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