Facts and myths about use and effect of statins in patients with dyslipidaemia - a survey of physicians.

Keywords

statins, primary health care, family medicine, dyslipidaemia

Abstract

Introduction

Statins are the primary medications used to treat lipid disorders. However, numerous myths surrounding statin therapy lead to patient non-adherence and therapy discontinuation. The aim of this study was to assess the most common patient concerns regarding statin use.

Material and methods

A survey was conducted targeting doctors using an online questionnaire The first section included questions regarding socio-economic status, while the second focused on patient experiences related to refusing statin treatment due to fears of specific side effects, encounters with side effects during therapy, and estimates of the percentage of patients who discontinue treatment. The concluding section addressed the most common reasons for treatment termination from the perspective of practitioners, along with efforts to educate their patients.

Results

260 questionnaires were collected. Notably, 84% and 81% of doctors reported encountering refusals of statin treatment due to patients' fears of liver and muscle damage, respectively. The majority of respondents indicated that 10-20% of patients discontinue treatment on their own, despite significant side effects occurring in less than 10% of cases. Muscular symptoms were cited as the reason for discontinuing therapy in 75% of cases, while misinformation regarding statin side effects contributed to 53% of discontinuations. Additionally, 96.5% of doctors acknowledged efforts to educate their patients about statins.

Conclusions

Many harmful beliefs about the side effects of statins persist among patients, resulting in nonadherence to treatment. The most prevalent concerns involve fears related to muscle and liver damage. These issues can be mitigated through targeted education for both patients and healthcare professionals.

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Introduction:

Cardiovascular disease is the leading cause of death in developed countries. [1] A major risk factor for cardiovascular disease is lipid disorders, so the treatment of dyslipidaemia should always be considered within the context of cardiovascular disease prevention. [2] [3] The most used medications for treating lipid disorders are 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors, commonly referred to as statins [4]. Statins have been shown to inhibit the production of apolipoprotein B-100 in hepatocytes and to reduce the production of very low-density lipoprotein (VLDL). [7] [8]. Their effects are pleiotropic and extend beyond lipid metabolism. For example, statins use improves prognosis in people with acute kidney injury and prevents the occurrence of colorectal cancer. [9], [10], [11] They are also s used in the primary and secondary prevention of ischaemic heart disease. They reduce the risk of coronary incidents, stroke, and death from cardiac causes. [12], [13] Statins not only prolong life but also improve the quality of life. [14]

Despite the substantial scientific evidence supporting the benefits of statins, numerous myths about their side effects have grown over the years. This issue is compounded by the antistatin movement, dissemination of false information about statin therapy and lack of patient education resulting in fear of the side effects. [15] An important clinical problem is the gap between those eligible for treatment with statins to prevent cardiovascular disease and those treated. Studies indicate that around 10% of patients refuse treatment with statins, and around 30% discontinue therapy. Fear of side effects was the most common reason for giving up or stopping treatment. [16] A meta-analysis including data from many countries around the world showed that approximately 42% of statin users discontinued treatment during a follow-up period ranging from 6 months to 12 years. [17] Statin withdrawal is associated with increased cardiovascular incident rates and mortality compared to those continuing prescribed therapy [18]. Studied and described side effects of statins are myalgia, increased liver enzyme values, and increased risk of developing diabetes. [19]

Side effects associated with the use of statins in clinical trials are relatively rare. However, in their clinical practice, doctors often encounter the patient's refusal to include a statin in their treatment. Despite the existence of many studies that verify and assess the frequency of given side effects, there are no studies that assess the scale of "statin phobia" from the perspective of the doctor prescribing treatment.

The aim of this work was to investigate the most common concerns patients raised with their physicians before the implementation of statin treatment, which led to refusal to consent to therapy and to find out the most common reasons for discontinuing statins by doctors. Their identification will enable efforts to counter disinformation by citing knowledge based on scientific evidence.

Materials and methods

A CAWI (computer-assisted web interview) type survey was conducted using a proprietary questionnaire. The questionnaire was distributed online, mainly via Facebook, where it was posted in doctors' groups (membership of the groups is conditional on the presentation of a medical licence). The mailing database of the Polish Society of Family Medicine was also used. Results were collected over three months, from August to November 2023.

Before completing the survey, respondents were informed of its objectives and how the results would be used, after which they gave their informed consent to participate in the study. Participation in the survey was fully anonymous and voluntary, and the participant had the opportunity to stop the survey at any stage. They were also asked to provide an e-mail address.

The author's questionnaire consisted of single and one multiple-choice questions. The first part included questions on informed consent and being a doctor. If the answer to one of these questions was negative, the survey was not taken into consideration. The next part concerned the respondent's socio economic status, including age, gender, length of service in years, and stage of the doctor's career (specialist or in the process of specialising in family medicine, doctor without specialisation, specialist or in the process of specialising in a field other than family medicine). Subsequently, the participant was asked whether, in his/her work, he/she encounters refusal of treatment with statins from patients due to fear of a specific side effect. Liver damage, muscle damage, dementia, erectile dysfunction, development of diabetes, cataracts, and prostate cancer were considered. They were then asked to estimate what percentage of patients discontinue statins on their own without first consulting their doctor based on experience from clinical practice. The

doctor was then asked whether he or she had encountered adverse reactions to these drugs in his or her patients and, if so, in what percentage. They were also asked about the most common reason for the decision to discontinue appropriate treatment in cases where this situation occurred. The final question concerned the issue of the doctor undertaking education of his patients.

A questionnaire in English has been included in the supplementary materials. The authors of the study made every effort to eliminate potential errors in survey responses. To limit the multiple completion of the survey by the same user, the e-mail address provided could only be used once. The questionnaire could not be sent if answers to any of the questions were omitted.

The study was conducted following the Declaration of Helsinki, and approval was obtained from the Bioethics Committee of the Medical University of Wroclaw.

Statistical Analysis

The variables analysed were qualitative and quantitative. Normality of distribution was assessed using the Shapiro-Wilks test. Quantitative variables were presented in the form of mean value and standard deviation. Qualitative variables were presented in the form of percentages. Comparison of qualitative variables was made using the Chi square test. Statistical significance was assumed at the level of <0.05. Calculations were performed using Statistica 13 software by TIBCO Software Inc. (Palo Alto, CA, USA).

Results

1. Characteristics of the study group

The survey was completed by 260 doctors, 188 women (72%) and 72 (28%) men. Most respondents were doctors working in primary care residents and family medicine specialists 80%. Most respondents were indviduals undergoing specialization (52%). Specialists and doctors without specialization constituted 41% and 7%, respectively. The largest group consisted of doctors with \leq 5 years of experience (51%), followed by doctors with between 5 and 10 years of experience (29%). The smallest group were doctors with more than 10 years of experience (20%). The average length of service in primary care was 8 years, SD 7.25.(Table 1).

Table 1. Characteristics of the study group.

2. Reasons for refusing treatment with statins

Less than 80% of doctors faced refusal of statin treatment from patients due to fear of liver or muscle damage. Other reasons were indicated much less frequently (Table 2, Figure 1.).

Table 2. Doctors who faced refusal of treatment with statins due to a given concern

Respondents indicated that around 10-20% of patients discontinue statins on their own. More than ¾ of doctors encountered adverse effects of statins in their practice, which occurred in less than

10% of treated patients. A small proportion of patients (<10%) required treatment discontinuation for medical reasons. The most frequently cited reasons for doctors deciding to discontinue statins were myalgia or a high increase in CK, disagreement with treatment due to misinformation about the side effects of statins, drug intolerance, and liver enzyme elevations (Table 3, Figure 2.). As many as 96.5% of doctors declared, that they attempt to educate patients.

Table 3. Table 3. Doctor's reasons for discontinuing therapy.

3. Comparison of results in terms of gender and work experience

The results were compared in terms of the impact of gender and seniority. A detailed summary is provided in table 4. During the study, it was observed that doctors with longer work experience were statistically more likely to encounter side effects of statins in their patients and were more likely to admit to discontinuing treatment due to muscle pain or elevated liver enzymes. Physicians with the shortest professional experience (\leq 5 years) were less likely to report the experience of refusing statin treatment due to the patient's fear of developing dementia and diabetes. There were no significant differences in patient education with a negative attitude toward statins in groups divided by gender and work experience.

Table 4. Comparison of results in terms of gender and work experience

Discussion

In the present study, the practical experience of physicians with statin therapy for dyslipidaemia patients was reviewed, mainly in terms of refusal and discontinuation of the therapy. The most common reasons for not taking or discontinuing treatment were due to patients' fear of liver and muscle damage, which in most cases were not justified. Doctors indicated that a low percentage of patients required termination of therapy. This is confirmed by a large meta-analysis from 2022 [20], which analyzed over 4 million patients using statins, and side effects occurred in only 9.1% of them. Therefore, in the remainder of this article, we have undertaken to review all the patients' fears of statin treatment for veracity and medical justification. Many of these are misconceptions whose harmfulness must be combated. We believe that an explanation based on factual medical data will help doctors in daily practice to dispel myths and contribute to better therapeutic adherence.

One of the most common patients' concerns about statin treatment is the fear of liver damage. Scientific reports show that this fear is unfounded. The mechanism responsible for the adverse effects of statins on the liver, causing an increase in liver enzymes, has not been fully elucidated. [21]. [22] A transient increase in aminotransferase activity occurs during the first 12 weeks of treatment and usually resolves spontaneously. The increase in these enzymes does not correlate

with histopathological changes and, therefore, does not meet the criteria for liver damage [23]. A review of large, randomised trials and case reports of patients treated with statins by Law and Rudnicka found that liver and biliary dysfunction during the use of these drugs was comparable to placebo [24]. In a retrospective study, Smith et al. showed a significant increase in ALT and AST activity in only 1% of patients treated with statins. Charles et al. found elevated ALT activity in only 0.3% of patients who took a single statin for 4 years. [25] [26] Denus et al. conducted a meta-analysis of 13 randomised, controlled clinical trials. They evaluated almost 50,000 patients treated with statins for lipid disorders as part of cardiovascular disease prevention. The incidence of elevated serum aminotransferases was comparable in the treatment and placebo groups [27]. However, it is important to note that a contraindication to taking statins, according to the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) guidelines, is chronic liver disease with serum ALT and AST activity exceeding three times the upper limit of normal. The guideline recommends the determination of aminotransferases eight weeks after starting treatment with statins or after increasing the drug dose. An increase in ALT values less than three times the upper limit of normal is not a reason to discontinue treatment [28].

Another concern of patients was muscle damage during statin treatment, which was declared by 84% of respondents. The association of muscular symptoms with statin intake SAMS (*Statinassociated muscle symptoms*). Typically, it is characterised by symmetrical pain, weakness, and cramps in the xiphoid muscles, primarily the thigh, buttock, and trunk muscles. Symptoms generally appear within 4-6 weeks of starting treatment, less frequently after a longer period of use, when it is most often due to a change in dose or the administration of another drug affecting the pharmacokinetics of statins [29]. In most cases, SAMS is not accompanied by an increased CK activity, in contrast to the most severe muscular complication, rhabdomyolysis. Where a significant increase in CK 40 times above the upper limit of normal myoglobinaemia and myoglobinuria can be observed, which can lead to acute renal failure. It is a life-threatening condition that occurs infrequently, with an average of 1 per 100,000 patients treated with statins [24].

Clinical studies show that SAMS affect 7-29% of patients, which is not supported by randomised placebo-controlled blinded studies, where the percentage is much lower, ranging from 1.5-5%. [30], [31] In *The Effects of Statins on Muscle Performance* (STOMP) study involving 420 volunteers randomly allocated to test and control groups, symptoms of myalgia were reported by 9.4% of those treated with 80 mg atorvastatin and 4.6% of those receiving placebo. [32] In other randomised trials, the frequency of SAMS was similar in both groups. Studies have been conducted using high doses of statins in patients. Not enough data were available to perform subgroup analyses based on dosage [33], [34], [35]. The risk of SAMS increases with statin dose but also with the presence of other risk factors (genetic factors, patient characteristics, and interactions with other drugs) [36].

In case of suspicion of SAMS in a patient taking statins, the physician should order a serum CK analysis. However, it should be remembered that high-intensity physical exertion, the use of drugs that inhibit the metabolism of statins (fibrates, antifungal azole drugs, macrolide antibiotics), drugs and substances that negatively affect muscle tissue (steroids, immunosuppressants and antipsychotics, i.e., steroids and antipsychotics such as haloperidol, risperidone, opioids, alcohol) are often responsible for muscle complaints or the nocebo effect [29]. The nocebo effect is related to the perception of discomfort associated as a side effect of the drug through the patient's negative

attitudes towards its use and the expectation that a particular side effect may occur. [37] The Samson study, which included 60 patients with a history of statin treatment interruption due to SAMS, assessed the above phenomenon. During the monthly periods, the subjects were randomised to alternately take 20 mg of atorvastatin or a placebo or remain pill-free. The cycle was repeated four times. The frequency of reported SAMS was similar in both groups; those receiving the drug and placebo. [38]

Approximately 17% of physicians have encountered the opinion that statins cause dementia. The incidence of dementia is age-related, and with an increasingly ageing population, the number of people with dementia is steadily rising. [39] Numerous studies have been carried out to investigate the possible effects of statins on the development of dementing disorders. In contrast, data from the literature indicates the opposite. [40] The use of statins has been shown to have a beneficial effect in reducing the incidence of general dementia, Alzheimer's disease, and mild cognitive impairment. This is because statins inhibit the formation of many intermediates in the cholesterol synthesis pathway. Some of these compounds are involved in the deposition of amyloid and senile plaques in the brain, responsible for Alzheimer's disease. [41] There was also a 10-year follow-up of patients with the ApoE4/ApoE4 genotype. This study showed that the incidence of Alzheimer's disease was significantly lower in statin users than in the control group. [42] The protective effect of statins against dementia is also confirmed by a large study in Taiwan, which also confirms the inversely proportional correlation between statin dose and risk of dementia [43].

The experience of patients' fear of statins due to the alleged risk of erectile dysfunction was reported by 8% of doctors. Statins have been shown to improve vascular endothelial function by reducing the concentration of low-density lipoproteins that act adversely on it. As a result, nitric oxide activity in the walls of the penile capillaries increases and erectile function is improved. This effectiveness has been confirmed in several studies. [44], [45] On the other hand, statins may impair erectile function as they reduce the synthesis of testosterone. Several studies supporting this thesis can be found in the literature. Meta-analyses of randomised placebo-controlled trials addressing this topic come to the aid of assessing the effect of statins on erectile function. One meta-analysis involving a review of seven studies on the effects of rosu- and atorvastatin on erection found positive effects on erection. A limitation of this meta-analysis was the small group of included patients (686) and the fact that it was characterised by high heterogeneity. [46] The Hope 3 study involving a group of 2153 patients and a follow-up period of 5.8 years was very important. Rosuvastatin and its effect on erection compared with placebo were analysed. The results showed a slight improvement among patients taking statins compared to placebo. [47]

Undoubtedly, the topic of the effect of statins on erectile function has not been definitively investigated, especially when studies reporting a decrease in testosterone levels during therapy with 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors and thus a possible induction of hypogonadism [48], [49]. Although the meta-analyses and studies cited reveal a positive effect of statins on erectile function, there is a need for further, larger-group and well-designed placebo-controlled studies investigating this correlation.

Another myth about statins experienced by 4% of doctors was the alleged risk of cataracts during their use. Statins have not been shown to increase the risk of developing cataracts. Metaanalyses of randomised placebo-controlled trials have not proven a keratogenic effect of statins [50]. On the contrary, some studies have suggested a protective effect of statins on the risk of cataracts, but the results were not reliable enough to draw a definite conclusion. Given the significant benefits of statins in patients with cardiovascular conditions, the presumed risk of cataracts should not deter their use.

3.5 % of doctors declared that they had faced refusal of treatment with statins because of patients' fear of developing prostate cancer. Statins have not been shown to increase the risk of prostate cancer. On the contrary, according to meta-analyses of the studies published to date on this topic, statins may reduce this risk, especially of advanced and fatal cancers [51]. It is possible that statins will be one of the therapeutic pathways for prostate cancer in the future, but further research is needed for this to reach the strength of a recommendation.

The fear of developing diabetes because of treatment with statins was encountered by 20 % of doctors. Statins, niacin, thiazide diuretics, and beta-blockers are categorised as diabetogenic drugs. [18] In the JUPITER study (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin), patients treated with rosuvastatin 20 mg/dl for 1.9 years with one or more risk factors for diabetes had 28% more cases of diabetes compared with placebo. In patients without risk factors for diabetes treated with rosuvastatin 20 mg/dl, there was no increased incidence of diabetes. [53] In the SPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels) study, 34% of those taking statins developed diabetes within 4.9 years. [54][55] A large retrospective cohort study from 2021 found that statin use was associated with diabetes progression, including a greater likelihood of starting insulin treatment, significant hyperglycaemia, acute glycaemic complications, and increased prescriptions for hypoglycaemic drugs. Secondary analysis showed a dose-dependency of statin and faster progression of diabetes. [56] A 2024 metaanalysis assessed the effect of statin therapy on new-onset diabetes. It found that statins cause a modest, dose-dependent increase in the number of new-onset diabetes diagnoses. However, the adverse effects of statins on cardiovascular risk that may result from these small increases in glycemia are already accounted for by the overall reduction in cardiovascular risk seen with statin therapy in these studies. [57] During treatment with statins, patients who are obese, have elevated triglycerides, and suffer from hypertension are most at risk of developing diabetes. Patients with the above burdens are at high risk of developing diabetes even if they are not taking statins. Patients without risk factors for diabetes treated with statins did not show an increased incidence of diabetes. [18,58]

The authors are aware of the limitations of the study, which undoubtedly include the data collection methodology. The survey was distributed through a social network and the mailing database of the Polish Society of Family Medicine, but the authors are unable to provide the percentage of respondents who completed the survey from each source. This resulted in a clear advantage for doctors of this specialty. Additionally, probably due to the fact that more women work in primary health care and that women are more willing to participate in surveys, men constituted only 32%. Moreover, the questions in the questionnaire were based on the subjective estimate of the respondent and did not specify the period of time to be taken into account. This contributed to a high generalization of the results. A significant limitation was also the superficially collected interview about the characteristics of the study group. There were no questions about the

respondent's place of residence and work. This prevented better comparison of results and identification of risk factors for given responses.

Doctors are often faced with refusal of treatment with statins and discontinuation of therapy due to circulating misconceptions among patients that are not fully understood. We hope that the arguments cited based on factual medicine will make it easier for doctors to educate their patients. Increasing the proportion of patients properly treated for dyslipidaemia will translate into a decrease in cardiovascular mortality.

Summary

Many misconceptions about the side effects of statins circulate among patientsoften leading to refusals to start or continue therapy. . In our study group, nearly 80 % of the doctors interviewed had encountered refusal of statin treatment from patients due to fear of liver or muscle damage. Scientific studies clearly show that adverse effects in patients treated with statins are rare, and their incidence is comparable to the placebo group. Statins play a crucial role in the prevention of cardiovascular disease, and emphasis should be placed on educating patients and healthcare professionals to reduce misconceptions about the side effects of these drugs. One proposed solution is to create and place information slots in the form of advertisements on television and radio. It would be enough to mention facts about the huge share of lipid disorders in the cause of death and how to deal with them with a healthy lifestyle and statins. Additionally, medical facilities could provide information brochures that patients could read while waiting for a medical appointment. However, doctors should have the opportunity to use reliable knowledge provided at scientific conferences and in open access articles. It is important that education is carried out on a large scale Scientific Societies such as the Polish Lipid Association or the Polish Society of Family Medicine are particularly important in the continuous education of doctors and improving their competences in the area of lipid-lowering therapy. In the case of high resistance to treatment with statins, it is worth offering patients other cholesterol-lowering substances, for example alicrocumab, which, according to research, provided clinically significant reductions in LDL-C. [59]

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Conflicts of Interest

The authors declare no conflicts of interest

Institutional Review Board Statement

The study was conducted in accordance with the Declaration of Helsinki and approved by the Bioethics Committee of the Medical University of Wroclaw (approval number: KB 308/2023N, approval date: 26 October 2023).

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study upon filling in the questionnaire.

Data Availability Statement

The database used in this study is available upon request. The data are not publicly available due to privacy restrictions.

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Table 1. Characteristics of the study group.

	N (%)						
	M ± SD						
Sex	Female	188 (72%)					
	Male	72 (28%)					
Tł	7.84 ± 7.25						
	resident or specialist in family medicine	207 (80%)					
Career stage	resident or specialist in another field	35 (13%)					
	doctor without specialisation	18 (7%)					

Reasons for refusing consent to therapy	Doctors who faced refusal N (%)			
liver damage	206 (81)			
muscle damage	214 (84)			
dementia	47 (17)			
erectile dysfunction	24 (8)			
diabetes mellitus	52 (20)			
cataract	9 (4)			
prostate cancer	11 (3.5)			

Table 2. Doctors who faced refusal of treatment with statins due to a given concern

Table 3. Doctor's reasons for discontinuing therapy.

Doctor's reasons for discontinuing statins N (%)				
Myalgia or a significant increase in CK levels	195 (75)			
Increased liver enzyme	88 (34)			
Intolerance	130(50)			
Cataract	3 (1)			
Patients' false beliefs and lack of consent	138 (53)			
Others	16 (6)			

Variable	Work experiance			Sex					
	≥5	6-10	>10	р	Female	Male	р		
Reasons for refusing consent to therapy									
liver damage	98 (74.3)	63 (84.0)	45 (84.9)	0.131	156 (83.0)	50 (69.4)	0.016		
muscle damage	108 (81.8)	58 (77.3)	48 (90.6)	0.151	159 (84.6)	55 (76.4)	0.122		
dementia	14 (10.6)	21 (28.0)	12 (22.6)	0.004	32 (17.0)	15 (20.8)	0.474		
erectile dysfunction	11 (8.3)	8 (10.7)	5 (9.4)	0.858	17 (9.0)	7 (9.7)	0.865		
diabetes mellitus	17 (12.9)	22 (29.3)	13 (24.5)	0.011	38 (20.2)	14 (19.4)	0.899		
cataract	2 (1.5)	4 (5.3)	3 (5.7)	0.218	4 (2.1)	5 (6.9)	0.057		
prostate cancer	5 (3.8)	3 (4.0)	3 (5.7)	0.843	7 (3.7)	4 (5.6)	0.511		
	Do	ctor's reasor	ns for discont	tinuing statir	IS				
Myalgia or a significant increase in CK levels	60 (45.5)	48 (64.0)	41 (77.4)	<0.001	107 (56.9)	42 (58.3)	0.863		
Increased liver enzyme	25 (18.9)	20 (26.7)	22 (41.5)	0.006	52 (27.7)	15 (20.8)	0.261		
Intolerance	47 (35.6)	29 (38.7)	22 (41.5)	0.739	70 (37.2)	28 (38.9)	0.805		
Cataract	1 (0.8)	0 (0.0)	1 (1.9)	0.485	0 (0.0)	2 (2.8)	0.021		
Patients' false beliefs and lack of consent	52 (39.4)	30 (40.0)	23 (43.4)	0.878	81 (43.1)	24 (33.3)	0.151		
Others	4 (3.0)	2 (2.7)	5 (9.4)	0.107	9 (4.8)	2 (2.8)	0.471		
Attempts to educate patients negative about statins	129 (97.7)	72 (96.0)	50 (94.3)	0.499	183 (97.3)	68 (94.4)	0.253		
Side effects after using statins	87 (65.9)	61 (81.3)	50 (94.3)	<0.001	147 (78.2)	51 (70.8)	0.212		

Table 4. Comparison of results in terms of gender and work experience



Figure 1. Doctors who faced refusal of treatment with statins due to a given concern



Figure 2. Docto's reasons for discontinuing statins