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The dynamics of atherogenic lipoproteins and estrogens during the management of dyslipidemia with PCSK9 inhibitors in patients with various comorbidities

Kuznetsov A. A.[1], Mal G. S.[2]

[1] Moscow Regional Hospital named after Prof. V.N. Rozanov, Moscow Region, Russia.
[2] Kursk State Medical University of the Ministry of Healthcare of Russian Federation, Kursk, Russia.

AUTHORS

Andrey A. Kuznetsov*, M.D., physician of the Department of Cardiology of the Moscow Regional Hospital named after Prof. V.N. Rozanov, Moscow Region, Russia.
Galina S. Mal*, M.D., doctor of medical sciences, professor, Head of the Department of Pharmacology of Kursk State Medical University of the Ministry of Healthcare of Russian Federation, Kursk, Russia.

Abstract

Objective. To assess the dynamics of atherogenic lipoproteins and estrogens during the management of dyslipidemia with PCSK-9 inhibitors in patients with coronary artery disease (CAD) and various comorbidities.

Materials and methods. The study included 114 men with CAD and very high cardiovascular risk. All patients were divided into three groups: group 1 — patients with CAD (n=39), group 2 — patients with CAD in combination with type 2 diabetes mellitus (T2DM) (n=38), group 3 — patients with CAD in combination with stages IIIA-IIIB of chronic kidney disease (CKD) (n=37). All study participants were administered with intense treatment with statins + ezetimibe. In case when target levels of low-density lipoprotein cholesterol (LDL–C) were not achieved, alirocumab was added to treatment with the control of lipid profile and estrogens levels for 12 months.

Results. In group 1 97.4 % of patients (n=38) achieved target LDL–C level that decreased by 73.9 % from 4.41±0.19 mmol/l to 1.15±0.15 mmol/l (p<0.001); in group 2 94.7 % of patients (n=36) achieved target LDL–C level that decreased by 74.2 % from 4.62±0.25 mmol/l to 1.19±0.12 mmol/l (p<0.001), in group 3 91.9 % of patients reached target values (n=34) and LDL–C decreased by 73.5 % from 4.60±0.20 mmol/l to 1.22± 0.09 mmol/l (p<0.001). The level of estradiol after 12 months after treatment with alirocumab increased by 8.3 % (p=0.39) in group 1, by 7.7 % (p=0.36) — in group 2, by 8.5 % (p=0.31) — in group 3.

Conclusion. Thus, the use of PCSK9 inhibitors in combination with optimal lipid-lowering therapy in patients with very high cardiovascular risk showed clear effectiveness in patients with CAD without comorbidities. In all study groups, plasma estradiol level statistically insignificantly increased after alirocumab treatment.

* Corresponding author. Tel.: +7 977-684-2715. E-mail: dr.cardiologist.kuznetsov@yandex.ru

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Introduction

Cardiovascular mortality has been one of the most important issues of cardiology for a long time. Despite all the advances of modern medicine, cardiovascular diseases (CVDs) and coronary artery disease (CAD) in particular remain the main causes of death worldwide [1]. In recent years, the feasibility of invasive treatment of coronary arteries has increased, however, the pharmacological treatment remains the first-line therapy for stable CAD and its secondary prevention [2, 3]. The pathophysiologic substrate for CAD is atherosclerosis that progresses due to the influence of several risk factors. The main modifiable cardiovascular risk factor is dyslipidemia that is reflected by the increase of low-density lipoprotein cholesterol (LDL–C) [4]. In addition to dyslipidemia, many studies have established that the level of female sex hormones plays a pivotal role along with many less significant risk factors for the development of CAD [5–7]. Back in 1965, A.L. Myasnikov suggested that estrogen could activate the phagocytic function of reticuloendothelial system that contributed to elimination of cholesterol.

Previously, the authors have shown the improvement of cholesterol:phospholecetin index that could prevent the development of atherosclerosis [8, 9]. Most authors point out that estrogens improve plasma lipid profiles (decrease the level of LDL–C and total cholesterol, increase the level of high-density lipoprotein cholesterol (HDL–C) [10–13], as well as cholesterol metabolism in the vascular wall (inhibits the processes of its uptake and degradation) that explains anti-atherosclerotic mechanism of endogenous estrogens and estrogen replacement therapy [14–16].

According to the latest clinical guidelines, the decrease of atherogenic lipoproteins in response to drug therapy in patients with CAD should be assessed by the achievement of target LDL–C levels, depending on cardiovascular risk (CVR) category [17]. For a long time, the main lipid-lowering medications were hydroxymethylglutaryl-coenzyme-A reductase inhibitors (statins), however only 21 % of patients, who received such therapy, achieved target LDL–C levels [18]. In case when target LDL–C levels couldn't be achieved with optimal lipid-lowering therapy, it is recommended to prescribe other groups of lipid-lowering medications — monoclonal antibodies, proprotein convertase subtilisin/kexin type 9 (PCSK9) enzyme inhibitors [19] that showed the achievement of target LDL–C parameters in over 90 % of patients [20].

To date, data on estrogens dynamics during the treatment with PCSK9 inhibitors are limited. Some studies have shown lower concentration of PCSK9 in men compared with women [21]. In addition, the level of PCSK9 enzyme increases with age in women, while decreases in men [22]. This fact may be explained by the influence of female sex hormones — increased level of estrogen contributes to the decrease of PCSK9 [23].

The aim of this study is the assessment of atherogenic lipoproteins and estrogen dynamics in patients with CAD who were prescribed with PCSK9 with several concomitant diseases.

Materials and methods

This open prospective study was carried out at Moscow Regional Hospital named after prof. V.N. Rozanov. The study was approved by the local ethics committee (protocol No. 3 dated March 16, 2020, Kursk State Medical University of the Ministry of Healthcare of Russian Federation), all the participants signed an informed consent form. All study participants had permanent registration at Moscow Region and were included into the preferential category of citizens

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(PCSK9 inhibitors in the Moscow Region are provided according to regional program and by the means of federal compulsory medical insurance fund using the clinical and statistical group ds36.004).

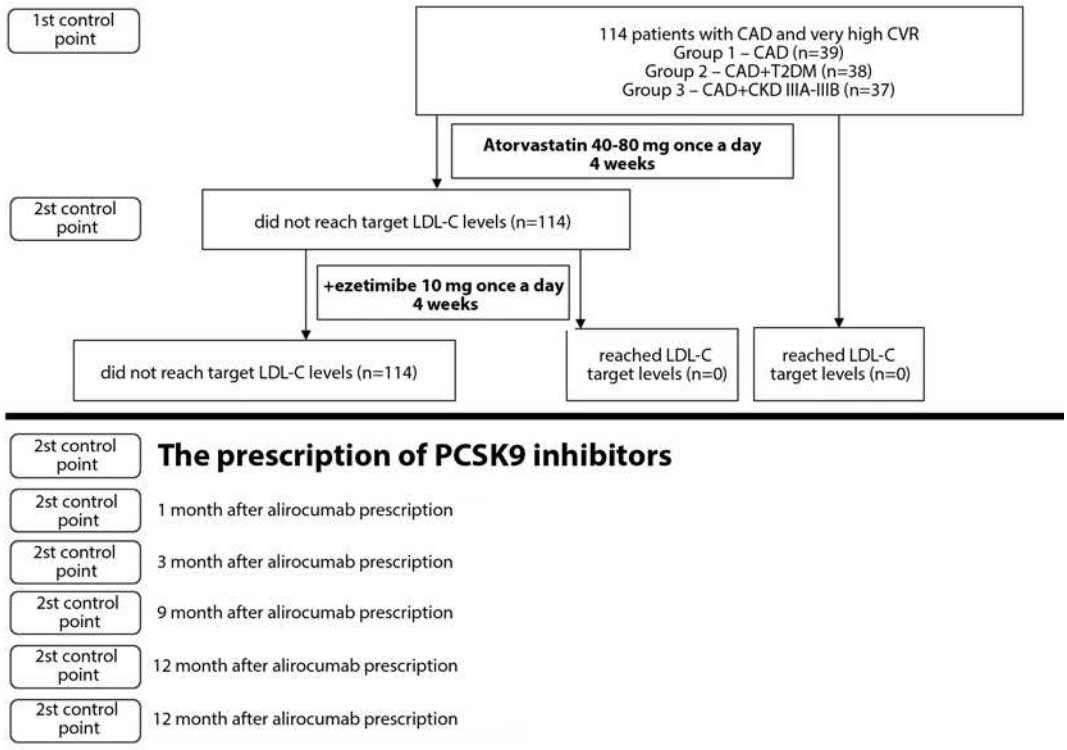
The study included 114 men (mean age 59.22 ± 5.74 years) with CAD, very high CVR and primary dyslipidemia, who required secondary prevention of CVD. Study participants were divided into 3 groups depending on the presence of concomitant diseases: group 1 — with CAD only (n= 39); group 2— with CAD and type 2 diabetes mellitus (T2DM) (n=38); group 3 — with the presence of CAD and stages IIIA-IIIB of chronic kidney disease (CKD) (n=37).

All the patients were examined during 8 visits. Study design is presented in Scheme 1. The first visit included standard medical examination and the prescription of maximum tolerated dose of atorvastatin. After 4 weeks, at second visit, the achievement of target LDL–C level according to the European Society of Cardiology (ESC) was assessed [17]. In case when target parameters were not achieved, patients were prescribed with 10 mg of ezetimibe once a day. At the third visit, 4 weeks after, the effect of lipid-lowering therapy was repeatedly assessed. Patients who showed LDL–C level over 1.4 mmol/l were prescribed with 150 mg of alirocumab additionally to previous treatment, subcutaneously once every 14 days (PRALUENT, SANOFI, France). The analysis of lipid profile and estradiol levels, after the prescription of alirocumab, was carried out at the next 5 control points: at 1st, 3d, 6th, 9th and 12th month of treatment.

The study inclusion criteria were: male gender, age from 50 to 69 years, confirmed diagnosis of CAD, very high CVR, lack of achievement of LDL–C target goals with the prescription of atorvastatin and ezetimibe in maximum tolerated dose, the absence of contraindications for the prescription of PCSK9 inhibitors.

The non-inclusion criteria were: the achievement of LDL–C targets with the prescription of atorvastatin and ezetimibe in maximum tolerated dose, stage III chronic heart failure (according to Vasilenko-Strazhesko classification) with left ventricular ejection fraction less than 30 %, individual intolerance to PCSK9 inhibitors, the decrease of LDL–C level of less than 0,5 mmol / l, obesity with a body mass index of less than 40.5; fasting triglycerides (TG) level over 4.52 mmol /l.

Fasting blood samples for biochemical assays were collected once, from the cubital vein in the morning, 12 hours after the last meal. The analysis was carried out using automatic biochemical analyzer BS-120 Mindray (China). The lipid panel included the param-



Scheme 1. Study design

eters of total cholesterol (TC), LDL–C, high-density lipoproteins cholesterol (HDL–C), triglycerides (TG).

The statistical analysis was performed using SPSS 23.0 software (IBM USA). The normality of distribution was assessed using the Kolmogorov–Smirnov test with the Lilliefors correction (for the entire sample) or the Shapiro–Wilk test (for groups with less than 50 participants). Quantitative features are presented as M ± SD for normally distributed parameters, where M is the arithmetic mean, SD — the standard deviation; the parameters that deviated from normal distribution are presented as median and quartiles (Me [Q1; Q3]). The qualitative parameters are presented in absolute numbers and/or percentage. The significance of differences between groups quantitative variables was assessed using the Kruskal–Wallis test (between three groups) and Mann–Whitney test (between two groups), the Wilcoxon test was used for dependent samples. Two-tailed Fisher's or chi-squared tests were used to assesses differences between quality variables. A p-value of <0.05 was taken to infer statistical significance.

Results

Before the inclusion into the study all the patients had comparable lipid panel parameters and comorbid diseases. Clinical characteristics of patients at baseline are presented in table 1.

The primary screening of the study participants showed that the vast majority of patients had classes 1–2 of obesity, arterial hypertension, and the history of smoking. Before the inclusion into the study, patients were prescribed with various dosages of statins without the achievement of LDL–C targets. At the first visit, atorvastatin at a maximum dose of 80 mg/day was administered in all patients. Atorvastatin intolerance was confirmed in 16.7% of patients (n=19) and required complete medication discontinuation in 12 patients and dose reduction to 40 mg in 5 patients. After 4 weeks of treatment, LDL–C level was assessed. In group 1, the level of LDL-C decreased from 4.41±0.19 mmol/l to 2.63±0.15 mmol/l (p<0.001), in group 2 — from 4.62±0.25 mmol/l to 2.71±0.09 mmol/l (p<0.001), group 3 — from 4.60±0.20 mmol/l to 2.69±0.08 mmol/l (p<0.001). At this point all patients were prescribed with ezetimibe, which caused the intensification of lipid-lowering response. Four weeks after, LDL–C reached 2.28±0.08 mmol/l in group 1, 2.32±0.07 mmol/l — in group 2, 2.33±0.07 mmol/l — in group 3. Since none of the patients reached LDL–C targets, alirocumab was added to treatment in all patients with the control of estradiol levels at all subsequent control points. Further dynamics of lipid profile and estradiol in the study groups are presented in figure 1.

Alirocumab intolerance was reported in 6 patients and lead to the exclusion of these patients from the study. In 12 months after the prescription of PCSK9 inhibitors, 108 patients achieved LDL–C targets; in group 1–97.4% (n=38), in group 2–94.7% (n=36), in group 3–91.9% (n=34). The final LDL–C level in group 1 was 1.15±0.15 mmol/l that was 73.9% lower compared with baseline, in group 2–1.19±0.12 mmol/l and decreased by 74.2%, in group 3–1.22±0.09 mmol/l

Table 1. **Clinical characteristics of patients at baseline**

Parameters	CAD (n= 39)	CAD+ T2DM (n= 38)	CAD+ CKD IIIA-IIIB (n= 37)	p
Age, years	60,94± 5,88	60,55± 6,21	59,22± 5,74	0,43
Obesity — class 1–2	59% (N=23)	63% (N= 24)	70% (N= 26)	—
Smoking	74% (N=29)	84% (N= 32)	92% (N= 34)	—
Arterial hypertension	90% (N=35)	90% (N= 34)	86% (N= 32)	—
Myocardial infarction	39% (N=15)	53% (N= 20)	38% (N= 14)	—
PCI/CABG	54% (N=21)	68% (N= 26)	46% (N= 17)	—
Lower extremity atherosclerosis	31% (N=12)	32% (N= 12)	27% (N= 10)	—
Atrial fibrillation	31% (N=12)	39% (N= 15)	30% (N= 11)	—
TC, mmol/l	6,45± 0,29	6,67± 0,21	6,69± 0,15	0,001
LDL–C, mmol/l	4,41± 0,18	4,62± 0,24	4,60± 0,20	0,001
HDL–C, mmol/l	0,70± 0,08	0,71± 0,09	0,69± 0,11	0,15
TG, mmol/l	2,09± 0,46	2,06± 0,40	1,99± 0,39	0,49
Atherogenic index	8,24± 1,12	8,55± 1,17	8,92± 1,24	0,14

Note. Significance levels are indicated for the Kruskal–Wallis test.
p — the level of significance of differences between study groups, quantitative variables are presented as means and standard deviations (M±SD); qualitative variables are presented as %.

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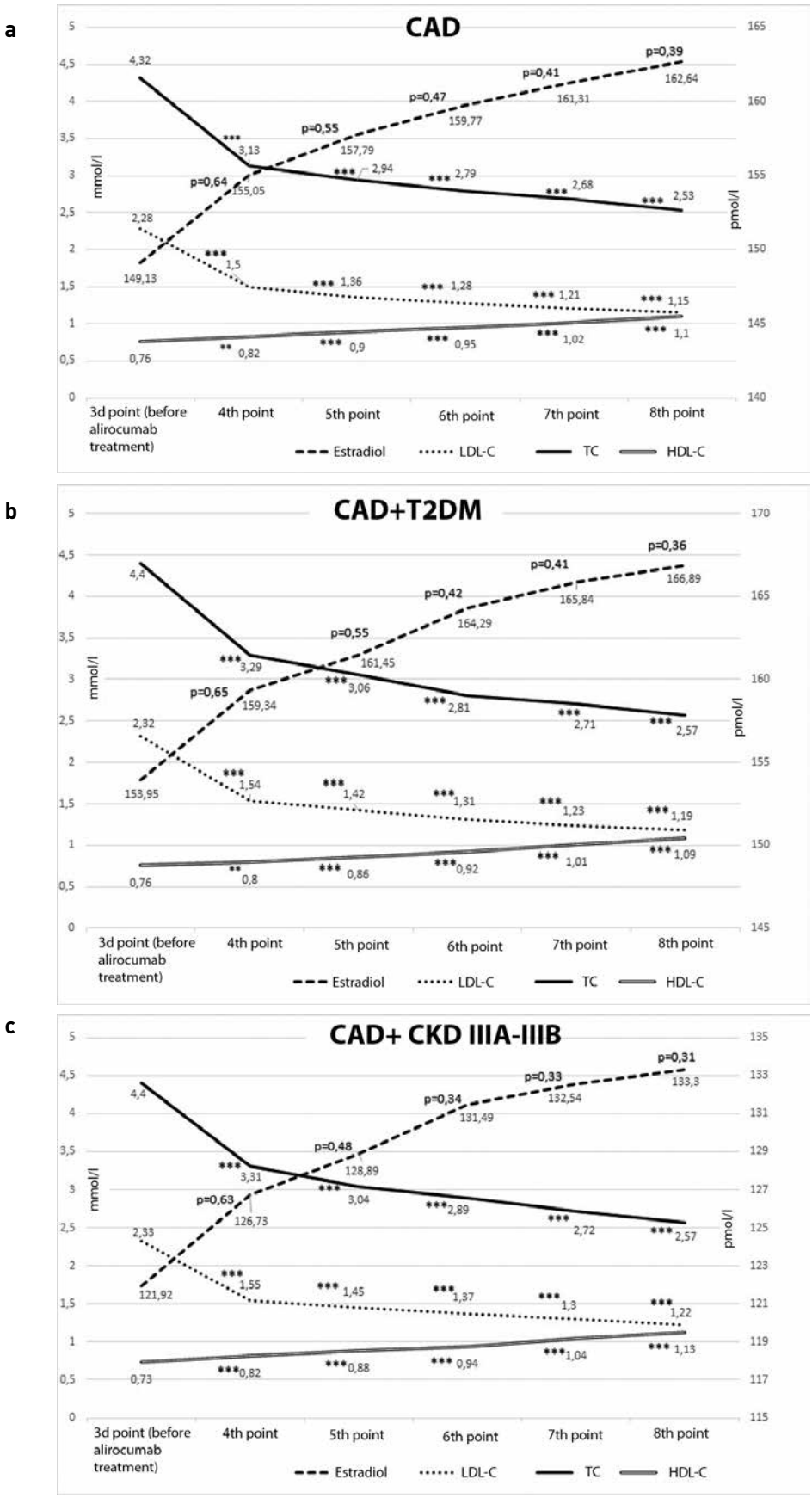

Figure 1. The dynamics of lipid profile and estradiol during 12-months alirocumab treatment: a — in patients with CAD, b — in patients with CAD in combination with T2DM, c — in patients with CAD and IIIA–IIIB stages of CKD.

and decreased by 73.5%. Alirocumab showed statistically significant (p<0.001) changes of all lipid profile parameters already 4 weeks after treatment initiation (2 injections). The TC level decreased from 4.32±0.08 mmol/l to 3.13±0.15 mmol/l (p<0.001) 4 weeks after and to 2.53±0.16 mmol/l (p<0.001) 12 months after the addition of alirocumab in group 1; from 4.40±0.08 mmol/l to 3.29±0.08 mmol/l (p<0.001) 4 weeks after and reached 2.57±0.09 mmol/l (p<0.001) 12 months after in group 2; from 4.40±0.08 mmol/l to 3.31±0.11 mmol/l (p<0.001) 4 weeks after and reached 2.57±0.11 mmol/l (p<0.001) 12 months after in group 3. The TG level decreased from 1.94±0.42 mmol/l to 1.74±0.36 mmol/l (p=0.04) in 4 weeks and to 1.13±0.34 mmol/l (p< 0.001) in 12 months of alirocumab treatment in group 1; from 1.94±0.37 mmol/l to 1.74±0.36 mmol/l (p=0.02) in 4 weeks and to 1.11±0.34 mmol/l (p<0.001) in 12 months in group 2; from 1.81±0.33 mmol/l to 1.64±0.31 (p=0.02) in 4 weeks and to 1.07±0.31 mmol/l (p<0.001) in 12 months in group 3, respectively. The level of HDL–C in group 1 increased from 0.76±0.08 mmol/l to 0.82±0.08 mmol/l (p<0.01) after 4 weeks of treatment and to 1.10±0.07 mmol/l (p<0.001) in 12 months; in group 2 — from 0.76±0.07 mmol/l to 0.80±0.06 mmol/l (p<0.01)in 4 weeks and to 1.09±0.08 mmol/l (p<0.001) in 12 months; in group 3 — from 0.73±0.07 mmol/l to 0.82±0.08 mmol/l (p<0.001) in 4 weeks and to 1.13±0.06 mmol/l (p<0.001) in 12 months. The analysis of estradiol dynamics showed high variability of this parameter in all groups that is most likely associated with the individual features of endocrine status in men (Fig. 2). The level of estradiol increased by 8.3% — from 149.13±87.30 pmol/l to 162.64±86.14 pmol/l (p=0.39) during the study follow-up; in the group 2 — by 7.7% — from 153.95±71.50 pmol/l to 166.89±71.01 pmol/l (p=0.36); in group 3 — by 8.5% — from 121.92±67.16 pmol/l to 133.30±68.40 pmol/l (p=0.31).

Discussion

In current study patients with CAD and very high CVR were prescribed with hypolipidemic therapy with PCSK9 inhibitors for 12 months. The achievement of target LDL–C level was the objective of treatment.

Over 90% of all study participants reached target LDL–C parameters. The most prominent response to alirocumab treatment was observed in patients with CAD without concomitant diseases (group 1), where the final LDL–C level was 1.15±0.15 mmol/l, in patients with CAD in combination with T2DM (group 2), the final LDL–C level was 1.19±0.12 mmol/l, and in patients with CAD in combination with IIIA-IIIB stages of CKD (group 3) the hypolipidemic effect was the lowest and the final LDL–C level was 1.22±0.09 mmol/l that is consistent with the data of large clinical studies confirmed by meta-analyses, such as FOURIER [24], where 97% of patients with CAD reached LDL–C target values and ODYSSEY OUTCOMES [25], where after

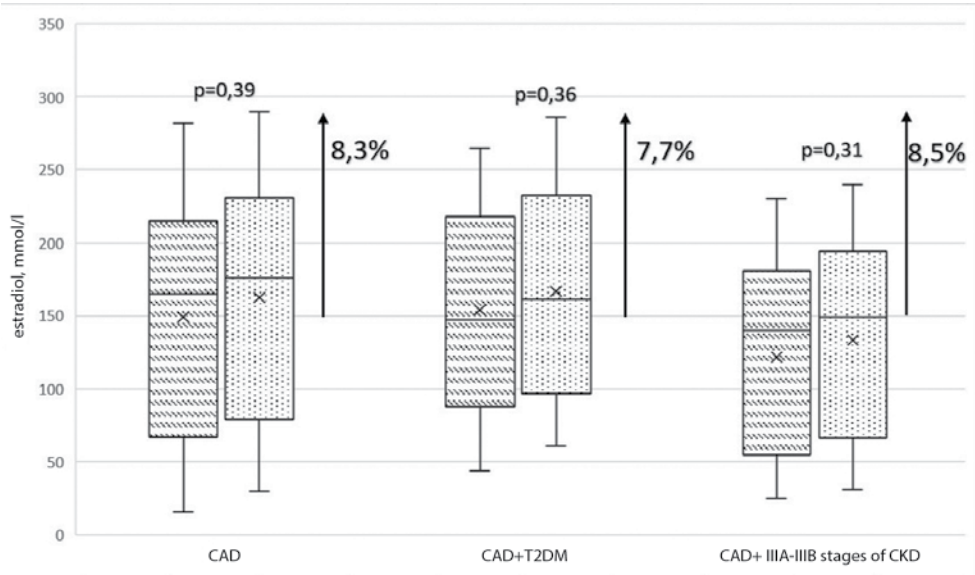

Figure 2. The dynamics of estradiol in study groups before and after the treatment with alirocumab.
Note. Significance levels are indicated for the Wilcoxon T-test; p — the significance of differences in estradiol level between baseline and the end of treatment with alirocumab.

12 months of alirocumab use, average LDL–C level reached 1.2 mmol/l that is not consistent with the results of smaller foreign and domestic trials.

Thus, according to the results of similar clinical study from Netherlands, the prescription of PCSK9 inhibitors allowed to achieve LDL–C level of < 1.8 mmol/l in 67.1 % of patients [26]. According to data from Israel Lipid Center, combined lipid-lowering therapy with PCSK9 inhibitors allowed 50 % of patients to achieve LDL–C concentration of < 1.8 mmol/l [27]. According to the retrospective chart review study from the National Research Center for Therapy and Preventive Medicine, the prescription of PCSK9 inhibitors additionally to optimal lipid-lowering therapy resulted in LDL–C of < 1.8 mmol in 78.3 % of patients and < 1.4 mmol / l — in 57.7 % of patients [28] that is significantly lower compared with the results of our study and may be explained by higher baseline LDL–C levels in the above studies, and the inclusion of patients with familial hypercholesterolemia.

In current study, total LDL–C level decrease reached 73.9 % in group 1, 74.2 % — in group 2, 73.5 % — in group 3 that differs from the results of studies from other countries. According to the results of large multicenter FOURIER and ODYSSEY OUTCOMES [24, 25] studies, the total reduction of LDL–C reached 85 % that is significantly higher compared with our results, and can be associated with longer use of PCSK9 inhibitors (36 months). According the French Lipid Center, the prescription of triple lipid-lowering therapy (statin + ezetimibe + PCSK9 inhibitor) resulted in the reduction of LDL–C level only by 66.3 % from baseline [29], which is lower compared with our study and may be associated with the inclusion into this study of patients with heterozygous familial hypercholesterolemia.

Our study showed good statin tolerability (16.7 %) and low incidence of adverse reactions to PCSK9 inhibitors intake (5 %). In other lipid centers and according to outpatient practice, statin intolerance ranges from 31.6 % to 77.0 % [27–28, 30–31], intolerance to PCSK9 inhibitors — from 10.0 % to 15.5 % [26, 27].

Estradiol blood level statistically insignificantly increased in all study groups after the addition of alirocumab into treatment. In group 1, estrogen level increased by 8.3 % 12 months after the prescription of PCSK9 inhibitors, in group 2 — by 7.7 %, in group 3 — by 8.5 %, respectively. It is noteworthy that this indicator had high variability (from 21 to 282 pmol/l), associated with individual characteristics of patient's endocrine status.

Conclusion

Thus, the use of PCSK9 inhibitors in combination with optimal lipid-lowering therapy in patients with very high CVR showed the most pronounced response in patients with CAD without comorbid diseases. Patients with comorbidities (CAD with T2DM and IIIA-IIIB stages of CKD) showed lower response to alirocumab. At the same time, over 90 % of patients reached LDL–C targets.

The level of estradiol statistically insignificantly increased in all study groups that may be associated with HDL–C increase.

The obtained results require further investigation in the framework of large clinical trials.

Conflict of interest: none declared.

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