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Adherence to Statins Use and Risk of Dementia among Patients with Diabetes and Comorbid Hyperlipidemia

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Abstract

The results from previous observational studies and clinical trials about the neuroprotective benefits of statins use for the prevention of dementia are contradictory. It is unclear whether the neuroprotective benefits are experienced in a specific group with a higher risk of dementia, such as patients with concurrent diabetes and hyperlipidemia. We aimed to examine the association between adherence to statins and the risk of dementia among patients with diabetes and comorbid hyperlipidemia. This was a retrospective study with a new user design. We used data from the Taiwan National Health Insurance Research Database to identify patients with diabetes and comorbid hyperlipidemia. The occurrence of dementia was the study outcome. The adherence to statins was the exposure, which was measured by the proportion of days covered (PDC) of statins. The good adherence included patients with ≥80% PDC of statins. Cox proportional hazards regression models were used to evaluate the association between adherence to statins and dementia. Among 18,125 included individuals with diabetes and comorbid hyperlipidemia, 33.5% had good adherence to statins. Compared to poor adherence to statins, good adherence to statins was not significantly associated with a reduced risk of dementia (hazard ratio = 0.94; 95%confidence interval = 0.70–1.24) among patients with diabetes and comorbid hyperlipidemia. Good adherence to statins was not found to be associated with the risk of dementia among patients with diabetes and comorbid hyperlipidemia in Taiwan. Future studies with a more diverse study population are needed to evaluate the neuroprotective effects of statins use on dementia prevention.

Keywords

adherence, dementia, diabetes, hyperlipidemia, statins

What do we already know about this topic?
Statins have potential benefits of delaying dementia, although there is no cure for dementia currently.

How does your research contribute to the field?
Adherence to statins was not found to be associated with a reduced risk of dementia among diabetic patients with comorbid hyperlipidemia.

What are your research's implications toward theory, practice, or policy?
Healthcare providers should have a more conservative attitude toward the effectiveness of statins on dementia before further studies with a longer follow-up period and a more precise definition of good adherence to statins.

Introduction

Dementia is a progressive neurodegenerative disease that gradually impairs memory and cognitive function among patients. There are 7.7 million new cases of dementia each year globally, and the incidence is still increasing.[1] Patients with diabetes have a nearly two-fold higher risk of developing dementia than individuals without diabetes and the majority of them are type 2 diabetes due to the age of the populations involved.[2] Patients with hyperlipidemia also have an increased risk of developing dementia.[3] Patients with diabetes and hyperlipidemia are more likely to develop

dementia than patients with diabetes alone.[3] Furthermore, hyperlipidemia commonly cooccurs with diabetes.[3] Compared to patients without diabetes, patients with diabetes have been shown to have a six-fold probability of developing hyperlipidemia.[3] Therefore, patients with concurrent diabetes and hyperlipidemia have an increased risk of developing dementia.

Patients with hyperlipidemia often require statins as medication treatment. In addition to lowering cholesterol, statins use has been suggested to have a neuroprotective effect.[4-7] Prior studies reported the potential mechanisms for neuroprotective effect of statins to reduce the risk of dementia including (1) lowering the cholesterol level, (2) decreasing cardiovascular risk factors, (3) reducing the deposition of β-amyloid plaques, (4) increasing vascular dilation through endothelial nitric oxide (NO) synthase, and then increasing cerebral blood flow, and (5) inhibiting inflammatory and oxidative stress markers that relevant to hyperlipidemia.[4,6-13]

However, meta-analyses of randomized controlled trials[14] and meta-analyses of observational studies[5,15] have reported contradictory results about the potential neuroprotective benefits of statins in the prevention of dementia. Observational studies have shown that statins use reduced the risk of dementia among patients with diabetes and patients with hyperlipidemia.[5,15] In contrast, the protective effect of statins use on dementia was not observed in clinical trials.[14]

Previous observational studies that reported a positive association between statins use and the prevention of dementia had several limitations in not considering adherence to statins, using a prevalent user design, and often only including statins nonusers as the reference group.[16,17] For example, patients with high cardiovascular risk or with previous stroke are more likely to have good adherence. Prevalent statins users are less likely to be susceptible to its side effects and more likely to have good adherence to statins than new statins users. Furthermore, studies that included statins nonusers as the reference group (ie, studies that lacked an active comparator) may have either overestimated or underestimated the neuroprotective effect. These major limitations from previous studies could lead to bias when assessing the neuroprotective effect of statins on the prevention of dementia and further limit the assessment of the association between statins use and dementia when considering adherence. Thus, it is important to know whether neuroprotective benefits from statins are experienced in a specific patient group with a high risk of developing dementia, such as patients with concurrent diabetes and hyperlipidemia. Therefore, we conducted a pharmacoepidemiologic study that aimed to examine whether good adherence to statins was associated with a reduced risk of developing dementia among individuals with diabetes and comorbid hyperlipidemia.

Materials and Methods

Data Source

The data for this study were collected from Longitudinal Cohort of Diabetes Patients (LHDB) in National Taiwan Insurance Research Database (NHIRD). NHIRD is an administrative claims database that contains beneficiaries' demographic characteristics, diagnoses, inpatient and outpatient procedures, medication prescriptions, and enrollment information of the enrollees in Taiwan National Health Insurance program. The program is a single-payer compulsory insurance plan that covers 99.5% of the Taiwan population.[18] The analyzed LHDB contains a random sample of 120 000 incident cases of diabetes in each calendar year from 2003 to 2006, and all of the participants were followed up to 2013 as a longitudinal cohort.[19]

Study Design and Participants

We only included type 2 diabetes individuals with comorbid hyperlipidemia and statins use. The enrollment period was from 2003 to 2007. To be included in the study cohort, individuals needed to have the diagnosis of hyperlipidemia (ICD-9-CM = 272.0–272.4) ≥1 month after the diagnosis of diabetes (ICD-9-CM code = 250.xx, except for 250.x1 and 250.x3); this ensured that hyperlipidemia was a comorbid with diabetes. We used statins prescriptions to ensure the validity of the hyperlipidemia diagnosis. The index date was the date of the first statins prescription after the diagnosis of hyperlipidemia. To verify new users of statins, individuals receiving any statins during the 1-year pre-index period were excluded. The study design is illustrated in Figure 1.

Individuals were excluded if they had dementia (ICD-9-CM code = 290.0-290.4, 294.1, 294.2, 331.0-331.2), Huntington's disease (ICD-9-CM code = 333.4), Creutzfeldt-Jakob disease (ICD-9-CM code = 046.11, 046.19), cerebral degeneration (ICD-9-CM code = 331.8), or Parkinson's disease (ICD-9-CM code = 332.0, 332.1) during the 1-year pre-index period. Moreover, individuals aged under 50 were excluded.

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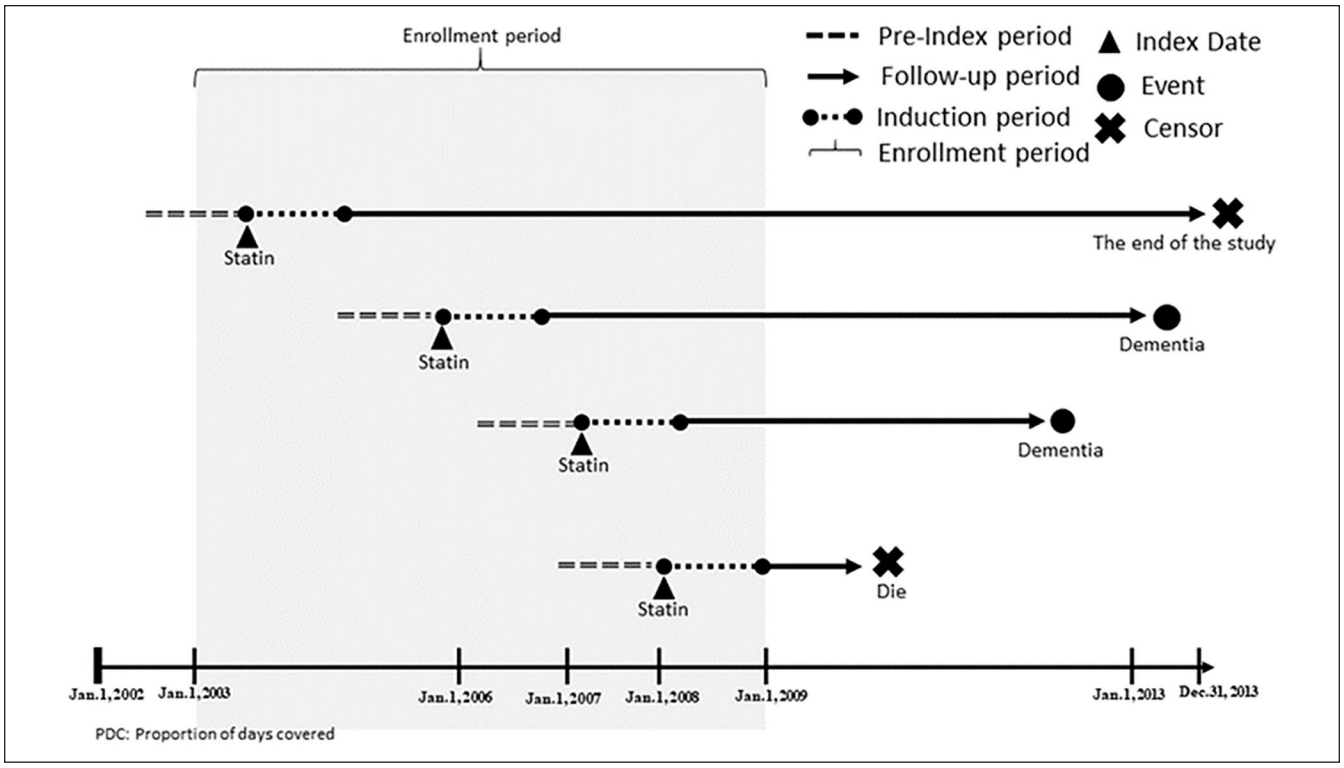

Figure 1. Illustration of the study design.

The active comparator design was used to categorize individuals into the good adherence group and the reference group. The interval-based proportion of days covered (PDC) of statins use over a 1-year period starting from the index date was used to measure adherence. The one-year period after the index date was the induction period for dementia. The induction period was designed to exclude the event of dementia caused by factors other than the level of statins use. The period also allowed us to calculate the PDC of statins use. The follow-up period was the time between the end of the induction period (the date that was 1 year later than the index date) and the date of incident dementia or the date of censoring. The maximum follow-up time was 10 years in all eligible individuals. Figure 2 shows the enrollment process for the study population.

Outcomes Measures

The outcome of this study was the incidence of dementia. The definition of incident dementia was the first inpatient or outpatient diagnosis of dementia (ICD-9-CM code: 290.0-290.4, 294.1, 294.2, 331.0-331.2) during the follow-up period.

Primary Exposure

The primary exposure was defined as whether patients had good adherence to statins. Adherence was measured by the PDC. NHIRD includes information on days' supply, and the PDC was assessed as the cumulative number of days on statins according to the prescription records divided by the one-year period after the index date. The PDC was recommended by Pharmacy Quality Alliance as the preferred method to calculate chronic medication adherence.[20] The active comparator design was used with patients categorized into the good adherence group and the reference group. Patients were in the good adherence group if the PDC $\geq$ 80%, and patients were in the reference group if they had a PDC between 20% and 80%, in accordance with clinical evidence providing support for a standard PDC threshold of 80%.[20] To make the 2 groups more comparable, we excluded patients with a PDC $<$ 20% because these patients could be temporary statins users. Furthermore, very poor adherence could be driven by many confounders, including social economic status, regional factors, education level, or mental disorders. Most of these confounders could not be fully assessed and ruled out in our claim-based study. To ensure validity, we further assessed whether patients switched between the use of different types of statins and other anti-hyperlipidemic drugs. If the users switched between different kinds of statins or switched to a combination of statins, the number of days on any statin treatments was counted for the PDC. In contrast, if the users switched to other anti-hyperlipidemic drugs without statins, the number of days for those treatments was excluded from the cumulative number of days covered by statin therapy.

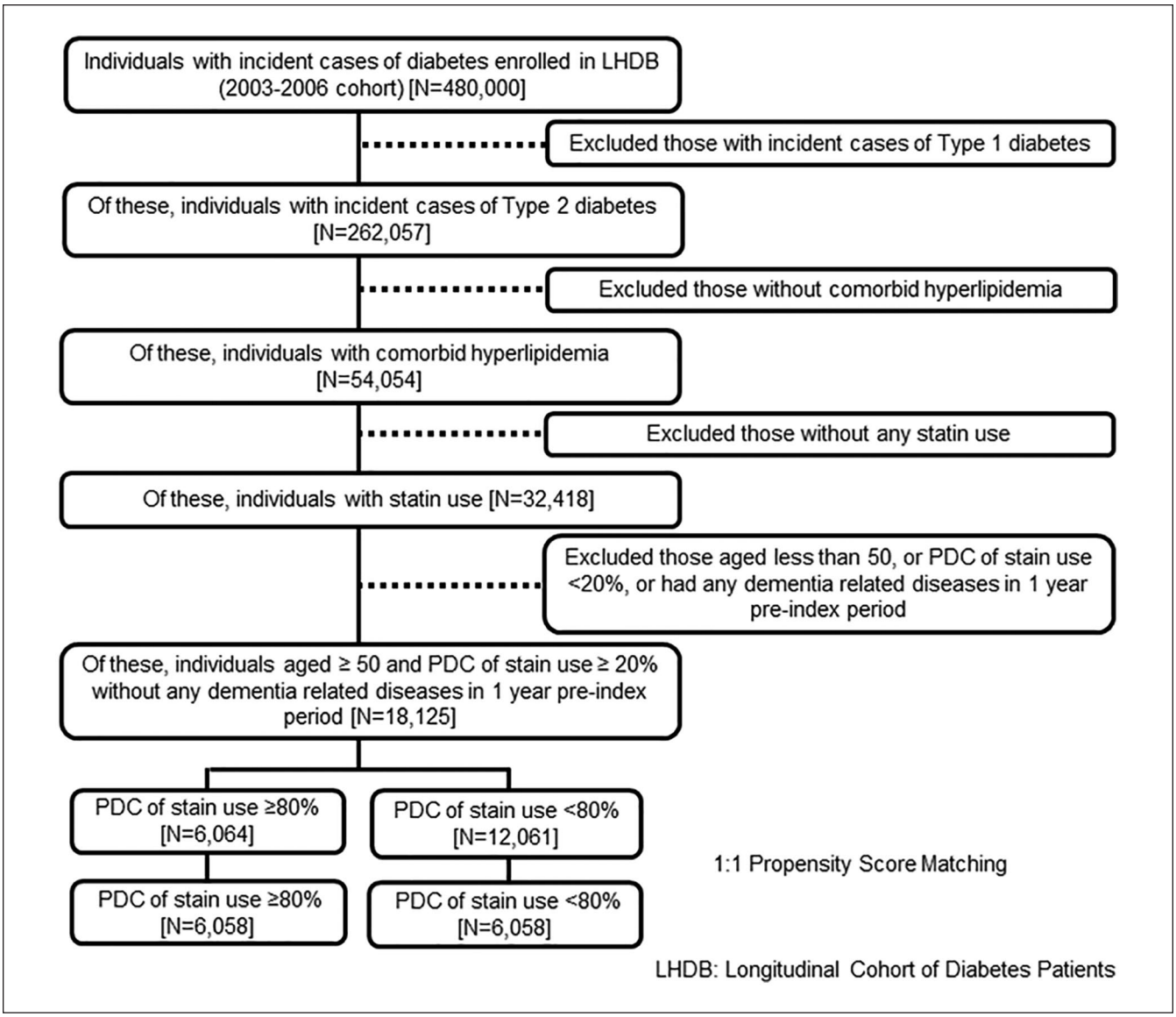

Figure 2. The enrollment process of the study population.

Covariates

Covariates in the study were categorized into demographic and clinical characteristics. The demographic characteristics included age, gender and region, and these 3 covariates were assessed on the index date. Clinical characteristics included diabetes severity, hyperlipidemia severity, comorbidities and medication-related variables. All covariates were measured in the one-year pre-index period.

Diabetes severity was measured by the diabetes disease duration and the number of oral hypoglycemic agents that patients used. The diabetes disease duration was defined by the year when the individual was first diagnosed with type 2 diabetes. The number of oral hypoglycemic agents was determined according to the inpatient or outpatient records of prescriptions over the 1-year pre-index period.

Hyperlipidemia severity was measured by the mean defined daily dose of statins and the intensity of statins. The mean defined daily dose of statins was based on the first year of statin therapy. The prescriptions in any kind of statins were converted into the number of defined daily doses (DDDs). DDD is the assumed average maintenance dose per day for statins.[21] The intensity of statins can be classified into high-intensity, moderate-intensity, and lower-intensity statin therapy in accordance with the American College of Cardiology/American Heart Association guidelines on the treatment of blood cholesterol.[22] The intensity of statins was based on the average expected LDL-C response to a specific statin and dose.

Comorbid diseases were measured during the pre-index period, including cardiovascular diseases, cerebrovascular events, peripheral vascular diseases, chronic pulmonary

disease, psychiatric disorders, nephropathy, hypertension, thyroid diseases, liver disease, malignancy, and autoimmune diseases.

Medication-related variables were divided into 8 prescription categories and defined based on the pre-index period. They were antihypertensive treatment, other antihyperlipidemic drugs, antithrombotic medications, antidepressants, benzodiazepines, antipsychotic medications, anticholinergic drugs, and digitalis glycosides.

Statistical Analyses

The propensity score was used to match characteristics between the good adherence and comparison groups in our study. The 1:1 propensity score matching through the greedy matching process was performed.[23]

Descriptive statistics were used to describe and compare the demographic and clinical characteristics between the good adherence and comparison groups. For continuous variables, an independent samples t-test was used. For categorical variables, the chi-square test was used. A Cox proportional hazards model was performed to study the time to dementia diagnosis and to compare the hazard ratio (HR) of incident dementia between the exposure group and the reference group. Individuals were censored at the time of the following situations: the end of the study period on December 31, 2013, the earliest date of insurance withdrawal, or at the time of death if they died during follow-up before dementia diagnosis. All the data analyses were conducted using SAS software, version 9.4 (SAS Institute, Cary, North Carolina, USA). In this study, a two-tailed p value <0.05 was considered statistically significant.

Sensitivity Analysis

We further conducted a time-dependent Cox proportional hazards model in the sensitivity analysis. When a key independent variable or covariates change during the follow-up period, it is appropriate to use time-varying explanatory variables. In our study, the key independent variable was good adherence to statins, which was a variable that would keep varying in the follow-up period. Therefore, the time-dependent status of statins use was incorporated into the Cox proportional hazards model. The status of statins use was identified yearly in the follow-up period. If the participants' PDC of statins use in a year was $\geq 80\%$, they were in the good adherence group in that year. In contrast, if the participants' PDC of statins use in a year was $<80\%$, they were in the reference group in that year. This study was reviewed and obtained an exemption and a waiver for informed consent from the Taipei Medical University Joint Institutional Review Board (TMU-JIRB No: N201704057).

Results

Table 1 shows the characteristics of the study population before and after propensity score matching. Among 18 125 eligible individuals with type 2 diabetes and comorbid hyperlipidemia, 6064 had good adherence to statins. After 1:1 propensity score matching, 6058 individuals with type 2 diabetes and comorbid hyperlipidemia were in the good adherence group, and 6058 were in the comparison group. After 1:1 propensity score matching, most characteristics between patients with and without good adherence to statins were balanced.

Table 2 indicates the incident rates and results from the Cox proportional hazard model after propensity score matching. Of 6058 good adherence statins users, 272 people had diagnoses of dementia over a mean follow-up time of 6.57 years. The hazard of incident dementia among individuals with type 2 diabetes and comorbid hyperlipidemia was not statistically different between the good adherence group and the comparison group (HR = 0.94; 95% CI = 0.80-1.11). Similar results were observed in the sensitivity analysis, which considered statins use as a time-varying exposure (HR = 0.93; 95% CI = 0.70-1.23).

Discussion

In this large cohort study with an active comparator design, good adherence to statins were not found to be associated with a lower risk of dementia than poor adherence to statins among individuals with type 2 diabetes and comorbid hyperlipidemia. The results were consistent in the sensitivity analysis. Our findings provided evidence that good adherence to statins did not lower the risk of dementia among individuals with diabetes and comorbid hyperlipidemia.

The prevalence of good adherence to statins in our study (33.5%) was lower than that (nearly 50%) in previous studies.[24,25] This could be explained by 2 reasons. First, our study population included patients with diabetes and comorbid hyperlipidemia. Unlike patients with hyperlipidemia who may only need to use statins,[25] patients in our study needed to take statins and diabetic drugs, which could lower the rate of good adherence because previous studies showed that polypharmacy increased the complexity of the medication regimen and decreased adherence.[26,27] Second, the length of the PDC measurement period was shorter than that in previous studies.[24] A longer PDC measurement period tends to lead to a higher rate of good medication adherence. When compared with a prior study using the same PDC measurement period as we did (ie, 1 year) among patients with diabetes, a similar prevalence of good adherence, ranging from 34.9% to 37.6%, was found between the study and our study.[28]

Table 1. Characteristics of Good Adherence to Statin Group and Low Adherence to Statin Group among Patients with Concurrent Diabetes and Hyperlipidemia.

	Before propensity score matching					After propensity score matching				
	Good adherence to statin (N = 6064)		Poor adherence to statin (N = 12061)		Absolute standardized differences	Good adherence to statin (N = 6058)		Poor adherence to statin (N = 6058)		Absolute standardized differences
	No.	(%)	No.	(%)		No.	(%)	No.	(%)	
Age, mean (SD)	62.34	8.8	62.32	8.9	0.15	62.34	8.9	62.34	8.8	0.03
Male	2778	45.8	5737	47.6	0.26	2777	45.8	2767	45.7	0.02
Region										
Northern	1984	32.7	3663	30.4	0.52		32.7	2007	33.1	0.05
Northwestern	718	11.8	1455	12.1		718	11.9	684	11.3	
Central	1093	18	2214	18.4		1093	18	1060	17.5	
Southwestern	836	13.8	1816	15.1		836	13.8	864	14.3	
Southern	1082	17.8	2154	17.9		1081	17.9	1103	18.2	
Eastern and others	351	5.8	759	6.3		351	5.8	340	5.6	
Diabetes cohort										
2003	2066	34.1	4234	35.1	0.82	2065	17	2059	17	0.06
2004	1721	28.4	3509	29.1		1716	14.2	1732	14.3	
2005	1393	23	2639	21.9		1393	11.5	1382	11.4	
2006	884	14.6	1679	13.9		884	7.3	885	7.3	
Number of OHAs										
0 class of OHAs	160	2.6	425	3.5	0.53	160	2.6	151	2.5	0.15
1 class of OHAs	1210	20	2627	21.8		1209	20	1260	20.8	
2 classes of OHAs	2400	39.6	4943	41		2399	39.6	2371	39.1	
3 classes of OHAs	1418	23.4	2591	21.5		1416	23.4	1411	23.3	
4 classes of OHAs	621	10.2	1035	8.6		621	10.3	617	10.2	
5 classes of OHAs	200	3.3	364	3		200	3.3	204	3.4	
6 classes of OHAs	55	0.9	76	0.6		53	0.9	44	0.7	
Insulin	1289	21.3	2249	18.7	0.32	1287	21.2	1258	20.8	0
MDDD of statins										
MDDD $>$ 0.61	2193	36.2	4398	36.5	0.03	2191	36.2	2237	36.9	0.04
MDDD $\leq$ 0.61	3871	63.8	7663	63.5		3867	63.8	3821	63.1	
Intensity of statins										
High	218	3.6	405	3.4	0.17	217	3.6	223	3.7	0.03
Moderate and low	5846	96.4	11656	96.6		5841	96.4	5835	96.3	
Atrial fibrillation	111	1.8	208	1.7	0	111	1.83	107	1.77	0.02
Heart failure	418	6.9	813	6.7	0.28	418	6.9	419	6.92	0.01
Coronary artery disease	1653	27.3	3113	25.8	0.21	1650	27.24	1663	27.45	0.06
Atherosclerosis	159	2.6	348	2.9	0.40	159	2.62	157	2.59	0.01
Transient cerebral ischemia	204	3.4	458	3.8	0.40	204	3.37	208	3.43	0.02
Stroke	485	8	869	7.2	0.62	485	8.01	478	7.89	0.01
Diabetic PVD	245	4	538	4.5	0.28	245	4.04	236	3.9	0.01
Other peripheral vascular disease	197	3.3	458	3.8	0.12	197	3.25	193	3.19	0.02
Arteries of the extremities	37	0.6	65	0.5	0.00	37	0.61	30	0.5	0.04

(continued)

Table 1. (continued)

	Before propensity score matching					After propensity score matching				
	Good adherence to statin (N = 6064)		Poor adherence to statin (N = 12061)		Absolute standardized differences	Good adherence to statin (N = 6058)		Poor adherence to statin (N = 6058)		Absolute standardized differences
	No.	(%)	No.	(%)		No.	(%)	No.	(%)	
Chronic obstructive pulmonary disease	332	5.5	696	5.8	0.41	331	5.46	328	5.41	0.03
Sleep apnea	51	0.8	79	0.7	0.00	51	0.84	50	0.83	0.02
Depression	317	5.2	629	5.2	0.40	317	5.23	312	5.15	0.04
Schizophrenia	30	0.5	79	0.7	0.00	30	0.5	33	0.54	0.02
Bipolar	42	0.7	98	0.8	0.00	42	0.69	47	0.78	0.00
Anxiety	1347	22.2	2757	22.9	0.33	1347	22.24	1324	21.86	0.03
Chronic kidney disease	286	4.7	565	4.7	0.60	286	4.72	264	4.36	0.02
Hypertension	4360	71.9	8364	69.4	0.29	4356	71.9	4317	71.26	0.07
Liver disease	1724	28.4	3892	32.3	0.07	1722	28.43	1686	27.83	0.01
Autoimmune diseases	2	0.03	2	0.02	0.00	2	0.03	2	0.03	0.00
Malignancy	392	6.5	689	5.7	0.28	392	6.47	380	6.27	0.02
Thyroid diseases	355	5.9	659	5.4	0.40	355	5.86	334	5.51	0.04
Beta-Blockers	3087	50.91	5843	48.45	0.03	3085	50.92	3129	51.65	0.03
ACEI	2667	43.98	5022	41.64	0.19	2664	43.97	2699	44.55	0.03
CCB	3503	57.77	6641	55.06	0.42	3501	57.79	3525	58.19	0.02
Diuretics	2695	44.4	4856	40.3	0.27	2694	44.5	2655	43.8	0.01
ARB	2145	35.4	3508	29.1	0.36	2141	35.3	1986	32.8	0.08
Fibrate	872	14.4	2357	19.5	0.59	871	14.4	901	14.9	0.01
Bile acid sequestrants	13	0.2	16	0.1	0.00	13	0.2	6	0.1	0.02
lipid modifying agents	107	1.8	191	1.6	0.00	107	1.8	80	1.3	0.05
Nicotinic acid	10	0.16	31	0.3	0.00	10	0.2	12	0.2	0.02
Vitamin K antagonists	106	1.8	143	1.2	0.28	106	1.8	75	1.2	0.05
Aspirin	2397	39.5	4638	38.5	0.35	2394	39.5	2409	39.8	0.02
Clopidogrel	377	6.2	488	4.05	0.28	375	6.2	287	4.7	0.07
Cilostazol	120	2	201	1.7	0.28	120	2	112	1.9	0.02
Ticlopidine	122	2	216	1.8	0.00	121	2	121	2	0.04
Dipyridamole	1214	20	2457	20.4	0.11	1212	20	1282	21.2	0.00
Antidepressants	1063	17.5	2062	17.1	0.35	1063	17.6	1070	17.7	0.02
Benzodiazepines	3773	62.2	7468	61.9	0.12	3772	62.3	3750	61.9	0.05
Typical antipsychotics	128	2.1	261	2.2	0.01	128	2.1	111	1.8	0.01
Atypical antipsychotics	301	5	697	5.8	0.01	301	5	308	5.1	0.01
Nonselective COX inhibitors	5611	92.53	11125	92.2	0.50	5607	92.6	5601	92.5	0.04
Selective COX-2 inhibitors	828	13.65	1526	12.7	0.21	828	13.7	848	14	0.04
Anticholinergic drugs	5706	94.1	11308	93.8	0.28	5703	94.1	5696	94	0.03
Digitoxin	294	4.85	532	4.4	0.28	294	4.85	281	4.64	0.02
Metildigoxin	6	0.1	18	0.2	0.00	6	0.1	6	0.1	0.01

T2DM = type 2 diabetes mellitus; SD = standard deviation; OHA = oral hypoglycemic agents; MDDD = mean defined daily dose; PVD = peripheral vascular diseases; ACEI = angiotensin-converting-enzyme; CCB = calcium channel blocker; ARB = angiotensin receptor blockers.

Table 2. Association between Adherence to Statin and Risk of Dementia: Results from Cox Proportional Hazard Model after Propensity Score Matching.

Group	Number of dementia events	Follow-up (years)		Cox proportional hazard model	
		Total	Mean	Hazard ratio	95% CI
Good adherence group [PDC ≥ 80%] (N = 6058)	272 (4.5%)	39 773	6.57	0.94	(0.80-1.11)
Reference group [80% < PDC] (N = 6058)	300 (5.0%)	40 282	6.65	Reference	

CI = confidence interval; PDC = proportion of days covered.

In our study, good adherence to statins was not associated with a lower risk of dementia among individuals with concurrent diabetes and hyperlipidemia. Our findings were different from several previous observational studies that indicated the protective effect of statins on dementia.[5,16,29] The difference could result from 2 reasons. First, the active comparator design used in our study decreased the bias from confounding by indication. Instead, previous studies often compared the effect of statins on the risk of dementia between statins users and nonusers.[16,29] Selecting nonusers as the reference group could induce bias due to the indication effect or the sick-stopper effect, leading to the overestimation or underestimation of the neuroprotective effect of statins on the prevention of dementia. For example, the indication bias could lead to an underestimation of the protective effect, but the sick-stopper effect from older and frail patients could lead to an overestimation of the effect. Unlike previous studies, our current study had 2 groups with similar treatment indications, which led to more robust evidence.

Second, the definition of statins without considering medication adherence in most previous observational studies could not thoroughly reflect the effectiveness of statins in real-world settings.[5,16,29,30] Previous studies defined statins use often with the assumption of good adherence but did not actually measure adherence.[17] However, adherence to statins could substantially decline over time in the real world.[31] The current study measured adherence and considered the effectiveness of statins, which could provide better evidence for real-world experiences. Therefore, the protective effect of statins on the risk of dementia observed in previous observational studies could be biased due to not precisely measuring statins adherence.[32,33]

From a clinical perspective, healthcare providers should have a more conservative attitude toward the effectiveness of statins on dementia. The protective effect of statins on dementia reported in previous studies was a concern. Adherence to statins was not associated with a reduced risk of dementia in our study, so healthcare providers still need to closely monitor high-risk patients with good statins adherence. From a research perspective, we consider our findings to reflect more real-world situations. In our study, we closed the gap of the inconsistent association between statins and dementia and provided a more robust result with a rigorous pharmacoepidemiologic study design that assessed statins adherence with an active comparator.

Our study had several strengths. First, the active comparator design could largely reduce bias due to the confounding by indication effect. Second, the assessment of new drug users could eliminate the prevalent user bias. Third, we created an induction period to ensure that the outcome occurred after the exposure, thus reducing exposure misclassification and preventing protopathic biases. Finally, we captured the time-varying status of statins use in a sensitivity analysis to confirm the consistent association between good adherence to statins and risk of dementia.

Regardless of the strengths, the study still had several limitations. First, the follow-up time was relatively short for the disease progression. However, compared to previous studies with only a 3 to 4 year follow-up period,[34,35] this study provided a relatively longer follow-up period. Second, propensity score matching could only reduce measurable confounders but not unmeasurable confounders (eg, apolipoprotein E [ApoE] genotype). Prior studies showed that the proportion of subjects with the ApoE genotype was significantly higher among patients with dementia than among patients without dementia (64.3% vs 35.8%; $P < .01$).[36] Mutations in this gene result in an accumulation of β-amyloid plaques.[37] Third, the measurement of adherence in this study was based on the prescription records rather than the patients' real compliance. We used the PDC to measure adherence, which is a reliable and valid method recommended by the Pharmacy Quality Alliance for measuring adherence in the claims data.[20] The PDC threshold of 80% is the level at which the medication has a reasonable likelihood of achieving the most clinical benefit. Fourth, in the outcome measurement, we defined the incident dementia using the first inpatient or outpatient diagnosis. Considering dementia as a progressive neurodegenerative disease, it is less likely to misclassify the individuals with dementia into individuals without dementia when using the first inpatient or outpatient diagnosis. However, a single diagnosis of dementia might still not indicate a true diagnosis because the diagnosis code might be used for other insurance claims purposes. In addition, previous studies found statin use could be protective for patients with mild cognitive impairment (MCI).[38,39] However, patients with MCI were less likely to be captured in claim-based data. Thus, a misclassification bias could still exist. Fifth, we use adherence as the exposure, which could lead to a healthy user bias and could not completely separate the neuroprotective effect of statins use from health behaviors

such as good statins adherence. Sixth, the diagnosis of dementia can be more precise with neuropsychological functioning and testing scores in additional to the diagnosis code from inpatient or outpatient records. Due to the nature of the data, we were unable to obtain those scores. However, in Taiwan National Health Insurance regulation, the specificity of dementia is relatively high because it is required to pass several evaluations (eg, Clinical Dementia Rating, Comprehensive Neuropsychological Test, brain computed tomography and blood test) assessed by psychiatrists. Therefore, it is less likely to misclassify individuals without dementia as with dementia, and then less likely to bias our results. Finally, the generalizability in this study may be limited to individuals with type 2 diabetes and comorbid hyperlipidemia in Taiwan.

Conclusion and Relevance

In conclusion, good adherence to statins was not found to be associated with a reduced risk of dementia among patients with diabetes and comorbid hyperlipidemia. Healthcare providers should be aware that the neuroprotective effect of statins among patients with concurrent diabetes and hyperlipidemia may not be as strong as reported in previous studies. Future studies with a more diverse study population are needed to further evaluate the neuroprotective effect of statins on dementia prevention.

Authors' Note

Jin-Liern Hong is currently an employee of Takeda. The results were presented in part at the 2018 International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Conference, May 19 to 23, 2018, Baltimore, MD, USA.

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Author Contributions

Chung-Hsuen Wu oversaw the implementation and quality assurance of the study, contributed to the interpretation of these results, and critically reviewed the manuscript. Ching-Yuan Chang conceived of the study, conducted the analyses, and drafted the manuscript. Fang-Ju Lin and Jin-Liern Hong contributed to the interpretation of these results and critically reviewed the manuscript.

Declaration of Conflicting Interests

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