Use of Lipid-Modulating Drugs in Complicated Course of Coronary Heart Disease

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We present the results of the study of lipid-modulating drugs (pravastatin, atorvastatin, simvastatin, and fibrate gemfibrozil) in complicated coronary heart disease (acute coronary syndrome without *ST* elevation, chronic heart failure. In acute coronary syndrome statins produced a positive effect on some studied parameters, while in heart failure only the safety of short-term therapy with statins was demonstrated.

Key Words: *coronary heart disease; statins; acute coronary syndrome; inflammation; heart failure*

The deseases associated with atherosclerotic involvement of vessels, first of all, coronary arteries, rank first among mortality causes in developed countries. A large contribution into mortality and disability is made by acute coronary syndromes (ACS) and heart failure determined by progression of coronary heart disease (CHD). Prevention of complication of this pathology is an urgent problem of cardiology. Studies performed during the last decade showed that among a wide variety of preparations, only limited number of drugs substantively prevent coronary events and, more important, reduce overall mortality: acetylsalicylic acid, β-adrenoceptor blockers, inhibitors of angiotensin-converting enzyme, and hypolipidemic drugs, especially statins. The latter are effective in both primary and secondary prophylactics. It should be noted that their efficiency was proven against the background of treatment with other above-listed active preparations. The efficiency of these preparations is higher in high-risk patients. In this context we hypothesized that the use of these preparations during CHD complications or exacerbations can be associated with maximum clinical effect.

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Atherosclerotic plaque rupture leading to ACS development occurs primarily in vulnerable plaques characterized by the presence of a large lipid core with high cholesterol (CH) content and thinned cap with high content of inflammation cells and reduced content of collagen and smooth muscle cells. Moreover, an important role in destabilization of the plaque is played by local predisposition to vasospastic reaction due to endothelial dysfunction. At last, an important role in the development of ACS after plaque rupture is played by activity of platelets and procoagulant activity of the blood [15].

However, despite introduction of new potent antiplatelet agents and anticoagulants, the incidence of unfavorable outcomes in ACS is still high. Thus, along with the search for new antithrombotic preparations, interventions aimed at suppression of destabilization processes in the atherosclerotic plaque are of crucial importance. However, now patient has to take 4-5 drugs simultaneously and further increase in their number can lead to unpredictable interactions and side effects.

A possible solution of this problem is the use of 3-hydroxy-3-methyl-glutaryl coenzyme A reductase inhibitors (statins) widely prescribed in chronic CHD. Statins produce a number of so-called "nonlipid" or pleiotropic effects potentially modulating the main elements of CHD pathogenesis. They pos-

sess anti-inflammatory activity, normalize endothelium-dependent vascular reaction, and to a certain extent reduce prothrombotic activity of the blood [9].

There are no unambiguous data on the effect of statins during CHD exacerbation (especially starting from day 1 of CHD exacerbation). Despite positive results of some wide-scale trials with statins in ACS (PROVE IT, MIRACL) [18], this approach is doubted by some authorities. Theoretically, the positive pleiotropic effects of statins observed during the chronic course of CHD can be unfavorable during exacerbation. Moreover, it is not quite clear, whether the choice of the dose of statins can be guided by the level of lipids, because this parameter considerably decreases during ACS. Finally, it remains unclear whether statins with pronounced and moderate hypolipidemic activity in equivalent doses produce similar nonlipid effects and whether peiotropic effects of statins depend of their dose. On the other hand, the results of PACT [19], ATOZ [10], and meta-analysis of all trials on early treatment with stains in CHD published in the middle of 2006 cast doubts on the efficiency of this approach.

Some recent published data suggest that some other hypolipidemic interventions can stabilize the atherosclerotic plaque. For instance, experiments showed that agonists of PRAR (nuclear peroxisome-proliferator activated receptor), *e.g.* well-known hypolipidemic drugs fibrates, produce an antiinflammatory effect on vulnerable plaque [14]. It was hypothesized that the so-called nonlipid, or pleiotropic effects of statins and the effects of PPAR agonists (in particular, fibrates) can be mediated through the same mechanisms [16]. Gemfibrozil was chosen because it is best studied and its beneficial effect in secondary prophylactics of CHD was proven [17].

The data on the use of statins in patients with severe heart failure caused by CHD are scanty [11]. Some meta-analyses and epidemiological studied showed that low CH levels in circulatory insufficiency are associated with poor prognosis [8]. It is not clear in this case, whether the decreased lipid level is the cause or reflects grave state of the patient? Some pilot studies, primarily with atorvastatin or rosuvastatin, demonstrated the positive effects of statins on surrogate end-points in this group of patients [13]. We found no relevant data on the use of simvastatin in this clinical situation, although this statin is most widely used in our country. Moreover, simvastatin is best studied in many trials with definite end-points, in particular, in experiments with reduction of the total mortality in high-risk patients [12].

The effects of hypolipidemic drugs, primarily statins, in patients with complicated CHD are studies in the Laboratory of Clinical Cardiology (Institute of Physicochemical Medicine) since 1996.

The aim of this study was to evaluate the effects of lipid-lowering preparations in no-*ST*-elevation ACS (ACS_{NE}) under conditions of combined antithrombotic therapy and in chronic heart failure resulting from CHD.

MATERIALS AND METHODS

The ACS_{NE} group (Table 1) included men and postmenopausal women receiving no hormone-replacement therapy with ACS without stable ST elevation on day 1 after the development of anginal attack, which was the cause of hospitalization. Patients with secondary ACS (with acute heart failure, arrhythmias, severe anemias, *etc.*), with pronounced dyslipidemias, and patients regularly receiving statins were not included in the study. Other exclusion criteria routinely used in controlled clinical trials were also used.

The group of patients with congestive heart failure against the background of chronic CHD (Table 1) comprised men and postmenopausal women receiving no hormone-replacement therapy with evident CHD and clinical signs of circulatory insufficiency (NYHA functional class II-IV) and left-ventricular disfunction (ejection fraction<35%). This group did not include patients with recent ACS, receiving statins, and patients with evident systemic inflammation.

In series I, we evaluated the effect of short-term course of pravastatin in ACS_{NE} by changes in inflammatory markers, parameters of hemostasis, and heart rhythm variability and compared them with the hypolipidemic effects of the test drug. Pravastatin is one of the best clinically studied statins. Moreover, there are convincing experimental data that pravasatin produces more pronounced pleiotropic (nonlipid) effects compared to other statins. This is why pravastatin also served as the reference drug in series II. In series II, we compared the effects of short-term course of pravastatin and atorvastatin in various doses in ACS_{NE} by changes in inflammatory markers and parameters of hemostasis and compared them with the hypolipidemic effects of the test drugs. In series III, we studied the effect of early treatment with PPAR-α agonist gemfibrozil on inflammatory markers and parameters of hemostasis in ACS_{NE}. In series IV we evaluated the effect of simvastatin on inflammatory markers and markers of circulatory insufficiency in patients with chronic heart failure against the background of CHD.

TABLE 1. Groups of Patients

Parameter	Series								
	I			II		III		IV	
	control	pravastatin, up to 60 mg	atorvastatin, 10 mg	atorvastatin, 40 mg	pravastatin, 40 mg	control	gemfibrozil, 1200 mg	control	simvastatin, 40 mg
Number of patients	20	20	30	29	31	21	21	31	32
Men, %	85	90	52	43	58	53	47	81	78
Age, years	56.2±7.8	49.4±9.0*	64.6±10.6	65.1±9.2	61.5±10.0	69.9±11.4	77.8±15.7	65.5±9.2	65.8±8.7
Arterial hypertension, %	65	70	79	83	87	48	76	77	78
Diabetes mellitus, %	10	0	16	13	10	10	14	45	41
Smokers, %	60	55	17	20	16	33	19	68	56
Myocardial infarction, %	20	5	35	33	33	25	30	87	94
Total CH, mmol/liter	5.7±1.2	6.2±1.1	5.8±1.3	5.7±1.2	5.6±1.2	5.7±1.0	5.9±1.4	5.3±1.2	5.4±1.1
TG, mmol/liter	2.1±1.3	2.1±1.2	1.5±1.3	1.4±0.9	1.3±1.0	1.4±0.6	1.4±0.8	1.4±0.9	1.4±0.6
HDL CH, mmol/liter	0.9±0.2	1.0±0.3	1.2±0.3	1.1±0.3	1.1±0.3	1.0±0.3	1.0±0.3	0.9±0.3	0.9±0.2
LDL CH, mmol/liter	3.8±0.9	4.2±0.9	3.9±1.0	4.0±1.1	3.8±1.1	4.1±0.9	4.3±1.3	3.8±1.0	3.9±1.0
vWF, %	55.7±9.7	58.1±11.6	45±11	50±10	49±9	50.7±9.9	50.4±11.0	29.4±4.7	28.5±5.7

Note. *$p<0.05$ for differences between groups in one series.

In series I, pravastatin was given *per os* in doses of 20-60 mg/day depending on the initial level of LDL CH for 3 months. In series II, the patients received atorvastatin (the most potent statin) for 2 weeks; hypolipidemic activity of 10 mg atorvastatin is equivalent to that of 40 mg pravastatin. For evaluation of the efficiency and safety of aggressive hypolipidemic intervention in comparison with more moderate lipid-lowering therapy, we used atorvastatin in a dose of 40 mg. In series III, gemfibrozil (1200 mg/day, 3 months) was used as an alternative hypolipidemic intervention, because it is the only fibrate with proven clinical efficiency in secondary prophylactics of CHD.

In series IV, simvastatin (40 mg/day, 4 months) was chosen for the therapy of patients with heart failure, because this preparation, apart from proven efficiency, is most widely used and (which is of no small importance) available in our country.

Statistical processing of clinical end-points was not performed because of low number of patients. Changes in markers of inflammation and hemostasis in relation to changes in blood lipids were used as surrogate end-points. Blood lipids were measured routinely, LDL CH content was calculated.

The effect of the studied preparations on inflammatory component was evaluated using highly sensitive tests for C-reactive protein (C-RP) as the best studied prognostic marker. Serum amyloid A, IL-6, and soluble CD40 ligand served as additional indexes of inflammation. In patients with heart failure, the levels of TNF-α and N-terminal pro-brain natriuretic peptide were also measured for objectivization of the severity of their status. These parameters were measured in accordance with international recommendations. For exclusion of patients with inflammatory disease, a semiquantitative screening test for elevated C-RP was performed during the first visit (except series I).

In some patients, fibrinogen (parameter of antithrombotic activity and an acute-phase protein) and von Willebrand factor (vWF, factor reflecting the state of platelets and endothelial function) were measured. Published data suggest that statins and fibrates affect these parameters in chronic states.

In some patients, spontaneous and ADP-induced platelet aggregation was evaluated on a Biola laser analyzer by two methods: by light-transmission curve (after Born) and by measuring the mean size of aggregates.

For exclusion of subjective influences, the studied parameters in frozen blood were simultaneously measured by an independent investigator, who did not know randomization codes.

Treatment with high doses of statins was controlled by targeted questioning on myalgias and repeated measurements of liver enzymes (ALT, AST) and creatine phosphokinase.

RESULTS

In series I, the level of LDL CH considerably decreased against the background of pravastatin treatment as soon as on days 4-7, the maximum decrease was observed on day 14 (by 34% on average, Fig. 1, *a*). Total CH decreased at all terms of the study, the maximum decrease (-23%, $p<0.05$) was also observed on day 14. In 15 patients receiving pravastatin, the desired level of LDL was attained on days 4-30, while in controls demonstrating a tendency to LDL decrease this parameter on day 14 decreased by 12% in only 5 patients. Changes in triglyceride (TG) and HDL content in the experimental group were insignificant, while in

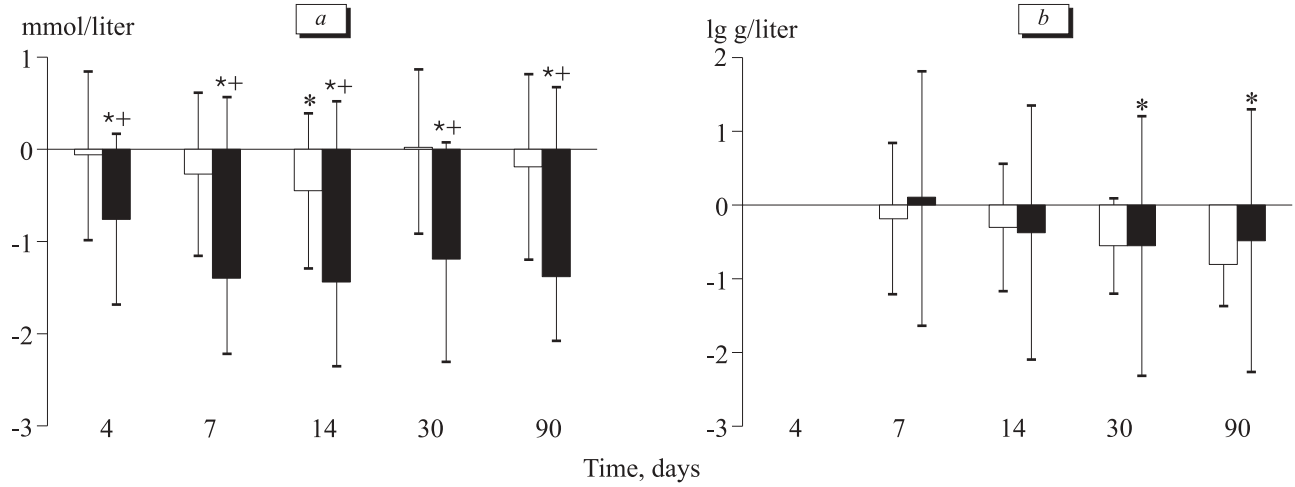

Fig. 1. Changes in LDL CH (*a*) and C-RP (*b*) in series I. Light bars: control ($n=13$), dark bars: pravastatin ($n=10$). $^{*}p<0.05$ compared to initial values, $^{+}p<0.05$ compared to the control.

the control group the content of TG significantly increased on days 4-7 and starting from day 14 this parameter did not differ from the initial level [1].

After driving C-RP and serum amyloid A values to a normal distribution by taking the logarithm, the content of C-RP significantly decreased compared to the initial level on days 30 and 90 only in the pravastatin group. Figure 1 shows changes in the level of C-RP only for patients, for whom these data were obtained. When comparing the changes in serum amyloid A content in both groups from the initial level by parametric methods, no reliable differences were found.

No significant changes in spontaneous and ADP-induced (2.5 μmol) aggregation of platelets from the initial levels were observed in both groups; the groups also did not significantly differ by these parameters. Only analysis of platelet aggregation induced by 5 μmol ADP showed that in the control group the tendency to activation of platelet aggregation became significant by some parameters on days 14 and 30 [2]. None cases of myalgia were noted during the 3-month observation period; creatine phosphokinase activity did not surpass the normal by more than 3-fold. Two patients (experimental group) were excluded from the study because of increased transaminase activity and skin rash. One patient receiving pravastatin died of acute myocardial infarction on day 13.

Potent and rapid hypolipidemic effect of pravastatin was not associated with deterioration of the clinical course of the disease. Bicycle ergometry revealed a tendency to improvement of exercise tolerance in the group receiving pravastatin compared to the control group. Heart rhythm variability parameters were also higher in the experimental group, however, the difference from the control group was insignificant. Only on day 7 of treatment, the low-frequency range power was higher than in the control [3].

Thus, the use of pravastatin in medium and high doses during the most acute phase of unstable angina pectoris in patients with normal and moderately elevated LDL CH led to a rapid decrease in total CH and LDL CH, which attained maximum on day 14. In the experimental group, the level of LDL CH was lowered to the target level 100 mg/dl in 15 of 20 cases within one month. This pronounced hypolipidemic effect was not accompanied by significant changes in spontaneous and ADP-induced platelet aggregation.

In series II, total CH and LDL CH significantly decreased on day 7 of statin treatment in all groups and by day 14 this decrease was even more pronounced. As was expected, treatment with 40 mg/day atorvastatin led to more pronounced decrease in total CH and LDL CH compared to 10 mg/day atorvastatin and 40 mg/day pravastatin ($p<0.05$ for days 7 and 14). By day 7, the relative decrease in total CH was 15, 20, and 12% and LDL CH was 22, 26, and 20% in groups receiving 10 and 40 mg/day atorvastatin and 40 mg/day pravastatin, respectively. By day 14, total CH in groups receiving 10 and 40 mg/day atorvastatin and 40 mg/day pravastatin decreased by 23, 31, and 17% and LDL CH decreased by 33, 41, and 23%, respectively. HDL CH also significantly decreased in all three groups by day 7 and remained low to day 14 ($p<0.01$); no significant differences between groups were noted throughout the observation period. In all three groups, TG level significantly increased compared to the initial level by day 7. A tendency to TG decrease was noted by day 14. The difference from the initial level became insignificant in patients receiving atorvastatin in both doses, but remained significant in patients receiving pravastatin.

Patients refusing statin therapy, patients taking anti-inflammatory drugs throughout the observation period, and patients with acute inflammatory diseases (respiratory infection, phlebitis) were excluded from the analysis before measuring inflammation markers: 7 patients from the group receiving 10 mg atorvastatin, 6 patients from the group receiving 40 mg atorvastatin, and 6 patients from the group receiving 10 mg pravastatin.

The mean initial values of C-RP were similar in all three groups (5.90, 8.04 and 4.83 mg/liter for groups receiving 10 and 40 mg/day atorvastatin and pravastatin, respectively). Analysis of the dynamics of C-RP content revealed no significant changes in this parameter, although it tended to increase in the pravastatin group and to decrease in atorvastatin group by day 14 of the study. When two atorvastatin groups were united, the decrease in C-RP content became significant (by 18% on day 14). No significant differences in the level of C-RP between the united atorvastatin group and pravastatin group were revealed at all terms of the experiment. No relationship between the decrease in blood lipid content and C-RP concentration were found.

The distribution of IL-6 levels differed from normal, and therefore these data were analyzed using nonparametric methods. Visual differences between the groups in the initial medians of IL-6 levels were statistically insignificant. The level of IL-6 did not change during the 14-day period, while treatment with atorvastatin in low and medium doses led to a minor decrease in this parameter by days 14 and 7, respectively. No significant changes in IL-6 level were found after uniting the two atorvastatin groups [4].

In patients receiving pravastatin, plasma level of the thrombin–antithrombin complex (TAT) decreased on day 7 and 14 by 10.17% ($p<0.01$) and 17% ($p<0.01$) from the initial level, respectively (Fig. 2). The content of thrombin 1+2 fragment decreased by 3.5% ($p<0.05$) on day 14, as well as the level of D-dimer (14% from the initial level, $p<0.01$). The level of vWF significantly increased by 6.95% from the initial value on day 7, but on day 14 the difference from the initial value became statistically insignificant (Fig. 2, *b*).

In patients receiving atorvastatin, the dynamics of these parameters was opposite to that in the pravastatin group. The level of TAT in patients receiving 10 mg/day atorvastatin increased on days 7 and 14 by 8% ($\delta<0.05$) and 13% ($\delta<0.01$), respectively, and in patients receiving 40 mg/day by 12 ($p<0.01$) and 16%, respectively, (Fig. 2, *c*). The increase in this parameter on day 14 was also significant in comparison with day 7 ($p<0.05$ for 10 mg/day and $p<0.01$ for 40 mg/day).

The level of prothrombin 1+2 fragment significantly increased on day 7 and remained at this level until day 14 in both atorvastatin subgroups (Fig. 2, *a*). On days 7 and 14, this parameter increased by 19.6% ($p<0.01$) and 19.1% ($p<0.01$) from the initial level in patients receiving 10 mg/day, and by 23.3% ($p<0.01$) and 23.8% ($p<0.01$) in patients receiving 40 mg/day, respectively.

The level of D-dimmer increased on day 7 (Fig. 2, *d*), but this increase was significant only in the subgroup receiving 10 mg/day atorvastatin (56%, $p<0.01$ compared to the initial level). On day 14, the level of D-dimmer did not significantly differ from the control in both subgroups.

The level of vWF decreased; this decrease was more pronounced in the subgroup receiving 40 mg/day atorvastatin. On days 7 and 14, vWF level

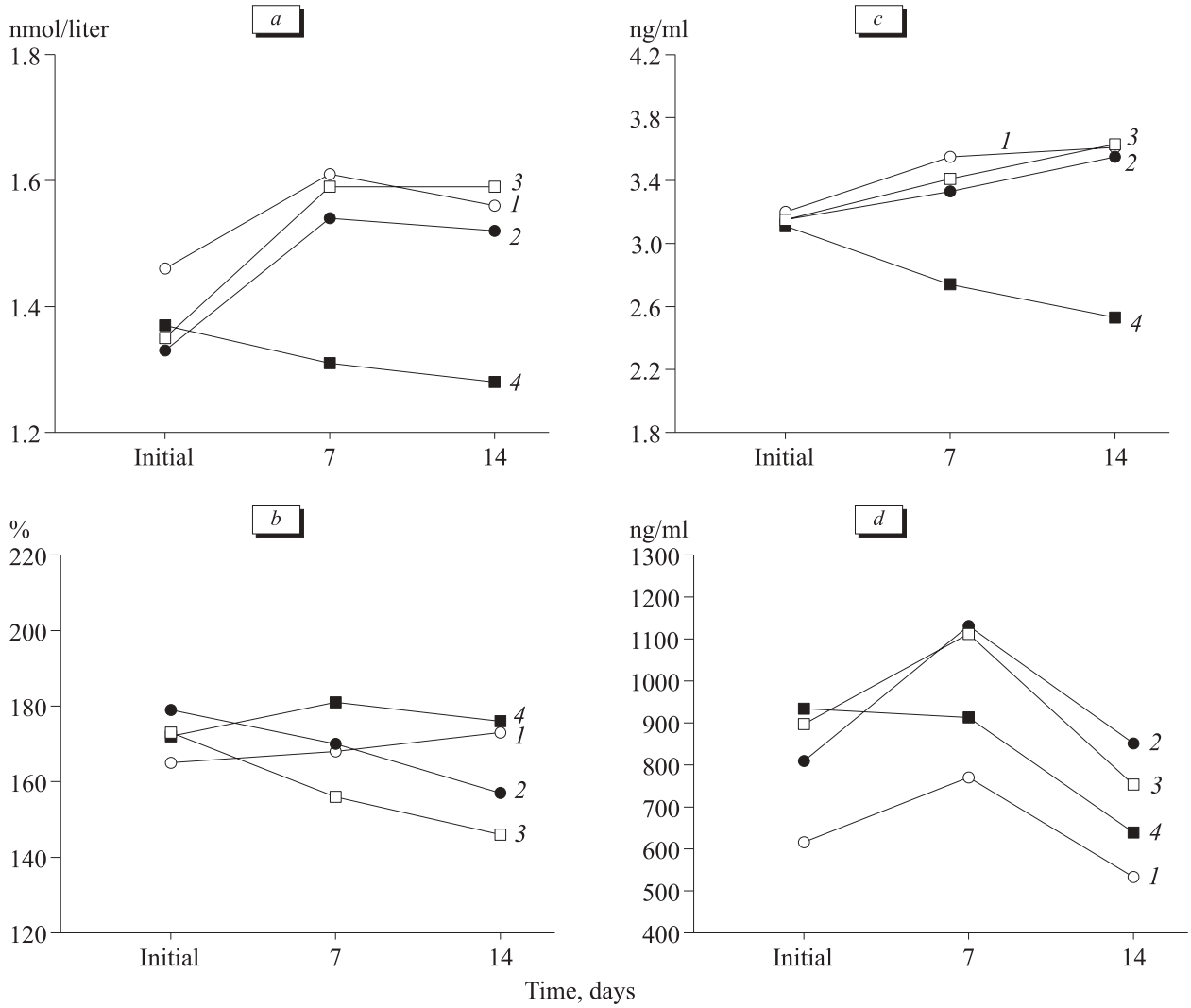

Fig. 2. Parameters of hemostasis in series II. *a*) prothrombin 1+2 fragment, *b*) vWF, *c*) TAT, *d*) D-dimer. *1*) control, *2*) atorvastatin, 10 mg, *3*) atorvastatin, 40 mg, *4*) pravastatin, 40 mg.

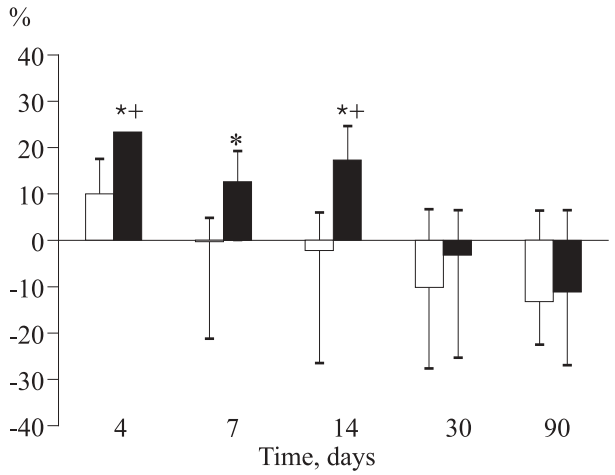

Fig. 3. Changes in vWF level in series III. Light bars: control, dark bars: gemfibrozil. *$p<0.05$ compared to initial values, $^{+}p<0.05$ compared to the control.

decreased by 4.4% ($p<0.01$) and 8.3% ($p<0.01$) in patients receiving 10 mg/day, and by 12% ($p<0.01$) and 16% ($p<0.01$) in patients receiving 40 mg/day, respectively. The decrease in this parameter on day 14 compared to day 7 was also significant ($p<0.01$ for both groups).

On days 7 and 14, the level of TAT significantly increased compared to the initial level by 14% ($p<0.05$) and 16.79% ($p<0.01$), respectively. The content of prothrombin 1+2 fragment significantly increased by 13.7 and 11% from the initial level on days 7 and 14, respectively. The initial level of D dimmer in the control group was lower that in the experimental group probably because of lower number of patients with high creatine phosphokinase activity (11% compared to 31% in each experimental group). The level of D dimmer significantly increased by 37.6% on day 7, but slightly decreased by 7% on day 14 compared to the initial value. The levels of vWF on days 7 and 14 did not differ from the initial values [5].

In patients of the experimental groups we found a weak, but significant direct correlation between changes in vWF and total CH ($r=0.25$, $p=0.018$) and between vWF and LDL CH ($r=0.23$, $p=0.032$). Quartile analysis showed that on day 14 vWF significantly ($p=0.021$) decreased in patients with maximum decrease in LDL CH ($n=20$) and remained unchanged in patients with minimum decrease in this parameter ($n=21$). Similarly, vWF significantly ($p=0.0056$) decreased in patients with maximum decrease in total CH and remained unchanged in patients with minimum decrease in this parameter. A weak, but significant inverse correlation was found between the levels of TAT and total CH ($r=-0.22$, $p=0.039$). Quartile analysis revealed no significant relationship between the levels of TAT and total CH [6].

In series III, the levels of total CH and LDL CH moderately decreased in the experimental group starting from days 7-14, the level of TG markedly decreased on days 30-90, and the level of HDL CH moderately decreased during the first few days of treatment and then did not differ from the initial value. In the control group, the content of TG considerably increased and the content of HDL CH decreased on days 7-14. None lipid parameters differed from the initial values in the control group on days 30-90.

Treatment with gemfibrozil in ACS had practically no effect on the studied markers of inflammation: C-RP measured using a highly sensitive test and the content of soluble CD40 ligand. Since the distribution of C-RP values differed from normal, we found the logarithm of experimental points and after verification of normal distribution the data were analyzed using parametric methods. The marker tended to decrease in both groups, but in the control group the decrease in C-RP level was observed only on day 30, while in the experimental group this decrease remained significant on days 30 and 90 after randomization. In both groups, the content of soluble CD40 ligand significantly increased starting from day 7. No significant intergroup differences were noted.

vWF in the control group significantly increased during the first week of ACS, but then decreased (Fig. 3). In the gemfibrozil group, the increase in vWF level was more pronounced. This parameter surpassed the initial value and the corresponding parameter in the reference group on days 4-14 of therapy. But then the difference from the control and initial values disappeared (Fig. 3).

In none cases gemfibrozil therapy of ACS starting from the first days in hospital was accompanied by elevation of creatine phosphokinase activity by more than 10 times compared to the normal level or stable elevation of liver transaminases by more than 3 times. The increase in ALT activity by more than 2 times compared to the normal was noted in 4 patients from the control group and in 1 patient from the experimental group (single increase, the drug was not discontinued). In one patient gemfibrozil was discontinued on day 3 because of diarrhea. Statistical analysis of clinical outcomes was not performed because of low number of patients.

In series IV, 5 patients dropped out during the first month of the study. Two patients in each group were excluded because of refusal or violation of the treatment regimen, one patient from the control group was excluded because of acute cerebral cir-

TABLE 2. Biochemical and Echocardiographic Parameters in Series IV (*M*±*m*)

Parameter	Control		Simvastatin	
	initial	after 4 months	initial	after 4 months
Total CH, mmol/liter	5.3±1.2	5.4±0.9	5.4±1.1	3.8±0.9^{+}
TG, mmol/liter	1.41±0.90	1.33±0.50	1.4±0.6	1.1±0.4^{++}
HDL CH, mmol/liter	0.9±0.3	1.03±0.30^{+}	0.9±0.2	1.05±0.24^{+}
LDL CH, mmol/liter	3.8±1.0	3.7±0.9	3.9±1.0	2.2±0.8^{+}
C-RP, mg/liter*	4.3 (1.9; 6.8)	2.5 (1.5; 5.5)	1.6 (0.9; 3.6)	0.9 (0.5; 2.7)
TNF-α*	0.7 (0.5; 1.5)	0.7 (0.5; 1.1)	1.0 (0.7; 1.3)	0.9 (0.4; 1.8)
End-diastolic volume, cm^3*	189 (161; 218)	173 (148; 226)	190 (162; 222)	183 (151; 214)
End-systolic volume, cm^3*	137 (117; 147)	120^{+} (91; 154)	133 (115; 165)	117^{+} (98; 144)
vWF, %	29.4±4.7	33.5±4.0^{+}	28.5±5.7	34.2±5.0^{+}
Maximum early diastolic filling rate (E), m/sec	0.7±0.2	0.6±0.2	0.7±0.2	0.6±0.2
Maximum atrium contraction rate (A), m/sec	0.7±0.3	0.8±0.2	0.7±0.3	0.7±0.2^{++}
E/A*	0.8 (0.7; 1.4)	0.8 (0.7; 1.0)	1.0 (0.7; 1.9)	0.8^{++} (0.7; 1.1)

Note. *Data are presented as medians and 25-75 percentiles. $^{+}p<0.001$, $^{++}p<0.05$ compared to initial values.

culation disorders. After 2 months, 2 patients from the statin group dropped out: 1 patient was excluded because she needed electrocardioversion for atrial flutter and 1 patient refused repeated testing after ophthalmologic surgery.

The final analysis comprised 63 patients: 32 patients from the experimental group and 31 controls.

One month after treatment, the patients receiving simvastatin had lower level of LDL CH, which persisted to the end of the experiment. After 4 months, LDL CH in the experimental group decreased by 42% from the initial level. In the control group this parameter little changed (Table 2). The level of LDL CH below 2.6 mmol/liter after 1 and 4 months of simvastatin therapy was attained in 21 (65.5%) and 23 (72%) patients, respectively. Similar changes were observed for CH and TG: these parameters significantly decreased in the experimental group (by 30 and 14%, respectively, after 4 months) and remained unchanged in the control group. The level of HDL CH significantly increased in all patients [7].

Thus, short-term treatment with statins in addition to the standard therapy on day 1 of ACS development was accompanied by pronounced hypolipidemic effect starting from days 4-7 of treatment. This effect was clearly seen despite "acute" decrease of LDL CH typical of ACS. Moreover, we observed a decrease in the content of typical inflammatory marker C-RP during the first 14-30 days of therapy. The use of fibrates (gemfibrozil) was also associated with a decrease in lipid levels, but at later terms, and was not accompanied by C-RP changes. Moreover, we observed negative changes in vWF content.

In patients with moderate and severe chronic heart failure, short-term treatment with simvastatin in a dose of 40 mg in addition to standard therapy considerably decreased lipid levels and C-RP content in the blood. These changes were not accompanied by echocardiographic characteristics of the functional state of the left ventricle compared to the control.

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