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Hyporesponse to statin therapy in patients with carbohydrate metabolism disorders following acute coronary syndrome

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The aim of the study was to investigate the frequency of hyporesponse to statin therapy among patients with impaired carbohydrate metabolism after acute coronary syndrome (ACS) in short-term follow-up.

Methods. A retrospective analysis of the medical records of 1500 patients admitted for cardiologic follow-up after ACS was performed. The data of patients who did not receive statins before the development of ACS (400 patients; mean age — 63.42±9.64 years, including 286 (71.5%) men) were included in the analysis. Carbohydrate metabolism disorders (CMD) according to WHO and Russian Association of Endocrinologists criteria were present in 124 patients (type 2 diabetes mellitus (type 2 DM) — in 71 patients; prediabetes — in 53 patients). All patients were prescribed high-dose statin therapy, namely atorvastatin (40 mg or more daily). Low-density lipoprotein (LDL) cholesterol was assessed at baseline and after 1 month of therapy. Hyporesponse to statins was defined as the percentage reduction in LDL cholesterol of <15% from baseline during 1 month of therapy. Suboptimal response was defined as an LDL reduction of less than 50% after 1 month of therapy.

Results. The frequency of hyporesponse was 26.75% (n=107). Depending on the history of carbohydrate me-

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tabolism disorders (type 2 DM, prediabetes), patients were divided into 2 groups: group 1 (CMD, n=124), group 2 (without CMD, n=276). After 1 month of follow-up in the total group, the rate of hyporesponse was 26.75%. In group 1 and group 2, the rate of hyporesponse to statin therapy was 25.81% and 27.54%, respectively (p=0.719). The frequency of suboptimal response in the CMD group was 56.45%. Patients with CMD and hyporesponse to statins were characterized by lower baseline LDL levels.
Conclusion. The absolute majority of patients with CMD after ACS do not achieve the LDL-lowering goal after 1 month of high-intensity statin therapy. Hyporesponse to statins is seen in a quarter of this group. Lower baseline LDL levels increase the likelihood of hyporesponse to statins.

Keywords: statins, hyporesponse, diabetes mellitus, prediabetes.

Conflict of interests: none declared.

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Introduction

The amount of cases of type 2 diabetes mellitus (T2DM) is increasing at an alarming rate worldwide. As a prevalent and serious disease, T2DM places a significant burden on patients, their families and the healthcare system. T2DM is a significant risk factor (RF) for cardiovascular diseases (CVD) such as: coronary heart disease (CHD), stroke, peripheral arterial disease (PAD), heart failure (HF). Patients with T2DM have a 2–4 times higher risk of developing CVD than patients without diabetes [1]. Prediabetes is an independent risk factor for cardiovascular morbidity and mortality [2]. A meta-analysis of 102 prospective studies found that patients with a glycemic level of 6.1–7.0 mmol/L had a 17% higher risk of CHD, and those with a glycemic level of 5.6–6.1 mmol/L had an 11% higher risk of CHD than those with a glycemic level < 5.6 mmol/L [3].

According to current guidelines, the first-line therapy for patients of very high cardiovascular risk is high-intensity statin therapy with a target low-density lipoprotein cholesterol (LDL-C) level of ⩾50% of baseline, with a goal of <1.4 mmol/L achieved [4]. Indeed, "there is no longer a 'hypothesized role for LDL-C,' but rather an established fact that elevated LDL-C levels have a causal relationship with CVD of atherosclerotic etiology and that the maximal reduction of LDL-C and other apoliprotein B (apoB)-containing lipoproteins leads to a reduction in cardiovascular mortality" [4].

Some data suggest that the use of statins may be associated with the prevention of HF in patients after acute coronary syndrome (ACS) [5, 6]. The benefit of statin therapy in terms of impact on the prognosis of HF remains controversial. Further investigation of the role of statins in preventing the development or progression of HF is all the more interesting because of the variable hypolipidemic response to drug administration. For example, a recent retrospective observational study (4.4 years of follow-up) showed that hyporesponse to statins increased the risk of HF in patients after myocardial infarction (MI) [7]. In this observational study, hyporesponse to statins was more frequent in patients with dyslipidemia and in patients with T2DM. Assessing the prevalence of hyporesponse to statin therapy in patients with CMD after ACS may be the first step in assessing the clinical significance of this phenomenon in relation to the development of HF and a step towards optimizing lipid-lowering therapy.

Methods

We retrospectively analyzed the medical records of ACS patients admitted to the outpatient phase of cardiac rehabilitation. From January 1, 2020 to January 1, 2021, 1500 patients who underwent ACS and coronary stenting were admitted for observation in the first 3 days after discharge from hospital vascular departments. Patients received medical therapy including dual antiplatelet therapy, high-dose statin therapy, beta-adrenergic blockers, renin-angiotensin-aldosterone system antagonists, and diuretics. Inclusion criteria were: history of ACS of 1 month or less, no statin use before the cardiovascular event, no con-

traindications to statin prescription. Exclusion criteria were: use of statins in any therapeutic dose before the cardiovascular event, incomplete information from outpatient records. Parameters studied included: LDL-C, recurrent cardiovascular events and HF. The study protocol was approved by the ethics committees of our institutions. Atorvastatin was started within 24 hours after coronary stenting. The choice of atorvastatin dose was made by the treating physician. LDL-C levels were measured on admission and 1 month after initiation of statin therapy in all patients. Hyporesponse to statins was defined as a percent decrease in LDL-C levels <15% of baseline before 1 month after initiation of statins. High-intensity statin therapy was defined as atorvastatin ⩾40 mg daily.

All analyses were performed using the program Statistica 13.3 (StatSoft Russia). In case of non-normal distribution, data were presented as median (Me), lower (LQ) and upper quartiles (UQ), in case of normal distribution — as sample mean and standard deviation. The Mann-Whitney test was used when two independent samples were compared quantitatively, and the χ^2 test for independent samples was used when groups were compared qualitatively. In all cases, the critical p level was considered to be < 0.05.

Results

According to the inclusion/exclusion criteria, data from 400 patients (mean age 63.42±9.64 years, 286 (71.5%) men) were included in the retrospective analysis. More than 50% of the patients had a history of MI. Coronary revascularization was performed in almost all cases. The majority of patients had arterial hypertension (AH) — 383 patients (95.75%). More than half of the patients were diagnosed with HF — 269 patients (67.25%), with a prevalence of preserved ejection fraction (EF), functional class (FC) 2 (Table 1).

All patients were prescribed antiplatelet and hypolipidemic therapy in the form of atorvastatin. Most patients were taking beta-adrenergic blockers (89.75%), renin-angiotensin system inhibitors, mostly angiotensin-converting enzyme inhibitors (ACEi) (75.25%), and diuretics in 18.25% of patients. LDL–C was assessed at baseline using medical records provided to patients at discharge and again at 1 month. Hyporesponse to statins was defined as the percentage of LDL-C reduction <15% from baseline within 1 month of statin treatment. When LDL-C was analyzed in the entire group, the prevalence of hyporesponse after 1 month of therapy was 26.75% (107/400) (Figure 1). The majority were men (n=71; 66.35%). The baseline LDL-C level in patients with a hyporesponse to statins was 2.66 mmol/L (2.2; 3.3) and was lower than in patients with a greater reduction in LDL-C (3.3 (2.5; 4.0); p=0.000).

Table 1. **Clinical characteristics of the group**

Characteristic	Values
Age, years	63.42±9.64 years
Male gender	286/71.5
MI	296/74
Unstable angina pectoris	104/26
Revasculzrization	384/96
Coronary artery bypass surgery	35/9
Stenting	349/91
AH	383/95.75
Atrial fibrillation	40/10
Supraventricular arrhythmias	79/19.75
Ventricular arrhythmias	74/18.5
Sick sinus syndrome	3/0.75
Conduction disorders of the atrioventricular or sinoatrial block type	16/4
Bundle branch block	50/12.5
Chronic HF (CHF), total	269/67.25
CHF with preserved LV EF	188/69.88
CHF with reduced LV EF	16/5.94
CHF with mid-range LV EF	65/24.16
FC 1	98/36.43
FC 2	146/54.27
FC 3	25/9.29
T2DM	71/17.75
Pre-diabetes	53/13.25

Note. Data are presented as N (%) or mean ± standard deviation.

Carbohydrate metabolism disorders were present in 124 patients (31.00%; group 1), carbohydrate metabolism disorders (CMD) were absent in 276 patients (group 2). Patients with CMD were older and had a higher body mass index (BMI) (Table 2).

Initial levels of TC, LDL-C, triglycerides (TG), and high-density lipoprotein cholesterol (HDL-C) did not differ between groups (Table 3). After 1 month, patients in group 1 had higher TG levels and hypertriglyceridemia was more frequent. After 1 month of follow-up, LDL-C levels <1.4 mmol/L were observed in a minority of patients in both groups; achievement of the hypolipidemic therapy goal (LDL-C <1.4 mmol/L or LDL-C reduction by ⩾50%) was equally frequent in groups 1 and 2 (23% and 16%, respectively; p=0.092). Hyporesponse to statins was observed in 32 patients in group 1 (25.81%) and 76 patients in group 2 (27.54%; p=0.719). Suboptimal response (< 50% LDL-C reduction) was observed in every second pa-

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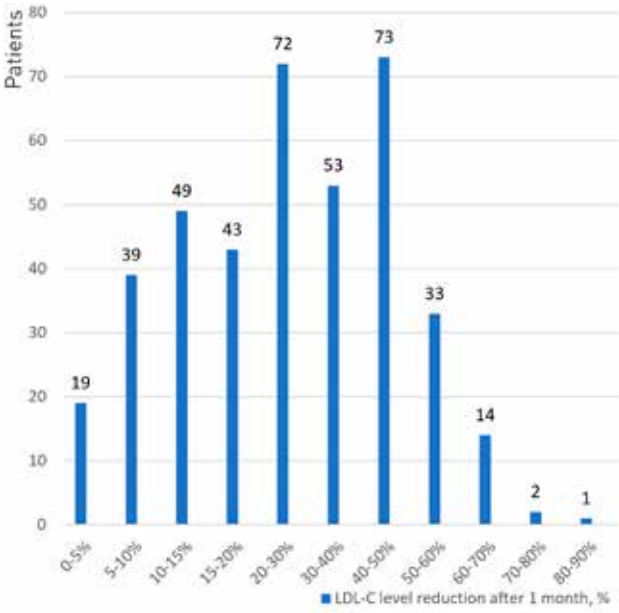

Fig. 1. Distribution of percent change in LDL–C levels in all subjects after 1 month

Table 2. **Clinical characteristics of patient groups**

Characteristic	Group 1, n=124	Group 2, n=276	p
Age, years	64.99±8.25	62.72±10.14	0.024
BMI, kg/m^2	30.05±5.36	28.33±4.86	0.002
Male gender	77 (62.1)	209 (75.7)	0.005
MI	40 (32.26)	84 (30.44)	0.715
Revascularization	117/94.35	268 (97.10)	0.181
Coronary artery bypass surgery	12/10.25	12 (4.48)	0.038
Stenting	112/84.67	256 (95.52)	0.407
AH	121 (97.58)	262 (94.93)	0.224
Atrial fibrillation	14 (11.29)	26 (9.42)	0.564
Obesity/overweight	102 (82.26)	215 (77.9)	0.320
CHF, total	85/68.54	181 (65.58)	0.561
CHF with preserved LV EF	60/70.58	140 (77.34)	0.665
CHF with reduced LV EF	1/1.17	11 (6.08)	0.085
CHF with mid-range LV EF	24/28.23	30 (16.57)	0.022
FC 1	31/36.47	68 (37.57)	0.938
FC 2	50/58.82	94 (51.93)	0.227
FC 3	4/4.70	17 (9.39)	0.224
LV EF (%)	57.5 (50; 64)	57 (51.8; 63)	0.598
Atorvastatin, 40 mg	8 (6.45)	7 (3.26)	0.057
Atorvastin, 80 mg	116 (93.54)	269 (96.74)	0.057
β-blockers	117 (94.35)	243 (88.04)	0.052
ACEi or ARBs	118 (95.16)	257 (93.12)	0.434
Slow calcium channel blockers	34 (37.42)	60 (21.74)	0.215
Diuretics	26 (20.97)	47 (17.03)	0.346
DAPT, double antiplatelet therapy	110 (88.70)	250 (90.58)	0.564
Oral anticoagulant.	14 (11.29)	26 (9.42)	0.564
Metformin	66 (53.22)	—	—
Gliclazide	58 (46.77)	—	—
Insulin	22 (17.74)	—	—

Note. Data are presented as N (%) or mean ± standard deviation.

Table 3. **Characterization of lipid metabolism baseline and response to statin therapy in the groups**

Parameter	Group 1, n=124	Group 2, n=276	p
Baseline lipid levels			
TC, mmol/l	4.79 (4.0;5.56)	4.7 (4.0; 5.58)	0.881
LDL–C, mmol/l	3.2 (2.48; 3.80)	3.15 (2.5; 3.91)	0.639
TG, mmol/l	1.65 (1.1; 2.30)	1.50 (1.09; 2.0)	0.095
HDL–C, mmol/l	1.09 (0.92; 1.22)	1.10 (0.90; 1.36)	0.096
Hypertriglyceridemia	53 (42.7)	95 (34.4)	0.111
Lipid levels after 1 month			
TC, mmol/l	3.78 (3.20;4.50)	3.80 (3.32; 4.21)	0.535
LDL–C, mmol/l	2.10 (1.62; 2.62)	2.20 (1.80; 2.60)	0.226
TG, mmol/l	1.41 (1.10; 1.90)	1.40 (0.99; 1.60)	0.023
HDL–C, mmol/l	1.00 (0.80; 1.17)	1.03 (0.90; 1.20)	0.069
Hypertriglyceridemia	37 (29.8)	56 (20.3)	0.036
LDL–C <1,4 mmol/l	13 (10.48)	17 (6.16)	0.129
Decrease in LDL–C level after 1 month of therapy			
0-5 %	3 (2.42)	15 (5.43)	0.179
5-10 %	14 (11.29)	25 (9.06)	0.486
10-15 %	15 (12.09)	36 (13.04)	0.793
15-20 %	9 (7.26)	32 (11.59)	0.186
20-30 %	27 (21.77)	47 (17.03)	0.258
30-40 %	17 (13.71)	35 (12.68)	0.777
40-50 %	17 (13.71)	54 (19.56)	0.156
50-60 %	14 (11.29)	21 (7.61)	0.228
60-70 %	8 (6.45)	8 (2.89)	0.093
70-80 %	0	2 (0.72)	0.854
80-90 %	0	1 (0.36)	0.681
≥50 %	22 (17.74)	29 (10.51)	0.045
LDL–C <1.4 mmol/l or decrease in LDL–C by ≥ 50 %	29 (23.39)	45 (16.30)	0.092

Note. Data are presented as N (%) or median (interquartile range).

tient with CMD (56.45 %) and in 39.13 % of cases in group 2 (p=0.405).

In group 1, baseline LDL-C in the hyporesponders was 2.7 (2.1; 3.30) mmol/l and was significantly lower than in the responders (3.28 mmol/l (2.7; 3.9), p=0.006). Consistently, TC was also lower: 4.1 (3.5; 4.83) and 5.0 (4.2; 5.7) respectively; p=0.001. In group 1, the frequency of atorvastatin 40 mg and atorvastatin 80 mg/day did not differ between responders and hyporesponders. Particularly, atorvastatin 40 mg was used in 12.5 % of hyporesponders and 4.35 % of responders (p=0.230). In group 2, the baseline LDL-C level in hyporesponders was 2.6 (2.27; 3.19) mmol/l and was also significantly lower than in responders (3.4 mmol/l (2.80; 4.09)), p=0.000. In group 2, atorvastatin 40 mg was used more frequently in hyporesponders (7.89 % vs. 2.0 %, respectively, p=0.001).

Discussion

Achieving target lipid levels is aimed at reducing the risk of atherosclerotic CVD. HMG-CoA reductase inhibitors (statins) have been shown to reduce the incidence of CHD in patients with and without diagnosed CVD [8, 9]. Numerous data suggest that the use of statins may be associated with the prevention of HF in patients after ACS [10]. The results of a large meta-analysis of 17 randomized clinical trials (RCTs) (n=132,568, mean age 63 years, 29 % women) showed that statin therapy was associated with a reduced risk of hospitalization for HF [11]. A combined analysis of the data showed a reduction in the incidence of hospitalization for HF and a reduction in the incidence of MI if statins are used [12]. A recently published retrospective cohort study in a group of patients with atrial fibrillation showed a reduction in the risk of HF, HF-related death, and all-cause mortality independent of LDL-C cholesterol levels [13]. At the same time, an observational study using data from the Swedish nationwide MI registry showed that patients with a larger reduction in LDL-C (1.85 mmol/l) compared with a smaller reduction (0.36 mmol/l) had lower risk ratios for all outcomes assessed, and in particular for hospitalization due to HF (OR: 0.73; 95 % CI 0.63–0.85) [14]. A RCT in patients with ACS and dyslipidemia showed that hospitalization for HF was significantly reduced in the intensive therapy group (pitavastatin + ezetimibe) compared with pitavastatin monotherapy [15]. ESC experts recommend the use of statins for the prevention of HF in high-risk individuals [16].

It is well known that there is a large variability in the response to statins as well as in the % reduction of LDL-C. According to the Russian registry (REGION-IM) of patients with MI, LDL-C ⩽1.4 mmol/l was achieved in 23 % of cases on hypolipidemic therapy. In addition, the target LDL-C level was achieved in 21 % of patients receiving statin monotherapy and in 44 % of patients receiving statin + ezetimibe combination therapy. [17]. In another European study, despite the use of high-intensity statin monotherapy, more than half of the patients hospitalized with ACS (82.9 %) did not achieve target LDL-C levels [18]. The mechanisms that increase cardiovascular risk in this group of patients may be not only higher LDL-C levels, but also decreased pleiotropic effects such as the anti-inflammatory one [19, 20].

In a retrospective observational study (follow-up period — 4.4 years), hyporesponse to statins was shown to increase the risk of HF in post-MI patients [7]. A study by Kuyama N. et al. showed that baseline levels of mature PCSK9 (proprotein convertase subtilisin/kexin type 9) were associated with hyporesponse to statins. This suggests that mature PCSK9 may be a potential determinant of statin hyporesponse [21]. Statin-mediated increases in circulating PCSK9 levels may contribute to inflammation and impair endothelial permeability, including nitric oxide production [22]. Since systemic inflammation is a known component of HF pathogenesis, mediated by increased expression of endothelial adhesion molecules and production of reactive oxygen species [23], an unfavorable inflammatory activity profile may be another factor in the occurrence of HF in statin hyporesponders. According to some data, circulating PCSK9 levels are a significant predictor of the combined endpoint of all-cause death and hospitalization in patients with HF [24].

Other individual characteristics, including age, sex, body weight, cigarette smoking, inflammation, chronic kidney disease, DM, baseline lipid levels, and some genetic variations, may also be possible the determinants of poor response to statins [25–27].

In our observation, the hyporesponse (LDL-C reduction ⩽ 15 %) to high-dose atorvastatin therapy was registered in 28 % of cases in patients after ACS and coronary revascularization after 1 month of therapy. The frequency of hyporesponse registered in our observation was higher than in the previous study by Tsuda K. et al. (2020). According to the results of the Japanese study, hyporesponse was observed in 15.2 % of cases (77/505) of statin therapy [7]. Similarly, we found no evidence of a greater rate of hyporesponse or suboptimal response to statins in the group of patients with CMD. A significantly lower baseline LDL-C level was observed in the group of patients with CMD and in group 2 of hyporesponders, which is consistent with the results of previous studies [7, 18].

Conclusion

According to the data of the retrospective analysis of the outpatient records of patients who were followed up in the clinic after ACS and had CMD (T2DM, prediabetes), hyporesponse to statin therapy was observed in 25.81 % of cases, suboptimal response to statins in 56.45 % of cases. There was no evidence of a higher frequency of hyporesponse and subop-

timal response to statin therapy in the group of patients with CMD compared to patients without CMD. Hyporesponders with CMD had significantly lower baseline LDL–C levels.

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