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BRIEF REPORT

Impact of Prasugrel Reload Dosing Regimens on High On-Treatment Platelet Reactivity Rates in Patients on Maintenance Prasugrel Therapy

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In acute coronary syndrome (ACS) patients undergoing percutaneous coronary interventions (PCI), prasugrel is associated with a greater reduction in atherothrombotic events, albeit at the expense of increased bleeding, compared with clopidogrel (1). However, despite its greater antiplatelet potency compared with clopidogrel, recent investigations have shown that prasugrel-treated patients may still have high on-treatment platelet reactivity (HPR) and remain at risk for ischemic recurrences (2). Of note, these pharmacodynamic (PD) assessments were limited to a single assay and HPR cutoff value, potentially overestimating the true prevalence of HPR, which would be more comprehensively defined by using multiple assays and other recommended cutoff values (2,3). In addition, PD assessments were performed in the peri-PCI period, during which spuriously higher rates of HPR are measured and which decrease over time once patients are in their steady-state maintenance phase of therapy (3,4). This may explain why results of PD testing performed remote from PCI have greater prognostic significance than those obtained in the peri-PCI period (4). To date, there is limited information on the PD effects of prasugrel and rates of HPR using multiple PD assays and cutoff values while patients are in their steady-state phase of treatment.

This is a post-hoc analysis of a prospective, randomized, PD study recently reported in *JACC* (5). Details of the inclusion and exclusion criteria and study design for the main trial have been published previously (5). In brief, patients in a steady-state phase of prasugrel maintenance therapy (10 mg daily) for at least 14 days after an ACS undergoing PCI were studied. Patients were randomized (1:1:1 fashion) to receive 10, 30, or 60 mg of prasugrel, and PD testing was conducted at 3 time points: baseline, and 1 and 4 h following dosing. Baseline PD assessments were representative of trough levels of platelet reactivity (last maintenance dose taken 18 to 24 h before blood sampling). Platelet function assays included flow cytometric analysis of the phosphorylation status of the vasodilator-stimulated phosphoprotein (VASP), VerifyNow P2Y12 assay (Accumetrics, San Diego, California), and light transmission aggregometry (LTA) using 5 and 20 μmol/l adenosine diphosphate (ADP) as stimuli. In the present analysis, established cutoff points that have been associated with adverse ischemic events were used to define HPR: platelet reactivity index (PRI) $\geq$50% for VASP assay; $P2Y_{12}$ reaction units (PRU) >230 for the VerifyNow P2Y12 assay; and >46% and >59%

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maximal platelet aggregation (MPA) for LTA using 5 and 20 μmol/l ADP, respectively (3). Categorical variables were expressed as frequencies and percentages. Intragroup comparisons of HPR were performed with the McNemar test or binomial exact. Chi-square test or Fisher exact test (according to application conditions) were used to compare the percentage of patients with HPR among treatment groups (intergroup comparisons). A p value <0.05 was considered statistically significant for all comparisons.

A total of 64 patients who completed all time periods were studied: 10 mg (n = 22), 30 mg (n = 21), and 60 mg (n = 21). In the overall study population, the percentage of HPR patients at baseline ranged from 6.3% to 12.5%, depending on the assay used (VASP: 12.5%, VerifyNow P2Y12: 7.8%, LTA ADP 5 μM: 9.4%, LTA ADP 20 μM: 6.3%). Although nonstatistically significant p values were obtained for all intra- or intergroup comparisons, the 30-mg and 60-mg dosing regimens achieved numerically lower HPR rates compared with the 10-mg dosing at 1 and 4 h using all assays (Table 1). In particular, following a 10-mg dose, rates of HPR remained either unchanged or reduced, depending on the assay used, ranging from 0% to 9.1% (Table 1). Following a 30-mg or 60-mg dose, rates of HPR decreased at 1 and 4 h. However, HPR rates were always null only with a 60-mg dose.

The findings of the present investigation conducted in patients who suffered an ACS and underwent PCI demonstrate that: 1) trough levels of platelet reactivity (18 to 24 h after last maintenance dose) in patients in their steady-state phase of prasugrel therapy are overall low, ranging from 6.3% to 12.5%, depending on the assay used; 2) 4 h following a 10-mg dose (approximating peak platelet reactivity levels), HPR rates were overall reduced, ranging from 0% to 9.1% depending on the assay used; and 3) following a 30-mg or 60-mg dose, HPR rates were reduced with all assays with only 1 patient persisting with HPR after a 30-mg dose and no patients with HPR after a 60-mg dose. Several take-home messages derive from these observations. First, similar to the more established experience with clopidogrel, in prasugrel-treated patients, rates of HPR may be subject to variability according to the PD assay used, with VASP-PRI showing the highest rates (3). However, HPR rates defined by VASP-PRI assessed in our study population in their steady-state phase of maintenance prasugrel therapy were markedly lower (12.5% for trough levels and 9.1% for peak levels after maintenance dose) than those previously reported from PD assessments following a 60-mg loading dose administration conducted in the peri-PCI period (25% HPR rate) (2). These observations suggest that not only the assay chosen, but also the timing of PD assessments has an important impact on more accurately defining HPR rates. This is in line with findings from PD studies with clopidogrel showing that response rates performed remote from the peri-PCI period, once patients are in their steady-state phase of treatment, not only improve, but also have better prognostic value (4). Further, our study results may also have practical implications for prasugrel-treated patients requiring subsequent revascularization (e.g., due to chronic progression of coronary atherosclerotic disease processes or staged PCI). We acknowledge the inherent limitations of this investigation as being a post hoc analysis of a

Abbreviations and Acronyms

ACS = acute coronary syndrome

ADP = adenosine diphosphate

HPR = high on-treatment platelet reactivity

LTA = light transmission aggregometry

MPA = maximal platelet aggregation

PCI = percutaneous coronary interventions

PD = pharmacodynamic

PRI = platelet reactivity index

PRU = $P2Y_{12}$ reaction units

VASP = vasodilator-stimulated phosphoprotein

Table 1. HPR Rates Measured With Different Platelet Function Assays in Patients on Maintenance Prasugrel Therapy Before and After Escalating Prasugrel Dosing Regimens

HPR Definition	Time Point	Overall (N = 64)	10 mg (n = 22)	30 mg (n = 21)	60 mg (n = 21)
VASP ≥50% PRI	Baseline	8 (12.5%)	5 (22.7%)	2 (10.5%)	1 (4.8%)
	1 h	2 (3.1%)	2 (9.1%)	0 (0%)	0 (0%)
	4 h	2 (3.1%)	2 (9.1%)	0 (0%)	0 (0%)
VN-P2Y12 >230 PRU	Baseline	5 (7.8%)	2 (9.1%)	2 (9.5%)	1 (4.8%)
	1 h	3 (4.7%)	2 (9.1%)	1 (4.8%)	0 (0%)
	4 h	1 (1.6%)	1 (4.5%)	0 (0%)	0 (0%)
LTA (ADP 5 μM) >46% MPA	Baseline	6 (9.4%)	2 (9.1%)	2 (9.5%)	2 (9.5%)
	1 h	2 (3.1%)	1 (4.5%)	1 (4.8%)	0 (0%)
	4 h	2 (3.1%)	1 (4.5%)	1 (4.8%)	0 (0%)
LTA (ADP 20 μM) >59% MPA	Baseline	4 (6.3%)	1 (4.5%)	2 (9.5%)	1 (4.8%)
	1 h	1 (1.6%)	1 (4.5%)	0 (0%)	0 (0%)
	4 h	1 (1.6%)	0 (0%)	1 (4.8%)	0 (0%)

ADP = adenosine diphosphate; HPR = high on-treatment platelet reactivity; LTA = light transmittance aggregometry; MPA = maximal platelet aggregation; PRI = platelet reactivity index; PRU = $P2Y_{12}$ reaction units; VASP = vasodilator-stimulated phosphoprotein assay; VN-P2Y12 = VerifyNow P2Y12 assay.

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PD study. Indeed, a prospective randomized study powered to detect differences in outcomes is warranted to support the clinical implications of our analysis. The findings of the present investigation show that an additional loading dose of prasugrel is useful to overcome HPR; in particular, there were no cases of HPR following a 60-mg loading dose. Therefore, although our study does not provide any insights on the safety or efficacy of a 60-mg loading dose strategy in patients already on chronic prasugrel, it is well established that HPR rates are associated with increased peri-PCI complications. Therefore, our study offers information on the PD effects of reloading patients on chronic prasugrel therapy and strategies to minimize HPR rates.

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