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Patient-Reported Symptom Burden Following Initiation of Statin Therapy: A Prospective Observational Study

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Abstract

Statins are one of the key drugs used to lower the risk of developing heart disease, but adverse symptoms experienced by the patients post medication are the foremost reason for non-adherence to the treatment. This research work was performed to evaluate the extent, timeline and factors associated with the symptoms reported by patients who were on statins for the first 12 weeks. An observational study was carried out on 248 patients prescribed with statins, among which 232 completed the study. Patients' burden of symptoms was assessed using an eight-questionnaire (score between 0-80) initially and 2-, 4-, 8- and 12-weeks post treatment. Analyses of the data collected were done using paired t-test, linear mixed effects model and multivariable logistic regression analysis using SPSS version 26.0. Of patients, 73.7% experienced one or more clinically significant symptoms in week 12, including, mainly, muscle pain (41.4%), muscle cramps (31.9%) and fatigue (30.6%). Clinically significant worsening was seen in 53.4% of patients, with higher frequency in high intensity versus moderate intensity therapy (67.4% vs 44.3%; $p = 0.001$). High intensity therapy (OR adjusted 2.58; 95% CI 1.43–4.65), being female (OR adjusted 1.94; 95% CI 1.08–3.49), polypharmacy (OR adjusted 1.87; 95% CI 1.04–3.36), and baseline concerns regarding ADRs (OR adjusted 2.21; 95% CI 1.24–3.94) independently predicted worsening. Modification of therapy occurred in 14.2% of patients, with higher frequency in the group experiencing worsening (23.4% vs 3.7%; $p < 0.001$). The mean LDL decreased by 42.4%. Burden of symptoms following statins initiation is considerable and front-loaded, and early structured assessment of symptoms can help to maintain therapy for a long time.

Keywords: Statins; Symptom Burden, Patient-Reported Outcomes, Statin Intolerance, Treatment Persistence, Cardiovascular Prevention, Prospective Study.

1 INTRODUCTION

1.1 Overview of Statin Therapy and Cardiovascular Prevention

Statins are one of the most commonly used drugs that lower the levels of cholesterol and prevent atherosclerotic diseases of the cardiovascular system. Efficacy of these drugs is related to the constant therapy and regular adherence to it. But there are people who either stop taking statins or take them in an irregular way due to muscle pain, weakness, cramps, and tiredness (Backes et al., 2017; Cheeley et al., 2022; Reith et al., 2022).

1.2 Patient Experiences Following Statin Treatment

Symptoms that could be experienced by patients beginning on statins include musculoskeletal pains, fatigue, and insomnia among others. There may be cases where such symptoms occur even before patients begin taking these drugs, thus posing challenges when determining the direct cause of such symptoms. Intensity of the medications, patient expectations, medical conditions, and other medications being taken by patients can have an effect on the reportage of such symptoms (Davis & Weller, 2021; De Vera et al., 2014; Herrett et al., 2021).

1.3 Research Motivation and Study Significance

The existing body of research on statin-related symptoms is based on either clinical trials or retrospective studies. Yet, this kind of research may fail to fully encompass the information provided by patients themselves. Regular assessment of the symptoms in the initial phase of the therapy allows identifying the course of development of the symptoms and patients, who may be at risk of changing their treatment.

1.4 Study Aim and Specific Objectives

The aim of this study was to evaluate patient-reported symptom burden following the initiation of statin therapy over twelve weeks and identify factors associated with clinically relevant symptom worsening.

The objective of this research was to assess the patient's symptom burden after the administration of statins over twelve weeks and the factors that contribute to clinically significant worsening of symptoms.

- Specifically, the objectives were:
- Assess the change in symptom burden from baseline to twelve weeks.
- Determine the prevalence of symptoms at follow-up.
- Compare the patterns of symptoms among moderate intensity and high intensity statin therapy.
- Identify the factors that contribute to worsening of symptoms.

- Evaluate the link between symptom worsening, modification of treatment, and LDL cholesterol lowering.

2 REVIEW OF LITERATURE

2.1 Patterns of Symptoms Among Statin Users

Several studies have emphasized the significance of muscle symptoms for patients who are on statins. Complaints include pain, cramping, muscle weakness, and discomfort. This can affect whether patients continue their medication or not (Katamesh et al., 2024; Sarzani et al., 2024). The reluctance of patients and the effect of expectations about treatments on adverse symptoms have also been studied (Shah et al., 2024).

2.2 Factors Influencing Symptom Development and Treatment Continuity

Various factors can be implicated in the development of symptoms related to statins and discontinuation of therapy. These factors may consist of medication strength, patient-related features, pre-existing medical conditions, and concerns about possible side effects (Stroes et al., 2015). The issue of statin intolerance and its influence on the quality of patients' lives has been discussed before (Tsushima & Hatipoglu, 2023).

2.3 Research Gap

There have been few studies done that combine a standardized self-report symptom questionnaire, serial measurements over the first twelve weeks, comparison of moderate intensity versus high intensity treatments, and symptom burden in relation to treatment adjustment and lipid levels in the same population. This study fills this research gap by studying new patients starting treatment for twelve weeks and measuring symptom burden and its effects.

3 METHODOLOGY

3.1 Research Design and Clinical Setting

An observational study was performed on consecutive patients attending out-patient clinics of a tertiary care teaching hospital of cardiology and general medicine. Subjects were followed up for 12 weeks after starting treatment for a duration of 12 months. The study proposal was approved by the Institutional Ethics Committee, written informed consent was taken from all subjects, and the study was done in compliance with STROBE guidelines for observational studies.

3.2 Participant Recruitment and Selection Criteria

Sample size determination was carried out for a single proportion by using $n = Z^2p\ (1 - p)/d^2$ with 95% confidence level, 50% expected proportion, and 6.5% absolute precision, leading to a minimum sample size of 228 subjects. Considering the possibility of loss to follow-up of 8% subjects, 248 subjects were recruited. Out of these subjects, 232 (93.5%) subjects participated in the twelve-week

evaluation and comprised the analysis population. The rest of the 16 subjects were either lost to follow-up (n=11) or withdrawn from the study (n=5). Adults 18 years or above age who were prescribed a statin drug for the first time, without any statin usage in the previous 12 months were the eligible subjects. Patients with the known intolerance to statins, presence of active liver diseases, elevated creatine kinase > three times upper limits of normal at baseline, hypothyroidism without any treatment, terminal illnesses, and cognitive dysfunction preventing self-reporting were excluded from this study.

3.3 Baseline Evaluation and Follow-Up Procedure

Prior to initiating treatment, age, sex, indication for therapy (primary/secondary prevention), diabetes mellitus, hypertension, number of drugs taken on a daily basis, and fasting LDL cholesterol levels (LDL-C) were documented by experienced investigators. Patients were asked whether they have any worries about possible side-effects from statins (yes/no). Completion of the symptom questionnaire was required to determine the symptom load prior to treatment. Statin and statin dose were selected by the treating physician, independent of the research project. Treatment was defined as being of moderate intensity (atorvastatin 10–20 mg, rosuvastatin 5–10 mg, or simvastatin 20–40 mg) or high intensity (atorvastatin 40–80 mg or rosuvastatin 20–40 mg). Assessments were performed at 2, 4, 8, and 12 weeks either by clinic visit or phone interviews. Fasting LDL-C was assessed at 12 weeks. Interviews were conducted using the same protocol as clinic visits. The investigators collecting data were not responsible for prescribing statins.

3.4 Assessment of Patient-Reported Symptoms

Symptom burden was assessed via an eight-item questionnaire on muscle pain, muscle weakness, muscle cramps, fatigue, joint pain, sleep disruption, gastro-intestinal discomfort, and headache or dizziness. Scores for each of the eight items were collected on a scale of 0 (absent) to 10 (worst possible), during the past 7 days. The overall score thus could range between 0 and 80, with higher scores implying greater burden. Content validity was ensured through the panel of clinicians' review, pilot testing of the questionnaire was done prior to its administration, and Cronbach's alpha reliability was high (0.87). Clinically significant presence of a symptom was assumed if its item score was 4 or greater. Clinically significant worsening of symptoms was the primary endpoint and was defined as an increase of 10 points or more in the overall score from baseline to week 12. Other secondary endpoints included modification of the treatment regime (either discontinuation, lowering of the dosage, or changing to another medicine due to symptoms) and change of LDL-C.

3.5 Overall Study Workflow

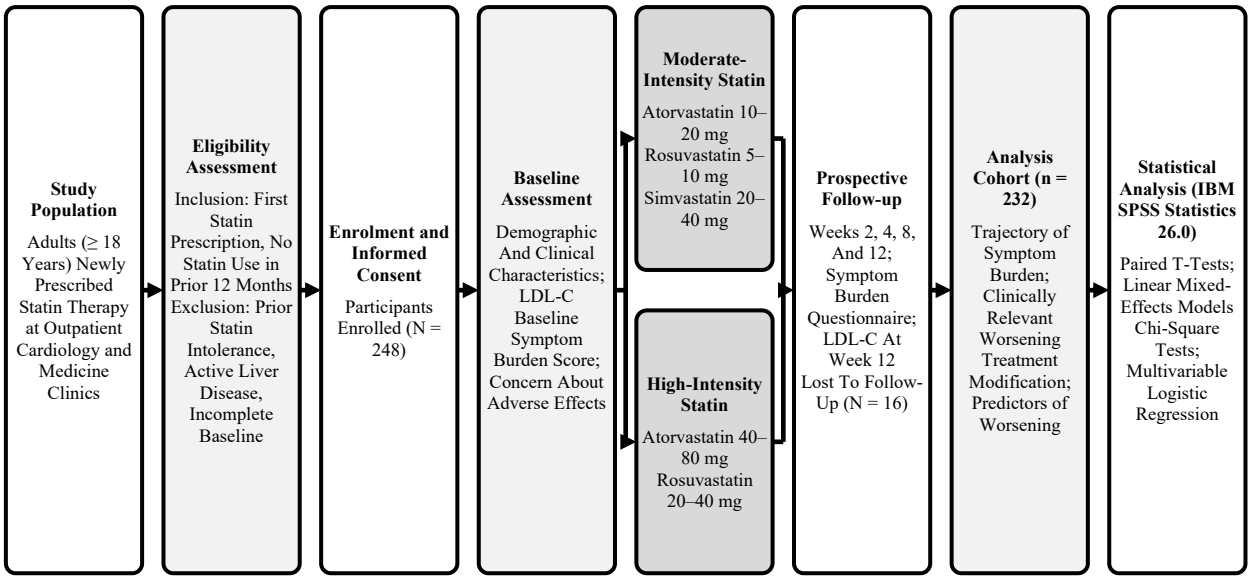


Figure 1: Study Design and Workflow Illustrating Participant Enrolment, Baseline Evaluation, Statin Intensity Classification, Follow-Up Assessments, And Statistical Analysis

The framework of the study is shown in figure 1. Adults meeting the criteria for the study were recruited and evaluated at baseline and then followed prospectively during their moderate or intensive statin treatment, as prescribed by their doctors. The burden of symptoms was assessed at each visit interval, and 232 patients completing follow-up constituted the study population.

3.6 Statistical Methods and Data Evaluation

Statistical analyses were done using IBM SPSS Statistics software, version 26.0. Descriptive statistics for continuous variables were presented as mean±standard deviation or median with interquartile range. Categorical variables were described as numbers and percentages. Paired t-test was used to compare the change in total score from baseline. Linear mixed-effect models were fitted to evaluate the trends of outcomes over time and differences between statin intensity groups, with time, intensity groups, and their interaction as fixed effect factors and random intercept at individual level. The chi-square test was applied to compare proportions. The multivariable logistic regression analysis included statin intensity, age, gender, diabetes, indications for treatment, polypharmacy (taking five or more medications daily), baseline symptom score and baseline concern about side effect score, and results were reported as adjusted odds ratio (aOR) with 95% confidence interval (CI). Item-level missing data were rare (<2%) and managed with mean imputation across the completed items of an individual. P-value <0.05 was considered statistically significant.

4 RESULTS

4.1 Demographic and Clinical Profile of Participants

The analysis sample consisted of 232 patients with mean age of 56.4 ± 10.7 years; among these, 126 (54.3%) were men, while 106 (45.7%) were women. Statins were prescribed for primary prevention in 143 patients (61.6%), while for secondary prevention – in 89 (38.4%). Diabetes was found in 98 patients (42.2%), hypertension – in 131 (56.5%), 84 (36.2%) patients used five or more drugs daily. Atorvastatin was prescribed in 118 (50.9%) patients, rosuvastatin – in 76 (32.8%), and simvastatin – in 38 (16.4%) cases. Moderate-intensity therapy was prescribed in 140 patients (60.3%), while high-intensity one – in 92 (39.7%). The worry about statin adverse effects before treatment was mentioned by 93 participants (40.1%). Mean baseline LDL-C was 142.6 ± 28.4 mg/dL. There were no differences in the baseline characteristics and in the baseline symptoms scores between the two groups, except for the fact that high-intensity therapy was prescribed more frequently for secondary prevention (65.2% vs 20.7%; $p < 0.001$).

4.2 Changes in Symptom Scores Over Time

The average total symptom burden score increased from 11.6 ± 8.4 at baseline to 22.4 ± 13.1 at week 4 and 22.8 ± 13.4 at week 12. The average increase from baseline to week 12 was 11.2 units (95% CI 9.5–12.9; paired $t = 13.12$, $p < 0.001$). Most of the change occurred in the first four weeks (average increase 10.8 units) after which the score leveled out at its highest point of 23.6 at week 8 and did not increase any more at week 12. There was a significant effect of time ($p < 0.001$) in the mixed-effects model. The trend differed depending on the intensity of the statin treatment (group × time interaction, $p = 0.002$). Patients receiving high-intensity treatment increased their score from 12.2 at baseline to 27.0 at week 12 (average change 14.8), while patients receiving moderate-intensity treatment increased from 11.2 to 20.0 (average change 8.8). The difference in change between the two groups was 6.0 units (95% CI 2.5–9.5; $p = 0.001$).

Figure 2 shows the total symptom burden score increased from baseline to Week 8 across all groups, with the high-intensity statin group showing the highest scores throughout the follow-up period. At Week 12, a slight reduction was observed in all groups, indicating a modest improvement in symptom burden.

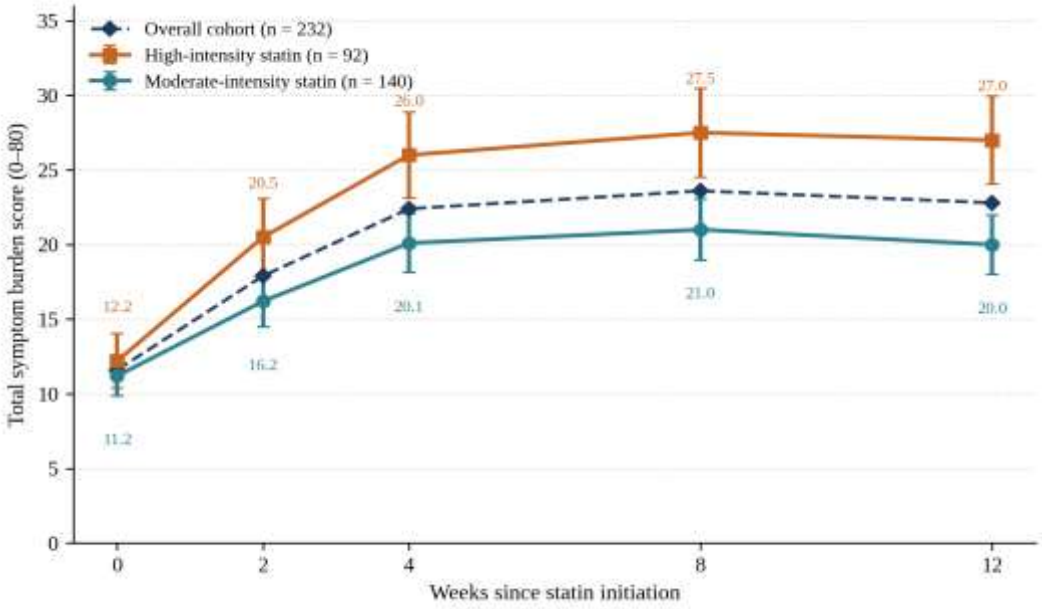


Figure 2: Mean Total Symptom Burden Score from Baseline to Week 12 By Statin Intensity. Error Bars Represent 95% Confidence Intervals

4.3 Prevalence of Individual Symptoms

Table 1: Prevalence of Clinically Relevant Symptoms (Item Score ≥ 4) and Symptom Severity During Follow-up (N = 232)

Symptom	Baseline, n (%)	Week 4, n (%)	Week 12, n (%)	Week 12 severity score, mean ± SD
Muscle pain	31 (13.4)	88 (37.9)	96 (41.4)	4.9 ± 3.1
Muscle weakness	22 (9.5)	61 (26.3)	68 (29.3)	3.6 ± 2.8
Muscle cramps	27 (11.6)	70 (30.2)	74 (31.9)	3.9 ± 2.9
Fatigue	35 (15.1)	66 (28.4)	71 (30.6)	3.8 ± 2.7
Joint pain	29 (12.5)	44 (19.0)	47 (20.3)	2.4 ± 2.5
Sleep disturbance	24 (10.3)	31 (13.4)	29 (12.5)	1.7 ± 2.2
Gastrointestinal discomfort	18 (7.8)	28 (12.1)	25 (10.8)	1.5 ± 2.0
Headache or dizziness	15 (6.5)	21 (9.1)	19 (8.2)	1.0 ± 1.7
Any clinically relevant symptom	**98 (42.2)**	**158 (68.1)**	**171 (73.7)**	—
Total symptom burden score (0–80)	**11.6 ± 8.4**	**22.4 ± 13.1**	**22.8 ± 13.4**	**22.8 ± 13.4**

The occurrence of clinically significant symptoms increased from baseline to week 4 in all eight symptoms and remained stable or slightly increased at week 12 (Table 1). Clinically significant symptom occurred in 98 participants (42.2%) at baseline, 158 (68.1%) at week 4, and 171 (73.7%) at week 12. Muscle pain had the biggest percentage increase, rising from 13.4% at baseline to 41.4% at

week 12, while muscle cramps (11.6% to 31.9%), muscle weakness (9.5% to 29.3%), and fatigue (15.1% to 30.6%) followed next. The percentage increase in joint pain was relatively small (12.5% to 20.3%), whereas sleep disturbance, gastrointestinal discomfort, and headache/dizziness remained largely unchanged from baseline. Muscle symptoms and fatigue were responsible for the majority of the new burden.

4.4 Factors Associated with Symptom Deterioration

A clinically relevant deterioration, which was defined as an increase of at least 10 points in the total score, was observed in 124 patients (53.4%). The patients on high-intensity therapy showed a greater incidence of deterioration (62 out of 92; 67.4%) compared to patients on moderate-intensity therapy (62 out of 140; 44.3%) ($\chi^2 = 11.91$, $p = 0.001$). In the multivariable model, high-intensity therapy was independently associated with a deterioration (aOR 2.58; 95% CI 1.43-4.65; $p = 0.002$), as well as female sex (aOR 1.94; 95% CI 1.08-3.49; $p = 0.027$), polypharmacy (aOR 1.87; 95% CI 1.04-3.36; $p = 0.036$), and having a concern about side effects at baseline (aOR 2.21; 95% CI 1.24-3.94; $p = 0.007$). A 5-point higher baseline symptom score corresponded to an increased odds of deterioration (aOR 1.19; 95% CI 1.03-1.38; $p = 0.020$). An age ≥65 years (aOR 1.61; 95% CI 0.86-3.01; $p = 0.136$), diabetes (aOR 1.12; 95% CI 0.63-1.99; $p = 0.699$), and secondary prevention (aOR 0.93; 95% CI 0.52-1.66; $p = 0.806$) were not associated with a deterioration.

4.5 Treatment Modification and LDL Cholesterol Response

The therapy was changed because of symptoms in 33 patients (14.2%), including 14 stops (6.0%) and 19 changes in dosage or medication switches (8.2%). Therapy changes were significantly more common in patients who had clinically relevant worsening (29 of 124; 23.4%) compared with those who did not have it (4 of 108; 3.7%) ($\chi^2 = 18.33$, $p < 0.001$). Nevertheless, even despite the high level of side effects, the mean value of LDL-C decreased from 142.6 ± 28.4 mg/dL at baseline to 82.1 ± 24.7 mg/dL after 12 weeks of treatment by 60.5 mg/dL (42.4%).

5 DISCUSSION

5.1 Interpretation of Major Findings

In this prospective study, a considerable increase in the symptom burden was reported after the use of statins, with a mean increase of 11.2 units on a scale of 80 units and the presence of clinically significant symptoms in 73.7% of patients at week twelve. This increase occurred during the first four weeks of treatment and then leveled off to a plateau, thus suggesting that the early weeks of treatment are the time when the symptoms occur the most. This increased burden included mainly muscle pain, cramps, weakness, and fatigue, while the burden related to sleep, gastrointestinal, and neurological systems did not change significantly.

The most significant variable that correlated with worsening was statin intensity. Patients on high-intensity statins were more likely to experience a greater increase in symptom burden, and their

odds for worsening were 2.6 times higher compared to the odds of other patients. Sex and polypharmacy, both factors related to different levels of medication exposure and the possibility of drug interactions, were also associated with worsening independently. The independent correlation between pre-existing concerns about adverse effects prior to treatment is indicative of the influence of patient expectations on symptom burden.

The fact that 42.2% of subjects had clinically significant symptoms before the initiation of treatment shows that there is an existing background burden of illness and that considering all post-treatment symptoms to have been caused by the medication would exaggerate its impact. The fact that the burden could be measured at baseline and at the follow-up is the biggest strength of this prospective study design. The fact that treatment changed in nearly one in four subjects who experienced clinically significant worsening, whereas less than one in twenty did not, shows that the questionnaire score is clinically significant. This pattern of results is meaningful from a practical standpoint. Since the scores reached a plateau from week 4 to week 8 and did not keep increasing, symptom burden in this group seemed to have remained stable rather than increased with continued treatment. The small reduction in mean scores from week 8 to week 12, especially for the moderate-intensity group, may be due to adaptation, resolving symptoms following dosage adjustments, or dropouts with high symptom burden; at this point, the current study cannot differentiate between these possibilities. However, the plateau implies that patients who make it past the first month without clinically significant symptoms will be less likely to have them afterwards.

5.2 Strengths and Limitations

Strengths of the study are its prospective design, measurement of symptoms prior to medication and at multiple time points, high rate of follow up, as well as the combination of patient-reported outcomes together with changes in treatment and lipids. There are limitations that have to be addressed. The lack of a control group makes it impossible to make causal inference about the cause of these symptoms. Statin and dosage were selected by the attending physician, which means that even after adjustment, the issue of confounding by indication cannot be ruled out. This is because the questionnaire used for symptom assessment has never been used elsewhere and has not been validated externally, as well as symptoms were self-reported.

6 CONCLUSION

This current prospective study brings into focus the need for monitoring patient-reported symptoms in the initial phase of statins' usage. The mean symptom burden score in the group of 232 participants who underwent twelve weeks of follow-up increased from 11.6 ± 8.4 to 22.8 ± 13.4, constituting a clinically significant mean difference of 11.2 points (95% CI: 9.5–12.9; $p < 0.001$). The maximum difference was found in the first four weeks. Clinically significant symptoms were experienced by 73.7% of participants, the most common being muscle pain (41.4%), muscle cramps (31.9%), and fatigue (30.6%). Symptoms worsened in 53.4% of participants and were significantly associated with

intensive statin treatment (aOR: 2.58; 95% CI: 1.43–4.65), being female, polypharmacy, and pre-treatment concerns about adverse effects. In addition, participants with symptoms worsening had a higher rate of treatment modification (23.4% vs 3.7%; $p < 0.001$), but with the mean LDL-C level reduction of 42.4%.

The key innovation in this study is the integration of baseline symptom assessment, follow-up symptom assessment, dose comparison, and lipid changes in one prospective design. The results obtained will help to include the screening for symptoms and personalized counseling into the management of statins. In future research, it would be necessary to test the eight-question questionnaire on a multicenter sample, conduct follow-ups for more than twelve weeks, use biological markers, and monitor symptoms using digital technologies. It would also be interesting to explore how personalizing the dose and timely intervention influence adherence to treatment and treatment adherence.

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