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Improve physician adherence to high-intensity statin in the secondary prevention of acute coronary syndrome

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***Abstract*---**Statin therapy is critical in reducing morbidity and mortality associated with cardiovascular disease. However, prescribed statins are only effective if patients take them regularly, a process known as medication adherence. Patient factors, physician factors, and health system factors all influence patient adherence to statin therapy, with interactions between the categories common. Physician factors include the doctor's adherence to guideline recommendations, office visits, and interactions with patients. A prospective interventional study was conducted in Iraq, Al-Muthanna Governorate, Al-Hussein Teaching Hospital during the period from October 2021 to March 2022. A convenient sampling method was adapted to enrol the participants in the current study which included two groups including the intervention and control group. In the intervention group, the researcher sought to use an educational program, mediated by clinical pharmacists, to improve physician adherence to secondary prevention of acute coronary syndrome in hospitalized patients at discharge. Regarding the prescription of statin to patients with age of <75 years, there was no significant difference between the study groups at the first visit after discharge in group A and after intervention in group B, while there was a significant difference at the end of follow up as 64.4% of patients in group A had high-intensity statin compared to 97% in group B.In conclusion, the pharmacist intervention resulted in a significant improvement in the physician's adherence to the recommended secondary prevention with subsequent a significant difference in the level of lipid between the study groups at the end of the study.

***Keywords*---**ACS, secondary prevention, Iraq, statin.

Introduction

Acute coronary syndrome encompasses both unstable angina and myocardial infarction (MI)(1). Unstable angina is defined as new-onset or rapidly worsening angina (crescendo angina), angina with little or no exercise, or angina at rest in the absence of cardiac injury(2). Clinically, MI is defined by the presence of acute myocardial injury, it includes ST-elevation MI (STEMI) and non ST-elevation MI (NSTEMI). STEMI is defined as severe and/or total coronary flow obstruction with transmural ischemia, predisposing to myocardial necrosis and pump dysfunction, whereas NSTEMI is defined as flow-limiting coronary stenosis with downstream myocardial ischemia, predisposing to myocardial necrosis and pump dysfunction(3, 4). According to a World Health Organization study conducted in 2017, death from coronary artery disease (CAD) accounted for approximately 18.5 % of all deaths in Iraq. The CAD mostly manifested as chronic stable angina or ACS.

The regular and correct administration of secondary preventive drugs improves the quality of life and survival, reducing cardiovascular events and mortality by up to 80%. As a result, the American Heart Association/American College of Cardiology (AHA/ACC) guidelines recommend prescribing secondary prevention medications to all patients who do not have contraindications before discharge(5). Secondary prevention treatments, including behavioural advice (diet, exercise and smoking cessation) and cardioprotective medications (aspirin or other antiplatelet, beta-blockers, statins, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers), are effective in reducing the risk of repeat ischaemic events in ACS(6). Statin therapy, which has been shown to reduce the risk of MI, death, and stroke, remains the cornerstone of lipid management for secondary prevention. In patients with no contraindications, high-intensity statin therapy reduces LDL cholesterol levels by 50°/o or more and is preferred over moderate-intensity therapy(7, 8).

Low intensity statin include pravastatin 10-20 mg, lovastatin 10-20 mg, simvastatin 5-10 mg, atorvastatin 5 mg, and rosuvastatin 2.5 mg. Moderate intensity statin include pravastatin 40-80 mg, lovastatin 40-80 mg, simvastatin 20-40 mg, atorvastatin 10-20 mg, and rosuvastatin 5-10 mg. High intensity statin include atorvastatin 40-80 mg and rosuvastatin 20-40 mg(9). In general, statin enters the systemic circulation both actively and passively via the ATP-binding cassette (ABC) and solute carrier family (SLC) gene families. The cytochrome P450 (CYP) and UDP-glucuronosyltransferase (UGT) enzyme families are responsible for statin metabolism, and they primarily act in the liver and, to a lesser extent, the kidney(10). Statins work by competitively inhibiting the active site of hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase, the first and most important rate-limiting enzyme in the mevalonate pathway. Inhibiting this site prevents substrate access, preventing HMG-CoA conversion to mevalonic acid. This reduces hepatic cholesterol synthesis, which leads to increased production of microsomal HMG-CoA reductase and cell surface LDL receptor expression. This promotes increased clearance of LDL-c from the bloodstream and, as a result, a 20% to 55% reduction in circulating LDL-c levels(11).

The prevalence of statin intolerance is also widely debated, in part because of difficulties in identification and diagnosis(11). Statin intolerance, or the inability to continue statins due to adverse symptoms or abnormal lab values, affects approximately 5–10% of statin users. Statin use is also associated with elevated liver enzymes and an increased risk of incident diabetes, but studies show that these people benefit from statins(12). Statin-Associated Muscle Symptoms are by far the most common and serious adverse event, accounting for up to 72% of all statin adverse events. These can manifest as myalgia, myopathy, myositis with elevated CK (creatinine kinase), or, in the most severe cases, rhabdomyolysis, with some people also reporting joint and abdominal pain(11). Higher intensity therapy may increase the likelihood of statin-associated muscle symptoms(13). Statin therapy plays a central role in decreasing the morbidity and mortality associated with cardiovascular disease. However, prescribed statins are only effective if they are taken by patients regularly, known as medication adherence. The factors that influence patient adherence to statin therapy can be categorized into patient factors, physician factors, and health system factors, often with interactions between the categories. Physician factors include the physician's adherence to applying guideline recommendations, office visits, and their interactions with patients(14).

Aim of the study

Assessment of the effect of pharmacist educational intervention in improving the adherence of the physicians to guideline-recommended high-intensity statin use in the secondary prevention of ACS and evaluation of the clinical benefit of this intervention.

Patients and Methods

Study design and setting

A prospective interventional study was carried out in Iraq, Al-Muthanna Governorate, Al-Hussein Teaching Hospital, from October 2021 to March 2022.

Ethical consideration

The Ethics and Scientific Committee of the Faculty of Pharmacy/University of Kufa and the Scientific Committee of Researches of An Al-Muthanna Health Directorate proposed and approved this study. After thoroughly and clearly explaining the purpose of the study, patients verbally provided fully informed consent.

Study population

Sampling method and inclusion criteria

A convenient sampling method was adapted to enrol the participants in the current study which included two groups.

- Group A: A total of 150 patients who were diagnosed with ACS (STEMI, NSTEMI, or UA) were selected, 39 of them were excluded due to loss of

follow up. The participants in this group were followed for two months before the intervention.

- Group B: A total of 134 patients who were diagnosed with ACS (STEMI, NSTEMI, or UA) were matched with the participants in group B regarding the age, gender, and body mass index (BMI), and diagnosis were selected. The participant's selection was done before the intervention and the follow up was done two months after the intervention. During follow up, 17 participants were excluded due to loss of follow up. Then six participants were excluded to have a total number of 111.

Exclusion criteria

Patients were excluded if they have a contraindication to use statin for the secondary prevention of acute coronary

Data collection

The researcher collected the data of the enrolled patients by using a structured questionnaire through direct interviews and examination. The questionnaire was prepared by the researcher after reviewing similar articles with revision of the supervisor, it included closed-ended questions and was divided into two sections:

- Section A: It included the data of enrolled patients at the time of discharge from the hospital before intervention and is composed of three parts:
  - Part one: It included Sociodemographic of the participants including age, gender, residency, occupation, and smoking state.
  - Part two : It included medical history, surgical history, and drug history.
  - Part three: It included the information about the present disease which contained the diagnosis, prescribed statin by the physician, and the results of the laboratory investigations.
- Section B: It contained the prescribed drugs by the physician at the first follow up visit after discharge in group A and after the first visit after intervention in group B. In addition to the results of the laboratory investigations that were done 2 months after the first follow up visit.

Intervention

In this study, the researcher used an educational program, mediated by clinical pharmacists, to improve physician adherence to high-intensity statin secondary prevention of acute coronary syndrome for hospitalized patients at discharge. The intervention was done through many activities including:

- A scientific lecture was prepared by the researcher depending on the “ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults” and delivered in the presence of the specialist doctors in the selected hospital, with an open discussion between the specialists, and between them and the researcher.
- Organizing indicative posters and placing them in specific clear places.

- Organizing brochures including a summary of statin drugs guidelines and distributing them to specialists.

Statistical Analysis

Microsoft Excel 2019 and software package of social science (SPSS) version 22 was used for data entry and analysis. The descriptive analysis focused on frequencies and percentages. Continuous variables were presented as mean (±Standard Deviation (SD)) and were compared by using the paired t-test. Categorical data were presented as proportions and the chi-square test was used to measure the statistical difference between the two proportions. A P-value of less than 0.05 will be considered statistically significant.

Definition of variables

The weight and height were measured and accordingly, the BMI was calculated according to the formula:
BMI= weight (Kg) / **(**height (m)**)^{2}**[15]

Results

A total of 222 patients were enrolled in the current study. There were no significant differences between the study groups regarding gender, age, residency, education, and employment (Table 3.1).

Table 3.1
Sociodemographic characteristics of the participants (N=222)

Characteristics		Group A N=111	Group B N=111	P-value
		N (%)	N (%)	
Gender	Female	28 (26.7)	27 (26.5)	0.975
	Male	77 (73.3)	75 (73.5)	
Age group	≤40	6 (5.4)	8 (7.2)	0.775
	41-50	22 (19.8)	20 (18.0)	
	51-60	34 (30.6)	37 (33.3)	
	61-70	35 (31.5)	28 (25.2)	
	≥71	14 (12.6)	18 (16.2)	
Smoking	Yes	27 (24.3)	35 (31.5)	0.231
	No	84 (75.7)	76 (68.5)	

No significant difference was obtained between the study groups regarding the current diagnosis (Figure 3.1).

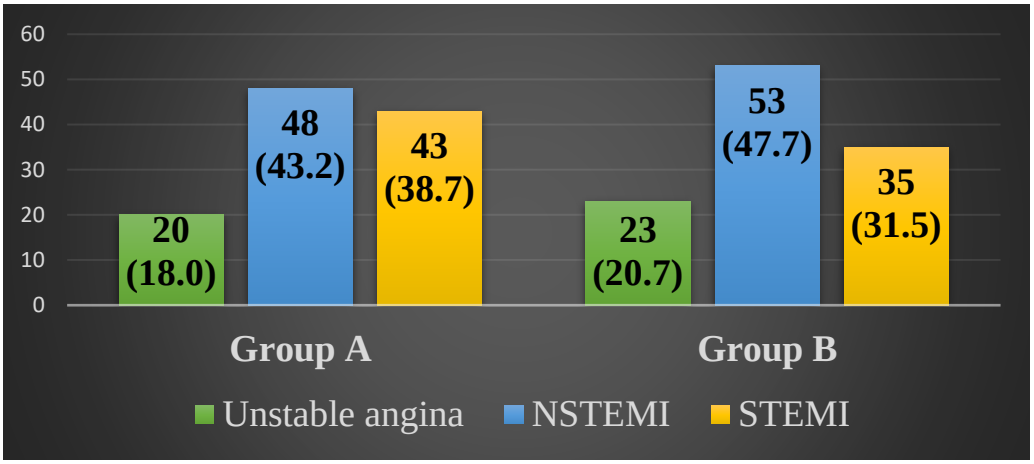

Figure 3.1. Distribution of the participants according to the diagnosis

Regarding the prescription of statin to patients with age of <75 years, there was no significant difference between the study groups at the first visit after discharge in group A and after intervention in group B, while there was a significant difference at the end of fellow up as 64.4% of patients in group A had high-intensity statin compared to 97% in group B (Table 3.2)

Table 3.2
Prescribed statin before and after the intervention in patients less than 75 years old

Statin	Group A N=101	Group B N=99	P-value
	N (%)	N (%)	
At the beginning			
Not received	7 (6.9)	6 (6.1)	0.681
Low intensity	1 (1.0)	0 (0.0)	
Medium intensity	26 (25.7)	22 (22.2)	
High intensity	67 (66.3)	71 (71.7)	
After the intervention in the group B			
Not received	4 (4.0)	0 (0.0)	<0.001
Low intensity	3 (3.0)	0 (0.0)	
Medium intensity	29 (28.7)	3 (3.0)	
High intensity	67 (64.4)	96 (97.0)	

There was no significant difference between the study groups at the first visit after discharge in group A and after intervention in group B among patients with an age of ≥75 years regarding statin prescription, while there was a significant difference at the end of fellow up as 50% of patients in group A had medium intensity statin compared to 100% in group B (Table 3.3).

Table 3.3
Prescribed statin before and after the intervention in patients ≥75 years old

Statin	Group A N=6	Group B N=9	P-value
	N (%)	N (%)	
At the beginning			
Not received	1 (16.7)	1 (11.1)	0.766
Low intensity	0 (0.0)	0 (0.0)	
Medium intensity	4 (66.7)	5 (55.6)	
High intensity	1 (16.7)	3 (33.3)	
After the intervention in the group B			
Not received	0 (0.0)	0 (0.0)	<0.018
Low intensity	0 (0.0)	0 (0.0)	
Medium intensity	3 (50.0)	9 (100.0)	
High intensity	3 (50.0)	0 (0.0)	

Regarding the prescription of statin to patients with age of <75 years and had CKD, there was no significant difference between the study groups at the first visit after discharge in group A and after intervention in group B, while there was a significant difference at the end of fellow up as 25% of patients in group A had high-intensity statin compared to 100% in group B (Table 3.4)

Table 3.4
Prescribed statin before and after the intervention in patients <75 years old with CKD

Statin	Group A (N=4)	Group B (N=3)	P-value
	N (%)	N (%)	
At the beginning			
Not received	0 (0.0)	0 (0.0)	0.147
Low intensity	0 (0.0)	0 (0.0)	
Medium intensity	2 (50.0)	0 (0.0)	
High intensity	2 (50.0)	3 (100.0)	
After the intervention in the group B			
Not received	0 (0.0)	0 (0.0)	0.047
Low intensity	0 (0.0)	0 (0.0)	
Medium intensity	1 (25.0)	3 (100.0)	
High intensity	3 (75.0)	0 (0.0)	

There was a significant difference between the study groups regarding triglyceride, cholesterol, LDL, and HDL at the end of follow up, the better improvement was in group B (Table 3.5).

Table 3.5
Lipids distribution according to the study groups before and after the intervention

Lipid profile	Group A N=111	Group B N=111	P-value
	Mean (SD)	Mean (SD)	
At the beginning			
Triglyceride	191.32 (7.2)	189.98 (5.1)	0.113
Cholesterol	205.17 (6.4)	203.47 (6.5)	0.051
LDL	104.02 (8.1)	101.79 (9.8)	0.067
HDL	45.02 (7.5)	46.95 (8.3)	0.072
After the intervention in the group B			
Triglyceride	185.54 (7.8)	183.06 (6.1)	0.009
Cholesterol	181.58 (7.3)	170.94 (17.6)	<0.001
LDL	95.66 (11.1)	92.81 (8.3)	0.041
HDL	48.02 (8.3)	49.04 (6.9)	0.319

Discussion

The most important finding of the current study was 66.3% of patients in group A and 71.7% in group B statin according to the guild lines. In addition, no significant difference between the study groups regarding the prescription of statin, while a significant difference at the end of follow up. In comparison, Geva et al concluded that Physician adherence was highest when lipid profile screening was appropriate according to guidelines (63.9%), lowest when pharmacotherapy up-titration was appropriate (27.6%), and highest when pharmacotherapy initiation was appropriate (21%)(16). Another study revealed that the majority of physicians (69%) were aware of the 2013 ACC/AHA guideline; however, 79.9% had yet to adopt some facets (e.g., using LDL-C as the target of therapy)(17). In Vietnam, a study that was done there revealed that 94.1% of patients with ACS were prescribed to use the recommended dose of statin(18).

The current study revealed that males constituted more than half of the sample. Although classic CVD risk factors are the same in men and women, there are variances in the prevalence and impact of these risk variables. This is especially true in ACS because women with ACS are typically older and have more comorbidities, such as hypertension, dyslipidemia, diabetes, heart failure, and atrial fibrillation(19). Another finding was more than half of the patients were with an age of more than 50 years. In comparison, another study postulated that Cardiovascular disease is very common among the elderly. Patients aged 75 years old and up account for one-third of those admitted to hospitals with acute ischemia episodes and more than half of all cardiac deaths. One of the most important risk indicators in patients admitted with NSTEMI has been age(20). In agreement with these findings, Alexandre et obtained several gender-related differences in patients with ACS regarding the demographic characteristics, coronary artery disease pattern and applied treatment(21).

About one-third of patients in the current study was a smoker. In comparison, about 41% of patients were current smokers in another study that was done in

Portugal(22). In Sri Lanka, Smoking was found in 55.8% of STEMI patients, 39.8% of UA patients, and 35.5% of NSTEMI patients, demonstrating a strong link between smoking and STEMI(23). Regarding the BMI, more than half of the patients in the current study were overweight or obese. The same findings were obtained by another study that postulated that the mean BMI of the patients were higher than the controls(24). After the intervention, a significant improvement in the lipid profile of the patients in the intervention group compared to an insignificant improvement in the control group. In comparison, according to another study, 474 individuals (90.6%) were prescribed statins at discharge. throughout the 6-month follow, 50 (9.5%) individuals dead. Patients not taking statins had a trend toward greater mortality(25).

Conclusion

The pharmacist intervention resulted in a significant improvement in the physician's adherence to the recommended statin as secondary prevention of the ACS with subsequent a significant difference in the level of lipid between the study groups at the end of the study.

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