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The appropriateness of the use of statins for the secondary and primary prevention of atherosclerotic cardiovascular disease: a cross-sectional study from Jordan

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Abstract. – OBJECTIVE: The appropriate use of statins to lower blood cholesterol remains the main strategy for primary and secondary prevention of atherosclerotic cardiovascular diseases (ASCVD). Here, we aim to examine the pattern of statin use and the appropriateness of dyslipidemia treatment in patients with or without established ASCVD according to the latest American Heart Association/American College of Cardiology (AHA/ACC) guidelines.

SUBJECTS AND METHODS: This is a cross-sectional study conducted in the largest tertiary government hospital in Jordan. Data was collected through face-to-face interviews and the review of medical records.

RESULTS: A total of 752 patients were enrolled, 740 (98.4%) patients were on atorvastatin, 8 (1.1%) were on simvastatin, 3 (0.4%) were on rosuvastatin, and 1 (0.1%) was on fluvastatin. The majority of patients, 550 (73.1%), used statins for secondary prevention. Only half of the patients, 367 (49.7%), received statin treatment at the intensity recommended by the guidelines. A large percentage of patients, 306 (40.7%), were undertreated with statins, and the management of dyslipidemia was not accompanied by appropriate follow-up. Based on the latest guidelines' recommendations, older age ($p = 0.027$), longer duration of statin use ($p = 0.005$), increased number of ASCVDs ($p < 0.001$), using statins other than atorvastatin ($p = 0.004$), and a history of angina ($p < 0.001$) or stroke ($p < 0.001$) were associated with undertreatment with statins.

CONCLUSIONS: The use of statins was not in concordance with the guidelines. Many of the patients surveyed were undertreated and adequate follow-up to identify the extent of patients' compliance and response was missing.

Key Words:
Statin, Dyslipidemia, Atherosclerotic cardiovascular disease, ASCVD, Prevention, Guidelines, Jordan.

Introduction

Cardiovascular disease (CVD) has remained the leading cause of death and poor quality of life worldwide for the past two decades[1]. Among CVD, atherosclerotic cardiovascular disease (ASCVD), such as coronary artery disease, cerebrovascular disease, and peripheral arterial disease, is highly preventable by managing modifiable risk factors in patients with established ASCVD (secondary prevention) and those at high risk of developing ASCVD (primary prevention)[2]. Many studies[3-6] show a causal relationship between the development of ASCVD and smoking, hyperglycemia, and, most importantly, dyslipidaemia.

Targeting low-density lipoprotein cholesterol (LDL-C) is the main focus of current and previous guidelines[7-9] on the management of blood cholesterol for the primary and secondary prevention of ASCVD. Lowering LDL-C by about 40 mg/dl can reduce the risk of cardiovascular events by a fifth[10]. Unlike in the management of other modifiable risk factors such as blood pressure and plasma glucose, intensive lowering of plasma LDL-C levels is not associated with any known risks (e.g., hypotension and hypoglycemia when treating hypertensive and diabetic patients, respectively)[11,12]. Therefore, there is no

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universal lower limit when lowering LDL-C levels. Instead, current American[8] and European[13] guidelines recommend intensive lowering of LDL-C to the lowest levels possible, with the European guidelines advocating for a more ambitious goal for LDL-C levels of less than 55 mg/dl in very high-risk patients compared with the target advised by the American guidelines of less than 70 mg/dl.

To achieve low LDL-C levels, potent pharmacological therapies are needed. Statins are the mainstay treatment for dyslipidaemia[8]. Statins lower LDL-C by inhibiting the 3-hydroxy-3-methylglutaryl-coenzyme (HMG-CoA) reductase, upregulating the hepatic LDL-receptors and increasing LDL clearance[14]. Depending on the individual drug and dose, statins alone can reduce LDL-C by 30-50% or more[15]. Compared with other LDL-C-lowering drugs, statins are considered effective, safe, and cheap and have been studied extensively. However, if target LDL-C levels cannot be reached using statin monotherapy or if the patient shows signs of statin intolerance, non-statin alternatives such as ezetimibe (a cholesterol absorption inhibitor) or proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitors can be used/added[8].

The use of high-intensity statins (atorvastatin ≥ 40 mg/day or rosuvastatin ≥ 20 mg/day) has been on the rise since 2011 with the highest increase observed after the release of the 2018 American Heart Association/American College of Cardiology (AHA/ACC) guidelines on the management of blood cholesterol, where the recommendation for high-intensity statin use in patients older than 75 years with ASCVD became a class II recommendation[8,16]. According to these guidelines, high-intensity statins should be used in patients with clinical ASCVD or a high risk of ASCVD to reduce LDL-C to less than 70 mg/dl or 50% of the baseline LDL-C. Statin use was also associated with reduced cardiovascular mortality in certain subgroups of patients, such as non-dialysis chronic kidney disease patients, with a relative risk of 0.77, and 95% confidence interval of 0.69-0.87[17].

Despite the surge in the use of high-intensity stations, some patient groups, such as females and patients with cerebrovascular and peripheral arterial disease, are still undertreated with statins as the intensity of the statin prescribed is inadequate or they are not treated with statins at all[16,18].

Given the above, the appropriate monitoring of the fasting lipid profile of patients with established ASCVD or at high risk of developing ASCVD is crucial to avoid the underuse of LDL-C-lowering drugs. The guidelines[8] recommend monitoring the fasting lipid profile of patients on statins every 4-12 weeks after initiation or adjustment of the treatment, and one to four times annually once the patient is at the target LDL-C levels to evaluate the efficacy and safety of and patients' adherence to treatment. Despite the belief that the lower the LDL-C levels, the better, monitoring for statin overuse is also essential[11-13]. The risk of liver injury and/or muscle damage increases with high-dose statins[19]. In a recent review[20], statins were involved in 4.3% of drug-induced liver injury. Therefore, exposing patients to unnecessarily high doses of statins is considered a medication error that can result in many preventable adverse drug reactions that jeopardize patients' health and quality of life[21]. Additionally, despite the availability of lower-cost generic statins, the unjustified use of high doses of statins or of statins at all leads to needless costs that strain the finances of the payer and exhaust the healthcare system[22].

Many US studies[16,18,23-26] describe the pattern of statin use in the primary and secondary prevention of ASCVD and the extent of clinicians' compliance with the latest guidelines. However, no studies currently describe the use of statins in similar populations in Jordan.

This research aims to study the pattern of statin use and the appropriateness of dyslipidemia treatment in patients with or without established ASCVD in Jordan according to the latest AHA/ACC guidelines.

Subjects and Methods

This was a cross-sectional study conducted from January to April 2022 in a tertiary government hospital. Al Basheer Hospital is the largest government hospital in Jordan, with a capacity of 1,000 beds. Patients visiting the outpatient clinics in the Cardiology Department and the non-intensive care medical wards were approached for enrolment in the study. Patients who had been on statins for at least two months at the time of enrolment were included in the study. Institutional Review Board (IRB) approval from the Ministry of Health (MOH), Jordan, was obtained before the study's launch and all experiments were performed per relevant guidelines and regulations. Data was collected by filling in a data collection

sheet with the necessary information. Additional information was obtained from electronic medical records. Patients were asked to sign an informed consent form before the interview and the collection of data.

Data Collection

After an intensive review of the current literature, the study researchers participated in the development of the patient interview data collection sheet to ensure that it would capture all the required information in a concise and time-suitable manner. A pilot study was conducted on 20 patients to determine the appropriateness of the questions, identify any additional information needed, and estimate the time needed to complete the data collection. Adjustments to the data collection sheet were made accordingly. The results from the pilot study were excluded from the final analysis.

Data collection and processing consisted of three parts. Part one covered demographic and general information and was collected through direct interviews with the patients, and part two involved gathering data from the patients' electronic hospital medical records. Finally, part three was conducted by two clinical pharmacists and involved assessing the appropriateness of statin therapy in reference to the recent dyslipidemia guidelines and patients' medical history and risk factors. The 10-year risk of heart disease or stroke was calculated using the online calculator based on the ASCVD algorithm published in the 2013 ACC/AHA Guidelines on the Assessment of Cardiovascular Risk[27].

Data from the first 50 cases surveyed were assessed by the two researchers concomitantly to provide a uniform understanding of the guidelines and consistent decisions on compliance with the guidelines. The remaining cases were evaluated by only one of the researchers. Any conflicting opinions were resolved by referring the issue to a third researcher.

Sample Size

Equation 1 was used for observational studies to determine the optimal sample size. Where n is the sample size, Z is the statistic corresponding to the level of confidence (for a 95% confidence interval, Z is 1.96), P is the expected prevalence (according to the results of similar studies), and d is precision, d = 0.05. This equation results in the largest sample size when P = 0.50 and 1-P is 0.50. Using these values, the optimal sample size for this study was a minimum of 380 patients. However, a larger sample size was targeted to make the research more representative.

$$n = \frac{Z^2\, P\,(1\text{-}P)}{d^2} \qquad \text{Equation 1}[28]$$

Equation 1. The sample size for cross-sectional studies.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, version 23 (IBM Corp., Armonk, NY, USA). Categorical data were presented as frequency (%) and continuous data were described as mean ± (SD). An independent sample *t*-test was used to detect statistical differences between the variables in continuous data. A Chi-squared test (χ^2) was used to detect statistically significant differences between categorical variables. *p*-values of ≤ 0.05 were considered statistically significant.

Results

A total of 752 patients were enrolled in the study, of which 124 (16.5%) were inpatients and 628 (83.5%) were outpatients. The average age of the participants was 58.97 ± 11.30, and their average body mass index was 30.38 ± 6.52. The general characteristics of the patients are described in Table I.

Diabetic patients had an average duration of diabetes of 11.80 ± 9.19 years. The total average number of ASCVD cases was 1.28 ± 1.01. Thirty percent of the patients had at least two medical conditions and 81.9% of the patients had at least four medical conditions, generating a total average of 3.32 ± 1.40 medical conditions per patient. The frequency of different medical conditions is reported in Table II.

The duration of statin use ranged from 2 months (37, 5%) to 33 years (1, 0.13%), with a median use of 4.0 years. Half of the patients surveyed had been on statins for at least 4 years, and 86% of the patients had been on statins for at least 10 years. The patients were asked to estimate their adherence to statin therapy. The lowest compliance was assigned a value of 10%, and the highest a value of 100%. Most of the patients complied with their statin treatments at an average compliance level of 91.49%. No statistically significant

Table I. General characteristics of the participants (N = 752).

	Frequency (%)		Frequency (%)
Gender (N = 752)		**Reason for admission of inpatients (N = 124)**	
Male	484 (64.4%)	Acute coronary syndrome (ACS)	9 (7.3%)
Female	268 (35.6%)	Infection	7 (5.6%)
Nationality (N = 732)		Cerebral vascular accident (CVA)	21 (16.9%)
Jordanian	705 (96.3%)	Decompensated heart failure	14 (11.3%)
Syrian	11 (1.5%)	Shortness of breath	9 (7.3%)
Palestinian	11 (1.5%)	Chest pain	7 (5.6%)
Iraqi	3 (0.4%)	Venous thromboembolism (VTE)	5 (4.0%)
Egyptian	2 (0.3%)	Acute kidney injury	4 (3.2%)
Social status (N = 746)		Dialysis	4 (3.2%)
Married	622 (83.4%)	Myocardial infarction	12 (9.7%)
Single	24 (3.2%)	Other	24 (19.4%)
Divorced	16 (2.1%)	Not available	8 (6.5%)
Widower	84 (11.3%)	**Working status (N = 733)**	
Monthly income		Not working	444 (60.6%)
Less than 200	265 (37.5%)	Working	151 (20.6%)
200-400	344 (48.7%)	Retired	138 (18.8%)
400-800	87 (12.3%)	**Education level (N = 696)**	
More than 800	11 (1.6%)	Less than high school	429 (61.6%)
Physical activity		High school	191 (27.4%)
Low	268 (35.6%)	BSc or higher	76 (10.95)
Moderate	294 (39.1%)		
High	190 (25.3%)		
Smoking (N = 745)			
No	427 (57.3%)		
Yes	318 (42.7%)		

difference in adherence to statin treatment was observed between the sexes or between the use of statins for secondary or primary prevention (p = 0.896, 0.893 respectively). However, significant discrepancies in compliance were found between patients on high or moderate-intensity statins. Adherence to high-intensity statins was significantly greater than to moderate-intensity statins, namely, 93.50 ± 20.06 compared with 89.68 ± 24.91 (p = 0.020).

The reasons for low compliance, as reported by patients, were the drug side effects such as myopathy, muscle pain, changes in taste, stomach upset, and headache. Other causes of incompliance included laziness, polypharmacy, and forgetfulness, as illustrated in Figure 1.

A total of 740 (98.4%) patients were on atorvastatin, 8 (1.1%) were on simvastatin, 3 (0.4%) were on rosuvastatin, and 1 (0.1%) was on fluvastatin. Half of the patients, 373 (50.4 %), were taking atorvastatin at a daily dose of 20 mg, 363 (49.1%) were on 40 mg once daily, 3 (0.4%) were on 10 mg once daily, and 1 (0.1%) was on 80 mg once daily. All rosuvastatin patients were on 10 mg once daily, while the sole patient on fluvastatin was on 80 mg once daily, and all eight patients on simvastatin were on 20 mg once daily.

Only 47 patients (6.3%) had their statin dose attempted to change, and none from the rosuvastatin, simvastatin, or fluvastatin groups. Nine of the 47 patients were on 20 mg of atorvastatin daily and the rest were on 40 mg daily.

Patients had average LDL-C levels of 101.31 ± 42.48 mg/dL. No significant differences were found in LDL-C, triglycerides (TG), and total cholesterol (TC) between patients on different types of statins (p = 0.152, 0.306, and 0.42, respectively). However, a statistically significant difference in HDL was found between different treatment groups (p = 0.016). The variations in LDL, HDL, TC, and TG values between patients on different types of statins are illustrated in Table III.

There were no significant differences in LDL-C, TC, and TG observed between patients on 20 mg daily and 40 mg daily of atorvastatin (p = 0.67, 0.77, and 0.547, respectively). In the group of patients who were receiving 20 mg of atorvastatin daily, only 29.8% had LDL-C < 70 mg/dL and 56.9% had LDL-C < 100 mg/dL. Patients on 40 mg of atorvastatin daily (21.9%) had LDL-C < 70 mg/dL and 51.6% had LDL-C < 100 mg/dL.

Almost half of the patients, or 357 (47.5%), were on high-intensity statins and 395 patients (52.5%) were on moderate-intensity statins.

Table II. Frequency of different medical conditions.

	Frequency (%)		Frequency (%)
Diabetes		**Cancer**	
Yes	476 (63.3%)	Yes	22 (2.9%)
No	276 (36.7%)	No	730 (97.1%)
Heart failure		**Chronic obstructive pulmonary disease**	
Yes	313 (41.6%)	Yes	38 (5.1%)
No	439 (58.4%)	No	714 (94.9%)
Angina		Asthma	
Yes	369 (49.1%)	Yes	46 (6.1%)
No	383 (50.9%)	No	706 (93.9%)
Peripheral arterial disease		**Hypothyroidism**	
Yes	108 (14.4%)	Yes	89 (11.8%)
No	644 (85.6%)	No	663 (88.2%)
Myocardial infarction		**Human immunodeficiency virus (HIV)**	
Yes	312 (41.5%)	Yes	2 (0.3%)
No	440 (58.5%)	No	750 (99.7%)
Stroke		**Psoriasis**	
Yes	171 (22.7%)	Yes	20 (2.7%)
No	581 (77.3%)	No	732 (97.3%)
Hypertension		**Rheumatoid arthritis**	
Yes	639 (85.0%)	Yes	55 (7.3%)
No	113 (15.0%)	No	697 (92.7%)
Dyslipidemia			
Yes	627 (83.4%)		
No	125 (16.6%)		

One hundred and sixty-eight patients (22.3%) had no LDL-C tests at all, according to their electronic medical records. The number of patients who had an LDL-C test in the past year was 403 (72.1%), and only 277 (47.9%) had this test in the previous six months. The time since a patient's last LDL-C test ranged from 0.07 years to 10.30 years, with a median of 0.60 years.

A total of 202 patients (26.9%) took statins for the primary prevention of ASCVD and 550 patients (73.1%) used statins for the secondary prevention of ASCVD, (Table IV). The online calculator was used to estimate the 10-year primary risk of ASCVD in patients without pre-existing CVD. In total, 166 of the 202 patients who took the statins for primary prevention had com-

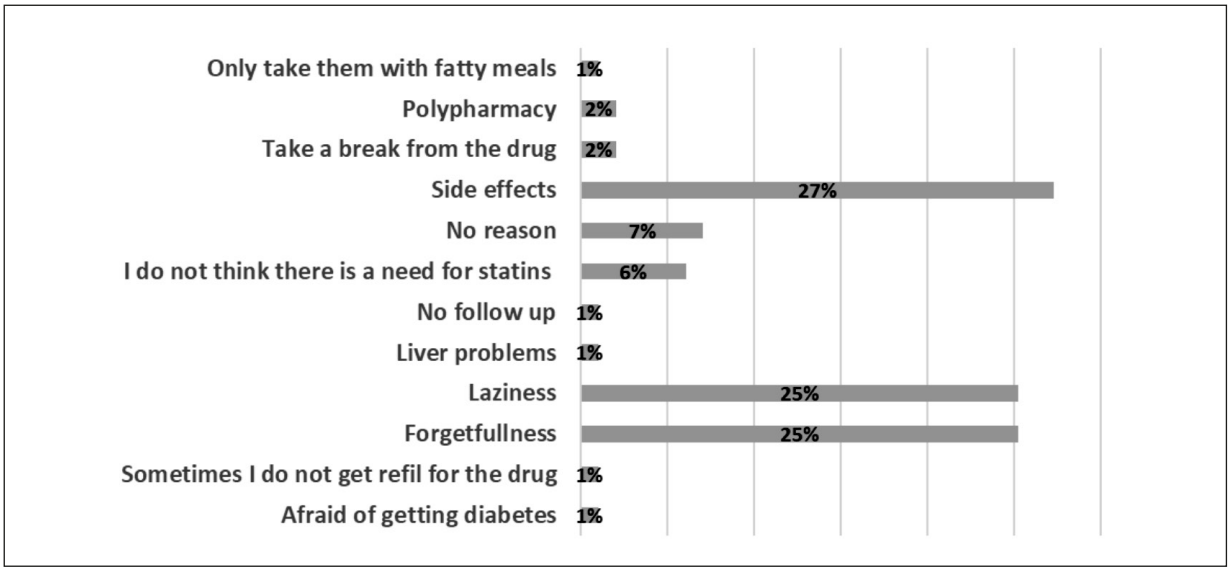

Figure 1. Reasons for treatment non-compliance in patients taking statins (N=99).

Table III. LDL-C, HDL, TC, and TG values of patients on different types of statins.

Type of statin	LDL-C mean ± SD	HDL mean ± SD	Total cholesterol mean ± SD	Triglycerides mean ± SD
Rosuvastatin (N = 3)	48.00 (n = 1, 33.33%)	22 (n = 1, 33.33%)	134 (n = 1, 33.33%)	320 (n = 1, 33.33%)
Atorvastatin 20 mg (N = 373)	100.39 ± 43.71 (n = 299, 80.16%)	41.08 ± 12.52 (n = 297, 79.62%)	178.34 ± 55.74 (n = 315, 84.45%)	184.85 ± 127.01 (n = 315, 84.45%)
Atorvastatin 40 mg (N = 363)	101.89 ± 40.70 (n = 275, 75.76%)	38.95 ± 12.48 (n = 277, 76.31)	176.91 ± 65.20 (n = 295, 81.27%)	190.94 ± 121.45 (n = 294, 80.99%)
Simvastatin (N = 8)	136.80 ± 42.75 (n = 5, 62.50%	56.20 ± 14.33 (n = 5, 62.50%	218.30 ± 39.98 (n = 5, 62.50%	143.00 ± 63.85 (n = 5, 62.50%
Fluvastatin (N = 1)	82.00 (n = 1, 100%)	36.00 (n = 1, 100%)	189.00 (n = 1, 100%)	355.00 (n = 1, 100%)

plete data for the online calculator. One hundred and six patients out of these 166 (63.86%) were at elevated risk (10-year ASCVD risk of 7.5% or higher) and 60 patients (36.14%) were at low risk (10-year ASCVD risk < 7.5%).

The LDL-C levels of patients on statins for the secondary or primary prevention of ASCVD were not statistically different. The average level of LDL-C in patients receiving statins for secondary prevention was 100.88 ± 41.11 compared with 102.33 ± 45.68 for those receiving statins for primary prevention ($p = 0.717$).

The LDL-C values of 139 patients (25.3%) receiving statins for secondary prevention were missing from their electronic medical records, meaning that they were not tested for lipid blood levels at any of the Ministry of Health labs across Jordan. A total of 411 patients had LDL-C values recorded and only 107 of them (26.0%) had LDL-C levels < 70 mg/dL. Further analysis of the groups receiving statins for secondary prevention revealed that among the 274 patients who were prescribed a statin dose that matched the recommendations, 202 had their LDL-C levels measured, of which only 44 (21.8%) had LDL-C levels < 70 mg/dL.

Only half of the patients surveyed, 367 (49.7%), received statin treatment at the intensity recommended by the guidelines, and 372 (50.3%) were prescribed a statin regimen that was not in agreement with the guidelines. Thirteen patients were excluded because they were older than 70 years of age and the physician's clinical judgment was a deciding factor.

The detailed analysis of the patients who were undertreated with statins (306) as compared with the remaining statin patients (445), showed that older patients ($p = 0.027$), patients who had been using stains for a longer duration ($p = 0.005$), patients with more ASCVD ($p < 0.001$), patients using stains for secondary prevention of ASCVD ($p < 0.001$) or with a high 10-year risk ($p < 0.001$), patients who were using statins other than atorvastatin ($p = 0.004$), and patients with a history of angina ($p < 0.001$) or stroke ($p < 0.001$) were more likely to be undertreated with statins based on the latest guidelines' recommendations (Table V).

Discussion

Despite ample scientific evidence of the importance of dyslipidemia management in the reduction of primary and secondary atherosclerotic cardiovascular events, reports[16] reveal the inappropriate management of dyslipidemia and the loss of this crucial opportunity to reduce ASCVD risk. Similar findings were revealed in our study, where almost half of the patients who used statins for the secondary prevention of ASCVD were undertreated (i.e., the intensity of statins prescribed was lower than that recommended by the AHA/ACC guidelines). In the primary prevention group, 15% of patients were undertreated but a higher percentage (23.3%) were overtreated. Although statins are generally safe, patients should not be exposed to higher-intensity statins than that recommended by the guidelines, especially if there is no adequate follow-up.

Most of the patients in the study have been using statins for a long time. Treatment compliance, as self-reported by the patients, was good. There were numerous reasons for non-compliance, but only a quarter of those with adherence issues reported side effects. In general, statins are considered safe, have very few and rare side effects (e.g., myopathy and liver toxicity), and their benefits outweigh their risks[29-31].

Table IV. Appropriateness of the administered doses of statins in different groups.

	Administered intensity matches the recommended	Administered intensity is lower than recommended	Administered intensity is higher than recommended	Statin is administered based on the physician's clinical judgment (patient > 75 years)	The patient should not receive statin	Not enough information to make a decision
All patients (N = 752)	367 (48.8%)	306 (40.7%)	47 (6.3%)	12 (1.6%)	19 (2.5%)	1 (0.1%)
Secondary prevention (N = 550)	274 (49.8%)	276 (50.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Primary prevention (N = 202)	93 (46.0%)	30 (14.9%)	47 (23.3%)	12 (5.9%)	19 (9.4%)	1 (0.5%)

Table V. Differences in the percentage of undertreated patients between different groups.

	Undertreated (statin intensity is lower than recommended) No	Undertreated (statin intensity is lower than recommended) Yes	*p*-value
Gender			0.420
Female	164 (61.2%)	104 (38.8%)	
Male	281 (58.2%)	202 (41.8%)	
Monthly income			0.356
Less than 200	166 (62.6%)	99 (37.4%)	
200-400	191 (55.7%)	152 (44.3%)	
400-800	53 (60.9%)	34 (39.1%)	
More than 800	4 (63.6%)	7 (36.4%)	
Smoker			0.153
No	262 (61.4%)	165 (38.6%)	
Yes	178 (56.2%)	139 (43.8%)	
Education level (N = 696)			0.507
Less than high school	244 (57.0%)	184 (43.0%)	
High school	118 (61.8%)	73 (38.2%)	
BSc or higher	46 (60.5%)	30 (39.5%)	
Did the physician attempt to increase the dose of statin?			0.001
No	406 (57.7%)	298 (42.3%)	
Yes	39 (83.0%)	8 (17.0%)	
10-year cardiovascular risk for patients on statins for primary prevention			< 0.001
≥ 7.5 (high risk)	77 (72.6%)	29 (27.4%)	
< 7.5 (low risk)	60 (100.0%)	0 (0.0%)	
Intensity of statin			< 0.001
High intensity	356 (99.7%)	1 (0.3%)	
Low intensity	89 (22.6%)	305 (77.4%)	
Angina			< 0.001
No	272 (71.2%)	110 (28.8%)	
Yes	173 (46.9%)	196 (53.1%)	
Peripheral arterial disease			0.0570
No	390 (60.7%)	353 (39.3%)	
Yes	55 (50.9%)	53 (49.1%)	
Myocardial infarction			0.300
No	267 (60.8%)	172 (39.2%)	
Yes	178 (57.1%)	134 (42.9%)	
Stroke			< 0.001
No	365 (62.9%)	215 (37.1%)	
Yes	80 (46.8%)	91 (53.2%)	
Statin treatment is for:			< 0.001
Primary prevention	171 (85.1%)	30 (14.9%)	
Secondary prevention	274 (49.8%)	276 (50.2%)	
Type of statin			0.004
Rosuvastatin (N = 3)	0 (0%)	3 (100%)	
Atorvastatin (N = 739)	444 (60.1%)	295 (39.9%)	
Fluvastatin (N = 1)	0 (0%)	1 (100%)	
Simvastatin (N = 8)	1 (12.5%)	7 (87.5%)	

	Undertreated (statin intensity is lower than recommended) No Mean ± SD	Undertreated (statin intensity is lower than recommended) Yes Mean ± SD	*p*-value
Body mass index	30.47 ± 6.70	30.27 ± 6.26	0.686
Number of ASCVD	1.09 ± 1.06	1.55 ± 0.88	< 0.001
Duration of statin therapy	5.28 ± 5.69	6.58 ± 6.54	0.005
Age	58.34 ± 11.44	60.19 ± 10.99	0.027

A very small percentage of patients had the dosage of statins increased during the course of treatment, meaning that most of the patients surveyed remained on the same dosage throughout the treatment. Low doses of statins can initially be prescribed to promote tolerance and reduce the risk of side effects; however, a further increase in the dosage to the desired intensity of statin to achieve LDL-C level goals is essential.

No significant differences were detected between patients on atorvastatin at 20 mg daily or 40 mg daily. This implies that the average LDL-C values of patients who were receiving high-intensity statins were the same as those receiving moderate-intensity statins, although logic dictates that these values should be lower. We do not have access to the baseline LDL-C values, so there is no way to determine the reduction in these values. These findings also suggest that patients on high-intensity statins did not reach the target LDL-C levels and require additional drugs for effective treatment, such as ezetimibe (an inhibitor of cholesterol absorption) or proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitors[8].

The most commonly reported indications[32] for ordering lipid tests were monitoring and the follow-up of statin dosage change.

To ensure that LDL-C targets are achieved, frequent lipid profile tests are essential. Ideally, these tests should be carried out one to four times annually once the patient has reached their target LDL-C levels to evaluate the efficacy and safety of and patient adherence to treatment[8]. In this study, one-third of the patients had not received any LDL-C tests in the previous year, which demonstrates a lack of follow-up and suggests the underestimation of the importance of regular lipid profile testing to determine adherence to treatment and the need for additional drugs. This might be due to a lack of knowledge among physicians or an attempt to reduce costs. The monitoring of lipid levels has a weak to moderate ability to detect non-adherence[33] and, unfortunately, any patients on statins for the secondary prevention of ASCVD typically stop using statins after only a short time[34,35].

Adherence to statin therapy is associated with favorable outcomes. Bitton et al[36] revealed that high adherence has positive effects on health outcomes and annual costs related to the secondary prevention of coronary artery disease[36,37]. An inverse association between statin adherence and death from all causes in patients with ASCVD has also been revealed by Rodriguez et al[38]. In the present study, no significant differences in adherence between males and females or patients using statins for secondary or primary prevention were observed. However, adherence to high-intensity statin treatment was found to be higher than for moderate-intensity statin treatment. These results contradict the findings of Rodriguez et al[38] who found that women were less adherent (OR, 0.89; 95% CI, 0.84-0.94), as were younger. Also, older patients were less likely to adhere compared to those aged 65 to 74. Additionally, patients taking moderate-intensity statin therapy were more adherent than patients taking high-intensity statin therapy (OR, 1.18; 95% CI, 1.16-1.20)[38].

The target level for LDL-C in secondary prevention is < 70 mg/dL. LDL-C levels in patients on atorvastatin at 20 mg daily were not different from those in patients on 40 mg daily. This could be explained by differences in baseline LDL-C values, compliance issues, or differences in patients' responses to statins. Response to statin therapy is not consistent and there is, in fact, wide variation in responses to this treatment[39,40]. Low rates of achieving lipid goals were discovered in all risk groups, especially in high-risk patients and patients with coronary heart disease[41]. A diminished response to statins is associated with an increased risk of CVD[42]. Pharmacogenomics partly explains this phenomenon, where patients receiving statins can be divided into non-responders and high responders[43]. Follow-up is necessary to ensure that patients have the appropriate response to statins, and if this is not established, other modalities for lipid-lowering can be used.

Even when statins are used at an optimum intensity and LDL-C levels reach recommended targets, residual ASCVD risk still exists[44,45]. Many factors contribute to this risk, such as non-low-density lipoproteins and atherogenic processes unrelated to LDL-C and patient genetics and behaviors[46].

Although the safety of statin use in terms of drug-drug interactions was not an objective of this study, it is important to note that optimizing dyslipidemia management includes the prevention of clinically significant drug-drug interactions, especially since patients with cardiovascular disease are subjected to polypharmacy. These interactions can either lead to reduced efficacy or increased risk of toxicity. The most common statin drug-drug interactions are through the cytochrome P-450 enzyme system[47,48] and P-glycopro-

tein (P-gp)[49,50]. In addition, the coadministration of a statin with a fibrate for further reductions in lipid levels predisposes patients to increased muscle-related toxicity[51]. Fenofibrate or fenofibric acid is favored over gemfibrozil in combination therapy[52]. To avoid these interactions, a complete and thorough review of the patient's medications should be conducted regularly to improve patient safety.

Limitations

Our study has several limitations given its cross-sectional design, such as the lack of data on baseline LDL-C levels and the incomplete history of the surveyed patients' statin use. Additionally, we were unable to obtain any lipid profile tests that the patients might have had outside Ministry of Health laboratories. Despite these limitations, this study provides valuable information on the use of statins for the secondary and primary prevention of ASCVD in Jordan and helps to reflect the situation in the Middle East and other developing regions. Moreover, the study sheds light on the missed opportunities to reduce the morbidity and mortality of CVD through the judicious use of statins according to recent evidence-based guidelines. The study highlights the need to identify patients who need their statin dose adjusted or would benefit from the introduction of additional drugs to reduce their risk of ASCVD.

Conclusions

Ample evidence supports the importance and efficacy of statins in the secondary and primary prevention of ASCVD in reducing morbidity and mortality. In this study, we revealed for the first time the inappropriate use of statins, especially undertreatment for secondary prevention, in a population in Jordan. Patients who received the appropriate intensity statins and those who received an intensity lower than that recommended did not achieve the desired LDL-C targets. This indicates the need for dose adjustment or the introduction of additional drugs to manage the patients' LDL-C levels. Adequate follow-up using frequent lipid profile tests was lacking. This denies patients the accurate assessment of their response to statins and keeps medical professionals in the dark regarding patients' compliance with statin treatment and the need to increase statin dosages or introduce new drugs into a patient's treatment plan.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Authors' Contribution

Lobna Gharaibeh: study design, conceptualization, data analysis, manuscript writing, proofreading, supervision. Sura Al Zoubi: study design, manuscript writing, proofreading, supervision. Hanan Sartawi: study design, conceptualization, data curation, data analysis, supervision. Diana Ayyad: study design, conceptualization, data curation, data analysis, supervision. Mai Hawamdeh: study design, conceptualization, data curation, data analysis. Raya Alrashdan: study design, conceptualization, data curation, data analysis. All authors reviewed the manuscript.

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Data Availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Ethics Approval

Approval (number MBA Ethical Committee 14944) from the Institutional Review Board (IRB), Ministry of Health (MOH) was obtained before the study's launch and all experiments were performed per relevant guidelines and regulations.

Informed Consent

Patients were asked to sign an informed consent form before the interview and the collection of data.

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