



Diabetes mellitus, glucose control parameters and platelet reactivity in ticagrelor treated patients



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ABSTRACT

Introduction: Despite the recent advances, prognostic difference between diabetic and non diabetic patients is still marked after an acute coronary syndrome. Diabetes mellitus and poor glycemic control represent well established pro-thrombotic conditions, as inadequate glycemic control can lead to impaired responsiveness to antiplatelet therapies. Among new antiplatelet agents, ticagrelor has provided more potent platelet inhibition, potentially offering benefits in reducing residual high-on treatment platelet reactivity. However, no study has so far investigated the relationship between diabetes mellitus and platelet reactivity in patients treated with ticagrelor after an acute coronary syndrome (ACS).

Methods: In patients treated with acetylsalicylic acid (100–160 mg) and ticagrelor (90 mg twice a day) platelet reactivity was assessed at 30–90 days post-discharge for an ACS. Diabetic status was defined before discharge. Multiple-electrode aggregometry was used to assess platelet function. High residual platelet reactivity was defined as ADP-test results >417 AU * min.

Results: Diabetes was observed in 86 out of 224 patients (38.4%). Diabetes was significantly associated with older age, higher BMI, renal failure, hypertension, treatment with diuretics, higher levels of WBC, glycaemia, HbA1c, and lower levels of HDL-cholesterol. Platelet reactivity was higher in diabetic patients as compared to non-diabetic ones for all the different activating stimuli tested. A total of 29 patients (12.9%) displayed high-residual platelet reactivity with ticagrelor with an almost double rate in diabetics as compared to non-diabetics (18.8% vs 9.4%, $p = 0.06$; adjusted OR[95%CI] = 2.12[1.1–4.1], $p = 0.025$). A progressive increase of platelet reactivity was observed for higher HbA1c levels ($r = 0.15$, $p = 0.029$).

Conclusion: The present study shows that diabetic patients display higher platelet reactivity despite dual antiplatelet therapy. In fact, diabetes mellitus emerged as independent predictor of high-residual platelet reactivity in post-ACS patients treated with ticagrelor.

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1. Introduction

Diabetes mellitus still represents one of the main determinants of cardiovascular risk, accounting for about one third of patients admitted for an acute coronary syndrome (ACS) [1].

Moreover, despite the introduction of new-generation drug eluting stents, new implantation techniques and pharmacological strategies [2–4], diabetes is still associated with an increased rate of thrombotic complications and worse prognosis after percutaneous coronary revascularization (PCI), justifying a more aggressive management [5–7].

Enhanced platelet reactivity and reduced effectiveness of antiplatelet therapies play a central role in increasing the ischemic burden of diabetic patients, and especially among patients with inadequate glycemic control, where hyperglycemia, oxidative stress and enhanced inflammatory response can induce platelet activation. In fact, a higher rate of residual high-on treatment platelet reactivity (HRPR) has been shown in diabetic patients, as compared to non-diabetic patients, during clopidogrel treatment, thus negatively influencing cardiovascular outcomes [8,9].

Newly developed antiplatelet agents, inhibiting platelet P2Y₁₂ receptor, have only partially overcome the phenomenon of impaired effectiveness observed with clopidogrel, providing a more powerful and predictable antiplatelet effect [10,11]. In particular, ticagrelor, a reversible, direct-acting P2Y₁₂ blocker, has demonstrated in the PLATO-trial a reduction in major cardiovascular events among patients with

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diabetes that was consistent with the results in the overall cohort of patients [12,13]. However, a recent meta-analysis has suggested an association between diabetic status and platelet reactivity during ticagrelor maintenance therapy [14]. Therefore, the aim of the current study was to evaluate the relationship between diabetes mellitus, glucose control parameters and platelet reactivity, and the occurrence of HRPR in patients treated with ticagrelor after an acute coronary syndrome (ACS).

2. Methods

We included patients admitted for an ACS to the Division of Cardiology, “Maggiore della Carità” Hospital, Eastern Piedmont University in Novara, Italy, from September 2013 to October 2014. Invasive treatment with coronary angiography and eventual coronary stenting was not a required inclusion criteria. 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 30–90 days from discharge. The study was approved by our local Ethical Committee and informed consent was obtained by all patients.

Main baseline 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 was > 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 [15]. Compliance was assessed by medical interview. Exclusion criteria were patients' refusal or if the patient had given up ticagrelor therapy.

2.1. Biochemical measurements

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 [16]. Blood cells 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).

2.2. Platelet aggregation

Platelet aggregation was determined by Multiplate electrical impedance aggregometry (MEA), within 1–2 h from the morning dose of ticagrelor. The aggregation tests were performed from 30 min to 2 h from blood collection [17]. Platelets 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, defining platelet function as the area under curve (AUC or AU * min). HRPR for ticagrelor was defined for ADP test above 417 AU * min (normal range: [417–1030]) [18]. The test was repeated in patients with HRPR to confirm the findings. The previously described cut-off value of 468 AU * min was also applied for the definition of HRPR with Ticagrelor [19].

2.3. Statistical analysis

Statistical analysis was performed using SPSS 17.0 statistical package. Patients were grouped according to diabetic status. Continuous data were expressed as mean ± SD and non-numerical binary data as percentage. Analysis of variance and the chi-square test were used for continuous and non-numerical binary variables, respectively.

Linear regression analysis was performed to compare glycemic control parameters and platelet reactivity at ADP-test. Multiple logistic regression analysis was performed to evaluate the relationship between glycemic status and HRPR after correction for baseline differences (all variables displaying a significant association with vitamin D levels at univariate analysis), that were entered in the model in block. Multiple linear regression analysis was conducted to evaluate the relationship between ADP test results and glycemic control (standardized beta coefficient) after correcting for significant continuous variables at univariate analysis. Partial correlation test was also performed for additional cross-validation. A *p* value < 0.05 was considered statistically significant.

3. Results

Our population is represented by a total of 224 patients, including 86 (38.4%) diabetic patients.

3.1. Diabetic status and platelet reactivity

Table 1 shows main baseline clinical features according to diabetic status. Diabetic patients were older (*p* = 0.05), with a higher BMI (*p* = 0.009), larger prevalence of renal failure (*p* = 0.016), hypertension (*p* = 0.02) and were more frequently receiving a chronic therapy with diuretics (*p* = 0.02). Diabetes mellitus directly related with White Blood Cells Count, glycaemia, HbA1c and HDL-cholesterol (*p* < 0.001, respectively).

Platelet reactivity was higher in diabetic as compared to non-diabetic patients (*p* = 0.046 for ASPI test, *p* = 0.013 for COL test, *p* = 0.04 for TRAP test and *p* = 0.002 for ADP test, as in Table 1). A total 29 patients (12.9%) out of 224 displayed HRPR (ADP test ≥ 417 AU * min) in treatment with ticagrelor, with an almost double rate of HRPR patients in the presence of diabetes mellitus, although such a marked absolute difference did not reach statistical significance (18.8% vs 9.4%, *p* = 0.06, Fig. 1).

In fact, at multivariate analysis, after correction for baseline differences (age ≥ 75 years, BMI, renal failure, hypertension, diuretics, White Blood Cells Count, glycaemia, HbA1c and HDL-cholesterol), diabetes emerged as an independent predictor of HRPR with ticagrelor (OR[95%CI] = 2.12[1.1–4.1], *p* = 0.025). Results are shown in Table 2.

At linear regression analysis, as displayed in Fig. 2A, a direct relationship was identified between platelet reactivity at ADP test and HbA1c (*r* = 0.15, *p* = 0.029), but not with fasting glycemia (*r* = 0.08, *p* = 0.20, Fig. 2B). The association between glycosylated haemoglobin and ADP test results were confirmed by partial regression analysis (beta = 0.142, *p* = 0.05).

4. Discussion

The present study represents one of the largest cohorts of patients treated with Ticagrelor for a recent ACS, where the role of diabetes mellitus (DM) and glycemic control on platelet reactivity were assessed. Our main finding is that diabetes mellitus is independently associated with higher platelet reactivity. In addition, we have observed a significant linear association between HRPR and glycosylated haemoglobin levels, but not with fasting glycaemia.

Diabetes mellitus represents a major public health concern, in particular for its progressively increasing prevalence and unfavorable cardiovascular prognosis. In fact, the improvements in the management of ACS and in revascularization strategies have proven largely unsatisfactory among diabetic patients, that still display a far higher risk of long-term mortality and acute ischemic events [20–22] as compared to non diabetics [23–26].

Platelet hyper-reactivity can be held responsible for a relevant part of the thrombotic risk increase among diabetic patients, thus explaining the great efforts accomplished to establish an optimal antiplatelet

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