COMPARISON OF PLASMA COAGULABILITY AFTER SHORT-TERM TREATMENT WITH ROSUVASTATIN VERSUS ATORVASTATIN IN UNSTABLE ANGINA PATIENTS

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ABSTRACT

Statins are the integral medications for the management of patients with acute coronary syndrome including unstable angina (UA) with multiple pleiotropic effects. However, the influence of statins on the coagulation system is controversial. Our study aimed to explore the effects of atorvastatin and rosuvastatin in high doses on some coagulation parameters (prothrombin pool (PP) and soluble fibrin-monomer complexes (SFMC) concentration) after a 7-days follow-up period in patients with UA. We recruited 50 patients aged 55 to 70 years with progressive UA. Standard therapy according to ESC guidelines 2020 was recommended for all patients. Before treatment onset, they were divided into 2 groups: group A – 26 patients were prescribed atorvastatin, group R – 24 patients with rosuvastatin treatment. The blood samples to analyze the concentration of PP and SFMC were collected twice – before the treatment onset and 7 days after. We revealed significant decrease in PP concentration (p=0,02) and increase in SFMC concentration (p=0,01) in group A patients while there were no significant changes of investigated parameters (p=0,94, p=0,57 respectively) in group R. Additionally, we have noted significant negative correlation between baseline PP concentration and direction of PP changes (r=-0,803, p<0,001) as well as PP changes direction and SFMC concentration after treatment (r=-0,655, p<0,001). Thus, we may consider that atorvastatin and rosuvastatin are characterized by different influences on coagulation in patients with progressive UA with standard basic treatment. The rebound coagulation system activation after anticoagulant discontinuation is more pronounced in UA patients against a background of atorvastatin treatment in comparison with rosuvastatin.

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Introduction. Statins (3-hydroxy-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors) are considered a cornerstone in prevention and treatment of atherosclerosis and its complications [1, 2], as it was shown that this group of medicines reduces the risk of major vascular events [3] as well as cardiovascular and all-cause mortality [4].

While the enormous targeted investigations were performed to analyze the data regarding the direct pharmacological hypolipidemic mechanism of statins [5], the plethora of statins' pleiotropic effects was revealed [6]. Most of them are explained by the anti-inflammatory properties of statins [7]. Thus, statins adjust two main pathogenetic mechanisms of coronary artery disease progression, particularly dyslipoproteinemia and inflammation. It was found that even short-term treatment with statins influence on coronary heart disease, which is of high importance regarding the management of patients with acute coronary syndrome [8].

Far less attention is paid to the influence of statins onto the hemostasis, though the latter imbalance occupies a fitting first place especially in case of coronary artery disease destabilization, when atherothrombosis occurs [2].

Traditionally, acute cardiovascular events are reckoned to be connected tightly with the formation of platelet-rich thrombi. But the insufficient effect of even double antiplatelet therapy and finally results of autopsy findings with fibrin-rich thrombi that cause myocardial infarction suggest the underestimated role of the coagulation with thrombin as the central enzyme [9] and its precursor prothrombin. Consequently, it stands to reason that anticoagulants are mandatory medicines for the management of patients with acute coronary syndrome [2]. Soluble fibrin monomer complex (SFMC) which is famous for its diagnostic potential in patients with myocardial infarction and unstable angina (UA) [10] is one of the coagulation cascade intermediate products with further fibrin polymer formation as the direct way to thrombosis occurrence [11].

Ancillary effects of statins on the coagulation system were described in several reviews but with a note about rather controversial results of studies. There is some data about the influence of statins on thrombin and fibrin [12, 13].

Thus, the main target of our study was to investigate whether the difference between statins regarding changes in blood plasma coagulability exists. Among all types of statin, it was chosen atorvastatin and rosuvastatin as the most widely used representatives of this group which vary in their lipophilicity, elimination half-life, potency, and the mevalonic acid pathway influence [14]. For this purpose, we have analyzed 2 parameters: SFMC and prothrombin pool (PP) which reflects the concentration of all molecules with epitopes of prothrombin origin [15]. A 7-days follow-up period (36 hours after anticoagulant withdrawal) was of high interest for us as just at this time the risk of thrombotic events increases.

Materials and Methods. In our prospective observational study, we recruited 50 patients aged between 55 and 70 years old (19 females (38%)) which were hospitalized to the cardiology department with an established diagnosis of progressive unstable angina. Also, we included only those patients who had not been taking statins for at least 3 months (mainly, because of low compliance with treatment).

The protocol of the study was approved by the Research Ethics Committee of the Bogomolets National Medical University. The patients gave written consent to participate after the explanation of the survey design.

All patients received conservative standardized treatment according to the current ESC Clinical Practice Guidelines [2], particularly anticoagulant (enoxaparin 1 mg/kg twice daily 3 days, 0,5 mg/kg twice daily 2 days subcutaneously**),** acetylsalicylic acid (ASA) 75 mg once daily, clopidogrel 75 mg once daily, bisoprolol in dosage depending on heart rate (HR) and blood pressure (BP) once daily, angiotensin-converting enzyme inhibitor (ACEi) (enalapril/ramipril/perindopril in individual dosage), nitrates in infusion once daily and 20 mg in tablets twice daily, pantoprazole 20 mg once daily. But depending on statin therapy which was prescribed the patients we formed 2 groups. The patients of group A have been treated with atorvastatin 60 mg per day, while the patients of group R were recommended rosuvastatin 20 mg per day. Such a dosage is believed to be equivalent to these medicines [16]. The follow-up period was 7 days.

The exclusion criteria were conditions with a possible thrombophilic state such as heart defects, persistent atrial fibrillation / atrial flutter, cardiomyopathies, non-ischemic myocardial injuries, heart failure IIB-III stage, endocrinological disorders, active infection, chronic diseases in the period of exacerbation, blood diseases including coagulopathies, anemia of II-III stage, glomerular filtration rate less than 60 ml/min./1,73 m2, hepatic dysfunction, malignancy, traumas, and bleedings within 6 months before this study, myocardial infarction or stroke within 1 year before this survey.

Immediately after admission the patients passed the general clinical examination with anamnesis gathering, ECG at rest registration, qualitative troponin I test.

If according to the preliminary information the patient met inclusion criteria we collected blood samples for hemostatic parameters under investigation (PP, SFMC) before initiation of treatment. We controlled above mentioned hemostatic parameter after 7 days of treatment (36 hours after enoxaparin discontinuation). Blood samples were taken by phlebotomy in sodium citrate, centrifugated, aliquoted, and frozen until use. We determined SFMCs concentration by colorimetric orthophenanthroline method. We used ELISA immune assays with primary and secondary antibodies following the manufacturer's instructions (Santa Crus Biotechnology, CA, USA) to evaluate PP concentration.

Also, we performed echocardiography as well as a basic routine blood analysis set (hepatic and renal panel, complete blood count, lipidogram) and hs-Troponin I test.

We used SPSS (version 22, IBM Corp, USA) for data analysis. Test for normality was provided with the Shapiro Wilk test. We presented numerical data as the median with interquartile range (Me(IQR)), while nominal variables were reported in absolute values (percentage) and compared by using the chi-squared test ($\chi 2$). We used the Mann-Whitney (U) test for unpaired samples and the Wilcoxon test (W) for paired samples to weigh the differences between numerical variables. The correlation between variables was examined with the use of Pearson or Spearman correlation depending on the type of variables. P-value <0,05 was considered statistically significant.

Results. In our survey we included 50 patients (age 66,0 (60,0-67,0) years, 19 females (38,0%)) with progressive UA. In general, both groups are comparable, and some peculiarities of the investigated population are reported in further tables.

Baseline characteristics of patients are presented in table 1. There was no significant difference between groups including preliminary treatment. The latter is rather important while taking into account multiple indirect influences of medicines onto coagulation. Relatively low compliance with the treatment should be mentioned in recruited patients.

Table 1. Baseline characteristics of patients

Parameter	Group A	Group R	p
Age, years	63,0(60,0-67,3)	66,0 (64,0-67,0)	0,39
Females, n (%)	8 (42,1)	11 (57,9)	0,27
BMI, kg/m^2,	30,6 (27,2-32,7)	28,3 (26,7-30,0)	0,06
Preliminary treatment			
RAASi, n (%)	18 (69,2)	19 (79,2)	0,07
Diuretic, n (%)	6 (23,1)	7 (29,2)	0,75
CCB, n (%)	2 (7,7)	2 (8,3)	0,89
β-blocker, n (%)	13 (50,0)	14 (58,3)	0,14
ASA, n (%)	8 (30,8)	11 (45,8)	0,38
Nitrate, n (%)	2 (7,7)	5 (20,8)	0,23
BMI – body mass index; RAASi – inhibitor of renin angiotensin aldosterone system; CCB – calcium channel blocker, ASA – acetylsalicylic acid			

Table 2 represents 3 main groups of criteria according to which the diagnosis was established, particularly clinical features, biochemical marker (hs-cTn) and ECG changes while admission. Though in general two groups are consistent, hs-cTn concentration tends to be higher in group R.

Table 2. Diagnostic criteria of unstable angina among the groups

Parameter	Group A	Group R	p
Complaints while admission			
Typical pain, n (%)	16 (61,5)	17 (70,8)	0,12
Atypical pain, n (%)	6 (23,0)	6 (25,0)	0,72
Dyspnoe (equivalent), n (%)	2 (7,7)	1 (4,2)	0,24
hs-cTn, pg/ml	21,95 (17,72-28,62)	27,00 (22,25-30,95)	0,08
HR, beats/min.	76,0 (70,0-83,0)	72,0 (70,0-78,0)	0,17
ST-segment depression, n (%)	16 (61,5)	20 (83,3)	0,09
T wave variability, n (%)	15 (57,7)	17 (70,8)	0,38
New-onset LBBB, n (%)	2 (7,7)	0	0,49
hs-cTn – high sensitive cardiac troponin; HR – heart rate; LBBB – left bundle branch block			

Chest pain was the prevailing complaint in observed patients (90,0%). 33 patients (66%) suffered from typical retrosternal pain which was provoked by minimal physical exertion or even at rest, others described the discomfort in cardiac region (6, (12,0%)), in scapular region (6, (12,0%)), dyspnoe as the only possible equivalent of pain (3 (6%)) or just general fatigue which occurs suddenly (2 (4%)). Other additional complaints included dyspnoe (70,4%), palpitation (59,8%), headache (40,5%), dizziness (40,8%). In general, regarding complaints the groups were comparable.

The results of basic biochemical tests, echocardiography and BP while admission are demonstrated in table 3. Lipidogram parameters of both groups patients were above recommended targeted levels for high-risk patients while other biochemical characteristics were within normal ranges.

Table 3. General baseline laboratory and instrumental characteristics

Parameter	Group A	Group R	p
TC, mM/L	6,03 (4,85-6,82)	4,99 (4,57-6,61)	0,16
LDL-C, mM/L	3,45 (2,19-4,66)	3,02 (2,62-3,35)	0,11
HDL-C, mM/L	1,20 (1,07-1,67)	1,42 (0,97-1,84)	0,64
TGs, mM/L	2,27 (1,60-2,83)	1,97 (1,26-2,27)	0,08
ALT, IU/L	0,75 (0,65-0,92)	0,75 (0,65-0,83)	0,19
AST, IU/L	0,60 (0,50-0,70)	0,55 (0,50-0,64)	0,45
GFR, mL/min/1,73 m^2	60,0 (47,0-81,0)	59,5 (45,0-71,0)	0,55
Glucose, mM/L	4,8 (3,9-5,8)	5,0 (4,3-5,6)	0,38
WBC, $x10^9$/L	7,8 (6,8-8,2)	7,8 (5,8-9,6)	0,53
RBC, $x10^{12}$/L	5,0 (4,5-5,3)	4,8 (4,3-5,1)	0,13
Hb, g/L	145,0 (132,0-148,0)	138,0 (133,0-146,0)	0,17
Platelets, $x10^9$/L	256,0 (201,0-292,0)	243,5 (170,0-384,0)	0,94
EDV, mL	118,0 (109,0-129,0)	113,0 (100,0-121,0)	0,34
ESV, mL	43,2 (33,7-68,0)	42,0 (39,0-63,0)	0,54
IVS, mm	1,21 (1,11-1,40)	1,21 (1,10-1,24)	0,32
EF, %	55,5 (50,0-61,0)	61,0 (55,2-63,0)	0,14
sBP, mmHg	150,0 (140,0-160,0)	147,5 (120,0-160,0)	0,91
dBP, mmHg	90,0 (82,0-92,5)	86,0 (80,0-93,0)	0,52

TC – total cholesterol; LDL-C – low-density lipoprotein cholesterol; HDL-C – high-density lipoprotein cholesterol; TGs – triglycerides; ALT – alanine transaminase; AST – aspartate transaminase; GFR – glomerular filtration rate; WBC – white blood cells; RBC – red blood cells; Hb – hemoglobin; EDV – end-diastolic volume; ESV – end-systolic volume; IVS – interventricular septum; EF- ejection fraction; sBP – systolic blood pressure; dBP – diastolic blood pressure

The investigated patients were characterized by hypertensive left ventricular hypertrophy with preserved ejection fraction. Also, while admission the normal blood pressure was registered only in 6 patients (12%).

To sum up all above-mentioned the groups were comparable by main characteristics.

The dynamic changes of investigated hemostatic parameters are shown in table 4.

Table 4. The concentration of prothrombin pool (PP) and soluble fibrin-monomer complexes (SFMC) before the treatment and after 7 days follow-up period

Variable	Group A n=26			Group R n=24			$p^{\S}$	$p^{\#}$
	Before	After	p*	Before	After	p*		
PP, rel.units/mL	0,163 (0,158-0,175)	0,158 (0,151-0,164)	0,02	0,166 (0,158-0,178)	0,168 (0,157-0,174)	0,94	0,62	0,001
SFMC, µg/mL	15,5 (10,0-17,0)	18,0 (15,8-21,0)	0,01	19,0 (15,0-22,5)	18,5 (16,0-22,7)	0,57	0,01	0,31

PP – prothrombin pool; SFMC – soluble fibrin monomer complexes; before – at baseline; after – after 7-days follow-up period; * - paired-test (W) in each group as compared to baseline; § - p of intergroup comparison at baseline (unpaired U-test); # - p of intergroup comparison after follow-up period (unpaired U-test)

Before treatment PP concentration did not significantly differ between groups in contrast to SFMC concentration which was higher in group R. The same baseline trend was regarding hs-cTn concentration. However, after treatment, we registered the opposite relationship between the investigated parameters of groups. Thus, while the SFMC's concentration between groups was compatible, the PP concentration in group R was significantly higher than in group A. At the same time there were no significant changes of PP (-0,59 (-2,46-2,90)%) and SFMCs (-0,36 (-19,6-8,6)%) concentration in group R unlike group A in which we noted significant decrease in PP concentration by 4,9% (-4,9(-10,8-1,84)%) and increase in SFMC concentration by 10,8 (2,7-21,3)%.

We have noticed intragroup differences in direction of changes that are presented in Table 5. A percentage of SFMC changes with the upward direction was significantly higher in group A. Meanwhile, no significant difference was noted in group R, though the downward trend of PP concentration in group A was in 65,4% of patients.

Table 5. Peculiarities of coagulation parameters changes among

Variable	Group A		Group R		p
	Decrease, n (% of group)	Increase, n (% of group)	Decrease, n (% of group)	Increase, n (% of group)	
PP, rel.units/mL	17 (65,4)	9 (34,6)	13 (54,2)	11 (45,8)	0,42
SFMC, μg/mL	5 (19,2)	21 (80,8)	12 (50,0)	12 (50,0)	0,02

Finally, we have checked correlations between investigated parameters in observed groups. In terms of group A it was found strong negative correlation between PP concentration before treatment and direction of PP changes (r=-0,803, p<0,001), direct correlation of mild strength between PP and SFMC concentrations before treatment (r=0,626, p=0,001) as well as concentrations of PP before treatment and SFMC after (r=0,447, p=0,02). Also, negative relations of mild strength were noticed between PP changes direction and SFMC before treatment (r=-0,530, p=0,005) as well as after (r=-0,655, p<0,001).

In the group R we have noticed direct correlation between PP concentration before and after treatment (r=0,912, p<0,001) as well as SFMC concentration before and after (r=0,746, p<0,001). Though there were no significant relations between PP and SFMC concentrations before and after treatment, we have noted indirect relations between directions of PP and SFMC concentration changes (r=-0,585, p=0,003).

Discussion. The results of our study confirm several statements regarding statins' influence on organism and drug-drug relations, however, with some practical supplement.

Currently, there is no doubt in the short-term positive effects of high-dose statin therapy on the course of ACS. Zhi-Jian Liu et al. reported a significant decrease in high sensitive C reactive protein and malonaldehyde as markers of inflammation and oxidative stress respectively in patients with acute myocardial infarction and successful primary percutaneous coronary intervention received high-dose atorvastatin therapy in comparison with moderate after only 7 days follow-up period [17].

However, as far as we know almost no data is regarding the effects of statins on blood plasma coagulability after a short follow-up period as most investigators have described the data regarding a more prolonged period of statins' treatment. In general, it was mentioned that a decrease in thrombin generation is highly suggestive [18], especially in patients with hypercholesterolemia [19]. Tonu S. et al. registered a significant increase in prothrombin time after 8 weeks of treatment with atorvastatin and rosuvastatin in low doses [20]. Fenton et al. found out that simvastatin downregulated thrombin generation as prothrombin fragments F1+F2 in the blood plasma of type 2 diabetes patients were lowering after the treatment period [21]. On the other hand, it was reported no influence of statin on thrombin generation in patients with ACS [22].

The data regarding statins' influence on fibrinogen concentration as the source of SFMC are not less controversial. However, predominantly it was shown the impaired fibrinogen cleavage, decrease the amount of fibrinopertides after statin treatment, changes of fibrin clot characteristics [12].

In our study, we have registered a significant decrease in PP concentration and an increase in SFMC concentration in patients with progressive unstable angina after 7 days atorvastatin course unlike in patients after the rosuvastatin course no significant changes of both parameters were noted.

At first glance, a decrease in PP concentration is considered to be a good prognostic sign. However, an increase in SFMC concentration is supposed to be a marker of increased risk of thrombotic complications. We presume such condition may be connected with the "exhaustion" of PP after intensified coagulation with the active formation of SFMC. Such a decrease in coagulation potency may be in consequence of rebound thrombin generation after anticoagulant discontinuation [23].

The negative correlation between PP concentration before treatment and direction of PP changes as well as the positive relation between the concentration of PP before and SFMC after treatment come in support of our assumption.

In terms of rosuvastatin, a few peculiarities should be defined. Some pleiotropic effects of statins are supposed to be connected with the nonsterol isoprenoid pathway. It was shown the reduced expression of ubiquinone, dolichol synthesis, and protein prenylation pathway in recombinant yeast strain with human HMGR by atorvastatin whereas rosuvastatin caused diverse effects (expression of BTS1, COQ3, RER2 and downregulation of COQ2, CAT5, SEC59) [14]. Such finding direct to the possibility of intragroup distinctions between accessory effects of statins.

Another point that should be mentioned is drug interactions between clopidogrel as medicine for double antiplatelet therapy and statins. While rosuvastatin is transformed by CYP2C9, clopidogrel and atorvastatin are metabolized by CYP3A4 isoenzyme of cytochrome P450 (CYP) [24]. The latter peculiarity of atorvastatin may cause an increase in major adverse thrombotic events [25]. The observed trend in the rosuvastatin group may be connected with either the above-mentioned facts.

We are inclined to qualify the absence of dynamic in group R after enoxaparin withdrawal as a better trend than a decrease in PP along with an increase in SFMC concentration.

Conclusions.

1. Statins are characterized by different influences on coagulation in patients with UA.
2. The rebound thrombin generation after enoxaparin discontinuation is less marked in UA patients against a background of rosuvastatin treatment in comparison with atorvastatin.
3. Rosuvastatin should be preferable to atorvastatin for patients with unstable angina if there was no previous statin treatment.

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Declaration of Interest Statement. None

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