ORIGINAL ARTICLE

Utilization of statins in patients with type 2 diabetes mellitus: the practice in a lower middle income South Asian country

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Abstract

Background Cardiovascular disease (CVD) is a major cause of morbidity and mortality among patients with type 2 diabetes. Statin reduces CVD risk. The ACC/AHA 2018 guideline on dyslipidemia recommends all patients with type 2 diabetes mellitus to be given moderate-intensity statin. We aimed to determine the prescription practices of statins among patients with type 2 diabetes mellitus.

Methods A cross-sectional study was conducted from February to April 2021. Patients with type 2 diabetes mellitus between 40 and 75 years were recruited from the University Medical Clinic and Endocrine Clinic at Colombo South Teaching Hospital, Sri Lanka.

Results Four hundred seventy-one patients were enrolled with a mean age of 59.05 (± 9.139) years. The mean duration of diabetes was 10.97 (± 9.57) years. Four hundred forty-one (93.6%) patients were on statin and 30 (6.4%) patients were not on statin therapy. Those not on statins were not prescribed statins.

Conclusions There were 163 (34.61%) patients who required high intensity. Though only 3 (1.73%) were on high-strength statin, the rest were on moderate (152, 93.25%), low (4, 2.45%), and none (4, 2.45%). Among patients with prior history of atherosclerotic cardiovascular disease (ASCVD) and the high-risk category according to the 10-year ASCVD risk estimation (155, 32.91%), only 17 (10.97%) have achieved optimal LDL therapeutic targets (55mg/dL). A large proportion of the study population received statin therapy for primary and secondary prophylaxis. However, the majority were on suboptimal doses of statin and have not achieved therapeutic targets with regard to LDL-C levels. The findings highlight the importance of improving statin therapy and optimizing lipid management according to evidence-based guideline recommendations.

Keywords Statin · Type 2 diabetes mellitus · Sri Lanka · South East Asia · Atorvastatin · Rosuvastatin · Audit · Dyslipidemia · Lipid

Background

Cardiovascular disease (CVD) affects nearly one-third of the population and currently, it is a major cause of mortality worldwide [1]. According to the 2018 World Health Organization Non-communicable Diseases (NCD) Country Profiles, 83% of deaths in Sri Lanka are caused by NCD and 34% of the total mortality was due to cardiovascular disease (CVD). The prevalence of diabetes mellitus is increasing in Sri Lanka. Local studies show that one out of five adults in Sri Lanka has either diabetes mellitus or pre-diabetes [2].

Apart from lifestyle modifications, optimal pharmacotherapy plays a pivotal role in achieving therapeutic targets in the reduction of associated morbidity and mortality diabetes [3]. Statins are one such drug that has shown to be beneficial in large-scale trials and recommended in current guidelines in patients with type 2 diabetes mellitus (T2DM). Each 1 mmol/L (38.7 mg/dL) lowering in LDL-C reduced the mortality and major adverse cardiovascular events by 0.80 (95% CI, 0.77–0.83), consistently in both primary and secondary prevention [4]. The 2018 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease recommends

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the use of moderate-intensity statin in type 2 diabetes mellitus who are 40–75 years old [5]. The American Diabetes Association (ADA) published the standards on medical care for patients with type 2 diabetes, which includes recommendation for initiating lipid-lowering therapy and prescription of moderate-intensity statins for those with no additional risk factors, and high-intensity statins for those with either CVD risk factors or overt CVD. Although guidelines emphasize the remarkable value of statin in primary and secondary prevention of CVD, little is known about the prescription pattern of statin in Sri Lanka. Using a large cohort of patients, the present study focused on statin eligibility based on ACC/AAHA 2018 guidelines and patient characteristics associated with receiving statin therapy in patients with type 2 diabetes.

Methods

Study design

We conducted a cross-sectional study from February to April 2021 among patients with type 2 diabetes mellitus attending the University Medical Clinic and Endocrine Clinic at Colombo South Teaching Hospital, Sri Lanka. This is one of the largest tertiary care hospitals in the country.

Data source and patient selection

Patients with diabetes between 40 and 75 years were recruited and type 1 diabetes mellitus patients, immunocompromised patients, and pregnant women were excluded. The study was conducted using a data extraction sheet which recorded the demographic data and clinical parameters and the investigations (FBS, serum creatinine, HbA1C, and lipid profile).

The latest investigations available within 1 year were taken into account. Data was analyzed using IBM SPSS version 21. Nominal variables were presented as the number of cases and percentages, and continuous variables were presented as means ± standard deviations. Comparison of clinical and demographic factors by gender and statin use was achieved by using the chi-square or Fisher's exact tests for categorical variables. The significance level was set at $p < 0.05$.

Statin eligibility criteria

Statin treatment regimens of the study groups were compared with the treatment recommendations of 2018 ACC/AHA guidelines.

Definitions of variables

Demographics

Education up to grade five and above grade five was considered as primary education and secondary education, respectively.

Comorbidities

The diagnosis of hypertension was based on the self-reported history of hypertension, documentation on clinic records, and the use of hypertension-lowering medications or sustained blood pressure $\geq 140/90$ mmHg in more than one visit. We considered CVD as coronary artery disease (CAD), CVA (ischemic strokes, transient ischemic strokes), and peripheral arterial disease (PAD). CAD was any documented definite or probable myocardial infarction, CAD-related revascularization (surgery, angioplasty, stenting, or any combination of these), or stable angina in participants' medical records. Data on CVA and PDA were extracted from participants' medical records as defined by the treating physician. Smoking status was a documented self-report of current smoking habits. History of dyslipidemia was obtained by patients' medical records. We estimated glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease (MDRD), and classified patients with eGFR < 60 ml/min/1.73 m^2 as having CKD. Dipstick proteinuria appeared as negative (−), trace, (+), (++), or (+++) in the dataset. Individuals with $\geq$ (+) dipstick proteinuria results were considered as having nephropathy.

Cardiovascular risk and statin therapy

We estimated 10-year cardiovascular risk of the patients using ASCVD risk estimator plus and categorized them as low (< 5%), borderline (5 to < 7.5%), intermediate (≥ 7.5 to < 20%), and high (≥ 20%). All patients with type 2 DM were considered as statin eligible. Intensity of statin therapy was defined according to the ACC/AHA 2018 guideline. Atorvastatin 40–80 mg and rosuvastatin 20–40 mg were defined as high-intensity statin therapy and atorvastatin 10–20 mg and rosuvastatin 5–10 mg were defined as moderate-intensity statin therapy. Prescription of statin for patients with previous documented CVD was considered as secondary prevention and the rest as for primary prevention. Statin use was measured based on the prescription records during the patients' clinic follow-up as all records at CSTH were not computerized.

Results

Basic characteristics

Four hundred seventy-one type 2 diabetes mellitus patients were enrolled. The mean age of the study population was 59.05 (± 9.139) years. Three hundred fourteen (66.7%) were female and 157 (33.3%) were male. The mean diabetic duration was 10.97 (± 9.57) years with 243 (51.6%) patients having type 2 diabetes mellitus over 10 years.

Among the participants, the cardiovascular risk factors detected were hypertension in 333 (70.7), dyslipidemia in 115 (24.4%), and smoking in 8 (1.7%). Chronic kidney disease (CKD) was detected in 114 (24.2%) patients and 126 (26.8%) had nephropathy. However, albuminuria was not investigated in 288 (61.1%) patients. Macrovascular complications of diabetes were reported in 60 (12.74%) patients: coronary artery disease in 55 (11.7%), peripheral vascular disease in 4 (0.8%), and cerebrovascular disease in 9 (1.9%).

An overview of the main characteristics of the study population is summarized in Table 1.

Characteristics of statin therapy

Statins were prescribed for 441 (93.6%) patients. Thirty (6.4%) patients were not on statin therapy. Out of the patients who were on statin, 60 (13.61%) were prescribed statins for secondary prevention and 381 (86.39%) for primary prevention. The most frequently prescribed statin therapy was atorvastatin (97.28%) followed by rosuvastatin (2.72%).

In relation to the statin-non-prescribed group, the statin-prescribed group was more likely to be hypertensive (43.33% vs 72.56%; $p = 0.001$), more likely to have dyslipidemia (6.67% vs 25.62%; $p = 0.019$), and likely to have a history of ischemic heart disease (0% vs 12.47%; $p = 0.040$). Factors associated with statin prescription are summarized in Table 2. A log-binomial model was fitted to examine the adjusted associations between statin prescription and various factors among the diabetic patients in the study. The best fit resulted with the covariates displayed in Table 3. Diagnosis of hypertension, borderline, and high-risk ASCVD groups were found to be associated with an increased likelihood of receiving statin therapy.

In our study, there were 60 (15.1%) patients with prior history of atherosclerotic cardiovascular disease (ASCVD), 8 (1.7%) patients LDL level ≥ 190 mg/dL, and 95 (20.2%) patients with 10-year cardiovascular risk > 20% requiring high-intensity statin therapy according to the 2018 ACC/AHA guideline on the management of blood cholesterol. Out of them, only 3 (1.73%) were prescribed with high-intensity statins. The rest were prescribed with moderate-intensity

Table 1 Main characteristics of the study population

Characteristics	Frequency (n)	Percent (%)
Gender		
Female	314	66.7
Male	157	33.3
Duration of diabetes		
< 10 years	228	48.4
≥ 10 years	243	51.6
Educational status		
≤ Primary education	68	14.4
≥ Secondary education	360	76.4
N/A	43	9.1
Hypertension		
Yes	333	70.7
No	138	29.3
Dyslipidemia		
Yes	115	24.4
No	356	75.6
Smoking		
Yes	8	1.7
No	463	98.3
Atrial fibrillation		
Yes	3	0.6
No	468	99.4
Rheumatoid arthritis		
Yes	7	1.5
No	464	98.5
Nephropathy		
Yes	126	26.8
No	57	12.1
N/A	288	61.1
CKD		
Yes	114	24.2
No	357	75.8
IHD		
Yes	65	13.8
No	406	86.2
PVD		
Yes	5	1.1
No	466	98.9
Stroke		
Yes	10	2.1
No	461	97.9
ASCVD category		
Low	160	34
Borderline	37	7.9
Intermediate	109	23.1
High	94	20.0
Established ASCVD	71	15.1

(152, 93.25%) and low-intensity (4, 2.45%) statins. Four patients (2.45%) were not given statins. The statin prescription pattern in study population is summarized in Figure 1.

Table 2 Factors associated with statin prescription among statin-eligible patients with type 2 diabetes (N = 471)

Characteristics	Subcategory	Statin not prescribed (n = 30)	Statin prescribed (n = 441)	p value
Gender	Females	21 (70.00%)	293 (66.44%)	0.689
	Males	09 (30.00%)	148 (33.56%)	
Age	40–64 years	24 (80.00%)	295 (66.89%)	0.137
	65–75 years	06 (20.00%)	146 (33.11%)	
Clinic	Endocrine	30 (100.00%)	435 (98.64%)	0.520
	Medical	00 (0.00%)	06 (1.36%)	
Education status	≤ Primary education	03 (10.00%)	65 (14.74%)	0.589
	> Primary education	23 (76.67%)	337 (76.42%)	
	NA	04 (13.33%)	39 (8.84%)	
Duration of diabetes	< 10 years	19 (63.33%)	209 (47.39%)	0.091
	≥ 10 years	11 (36.67%)	232 (52.61%)	
Hypertension	Yes	13 (43.33%)	320 (72.56%)	0.001
	No	17 (56.67%)	121 (27.44%)	
Dyslipidemia	Yes	02 (6.67%)	113 (25.62%)	0.019
	No	28 (93.33%)	328 (74.38%)	
Smoking	Yes	00 (0.00%)	08 (1.81%)	0.457
	No	30 (100.00%)	433 (98.19%)	
CKD	Yes	05 (16.67%)	109 (24.72%)	0.319
	No	25 (83.33%)	332 (75.28%)	
Nephropathy	Yes	04 (13.33%)	122 (27.66%)	0.210
	No	05 (16.67%)	52 (11.79%)	
	NA	21 (70.00%)	267 (60.54%)	
IHD	Yes	00 (00.00%)	55 (12.47%)	0.040
	No	30 (100.00%)	386 (87.53%)	
PVD	Yes	00 (0.00%)	04 (0.91%)	0.600
	No	30 (100.00%)	437 (99.09%)	
Stroke	Yes	00 (0.00%)	09 (2.04%)	0.430
	No	30 (100.00%)	432 (97.96%)	
ASCVD	Low	14 (46.67%)	152 (34.47%)	0.119
	Borderline	04 (13.33%)	33 (7.48%)	
	Intermediate	08 (26.67%)	105 (23.81%)	
	High	04 (13.33%)	91 (20.63%)	
	Previous	00 (0.00%)	60 (13.61%)	

Table 3 Adjusted relative risks for associations between various factors and statin prescription

Characteristics	Risk ratio	95% CI	p value
Sex (male)	1.0028777	0.9661957–1.0409524	0.87986
Age	1.0002212	0.9973583–1.0030923	0.87981
Duration of diabetes	1.0003480	0.9997019–1.0009946	0.29120
CKD	1.0006030	0.9942884–1.0069576	0.85196
Dyslipidemia	1.0282467	0.9345710–1.1313118	0.56763
Hypertension	1.1011756	1.0034628–1.2084033	0.04206
Smoking	1.0040577	0.9968161–1.0113519	0.27287
ASCVD—borderline	0.9747494	0.9747494–0.9747494	0.00029
ASCVD—intermediate	1.0439577	0.9672446–1.1267551	0.26928
ASCVD—high	1.0226453	1.0226453–1.0226453	0.00057
Previous ASCVD	1.0498369	0.9520481–1.1576699	0.32960

Fig. 1 Prescription of statin: Intensity vs risk category
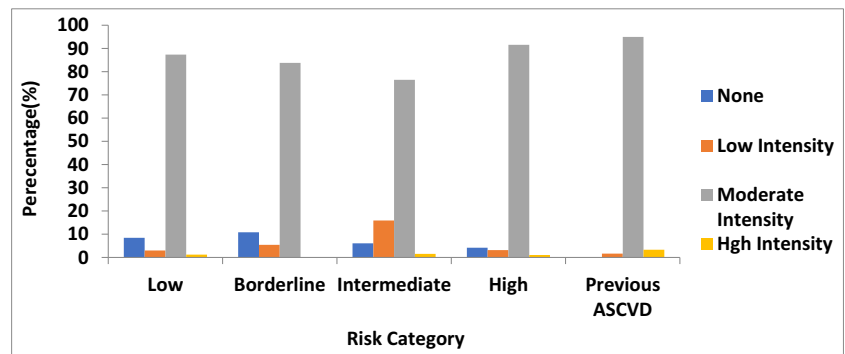
LDL therapeutic target achievement

In further analysis of patients with prior history of ASCVD and high-risk category according to the 10-year ASCVD risk estimation, only 17 (10.97%) have achieved optimal LDL therapeutic targets.

Reasons for non-prescription of statins

All 30 patients who were not on statins were patients who should have been prescribed statins for primary prevention. Only patients who needed primary prevention were not prescribed statin. Side effects due to statin, drug interactions, and non-compliance were assessed as causes for not prescribing statins. None of the patients who were not on statins was not prescribed due to the above causes. The patients who were not prescribed statins were not aware that they should have been prescribed a statin. None of the patients who were not on statins had discontinued statin, nor intolerant or had contraindications for statins.

Discussion

This study was based on the current evidence for statin prescription. A significant proportion of our study population received statin therapy which is commendable. An observational cohort study conducted to evaluate the global pattern of comprehensive cardiovascular risk factor management with type 2 diabetes patients reported that only 48.5% of South Asians were prescribed with statin [6]. In a multicenter study conducted in India, similar results of only 55.2% were prescribed statin [7]. The statin prescription rate in our study was much higher. Sri Lanka is a resource-poor country similar to India. The Sri Lankan health system is free for all in the state sector. The high adherence to statin prescription for all type 2 diabetes patients is noteworthy. The statins were prescribed preferably for diabetics with IHD and hypertension. This indicated the clinicians understand the CVD risk factors in diabetes as the presence of these risk factors enhances the risk

in patients with diabetes. The fact that should be promoted as knowledge is that all diabetics require statins and not just the ones with high CVD risk.

Under-prescription of statin in our population is a major concern as statin therapy is associated with a measurable reduction of cardiovascular mortality and morbidity at a low cost. All the patients who were not on statins in our study were not on them as the prescribers have not prescribed them. As a country with universal free health care, prevention of type 2 diabetes mellitus–related cardiovascular morbidity is cost-effective. In previous studies, the reason practitioners did not prescribe lipid-lowering agents in patients with type 2 diabetes has been related to patient factors and physician factors. Patient factors included compliance issues or refusal due to expected or perceived side effects. Physician factors included, patients not at high risk, patients at treatment targets, short life expectancy, and expected compliance issues [8, 9].

Despite the high prescription rate of statin, majority of the patients were on suboptimal doses. A majority who should be on high doses were prescribed with moderate-intensity statin. The statin intensity makes a difference in the achievement of LDL goals. The LDL reduction is proportionate to the intensity of statins. The fact that patients who should have been started on high intensity have been given only moderate intensity is discouraging. Steinberg et al. found that statins are under-dosed frequently in day-to-day clinical practice [10]. In another study done in India, a low prescription rate of high-strength statins (12.7%) was seen which is consistent with our findings [7]. Lack of sensitivity to contemporary evidence-based recommendations and individual perspectives of possible side effects of statin such as muscle toxicity strengthened by the paucity of population-based evidence could have affected the substandard prescription pattern and low level of therapeutic target accomplishment. Several studies done in Sri Lanka have shown side effects of stains to be minimal [11]. Therefore, statins at the appropriate intensity should be prescribed to patients. This requires further education of the clinicians to encourage them to use high-intensity statins when clinically indicated.

None of the patients in the study was not given high-intensity statin due to side effects. This requires further

education of the clinicians to encourage them to use high-intensity statins when clinically indicated.

A notable proportion, even among the patients who needed secondary prevention of CVD and high-risk 10-year ASCVD category have not achieved the therapeutic goals. The importance of checking lipid profiles regularly and optimizing statin therapy adding on therapy such as ezetimibe to reach LDL goals needs to be emphasized. A study conducted to estimate control of modifiable risk factors in diabetes patients in primary care setting and attainment of therapeutic goals of LDL-C levels in routine clinic practice in a tertiary care setting in Sri Lanka reported low-level achievement of therapeutic goals. Only 24.3% and 12.9% have achieved the therapeutic target in those studies respectively which is compatible with our findings [13, 14]. The reason for not achieving LDL goals could be unawareness of the importance of reaching goals among the prescribers. Analysis of statin non-prescribed group and non-achievement of therapeutic goals is suggestive of clinical inertia. However, further evaluation of root causes for the gap between clinical practice and the current guidelines needs further studies of qualitative nature to understand the prescribing practice of the doctors.

Conclusion

In conclusion, this study shows that despite the high rate of statin utilization, prescription of the right intensity of statin according to the risk category is substantially far below the current recommendations.

Limitations

There are several limitations of this study. The study was done in a single center and this was carried out during the 3rd wave of the COVID-19 pandemic, limiting patients' clinic attendance and the number of investigations done during the period of the study.

Declarations

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