients treated with ticagrelor or prasugrel can be drawn. Therefore, our results could be considered preliminary, though hypothesis generating.

In DM patients with ACS who had been pretreated with clopidogrel and underwent PCI, ticagrelor achieved a significantly higher platelet inhibition than prasugrel. Both antiplatelet agents effectively treated HPR. The relevance of these findings to the clinical efficacy and safety

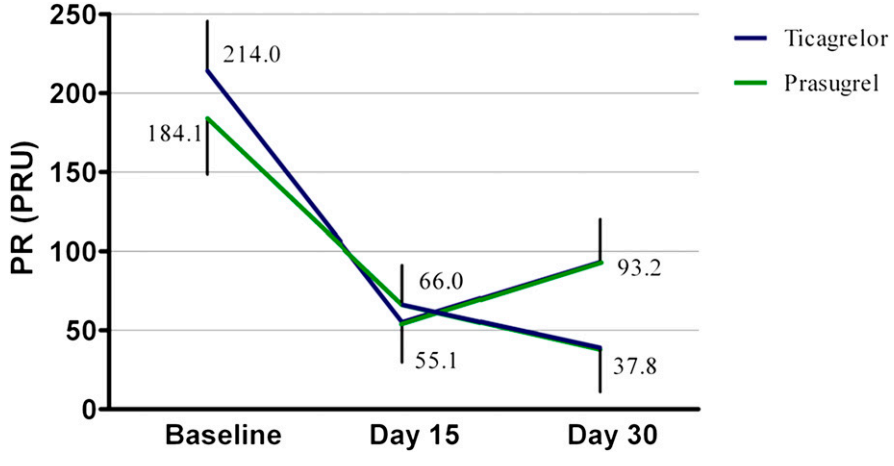

Figure 2—*PR (in PRU) by treatment sequence, LS estimates, and 95% CIs are presented.*

Table 3—*Platelet inhibition (%) at the end of treatment periods*

End point	*N*	Ticagrelor LS estimates (95% CI)	*n*	Prasugrel LS estimates (95% CI)	*n*	LS mean difference (95% CI)	*P* value
PR day 15 (precrossover)	30	78.3 (61.3–83.2)	15	72.3 (61.3–83.2)	15	5.9 (−9.8 to 21.6)	0.4
PR day 30 (postcrossover)	30	83.5 (72.7–94.2)	15	64.8 (54.0–75.6)	15	18.6 (3.2–34.1)	0.02
Combined data (pre- and postcrossover)	60	81.7 (74.2–89.3)	30	67.7 (60.1–75.2)	30	14.0 (6.1–22.0)	0.001

of ticagrelor and prasugrel in DM patients needs further elucidation.

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D.A. wrote the manuscript. I.X. and K.S. researched and analyzed data. E.M., A.S., and E.T. researched data. P.D. contributed to discussion and reviewed and edited the manuscript. D.A. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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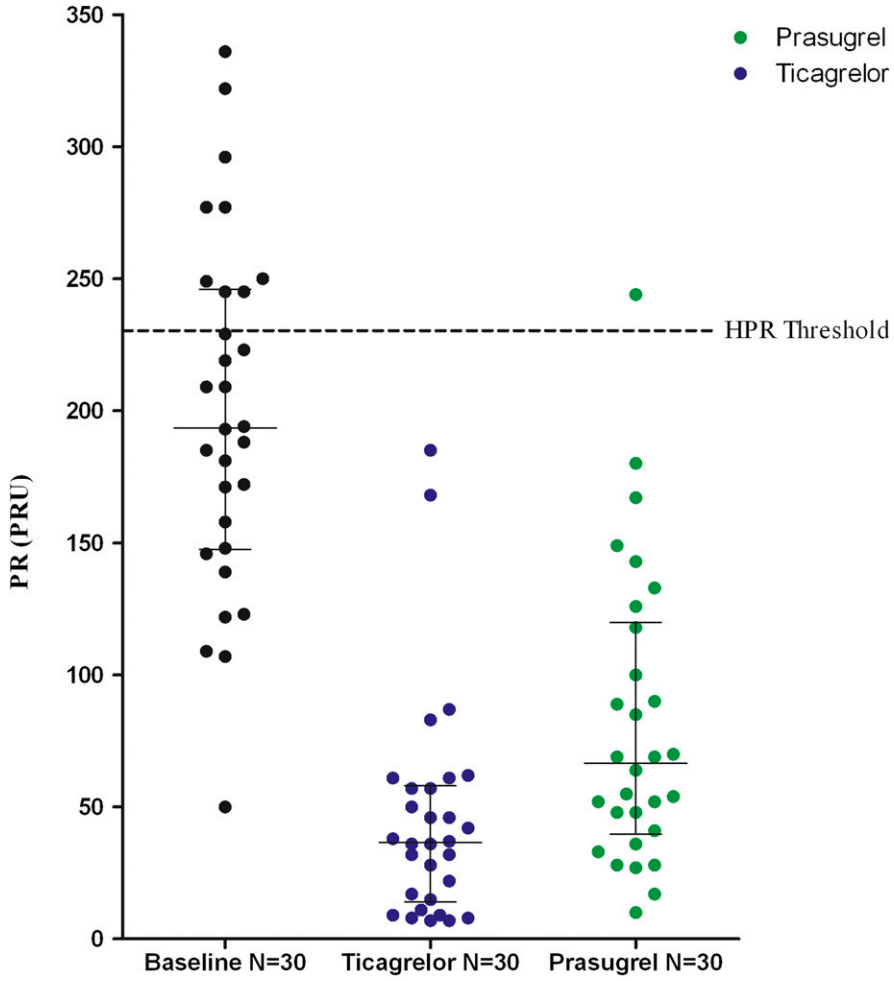

Figure 3—*Individual PR values according to treatment. Combined data for the precrossover and postcrossover periods are depicted. Lines represent medians, and error bars represent interquartile range.*

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