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Prevalence and predictors of high-on treatment platelet reactivity with ticagrelor in ACS patients undergoing stent implantation

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ABSTRACT

Background: Residual high-on treatment platelet reactivity (HRPR) predicts outcomes and major cardiovascular events. Ticagrelor has provided pharmacological and clinical evidence of more predictable and more potent antiplatelet effect as compared to clopidogrel. However, so far, few data have investigated the prevalence and predictors of HRPR in unselected patients treated with ticagrelor, that is therefore the aim of the current study.
Methods and results: Our population is represented by 195 patients undergoing coronary stenting for ACS and receiving ASA and ticagrelor. Platelet function was assessed by multiplate impedance aggregometry (MEA) between 1 and 3 months after stenting. Main clinical features and biochemistry parameters were collected. HRPR for ticagrelor was defined for aggregation > 417 AUC after MEA-ADP stimulation. A total of 26 patients, (13.3%), displayed HRPR with ticagrelor. Older age (≥70 years, $p = 0.002$), hypertension ($p = 0.02$) previous myocardial infarction ($p = 0.04$), therapy with nitrates and beta-blockers ($p = 0.02$), diuretics ($p = 0.03$) and fasting glycaemia ($p = 0.05$) were associated to HRPR with ticagrelor. By multivariate analysis, age ≥ 70 years (OR [95%CI] = 4.6[1.55–13.8], $p = 0.006$), concomitant therapy with beta-blockers (OR [95%CI] = 3.2[1.06–9.6], $p = 0.04$) and platelets count (OR[95%CI] = 1.0007 [1–1.016], $p = 0.05$) were identified as independent predictors of HRPR with ticagrelor.
Conclusion: The present study firstly demonstrates that the occurrence of HRPR in patients treated with ticagrelor is not so futile, as it was observed in 13% of patients treated with ticagrelor. Older age, beta-blockers administration and platelets count are independent predictors of HRPR with ticagrelor.

1. Background

Percutaneous coronary revascularization has contributed to the relevant reduction in mortality observed in the last decades in the treatment of patients with acute myocardial infarction [1,2]. Adjunctive mechanical devices and pharmacological therapies have further improved these results [3–6] that, however, still remain unsatisfactory in high-risk subgroups of patients [7,8]. Dual antiplatelet therapy currently represents the gold standard for the prevention of ischemic and thrombotic events in acute coronary syndrome patients and in those undergoing percutaneous stent implantation, with a pivotal role played by new ADP-antagonists [9–12]. In fact, almost 30% of patients do not achieve an adequate platelet inhibition with clopidogrel, due to its complex metabolic pathways and genetic factors that can cause an impaired transformation of clopidogrel into its active metabolites [13]. Residual high-on treatment platelet reactivity (HRPR) has been associated with worse cardiovascular outcomes and a higher rate of major ischemic events, and especially to an increased risk of stent thrombosis [14–16].

New ADP-antagonists have partially overcome the problems of interindividual response variability, due to an easier metabolic activation (Prasugrel) or being directly active drugs (Ticagrelor), thus achieving a more powerful and predictable inhibition of platelet aggregation and faster onset of action. Particular attention has been paid to ticagrelor, being the first reversible oral ADP antagonist [17]. In addition, due to its peculiar adenosine-like structure, it may display potential pleiotropic effects [18–20] that may contribute to explain the significant benefits in mortality obtained with ticagrelor, but not with prasugrel, as compared to clopidogrel [21,22].

Even though recent evidence has emerged on the impact of circulating and genetic factors on the response to ticagrelor [23,24], no study has so far extensively attempted to evaluate the prevalence and

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predictors of HRPR with ticagrelor, that was, therefore, the aim of the present study.

2. Methods

We included patients admitted for acute coronary syndromes to the Division of Cardiology, "Maggiore della Carità" Hospital, Eastern Piedmont University in Novara, Italy, from September 2013 to September 2014 and undergoing percutaneous coronary revascularization. All patients receiving at discharge dual antiplatelet therapy with ASA (100 to 160 mg daily) and ticagrelor (90 mg every 12 h) were scheduled for chemistry and platelet function tests 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 to dual antiplatelet therapy 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 mm Hg and/or diastolic pressure > 90 mm Hg 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 [25]. Compliance was assessed on the day of the scheduled platelet function test. Exclusion criteria were patients' refusal or if the patient had given up ticagrelor therapy.

3. Biochemistry analysis

Blood samples were drawn in the early morning, following a fasting period of 12 h. Glucose, creatinine, glycosylated haemoglobin and lipid profile were determined as previously described [26]. Blood cell count was performed in a blood sample collected in tripotassium EDTA (7.2 mg) tubes. These blood samples were analysed within 2 h of venipuncture by automatic blood cells counter (A Sysmex XE-2100).

4. Platelet aggregation

Platelet aggregation was determined by multiplate electrical impedance aggregometry (MEA), within 1–2 h from morning dose assumption of ticagrelor. The aggregation tests were performed from 30 min to 2 h from blood collection [27]. 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 ticagrelor was defined for ADP test above 417 AUC; (normal range: [417–1030]). [28]. The previously reported [29] cut-off of >468 AUC (46 AU) was also applied to define poor ticagrelor responders. The test was repeated in patients with HRPR to confirm the finding.

5. Statistical analysis

All statistical analyses were performed by SPSS Statistics Software 17.0. (SPSS Inc., Chicago, Illinois). Continuous variables were represented as mean ± SD, while categorical variables as percentage. Patients were grouped according to quartile values of ADP-test or 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. Linear regression analysis was performed between platelet aggregation AUC and continuous variables associated to HRPR. Forward multiple logistic regression analysis was performed to evaluate independent predictors of HRPR, among the variables significantly associated to HRPR at univariate analysis (all variables with $p < 0.10$). A p value < 0.05 was considered statistically significant.

6. Results

Our population is represented by 195 post-ACS patients undergoing coronary stenting. The main demographic, clinical and laboratory features of our population are listed in Table 1. HRPR with ticagrelor was observed in 26 patients (13.3%). The test was repeated in all patients with HRPR, confirming the finding in all of them.

As shown in Fig. 1, mean platelet reactivity at MEA-ADP test was 532 ± 129.2 in HRPR patients vs 239.3 ± 92.1 in patients without HRPR ($p < 0.001$). As shown in Table 1, patients with HRPR were older (≥70 years, $p = 0.002$), more frequently affected by hypertension ($p = 0.02$) and previous myocardial infarction ($p = 0.04$), more often chronically treated with nitrates, beta-blockers ($p = 0.02$) and diuretics ($p = 0.03$) and had higher fasting glycaemia ($p = 0.05$). No differences were observed in other demographic, clinical or angiographic variables.

As shown in Fig. 2, the prevalence of HRPR was quite stable in different high-risk subgroups of patients, such as diabetic patients and those with chronic kidney disease, whereas it was relevantly increased in elderly patients (≥70 years), female gender and patients with hypertension.

At multivariate analysis age ≥ 70 years (OR [95%CI] = 4.6 [1.55–13.8], $p = 0.006$), concomitant therapy with beta-blockers (OR [95%CI] = 3.2[1.06–9.6], $p = 0.04$) and platelets count (OR[95%CI] = 1.0001 [1–1.016], $p = 0.05$) were identified as independent predictors of HRPR with ticagrelor. In fact, as shown in Fig. 3, a linear relationship was observed between platelet aggregation values and age ($r = 0.16$, $p = 0.03$) and platelet count ($r = 0.23$, $p = 0.001$).

Similar findings were observed when considering AUC > 468 as the cut-off point for poor response to ticagrelor. In fact, 18 patients (9.2%) displayed platelet reactivity values above the therapeutic range. Independent predictors were confirmed to be age ≥ 70 years (OR [95%CI] = 5.3[1.37–20.5], $p = 0.02$), and platelets count (OR[95%CI] = 1.001 [1–1.013], $p = 0.045$).

7. Discussion

The present study represents the first attempt to define the occurrence of HRPR in patients treated with ticagrelor by the use of multiplate. We identified HRPR with ticagrelor in about 13% of patients and especially among elderly and in the presence of elevated platelet count.

Larger attention has been paid to optimization of antiplatelet therapy in the setting of ACS [30], especially in patients undergoing stent implantation, with the aim to reduce the risk of stent thrombosis and improve overall clinical outcomes. In fact, the occurrence of stent thrombosis still remains relatively high, due to the larger and larger complexity of current ACS patients, with negative impact of survival [31–33].

Ticagrelor is a newly developed, potent antiplatelet agent, reversibly binding P2Y12, the platelet ADP-receptor. Great enthusiasm has followed its introduction, potentially solving the problem of HRPR and interindividual response variability of thienopyridines, leading to a widespread use of ticagrelor and its validation in guidelines especially in high-risk patients, as in those experiencing an ACS [10,34].

In fact, in the PLATO trial [22], ticagrelor decreased the incidence of major adverse cardiovascular events (MACE) and total mortality in patients with ACS, being so far the only ADP-antagonist to achieve such a survival benefit. It is relevant to underscore that the beneficial effects in mortality were observed only with ticagrelor but not prasugrel, despite the more contained reduction in the relative risk of stent thrombosis (25% with ticagrelor vs 54% with prasugrel). Indeed, the presence of additional pleiotropic effects, via the adenosine A2a pathway, has been claimed as a potential explanation [35].

However, recent evidence has emerged that, in real life STEMI patients, a more delayed effect of ticagrelor could occur, being conditioned not only by higher baseline platelet reactivity but also by

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