Statins Can Delay Insulin Use and Reduce Diabetes-related Diseases in Asian Patients With Type 2 Diabetes

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Abstract: We evaluated the role of statins in delaying insulin use and diabetes-related diseases in Asian patients with type 2 diabetes mellitus (T2DM) because statins can cause new-onset diabetes.

We used data from the Longitudinal Health Insurance Database in this retrospective cohort study. The 12,470 T2DM patients were categorized into 2 cohorts: a statin cohort comprising 2545 patients who received statin therapy for at least 6 months (180 days) before the index date and a nonstatin cohort comprising 9925 patients who did not receive statin therapy. The control-to-case ratio was set at approximately 4:1. Univariable and multivariable Cox proportional hazards regression analyses were performed to evaluate the risk of diabetes-related events and insulin use on receiving statin treatment.

Patients in the statin cohort had a 48% lower risk of diabetes-related coma than those in the nonstatin cohort (95% confidence interval = 0.29–0.92). Patients with >730 days of statin therapy had a significantly lower risk of insulin use, diabetes-related disorders of the eye and neurons, and peripheral circulatory disorders. Compared with patients in the nonstatin cohort, the risk of insulin use, diabetes-related coma, and diabetes-related

disorders of the eye and neurons was lower in patients on a cumulative defined daily dose (cDDD) of statins for >475 days.

These results suggest that longer duration of statin use and higher cDDD of statins can delay insulin use in Asian patients with T2DM.

Abbreviations: CHD = coronary heart disease, CIs = confidence intervals, GLUT = glucose transporter, HbA1c = hemoglobin A1c, HRs = Hazard ratios, ICD-9-CM = International Classification of Diseases, IRR = incidence rate ratio, LHID 2000 = The Longitudinal Health Insurance Database 2000, NHIRD = National Health Insurance Research Database, NHRI = the National Health Research Institutes, Ninth Revision = Clinical Modification, T2DM = type 2 diabetes mellitus.

INTRODUCTION

Statins, or hydroxmethylglutaryl-coenzyme-A (HMG-CoA) reductase inhibitors, are a medication widely prescribed worldwide[1] to reduce hyperlipidemia-related atherosclerotic complications such as stroke or acute myocardial infarction.[2,3] Statins not only reduce hyperlipidemia but also attenuate expression of inflammatory markers such as C-reactive protein.[4] UK Prospective Diabetes Study 23 (UKPDS 23) reported that low-density lipoprotein cholesterol (LDL-C) is the strongest predictor of the risk of coronary heart disease (CHD) in patients with diabetes.[5] Five major contributors to CHD risk, namely, LDL-C, HDL-C, hemoglobin A1c (HbA1c), systolic blood pressure, and smoking, were mentioned in UKPDS 23, and the data in this study support the need for reducing LDL-C levels to reduce CHD risk in patients with type 2 diabetes mellitus (T2DM). In addition, the Multiple Risk Factor Intervention Trial showed that total cholesterol, smoking, and blood pressure can predict the occurrence of cardiovascular diseases in diabetic and nondiabetic patients.[6] On the basis of these findings and according to the guidelines of the American Diabetes Association, statins have always been the preferred first-line medication for diabetic patients with hyperlipidemia. However, the Food and Drug Administration in the United States suggests that statin therapy can increase HbA1C and fasting blood glucose levels.[7] The associations between statin therapy and new-onset diabetes have been widely discussed recently.[8] Further analysis of previous clinical trials suggests that patients with T2DM risk factors are at a high new-onset diabetes risk after statin use.[9,10] We investigated the role of statin therapy in improving glycemic control or reducing T2DM-related complications in patients. One of the reasons for providing insulin therapy to patients with T2DM is that T2DM is a progressive disease with β-cell failure.[11] Our hypothesis is that statins can delay insulin use in patients with T2DM, and if proven, it may act as direct or indirect evidence to confirm that although statins can cause new-onset diabetes, they may be used for diabetic control.

METHODS

Data Source

National Health Insurance (NHI) is a single-payer mandatory insurance program that was implemented in Taiwan in 1995 and covers all forms of health care for the residents of Taiwan (http://www.nhi.gov.tw/english/index.aspx). NHI covers outpatient, inpatient, emergency, dental, and traditional Chinese medicine services, as well as prescription drugs. This retrospective cohort study used data from the Longitudinal Health Insurance Database (LHID), a subset of the National Health Insurance Research Database (NHIRD), which was released by the Taiwan Bureau of National Health Insurance. The LHID was constructed in 2000 by randomly selecting 1,000,000 enrollees from the Registry for Beneficiaries of the NHI program. No significant differences were observed in distributions of sex, age, and health costs between patients in the LHID and in the NHRI (http://nhird.nhri.org.tw/en/Data_-Subsets.html#S3). The patients were identified and diagnosed on the basis of International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) codes. This study was exempted by the Institutional Review Board of China Medical University in Central Taiwan (CMU-REC-101–012).

Sampled Participants

Patients aged 20 years or older and diagnosed with T2DM from 2000 to 2010 were selected from the LHID for this study. The retrospective cohort comprised 12,470 T2DM patients. The index date was defined as the date of T2DM diagnosis. Patients were categorized into 2 cohorts: a statin cohort comprising 2545 patients who received statin therapy for at least 6 months (180 days) before the index date and a nonstatin cohort comprising 9925 patients who did not receive any statin therapy. The controls in the nonstatin cohort were randomly assigned the same index date as the patients in the statin cohort. The patients in the nonstatin cohort were frequency-matched for age (in 5-year bands), sex, the year of statin use, and the index year of T2DM diagnosis. The control-to-case ratio was set at approximately 4:1 to enhance the power of statistical tests. Patients in both cohorts with a history of diabetes-related eye disorders (ICD-9-CM 250.5), diabetes-related peripheral circulatory disorders (PCDs) (ICD-9-CM 250.7), diabetes-related ketoacidosis (ICD-9-CM 250.1), diabetes-related renal manifestations (ICD-9-CM 250.4), diabetes-related coma (ICD-9-CM 205.2 and 250.3), and diabetes-related neurological disorders (ICD-9-CM 250.61 and 250.63); patients with insulin use before the index date; patients aged younger than 20 years; and patients with incomplete information were excluded.

Measurement of Outcomes

The study events included diabetes-related disorders of the eye and neurons, diabetes-related PCD, diabetes-related ketoacidosis, diabetes-related renal manifestations, diabetes-related coma, and insulin use. All patients were followed-up from the index date to the event occurrence date, withdrawal from the NHI system, or the end of the follow-up period (December 31, 2011).

Variables of Interest

The potential comorbidities and medications for diabetes-related events included coronary artery disease (ICD-9-CM 410–414), hypertension (ICD-9-CM 401–405), hyperlipidemia (ICD-9-CM 272), and chronic kidney disease (ICD-9-CM 585) and thiazolidinediones, sulfonylurea, and metformin. All comorbidities and medications were defined before the index date.

Statistical Analysis

The χ^2 and Student *t* tests were used to assess the differences for the categorical and continuous variables between the statin and nonstatin cohorts. The incidence (per 1000 person-y) of diabetes-related events and insulin use was calculated for both cohorts. Univariable and multivariable Cox proportional hazards regression analyses were performed to estimate the risk of diabetes-related events and insulin use on receiving statin treatment. Hazard ratios (HRs) and 95% confidence intervals (CIs) were provided in the Cox models. The multivariable models were adjusted for factors such as age; sex; comorbidities such as coronary artery disease, hypertension, hyperlipidemia, and chronic kidney disease; and medications such as thiazolidinediones, sulfonylurea, and metformin, which differed significantly between the 2 groups, as listed in Table 1. The defined daily dose, recommended by the World Health Organization, is the assumed average maintenance dose per day of a drug. We calculated the cumulative defined daily dose (cDDD) was calculated the total prescribed defined daily dose of each type of statin for statin users. In addition, we evaluated the effect of statin use duration (≤ 365, 366–730, and >730 days) and cDDD (≤ 265, 266–475, and >475 days) for the risk of diabetes-related events and insulin use. We used SAS software (Version 9.3 for Windows; SAS Institute Inc, Cary, NC) for all data analyses. A 2-tailed *P* value of <0.05 was considered statistically significant.

TABLE 1. Comparisons in Demographic Characteristics and Comorbidities in Type 2 Diabetes Mellitus Patient With and Without Statin

	Statin		
	No (N = 9925)	Yes (N = 2545)	*P*
Sex	n (%)	n (%)	0.52
Women	5404 (54.5)	1404 (55.2)	
Men	4521 (45.6)	1141 (44.8)	
Age stratified			0.51
≤ 49	1500 (15.1)	375 (14.7)	
50–64	4575 (46.1)	1151 (45.2)	
65+	3850 (38.8)	1019 (40.0)	
Age, mean±SD*	61.4 (11.1)	61.7 (11.1)	0.19
Comorbidity			
Coronary artery disease	2676 (27.0)	1204 (47.3)	<0.001
Hypertension	6111 (61.6)	2167 (85.2)	<0.001
Hyperlipidemia	4113 (41.4)	2406 (94.5)	<0.001
Chronic kidney disease	137 (1.38)	74 (2.91)	<0.001
Medication			
Thiazolidinediones	57 (0.57)	65 (2.55)	<0.001
Sulfonylurea	2397 (24.2)	553 (21.7)	0.01
Metformin	2760 (27.8)	804 (31.6)	<0.001

Chi-Square Test.
* *t* Test.

RESULTS

Most participants were women and 50 to 64 years' old. The mean ages of patients in the statin and nonstatin cohorts were 61.7 (SD = 11.1) and 61.4 (SD = 11.1) years, respectively.

Patients in the statin cohort were more likely to have coronary artery disease, hypertension, hyperlipidemia, and chronic kidney disease than those in the nonstatin cohort ($P < 0.001$). Thiazolidinediones and metformin medication were more prevalent in the statin cohort at the baseline ($P < 0.001$) compared with the nonstatin cohort.

Table 2 shows the incidence rates of diabetes-related events and insulin use for both cohorts and the HR of the statin to the nonstatin cohorts. The statin cohort (1.46 per 1000 person-years) had a lower incidence of diabetes-related coma than the nonstatin cohort (2.84 per 1000 person-years). Patients in the statin cohort had a 48% lower risk of diabetes-related coma than those in the nonstatin cohort (95% confidence interval = 0.29–0.92). The associations between the duration of statin use and the risk of diabetes-related events and insulin use are shown in Table 3. Patient with ≤365 days of statin therapy were at significantly higher risks of diabetes-related renal manifestations, diabetes-related disorders of the eye and neurons, and insulin use compared with patients in the nonstatin cohort. Patients with >730 days of statin therapy had significantly lower risks of diabetes-related disorders of the eye and neurons, diabetes-related peripheral circulatory disorders, and insulin use than those in the nonstatin cohort.

Furthermore, based on estimation of the risk of diabetes-related events and insulin use on the basis of cDDD for statin, the patients with statin therapy exhibited an association with diabetes-related events and insulin use (Table 4). Patients receiving ≤265 cDDD of statin therapy had significantly higher risks of diabetes-related renal manifestations, diabetes-related eye disorders, and insulin use, than those in the nonstatin cohort.

The risk of diabetes-related coma, diabetes-related eye disorders of the eye and neurons, and insulin use was lower in patients who received >475 cDDD of statin therapy than those in the nonstatin cohort.

DISCUSSION

Statin, New-onset Diabetes, and T2DM Control

According to the West of Scotland Coronary Prevention Study, a protective effect of pravastatin can prevent new-onset diabetes.[12] However, other statins, such as atorvastatins, rosuvastatins, and simvastatins, can increase the fasting blood glucose and HbA1c levels.[9,13,14] In our study, as shown in Table 2, fewer diabetic patients used insulin to control T2DM in the statin cohort, although the crude HR was significant instead of the adjusted HR. As shown in Table 3, >730 days instead of 365 days of statin therapy can substantially reduce insulin use in diabetic patients. In addition, previous studies on statins, such as the Study of Heart and Renal Protection for simvastatin[15] and the Lescol Intervention Prevention Study for fluvastatin,[16] have reported that the beneficial duration of statin use was >1 year. Moreover, statin use for >475 cDDD can reduce insulin use in diabetic patients. Our finding differs from that of a previous study that suggested that intensive-dose statin therapy compared with moderate-dose statin therapy increases new-onset diabetes.[17]

Statins and Insulin

Simvastatin and atorvastatin are lipophilic statins. These statins have been reported to reduce insulin secretion. One possible mechanism is the inhibition of glucose-stimulated elevations of free calcium in pancreatic β-cells.[18,19] High-dose statin therapy with simvastatin significantly reduces insulin secretion[18]; however, these studies could not explain our

TABLE 2. Comparison of Incidence Densities of Diabetes-related Events and Insulin Use Hazard Ratio Between Type 2 Diabetes Mellitus Patient With and Without Statin

| | Statin | | | | | | | |
| | No | | | Yes | | | | |
	Event	PY	Rate[†]	Event	PY	Rate[†]	Crude HR[‡] (95% CI)	Adjusted HR[§] (95% CI)
Diabetes-related diseases								
Ketoacidosis	71	41295	1.72	15	10920	1.37	0.80 (0.46, 1.39)	0.76 (0.41, 1.41)
Coma	117	41266	2.84	16	10931	1.46	0.52 (0.31, 0.87)[*]	0.52 (0.29, 0.92)[*]
Renal manifestations	731	39702	18.4	231	10434	22.1	1.20 (1.04, 1.39)[*]	1.09 (0.92, 1.29)
Eye involvement	364	40620	8.96	110	10652	10.3	1.15 (0.93, 1.42)	1.11 (0.87, 1.42)
Neurological	624	39528	15.8	152	10499	14.5	0.92 (0.77, 1.10)	0.86 (0.71, 1.06)
PCD	322	40553	7.94	67	10782	6.21	0.79 (0.60, 1.02)	0.83 (0.61, 1.11)
Medication								
Insulin use	4622	30948	149.3	1140	8354	136.5	0.92 (0.86, 0.98)[**]	0.94 (0.87, 1.01)

CI = confidence interval, HR = relative hazard ratio, PCD = peripheral circulatory disorder, PY = person-years.

[*] $P < 0.05$.

[**] $P < 0.01$.

[***] $P < 0.001$.

[†] Rate, incidence rate, per 1000 person-years.

[‡] Crude HR: The relative hazard ratio without adjustment for age, sex, and co-morbidities of coronary artery disease, hypertension, hyperlipidemia, and chronic kidney disease and medication of thiazolidinediones, sulfonylurea, and metformin by univariable Cox proportional hazards regression.

[§] Adjusted HR: The relative hazard ratio with adjustment for age, sex, co-morbidities and medication by multivariable Cox proportional hazards regression.

TABLE 3. Incidence and Adjusted Hazard Ratio of Diabetes-related Events and Insulin Use Stratified by Duration of Statin Use

Statin exposed	N	Event	Rate[†]	Crude HR[‡] (95% CI)	Adjusted HR[§] (99.5% CI)
Diabetes-related ketoacidosis					
No use	9925	71	1.72	1.00	1.00
Duration on statin					
≤365 days	344	5	0.87	1.64 (0.60, 4.49)	1.38 (0.49, 3.91)
366–1095 days	1093	4	1.21	0.90 (0.41, 1.95)	0.82 (0.36, 1.85)
>1095 days	1108	6	3.19	0.47 (0.17, 1.28)	0.46 (0.16, 1.31)
Diabetes-related coma					
No use				1.00	1.00
Duration on statin	9925	117	2.84		
≤365 days	344	2	0.35	0.75 (0.24, 2.35)	0.69 (0.21, 2.23)
366–730 days	1093	8	2.42	0.54 (0.25, 1.17)	0.56 (0.25, 1.23)
>730 days	1108	6	3.18	0.42 (0.19, 0.96)[*]	0.43 (0.18, 1.01)
Diabetes-related renal manifestations					
No use	9925	731	18.4	1.00	1.00
Duration on statin					
≤365 days	344	79	14.2	1.69 (1.23, 2.32)[**]	1.43 (1.03, 1.98)[*]
366–730 days	1093	64	20.1	1.33 (1.08, 1.63)[**]	1.18 (0.95, 1.48)
>730 days	1108	88	52.8	0.96 (0.77, 1.20)	0.89 (0.70, 1.13)
Diabetes-related eye involvement					
No use	9925	364	8.96	1.00	1.00
Duration on statin					
≤365 days	344	39	6.90	1.96 (1.29, 2.96)[**]	1.74 (1.14, 2.69)[*]
366–730 days	1093	27	8.34	1.48 (1.12, 1.95)[**]	1.42 (1.05, 1.92)[*]
>730 days	1108	44	24.9	0.64 (0.43, 0.93)[*]	0.62 (0.42, 0.93)[*]
Diabetes-related neurological					
No use	9925	322	7.94	1.00	1.00
Duration on statin					
≤365 days	344	22	3.87	1.72 (1.22, 2.41)[**]	1.51 (1.06, 2.15)[*]
366–730 days	1093	14	4.27	1.15 (0.91, 1.45)	1.06 (0.83, 1.37)
>730 days	1108	31	17.0	0.51 (0.37, 0.70)[***]	0.49 (0.35, 0.68)[***]
Diabetes-related PCD					
No use	9925	624	15.8	1.00	1.00
Duration on statin					
≤365 days	344	55	9.85	0.99 (0.54, 1.80)	0.99 (0.53, 1.82)
366–730 days	1093	49	15.4	1.08 (0.77, 1.51)	1.12 (0.78, 1.62)
>730 days	1108	48	27.7	0.46 (0.29, 0.74)[**]	0.49 (0.30, 0.81)[**]
Insulin use					
No use	9925	4622	149.3	1.00	1.00
Duration on statin					
≤365 days	344	414	84.5	1.55 (1.35, 1.79)[***]	1.45 (1.25, 1.68)[***]
366–730 days	1093	326	126.3	1.13 (1.04, 1.24)[**]	1.16 (1.05, 1.27)[**]
>730 days	1108	400	458.8	0.63 (0.57, 0.70)[***]	0.65 (0.58, 0.72)[***]

CI = confidence interval, HR = relative hazard ratio, PCD = peripheral circulatory disorder.
[*] $P < 0.05$.
[**] $P < 0.01$.
[***] $P < 0.001$.
[†] Rate, incidence rate, per 1000 person-years.
[‡] Crude HR: The relative hazard ratio without adjustment for age, sex, and co-morbidities of coronary artery disease, hypertension, hyperlipidemia, and chronic kidney disease and medication of thiazolidinediones, sulfonylurea, and metformin by univariable Cox proportional hazards regression.
[§] Adjusted HR: The relative hazard ratio with adjustment for age, sex, co-morbidities, and medication by multivariable Cox proportional hazards regression.

findings. Statins can reduce isoprenoids produced in the cholesterol synthetic pathway. Isoprenoids can upregulate the insulin-responsive glucose transporter (GLUT)-4 expression, and this protein enhances glucose uptake.[20] Lovastatin can reduce insulin sensitivity through downregulation of GLUT-4 and upregulation of GLUT-1 in 3T3-L1 adipocytes.[21] A decrease in the availability of isoprenoids or adiponectin after statin use could result in

insulin resistance, and finally, it may worsen glycemic control in diabetic patients. However, certain studies have reported that statins could reduce insulin resistance[22] or stimulate adiponectin secretion.[23] We adjusted for metformin and thiazolidinedione medication in our analysis, which were confounders for insulin resistance. Significant adjusted HRs showed that statins can delay insulin use in diabetic patients.

TABLE 4. Incidence and Adjusted Hazard Ratio of Diabetes-related Events and Insulin Use Stratified by cDDD of Statin

Statin exposed	N	Event	Rate[†]	Crude HR[‡] (95% CI)	Adjusted HR[§] (99.5% CI)
Diabetes-related ketoacidosis					
No use	9925	71	1.72	1.00	1.00
Dose of statin use					
≤265 cDDD	639	6	2.18	1.25 (0.54, 2.88)	1.10 (0.46, 2.64)
266–475 cDDD	633	5	1.99	1.15 (0.47, 2.86)	1.05 (0.41, 2.70)
>475 cDDD	1273	4	0.71	0.41 (0.15, 1.13)	0.42 (0.15, 1.18)
Diabetes-related coma					
No use	9925	117	2.84	1.00	1.00
Dose of statin use					
≤265 cDDD	639	7	2.53	0.89 (0.42, 1.91)	0.83 (0.37, 1.84)
266–475 cDDD	633	5	1.99	0.70 (0.29, 1.72)	0.69 (0.27, 1.74)
>475 cDDD	1273	4	0.71	0.25 (0.09, 0.68)[**]	0.26 (0.09, 0.72)[*]
Diabetes-related renal manifestations					
No use	9925	731	18.4	1.00	1.00
Dose of statin use					
≤265 cDDD	639	76	30.1	1.63 (1.29, 2.06)[***]	1.42 (1.11, 1.82)[**]
266–475 cDDD	633	59	24.5	1.32 (1.01, 1.72)[*]	1.15 (0.87, 1.52)
>475 cDDD	1273	96	17.5	0.95 (0.77, 1.18)	0.88 (0.70, 1.11)
Diabetes-related eye involvement					
No use	9925	364	8.96	1.00	1.00
Dose of statin use					
≤265 cDDD	639	43	16.3	1.80 (1.31, 2.47)[***]	1.63 (1.17, 2.29)[**]
266–475 cDDD	633	37	15.3	1.70 (1.21, 2.39)[**]	1.65 (1.16, 2.36)[**]
>475 cDDD	1273	30	5.36	0.60 (0.41, 0.87)[**]	0.59 (0.40, 0.87)[**]
Diabetes-related neurological					
No use	9925	322	7.94	1.00	1.00
Dose of statin use					
≤265 cDDD	639	24	8.87	1.44 (1.10, 1.89)[**]	1.27 (0.96, 1.69)
266–475 cDDD	633	19	7.71	1.21 (0.89, 1.63)	1.14 (0.84, 1.56)
>475 cDDD	1273	24	4.28	0.55 (0.41, 0.74)[***]	0.52 (0.38, 0.71)[***]
Diabetes-related PCD					
No use	9925	624	15.8	1.00	1.00
Dose of statin use					
≤265 cDDD	639	58	22.8	1.12 (0.74, 1.69)	1.11 (0.72, 1.72)
266–475 cDDD	633	46	19.1	0.97 (0.61, 1.53)	1.00 (0.62, 1.62)
>475 cDDD	1273	48	8.65	0.54 (0.36, 0.82)[**]	0.58 (0.38, 0.91)[*]
Insulin use					
No use	9925	4622	149.3	1.00	1.00
Dose of statin use					
≤265 cDDD	639	358	208.9	1.38 (1.24, 1.54)[***]	1.32 (1.18, 1.47)[***]
266–475 cDDD	633	291	160.5	1.07 (0.95, 1.20)	1.10 (0.97, 1.25)
>475 cDDD	1273	491	101.7	0.69 (0.63, 0.76)[***]	0.71 (0.65, 0.79)[***]

cDDD = cumulative defined daily dose, CI = confidence interval, HR = relative hazard ratio, PCD = peripheral circulatory disorder.
[*] $P < 0.05$.
[**] $P < 0.01$.
[***] $P < 0.001$.
[†] Rate, incidence rate, per 1000 person-years.
[‡] Crude HR: The relative hazard ratio without adjustment for age, sex, and co-morbidities of coronary artery disease, hypertension, hyperlipidemia, and chronic kidney disease and medication of thiazolidinediones, sulfonylurea, and metformin by univariable Cox proportional hazards regression.
[§] Adjusted HR: The relative hazard ratio with adjustment for age, sex, co-morbidities, and medication by multivariable Cox proportional hazards regression.

Statins and Diabetes-related Diseases

In the Scandinavian Simvastatin Survival Study, simvastatins significantly reduced CHD incidence and total mortality in diabetic patients with high LDLC levels.[24] Our analysis showed that longer duration of statin use and higher cDDD of statin therapy can reduce diabetes-related diseases such as coma, renal manifestations, eye disorders, and PCD. From our analyses of diabetes-related ketoacidosis and coma, we infer that statin therapy can be used for diabetic control in Asian patients.

CONCLUSION

In our study, longer duration and higher cDDD of statin therapy can delay insulin use and reduce diabetes-related diseases in diabetic patients.

Limitations

First, additional data such as drinking, smoking, body mass index, nutritional state, or red rice use are unavailable in the NHIRD, and therefore unknown confounders may have affected the results of this study. Second, to understand the association between insulin and statins in patients with T2DM, we could use only the cDDD of statins for our analysis.

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