Switching Acute Coronary Syndrome Patients From Prasugrel to Clopidogrel

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Objectives This study sought to assess the consequences of switching prasugrel to clopidogrel on platelet inhibition and clinical outcomes after an acute coronary syndrome (ACS).

Background Many ACS patients are switched from prasugrel to clopidogrel within the recommended 1-year duration of treatment.

Methods Platelet reactivity was measured with the VerifyNow P2Y12 assay (Accumetrics, San Diego, California) in 300 ACS patients treated for 15 days with prasugrel 10 mg. Patients displaying low on-treatment platelet reactivity (LPR) and/or at high risk of bleeding were switched to clopidogrel 75 mg and tested again 15 days later. The rate of patients with high on-treatment platelet reactivity (HPR), P2Y12 reaction units (PRU) >208, and LPR (PRU <0) were evaluated before and after the switch. Bleeding and ischemic events were also recorded.

Results On a regimen of prasugrel 10 mg, the rate of patients with LPR was 45.6% (n = 137), whereas 4.3% (n = 13) had HPR. A group of 31 patients (10.3%) was switched to clopidogrel 75 mg, of whom 29 had LPR (93.5%) on a regimen of prasugrel. On-treatment platelet reactivity (PRU) increased from 14 ± 4 on a regimen of prasugrel to 155 ± 15 on a regimen of clopidogrel (p = 0.0001), resulting in a much lower rate of patients with LPR (9.7%). The rate of patients with HPR increased from 0% with prasugrel to 29% (n = 9) with clopidogrel. The rate of minor bleeding decreased after the switch from 32.2% to 9.7%; p = 0.03.

Conclusions An LPR is frequent in patients treated with prasugrel 10 mg. Early switching from prasugrel 10 mg to clopidogrel 75 mg reduces the number of patients with LPR and minor bleeding events but unmasks a group of nonresponders to clopidogrel with unknown consequences on clinical outcomes. (J Am Coll Cardiol Intv 2013;6:158–65) © 2013 by the American College of Cardiology Foundation
Prasugrel has been the first P2Y\textsubscript{12} antagonist available to overcome clopidogrel poor response with a significant improvement in clinical outcome of acute coronary syndrome (ACS) patients (1). Prasugrel has become a first-line therapy especially in ST-segment elevation myocardial infarction patients (2) and in diabetic patients (3) undergoing primary percutaneous coronary intervention (PCI). American and European guidelines recommend dual antiplatelet therapy for 1 year after an acute ACS; maintenance therapy with prasugrel relies on a daily dose of 10 mg or a reduced dose of 5 mg in elderly patients (>75 years) and in low body weight (<60 kg) patients (4,5). Despite the evidence for a consistent and sustained clinical benefit with prasugrel in the long term, many physicians switch their patients to clopidogrel before the end of the recommended 1-year period of treatment. The main reason for a strategy of switching seems to be safety concerns. However, the pharmacodynamic and clinical impact of switching prasugrel to clopidogrel is unknown. The aim of our study was to assess platelet reactivity and clinical outcomes in ACS patients before and after a switch from prasugrel 10 mg to clopidogrel 75 mg.

**Methods**

**Study design.** Acute coronary syndrome patients treated by PCI and prasugrel 10 mg at the Pitié-Salpêtrière hospital in Paris were prospectively monitored for platelet reactivity 15 days after hospital discharge. After clinical examination and platelet function monitoring, some patients were switched to clopidogrel 75 mg maintenance dose. The decision was left to the discretion of the physician, and the reasons for the switch were recorded. A second platelet reactivity measurement was carried out 15 days later in patients who were switched to clopidogrel. Platelet reactivity was evaluated with the VerifyNow P2Y\textsubscript{12} assay (Accumetrics, San Diego, California), light transmission aggregometry (LTA), and the vasodilator-stimulated phosphoprotein (VASP) platelet reactivity index (PRI) according to methods and definitions used in previous studies (6,7). Clinical follow-up evaluated bleeding and ischemic events up to 30 days. Patient characteristics were entered into a prospective web-based registry (ONASSIST [ONline ASSIstance for Stent Thrombo sis] registry) regrouping clinical and biological data as well as the identification of drug intake to evaluate potential drug–drug interaction.

**Study population.** Patients entered in the prospective ONASSIST registry for this study were treated by prasugrel 10 mg maintenance dose, the only dosage available in France (8). Exclusion criteria for participation to the study were any contraindication to prasugrel, glycoprotein IIb/IIIa antagonist administration within 7 days before inclusion, and a low platelet count <100,000/ml. The Pitié-Salpêtrière University Hospital Ethics Committee approved the protocol, and the study was conducted in accordance with the Declaration of Helsinki.

**Platelet function tests. VerifyNow P2Y\textsubscript{12} assay.** For the VerifyNow P2Y\textsubscript{12} assay (Accumetrics, San Diego, California), samples were run according to the package insert. Results were expressed in P2Y\textsubscript{12} reaction units (PRU) in response to iso-Thrombin Receptor Activating Peptide and to adenosine diphosphate (ADP)-prostaglandin E1 (PGE\textsubscript{1}) and in percentage of inhibition corresponding to the ratio of the results of the ADP-PGE\textsubscript{1} and iso-Thrombin Receptor Activating Peptide channels.

**LTA.** Blood was collected into Becton-Dickinson (Franklin Lakes, New Jersey) 3.2% citrate vacutte tubes. Platelet-rich plasma was obtained by centrifugation of citrated whole blood at 1,000 g for 10 min at 20°C. Platelet-poor plasma was obtained by further centrifugation at 4,500 g for 15 min. In vitro platelet aggregation in platelet-rich plasma was measured at 37°C by LTA (model 490-4D; Chrono-Log Corp., Kordia, the Netherlands) and was induced by the addition of ADP (Sigma-Aldrich, Saint-Quentin Fallavier, France) at a final concentration of 20 μmol/l. All measurements were performed in duplicate and results were expressed in maximal platelet aggregation (MPA) and residual platelet aggregation (RPA) measured at 6 min. Pre-specified criteria used to define non-evaluable samples were lack of sufficient signal, hemolysis, and platelet count <100,000/ml and an unstable baseline.

**VASP-PRI.** The phosphorylation of the VASP was measured with a Beckman Coulter FC500 cytometer (Beckman Coulter, Villepinte, France) or with enzyme-linked immunoadsorbent assay VASP-P technique (Thermo Scientific Multiskan Ascent, BioCytex, Stago, Paris, France) according to manufacturer instructions and previous studies. Blood samples were incubated in vitro with ADP and PGE\textsubscript{1} before fixation. The VASP PRI measured by flow cytometer was calculated from the median fluorescence intensity (MFI) of each condition according to methods expressed in P2Y\textsubscript{12} reaction units (PRU) in response to iso-Thrombin Receptor Activating Peptide and to adenosine diphosphate (ADP)-prostaglandin E1 (PGE\textsubscript{1}).

**Abbreviations and Acronyms**

- **ACS**: acute coronary syndrome
- **ADP**: adenosine diphosphate
- **BARC**: Bleeding Academy Research Consortium
- **HPR**: high on-treatment platelet reactivity
- **LPR**: low on-treatment platelet reactivity
- **LTA**: light transmission aggregometry
- **MFI**: median fluorescence intensity
- **MPA**: maximal platelet aggregation
- **PCI**: percutaneous coronary intervention
- **PGE\textsubscript{1}**: prostaglandin E1
- **PRI**: platelet reactivity index
- **PRU**: P2Y\textsubscript{12} reaction units
- **RPA**: residual platelet aggregation
- **VASP**: vasodilator-stimulated phosphoprotein
to the formula: VASP PRI = ([MFI (PGE₁) - MFI (PGE₁ + ADP)]/MFI [PGE₁]) × 100.

**Study endpoints.** The main endpoint was the variation in the rate of both high on-treatment platelet reactivity (HPR) and low on-treatment platelet reactivity (LPR) before and after the switch from prasugrel 10 mg maintenance dose to clopidogrel 75 mg maintenance dose, with the PRU from the VerifyNow P2Y₁₂ platform assay with the predefined thresholds of PRU > 208 for HPR (9) and PRU < 30 for LPR (10), respectively.

Other endpoints were the variations in the rate of HPR and LPR before and after the switch, with VASP index and LTA with cutoff values of PRI > 50% and percentage of residual platelet inhibition > 46.2% or maximal platelet inhibition > 59% for HPR with VASP and LTA, respectively (11,12). Due to the lack of a consensus definition of LPR with VASP and LTA, the thresholds were determined retrospectively as the 25th percentile of values of our overall database and calculated as a PRI < 10%, RPA < 1%, and MPA < 20.5%, respectively.

The therapeutic window was defined as: 1) PRU between 30 and 208; 2) PRI between 10% and 50%; 3) RPA between 1% and 46.2%; or 4) MPA between 20.5% and 59%.

Another endpoint was the variation in the rate of minor and major bleeding events according to the Bleeding Academy Research Consortium (BARC) classification (13) and ischemic events, stent thrombosis, and myocardial infarction up to 30 days.

**Statistical analysis.** On the basis of previous platelet function studies (6), at least 30 switched patients were needed to yield 90% power with an alpha-risk error of 0.05, assuming a 40% SD to demonstrate that switching from prasugrel to clopidogrel led to a 90% higher level of platelet reactivity as measured by the VerifyNow P2Y₁₂.

Normal distribution of the variables was evaluated for continuous variables after a normal distribution are assumed a 40% SD to demonstrate that switching from prasugrel to clopidogrel led to a 90% higher level of platelet reactivity as measured by the VerifyNow P2Y₁₂. Normal distribution of the variables was evaluated for continuous variables with the Kolmogorov-Smirnov test. Continuous variables after a normal distribution are presented as mean ± SD and were compared with Student unpaired t test or paired t test when appropriate. Categorical variables are presented as counts and percentages and were compared by means of the chi-square test or Fisher exact test. Results are reported as mean ± SD for the detailed analyses. All p values are 2-sided, and a value of p < 0.05 was considered significant. All analyses were performed with PRISM (version 5; Graph Pad, San Diego, California). All the authors had full access to and take full responsibility for the integrity of the data.

<table>
<thead>
<tr>
<th>Table 1. Baseline Characteristics</th>
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<td>2-vessel disease, %</td>
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<td>Calcium antagonist, %</td>
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<td>Statins, %</td>
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<td>Proton pump inhibitors, %</td>
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Values are Mean ± SD; *p < 0.05.

ACE = angiotensin-converting enzyme; ASA = acetylsalicylic acid; BMI = body mass index; CAD = coronary artery disease; CrCl = creatinine clearance; EF = ejection fraction.
Results

Study population. Of 345 ACS consecutive patients who entered the prospective ONASSIST registry being exposed to a daily 10-mg maintenance dose of prasugrel, 300 patients agreed to participate in the study and had a platelet function-testing visit 15 days after hospital discharge. Our study population was a high-risk population, with one-third of ST-segment elevation myocardial infarction patients who underwent primary PCI and one-third of diabetic patients who presented with non-ST-segment elevation myocardial infarction and had PCI performed. Baseline characteristics are presented in Table 1.

Platelet response to prasugrel 10 mg. The rate of patients with HPR and LPR at the first visit was 4.3% (n = 13 of 300) and 45.6% (n = 137 of 300), respectively, according to the predefined PRU cutoff levels of >208 and <30 (Fig. 1). With the other platelet function tests, the rates of HPR were 2.0% with RPA, 2.6% with MPA, and 6.7% with VASP testing. The rates of LPR with VASP, RPA, and MPA were 24.3%, 38.6%, and 24.7%, respectively.

A total of 31 prasugrel-treated patients (10.3%) were switched to a clopidogrel maintenance dose of 75 mg after the first monitoring-visit. Baseline characteristics of patients who were switched to clopidogrel versus those who were maintained on a regimen of prasugrel 10 mg are presented in Table 1. Switched patients were significantly older and displayed a lower body weight and a higher rate of LPR. The LPR was observed in 93.5% versus 39.8% in switched versus nonswitched patients (p < 0.0001). One patient without LPR was switched to clopidogrel because of a suspected allergic reaction (skin rash), and 1 was switched because of a bleeding BARC 2 (hematemesis).

Pharmacodynamic impact of the switch. The switch from prasugrel to clopidogrel led to a 10-fold increase in PRU level (from 14.23 ± 22 before switching to 155.0 ± 87 after switching, p < 0.000 1). One-third of the patients who switched to clopidogrel displayed HPR, whereas there was none on a prasugrel regimen. The rate of LPR was reduced by 10-fold and finally present in >10% of patients maintained on a regimen of clopidogrel (Fig. 2). The other tests showed consistent results as presented in Table 2. The rates of HPR on clopidogrel 75 mg were 19%, 22.6%, and 38% with RPA, MPA, and VASP-PRI, respectively. In contrast, the rates of LPR were 0%, 6.5%, and 10% with RPA, MPA, and VASP-PRI, respectively (p < 0.000 1) (Fig. 3). In the switched group, the clinical characteristics associated with a poor response to clopidogrel were age (62.63 ± 12.03 vs. 71.63 ± 9.69, p = 0.056) and creatinine clearance (95.40 ± 27.39 vs. 67.33 ± 20.57, p = 0.01).

Figure 1. On-Treatment Platelet Reactivity With Prasugrel 10 mg at 15 Days
The rates of high on-treatment platelet reactivity were 4.3%, 6.7%, 2%, and 2.6% with VerifyNow (Accumetrics, San Diego, California), vasodilator-stimulated phosphoprotein measurement, residual platelet aggregation (RPA), and maximal platelet aggregation (MPA), respectively. The rates of low on-treatment platelet reactivity were 45.6%, 24.3%, 38.7%, and 24.7% with Verify Now, vasodilator-stimulated phosphoprotein, RPA, and MPA, respectively. ADP = adenosine diphosphate; PRI = platelet reactivity index; PRU = P2Y12 reaction units.
from prasugrel to clopidogrel. The first finding is that high on-prasugrel platelet reactivity is a rare phenomenon found in <1 of 20 patients, whereas one-half of patients display low on-prasugrel platelet reactivity. The second finding is that prasugrel-treated patients who are switched to clopidogrel on the basis of LPR also display clinical characteristics known to be associated with an increased risk of bleeding (e.g., age >75 years old, low-weight). Third, the switch strategy led to an important reduction of platelet inhibition unmasking high platelet reactivity in one-third of patients taking clopidogrel, some of these patients exhibiting real pharmacodynamic resistance to clopidogrel. The switch strategy is also associated with less frequent minor bleeds.

Switching from a potent platelet inhibitor with a higher bleeding hazard to a weaker agent of the same class of thienopyridines might be justified, especially in patients at higher risk of bleeding. According to TRITON (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel) post-hoc analyses, elderly patients (over 75 years old) and low body weight patients (under 60 kg) have a higher risk of bleeding on a regimen of prasugrel 10 mg maintenance dose, altering the net clinical benefit of prasugrel in these patients (15). Therefore, we report here in a real-life ACS population that LPR identification by monitoring as well as factors such as advanced age, low body weight, or presence of nuisance bleeding are associated with the decision of switching from prasugrel to clopidogrel. Low on-treatment platelet reactivity is also found in the nonswitched population but to a much lower extent; the good tolerance of the drug and the absence of obvious risk factor for bleeding might explain the decision of keeping these patients maintained on a regimen of prasugrel 10 mg maintenance dose, altering the net clinical benefit of prasugrel in these patients (15).

Short-term outcomes. Clinical follow-up was obtained in all patients at 1-month follow-up. There was no Thrombolysis In Myocardial Infarction major bleeding with prasugrel. Bleeding Academy Research Consortium 1 and BARC 2 bleedings were reported in one-fifth of patients exposed to prasugrel 10 mg maintenance dose (17.1% and 3.2%, respectively). In the overall population there was no ischemic event after 1-month follow-up. Of interest, patients who were switched to clopidogrel tended to have a higher rate of bleeding under prasugrel 10 mg maintenance dose than those who were not switched (32.3% vs. 18.1%, respectively; p = 0.078). Patients switched to clopidogrel 75 mg and reevaluated after the shift have a decreased rate of bleeding events during the clopidogrel period when compared with the first period on a regimen of prasugrel 10 mg. Indeed, bleeding events (BARC 1 and 2) decreased from 32.2% under prasugrel to 9.7% during the clopidogrel period (p = 0.03) (Fig. 4).

**Discussion**

If the pharmacological impact of switching from clopidogrel to prasugrel has been evaluated in several studies (7,14), this investigation is, to our knowledge, the first “real-life” evaluation of a pharmacodynamically driven switch strategy from prasugrel to clopidogrel. The first finding is that high on-prasugrel platelet reactivity is a rare phenomenon found in <1 of 20 patients, whereas one-half of patients display low on-prasugrel platelet reactivity. The second finding is that prasugrel-treated patients who are switched to clopidogrel on the basis of LPR also display clinical characteristics known to be associated with an increased risk of bleeding (e.g., age >75 years old, low-weight). Third, the switch strategy led to an important reduction of platelet inhibition unmasking high platelet reactivity in one-third of patients taking clopidogrel, some of these patients exhibiting real pharmacodynamic resistance to clopidogrel. The switch strategy is also associated with less frequent minor bleeds.

Switching from a potent platelet inhibitor with a higher bleeding hazard to a weaker agent of the same class of thienopyridines might be justified, especially in patients at higher risk of bleeding. According to TRITON (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel) post-hoc analyses, elderly patients (over 75 years old) and low body weight patients (under 60 kg) have a higher risk of bleeding on a regimen of prasugrel 10 mg maintenance dose, altering the net clinical benefit of prasugrel in these patients (15). Therefore, we report here in a real-life ACS population that LPR identification by monitoring as well as factors such as advanced age, low body weight, or presence of nuisance bleeding are associated with the decision of switching from prasugrel to clopidogrel. Low on-treatment platelet reactivity is also found in the nonswitched population but to a much lower extent; the good tolerance of the drug and the absence of obvious risk factor for bleeding might explain the decision of keeping these patients maintained on a regimen of prasugrel, especially with monitoring values in the target window of efficacy without excess platelet inhibition. We believe that the combination of an unfavorable safety profile...

**Table 2. Results of Different Platelet Function Tests Before and After Switch**

<table>
<thead>
<tr>
<th>Test</th>
<th>Prasugrel 10 mg</th>
<th>Clopidogrel 75 mg</th>
<th>p</th>
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<tbody>
<tr>
<td>VerifyNow (P2Y12)</td>
<td>31 (100%)</td>
<td>31 (100%)</td>
<td></td>
</tr>
<tr>
<td>Base (iso-TRAP) (PRU)</td>
<td>283.7 ± 53.07</td>
<td>285.5 ± 42.37</td>
<td>0.88</td>
</tr>
<tr>
<td>Patient (ADP-PGE1) (PRU)</td>
<td>14.23 ± 21.98</td>
<td>15.50 ± 87.24</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>% inhibition</td>
<td>94.67 ± 8.36</td>
<td>47.17 ± 27.44</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LTA</td>
<td>31 (100%)</td>
<td>31 (100%)</td>
<td></td>
</tr>
<tr>
<td>MPA ADP 20 µmol/l</td>
<td>20.11 ± 10.47</td>
<td>43.84 ± 15.19</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>RPA ADP 20 µmol/l</td>
<td>2.22 ± 5.80</td>
<td>26.45 ± 19.59</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>VASP</td>
<td>12.55 ± 11.90</td>
<td>43.63 ± 21.82</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Values are mean ± SD.  
ADP-PGE1 = adenosine diphosphate prostaglandin E1; iso-TRAP = iso-Thrombin Receptor Activating Peptide; LTA = light transmission aggregometry; MPI = maximal platelet aggregation; PRI = platelet reactivity index; PRI = P2Y12 reaction units; RPA = residual platelet aggregation; VASP = vasodilator-stimulated phosphoprotein.
of the patient and LPR measured by monitoring convinced the physicians to switch from prasugrel to clopidogrel. The switch could be driven by cost issues, low education level, and compliance reasons—in addition to medical reasons related to safety concerns—and expose the patients to complications. In the present study, patients were all fully supported by our universal health care system, and drug cost was not considered in the decision to switch treatment.

High on-treatment platelet reactivity is well-defined for clopidogrel (11) and has been clearly identified as a risk marker for ischemic events (16,17). High on-treatment platelet reactivity can also exist with prasugrel in ACS patients after a loading dose of 60 mg (18) and to a lower extent (6% of treated patients) on the maintenance dose of 10 mg (19). In contrast, only a few studies have investigated low on-clopidogrel platelet reactivity, because it is infrequent and less well-defined (20). The same problem of definition applies to the new P2Y12 inhibitors prasugrel and ticagrelor. There is a lack of data and no consensus on the definition of LPR with VASP and LTA, because it has rarely been an issue with clopidogrel. However, low on-clopidogrel platelet reactivity is associated with a higher risk of bleeding (21,22). The definition of low on-prasugrel platelet reactivity in our study is also arbitrary. With our definitions, it is present in more than one-third of the treated population, a finding coherent with previous reports (7).

The underlying concept that is presented here is the tailored antiplatelet therapy approach. Pharmacological studies support the existence of a “sweet spot” for P2Y12 receptor inhibition that might decrease the risk of both bleeding and thrombotic events (23,24). As expected, selective switch from prasugrel to clopidogrel increased the rate of ACS patients in the “therapeutic target window” of platelet inhibition, defined in our study between 30 and 208 PRU. This might be because the patients selected are good responders to thienopyridines in general. In our work, most of the switched patients had LPR, and the switching strategy rarely exposed patients to the risk of clopidogrel resistance and potentially to a higher ischemic risk. If the switch were more systematic without platelet function monitoring, the risk of resistance to clopidogrel would be higher and possibly more detrimental clinically. We fully acknowledge that, despite the rationale for individualized antiplatelet therapy, the clinical benefit of such a tailored approach based on platelet function testing has not yet been proven. Previous studies on tailored therapy (25,26) were either neutral or stopped, due to low event rates or slow recruitment. However, there is more evidence to use an approach with pharmacodynamic information to improve and understand a particular case, such as stent thrombosis (27). Our finding emphasizes the need for more clinical studies on tailored antiplatelet therapy, especially with the newest agents, such as prasugrel and ticagrelor. The results

![Figure 3. Pharmacological Response Before and After the Switch](image-url)
of the ARCTIC (Double Randomization of a Monitoring Adjusted Antiplatelet Treatment Versus a Common Antiplatelet Treatment for DES Implantation, and Interruption Versus Continuation of Double Antiplatelet Therapy) trial (28) are expected to add important information on a personalized approach of antiplatelet therapy. Reaching the sweet spot of platelet inhibition to reduce both the ischemic and bleeding risks still represents a challenge in the treatment of ACS.

Study limitations. This study has limitations and biases inherent to registries that evaluate a “real-life” population. It has to be noted that the decision of switching the patients from 1 drug to the other was left to the discretion of the physician, who was aware of the results of the pharmacodynamic tests. The current work is a pilot study with a limited sample size, and therefore our results should be interpreted as being only exploratory. The limited number of switched patients and the short-term follow-up might limit our conclusions, but we might also underestimate the value of testing with such a short-term study.

Conclusions

Switching from prasugrel to clopidogrel results in a significant increase of platelet reactivity and less minor bleeding, but it also unmasks a group of poor responders to clopidogrel with potential consequences on ischemic events. Monitoring platelet response to treatment in ACS patients might help optimize the net clinical benefit, but it remains to be proven in large clinical trials.

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REFERENCES


Key Words: P2Y12 receptor antagonist □ platelet reactivity □ switch.