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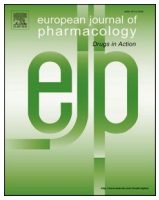

Effects of proprotein convertase subtilisin-kexin type 9 inhibitors on inflammatory and hemostatic parameters in post myocardial infarction patients

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ABSTRACT

Despite progress in treatment, elevated levels of low-density lipoprotein cholesterol (LDL-C) and lipoprotein (a) (Lp(a)), represent a significant part of the residual risk. Both are associated with inflammation and the coagulation fibrinolytic system. The purpose of our research was to evaluate the effect of proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i) on lipid parameters and indicators of inflammation, coagulation and fibrinolysis. We included 100 post myocardial infarction (MI) patients with insufficiently controlled LDL-C values despite the maximum dose of statin, and highly elevated Lp(a). Patients received alirocumab or evolocumab (150 mg sc or 140 mg sc every two weeks, respectively), or placebo for 6 months.

In patients receiving PCSK9i, a significant decrease in total cholesterol (TC), LDL-C, triglycerides (TG) and Lp (a), and an increase in high density lipoprotein cholesterol ($p < 0.001$ for all) was found. Before treatment, the concentrations of TC, LDL-C and TG correlated with the concentrations of thrombin activatable fibrinolysis inhibitor ($r = 0.41$, $p < 0.001$; $r = 0.353$, $p < 0.001$; $r = 0.311$, $p = 0.003$, respectively), and plasminogen activator inhibitor-1 ($r = 0.302$, $p = 0.007$; $r = 0.218$, $p = 0.049$; $r = 0.278$; $p = 0.013$, respectively). The concentrations of TC and LDL-C correlated with overall fibrinolytic potential ($r = -0.220$, $p = 0.034$; $r = -0.207$, $p = 0.047$, respectively). The concentration of TG was related to the concentration of interleukin 6 ($r = 0.290$, $p = 0.004$) and interleukin 8 ($r = 0.332$, $p = 0.001$). No correlations between Lp(a) and inflammatory or hemostatic variables were found. No associations were found after treatment. Our results show that inflammatory cytokines and fibrinolytic parameters are related to LDL-C and not Lp(a) in post-MI patients before and with neither of them following PCSK9i treatment.

The trial registration number: NCT04613167, Date of registration: November 3, 2020.

1. Introduction

Low-density lipoprotein cholesterol (LDL-C) lowering with statins greatly reduces the cardiovascular complications (Schubert et al., 2021). However, these beneficial effects cannot be attributed solely to LDL-C reduction, but also to the so-called pleiotropic effects of statins. These effects are not directly related to lipids, but to reduction of inflammation and changes in hemostasis (Oesterle et al., 2017). Statins thus improve the properties of the arterial vessel wall (Masoura et al., 2011), as well as lower the values of high-sensitivity C-reactive protein (hs-CRP), in particular in patients with high baseline values of this marker (Nissen et al., 2005). Despite that statins lower LDL-C by at least 50%, a large proportion of patients with coronary artery disease (CAD) still have their values well above the target (Gitt et al., 2017). Many patients also have increased lipoprotein (a) (Lp(a)) values, which independently of LDL-C increase the future cardiovascular risk (Erqou et al., 2009). The increased concentration of Lp(a) is associated with both, inflammation and hemostasis (Ugovšek and Šebeštjen, 2022). Lp(a) upregulates the inflammatory cytokines such as interleukin (IL)-1β, IL-6, IL-8, tumor necrosis factor-α (TNF-α), and the adhesion molecules on endothelial cells such as vascular cell adhesion protein-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), E-selectin, P-selectin and others (Simantiris et al., 2022). Despite that Lp(a) levels are more than 90% genetically determined, inflammatory markers can also increase its

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concentration (Müller et al., 2015). Statin treatment reduces hs-CRP, the most well-recognized inflammatory marker. The decrease in hs-CRP independently of a decrease in LDL-C also predicts the occurrence of new coronary events (Ridker et al., 2008). Statins also reduce TNF-α that in conjunction with IL-6 stimulate the synthesis of acute-phase proteins (Ascer et al., 2004). Many pleotropic effects of statins have been known for a long time, but new ones appear every day, and there are even more discoveries in the field of mechanisms of these effects of statins that do not depend on their lipolytic action (German and Liao, 2023). Treatment with proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i) showed no effect on hs-CRP. However, the vast majority of these patients were previously treated with statins (Ruscica et al., 2019; Scicali et al., 2021). Only one study found a reduction of IL-6 and TNF-α following PCSK9i treatment in statin naïve patients (Basiak et al., 2022b). The improvement of the properties of the arterial vessel wall after treatment with PCSK9i does not depend on their effect on LDL-C, which is otherwise their main property (Schremmer et al., 2023).

Due to high structural similarity between apolipoprotein a (apo(a)), which is a component of Lp(a), and plasminogen, Lp(a) is also involved in hemostasis. Lp(a) competes with plasminogen for binding sites on plasmin, thus possessing a prothrombotic effect. Lp(a) also increases the activation of platelets and the synthesis of plasminogen activator inhibitor-1 (PAI-1), thereby inhibiting fibrinolysis (Stulnig et al., 2019). All these effects cause an increased prothrombotic risk in subjects with elevated Lp(a). Statin treatment in CAD patients stimulates fibrinolysis (Seljeflot et al., 2002) that is not due to the LDL-C reduction (Dangas et al., 2000). Data on the effect of PCSK9i on hemostasis are very scarce. Statin-intolerant patients with familial hypercholesterolemia showed no changes in D-dimer and fibrinogen, which are the most robust markers of accelerated fibrinolysis (Schol-Gelok et al., 2018). In statin naïve high risk patients (Basiak et al., 2022b), PCSK9i decreased both, fibrinogen and PAI-1 (Basiak et al., 2022a). Thrombin activatable fibrinolysis inhibitor (TAFI) is activated by thrombin and downregulates fibrinolysis by preventing the connection between fibrinogen and tissue type plasminogen activator (t-PA) (Mosnier and Bouma, 2006). TAFI activity is an independent predictor for future cardiovascular events in patients with acute myocardial infarction (MI) (Leenaerts et al., 2015), as well as for refractiveness in patients with unstable angina pectoris (Brouwers et al., 2003). Atorvastatin in patients with hypercholesterolemia improves fibrinolysis through reduced thrombin formation and thus also TAFI activity (Bruni et al., 2004).

Here, we aimed to determine whether PCSK9i in post-MI patients with very high Lp(a) affect inflammation and hemostasis. We were also interested whether these effects are related to changes in LDL-C and Lp(a), since PCSK9i effectively reduce both.

2. Materials and methods

2.1. Patients

The current study was performed using a patient cohort as published previously (Rehberger Likozar and Šebeštjen, 2022). Briefly, 100 patients in stable phase after MI (first acute coronary syndrome before the age of 55) and elevated Lp(a) (above 1000 mg/L or an Lp(a) level above 600 mg/L and an LDL-C level of more than 2.6 mmol/L) were included. Patients were randomized (according to a randomisation list) to three groups: standard lipid-lowering therapy with no PCSK9i (control; N = 31), or alirocumab 150 mg SC (N = 35) or evolocumab 140 mg SC (N = 34), every two weeks.

All the procedures performed in this study that involved human participants were carried out in accordance with the ethical guidelines of the 1964 Declaration of Helsinki. Approval for this study was obtained from the National Medical Ethics Committee of the Republic of Slovenia (reference number: KME 0120-357/2018/8). The study was registered with CinicalTrials under the number NCT04613167.

All patients signed a written informed consent prior to inclusion in the study.

2.2. Clinical examination

The blood pressure was measured in the sitting position after a minimum of 10 min of rest and the average of three measurements was determined. Anthropometric parameters were determined, and body mass index (BMI) was calculated.

2.3. Biochemical analysis

The blood for laboratory analyzes was taken in the morning after 12 h of fasting. Samples were collected from the antecubital vein into vacuum-sealed 5 ml tubes containing clot activator (Vacutube, LT Burnik, Slovenia). Serum was obtained by 15-min centrifugation at 2000×*g*. Total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), apo A1 and B were determined in the fresh serum by standard colorimetric or immunologic assays on an automated biochemistry analyzer (Fusion 5.1; Ortho-Clinical Diagnostics, USA). The same biochemistry analyzer was used to determine Lp(a) with the Denka reagent (Randox, UK), which contains apo(a) isoform-insensitive antibodies, and therefore showed minimal apo(a) size-related bias. The Friedewald formula (Friedewald et al., 1972) was used to calculate LDL-C. TAFI activity in plasma was measured using the chromogenic method utilizing Pefakit® TAFI reagents (Pentapharm, Switzerland) on an automated coagulation analyzer CS-2500 (Sysmex, Japan). PAI-1 antigen in plasma was measured using a classic sandwich ELISA (ASSERACHROM PAI-1, Diagnostica Stago, France). Measurements of TNF-α, hs-CRP, IL-6, IL-8, and IL-10 levels in serum were performed using the Luminex's xMAP® Technology utilizing magnetic beads coupled with specific antibodies, which allowed multiplexing. All analysis was performed according to manufacturer's instructions (R&D Systems, UK). Overall coagulation potential (OCP), overall hemostatic potential (OHP) and overall fibrinolytic potential (OFP) were measured and calculated as described before (Anžej Doma et al., 2013).

2.4. Statistical analysis

Kolmogorov–Smirnov tests were used to assess the distribution of the variables. Variables showing normal distributions are expressed as means ±standard deviations. The non-normally distributed variables are expressed as medians and range (lower and upper quartiles). Changes/deltas in variables were calculated using the following formula: (variable after 6 months of treatment-variable at beginning of the study)/variable at the beginning of the study and expressed as percentage. Pearson and Spearman correlation analysis was performed to determine the correlation between the parameters. The difference between the parameters at baseline and after 6 months of treatment were calculated using paired samples *t*-test or Mann-Whitney test. GPower was used to perform the power of the study calculations. The required sample size was determined using the *apriori* analysis with the 0.80 power of the study, 0.15 effect size and 0.05 α error probability (Faul et al., 2009). Statistical analysis was performed using IBM SPSS Statistics for Windows, (Version 25.0. Armonk, NY: IBM Corp.) and GraphPad Prism version 8 for Windows (GraphPad Software, San Diego, CA, USA; www.graphpad.com).

3. Results

3.1. Patient characteristics

A total of 100 patients with clinically stable CAD of at least 6 months after MI, with mean age at first coronary event of 43 years were included in the study. Most of them were male (86%), 11.4% were diabetics and 5.7% were active smokers. All the patients were receiving statins at the highest tolerated dose without/with ezetimibe, angiotensin-converting

enzyme inhibitors/angiotensin receptor blockers, β-blockers, and antiplatelet therapy. The 100 patients were recruited in this study during the period of November 2020 to May 2021 and followed for 6 months. All included patients showed clinically stable CAD of at least 6 months after MI, with mean age at first coronary event <55 years. The patients were randomized to the control (N = 31), alirocumab (N = 35) and evolocumab (N = 34) groups. Given that there were no differences between the groups of patients who received active treatment, we analyzed them as one group. One patient in the alirocumab group did not finish the study due to problems associated with COVID-19 disease.

The mean ages of the groups showed no significant differences (47.5 ± 9.5, 50.7 ± 7.2 years, respectively; p = 0.350).

There were also no significant differences between the groups for systolic (124 ± 10, 128 ± 16 mmHg, respectively; p = 0.354) and diastolic (76 ± 8, 77 ± 8, mmHg, respectively; p = 0.919) blood pressures, and these values did not change during the study. There were 3 (9.7%), 9 (13,0%) current smokers in the respective groups; the distribution of these smokers was not statistically significant between the groups (chi-squared test, p = 0.547). For diabetes mellitus, there were 7 (20.0%), 7 (10.0%) patients across the groups, respectively; the differences between the groups here were not statistically significant (chi-squared test, p = 0.190).

3.2. Lipid parameters

As expected, treatment with PCSK9i led to significant reductions in TC, LDL-C, apo B and TG. At the same time, there was also a significant increase in HDL-C, apo A1 and total PCSK9 in the treated group. A significant increase in apo A1 and total PCSK9 also occurred in the placebo group, but the increase was more pronounced in the PCSK9i group (Table 1).

Table 1
Lipoproteins and total PCSK9 at baseline and after 6 months of treatment.

Parameter	Group	Baseline	After 6 months	p
Total	Placebo	4.29 ± 0.99	4.38 ± 0.93	0.425
cholesterol	PCSK9i	4.25 ± 0.81	2.74 ± 0.95	**<0.001**
(mmol/L)	p	0.812	**<0.001**	
LDL	Placebo	2.40 ± 0.99	2.43 ± 0.80	0.735
cholesterol	PCSK9i	2.31 ± 0.70	0.88 ± 0.82	**<0.001**
(mmol/L)	p	0.871	**<0.001**	
HDL	Placebo	1.12 ± 0.23	1.20 ± 0.31	0.010
cholesterol	PCSK9i	1.20 ± 0.28	1.27 ± 0.32	**<0.001**
(mmol/L)	p	0.227	0.369	
Triglycerides	Placebo	1.62 (1.00–2.16)	1.64 (1.11–2.09)	0.600
(mmol/l)	PCSK9i	1.50 (1.06–2.11)	1.20 (0.78–1.81)	**<0.001**
	p	0.840	**0.025**	
Apo A1	Placebo	1.23 (1.16–1.34)	1.27 (1.20–1.43)	**0.002**
(g/L)	PCSK9i	1.30 (1.20–1.46)	1.35 (1.22–1.55)	**0.001**
	p	0.170	0.186	
Apo B	Placebo	0.80 (0.73–1.00)	0.82 (0.67–0.96)	0.099
(g/L)	PCSK9i	0.82 (0.63–0.98)	0.35 (0.35–0.48)	**<0.001**
	p	0.565	**<0.001**	
Lp(a)	Placebo	1491 (1185-1739)	1397 (1224-1574)	0.701
(mg/L)	PCSK9i	1416 (1201-1781)	1133 (820-1664)	**<0.001**
	p	0.915	**0.035**	
Total PCSK9	Placebo	240.3 (195.1–364.4)	352.1 (251.1–469.0)	**0.007**
(ng/L)	PCSK9i	285.7 (210.0–401.3)	2784.3 (2508.4–3185.8)	**<0.001**
	p	0.265	**<0.001**	

Data are medians (lower-upper quartile) or means ± standard deviation. The differences between the two groups were calculated with *t*-test or Mann-Whitney test. The difference between the parameters at baseline and after 6 months of treatment within each group were calculated using paired samples *t*-test or Wilcoxon matched-pairs signed-rank test.
LDL-C, low-density lipoprotein; HDL-C, high-density lipoprotein; Apo A1, apolipoprotein A1; Apo B, apolipoprotein B; Lp(a), lipoprotein(a); PCSK9i, PCSK9 inhibitor.

3.3. Inflammatory markers

No significant decrease in the concentration of the inflammatory markers, i.e., hs-CRP, IL-6, and IL-8, was observed in any of the groups. Nevertheless, the difference in IL-8 change between the groups was statistically significant (p = 0.026). The concentration of TNF-α in the group treated with PCSK9i did not significantly decrease, however the concentration of TNF-α in the placebo group increased, hence the difference in TNF-α changes between treated and placebo group was statistically significant (p = 0.016). Similarly, statistically significant difference between the treated and placebo group was observed in IL-6 changes (p = 0.005). The concentration of VCAM1 increased in the PCSK9i treated group, while there were no significant changes in the placebo group. The concentration of VCAM1 between PCSK9i treated and placebo group was marginally statistically significantly different at the end of the study (p = 0.082), but the difference in changes was not (p = 0.122) (Table 2).

3.4. Hemostatic parameters

Treatment with PCSK9i significantly increased the concentration of PAI-1 (p = 0.015), while a significant increase in PAI-1 also occurred in the placebo group (p = 0.007). Treatment with PCSK9i increased the concentration of TAFI with borderline significance (p = 0.062). The difference between the changes in the concentration between groups was statistically significant for PAI-1 (p = 0.004), but not for TAFI (p = 0.749). There were no statistically significant results in the concentration of FVIII, platelets and D-dimer in any of the groups. OCP increased significantly in the placebo group, with no change in the PCSK9i group. The difference between the two changes was statistically significant (p = 0.049). However, we did not find any significant differences or changes in OFP or OHP (Table 3).

3.5. Relationship between lipid, inflammatory and hemostatic variables

Before the treatment, the concentrations of TC, LDL-C and TG correlated with the concentration of TAFI (r = 0.41, p < 0.001, r = 0.353, p < 0.001, and r = 0.311, p = 0.003, respectively) and PAI-1 (r = 0.302, p = 0.007, r = 0.218, p = 0.049 and r = 0.278, p = 0.013, respectively). D-dimer correlated with TC (r = 0.207, p = 0.047) (Fig. 1).

Table 2
Inflammatory markers at baseline and after 6 months of treatment.

Marker	Group	Baseline	After 6 months	p
hs-CRP (mg/L)	Placebo	0.80 (0.39–2.23)	0.79 (0.36–1.96)	0.542
	PCSK9i	0.87 (0.37–1.93)	0.83 (0.31–1.65)	0.666
	p	0.592	0.540	
TNF-α (ng/L)	Placebo	3.74 (2.99–5.02)	3.91 (3.05–5.57)	0.194
	PCSK9i	3.91 (3.36–5.36)	3.33 (2.53–6.47)	0.557
	p	0.336	0.072	
IL-6 (ng/L)	Placebo	1.69 (1.19–2.18)	1.69 (1.20–2.99)	0.486
	PCSK9i	1.69 (1.20–2.53)	1.36 (1.16–2.18)	0.126
	p	0.807	0.089	
IL-8 (ng/L)	Placebo	12.05 (10.80–16.10)	11.50 (10.80–17.00)	0.457
	PCSK9i	13.50 (10.65–18.30)	15.50 (10.80–24.83)	0.136
	p	0.594	0.198	
VCAM-1 (ng/L)	Placebo	0.68 (0.56–0.83)	0.60 (0.53–0.82)	0.563
	PCSK9i	0.62 (0.51–0.89)	0.71 (0.56–0.90)	**0.025**
	p	0.875	0.082	

Data are medians (lower-upper quartile) or means ± standard deviation. The differences between the two groups were calculated with *t*-test or Mann-Whitney test. The difference between the parameters at baseline and after 6 months of treatment within each group were calculated using paired samples *t*-test or Wilcoxon matched-pairs signed-rank test.
hs-CRP, high-sensitivity C-reactive protein; TNF-α, tumor necrosis factor-α; IL, interleukin; VCAM-1, vascular cell adhesion protein-1; PCSK9i, PCSK9 inhibitor.

Table 3
Markers of hemostasis at baseline and after 6 months of treatment.

Marker	Group	Baseline	After 6 months	p
TAFI (%)	Placebo	94.40 ± 15.95	95.86 ± 15.03	1.000
	PCSK9i	99.18 ± 15.46	101.18 ± 15.40	0.062
	p	0.196	0.234	
PAI-1	Placebo	25.00 (18.00–41.00)	36.00 (25.00–59.75)	**0.007**
(ng/mL)	PCSK9i	36.50 (22.25–56.75)	45.00 (36.00–72.00)	**0.015**
	p	0.162	0.121	
FVIII	Placebo	1.46 (1.19–1.64)	1.42 (1.20–1.70)	0.336
(IU/mL)	PCSK9i	1.56 (1.24–1.74)	1.54 (1.26–1.80)	0.441
	p	0.431	0.489	
Platelets	Placebo	229 (204-262)	220 (195-279)	0.501
(x 10^9/L)	PCSK9i	228 (198-274)	225 (195-271)	0.093
	p	0.902	0.945	
D-dimer	Placebo	340 (190-544)	354 (208-554)	0.089
(μg/L)	PCSK9i	270 (190-482)	297 (193-462)	0.979
	p	0.565	0.311	
OCP	Placebo	22.50 (20.10–26.90)	22.70 (19.20–25.50)	**0.032**
(Abs-sum)	PCSK9i	23.45 (19.78–28.13)	24.50 (19.80–28.80)	0.503
	p	0.687	0.109	
OFP (%)	Placebo	71.59 ± 7.27	71.30 ± 8.10	0.659
	PCSK9i	71.54 ± 8.32	71.82 ± 8.02	0.853
	p	0.706	0.809	
OHP	Placebo	6.30 (5.40–8.30)	6.10 (4.78–8.35)	0.886
(Abs-sum)	PCSK9i	6.60 (4.73–8.65)	6.30 (5.10–7.80)	0.226
	p	0.827	0.459	

Data are medians (lower-upper quartile) or means ± standard deviation. The differences between the two groups were calculated with *t*-test or Mann-Whitney test. The difference between the parameters at baseline and after 6 months of treatment within each group were calculated using paired samples *t*-test or Wilcoxon matched-pairs signed-rank test.
TAFI, thrombin activatable fibrinolysis inhibitor; PAI-1, plasminogen activator inhibitor-1; FVIII, factor VIII; OCP, overall coagulation potential; OFP, overall fibrinolytic potential; OHP, overall hemostatic potential; PCSK9i, PCSK9 inhibitor.

The concentration of TC and LDL-C correlated with OFP ($r = -0.220$, $p = 0.034$ and $r = -0.207$, $p = 0.047$, respectively) (Fig. 1), and total PCSK9 concentration correlated with OHP ($r = -0.309$, $p = 0.003$) and OFP ($r = 0.205$, $p = 0.049$) (Fig. 2). The concentration of TG was related to the concentration of IL-6 ($r = 0.290$, $p = 0.004$) and IL-8 ($r = 0.332$, $p = 0.001$) (Fig. 2). We did not find any correlations between Lp(a) concentration and inflammatory or hemostatic variables. Interestingly, in the PCSK9i treated group all these associations became insignificant after 6 months of treatment, only the association between TC and FVIII remained significant ($r = 0.335$, $p = 0.007$).

We did not observe any association between the changes in lipid and inflammation parameters after 6 months of treatment (Table 4). However, we did detect the significant correlations between the changes in lipid and hemostatic parameters after 6 months of treatment (Table 5). The change in total cholesterol significantly correlated with the change in TAFI ($\rho = 0.325$; $p = 0.010$). The change in HDL cholesterol was related to the change in D-dimer ($\rho = 0.321$; $p = 0.013$). The change in triglycerides was related to the change in TAFI ($\rho = 0.289$; $p = 0.023$), in OFP ($\rho = 0.307$; $p = 0.012$) and in OHP = (ρ −0.306; 0.012). The change in Lp(a) was related to the change in D-dimer ($\rho = -0.307$; $p = 0.020$) and OCP ($\rho = 0.389$; $p = 0.002$) (Table 5).

4. Discussion

To the best of our knowledge, our study is the first to examine the effects of PCSK9i on the parameters of inflammation and hemostasis, and to determine their association with lipid changes in stable post-MI patients with high Lp(a) value already treated with statins at the highest tolerated dose. Our results show that, before treatment the concentration of both, TC and LDL-C is mainly related to indicators of the coagulation fibrinolytic system, while the concentration of TG is also related to indicators of inflammation.

4.1. Impact of PCSK9i treatment on lipid parameters

As expected, treatment with PCSK9i significantly reduced the concentrations of TC, LDL-C, and TG as well as Lp(a). A significant increase in the concentration of HDL-C found in our study was equally expected (Sabatine et al., 2017; Schwartz, 2018). At the end of the study, all patients achieved LDL-C treatment target (Authors/Task Force Members et al., 2019). On the contrary, the Lp(a) values at the end of the study were high above the desirable levels (Authors/Task Force Members et al., 2019) despite the statistically significant and anticipated reduction between 20% and 40% (Sabatine et al., 2017; Schwartz et al., 2018). This might be the reason that no associations between Lp(a) concentration and both, inflammatory and coagulation fibrinolytic system indicators were found. Despite the well-recognized pathophysiological connection between Lp(a) and the previously mentioned parameters (Simantiris et al., 2022), we have no data whether a plateau for Lp(a) level exists, above which no further influence on inflammatory and hemostasis parameters is possible. This may also be supported by the two findings in our study; first, we found non-significant correlation between changes in these parameters and Lp(a) (data not shown), and second, as already mentioned, our patients possessed high above on-target values of Lp(a) after PCSK9i treatment. The answer to this question may be given by further research with drugs specific for lowering Lp(a).

4.2. Effects of PCSK9i treatment on parameters of inflammation, coagulation and fibrinolysis

Similar to our study, the EQUATOR study (Baruch et al., 2017) showed that treatment with PCKS9i has no effect on the levels of hs-CRP, IL-6 or TNF-α in patients previously treated with statins at the highest tolerated dose. The completely opposite results were found in the study by Basiak et al. (2022b), where treatment with PCKS9i significantly reduced all, hs-CRP, IL-6 and TNF-α. However, we must be aware that the patients in Basiak et al. study did not receive any therapy, although they were characterized as being at high risk with unstable atherosclerotic plaques in the carotid arteries. Moreover, their baseline LDL-C values were more than two times higher and their hs-CRP values were more than three times higher compared to our or the EQUATOR study. Moreover, the patients in Basiak et al. study did not sustain MI and their Lp(a) values were not measured, so the direct comparison of the results is not possible. Hoogeveen et al. showed that treatment with PCSK9i in patients with statin-intolerant familial hypercholesterolemia led to a reduction in local inflammation in the atherosclerotic plaque as measured by 18F-fluoro-deoxyglucose positron-emission tomography/-computed tomography (18F-FDG PET/CT), although there was no reduction in hs-CRP (Hoogeveen et al., 2019). In contrast, Stiekema et al. showed no reduction in local inflammation in patients previously treated with statins (Stiekema et al., 2019). However, an important difference between the two studies was that patients in the latter study possessed significantly higher Lp(a) values at the beginning and at the end of the study.

Reduced fibrinolytic potential significantly contributes to the formation of a thrombus and the resulting acute cardiovascular event upon rupture of the atherosclerotic plaque. TAFI attenuates fibrinolysis by inhibiting tPA-mediated plasminogen activation (Masuda et al., 2012). In patients with hypercholesterolemia without any therapy, the values of TAFI activity were increased compared to healthy controls, but after treatment with atorvastatin, the values were similar in both groups (Bruni et al., 2004). Patients with MI in the acute phase (either ST elevation MI or non ST elevation MI) had significantly increased values of TAFI activity in femoral artery samples compared to patients with hemodynamically insignificant changes in the coronary arteries (Leenaerts et al., 2015). It is also important to note that TAFI activity in samples taken intracoronary before percutaneous revascularization was significantly higher than in peripheral arterial blood. The latter indicates

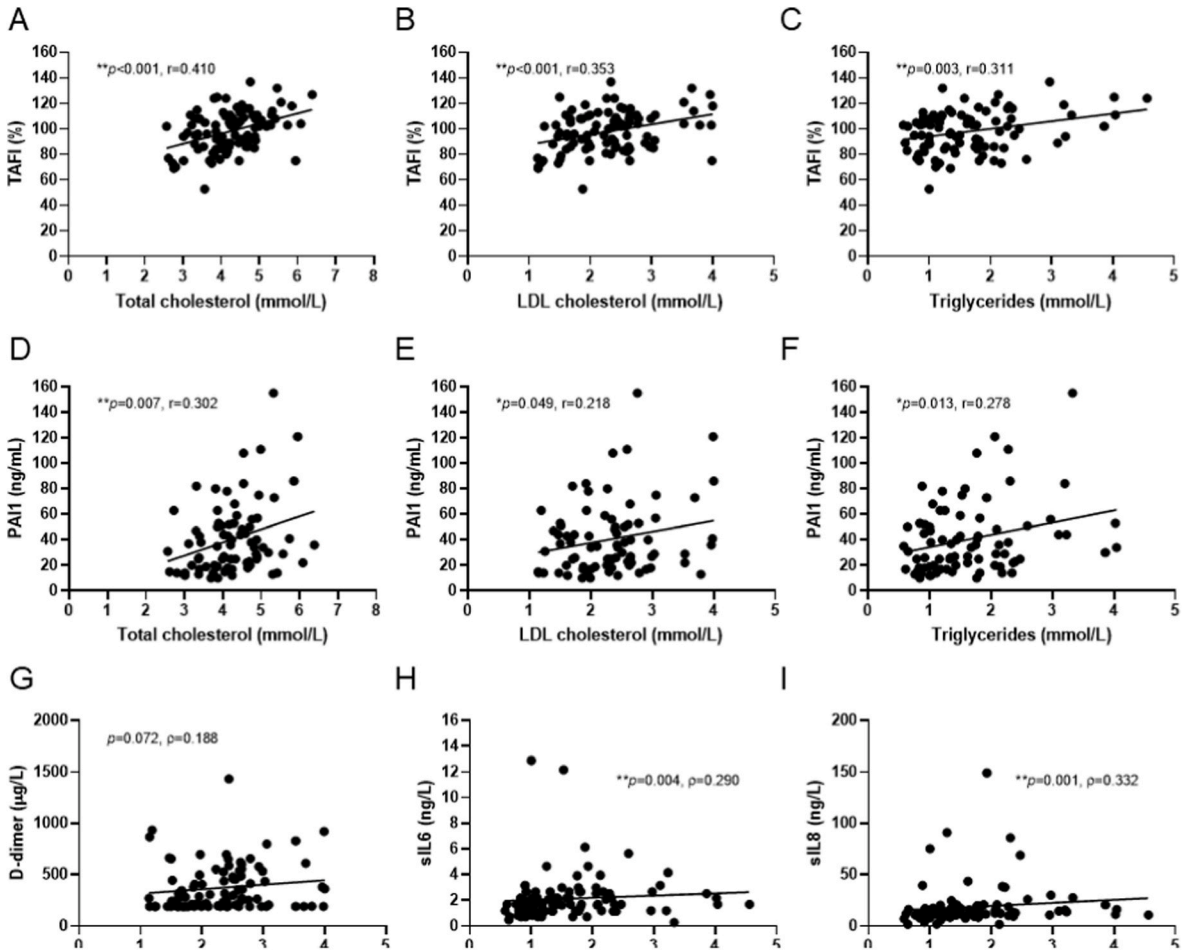

Fig. 1. Correlations between lipid and fibrinolytic parameters (**A-G**), and between lipid and inflammatory parameters (**H–I**). Pearson or Spearman correlation analysis was used to calculate the correlation coefficient (r or ρ) and p.

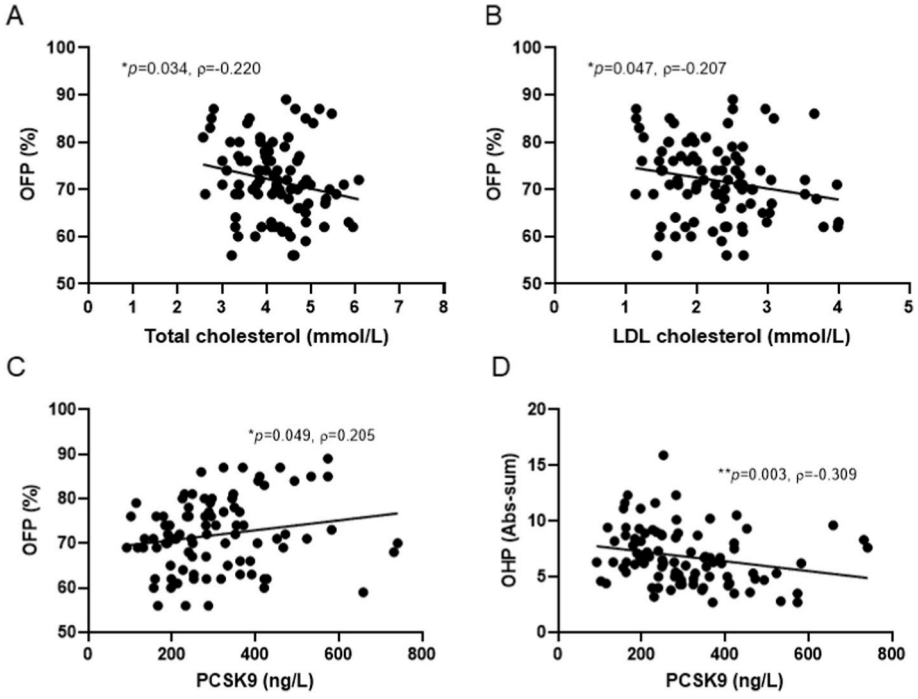

Fig. 2. Correlation between overall fibrinolytic potential and total cholesterol, LDL cholesterol and PCSK9 (**A-C**), and between overall hemostatic potential and PCSK9 (**D**). Spearman correlation analysis was used to calculate the correlation coefficient (ρ) and p.

Table 4
Correlations between the changes in lipid and inflammation parameters after 6 months of treatment.

Parameter		Δ hs-CRP	Δ IL-6	ΔIL-8	Δ TNF-α	Δ VCAM-1
Δ Total cholesterol	ρ	−0.008	−0.026	−0.058	−0.095	−0.176
	p	0.951	0.834	0.646	0.450	0.159
Δ LDL cholesterol	ρ	−0.019	−0.153	−0.134	0.095	−0.183
	p	0.880	0.220	0.284	0.449	0.141
Δ HDL cholesterol	ρ	−0.181	0.165	0.011	−0.040	0.056
	p	0.142	0.186	0.929	0.753	0.658
Δ Triglycerides	ρ	−0.003	−0.079	−0.142	−0.156	−0.108
	p	0.982	0.530	0.257	0.212	0.390
Δ Lp(a)	ρ	0.179	−0.139	−0.071	−0.173	−0.160
	p	0.153	0.273	0.579	0.171	0.206

Spearman correlation analysis was used to calculate the correlation coefficient (ρ) and p. Changes (Δ) were obtained by calculating the differences between the value of the parameter after 6 months and at baseline. hs-CRP, high-sensitivity C-reactive protein; IL, interleukin; TNF-α, tumor necrosis factor-α; VCAM-1, vascular cell adhesion protein-1.

increased local activity of TAFI, which could significantly contribute to thrombus formation. In the AtheroGene study (Tregouet et al., 2009), increased TAFI activity, not antigen concentration, emerged as an independent predictor of future cardiovascular events in 1866 patients with confirmed CAD. In our study, TAFI activity before treatment was strongly positively correlated with the values of TC, LDL-C and TG. We observed a significant decrease in all three lipid parameters, but no changes in TAFI activity after PCSK9i treatment. We can conclude that the reduction of these values alone does not affect the TAFI activity. Despite the significant decrease in Lp(a), very high above the target Lp (a) levels after PCSK9i treatment could be the reason for the unchanged TAFI activity. In a small group of patients with elevated Lp(a) values, who were mostly treated with statins, treatment with specific Lp(a) lowering agents IONIS-APO(a)Rx, which lowered Lp(a) by 70%, did not cause significant changes in PAI-1 and TAFI antigen (Boffa et al., 2019). However, the patients in our study had on average three times higher baseline Lp(a) values compared to this patient cohort. In any case, the significant increase in PAI-1 antigen concentration in the placebo group, is somewhat surprising. PAI-1, which is released from endothelial cells, is one of the major inhibitors of fibrinolysis which inhibits t-PA (Folsom, 2001). There are very few studies on the effect of PCSK9i on parameters of coagulation and fibrinolysis. Basiak et al. studied the effect of PCSK9i on coagulation and fibrinolysis parameters in patients naïve to any lipolytic therapy (Basiak et al., 2022a). On the other hand, many studies have shown that treatment with statins significantly reduces the concentration of PAI-1 (Sahebkar et al., 2016). However, the reason that no effect on PAI-1 was observed in our study might be that we have included only patients who were previously treated with the maximum tolerated dose of statins. Of note, PAI-1 is derived from several sources, including the vascular endothelium (Song et al., 2017), adipose tissue, and the liver (Bastelica et al., 2002). Considering that these different sources are influenced by many other factors and not only PCSK9i treatment, this could be the reason why there was an increase in the PAI-1 concentration even in the placebo group. Like PAI-1, VCAM-1 is also secreted from endothelial cells, and the secretion of both is accelerated by pro-inflammatory cytokines, primarily by TNF-α and also by oxidized LDL-C (Cook-Mills et al., 2011). At a first glance, it seems that PCSK9i treatment leads to activation of the endothelium, which would lead to an acceleration of the atherosclerotic process. However, we must take into account that our study included high risk patients with impaired endothelial function (Boulanger, 2018). Regeneration of the endothelium is a two-phase process, first the activation of the endothelial cells followed by the improvement in its function (Mcdonald et al., 2018). The time course of regeneration could be determined by the long-term research, and above all by more frequent blood sampling.

4.3. Associations between lipids, inflammation and hemostasis

Before the start of the PCSK9i treatment, the concentrations of PAI-1 antigen and the TAFI activity, as important components of the fibrinolytic process, were associated with the concentrations of TC and LDL-C. Total and LDL-C concentrations were significantly negatively correlated with OFP. Despite the different measuring methods, the endogenous fibrinolytic potential emerged as an important prognostic factor in patients with an acute cardiovascular event (Okafor and Gorog, 2015). After 6 months of treatment with PCSK9i, the relationship between the concentration of TC and LDL-C and individual parameters of the fibrinolytic system as well as OFP, was no longer significant. In patients without clinically evident atherosclerosis the concentration of IL-6 was not only associated with the concentration of TG, but also proved to be an independent predictive factor for future cardiovascular events (Luc et al., 2003).

The concentrations of TC and LDL-C as well as TG at the end of our study were below the recommendations of the current guidelines. It seems that further reduction of TC and LDL-C in particular might not contribute to further reduction of the remaining risk. On the other hand, there is still space for improvement of the Lp(a) values, as these values in our patients remained significantly higher than desired (Authors/Task Force Members et al., 2019) even after PCSK9i treatment.

Our finding that changes in the values of lipid parameters were not associated with the changes in the concentrations of inflammatory parameters is not surprising. Similarly to previous studies, the additional treatment with PCSK9i did not contribute to the reduction of inflammatory parameters in patient pretreated with statins (Hoogeveen et al., 2019; Scicali et al., 2021). On the contrary, treatment with PCSK9i significantly reduced the concentration of inflammatory parameters in statin naïve patients (Basiak et al., 2022b). It might be that statin treatment lowers the values of inflammatory parameters to the point that further reduction is not possible.

Table 5
Correlations between the changes in lipid and hemostatic parameters after 6 months of treatment.

Parameter		Δ TAFI	Δ PAI-1	Δ FVIII	Δ Platelets	Δ D-dimer	Δ OCP	Δ OFP	Δ OHP
Δ Total cholesterol	ρ	**0.325**	0.187	0.237	0.119	−0.12	−0.171	0.102	−0.163
	p	**0.010**	0.202	0.074	0.332	0.928	0.169	0.416	0.191
Δ LDL cholesterol	ρ	0.147	0.083	0.022	−0.019	−0.196	−0.030	0.194	−0.204
	p	0.253	0.574	0.868	0.875	0.137	0.813	0.119	0.100
Δ HDL cholesterol	ρ	0.205	−0.026	0.230	0.125	**0.321**	−0.154	−0.119	0.104
	p	0.109	0.862	0.082	0.312	**0.013**	0.217	0.341	0.407
Δ Triglycerides	ρ	**0.289**	0.001	0.129	0.118	−0.075	−0.117	**0.307**	**−0.306**
	p	**0.023**	0.993	0.333	0.338	0.571	0.348	**0.012**	**0.012**
Δ Lp(a)	ρ	0.062	−0.056	−0.022	0.098	**−0.307**	**0.389**	0.204	−0.036
	p	0.638	0.708	0.847	0.432	**0.020**	**0.002**	0–106	0.777

Spearman correlation analysis was used to calculate the correlation coefficient (ρ) and p. Changes (Δ) were obtained by calculating the differences between the value of the parameter after 6 months and at baseline. FVIII, factor VIII; OCP, overall coagulation potential; OFP, overall fibrinolytic potential; OHP, overall hemostatic potential; PAI-1, plasminogen activator inhibitor-1; TAFI, thrombin activatable fibrinolysis inhibitor.

Given the well-recognized association between the increased triglyceride concentration and reduced fibrinolytic activity (Mussoni et al., 1992), our results also showed that a decrease in triglyceride concentration is associated with the indicators of improved fibrinolytic potential such as TAFI, OFP and OHP. D-dimer is a highly sensitive marker of accelerated intravascular fibrinolysis (Olson, 2015). Hence, the decrease in Lp(a) concentration associated with elevated D-dimer values in our patients indicates an accelerated fibrinolytic activity. Although OFP did not increase after 6 months of treatment in our study, the decrease in Lp(a) concentration correlated with OCP, also indicating a shift towards fibrinolysis. Unfortunately, in the current study we did not measure platelet activity, that also plays an important role in the formation of a thrombus following a rupture of an atherosclerotic plaque (Ugovšek and Šebeštjen, 2022). However, previous study showed that the reduction of platelet activity is one of the mechanisms of PCSK9i (Cammisotto et al., 2021).

5. Conclusions

In our research, we found that fibrinolytic parameters and, above all, the total fibrinolytic activity are related mainly to the concentration of LDL-C and not Lp(a) in post-MI patients with insufficiently regulated LDL-C values and highly elevated Lp(a) values. The same applies to the inflammatory cytokines. After treatment, however, the hemostatic and inflammatory parameters were not associated with LDL-C nor Lp(a). At a first glance, this may be surprising, but we must be aware of that all our patients had greatly increased Lp(a) values. Treatment with PCSK9i reduced LDL-C levels by 70% and below the values recommended by the latest guidelines. On the other hand, the values of Lp(a), that is associated with other risk factors such as inflammation and the coagulation fibrinolytic system, remained high above the recommended values. Of course, the question arises as to whether a more pronounced decrease in Lp(a) values would additionally affect the indicators of inflammation, coagulation and fibrinolysis. At the same time, the question is what is the target Lp(a) level at which such changes would occur. The next question is whether the relationship between Lp(a) concentration and indicators of inflammation, coagulation and fibrinolysis is directly proportional, or whether there is a threshold of Lp(a) concentration below which it no longer affects the above-mentioned indicators. Research with Lp(a)-specific drugs could provide some answers to these questions, presuming that the indicators of inflammation, coagulation and fibrinolysis will be measured in addition to Lp(a) values (Shiyovich et al., 2023; Yeang et al., 2022). The results of our research suggest that the parameters of inflammation, coagulation and fibrinolysis in post MI patients are no longer related to lipid parameters after treatment with PCSK9i. Whether the additional Lp(a) lowering to the recommended values would affect these parameters, still needs to be resolved.

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Ethics approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the National Medical Ethics Committee of the Republic of Slovenia (reference number: KME 0120-357/2018/8).

CRediT authorship contribution statement

Andreja Rehberger Likozar: Writing – original draft, Investigation, Data curation, Conceptualization. **Sabina Ugovšek:** Writing – original draft, Investigation, Data curation, Conceptualization. **Miran Šebeštjen:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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