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High On-Treatment Platelet Reactivity After Prasugrel Loading Dose and Cardiovascular Events After Percutaneous Coronary Intervention in Acute Coronary Syndromes

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Objectives The aim of this study was to investigate the relationship between platelet reactivity (PR) after a loading dose (LD) of prasugrel and thrombotic events.

Background Post-treatment PR has been shown to be strongly associated with the occurrence of major adverse cardiac events (MACE) after percutaneous coronary intervention (PCI) in the clopidogrel era. Prasugrel is a new $P2Y_{12}$–adenosine diphosphate receptor with a higher potency on PR.

Methods A prospective multicenter study included patients who underwent successful PCI for acute coronary syndromes and received prasugrel therapy. Vasodilator-stimulated phosphoprotein (VASP) index was measured after the prasugrel LD. High on-treatment PR was defined as a VASP index ≥50%. MACE included cardiovascular death, myocardial infarction, and definite stent thrombosis at 1 month.

Results Three hundred one patients were enrolled. The mean VASP index after 60 mg of prasugrel was 34.3 ± 23.1%. High on-treatment PR was observed in 76 patients (25.2%). Patients experiencing thrombotic events after PCI had significantly higher VASP indexes compared with those free of events (64.4 ± 14.4% vs. 33.4 ± 22.7%; range: 51% to 64% and 5% to 47.6%, respectively; $p = 0.001$). Kaplan-Meier analysis comparing good responders and patients with high on-treatment PR demonstrated a significantly higher rate of MACE in patients with suboptimal PR inhibition (log-rank $p < 0.001$). Receiver-operating characteristic curve analysis found a cutoff value of 53.5% of the VASP index to predict thrombotic events at 1 month ($r = 0.86$, $p < 0.001$). Patients with minor or major Thrombolysis In Myocardial Infarction unrelated to coronary artery bypass grafting bleeding and those without had similar VASP indexes (30 ± 17.8% vs. 34.3 ± 23%, $p = 0.70$).

Conclusions Despite the use of prasugrel, a significant number of patients undergoing PCI in the setting of acute coronary syndromes do not achieve optimal PR inhibition. Such patients have a higher risk for MACE after PCI. (J Am Coll Cardiol 2011;58:467–73) © 2011 by the American College of Cardiology Foundation

The addition of clopidogrel to aspirin in patients undergoing percutaneous coronary intervention (PCI) for acute coronary syndromes (ACS) has enabled a dramatic decrease in the rate of thrombotic events (1). However, clopidogrel

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Abbreviations and Acronyms

ACS = acute coronary syndromes
ADP = adenosine diphosphate
CABG = coronary artery bypass grafting
CV = cardiovascular
HTPR = high on-treatment platelet reactivity
LD = loading dose
MACE = major adverse cardiac event(s)
MFI = mean fluorescence intensity
PCI = percutaneous coronary intervention
PGE_1 = prostaglandin E_1
PR = platelet reactivity
ROC = receiver-operating characteristic
TIMI = Thrombolysis In Myocardial Infarction
VASP = vasodilator-stimulated phosphoprotein

has 3 main limitations: a slow onset of action, mild potency, and large interindividual variability in response (2,3). Of importance, several studies have highlighted a link between high on-treatment platelet reactivity (HTPR), or suboptimal platelet reactivity (PR) inhibition, as measured by platelet assays after a clopidogrel loading dose (LD) and the occurrence of thrombotic events after PCI (3,4). The vasodilator-stimulated phosphoprotein (VASP) index is the most specific platelet assay to assess PR inhibition related to $P2Y_{12}$–adenosine diphosphate (ADP) receptor antagonists. A recent consensus has been published, on the basis of receiver-operating characteristic (ROC) curve analysis, regarding the predictive value of various platelets assays to predict major adverse cardiac events (MACE) after PCI. In this consensus report, HTPR was defined as a VASP index ≥50% (3). This cutoff value exhibited very high negative predictive value for thrombotic events in several trials and has therefore been used to tailor therapy to improve clinical outcomes in patients undergoing PCI (5,6).

Prasugrel is a third-generation thienopyridine that has demonstrated faster and more potent $P2Y_{12}$-ADP receptor inhibition than clopidogrel (7). Like clopidogrel, prasugrel is a prodrug that requires bioactivation steps, including biotransformation by hepatic cytochromes into actives metabolites. In TRITON–TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel–Thrombolysis In Myocardial Infarction 38), prasugrel therapy resulted in a significant reduction in MACE after PCI compared with clopidogrel in patients with ACS (8). Its benefit, within the first 30 days, was related to a reduction in recurrent thrombotic events, including early stent thrombosis. This benefit is related to the favorable pharmacodynamic profile of prasugrel compared with clopidogrel, as these 2 drugs share similar active metabolites (9). Interestingly, in a recently published substudy of TRITON–TIMI 38, the investigators observed a relatively high rate of HTPR, as defined using the consensus definition, in patients receiving prasugrel therapy (10). However, to date, a potential link between PR inhibition and recurrent thrombotic events after PCI has not been evaluated in patients receiving prasugrel therapy. In the present study, we aimed to investigate the relationship between PR inhibition and the occurrence of MACE in patients undergoing successful PCI for ACS and receiving prasugrel.

Methods

A prospective multicenter study was performed. Patients presenting with ACS and undergoing successful PCI who received prasugrel and gave informed consent to participate in the study were eligible. Patients were enrolled in the study between February and September 2010. The protocol was approved by each of the local ethics committees and was in accordance with the Declaration of Helsinki.

Exclusion criteria were failed PCI, cardiac arrest, contraindications to antiplatelet therapy, a platelet count <100 g/l, history of bleeding diathesis, concurrent severe illness with expected survival <1 month, surgery within 1 month or scheduled in the following year, age over 75 years, warfarin or other oral anticoagulant therapy, weight <60 kg, history of stroke, noncompliance with therapy, or an inadequate prasugrel LD. Five patients were excluded from the study because they did receive concomitant anticoagulant therapy (warfarin) after PCI.

PR measurements. Blood samples for VASP index analysis were drawn by atraumatic venipuncture of the antecubital vein at least 6 h and within 12 h after prasugrel LD. The initial blood drawn was discarded to avoid measuring platelet activation induced by needle puncture; blood was collected into a Vacutainer (Becton, Dickinson and Company, Franklin Lakes, New Jersey) containing 3.8% trisodium citrate and filled to capacity. The Vacutainer was inverted 3 to 5 times for gentle mixing and sent immediately to the hemostasis laboratory. VASP index phosphorylation analysis was performed within 24 h of blood collection by an experienced investigator using Platelet VASP kits (Diagnostica Stago, Asnières, France) (4,5). Briefly, a citrated blood sample was incubated with prostaglandin E_1 (PGE_1) or with PGE_1 and ADP 10 μmol/l for 10 min and fixed with paraformaldehyde, after which the platelets were permeabilized with a nonionic detergent. Analyses were performed on an EPICS XL-MCL flow cytometer (Beckman Coultronics, Margency, France), the platelet population was identified from its forward and side scatter distribution, and 10,000 platelets were gated. VASP index was calculated from the mean fluorescence intensity (MFI) of samples incubated with PGE_1 or PGE_1 and ADP according to the formula: $VASP = [(MFI_{PGE1} - MFI_{PGE1\_ADP})/MFI_{PGE1}] \times 100$. HTPR was defined as a VASP index ≥ 50% according to the consensus definition (3).

PCI. PCI was performed according to international guidelines, using a standard technique through the radial or femoral route. Successful stent implantation was achieved in all patients. Either a drug-eluting or a bare-metal stent was used according to French Society of Cardiology guidelines. The sheath was removed immediately at the end of the procedure in all cases. Routine care before and after the procedure was undertaken for all patients, including pre-