


Lipid exchange and inflammatory markers in patients with coronary artery disease and atrial fibrillation

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Aim. To investigate lipid exchange violations, inflammatory markers levels, their connections in coronary artery disease (CAD) patients with atrial fibrillation (AF) and their role in AF paroxysm development and duration.

Materials and methods. 300 patients were divided into three groups: 27 patients without CAD and arrhythmias formed the control group (CG), 149 patients with CAD but without arrhythmias were included in the main group, and 124 patients with CAD and AF paroxysm were in the comparison group. The average duration of AF paroxysm in the studied group was 2 [1; 3] days (mean [95 % CI]). Such indexes were examined: total cholesterol (TC), triglycerides (TG), low-density lipoproteins (LDL), high-density lipoprotein (HDL), lipoprotein (α) (Lp(α)), apolipoprotein A1 (ApoA1), apoprotein B (ApoB), C-reactive protein (CRP) and interleukin 6 (IL-6).

Results. According to our data, CAD is characterized by significant lipid exchange violations (increasing TC, LDL, TG, Lpα, ApoB and decreasing HDL; $p < 0.05$) and increasing inflammatory markers (CRP, IL-6). The presence of AF paroxysm in CAD patients deepened such changes (increasing ApoB, IL-6, CRP; $p < 0.05$) and ApoB/ApoA1 ratio was increased ($p < 0.05$). Significant strong and middle strength correlations between inflammatory markers (CRP, IL-6) and lipid exchange indexes (LDL, TG, ApoA1, ApoB, ApoB/ApoA1) were found ($p < 0.05$). For validation the role of lipid exchange and inflammation in AF pathogenesis ROC curve was performed: $LDL + 1.6 \times CRP$, the area under ROC curve 0.8519 ($p < 0.05$). This formula can help us to predict the development of AF paroxysm in CAD patients. Moreover, a linear regression equation was created: $AF\ Paroxysm\ Duration\ (days) = 0.91 \times IL-6 - 0.95$ ($p < 0.05$), which will help to predict AF paroxysm duration in CAD patients, too.

Conclusions. AF paroxysm occurrence in CAD patients is based on dyslipidemia and inflammation. It is connected with increasing IL-6, CRP, ApoB/ApoA1 levels. The duration of AF paroxysm in CAD patients directly depends on the IL-6 level.

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Ліпідний обмін і маркери запалення в пацієнтів з ішемічною хворобою серця та фібриляцією передсердь

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Мета роботи – вивчити порушення ліпідного обміну, рівень маркерів запалення, їхній зв'язок у хворих на ішемічну хворобу серця (ІХС) із фібриляцією передсердь (ФП) і роль у розвитку та тривалості пароксизму ФП.

Матеріали та методи. Обстежили 300 хворих, яких поділили на три групи: 27 осіб без ІХС та аритмії залучили в контрольну групу (КГ), 149 пацієнтів із ІХС, але без аритмії – в основну, 124 хворих на ІХС із пароксизмом ФП – у групу порівняння. Середня тривалість пароксизму ФП у групі дослідження становила 2 [1; 3] дні (середнє [95 % ДІ]). Оцінювали такі показники: загальний холестерин (ЗХ), тригліцериди (ТГ), ліпопротеїди низької щільності (ЛПНЩ), ліпопротеїди високої щільності (ЛПВЩ), ліпопротеїн (α) (Lp(α)), аполіпопротеїн А1 (АроА1), апопротеїн В (АпоВ), С-реактивний білок (СРБ) та інтерлейкін 6 (ІЛ-6).

Результати. За результатами, що отримали, у хворих на ІХС визначили дисліпідемію (підвищення ЗХ, ТГ, ЛПНЩ, Lp(α), АроВ і зниження ЛПВЩ, $p < 0,05$) та підвищення маркерів запалення (СРБ, ІЛ-6). Наявність пароксизму ФП у хворих на ІХС поглиблювала ці зміни (зростали АроВ, ІЛ-6, СРБ, $p < 0,05$), співвідношення АроВ/АроА1 підвищене ($p < 0,05$). Виявили також значущі сильні та середньої сили кореляції ($p < 0,05$) між маркерами запалення (СРБ, ІЛ-6) та показниками ліпідного обміну (ЛПНЩ, ТГ, АроА1, АроВ, АроВ/АроА1). Для підтвердження ролі ліпідного обміну та запалення в патогенезі ФП побудували ROC-криву: $ЛПНЩ + 1,6 \times СРБ$; площа під ROC-кривою – 0,8519 ($p < 0,05$).

Ця формула може допомогти передбачити розвиток пароксизму ФП у хворих на ІХС. Склали рівняння лінійної регресії: тривалість пароксизму ФП (дні) = $0,91 \times ІЛ-6 - 0,95$ ($p < 0,05$), що дає змогу прогнозувати тривалість пароксизму ФП у пацієнтів з ІХС.

Висновки. В основі виникнення пароксизму ФП у хворих на ІХС лежать процеси дисліпідемії та запалення, що проявляється підвищенням ІЛ-6, СРР, АроВ/АроА1. Тривалість пароксизму ФП у хворих на ІХС прямо залежить від рівня ІЛ-6.

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Coronary artery disease (CAD) is a pathological process characterized by atherosclerotic plaque accumulation in the epicardial arteries. It is chronic serious progressive condition that increases the risk of cardiovascular events and death. Lipid exchange violations and inflammation are the basic pathogenetic mechanisms of CAD occurrence [1].

Atrial fibrillation (AF) is the most common arrhythmia in adults. It is associated with substantial morbidity and mortality. CAD is one of the known AF risk factors, as inflammatory diseases and lipid profile disturbances. Also, CAD and AF have a lot of the same risk factors as smoking, obesity, physical inactivity, etc. All ones increase the risk of AF occurrence in CAD patients more than 3 times. One of the strategies in AF treatment is the detection and management of cardiovascular risk factors, including CAD [2,3].

Such dyslipidemia characteristics are increasing the risk of cardiovascular events such as hypercholesterolemia, hypertriglyceridemia, increased low-density lipoproteins (LDL) and lipoprotein (α), decreased high-density lipoproteins (HDL). Also, CAD is characterized by increasing inflammatory markers such as C-reactive protein (CRP) [4]. Despite a deep long-term study of the role of dyslipidemia and inflammatory markers in CAD and AF pathogenesis, there are still unclear points, for example: their connections, their peculiarities in CAD and AF comorbidity.

Aim

To investigate lipid exchange violations, inflammatory markers levels, their connections in CAD patients with AF and their role in AF paroxysm development and duration.

Materials and methods

300 patients were examined and divided into three groups: 27 patients without CAD and arrhythmias formed the control group (CG), 149 patients with CAD but without arrhythmias were included in the main group, and 124 patients with CAD and AF paroxysm were in the comparison group. There were no significant changes in age and gender in the study groups (Table 1), so analysis of cardiometabolic risk factors peculiarities in connection with age, gender was not the aim of our study. Middle AF paroxysm duration in the studied group was 2 [1; 3] days (mean [95 % CI]). CAD and AF diagnosis were based on the latest ESC guidelines [1,2].

Inclusion criteria were based on results of objective clinical examination (typical patients' compliance and history), resting 12-lead electrocardiogram (ECG), transthoracic echocardiography, ultrasound of the carotid arteries, lipid profile, invasive coronary angiography. We selected patients who had atherosclerotic plaques presence in coronary arteries during invasive coronary angiography by anamnesis morbi for CAD diagnosis decision. AF paroxysm was found by resting 12-lead ECG. ECG was done by CardioLab ECG complex (Kharkiv, 2017). Carotid ultrasound and

echocardiography were done by Toshiba Aplio 400 color Doppler ultrasound system (Japan, 2016).

Exclusion criteria include reported malignancies, chronic kidney disease (Glomerular Filtration Rate, GFR <60 mL/min), valvular AF, heart failure Class III to IV (by New York Heart Association), left ventricular dysfunction (ejection fraction <45 %), thyroid pathology, inflammatory bowel disease, irritable bowel syndrome, vegetarians and vegans, pregnancy, taking probiotics and antibiotics for a month before the study. No significant difference in risk factors at baseline was seen between study groups, they were compatible ($p > 0.05$).

Informed consent was obtained from all patients in accordance with the Declaration of Helsinki. The study was conducted at the base and was approved by the ethical commission of the Kyiv City Clinical Hospital No. 12. Clinical and laboratory characteristics of the study groups are shown in Table 1.

Lipid profile was investigated by total cholesterol (TC), triglycerides (TG), LDL, HDL, lipoprotein (α) (Lp(α)), apolipoprotein A1 (ApoA1), apoprotein B (ApoB); inflammatory markers were CRP and interleukin 6 (IL-6). Atherogenic index of plasma (AIP) was calculated by $\log(TG/HDL)$ [5]. Patient's blood sampling was performed on an empty stomach from the cubital vein on the day of hospitalization. Hymalyzer 2000 was used for the detection TC, TG, HDL, LDL (reagent produced by HUMAN GmbH), ApoA1, ApoB, Lp(α) and CRP (reagent produced by Dialab) – by flow cytometry. Hymareader 2106 (ELISA) was used for the detection IL-6 – reagents produced by Vector Best. All analyses were done in Bogomolets National Medical University on the Department of Internal Medicine No. 4 based on Kyiv City Clinical Hospital No. 12 (certificate No. ПТ-257/21).

Results were presented as mean \pm standard error for continuous variables or median [95 % confidence interval (CI)] for categorical variables. Variables distribution for normality is checked by the Pearson criterion. Data were compared using Scheffe's multiple comparison method with two critical regions by the type of distribution. Pearson's rank correlation coefficient was calculated. ROC curve analysis for lipid and inflammatory indexes and linear regression model were done [6,7]. All calculations were done in MATLAB R2014a (License number 271828).

Results

The main and comparison groups have a significant increase of TC (32.64 % and 43.06 % respectively), TG (80.36 % and 55.36 % respectively), LDL (70.78 % and 72.73 % respectively), Lp(α) (41.17 % and 54.95 % respectively), ApoB (85.12 % and 140.50 % respectively), CRP (136.26 % and 232.97 % respectively), IL-6 (65.22 % and 103.11 % respectively) and decreasing HDL (16.09 % and 29.31 % respectively) compared with CG ($p < 0.05$). ApoB/ApoA1 ratio was significantly higher in mean (143.64 %) and comparison (163.64 %) groups from CG both ($p < 0.05$). AIP was also significantly higher in mean and com-

Table 1. Baseline characteristics of studied groups, mean \pm standard error

Parameter, units of measurement	CAD	CAD + AF	CG	p1-2	p2-3	p1-3
Age, years	67.71 \pm 3.90	67.96 \pm 0.94	56.25 \pm 2.18	0.8427	0.2656	0.3514
Men, %	48.99	47.97	48.15	0.9802	0.9802	0.9802
BMI, kg/m ²	27.02 \pm 0.33	26.93 \pm 0.43	28.12 \pm 2.10	0.6912	0.6912	0.6912
Smoking, %	51.01	41.46	40.74	0.6529	0.6529	0.6529
Uric acid, mmol/l	380.50 \pm 28.16	404.90 \pm 36.11	310.2 \pm 29.12	0.6270	0.0418	0.0457
Total bilirubin, mmol/l	11.30 \pm 0.09	12.40 \pm 0.08	11.7 \pm 0.11	0.7652	0.7652	0.7652
GFR, ml/min	62.03 \pm 2.31	67.73 \pm 1.98	84.01 \pm 5.48	0.5632	0.0388	0.0415

Table 2. Lipid exchange and inflammatory signs, mean \pm standard error

Parameter, units of measurement	CAD	CAD + AF	CG	p1-2	p2-3	p1-3
TC, mmol/l	5.73 \pm 0.37	6.18 \pm 0.31	4.32 \pm 0.21	0.3361	0.0481	0.0425
TG, mmol/l	2.02 \pm 0.18	1.74 \pm 0.14	1.12 \pm 0.09	0.2011	0.0210	0.0338
LDL, mmol/l	2.63 \pm 0.29	2.66 \pm 0.24	1.54 \pm 0.11	0.1982	0.0405	0.0387
HDL, mmol/l	1.46 \pm 0.13	1.23 \pm 0.14	1.74 \pm 0.12	0.1694	0.0371	0.0420
Lp(α), mg/dl	22.53 \pm 1.26	24.73 \pm 1.48	15.96 \pm 1.23	0.4412	0.0476	0.0218
ApoA1, g/l	2.02 \pm 0.16	2.34 \pm 0.27	1.62 \pm 0.09	0.2618	0.2618	0.2618
ApoB, g/l	2.24 \pm 0.19	2.91 \pm 0.13	1.21 \pm 0.18	0.0445	0.0217	0.0210
ApoB/ApoA1	1.34 \pm 0.21	2.00 \pm 0.19	0.55 \pm 0.07	0.0451	0.0091	0.0427
AIP	0.10 \pm 0.05	0.02 \pm 0.03	-0.32 \pm 0.11	0.4270	0.0118	0.0077
CRP, mg/l	2.15 \pm 0.20	3.03 \pm 0.19	0.91 \pm 0.12	0.0095	0.0088	0.0414
IL-6, pg/ml	2.66 \pm 0.16	3.27 \pm 0.16	1.61 \pm 0.09	0.0307	0.0079	0.0466

Table 3. Correlations between lipids exchange indexes and inflammatory markers, $p < 0.05$

Lipids exchange signs / Inflammatory markers	CRP	IL-6
TC	0	0
TG	0.380	0.706
LDL	0.328	0.312
HDL	0	-0.384
Lp(α)	0	0
Apo A1	-0.472	-0.765
Apo B	0.747	0.717
AIP	0.463	0.504
ApoB/ApoA1	0.495	0.745

+: moderate positive correlation, $0.3 < r < 0.7$; ++: strong positive correlation, $r > 0.7$; 0: no significant correlations; -: moderate negative correlation, $-0.3 > r > -0.7$; --: strong negative correlation, $r < -0.7$.

parison groups from CG both ($p < 0.05$). Also, it is higher than reference ranges as independent predictor of acute myocardial infarction [5]. In the comparison group significant increase of ApoB (29.91 %), CRP (40.93 %), IL-6 (22.93 %) levels and ApoB/ApoA1 ratio (49.25 %) were detected compared to the main group. The results are shown in *Table 2*.

Moreover, we explore the correlations between inflammatory markers and dyslipidemia indexes. The reliable correlations between CRP (total number = 6), IL-6 (total number = 7) and lipid exchange indexes were found. It is interesting fact that all proatherogenic lipid indexes [1] directly correlated with inflammatory markers due to our data ($p < 0.05$). The results are shown in *Table 3*.

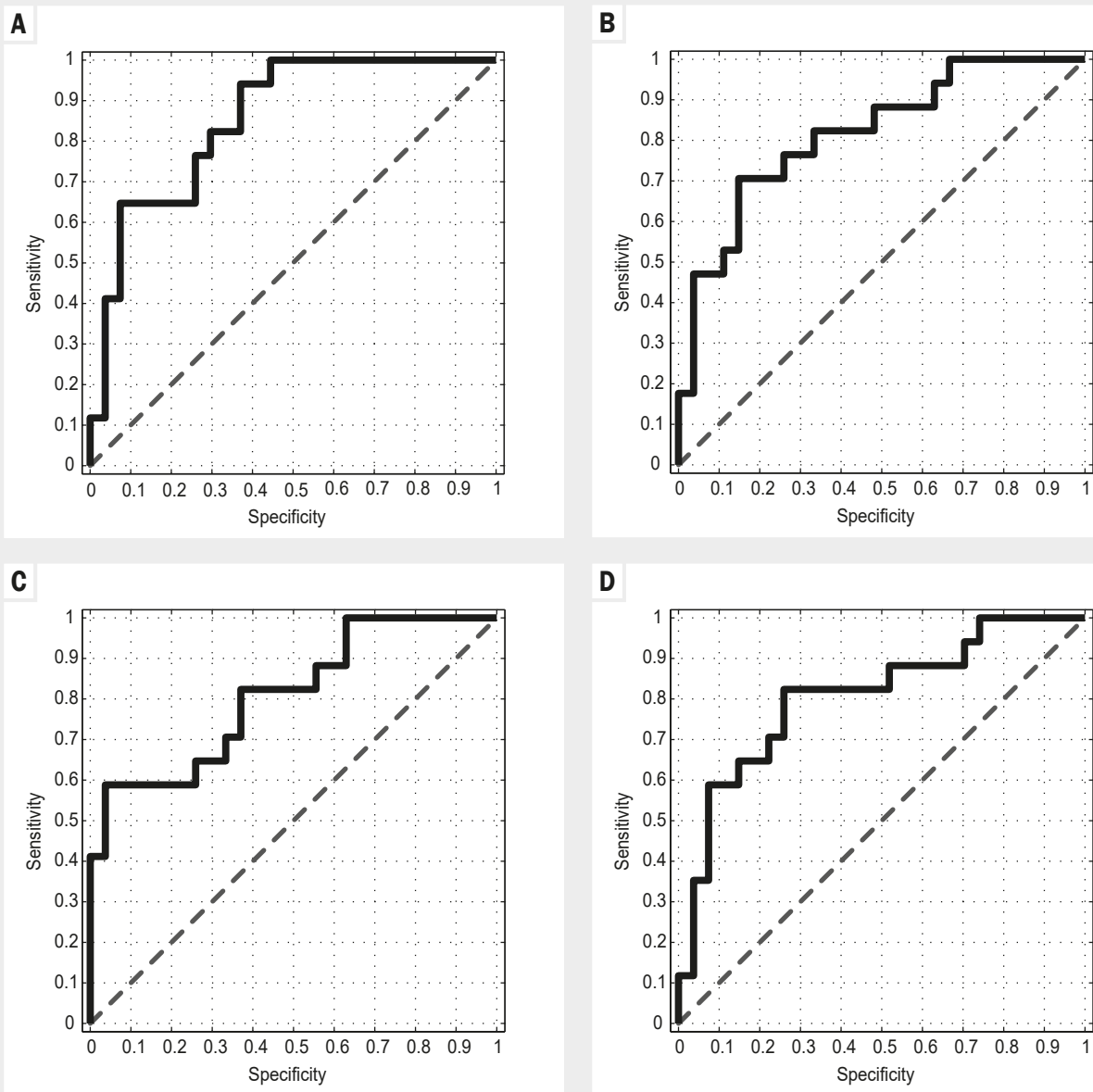


Fig. 1. ROC curve analysis for lipid and inflammatory indexes for the main and comparison groups, $p < 0.05$. **A:** LDL + 1.6 × CRP, the area under ROC curve 0.8519; **B:** ApoB + 0.8 × CRP, the area under ROC curve 0.8126; **C:** LDL – 1.6 × ApoA1, the area under ROC curve 0.8083; **D:** AIP – 0.6 × CRP, the area under ROC curve 0.8061.

In our study ROC analysis was performed to prove the diagnostic value of lipid indexes and inflammatory markers for the main and comparison groups. It was done individually for each sign and for their combinations for further validation of their diagnostic values. We were looking for optimal combinations that can be used as prognostic markers of risk AF paroxysm in CAD patients, where the area under the ROC curve exceeded 0.8 for different indexes and their combinations, while the p value was significant ($p < 0.05$). It was performed for the main and comparison groups. Results are shown in Fig. 1.

In formulas A, B, C, D, which are presented in Fig. 1, the coefficient k is obtained from the solution of the problem of maximizing the AUC value for the binary classification criteria in the class $X1 + k \times X2$. Due to the finiteness of the training sample, the

optimal value of k is determined by the interval. The value given in the article is a representative of this interval, chosen based on the brevity of its decimal representation.

Due to obtained data analysis of the linear regression was done between AF paroxysm duration and lipids exchange, inflammatory indexes. Such linear regression equation was established, $p = 0.0318$: AF paroxysm duration (days) = $0.91 \times IL - 0.95$.

As we can see, by IL-6 level AF paroxysm duration in CAD patients can be predicted.

Discussion

The role of dyslipidemia and inflammation, their connection in CAD pathogenesis is already known. CAD is associated with

such lipid changes: hypercholesterolemia, hypertriglyceridemia, elevated LDL, Lp(α), ApoB and decreased HDL plasma levels [1,8,9]. Also, CAD is characterized by increasing AIP, which is the significant predictor of the occurrence of cardiovascular events (acute myocardial infarction and stroke) [5] and ApoB/ApoA1 ratio, that is proarrhythmic index [12]. Chronic long-term persistent dyslipidemia leads to increasing plasma inflammatory markers such as CRP and IL-6 [4]. In our study we got the same results, that have proved the previous data.

Moreover, correlations between inflammatory markers and lipid indexes can determine their role in CAD development. In accordance with our data CRP and IL-6 have significant direct strong and middle strength positive correlations with TG, LDL, ApoB, PAI, ApoB/ApoA1 and negative with ApoA1 plasma level. Also, IL-6 has negative middle strength correlation with HDL plasma level. This mostly matches literature data [8,9], but we provided the more wide lipid spectrum analysis that includes more indexes for deeper pathogenetic understanding.

The main importance is that we investigate changes in lipids profile indexes and inflammatory markers in patients with CAD and AF paroxysm. A significant increase of ApoB, CRP, IL-6 and decreasing ApoA1 was found. The latest data on the role of dyslipidemia in AF paroxysm still remains unclear and controversial. Despite the well-known opinion that AF is positively linked with TC, TG, LDL and negatively correlated with HDL levels [2,10], some data claimed that lower level of TC, TG, LDL is common for AF patients [11]. Also, the role of ApoB in AF paroxysm pathogenesis is still unclear: some authors say that decreased ApoB is associated with AF paroxysm [10], while other data declare that increased ApoB and ApoB/ApoA1 ratio leads to AF paroxysm [10,12]. Other data matches the antiatherogenic and antiarrhythmic HDL and ApoA1 [10,11,12,13], which coincide with our results.

We can explain this by differences in the formation of studied groups: in our study exclusion criteria were valvular AF, heart failure Class III to IV (by New York Heart Association), left ventricular dysfunction (ejection fraction <45 %), thyroid pathology, because we tried to understand the role of CAD in AF paroxysm pathogenesis. Moreover, most of our patients did not receive statins 3 months before plasma test.

ROC curve analysis was done in our work to validate the role of lipid indexes and inflammatory signs in AF paroxysm pathogenesis of CAD patients. $LDL + 1.6 \times CRP$ – characterized by the higher area under ROC curve 0.8519 ($p < 0.05$), so can be used for AF paroxysm prediction in CAD patients.

By our results AF paroxysm duration significantly linearly depends on IL-6 levels. It can be explained that increased IL-6 leads for atrium Ca^{2+} exchange abnormalities, reentry formation [13] as well as IL-6 increased intramyocardial fibrosis [15].

Conclusions

1. CAD is characterized by significant lipid exchange violations (increasing TC, LDL, TG, Lp(α), ApoB and decreasing HDL; $p < 0.05$) and increasing inflammatory markers (CRP, IL-6).

2. The presence of AF paroxysm in CAD patients deepens such changes (increasing ApoB, IL-6, CRP; $p < 0.05$). As for AF paroxysm in CAD patients ApoB/ApoA1 ratio was increased ($p < 0.05$).

3. Significant strong and middle strength correlations between inflammatory markers (CRP, IL-6) and lipid exchange indexes (LDL, TG, ApoA1, ApoB, AIP, ApoB/ApoA1) were found ($p < 0.05$).

4. For validation the role of lipid exchange and inflammation in AF pathogenesis ROC curve was created: $LDL + 1.6 \times CRP$, the area under ROC curve 0.8519 ($p < 0.05$). This formula can help us to predict AF paroxysm in CAD patients.

5. The linear regression equation was performed: $AF\ Paroxysm\ Duration\ (days) = 0.91 \times IL-6 - 0.95$ ($p < 0.05$), which will help to predict AF paroxysm duration in CAD patients.

Perspectives of subsequent scientific research: It will be interesting to investigate more inflammatory markers and to check their connections with dyslipidemia in patients with CAD and AF.

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