Forming statin response in patients with coronary heart disease in presence of acute respiratory viral infections by means of genetic markers

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Abstract

Introduction. The present study evaluated the interaction of statin response and genetic polymorphism of interleukin (IL-1β, IL-6, IL-4, IL-10) genes with the course of atherosclerosis and coronary heart disease (CHD) in patients with CHD combined with acute respiratory viral infections (ARVI).

Objectives. Studying variability of Rosuvastatin response in patients with CHD combined with ARVI, taking cytokine gene polymorphism into account.


Results and discussion. In CHD patients at Visit I, the target level of low-density lipoprotein cholesterol (LDL-C) was reached by 55.7% of participants. At Visit II, the target LDL-C level was reached by 49.7% of patients, which coincided with ARVI detection in some patients.

In CHD patients with ARVI at Visit II, the IL-1β level increased to 33.00 pg/ml (N=5.00 pg/ml), IL-6 – 19.20 pg/ml (N=9.00 pg/ml); at Visit VI those levels decreased to 20.70 pg/ml and 12.80 pg/ml. The IL-4 level was 8.30 pg/ml (N=13.00 pg/ml), while IL-10 level was 19.40 pg/ml (N=31.00 pg/ml), with their increase at Visit VI to 15.80 pg/ml and 33.50 pg/ml.

CHD patients without ARVI did not develop interleukin level changes. At Visit II, the IL-1β level was 10.30 pg/ml, IL-6 level was 12.40 pg/ml, and at Visit VI, they were 13.00 pg/ml and 14.00 pg/ml. The IL-4 and IL-10 levels at Visit II were 19.70 pg/ml and 32.30 pg/ml; at Visit VI, those levels were 23.20 pg/ml and 34.20 pg/ml. The following associations were demonstrated: –511CT / increased IL-1β, LDL-C synthesis; –511CC / LDL-C level increase; –174GG / IL-6, LDL-C level increase; –1082GG / IL-10 level increase, cholesterol and CRP level decrease; –589TT / CRP, IL-4 level increase.

Conclusion. Genotypes –511CT, –174GG, –1082AA in all patients required 20 mg/day Rosuvastatin dose to reach the target LDL-C level.

Keywords
cytokines, Rosuvastatin, gene polymorphism, hyperlipidemia
Introduction

CHD continues to be leading in the structure of mortality and disability among diseases of the cardiovascular system (CVS).

In 2017, 53.3% lethal outcomes in the Russian Federation are attributed to CHD (Boytsov et al. 2017).

Absence of drug response to pharmacological hyperlipidemia (HLP) correction is diagnosed in every fifth patient (Sychev 2011).

Being a multifactorial disease, CHD is associated with genetic factors and environmental factors; it is also subject to chronopharmacology laws. According to the results of epidemiological studies, chronic CHD destabilization was detected in different seasons (Pankrushina and Sudakova 2014).

There is a seasonal trend in the increase in the number of hospitalizations for patients with CHD, due to intercurrent infections in autumn and spring (Surnin et al. 2011, Gribovskaya et al. 2015). Pharmacotherapy of patients in these conditions is changed compared to the standard management. This requires a search for modern pharmacological approaches to correct the treatment in this patients’ group.

One of the main pathogenetic causes of atherosclerosis development is inflammation, being an important atherogenesis component (Surnin et al. 2011, Gribovskaya et al. 2015) (Fig. 1).

Inflammation is a sign of the impact of various factors damaging vascular endothelium. A number of studies demonstrate the relation between an increase in the proinflammatory cytokine level (TNF-α, IL-1β, IL-6) and the signs of atherosclerosis destabilization and CHD (Golyshko 2010, Pankrushina and Sudakova 2014, Shevchenko 2015). Any acute infection may be the etiological factor which activates chronic inflammation in the atherosclerotic plaque, involving the cytokine system (Pankrushina and Sudakova 2014, Gribovskaya et al. 2015).

Quite a few articles demonstrate the relation between the clinical and laboratory status of CHD patients who have had ARVI and influenza (Golyshko 2010, Surnin et al. 2015, Gribovskaya et al. 2018).

An infectious process acts as a trigger that destabilizes the course of atherosclerosis and CHD. There is laboratory and instrumental evidence for this (Surnin et al. 2011, Pankrushina and Sudakova 2014). However, no endogenous components, which are essential for cardiovascular destabilization, have been studied.

ARVI is characterized by the imbalance of cytokine interaction against the background of chronic infection (herpes virus, cytomegalovirus), which becomes irreversible with the inflammatory process activation (Zykov et al. 2011, Surnin et al. 2011). Thus, pharmacological HLP correction should be changed considering the aggravating background (concomitant viral infection).

The present study evaluated the relation between genetic polymorphism of pro- and anti-inflammatory cytokine genes (IL-1β, IL-6, IL-4, IL-10) and a statin response degree. Besides, changes of patient’s biochemical, immunological, and morphometric statuses were monitored in various Rosuvastatin dose regimens.

Failure to reach the target LDL-C level in the studied patients was associated with insufficient intensity of
Rosuvastatin pleiotropic effects in CHD patients in presence of an acute infectious illness.

Consequently, genetic aspects caused by interleukin gene polymorphism impact the implementation of pleiotropic statin effects, ensuring patients’ compliance with HLP pharmacotherapy.

Thus, before the start of treatment, genetic tests are required to possibly predict its efficacy, i.e. achieving the target LDL-C level. This will enable individualization of HLP pharmacotherapy in this patient group.

**Objectives:** to study drug response variability when evaluating hypolipemic and pleiotropic Rosuvastatin effects in CHD patients and in those where it is combined with an acute infectious illness.

### Materials and methods

The study involved 170 CHD patients, 120 of whom also had infections (ARVI).

The inclusion criteria for the patients were as follows: males and postmenopausal females aged 41-60 years; stable angina of functional class (FC) I-II (Diagnostics and correction of lipid metabolism disorders in order to prevent and treat atherosclerosis. Russian recommendations of the All-Russian Scientific Society of Cardiologists (V revision) 2018); acute infectious process caused by influenza virus, cytomegalovirus (CMV), or Chlamydia pneumoniae; isolated or combined hypercholesterolemia – HC (patients with cholesterol level>5.5 mmol/l, triglycerides>1.7 mmol/l) (Diagnostics and correction of lipid metabolism disorders in order to prevent and treat atherosclerosis. Russian recommendations of the All-Russian Scientific Society of Cardiologists (V revision) 2018); no contraindications to HMG-CoA-reductase inhibitors; prior therapy with 4th generation statins as hypolipemic treatment, with starting dose of 10 mg/day; patient informed consent for study participation.

The exclusion criteria were as follows: individual Rosuvastatin intolerability; side effects of the treatment administered (3-fold liver enzyme increase); patient’s refusal to continue the treatment; comorbid diseases requiring pharmacotherapy which could impact lipid metabolism.

HC was verified based on the inclusion criteria, the presence of increased lipid metabolism parameters, as well as subclinical and clinical atherosclerosis signs. The patients with secondary lipid metabolism parameters were excluded from the study.

CHD disease and FC of stable angina were confirmed according to the clinical signs and the exercise stress test performed in pre-hospital settings.

The study was performed using a simple prospective method. The design was approved at the meeting of the Regional Ethics Committee of KSMU on 12th May 2017 (Fig. 2).

All the patients underwent a standard general clinical examination. At each study point, the LDL-C and cholesterol (C) levels were determined in the blood serum using an enzymatic calorimetric method and diagnostic “Analytic” kits manufactured by Vitalab Flexor E (Netherlands).

HLP pharmacotherapy was performed using 4th generation statins (Rosuvastatin, starting dose of 10 mg/day) according to the recommendations (Diagnostics and correction of lipid metabolism disorders in order to prevent and treat atherosclerosis. Russian recommendations of the All-Russian Scientific Society of Cardiologists (V revision) 2018).

Visit I: screening and inclusion of CHD patients into the study.

Visit II: dividing the patients into 2 subgroups based of the target LDL-C level (determined at the moment of hospitalization of some patients with ARVI into the Regional Clinical Infectious Hospital) to be reached.

If the target LDL-C level (1.8 mmol/l) was not reached during Rosuvastatin administration on Day 7 from ARVI onset (Visit III) (Diagnostics and correction of lipid metabolism disorders in order to prevent and treat atherosclerosis. Russian recommendations of the All-Russian Scientific Society of Cardiologists (V revision) 2018), the patient was switched to the 20 mg/day dose. On subsequent visits, reaching the target LDL-C level was checked, with further dose titration.

Infection verification was performed based on the clinical signs, using virological (polymerase chain reaction (PCR) of nasopharyngeal smears) and immunological (enzyme-linked immunosorbent assay (ELISA) of blood serum) methods. The virological spectrum was as follows: CMV – 29.1%, Influenza A – 40.1%, and Chlamydia pneumoniae – 30.8%.

Taking into account the detected causative agent, pharmacotherapy of the main disease included, according to the recommendations (Clinical protocols. National Scientific Society of Infectiologists 2014), the following: antiviral drugs (Oseltamivir – 0.75 g BID, Umifenovir – 0.2 g QID) and antibiotics in case of bacterial complications (macrolides: Azithromycin – 0.5 g OD, or 3rd generation cephalosporins – Ceftriaxone 1.0 g BID i/m). Symptomatic treatment included antipyretics – analides (Paracetamol 0.5 g). Oseltamivir was administered in 19% of cases, Ceftriaxone – in 40% of cases, Azithromycin – in 23% of cases, and Umifenovir – of in 81% cases.

Interleukin concentration in blood serum was determined using an ELISA method on a Tecan analyzer, using Vector Best CJSC kits.

Genomic deoxyribonucleic acid (DNA) isolation was performed on frozen (-20°C) venous blood using phenol-chloroform extraction. Genotyping of polymorphisms IL-1β –511C>T (annealing t -57°C, Mg – 3.5), IL-6 –174G>C (annealing t -45°C, Mg – 2.5), IL-4 –589C>T (annealing t -57°C, Mg – 2.5), IL-10 –1082G>A (annealing t -51°C, Mg – 2.5) was performed using a PCR method on a CFX96 Bio-Rad Laboratories amplifier (USA) with commercial TaqMan SNP Genotyping Assays reagent kits manufactured by Applied Biosystems (USA). The DNA isolation method was developed at the
Department of Biology, Medical Genetics, and Ecology of KSMU.

To confirm statistical significance of the obtained results, Microsoft Excel Office 2007 software package was used. The character of quantitative feature distribution and normality were evaluated using Student t-test. The parameters were considered statistically significant at the level P<0.05. To detect the power and direction of relations between the features under study, the correlation analysis was performed, with the calculation of the correlation coefficient (r).

**Results and discussion**

This research, conducted in the comparable subgroups of CHD patients with ARVI and those without ARVI, evaluated the efficacy of HLP pharmacotherapy when applying Rosuvastatin monotherapy (10 mg/day).

CHD patients at Visit I demonstrated the hypolipidemic effect of Rosuvastatin (10 mg/day) in the form of 55.7% patients achieving the target LDL-C level, out of whom isolated HC was found in 30.1% of the patients, and combined HC – in 25.6% of the patients.

Four weeks after inclusion into the study (Visit II), an individual evaluation of hypolipidemic efficacy correction was performed, based on achieving the target LDL-C level. At this visit, some cases of patients being hospitalized into the Regional Clinical Infectious Hospital with ARVI signs were registered.

Thus, the signs of CHD destabilization were the changed lipid profile parameters, with voiding the LDL-C level previously reached using a standard Rosuvastatin dose (10 mg/day).

At Visit II, a decrease in the achieved target level was detected in 61.7% CHD patients, among whom 33.1% of patients had isolated HC, and 28.6% of CHD patients had combined HC.

The clinical signs of CHD destabilization were not registered, which was confirmed by consequent electrocardiogram (ECG) registration over time.

The data obtained on destabilization of the atherosclerosis course facilitated the change of the standard treatment with the titration of the used Rosuvastatin dose.

The patients were followed up 7 days (Visit III), 14 days (Visit IV), 28 days (Visit V), and 3 months (Visit VI) after the ARVI onset, according to the study design.

Starting from Visit II, the patients underwent HLP treatment adjustment with Rosuvastatin 10 mg/day and Rosuvastatin 20 mg/day. The percentage of CHD patients with ARVI and isolated HC evaluated at Visit III demon-
strated that 50% of patients had reached the target LDL-C level when taking 10 mg Rosuvastatin and 55% patients – when taking a 20 mg dose (Fig. 3).

The subsequent follow-up points demonstrated the target cholesterol level was reached in 53% and 60% (Visit IV), in 58% and 63% (Visit V), in 64% and 67% patients (Visit VI) when applying the corresponding dose regimens.

In CHD patients with ARVI and combined HC, at Visit III, 47% of patients reached the target level on 10 mg Rosuvastatin and 52% – on 20 mg dose (Fig. 4).

Further follow-up showed that the target LDL-C level was reached in 50% and 56% (Visit IV), 56% and 60% (Visit V), 62% and 64% (Visit VI) of patients. Thus, the dose regimen adjustment for statin therapy up to 20 mg of Rosuvastatin promoted an increase of its hypolipidemic effect.

Pharmacological HC correction was performed in CHD patients without ARVI signs within the same period (Fig. 5).

In CHD patients with isolated HC, Rosuvastatin at a dose of 10 mg dose facilitated reaching the target LDL-C level in 54% (Visit I), 50% (Visit II), 54% (Visit III), 57% (Visit IV), 60% (Visit V), and 65% (Visit VI) of patients.

Accordingly, Rosuvastatin at a dose of 20 mg to reaching the target LDL-C level in 60% (Visit III), 64% (Visit IV), 68% (Visit V), and 72% (Visit VI) of patients.

For CHD patients with combined HC, at Visits I and II, HLP pharmacotherapy with Rosuvastatin at a dose of 10 mg/day led to reaching the target LDL-C level in 43% and 46% patients (Fig. 6). With further dose regimen correction, at Visit III, the target level (Rosuvastatin administered at a dose of 10 mg/day) was reached in 50% of patients, and in 58% of patients – at a 20 mg/day dose.

Visit IV was characterized by 53% of patients (10 mg/day) and 62% participants (20 mg/day) reaching the target level. At Visit V, the target level was reached in 56% (10 mg/day) and in 66% (20 mg/day) of patients. At Visit VI, 69% (20 mg/day) and 60% patients (10 mg/day) reached the target cholesterol level.

With pharmacological correction of HLP with Rosuvastatin, the hypolipidemic effect criterion was demonstrated with 67% of the studied patients reaching the target LDL-C level on Week 12 of pharmacotherapy (Fig. 7).

Along with the lipid metabolism parameters, the morphometric parameters (intima media thickness (IMT) of commons carotid arteries (CCA)) were also studied. The IMT examination allowed evaluating the efficacy of HLP pharmacotherapy (Table 1).

In the CHD patients included into the study, the IMT determined in the outpatient settings did not exceed 1.50 mm.

In CHD patients with ARVI, IMT at Visit I was 1.23±0.10 mm. Further pharmacotherapy with Rosuvastatin at a dose of 10 mg/day led to a decrease in IMT to 1.15±0.05 mm at Visit VI, and with Rosuvastatin at a dose of 20 mg – to 1.00±0.01 mm.

Thus, treatment with different doses of Rosuvastatin facilitated a significant IMT decrease when applying the both dose regimens.
The analysis of IMT changes in the CHD patients without ARVI ($p_{I-VI} < 0.05$), when Rosuvastatin is administered at a dose of 10 mg/day, showed IMT regression by 9%, while with 20 mg administration ($p_{I-VI} < 0.05$) – by 8.8%. No statistically significant differences were detected in the groups among the CHD patients with isolated and combined HC, but without ARVI.

Thus, a more significant pleiotropic effect was detected for Rosuvastatin administered at 20 mg/day in CHD patients with or without ARVI.

However, to achieve IMT regression in patients with comorbid diseases, Rosuvastatin dose titration up to 20 mg/day was required for the majority of patients (63%), which was inferior to the data obtained in CHD patients without ARVI (68%).

The obtained data accorded with those from large-scale multicenter trials, e.g. ASTEROID (2005), ORION (2005), METEOR (2006), SATURN (2011), which evaluated Rosuvastatin impact on atherosclerotic plaque regression. However, disease duration in those studies was at least two years, while the used doses of Rosuvastatin reached 40-80 mg QD, without taking acute inflammation (Melnyk et al. 2010, Skvortsov et al. 2013).

While studying the changes of hypolipidemic and pleiotropic components of Rosuvastatin pharmacological effect, their relations and interdependence were of great interest (Fig. 8).

Evaluation of relations between IMT in different Rosuvastatin dose regimens and lipid panel parameters demonstrated that there was a direct and very weak correlation between IMT and C when Rosuvastatin was administered at a dose of 10 mg. After titration of Rosuvastatin dose to 20 mg/day, a weak correlation relationship was diagnosed between IMT and C.

When studying IMT and LDL-C level changes during HLP pharmacotherapy with Rosuvastatin at a dose of 10 mg/day, a direct and very weak correlation was observed. Rosuvastatin administered at a dose of 20 mg provided for a weak correlation relationship between LDL-C and IMT.

In the context of pleiotropic statin effect, studying an anti-inflammatory activity is of utmost interest, along with studying a hypolipidemic one.

Pathogenetic mechanisms of atherosclerotic process progression are related to the participation of viral agents (direct cytopathic action on the vascular wall with the development of endothelial dysfunction) (Loktionova et al. 2012). Thus, when causative agent permeates, the activity of immune cells increases, and chronic inflammation is activated in atherosclerotic plaques (Loppnow et al. 2011, ...
Consequently, ARVI is a predictor of atherosclerosis progression. The interleukin levels in blood serums were determined in CHD patients at Visit II and further on, during the follow-up up to Week 12 (Visit VI) (Fig. 9).

Cytokine profile follow-up in CHD patients with ARVI when administering Rosuvastatin at a dose of 10 mg revealed an increase in the interleukin-1 level to 33.00 pg/ml at Visit II, with ARVI verification compared to the normal one (5.00 pg/ml), with a further decrease. At Visit VI (3 months after ARVI), it was 20.70 pg/ml after HLP pharmacotherapy.

The IL-6 level at Visit II was 19.20 pg/ml, with a further decrease to 12.80 pg/ml. The cytokine profile data obtained at Visit II in CHD patients with ARVI were caused by the activation of inflammatory processes at the moment of viral infection onset.

Further changes of pro-inflammatory cytokine parameters towards a progressive decrease were related to specific features of the clinical status of ARVI patients (transition to reconvalescence period, starting from Day 7 – Visit III) and implementation of Rosuvastatin pleiotropic effects.

Pro-inflammatory cytokine (IL-4 and IL-10) levels in CHD patients with ARVI at Visit II were characterized by low parameters. Thus, the IL-4 level at Visit II was 8.30 pg/ml, with a subsequent increase at Visit VI to 15.80 pg/ml. The IL-10 level at Visit II was 19.40 pg/ml, while at Visit VI it increased to 33.50 pg/ml.

These changes were due to manifestations of active inflammatory process at Visit II, with the trend to further restore cytokine status balance by the end of the follow-up (Week 12).

Three months after a viral infection, the patients reached the cytokine levels comparable with the results obtained in CHD patients without viral infection signs (p>0.05).

CHD patients without ARVI signs revealed a slight variability of the pro-inflammatory interleukin parameters throughout the 12-week case follow-up (Fig. 10).

The IL-1β level fluctuated from 10.30 pg/ml at Visit II to 13.00 pg/ml at Visit VI. The IL-6 parameter changed from 12.40 pg/ml at Visit II to 14.00 pg/ml at Visit VI.

The IL-1β and IL-6 levels were characterized by stable parameters throughout the whole follow-up period and were significantly lower than those in CHD patients with viral infection (p<0.05).

This pattern can be explained by stable balance of pro-inflammatory cytokines during the chronic inflammatory process in chronic CHD patients without infection (Loppnow et al. 2011, Zykov et al. 2011).

The IL-4 and IL-10 parameters in CHD patients without ARVI signs were significantly higher (P˂0.05) compared to the group of CHD patients with ARVI (Fig. 10). This is due to the suppression of inflammation in the atheroscle-
As known, IL-6 regulates the response of the acute inflammation phase (Guan et al. 2012, Shevchenko 2015). For the IL-6 gene, –174GG genotype demonstrated the most significant effect on the production of this cytokine. Its blood serum concentration at Visit II increased to 32 pg/ml compared to other genotypes of the IL-6 gene (P<0.05), which agrees with data from foreign trials (Chen et al. 2012).

The analysis of association of IL-6 gene genotypes with the quantitative lipid level showed that in carriers of –174GG genotype, the LDL-C level exceeded such for other IL-6 genotypes – 2.51 mmol/l (P<0.05). This proved the destabilization of the lipid transport system in case of acute inflammation (Babu et al. 2012) and the insufficient intensity of lipid- and non-lipid effects of Rosuvastatin at a dose of 10 mg/day, which showed in failure to reach the target LDL-C level.

It was shown that the presence of –589 C/T polymorphism of the IL-4 gene located in the promotor region led to replacing cytosine (C) for thymine (T) in position –589, with an increased transcriptional gene activity (Chen et al. 2012, Shevchenko 2015). As known, IL-6 regulates the response of the acute inflammation phase (Guan et al. 2012, Shevchenko 2015). For the IL-6 gene, –174GG genotype demonstrated the most significant effect on the production of this cytokine. Its blood serum concentration at Visit II increased to 32 pg/ml compared to other genotypes of the IL-6 gene (P<0.05), which agrees with data from foreign trials (Chen et al. 2012).

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Thus, for carriers of the homozygous –589CC genotype of the IL-4 gene, the anti-inflammatory activity of IL-4 decreased (Shevchenko 2015). In the present study, IL-4 and CRP production was increased in carriers of the –589TT genotype compared to the presence of other genotypes (P<0.05).

IL-10, which suppresses the production of pro-inflammatory cytokines and antigen-presenting functions of macrophages, serves as a cellular immunity inhibitor. The presence of G/G genotype of the G-1082A locus is related to the anti-inflammatory immunity activation (Chen et al. 2012). Detection of homozygous A/A genotype was associated with low IL-10 production (r=0.32, P=0.01), which led to prolonged preservation of an increased number of pro-inflammatory cytokines and an increased inflammatory process chronicity (Babu et al. 2012). The present study demonstrated IL-10 synthesis in carriers of homozygous –1082GG genotype.

The analysis of impact of genetic polymorphisms of pro- and anti-inflammatory cytokine genes in CHD pa-
patients without ARVI on the pharmacological response of Rosuvastatin at a dose of 10 mg/day revealed a weak direct correlation between the IL-1β and IL-6 levels (10.30 pg/ml and 12.40 pg/ml) and –511TT and –174GC genotypes, respectively (r=0.46, P=0.001) (Fig. 12).

Carriers of –511TT genotype were diagnosed with the lowest LDL-C level and a high HDL-C level (p<0.05), which confirmed the implementation of a hypolipidemic Rosuvastatin effect. Carriers of –511CC genotype had the increased LDL-C levels.

Carriership of homozygous –1082GG genotype demonstrated the association with the decreased CRP and the level of C (r=0.6, P=0.003), which confirmed the activation of anti-inflammatory processes in patients with chronic inflammation. When the anti-inflammatory cytokine (IL-4, IL-10) level increased, the C level decreased (r=0.47, P<0.05).

The analysis of correlation between pro-/anti-inflammatory cytokine gene genotypes revealed the activity of genotypes –511TT (IL-1β gene), –174CC (IL-6 gene), –589TT (IL-4 gene), and –1082GG (IL-10 gene) in maintaining chronic inflammation stability (r=0.46, P=0.012).

Thus, one can parallel the implementation of the anti-inflammatory Rosuvastatin effect in CHD patients with ARVI. The anti-inflammatory effect is due to genetic polymorphism of pro-/anti-inflammatory cytokine genes (Chen et al. 2012, Yu et al. 2012).

The obtained correlations contributed to the preparation of a personalized HLP pharmacotherapy algorithm in CHD patients in presence of ARVI (Fig.13).

Conclusion

1. A Personalized approach to HLP pharmacotherapy in CHD patients in presence of an acute infectious process proved the necessity of Rosuvastatin dose titration to 20 mg/day in order to reach the target LDL-C level in 27% of patients, who failed to responding to a 10 mg/day dose.

2. The presence of heterozygous –511CT genotype for –511C>T polymorphism of the IL-1β gene, homozygous –174GG genotype for –174G>C polymorphism of the IL-6 gene, and homozygous –1082AA genotype for polymorphism –1082G>A of the IL-10 gene did not lead to reaching the target LDL-C level in Rosuvastatin 10 mg/day monotherapy.

3. Carriership of these genotypes required pharmacotherapy with Rosuvastatin 20 mg/day to reach the target LDL-C level.

4. 33% of the studied patients who had higher levels of lipid transport system parameters at the moment of inclusion into the study did not reach the target LDL-C levels on HLP pharmacotherapy with Rosuvastatin 20 mg/day.

References

Author contributions

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