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RESEARCH

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

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Abstract

Background: 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 (CHD) in a real-world clinical setting.

Methods: A cross-sectional observational study was conducted in 10 regions of Russia in clinics with the participation of 166 physicians and 959 patients with CHD aged ≥ 65 years (mean age 69 years, 47.5% women). Medical records were reviewed for medical history, blood lipid levels, and statin type and dosage. A questionnaire was applied to evaluate statin-associated muscle symptoms and reasons for refusal or termination of statin intake.

Results: Risk factors for atherosclerosis in patients were as follows: arterial hypertension–93%, obesity–59.6%, type 2 diabetes mellitus–24.6%, smoking–20.4%. Myocardial infarction and stroke were reported in 31.6% and 9.1% of patients, respectively. Statins were prescribed to 77% of patients. The main reasons for poor adherence to statin therapy were fear of adverse events (46%), lack of motivation to continue treatment (29.4%), polypharmacy (27.6%), memory impairment (26.5%) and insufficient treatment effectiveness (18.8%). Only 11.7% of patients discontinued statin intake due to side effects, whereas 13.5% of patients interrupted treatment because of cost. Muscle symptoms of mild to moderate severity occurred in 9.2% of patients; the rate of increase in serum creatine kinase was 0.83%.

Conclusion: Elderly patients with CHD have demonstrated poor adherence to statin therapy in real-world clinical settings. The incidence of statin-associated muscle symptoms was approximately 10%.

Keywords: Statins, adherence, older 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]. A large-scale meta-analysis of the Cholesterol Treatment Trialists, which included 170,000 patients from 26 trials, showed that a 1 mmol/L reduction in plasma LDL-C was associated with a 10% reduction in all-cause death, a 20% reduction in coronary heart disease (CHD) death, a 23% reduction in major adverse cardiovascular events, and a 17% reduction in stroke [5]. The current treatment strategy is to use statins at the maximum tolerated dose [2, 3]. However, in real-world clinical practice, statins are often prescribed at inadequate doses, which lead to failure to achieve target LDL cholesterol levels in most patients.

Poor adherence to statin therapy is linked to a significantly increased risk of cardiovascular events and death [6, 7]. Reasons for non-adherence fall into three categories: patient-related, physician-related, and health care system-related. Patient-related factors (skepticism, lack of symptomatic benefit, perceived or actual side effects) have a greater impact on adherence [8].

Side effects are considered the most common reason

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Table 1. Characteristics of patients.

Parameters	Total cohort (n = 958)	Male (n = 503)	Female (n = 455)	P (Male *vs.* Female)
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	15.3	17.1	13.2	< 0.05
IV	2.4	4.4	0.2	< 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

Note: LDL, low-density lipoprotein; HDL, high-density lipoprotein.

for statin discontinuation, and statin-associated muscle symptoms (SAMS) are one of the leading causes of statin non-adherence [9]. Observational studies and registries indicate that the incidence of SAMS can vary from 11% to 29% [9-11]. Patients may report mild to moderate muscle pain or weakness, which is often not associated with increased creatine kinase activity [9]. Muscle symptoms are often overlooked by clinicians and, as a result, their incidence in different patient populations is poorly defined.

More than 80% of patients who die from CHD are over 65 years of age [12]. A previous meta-analysis of 24,674 elderly patients without known ASCVD found that statins reduced the incidence of myocardial infarction by 39% and stroke by 24% [13]. The Cholesterol Treatment Trialists meta-analysis showed a relative risk reduction of major cardiovascular events in patients of all ages receiving statin therapy [5]. According to the 2019 European Society of Cardiology/European Atherosclerosis Society guidelines, statin therapy in older patients should be initiated at a low dose and gradually increased up to the target values of LDL-C, as recommended for younger patients [3].

The 2018 American College of Cardiology/American Heart Association recommendations advise limiting the prescription of high-intensity statin regimen in patients > 75 years of age [10]. Attention should be paid to safety issues and the risk of adverse events when prescribing statins to older patients. Older patients have comorbidities and are taking multiple medications that increase the likelihood of side effects, including myalgia, with or without increased creatine kinase. According to the World Health Organization, more than 50% of patients over the age of 55 develop musculoskeletal symptoms [14].

Thus, the evaluation of low statin adherence in a cohort of elderly patients is very important. This paper describes the first large program in Russia aimed at studying statin prescription rates and adherence, related muscle symptoms, and identification of the causes of treatment failure and poor adherence to statins in elderly patients (≥ 65 years) with CHD in a real clinical setting.

Material and methods

This cross-sectional observational study was conducted in 10 regions of Russia in outpatient clinics involving 166

Table 2. Reasons for poor adherence to statin therapy.

Causes	Patient groups, %			P (Male *vs.* Female)
	Total (n = 446)	Male (n = 240)	Female (n = 204)	
Fear of adverse events	46.0	46.3	46.1	> 0.05
Lack of motivation	29.4	33.3	25.0	< 0.05
Polypharmacy	27.6	25.0	30.9	< 0.05
Memory impairment	26.5	25.0	28.4	< 0.05
Insufficient effectiveness	18.8	16.2	22.1	< 0.05
Lack of knowledge	17.3	17.9	16.8	> 0.05
Physician`s recommendation	13.5	15.4	11.3	> 0.05
Adverse effects	11.7	10.8	12.8	< 0.05
Drug cost	7.6	8.3	6.9	< 0.05

physicians and 959 patients with CHD aged ≥ 65 years (mean age 68.9 ± 0.2 years, 47.5% women).

Inclusion criteria were as follows: age ≥ 65 years, presence of primary hyperlipidemia (Fredrickson types IIa and IIb) and confirmed 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 medical history, blood lipid levels, and statin type and dosage. A questionnaire was applied to evaluate statin-associated muscle symptoms and reasons for refusal or termination of statin intake.

SAS software (version 6.12) was used for statistical analysis. For continuous variables, the mean ± standard error of the mean was applied. Categorical parameters were presented as percentages. One-way analysis was performed and the presence of collinearity among variables was assessed. Logistic regression was applied to calculate odds ratios (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 included patients, 62.7% were in the age group 65–69 years, 26.3% in the age group 70–74 years, 8.7% in the age group 75–79 years, and 2.3% in the age group ≥ 80 years (Table 1). Almost half of the participants were women; 721 patients suffered from angina pectoris. One third of the patients suffered from myocardial infarction (MI). Most patients had arterial hypertension. One fifth of the patients were current smokers. Obesity and type 2 diabetes were more common in women. Most patients were receiving antihypertensive medication and had elevated levels of LDL-C and triglycerides.

Statins have been prescribed to most patients (n = 738, 77%), but only 294 (39.8%) took them regularly. The remaining patients either did not take statins at all (n = 138) or took them intermittently (n = 306). The main reasons for poor adherence to statin therapy were fear of adverse events (46%), lack of motivation (29.4%), polypharmacy (27.6%), memory impairment (26.5%), and insufficient effectiveness (18.8%) (Table 2).

Other reasons were lack of knowledge about the need for continuous drug intake, recommendation by another physician, and adverse events. Only 7.6% of patients complained about the cost of the drug.

The majority of patients (65.8%) had taken statins for 3 months, 30.1% for 4 to 12 months, and 27.3% for up to 5 years (Figure 1). Only 6.9% of patients took statins continuously for more than 5 years.

Better adherence to statins was more common among women, those with a family history of CHD, previous myocardial infarction, no history of muscular symptoms, use of beta-blockers, and knowing cholesterol level (Table 3). Multivariate analysis showed that the probability of statin discontinuation markedly increased in patients with memory problems, smoking, in case of another physician's recommendation or no recommendation, due to polypharmacy, drug cost, lack of cholesterol control, and lack of and disbelief in treatment efficacy, and presence or fear of side effects (Table 4).

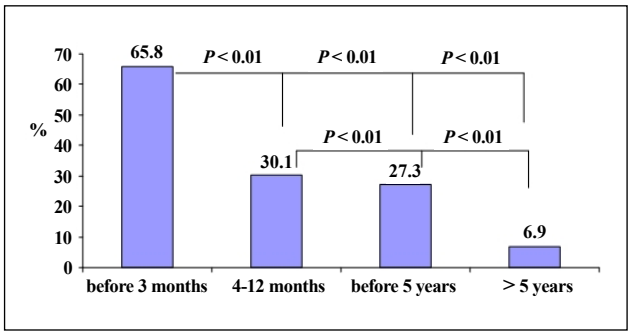

Figure 1. Duration of statin intake by older CHD patients.

Only 14.5% of elderly patients were on a high-intensity statin regimen (male 15.5%, female 9.9%), of whom 88% were treated with atorvastatin and 12% with rosuvastatin. In individuals continuously taking statins, creatine kinase levels were increased above the normal range in 0.83% (5

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

Parameters	Duration of statin intake		*P*
	< 3 months (n = 225)	> 1–5 years (n = 214)	
Male	131 (58.2)	113 (52.3)	0.048
Higher education	125 (57.7)	140 (65.4)	0.055
Knowing cholesterol levels	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
History of myocardial infarction	84 (37.3)	103 (48.1)	0.001
History of stroke	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

Note: Data presented as n (%).

Table 4. Factors associated with the statin discontinuation and duration of treatment.

Variables	OR	95% CI	*P*
Reasons for statin discontinuation			
Memory impairment	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
Drug cost	3.86	1.72–8.71	0.001
Absence of cholesterol measurements	3.16	1.98–5.06	0.0001
Lack of treatment efficacy	2.93	2.34–3.85	0.0001
Disbelief in treatment efficacy	2.28	1.45–3.59	0.0004
Side effects	2.04	1.14–3.66	0.017
Fear of side effects	1.68	1.23–2.30	0.001
Polypharmacy	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
Knowing cholesterol level	1.47	1.13–1.92	0.004
Motivation for 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
History of myocardial infarction	1.57	1.19–2.05	0.001
History of stroke	2.04	1.53–2.70	0.001
Stroke in the past	1.63	1.04–2.56	0.032

out of 600 patients). Mild to moderate muscle symptoms were observed in 55 (9.2%) patients, regardless of gender.

Discussion

The main finding of our study is that in real clinical practice in Russia, about 60% of elderly patients did not have a clear understanding of the importance of constant use of statins. We included almost 1000 CHD patients ≥ 65 years of age who were clearly eligible for statin therapy, but 23% of them had not received a statin recommendation from their physicians. Among others, 18.7% of patients refused to take statins or 41.5% took statins intermittently. In our study, the leading reason for inconsistent use of statins (46% of cases) was fear of adverse events, although side effects in those taking statins developed four times less frequently than expected (only 11.7% of patients). The second most common reason for non-adherence to treatment (29% of cases) was lack of motivation for treatment due to a lack of belief in its effect. About 27% of patients reported memory impairment, which was also a major barrier to chronic statin use. Polypharmacy was another reason for treatment discontinuation. Women were more likely to experience side effects, leading to higher rates of treatment discontinuation. This provided better control of LDL-C levels in men compared to women, although men had less faith in the ability of statins to prolong their lifespan. Poor control of cholesterol levels, despite taking the drug, was the reason for refusal to take statins in every fifth patient. Adherence to statin treatment increased significantly when target LDL-C levels were achieved. The most important evidence base is that high adherence to statins provides a significant reduction (59%) in cardiovascular risk in patients with target LDL cholesterol levels [15]. It is well known that polypharmacy, comorbidity, the presence of multiple risk factors, and high LDL-C levels at baseline at any age significantly reduce adherence to statin therapy. [16, 17]. Only a persuasive, convincing, and detailed explanation of the necessity of taking lipid-lowering drugs for cardiovascular risk reduction can increase adherence of older patients to the therapy. A large observational 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 for primary prevention [18]. In 542 hospitalized patients with angiographically confirmed CAD with a mean age of 69 years from an area with the highest CAD mortality rate, only 85% of patients were receiving statins at discharge, with a further decline in statin adherence of 15.7% at 12 months of follow-up [19]. Similarly, in a large study of 62,070 patients (mean age 66 years, 65% male), statin therapy was associated with 25% relative reduction of 3-year risk of major cardiovascular events ($P < 0.0001$) [20]. In a study of 347,104 patients with ASCVD, it was found that the lower the adherence to statin therapy, the higher the risk of all-cause mortality [21].

The USAGE (Understanding Statin Use in America and Gaps in Education) Internet survey assessed the behavior of 10,138 US adults who were former or current statin users. Muscle symptoms were reported by 60% and 25% of former and current users, respectively [22]. The primary reasons for switching from one statin to another were cost (32%) and SAMS (33%), whereas the primary reason for discontinuation was side effects (62%). Lack of efficacy was mentioned only 13% of respondents [23]. Nearly half of the participants switched a statin at least once [22]. In

our study, we assessed the reasons for discontinuation, but not for switching statins. Also, the USAGE survey demonstrated that females were more likely to have discontinued statin intake than males [24], whereas we found no differences in statin discontinuation between women and men. Importantly, the larger ACTION (Adherence and concerns with statins and medication discussions with physicians) survey confirmed the main findings of USAGE [25]. Gender differences in treatment adherence may be due to biological or social reasons. Women are less likely than men to believe that statins are safe and effective. Women perceive themselves to be at low risk of fatal cardiovascular events [26, 27].

Adherence is typically measured as a single fixed average over the entire follow-up period, but should be considered over time and across behaviors. A retrospective cohort study that controlled for time-dependent factors influencing prior adherence and the temporal sequence between factors found that adherence to statins in women reduced the risk of cardiovascular events by approximately one-fifth compared with non-adherence [28]. Thus, adherence is a complex behavior that requires training, motivation, and lifestyle changes. Other factors, such as socioeconomic status, also play a role. In previous studies, adherence to statin treatment was lower in women than in men [29]. There are no studies on gender differences in adherence to statins in the Russian population. The lack of gender differences in adherence in our study may be country-specific.

Our study reveals two important trends in current statin therapy. First, the cost of statins is not a limiting factor for their use in clinical practice. Second, the number of side effects with statins was much lower than expected. Elevations in creatine kinase levels associated with statins occurred in less than 1% of patients, while mild to moderate muscle symptoms were observed in 9.2% of patients. The PRIMO (Prediction of muscle risk in observation) study conducted in France in patients with hyperlipidemia (30% aged ≥ 65 years) treated with high-dose statins showed that the incidence of mild to moderate muscle symptoms was 10.5% [11]. In our study, only 14.5% of participants received high-intensity statin therapy, and overall, statin-related muscle symptoms (including asymptomatic creatine kinase elevations) were observed in 10% of participants. Moreover, we showed that statin therapy in older patients was administered for the first 3 months, after which adherence to treatment sharply decreased. Prescribing statins to older patients would likely be justified by a balanced approach based on the benefits of statins with the lowest risk of adverse events. It is assumed that proper treatment of an elderly patient requires mutual understanding and agreement between the patient and the physician [22]. Ensuring the quality of life of an elderly patient is an important issue in terms of medical care. We need to expand and improve outpatient care for this group of patients, avoiding polypharmacy as much as possible and providing medications based on expected benefits and potential risk of complications.

Our study has several limitations. First, physicians involved in the study retrospectively analyzed medical records and questionnaires filled by patients. Second, we cannot exclude the possibility that some patients may have provided inaccurate information about their attitudes toward statin treatment due to cognitive problems. However, our study provides novel and valuable information on statin adherence in elderly patients in a real-world setting.

Conclusions

Elderly patients with CHD in real-world clinical settings in Russia demonstrated poor adherence to statin therapy, and the incidence of statin-associated muscle symptoms was about 10%.

Declarations

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Conflicts of interest: Authors declare no conflict of interests.

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Ethical approval: This study was conducted in accordance with the Helsinki Declaration and approved by the Institutional Review Board/Ethics Committee.

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