



Statin Utilization Patterns among Type 2 Diabetes Mellitus Patients with High Cardiovascular Disease Risks in Ethiopia

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ABSTRACT

Background: Cardiovascular disease is a leading cause of morbidity and mortality among type 2 diabetes mellitus (T2DM) patients. It has been proved & recommended by most guidelines that statins are effective for primary or secondary cardiovascular diseases prophylaxis. The aim of the study was to assess the pattern of statin use among T2DM patients with high risk of cardiovascular diseases.

Methods: Hospital-based cross-sectional study was conducted among T2DM patients from February to April 2018 at Jimma University Medical Center. Patient-specific data including clinical characteristics, laboratory work ups and medication records were collected using a structured data collection tool.

Results: From a total of 150 study participants, 93(62%) of them were males. Majority of the patient, 112(74.7%), were between age of 40-64 years (mean \pm SD of 46.65 \pm 19.61 years). About 55(36.67%) of participants were on statin therapy for treatment & prophylaxis. Age between 65 to 74 years (AOR = 3.006; 95% CI: 1.440–6.277; P=0.003), disease co-morbidity (AOR 4.486; 95% CI: 2.080–9.673; P<0.001) & elevated blood cholesterol (AOR = 1.422; 95% CI: 1.244–1.622; P=0.033), living with diabetes mellitus for more than 10 years (AOR=2.45; 95% CI: 1.524- 3.891; P=0.027) & uncontrolled blood sugar (AOR=2.127; 95% CI: 1.833–2.457; P=0.0241) were independent predictor of statin use.

Conclusion: The majority of patients with type 2 diabetes were not receiving statins. Further interventions to improve statin use should be considered for these high-risk patients.

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Introduction

Diabetes mellitus (DM) is an endocrinological disorder arising from insulin deficiency or due to the ineffectiveness of the insulin produced by the body. This results in high blood glucose and with time, to neurological, cardiovascular, retinal and renal complications. It is the condition in which the body does not properly process carbohydrate for use as energy(1). Despite the different classification scheme of DM, there are 2 major types

(Type 1 & Type 2). Type 1 diabetes (T1DM) may account for 5 percent to 10 percent of all diagnosed cases of diabetes. Risk factors are less well defined for T1DM than for type 2 diabetes (T2DM), but autoimmune, genetic, and environmental factors are involved in the development of this type of diabetes(2). T2DM may account for about 90 percent to 95 percent of all diagnosed cases of diabetes. Risk factors for T2DM diabetes include older age, obesity, and family history of diabetes, prior history of gestational

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diabetes, impaired glucose tolerance, physical inactivity, and race/ethnicity(3).

Patients with T2DM are more likely to develop the cardio-and cerebrovascular disease than individuals without diabetes. It has been estimated that patients with diabetes without a prior myocardial infarction have a risk for myocardial infarction as high as patients without diabetes, but with a history of myocardial infarction(4). In addition, mortality rates following myocardial infarction are higher among patients with diabetes(5). Around 60% of patients with diabetes die from any type of cardiovascular disease (CVD) or stroke(6). Therefore, the control of cardiovascular risk factors, including dyslipidemia, is essential. That is why the optimization of lipid-lowering therapy use among T2DM patients should be considered as one of the significant approaches to decrease the overall CVD burden. People with diabetes have been shown to incur many clinical benefits from lipid-lowering therapy(7). Statin therapy is considered as the cornerstone of clinician's efforts toward primary and secondary CVD prevention in patients with T2DM(8). They are used for primary and secondary prevention of cardiovascular diseases. When it is used to treat dyslipidemia in patients without any history of CVD or atherosclerotic vascular disease is termed as primary prevention and when used in patients with a history of CVD or CVD risk factors is said to be secondary prevention.

Low-density lipoprotein (LDL) level less than 100mg/dl for patients with cardiac diseases or cardiac risk factors and less than 70mg/dl is suggested by recent guidelines for patients with high risk(9, 10). Patients with T2DM are deemed as prime candidates for receiving statin therapy, which has been endorsed by most of the clinical practice guidelines (CPGs)(11, 12). Although statins are proven to reduce CVD-related events and all-cause mortality significantly(13), underutilization of statins in patients at high risk for atherosclerotic cardiovascular diseases, such as those over 40 years with T2DM is reported in the form of inappropriate dosing, discontinuation, and adherence issues(14). To our knowledge, this is the first study addressing the utilization pattern of statins in type 2 diabetic patients in Ethiopia. As well currently prevalence of diabetes is increasing, this is indicative to control morbidity related to metabolic complications. Hence, the study was undertaken to determine the patterns of statin use among ambulatory type 2 diabetic patients with high cardiovascular risks and to identify factors associated with its a Jimma University Medical Center, Ethiopia.

Methods

The study was conducted at Jimma University Medical Center (JUMC) in Ethiopia. JUMC is the only teaching and referral hospital in the South-Western part of the country with a bed capacity of 600. It provides services for approximately 9000 inpatient and 80,000 outpatient clients per year with a catchment population of about 15 million people. The study was conducted from February

30- April 30, 2018. An institutional based cross-sectional study was conducted among type 2 diabetic patients on follow-up, who fulfilled inclusion criteria. Ethical clearance & approval was obtained from the institutional review board (IRB) of Jimma University. The data that were collected from the JUMC ambulatory clinic was preceded by a formal request letter from Jimma University. The raw data were not made available to anyone and not used as the determinant of the participant. All steps in data collection and compilation were conducted and supervised by the principal investigator. Strict confidentiality was assured through anonymous recording and coding of questionnaires and placed in a safe place.

We included patients who were older than 40years; have at least 6 months follow-up, whose medical records were legible and have complete. Type 1 DM patients were excluded from the study.

The sample size was determined by using the single population proportion formula, assuming a 95% confidence interval (CI), assuming a prevalence of 50% for statin utilization among T2DM patients, as no study has done previously, a 5% margin of error. Simple random sampling technique was used to select study participants after obtaining the patient list from Chronic Illness Clinic Registration Book, which had lists of 1867 diabetic patients; from these patients with type 2 DM were 967 and about 246 were above 40 years old. Then, finally, the corrected statistical sample size was 150 type 2 DM patients.

A structured data collection questionnaire was developed by researchers from relevant pieces of literatures. Patient chart review and self-report were used to determine the various variables. Two trained clinical nurse professionals were recruited as data collectors & they interviewed the study participants and reviewed patient charts and medical records for the respective information such as participants' socio-demographic and clinical characteristics, laboratory work ups and medication records. Before data collection pre-test was done for data collection validity on 5% of study participants, which were not included into the final analysis. Before entry to SPSS for analysis, data was cleared, categorized, compiled and coded and also checked for completeness, accuracy. Any erroneous, ambiguous and incomplete data were excluded.

Data were entered into the computer using EpiData version 3.1 and exported to the Statistical Package for Social Science (SPSS) version 22.0 for analysis. Differences between mean values were evaluated using Student's t-test while proportions were compared using the Pearson's Chi-square test. Bivariate and multivariable logistic regressions were performed to assess seemingly significant predictors of statin use. Independent variables with a p-value less than 0.1 on bivariate analysis were a candidate for multivariable logistic regressions. Categorical and continuous data were expressed as percentages and mean \pm standard deviation respectively.

Descriptive statistics were applied for the analysis of patient characteristics, including means, standard deviations (SD), medians, and percentiles and categorical variables were analyzed by using the chi-square test. A p-value of <0.05 was considered to be statistically significant.

Operational Definitions

- **Co-morbidity:** Diseases or disorders that exist together with an index disease or co-occurrence of two or more diseases or disorders in an individual(15).
- **Controlled BP:** BP < 140/90 mmHg in hypertensive diabetic patients of all ages(16).
- **Uncontrolled BP:** BP \geq 140/90 mmHg in hypertensive diabetic patients of all ages(16).
- **Controlled blood sugar:** Fasting blood sugar between 80 mg/dL 130 mg/dL(4.4–7.2 mmol/L)(17).
- **Uncontrolled blood sugar:** Fasting blood sugar greater than 130 mg/dL(17).
- **Patients with high cardiovascular disease risks:** Type 2 diabetic mellitus patients with age of greater than or equal to 40 years.
- **Elevated Lipid:** is characterized by non-HDL cholesterol exceeding 130 mg/dL (3.36 mmol/L) and/or LDL cholesterol exceeding 100 mg/dL (2.59 mmol/L).

Table 1. Clinical and behavioral characteristics of study participants at JUMC; April, 2018

Variables		Frequency	Percentage
Presence of co-morbidity	Yes	99	66.0
	No	51	34.0
Type of comorbidity	Hypertension	57	51.35
	CHF	21	18.92
	PAD	8	7.21
	Neuropathy	5	4.50
	Nephropathy	7	6.31
	Stroke	6	5.41
	Others**	7	6.31
Exercise	Regularly	34	22.67
	Sometimes	82	54.66
	Never at all	34	22.67
Age at diagnosis with DM (years)	<40	50	33.33
	>40	100	66.67
Time since DM diagnosis(years)	\leq 10	107	71.33
	>10	43	28.67
Alcohol use	Never	62	41.33
	Occasionally	76	50.67
	Regularly	12	8
Smoker	Yes	18	12
	No	132	88
Chat chewer	Yes	79	52.7
	No	71	47.3
Lipid panel status	Normal	21	14
	Elevated	6	4
	Unknown	123	82
Glycemic status	Controlled	61	40.67
	Not controlled	89	59.33
Blood Pressure Status	Normal	93	62
	Controlled	24	16
	Not controlled	33	22

CHF, Congestive heart failure; PAD, Peripheral arterial disease; DM, Diabetes mellitus. **Dyspepsia, Asthma, Retinopathy

Results

From a total of 150 type 2 DM patients, 93(62%) of them were males. About 74.7% of the patients were aged between 40-64 years, with mean \pm SD of 46.65 ± 19.61 years and 64% of them had current body mass index (BMI) between 21-25 Kg/m². Of all patients, 74.7 % of them were married and more than half of the study participants were living in an urban area. About one of fourth of patients was unemployed and 18% of them had no regular income (Table 1). Out of all patient, about 99(66%) had co-morbidities; with

which hypertension accounts 51.3% of all co-morbidities and follow by heart failure (18.9%). About two-thirds of the patients were diagnosed with DM when they are above 40 years of age and around 71.3% were diagnosed in the last 10 years. With regards to behavioral measures of respondents, about half of them were occasional alcohol drinker & 52.7% of them were chat chewer. Eighty-two percent of patients had unknown lipid panel status. About 59.33% & 22% of respondents had uncontrolled blood sugar and blood pressure, respectively (Table 2).

Table 2. Statin use pattern among study participants at JUMC; April, 2018

Variables		Frequency	Percentage	
Reason for use of statin	Primary prophylaxis	16	29.10	
	Secondary prophylaxis	35	63.63	
	Treatment	4	7.27	
Types of statin	Lovastatin	28	50.91	
	Simvastatin	13	23.64	
	Atorvastatin	14	25.45	
Intensity of statin	High intensity	Lovastatin	3	5.45
		Simvastatin	1	1.82
		Atorvastatin*	14	25.45
	Moderate intensity	Lovastatin	15	27.27
		Simvastatin	3	5.45
		Atorvastatin	0	0
	Low intensity	Lovastatin	10	18.18
		Simvastatin	9	16.36
		Atorvastatin	0	0

*40mg of Atorvastatin was considered as high-intensity statin

Among 150 patients 55(36.67%) of them were on statin therapy and they used it for prophylaxis [primary, 29.10% & secondary, 63.63%] and 7.27% of them were treated.

About half of statin user was on lovastatin regimen and one-fourth of them were taking atorvastatin. All of the atorvastatin users were on high-intensity dose (Table 3).

Table 3. Factors associated with statin use among study participants at JUMC; April 2018

Variables On statin		Statin Use		COR(95% CI)	P-value	AOR(95% CI)	P-value
		On sta- tin	Not on statin				
Gender	Male	24	69	1			
	Female	31	26	1.288 (0.554-2.992)	0.557		
Age (yrs)	40-64	28	84	1		1	
	65-74	19	10	2.941(1.168-7.406)	0.022	3.006(1.440-6.277)	0.003
	≥ 75	8	1	2.794(0.637-12.261)	0.173	2.681 (1.312-5.501)	0.087
BMI (kg/m ²)	18-20	14	22	1		1	
	21-25	34	62	1.921 (0.364-2.328)	0.062	1.356 (1.009-12.673)	0.085
	>25	7	11	1.438 (0.833-2.317)	0.031	1.213 (0.931-4.091)	0.121

Table 3. Continued

Variables On statin		Statin Use		COR(95% CI)	P-value	AOR(95% CI)	P-value
		On statin	Not on statin				
Residence	Rural	26	46	1			
	Urban	29	49	0.667(0.296-1.504)	0.329		
Educational status	Cannot read & write	7	32	1			
	Primary school	11	40	0.956(0.209-4.377)	0.954		
	Secondary school	21	21	1.621(0.397--6.618)	0.501		
	College and above	16	2	1.402(0.330-5.962)	0.647		
Marital Status	Widowed	2	4	1			
	Married	46	66	0.767 (0.17, 3.32)	0.121		
	Divorced	7	25	1.037(0.004-9.336)	0.333		
Monthly Income(ETB)	No regular Income	11	16	1		1	
	<1000	6	9	1.143(0.899-4.011)	0.604	1.23 (1.195-4.15)	0.621
	1000- 3000	20	32	1.455(0.353-6.000)	0.296	1.68 (1.68- 4.276)	0.711
	≥3000	18	38	2.118(0.518-8.650)	0.086	0.831(0.476-1.450)	0.514
Living Situation	Living alone	9	13	1			
	Living with immediate family	20	43	0.652(0.273-1.556)	0.335		
	Living with Extended family	26	39	0.565(0.145-2.195)	0.409		
Job/ Occupation	Unemployed	11	25	1		1	
	Gov't employee	17	31	2.105(0.602-7.357)	0.21	0.978 (1.114-9.090)	0.754
	Non-Gov't employee	19	8	1.091(0.204-4.893)	0.078	1.241 (0.88–1.34)	0.323
	Self-employed	8	31	1.09(1.164-13.745)	0.080	0.903(0.542-1.507)	0.697
Presence of co-morbidity	No	17	34	1		1	
	Yes	38	61	2.132 (1.304-13.071)	0.043	4.486(2.080-9.673)	<0.001
Time since DM diagnosis (years)	<10	34	73	1		1	
	≥10	21	22	1.067(1.007-14.659)	0.021	2.45 (1.524- 3.891)	0.027
Age at diagnosis with DM (years)	<40	19	31	1			
	≥40	36	64	1.513 (0.819–2.657)	0.13		
Alcohol use	Never	23	39	1			
	Occasionally	25	51	0.634 (0.525–0.732)	0.231		
	Regularly	7	5	0.861 (0.765–0.919)	0.140		
Smoker	No	7	11	1		1	
	Yes	48	84	1.102 (0.913–1.321)	0.026	1.124 (0.914–1.337)	0.182
Chat Chewer	No	30	49	1			
	Yes	25	46	0.992 (0.821–1.203)	0.341		
Lipid panel status	Normal	9	12	1		1	
	Elevated	6	0	1.791 (1.513–2.110)	0.041	1.422 (1.244–1.622)	0.033
	Unknown	40	83	1.262 (1.102–1.456)	0.025	1.842 (0.610–7.112)	0.065
Glycemic status	Controlled	24	37	1		1	
	Not controlled	31	58	1.643 (1.291–2.077)	0.056	2.127 (1.833–2.457)	0.0241
Blood Pressure status	Normal	32	61	1			
	Controlled	8	16	0.293 (0.787–1.246)	0.901		
	Not controlled	15	18	1.102 (0.913–1.321)	0.251		

The association of independent variables with the dependent variable was investigated using both univariate and multivariate logistic regression techniques. In univariate logistic regression analysis; age, body mass index, monthly income, occupation, smoking, the presence of co-morbidity, long duration with diabetes, elevated & unknown lipid panel and uncontrolled blood sugar showed association with current statin use and hence, were used in multivariate analysis. On multivariate analysis age showed statistically significant association with statin use; in that patients age between 65 to 74 years were three times (adjusted odds ratio(AOR) = 3.006;95% CI: 1.440–6.277; P = 0.003) more likely to use statin than those <64 years old. And also diabetic patients with age greater than 75 years old had more than 2 times odds of utilizing statin (AOR = 2.681; 95% CI: 1.312–0.501; P = 0.087). On univariate analysis patients with uncontrolled blood sugar had more probability of using statin (crude odds ratio (COR)=1.643; 95% CI: 1.291–2.077; P=0.056) compared to patients with controlled glycaemia. Likewise smoker (COR=1.102; 95% CI: 0.913–1.321; P=0.026), long time with diabetes (COR=1.067; 95% CI: 1.007-14.659; P=0.021) & patients who had income had higher odds of utilizing statin.

On multivariate analysis, patients with co-morbidity showed more than four times (AOR=4.486; 95% CI: 2.080–9.673; P<0.001) more chance of utilizing statin than patients without co-morbidity, which is statistically significant. The utilization of statin was more likely among patients with elevated blood cholesterol (AOR = 1.422; 95% CI: 1.244–1.622; P = 0.033) than patients with known lipid panel status. Age between 65 to 74 years (AOR=3.006; 95% CI: 1.440-6.277; p=0.003), living with DM for more than 10 years (AOR=2.45; 95% CI: 1.524- 3.891; p=0.027) and uncontrolled blood sugar (AOR=2.127; 95% CI: 1.833–2.457; p=0.0241) showed statistically significant association with utilization of statin (Table 3).

Discussions

Diabetes Mellitus now become a pandemic with a rising trend in both morbidity and mortality. Management of T2DM is based on control of hyperglycemia and also preventing the complications. Over the past few decades, integrated health delivery systems have evolved, and continue to increase in number. As a result of the evolution of these systems, the way that diabetes-related care is delivered and management of its comorbid conditions have changed considerably. As hyperlipidemia is one of the most prominent risk factors for coronary heart disease (CHD), a key approach to reducing the risk of CVD in both primary and secondary prevention is to decrease LDL-C (26). Several clinical trials have additionally indicated that there are subgroups of statin-treated patients who could benefit from a more intense lipid-lowering therapy (LLT)

regimen (34). Reduction in CV event rates by improved treatment strategies could also mean an opportunity to lower future healthcare costs.

Our current study finding showed that among 150 type 2 diabetic patients, 55(36.67%) of them were on a statin as primary prophylaxis, secondary prophylaxis, and treatment. This is higher than reports from Scotland(18) & Germany (19), in which only 25% of patients were with statin prescriptions. Prescription frequencies were higher in secondary prevention, which is also similar to study from Germany(19). As recommended in different clinical practice guidelines (CPGs) most of our patients were on secondary prophylaxis. Patients with diabetes between 40 and 75 years and LDL-C of 70–189 mg/dl and without coronary artery disease or stroke are ideal candidates to receive statin therapy as primary prophylaxis. Moreover, if patients with diabetes had already documented coronary artery disease or stroke, there was more emphasis on receiving statins as a fundamental part of their therapeutic plan for secondary CVD prophylaxis(20).

We identified five (5) major parameters that were significantly associated with statin prescription: older age >65 years, the presence of comorbidity, elevated blood cholesterol living more than 10 years with DM and uncontrolled blood sugar.

In this current study, age was one of the determinants for use of the statin. This is similar to reports from the USA(21) and Europe(22), which showed an increasing trend in the total number of adults eligible to receive statin therapy, especially among older adults without CVD. Besides this, studies described statin prevalence using population-based prescription drug databases stratified by age and sex, and generally indicate that statin use increases with age(23, 24). This age-based increase in the use of statin generally appropriate as cardiovascular risk increases with age so that statin use increases with age. However, some study result by Teeling et al., (25) & Ko et al., (26) were in paradox with our study result, that an odds of statin use is less among elderly. This is may be due to a slight difference in study populations.

Interestingly, smokers had higher odds of receiving a statin than never smokers, which is similar to a former report from Germany(19). It could be postulated as smoking is considered a major risk factor for CVD as oxidative stress from tobacco smoke increase risks as well as it is component of risk score which will increase the total score of patient's risk for developing CV events. In our current study, BMI had also a significant association with statin utilization. Patients with higher BMI showed higher odds of statin prescription, which is in agreement with a study from Germany(19) and reports by Agalliu et al., (27)and Neutel et al., (28). Different converging lines of evidence suggest that hyperlipidemia is associated with a higher BMI. And also BMI is a convenient and valid measure of adiposity, which will have a direct relation with hyperlipidemia and

in turn results in consumption of statin as preventative as well as treatment strategies.

In this current report, comorbidities were also significantly associated with statin utilization. It presences increase the probability of statin use by more than 4 times (AOR 4.486; 95% CI: 2.080–9.673; $P < 0.001$). This result is in line with studies from Germany(19), Scotland(18), & Malaysia (29). Most of our study participants were comorbid with hypertension, congestive heart failure (CHF), peripheral arterial disease, stroke, and others, whom will benefit from statin therapy/prophylaxis and also currently recommended to initiate statin for patients with such high risk for CV events.

The American Diabetic Association recommends lifestyle intervention (diet, weight loss, increased physical activity) to improve the lipid profile in all patients with diabetes(30). In patients with clinical cardiovascular disease (CVD) or over age 40 years with other CVD risk factors, statin therapy should be added to lifestyle intervention regardless of baseline lipid levels. For patients without clinical CVD and under age 40 years, statin therapy can be considered in addition to lifestyle intervention if LDL cholesterol remains above 100 mg/dL or in those with multiple CVD risk factors. Likewise, in this current study, the odds of using statin were higher among diabetic patients with elevated cholesterol. It is obvious that a patient with dyslipidemia needs a statin prescription.

Patients with type 2 diabetes have an increased prevalence of lipid abnormalities, contributing to their high risk of atherosclerotic cardiovascular disease (ASCVD). As they live longer, the risk of metabolic increases and in fact these patients will need lipid-lowering therapy. In our current study living long duration (i.e. greater than 10 years) with DM was significantly associated with the use of a statin. This is related to a proportional increase in age with CVD risk.

Uncontrolled blood sugar had also a statistically significant association with statin use. Patients with poor glycemic control utilize statin 2 times more than with their counterparts. This may be related to the fact that defects in insulin action and hyperglycemia could lead to changes in plasma lipoproteins in patients with diabetes(31), which in turn necessitate statin prescription.

The study has limitations. As it was performed in only one tertiary hospital and small sample size, it may not reflect the pattern of statin use in other facilities of Ethiopian hospitals. As the strength of the study, to our knowledge, this is the first study addressing the various predictors of statin prescription in patients with type 2 diabetes in Ethiopia.

Despite contemporary recommendations that all people with diabetes should be treated with statins, the majority of patients (about two thirds) with type 2 diabetes mellitus were not receiving statins. Age between 65 to 74 years, the presence of comorbidity, elevated blood cholesterol, living long duration with DM and uncontrolled blood sugar were

an independent predictor of statin use. Further interventions to improve statin use should be considered for these high risks for CVD patients. Prescribing interventions should focus on hospital healthcare professionals who are in a position to optimize medications for CVD prophylaxis among patients with type 2 diabetes mellitus.

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