Contents available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

International Diabetes Federation

Risk of macrovascular complications in statin-treated patients developing diabetes

Yin-Huei Chen [a], Yu-Cih Yang [b,c], Weishan Chen [b,c], Yen-Nien Lin [d,e,f], Yi-Chih Hung [a,e,*]

[a] Division of Endocrinology and Metabolism, Department of Medicine, China Medical University Hospital, Taichung, Taiwan
[b] Management Office for Health Data, China Medical University Hospital, Taichung, Taiwan
[c] College of Medicine, China Medical University, Taichung, Taiwan
[d] Division of Cardiovascular Medicine, Department of Internal Medicine, China Medical University Hospital, Taichung, Taiwan
[e] Graduate Institute of Clinical Medical Science, China Medical University, Taichung, Taiwan
[f] Cardiovascular Research Laboratory, China Medical University Hospital, Taichung, Taiwan

ARTICLE INFO

Article history:
Received 25 July 2019
Received in revised form
11 September 2019
Accepted 23 September 2019
Available online 24 September 2019

Keywords:
Statin
Hyperlipidemia
Diabetes mellitus
Macrovascular complications
Cohort study

ABSTRACT

Aims: To assess the risk of macrovascular complications in patients developing diabetes from statin treatment.

Methods: In this population-based cohort study, 40,409 participants who began to receive statin therapy between 2000 and 2012 were enrolled in to the study group, and another 1:1 matched adults without statin treatment during the same period served as the control group. Both groups were followed up to identify individuals who later developed diabetes. After a follow-up identification of diabetes, diabetes and non-diabetes cohorts were subjected to an analysis for the risk of macrovascular events between diagnosis of diabetes and December 31, 2013.

Results: Compared with individuals without statin therapy, statin-treated patients had a higher risk of developing diabetes (adjusted hazard ratio: 2.46; 95% confidence interval: 2.37–2.57). Compared with statin-treated patients without diabetes, statin-treated participants developing diabetes had a higher overall incidence of macrovascular complications (adjusted hazard ratio: 1.74; 95% confidence interval: 1.62–1.88). Moreover, compared with that of other diabetogenic statins, patients taking pravastatin had a lower risk of developing diabetes (adjusted hazard ratio: 0.63; 95% confidence interval: 0.55–0.73) and macrovascular events (adjusted hazard ratio: 0.64; 95% confidence interval: 0.42–0.98).

Conclusions: According to these findings, prescribing statins that have a neutral effect on glucose homeostasis may be advisable for Asian populations.

Abbreviations: CV, cardiovascular; NHI, Taiwan national health insurance; NHIRD, the Taiwan national health insurance research database; LHID, the longitudinal health insurance database; ACS, acute coronary syndrome; MI, myocardial infarction; PDC, proportion of follow-up days on statin use; HTN, hypertension; CHF, congestive heart failure; CKD, chronic renal disease; WOSCOPS, the West of Scotland coronary prevention study; JUPITER, justification for the use of statins in prevention: an intervention trial evaluating rosuvastatin

* Corresponding author at: Division of Endocrinology and Metabolism, Department of Medicine, China Medical University Hospital, 2 Yuh-Der Road, Taichung 40447, Taiwan.
E-mail address: viennaspring2061@yahoo.com.tw (Y.-C. Hung).

https://doi.org/10.1016/j.diabres.2019.107870
0168-8227/

1. Introduction

Statins are the most commonly prescribed medicines for hyperlipidemia with a capability of decreasing cardiovascular (CV) risk. However, the application of statin has been associated with an increased risk of diabetes [1–6], particularly in patients with risk factors for diabetes, including those of Asian descent [7]. Since the precise mechanism for statins-induce diabetes is unknown and the glycemic effect of statins may be associated with adverse CV events, many physicians are reluctant to prescribe statins for patients who are considered to be at high risk of developing diabetes. Based on data from several epidemiological studies establishing a relationship between CV risk and glycemic control [8–10], it was estimated that a 0.1–0.3% statin-induced increase in HbA_{1c} might increase CV risk by 2–6% in a large patient population with fasting glycemia within the high-normal to diabetic range [11]. Although naive type 2 diabetes is associated with an increase in CV risk, limited information is available regarding whether statins-induced diabetes may lead to CV complications [12]. One recently published population-based cohort study showed that statin-induced diabetes might be prognostically less adverse than diabetes that was unlikely related to statins [13].

Therefore, to investigate the clinical relevance of increased serum glucose levels in patients treated with statins, a population-based cohort study using the database of the Taiwan National Health Insurance (NHI) program was conducted to assess the risk of macrovascular complications among statin-treated patients who later developed diabetes. We also evaluated and compared the risk of macrovascular events among patients taking less diabetogenic statin (pravastatin) and patients treated with other diabetogenic statins.

2. Methods

2.1. Data source

The Taiwan National Health Insurance Research Database (NHIRD) contains the annual reimbursement claim data from the National Health Insurance program, which has been the universal health insurance system in Taiwan since 1996 and covered approximately 99% of the Taiwanese population by 1998 [14]. The Longitudinal Health Insurance Database (LHID), which is a subset of the NHIRD, includes historical claims data for one million people randomly sampled from the whole insured population for the years 1996 to 2000. Before being released for research, all personal identification data in the LHID are delinked to protect patient privacy by the National Health Research Institute via an anonymized number system to link each claimant's demographic information to the LHID. The NHIRD uses the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) to categorize disease diagnoses based on outpatient and inpatient data.

2.2. Ethical approval

This study was approved by the Ethics Review Board of China Medical University (CMUH-104-REC2-115), who waived the need for informed consent based on the retrospective study design.

2.3. Study population

Based on their treatment history with statin, participants were allocated to the study group (treated with statin) or the control group (not treated with statin).

The study group comprised patients aged 18–85 years who had been newly treated with statin between 2000 and 2012. The index day was defined as the date of first prescription of statin. We excluded patients diagnosed as having macrovascular events (i.e., acute coronary syndrome [ACS] or myocardial infarction [MI][ICD-9-CM codes 410 and 411], or stroke [ICD-9-CM codes 430–438]) or diabetes (ICD-9-CM codes 250 or treated with antidiabetic agents), before the index day, individuals diagnosed with gestational diabetes mellitus (ICD-9-CM code 648.83), pancreatic disease (ICD-9-CM code 577), alcoholism (ICD-9-CM code 303), obesity (ICD-9-CM code 278, A code A183), or polycystic ovarian syndrome (PCOS)(ICD-9-CM code 256.4), and those who had undergone bariatric surgery (ICD-9-CM code V45.86) or had taken steroids more than 3 months before the index day. Using frequency matching, each patient without statin treatment was matched for one stain-treated patient by age, gender and index year. Follow-up was terminated on the development of diabetes (ICD-9-CM codes 250 or treated with antidiabetic agents), a withdrawal from the insurance system, or on December 31, 2013, whichever was the earliest. The overall incidence of diabetes of the two groups were subsequently compared.

After the exclusion of patients treated with glucose-lowering agents, subjects were categorized based on whether they were treated with statin and whether they were diagnosed with diabetes into four groups, including one group of statin-untreated patients without diabetes, one group of statin-untreated patients with diabetes, one group of statin treated-patients without diabetes, and one group of statin-treated patients developing diabetes. The overall incidence rates of macrovascular events were compared between the group of statin-untreated patients without diabetes and other three groups, as well as between the group of statin-treated patients without diabetes and other three groups. Moreover, we evaluated the effect of diabetes on the risk of macrovascular events according to the proportion of follow-up days on statin use (PDC). We also evaluated the risks of developing diabetes and macrovascular events of patients taking pravastatin and other statins. "Patients taking pravastatin" referred to those who only took pravastatin during the follow up period whereas "Patients taking other statins" referred to those who took statins other than pravastatin during the follow-

up period. Patients who initiated high intensity statin therapy, defined as patients treated with atorvastatin ≧40 mg/day, or rosuvastatin ≧20 mg/day, were excluded. Propensity score matching [15] was adopted to match each patient taking pravastatin with a patient taking other statins regarding to age, gender, follow up duration, intensity of initial statin

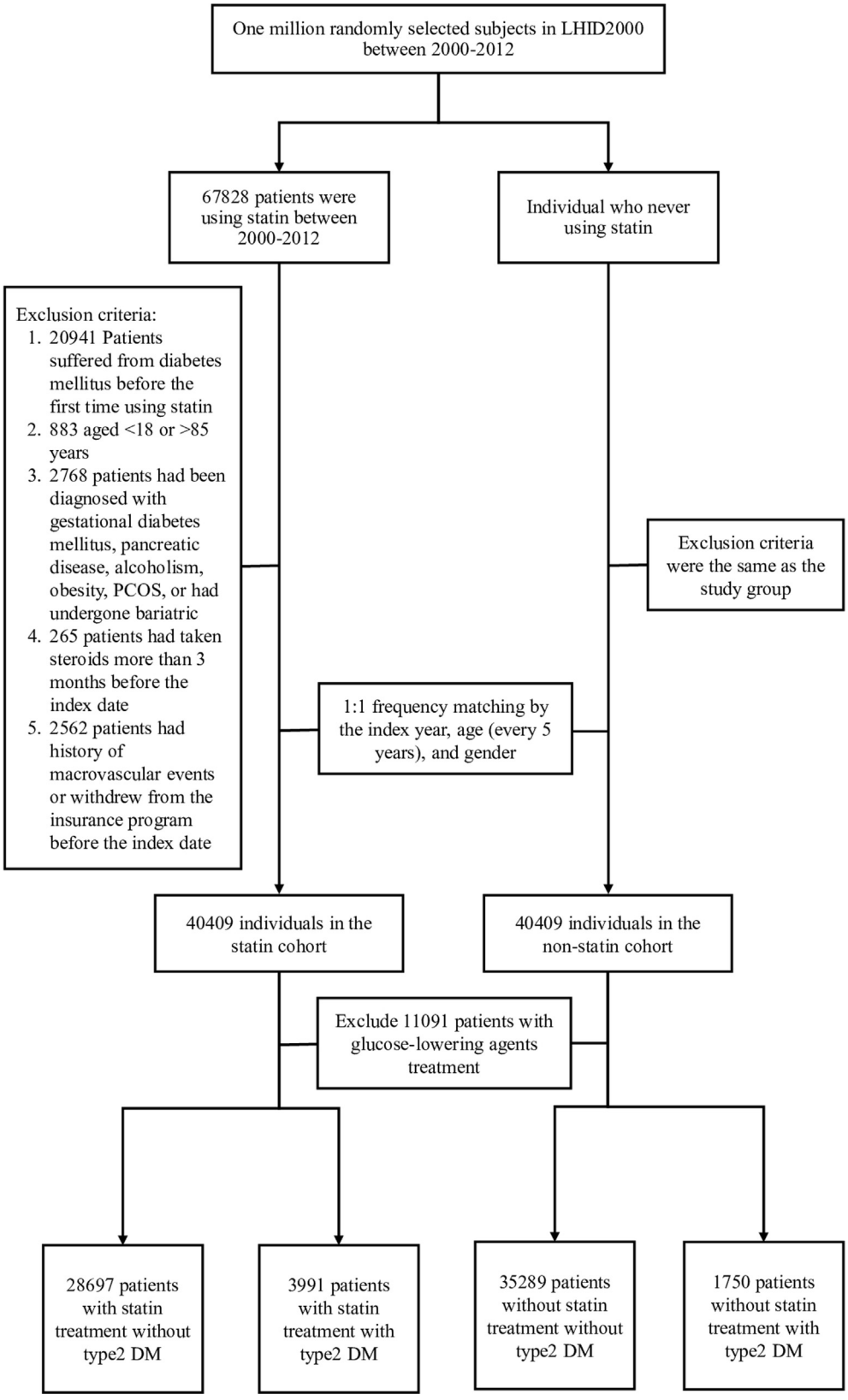

Fig. 1 – Flow-chart of cohort selection.

therapy, the administration of other cholesterol lowering agents, the presence or absence of hypertension (HTN) (ICD-9-CM codes 401–405), congestive heart failure (CHF)(ICD-9-CM codes 428), arrhythmia(ICD-9-CM codes 427), and chronic renal disease (CKD)(ICD-9-CM codes 585), administration of antihypertensive medication, aspirin, clopidogrel, and warfarin. The overall incidence rate of diabetes in the two groups were compared. In addition, patients with preexisting macrovascular events prior to diabetes and participants taking glucose-lowering agents were excluded, and the overall incidence rates of macrovascular events in patients taking pravastatin and other statins were subsequently evaluated.

2.4. Statistical analysis

The chi-square test and Student's *t*-test were used to compare the differences of categorical variables and continuous variables between groups, respectively. The incidence rate of an event was estimated using the number of events and person-years. The hazard ratio (HR) and 95% confidence interval (CI) for the risk of events were estimated using univariate and multivariate Cox proportional hazard regression models. The multivariate model was adjusted for age, gender, comorbidities and medications listed in Table 3. The cumulative incidence of macrovascular events was assessed using the Kaplan–Meier method and differences between groups were determined via a log-rank test. All statistical analyses were performed using SAS statistical software (Version 9.4 for Windows; SAS Institute, Inc., Cary, NC, USA). Statistical significance was defined at $P < 0.05$.

3. Results

Fig. 1 shows the flow-chart of cohort selection in this study. With 40,409 matched individuals in each cohort, the demographic characteristics of these two cohorts are presented in Table 1. Most patients were aged 45–64 years with 54.1% patients being females. The average duration of statin treatment and the follow-up period was approximately 6.98 years and 7 years, respectively. As shown in Table 1, the overall incidence of diabetes in the study group was 2.78 per 100 person-years, which was higher than that in the control group (1.13 per 100 person-years), to give an adjusted hazard ratio (aHR) of 2.46 (95% CI: 2.37–2.57; $P < 0.01$).

As shown in Table 2, among remaining participants after the exclusion of 11,091 patients with glucose-lowering agents treatment, 35,289 participants were statin-untreated patients without diabetes, 1750 patients were statin-untreated patients with diabetes, 28,697 patients did not develop diabetes after receiving statin treatment, and 3991 statin-treated patients developed diabetes. The demographic characteristics of these four cohorts revealed that most patients were aged 45–64 years with 54% patients being females. The mean follow-up duration in the four cohorts was 5.6, 4.2, 3.8 and 3.7 years, respectively. While less than 5% of patients used other cholesterol-lowering agents, the usages of anti-hypertensive medication and anti-platelet/anti-coagulant agents was shown in Table 2 and comorbidities including CHF, CKD, HTN, and arrhythmia were also shown in Table 2.

With the risk of macrovascular events of the study group shown in Table 3, to compare with statin-untreated patients without diabetes, the risk of developing macrovascular events was higher among statin-untreated patients with diabetes (aHR: 2.84; 95% CI: 2.55–3.15; $P < 0.01$), statin-treated patients without diabetes (aHR: 1.93; 95% CI: 1.84–2.04; $P < 0.01$), and statin-treated patients who developed diabetes (aHR: 3.39; 95% CI: 3.14–3.66; $P < 0.01$). Compared with statin-untreated patients without diabetes, the risk of developing particular types of macrovascular events including MI, stroke and ACS were also higher among statin-untreated patients with diabetes, statin-treated patients without diabetes, and statin-treated patients developing diabetes. Compared with statin-treated patients without diabetes, the risk of

Table 1 – Demographic data and risk of diabetes of statin-treated participants and statin-untreated patients.

	Statin treatment				
	Yes (n = 40409)		No (n = 40409)		*p*-value
	n	%	n	%	
Age, years					>0.99
<45	7008	17.3	7008	17.3	
45–64	22,102	54.7	22,102	54.7	
≥65	11,299	28.0	11,299	28.0	
mean (SD)	56.85 (12.6)		56.71 (12.7)		0.12
Gender					>0.99
Female	21,862	54.1	21,862	54.1	
Male	18,547	45.9	18,547	45.9	
Duration of statin treatment, years (SD)	6.98 (4.93)				
Follow-up duration, years (SD)	7.12 (4.26)		7.39 (3.87)		<0.0001
Event (Diagnosed as having diabetes)	8025		3387		
PY	287,825		298,662		
IR	2.87		1.13		
Crude HR (95% CI)	2.46 (2.36–2.56)		1 (Reference)		<0.0001
Adjusted HR (95% CI)	2.46 (2.37–2.57)		1 (Reference)		<0.0001

developing macrovascular events was higher among statin-treated patients developing diabetes (aHR: 1.74; 95% CI:1.62–1.88; $P < 0.01$). Compared with statin-treated patients without diabetes, the risk of developing particular types of macrovascular events including MI, stroke and ACS were also higher among statin-treated patients with diabetes.

Our analysis also revealed that the incidence of macrovascular complications among the study group regardless of statin compliance was higher than that among the control group (PDC $\leq$ 50%: aHR: 1.56; 95% CI 1.10–2.23; $P = 0.012$; and PDC > 50%: aHR: 1.50; 95% CI 1.16–1.95; $P < 0.01$). P for trend was 0.9 (Supplementary Table 1).

Table 4 shows the baseline characteristics of patients taking pravastatin and other statins. Each cohort comprised 3061 matched individuals with very similar demographic characteristics between cohorts. Most patients were aged from 45 to 64 years with 55% patients being females. The average treatment duration with pravastatin was longer than those with other statins treatment (8.26 and 7.35 year for pravastatin and other statins, respectively; $P < 0.01$). The mean duration of follow-up was approximately 10 years. Approximately 60% of the patients initiated moderate intensity statin therapy and 40% of the patients started with low intensity statin therapy. In both cohorts, other cholesterol-lowering agents were used by less than 10% of patients. The incidence of congestive heart failure (CHF), chronic renal disease (CKD), hypertension (HTN), and arrhythmia was approximately 3%, 2%, 37%, and 7% in both cohorts, respectively. With a similar number of patients being treated with anti-hypertensive medication, approximately 2%, 0.3%, and 0.2% of patients in both groups were treated with aspirin, clopidogrel, or warfarin, respectively.

Table 5 shows the comparison of the risk of diabetes and macrovascular events between pravastatin and other statins users. Compared with patients taking other statins, pravastatin users had a lower risk of developing diabetes (aHR: 0.63; 95% CI: 0.55–0.73; $P < 0.01$) and macrovascular events (aHR: 0.64; 95% CI: 0.42–0.98; $P = 0.04$).

Fig. 2 shows the cumulative incidence of macrovascular events which was significantly higher in statin-untreated patients with diabetes, statin-treated patients without diabetes, and statin-treated patients developing diabetes than statin-untreated patients without diabetes (log-rank test, $P < 0.01$).

4. Discussion

Our findings revealed that patients treated with statins and subsequently developed diabetes had a higher risk of macrovascular complications than statin-treated patients without diabetes. Moreover, compared with other diabetogenic statin users, patients taking pravastatin was associated with a lower risk of developing diabetes and macrovascular complications. Therefore, prescribing statins that have a neutral effect on glucose homeostasis may be advisable, particularly among Asian populations.

The relation between statins and the development of diabetes was first reported in the West of Scotland Coronary Prevention Study (WOSCOPS) in 2001. This randomized placebo-controlled trial of 40 mg pravastatin revealed a 30% reduction in the incidence of new-onset diabetes [16]. However, the WOSCOPS trial did not apply standard diagnosis criteria of diabetes and that all participants were only men, which could have contributed to heterogeneity. After WOSCOPS, several trials tried to assess the protective effects of atorvastatin and simvastatin and these studies showed an increase risk of new onset diabetes [17]. Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial also showed an increased incidence of new-onset diabetes in the statin group [18].

The exact mechanism regarding the increased risk of diabetes in statin-treated patients is unknown and remains an interesting area of research. Statins have not clearly been shown to increase the microvascular complications of diabetes and the clinical significance of the glycemic effect of statins is uncertain [17]. Research focusing on the adverse prognostic effects of statin-induced diabetes is rare. Because - patients with diabetes might use different classes of drugs or combination therapy, such as a fixed-dose combination or free combination and glucose- lowering agents may have effects on CV events, we excluded patients taking glucose-lowering agents after being diagnosed as having diabetes to eliminate such effect. Generally speaking, glucose lowering agents are prescribed for patients with severe diabetes such as those with HbA1c > 7%, while diet and exercise treatment are recommended for patients with mild diabetes such as those with HbA1c < 7%. Therefore, the severity of diabetes of patients in our study are likely mild. Our study showed that statin-untreated patients with diabetes, statin-treated patients without diabetes and statin-treated patients with diabetes had higher risks of developing macrovascular complications compared with statin-untreated patients without diabetes. In addition, patients treated with statins and subsequently developed diabetes also had a higher risk of macrovascular complications than statin-treated patients without diabetes. According to the findings of our study, the diabetogenic action of statins was associated with adverse CV effects. Moreover, we also evaluate the risk of diabetes and macrovascular complications after taking statin that has a neutral or possibly beneficial effect on glucose homeostasis. Because physicians may prescribe pravastatin for patients with lower CV risk throughout the observational period, we used propensity score matching to match almost all baseline characteristics and adjusted for potential confounders while analyzing the risk of macrovascular events between pravastatin and other statins users. Compared with patients treated with other diabetogenic statins, patients taking pravastatin was associated with a decreased risk of diabetes and macrovascular complications. Therefore, for Asian patients whom statin therapy is being considered, treatment with a statin that has a neutral and possibly beneficial effect on glucose homeostasis may be recommended.

The relationship between duration of statin therapy and risk of newly diagnosed diabetes is unclear [19]. An analysis of study-level data from 20 major statin trials found no relationship between the length of those statin trials and the risk of newly diagnosed diabetes attributable to statin therapy [20]. However, according to one population-based cohort study published recently, the greater the adherence to statins,

Table 2 – Demographic data of the study cohorts.

	Statin-untreated patients without diabetes (n = 35289)		Statin-untreated patients with diabetes (n = 1750)		Statin-treated patients without developing diabetes (n = 28697)		Statin-treated patients developing diabetes (n = 3991)		*p*-value
	n	%	n	%	n	%	n	%	
Age, years									<0.0001
<45	6619	18.7	111	6.34	4829	16.8	588	14.7	
45–64	19,199	54.4	977	55.8	15,287	53.3	2264	56.7	
≥65	9471	26.9	662	37.8	8581	29.9	1139	28.6	
Mean (SD)	56.1 (12.8)		61.0 (10.5)		57.3 (12.8)		57.4 (11.7)		<0.0001
Gender:									0.18
Female	19,087	54.1	990	56.6	15,570	54.3	2137	53.5	
Male	16,202	45.9	760	43.4	13,127	45.7	1854	46.5	
Follow-up duration, years (SD)	5.69 (6.01)		4.20 (6.95)		3.86 (6.79)		3.79 (7.09)		<0.0001
Other cholesterol-lowering agents:									
Fibrate	69	0.20	7	0.40	145	0.51	30	0.75	<0.0001
Niacin	8	0.02	0	0	6	0.02	0	0	<0.0001
Others	13	0.04	2	0.11	35	0.12	1	0.03	0.0006
Comorbidity:									
Congestive heart failure	1517	4.30	97	5.54	2162	7.53	308	7.72	<0.0001
Chronic renal failure	485	1.37	23	1.31	894	3.12	77	1.93	<0.0001
Hypertension	10,953	31.0	835	47.7	16,636	57.9	2350	58.8	<0.0001
Arrhythmia	2944	8.34	182	10.4	4055	14.1	449	11.2	<0.0001
Anti-hypertensive medication:									
ACEI	301	0.85	23	1.31	457	1.59	79	1.98	<0.0001
ARB	439	1.24	29	1.66	592	2.06	89	2.23	<0.0001
α-blocker	140	0.40	11	0.63	225	0.78	39	0.93	<0.0001
β-blocker	516	1.46	36	2.06	705	2.46	122	3.06	<0.0001
CCB	560	1.59	34	1.94	757	2.64	113	2.83	<0.0001
Diuretics	263	0.75	22	1.26	376	1.31	58	1.45	<0.0001
Other anti-hypertensive drugs	88	0.25	4	2.51	141	0.49	23	0.58	<0.0001
Anti-platelet/anti-coagulant agents:									
Aspirin	410	1.16	39	2.23	647	2.25	105	2.63	<0.0001
Clopidogrel	93	0.26	10	0.57	189	0.66	24	0.60	<0.0001
Warfarin	39	0.11	2	0.11	47	0.16	6	0.15	0.32

ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker.

Table 3 – Incidence and hazard ratio of macrovascular events from the study cohorts.

Subgroup	Event	N	PY	IR	Crude		Adjusted		Crude		Adjusted	
					HR (95%CI)	*p*-value	HR (95%CI)	*p*-value	HR (95%CI)	*p*-value	HR (95%CI)	*p*-value
Statin-untreated patients without diabetes	Total	7278	200,991	3.62	1.0 (reference)		1.0 (reference)		0.45 (0.43–0.47)	<0.0001	0.51 (0.49–0.54)	<0.0001
	MI	401	200,991	0.19	1.0 (reference)		1.0 (reference)		0.21 (0.18–0.25)	<0.0001	0.23 (0.19–0.28)	<0.0001
	Stroke	6537	200,991	3.25	1.0 (reference)		1.0 (reference)		0.51 (0.48–0.54)	<0.0001	0.58 (0.55–0.61)	<0.0001
	ACS	359	200,991	0.17	1.0 (reference)		1.0 (reference)		0.29 (0.24–0.35)	<0.0001	0.36 (0.29–0.43)	<0.0001
Statin-untreated patients with diabetes	Total	873	7350	11.8	3.46 (3.11–3.84)	<0.0001	2.84 (2.55–3.15)	<0.0001	1.57 (1.42–1.74)	<0.0001	1.46 (1.32–1.62)	<0.0001
	MI	55	7350	0.74	4.02 (2.75–5.89)	<0.0001	3.45 (2.35–5.05)	<0.0001	0.87 (0.60–1.24)	0.44	0.81 (0.56–1.17)	0.27
	Stroke	754	7350	10.2	3.22 (2.87–3.62)	<0.0001	2.63 (2.35–2.95)	<0.0001	1.66 (1.48–1.86)	<0.0001	1.53 (1.36–1.72)	<0.0001
	ACS	69	7350	0.93	6.56 (4.72–9.13)	<0.0001	5.53 (3.97–7.70)	<0.0001	1.94 (1.42–2.65)	<0.0001	1.99 (1.45–2.72)	<0.0001
Statin-treated patients without developing diabetes	Total	11,173	110,892	10.0	2.20 (2.09–2.31)	<0.0001	1.93 (1.84–2.04)	<0.0001	1.0 (reference)		1.0 (reference)	
	MI	1266	110,892	1.14	4.63 (3.91–5.47)	<0.0001	4.22 (3.55–5.02)	<0.0001	1.0 (reference)		1.0 (reference)	
	Stroke	9200	110,892	8.29	1.93 (1.83–2.04)	<0.0001	1.71 (1.62–1.81)	<0.0001	1.0 (reference)		1.0 (reference)	
	ACS	743	110,892	0.67	3.37 (2.80–4.06)	<0.0001	2.77 (2.28–3.36)	<0.0001	1.0 (reference)		1.0 (reference)	
Statin-treated patients developing diabetes	Total	2240	15,148	14.7	3.63 (3.37–3.92)	<0.0001	3.39 (3.14–3.66)	<0.0001	1.65 (1.53–1.77)	<0.0001	1.74 (1.62–1.88)	<0.0001
	MI	246	15,148	1.62	6.75 (5.32–8.56)	<0.0001	6.32 (4.96–8.04)	<0.0001	1.45 (1.18–1.79)	0.0003	1.49 (1.21–1.84)	0.0001
	Stroke	1835	15,148	12.1	3.20 (2.94–3.48)	<0.0001	3.01 (2.76–3.28)	<0.0001	1.65 (1.52–1.79)	<0.0001	1.75 (1.61–1.90)	<0.0001
	ACS	169	15,148	1.11	6.80 (5.28–8.75)	<0.0001	5.91 (4.57–7.63)	<0.0001	2.01 (1.60–2.52)	<0.0001	2.12 (1.69–2.67)	<0.0001

PY, person-years; IR, incidence rate, per 100 person-years; HR, hazardratio; CI, confidence interval; ACS, acute coronary syndrome; MI, myocardial infarction.
Models adjusted for age, gender, comorbidities and medications listed in Table 2.

Table 4 – Baseline characteristics of patients taking pravastatin and other statins.

Variable	Original population				p-value*	PS-matching population				p-value*
	Pravastatin (n = 3436)		Other statin (n = 11940)			Pravastatin (n = 3061)		Other statin (n = 3061)		
	N	%	N	%		N	%	N	%	
Age, years					<0.0001					0.34
<45	868	25.3	1918	16.1		728	23.8	680	22.2	
45–64	1811	52.7	6383	53.5		1625	53.1	1662	54.3	
≥65	757	22.0	3639	30.4		708	23.1	719	23.5	
mean (SD)	53.8 (12.8)		57.6 (12.5)		<0.0001	54.4 (12.7)		54.6 (12.8)		0.36
Gender:					0.55					0.27
Female	1905	55.4	6687	56.0		1685	55.1	1727	56.4	
Male	1531	44.6	5253	44.0		1376	44.9	1334	43.6	
Duration of statin treatment, years (SD)	8.72 (6.10)		4.26 (6.57)		<0.0001	8.26 (6.10)		7.35 (6.43)		<0.0001
Follow-up duration, years (SD)	11.8 (2.57)		6.84 (4.34)		<0.0001	11.5 (2.53)		10.2 (3.76)		<0.0001
Initial statin therapy	2103 (61.2)		6734 (56.4)		<0.0001	1907 (62.3)		1845 (60.3)		0.21
Moderate intensity*										
Low intensity**	1333 (38.8)		5206 (43.6)		<0.0001	1154 (37.7)		1216 (39.7)		0.22
Other cholesterol-lowering agents:										
Fibrate	9	0.26	69	0.58	0.02	9	0.29	15	0.49	0.21
Niacin	0	0	1	0.01	0.59	0	0	0	0	–
Others	1	0.03	14	0.12	0.14	1	0.03	2	0.07	0.56
Comorbidity:										
Congestive heart failure	98	2.85	858	7.19	<0.0001	98	3.20	105	3.43	0.61
Chronic renal failure	59	1.72	300	2.51	0.006	59	1.93	55	1.80	0.70
Hypertension	1135	33.0	7035	58.9	<0.0001	1134	37.0	1179	38.5	0.23
Arrhythmia	221	6.43	1532	12.8	<0.0001	219	7.15	221	7.22	0.92
Anti-hypertensive medication:										
ACEI	46	1.34	192	1.61	0.25	38	1.24	41	1.34	0.73
ARB	44	1.28	247	2.07	0.002	41	1.34	42	1.37	0.91
α-blocker	20	0.58	91	0.76	0.27	17	0.56	16	0.52	0.86
β-blocker	94	2.74	312	2.61	0.69	79	2.58	71	2.32	0.50
CCB	74	2.15	335	2.81	0.03	67	2.19	79	2.58	0.31
Diuretics	39	1.14	136	1.14	0.98	33	1.08	38	1.24	0.55
Other anti-hypertensive drug	12	0.35	59	0.49	0.26	11	0.36	8	0.26	0.49
Anti-platelet/anti-coagulant agents:										
Aspirin	76	2.21	269	2.25	0.88	62	2.03	66	2.16	0.72
Clopidogrel	10	0.29	61	0.51	0.09	9	0.29	14	0.46	0.29
Warfarin	4	0.12	18	0.15	0.63	4	0.13	6	0.20	0.52

ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; PS, propensity score.

* Moderate-intensity statins: 10 mg/day ≤ atorvastatin < 40 mg/day, 5 mg/day ≤ rosuvastatin < 20 mg/day, 20 mg/day ≤ simvastatin, pravastatin ≥ 40 mg/day, lovastatin ≥ 40 mg/day and fluvastatin ≥80 mg/day.

** Low-intensity statins: atorvastatin < 10 mg/day, rosuvastatin < 5 mg/day, simvastatin < 20 mg/day, pravastatin < 40 mg/day, lovastatin < 40 mg/day and fluvastatin < 80 mg/day.

Table 5 – Incidence and hazard ratio of diabetes and macrovascular events between patients taking pravastatin and other statins.

Statin taken	DM	PY	IR	Crude		Adjusted	
				HR (95%CI)	*p*-value	HR (95%CI)	*p*-value
Pravastatin	449	22,515	1.99	0.62 (0.54–0.71)	<0.0001	0.63 (0.55–0.73)	<0.0001
Other statins	641	25,284	2.53	1 (Reference)		1 (Reference)	
	Macrovascular events	PY	IR	Crude		*Adjusted*	
				HR (95%CI)	*p*-value	HR (95%CI)	*p*-value
Pravastatin	47	25,294	0.18	0.66 (0.43–1.01)	0.05	0.64 (0.42–0.98)	0.04
Other statins	79	22,515	0.35	1 (Reference)		1 (Reference)	

PY, person-years; IR, incidence rate, per 100 person-years; HR, hazard ratio; CI, confidence interval.

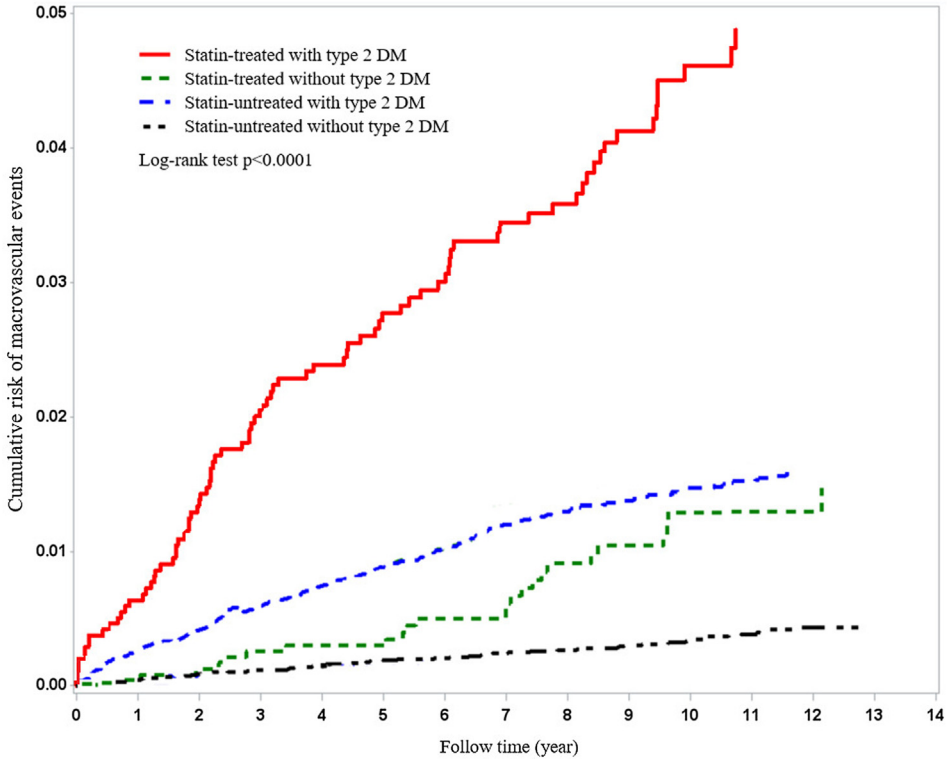

Fig. 2 – Cumulative incidence of macrovascular events in statin-treated patients without diabetes, statin-untreated patients with diabetes, statin-treated patients without developing diabetes and statin-treated patients developing diabetes.

the greater the likelihood of statin-induced diabetes [13]. The findings of Corrao et al revealed that compared with patients who took statins but did not developed diabetes, patients taking statins who developed diabetes had a prognostically lower macrovascular risk as adherence to statin increased [13]. In our study, we investigated the risk of macrovascular events in individuals whose adherence to statins was $\leq$ 50% (low compliance) and > 50% (high compliance). In contrast to the findings of Corrao et al. [13], we found that the incidence of macrovascular complications in patients with diabetes was higher than those in patients without diabetes (*P* for trend 0.9), regardless of high or low statin compliance. Therefore, patients taking statins should be screened for the development of diabetes and receive advice for lifestyle intervention regardless of their level of statin compliance or duration of statin therapy, especially for Asian populations.

Our study had several strengths. First of all, the use of the administrative database prevented underreporting of medical visits. Secondly, its national population-based design enable our study to be highly representative of the general population and prevented selection bias. Thirdly, the risk of misclassification by excluding many patients likely to have had other types of diabetes (those diagnosed with pancreatitis or alcoholism, or those taking steroids) was reduced. Fourthly, we used propensity score matching to match almost all baseline characteristics and adjusted for potential confounders while

analyzing the risk of macrovascular events between pravastatin and other statins users.

Nevertheless, this study has several limitations. First of all, this is an observational study which may be affected by bias and poor controlling of confounding. Secondly, all patient identities were encrypted for reasons of privacy and data security and therefore, we were unable to contact patients to discuss their use of statins. Thirdly, several potential confounding factors, such as serum glucose level, lipid panel, blood pressure, body weight, and smoking status were not included in the database. Fourthly, although experts from the NHI program regularly review randomly selected medical records to confirm the diagnosis from all hospitals, bias may still arise from miscoding. However, the diagnoses in the NHIRD have previously been validated [21,22]. Finally, as our study included only Taiwanese patients, and these patients may have been at greater risk of diabetes due to their Asian descent, our results may not be applicable to other populations.

In conclusion, we found that patients treated with statins and subsequently developed diabetes were at a higher risk of developing macrovascular complications than statin-treated patients without diabetes. In addition, compared with patients taking other diabetogenic statins, patients taking pravastatin was associated with a decreased risk of diabetes and macrovascular complications. Therefore, prescribing statins that have a neutral or beneficial effect on glucose homeostasis may be advisable for Asian populations. Further studies to determine the clinical significance of statin-induced diabetes on CV complications are required to confirm this finding.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

None.

Author's contribution

Yin-Huei Chen: manuscript preparation.

Yu-Cih Yang: data analysis and interpretation.

Weishan Chen: data analysis and interpretation.

Yen-Nien Lin: critical discussion.

Yi-Chih Hung: study design, manuscript preparation, data interpretation, manuscript revision and approval.

Funding

This work was supported by grants from the Ministry of Health and Welfare, Taiwan (MOHW108-TDU-B-212-123004), China Medical University Hospital, Academia Sinica Stroke Biosignature Project (BM10701010021), MOST Clinical Trial Consortium for Stroke (MOST 107-2321-B-039-004), Tseng-Lien Lin Foundation, Taichung, Taiwan, and Katsuzo and Kiyo Aoshima Memorial Funds, Japan.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2019.107870.

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