Research Article

Statins adherence and associated muscle symptoms in elderly coronary heart disease patients

Marina G. Bubnova[1], Marat V. Ezhov[2*], David M. Aronov[1]

[1] National Medical Research Center of Therapy and Preventive Medicine, Ministry of Health of the Russian Federation, Moscow, Russia

[2] National Medical Research Center of Cardiology n.a. ac. E.I. Chazov, Ministry of Health of the Russian Federation, Moscow, Russia

*Correspondence: Marat V. Ezhov

Address: Academician Chazov street, Moscow, 121552, Russia

Email Address: MVEzhov@cardio.ru (M.V.E.),

Abstract

Aim. The purpose of the study was to assess adherence to statin therapy and the incidence of statin-associated muscle symptoms in elderly patients with coronary heart disease in real clinical settings. **Methods and results.** This cross-sectional observational study was conducted in outpatient departments from 10 Russian regions with 166 physicians and included 959 patients aged ≥65 years (mean age 68.9±0.2 years, 47.5% women) with proven coronary heart disease. There was a high frequency of atherosclerosis risk factors: 93% of patients had arterial hypertension, 59.6% were obese, 24.6% had type 2 diabetes, and 20.4% were current smokers. Myocardial infarction and stroke were documented in 31.6% and 9.1% of patients, respectively. Statins were recommended in 77% of the patients, of which 18.7% refused to take the medication, and 41.5% took the treatment course. The main causes of poor adherence to statin therapy were fear of adverse events (46%), lack of motivation to maintain treatment (29.4%), polypharmacy (27.6%), memory impairment (26.5%), and lack of treatment efficacy (18.8%). Only 11.7% of patients stopped statin intake because of adverse events, whereas 13.5% of patients terminated statins treatment due to the treatment cost. Muscle symptoms of mild to moderate severity occurred in 9.2% of patients, and the frequency of increased creatine kinase level was 0.83%. **Conclusion.** Elderly coronary heart disease patients demonstrated poor adherence to statin therapy in real clinical settings. The frequency of statin-associated muscle symptoms was about 10%.

Key words: statins, adherence, elderly patients, coronary heart disease, statin-associated muscle symptoms.

Introduction

Epidemiological, genetic, and randomized clinical studies have confirmed the key role of low-density lipoprotein cholesterol (LDL-C) in the development of atherosclerotic cardiovascular disease (ASCVD) [1-4]. Statins are the first-line drugs for the treatment of hypercholesterolemia and atherosclerosis [2,3]. Large-scale meta-analysis of the Cholesterol Treatment Trialists included 170,000 patients from 26 trials, and showed that decreasing blood plasma LDL-C by 1 mmol/L is associated with a reduction in all-cause death by 10%, coronary heart disease (CHD) death by 20%, major adverse cardiovascular events by 23%, and stroke by 17% [5]. In the current treatment strategy, statins are used at the maximum tolerated dose [2,3]. However, in a real clinical practice, they are often prescribed at inadequate doses, which leads to failure in achieving the target level of LDL-C in the majority of patients. Another problem is poor adherence to statin therapy, which is attributed to both subjective and objective reasons. Observational studies and registries show that the incidence of statin-associated muscle symptoms (SAMS) may vary from 11% to 29% [6-8]. Patients may report the presence of muscle pain or weakness of mild-to-moderate intensity, which is often not associated with increased activity of creatine kinase [6]. Muscle symptoms may often be missed by physicians, and as a result, their occurrence is not clearly defined in different cohorts.

More than 80% of patients who die of CHD are older than 65 years [9]. A previous meta-analysis of 24,674 elderly patients without established ASCVD demonstrated that statins lowered the incidence of myocardial infarction by 39%, and of stroke by 24% [10]. Cholesterol Treatment Trialists meta-analysis showed a relative risk reduction of major cardiovascular events in patients of all ages on statin therapy [5]. According to the 2019 European Society of Cardiology/European Atherosclerosis Society Guidelines, statin therapy in elderly patients should be initiated at a low dose that is gradually increased up to the target values of LDL-C, similar to the recommendation for younger patients [3]. The American College of Cardiology/American Heart Association 2018 Recommendations advise limiting the prescription of high-intensity statin regimen in patients > 75 years [7]. Attention should be paid to safety issues and risk of adverse events when prescribing statins to elderly patients. Elderly patients have co-morbidities and take a number of drugs that increase the probability of adverse events and myalgia, with or without creatine kinase elevation. With aging, the risk of musculoskeletal diseases significantly increases. According to the World Health Organization, more than 50% of patients over 55 years develop diseases limiting the function of muscles and joints [11]. Thus, investigation of causality for low adherence to statin therapy in a cohort of elderly patients is very important.

This paper describes the first major program in Russia, which aimed to study the frequency of statin prescription, related muscle symptoms, and identification of causes of treatment failure and poor adherence to statins in elderly patients (≥65 years) with CHD in a real clinical setting.

Material and methods

The study was conducted in outpatient departments from 10 Russian regions with 166 physicians. In total, 959 patients were enrolled who met the following criteria: age ≥ 65 years, the presence of primary hyperlipidemia (IIa and IIb Fredrickson type classification), and documented CHD. This study was conducted in accordance with the Helsinki Declaration and approved by the Institutional Review Board/Ethics Committee. All subjects provided informed consent to participate in the study. Medical records were reviewed for the history, blood lipid levels, type and dosage of statin. A questionnaire was applied to evaluate statin associated muscle symptoms and the reasons for refusal or termination of statin intake. SAS software (version 6.12) was used for statistical analysis. For continuous variables, the mean ± standard deviation was applied. The normality of distribution was assessed with the Shapiro-Wilkes test. Categorical parameters were presented as percentages. A logistic regression was applied to calculate the odds ratio (OR). A binary logistic regression model was used to build a 95% confidence interval (CI) and a point estimate of the OR. Differences were considered statistically significant at $p<0.05$.

Results

Among the enrolled patients, 62.7% were between 65 and 69 years of age, 26.3% were 70–74 years, 8.7% were 75–79 years, and 2.3% were ≥80 years (Table 1). Almost half of the participants were women; 721 patients suffered from angina pectoris. Each third patient had suffered myocardial infarction. The examined cohort revealed a high prevalence of arterial hypertension. One in five patients were current smokers. More women had obesity and type 2 diabetes. Most patients were receiving antihypertensive drugs and had elevated mean levels of LDL-C and triglycerides.

Table 1. Characteristics of study patients.

Parameters	Total cohort *n* = 958	Males *n* = 503	Females *n* = 455	P (Males vs. Females)
Age, years	69.8 ± 0.2	69.4 ± 0.2	70.3 ± 0.2	0.002
Angina pectoris, class %				
I	6.8	8.2	5.3	>0.05
II	53.2	51.3	55.4	>0.05

III IV	15.3 2.4	17.1 4.4	13.2 0.2	<0.05 <0.05
Myocardial infarction in the past, %	31.6	40	22.4	0.001
Arterial hypertension, %	93	91.5	94.8	<0.05
Stroke in the past, %	9.1	7.9	10.3	>0.05
Smoking, %	20.4	33.4	5.9	0.001
Obesity, %	59.6	53.8	66.8	0.001
Type 2 diabetes, %	24.6	19.1	30.8	0.001
Body mass index, kg/m^2	29.4 ±0.1	28.6 ±0.2	30.2 ±0.2	0.0001
Total cholesterol, mmol/L	6.85 ±0.04	6.77 ±0.05	6.95 ±0.06	<0.05
LDL cholesterol, mmol/L	4.62 ±0.04	4.52 ±0.05	4.73 ±0.06	<0.01
Triglycerides, mmol/L	2.19 ±0.03	2.21 ±0.04	2.17 ±0.05	>0.05
HDL cholesterol, mmol/L	1.14 ±0.01	1.04 ±0.02	1.23 ±0.02	0.0001
Glucose, mmol/L	5.71 ±0.04	5.62 ±0.06	5.81 ±0.06	<0.05
Creatinine, μmol/L	90.6 ±0.8	92.6 ±1.1	88.1 ±1.2	<0.01

Data are presented as the mean ± standard deviation or in percentages. LDL – low density lipoprotein; HDL – high density lipoprotein.

Most patients (*n* = 738, 77%) were prescribed statins, more frequently in males (76.5 vs. 70.6%, P < 0.05); however, only 294 (39.8%) took them regularly. The remaining patients either did not take the statins at all (*n* = 138) or took them intermittently (*n* = 306). The predominant causes that some patients (*n* = 446, 240 males and 204 females) completely refused to take the statins were concerns about the side effects mentioned in the drug leaflet, lack of faith in the drug benefit, intake of many pills, and forgetfulness (Table 2).

Table 2. Causes of statin intake refuse by elderly patients.

Causes	Patient groups, %			P (Males vs. Females)
	Total (*n* = 446)	Males (*n* = 240)	Females (*n* = 204)	
Concerns about side effects described in the drug leaflet	46.0	46.3	46.1	>0.05
Disbelief in the drug benefit	29.4	33.3	25.0	<0.05
Many pills	27.6	25.0	30.9	<0.05

Forgetfulness	26.5	25.0	28.4	<0,05
Poor cholesterol control	18.8	16.2	22.1	<0.05
Lack of knowledge about the need for the continuous drug intake	17.3	17.9	16.8	>0.05
Physician`s recommendations	13.5	15.4	11.3	>0.05
Adverse effects	11.7	10.8	12.8	<0.05
Lack of financing	7.6	8.3	6.9	<0.05

Other reasons noted by the patients were as follows: poor cholesterol control, despite taking the medication; lack of knowledge about the need for continuous drug intake; the drug was discontinued by another doctor; and adverse events when taking a statin. Only 7.6% of patients (mostly males) complained about the lack of funds. The questionnaire review showed that 59.2% of patients agreed with the need to remain on the medication for life. More females (61.8%) than males (56.9%) had this awareness (P = 0.049). At the same time, 12.8% of the elderly patients felt that constant use of the medication was harmful, and 24.2% did not believe that the lifelong use of drugs was necessary (males vs. females 27.4% and 20.9%, P = 0.022). One-third of patients (32.5%) stopped taking the medication because they were not feeling well. This happened although 69.3% of them confirmed that the doctor had explained the purpose of statin intake and potential adverse events in the case of statin discontinuation. According to multivariate analysis, the factors that increased the likelihood of complete refusal of statin intake by elderly patients were: belief that the drug was unnecessary (OR 8.14, 95% CI 4.14–15.99; P = 0.0001), concern about the potential harm of statins (OR 4.11, 2.52–6.70; P = 0.0001), absence of effect on life longevity (OR 2.72, 1.65–4.49; P = 0.0001), and lack of money (OR 2.56, 1.18–5.57; P = 0.018). The probability of statin termination was higher in cases of polypharmacy (OR 1.65, 1.01–2.71; P = 0.045), especially in concomitant use of antidepressants (OR 3.02, 1.11–8.24; P = 0.031), and the presence of thyroid disease (OR 1.99, 1.37–2.88; P = 0.0003), obesity (OR 1.49, 1.01–2.20; P = 0.047), or chronic obstructive pulmonary disease (OR 1.20, 1.05–1.34; P = 0.042). The majority (65.8%) of patients had taken statins for 3 months, 30.1% from 4 to 12 months, and 27.3% up to 5 years (**Figure 1**). Only 6.9% of patients took statins continuously for more than 5 years.

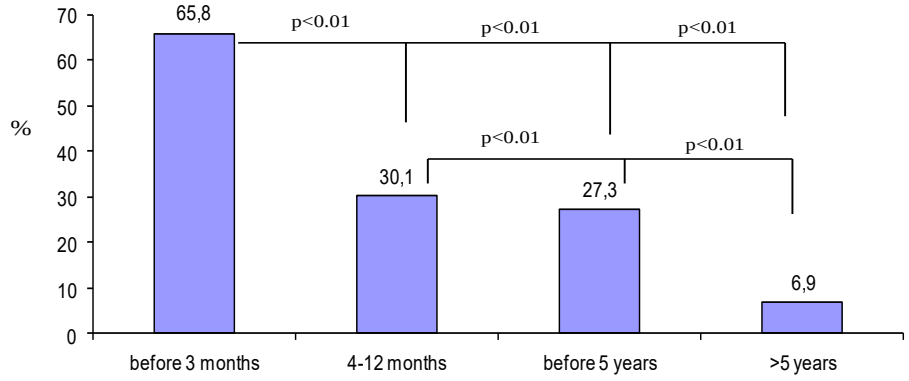

Figure 1. Duration of statin intake by elderly CHD patients.

The long-term use of statins was more common in women, those with a family history of CHD, previous myocardial infarction, history of muscles symptoms, and knowledge of cholesterol level (Table 3).

Table 3. Characteristics of elderly patients depending on duration of statin intake.

Parameters	Duration of statin intake		P
	<3 months (*n* = 225)	>1–5 years (*n* = 214)	
Males	131 (58.2)	113 (52.3)	0.048
≥70 years	75 (33.3)	75 (35.1)	0.194
Higher education	125 (57.7)	140 (65.4)	0.055
Knowledge of cholesterol level	96 (42.7)	131 (61.2)	0.001
Smoking	53 (23.6)	36 (16.8)	0.062
Family history of CHD	122 (54.2)	132 (61.7)	0.006
Arterial hypertension	210 (93.3)	202 (94.4)	0.063
Obesity	123 (54.7)	117 (54.7)	0.126
Type 2 diabetes	63 (28)	52 (24.3)	0.077
Myocardial infarction in the past	84 (37.3)	103 (48.1)	0.001
Stroke in the past	15 (6.7)	24 (11.2)	0.056
History of muscles symptoms	20 (8.9)	14 (6.5)	0.015
Use of beta-blockers	126 (56)	159 (74.3)	0.001

Data presented as n (%)

Multivariate analysis showed that the probability of termination of statin intake markedly increased in patients with forgetfulness, in the absence of the doctor's

recommendation for long-term drug use, in cases of taking many pills, lack of money, lack of cholesterol control, and poor efficacy of the cholesterol-lowering therapy (Table 4). The presence of smoking increased the probability of statin discontinuation by 1.5-fold.

Table 4. Factors associated with the discontinuation of regular intake of statins and the duration of statin therapy among elderly patients.

Variables	OR	95% CI	P
Factors increasing the probability of statin intake termination			
Patient forgetfulness	10.01	5.71–17.53	0.0001
Another physician recommendation	5.61	3.94–7.99	0.0001
Absence of the physician recommendation	5.59	3.74–8.37	0.0001
Lack of money	3.86	1.72–8.71	0.001
Absence of cholesterol measurements	3.16	1.98–5.06	0.0001
Lack of efficacy of lipid-lowering therapy	2.93	2.34–3.85	0.0001
Lack of trust in treatment	2.28	1.45–3.59	0.0004
Adverse events	2.04	1.14–3.66	0.017
Fear of adverse events	1.68	1.23–2.30	0.001
Intake of many drugs	5.14	3.25–8.13	0.0001
Smoking	1.49	1.06–2.09	0.024
Factors increasing the probability of long-term statin intake			
Physician recommendation	5.53	3.60–8.47	0.0001
Regular control of cholesterol level	3.64	2.17–6.12	0.0001
Knowledge of cholesterol level	1.47	1.13–1.92	0.004
Explanation of the need of statins intake	2.42	1.79–3.27	0.0001
Beta-blockers intake	2.22	1.67–2.94	0.0001
Concomitant diseases	3.45	1.21–9.84	0.020
Family history of the CHD	1.57	1.19–2.05	0.001
Myocardial infarction in the past	2.04	1.53–2.70	0.001
Stroke in the past	1.63	1.04–2.56	0.032

Only 14.5% of elderly patients were on a high-intensity statin regimen (males 15.5%, females 9.9%), of them 88% were on atorvastatin, and were12% on rosuvastatin. In those continuously taking statins, creatine kinase level increased above the normal range in 0.83% (5 of 600 patients). Muscle symptoms of mild to moderate severity occurred in 55 (9.2%) patients independently of sex.

Discussion

In this study, we enrolled patients ≥65 years with documented CHD, in whom statin therapy was explicitly indicated, but 23% of the elderly patients with CHD did not receive recommendations to take statins. The problem is that patients either refused to use statins (18.7%) or preferred the course intake (41.5%). In our study the leading cause (46% of cases) of the non-continuous use of statins was the fear of adverse events, although side effects in those taking statins developed 4-fold less than had been expected (only 11.7% of patients). The second cause (29% of cases) was the lack of motivation for treatment due to disbelief in its effects. About 27% of patients complained of cognitive symptoms, and this was also a major barrier to the continuous use of statins. Polypharmacy was another cause for discontinuation. More elderly women than men developed adverse events (12.8% vs. 10.8%), which caused them to stop taking the statin. Refusal by elderly men to take the statin was less common. This ensured the slightly better control of LDL-C in men compared to women, although the male subjects had less belief in the ability of a statin to extend their lifespan. Poor control of cholesterol levels, despite taking the medication, was the reason for refusing to take statins in each fifth patient. Adherence to statin treatment significantly increased when the target level of LDL-C is reached. Wei *et al.* [12] showed that patients with the target level of LDL-C on the background of high adherence to the therapy versus those who forgot to take a statin, showed remarkable reduction of risk of cardiovascular events by 59%. Hence, in real clinical practice in Russia, 60% of the elderly patients lacked a clear understanding of the importance of continuous statin intake. It is well known that parameters such as polypharmacy, comorbidity, presence of multiple risk factors, and high levels of LDL-C at baseline at any age significantly reduce adherence to statin therapy [13,14]. Only a persuasive, convincing, and detailed explanation of the necessity of taking lipid-lowering drugs for cardiovascular risk reduction will increase adherence of elderly patients to the therapy.

Large observational primary prevention study of 19,518 subjects older than 65 years had shown that all-cause mortality rate was 34% lower and cardiovascular disease events were 20% fewer among those who had adhered to statin treatment [15]. In 542 hospitalized patients with angiographically documented CHD with mean age 69 years from the district with the highest incidence and mortality for CHD it was shown that at discharge only 85% were being treated with a statin with further decreasing adherence for statins by 15.7% for 12 months follow-up [16]. Similarly, in a large study with 62,070 patients (mean age 66 years, 65% males) statin therapy was associated with 25% relative reduction of 3-year risk of major cardiovascular events ($P < 0.0001$) [17]. An analysis of 347,104 patients with ASCVD found an association between low adherence to statin therapy and a greater risk of all-cause mortality [18].

The USAGE (Understanding Statin Use in America and Gaps in Education) internet survey assessed behaviour of 10,138 US adult former or current statin users. Muscle symptoms were reported by 60% and 25% of former and current users, respectively [19]. The primary reason for switching from one statin to another was cost (32%) and SAMS (33%), whereas the primary reason for discontinuation was side effects (62%). Lack of efficacy was mentioned only in 13% of respondents [20]. Nearly half of all participants switched a statin at least once [19]. In our study we assessed the reasons for discontinuation but not for switching of statins. Also, the USAGE survey demonstrated that females were more likely to have discontinued statin intake than males [21], whereas in our study we did not find differences between sexes in statin termination. Importantly, the recent larger ACTION (Adherence and Concerns with STatins and MedicatION Discussions With Physicians) survey key results confirmed findings in USAGE [22].

Our study identified two relevant trends in contemporary therapy with statins. First, the cost of a statin is not a limiting factor of its widespread use in clinical practice. This was confirmed by the fact that every fourth patient did not take a statin administered free of cost. Second, the number of adverse events on statins was much lower than was anticipated. The increase of creatine kinase associated with statins was registered in 0.83% of patients, while mild-to-moderate muscle symptoms were revealed in 9.2% of the patients. The PRIMO (Prediction of Muscular Risk in Observational Conditions) study conducted in France in patients with hyperlipidemia and treated with high doses of statins showed that the incidence of mild-to-moderate muscle symptoms was 10.5% [8], and, notably the number of patients ≥65 years reached 30.2%. The high-intensity statin therapy in our study was obtained by only 14.5%, while the remaining 85.5% received low or moderate doses of statins.

On the whole, in the Russian program, statin-associated muscle symptoms (including an asymptomatic increase in creatine kinase) occurred in 10% of the participants. Older and younger adults as well as women were less likely to adhere to statins. The administration of statins for elderly patients is certain to be justified by a balanced approach based on the use of a statin with the lowest risk of adverse events. Besides advanced age, reduced body mass, hypothyroidism, muscle disease history, type 2 diabetes, alcohol abuse, polypharmacy are factors that significantly increase the risk of myopathy. Numerous clinical studies have confirmed the importance of continuous statin intake (survival curve divergence occurs at least after 2 years) [5]. In fact, statin therapy in elderly patients is carried out during the first 3 months, after which adherence to treatment drops sharply.

Conclusion

It is now clear that old age is not an obstacle to the active use of statins to prevent cardiovascular events. It is assumed that the correct treatment of an elderly patient

requires mutual understanding and agreement between the patient and the doctor [19]. Ensuring the quality of life of an elderly patient is an important problem from the point of view of practical medical care. We must expand and improve outpatient care in this patient population, avoiding polypharmacy as much as possible and delivering drugs based on expected benefits and potential risk of complications.

In conclusion, elderly patients with coronary heart disease in real clinical settings in Russia demonstrated poor adherence to statin therapy, and the frequency of statin-associated muscle symptoms was about 10%.

Study limitation

The study obtained retrospective information from elderly patients about their disease state and statins or other medication intake and any adverse events.

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Disclosures

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