Impact of new P2Y12 blockers on platelet reactivity and clinical outcomes after acute coronary syndrome: Insight from a large single center registry

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ABSTRACT

Background: We retrospectively studied the impact of the introduction of new P2Y12 inhibitors (prasugrel, ticagrelor) on platelet reactivity and clinical outcomes after Acute Coronary Syndrome (ACS) from a large single center registry.

Methods: Consecutive patients admitted for ACS since 2007 and discharged on dual antiplatelet therapy were enrolled. Biological response was assessed one month after discharge by PRI VASP and ADP-induced aggregation (%ADP). Patients were classified according to PRI VASP as very low on-treatment platelet reactivity (VLTPR) (PRI VASP ≤ 10%), low on-treatment platelet reactivity (LTTPR) (PRI VASP ≤ 20%) and high on-treatment platelet reactivity HTPR (PRI VASP > 50%). Ischemic and bleeding complications were reported.

Results: 1999 patients were analyzed, 605 before (July 2007–February 2010) and 1394 after introduction of new P2Y12 blockers (February 2010–August 2013). After introduction, we reported a significant lower PRI VASP values (38% ± 0.53 vs. 42% ± 0.81 p = 0.001), %ADP aggregation (52% ± 0.4 vs. 54% ± 0.6 p = 0.03) and HTPR incidence (22% versus 34% OR [95% CI]:0.65 [0.53–0.80]; p < 0.001). Conversely, incidence of VLTPR and LTTPR were significantly higher after the introduction of new P2Y12 inhibitors: 6% versus 3% (OR [95% CI]:2.0 [1.2–3.3]; p < 0.001) and 19% versus 8% (OR [95% CI]:2.8 [2.0–3.9]; p < 0.001) respectively. Clinical follow-up confirmed biological findings with higher incidence of bleeding 10% versus 5% (OR [95% CI]:2.1 [1.4–3.2]; p < 0.001) and lower incidence of stent thrombosis 1.3% versus 3.3% (OR [95% CI]:0.39 [0.20–0.73]; p < 0.01) with new P2Y12 blockers.

Conclusion: The introduction of new P2Y12 inhibitors modified both platelet reactivity and clinical outcome of ACS patients, with higher rate of hyper responders and bleedings, and lower rate of non responders and thrombotic events.

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1. Introduction

Oral antiplatelet therapy including aspirin and P2Y12 inhibitors are widely used with proven benefit for the prevention of recurrent ischemic events after acute coronary syndrome (ACS) and current guidelines recommend the use of dual antiplatelet therapy (DAPT) since CURE results in 2001 [1–6]. Clopidogrel has been considered as the gold standard therapy [6] before new P2Y12 blockers demonstrated their clinical benefit in large randomized controlled trials [7,8]. When first introduced, prasugrel had proved its superiority over clopidogrel in the TRITON study; nevertheless its use was associated with an increased bleeding risk [7]. Ticagrelor, the latest P2Y12 receptor inhibitor commercialized in 2012, provided significant reduction of mortality and prevention of major adverse cardiac outcomes but with a significant excess of major bleedings compared to clopidogrel [8]. New P2Y12 blockers have greater potency and faster onset than clopidogrel for which response is highly variable [9]. Individual response to antiplatelet agents exists and clinical relevance of platelet function testing has been demonstrated for ischemic
and bleedings events [10–12]. Transition from controlled clinical studies to daily practice is important for new drug evaluation and modification of ACS landscape after therapeutic evolution should be assessed continuously after introduction of new drugs' effectiveness. Therefore, the present study aimed to assess in a large registry the evolution of platelet reactivity and clinical outcomes after ACS before and after introduction of new P2Y12 blockers.

2. Methods

All consecutive patients admitted in our institution for Non ST Elevation ACS (NSTE ACS) or ST Elevation Myocardial Infarction (STEMI), between July 2007 and August 2013, were eligible if they had undergone successful percutaneous coronary intervention (PCI). Patients were treated with a loading dose of antplatelet therapy before PCI (i.e. clopidogrel 600 mg, prasugrel 60 mg or ticagrelor 180 mg). All patients were treated at discharge with a P2Y12 inhibitor in association with aspirin 75 mg for one year. P2Y12 blockers used were clopidogrel 75 mg/d, clopidogrel 150 mg/d, prasugrel 10 mg/d or ticagrelor 90 mg twice a day. Two periods were defined before and after introduction of new P2Y12 (prasugrel was the first drug to be introduced in February 2010). Clinical follow-up was performed for all patients at one month and six months. Biological response was assessed at one month clinical follow-up by % platelet reactivity index vsadilator-stimulated phosphoprotein (PRI VASP) and ADP-induced aggregation (%ADP). Based on PRI VASP, patients were classified as: very low on-treatment platelet reactivity (VLTPR = PRI VASP ≤ 10%) [13], low on-treatment platelet reactivity (LTPR = PRI VASP ≤ 20%) [14], high on-treatment platelet reactivity (HTPR = PRI VASP > 50%) [15] or normoresponders (20% < PRI VASP ≤ 50%). Adherence was systematically assessed during the two follow-up visits. The exclusion criteria were a history of bleeding diathesis, prior stroke or transient ischemic attack for prasugrel therapy, the two follow-up visits. The exclusion criteria were a history of bleeding diathesis, prior stroke or transient ischemic attack for prasugrel therapy, the two follow-up visits. The exclusion criteria were a history of bleeding diathesis, prior stroke or transient ischemic attack for prasugrel therapy, the two follow-up visits. The exclusion criteria were a history of bleeding diathesis, prior stroke or transient ischemic attack for prasugrel therapy, the two follow-up visits. The exclusion criteria were a history of bleeding diathesis, prior stroke or transient ischemic attack for prasugrel therapy.

The clinical endpoint was the occurrence of bleeding events according to the Bleeding Academic Research Consortium definitions with type 1, 2, 3 or 5 (type 4 was not expected while no patient had planned coronary artery bypass grafting) [17] and ischemic complications (definite or possible stent thrombosis using the Academic Research Consortium definition) [18] during the first six months. Radial access is widely used in our center and access-site bleedings less dependent of platelet inhibition; we collected only the non-access site bleeding complications.

The primary endpoints of the present study were defined as:

- Evolution of platelet reactivity status before and after new P2Y12 inhibitors introduction.
- Bleeding complications and stent thrombosis before and after new P2Y12 inhibitors introduction.

Statistical analysis was performed using PASW Statistics version 17.0. Continuous variables were reported as means and standard deviation or as medians and range (according to their distribution), and categorical variables were reported as count and percentages. Standard 2-sided tests were used to compare continuous characteristics (Student t or Mann–Whitney U tests) or categorical characteristics (chi-square or Fisher exact tests) among patient groups. Odds ratios (OR) were estimated with a 95% confidence interval. For all tests, statistical significance was defined as p < 0.05.

3. Results

1999 consecutive patients undergoing PCI with coronary stenting for ACS between 2007 and 2013 were prospectively included in our registry. Prasugrel was used for the first time in February 2010 and ticagrelor was introduced in February 2013. We included 605 patients in the “before” cohort and 1394 in the “after” cohort. Characteristics of the two cohorts are reported and compared in Table 1. We observed significant differences concerning use of GP IIb/IIIa inhibitors (38% before vs. 30% after p = 0.01) and LDL-Chol level was lower at one month in the “after” cohort (p = 0.02). Before the introduction of new P2Y12 agents, 117 patients (19%) were on clopidogrel 75 mg and 488 (81%) on clopidogrel 150 mg. After, we observed 295 patients (21%) on clopidogrel 75 mg, 466 (33%) on clopidogrel 150 mg, 566 (41%) on prasugrel, and 67 (5%) on ticagrelor. Drug eluting stents (DES) were used in 66% of the after-cohort patients (460 on clopidogrel, 423 on prasugrel and 37 on ticagrelor).

No difference concerning antiagcoagulation protocol was reported in the after cohort compared with before. We observed a significant evolution of platelet reactivity with significantly lower %PRI VASP and %ADP aggregation after than before introduction: 38% ± 0.53 vs 42% ± 0.81, p = 0.001 and 52% ± 0.4 vs. 54% ± 0.6, p = 0.03 respectively (Fig. 1A and B).

Incidence of VLTPR and LTPR were significantly higher than before: 6% (n = 84) vs. 3% (n = 19) (OR [95% CI]: 2 [1.2–3.3]; p < 0.01) and 19% (n = 270) vs. 8% (n = 48) (OR [95% CI]: 2.8 [2.0–3.9]; p < 0.01) respectively. Conversely, incidence of HTPPR was higher than after before: 34% (n = 204) vs. 22% (n = 345) (OR [95% CI]: 1.5 [1.3–1.9]; p < 0.01) (Fig. 2). We observed 9% of bleeding complications (n = 170) in the global cohort, corresponding to 5% (n = 140) after (OR [95% CI]: 1.5 [1.3–1.7]; p < 0.01).

Table 1

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All patients (n = 1999)</th>
<th>Before (n = 605)</th>
<th>After (n = 1394)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female gender (n, %)</td>
<td>411 (21%)</td>
<td>116 (19%)</td>
<td>295 (21%)</td>
</tr>
<tr>
<td>Age (years; m ± SD)</td>
<td>64.1 ± 12.5</td>
<td>64.6 ± 12.4</td>
<td>64.0 ± 12.5</td>
</tr>
<tr>
<td>BMI (kg/m²; mean ± SD)</td>
<td>26.8 ± 4.3</td>
<td>26.7 ± 4.3</td>
<td>26.9 ± 4.3</td>
</tr>
<tr>
<td>Hypertension (n, %)</td>
<td>1121 (56%)</td>
<td>364 (60%)</td>
<td>757 (54%)</td>
</tr>
<tr>
<td>Type II diabetes (n, %)</td>
<td>570 (29%)</td>
<td>174 (29%)</td>
<td>396 (28%)</td>
</tr>
<tr>
<td>Dyslipidemia (n, %)</td>
<td>1075 (54%)</td>
<td>338 (56%)</td>
<td>737 (53%)</td>
</tr>
<tr>
<td>Current smoker (n, %)</td>
<td>714 (36%)</td>
<td>233 (39%)</td>
<td>481 (35%)</td>
</tr>
<tr>
<td>Previous CAD (n, %)</td>
<td>616 (31%)</td>
<td>129 (21%)</td>
<td>487 (35%)</td>
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<td>Beta blocker (n, %)</td>
<td>1362 (68%)</td>
<td>446 (74%)</td>
<td>916 (66%)</td>
</tr>
<tr>
<td>ACE-inhibitors (n, %)</td>
<td>1334 (67%)</td>
<td>439 (73%)</td>
<td>895 (64%)</td>
</tr>
<tr>
<td>New P2Y12 inhibitor (n, %)</td>
<td>633 (32%)</td>
<td>0</td>
<td>633 (45%)</td>
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<tr>
<td>STEmI (n, %)</td>
<td>585 (29%)</td>
<td>191 (32%)</td>
<td>394 (28%)</td>
</tr>
<tr>
<td>Number stent (n ± SD)</td>
<td>1.3 ± 0.6</td>
<td>1.2 ± 0.6</td>
<td>1.3 ± 0.7</td>
</tr>
<tr>
<td>DES (n, %)</td>
<td>1186 (59%)</td>
<td>266 (44%)</td>
<td>920 (66%)</td>
</tr>
<tr>
<td>Stent length (m ± SD)</td>
<td>202.2 ± 12.2</td>
<td>182.2 ± 9.7</td>
<td>210.2 ± 13.1</td>
</tr>
<tr>
<td>Gp 2b3a inhibitor (n, %)</td>
<td>636 (32%)</td>
<td>229 (38%)</td>
<td>407 (30%)</td>
</tr>
<tr>
<td>EF (%; m ± SD)</td>
<td>54.9 ± 8.4</td>
<td>54.8 ± 8.3</td>
<td>55.2 ± 8.3</td>
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<tr>
<td>Insulin (mUI/l; m ± SD)</td>
<td>13.6 ± 16.1</td>
<td>13.7 ± 12.0</td>
<td>13.8 ± 17.4</td>
</tr>
<tr>
<td>CRP (mg/l; m ± SD)</td>
<td>5.5 ± 14.4</td>
<td>5.3 ± 17.0</td>
<td>5.6 ± 13.1</td>
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<tr>
<td>Triglyceride (G/L; m ± SD)</td>
<td>1.3 ± 0.8</td>
<td>1.2 ± 0.7</td>
<td>1.3 ± 0.9</td>
</tr>
<tr>
<td>Cholesterol (G/L; m ± SD)</td>
<td>1.5 ± 0.4</td>
<td>1.5 ± 0.4</td>
<td>1.5 ± 0.4</td>
</tr>
<tr>
<td>HDL (G/L; m ± SD)</td>
<td>0.8 ± 0.3</td>
<td>0.9 ± 0.3</td>
<td>0.8 ± 0.3</td>
</tr>
<tr>
<td>HbA1c (%; m ± SD)</td>
<td>6.3 ± 1.0</td>
<td>6.2 ± 1.0</td>
<td>6.3 ± 1.1</td>
</tr>
</tbody>
</table>

M: mean; SD: standard deviation; STEMI: ST elevation myocardial infarction; NSTEmI: non ST elevation myocardial infarction; EF: ejection fraction; CAD: coronary artery disease; HDL: high density lipoprotein; LDL: low density lipoprotein; HbA1C: glycosylated hemoglobin; ACE: angiotensin-converting enzyme; GP: platelet glycoprotein; DES: drug eluting stent.
CI]: 0.47 [0.31–0.70]; p < 0.01). Among previous bleedings we reported 24 BARC 1 (80%), 4 BARC 2 (13%) and 2 BARC 3 (7%) versus 100 BARC 1 (77%), 22 BARC 2 (17%), and 8 BARC 3 (6%) in the after cohort.

Conversely, incidence of stent thrombosis was higher before than after introduction of new P2Y12 blockers: 3.3% (n = 20) vs. 1.3% (n = 18) (OR [95% CI]: 2.6 [1.4–4.9]; p < 0.01) (Fig. 3).

Patients in the after cohort suffering from ST corresponded to 10 on clopidogrel, 7 on prasugrel and one on ticagrelor. In 9 patients DES were used. Bleeding complications were reported in 44 patients on clopidogrel, 82 patients on prasugrel and 14 patients on ticagrelor.

In the overall population, we observed significantly lowers levels of PRI VASP (27.6% ± 1.3 vs. 40.1% ± 0.5, p < 0.001) and %ADP (41.7% ± 1.1 vs. 53.6 ± 0.4, p < 0.001) in patients with bleeding complications in comparison with patients without bleeding complications. This difference remains significant in the two cohorts before and after (p < 0.01 for both). Also, we confirmed that VLTPR (OR [95% CI]: 4.1 [2.6–6.5]; p < 0.001) and LTPR (OR [95% CI]: 4.5 [2.9–5.6]; p < 0.001) are strong predictors of bleeding complications.

Fig. 1. A and 1B: Comparison of platelet inhibition before and after introduction of new P2Y12 agents. We observed a significant evolution of platelet reactivity with significantly lower %PRI VASP and %ADP aggregation after than before introduction of new P2Y12 blockers. PRI VASP (Platelet Reactivity Index Vasodilator-Stimulated Phosphoprotein).

Fig. 2. Platelet reactivity status evolution since introduction of new P2Y12 inhibitors. Incidence of VLTPR and LTPR were significantly higher after than before, inversely HTPR is less frequent after. VLTPR (Very Low on Treatment Platelet Reactivity); LTPR (Low on Treatment Platelet Reactivity); HTPR (High on Treatment Platelet Reactivity).

Fig. 3. Stent thrombosis and bleeding complication comparison before and after introduction of new P2Y12 inhibitors. Stent thrombosis significantly decreases and conversely bleeding complications are more frequent during the “after” period.

4. Discussion

The key observation of the present study is a marked shift in clinical and biological pattern of ACS patients since the introduction of newer P2Y12 blockers. These agents provide a more potent platelet inhibition, and decrease resistance status and ischemic complications but are associated with more bleeding events and hyperresponse.

Prasugrel is a thienopyridine, pro-drug converted into an irreversible P2Y12 receptor inhibitor, similar to the one originated from clopidogrel, but which different metabolisms lead to higher and faster platelet inhibition in patients with coronary artery disease [19]. Ticagrelor is an oral, direct, and reversible P2Y12 inhibitor, which has a shorter half-life and requires twice-daily intakes [20]. Both two drugs have a rapid onset of action and are less affected by CYP2C19 polymorphisms. Both TRITON and PLATO trials proved the superiority of new P2Y12 blockers on clopidogrel concerning ischemic end points (death, myocardial infarction, stroke, stent thrombosis and urgent revascularization) [7,8]. Nevertheless, this high efficacy is counterbalanced by an excess of bleeding...
complications [21]. Our cohort confirms that in real world practice these observations about all-comer ACS patients are relevant. Stent thrombosis is the major complication feared by interventional cardiologists after stent implantation and evidence has accumulated that the persistence of thrombotic events after PCI might be related to specific limitations of clopidogrel [22]. Following numerous studies, it had been confirmed that insufficient P2Y12 receptor inhibition (HTPR) is associated with a higher risk for thrombotic events after PCI [23–25]. Introduction of a loading dose and new antiplatelet agents significantly participated in the decline of stent thrombosis. New DES are also implicated in the literature on reduction of ischemic complications [26]. In our cohort the few number of ST does not allow a comparison between DES and bare metal stent concerning ST (9 patients suffering from ST were implanted with DES). Accordingly, in our registry we observed an important decrease in the %HTPR patients and the occurrence of stent thrombosis since the introduction of new P2Y12 blockers. Integrating these findings, clinicians should be concerned about ischemic events but also bleeding complications [27]. Some trials have shown that excessive platelet inhibition on clopidogrel is a predictor of major bleeding events [28–30]. More recently, VLTPR was found to be a strong and independent biological predictor of bleeding complications on thienopyridines, [13]. We observed that the introduction of new P2Y12 leads to a significant increase in %VLTPR and %HTPR patients associated with 10% bleeding risk in actual ACS patients. In our cohort the majority of bleeding events are BARC1 nuisance bleedings (77%). However, these bleedings have significant clinical relevance while they might lead to treatment discontinuation [31,32]. Also, comparison of the new P2Y12 blockers is still an unaddressed question for clinical outcomes and no properly sized randomized clinical trial will be performed to provide a definite answer. A recent biological study from our group showed that ticagrelor is associated with higher platelet inhibition and higher incidence of ‘hyper response’ than prasugrel one month after ACS [33]. Three meta-analysis compared prasugrel to ticagrelor failing to prove superiority on mortality [34–36]. Comparison of prasugrel versus ticagrelor found no significant differences in death, MI and stroke. Prasugrel, when compared to ticagrelor, was associated with a decrease in stent thrombosis. Major bleeding not related to bypass surgery was similar between the two agents. Also, platelet testing might play a role in stratifying ischemic and bleeding risk and evaluating ischemic versus bleeding risk but not guiding antiplatelet agent choice. Randomized studies assessing a personalized therapy based on platelet testing did not prove the efficiency of this strategy [23,37,38]. These studies included mainly patients with stable coronary artery disease and did not focus on ACS patients undergoing PCI. Actually, platelet function testing should be used to try tailoring therapy and to reach an optimal level of platelet inhibition, protecting patients against thrombosis without reaching an excessive level of inhibition that would predispose patients to bleeding, aiming for a ‘therapeutic window’. Also, new P2Y12 agents could possibly be avoided in patients with high bleeding risk, such as those with previous stroke, non diabetic, advanced age, severe renal failure or low weight where clopidogrel will continue to maintain a major role, defining a tailored approach based on patient’s characteristics. Platelet testing can help clinicians stratifying ischemic versus bleeding risk and should be included in global risk estimation, mostly guided by clinical risk evaluation. Association of aspirin and P2Y12 blocker is recommended during one year after ACS [1,2], covering a first high thrombotic phase, however long term treatment exposes patients to bleeding risk, and new strategies for DAPTI are required. The ongoing GLOBAL LEARDERS trial (NCT 01813435) will test, in a randomized study concerning all-comers stent procedures, a new strategy with 1 month DAPT followed by 23 month ticagrelor alone versus 12 month DAPT followed by aspirin alone indefinitely on safety/efficacy balance. Few studies evaluating a switching therapy based on the platelet reactivity showed reach objectives only concerning biological platelet inhibition [39–41]. With new P2Y12 blockers achieving a significant reduction in stent thrombosis occurrence, actual challenges are the reduction of long term bleeding events. This evaluation should take place in a “dynamic therapy”, switching a high potent treatment once passed the first ischemic phase, to clopidogrel which could reduce bleeding events. Clinical impact of these findings warrants further investigation to recommend P2Y12 inhibitor switching according to individual risk.

5. Study limitations

The intrinsic limitations of this study result from the observational characteristic of a registry and its retrospective analysis. Also, we included few patients on ticagrelor, due to the recent commercialization of this drug in our country.

6. Conclusion

Introduction of new P2Y12 inhibitors leads to a modification on ACS patient’s profile, increasing hyper responders versus low responders. Meanwhile, the same trend was observed for clinical outcomes with less stent thrombosis and more bleeding. This evolution modifies targets during long term management of ACS patients on DAPT.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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References