Statin Use and the Risk of Dementia in Patients with Stroke: A Nationwide Population-Based Cohort Study

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Background: Patients with stroke have an increased risk of dementia. Some studies have found that statin use might lower the risk of incident dementia; however, there is still a lack of data from patients with stroke. Therefore, the aim of our study was to investigate the impact of statin use on the risk of dementia in patients with stroke. *Methods:* We used the National Health Insurance Research Database in Taiwan to identify 14,807 patients diagnosed with stroke from 1997 to 2005. These patients were classified as statin users and nonusers. Propensity score matching was performed to balance selected confounders between the statin users and nonusers. Cox proportional hazard regression models were used to evaluate the association between statin use and the risk of dementia. *Results:* During the follow-up period (median, 7.5 years), 1895 patients were diagnosed with incident dementia. Statin use was associated with a significantly lower incidence of dementia (adjusted hazard ratio, .81; 95% confidence interval, .73-.89) than nonuse was. In particular, lipophilic and high-potency statins were associated with lower risk of dementia. Statin exposure duration was inversely related to the risk of dementia ($P < .001$ for the trend). No significant effect modification for the relationship between statin use and the risk of dementia was found for either age or sex. *Conclusion:* In this nationwide cohort study, statin use was associated with decreased risk of dementia among patients with stroke. The use of high-potency statins, lipophilic statins, and prolonged exposure to statins may be associated with greater benefits.

Key Words: Dementia—statins—stroke—Epidemiology

Introduction

Stroke is a leading cause of death and disability worldwide.[1,2] The number of stroke survivors in 2010 was nearly 33 million worldwide, and this number is expected to increase as life expectancy increases. Several reviews and cohort studies demonstrated that stroke is associated with an increased risk of cognitive decline and dementia, including Alzheimer's disease and vascular dementia.[3-5] Patients with stroke with concurrent dementia may have increased mortality rates, increased rates of institutionalization, and are more dependent upon family and healthcare providers.[6,7] These patients also tend to have poor quality of life and their care places a great burden on their families and the healthcare system. The increased incidence of stroke and the association between stroke and dementia onset implies that preventing poststroke dementia is crucial to the financial and healthcare system. Thus, minimizing the impact of poststroke dementia is a major public health issue.

Evidence suggests that hyperlipidemia is associated with an increased risk of dementia.[8] Statins, 3-hydroxyl-3-methylglutaryl coenzyme A reductase inhibitors, are commonly used to reduce serum cholesterol levels. Statin therapy may also reduce the risk of dementia either directly by lowering lipid levels or through other pleiotropic effects such as reduction of β-amyloid and serum apolipoprotein levels,[8] antithrombotic effects, and anti-inflammatory effects.[9,10] Studies on the

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association between statin use and the risk of dementia are inconsistent. Some observational studies found a significant association between statin use and reduced risk of dementia,[11,12] while two short-term clinical trials have failed to show beneficial effects on cognitive function.[13,14] Furthermore, several case reports have suggested a potential association between statin use and cognitive impairment.[15,16] However, these previous studies did not focus on patients with stroke, who have a higher risk of dementia.

Given the prevalence of statin use for the secondary prevention of recurrent stroke, it is important to clarify the association between statin use and the risk of dementia in patients with stroke. Thus, we conducted a nationwide, long-term follow-up study to investigate whether statin use was positively or negatively associated with risk of dementia in patients with stroke.

Methods

Data Source

In Taiwan, the mandatory health insurance program, National Health Insurance (NHI) program, was launched in 1995. As a single-payer insurance program, NHI approximately covered over 99.9% of the Taiwanese population by the end of 2010. For research purposes, the National Health Research Institutes (NHRI) retrieved claim data from the NHI program and constructed the National Health Insurance Research Database (NHIRD). The NHIRD contains comprehensive claim data for all beneficiaries, including hospitalization and ambulatory visits. All diagnoses, treatments, procedures, and prescriptions were recorded. In this database, International Classification of Diseases, Ninth Revision, Clinical Modification (ICD9-CM) was used for diagnosis and the NHI codes were used for prescriptions, treatments, and procedures. All personally identifiable data were scrambled to ensure patient privacy. The Longitudinal Health Insurance Database (LHID) 2005 is a subset of NHIRD. One million samples were randomly selected from all beneficiaries. The LHID 2005 was confirmed to have no significant differences in sex, age, and medical cost from the NHIRD.

This study was approved by the Institutional Review Board of the Mackay Memorial Hospital, Taipei, Taiwan (No. 15MMHIS222e). Informed consent was waived owing to the use of deidentified claim data in the NHIRD.

We conducted a retrospective cohort study on the association between statin use and the risk of incident dementia in patients with stroke. The study population consisted of patients admitted to the hospital, diagnosed with ischemic or hemorrhagic stroke (ICD9-CM code: 430.xx-438.xx) between January 1, 1997 and December 31, 2005. To ensure the accuracy of the stroke diagnosis, we only recruited patients who were admitted to the hospital with an initial diagnosis of stroke and then subjected to a computed tomography scan or magnetic resonance imaging during admission. Patients younger than 20 years old or patients previously diagnosed with any type of dementia prior to stroke onset were excluded. Based statin prescriptions during the follow-up period, patients with stroke were classified as statin users or nonusers (matched controls). Patients with at least one statin prescription during the follow-up period were defined as statin users, and the remaining patients were defined as nonusers. To ensure that the patients were new statin users, patients with any statin prescription 1 year before index hospitalization were not enrolled. Given the differences in baseline characteristics and dementia risk between the statin users and nonusers, we applied propensity score matching at a ratio of 1:1 for stroke patients with and without statin use. The propensity score, which predicted the probability of statin use, was calculated using logistic regression on the basis of the patients' demographics (age and sex), and baseline comorbidities (diabetes, hypertension, hyperlipidemia, atrial fibrillation, sleep apnea, and ischemic heart disease). To prevent the immortal time bias, the index date for the start of follow-up was the date of first prescription for statin users. Statin nonusers were assigned the same index date according to the corresponding index date for a statin user. Finally, a total of 4974 pairs of propensity score-matched statin user and controls were identified.

Using the prescription records in the NHIRD, we collected information on statin use during the follow-up period. For each statin prescription, detailed information on drug type, quantity, dispensing date, and days of drug supply were collected. These drugs included atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, and simvastatin. To investigate the association between the pharmacologic characteristics of statins and the risk of dementia, these statins were classified as (1) high-potency (rosuvastatin, atorvastatin, and simvastatin) and low-potency (lovastatin, fluvastatin, and pravastatin) statins according to their lipid-lowering activities, which were estimated using half maximal inhibitory concentration (IC50), and as (2) lipophilic (atorvastatin, lovastatin, fluvastatin, and simvastatin) and hydrophilic (pravastatin and rosuvastatin) statins.[17] The cumulative duration of statin exposure was assessed by the summation of day supplements in each prescription during the follow-up period.

The following covariates that could plausibly confound associations between statin use and incident dementia were extracted from the NHIRD: demographic factors at index date (including patient age and sex), socioeconomic status variables (including baseline values of insurable income, and urbanization level of residence), baseline medical comorbidities (including diabetes [ICD9-CM codes 250.X], hypertension [ICD9-CM codes 401.X-405.X], hyperlipidemia [ICD9-CM codes 272.X], atrial fibrillation [ICD9-CM codes 427.31], sleep apnea [ICD9-CM codes

780.51, 780.53, 780.57], and ischemic heart disease [ICD9-CM codes 410.X-414.X]), and concomitant medication use (including hypoglycemic agents, angiotensin II receptor blockers, β-blockers, calcium channel blockers, angiotensin converting enzyme inhibitors, antiplatelet agents, and anticoagulants).

The outcome of interest was the incident diagnosis of dementia during the follow-up period. In order to ensure the accuracy of the dementia diagnosis, the dementia patients were defined as having the primary diagnosis of dementia (ICD9-CM codes: 290.0x-290.4x, 294.1x-294.2x, and 331.0x-331.2x) when they had outpatient or inpatient visits from the index date to the end of the study. All patients were continuously followed from the index date to the date of incident dementia diagnosis. If an event (dementia) did not occur, the case was regarded as censored at the end of study, death, or withdrawal from insurance.

Statistical Analyses

Differences in demographic data and clinical characteristics between statin users and nonusers were examined using chi-square tests for categorical variables and *t*-tests for continuous variables. We calculated the incidence rate of incident dementia in the two groups by dividing the number of cases by the number of person-years of follow-up. The difference in the incidence of dementia between the statin users and nonusers was estimated using Kaplan−Meier analysis with a log-rank test. We used the Cox proportional hazards model to estimate hazards ratios (HRs) and 95% confidence intervals (CIs) for dementia incidence in relation to statin use by adjusting for potential confounding variables. Variables not sufficiently balanced after propensity score matching and those associated with the risk of dementia were also included in the model. The proportional hazard assumption was assessed using a graphical method. We further applied a separate Cox proportional hazards model to explore the associations between statin use and the risk of dementia on the basis of the type, potency, lipophilicity, and duration of use in years (<1 year, 1-3 years, and ≥3 years), respectively. The reference group consisted of patients who did not use statins during the follow-up period. Stratified analyses using an interaction term were performed on subgroups of the patients with different ages and sex, stroke subtypes, and presence of hyperlipidemia to test whether the effect of statins was consistent for different groups. We used SAS Version 9.1.3 software (SAS Institute Inc, Cary, NC) for statistical analysis. All statistical tests were two-tailed, and $P < .05$ was regarded as significant.

Results

Between January 1997 and December 2005, we identified 14,807 patients diagnosed with stroke, including 5527 statin users and 9280 statin nonusers. Statin users tended to be young, female, and more likely to have hypertension, diabetes, or hyperlipidemia and ischemic heart disease. After propensity score matching, 4724 pairs of statin users and nonusers with comparable age, sex, and

Table 1. *Baseline characteristics in the overall and propensity-score matched stroke cohort*

	Overall cohort			Propensity-score matched cohort		
	Statin users	Statin nonusers	*P*	Statin users	Statin nonusers	*P*
Patients (no.)	5527	9280		4724	4724	
Mean age (SD), years	61.8 (11.4)	66.5 (14.1)	<.001	62.7 (11.3)	62.2 (14.7)	.06
Sex			<.001			.95
Female	2585 (47%)	3751 (40%)		2115 (45%)	2118 (45%)	
Male	2942 (53%)	5529 (60%)		2609 (55%)	2606 (55%)	
Comorbidities						
Diabetes	2253 (41%)	2467 (27%)	<.001	1687 (36%)	1658 (35%)	.53
Hypertension	4222 (76%)	6361 (69%)	<.001	3497 (74%)	3480 (74%)	.69
Hyperlipidemia	2386 (43%)	1751 (19%)	<.001	1601 (34%)	1532 (32%)	.13
Atrial fibrillation	995 (18%)	1020 (11%)	<.001	613 (13%)	615 (13%)	.96
Ischemic heart disease	1902 (34%)	3155 (34%)	.61	1593 (34%)	1585 (34%)	.86
Medications						
Antidiabetic agents	1873 (34%)	2034 (22%)	<.001	1404 (30%)	1334 (28%)	.11
ARBs	974 (18%)	1441 (16%)	<.001	777 (17%)	823 (17%)	.21
β-blocker	3305 (60%)	4940 (53%)	<.001	2765 (59%)	2705 (57%)	.21
Calcium channel blocker	3127 (57%)	4879 (53%)	<.001	2616 (55%)	2642 (56%)	.59
ACEIs	2498 (45%)	3619 (39%)	<.001	2042 (43%)	1931 (41%)	.02
Antiplatelets	4639 (84%)	6842 (74%)	<.001	3922 (83%)	3433 (73%)	<.001
Anticogulant	774 (14%)	1020 (11%)	<.001	472 (10%)	236 (5%)	<.001

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers.
All data are presented as *n* (%), except where otherwise indicated.

comorbidities were used in the analysis of the relationship between risk of dementia and statin use. The demographic and clinical characteristics of these cohorts are summarized in Table 1.

During the follow-up period (median, 7.5 years), 767 patients (16.2%) were diagnosed with incident dementia among statin users; 1128 (23.9%), among nonusers. The cumulative incidence rates of dementia were lower among statin users than among their matched controls ($P < .001$, log-rank test) (Fig 1). The crude and adjusted relative hazard risks of the associations between statin use and incident dementia are shown in Table 2. Compared with the nonusers, statin users had lower risks of incident dementia after adjusting for potential confounding factors (HR .81; 95% CI, .73-.89). Significantly decreased dementia risk was found for rosuvastatin (HR .53; 95% CI: .41-.68), fluvastatin (HR .76; 95% CI: .61-.95), atorvastatin (HR .78; 95% CI: .68-.89), and simvastatin (HR .82; 95% CI: .69-.98). Regarding the pharmacologic characteristics of statins, high-potency statin users (HR .72; 95% CI: .65-.802) had a decreased risk of incident dementia compared with nonusers. Additionally, lipophilic statin users were associated with a significant decrease in dementia risk when compared with nonusers (HR .78; 95% CI: .71-.86). There was a trend toward significance between the duration of statin use and decreased dementia risk; patients using statins >1 year had a significant increase in the relative hazards of dementia compared with nonusers. However, statin use <1 year did not provide any protective effects against the occurrence of dementia (HR 1.25; 95% CI: 1.12-1.39). The results indicated that patients who received a longer duration of statin treatment during follow-up had significantly better outcomes than those who never used statins. In the subgroup analyses, we found that age, gender, and stroke subtypes did not significantly modify the association between statin use and dementia risk. Statin had more prominent association in patients with hyperlipidemia than in those without hyperlipidemia (P for interaction <.001) (Table 3).

Discussion

In this nationwide cohort study, we found that statin use was associated with a 17% lower risk of incident dementia in patients with stroke. The potency, solubility, and cumulative duration of statin use were major factors in the reduction of dementia risk. The reduced dementia risk with statin use was greater in high potency, lipophilicity, and long-term cumulative statin users. The results remained consistent in analyses stratified by gender and different age groups.

There is substantial data supporting the use of statins in the secondary prevention of stroke.[9,18] However, the role of statins in the improvement of cognitive function and the prevention of dementia are still highly debatable. Numerous studies, including observational studies and randomized controlled trials, have reported conflicting results regarding the association between statin use and dementia prevention. For instance, a 4-month randomized controlled trial evaluated the effects of simvastatin versus placebo on cognitive function and found that simvastatin use improved selected measures of cognitive function.[19] Conversely, other randomized controlled trials, such as Heart Protection Study and the Prospective Study of Pravastatin in the Elderly at Risk, failed to demonstrate the effectiveness of statins on cognitive function.[13,14] Although these studies were focused on changes in cognitive function, they were limited by relatively short follow-up times. The Ginkgo Evaluation Study of 3609 cognitively healthy elderly patients indicated that current statin use was associated with a reduction in the incidence of all-cause dementia (HR .79; 95% CI .65-.96).[12] In a population-based observation study, Chen et al. reported that statin use reduced the risk of dementia in a diabetic cohort

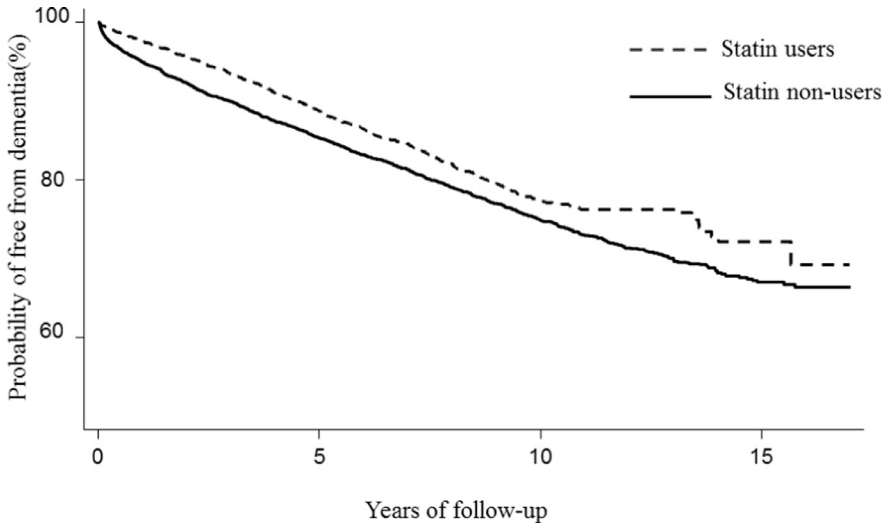

Figure 1. *Kaplan–Meier curve for incidence of dementia in patients with stroke categorized by statin use.*

Table 2. *Incidence rate and relative risk of dementia associated with statin use in the propensity-score matched stroke cohort*

	No. of events	Person-years	Incidence rate†	Propensity score-matched	
				Crude HR (95% CI)	Adjusted* HR (95% CI)
Statin use					
None	1128	37,537	30.1	1 (Reference)	1 (Reference)
Yes	767	30,304	25.3	.82 (.075-.90)	.81 (.73-.89)
Type of statin					
None	1128	37,537	30.1	1 (Reference)	1 (Reference)
Rosuvastatin	63	4088	15.4	.49 (.38-.63)	.53 (.41-.68)
Atorvastatin	281	11,573	24.3	.77 (.68-.88)	.78 (.68-.89)
Fluvastatin	80	3209	24.9	.80 (.63-1.00)	.76 (.61-.95)
Simvastatin	151	5816	26.0	.83 (.70-.99)	.82 (.69-.98)
Pravastatin	73	2356	31.0	.99(.78-1.25)	.86 (.68-1.09)
Lovastatin	119	3261	36.5	1.16 (.96-1.40)	1.00 (.83-1.21)
Potency of statin					
None	1128	37,537	30.1	1 (Reference)	1 (Reference)
High	583	26,316	22.1	.72 (.65-.80)	.72 (.65-.80)
Low	184	3988	46.1	1.43 (1.22-1.67)	1.21 (1.03-1.42)
Solubility of statin					
None	1128	37,537	30.1	1 (Reference)	1 (Reference)
Lipophilic	697	28,718	24.3	.79 (.72-.87)	.78 (.71-.86)
Hydrophilic	70	1586	44.1	1.26 (.99-1.61)	1.21 (.95-1.55)
Duration of statin use					
None	1128	37,537	30.1	1 (Reference)	1 (Reference)
< 1 year	477	10,448	45.7	1.40 (1.25-1.56)	1.25 (1.12-1.39)
1-3 years	195	7704	25.3	.81 (.70-.95)	.78 (.67-.91)
>3 years	95	12,152	7.8	.26 (.21-.032)	.28 (.23-.35)

Abbreviations: CI, confidence interval; HR, hazard ratio.
*Adjusted for age, sex, socioeconomic status, comorbidity, and medication.
†Per 10^3 person-years.

(HR .48; 95% CI .30-.76).[20] In contrast, a retrospective longitudinal study found no difference in the risk of subsequent onset of dementia and Alzheimer's disease among current and former users of statins compared with nonusers among patients with chronic heart failure over a 2-year follow-up period.[21] These inconsistencies might arise from differences in sample size, study design, target outcome, and enrolled study population. However, none of the aforementioned studies focuses on patients with stroke. In the present study, we found that statin use might also have a favorable effect on decreasing the risk of subsequent dementia in stroke patients who were at high risk of dementia and had more comorbidities than the general population. To our knowledge, this is the first large-scale study to investigate the link between statin use and the risk of dementia in the patients with stroke.

Table 3. *Relative risk of dementia associated with statin use by sex, age groups, stroke subtypes, and hyperlipidemia*

	Hazard ratio* (95% CI)	*P* for interaction
All patients	.81 (.73-.89)	
Sex		.32
Male	.75 (.66-.86)	
Female	.87 (.76-.99)	
Age, years		.87
<65 years	.81 (.68-.97)	
65-75 years	.82 (.71-.95)	
>75 years	.77 (.64-.92)	
Stroke subtypes		.07
Ischemic	.79 (.71-.87)	
Hemorrhage	.80 (.61-1.05)	
Hyperlipidemia		<.001
Yes	.63 (.54-.74)	
No	.91 (.80-1.02)	

Abbreviation: CI, confidence interval.
*Adjusted for age, sex, socioeconomic status, comorbidity, and medication.

The mechanism underlying the association between statin treatment and decreased dementia risk in patients with stroke may be complex. First, several studies showed that atherosclerosis was involved in the pathogenesis of stroke and dementia. Chronic cerebral hypoxia and hypoperfusion secondary to atherosclerosis may contribute to white-matter lesions or leukoaraiosis, which may trigger and modify the progression of Alzheimer's disease and vascular dementia.[22] Statins may have antiatherocslerotic effects based on the improvement of endothelial dysfunction and reversal of coagulation and platelet abnormalities after statin treatment. A previous study showed that statins enhanced vasomotor reactivity and increased cerebral

blood flow in patients with subcortical vessel disease.[23] Second, cerebral ischemia increases the expression of amyloid precursor protein and reduces the clearance of β-amyloid from the brain, which are the pathological hallmarks of Alzheimer's disease.[24] Statins may reduce the production of β-amyloid by the inhibition of cholesterol biosynthesis to decrease amyloid production.[8] Third, patients with stroke often experience acute or chronic systemic inflammation. Several studies have suggested that increased systemic inflammation is associated with increased risk of dementia.[25] Statin treatment is associated with reduction in serum cytokine levels and C-reactive protein levels that might lower the risk of dementia in patients with stroke.[26]

The effect of statins on the risk of dementia among patients with stroke might differ on the basis of the potency and solubility of the statin treatment. An in vitro study revealed that the neuroprotective effect of statins was related to the ability of statins to penetrate the blood−brain barrier.[27] Some studies have found that higher the lipid-solubility of a statin, the greater its ability to cross the blood−brain barrier and affect the central nervous system. Our results were concurrent with those of previous studies that showed that the use of a lipophilic statin, but not a hydrophilic statin, might reduce the risk of further dementia in patients with stroke.[12,28] Many studies have demonstrated that statin potency is correlated with the protective effects of statins in cardiovascular and cerebrovascular diseases.[29] Our study also found that statin potency played an important role in reducing the risk of incident dementia. Reports have suggested an association between the risk of incident dementia and the cumulative duration of statin use among the patients with stroke.[30] Our studies also found that statin use for more than 1 year was associated with reduced risk of dementia.

In subgroup analyses, the significant protective effects of statins for incident dementia were only found in the stroke patients with hyperlipidemia but not in the stroke patients without hyperlipidemia, which may be ascribed from higher risks of dementia in patients with hyperlipidemia. Recent studies suggest that hyperlipidemia is a risk factor of cognitive impairment and dementia.[31,32] Our results indicated the clinical importance of statin use in the stroke patients with hyperlipidemia for preventing the risk of dementia. Further study is needed to confirm the hypothesis.

The strengths of our study included the use of a nationwide dataset, which can capture all validated cases of stroke from the entire country, and allow for continuous tracing of statin exposure duration and the risk of dementia for each case. In addition, we analyzed a large sample of subjects, with multiple comorbidities and abundantly prescribed comedications, which represents the population of patients with stroke in real-world practice setting. Finally, we used multiple strategies to minimize confounders and bias. The propensity score matching method was used to avoid bias owing to confounding by indication. We excluded patients with a history of statin prescription 1 year before the diagnosis of stroke to mitigate the prevalent user bias.[33] Nevertheless, some potential limitations should also be noted. First, the diagnosis of stroke and dementia was based on the ICD9-CM coding, and there were concerns regarding the accuracy of medical coding in the claims data. Coding of dementia from LHID was shown to have good validity in previous studies.[34] To ensure the accuracy of the diagnostic codes of stroke, only patients admitted for stroke with essential diagnostic procedures, including computed tomography scan or magnetic resonance imaging were enrolled; however, coding errors cannot be completely ruled out. However, the error might be equal between statin users and nonusers, and would not be expected to bias the associations. Second, although we used the propensity score matching method to balance a wide range of dementia risk factors between statin users and nonusers, we cannot rule out the effects of unmeasured confounders. Third, because of the inherent limitations of the insurance claims data, no information on other critical confounding variables such as lifestyle factors, education, and laboratory examinations was obtained for further analysis. Although we attempted to include comorbidities and insurable wages as proxies for health status and socioeconomic status in the models, they may not be perfect proxies. Fourth, Alzheimer's dementia and vascular dementia often co-occur as a mixed dementia, thereby complicating diagnosis. To accurately differentiate the Alzheimer's type and other types of dementia is difficult, owing to the frequently overlapping clinical features and related underlying pathology.[35] We did not distinguish the risks between statin use and Alzheimer's disease and other types of dementia. Finally, information regarding over-the-counter purchase of statins was not available in the claims database, which could lead to misclassification of exposure. However, this misclassification is unlikely because all statin products are reimbursable by the NHI program in Taiwan.

Conclusion

In this nationwide population-based cohort study, statin use was associated with decreased risk of dementia in patients with stroke. The use of high potency, lipophilic statins, and prolonged exposure to statins resulted in greater benefit for these patients. As statins are among the most prescribed medications for patients with stroke, and dementia is already a major cause of disability worldwide, these findings may be important and warrant further investigation. Further studies specifically designed for patients with stroke are warranted to investigate the underlying biological mechanisms that may mediate decreased dementia risk with statin use and confirm the

impact of statins on the dementia risk in this particular population.

References

1. Chan L, Lin YD, Liu CH. World Stroke Day in Taiwan: Raising Public Awareness of Stroke. Int J Gerontol 2017;10:175-179.
2. Hu HY, Chi WC, Chang KH, et al. The World Health Organization Disability Assessment Schedule 2.0 can predict the institutionalization of patients with stroke. Eur J Phys Rehabil Med 2017;53:856-862.
3. Ivan CS, Seshadri S, Beiser A, et al. Dementia after stroke: the Framingham Study. Stroke 2004;35:1264-1268.
4. Caratozzolo S, Mombelli G, Riva M, et al. Dementia after three months and one year from stroke: new onset or previous cognitive impairment? J Stroke Cerebrovasc Dis 2016;25:2735-2745.
5. Hu GC, Chen YM. Post-stroke dementia: epidemiology, mechanisms and management. Int J Gerontol. 2107;11:210-214.
6. Barba R, Morin MD, Cemillan C, et al. Previous and incident dementia as risk factors for mortality in stroke patients. Stroke 2002;33:1993-1998.
7. Pasquini M, Leys D, Rousseaux M, et al. Influence of cognitive impairment on the institutionalisation rate 3 years after a stroke. J Neurol Neurosurg Psychiatry 2007;78:56-59.
8. Tamboli IY, Barth E, Christian L, et al. Statins promote the degradation of extracellular amyloid {beta}-peptide by microglia via stimulation of exosome-associated insulin-degrading enzyme (IDE) secretion. J Biol Chem 2010;285:37405-37414.
9. Toyoda K, Minematsu K, Yasaka M, et al. The Japan Statin Treatment Against Recurrent Stroke (J-STARS) Echo Study: rationale and trial protocol. J Stroke Cerebrovasc Dis 2017;26:595-599.
10. Wassmann S, Laufs U, Baumer AT, et al. HMG-CoA reductase inhibitors improve endothelial dysfunction in normocholesterolemic hypertension via reduced production of reactive oxygen species. Hypertension 2001;37:1450-1457.
11. Beydoun MA, Beason-Held LL, Kitner-Triolo MH, et al. Statins and serum cholesterol's associations with incident dementia and mild cognitive impairment. J Epidemiol Community Health 2011;65:949-957.
12. Bettermann K, Arnold AM, Williamson J, et al. Statins, risk of dementia, and cognitive function: secondary analysis of the ginkgo evaluation of memory study. J Stroke Cerebrovasc Dis 2012;21:436-444.
13. Shepherd J, Blauw GJ, Murphy MB, et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. Lancet 2002;360:1623-1630.
14. Heart Protection Study Collaborative G. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet 2002;360:7-22.
15. Galatti L, Polimeni G, Salvo F, et al. Short-term memory loss associated with rosuvastatin. Pharmacotherapy 2006;26:1190-1192.
16. Wagstaff LR, Mitton MW, Arvik BM, et al. Statin-associated memory loss: analysis of 60 case reports and review of the literature. Pharmacotherapy 2003;23:871-880.
17. Meor Anuar Shuhaili MFR, Samsudin IN, Stanslas J, et al. Effects of different types of statins on lipid profile: a perspective on Asians. Int J Endocrinol Metab 2017;15:e43319.
18. Manktelow BN, Potter JF. Interventions in the management of serum lipids for preventing stroke recurrence. Cochrane Database Syst Rev 2009:CD002091.
19. Carlsson CM, Gleason CE, Hess TM, et al. Effects of simvastatin on cerebrospinal fluid biomarkers and cognition in middle-aged adults at risk for Alzheimer's disease. J Alzheimers Dis 2008;13:187-197.
20. Chen JM, Chang CW, Chang TH, et al. Effects of statins on incident dementia in patients with type 2 DM: a population-based retrospective cohort study in Taiwan. PLoS One 2014;9:e88434.
21. Chitnis AS, Aparasu RR, Chen H, et al. Use of statins and risk of dementia in heart failure: a retrospective cohort study. Drugs Aging 2015;32:743-754.
22. Snowdon DA, Greiner LH, Mortimer JA, et al. Brain infarction and the clinical expression of Alzheimer disease. The Nun Study. JAMA. 1997;277:813-817.
23. Giannopoulos S, Katsanos AH, Tsivgoulis G, et al. Statins and cerebral hemodynamics. J Cereb Blood Flow Metab 2012;32:1973-1976.
24. Whitehead SN, Cheng G, Hachinski VC, et al. Progressive increase in infarct size, neuroinflammation, and cognitive deficits in the presence of high levels of amyloid. Stroke 2007;38:3245-3250.
25. Swardfager W, Winer DA, Herrmann N, et al. Interleukin-17 in post-stroke neurodegeneration. Neurosci Biobehav Rev 2013;37:436-447.
26. Wang Q, Yan J, Chen X, et al. Statins: multiple neuroprotective mechanisms in neurodegenerative diseases. Exp Neurol 2011;230:27-34.
27. Riekse RG, Li G, Petrie EC, et al. Effect of statins on Alzheimer's disease biomarkers in cerebrospinal fluid. J Alzheimers Dis 2006;10:399-406.
28. Haag MD, Hofman A, Koudstaal PJ, et al. Statins are associated with a reduced risk of Alzheimer disease regardless of lipophilicity. The Rotterdam Study. J Neurol Neurosurg Psychiatry. 2009;80:13-17.
29. Dormuth CR, Hemmelgarn BR, Paterson JM, et al. Use of high potency statins and rates of admission for acute kidney injury: multicenter, retrospective observational analysis of administrative databases. BMJ 2013;346:f880. https://www.bmj.com/content/346/bmj.f880.long.
30. Wu CK, Yang YH, Lin TT, et al. Statin use reduces the risk of dementia in elderly patients: a nationwide data survey and propensity analysis. J Intern Med 2015;277:343-352.
31. Reitz C. Dyslipidemia and the risk of Alzheimer's disease. Curr Atheroscler Rep 2013;15:307.
32. Zambon D, Quintana M, Mata P, et al. Higher incidence of mild cognitive impairment in familial hypercholesterolemia. Am J Med 2010;123:267-274.
33. Ray WA. Evaluating medication effects outside of clinical trials: new-user designs. Am J Epidemiol 2003;158:915-920.
34. Lin FC, Chuang YS, Hsieh HM, et al. Early statin use and the progression of Alzheimer disease: a total population-based case-control study. Medicine (Baltimore) 2015;94:e2143.
35. Wiederkehr S, Simard M, Fortin C, et al. Comparability of the clinical diagnostic criteria for vascular dementia: a critical review. Part I. J Neuropsychiatry Clin Neurosci. 2008;20:150-161.