

The Association Between Long-term Statin Therapy and New-onset Diabetes in Patients with Cardiovascular Risk Factors in the United Arab Emirates

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Abstract

Objectives: Statins are the most widely prescribed lipid-lowering agent for primary and secondary cardiovascular disease (CVD) prevention. However, despite the cardiovascular benefits, some risks exist, such as the risk of new-onset diabetes mellitus (NODM) among statin users. In the United Arab Emirates (UAE), which has one of the highest prevalences of CVD globally, the relationship between long-term statin use and NODM has never been studied. Therefore, this study described the incidence and risk of NODM associated with statin therapy among UAE patients with cardiovascular risk factors.

Methods: Retrospective data were captured from April 2008 until January 2020. Propensity score matching was applied to carefully match statin users to an equal number of nonusers and thus decrease baseline variability. Multivariable Cox proportional hazards regression analysis estimated the risk of NODM in statin users compared to statin nonusers.

Results: Patients (n = 631) with one or more vascular risk factors were followed for a median of 10.1 years (interquartile range 7.9, 10.9 years). At baseline in the matched cohort, age- and sex-adjusted incidence rates among statin users were higher than those among nonusers (21.2 events per 1,000 person-years versus 8.3 events per 1,000 person-years, respectively). Furthermore, statin therapy users were more than three times as likely to develop NODM over 10 years compared to statin nonusers. It was estimated that 19.2 patients (95% CI: 10.9, 90.9) would need to be treated with statins for 10 years for one patient to develop NODM.

Conclusions: Long-term statin use among Emirati patients was associated with increased NODM risk. However, the number of patients who needed to be treated with statins to cause NODM was low. While this risk is small relative to the benefits of treating CVD, clinicians should closely monitor new users of statin therapy at risk of diabetes in the UAE.

Keywords: statins, diabetes, dyslipidemia, cardiovascular disease, incidence, risk factor, United Arab Emirates.

Introduction

Statins are the most prescribed lipid-lowering agent for primary and secondary cardiovascular disease prevention. The risk of ischemic heart disease events and stroke is reduced by 60% and 17%, respectively, when the low-density lipoprotein-cholesterol (LDL-cholesterol) concentration is decreased by approximately 1.8 M with statin therapy.¹ Robust evidence for the benefit and safety of statin use over the last three decades has informed the updates to lipid-lowering guidelines and treatment choices,^{2,3} resulting in increased statin use from 838.1/100,000 persons in 2003 to 1,626.9/100,000 persons in 2015.⁴ However, despite the benefits, there are some risks. Recent data from randomized clinical trials^{5,6} have shown an increase in statin-induced new-onset diabetes mellitus (NODM), resulting in a 10% to 45% higher risk of NODM.⁷ Based on these risks, the Food and Drug Administration in the United States, as well as the European Medicines Agency, issued a warning relating to an increase in the incidence of diabetes among statin users.⁸

The use of statins globally, which includes the United Arab Emirates (UAE), could be dramatically increased based on recent changes to the evidence-based guidelines.⁹ Therefore, patients at higher risk for NODM must have their management plans individualized. The prevalence of dyslipidemia in the UAE is 44%,¹⁰ whereas the incidence of cardiovascular disease (CVD) is 12.7 per 1,000 person-years¹¹ and diabetes incidence is 16.3 cases per 1,000 person-years among overweight and obese UAE nationals.¹² These findings help to contextualize the present burden for statin use and diabetes management.

Studies conducted globally on statin-related NODM were mainly in Western countries, with a few published from the Middle East region.⁷ This study will compare the incidence of NODM among Emirati patients with cardiovascular risks and receiving statin therapy to that of statin nonusers, as well as the association between statin therapy and incident diabetes, thus adding to the epidemiological data on statin-related NODM in the Gulf region of the Middle East.

Methods

This is a retrospective observational analytical cohort study design. The study site was Tawam Hospital, Al Ain, Abu Dhabi, UAE. Electronic medical records (EMRs) of adult UAE nationals visiting outpatient clinics at the large local tertiary care hospital in Al Ain from 1st April 2008 to 31st December 2008 were reviewed retrospectively.

The sample size for the study was determined using a formula appropriate for estimating incidence in a population¹³ A sample size of 300 participants was calculated, considering an expected 13% incidence of DM,¹² and using 80% statistical power with a 2-sided significance level of 0.05.

UAE national patients aged ≥ 18 years with one or more cardiovascular risk factors, such as hypertension (defined as having systolic blood pressure [SBP] ≥ 140 mmHg or diastolic blood pressure [DBP] ≥ 90 mmHg or receiving antihypertensive medications), dyslipidemia (defined as patients receiving statin therapy or having an established diagnosis of dyslipidemia at baseline), overweight (defined as having a body mass index [BMI] 25–29.9 kg/m²; BMI was calculated as the weight [kg] divided by the height [m²]), obesity (defined as BMI ≥ 30 kg/m²), smoking history (current smokers or those with past smoking history were considered smokers), history of coronary heart disease (CHD) (defined as patients with a documented history of a coronary event, coronary revascularization procedure or a diagnosis established by a cardiologist), history of stroke (defined as patients with a documented history of cerebrovascular accident or transient ischemic attack), documented history of peripheral arterial disease (PAD), and history of chronic kidney disease (defined as an eGFR < 60 mL/min \cdot 1.73 m²; the CKD-EPI Creatinine Equation [2021], which includes serum creatinine, was used to estimate glomerular filtration rate [eGFR]).¹⁴

Statin therapy was determined by reviewing drug prescriptions and clinicians' assessment plans for patients in the EMRs. Patients who were newly prescribed at least one statin therapy, such as atorvastatin, rosuvastatin, simvastatin, pravastatin, lovastatin, or fluvastatin, during the index period (1st April to 31st December 2008) for more than 90 days were identified as statin users, whereas patients with no records of statin therapy use during the index period were considered nonstatin users. Patients with a diagnosis of DM, on medications for DM, with an HbA1c $\geq 6.5\%$ prior to

the index date, or missing HbA1c baseline data were excluded. In addition, patients receiving statin therapy prior to the study entry date were excluded (Figure 1).

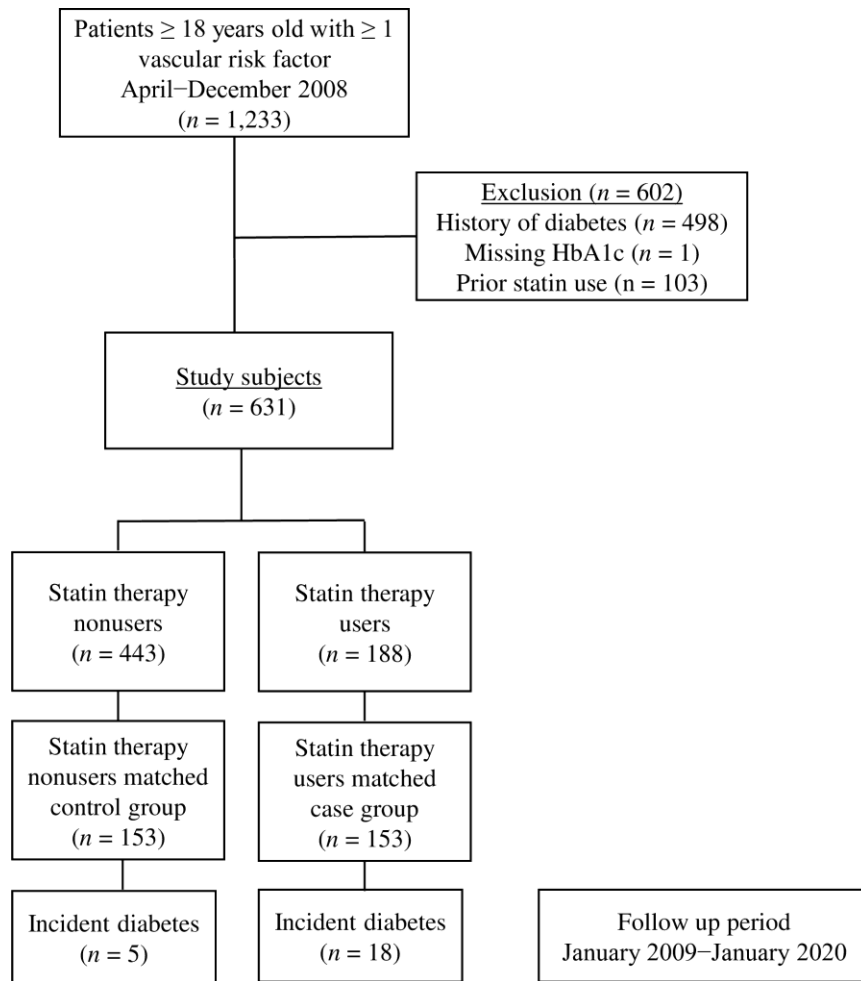


Figure 1: Subject selection flowchart, statin therapy.

The following baseline information was collected from the patients’ EMRs for analysis: age, sex, smoking status, family history of diabetes (defined as a first-degree relative having a history of diabetes), history of CHD, stroke, and PAD, and clinical parameters, such as BMI, SBP, and DBP. Treatment modalities such as antihypertensive medication and statins and laboratory results such as low-density lipoprotein-cholesterol (LDL-C), eGFR, and HbA1c were included.

The primary outcome measured is incident diabetes defined as a follow-up HbA1c measurement of $\geq 6.5\%$ on at least two separate days over any period. This was identified by an annual review of patients’ hospital records until 31st January 2020. The date of incident diabetes diagnosis was based on the earliest abnormal laboratory test result. The follow-up time for developing NODM was determined for each patient from the index date to the diagnosis of NODM, last outpatient visit, or until 31st January 2020, whichever occurred first.

Multiple (five) imputations using the predictive mean matching technique were performed for missing data: Family history of diabetes had 20.6% missing, LDL-C had 4.4% missing, creatinine had 1.1% missing, whereas height, weight, SBP, and DBP each had $<1\%$ missing. The missing values all occurred at random. The imputed dataset that was created was then utilized in all analyses. Rubin’s rules were used to combine the results across the imputed datasets.¹⁵

Propensity score matching was used to account for variations in baseline characteristics between the statin user group and the statin nonuser group and to construct the matched cohort.^{16,17} The propensity score was estimated using the multivariable logistic regression model with statin user group as the dependent variable and the covariates of age, history of CHD, history of stroke, sex, history of smoking, antihypertensive medication, SBP, DBP, BMI, LDL-C, eGFR, and HbA1c. The nearest neighbor matching algorithm with a 1:1 matching ratio and a caliper width = 0.2 of the propensity score was used.

In the original unmatched and matched cohorts, the differences in baseline characteristics between statin users and statin nonusers were tested using Fisher’s exact test (two-tailed) for categorical variables, an independent-samples t test for normally distributed continuous variables, and a Mann–Whitney U test for nonnormally distributed continuous variables. Normally distributed continuous variables are presented as the means and standard deviation (SD), whereas nonnormally distributed continuous variables are presented as medians and interquartile ranges (IQRs). Categorical variables are presented as proportions. The age- and sex-adjusted incidence rates of NODM per 1,000 person-years for statin and nonstatin users were calculated using Poisson regression.¹⁸

The association between incident diabetes and statin users and nonusers was evaluated using multivariable Cox proportional hazard models. The multivariable Cox regression model was adjusted for the following covariates: age, sex, history of smoking, family history of diabetes, SBP, DBP, LDL-C, BMI, and statin use. The results were recorded as hazard ratios (HRs) and 95% confidence intervals (CIs).

The number of patients who must be treated for one of them to experience an adverse reaction because of the therapy (number needed to harm [NNH]) was estimated using the method based on the restricted mean survival time.¹⁹ Postestimation sensitivity analysis to assess unmeasured confounding was conducted using the E-value package in R software.²⁰ The E-value is a novel method for estimating unmeasured confounding. It is described as the lowest strength of association that an unmeasured confounder required to fully explain a certain therapy–outcome association, depending on the measured covariates. A high E-value indicates that significant unmeasured confounding is required to explain an effect estimate, whereas a low E-value indicates that minimal unmeasured confounding is required to explain an effect estimate.

All statistical analyses were performed using SPSS version 28 (IBM Corp., Armonk, NY, USA) and R software, version 4.1.2 (The R Foundation, Vienna, Austria). Two-sided p values < 0.05 were considered statistically significant.

The study was ethically approved by the Tawam Human Research Ethics Committee (MF2058-2022-841). All methods were carried out in accordance with the ethical standards of the Helsinki Declaration. Patients’ records and information were anonymized and de-identified at the time of data entry; therefore, the requirement for informed consent was waived by the Tawam Human Research Ethics Committee.

Results

In our study, 631 adult patients with one or more cardiovascular risk factors at baseline were identified (Figure 1). Among them, 188 (29.8%) patients initiated at least one statin therapy during the index period, of which 116 patients were prescribed atorvastatin, 42 rosuvastatin, 21 simvastatin, 6 pravastatin, 1 fluvastatin, and 2 unknown statin class types. In the original cohort, there were several differences in the baseline characteristics between the statin user and nonuser groups (Table 1). Patients receiving statin medications were older and primarily women, had a higher proportion of patients receiving blood pressure-lowering medication, and had a higher prevalence of CHD than nonusers. In addition, statin users had higher BMIs, SBPs, HbA1c levels, and LDL-C levels at baseline than nonusers. Interestingly, statin nonusers had a higher proportion of patients with a family history of diabetes compared to statin users (50.8% versus 32.4%, respectively). After applying propensity score matching, 153 statin users and 153 nonusers with similar baseline variables were identified.

Table 1: Baseline characteristics of the study cohort stratified by statin medication use.

Characteristic	Original cohort	Matched cohort ^a
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	Statin therapy nonusers (n = 443)	Statin therapy users (n = 188)	p value	Statin therapy nonusers (n = 153)	Statin therapy users (n = 153)	p value
Age (years), mean (SD)	40.1 (15.0)	56.0 (12.9)	<0.001	53.6 (14.2)	54.3 (12.8)	0.646
Sex, n (%)						
Men	251 (56.7)	76 (40.4)	<0.001	64 (41.8)	68 (44.4)	0.729
Women	192 (43.3)	112 (59.6)		89 (58.2)	85 (55.6)	
Smoking, n (%)	90 (20.3)	30 (16.0)	0.223	26 (17.0)	25 (16.3)	1.000
CHD, n (%)	4 (0.9)	19 (10.1)	<0.001	4 (2.6)	9 (5.9)	0.256
Stroke, n (%)	12 (2.7)	9 (4.8)	0.224	8 (5.2)	8 (5.2)	1.000
PAD, n (%)	2 (0.5)	3 (1.6)	0.160	2 (1.3)	1 (0.7)	1.000
BP-lowering medication, n (%)	108 (24.4)	126 (67.0)	<0.001	87 (56.9)	92 (60.1)	0.643
Statin type, n (%)		n = 186			n = 151	
Atorvastatin		116 (62.4)			90 (59.6)	
Rosuvastatin		42 (22.6)			37 (24.5)	
Simvastatin		21 (11.3)			18 (11.9)	
Pravastatin		6 (3.2)			5 (3.3)	
Fluvastatin		1 (0.5)			1 (0.7)	
Family history of diabetes, n (%)	225 (50.8)	61 (32.4)	<0.001	53 (34.6)	54 (35.8)	1.000
BMI, kg/m ² , median (IQR)	27.8 (24.4, 32.0)	29.7 (25.8, 32.7)	0.010	29.9 (26.0, 33.6)	29.7 (26.0, 32.2)	0.561
SBP, mmHg, mean ± SD	125.3 (16.4)	130.2 (15.4)	<0.001	130.7 (18.4)	129.6 (16.1)	0.599
DBP, mmHg, mean ± SD	76.2 (11.6)	76.5 (10.7)	0.782	77.7 (13.9)	77.0 (11.0)	0.622
HbA1c, %, mean ± SD	5.5 (0.5)	5.7 (0.5)	<0.001	5.7 (0.4)	5.7 (0.5)	1.000
LDL-C, M, mean ± SD	3.2 (0.8)	3.5 (1.1)	0.002	3.5 (0.9)	3.5 (1.1)	0.798
eGFR, mL/min·1.73 m ² , median (IQR)	114.0 (101.5, 124.0)	100.5 (87.0, 109.0)	<0.001	102.0 (92.0, 112.0)	103.0 (93.0, 109.0)	0.556
Follow-up HbA1c, %, median (IQR)	5.5 (5.2, 5.8)	5.8 (5.5, 6.1)		5.6 (5.4, 6.0)	5.8 (5.5, 6.1)	

SD = standard deviation; *CHD* = coronary heart disease; *PAD* = peripheral artery disease; *BP* = blood pressure; *HbA1c* = hemoglobin A1c; *BMI* = body mass index; *SBP* = systolic blood pressure; *DBP* = diastolic blood pressure; *LDL* = low-density lipoprotein-cholesterol; *eGFR* = estimated glomerular filtration rate; *CI* = confidence intervals
^a Matched cohort constructed using propensity score matching

Patients were followed for a median of 10.1 years (IQR 7.9, 10.9 years). During the follow-up period for the original cohort, 20 patients (10.6%) on statins developed NODM. The age- and sex-adjusted incidence rate was 26.9 events per 1,000 person-years in statin users compared to 8.4 events per 1,000 person-years in nonusers. Furthermore, statin use in the original cohort was associated with a more than a twofold risk of developing NODM (adjusted HR = 2.46, 95% CI: 1.11, 5.45, p value = 0.027) compared to nonusers (Table 2).

Table 2. Incidence rate and HR for the association between statin therapy use and the risk of NODM in the original and matched cohorts.

Original cohort

Matched cohort^a

		NODM cases, <i>n</i> (%)	Incidence rate of NODM ^b (95% CI)	Adjusted ^c HR (95% CI)	NODM cases, <i>n</i> (%)	Incidence rate of NODM ^b (95% CI)	Adjusted ^c HR (95% CI)
Statin users	therapy	20 (10.6)	26.9 (16.0–45.3)	2.46 (1.11–5.45) ^d	18 (11.8)	21.2 (13.8–32.5)	3.24 (1.13–9.26) ^e
Statin nonusers	therapy	12 (7.8)	8.4 (4.7–15.1)	Reference	5 (3.3)	8.3 (3.4–20.4)	Reference

NODM = new-onset diabetes; *HR* = hazard ratio; *CI* = confidence intervals; *BMI* = body mass index; *SBP* = systolic blood pressure; *DBP* = diastolic blood pressure; *LDL-C* = low-density lipoprotein-cholesterol

^a Matched cohort constructed using propensity score matching

^b Age- and sex-adjusted incidence rate per 1,000 person-years

^c Cox regression model adjusted for age, sex, history of smoking, family history of diabetes, SBP, DBP, LDL-C, and BMI

^d *p* = 0.027

^e *p* = 0.028

Similarly, a statistically significant risk of NODM was associated with the use of statin therapy in the matched cohort, in contrast to the risk associated with statin nonuse. (Table 2 and Figure 2). In this cohort, 18 statin users (11.8%) developed NODM. The age- and sex-adjusted incidence rates in statin users and nonusers were 21.2 events per 1,000 person-years versus 8.3 events per 1,000 person-years, respectively. The adjusted HR was estimated to be 3.24 (95% CI: 1.13, 9.26, *p* value = 0.028). Figure 2 shows the multivariable-adjusted Cox regression probability curve that indicates a significantly higher rate of NODM occurrence among statin users compared to statin nonusers over the follow-up period. Furthermore, the likelihood of developing NODM started as early as within one year of initiating statin therapy.

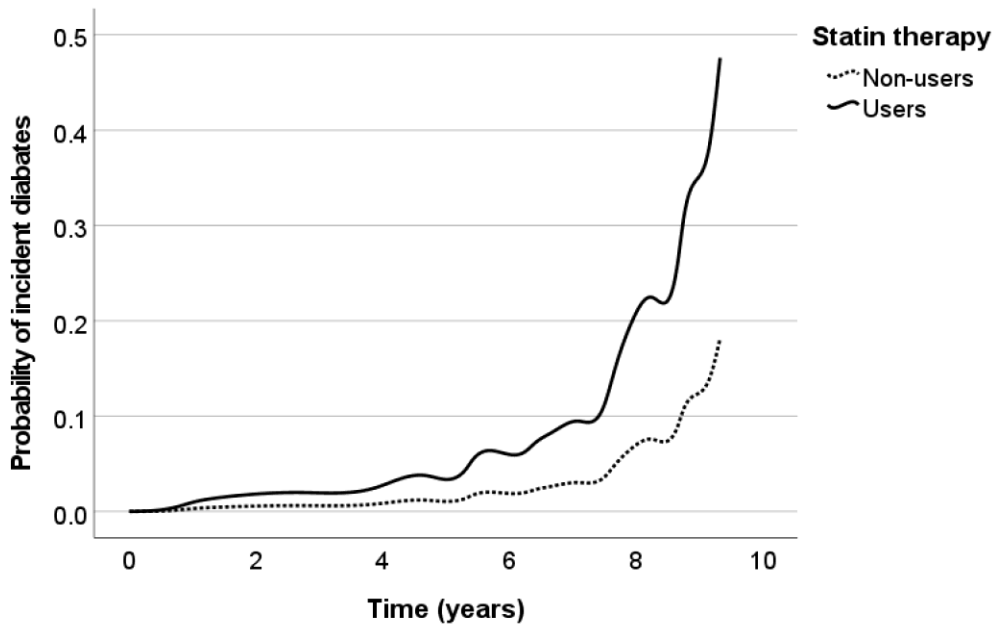


Figure 2: Multivariable-adjusted Cox regression probability curve comparing statin therapy users and nonusers in the propensity score-matched cohort.

It was estimated that 19.2 patients (95% CI: 10.9, 90.9) in the matched cohort would need to be treated with statins for 10 years for one patient to develop NODM (NNH).

As seen in the adjusted Cox regression analysis results of the matched cohort reported in Table 2, the E-values for the point estimate and lower confidence bound for NODM were 5.93 and 1.52, respectively.

Subgroup analyses were conducted to assess the association between statin use and the risk of NODM among the different cardiovascular disease risk factor subgroups in the matched cohort (Supplemental Table S1). The age- and sex-adjusted incidence rate was highest among the smoking subgroup (46.4 events per 1,000 person-years), while the incidence rate in the overweight and obesity subgroup was 23.8 per 1,000 person-years, and 25.8 events per 1,000 person-years in the hypertension subgroup.

Discussion

The development of NODM among statin users in recent years has become an emerging concern because diabetes is recognized as a significant risk factor for CVD. This outcome is confined not only to patients using statins in the general population but also to those with CVD.^{5,21} We observed that over a 10-year follow-up, Emirati patients presenting with cardiovascular risk factors and receiving statin therapy had a significantly increased risk of NODM compared to statin nonusers. The risk was noted in both the original and matched cohorts in this study. Participants using statins may differ from those not using statins, and these differences may influence the risk of incident diabetes. Thus, we identified a matched cohort to reduce bias; the resultant effect of statin therapy on NODM remained but with a higher risk than that observed in the original cohort.

The predictive risk of developing NODM has varying results in different populations and countries when compared to the results in the present study. The results from the Netherlands²² and Korea²³ showed a 38% and 66% risk, respectively, whereas data from meta-analyses showed a 44%²⁴ and 61%²⁵ risk for incident diabetes. The varied trends could be explained by varying methodologies, diverse study populations,^{26,27} the use of different statins with differing doses and intensities,⁶ and varying methods of diagnosing diabetes.²⁸

It is well documented that diabetes is a significant risk factor for CVD. Multiple trials suggesting the increased risk of NODM associated with long-term statin use as well as higher intensity and cumulative statin dosing⁶ guided both the Food and Drug Administration and the European Medicine Agency toward issuing a warning. Sattar et al. reported in their meta-analysis that 255 (95% CI: 150, 852) patients would have to be treated with a statin for 4 years for one extra patient to develop incident diabetes, as well as to reduce the number of major CVD events by 5.4.²¹ In our study's matched cohort, it is estimated that 19.2 patients would need to be treated with statins for 10 years for one patient to develop NODM (NNH). Thus, the risk for NODM is small relative to the reduction in CVD events over time. The findings of a recent meta-analysis on randomized controlled trials strongly support that the absolute benefits of statin therapy far outweigh any adverse effects of NODM.⁶ Additionally, it must be noted that most of the published data support a decrease in cardiovascular and all-cause mortality among statin users.^{5,29} Therefore, the decision to prescribe statins should be encouraged, particularly for those with CVD risk factors and/or established CVD.

Much of the available evidence on statin-induced diabetes is mainly from Western countries and is more often based on post hoc analyses of randomized controlled trials or results from meta-analyses. This retrospective observational study of statin-induced diabetes, a first in the UAE, supports and extends previous reports on the evidence showing a risk for the development of NODM with statin treatment while adding to the epidemiological information within the Gulf region of the Middle East.^{7,30-33} The current evidence validates a low risk for the development of NODM both in absolute terms and when compared to the benefit in CVD event reduction. Therefore, periodic screening for diabetes by healthcare providers in persons at risk for the development of NODM with regular measurements of fasting plasma glucose or HbA1c is recommended.

There are several limitations that are relevant when interpreting the findings. First, data on the statin dosages as well as the changes in statin use and doses over time were not available. Further studies and independent confirmation of the causality between statin use and NODM in larger clinical trials are warranted. Second, the data were from a single site, and thus, generalizations of our results should be made with caution. However, although our results may not be generalizable and considering that our patients on statins had one or more cardiovascular risk factors, our results may hold important clinical implications for the reduction of cardiovascular risk. Third, unmeasured confounding may have occurred despite adjusting for all major risk factors for diabetes. However, using the E-value method in the

sensitivity analysis suggested that the observed 10-year HR of 3.24 for NODM in the matched cohort could be explained only by an unmeasured confounder that was associated with both statin therapy and NODM risk with a risk ratio of more than 5.93. This risk ratio value is greater than that of the diabetes-related risk factors that were included in this study's multivariable Cox regression model (Supplemental Table S2). Therefore, it is unlikely that an unmeasured confounder to counteract the impact of statin use demonstrated in this study exists. Finally, the variability in follow-up intervals among participants may have introduced attrition bias, potentially impacting the study findings.

Conclusion

Our study's results demonstrate an association between statin use and increased NODM risk, aligning with previous research findings and highlighting the importance of pharmacovigilance. While research has confirmed the significant benefits of statin therapy, outweigh the risk of NODM, especially in patients with significant cardiovascular risk on long-term statin therapy, clinicians need to be attentive in monitoring high-risk patients for the development of diabetes. This includes individuals with established risk factors, both among naïve statin users and those currently on statin therapy.

Disclosure

The authors declared no conflicts of interest. No funding was received for this study.

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Supplemental Table S1: Incidence rate and HR for the association between statin therapy use and the risk of NODM among the different cardiovascular disease risk factor subgroups in the matched cohort

Subgroup (statin therapy users)	NODM cases, <i>n</i> (%)	Matched cohort ^a	
		Incidence rate of NODM ^b (95% CI)	Cox regression model
			Adjusted HR (95% CI)

Hypertension (n=104)	15 (14.4)	25.8 (16.3–40.9)	1.82 (0.62–5.39)	0.278
Overweight and obesity (n=125)	17 (13.6)	23.8 (15.5–36.5)	2.77 (0.89–8.66)	0.079
Smoking (n=25)	5 (20.0)	46.4 (15.1–108.0)	3.37 (0.31–36.77)	0.318
Chronic kidney disease (n=6)	0 (0.0)	0.0 (0.0–0.0)	Not applicable	Not applicable
Cardiovascular disease^c (n=18)	3 (16.7)	35.0 (12.4–98.6)	0.02 (0.00–67.23)	0.802

NODM = new-onset diabetes; *HR* = hazard ratio; *CI* = confidence intervals

^a Matched cohort constructed using propensity score matching

^b Age- and sex-adjusted incidence rate per 1,000 person-years

^c Defined as a history of coronary heart disease, stroke, or peripheral arterial disease

Supplemental Table S2. Predictors of incident diabetes (multivariable Cox proportional hazards model)

Characteristic	Before matching (n = 631)		After matching ^a (n = 306)	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age (years)	1.00 (0.97, 1.03)	0.944	0.99 (0.95, 1.02)	0.464
Sex (men)	2.27 (0.93, 5.57)	0.072	1.38 (0.50, 3.80)	0.537
Smoking	1.37 (0.56, 3.35)	0.491	2.37 (0.81, 6.95)	0.116
Statin therapy	2.46 (1.11, 5.45)	0.027	3.24 (1.13, 9.26)	0.028
Family history of diabetes	0.59 (0.26, 1.34)	0.205	0.41 (0.15, 1.13)	0.084
BMI (kg/m ²)	1.02 (0.96, 1.08)	0.495	0.98 (0.91, 1.06)	0.622
SBP (mmHg)	1.00 (0.97, 1.03)	0.924	1.01 (0.97, 1.05)	0.670
DBP (mmHg)	1.01 (0.96, 1.05)	0.808	1.01 (0.96, 1.06)	0.681
LDL-C (M)	0.89 (0.61, 1.30)	0.541	0.90 (0.59, 1.39)	0.646

HbA1c = hemoglobin A1c; *BMI* = body mass index; *SBP* = systolic blood pressure; *DBP* = diastolic blood pressure; *LDL* = low-density lipoprotein-cholesterol; *CI* = confidence intervals; *HR* = hazard ratio

^a Matched cohort constructed using propensity score matching