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Does Pentraxin-3 contribute to the reduction of low-density lipoprotein levels by statin therapy?

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Abstract

Statins have been shown to decrease inflammatory markers, especially high sensitivity C reactive protein (hsCRP), in a dose-dependent manner. Pentraxin-3 (PTX3) is another important inflammatory biomarker from the pentraxin family that provides useful prognostic information and facilitates diagnostics of cardiovascular diseases. This study investigated the effect of statin therapy on PTX3 and hsCRP concentrations and whether statins acted synergistically with PTX3 and hsCRP concentrations in lowering LDL-C. The study group consisted of 90 patients undergoing coronary angiography.

The results showed that statins reduced PTX3 concentrations (p=0.031). PTX3 and hsCRP levels were significantly different between subclinical and severe stenosis groups (p=0.011 and p=0.009, respectively). Statin therapy was significantly associated with lower PTX3 and LDL-C levels in multiple logistic analyses. The probability that statin therapy would achieve target LDL-C values was highest in patients with low PTX3 values (OR=3.683, p=0.040), while multiplicative interaction was 23.3.

The effect of statins on PTX3 reduction was higher than on hsCRP. It can be suggested that statin therapy was more successful in patients with low PTX3 values.

Key words: Pentraxin-3, hsCRP, statins, coronary angiography, multiplicative interaction, LDL-C

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Introduction

The role of statins in reducing cardiovascular risk was proven in recent years, both in primary and secondary prevention. Statins are now an integral part of therapy after serious cardiovascular events, and 2018 AHA/ACC (American Heart Association/American College of Cardiology) guidelines recommend the introduction of high-intensity statin therapy as secondary prevention in the presence of atherosclerotic cardiovascular disease, with a target of 50% reduction in low-density lipoprotein cholesterol (LDL-C) compared to baseline values (1). Similarly, ESC/EAS (European Society of Cardiology/European Atherosclerosis Society) 2019 guidelines recommended introducing intensive statin therapy in patients with cardiovascular disease to achieve LDL-C levels below 1.8 mmol/L or a 50% reduction (2).

Experimental studies showed that statin treatment increased the levels of antiatherogenic high-density lipoprotein cholesterol (HDL-C) and its major apolipoprotein A-1 (apoA-I), besides reducing LDL cholesterol by acting on intracellular signalling molecules (3). The inhibition of prenylation process in cholesterol synthesis caused by statins hits the number of signal transduction molecules in the vascular and myocardial signalling pathways (4). Direct inhibition of the prenylation of vascular cells explains the rapid pleiotropic effects of statins on a vascular wall (5). It has been shown that statins, in a dose-dependent manner, decrease inflammatory markers, especially C-reactive protein (CRP) (6). The statin effects on LDL-C and high-sensitive CRP (hsCRP) are mediated by various mechanisms (7). It is believed that statins act directly on hepatocytes and prevent the cytokine-mediated expression of CRP (8).

Apart from CRP, another important inflammatory biomarker from the pentraxin family is pentraxin-3 (PTX3). PTX3 is highly expressed in advanced atherosclerosis tissues, including macrophages and endothelial cells. Morikawa et al. showed that atorvastatin and pitavastatin in cultured cells reduce PTX3 mRNA levels in a dose-dependent manner (9). A study by Baetta et al. indicated that atorvastatin decreases the production and release of PTX3 in human endothelial cells through a post-transcriptional effect. These authors suggested that statins reduce the expression of PTX3 in vascular cells through the inhibition of protein geranylgeranylation (10). The suppression of PTX3 expression by statins may decrease the total risk of cardiovascular diseases. At present, there is not enough data on the statin therapy effect on PTX3 concentration. It is important to mention that most data regarding the role of statins on PTX-3 in atherosclerosis are derived from *in vitro* studies.

In contrast, the number of studies on human samples is limited. In addition, the JUPITER study showed that subjects with LDL-C lower than 3.36 mmol/L and hsCRP above 2 mg/L treated with statins had a reduced number of myocardial infarctions, stroke onsets, revascularisation procedures, and premature death (11). To our knowledge, no published reports have examined the combined effect of statin use and PTX-3 concentration on LDL-C.

To better understand the impact of statins on inflammatory markers, we investigated the effect of statin therapy on PTX3 and hsCRP concentrations in patients with coronary artery disease (CAD) and whether their concentrations and the use of statins acted synergistically in lowering of LDL-C.

Materials and methods

The study group included 90 CAD patients who were treated at the Institute of Cardiovascular Diseases of the Clinical Centre of Serbia in Belgrade and underwent coronary angiography. Indications for invasive diagnostic treatment were: myocardial infarction, stable angina pectoris, unstable angina pectoris or atypical chest pain with a positive history of familial cardiovascular disease.

All angiographic findings were reviewed by two cardiologists unaware that the patients were enrolled in the study. Of 90 CAD patients, 43 had subclinical stenosis (stenosis less than 50%), while 47 patients had severe stenosis (above 50% in one or more vessels).

Patients included in the study completed a questionnaire related to risk factors: (1) smoking at the time of angiography or at the onset of first symptoms; (2) diagnosis of hypertension (HT) indicated by systolic blood pressure ≥ 140 mm Hg and diastolic blood pressure ≥ 90 mm Hg or prescribed antihypertensive drugs; (3) body mass index (BMI); (4) duration of statins use (if they use). Reasons for excluding patients from study groups were: using other groups of lipid-lowering drugs than statins (fibrates, cholesterol absorption inhibitors, omega 3 fatty acids), a recently confirmed infection, comorbidities in terms of kidney disease, liver or malignancies, surgery, or severe trauma one month before the start of the study. Patients with hsCRP concentrations ≥10 mg/L, indicating the presence of a significant inflammatory condition (12), were also excluded. All patients were informed about the course of the study and signed an agreement before enrolling in the study. The study was planned according to the ethical principles following the Declaration of Helsinki (13). The ethics committees of the institutions participating in the study approved our study protocol in accordance with applicable regulations related to biomedical research.

Methods

Venous blood samples were collected from the patients after overnight fasting into collection tubes containing serum-separator gel for serum samples and ethylene diamine-tetraacetic acid (EDTA) for plasma samples. Lipid and lipoprotein parameters were determined in EDTA plasma, hsCRP and PTX3 in serum. Plasma and serum portions were stored at -80°C until assayed. Most biochemical markers were measured using an ILAB 600 analyser (Instrumentation Laboratory, Milan, Italy). Total cholesterol (TC) and triglycerides (TG) were assayed using routine enzymatic methods, and HDL-C was determined after phosphotungstic acid/$MgCl_2$ precipitation procedure using the same enzymatic method (14). The concentration of LDL-C was calculated using the Friedewald formula (15), while hsCRP was measured using a latex-enhanced immunoturbidimetric

method (Tina-quant CRP Roche, Indianapolis, USA). PTX3 was measured by ELISA (Human Pentraxin3 Duo Set ELISA R&D Systems, Minneapolis, USA).

Statistical analysis

For normally distributed continuous variables, the results are presented as arithmetic mean ± standard deviation, and for categorical variables, absolute frequencies are shown. Due to the curved distribution of TG, hsCRP and PTX3, the data were logarithmically transformed and presented as geometric means and 95% confidence intervals (CI). Continuous variables were compared by Student's t-test and two-way ANOVA, and categorical variables were analysed using Chi-square tests for contingency tables.

We examined the effect of statin therapy on inflammatory and lipid parameters using univariate and multivariate logistic regression analysis. Due to the absence of recommendations for PTX3 cut-off value, CAD patients were grouped so that patients with PTX3 in the upper tertile (PTX3≥5.23 ng/mL) were high PTX3 group, while patients with PTX3 values lower than the upper tertile were low PTX3 group. According to the recommendations (16), patients with hsCRP ≥3 mg/L, TC≥5.2 mmol/L and TG≥1.69 mmol/L concentrations were placed in a group with high values, and those with levels lower than those previously mentioned (hsCRP, TC and TG) created a low-value group. HDL-C levels below 1.03 mmol/L in males and below 1.29 mmol/L in females were defined as no-recommended values.

In addition, we calculated multiplicative interaction on the odds ratio (OR) scale (17). Multiplicative interaction describes whether the exposure to two factors together [statin therapy and low PTX3 or hsCRP levels (OR - two factors)] exceeds the product of the effects of the two exposures when considered separately [statin therapy without low PTX3 or hsCRP levels (OR - statin therapy) and low PTX3 or hsCRP levels without statin therapy (OR - low PTX3 or hsCRP)] on the presence of low LDL-C. Exposure to high PTX3 or hsCRP levels and the lack of statin therapy were considered the reference group (OR=1). We calculated multiplicative interaction according to the formula: OR - two factors/ (OR - statin therapy x OR - low PTX3 or hsCRP). Low LDL-C concentration (lower than 2.59 mmol/L) was coded 1, while LDL-C concentration higher than 2.59 mmol/L was coded 0. Multiplicative interaction higher than 1 indicates that the effect of both exposures together is higher than the product of the two exposures considered separately. In that case, interaction on the multiplicative scale is present (17).

A two-tailed value of $p<0.05$ was considered significant, and SPSS version 22 was used for calculations.

Results

All patients were classified into two groups: statin users (N=41) and nonusers (N=49). The concentrations of the inflammatory markers, as well as demographic characteristics, serum glucose and lipids in patients classified based on statin use are shown in Table I.

The concentrations of both investigated biomarkers of inflammation were higher in the statin nonusers' group (7.16 ng/mL vs 4.35 ng/mL for PTX3, and 4.79 mg/L vs 3.92 mg/L for hsCRP), but only for PTX3 the difference between groups was statistically significant (p=0.031). However, there was no difference between statin users and nonusers in LDL-C and HDL-C.

Table I Demographic characteristics and concentrations of examined laboratory parameters in patients with different statin use

Tabela I Demografske karakteristike i koncentracije ispitivanih laboratorijskih parametara kod pacijenata sa različitom upotrebom statina

Variable	Statin nonusers	Statin users	*p*
N	49	41	
Age, years	61.22 ± 12.43	60.66 ± 9.63	0.813
BMI, kg/m^2	26.77 ± 3.38	26.92 ± 3.97	0.854
Male, %	44	57	0.078
HT, %	32.7	27.5	0.360
Smokers, %	32.7	46.3	0.135
Stenosis prevalence %	57.1	53.7	0.156
Glucose, mmol/L	5.75 ± 1.63	5.46 ± 0.72	0.300
TC, mmol/L	5.23 ± 1.99	4.75 ± 0.95	0.166
TG, mmol/L[§]	1.51 (1.28-1.78)	1.50 (1.36-1.66)	0.938
HDL-C, mmol/L	1.13 ± 0.36	1.18 ± 0.30	0.477
LDL-C, mmol/L	3.34 ± 1.53	2.85 ± 0.83	0.079
hsCRP, mg/L[§]	4.79 (3.21-7.14)	3.92 (2.59-5.93)	0.606
PTX3, ng/mL [§]	7.16 (5.61-9.15)	4.35 (3.19-5.93)	0.031

Continuous variables are presented as mean ± SD, and categorical variables are presented as absolute and relative frequencies.

[§] For TG, hsCRP and PTX3 the geometrical mean and 95% confidence interval (CI) are presented (BMI – body mass index; HT– hypertension; TC – total cholesterol; TG – triglycerides; HDL-C – HDL-cholesterol; LDL-C – LDL-cholesterol; hsCRP – high-sensitivity C-reactive protein; PTX3 – pentraxin-3)

To assess the effect of the presence of stenosis and received statin therapy on the concentration of tested parameters, each group was additionally divided into sub-groups with either subclinical stenosis or with severe stenosis. The examined parameters were compared using two-way ANOVA with fixed factors (significant stenosis and statin therapy) (Table II). PTX3 and hsCRP levels were significantly different between subclinical and severe stenosis groups (p=0.011 and p=0.009, respectively). The highest PTX3 concentrations were found in statin nonusers with significant stenosis. We did not find a significant interaction between statin therapy and the presence of severe stenosis (p=0.680 for PTX3 and p=0.476 for hsCRP). Of all the examined lipid parameters, only the HDL-C concentration was different in the stenosis group (p=0.014), but interaction effect (between significant stenosis presence and statin therapy) on HDL-C was not proven (p=0.950).

Table II Concentrations of examined parameters in statin nonusers and users dependent on the presence of stenosis

Tabela II Koncentracije ispitivanih parametara kod pacijenata koji ne koriste i koji koriste statine u zavisnosti od prisustva stenoze

Variable	statin nonusers		statin users		
	subclinical stenosis	severe	subclinical stenosis	severe	*p**
N	19	30	20	21	
Male, %	39	52	53	60	0.096
PTX3, ng/mL§	4.77 (3.39-6.71)	8.19(6.26-10.72)	3.52 (2.40-5.16)	5.22 (3.19-8.52)	0.011
hsCRP, mg/L§	1.86 (1.02-3.82)	4.75 (3.07-7.34)	2.56 (1.36-3.75)	2.47 (1.65-3.70)	0.009
LDL-C, mmol/L	2.94 ± 1.10	3.62 ± 1.74	2.97 ± 0.89	2.75 ± 0.80	0.405
HDL-C, mmol/L	1.24 ± 0.31	1.06 ± 0.37	1.28 ± 0.33	1.01 ± 0.25	0.014
TC, mmol/L	4.88 ± 1.35	5.50 ± 2.35	4.98 ± 1.01	4.56 ± 0.89	0.775
TG, mmol/L§	1.34 (1.01-1.78)	1.62 (1.32-1.99)	1.49 (1.23-1.80)	1.52 (1.38-1.65)	0.279

*p** for difference between subclinical and severe stenosis groups by two-way ANOVA

Continuous variables are presented as mean ± SD, and categorical variables are presented as absolute and relative frequencies.

§ For TG, hsCRP and PTX3 the geometrical mean and 95% confidence interval (CI) are presented

(TC – total cholesterol; TG – triglycerides; HDL-C – HDL-cholesterol; LDL-C – LDL-cholesterol; hsCRP – high-sensitivity C-reactive protein; PTX3 – pentraxin-3)

Using the logistic regression analysis, we tested the influence of statin therapy on the presence of low or recommended concentrations of the investigated parameters after adjustment for the stenosis presence. The results showed that the treatment with statins led to a reduction in the PTX3 concentration, regardless of the presence of stenosis (OR=2.761, *p*=0.047). As expected, the results showed that statin therapy significantly increased the probability of low LDL-C concentrations after adjustment for stenosis (OR=2.626, *p*=0.041). However, it has not been proven that statin therapy significantly increases the probability of low hsCRP concentrations and low or recommended values for other lipid parameters (Table III). In multivariable analysis, including stenosis severity, age, BMI and HT presence, statin therapy was significantly associated with low PTX3 and LDL-C levels.

Table III Impact of the statin therapy on the presence of low or recommended concentrations of lipid and inflammatory parameters

Tabela III Uticaj terapije statinima na prisustvo niskih i preporučenih koncentracija lipida i inflamatornih parametara

Variable	OR (95% CI) unadjusted	p	Adjusted OR* (95% CI)	p	Adjusted OR** (95% CI)	p
PTX3, ng/mL	2.685 (1.015-7.106)	0.047	2.761 (1.013-7.524)	0.047	2.838 (1.019-7.908)	0.046
hsCRP, mg/L	2.100 (0.891-4.950)	0.090	2.085 (0.866-5.020)	0.101	2.428 (0.930-6.341)	0.070
LDL-C, mmol/L	2.597 (1.032-6.538)	0.043	2.626 (1.040-6.630)	0.041	2.998 (1.114-8.073)	0.030
HDL-C, mmol/L	1.420 (0.594-3.397)	0.430	1.219 (0.485-3.066)	0.674	1.267 (0.627-4.223)	0.317
TC, mmol/L	2.108 (0.822-5.408)	0.121	2.282 (0.875-5.990)	0.091	2.357 (0.829-6.808)	0.107
TG, mmol/L§	0.964 (0.388-2.396)	0.964	0.961 (0.359-2.251)	0.961	1.025 (0.370-2.841)	0.962

Adjusted OR*-adjusted for significant stenosis

Adjusted OR**-adjusted for significant stenosis, age, BMI and HT

PTX3≥5.23 ng/mL, hsCRP≥3 mg/L, TC≥5.2 mmol/L, TG≥1.69 mmol/L were coded 0 and corresponding values lower than previous specified values were coded 1. HDL-C levels≥1.55 mmol/L were coded 1 and HDL-C levels<1.55 mmol/L were coded 0.

(TC – total cholesterol; TG – triglycerides; HDL-C – HDL-cholesterol; LDL-C – LDL-cholesterol; hsCRP – high-sensitivity C-reactive protein; PTX3 – pentraxin-3)

In addition, we tested the multiplicative interaction of the exposure to both statin therapy and low PTX3 or hsCRP levels on low LDL-C concentration presence. Table IV indicates that statin use increases the probability of achieving target LDL-C values in combination with low PTX3 concentrations (OR-two factors =3.683, *p*=0.040). We observed the multiplicative interaction for low LDL-C (multiplicative interaction = 23.3) in statin users with PTX3 below 5.23 ng/mL. In testing the exposure to low hsCRP concentration and statin therapy, multiplicative interaction was not proven (Table IV).

Table IV Effects of statin therapy and inflammatory parameters on the target LDL-C level

Tabela IV Efekat terapije statinima i inflamatornih parametara na postizanje ciljnih koncentracija LDL-C

OR for LDL-C concentration lower than 2.59 mmol/L			
Reference group	**OR (low PTX3) (Without statin therapy)**	**OR (statin therapy) (high PTX3 level)**	**OR (two factors) (with statin therapy and low PTX3 level)**
1	0.510 (0.119-2.188) p=0.510	0.310 (0.031-3.111) p=0.319	3.683 (1.062-12.771) p=0.040
Reference group	**OR (low hsCRP) (Without statin therapy)**	**OR (statin therapy) (high hsCRP level)**	**OR (two factors) (with statin therapy and low hsCRP level)**
1	0.432 (0.077-2.407) p=0.338	2.903 (0.868-9.712) p=0.084	1.781 (0.539-5.888) p=0.344

Reference group was formed of statin nonusers (without statin therapy) and with high PTX3 (≥5.23 ng/mL) or hsCRP (≥ 3mg/L) levels;

Low PTX3 < 5.23 ng/mL; Low hsCRP, < 3mg/L

LDL-C concentration <2.59 mmol/L were coded 1 and LDL-C concentrations ≥2.59 mmol/L were coded 0

(LDL-C – LDL-cholesterol; hsCRP – high-sensitivity C-reactive protein; PTX3 – pentraxin-3)

Discussion

This study demonstrated that statins reduced PTX3 concentration, and that effect was particularly evident in patients with subclinical stenosis. Statin therapy significantly increased the probability of low PTX3 and LDL-C concentrations but not for low hsCRP concentrations. In addition, we have shown multiplicative interaction of statin therapy and low PTX3 on LDL-C levels.

According to our study findings, from the two examined inflammatory parameters (hsCRP and PTX3), statins reduced only PTX3 concentration. These results are partially consistent with the results of other studies. In a study by Hiro et al. (18), a significant decrease in PTX3 and hsCRP concentrations in patients with acute coronary syndrome was shown after treatment with pitavastatin and atorvastatin. Iwata et al. reported significantly reduced PTX3 concentrations in patients with stable angina treated with atorvastatin (10 mg/day) compared to patients without statin therapy (19). Ohbayashi and colleagues observed that PTX3 concentrations were decreased in hypercholesterolemic patients treated with pitavastatin (20). PTX3 concentration appears to be a more accurate indicator of local inflammatory response at sites of atherosclerotic lesions than CRP (21).

Genetic analysis showed that statins suppress the expression of PTX3 in endothelial cells (22). The proximal promoter of human PTX3 contains a nuclear factor κB (NF-κB) binding site and could be activated by the NF-κB pathway (23). The consequences of PTX3 activation by IKK/IκB/NF-κB pathway are up-regulation of iNOS expression and NO production. Considering that NO produced by iNOS can stimulate inflammation and necrosis and promote atherosclerosis, iNOS should be a key factor in PTX3-mediated endothelial cell injury (23). Some reports demonstrated that atorvastatin and lovastatin reduced proinflammatory cytokine expression in smooth muscle cells by inhibition of NF-κB activity (24). Based on all these data and the results of our study, we assume this is one of the mechanisms by which statins lead to PTX3 reduction, whereby statins eliminate the harmful effect of iNOS.

Studies conducted in a larger group of patients showed that the administration of statins successfully reduced LDL-C levels in patients with high CRP levels (7,25). Our study failed to demonstrate that, likely due to the small number of patients in the group. A PRINCE (Pravastatin Inflammation/CRP Evaluation) study showed that the administration of pravastatin at a 40 mg/day dose during 24 weeks significantly reduced CRP in serum of patients with and without cardiovascular disease risk, independently of changes in the concentration of LDL-C (26). Our study showed that patients treated with statins and with low PTX3 concentration had a significant probability of reaching desirable LDL-C levels, which was confirmed by the multiplicative interaction. It can be suggested that statin therapy was more successful in patients with low PTX3 values. The causalities between PTX3 and LDL-C levels are still unclear, but a study by Bosutti et al. showed that PTX3 mRNA levels were elevated in WBCs and adipose tissue of patients with high LDL-C levels (27). However, in the HELP LDL apheresis study, the authors concluded that total cholesterol and LDL-C were not associated with the LDL-apheresis related changes of PTX3 level (28). Despite the fact that the role of PTX3 in the vascular system is still not fully recognized, the question that arises from these results is whether statin therapy decreases LDL-C concentration and consequently, PTX3 level or the statin therapy causes better regulation of LDL-C levels due to low PTX3 concentration. Additional research is needed to investigate a potential positive statin effect on the endothelial wall through inhibition of PTX3 expression and the iNOS pathway. At the

same time, research is required to explore whether PTX3 determination would contribute to better patient selection for statin therapy.

As a limitation of this study, we must acknowledge that the subject groups were relatively small, and the observed relation between plasma PTX3 and cardiovascular risk factors was, although significant, somewhat weak. The effect of statin therapy on inflammatory parameters was tested in the study, but the division of patients according to the generic name of drug used was not performed. This was done as a cross-sectional study, and we did not determine a causal relationship between the parameters and the percentage of reduction in LDL-C.

Conclusion

Although the PTX3 role and the mechanism are still unclear, we found that the effect of statins on PTX3 reduction was higher compared to hsCRP. We also proved the synergism of low PTX3 levels and statin use on LDL-C reduction to desirable levels. It is necessary to further determine whether statin therapy modulates other risk factors, thereby reducing the need to release PTX3, as well as whether PTX3 can help in the selection of patients for statin treatment.

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Conflict of interest

None. The authors report no conflict of interest, including any financial, personal or other relationships with other people or organisations. All authors have read the journal's policy on disclosure of potential conflicts of interest.

Contribution statement

Vesna Vukovic Dejanović - manuscript writer, data interpretation;

Nataša Bogavac Stanojević - study design, statistical analysis, data interpretation, revision of the manuscript;

Vesna Spasojevic-Kalimanovska - final revision of the manuscript;

Dimitra Kalimanovska-Oštrić (as a medical doctor) - study design, data interpretation.

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Da li pentraksin -3 doprinosi sniženju koncentracije lipoproteina niske gustine i terapiji statinima?

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Kratak sadržaj

Pokazano je da statini snižavaju koncentracije inflamatornih markera, posebno visoko osetljivog C reaktivnog proteina (hsCRP), pri čemu je sniženje zavisno od doze leka. Pentraksin-3 (PTX3) je još jedan važan inflamatorni biomarker iz porodice pentraksina koji ima prognostičke karakteristike i olakšava dijagnozu kardiovaskularnih bolesti. U ovoj studiji je ispitivan efekat terapije statinima na koncentracije PTX3 i hsCRP, kao i sinergistički efekat terapije, koncentracija PTX3 i hsCRP u snižavanju LDL-C. U studiju je uključeno 90 pacijenata kojima je koronarnom angiografijom procenjeno suženje koronarnih krvnih sudova. Rezultati su pokazali da statini smanjuju koncentraciju PTX3 (p=0,031). Koncentracije PTX3 i hsCRP značajno se razlikuju između grupa sa subkliničkim (p=0,011) i teškim oblikom stenoze (p=0,009). Primenom multiple logističke regresione analize uočena je veza između terapije statinima i niskih koncentracija PTX3 i LDL-C. Verovatnoća da će terapija statinima postići ciljne vrednosti LDL-C bila je najveća kod pacijenata sa niskim vrednostima PTX3 (OR=3,683, p=0,040), dok je multiplikativna interakcija bila 23,3. Efekat statina na sniženje PTX3 bio je veći u odnosu na efekat koji ostvaruje na hsCRP. Može se sugerisati da je terapija statinima bila uspešnija kod pacijenata sa niskim vrednostima PTX3.

Ključne reči: Pentraksin-3, hsCRP, statini, koronarna angiografija, multiplikativna interakcija, LDL-C