Original Article

Unveiling Barriers and Investigating the Influence of High-Intensity Therapy on Statin-Induced Myalgia and Intolerance

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ABSTRACT

Background: We used the statin-associated muscle symptom clinical index (SAMS-CI) to evaluate misconceptions among cardiologists regarding the use of high-intensity statins (HIS) in relation to intolerance, including myalgia, and to determine the occurrence of HIS-induced myalgia in patients with acute coronary syndrome (ACS).

Methods: The present observational cohort study, performed in a tertiary care cardiac hospital in Karachi, Pakistan, consisted of 2 phases. Phase 1 involved an online survey among practicing cardiologists to identify obstacles to HIS prescription. The second phase involved observing 418 ACS patients who underwent HIS therapy. Myalgia was assessed using the SAMS-CI and categorized as unlikely (2–6), possible (7–8), or probable (9–11) cases of myalgia.

Results: In the first phase, 77.8% (35/45) of physicians favored prescribing HIS therapy. However, the commonly perceived barriers were myalgia (31%), tolerability (29%), and affordability (22%). In the second phase, 418 patients were included. Among them, 19 patients (4.54%) experienced muscle symptoms based on the SAMS-CI score. Subsequently, 5 patients were classified as unlikely and continued the same dosage, while 6 patients were categorized as possible, leading to a reduction in dosage to moderate intensity. Consequently, their symptoms were resolved, and they continued the moderate-intensity regimen. Statin use was discontinued for the remaining 8 patients in the probable category for 4 weeks until the symptoms resolved, after which moderate-intensity statins were resumed.

Conclusions: Most patients tolerated a lower targeted dose of HIS without experiencing objective symptoms. Therefore, we confidently conclude that a lower targeted dose of HIS is generally well tolerated in the ACS setting and should be considered by physicians. ***(Iranian Heart Journal 2024; 25(2): 47-55)***

KEYWORDS: Acute coronary syndrome, High-intensity statin, Intolerance, Myalgia, SAMS-CI

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Statins are the mainstay therapy for dyslipidemias and are considered the cornerstone in the management of cardiovascular disease (CVD). They are widely used medications due to their extensive therapeutic window [1] and hold a class I indication for secondary prevention in atherosclerotic coronary artery disease (CAD) up to the age of 75 (the 2018 ACC Cholesterol guidelines). The beneficial effects of statins result from their mechanism of action, which involves inhibiting the HMG-CoA reductase enzyme. This inhibition diminishes the synthesis of cholesterol, particularly low-density lipoprotein, in the liver. Statins also exhibit other pleiotropic effects, such as anti-atherosclerotic properties. [2]

As a result, statins lessen the burden of ischemic heart disease, thereby decreasing morbidity and mortality in both primary and secondary prevention. [3] Nonetheless, myotoxicity serves as a major adverse effect of statins, hindering the complete prevention of CVD. The clinical spectrum of myotoxicity includes myopathy, myalgia, myositis, and rhabdomyolysis, characterized by creatinine kinase levels exceeding 10 times the upper limit of normal. The incidence of myotoxicity varies, occurring in approximately 1 per 1000 people per year, depending on the specific statin, its dosage, and the presence of other risk factors. [1,4]

Observational studies estimate that 10% to 15% of statin users experience statin-related muscle side effects, ranging from mild myalgia to more severe muscle symptoms accompanied by significant creatinine phosphokinase elevations. [5] In some randomized controlled trials, approximately 1.5% to 3% of statin users and up to 10% to 13% of participants in prospective clinical studies developed myalgia. [6-9] The prevalence of statin-associated muscle symptoms contributes significantly to the high discontinuation rates of statin therapy, reaching up to 75% within 2 years of initiation. [4,10] Notably, the risk of these symptoms increases exponentially with higher doses. [11]

High-intensity statin therapy is less frequently prescribed in the South East Asian population, particularly in Pakistan, potentially due to concerns of statin intolerance, including statin-induced myalgia. However, there is a lack of documented scientific evidence regarding perceived statin intolerance among physicians. To further assess the significance of this perception, an online survey was conducted to identify perceived barriers to high-intensity statin therapy. Cardiac care physicians from across the province of Sindh, Pakistan, participated in this survey. The majority of the physicians reported intolerance or myalgia (60%) and affordability (22%) as major barriers to high-intensity statin therapy in our population. Consequently, in the current study, we utilized the statin-associated muscle symptom clinical index (SAMS-CI) to collect clinical evidence regarding statin-induced myalgia among patients with acute myocardial infarction.

METHODS

This prospective observational study was conducted at a tertiary care cardiac hospital after obtaining approval from the Ethics Review Committee of the National Institute of Cardiovascular Diseases (NICVD) with reference to ERC-03/2020. In the first phase of the research, an online survey questionnaire was developed. It featured possible obstacles in prescribing high-intensity statins, including statin intolerance, myalgia, affordability, physician discretion, and physician insight into the use of high doses. The survey was sent to 100 registered cardiologists out of 153 on the online portal of the College of Physicians and Surgeons Pakistan (CPSP).

In the second phase of the research, 418 patients were recruited from January 10, 2020, through October 9, 2020. They were commenced on a high-intensity statin regimen

(rosuvastatin [20–40 mg] or atorvastatin [40–80 mg]) after AMI (either ST–segment-elevation myocardial infarction [STEMI] or non–ST-segment-elevation myocardial infarction [NSTEMI]). Patients with preexisting muscle symptoms and those who declined to provide consent were excluded from this study. Informed consent was taken before inclusion, and baseline demographics and other data were collected through the questionnaire. The sample size for the study was calculated with an expected 10% incidence of myalgia. [5] At a 95% confidence level and a 3% margin of error, the sample size was calculated to be 385. Still, 418 patients were recruited in order to cater for the expected 8.5% loss to follow-up after 4 weeks. The proposed SAMS-CI score was composed of the distribution of the muscle symptoms, duration, and further response on de-challenge and re-challenge. Based on these parameters, the score was calculated, and SAMS-CI was categorized as unlikely (2–6), possible (7–8), and probable (9–11). Upon the presentation of the patients, we recorded their demographic and clinical characteristics, which encompassed age (expressed in years), weight (measured in kilograms), height (recorded in centimeters), body mass index (calculated in kilograms per square meter), sex, smoking status, diabetes mellitus, family history of CAD, obesity, and hypertension. These characteristics were defined operationally. The type and dosage of statin were documented. Symptoms of myalgia were recorded for all the patients according to the usual definition as suggested in the medical literature. All the collected data were recorded on a predesigned proforma. Confounding variables and bias were strictly controlled by following inclusion and exclusion criteria and stratification. The study population subsequently underwent follow-ups at 4, 8, and 12 weeks. The SAMS-CI score was calculated, and the patients were assessed clinically to determine statin-induced myalgia.

The data analysis of the collected data was performed using IBM SPSS (version 21). After quality assessment, the collected data were presented through descriptive statistics, such as mean ± standard deviation (SD) and frequencies (%). The data were stratified by confounding variables such as demographic and clinical characteristics, and the incidence and the SAMS-CI categorization of myalgia were assessed.

RESULTS

Forty-five cardiac care physicians completed the online survey questionnaire: 77.8% (35/45) of the physicians were in favor of prescribing high-intensity statin therapy in our population. Most of the respondents claimed to prescribe rosuvastatin (38/45) and the remaining atorvastatin (7/45). The most commonly reported reason for not prescribing high-intensity statin in our population was myalgia (31%), followed by tolerability (29%) and affordability (22%). The physicians' perceptions of barriers to high-intensity statin therapy are presented in Figure 1.

From 418 patients, 327 were males and 91 were females. The mean age was 55.6±11.14 years. Out of them, 376 patients were diagnosed with STEMI and 64 patients with NSTEMI. Additionally, 379 patients underwent percutaneous coronary intervention. All these patients were kept on a lower range of high-intensity statin, along with guideline-directed medical treatment. Moreover, 33.5% of the patients (n=140) had a reduced left ventricular ejection fraction, and normal ejection fraction was found in 51.2% (n=214).

Only 19 patients (4.54%) experienced muscle symptoms while taking high-intensity statins (rosuvastatin [20 mg] and atorvastatin [40 mg]), as indicated by the mean SAMS-CI score of 7.63±1.8. Among these, 5 patients (1.19%) showed no likelihood of developing myalgia and

continued the same dosage without experiencing any new symptoms.

In the case of 6 patients (1.43%), there was a possibility of myalgia according to the SAMS-CI score. As a result, their dosage was reduced to moderate-intensity statins (rosuvastatin [10 mg] and atorvastatin [20 mg]). Fortunately, their symptoms resolved, and they were able to continue the moderate-intensity statins.

Statin medication was discontinued for 8 patients (1.91%) in the probable category for a duration of 4 weeks until their symptoms subsided. Following the resolution of symptoms, these patients were prescribed moderate-intensity statins.

Although muscle symptoms are uncommon in this population, they were more pronounced in females (7.7%) than in males (3.7%). Patients older than 65 were more prone (6.1%).

A low left ventricular ejection fraction was associated with myalgia in 8.6% of the study population (n=12) compared with a normal ejection fraction in 1.9% (n=4). Serum creatinine did not correlate with statin-induced myalgia and was not a risk factor for muscle symptoms. CAD risk factors were not significantly associated with the adverse effects of statin.

On multivariable binary logistic regression analysis, female sex and reduced ejection fractions (<40%) were independent predictors of myalgia, with adjusted ORs of 5.04 (95% CI, 1.68 to 15.17; *P*=0.004) and 5.18 (95% CI, 1.57 to 17.04; *P*=0.007), respectively (Table 3).

Table 1: Demographic and Clinical Characteristics of the Patients Prescribed With High-Intensity Statin Therapy After Acute Myocardial Infarction

Characteristic	Total
Total (N)	418
Sex	
Male	78.2% (327)
Female	21.8% (91)
Age, y	55.6 ± 11.14
≤45	20.6% (86)
46–65	63.6% (266)
>65	15.8% (66)
Risk Factors	
Hypertension	45.9% (192)
Diabetes mellitus	35.9% (150)
Positive family history	5.3% (22)
Smoking	15.6% (65)
Obesity	2.2% (9)
Ejection Fraction (%)	
Reduced (<40%)	33.5% (140)
Preserved (≥40%)	51.2% (214)
Not assessed	15.3% (64)
Type of MI	
Anterior wall MI	7.4% (31)
Inferior wall MI	74.2% (310)
Lateral wall MI	3.1% (13)
NSTEMI	15.3% (64)
Serum Creatinine (ng/dL)	
Normal	79.2% (331)
Raised	9.3% (39)
Not assessed	11.5% (48)
Procedure	
Primary PCI	79.9% (334)
Early invasive PCI	10.8% (45)
Only LHC done	7.9% (33)
None	1.4% (6)

Postprocedural Complications	
None	97.8% (409)
Arrhythmias	0.7% (3)
Heart failure	1.2% (5)
Site bleeding	0.2% (1)
Follow-up After 4 Weeks	
Mortality	1.2% (5)
Readmission	3.1% (13)
Acute kidney injury	2.4% (10)
Heart failure	7.9% (33)
Myalgia	4.5% (19)
*SAMS-CI score	7.63 ± 1.8
Unlikely (2-6)	26.3% (5)
Possible (7-8)	31.6% (6)
Probable (9-11)	42.1% (8)

NSTEMI: non–ST-elevation myocardial infarction; PCI: percutaneous coronary intervention; LHC: left heart catheterization; SAMS-CI: statin-associated muscle symptom clinical index

Table 2: Incidence and SAMS-CI Distribution of Myalgia by Demographic and Clinical Characteristics

Characteristic	Total (N)	Myalgia		SAMS-CI Categorization			
		Row % (N)	*P* value	Unlikely (2-6)	Possible (7-8)	Probable (9-11)	*P* value
Sex							
Male	327	3.7% (12)	0.103	25% (3)	41.7% (5)	33.3% (4)	0.435
Female	91	7.7% (7)		28.6% (2)	14.3% (1)	57.1% (4)	
Age, y							
≤45	86	3.5% (3)	0.751	0% (0)	100% (3)	0% (0)	0.032
46–65	266	4.5% (12)		41.7% (5)	16.7% (2)	41.7% (5)	
>65	66	6.1% (4)		0% (0)	25% (1)	75% (3)	
Hypertension							
No	226	5.8% (13)	0.199	23.1% (3)	38.5% (5)	38.5% (5)	0.634
Yes	192	3.1% (6)		33.3% (2)	16.7% (1)	50% (3)	
Diabetes Mellitus							
No	268	5.6% (15)	0.168	20% (3)	40% (6)	40% (6)	0.252
Yes	150	2.7% (4)		50% (2)	0% (0)	50% (2)	
Positive Family History							
No	396	4.8% (19)	0.293	26.3% (5)	31.6% (6)	42.1% (8)	-
Yes	22	0% (0)		0% (0)	0% (0)	0% (0)	
Smoking							
No	353	4.2% (15)	0.498	33.3% (5)	20% (3)	46.7% (7)	0.095
Yes	65	6.2% (4)		0% (0)	75% (3)	25% (1)	
Obesity							
No	409	4.6% (19)	0.508	26.3% (5)	31.6% (6)	42.1% (8)	-
Yes	9	0% (0)		0% (0)	0% (0)	0% (0)	
Ejection Fraction (%)							
Reduced (<40%)	140	8.6% (12)	0.012	25% (3)	25% (3)	50% (6)	0.565
Preserved (≥40%)	214	1.9% (4)		25% (1)	25% (1)	50% (2)	
Not assessed	64	4.7% (3)		33.3% (1)	66.7% (2)	0% (0)	
Type of MI							
Anterior wall MI	31	6.5% (2)	0.830	50% (1)	0% (0)	50% (1)	0.843
Inferior wall MI	310	4.5% (14)		21.4% (3)	35.7% (5)	42.9% (6)	
Lateral wall MI	13	0% (0)		0% (0)	0% (0)	0% (0)	
NSTEMI	64	4.7% (3)		33.3% (1)	33.3% (1)	33.3% (1)	
Serum Creatinine (ng/dL)							
Normal	331	5.1% (17)	0.275	23.5% (4)	35.3% (6)	41.2% (7)	0.545
Raised	39	5.1% (2)		50% (1)	0% (0)	50% (1)	
Not assessed	48	0% (0)		0% (0)	0% (0)	0% (0)	

NSTEMI: non–ST-elevation myocardial infarction; SAMS-CI: statin-associated muscle symptom clinical index

Table 3: Multivariable Binary Logistic Regression Analysis for Myalgia

	Initial Solution		Final Solution	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Female	5.15 [1.54 - 17.27]	0.008	5.04 [1.68 - 15.17]	0.004
Age, y				
*≤45	1	-	-	-
46–65	3.83 [0.43 - 33.77]	0.227	-	-
>65	5.11 [0.49 – 53.0]	0.172	-	-
Risk Factors				
Hypertension	0.66 [0.21 - 2.09]	0.479	-	-
Diabetes mellitus	0.38 [0.10 - 1.52]	0.171	0.35 [0.09 - 1.34]	0.127
Positive family history	0 [0 - 0]	0.998	-	-
Smoking	1.25 [0.23 - 6.70]	0.796	-	-
Obesity	0 [0 - 0]	0.999	-	-
Reduced ejection fraction (<40%)	4.88 [1.36 - 17.48]	0.015	5.18 [1.57 - 17.04]	0.007
Type of MI				
*NSTEMI	1	-	-	-
Anterior wall MI	1.08 [0.15 – 8.00]	0.939	-	-
Inferior wall MI	0.85 [0.20 - 3.53]	0.822	-	-
Lateral wall MI	0 [0 - 0]	0.999	-	-
Raised serum creatinine	0.98 [0.19 - 5.07]	0.977	-	-

*reference category
NSTEMI: non–ST-elevation myocardial infarction

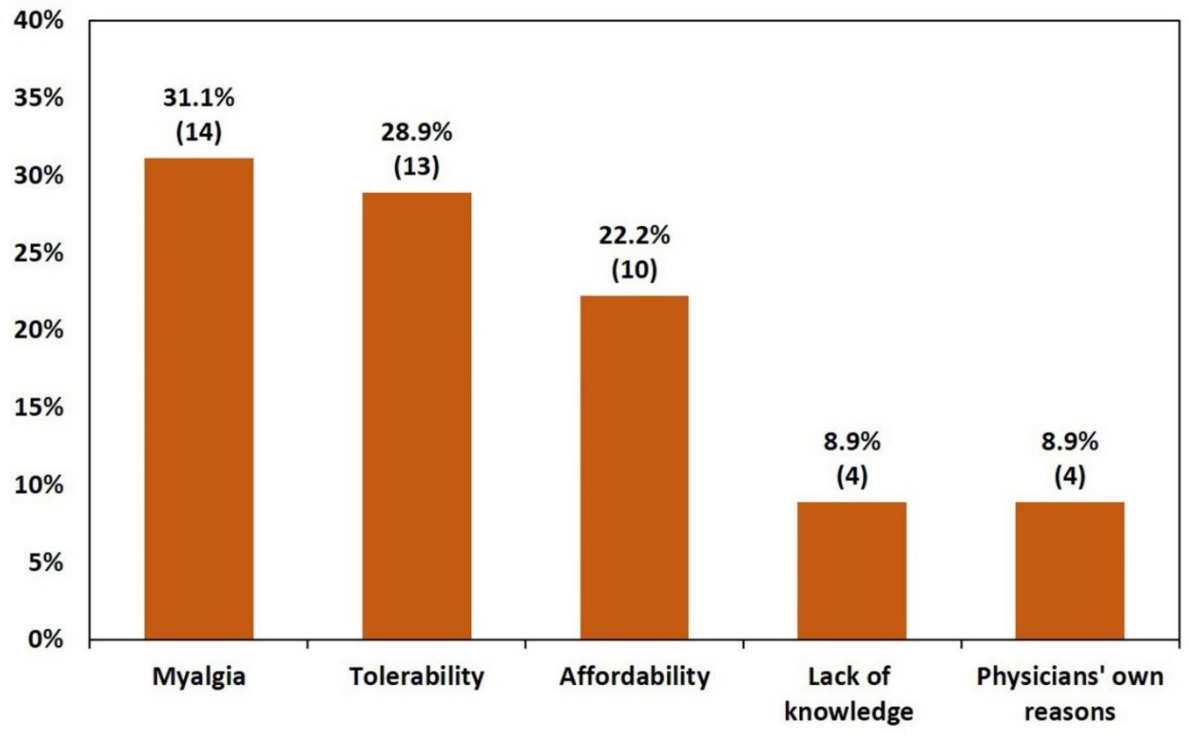

Figure 1: The image illustrates the physicians' perception of barriers to high-intensity statin therapy.

DISCUSSION

Statins serve as the fundamental and essential therapy for patients with acute coronary syndrome (ACS). However, many patients fail to achieve the target dosage of statins due to statin intolerance, often accompanied by myalgia. In the present study, we investigated physician perspectives on the prescription of high-intensity statins for secondary prevention in atherosclerotic CAD through an online survey. The survey revealed that statin intolerance, including myalgia (60%), was the primary reason cited by physicians for avoiding the prescription of high-intensity statins, even at lower dosages. Economic concerns for patients were also mentioned as a barrier. Based on these findings, a prospective observational study was initiated, as there were limited survey results or available data for comparison in South Asian countries. Notably, Japan and China have reported higher rates of statin intolerance, leading to limited statin doses being prescribed in those countries. [12, 13]

A clinical assessment of myalgia can be conducted effectively using the SAMS-CI score, enabling appropriate management as required. Therefore, in the present study, this scoring system was employed, revealing a prevalence of statin-induced myalgia of up to 4.5% when using lower doses of high-intensity statins, such as atorvastatin (40 mg) and rosuvastatin (20 mg). The majority of the studied patients tolerated the lower recommended dose of high-intensity statins well, with only 8 patients requiring a reduction in dosage to moderate intensity (rosuvastatin [10 mg] and atorvastatin [20 mg]) due to intolerance. A study conducted in France in an outpatient setting among 7925 hyperlipidemic patients receiving high-dose statin therapy under usual care reported muscle symptoms in only 10.5% (832) of the patients, with a median time of onset of 1 month. [14] These findings suggest a weak correlation between the use of high-intensity statins and the development of muscle symptoms, which may be outweighed by the cardiovascular benefits provided despite the presence of myalgia symptoms.

In the current study, muscle symptoms were evaluated based on patient-reported symptomatology using the SAMS-CI score rather than relying on laboratory evidence of creatinine kinase levels, as mentioned earlier. Nevertheless, Stein et al [15] in 1998 and Bakker-Arkema et al [16] in 2008 assessed myalgia without using a scoring system and by employing the definition described by the ACC/AHA/NHLBI. [17] These studies reported incidences of myalgia at 1.5% (n=521) and 2% (n=3500), respectively, in patients receiving high-dose statins.

The incidence of muscle symptoms was more prominent in females (7.7%), followed by older individuals (6.1%). This finding aligns with another study conducted by Parker et al [18] in 2015, which observed that nearly 60% of the subjects who experienced more pronounced muscle symptoms were older and/or women. Similarly, a clinical trial conducted in 2016 aimed to identify the occurrence and remission of statin-induced myopathy, taking into account patient perception and symptom characteristics from a sex perspective. This trial concluded that women reported a higher frequency of myopathy. [19]

Furthermore, contradicting our findings, a study conducted by Barter et al [20] in 2018, focusing on the clinical benefits of high vs low doses of statins in Japan, reported no evidence of serious adverse effects when using a higher dose compared with a lower dose of statin. Despite this disparity, the overall incidence of myalgia was lower with the use of high-intensity statins after ACS in our population.

Considering the clinical benefits associated with high-intensity statin therapy in atherosclerotic CVD, it is advisable for

cardiac care physicians to consider utilizing lower doses within the high-intensity range for statin therapy in our population. However, it is important to acknowledge the limitations of our study, such as the clinical assessment of myalgia without laboratory investigations and the fact that it was conducted at a single center.

Perspective

The findings of this study indicate that the benefits of statin therapy in reducing cardiovascular morbidity and mortality outweigh the risks of myopathy. Additionally, utilizing a lower recommended dose of a high-intensity range of statin allows patients with minimal muscle symptoms to adhere to this treatment regimen effectively.

CONCLUSIONS

High-intensity statin therapy is generally well tolerated in the ACS setting, particularly within the lower range of high-intensity dosages. We strongly recommend that physicians consider the incorporation of high-intensity statin therapy in ACS patients without hesitation. However, it is advisable to exercise caution and avoid the use of higher dosages within the high-intensity range in elderly individuals and female subjects.

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