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STATINS IN ACUTE CORONARY SYNDROMES

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SUMMARY

This review article provides results of recent studies (ARMYDA, NAPLES II, MIRACL, ARMYDA-ACS, JUPITER, LUNAR) with the use of inhibitors of HMG CoA reductase (statins) in patients with acute coronary syndrome and patients undergoing percutaneous coronary intervention. Based on the results of these clinical and experimental studies, lipid-lowering, anti-inflammatory and various other pleiotropic effects of statin therapy in acute forms of coronary heart disease have been proved. Also, the authors presented the main results and conclusions on the studies conducted in our center to study the effect of statins on the stunned myocardium, reperfusion injury of the myocardium in acute myocardial infarction.

Keywords: *statins; pleiotropic effects; acute coronary syndrome, percutaneus coronary interventions*

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Acute coronary syndrome (ACS) is an urgent problem in the whole world including Uzbekistan. According to the World Health Organization, cardiovascular diseases (CVD) are the main cause for death and disablement of the population on our planet. ST-segment elevation myocardial infarction (STEMI) takes the leading place among CVD. In spite of advances in the treatment of CVD including appearance of many effective drugs, use of angioplasty and surgical methods of treatment in the clinical practice, CVD take away the lives of 17.3 mln people annually what is 30% of all lethal cases in the world and it is prognosticated that this figure will increase up to 23.6 mln by 2030 [7].

CVD account for 55.4% in the mortality structure in Russia. In 90% of cases, mortality from CVD is associated with coronary heart disease (CHD) and myocardial infarction and other forms of cardiovascular pathology are responsible for only 10%.

The increase of morbidity and mortality because of cardiovascular pathology is also observed in Uzbekistan over the last two decades with mortality structure not differing from that in the world. According to data of R.D. Kurbanov et al. [1], about 11% of the adult population suffers from CHD. According to statistics of the American Heart Association, morbidity with primary MI is 550 thousand, the annual number of relapses reaches 200 thousand

with lethality because of STEMI being 82.5 thousand (15%); out of them 41 thousand of patients die within the first hour after development of symptoms [14].

Inhibitors of HMG CoA reductase or statins have been widely used in cardiovascular diseases over the last two decades [4, 15]. Many clinical trials showed that decrease of low density lipoprotein (LDL) level in the patients with CVD resulted in improved exercise tolerance due to atherosclerotic plaque stabilization with a strong correlation existing between the LDL level and improved patients' clinical status. The administration of statins in the early period after percutaneous coronary interventions (PCI) and in acute coronary syndromes may lead to reduced number of cardiovascular complications [6, 8], **decreased lipid level** (by 50%) relative to the baseline values may protect against repeated ischemic events [6, 25].

Several effects of statins have been known until today: these include anti-inflammatory action, correction of endothelial dysfunction, reduction of oxidative stress and decreased rate of thrombogenic reactions [20]. These non-hypolipidemic effects are called "pleiotropic effects".

In spite of the fact that the positive effect of statins on the course and prognosis after ACS has been studied in sufficient details within the limits of numerous randomized studies, our objective was to unite the results of studies concerning antithrombotic, anti-inflammatory and other pleiotropic effects exerted by statins in the patients with ACS during the first week after development of acute coronary syndrome and percutaneous coronary intervention. This paper is a review of the foreign literature in Russian.

Pathophysiology of acute coronary syndrome and arterial damage response

Acute coronary syndrome is a generalized name of several clinical conditions including acute myocardial infarction with ST-segment elevation (STEMI), myocardial infarction without ST-segment elevation (NSTEMI) and unstable angina. These conditions are often caused by atherosclerotic plaque erosion and rupture which result in partial or complete coronary artery obstruction. This is associated with thrombocyte activation and thrombogenesis in the affected zone. Cell adhesion proteins including P-proteins, which are produced in addition to thrombocyte aggregation, also provide for leukocyte activation. Thrombocyte activation results in generation of vasoconstrictors such as serotonin and thromboxane A2 what in its turn leads to blood flow reduction. The release of other vasoactive substances of the extracellular matrix and tissue is also possible [28], and endothelial damage may reduce the quantity of endothelial NO-synthase and nitrogen oxide. All these factors reduce the coronary blood flow and favor thrombogenesis. The mechanisms, which are comparable with that in acute coronary syndrome, e.g., rapid thrombocyte accumulation and leukocyte involvement, may be used for arterial damage response caused by stenting or angioplasty.

Statin therapy before percutaneous coronary intervention

It is best to assess the efficiency of therapy of thrombosis in the patients who underwent percutaneous coronary intervention (coronary artery angioplasty and stenting). The arterial trauma in these patients occurs at a certain planned moment (during the intervention), what, in its turn, helps to investigate the effects exerted by statins on inflammation, thrombosis and complications.

In the ARMYDA (Atorvastatin for Reduction of Myocardial Damage During Angioplasty) study, statins were administered to 153 patients with stable angina pectoris, who did not receive statins before inclusion in the study, 7 days before planned PCI. The study investigated myocardial necrosis markers. The quantitative assay of creatine phosphokinase MB-fraction (CPK-MB), troponin and myoglobin was performed in 8 and 24 hours. The level at primary diagnosis of myocardial infarction (basing on increased CHK-MB level) after PCI was 5% in patient group receiving statins and 18% in placebo group ($p = 0.025$). The maximum CPK-MB, troponin and myoglobin level in the patients receiving stations was lower than that in placebo group ($p < 0.01$) [16]. Researchers studied the efficiency of the "loading" statin dose in the patients with stable angina pectoris. The percentage of primary mortality caused by MI or unexpected mortality was 3.7% in patient group receiving the loading Atorvastatin dose and 9.4% in placebo group ($p = 0.037$). Besides that, decrease of the biomarker levels in the patients receiving high doses of Atorvastatin was more significant than that in the patients receiving the usual statin dose [9]. Thus, preliminary therapy with Atorvastatin in the dose of 40 mg/day for 7 days reduced considerably procedural myocardium damages during PCI.

The NAPLES II (Novel Approaches for Preventing or Limiting Events) study (2005-2008) investigated potential advantages of a single dose of Atorvastatin administered to the patients 24 hours before the percutaneous coronary intervention. The rate of MI associated with PCI was 9.5% in Atorvastatin group and 15.8% in control group ($p = 0.014$) in a group of 668 subjects [5]. The single administration of Atorvastatin in the dose of 80 mg resulted in reduced risk of MI (by 44%).

The analysis of the results obtained in 14 clinical trials showed that the use of statins before the percutaneous coronary intervention may lead to reduced risk of MI associated with PCI procedure [4, 5, 6, 17].

Early clinical significance of statins in acute coronary syndrome

The MIRACL (Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering) study is the first clinical trial concerning the results of the treatment with statins at early stages of acute coronary syndrome [26]. The MIRACL study involved 2100 subjects who received high doses of Atorvastatin (80 mg) during 1-4 days of the disease. A group of subjects receiving placebo was formed for comparison. The primary death, symptoms of MI and symptomatic myocardial ischemia were observed in 14.8% of cases in Atorvastatin group and in 17.4% in placebo group over the period of 16 weeks after the disease. The MIRACL study demonstrated clinical significance of statins in acute coronary syndrome what was achieved by lowering the blood cholesterol level. The results of the MIRACL study are evidence of the fact that the patients with ACS should receive statins right up to discharge from the hospital irrespective of the baseline low density lipoprotein cholesterol level.

The efficiency of the therapy with statins in acute conditions was assessed in the ARMYDA-ACS (Atorvastatin for Reduction of Myocardial Damage during Angioplasty) study. Similar to the MIRACL study, it was also performed in the population consisting of 171 patients receiving high doses (80 mg) of Atorvastatin. The administration of statins started when symptoms of the disease developed but not earlier than 12 hours after the intervention. Major cardiac events (MACE) were observed in 5% of cases in Atorvastatin group and in 17% in placebo group. Significant decrease of myocardial necrosis biomarkers such as CPK-MB and troponin I was found in Atorvastatin group what indicated its clinical efficiency in the patients with ACS undergoing percutaneous coronary intervention [18].

The manual on the treatment of the patients with myocardial infarction with ST-segment elevation published by the European Society of Cardiology in 2017 recommends the blood LDL level of <1.8 mmol/l (70 mg/dl) for the patients with ACS. And if the

baseline level is 1.8-3.5 mmol/dl it is recommended to decrease it by 50%. Besides that, it is recommended to measure the blood lipoprotein level again in order to determine whether it reached the target level 4-6 weeks after acute coronary syndrome [11].

The effect of statins on thrombocyte and thrombosis biomarkers in early period after development of ACS and PCI

Severe clinical complications associated with acute coronary syndrome and percutaneous coronary intervention result from thrombosis. Myocardial infarction due to subclinical and microvascular thrombosis is revealed only basing on determination of cardiac biomarkers and the statin therapy started early may enhance the efficiency of the treatment. Thrombocyte activation is one of the basic mechanisms of arterial thrombosis in acute coronary syndrome and after PCI. It was shown that early statin therapy reduces thrombocyte activation, vascular damage, thromboxane A2 production and decreases granular secretion by 30% [13]. Besides that, statins can enhance additionally the anti-aggregation properties of Aspirin [12].

One of the first short-term in vivo studies to investigate the effect of statins on thrombocyte activity was performed in 30 patients with hypercholesterolemia and in 20 healthy volunteers of comparable age and sex. V. Sanguigni et al. [25] determined the levels of soluble CD40L, the substance reflecting thrombocyte activation, tumor necrosis factor and thrombin generation. The CD40L, sCD40L and prothrombin F1+2 content in the patients with hypercholesterolemia was significantly higher than that in the healthy volunteers. The patients with hypercholesterolemia were randomized in groups. Fifteen patients who received Atorvastatin in the dose of 10 mg/day with simultaneous keeping to a diet (group 1) showed decreased level of CD40L (from 46.3 to 32.2 ng/ml), sCD40L (from 4.1 to 3.0 ng/ml) fragments and prothrombin F1+2 (from 2.0 to 1.4 nmol/l). These parameters practically did not change in 3 days in the patients of control group who were treated only with diet. This study showed that excessive CD40L expression in thrombocytes in the patients with hypercholesterolemia could result in higher plasma sCD40L and F1+2 levels which increase the risk of thrombogenesis. Atorvastatin in the dose of 10 mg had a direct antithrombotic effect by inhibition of CD40L thrombocytes and CD40L-mediated thrombin generation irrespective of its cholesterol-lowering action.

The effect of statins, in particular Rosuvastatin, on CD40L was investigated by P. Pignatelli et al. [32] in subjects keeping to the Mediterranean diet. Blood samples were taken 2 and 24 hours after single administration of Rosuvastatin in the patients with hypercholesterolemia. Thrombocyte activation and changes in CD40L quantity were not revealed in 2 and 24 hours in the patients keeping only to the Mediterranean diet and thrombocyte mobilization in the patients decreased by 30% and CD40L thrombocyte number lowered by 36% 2 hours after administration of Rosuvastatin dose. These parameters decreased by the 24th hour of the treatment.

The studies are also published concerning effects of statins on the substances and markers favoring thrombin generation. A. Undas et al. [31] investigated thrombin generation in wounds which were caused by skin incision in the patients receiving Simvastatin (40 mg) in the case in vivo. The administration of statin for 3 days slowed down thrombin generation initially to 0.258 nmol/l/s and to 0.175 nmol/l/s in 3 days and decreased factor Va level.

In the study performed by E. Atalar et al. [3], the use of Fluvastatin in high doses (80 mg) within 6 hours after development of acute coronary syndrome favored decrease of soluble endothelial protein C receptor [EPCR] level, what, in its turn, evidenced lowered thrombin activation. The free tissue factor pathway inhibitor [ftFPI], which inhibits factor Xa, also lowered in both groups with this parameter being higher in Fluvastatin group: 450% in Fluvastatin group and 155% in placebo group. The direct effects of these inhibitors and their influence of receptors lower the activity of cascade components of the blood coagulation system. Some data is evidence of the fact that 10 mg of Atorvastatin administered to the patients with ACS lowered antithrombin III [29], factor V and von Willebrand factor. These results were confirmed by other scientists [27]. All these studies revealed decreased biomarker level of blood coagulation cascade in patients with hypercholesterolemia suffering from ACS.

The effect of statin on venous thrombosis

The decrease of venous thromboembolism (pulmonary embolism and deep vein thrombosis) frequency is possible thanks to antithrombotic action of statins. The patients with increased C-reactive protein level and normal low density lipoprotein level were randomized in groups in the JUPITER study. The repeated investigation of the patients receiving Rosuvastatin in the dose of 20 mg/day revealed lower frequency of venous thromboembolism due to decreased thrombocyte aggregation activity [23].

Early effect of statins on inflammation

Some studies confirmed that statins could be used for several weeks or years to reduce inflammation. The above JUPITER study followed up the patients with increased C-reactive protein level and normal low density lipoprotein level [23]. The repeated investigations revealed that these parameter values were lower in the patients receiving Rosuvastatin than that in the subjects of placebo group.

A.C. Sposita et al. [27] found that statin lowered C-reactive protein level and this lowering depended on the doses received by the patient within 24 hours after onset of myocardial infarction. In the study performed by these authors, the patients were divided in 5 groups: patients not receiving statin; patients receiving statin in the dose of 20 mg, 40 mg, 80 mg per day and those who started to take statin in the dose of 80 mg/day 48 hours after onset of myocardial infarction. All patients continued to take statin in the initial dose for 7 days and were switched over to intake of Simvastatin in the dose of 20 mg/day from day 7. On the second day of the treatment, the patients who started to use statin earlier had significantly lower C-reactive protein level than the patients who began to take statin late. The dose-dependent effect of statins o the C-reactive protein level was found: so, the lower C-reactive protein level was reached when high statin doses were administered [23].

The effect of statins of lipid level in the patients with ACS

The LUNAR study performed comparative assessment of the effect of Rosuvastatin and Atorvastatin on LDL cholesterol level in the patients with ACS. 825 patients with acute coronary syndrome were randomized within 48 hours after development of the first symptoms for the treatment with Rosuvastatin in the dose of 20 mg, Rosuvastatin in the dose of 40 mg or Atorvastatin in the dose of 80 mg daily for 12 weeks. The repeated investigation was performed in 2, 6 and 12 weeks. The treatment efficiency regarding averaged lowering of LDL cholesterol level in 6 and 12 weeks was the primary endpoint. Besides that, changes in other lipoprotein levels including high density lipoprotein (HDL) cholesterol and also treatment safety were assessed too.

Rosuvastatin in the dose of 40 mg lowered LDL cholesterol level more effectively than Atorvastatin in the dose of 80 mg (by 46.8% and 42.7%, respectively; p=0.02). The decrease of LDL cholesterol

Table. Main randomized clinical trials with early administration of statins in ACS

Trial title, authors	Investigational drug	Clinical condition	Efficiency	Duration
ARMYDA	Atorvastatin	Stable angina pectoris, PCI	CPK-MB, troponin, myoglobin	7 days
ARMYDA-ACS	Atorvastatin	ACS, PCI	MACE, CPK-MB, troponin	12 days
NAPLES	Atorvastatin	PCI	CPK-MB, troponin	24 h
LUNAR	Rosuvastatin	ACS	Lipid profile	2, 6 and 12 weeks
MIRACL	Atorvastatin	ACS	Death, repeated MI	16 weeks
Sanguni et al.	Atorvastatin	Hypercholesterolemia	CD40L, sCD40L, F1+2	3 days
Undas et al.	Simvastatin	Hypercholesterolemia	Thrombin generation	3 days
Alyavi A.L., Kenjaev S.R. et al.	Atorvastatin	ACS	Myocardial stunning	3 days

level caused by administration of Rosuvastatin in the dose of 20 mg/day was equal to that observed in the patients receiving Atorvastatin in the dose of 80 mg/day. The HDL cholesterol level in the patients receiving Rosuvastatinin the doses of 40 and 20 mg confidently increased to a greater extent (by 11.9%, $p<0.001$ and by 9.7%, $p<0.01$, respectively) than when Atorvastatin in the dose of 80 mg was used (by 5.6%).

Rosuvastatin in the dose of 40 mg also proved to be confidently more effective than Atorvastatin in the dose of 80 mg regarding enhancement of pleiotropic effects while the action of Rusivastatin in the dose of 20 mg on these parameters were, as a rule, similar to that of Atorvastatin in the dose of 80 mg. The patients usually tolerated well all three therapeutic regimens for 12 weeks. The results obtained in the LUNAR study showed that Rosuvastatin in the dose of 40 mg/day administered to the patients with acute coronary syndrome lowered LDL cholesterol level, increased HDL cholesterol level and improved other parameters of blood lipids more effectively than Atorvastatin in the dose of 80 mg/day [20].

The effect of statins on reperfusion myocardial damage and myocardial stunning

Today scientists focused on investigation of the effect exerted by statins on reperfusion myocardial damage (myocardial stunning is one of its manifestations), systolic left ventricular dysfunction in acute myocardial infarction. In particular, A.L. Alyavi, S.R. Kenjaev et al. studied the effect of the high dose of Atorvastatin on myocardial stunning in 164 patients with acute coronary syndrome with ST-segment elevation with myocardial reperfusion in acute period at the Republican Scientific Center of Emergency Medicine. The patients were divided in two groups: the patients of group 1 received Atorvastatin in the dose of 20 mg/day on day 1 of the disease and group 2 received it in the dose of 80 mg/day. The patients were randomized by the "symptom – reperfusion" time, sex, age, clinical and anamnestic data and reperfusion method.

Stress-echocardiography with administration of Dobutamin in low doses was performed in the patients after condition stabilization in order to reveal myocardial stunning zones. The obtained results showed that the myocardial contractile function increased in 4.2±0.16 left ventricular segments in the patients receiving 80 mg of Atorvastatin and in 3.88±0.14 segments in the patients of group 2. The use of Atorvastatin in the high dose in acute coronary syndrome with ST-segment elevation reduced the degree of reperfusion damage and necrosis formation and favors the development of reversible myocardial dysfunction (myocardial stunning) zones [2].

Thus, as the literature analysis has shown, early administration of high statin doses in patients with acute coronary syndrome with ST-segment elevation has anti-inflammatory, antithrombotic, pleiotropic effects thereby improving treatment results. Besides that, early use of statins before percutaneous coronary interventions may enhance their efficiency and reduce the risk of complications.

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