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Original article

Prevalence and predictors of high-on treatment platelet reactivity during prasugrel treatment in patients with acute coronary syndrome undergoing stent implantation

Monica Verdoia (MD)[a], Patrizia Pergolini (MD)[b], Matteo Nardin (MD)[a], Roberta Rolla (MD)[b], Lucia Barbieri (MD)[c], Paolo Marino (MD)[a], Alessandro Carriero (MD)[d], Harry Suryapranata (MD, PhD)[e], Giuseppe De Luca (MD, PhD)[a,*] on behalf of the Novara Atherosclerosis Study Group

[a] Division of Cardiology, Azienda Ospedaliera-Universitaria "Maggiore della Carità", Eastern Piedmont University, Novara, Italy
[b] Clinical Chemistry, Azienda Ospedaliera-Universitaria "Maggiore della Carità", Eastern Piedmont University, Novara, Italy
[c] Division of Cardiology, Ospedale S. Andrea, Vercelli, Italy
[d] Division of Radiology Azienda Ospedaliera-Universitaria "Maggiore della Carità", Eastern Piedmont University, Novara, Italy
[e] Department of Cardiology, UMC St Radboud, Nijmegen, The Netherlands

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ABSTRACT

Background: ADP-antagonists such as prasugrel have reduced but yet not overcome the phenomenon of high-on treatment platelet reactivity (HRPR), that has been shown to increase the rate of major cardiovascular events after an acute coronary syndrome (ACS) or percutaneous coronary intervention (PCI). However, the exact prevalence and the principal determinants of suboptimal platelet inhibition in patients treated with dual antiplatelet therapy (DAPT) with prasugrel have not been completely clarified and were therefore the aim of the present study.

Methods: We included patients (<75 years and >60 kg) treated with DAPT (aspirin + prasugrel) after PCI, mainly for an ACS. Platelet function test evaluation was performed at 1–3 months from discharge. HRPR was assessed by multiplate impedance aggregometry and defined for results above upper limit of normal after ADP stimulation.

Results: We included 190 post-ACS patients. HRPR with prasugrel was observed in 19 patients (10%). The prevalence of HRPR was stable in different high-risk subgroups of patients (female gender, hypercholesterolemic, and chronic kidney disease) whereas it was increased in diabetic patients ($p = 0.045$), with a significant interaction between diabetic status and HRPR ($p = 0.04$). However, at multivariate analysis, an impaired metabolic status, with higher levels of glycosylated hemoglobin and low-density lipoprotein (LDL) cholesterol, but not diabetic status, emerged as independent predictors of HRPR with prasugrel [OR (95% CI) = 2.1 (1.32–3.33), $p = 0.002$ and OR (95% CI) = 1.03 (1.01–1.05), $p = 0.003$, respectively], with a stronger linear relationship between ADP-mediated platelet aggregation and glycosylated hemoglobin levels ($r = 0.24$, $p = 0.002$), than for LDL-cholesterol ($r = 0.13$, $p = 0.09$).

Conclusions: In post-ACS patients treated with PCI and receiving DAPT with prasugrel, HRPR is observed in about 10% of patients. Impaired metabolic status, and especially elevated glycosylated hemoglobin, emerged as independent predictors of the suboptimal effectiveness of prasugrel.

Introduction

Antithrombotic therapies represent a key point in the management of patients with acute coronary syndromes (ACS), where the innovations in the pharmacological field and early aggressive strategies have led to a significant improvement in clinical outcomes [1–4].

Antiplatelet ADP-antagonists such as prasugrel, in particular, have demonstrated a reduction in major adverse ischemic events [5], overwhelming those complex metabolic interactions that contribute to the interindividual variability or a more delayed platelet inhibition with clopidogrel [6,7].

* Corresponding author at: Ospedale "Maggiore della Carità", Eastern Piedmont University, C.so Mazzini, 18, 28100 Novara, Italy.
E-mail address: giuseppe.deluca@maggioreosp.novara.it (G. De Luca).

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However, recent studies have underlined the occurrence of a suboptimal platelet inhibition, or residual high-on treatment platelet reactivity (HRPR), even with newer antiplatelet drugs [8,9]. Indeed, inadequate platelet inhibition has been associated with a 2–9-fold increased risk of recurrent ischemic and thrombotic events, although it is still debated whether tailoring antiplatelet therapy could be more effective than a standard therapy in achieving a therapeutic window with dual antiplatelet therapy (DAPT) [10,11].

Variable rates (0–25%) of patients treated with prasugrel [12,13] have been reported to display HRPR, thus preventing the expected benefits of a more potent antiplatelet strategy, and especially in acute phase settings and in higher risk subsets of patients such as diabetics [14]. Nevertheless, in the absence of a standardized definition for HRPR assessment, the exact prevalence and clinical factors associated with an impaired response to prasugrel are still largely undefined, and were therefore the aim of the present study.

Methods

We included patients admitted to the Division of Cardiology, "Maggiore della Carità" Hospital, Eastern Piedmont University in Novara, Italy, from September 2013 to March 2016 and undergoing percutaneous coronary revascularization, mainly for an acute coronary syndrome. All patients receiving at discharge DAPT with aspirin (100–160 mg daily) and prasugrel (10 mg daily) were scheduled for chemistry and platelet function test evaluation at 1–3 months from discharge. The study was approved by our local Ethical Committee and informed consent was obtained by all patients.

Main demographic, clinical, and angiographic data, together with the indication for DAPT were recorded at discharge and included in a dedicated database, protected by password. Main cardiovascular risk factors were identified: hypertension was defined as systolic pressure >140 mmHg and/or diastolic pressure >90 mmHg or if the individual was taking antihypertensive medications. The diagnosis of diabetes was based on previous history of diabetes treated with or without drug therapies, fasting glucose >126 g/dl or HbA1c >6.5% at the moment of admission [15]. Compliance was assessed on the day of the scheduled platelet function test. Exclusion criteria were: patients' refusal or if the patient had given up prasugrel therapy, age ≥75 years, or body weight ≤60 kg.

Biochemistry analysis

Blood samples were drawn in the early morning, following a fasting period of 12 h. Glucose, creatinine, glycosylated hemoglobin, and lipid profile were determined as previously described [16]. Blood cell count was performed in a blood sample collected in tripotassium ethylenediaminetetraacetic acid (7.2 mg) tubes. These blood samples were analyzed within 2 h of venepuncture by automatic blood cells counter (A Sysmex XE-2100, Sysmex Europe GmbH).

Platelet aggregation

Platelet aggregation was determined by multiplate electrical impedance aggregometry (MEA) in the early morning (>12 h after last prasugrel dose). The aggregation tests were performed from 30 min to 2 h from blood collection [17]. Platelet aggregation was assessed after stimulation with arachidonic acid (0.5 mM) (ASPI test), collagen (3.2 μg/ml) (COL test), ADP (6.4 μM) with prostaglandin E1, and thrombin receptor activating peptide (TRAP-6; 30 μM). Results were expressed as arbitrary Aggregation Units (AU) and plotted against time recorded for 6 min, defining platelet function as the area under curve (AUC). HRPR for prasugrel was defined for ADP test above 417 AUC (normal range: 417–1030) [18,19]. The test was repeated in patients with HRPR to confirm the finding.

Statistical analysis

All statistical analyses were performed by SPSS Statistics Software 22.0 (IBM SPSS Inc., Chicago, IL, USA). Continuous variables were represented as mean ± SD, while categorical variables as percentages. For non-normally distributed variables median and interquartile range [IQR] were reported. Patients were grouped according to the definition of HRPR. Chi-squared and ANOVA test were appropriately used to compare clinical and laboratory features between patients with and without HRPR. Non-parametric test for the comparison of medians was applied for non-normally distributed variables. Linear regression analysis was performed between platelet aggregation AUC and continuous variables associated with HRPR. Forward multiple logistic regression analysis was performed to evaluate independent predictors of HRPR, among the variables significantly associated with HRPR at univariate analysis (all variables with $p < 0.05$). Odds ratios for continuous variables were considered per unitary linear increase. A p-value <0.05 was considered statistically significant.

Results

Our population is represented by 190 patients undergoing coronary stenting, mainly post-ACS. The main demographic, clinical, and laboratory features of our population are listed in Table 1. HRPR with prasugrel was observed in 19 patients (10%). The test was repeated in all patients with HRPR, confirming the finding in all of them.

As shown in Table 1, patients with HRPR were more frequently diabetic ($p = 0.015$) and displayed higher levels of glycosylated hemoglobin and low-density lipoprotein (LDL) cholesterol ($p = 0.003$ and $p = 0.001$, respectively) and white blood cells ($p = 0.05$). No differences were observed in other demographic, clinical, or angiographic variables, but for a higher prevalence of severe multivessel coronary disease in patients with HRPR ($p = 0.03$). Mean platelet reactivity in HRPR patients was markedly enhanced in response to all activating stimuli ($p < 0.001$ for ASPI test, ADP test, COL test, and TRAP test).

As shown in Fig. 1, the prevalence of HRPR was stable in different high-risk subgroups of patients, such as in female gender (10.1% vs. 9.1%, $p = 0.99$) and patients with chronic kidney disease (0% vs. 10.7%, $p = 0.37$), whereas it was relevantly increased in diabetic patients (15.9% vs. 6.5%, $p = 0.045$), with a significant interaction between diabetic status and HRPR ($p = 0.04$).

However, at multivariate analysis, an impaired metabolic status, with higher levels of glycosylated hemoglobin and LDL cholesterol, but not diabetic status, emerged as independent predictors of HRPR with prasugrel [OR (95% CI) = 2.1 (1.32–3.33), $p = 0.002$ and OR (95% CI) = 1.03 (1.01–1.05), $p = 0.003$, respectively]. Complete data from the multivariable model are shown in Table 2.

Moreover, as displayed in Fig. 2, a stronger linear relationship was observed between ADP-mediated platelet aggregation and glycosylated hemoglobin levels ($r = 0.24$, $p = 0.002$, Fig. 2A), than for LDL cholesterol ($r = 0.13$, $p = 0.09$, Fig. 2B).

Discussion

The present study represents one of the largest cohorts of patients chronically treated with prasugrel, where the prevalence and predictors of suboptimal platelet inhibition on DAPT were

Table 1
Main clinical and demographic features in study population and according to platelet reactivity (HRPR) with prasugrel.

Clinical features	Overall	Prasugrel responders ($n = 171$)	Prasugrel HRPR ($n = 19$)	p-Value
Age (mean ± SD)	62.8 ± 9.2	63 ± 9.3	61 ± 8.4	0.37
BMI (mean ± SD)	28.2 ± 6.3	27.9 ± 6.4	30.3 ± 5	0.13
Male sex (%)	82.6	82.5	84.2	0.99
Hypertension (%)	72.6	72.5	73.7	0.99
Active smokers (%)	33.2	31.6	47.4	0.32
Diabetes mellitus (%)	30.5	27.5	57.9	0.015
Hypercholesterolemia (%)	55.8	55.6	57.9	0.99
Previous MI (%)	24.2	25.1	15.8	0.57
Previous PCI (%)	40	39.8	42.1	0.99
Previous CABG (%)	10.1	9.9	11.2	0.70
Renal failure (%)	7.9	8.8	0	0.37
ACS presentation (%)	61.4	61.8	57.9	0.95
ACE inhibitors (%)	54.5	57.1	31.6	0.05
ARBs (%)	21.7	20.6	31.6	0.26
Statins (%)	86.8	87.1	84.2	0.72
Beta blockers (%)	89.9	91.2	78.9	0.11
Nitrates (%)	42.9	42.9	41.1	0.99
Ca-antagonists (%)	28.6	26.5	47.4	0.07
Diuretics (%)	29.6	30.6	21.1	0.60
Ejection fraction (% ± SD)	53.4 ± 8.2	53.3 ± 8.1	54.5 ± 8.8	0.53
Left main/trivessel CAD	43.2	40.4	68.4	0.03
Main chemistry parameters				
Glycemia (mean ± SD)	117.7 ± 36.9	116.3 ± 36.5	131.2 ± 38.8	0.11
HbA1c (mean ± SD)	6.3 ± 1	6.2 ± 1	7 ± 1.2	0.003
Creatinine (mean ± SD)	0.91 ± 0.3	0.91 ± 0.3	0.88 ± 0.2	0.59
Cholesterol HDL (mean ± SD)	40 ± 10.3	40.3 ± 10.4	37.5 ± 8.5	0.29
Cholesterol LDL (mean ± SD)	74.6 ± 0.3	72.4 ± 22.9	94.6 ± 48.2	0.001
C-reactive protein (mg/dl, mean ± SD)	0.04 [0.13–0.42]	0.11 [0.04–0.37]	0.32 [0.05–0.72]	0.23
Platelets (10^5 ml^{-1}; mean ± SD)	246.1 ± 62	244.7 ± 62.7	258.6 ± 57.4	0.36
Hemoglobin (mean ± SD)	13.7 ± 1.9	13.7 ± 1.9	14.1 ± 1.2	0.30
WBC (10^3 ml^{-1}; mean ± SD)	7.8 ± 1.9	7.8 ± 1.9	8.6 ± 1.9	0.05
COL test (AUC; mean ± SD)	417.3 ± 160	395 ± 144.7	608.2 ± 160.8	<0.001
ASPI test (AUC; mean ± SD)	377.3 ± 187.7	353.5 ± 171	590.4 ± 200.2	<0.001
TRAP test (AUC; mean ± SD)	1143.3 ± 299	1112.6 ± 288.7	1490.9 ± 246.9	<0.001
ADP test (AUC; mean ± SD)	282.2 ± 152.5	243.9 ± 83.6	626.7 ± 193.5	<0.001

CAD, coronary artery disease; BMI, body mass index; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; STEMI, ST-elevation myocardial infarction; ACS, acute coronary syndrome; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blockers; LDL, low-density lipoprotein; HDL, high-density lipoprotein; WBC, white blood cells.

addressed. We identified HRPR with prasugrel in about 10% of patients and especially among patients with diabetes.

Recent advances in antiplatelet pharmacological therapies have allowed the optimization of antithrombotic strategies, thus reducing the rate of stent thrombosis and recurrent ischemic events and providing significant benefits in the outcomes, especially in the setting of ACS [20–22].

However, increasing complexity of current ACS patients is rendering more and more challenging the balance between bleeding and thrombosis in the choice of DAPT strategies [23–25]. In fact, more advanced age and the higher rate of comorbidities, such as diabetes or renal failure, have dramatically raised the risk of bleeding complications, with negative consequences on the survival [26]. Nevertheless, these subsets of patients also display an enhanced pro-thrombotic status, with a baseline elevated platelet reactivity that has been previously associated with a suboptimal effectiveness of antiplatelet agents and recurrent ischemic events [27].

Previous studies, in fact, have documented the occurrence of HRPR in patients treated with DAPT, being associated with an increased rate of recurrent acute ischemic events and periprocedural thrombotic complications in patients treated with coronary stenting. In the recent collaborative analysis from different studies on the role of platelet reactivity for risk stratification after percutaneous coronary intervention, Aradi et al. [28] clearly

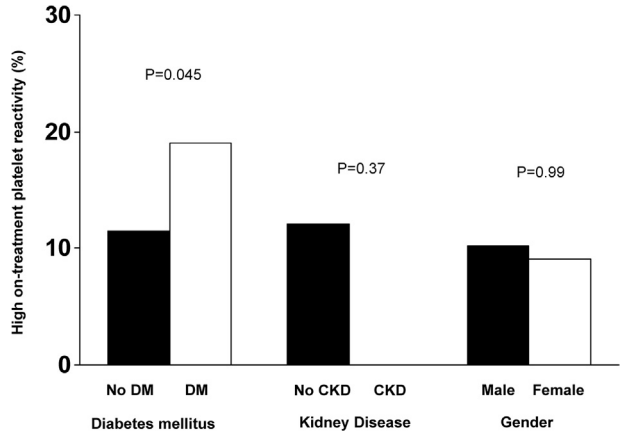

Fig. 1. Bar graph showing the prevalence of residual high-on treatment platelet reactivity in different subgroups of patients. DM, diabetes mellitus; CKD, chronic kidney disease.

Table 2
Results of the multivariate model for the identification of the predictors of high-platelet reactivity.

Variable	OR	95% CI	p-Value
HbA1c	2.1	1.32–3.33	0.002
LDL cholesterol	1.03	1.01–1.05	0.003
Diabetes mellitus	0.47	0.09–2.48	0.37
ACE-inhibitors	0.36	0.11–1.17	0.09
White blood cell count	1.18	0.89–1.56	0.26
Severe coronary artery disease	2.8	0.85–9.3	0.09

ACE, angiotensin-converting enzyme; LDL, low-density lipoprotein.

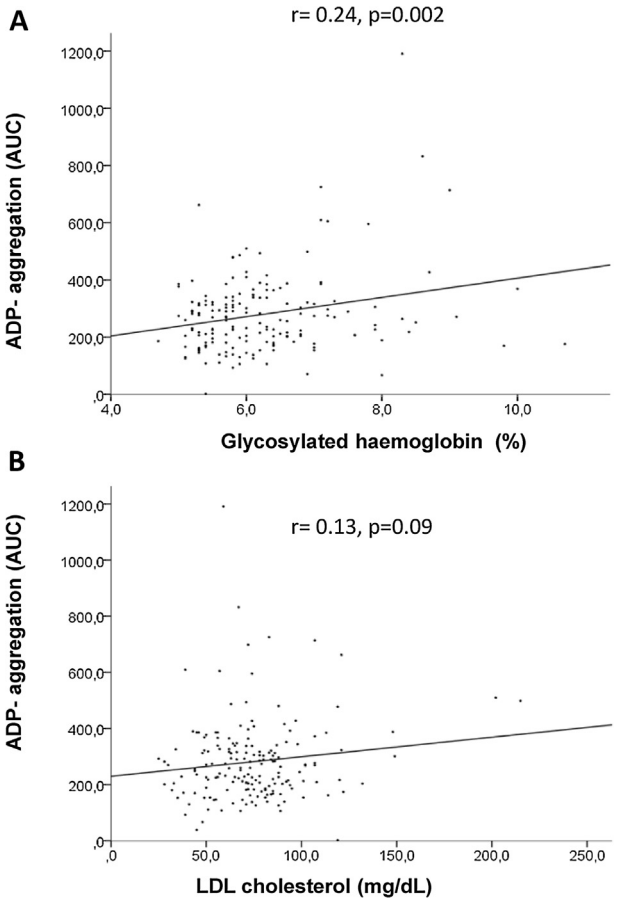

Fig. 2. Linear regression analysis displaying the relationship between area under the curve (AUC) at ADP multiplate test in prasugrel-treated patients and glycosylated hemoglobin (A, upper graph) and low-density lipoprotein cholesterol (LDL; B, lower graph).

showed in a cohort of over 20,000 patients undergoing PCI that HRPR had significantly higher risk for stent thrombosis [risk ratio (RR) and 95% CI: 2.73 (2.03–3.69), $p < 0.00001$], translating into increased mortality.

However, the majority of clinical data in these patients were obtained with clopidogrel, a pro-drug displaying a large inter-individual variability of effect, due to the several genetic and metabolic interactions with the processes leading to its activation [29].

The introduction of ADP-antagonists, such as prasugrel and ticagrelor, not requiring the same complex transformation as clopidogrel, has certainly provided a faster and more predictable platelet inhibition, thus translating into significant benefits in the prevention of recurrent ischemic events [30]. However, still suboptimal results have been achieved in higher thrombotic risk subsets of patients, such as diabetics, where we have recently reported a double rate of HRPR as compared to non-diabetic patients also with the more potent ticagrelor [31].

Among the ADP-antagonists, instead, prasugrel has demonstrated in the TRITON-TIMI 38 [32] a significant reduction in the rate of major adverse events in ACS patients undergoing invasive management, with even more positive results being achieved in diabetics rather than for subjects without diabetes (net clinical benefit with prasugrel 14.6% versus 19.2%; HR, 0.74; $p < 0.001$ in diabetics, 11.5% versus 12.3%; HR, 0.92; $p = 0.16$ in non-diabetics, p interaction = 0.05). An analogous conclusion, then, has been reached by Rossington et al. [33] in a meta-analysis of 4 randomized trials on diabetic patients with ACS, where prasugrel could reduce the rate of recurrent myocardial infarction, without increasing the risk of major bleedings, especially among patients managed with PCI.

Contrasting with the clinical data of TRITON-TIMI 38, instead, Laine and colleagues [34] reported in 100 diabetic post-ACS patients that ticagrelor achieved a significantly lower platelet reactivity as compared to prasugrel loading dose. In addition, similar results have been achieved by Alexopulos et al. in a cohort of 777 patients [35], thus raising potential concerns on the problem of suboptimal platelet inhibition also among prasugrel-treated patients, and especially in settings at higher thrombotic risk.

However, the magnitude of the problem of HRPR on prasugrel treatment is still largely undefined, with its rate varying among studies according to the methods and definitions applied [13,36].

The present study reports the data of 190 patients on a chronic maintenance therapy with prasugrel. We documented a rate of HRPR with prasugrel of 10% of the patients by the use of MEA.

In the SWAP-3 trial [37], among the 77 patients analyzed on prasugrel maintenance therapy, HRPR for prasugrel was 6.3% by light transmission aggregometry (LTA), a test that still represents the gold standard for assessing platelet function, with comparable levels of platelet inhibition being achieved by ticagrelor. Similarly, in the Optimizing anti-Platelet Therapy In diabetes MellitUS (OPTIMUS)-3 trial, that compared platelet reactivity with high-dose clopidogrel or prasugrel in a population of 35 diabetic patients, at 7 days, the poor responder rate ranged from 2.9% to 21.2% for prasugrel [38].

In a similar cohort of post-ACS patients, Siller-Matula et al. [39] documented HRPR with MEA aggregometry in 3% of the 107 subjects on prasugrel. However, their cohort included patients with younger age and lower rate of diabetes, hypertension, and other comorbidities as compared to our study, thus providing potential explanation for the difference in the prevalence of prasugrel poor-effectiveness. In fact, in a study by Cuisset et al., HRPR was much higher, occurring in about 8% of diabetic patients treated with prasugrel [40], thus not much dissimilar to the present results.

Moreover, in our study, we confirmed a higher rate of HRPR in diabetic patients, with a significant interaction between diabetic status and high platelet reactivity. However, at multivariate analysis only poor glycemic control, but not diabetes per se, emerged as an independent predictor of suboptimal platelet inhibition on prasugrel. Thus, it might be hypothesized that diabetic patients maintaining a good metabolic profile, could achieve a satisfactory platelet inhibition on prasugrel, therefore accounting for the positive results of this ADP-antagonist in the TRITON-TIMI 38 trial.

Indeed, Alexopulos et al. [41] have previously documented in 233 patients that the independent predictors of HRPR on prasugrel were the levels of baseline platelet reactivity, ACS at presentation, and active smoking. In our cohort of patients, indication to DAPT was an acute cardiovascular event in almost the overall cohort of patients, and moreover, diabetic status and impaired glycemic control can certainly have conditioned an elevation of baseline pre-treatment platelet reactivity.

In fact, hyperglycemia can have an impact on platelet function directly and by modulating the release of pro-oxidant and inflammatory substances, inducing P-selectin expression and amplification of platelet adhesion [42]. However, the strict association between glucose control parameters and platelet reactivity has been well established only in patients treated with clopidogrel, where Singla et al. [43] have documented higher platelet aggregation on DAPT in patients with HbA1c levels above 7%. On the contrary, no data on the topic have been so far reported in prasugrel-treated patients, where the present study firstly documents that the effectiveness of this antiplatelet drug can also

be conditioned by glucose homeostasis. In effect, however, a similar conclusion had been suggested from the TRITON-TIMI 38 study, reporting larger benefits from prasugrel among diabetic patients treated with insulin (7.9% reduction in major adverse events vs. 4.8% in the overall diabetic cohort) [44].

Therefore, more aggressive antiplatelet strategies, together with a more rigorous control of other risk factors, such as glycemic status, can certainly provide the largest advantages in patients with acute cardiovascular events, and especially in higher risk settings such as in diabetics.

Nevertheless, whether tailoring antiplatelet treatment according to platelet reactivity will provide any significant improvement in the outcomes is still a matter of debate [45,46], and future randomized trials will certainly provide more conclusive indications for the management of these patients at higher thrombotic risk.

Limitations

A first limitation can be considered the relatively small sample size. However, as we aimed to describe the prevalence of a phenomenon in a real-world setting, where few data have been reported so far, we preferred not to perform a sample size estimation. However, our study represents one of the largest cohorts of patients where platelet function was assessed and moreover our conclusions were consistent with previous reports on the topic [38]. Indeed, the reduced number of patients in certain higher-risk subsets of patients, such as subjects with renal failure, and the greater statistical power for continuous variables, could potentially have affected the conclusions of our multivariable model, however the independent predictors of HRPR in our findings are in line with the data achieved in similar studies with other antiplatelet agents [43,47].

Another limitation can be considered the timing of platelet aggregation. The choice of evaluating patients on chronic antiplatelet therapy, after at least one month, was made on purpose, as Gurbel et al. [48] previously reported that the prevalence of HRPR on antiplatelet therapy progressively decreased within the first 30 days of treatment.

In addition, our results in patients with HRPR were not confirmed by using LTA, that still represents the gold standard for platelet aggregation. However, a good correlation between ADP-mediated impedance platelet aggregometry and ADP-LTA has already been reported [49].

In our study, elderly patients and subjects with low body weight, representing potential indications to the adjustment of prasugrel dose, were excluded, and therefore data on these categories cannot be provided from the present study, as we wanted to enroll a population receiving a standardized prasugrel dose of 10 mg.

Finally, we did not perform a systematic follow-up of our patients and therefore, we cannot definitely evaluate the impact of prasugrel non-responsiveness on clinical outcomes.

Conclusions

In post-ACS patients treated with PCI and receiving DAPT with prasugrel, HRPR is not infrequent, occurring in about 10% of patients. Impaired metabolic status, and especially elevated glycosylated hemoglobin, emerged as the only independent predictor of suboptimal effectiveness of prasugrel.

Authors' contribution

Monica Verdoia, MD: (1) Conception and design; (2) Data collection; (3) Interpretation of the data; (4) Drafting of the article; (5) Final approval of the manuscript.

Lucia Barbieri, MD, Matteo Nardin, MD: (1) Interpretation of the data; (2) Data Collection; (3) Critical revision of the article for important intellectual content of the article; (4) Final approval of the manuscript.

Roberta Rolla, MD, Paolo Marino, MD: (1) Interpretation of the data; (2) Critical revision of the article for important intellectual content of the article; (3) Final approval of the manuscript.

Giorgio Bellomo, MD, Patrizia Pergolini, MD: (1) Interpretation of the data; (2) Critical revision of the article for important intellectual content of the article; (3) Evaluation of platelet reactivity; (4) Final approval of the manuscript.

Giuseppe De Luca, MD, PhD, Hatty Suryapranata, MD, PhD: (1) Conception and design; (2) Statistical analysis; (3) Interpretation of the data; (4) Drafting of the article; (5) Final approval of the manuscript; (6) Supervision.

Conflict of interest

The authors declare no funding source or conflict of interest to disclose.

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References

[1] De Luca G, Suryapranata H, Marino P. Reperfusion strategies in acute ST-elevation myocardial infarction: an overview of current status. Prog Cardiovasc Dis 2008;50:352–82.
[2] De Luca G, Suryapranata H, Stone GW, Antoniucci D, Tcheng JE, Neumann FJ, et al. Relationship between patient's risk profile and benefits in mortality from adjunctive abciximab to mechanical revascularization for ST-segment elevation myocardial infarction: a meta-regression analysis of randomized trials. J Am Coll Cardiol 2006;47:685–6.
[3] Navarese EP, De Luca G, Castriota F, Kozinski M, Gurbel PA, Gibson CM, et al. Low-molecular-weight heparins vs. unfractionated heparin in the setting of percutaneous coronary intervention for ST-elevation myocardial infarction: a meta-analysis. J Thromb Haemost 2011;9:1902–15.
[4] Savonitto S, De Luca G, Goldstein P, van T' Hof A, Zeymer U, Morici N, et al. Antithrombotic therapy before, during and after emergency angioplasty for ST elevation myocardial infarction. Eur Heart J Acute Cardiovasc Care 2017;6:173–90.
[5] Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, et al. TRITON-TIMI 38 Investigators Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2007;357:2001–15.
[6] Azmoon S, Angiolillo DJ. Switching antiplatelet regimens: alternatives to clopidogrel in patients with acute coronary syndrome undergoing PCI: a review of the literature and practical considerations for the interventional cardiologist. Catheter Cardiovasc Interv 2013;81:232–42.
[7] Nguyen TA, Diodati JG, Pharand C. Resistance to clopidogrel: a review of the evidence. J Am Coll Cardiol 2005;45:1157–64.
[8] Verdoia M, Sartori C, Pergolini P, Nardin M, Rolla R, Barbieri L, et al. Prevalence and predictors of high-on treatment platelet reactivity with ticagrelor in ACS patients undergoing stent implantation. Vascul Pharmacol 2016;77:48–53.
[9] Perl L, Lerman-Shivek H, Rechavia E, Vaduganathan M, Leshem-Lev D, Zemer-Wassercug N, et al. Response to prasugrel and levels of circulating reticulated platelets in patients with ST-segment elevation myocardial infarction. J Am Coll Cardiol 2014;63:513–7.
[10] Tantry US, Bonello L, Aradi D, Price MJ, Jeong YH, Angiolillo DJ, et al. Consensus and update on the definition of on-treatment platelet reactivity to adenosine diphosphate associated with ischemia and bleeding. J Am Coll Cardiol 2013;62:2261–73.
[11] Wisman PP, Roest M, Asselbergs FW, de Groot PG, Moll FL, van der Graaf Y, et al. Platelet-reactivity tests identify patients at risk of secondary cardiovascular events: a systematic review and meta-analysis. J Thromb Haemost 2014;12:736–47.
[12] Bonello L, Pansieri M, Mancini J, Bonello R, Maillard L, Barnay P, et al. High on-treatment platelet reactivity after prasugrel loading dose and cardiovascular events after percutaneous coronary intervention in acute coronary syndromes. J Am Coll Cardiol 2011;58:467–73.
[13] Cubero Gómez JM, Acosta Martínez J, Mendias Benítez C, Díaz De La Llera LS, Fernández-Quero M, Guisado Rasco A, et al. VERifyNow in DIabetes high-on-treatment platelet reactivity: a pharmacodynamics study on switching from clopidogrel to prasugrel. Acta Cardiol 2015;70:728–34.
[14] Ferreiro JL, Angiolillo DJ. Diabetes and antiplatelet therapy in acute coronary syndrome. Circulation 2011;123:798–813.

[15] De Luca G, Secco GG, Santagostino M, Venegoni L, Iorio S, Cassetti E, et al. Uric acid does not affect the prevalence and extent of coronary artery disease. Results from a prospective study. Nutr Metab Cardiovasc Dis 2012;22:426–33.
[16] Verdoia M, Schaffer A, Sartori C, Barbieri L, Cassetti E, Marino P, et al. Vitamin D deficiency is independently associated with the extent of coronary artery disease. Eur J Clin Invest 2014;44:634–42.
[17] Verdoia M, Pergolini P, Camaro C, Restifo M, Rolla R, Schaffer A, et al. PlA(1)/PlA (2) polymorphism does not influence response to Gp IIb-IIIa inhibitors in patients undergoing coronary angioplasty. Blood Coagul Fibrinolysis 2013;24:411–8.
[18] Vidali M, Rolla R, Parrella M, Cassani C, Manzini M, Portalupi MR, et al. Role of the laboratory in monitoring patients receiving dual antiplatelet therapy. Int J Lab Hematol 2012;34:484–94.
[19] Bonello L, Tantry US, Marcucci R, Blindt R, Angiolillo DJ, Becker R, et al. Consensus and future directions on the definition of high on-treatment platelet reactivity to adenosine diphosphate. J Am Coll Cardiol 2010;56:919–33.
[20] De Luca G, Smit JJ, Ernst N, Suryapranata H, Ottervanger JP, Hoorntje JC, et al. Impact of adjunctive tirofiban administration on myocardial perfusion and mortality in patients undergoing primary angioplasty for ST-segment elevation myocardial infarction. Thromb Haemost 2005;93:820–3.
[21] De Luca G, Dirksen MT, Spaulding C, Kelbæk H, Schalij M, Thuesen L, et al. Time course, predictors and clinical implications of stent thrombosis following primary angioplasty. Insights from the DESERT cooperation. Thromb Haemost 2013;110:826–33.
[22] Montalescot G, van't Hof AW, Bolognese L, Cantor WJ, Cequier A, Chettibi M, et al. Effect of pre-hospital ticagrelor during the first 24 h after primary percutaneous coronary intervention in patients with ST-segment elevation myocardial infarction: the ATLANTIC-H(24) analysis. JACC Cardiovasc Interv 2016;9:646–56.
[23] Bortnick AE, Epps KC, Selzer F, Anwaruddin S, Marroquin OC, Srinivas V, et al. Five-year follow-up of patients treated for coronary artery disease in the face of an increasing burden of co-morbidity and disease complexity. Am J Cardiol 2014;113:573–9.
[24] Lopes RD, Alexander KP, Manoukian SV, Bertrand ME, Feit F, White HD, et al. Advanced age, antithrombotic strategy, and bleeding in non-ST-segment elevation acute coronary syndromes: results from the ACUITY trial. J Am Coll Cardiol 2009;53:1021–30.
[25] Verdoia M, Pergolini P, Rolla R, Nardin M, Schaffer A, Barbieri L, et al. Advanced age and high-residual platelet reactivity in patients receiving dual antiplatelet therapy with clopidogrel or ticagrelor. J Thromb Haemost. 2016;14(January (1)):57–64.
[26] Mehran R, Pocock SJ, Stone GW, Clayton TC, Dangas GD. Associations of major bleeding and myocardial infarction with the incidence and timing of mortality in patients presenting with non-ST-elevation acute coronary syndromes: a risk model from the ACUITY trial. Eur Heart J 2009;30:1457–66.
[27] Stone GW, Witzenbichler B, Weisz G, Rinaldi MJ, Neumann FJ, Metzger DC, et al. Platelet reactivity and clinical outcomes after coronary artery implantation of drug-eluting stents (ADAPT-DES): a prospective multicentre registry study. Lancet 2013;382:614–23.
[28] Aradi D, Kirtane A, Bonello L, Gurbel PA, Tantry US, Huber K, et al. Bleeding and stent thrombosis on P2Y12-inhibitors: collaborative analysis on the role of platelet reactivity for risk stratification after percutaneous coronary intervention. Eur Heart J 2015;36:1762–71.
[29] Ancrenaz V, Daali Y, Fontana P, Besson M, Samer C, Dayer P, et al. Impact of genetic polymorphisms and drug-drug interactions on clopidogrel and prasugrel response variability. Curr Drug Metab 2010;11:667–77.
[30] Tomey M, Mehran R. Dual antiplatelet therapy dilemmas: duration and choice of antiplatelets in acute coronary syndromes. Curr Cardiol Rep 2013;15:405.
[31] Nardin M, Verdoia M, Sartori C, Pergolini P, Rolla R, Barbieri L, et al. Diabetes mellitus, glucose control parameters and platelet reactivity in ticagrelor treated patients. Thromb Res 2016;143:45–9.
[32] Wiviott SD, Braunwald E, Angiolillo DJ, Meisel S, Dalby AJ, Verheugt FW, et al. Greater clinical benefit of more intensive oral antiplatelet therapy with prasugrel in patients with diabetes mellitus in the trial to assess improvement in therapeutic outcomes by optimizing platelet inhibition with prasugrel-thrombolysis in myocardial infarction 38. Circulation 2008;118:1626–36.
[33] Rossington JA, Brown OI, Hoye A. Systematic review and meta-analysis of optimal P2Y12 blockade in dual antiplatelet therapy for patients with diabetes with acute coronary syndrome. Open Heart 2016;3. e960002.
[34] Laine M, Frère C, Toesca R, Berbis J, Barnay P, Pansieri M, et al. Ticagrelor versus prasugrel in diabetic patients with an acute coronary syndrome. A pharmacodynamic randomised study. Thromb Haemost 2014;111:273–8.
[35] Alexopoulos D, Vogiatzi C, Stavrou K, Vlassopoulou N, Perperis A, Pentara I, et al. Diabetes mellitus and platelet reactivity in patients under prasugrel or ticagrelor treatment: an observational study. Cardiovasc Diabetol 2015;14:68.
[36] Geisler T, Booth J, Tavlaki E, Karathanos A, Müller K, Droppa M, et al. High platelet reactivity in patients with acute coronary syndromes undergoing percutaneous coronary intervention: randomised controlled trial comparing prasugrel and clopidogrel. PLoS ONE 2015;10. e0135037.
[37] Franchi F, Faz GT, Rollini F, Park Y, Cho JR, Thano E, et al. Pharmacodynamic effects of switching from prasugrel to ticagrelor: results of the prospective, randomized SWAP-3 Study. JACC Cardiovasc Interv 2016;9:1089–98.
[38] Angiolillo DJ, Badimon JJ, Saucedo JF, Frelinger AL, Michelson AD, Jakubowski JA, et al. A pharmacodynamic comparison of prasugrel vs. high-dose clopidogrel in patients with type 2 diabetes mellitus and coronary artery disease: results of the Optimizing anti-Platelet Therapy In diabetes MellitUS (OPTIMUS)-3 trial. Eur Heart J 2011;32:838–46.
[39] Siller-Matula JM, Hintermeier A, Kastner J, Kreiner G, Maurer G, Kratochwil C, et al. Distribution of clinical events across platelet aggregation values in all-comers treated with prasugrel and ticagrelor. Vascul Pharmacol 2016;79:6–10.
[40] Cuisset T, Gaborit B, Dubois N, Quilici J, Loosveld M, Beguin S, et al. Platelet reactivity in diabetic patients undergoing coronary stenting for acute coronary syndrome treated with clopidogrel loading dose followed by prasugrel maintenance therapy. Int J Cardiol 2013;168:523–8.
[41] Alexopoulos D, Xanthopoulou I, Perperis A, Siapika A, Stavrou K, Tsoni E, et al. Factors affecting residual platelet aggregation in prasugrel treated patients. Curr Pharm Des 2013;19:5121–6.
[42] Angiolillo DJ, Fernandez-Ortiz A, Bernardo E, Ramírez C, Sabaté M, Jimenez-Quevedo P, et al. Platelet function profiles in patients with type 2 diabetes and coronary artery disease on combined aspirin and clopidogrel treatment. Diabetes 2005;54:2430–5.
[43] Singla A, Antonino MJ, Bliden KP, Tantry US, Gurbel PA. The relation between platelet reactivity and glycemic control in diabetic patients with cardiovascular disease on maintenance aspirin and clopidogrel therapy. Am Heart J 2009;158:784. e1–6.
[44] Hillegass WB, Brott BC, Dobbs JC, Papapietro SE, Misra VK, Zoghbi GJ. Oral antiplatelet therapy in diabetes mellitus and the role of prasugrel: an overview. Vasc Health Risk Manage 2011;7:445–59.
[45] Collet JP, Cuisset T, Rangé G, Cayla G, Elhadad S, Pouillot C, et al. Bedside monitoring to adjust antiplatelet therapy for coronary stenting. N Engl J Med 2012;367:2100–9.
[46] Siller-Matula JM, Francesconi M, Dechant C, Jilma B, Maurer G, Delle-Karth G, et al. Personalized antiplatelet treatment after percutaneous coronary intervention: the MADONNA study. Int J Cardiol 2013;167:2018–23.
[47] Schoos MM, Dangas GD, Mehran R, Kirtane AJ, Yu J, Litherland C, et al. Impact of hemoglobin A1c levels on residual platelet reactivity and outcomes after insertion of coronary drug-eluting stents (from the ADAPT-DES Study). Am J Cardiol 2016;117:192–200.
[48] Gurbel PA, Bliden KP, Hiatt BL, O'Connor CM. Clopidogrel for coronary stenting: response variability, drug resistance, and the effect of pretreatment platelet reactivity. Circulation 2003;107:2908–13.
[49] Paniccia R, Antonucci E, Maggini N, Romano E, Gori AM, Marcucci R, et al. Assessment of platelet function on whole blood by multiple electrode aggregometry in high-risk patients with coronary artery disease receiving antiplatelet therapy. Am J Clin Pathol 2009;131:834–42.