Inflammatory state does not affect the antiplatelet efficacy of potent P2Y12 inhibitors in ACS

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Abstract

Inflammation leads to atherosclerosis and acute coronary syndromes (ACS). We performed a prospective, observational study to assess association between the concentrations of inflammatory markers (high sensitivity C-reactive protein, hsCRP; high sensitivity interleukin6, hsIL-6; soluble CD40 ligand, sCD40L) and platelet reactivity in 338 patients with ACS treated with ticagrelor and prasugrel. We also assessed whether hsCRP, hsIL-6 and sCD40L are associated with standard inflammatory markers (white blood cell [WBC] and fibrinogen), and whether they differ according to patient diabetic status and pre-treatment with statins. Concentrations of hsCRP and concentrations of hsIL-6 and sCD40L were assessed using turbidimetric assay and enzyme-linked immunosorbent assay, respectively. Platelet reactivity was measured using multiple electrode aggregometry. There was only a weak inverse correlation between hsIL-6 and platelet reactivity ($r \leq -0.125$). In contrast, concentration of hsIL6 and hsCRP positively correlated with WBC count and fibrinogen ($r \geq 0.199$). Insulin-dependent diabetes mellitus (IDDM) was associated with higher concentration of hsIL-6 ($p=0.014$), whereas pre-treatment with statins - with lower concentration of hsIL-6 ($p=0.035$). In conclusion, inflammatory state does not affect the antiplatelet efficacy of potent P2Y12 inhibitors in the acute phase of ACS, confirming the safety and efficacy of potent P2Y12 inhibitors in patients with a high inflammatory burden.

Introduction

Chronic inflammation of the vessel wall underlies atherosclerosis and its major complications, such as acute coronary syndromes (ACS) [1-6]. In patients with stable coronary artery disease and/ or ACS, inflammation is reflected by elevated concentrations of inflammatory markers such as C-reactive protein (CRP), interleukin-6 (IL-6) or soluble CD40 ligand (sCD40L) [7-11]. Each of these markers was shown to have predictive value for future cardiovascular events, suggesting that measuring CRP, IL-6 and sCD40L after ACS may help to predict patient outcomes [12-14]. Accordingly, the results of "Canakinumab Antiinflammatory Thrombosis Outcome Study" (CANTOS) showed that decreasing inflammation by blocking the interleukin-1β pathway improves cardiovascular outcomes in patients with a history of ACS and elevated CRP, ultimately confirming the link between inflammation and recurrent cardiovascular events [15].

Patients after ACS receive a multitude of drugs, of which the anti-inflammatory effects are unknown. The standard treatment of ACS includes a dual antiplatelet therapy consisting of aspirin and a P2Y12 inhibitor such as clopidogrel, prasugrel or ticagrelor [16-23]. Because up to 30% of patients have high on treatment platelet reactivity (HTPR) under clopidogrel, prasugrel and ticagrelor are preferred over clopidogrel after ACS [24-29]. Whereas the anti-inflammatory effects of aspirin and clopidogrel are well-established [5,30-32], data regarding the anti-inflammatory effects of prasugrel and ticagrelor are scarce. It has been postulated that prasugrel has a greater anti-inflammatory potential than clopidogrel [33] and ticagrelor reduces inflammation at least as much as clopidogrel [34]. Further, although activated platelets contribute both to inflammation and thrombosis, whether the concentrations of inflammatory markers correspond to the extent of platelet inhibition in patients treated with prasugrel or ticagrelor is unknown. Finally, concomitant diabetes mellitus deteriorates prognosis after ACS [35], whereas pre-treatment with statins improves prognosis [36]. However, whether diabetes

and pre-treatment with statins affect inflammatory markers after ACS when treated with potent P2Y12 inhibitors has not been well characterised yet.

We aimed to investigate the association between the concentrations of inflammatory markers known to predict future cardiovascular events (high sensitivity [hs] CRP, hsIL-6 and sCD40L) [12-14] and platelet reactivity in patients with ACS treated with prasugrel or ticagrelor. In addition, we evaluated the dynamics of inflammatory parameters and platelet reactivity after PCI. We also assessed whether hsCRP, hsIL-6 and sCD40L are associated with standard inflammation markers, and whether they differ according to patient characteristics.

Methods

Study design

From May 2013 to April 2015 we performed a prospective, observational ATLANTIS INFLAMMATION study, a substudy of the "Association between the antiplatelet drug efficacy/safety and platelet function in patients treated with novel platelet inhibitors due to an acute coronary syndrome" (ATLANTIS-ACS; NCT01992484). The study protocol designed in accordance with the Declaration of Helsinki was approved by the Ethics Committee of the Medical University of Vienna. All participants provided written informed consent.

Study population

Patients were eligible for enrolment if they (i) were more than 18 years of age, (ii) presented with unstable angina pectoris (UAP), non-ST-segment elevation myocardial infarction (NSTEMI) or ST-segment elevation myocardial infarction (STEMI) at the General Hospital of Vienna, Austria, and (iii) were administered a loading dose of ticagrelor or prasugrel. Patients who participated in other clinical trials were excluded.

Study treatment

All patients routinely received a 60 mg loading dose and a 10 mg maintenance dose of prasugrel, or a 180 mg loading and a 90 mg maintenance dose twice daily of ticagrelor. The loading doses of ticagrelor or prasugrel were administered before percutaneous coronary intervention (PCI). In addition, all patients received a 300 mg loading dose and a 75 mg maintenance dose of aspirin. No exclusively study-related treatment was administered. All patients received standard treatment after AMI according to the guidelines, including statin, β-blocker, angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) and protein pump inhibitor (PPI), depending on the individual clinical characteristics and comorbidities. The study neither altered nor impaired any standard therapy necessary for the individual patient.

Clinical data collection

The following data were recorded on admission: demographic data (age, gender), weight, type of ACS and type of P2Y12 inhibitor administered (prasugrel, ticagrelor), cardiovascular risk factors (arterial hypertension, hyperlipidaemia, smoking status, family history of coronary artery disease and diabetes mellitus), history of cardiovascular disease (prior AMI, prior PCI, carotid artery disease, peripheral artery disease), angiographic data and pharmacotherapy administered at admission. Arterial hypertension was defined as (i) a history of hypertension and/ or the use of antihypertensive drugs or (ii) repetitive resting blood pressure values above 140/90 mmHg during in-hospital measurements, applied two to four times daily. Hyperlipidaemia was defined as (i) a history of lipid-lowering therapy or (ii) total cholesterol level above 200 mg/dl. Smoking was assessed as current, past and non-smoking. Diabetes mellitus was defined as (i) pathological oral glucose tolerance test, or (ii) a history of diabetes or anti-diabetic therapy. On admission, HbA1c was measured in all patients and oral glucose

tolerance test was performed, if necessary, to detect undiagnosed diabetes. In addition, routine laboratory parameters were recorded.

Samples collection and handling

Blood collection was performed during the hospital stay after primary PCI (days 1-3). Venous blood was collected in evacuated container tubes (Vacuette tubes; Greiner Bio-One, Kremsmuenster, Austria) containing (i) silica particles to prepare serum, (ii) lithium heparin to prepare plasma, and (iii) lepirudin to analyse platelet function. The latter two were cautiously filled to the right capacity and inverted 3 to 5 times for gentle mixing. To prepare serum, blood was left to clot for 30 minutes and the clot was removed by 20 minutes centrifugation at 1,300g. To prepare plasma, heparin blood was centrifuged within 30 min after blood collection at 2,5000 g for 15 minutes. Serum and plasma were aliquoted into 1.5 ml test tubes which were labelled with unique codes and stored at -80 °C until analysis.

Laboratory assays

Inflammatory markers

The concentration of hsCRP was measured in serum using a Cardiac CRP Latex High Sensitivity test on a Cobas 8000 c702 Module (Roche Diagnostics GmbH, Mannheim, Germany). This test is a turbidimetric immunoassay using latex particles coated with murine monoclonal anti-CRP antibodies and was showed to be to superior to other tests [37].

HsIL-6 and sCD40L were measured in heparin plasma using enzyme-linked immunosorbent assays (Human IL-6 high sensitivity ELISA and Human sCD40L Instant ELISA, respectively, Bender MedSystems GmbH, Vienna, Austria). All procedures were done according to the manufacturer´s instructions.

Platelet function

Platelet function was determined using Multiple Electrode Aggregometry (MEA) on a new generation impedance aggregometer (Multiplate Analyzer, Verum Diagnostica GmbH,

Munich, Germany) using AA test (arachidonic acid, 0.5 mM), and ADP test (ADP, 6.5 μM) according to the manufacturer's instructions. MEA measures the change of electrical impedance due to the adhesion and aggregation of platelets on the electrodes. The higher the aggregation, the larger the area under the curve (AUC). MEA was showed to be superior to other assays, such as vasodilator-stimulated phosphoprotein assay [38,39]. High on-treatment platelet reactivity (HTPR) determined with MEA was predictive for stent thrombosis, whereas low on-treatment platelet reactivity (LTPR) was predictive for bleeding in patients treated with clopidogrel [40,41]. After measuring platelet aggregation, all patients were divided into three groups: HTPR (AUC>46), medium on-treatment platelet reactivity (MTPR; AUC 20-45) and LTPR (AUC<20) [42-45].

Statistical analysis

We estimated an exploratory sample size of 338 patients to find an association between the concentrations of inflammatory markers and platelet reactivity in patients treated with prasugrel and ticagrelor, assuming the (i) correlation coefficient of 0.25, (ii) test power of 80%, (iii) significant two-sided alpha value below 0.05, and (iv) 25% of patients potentially lost to follow-up. Categorical variables were presented as number and percent and compared using Fischer's exact test. Continuous variables were presented as mean and standard deviation (SD) or median with interquartile range, depending on the distribution. Concentrations of inflammatory markers between patients treated with prasugrel and ticagrelor were compared using Mann–Whitney U test. The correlations between inflammatory markers and platelet reactivity were analysed by bivariate Spearman correlation coefficient. Statistical analysis was conducted using IBM SPSS Statistics, version 22.0 (IBM, New York, New York, United States).

Endpoints

The primary endpoint of the study was the association between the concentrations of hsCRP, hsIL-6 and sCD40L and platelet reactivity in ADP test. The secondary endpoints of the study were the: (i) correlation between the concentrations of hsCRP, hsIL-6 and sCD40L and platelet reactivity in AA test, (ii) dynamics of hsCRP, hsIL-6 and sCD40L and platelet reactivity after PCI, (iii) correlations between the hsCRP, hsIL-6 and sCD40L and standard inflammatory biomarkers (fibrinogen, WBC), and (iv) differences in hsCRP, hsIL-6 and sCD40L according to patient characteristics.

Results

Patient characteristics

Of the 338 patients enrolled in the study, 18 patients were excluded due to haemolysis of blood samples. Samples from 320 patients were used for the assessment of inflammatory markers (Table 1). All patients underwent coronary angiography. While 54% (n=174) were treated with ticagrelor, 46% received (n=146) prasugrel. Of the patient cohort, 62% were diagnosed with STEMI, 34% with NSTEMI and 4% with unstable AP. The majority of individuals displayed typical risk factors for ACS: 64% hypertension, 56% hyperlipidemia, 52% smoking, 48% family history of CAD, 20% diabetes with no significant difference between the three platelet reactivity groups (HTPR, MTPR, LTPR). Most patients received standard medication upon arrival in the hospital including statins (90%), beta blockers (89%), ACE-inhibitors or angiotensin receptor blockers (86%) and proton pump inhibitors (PPI) (74%). The laboratory data showed an overall high WBC count (10.96±3.98 G/L) and high levels of fibrinogen (390±96 mg/dl). Primary PCI was performed in 93% of the patients and most of them received unfractionated heparin prior to PCI (69% UFH vs. 5% LMWH vs. 7% no heparin).

The patient cohort was divided into three groups according to their platelet reactivity in response to ADP: LTPR, MTPR and HTPR. The minority of patients displayed the HTPR phenotype (3.2%), whereas 27% had MTPR and 70% LTPR. Platelet counts were 20% higher in the HTPR group compared to patients with LTPR (292±133 vs. 235±60 G/L; p=0.049). There was no difference in the three subgroups regarding the rate of ticagrelor and prasugrel administration (3.4% vs. 2.9% HTPR, p=0.69; 32% vs. 22% MTPR, p=0.17; 64% vs. 75% LTPR, p=0.16, respectively; Table 2).

Association between inflammatory markers and platelet reactivity

Patients treated with prasugrel and ticagrelor had comparable concentrations of hsCRP, hsIL-6 and sCD40L and comparable platelet reactivity (Table 2). The levels of inflammatory markers did not correlate with platelet reactivity, except for a week negative correlation between IL-6 and AA- and ADP-induced platelet aggregation (Table 3).

Dynamics of inflammatory parameters and platelet reactivity after PCI

HsIL-6 levels were highest when assessed one day after PCI and dropped quickly – at day three hsIL-6 levels were 47% lower as compared to day one (p<0.001; Figure 1). In contrast to hsIL-6 levels, hsCRP levels were lowest one day after PCI and increased 1.8-fold at day two and three (p<0.001; Figure 1). The levels of ADP-induced platelet aggregation were lowest one day after PCI (Figure 2) and increased slightly at days two and three (p<0.001; Figure 2). ADP-induced platelet aggregation dropped between hsIL-6 quartiles (p=0.007; Figure 3). When analyzed individually for each treatment group, this observation was confirmed for ticagrelor (p=0.034; Figure 3). In the prasugrel group, a similar trend was noticed, however without a statistical significance (p=0.26; Figure 3).

Correlations between hsCRP, IL-6, sCD40L and standard inflammatory markers

There were low to moderate correlations between hsCRP and IL-6 and standard inflammatory markers (fibrinogen and WBC). On the contrary, there was no correlation between sCD40-L and standard inflammatory markers (Table 4).

Associations between patients' characteristics and inflammatory parameters

Age, peripheral artery disease and creatinine levels were positively associated with increasing levels of IL-6 (Table 5).

Patients presenting with insulin dependent diabetes mellitus (IDDM) showed 52% higher levels of hsIL-6 when compared to patients without diabetes (p=0.014; Figure 4). In contrast, the levels of sCD40-L were 30% lower in patients presenting with IDDM as compared to no DM (p=0.043; Figure4). No association between DM and hsCRP was found.

An interpatient variability in hsIL-6 levels was noticed depending on the use of statins and abciximab. When treated with statins at the time of admission, patients showed 40% reduced levels of hsIL-6 as compared to no statin treatment (p=0.035; Figure 5). Concentrations of hsCRP and sCD40L did not differ according to pre-treatment with statins (data not showed). Patients treated with abciximab during PCI had 31% higher hsIL-6 levels as compared to patients not treated with abciximab (p=0.009; Table 5).

Discussion

The main finding of our study is that the inflammatory and/or preexisiting disease state does not alter the inhibitory effect of potent antiplatelet therapy (prasugrel or ticagrelor) in the acute phase of ACS, as proved by no correlation between the concentrations of hsCRP, IL-6 and sCD40L and platelet reactivity, despite similar dynamics of hsCRP and platelet reactivity. To increase the reliability of this finding, we showed positive correlations between hsCRP and

IL-6 and other markers of inflammation (WBC count and fibrinogen). Moreover, in our study administration of the potent platelet inhibitor abciximab on top of aspirin and P2Y12 inhibitor during PCI increased the concentration of IL-6, again indicating no relationship between platelet inhibition and inflammation.

Our result stand in contrast to the previously published findings. Other groups showed that platelet aggregation strongly correlates with the inflammatory state (CRP, WBC count and fibrinogen) in patients with stable coronary artery disease on long-term treatment with clopidogrel [46], and in patients with STEMI prior to PCI and treatment with P2Y12 inhibitor [47]. In contrast to the previous studies, in our study two potent P2Y12 inhibitors were used, which resulted in a very small number of patients with HTPR (<5%) and no difference between platelet reactivity in diabetic and non-diabetic patients, despite the well-established relationship between diabetes and higher platelet reactivity [48]. Hence, likely the main reason of the lack of correlation between the inflammation markers and platelet reactivity in our study is the use of two very potent platelet inhibitors that abrogate the effect of systemic inflammation and/or preexisiting disease state on platelet reactivity. Our results clearly demonstrate that the inflammatory state does not affect the antiplatelet efficacy of potent P2Y12 inhibitors, confirming the safety and efficacy of potent P2Y12 inhibitors in patients with a high inflammatory burden. Our results might also partly explain the superiority of prasugrel and ticagrelor over clopidogrel in the previous studies [16,23].

The only correlation found in our study was a weak negative correlation between the concentration of IL-6 negatively and platelet reactivity, confirmed by the opposite dynamics direction of these two parameters: whereas IL-6 decreases, platelet aggregation increases within the first 3 days after PCI. This paradoxical finding may be potentially explained by the differences in IL-6 signalling in the acute and chronic inflammation phase. Whereas the IL-6 “classic signalling” in the acute phase activates anti-inflammatory pathways which induce cell

and tissue regeneration, IL-6 “trans signalling” in the chronic phase has pro-inflammatory effect by the recruitment of monocytes to the inflamed area [49]. Hence, an increase in IL-6 concentration in the acute phase of AMI might be an important host defence mechanism, triggering immune responses to heal the infarcted myocardium [50,51].

Further, we found that patients with IDDM had higher concentrations of hsIL-6 in the acute phase of ACS, compared to patients without DM. Because DM is a chronic inflammatory state associated with pro-inflammatory effects of IL-6, the increased concentration of IL-6 in IDDM likely contributes to worse clinical outcomes after ACS. On the other hand, pulsatile interleukin-6 has been proposed as a treatment option for diabetic peripheral neuropathy [52], again indicating that chronic and short-term increase in IL-6 concentration may exert different immunomodulatory effects. However, since we did not measure the IL-6 concentrations prior to ACS, we cannot confirm that the increase in IL-6 concentration in IDDM patients was triggered by ACS and therefore short-term. Further, since we did not analyse clinical endpoints, we cannot determine the effect of increased IL-6 concentration in IDDM patients with ACS on cardiovascular outcomes.

In contrast to hsIL-6, the concentrations of sCD40L were lower in patients with IDDM, compared to to patients without DM. Insulin is known to inhibit platelet aggregation by suppressing the P2Y12 receptor pathway [53]. However, in DM patients the P2Y12 receptor is upregulated, leading to increased platelet reactivity and loss of responsiveness to antiplatelet effects of insulin [54]. Hence, one could expect that the hyperactive platelets in IDDM release more sCD40L (a marker of platelet activation), resulting in increased plasma concentrations of sCD40L. However, increased platelet reactivity in IDDM was observed only on clopidogrel and prasugrel [54-57], whereas the level of platelet inhibition was consistently high in insulin-treated patients on ticagrelor [58]. Because in our study most patients had LTPR while treated with prasugrel and ticagrelor, the lower concentrations of sCD40L in patients with IDDM likely

results from the high degree of platelet inhibition during treatment with potent P2Y12 antagonists.

Patients pre-treated with statins before ACS had lower concentration of hsIL-6 compared to statin-naïve patients. The anti-inflammatory effects of statin are well-established and include reduced recruitment of inflammatory cells, T cell activation and B cell differentiation, all of which are mediated by IL-6 [59-61]. Hence, our results indicate that the anti-inflammatory effects of statins are mediated by inhibition of IL-6 signalling prior to ACS.

Study limitations

The main limitation of the is the lack of end-points which would be independently associated either with the concentration of inflammatory markers or with platelet reactivity in the acute phase of ACS, making the study hypothesis-generating.

Conclusion

In conclusion, there is hardly any correlation between the concentrations of hsCRP, IL-6 and sCD40L and platelet reactivity in patients treated with potent P2Y12 inhibitors in the acute phase of ACS, suggesting the safety and efficacy of potent P2Y12 inhibitors in patients with a high inflammatory burden. IDDM aggravates, whereas pre-treatment with statins decreases inflammation after ACS.

Declaration of interest

The authors report no declarations of interest.

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Tables and figures

Table 1. Patient characteristics. Data are reported as mean ± standard deviation (SD) or n (number of patients) with percentages.

	Overall N=320	**LTPR N=225**	**MTPR N=85**	**HTPR N=10**	**p**
Age (years)	59±12	59±12	58±12	62±13	Ns
Gender (male) n (%)	256 (80)	179 (81)	67 (79)	10 (100)	Ns
Weight (kg)	83.7±16.0	83.2±15.8	84.9±16.7	83.5±15.1	Ns
Type of ADP-blocker n (%)					
Prasugrel	174 (54)	131 (58)	38 (45)	5 (50)	Ns
Ticagrelor	146 (46)	94 (42)	47 (55)	5 (50)	Ns
Type of ACS n (%)					
STEMI	199 (62)	144 (64)	50 (59)	4 (40)	Ns
NSTEMI	109 (34)	73 (32)	30 (35)	5 (50)	Ns
UAP	12 (4)	7 (3)	4 (5)	1 (10)	Ns
Risk factors / past medical history n (%)					
Hypertension	203 (64)	140 (62)	57 (67)	6 (60)	Ns
Hyperlipidemia	183 (56)	119 (53)	49 (58)	6 (60)	Ns
Smoking	171 (52)	119 (53)	42 (49)	6 (60)	Ns
Family history of CAD	158 (48)	102 (45)	43 (51)	7 (70)	Ns
Diabetes mellitus	67 (20)	47 (21)	16 (19)	2 (20)	Ns
Prior PCI	39 (12)	28 (12)	6 (7)	3 (30)	Ns
Prior myocardial infarction	73 (22)	51 (23)	17 (20)	3 (30)	Ns
Peripheral arterial occlusive disease	20 (6)	13 (6)	4 (5)	0 (0)	Ns
Cerebrovascular disease	13 (4)	10 (4)	1 (1)	1 (10)	Ns
Medication n (%)					
Statins	289 (90)	201 (89)	80 (94)	8 (80)	Ns

Beta-blocker	287 (89)	198 (88)	80 (94)	9 (90)	Ns
ACE-/ARB-Inhibitors	276 (86)	195 (86)	72 (85)	9 (90)	Ns
Calcium-Channel-Blocker	27 (8)	19 (8)	7 (8)	1 (10)	Ns
PPI	236 (74)	163 (72)	67 (79)	6 (60)	Ns
Antidiabetics	43 (13)	32 (14)	11 (13)	1 (10)	Ns
Laboratory data (mean±SD)					
Troponin T (µg/L)	0.67±1.69	0.56±1.41	0.97±2.33	0.77±1.47	Ns
Platelet count (G/L)	240±68	235±60	252±70	292±133	0.049
White blood cell count (G/L)	10.96±3.98	10.84±3.73	11.39±4.61	9.89±3.86	Ns
Creatinine (mg/dl)	0.98±0.34	1.00±0.38	0.96±0.24	0.88±0.21	Ns
Hemoglobin (g/dl)	14.5±1.78	14.5±1.79	14.7±1.38	13.9±1.90	Ns
Fibrinogen (mg/dl)	390±96	381±86	409±114	432±114	Ns
hsIL6 (pg/ml)	9.86±31.19	11.43±36.84	6.87±14.05	5.03±3.66	Ns
hsCRP (mg/L)	2.48±3.57	2.51±3.81	2.52±3.06	2.03±2.35	Ns
sCD40L (ng/ml)	1.49±2.61	1.42±2.01	1.47±2.14	0.66±0.44	Ns
Angiographic data					
Abciximab during PCI n (%)	106 (33)	87 (39)	17 (20)	2 (20)	Ns
Primary/early PCI n (%)	298 (93)	208 (92)	81 (95)	9 (90)	Ns
Number of stents per patient (mean±SD)	1.42±0.95	1.45±1.00	1.35±0.84	1.40±0.69	Ns
Total stent length (mm) (mean±SD)	31.4±20.9	31.9±22.4	30.6±17.2	28.1±14.3	Ns
Average stent diameter (mm) (mean±SD)	3.34±1.69	3.39±1.99	3.22±0.50	3.04±0.34	Ns

Data are reported as Mean ± standard deviation (SD), n (number of patients) or percentages; LTPR= low on treatment platelet reactivity; MTPR= medium on treatment platelet reactivity; HTPR= high on treatment platelet reactivity; CAD= coronary artery disease; PCI= percutaneous coronary intervention; STEMI=ST-elevation myocardial infarction; NSTEMI=none ST-elevation myocardial infarction; UAP= unstable angina pectoris; ACE-/ARB-Inhibitors= angiotensin-converting-enzyme-inhibitor/ angiotensin receptor blocker; PPI= proton pump inhibitor; UFH= unfractionated heparin; LMWH= low molecular weight heparin; Ns=not significant.

Table 2. Concentrations of inflammatory markers and platelet reactivity in patients treated with prasugrel and ticagrelor. Data are presented as median and interquartile range (25th-75th quartiles). Abbreviations: hsCRP: high sensitivity C-reactive protein; hsIL-6: high sensitivity interleukin-6; HTPR: high on-treatment platelet reactivity; LTPR: low on-treatment platelet reactivity; MTPR: medium on-treatment platelet reactivity; sCD40L: soluble CD40 ligand.

Parameter	**Prasugrel (n=174)**	**Ticagrelor (n=146)**	**p**
hsIL-6 (pg/ml)	3.90 (1.90-8.07)	3.52 (1.56-6.79)	0.23
hsCRP (mg/l)	1.16 (0.58-3.15)	1.04 (0.37-2.75)	0.16
sCD40L (ng/ml)	0.82 (0.51-1.46)	0.72 (0.49-1.31)	0.29
LTPR (%)	64	75	0.16
MTPR (%)	32	22	0.17
HTPR (%)	3.4	2.9	0.69

Table 3. Correlations between inflammatory markers and platelet reactivity. Abbreviations: AA: aggregation in response to arachidonic acid; ADP+PGE2: aggregation in response to adenosine diphosphate in presence of prostaglandin E1; ADP: aggregation in response to ADP; hsCRP: high sensitivity C-reactive protein; hsIL-6: high sensitivity interleukin-6; sCD40L: soluble CD40 ligand.

Spearman-Rho Correlation		**AA**	**ADP**
hsIL-6	coefficient of correlation	-0.125	-0.162
	P	0.026	0.004
hsCRP	coefficient of correlation	0.069	0.080
	P	0.22	0.16
sCD40L	coefficient of correlation	-0.045	0.003
	P	0.43	0.96

Table 4. Correlations between high sensitivity interleukin-6 (hsIL-6), high sensitivity C-reactive protein (hsCRP), soluble CD40 ligand (sCD40L) and fibrinogen, white blood cells (WBC). ** p<0.01

Spearman-Rho coefficient of correlation	**fibrinogen**	**WBC**
hsIL-6	0.266**	0.199**
hsCRP	0.344**	0.291**
sCD40-L	0.072	0.034

Table 5. Variables associated with high sensitivity interleukin-6 (hsIL-6) according to quartiles.

	Overall N=320	**1st N=80**	**2nd N=80**	**3rd N=80**	**4th N=80**	**P**
Age (years)	59±12	55±10	58±12	61±12	63±13	p<.001
Peripheral arterial occlusive disease	17 (5)	3 (4)	0 (0)	6 (8)	8 (10)	p=0.027
Laboratory data (mean±SD)						
Creatinine (mg/dl)	0.98±0.34	0.96±0.23	0.91±0.18	1.03±0.54	1.04±0.34	p=0.042
Medication						
Abciximab during PCI n (%)	107 (33)	21 (26)	22 (28)	27 (34)	37 (46)	p=0.009

Data are reported as mean ± standard deviation (SD), n (number of patients) or percentages;

Figure 1: Levels of high sensitivity interleukin-6 (hsIL-6) and high sensitivity C-reactive protein (hsCRP) according to the time point of blood sampling after primary percutaneous coronary intervention (PCI). Data are presented as median and interquartile range (25th-75th quartiles).

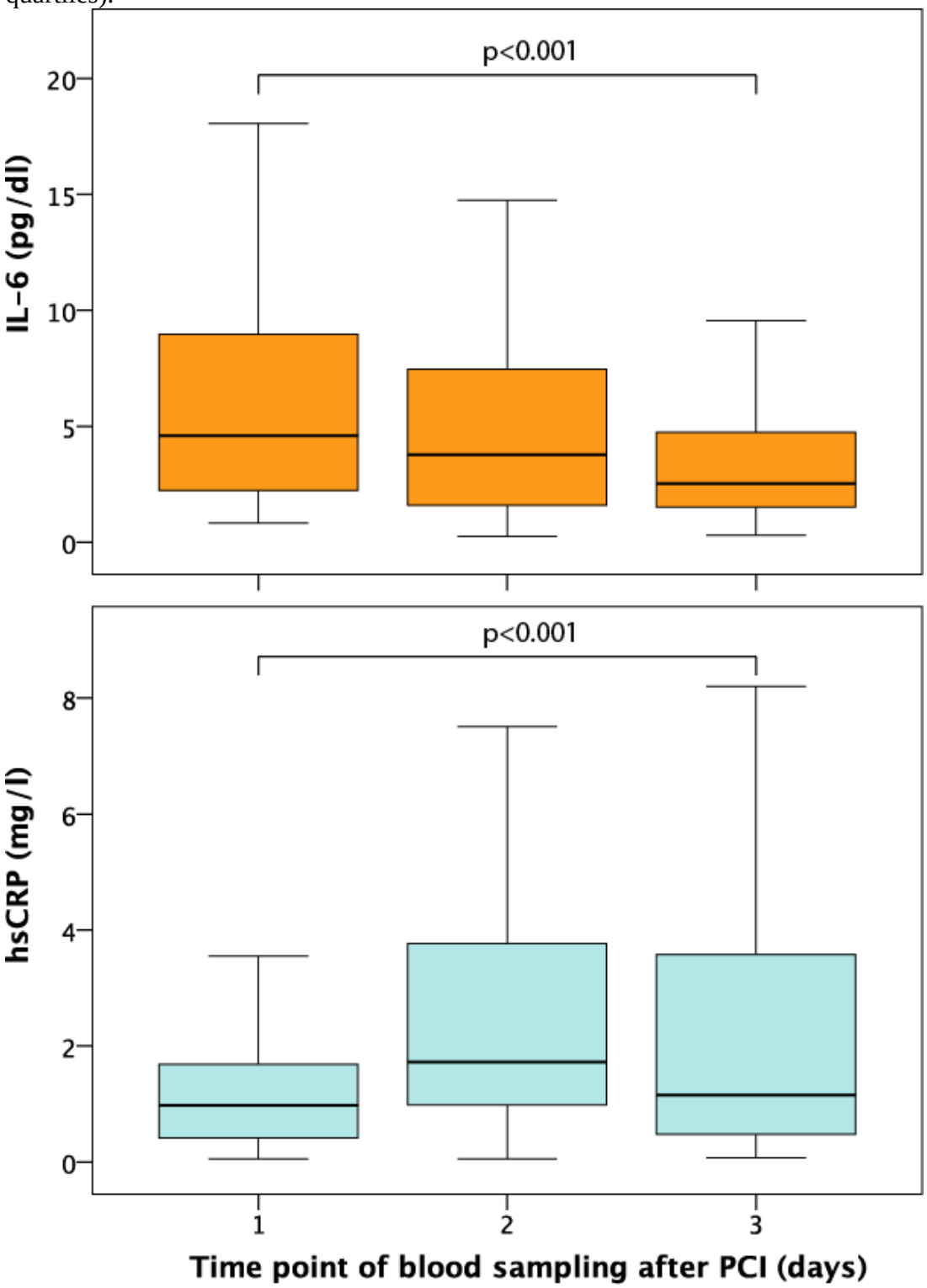

Figure 2: Adenosine diphosphate (ADP)-induced platelet aggregation according to the time point of blood sampling after primary percutaneous coronary intervention (PCI) measured with Multiplate elektrode aggregometry (MEA). Data are presented as median and interquartile range (25th-75th quartiles).

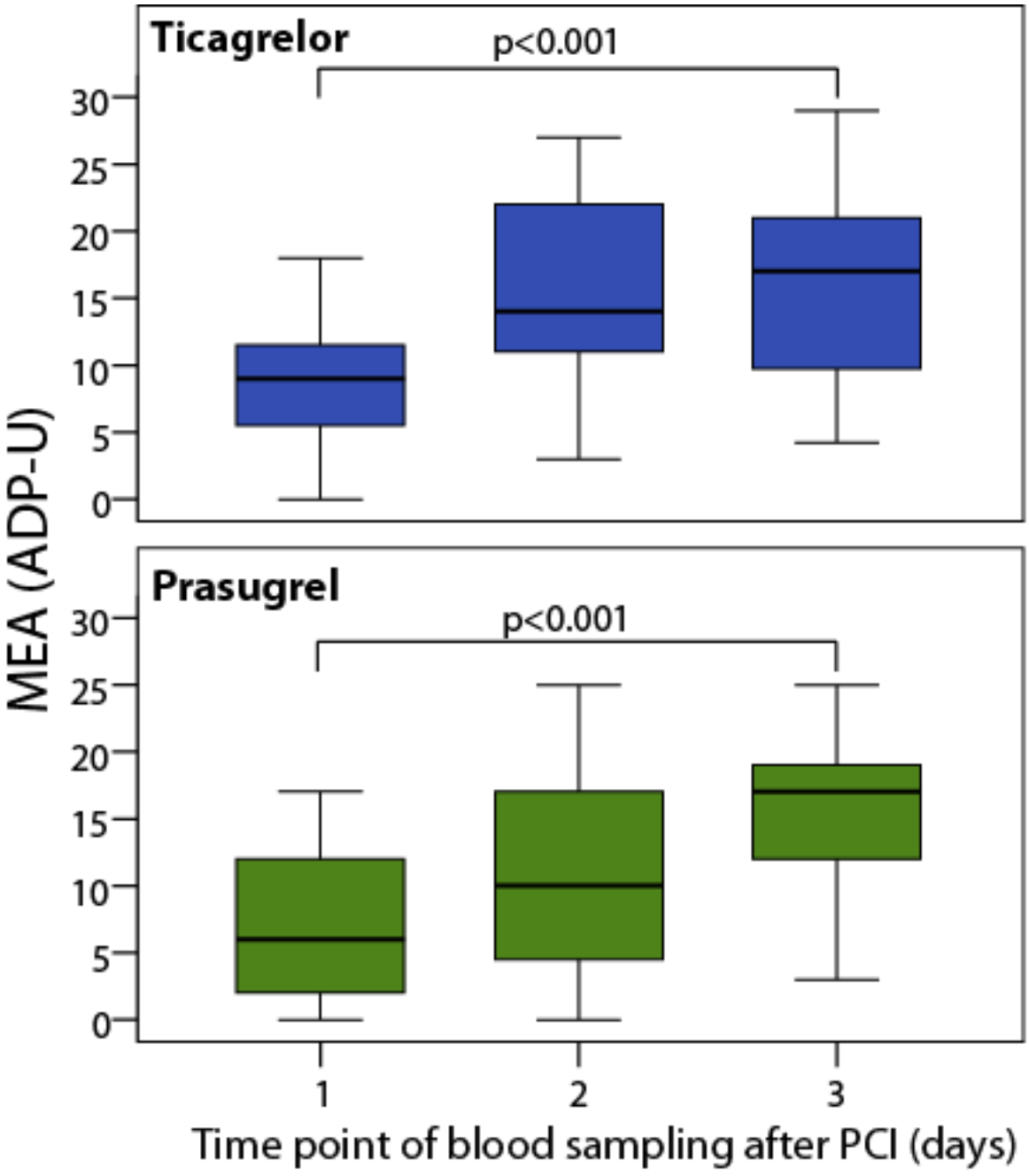

Figure 3. Adenosine diphosphate (ADP)-induced platelet aggregation according to high sensitivity interleukin-6 (hsIL-6) quartiles in the total population (upper panel) in patients treated with ticagrelor and prasugrel (lower panel) measured with Multiplate elektrode aggregometry (MEA).

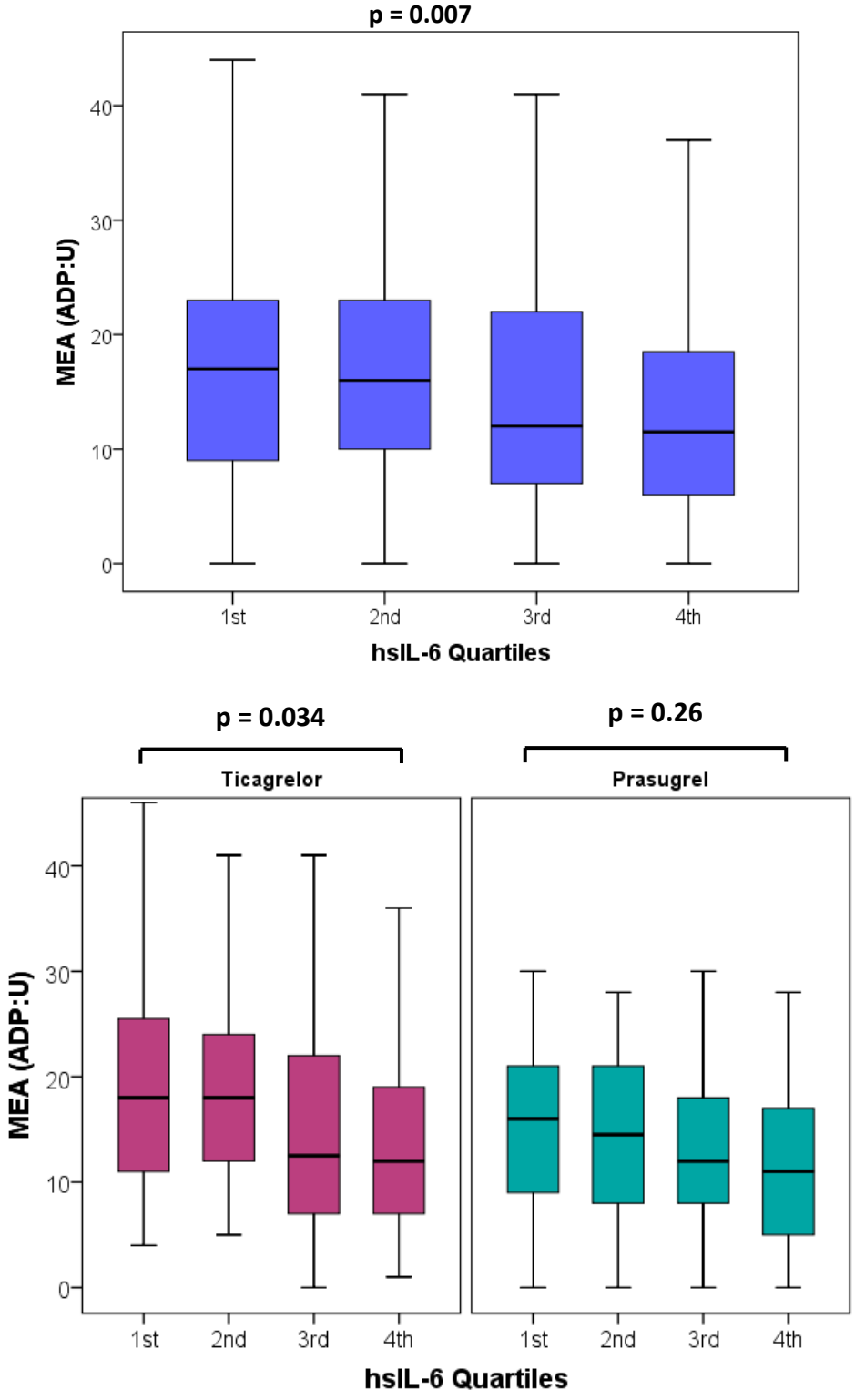

Figure 4. Concentrations of high sensitivity interleukin-6 (hsIL-6) and soluble CD40 ligand (sCD40L) according to patient diabetic status. Data are presented as median and interquartile range (25th-75th quartiles). NIDDM: not insulin dependent diabetes mellitus; IDDM: insulin dependent diabetes mellitus.

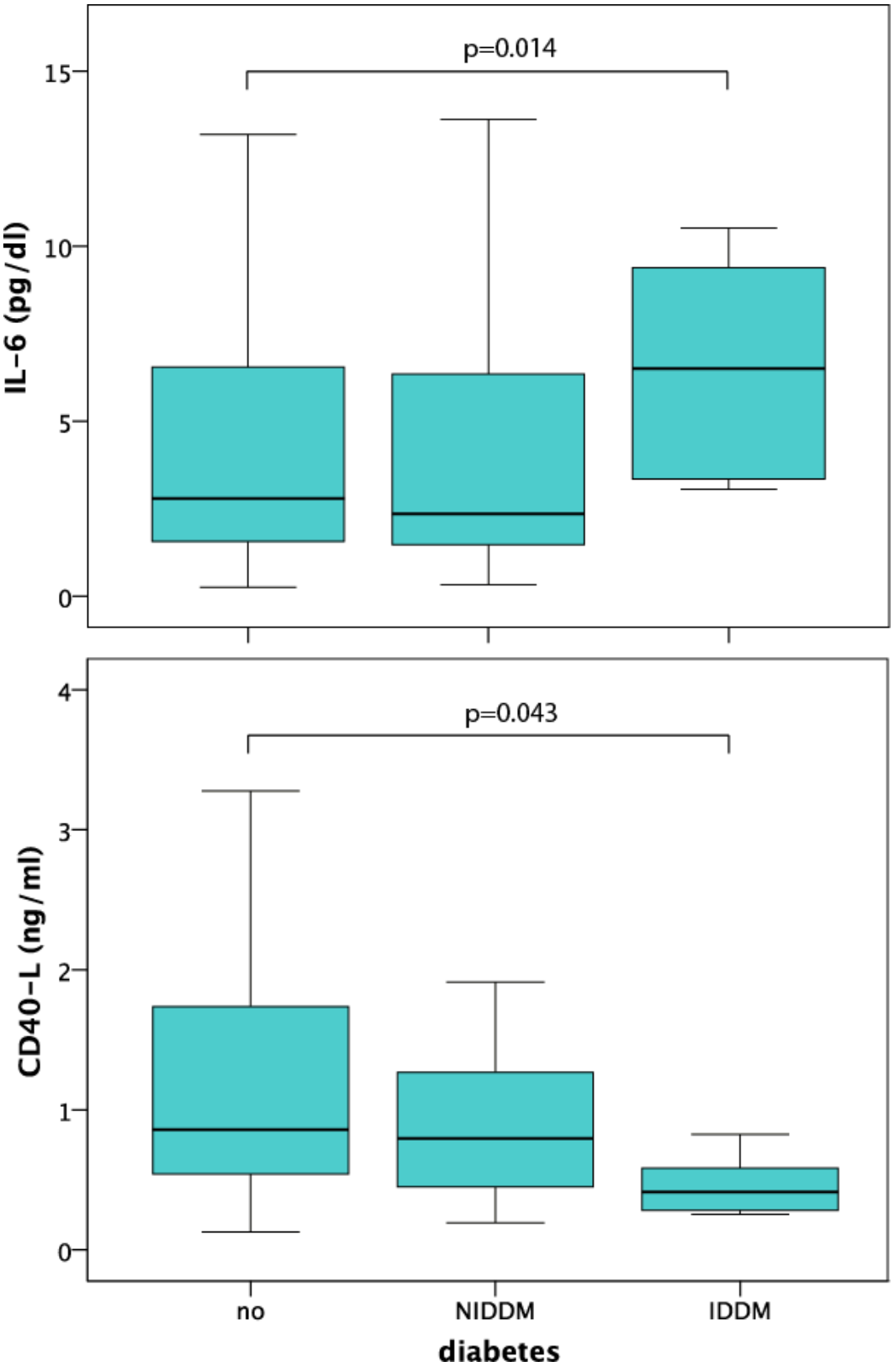

Figure 5. Concentrations of high sensitivity interleukin-6 (IL-6) according to pre-treatment with statins. Data are presented as median and interquartile range (25th-75th quartiles).