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Uric acid and high-residual platelet reactivity in patients treated with clopidogrel or ticagrelor

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Abstract *Background and Aim:* High residual platelet reactivity (HRPR) is still an important challenge, despite the advent of new potent ADP-antagonists. Therefore it is of extreme importance to identify factors that can influence platelet activation. Serum uric acid (SUA) has been largely addressed in the past as a possible risk factor for coronary artery disease, with a possible association with platelets hyperreactivity. So far no studies have assessed the role of serum uric acid on the response to dual antiplatelet therapy. Therefore, the aim of our study was to evaluate the impact of uric acid levels on platelet function in patients treated with dual antiplatelet therapy (DAPT) with clopidogrel or ticagrelor.
Methods and Results: We scheduled for platelet function assessment at 30–90 days post-discharge patients treated with DAPT (ASA + clopidogrel or ticagrelor) for an ACS or elective percutaneous coronary intervention (PCI). Platelet function was assessed by whole blood impedance aggregometry (Multiplate®-Roche Diagnostics AG), HRPR was considered for ASPI test >862 AU*min (for ASA) and ADP test values ≥417 AU*min (for ADP-antagonists).
Results: We included a total of 493 patients (262 were on ASA and clopidogrel and 231 on ASA and ticagrelor). Patients were divided according to quartiles of serum uric acid levels measured at the time of platelet aggregation assessment (Group 1 <4.6 mg/dL, $n = 114$; Group 2, 4.7–5.8 mg/dL, $n = 133$; Group 3, 5.9–6.8 mg/dL, $n = 124$; Group 4, >6.9, $n = 122$). Patients with higher uric acid levels were older, more often smokers, with history of hypertension and previous coronary artery bypass surgery and renal failure and were more often on therapy with diuretics at admission. Patients with higher SUA had higher triglycerides and fibrinogen. Uric acid levels did not influence ASPI, COL, TRAP and ADP tests. High residual platelet reactivity (HRPR) was observed in 1.5% of patients treated with ASA, with no difference according to SUA quartiles ($p = 0.60$), confirmed at multivariate analysis after correction for baseline confounders (adjusted OR[95%CI] = 1.05 [0.44–2.52], $p = 0.90$). HRPR for ADP-antagonists was observed in 23.6% of patients, with no difference according to SUA quartiles ($p = 0.47$); this result was confirmed also after correction for baseline confounders (adjusted OR[95% CI] = 1.04 [0.84–1.28], $p = 0.73$). Moreover, no association was found between HRPR and uric acid levels both among patients treated with clopidogrel ($p = 0.35$) or ticagrelor ($p = 0.74$), that was confirmed after correction for baseline confounding factors (adjusted OR[95%CI] = 1.18 [0.90–1.55], $p = 0.23$) and (adjusted OR[95%CI] = 0.96 [0.63–1.47], $p = 0.85$). The absence of association between SUA and platelet reactivity was confirmed at linear regression analysis both with clopidogrel ($r = 0.03$, $p = 0.55$) or ticagrelor ($r = -0.01$, $p = 0.85$).
Conclusion: This is the first large study showing that in patients receiving DAPT, uric acid levels

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do not influence response to ticagrelor and clopidogrel or the effectiveness of ASA.

Introduction

Platelet aggregation is a key point in the pathogenesis of coronary artery disease (CAD). In particular, among patients hospitalized after an acute coronary syndrome or undergoing elective coronary stent implantation, the use of an optimal dual antiplatelet therapy (DAPT) is of great importance in order to reduce mortality and recurrent thrombotic events [1,2]. Despite the introduction of new, more active antiplatelet agents [3–7] suboptimal platelet inhibition still represents an important challenge, especially for interventional cardiologists. To date, very few are known about the predictors of impaired response to antiplatelet therapies, especially ticagrelor.

Serum uric acid (SUA), a degradation metabolite of purines, has been addressed in past years as a possible risk factor for cardiovascular disease, in fact high SUA levels have been associated with the main determinants of atherosclerosis and metabolic syndrome. Hyperuricemia is a condition characterized by inhibited nitric oxide system, activation of the local rennin–angiotensin system, pro-inflammatory and proliferative actions and enhanced synthesis of reactive oxygen species with increased oxidative stress [8,9]. Moreover, elevated uric acid has been reported to promote vascular smooth muscle proliferation and to up regulate the expression of platelet-derived growth factor and monocyte chemoattractant protein-1 and to induce cyclo-oxigenase-2, that link uric acid to inflammation and potentially to platelet hyperreactivity [10–13]. However, elevated uric acid is commonly associated with additional several risk factors, that may by themselves influence platelet reactivity [14,15]. Few data have been reported so far on the impact of uric acid on platelet reactivity, especially in the era of new potent ADP antagonists. Therefore, aim of our study is to evaluate the impact of uric acid on high residual platelet reactivity (HRPR) in patients treated with DAPT with acetylsalicylic acid (ASA) and clopidogrel or ticagrelor.

Methods

We analyzed a total of 547 patients discharged from our Division of Cardiology, “Maggiore della Carità” Hospital, Novara, with dual antiplatelet therapy with ASA (100 mg daily) and ADP-antagonist (clopidogrel 75 mg daily or ticagrelor 90 mg b.i.d.) due to an acute coronary syndrome (ACS) or percutaneous coronary intervention (PCI) in elective patients from September 2009 to December 2014. Patients were scheduled for chemistry and platelet function tests evaluation at 30–90 days 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 DAPT were recorded at discharge and included in a dedicated database, protected by password. Hypertension was defined as systolic pressure >140 mmHg and/or diastolic pressure >90 mmHg or if the individual was taking antihypertensive medications. Diabetes mellitus was defined as previous diagnosis, specific treatment administration (oral drug or insulin), fasting glycaemia >126 mg/dL or HbA1c >6.5%. Chronic kidney disease was considered for history of renal failure at admission or in patients with an estimated glomerular filtrate (GFR) <60 mol/min/1.73 m^2 calculating by applying MDRD (Modification of Diet in renal Disease) formula.

Biochemical measurements

Blood samples were drawn at admission and at the time of platelet function assessment in all patients. Main biochemical chemistry was determined by standard methods. Glucose, creatinine, uric acid, blood cells count and lipid profile were determined by standard methods.

Platelet function assessment

Platelet aggregation was measured by whole blood tests, including impedance aggregometry (Multiplate®-multiple platelet function analyser; Roche Diagnostics AG). For Multiplate a whole blood sample was stored in Vacutainer standard lithium heparin tubes and analyzed within 1–2 h from collection [16]. Tests with different agonists were performed: arachidonic acid (ASPI test) for ASA, collagen, adenosine diphosphate (ADP) and prostaglandin E1 for ADP test and thrombin receptor activating peptide (TRAP-6). The results considered were expressed as arbitrary Aggregation Units (AU) and plotted against time, defining platelet function as the area under curve (AUC or AU∗min). HRPR was considered for AU∗min values above lower limit normal for ASA (HAPR) [range: 862–1344] or after ADP stimulation [range: 417–1030] respectively [17,18]. The previously reported [19] cut-off of >468 AU∗min (46 U) was also applied to define poor ticagrelor responders. The test was repeated in patients with HRPR to confirm the findings.

Statistical analysis

Statistical analysis was performed using SPSS 15.0 statistical package. Continuous data were expressed as mean ± SD and categorical data as percentage. Analysis of variance and the chi-square test were used for continuous and categorical variables, respectively. Patients were