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ORIGINAL RESEARCH

Adherence to Clinical Guidelines on STATIN Prescribing Among Diabetic Patients Aged 40–75 Years Old in a Primary Care Setting: A Cross-Sectional Study

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Background: Diabetes mellitus (D.M.) is a chronic metabolic disease caused by decreased insulin secretion, which increases the risk of cardiovascular diseases. Evidence has shown that statins reduce cardiovascular risk in patients with diabetes; moreover, most clinical guidelines recommend statins.

Objective: This study aimed to assess the level and status of adherence to guidelines on statin prescription in patients with diabetes mellitus in a primary care setting in Palestine.

Methods: A retrospective cross-sectional descriptive study was conducted at an ambulatory center in Palestine. Data were collected by auditing prescription records and reviewing medical charts of patients with diabetes who visited the clinic from February 15 to March 17, 2021. The collected data included patient characteristics, comorbidities, lipid profiles, and statin prescription. A chi-square test was used to evaluate the appropriateness of the prescribed statins with different demographic and clinical variables. Statistical significance was set at $p < 0.05$. Statistical Package for Social Sciences (SPSS) version 22 was used to analyze the data.

Results: Out Of 262 diabetic patients included in the analysis, 74% were prescribed appropriate statin therapy according to the American Diabetes Association (ADA) guidelines, and 24% of patients had inappropriate statin therapy or needed statins. Furthermore, 82.8% were on high-intensity statins, while 11% were not taking any statins. More than 60% of patients had uncontrolled diabetes and hypertension.

Conclusion: Most guidelines recommend statin therapy in diabetic patients owing to its benefits in preventing cardiovascular complications. In this study, most patients were on appropriate STATIN therapy; however, 50% of diabetic patients had LDL of more than 100 mg/dl, and 25% were not prescribed statins, increasing their risk of ASCVD. Therefore, we recommend strict adherence to the established guidelines on statins prescribed to patients with diabetes to prevent cardiovascular complications, save lives, and reduce healthcare costs.

Keywords: statin therapy, diabetes type II, hyperlipidemia, uncontrolled diabetes, CV risk

Introduction

Diabetes mellitus (DM) is a metabolic disease characterized by elevated blood glucose levels. It has many types, including type 1, type 2, maturity-onset diabetes of the young, gestational diabetes, and neonatal diabetes; however, the most prevalent is type 2.[1] Diabetes is caused by abnormalities in insulin secretion or sensitivity, which disturb tissue glucose uptake leading to symptoms of polydipsia, polyphagia, and polyuria.[1]

Diabetes mellitus is associated with many complications, including retinal, renal, and nervous system dysfunction. In addition, cardiovascular function is one of the most dangerous consequences of D.M.[2] Statistics show that adults with diabetes are two-four times more likely to die from heart disease than adults without diabetes.[3] Therefore, patient

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education and optimal medication therapy for diabetes are crucial for diabetic management and complications prevention.[4,5]

It is well established that people with diabetes have an increased risk of atherosclerotic cardiovascular disease (ASCVD).[6] Furthermore, diabetic patients with cardiovascular disease are at increased risk of death.[7] Patients above 40 years of age are at a higher risk of developing cardiovascular events, so there is a need to reduce the risk.[8] Statins reduce cholesterol levels and offer other benefits, including plaque stabilization, reduction of inflammation, reversal of endothelial dysfunction, and decreasing thrombogenicity,[9] thus reducing cardiovascular disease risk. Therefore, statin therapy is recommended for all diabetes patients over 40 years of age, regardless of their LDL concentration in the blood.[10,11]

Statins inhibit the hydroxymethylglutaryl-coenzyme A (HMGCoA) reductase enzyme responsible for the synthesis of mevalonic acid, the primary product of many isoprenoids, including cholesterol. In addition, there is an evidence that statins reduce LDL and VLDL assembly and secretion in an unknown mechanism.[12] In addition, statins block the synthesis of other isoprenoids, which helps reduce the severity of ischemia and block the heart. Furthermore, there is other evidence that statins work on the rhodopsin (Rho) kinase enzyme, which regulates the actin cytoskeleton; statin drugs inhibit Rho kinase and exert an anti-atherogenic effect, which helps in reducing the risk of many complications.[13]

In diabetic patients, statin therapy has been the drug class of choice to reduce LDL and prevent ASCVD.[14] In a meta-analysis, a relative reduction of a major cardiovascular event was associated with changes in LDL-C, suggesting that further lowering of LDL will reduce risks for ASCVD.[15] Therefore, statins are indicated for primary prevention for most diabetes patients 40 years of age and older and secondary prevention in diabetic patients with ASCVD. Several studies have demonstrated the effects of statins on primary and secondary cardiovascular prevention in different populations and statin groups.[16] For example, in a Canadian study to prove statin's effect in reducing the risk of cardiac events, the overall result was that daily treatment with statins resulted in a 27% reduction in CV events and a 25% reduction in stroke compared to placebo.[17]

According to the ADA and ACC/AHA guidelines, moderate-intensity statin and lifestyle modifications are recommended for all diabetic patients aged 40–75 without contraindication to statin therapy to achieve an LDL goal of less than 100 mg/dL. Furthermore, high-intensity statin therapy is recommended for patients with cardiovascular risk factors or overt cardiovascular disease to achieve the LDL goal of less than 70 mg/day.[18,19]

Even though statins should be prescribed for diabetic patients (> 40) regardless of their LDL laboratory values, monitoring their LDL is needed because some patients may have high LDL values even though they are using statins. It is imperative to consider this because high LDL values build up fatty deposits in the arteries, which reduce blood flow, leading to an increased risk of heart attack.[18,20]

Clinical guidelines have a clear recommendation for prescribing statins; however, inconsistencies have been reported in clinical practice; for example, an Australian cross-sectional study that included 8505 participants shows that only 44.2% of patients with prior CVD were prescribed blood pressure- and lipid-lowering medications and 47% of participant did not receive either medication for primary prevention CVD.[21] In addition, a large comparative study conducted in the USA to examine the frequency of high-risk patients not receiving high-potency statin revealed that only 1/4 of ASCVD patients were prescribed a high-intensity statin.

This retrospective study aimed to evaluate the appropriate prescription of statins for diabetic patients in an outpatient clinic based on the clinical guidelines offered by the American Diabetic Association and to provide recommendations to improve guideline adherence, optimize medication therapy, and prevent complications.

Methodology

A retrospective cross-sectional descriptive study was conducted at an ambulatory center in Bethlehem between February 15 and March 17, 2021, for all patients with diabetes who visited the clinic during that period. Data were collected, entered into an Excel datasheet, reviewed, and assessed by three clinical pharmacists. Clinical charts of 262 patients with type II diabetes were included; 49 were excluded from the study (10 were less than 40 years old, and 39 had incomplete documentation). In addition, sociodemographic and laboratory parameters, comorbidities, and statin prescription data were extracted. The demographic characteristics included age and sex. The clinical variables included low-

density lipoprotein (LDL), high-density lipoprotein (HDL), HbA1C, total cholesterol, triglycerides (TG), and atherosclerotic cardiovascular risk factors. The ethical committee of Birzeit University approved the study (reference number: BZUPNH2101).

Data were collected as categorical variables. Clinical pharmacists assessed and evaluated every patient chart based on the clinical guidelines for prescribing statin therapy.[10] The data were then imported into SPSS, recoded, and reclassified. The statin regimen was classified into high-dose intensity (atorvastatin 40–80 mg, rosuvastatin 20–40 mg) and moderate-dose intensity (atorvastatin 10–20 mg, rosuvastatin 5–10 mg). According to the American Diabetes Association guidelines, uncontrolled diabetes is defined as HbA1C> 7% in patients with no comorbidities. Patients with other comorbidities and low life expectancy may have higher A1C goal.[22] Furthermore, a blood pressure of more than 130/80 mmHg was considered uncontrolled based on the ADA guidelines. Patients were evaluated and categorized into appropriate statin therapy, inappropriate statin therapy, or need statin therapy based on the ADA guidelines.

Descriptive analysis was performed to present the data, followed by a chi-square test to evaluate the appropriateness of prescribed statins with different demographic and clinical variables. Statistical significance was set at $p < 0.05$. Multinomial logistic regression was then performed for the significant variables to predict categorical placement as a dependent variable. Finally, The Statistical Package for Social Sciences (SPSS) version 22 was used to analyze the data, compare the results and define the gap between statin prescription practice and guideline recommendations.

Data are presented as frequencies, percentages, and cross-tabulation between patients taking statin therapy, including age, gender, HbA1C, LDL, HDL, cholesterol, T.G., HTN, ASCVD, and patients who did not receive statin therapy. In addition, cross-tabulation tables were also generated between patients' LDL values and their comorbidities.

Ethical Committee

This study was approved by the ethical committee of Birzeit University (reference number: BZUPNH2101). The requirement for written informed consent from each patient was waived because this was an observational, retrospective study. This study complied with the ethical guidelines of the Declaration of Helsinki and patient data.

Results

Demographics and Characteristics

A total of 262 patients were enrolled in this study 50.8% were males. The majority (75.2%) were aged 50 to 75 years, 8.4% were between 40–49 years, and 16.4% were older than 75 years old. In addition, 16% of the participants were diabetic patients with no comorbidities. Atorvastatin is a statin prescribed for almost all patients. In addition, 82.8% of patients were prescribed high-intensity statin therapy, 6.1% were on moderate-intensity therapy, and 74% were on appropriate statin therapy (Table 1).

Clinical Variables

Patient clinical variables and objective findings are shown in Figure 1. Out Of 262 patients, 63.7% had uncontrolled diabetes with A1C levels >7%, 61% had uncontrolled hypertension >130/80 mmHg, 32.1% had total cholesterol levels over 200 mg/dl, and 48% had LDL >100 mg/dl. Figure 2 shows the correlation between LDL levels and comorbidities in patients with DM. High LDL levels differed among the comorbidities. For example, LDL levels of more than 100 mg/dl in 56.2% of patients with hypertension, 50% with no comorbidity, and 17.4% with ASCVD. Figure 3 shows the correlation between the percentage of patients with controlled or uncontrolled diabetes and the LDL levels. It shows that 53.3% of uncontrolled glycemic levels patients and 40% of controls levels have LDL levels of more than 100 mg/dl.

Statin Utilization

Table 2 shows the associations between statin use and sociodemographic, biochemical, and clinical characteristics. No significant differences were found between therapy appropriateness and being male or female in any age group or other clinical parameters except for comorbidity. However, patients with no comorbidities were more likely to be on an inappropriate statin regimen (71.4%) compared to those with ASCVD (4.3%), HTN (1%), or both (7.6%).

Table 1 Patients' Demographics, Comorbidities, and Therapy Frequency N=262

Category	Subcategory	Frequency n (%)
Gender	Male	133 (50.8%)
	Female	129 (49.2%)
Age	40–50	22 (8.4%)
	51–75	197 (75.2%)
	More than 75	43 (16.4%)
Comorbidities	None	42 (16.0%)
	ASCVD	23 (8.8%)
	HTN	105 (40.1%)
	ASCVD, HTN	92 (35.1%)
Statin use	Take statin (high intensity)	217 (82.8%)
	Take statin (moderate intensity)	16 (6.1`%)
	Did not take statin therapy	29 (11.1%)
Statin therapy evaluation	Appropriate statin therapy	194 (74.0)
	Not appropriate statin therapy	39 (14.9)
	Need statin therapy	29 (11.1)

Multinomial regression results revealed that patients with no comorbidity were at higher risk of being on an inappropriate statin or not having statin therapy (OR=45.918, 5.357), respectively, compared to patients with ASCVD and HTN. Furthermore, patients with HTN had a significantly lower risk of being on inappropriate statin therapy than patients with ASCVD and HTN. (Table 3)

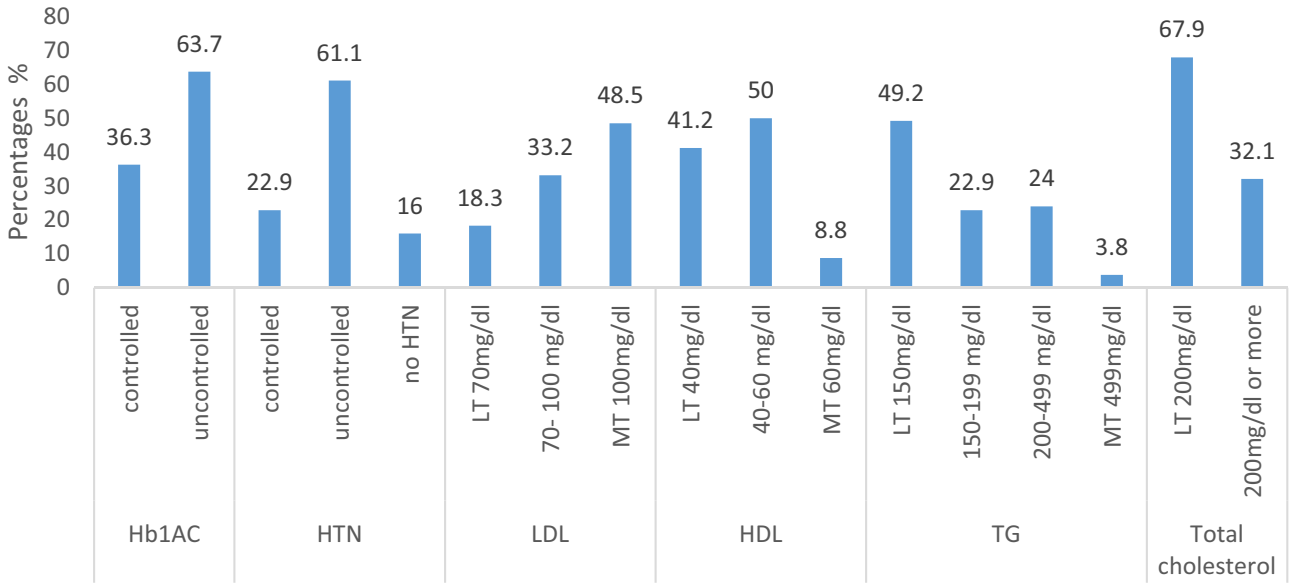

Figure 1 Patients' clinical variable frequency. (N= 262).

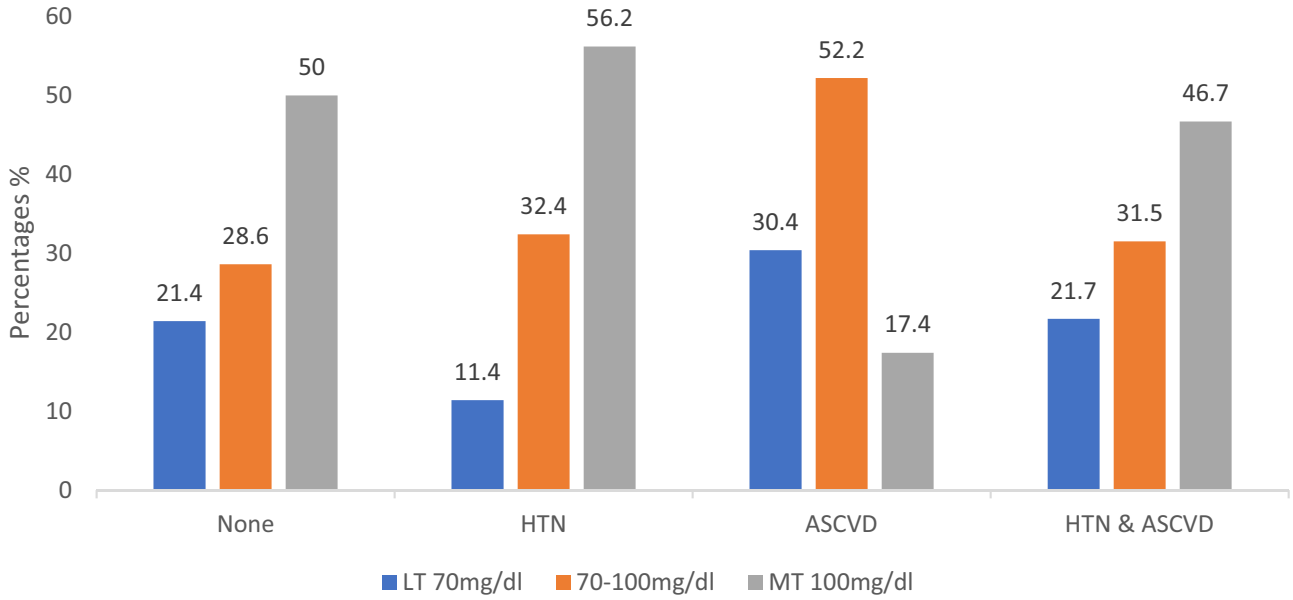

Figure 2 LDL and comorbidities. (N=262).

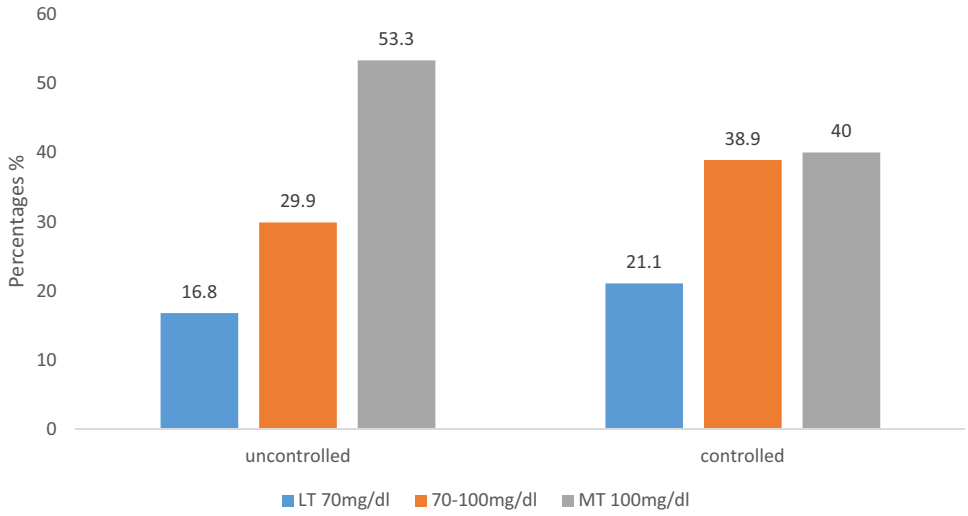

Figure 3 LDL and HBA1C.

Discussion

This study provided data on statin therapy utilization among diabetic patients in an outpatient clinic and compared their utilization in clinical practice with the recommendations of clinical guidelines. The majority of participants (three-quarters) were appropriately placed on a statin. This finding is much higher than those of other similar studies. For example, the Botswana study finding was 45.5% of 277 diabetic patients.[23] In an Indian study, only 55.2% of patients were on appropriate statin therapy,[24] and 42.5% of 120 patients in Bonga received statin.[25] On the other hand, only 16.8% of 1427 diabetic patients in Ghana took a statin.[26]

Inappropriate statin treatment was found in 14.9% of participants, such as a moderate- or low-intensity statin instead of high-intensity statin, increasing the risk of ASCVD. Furthermore, other patients received unnecessary high-intensity statin therapy, which was not indicated. This inappropriate utilization increases the adverse effects of the drug, myopathy, rhabdomyolysis, and increased liver enzymes.[27] This inappropriate utilization may be due to a limitation of the drug

Table 2 Statin Therapy Utilization

Category	Subcategory	Appropriate Statin Therapy n(%)	Not Appropriate Statin Therapy n(%)	Need Statin Therapy n(%)	P- value
Gender	Male	106 (79.7)	14 (10.5)	13 (9.8)	0.082
	Female	88 (68.2)	25 (19.4)	16 (12.4)	
Age	40–50	12 (54.5)	5 (22.7)	5 (22.7)	0.126
	51–75	149 (75.6)	30 (15.2)	18 (9.1)	
	More than 75	33 (76.7)	4 (9.3)	6 (14.0)	
Comorbidities	Non	7 (16.7)	30 (71.4)	5 (11.9)	<0.001
	ASCVD	19 (82.6)	1 (4.3)	3 (13.0)	
	HTN	93 (88.6)	1 (1.0)	11 (10.5)	
	ASCVD, HTN	75 (81.5)	7 (7.6)	10 (10.9)	
LDL	Less than 70	35 (72.9)	8 (16.7)	5 (10.4)	0.336
	LDL 70–100	71 (81.6)	10 (11.5)	6 (6.9)	
	LDL > 100	88 (69.3)	21 (16.5)	18 (14.2)	
HDL	Less than 40	83 (76.9)	12 (11.1)	13 (12.0)	0.140
	HDL 40–60	97 (74.0)	21 (16.0)	13 (9.9)	
	HDL >60	14 (60.9)	6 (26.1)	3 (13.0)	
HbA1C	Controlled	74 (77.9)	10 (10.5)	11 (11.6)	0.331
	Uncontrolled	120 (71.9)	29 (17.4)	18 (10.8)	
Cholesterol	Less than 200	134 (75.3)	25 (14.0)	19 (10.7)	0.799
	More than 200	60 (71.4)	14 (16.7)	10 (11.9)	
TG	Less than 150	93 (72.1)	22 (17.1)	14 (10.9)	0.497
	150–199	42 (70.0)	8 (13.3)	10 (16.7)	
	200–499	50 (79.4)	9 (14.3)	4 (6.3)	
	More than 499	9 (90.0)	0 (0.0)	1 (10.0)	

formulary at this institute due to drug availability and cost. Atorvastatin 40 mg is the only prescribed medication for all patients and the only statin medication in the formulary. Only one patient received rosuvastatin, which was purchased from a local pharmacy.

Only 11.1% of diabetic patients did not receive their recommended statin therapy; it is essential to consider the correlation between diabetes and increased risk of cardiovascular events, including coronary artery disease, stroke, peripheral arterial disease, cardiomyopathy, and congestive heart failure. Therefore, statin prescription was crucial for diabetic patients, regardless of whether their blood test values for LDL and total cholesterol were within normal ranges. Almost 10.9% of patients with total cholesterol <200 mg/dl need statin therapy.

Although three-quarters received statins as appropriate, more than half of the cases were classified as uncontrolled diabetic and hypertensive patients, increasing the risk of cardiovascular events. Additionally, approximately half of the

Table 3 Statin Therapy Utilization Among Comorbid Patients. (The Reference Category: Appropriate Statin Therapy)

Category	Subcategory	P-value	OR	CI (95%)
Not appropriate statin therapy	Non	<0.001	45.918	14.834–142.143
	ASCVD	0.602	0.564	0.065–4.865
	HTN	0.045	0.115	0.014–0.957
	ASCVD, HTN	Reference		
Need statin therapy	Non	0.013	5.357	1.426–20.130
	ASCVD	0.811	1.184	0.296–4.73
	HTN	0.796	0.887	0.358–2.201
	ASCVD, HTN	Reference		

patients had high LDL levels (>100 mg/dl). This is an alarming finding, where uncontrolled diabetes has been linked to complications, morbidity, mortality, and healthcare cost.[28] Uncontrolled D.M. increases the risk of high LDL levels, which is explained by the fact that hyperglycemia causes a reduction in LDL receptors and increases LDL blood levels.[29] Therefore, it is imperative to control D.M. and LDL because both increase macrovascular complications. Therefore, it is necessary to optimize treatment options to control diabetes, HTN, cholesterol, and weight through pharmacological or non-pharmacological interventions. Doctors, pharmacists, nurses, patients, and medical staff should collaborate to obtain the best outcomes. Another important finding of this study is the inappropriate management of hypercholesterolemia with LDL values higher than 100 mg/dL while on optimum statin therapy. Half of the patients with LDL more than 100 mg/dl mg/dL qualified for non-statin treatment to be added to the current statin based on the guidelines. The guidelines recommend the use of ezetimibe in addition to high-intensity statins to decrease LDL levels. Ezetimibe lowers cholesterol absorption and helps reduce the risk of complications in diabetic patients.[30]

There was a significant association with inappropriate statin prescription in diabetic patients with no comorbidity compared to patients with ASCVD or hypertension ($p < 0.05$). This finding demonstrates the lack of prescribing statins in diabetic patients for the primary prevention of ASCVD, which requires increased prescriber awareness and knowledge of clinical guidelines where statins are recommended in diabetic patients regardless of their ASCVD status.[31] Furthermore, providing continuing education and designing educational outreach programs to increase prescribers' knowledge and awareness of the benefit of statin therapy.[32] In addition, to improve prescribers' adherence to guidelines, the START/STOP criteria (a screening tool used to optimize medication therapy in the elderly) added Statin therapy for the primary prevention of cardiovascular disease in diabetes mellitus as part of the Alert to Right Treatment (START) which should be utilized in patients medication management.[33]

Conclusion

In this study, most patients received appropriate STATIN therapy; however, only half had LDL levels of more than 100 mg/dl, increasing their risk of ASCVD and thus qualifying them for ezetimibe therapy. Therefore, strict adherence to clinical guidelines is recommended to optimize treatment outcomes.

Strengths and Limitations of the Study

This was a retrospective study in which we retrieved data from patient charts; the data were limited to one institution. However, the drug formulary and clinical guidelines at that institution are followed by all outpatient clinics of the health ministry. Therefore, this study can be generalized to other outpatient clinics within the Ministry of Health throughout Palestine. However, the weaknesses and limitations of the research were inappropriate documentation and incomplete information. In addition, another limitation observed in this study is the use of a singular statin (atorvastatin), even

though there were different options, especially for patients with multi-drug therapy. However, this may not have affected the validity and applicability of our findings.

Disclosure

The authors report no conflicts of interest in this work.

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