

DOSE-DEPENDENT EFFECT OF STATINS ON THE PASSAGE OF CHD AMONG PATIENTS AFTER PRIMARY MYOCARDIAL INFARCTION

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Cardiovascular diseases remain the leading cause of death in the adult population. Treatment of patients with coronary heart disease (CHD) is crucial, as it is necessary to achieve a reduction in mortality. In recent decades, a number of scientifically based provisions have been adopted that have led to an improved prognosis for this category of patients, but acute myocardial infarction (AMI) remains one of the leading causes of death worldwide [1, 2].

Prevention of recurrent cardiovascular events in patients who have suffered from acute ST-segment elevation myocardial infarction (STEMI) is an important part of the treatment process and is associated with improved prognosis. Those who underwent the first event - they remain at an increased risk for a recurrent cardiovascular event, such as recurrent myocardial infarction, life-threatening arrhythmias, angina attacks, and death [3, 4].

According to modern clinical guidelines, patients after STEMI should be prescribed with double antiplatelet therapy, angiotensin converting enzyme inhibitors or angiotensin II receptor blockers, beta-blockers and statins. Recommendations of the European society of cardiology emphasize that statin therapy should be started or continued for all patients with AMI, if there are no contraindications to their use [5].

According to the results of studies, the target level of low-density lipoprotein cholesterol (LDL-C) was determined to be less than 1.81 mmol/l (70 mg/dL) in patients with AMI. Maintaining this level reduces the risk of recurrent cardiovascular events in patients after AMI. Therefore, currently, patients with AMI, regardless of whether or not interventional therapy, are recommended to prescribe statins at the highest possible dose, followed by titration of the dose to an effective one, which allows maintaining the target level of LDL-C [6].

Currently, the importance of achieving the target level of LDL-C in patients after AMI is at the forefront. However, a number of studies has shown that it is more important to reach this target level, rather than the hypolipidemic therapy regimen that allows this to be achieved. It was demonstrated that if stationary moderate intensity to adequately reduce LDL-C to recommended values, then the prognostic use of this therapy in reducing the risk of cardiovascular events like appointment as high dose. Also, the safety of using statins in maximum doses remains an extremely important issue, since it is often the cause of insufficient adherence of patients to treatment. Thus, although several extensive studies have been conducted to determine the optimal timing of statin therapy initiation and their clinical preferences, the administration of high doses of statins remains debatable. On the one hand, studies have established a dose-dependent effect on the course of CHD in patients after STEMI, and on the other hand, this advantage of high doses of statins should be weighed against side effects and the cost of treatment. All of the above determined the purpose of this study [7, 8].

The aim of the study was to determine the dose-dependent effect of statins on the course of CHD in patients after primary myocardial infarction.

Materials and methods. The results of the study are based on data from a comprehensive survey of 186 patients with STEMI. The sample of patients was conducted in the period from 2015 to January 2018 on the basis of the MI

“Regional medical center of cardiovascular diseases” of the Zaporizhzhia regional Council. All patients included in the study were taken to the hospital before 12 hours from the start of STEMI.

Criteria for inclusion in the study: male and female patients from 46 to 75 years of age; for women postmenopausal period is more than 1 year; presence of STEMI in the first 12 hours from the onset of the disease; informed consent of the patient to participate in the study.

Criteria for exclusion from the study: atrioventricular block of II-III degree; permanent form of atrial fibrillation; detection of congenital and acquired hemodynamically significant heart defects; III stage of chronic heart failure; detected left ventricular aneurysm; decompensated concomitant pathology; acute inflammatory diseases or exacerbation of chronic ones; history of coronary artery bypass grafting; oncological diseases.

All patients underwent a comprehensive clinical, instrumental and laboratory examination. AMI diagnosis verification was performed based on the ESC/ACCF/AHA/WHF Third universal definition of myocardial infarction (2012), taking into account the recommendations of the ESC Fourth universal definition of myocardial infarction (2018) [9, 10]. Distribution of patients into groups was performed depending on the statin dose:

- the first group included 131 patients with STEMI (median age 58.0 [52.0 ; 64.0] years) who used an middle-dose of statin;

- in the second group, there were 55 patients with STEMI (median age 60.0 [54.0 ; 65.0] years) who used a high-dose of statin.

All the patients had been collected blood samples for determination of CPK-MB and troponin I at the first contact. All patients underwent a lipidogram during screening and after 12 months. Total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol, and triglyceride (TG) levels were determined. The safety of statin treatment was determined by the level of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) during screening and in dynamics.

Treatment of patients. Patients were treated according to current European recommendations for the treatment of patients with STEMI. In the group of patients with STEMI, the following therapy was performed: a combination of systemic thrombolytic therapy (TLT) and stent implantation was performed in 45 (24.2 %) patients, systemic TLT was performed in 45 (24.2 %) patients, stent implantation - 89 (47.8 %) and 7 individuals (3.8 %) underwent conservative treatment. Further treatment of patients was performed using antiplatelet agents, selective beta-blockers, and ACE inhibitors. Statin was prescribed at an average dose of 103 (55.3 %) patients atorvastatin (Torvacard, Zentiva) 40 mg or rosuvastatin (Rosuward, Zentiva) 20 mg 1 time per day 28 (15.1 %) patients, taking into account the level of LDL-C in a high dose was prescribed 37 (19.9 %) patients atorvastatin 80 mg or rosuvastatin 40 mg inside 1 time per day 18 (9.7 %) patients. The cardiovascular event including a condition that required emergency medical attention: repeated myocardial infarction, ventricular tachycardia, angina attack.

Statistical processing of the obtained results. Statistical processing of the received data was performed on a personal electronic computer using the PSpP application software package (version 1.0.1, GNU Project, 1998-2017, GNU GPL license) and Apache OpenOffice (version 4.1, GNU GPL license). The obtained data are presented as the median and interquartile range of IU [Q25 ; Q75]. When testing statistical hypotheses, the null hypothesis was rejected at a level of statistical significance (p) below 0.05.

The processing of quantitative data was carried out by nonparametric or parametric methods depending on the distribution of the sample. The student's criterion (t -criterion) was used for parametric distribution: odd - for comparing independent samples and paired - for studying the dynamics of indicators within the group. Nonparametric methods were used for distribution other than

normal if two independent samples were compared, the Mann-Whitney method (U-criterion) was used, and the Wilcoxon method (W-criterion) was used to estimate dynamic changes within groups.

For dichotomous division of variables, ROC analysis (Receiver Operating Characteristic curve analysis) was used. We calculated the area under the ROC curve (AUC - Area under the ROC curve), the model was considered reliable when the AUC value is more than 0.5. The cut-off point was found using the J-Youden index.

The relative risk (RR, Relative Risk and its 95% confidence interval) was calculated using table 2x2 as the ratio of the frequency of cases among patients exposed to the studied factor to the frequency of cases among subjects who were not affected by this factor. The 95 % CI RR value that did not intersect 1 was considered reliable.

Results. Baseline characteristics for patients with STEMI included: age, sex, body mass index (BMI), the level of creatinine phosphokinase-myocardial band (CPK-MB) and cardiac troponin I (cTnI), the calculated left ventricle ejection fraction (LVEF) using Simpson's method. The data obtained is presented in table 1.

Table 1. Baseline characteristics for patients with STEMI

Characteristics	All patients (n = 186)	Middle-dose group (n = 131)	High-dose group (n = 55)
Age (years)	59,00 [52,00 ; 64,00]	58,00 [52,00 ; 64,00]	60,00 [54,00 ; 65,00]
Male:female	146:40	104:27	42:13
BMI (kg/m ²)	27,38 [24,80 ; 30,47]	27,06 [24,45 ; 30,44]	28,38 [25,83 ; 31,16]
CPK-MB (U/l)	40,43 [22,26 ; 82,90]	41,80 [22,04 ; 84,27]	38,16 [22,46 ; 82,43]
cTnI (ng/ml)	3,83 [0,87 ; 6,77]	4,43 [0,85 ; 6,80]	2,55 [0,90 ; 6,77]
LVEF (%)	55,04 [50,60 ; 61,70]	56,40 [51,10 ; 62,00]	53,69 [50,30 ; 60,33]

The number of patients with STEMI was 186, the middle-dose group included 131 patients, and the high-dose group - 55 patients. All the surveyed individuals were comparable in age and social status. The ratio of men to women was 4 to 1.

The *body mass index* value in the middle-dose group was 27.06 [24.45 ; 30.44] kg/m² versus 28.38 [25.83 ; 31.16] kg/m² in the high-dose group and had no significant difference ($p > 0.05$). CPK-MB and cTnI levels had no statistically significant difference between the patient groups ($p > 0.05$). The median LVEF in the middle-dose group was 56.40 [51.10 ; 62.00] % and was comparable to 53.69 [50.30 ; 60.33] % in the high-dose group ($p > 0.05$).

The lipid profile, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were determined during screening and after 12 months of treatment. The data obtained is shown in table 2.

During screening, the TC level in the high-dose group was 5.58 [4.78 ; 6.45] mmol/l and was significantly higher than the value of 4.99 [4.12 ; 5.83] mmol/l in the middle-dose group, ($p < 0.05$). After 12 months of combined therapy in both groups, the level of this indicator significantly decreased, respectively, to 4.34 [3.72 ; 4.86] mmol/l in the middle-dose group, and to 4.14 [3.74 ; 5.04] mmol/l in the second group, ($p < 0.05$). The values of TC after treatment were comparable, but the decline dynamics was significantly greater in the high-dose group by $\Delta_{12}\% = -26.49\%$ versus $\Delta_{12}\% = -15.84\%$ in the middle-dose group, ($p < 0.05$).

At the beginning of the observation, the HDL-C level was compared between the first and second groups of 1.27 [1.04 ; 1.46] mmol/l and 1.19 [1.02 ; 1.47] mmol/l, respectively, ($p > 0.05$). There were no statistically significant differences in this indicator after 12 months of follow-up between groups of 1.32 [1.11 ; 1.48] mmol/l

in the first group versus 1.31 [1.17 ; 1.58] mmol/l in the high-dose group, ($p > 0.05$). However, the increase in HDL-C was quite strong at $\Delta_{12}\% = +8.94\%$ in the high-dose group versus $\Delta_{12}\% = +5.41\%$ in the middle-dose group, ($p < 0.05$).

During screening, the LDL-C level in the high-dose group was 3.48 [2.69 ; 4.49] mmol/l and was significantly higher than the value of 3.03 [2.10; 3.62] mmol/l in the middle-dose group, ($p < 0.05$). The decrease in LDL-C after 12 months in the group of patients who used statin at an average dose was $\Delta_{12}\% = -29.15\%$ and was significantly less than the value of $\Delta_{12}\% = -50.54\%$ in the high-dose group, ($p < 0.05$). The values of this indicator after 12 months of treatment were comparable and amounted to 2.29 [1.78 ; 2.73] mmol/l in the first group and 1.80 [1.78 ; 2.86] mmol/l in the second group ($p > 0.05$).

Table 2. Changes in the lipid profile, AST and ALT among patients under the influence of treatment (Me [25 ; 75], n = 186)

Variable	Group	Screening	After 12 months	$\Delta_{12}\%$
TC (mmol/l)	Middle-dose group (n = 131)	4,99 [4,12 ; 5,83]	4,34 [3,72 ; 4,86]*	-15,84 [-20,18 ; -8,23]
	High-dose group (n = 55)	5,58 [4,78 ; 6,45]	4,14 [3,74 ; 5,04]*	-26,49 [-38,32 ; -21,60]
	p-	p = 0,008	p = 0,73	p < 0,05
HDL-C (mmol/l)	Middle-dose group (n = 131)	1,27 [1,04 ; 1,46]	1,32 [1,11 ; 1,48]*	5,41 [3,40 ; 7,69]
	High-dose group (n = 55)	1,19 [1,02 ; 1,47]	1,31 [1,17 ; 1,58]*	8,94 [7,20 ; 12,50]
	p	p = 0,85	p = 0,35	p < 0,05
LDL-C (mmol/l)	Middle-dose group (n = 131)	3,03 [2,10 ; 3,62]	2,29 [1,78 ; 2,73]*	-29,15 [-35,81 ; -17,70]
	High-dose group (n = 55)	3,48 [2,69 ; 4,49]	1,80 [1,78 ; 2,86]*	-50,54 [-70,22 ; -37,46]
	p	p = 0,004	p = 0,95	p < 0,05
TG (mmol/l)	Middle-dose group (n = 131)	1,41 [1,04 ; 2,05]	1,29 [0,97 ; 1,86]*	-9,09 [-13,43 ; -6,11]
	High-dose group (n = 55)	1,61 [1,17 ; 2,01]	1,42 [1,06 ; 1,74]*	-12,64 [-18,18 ; -9,30]
	p	p = 0,57	p = 0,97	p < 0,05
AST (U/l)	Middle-dose group (n = 131)	26,70 [16,47 ; 48,70]	23,35 [15,15 ; 41,43]*	-14,94 [-22,40 ; -6,98]
	High-dose group (n = 55)	33,10 [21,99 ; 54,92]	27,96 [20,59 ; 42,12]*	-14,43 [-25,43 ; -6,12]
	p	p = 0,16	p = 0,15	p = 0,25
ALT (U/l)	Middle-dose group (n = 131)	30,96 [19,70 ; 57,60]	27,16 [17,96 ; 45,40]*	-18,90 [-28,19 ; -11,35]
	High-dose group (n = 55)	26,90 [19,50 ; 39,05]	24,20 [19,37 ; 33,41]*	-11,83 [-19,75 ; -7,52]
	p	p = 0,11	p = 0,28	p = 0,008

Note. * - an indicator of the reliability of changes in dynamics.

The level of TG during screening was comparable between the groups ($p > 0.05$). There was a significant decrease by $\Delta_{12}\% = -9.09\%$ in the middle-dose group, while the decrease in the high-dose group by $\Delta_{12}\% = -12.64\%$ was significantly stronger ($p < 0.05$).

Analysis of the individual response to statin therapy showed that in the combination therapy group with an average statin dose of 131 patients, 49 people (37.7 %) reached the target LDL-C level of less than 1.81 mmol/l, while in the second group of 55 patients, there were significantly more of them - 30 (54.5%), ($p < 0.05$).

We have not registered any serious side effects from the use of statins by patients in both groups. However, there was an increase in hepatic transaminases in 5 (3.8 %) individuals and in the second group in 4 (7.3 %) patients, and it was not statistically significant between the groups ($p > 0.05$). At the same time, there was no increase in the level that would exceed the threshold value by three or more times, which did not require dose adjustment.

Then, using two data sets: the first patient who had an event ($n = 28$) and the second patient who did not have an event ($n = 158$), we performed ROC analysis and calculated the relative risk. The results are presented in table 3.

Table 3. The relative risk of occurrence for event among patients with STEMI

Variable	AUC	Sensitivity	Specificity	RR	95 % CI RR
Male/female	0,61	96,43	24,68	7.397	1.037 - 52.783
CPK-MB >73,98 (U/l)	0,60	46,43	74,05	2.119	1.082 - 4.148
Tnl >4,55 (ng/ml)	0,57	64,29	56,33	2.005	0.978 - 4.108
High dose statin/ Low dose statin	0,61	89,29	32,91	0.286	0.090 - 0.908

The results of the ROC analysis showed that for CPK-MB significantly (AUC = 0.60) at cut-off >73.98 U/l, the sensitivity value was 46.43 % and specificity was 74.05 % for the event. In the without event group were 117 patients below 73,98 U/l and 41 ones had a level higher than 73,98 U/l, in the event group respectively 15 patients below 73,98 U/l and 13 above 73,98 U/l. Relative risk for event was 2.119, 95 % CI 1.082 - 4.148. For variable Tnl the value of RR was unreliable because 95 % CI of RR crossed a 1.

In the event group were 27 males and only 1 female, in the without event group were 119 males and 39 females. Relative risk for event was 7.397, 95 % CI 1.037 - 52.783. Among the patients who had an event took a statin at an average dose were 25 people and 3 patients at a high dose, and without the event group took a statin at an average dose of 106 patients and 52 ones at a high dose. Relative risk for event was 0.286, 95% CI 0.090 - 0.908.

Taking into account the results of studies of cardiovascular mortality in patients after AMI, in the context of secondary prevention, statin therapy remains the cornerstone of lipid-lowering therapy. Early administration of intensive statin therapy reduces cumulative mortality rates [11, 12].

While current guidelines recommend using high doses of statins for all patients after AMI, no matter what the initial LDL-C level is, many clinicians still prescribe statins at an moderate dose. In our study, the initial LDL-C level between the middle-dose group and the high-dose group significantly differed (3.03 [2.10 ; 3.62] mmol/l vs 3.48 [2.69 ; 4.49] mmol/l, $p < 0.05$). Although the degree of LDL-C reduction was significantly higher with high-dose therapy (in the high-dose group -50.54 % vs -29.15 % middle-dose therapy, $p < 0.005$), however, both groups had comparable LDL-C levels after one year. A similar dose-dependen dynamics of the LDL-C level was recorded in the work of D. Hwang et al., that is, when using high doses of statins, there is a more pronounced decrease in LDL-C [13, 14].

For a long time it was believed that statins are drugs that have hepatotoxicity. Currently, these concerns are recognized by most experts as groundless: an increase in liver transaminases occurs in 0.5-2 % of cases, it is transient, and is not accompanied by any clinical symptoms [15].

Thus, based on the results, it can be argued that high-dose statin therapy is associated with a reduced risk of cardiovascular events. Our results could provide more clinical evidence for the use of statins in high doses for patients after AMI who do not have contraindications. However, it should be borne in mind that the degree of LDL-C reduction with statins varies significantly for each person, so achieving the target LDL-C levels may take a long time.

Conclusions. A high dose of statins in patients after acute myocardial infarction showed a greater effect in reducing the level of total cholesterol and low-density lipoprotein cholesterol than a moderate dose. Analysis of the effectiveness of lipid-lowering therapy showed that the achievement of the target LDL-C level less than 1.81 mmol/l was in 49 (37.7 %) in the middle-dose group, while the decrease in the high-dose group was significantly large and amounted to 54.5 %. Use by patients after AMI was associated with a decrease in the negative risk for event of 0.286, 95 % CI 0.090 - 0.908.

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