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Impact of statin therapy on the immature platelet count in patients with coronary artery disease: A single centre cohort study

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ABSTRACT

Background: Statins represent a pivotal therapy among patients with coronary artery disease (CAD), providing both lipid-lowering and pleiotropic, anti-thrombotic and anti-inflammatory benefits. Immature platelet count (IPC) has been proposed as the fraction of younger and potentially more reactive platelets, therefore potentially affecting the risk of major cardiovascular ischemic events. The aim of the present study was to evaluate the impact of statin therapy on IPC in patients with CAD.

Methods: Patients undergoing coronary angiography in a single centre were included. IPC levels were measured by routine blood cells count (A Sysmex XE-2100) as the product of immature platelet fraction (IPF) and platelet count, in patients naïve or chronically treated with statins at admission.

Results: We included in our study 642 patients, 61.2% treated with statins at admission. Patients on chronic statins were more often males, with a worse metabolic profile, but for lower total and LDL cholesterol, and a higher prevalence of major cardiovascular risk factors. The mean levels of IPC did not differ between statin treated and naive patients (7.9 ± 4.7 vs 7.7 ± 5, $p = 0.60$) and neither the distribution of IPC across tertiles ($p = 0.36$). In fact, at multivariate regression analysis, statin use was not independently associated with the rate of IPC above the 3rd tertile (adjusted OR[95%CI] = 1.19[0.80–1.79], $p = 0.39$).

Moreover, among the 190 patients that introduced the therapy with statins at admission, the levels of IPC and major platelet parameters did not differ at a median follow-up of 32 days, as compared to chronically treated or non-treated patients.

Conclusion: The present study shows that among patients with CAD the use of statins does not affect the immature platelet count or main platelet parameters.

1. Introduction

Advances in pharmacological therapy have significantly improved the outcomes of patients with coronary artery disease (CAD), reducing mortality and the risk of recurrent major ischemic events [1–3]. In particular, statins have emerged as a cardinal treatment in CAD, offering acute peri-procedural protective effects in patients undergoing coronary revascularization procedures and providing long-term reduction in the atherosclerotic burden [4,5]. In fact, besides their established lipid-lowering action, pleiotropic antithrombotic and anti-inflammatory effects have been described for statins, preventing vascular damage, improving endothelial function and lowering platelet reactivity [6]. However, previous studies have suggested that such benefits could be mostly limited to those high-intensity statin regimens, therefore drawing the attention to the identification of early markers of cardiovascular risk, allowing to target a more aggressive statin therapy only in high-risk patients.

Immature platelet count (IPC) has been proposed as an indicator of the fraction of younger, larger sized and potentially more reactive platelets [7], that have been associated with acute cardiovascular events and suboptimal platelet inhibition despite antiplatelet agents [8,9].

Moreover, it has been suggested that the persistence of elevated levels of immature thrombocytes could mirror the activity of an ongoing chronic vascular damage [10], translating in a peripheral consumption of mature platelets, and increased turnover and a more elevated risk of recurrent ischemic events, that could be potentially prevented with statins. Even though previous data have reported a reduction in mean platelet volume with statin therapy [11], no study has so far assessed

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the impact of the use of statins on the levels of immature platelets (IPC) among patients with CAD, that is therefore the aim of the current study.

2. Methods

We included a prospective cohort of patients undergoing coronary angiography and percutaneous coronary intervention (PCI) between December 2014 and August 2017 at the Ospedale "Maggiore della Carità", Novara, Italy and scheduled for a blood sample re-assessment after about 30–90 days from discharge. All patients were on dual antiplatelet therapy at discharge. Statin therapy was started after hospital admission, and always not before drawing the first blood sample (including IPC). A written informed consent was a required inclusion criterion. The study was approved by our local Ethical Committee. All demographic and clinical data were prospectively recorded in a dedicated database. Hypertension was defined as systolic pressure >140 mm Hg and/or diastolic pressure >90 mm Hg 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 renal failure was defined for history of renal failure or an admission glomerular filtration rate (GFR) <60 mol/min/1.73 m^2 by MDRD (Modification of Diet in renal Disease) formula. Elective patients were defined as those patients undergoing coronary angiography and PCI for indications different from an acute coronary syndrome, that was defined as by the presence of chest pain at rest lasting >20 min with or without an associated cardiac biomarkers elevation > ULN (respectively 0,04 μg/l for Troponin I and 5,00 μg/l for CK-MB) or electrocardiographic changes or wall motion abnormalities. High-intensity statin therapy was defined as atorvastatin ≥40 mg, rosuvastatin ≥20 mg or simvastatin 40 mg daily.

2.1. Biochemical measurements

Blood samples were drawn at admission, in elective patients a fasting period of 12 h was required. Glucose, creatinine, glycosylated haemoglobin and lipid profile were determined by standard methods [12]. Analogous fasting sample was obtained at the scheduled follow-up. Blood cells count was performed in a blood sample collected in tripotassium EDTA (7.2 mg) tubes and analysed within 2 h from drawing by an automatic blood cells counter (A Sysmex XE-2100). The percentage of reticulated platelets was defined as the percentage of immature platelets within the total platelet count or immature platelet fraction (IPF), determined by a fully automated sorting system (forward light scatter versus fluorescence scatterplot) of the Sysmex XE-2100 instrument, as previously described [13]. The expected Coefficient of Variation (CV) was ≤20% according to the manufacturer. The immature platelet count (IPC) was derived from the IPF percentage according to the total platelet count.

2.2. Statistical analysis

Statistical analysis was performed using SPSS 22.0 statistical package. Categorical data were provided as percentage, whereas continuous data were expressed as mean ± SD. Analysis of variance and the chi-square test were performed respectively for continuous and categorical variables. Patients were grouped according to the chronic use of any statins at admission (any statin and dose). IPC variations were considered as the relative difference between re-assessment and baseline measurement of IPC, as compared to the value at admission. Multiple logistic regression analysis was used to evaluate the relationship between IPC (above the 3rd tertile; ≥ 8.4 * 10^6/ml) and statin therapy, after correction for baseline confounding factors (all variables displaying a significant association at univariate analysis-p value <0.05), that were entered in the model in block. A p value <0.05 was considered statistically significant.

3. Results

We included in our study 642 patients, of whom 393 (61.2%) were treated with statins at admission. Among them, 239 patients received atorvastatin (60.8%); 81 (9.6%) rosuvastatin, 65 (16.5%) simvastatin, 7 patients pravastatin and 1 patient Fluvastatin. High-intensity statin was administered in 181 patients (46.1%). Main clinical and demographic features of included patients are listed in Table 1.

Patients on chronic statins were more often males ($p = 0.05$), with a higher rate of hypercholesterolemia, diabetes, previous MI or coronary revascularization ($p < 0.001$), displayed more often an elective indication ($p < 0.001$), and a more complex coronary disease ($p = 0.003$). Metabolic profile was worse in statin treated patients in terms of glycaemia and HbA1c ($p = 0.006$ and $p = 0.007$) and HDL-cholesterol ($p = 0.005$), despite displaying lower total and LDL-cholesterol ($p < 0.001$).

The mean levels of IPC did not differ between statin treated and statin non-treated patients (7.9 ± 4.7 vs 7.7 ± 5 * 10^6/ml, $p = 0.60$; Fig. 1A).

Also the mean IPF values were comparable (3.5 ± 2.5% vs 3.47 ± 2.27%, $p = 0.85$).

Table 1
Clinical characteristics according to statin treatment.

Baseline clinical characteristics	Statin naive ($n = 249$)	Chronic statins ($n = 393$)	p value
Age (mean ± SD)	68.2 ± 11.5	68.4 ± 9.7	0.85
Male sex (%)	73.9	80.7	0.05
BMI (mean ± SD)	27.3 ± 4.6	27.5 ± 4.5	0.54
Hypercholesterolemia (%)	46	67.4	<0.001
Renal failure (%)	20.1	17.6	0.47
Active smokers (%)	25.7	21.9	0.92
Diabetes mellitus (%)	30.1	46.1	<0.001
Hypertension (%)	75.5	74.8	0.85
History of MI (%)	9.3	30	<0.001
Previous PCI (%)	13.7	53.7	<0.001
Previous CABG (%)	3.2	17.6	<0.001
Indication to angiography			<0.001
Stable angina/silent ischemia (%)	29.9	47.3	
STEMI/ACS (%)	67.1	45	
Cardiomyopathy/valvular disease/arrhythmias (%)	10	7.7	
Concomitant medications			
ACE inhibitors (%)	54.2	48.9	0.19
ARB (%)	21.6	27.5	0.19
Beta blockers (%)	84.3	87.3	0.29
Nitrates (%)	43.8	50.9	0.09
Calcium antagonists (%)	25.7	30.8	0.18
Diuretics (%)	35.3	40.7	0.18
Acetylsalicylic acid (%)	92.4	95.2	0.17
P2Y12 inhibitor (%)	30.7	35.6	0.19
Coronary artery disease (%)			
Severe CAD (%)	34.9	47.1	0.003
Biochemistry parameters			
Platelets (10^6/ml; mean ± SD)	232.1 ± 68	239.5 ± 63	0.16
Haemoglobin (g/dl ± SD)	13.3 ± 1.8	13.3 ± 1.8	0.87
WBC (10^3/ml; mean ± SD)	7.8 ± 2.4	7.8 ± 2	0.93
Total cholesterol (mg/dL)	185.9 ± 40.3	143.7 ± 33	<0.001
HDL cholesterol (mg/dL)	41.8 ± 12.4	45.2 ± 17.5	0.005
LDL cholesterol (mg/dl)	113.5 ± 35.6	78.4 ± 28	<0.001
Glycaemia (mg/dL)	113.7 ± 33.4	123.1 ± 46.2	0.006
Glycosylated haemoglobin (%)	6.2 ± 1.1	6.4 ± 1.2	0.007
Creatinine (mg/dL)	1 ± 0.7	1 ± 0.5	0.61
C reactive protein (mg/dL)	0.6 ± 1.1	0.6 ± 1.5	0.75

CAD = coronary artery disease; MI = myocardial infarction; PCI = percutaneous coronary interventions; CABG = coronary artery bypass grafting; STEMI = ST-elevation myocardial infarction; ACS = acute coronary syndrome; CMD = dilated cardiomyopathy; LV = left ventricle; ACE = angiotensin converting enzyme; ARB = angiotensin receptor blockers.

Similarly, the distribution across IPC tertiles was not affected by the use of statins at admission (31 vs 36.1% in I tertile (<5.05 * 10^6/ml), 34.6 vs 30.5% in II tertile (5-05-8.39 * 10^6/ml) and 34.4 vs 33.3% in III tertile (≥8.4 * 10^6/ml), $p = 0.36$), as shown in Fig. 1B.

Results did not change when considering separately elective patients (7.77 ± 6 vs 7.88 ± 4.7 * 10^6/ml, $p = 0.17$) and ACS (7.63 ± 4.44 vs 7.86 ± 4.7 * 10^6/ml, $p = 0.64$), and in patients receiving high-intensity statins ($n = 181$) vs low-intensity (6.99 ± 3.3 vs 7.88 ± 4.8 * 10^6/ml, $p = 0.14$), as displayed in Fig. 2A and B, respectively.

In fact, at multivariate regression analysis (after correction for gender, hypercholesterolemia, diabetes, previous MI or coronary revascularization, clinical presentation, extent of coronary disease, glycaemia and HbA1c, total, LDL-cholesterol and HDL-cholesterol), statin use was not independently associated with the rate of IPC above the 3rd tertile (adjusted OR[95%CI] = 1.19[0.80–1.79], $p = 0.39$).

Moreover, we evaluated the cohort of 190 patients who introduced the therapy with statins at discharge: 165 (86.8%) received atorvastatin, while 21 rosuvastatin and 4 simvastatin. Compliance to statin therapy was documented in all patients by lipid-profile at follow-up (Table 2 Supplementary). The levels of IPC did not differ at a median follow-up of 32 days [IQR: 15–77], as compared to the patients already on statins at admission. In fact, the mean levels of IPC at re-assessment were similar among patients without statins ($n = 59$), patients starting statins after admission and chronically treated patients (7.34 ± 4.8 vs 7.87 ± 4.5 vs 7.89 ± 4.9 * 10^6/ml, $p = 0.71$) and also the variation of IPC

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