

Prescribing statins among patients with type 2 diabetes: The clinical gap between the guidelines and practice

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Background: Statins are recommended for cardiovascular protection for people with diabetes (high-risk groups). This study aimed to evaluate the gap between the guidelines of statin utilization and clinical practice among outpatients with type 2 diabetes regarding the patient's age and gender, to assess if this preventive drug is being satisfactorily utilized or not. **Materials and Methods:** In this cross-sectional study, patients aged <40 or >75 years, pregnant patients, and patients with type 1 diabetes, human immunodeficiency virus, or liver cirrhosis were excluded. Demographics, laboratory parameters, and prevalence of exposure to statin therapy were evaluated. This study was guided by the 2013 American College of Cardiology/American Heart Association cholesterol guidelines. IBM SPSS software was used for data management. **Results:** The study cohort involved 576 patients, with age being 58.3 ± 8.9 years. There were 50.5% of females and 49.5% of males. Overall 81.1% of patients aged 58.8 ± 8.8 years were statin users and 18.9% of patients aged 56.2 ± 9 years were statin nonusers. About 83.2% of females and 78.9% of males were prescribed statins. Statin medications included simvastatin 79.2%, atorvastatin 11.6%, lovastatin 5.8%, rosuvastatin 2.1%, and pravastatin 1.3%. Statin users' and nonusers' adherence was 56.5%, and 41.3% ($P = 0.004$), respectively. The adherence to medication plan of females and males was 55.7% and 51.6%, respectively ($P = 0.004$). **Conclusion:** Patients with diabetes who are at high risk of cardiovascular events, exposure to statin treatment is significantly less than perfect position both in females and males. Nearly one-fifth of the patients with type 2 diabetes are not using statins despite therapeutic necessities.

Key words: Age, clinical gap, gender, Malaysia, practice guidelines, statin medication, type 2 diabetes

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INTRODUCTION

Cardiovascular disease (CVD) affects one-third of patients and remains the main reason of death in the United States.^[1] At the same time, diabetes mellitus is recognized as a hazard equivalent to coronary heart disease (CHD). Reaching treatment targets is essential in preventing further morbidity and mortality resulting from CVDs.^[2,3] Some of the large-scale randomized controlled trials and observational studies have demonstrated the efficacy of statins in preventing cardiovascular morbidity and mortality in diabetic patients;^[4] therefore, statins have become the cornerstone

of hypercholesterolemia pharmacotherapy in patients with diabetes. Clinical practice guidelines recommend using statins as the first choice of drug in patients with mixed dyslipidemia or hypercholesterolemia.^[5]

The American Diabetes Association recommends that individuals with diabetes and a history of CVD aged from 40 to 75 years should be given a statin regardless of their baseline low-density lipoprotein cholesterol (LDL-C) concentration.^[6] Many studies have confirmed that a significant proportion of patients with diabetes in the community do not reach the predefined goals for optimal management of blood glucose, lipids,

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and blood pressure and suffer from comorbidities and polypharmacy.^[7-11] This failure to attain therapeutic targets has been reported in numerous researches from around the world, despite various patient populations, different clinical practice recommendations, and altered time frames.^[12]

This study was conducted to investigate the application of clinical practice guideline endorsements for the management of dyslipidemia in diabetic patients aged >40 and ≤75 years in actual practical clinical situations. At the same time, the study evaluates the gap between the guideline recommendation of statin utilization and practice among outpatients with type 2 diabetes mellitus with regard to their age and gender. The null hypothesis assumes that there is no gap between clinical practice and guidelines recommendations and also assumes no difference among females and males in the rate of prescribed statins.

MATERIALS AND METHODS

Study population

A cross-sectional study was conducted at the Endocrinology Clinic in Hospital Pulau Pinang, Malaysia, in October 2015–2016. The sociodemographic and prescription data for statin use were extracted from 827 patient files. The study enrolled individuals with type 2 diabetes mellitus aged 40–75 years. About 251 cases (186 patients <40 or >75 years old, 9 pregnant patients, 40 with type 1 diabetes, and 16 patients with liver cirrhosis) were excluded from the study. The experience of statin therapy in 576 patients was evaluated.

Procedure and variable assessment

A checklist was used for collecting patients'. Demographic characteristics include age, weight, height, gender, and ethnicity. The related clinical variables involve glycated hemoglobin (HbA1c), comorbidities, statin medications, and drug dosage and their duration. Data were collected from individuals, patients' medical records, and medical team. The principal investigator collected the data. A diabetologist estimated patients' adherence using 8-item Morisky Medication Adherence Scale. Adherence was classified as low adherence (scores >2), medium adherence (scores 1 or 2), and high adherence (scores = 0).^[13]

This study was guided by the 2013 American College of Cardiology/American Heart Association cholesterol guideline (AHA). Statin members were classified into high-dose intensity (HDI) group (atorvastatin 40–80 mg, rosuvastatin 20–40 mg, and simvastatin 60–80 mg daily), medium-dose intensity (MDI) group (atorvastatin 10–20 mg, lovastatin 40–60 mg, pravastatin 40–80 mg, rosuvastatin 5–10 mg, and simvastatin 20–40 mg daily), and low-dose intensity (LDI) group (simvastatin 10 mg,

pravastatin 10–20 mg, and lovastatin 20 mg daily).^[14] Uncontrolled glycemia was defined as HbA1c >7% for patients aged <65 years and ≥8% for patients aged ≥65 years based on the guidelines of American Diabetes Association 2016.^[15] This study was guided by the reporting guidelines for cross-sectional studies and Strengthening the Reporting of Observational Studies in Epidemiology (STROBE).^[16]

Statistical analysis

The data were managed using IBM SPSS software version 23.0 (SPSS Statistics for Windows, IBM Corp., Armonk, NY, USA). The Kolmogorov–Smirnov test was used to evaluate normality of the variables. Log transformation was performed on some of the skewed variables before analysis to reach a normal distribution.^[17] Nominal variables were demonstrated as a number and percentage, *n* (%). Parametric data were illustrated as the mean ± standard deviation (SD). Independent *t*-test was conducted to estimate the differences of means among the normally distributed continuous factors such as age, body mass index (BMI), period of diabetes, and HbA1c%. Mann–Whitney U-test was used when the distribution was skewed.^[18] Chi-square test evaluated the differences between the nominal variables such as ethnicity, family history of diabetes, HbA1c control, adherence, statin use, and gender. Kendall's tau_b or Spearman's correlation analysis was done for evaluating the relationship between statins and the other study variables, as appropriate. Linear and multinomial logistic regression analyses were done to predict the variable sharing in the decrease or increase of the utilization of statins in the management of diabetic dyslipidemia. *P* < 0.05 was considered statistically significant.

Ethical consideration

From the ethical perspective, this study followed the procedures of the registration in Clinical Research Centre in Hospital Pulau Pinang and the registration in National Medical Research Register (NMRR ID: NMRR-15-1068-25700).^[19] In addition, participants have signed an informed consent form, and all of the study procedures were conducted under the supervision of experts. All phases of the study were accredited by the local health authorities and the institutional Medical Ethics Committee before the initiation of this study. The confidentiality, data, and dignity of the patients are protected and used for the research and publication only.

RESULTS

This study enrolled a total of 576 patients, in the age range of 40–75 years, with mean ± SD of 58.3 ± 8.9 years. There were 50.5% of females and 49.5% of males. Statin users constituted 81.1% of cases, with age being 58.8 ± 8.8 years.

Statin nonusers constituted 18.9% of patients, with a mean age of 56.2 ± 9 years. Around 83.2% of women and 78.9% of men were given statins. Statin medicines included atorvastatin 11.6%, lovastatin 5.8%, pravastatin 1.3%, rosuvastatin 2.1%, and simvastatin 79.2%, as described in Figure 1. About 16.7% of patients were prescribed HDI-statin, 19.3% were prescribed LDI-statin, and 64% were prescribed MDI-statin as shown in Figure 2. Statin users had high adherence (56.5%), while statin nonusers had high adherence (41.3%) ($P = 0.004$) as demonstrated in Table 1. The adherence to medication plan of females and males was 55.7% and 51.6%, respectively ($P = 0.004$) as described in Table 2.

Binary logistic regression confirmed BMI, history of diabetes incidence, diabetic family history, HbA1c%, and uncontrolled glycemia ($HbA1c > 7\%$) as negative predictors for the utilization of statins among diabetic patients, whereas adherence works as a positive predictor for the usage of statins in diabetic dyslipidemia management (all $P < 0.05$). However, age and ethnicity are not predictors for the use of statins among type 2 diabetic persons ($P > 0.05$) as illustrated in Table 3.

DISCUSSION

In this study, about 20% of patients with type 2 diabetes mellitus aged between 40 and 75 years were not prescribed a statin. Besides, females had more exposure to statin therapy than males.

A robust body of evidence supports the cardiovascular benefits of beginning statin treatment. A Cochrane review article based on 18 randomized controlled trials with a total of 56,934 patients found that statin therapy reduced all-cause mortality. In addition, statin therapy reduced

fatal and nonfatal cardiovascular events and reduced the incidence of fatal and nonfatal stroke. Most of the standard clinical guidelines have recommended the utilization of statin treatment in patients with type 2 diabetes.^[20]

In 2010, the Cholesterol Treatment Trialists' collaboration achieved a meta-analysis of 26 trials with a total of more than 170,000 participants and follow-up of approximately 5 years. This meta-analysis found an overall decrease in all-cause mortality of 10% for every 1.0 mmol/L lessening in LDL-C levels (relative risk: 0.90, 95% confidence interval: 0.87–0.93) ($P < 0.001$).^[21] In addition, there were significant reductions in major vascular events.

Table 1: Variable distribution between statin user group and statin nonuser group among diabetic patients

Variance	Statin users (n=467)	Nonstatin users (n=109)	P
Age (years)	58.8±8.8	56.2±9	0.007
BMI (kg/m ²)	28.6±5.6	27.1±5.3	0.012
Gender, n (%)			
Male	225 (48.2)	60 (55)	0.803
Female	242 (51.8)	49 (45)	0.803
Ethnicity, n (%)			
Malay	186 (39.8)	28 (25.7)	0.028
Chinese	151 (32.3)	48 (44)	0.028
Indian	130 (27.8)	33 (30.3)	0.028
Family history of diabetes, n (%)	130 (27.8)	35 (32.1)	0.001
Period of diabetes	14.5±8.2	11.1±7	0.001
HbA1c, n(%)	349 (74.7)	39 (35.8)	0.001
HbA1c, (mean ± SD)	8.6±1.9	7.2±1.4	0.001
High adherence, n (%)	264 (56.5)	45 (41.3)	0.004
Medium adherence, n (%)	79 (16.9)	24 (22)	0.004
Low adherence, n (%)	124 (26.6)	40 (36.7)	0.004

Chi-square was used for nominal variables. Student t-test was performed for normally distributed variables. Mann-Whitney U-test was done for skewed variables. The P value is significant at level < 0.05 (two tailed), data are presented as mean±SD or n (%). BMI=Body mass index; HbA1c=Glycated hemoglobin; SD=Standard deviation

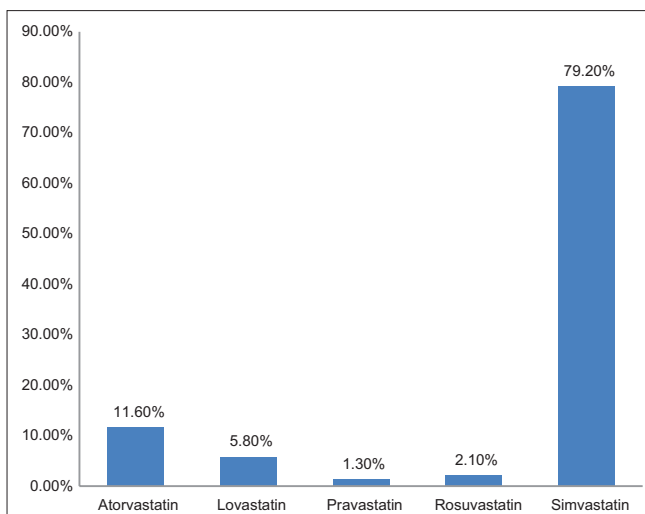


Figure 1: Statin distribution among outpatients with type 2 diabetes mellitus

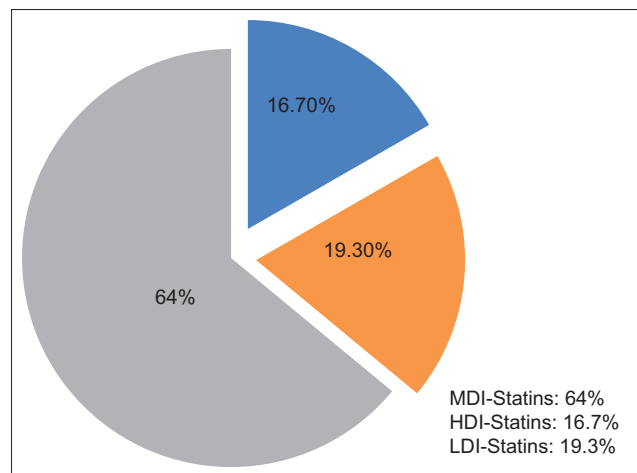


Figure 2: Distribution of statin dose intensity among outpatients with type 2 diabetes

Due to the overwhelming body of evidence supporting its use, statin therapy is recommended according to the guidelines of the AHA and the European Society of Cardiology.^[22,23]

In 2017, a study evaluated statin usage among people with diabetes and those with CHD in Vellore. Among 61 patients with CHD, 37.7% were on statins. Statin use among 422 persons with diabetes aged ≥40 years was 7.6% among rural patients and 13.4% among urban patients. Statin utilization for CHD was under 50% although higher than the use among people with diabetes, indicating the requirement to address this low percentage of usage among these high-risk cohorts.^[24]

In 2018, a national retrospective cohort of 899,664 veterans aged ≥40 years with diabetes mellitus (Brennan *et al.* 2018)

(from 2003 to 2011) classified the 9-year follow-up into 3-month periods. For each period, they assessed statin utilization, recognized as possession of ≥1-month supply. They inspected issues concomitant with statin uptake among baseline nonusers with a multivariate model. The baseline prevalence of statin usage was 43%, augmented by 1.8% per period ($P < 0.001$) and extended to a maximum of nearly 59%. Among baseline nonusers, statin consumption was 9% after year 1 and stretched to 36% by year 9. Factors accompanying statin uptake consist of the usage of hypoglycemic medications, HbA1c between 7% and 8.9% (53–74 mmol/mol), heart failure, hypertension, Hispanic ethnicity, and peripheral vascular disease. Statin usage is gradually growing among persons with diabetes and at fluctuating degrees within subgroups of this population. Policies that prioritize these subgroups for statin promotion may guide future, intervention-based research to enhance adherence to recent recommendations.^[25]

Table 2: Distribution of variables between diabetic female and male cohorts

Variance	Female (n=291)	Male (n=285)	P
Age (years)	58.1±8.7	58.5±9.1	0.628
BMI (kg/m ²)	28.2±5.6	28.5±5.5	0.584
Ethnicity, n (%)			
Malay	117 (40.1)	97 (34)	0.028
Chinese	99 (34.1)	100 (35.1)	0.028
Indian	75 (25.8)	88 (30.9)	0.028
Family history of diabetes, n (%)	89 (30.6)	76 (26.7)	0.001
Period of diabetes	14.1±7.7	13.7±8.4	0.517
HbA1c, n (%)	196 (73.6)	192 (67.4)	0.001
HbA1c, (mean ± SD)	8.5±1.9	8.3±1.8	0.233
High adherence, n (%)	162 (55.7)	147 (51.6)	0.004
Medium adherence, n (%)	47 (16.1)	56 (19.6)	0.004
Low adherence, n (%)	82 (28.2)	82 (28.8)	0.004
Statin users, n (%)	242 (83.2)	225 (78.9)	0.001
Statin nonuser, n (%)	49 (16.8)	60 (21.1)	0.001

Chi-square was used for nominal variables. Student t-test was performed for normally distributed variables. Mann–Whitney U-test was done for skewed variables. The P value is significant at level <0.05 (two tailed); data are presented as mean±SD; or n (%). BMI=Body mass index; HbA1c=Glycated hemoglobin; SD=Standard deviation

Elnaem *et al.* (2017) evaluated the patterns of statin treatment prescribed among hospitalized individuals with type 2 diabetes mellitus. The study involved patients aged between 40 and 75 years. The assessment of statin prescription indicated that 35% of patients were not given any statin, opposing to the national treatment recommendations. About 26% of the study participants were prescribed medications that interacted with statins.^[26] A significant percentage of the participants did not receive their recommended statin treatment for CVD avoidance, which is in concordance with our findings.^[27]

Variances in drug disposition, pharmacodynamics, and physiology contribute to the statement that females and males frequently respond differently to drugs. Hormonal influences can play a significant role. Sex/gender dissimilarities in dyslipidemia management with statins and more considerable trouble in attainment of the goals can be partly related to the sex/gender physiopathological divergences. Evidence supporting sex-based differences in

Table 3: Prediction of statin utilization in diabetic dyslipidemia management (n=576)

Independent variables	B	SE	Wald	df	P	OR	95% CI for OR	
							Lower	Upper
Age	-0.005	0.016	0.088	1	0.767	0.995	0.964	1.027
Adherence	0.675	0.165	16.795	1	0.001	1.964	1.422	2.713
BMI	-0.082	0.026	9.737	1	0.002	0.921	0.875	0.970
Diabetic family history	-0.554	0.274	4.072	1	0.044	0.575	0.336	0.984
Diabetic period	-0.048	0.018	7.211	1	0.007	0.953	0.920	0.987
Ethnicity	0.190	0.158	1.450	1	0.229	1.209	0.888	1.648
HbA1c (%)	-0.549	0.107	26.514	1	0.001	0.578	0.469	0.712
HbA1c control	-0.749	0.299	6.279	1	0.012	0.473	0.263	0.850
Constant	6.398	1.452	19.426	1	0.001			

Binary logistic regression was used to predict correlation. The P value is significant at level <0.05 (two tailed). Dependent variable=Statin usage; Independent variables=BMI, diabetic family history, diabetic period, HbA1c (%), HbA1c control. B=Intercept value; BMI=Body mass index; CI=Confidence interval; df=Degrees of freedom; HbA1c=Glycated hemoglobin; OR=Odds ratio; SE=Standard error

statin metabolism implicates differences in body fat content between males and females.^[28]

A recent systematic review and meta-analysis of 64 cohorts, including 858,507 persons and 28,203 coronary events, reported that females with diabetes have more than a 40% greater risk of incident CHD compared with diabetic males, this difference due to the higher percentage of females' body fat.^[29] The cause of these significant differences may partially stem from a shortage of control for cardiovascular hazard factors containing dyslipidemia among female patients with diabetes.^[30]

A Spanish revision which comprised available data for a total of 286,791 patients described that, while the percentage of females given lipid-lowering prescriptions was comparable to or even higher than that of males, LDL-C levels were remarkably uncontrolled in both women with and without CVD.^[31] These findings interpret the higher prevalence of statin use among females than males in our study.

CONCLUSION

People with type 2 diabetes mellitus who are at high risk of cardiovascular events, experience to statin treatment are significantly less than ideal condition both in males and females. Nearly 20% of the patients with type 2 diabetes are not using statins in spite of therapeutic necessities. Females were prescribed more statin than males. The utilization of statins decreases by the increase in BMI, diabetic period, HbA1c%, diabetic family history, and uncontrolled HbA1c. Efforts to confirm appropriate statin prescription and utilization can benefit in achieving better clinical outcomes of statin therapy and improve the patients' quality of life.

Study limitation

The study was done in a single center, wherever the time was constrained, and information accessibility in Hospital Pulau Pinang limited this study.

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Conflicts of interest

There are no conflicts of interest.

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