Early Statin Use and the Progression of Alzheimer Disease
A Total Population-Based Case-Control Study

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Abstract: The protective effect of statin on Alzheimer disease (AD) is still controversial, probably due to the debate about when to start the use of statin and the lack of any large-scale randomized evidence that actually supports the hypothesis. The purpose of this study was to examine the protective effect of early statin use on mild-to-moderate AD in the total Taiwanese population.

This was a total population-based case-control study, using the total population of Taiwanese citizens seen in general medical practice; therefore, the findings can be applied to the general population. The study patients were those with newly diagnosed dementia (ICD-9 290.x) and prescribed any acetylcholinesterase inhibitors (AChEIs) from the Taiwan National Health Insurance dataset in 1997 to 2008. The newly diagnosed eligible mild-to-moderate AD patients were traced from the dates of their index dates, which was defined as the first day to receive any AChEI treatment, back to 1 year (exposure period) to categorize them into AD with early statin use and without early statin use. Early statin use was defined as patients using statin before AChEI treatment. Alzheimer disease patients with early statin use were those receiving any statin treatment during the exposure period. Then, we used propensity-score-matched strategy to match these 2 groups as 1:1. The future randomized trial studies can confirm our findings.

There were 719 mild-to-moderate AD-paired patients with early statin use and without early statin use for analyses. Alzheimer disease progression was statistically lower in AD patients with early statin use than those without (P = 0.00054). After adjusting for other covariates, mild-to-moderate AD patients with early statin use exhibited a 0.85-risk (95% CI: 0.76–0.95; P = 0.0066) to have AD progression than those without.

Early statin use was significantly associated with a reduction in AD progression in mild-to-moderate AD patients. The future randomized trial studies can confirm our findings.

DOI: 10.1097/MD.0000000000000143

INTRODUCTION

Dementia is a chronic, progressive neurodegenerative disorder characterized by the decline of cognitive function. The World Health Organization (WHO) estimated that the proportion of dementia in the worldwide population aged 60 years and over will reach 22% by 2050.1 Alzheimer disease (AD) is the most common neurodegenerative dementia and is a leading cause of death in elderly persons.2 Evidence suggests that the precipitation of β-amyloid peptide and cholesterol homeostasis in the central nerve system play important roles in this multifactorial degenerative process.3–4 Thus, whether cholesterol-lowering agents such as statin can decrease the incidence/progression of AD has become a hot topic for research.

Statin use is associated with a decreased risk of cardiovascular ischemic events, statin was considered to have beneficial effects on neurodegeneration and cognitive functions through the inhibition of cholesterol biosynthesis to decrease amyloid production and tau hyperphosphorylation in the brain.5–6 However, these suggestive cognitive protective effects via statin use are still controversial, probably due to the debate about when to start the use of statin (before or after AD...
diagnosis) and what type (lipophilic or hydrophilic) of statin to use. Also, there is no any large-scale randomized evidence that actually supports the hypothesis. Thus, we hypothesized that the start of statin use before the diagnosis of mild-to-moderate AD can ameliorate the progression to severe AD and additionally, the protective potency between lipophilic and hydrophilic statins is different. To answer the aforementioned questions, we analyzed patients with mild-to-moderate AD in the total Taiwanese population in a period spanning >10 years (1997–2008).

**METHODS**

**Study Population and Data Collection**

The Taiwan National Health Insurance (NHI) dataset, run by the governmental authority as a mandatory and single-payer insurance system, was established on 01 March 1995 in Taiwan. After 1996, NHI claims data were digitalized and managed by Taiwan’s National Health Research Institutes, creating a large medical claims database known as the National Health Insurance Research Database (NHIRD). By December 2010, 23.074 million people were enrolled nationwide with a coverage rate of 99.6%.

Required by NHI Administration, the insurance system also records all patients with 30 categories of catastrophic illness such as malignant neoplasm, uremia, and chronic psychotic disorders that include dementia (International Classification of Diseases, Ninth Revision [ICD-9], code number 290.x), to become 1 NHI catastrophic illness registry file (eTable 1, http://links.lww.com/MD/A531). Patients with catastrophic illnesses were exempted from all copayment during the effective period in Taiwan, so the data are comprehensive.9,10

In Taiwan, before May 2010, only dementia patients with mild-or-moderate AD could be prescribed acetylcholinesterase inhibitors (AChEIs), including donepezil, rivastigmine, or galantamine, by Taiwan Neurology Society Board-certified neurologists and compensated by NHI for 1 year. If dementia patients become severe AD, based on the score of Clinical Dementia Rating (CDR), after 1 year, the prescription of AChEIs cannot be compensated by NHI and should no longer be supported by the government. Thus, our potential study patients were those with newly diagnosed dementia (ICD-9 290.x) and were prescribed any AChEIs from NHI catastrophic illness registry file between 01 January 1997 and 31 December 2008 in the entire Taiwan area. We excluded patients with (1) any diagnosis of cancer (ICD-9 140.xx-208.xx) and (2) age < 50 years and ≥ 80 years before the diagnosis of dementia. The index date was defined as the first date when the patient received the definite diagnosis of AD and started any AChEI treatment.

To get the permission of prescribing AChEIs for patients with mild-or-moderate AD, certified neurologists should send their patients’ detailed medical records to the Bureau of NHI for examination annually. The certified neurologists in Bureau of NHI thoroughly evaluated the patients’ medical history and a series of Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), biochemical laboratory data, brain image (Computer Tomography or Magnetic Resonance Imaging), Mini-Mental State Examination (MMSE), and CDR to judge whether the diagnostic criteria of mild-or-moderate AD was fulfilled and, if yes, the prescription of AChEI was granted and compensated by the NHI. CDR, a structured interview format, was used to assess current cognitive and functional status and its score is graded to mild (CDR = 1), moderate (CDR = 2), and severe (CDR = 3) in dementia patients. Thus, when the score of CDR was evaluated annually in AD patients increased from 1 or 2 to 3, which means from mild-to-moderate to severe, permission for prescribing AChEI granted by the Bureau of NHI was stopped.

**Propensity Score Matching**

The newly diagnosed eligible mild-to-moderate AD patients were traced from the dates of their index dates back to 1 year (exposure period) to categorize these AD patients into 2 groups: AD with early statins use and without early statins use. Early use of statin was defined as patients receiving any statin treatment in the exposure period.

Then, we used propensity-score-matched strategy to match the covariates, listed in Table 1 and eTable 2, http://links.lww.com/MD/A531, as 1:1 by using a “greedy” matching algorithm, with a maximum caliper of 0.1, for analysis.12,13 The matched study patients were followed up from their index dates until the stop of AChEI prescription, being dis-enrolled from the NHI program, death, up to 5 years from the index date, or the end of the study date (31 December 2008), whichever came first. This study was approved by the Institutional Review Board of Kaohsiung Medical University Hospital (KMUH). Because the patient identifiers are scrambled to the public for research purposes to protect confidentiality, the requirement for written or verbal consent from patients for data linkage study was waived.

**Use of Statins**

The detailed information about the prescription of statins in the exposure period were retrieved from both the inpatient and outpatient pharmacy prescription databases, which include drug types, dosage, started and ended dates of prescription, and total number of pills dispensed. According to their pharmacokinetic characteristics, statins were further classified into lipophilic and hydrophilic molecules. Lipophilic molecules included simvastatin, lovastatin, fluvastatin, and atorvastatin, whereas hydrophilic ones included pravastatin and rosuvastatin. The defined daily dose (DDD), a unit for assessing the standard dose of statins recommended by the WHO, was calculated. For example, the DDD was 15 mg for simvastatin, 10 mg for atorvastatin, and 20 mg for pravastatin. Then, cumulative DDD (cDDD) as the sum of dispensed DDD in the exposure period was calculated.

**Potential Confounders**

Information about age, gender, income, and co-morbidities, including hypertension, diabetes, cardiac dysrhythmia, congestive heart failure (CHF), peripheral artery disease (PAD), peptic ulcer, ischemic stroke, and ischemic heart disease (IHD), were also collected (eTable 2, http://links.lww.com/MD/A531). Comorbidities were defined in a patient if he or she was diagnosed for any of the aforementioned diseases on at least 2 outpatient claims or 1 inpatient claim during the exposure period.

To control for confounding agents, we included drugs that could potentially accelerate or reduce inflammation or cognitive function in the model. These drugs were anticoagulants, nonsteroidal anti-inflammatory agents (NSAID), antidepressants, benzodiazepine, and corticosteroid. Exposure to these drugs was defined as having a prescription of 1 of them at least 1 day after the index date to the occurrence of any event related to this study, being dis-enrolled from the NHI program, death, up to 5 years from the index date, or the end of the study period (31 December 2008), whichever came first.
Ascertaining of AD Patients With AChEIs Use
To evaluate the accuracy of information about the diagnosis of AD patients and the use of AChEIs, we searched any patients with both the diagnosis of ICD-9 290.x and the prescription of any AChEIs between 01 January 1998 and 31 December 1999 in KMUH, 1 medical center located in southern Taiwan. A total of 410 eligible patients were identified by the hospital computer. We randomly retrieved 100 medical charts from 100 case patients to comprehensively review their medical records up to 31 December 2013. After the exclusion of 11 patients who were not regularly followed-up in KMUH for 1 year and over, the remaining 89 patients were checked for information about the continuation of prescribing any AChEI and the score of CDR each year for 5 years. We found that 31 mild-to-moderate AD patients had CDR decline to become severe AD, and only 1 of them was continuously prescribed AChEIs. In contrast, none of the 58 mild-to-moderate AD patients who did not have CDR decline had their prescription of AChEIs stopped. The diagnostic accuracy of mild-to-moderate AD was 98.9% (88/89).

Statistical Analyses
Demographic characteristics, comorbidities, and potential confounding agents were tabulated by chi square or Fisher exact test, whichever appropriate, between 2 groups: mild-to-moderate AD with early statin use versus without early statin use. Kaplan–Meier analysis and log-rank testing were used to compare the distributions of mild-to-moderate AD progression in these 2 groups. The analysis of early statin use was also further categorized by lipophilic or hydrophilic. Cox proportional hazards modeling was used to compute hazard ratio (HRs) and 95% confidence interval (CI) for mild-to-moderate AD progression. The supremum test was performed for testing proportional hazards assumption. Covariates in the models were performed in 2 steps: (1) only include age, sex, diabetes, and hypertension, which were the most important factors for AD and (2) include all covariates listed in Table 1. Each participant accumulated person-time beginning from the index date until the termination of AChEIs prescription, dis-enrolment from the NHI program, death, up to 5 years from the index date, or the end of the study date (31 December 2008), whichever came first. The dose-response of cumulative statin use (cDDD) on the risk of mild-to-moderate AD progression was also calculated by quartile. Data analysis was performed using the SAS 9.3 statistical package; all \( P \)-values were 2-sided.

RESULT
The NHI catastrophic illness registry file contained 1,521,214 patients from the period of 01 January 1997 and 31 December 2008 (Fig. 1). In total, 6431 newly diagnosed
mild-to-moderate AD patients were included in this study. Among them, 724 patients were fulfilled mild-to-moderate AD with early statin use. After propensity score matching, 719 mild-to-moderate AD patients with early statin use were able to match 719 mild-to-moderate AD patients without early statin use for the final analyses. All covariates were comparable after matching (Table 1; eTable 3, http://links.lww.com/MD/A531). The percent of daily statin use in 719 mild-to-moderate AD patients with early statin use was 3–4% before the index date and, after the index date, the percent of daily statin use in 719 mild-to-moderate AD patients with early statin use started to approach that of patients without early statin use (eFigure 1, http://links.lww.com/MD/A531).

Among the 719 mild-to-moderate AD patients with early statin use, 581, 97, and 46 patients were prescribed lipophilic-only, hydrophilic-only, and both respectively, during the exposure period (Figure 1). Even excluding 46 patients prescribed both lipophilic and hydrophilic statins during the exposure period, all covariates were still comparable between AD patients with early statin use and without early statin use (eTable 4, http://links.lww.com/MD/A531).

Cumulative survival probability of AD progression was statistically lower in mild-to-moderate AD patients with early statin use than those without early statin use (P = 0.00054; Figure 2A). The significant protective effect of AD progression was more prominent in the lipophilic-only group (Figure 2B). After adjusting for age, sex, hypertension, and diabetes, mild-to-moderate AD patients with early statin use exhibited a 0.86-risk (95% CI = 0.77–0.96) to have AD progression than those without early statin use (P = 0.0099, Table 2, eTable 5, http://links.lww.com/MD/A531). The beneficial effects were still significant after further adjusting for other covariates (HR = 0.85, 95% CI = 0.76–0.96, P = 0.0066). Figure 3 shows the beneficial effects preventing AD progression was present in mild-to-moderate AD patients with early lipophilic-only statin use, but not in those with early hydrophilic-only statin use. The supremum test showed our data followed the proportional hazards assumption (P = 0.4180).

**DISCUSSION**

This study found that early statin use in mild-to-moderate AD patients was significantly associated with a reduction in AD progression.
aggravation. In addition, that beneficial effect was from lipophilic statin. To our best knowledge, this is the first population-based propensity-matched cohort study to explore the link between early use of statin and the risk of AD progression.

Cholesterol and its transport have been shown to be involved in the regulation of amyloid-beta peptides in senile plaques and tau hyperphosphorylation in neurofibrillary tangles, which are the pathological hallmarks of AD. Elevated cholesterol at the lipid rafts of the neuronal membrane, which contain the beta and gamma secretases, will result in increased cleavage of amyloid precursor protein (APP). The cleavage of APP by beta and gamma secretases results in nonsoluble products that aggregate as oligomers, protofibrils, and senile neuritic plaques. Statins inhibit the enzyme HMG-CoA reductase that catalyzes the rate-limiting step in cholesterol biosynthesis to reduce levels of circulating cholesterol and inhibit de novo cholesterol synthesis in the brain. Thus, statins may decrease amyloid-beta production and tau hyperphosphorylation in the brain. Besides, AD is associated with cerebrovascular damage and cerebral hypoperfusion. The progression of neuron loss and cognitive deterioration of Alzheimer disease are preceded by a slow decline in neurovascular regulation. Cerebral ischemia increases the expression of amyloid precursor protein and reduces the clearance of amyloid-β from the brain. Statins may increase endothelial nitric oxide synthase and reduce endothelin-1, leading to vasodilatation and increase in cerebral perfusion. In the studies of in vitro or in vivo, statin was proposed to have some neuroprotective effects through the

FIGURE 1. Study flowchart. AD = Alzheimer diseases, NIH = National Insurance Health. Index date (Day 0) indicates date of starting anti-AD agent.

Patients in the NIH catastrophic illness registry file during 01 January 1997 and 31 December 2008 (n = 1,521,214)

Patients with newly-diagnosed dementia (ICD code: 290.x) (n = 26,956)

3,834 Excluded Age < 50 or ≥ 80 yrs

Patients with dementia whose age 50-79 yrs (n = 23,122)

16,691 Excluded No prescription of any anti-AD agents (donepezil, rivastigmine, or galantamine)

Mild-to-moderate AD (n = 6,431)

Dichotomized by any prescription of statin between one year before index date and at index date (Day -365-0)

AD with early statin use, n = 724

AD without early statin use, n = 5,707

Matching by propensity score as 1 : 1 (5 patients cannot be matched)

AD with early statin use, n = 719

AD without early statin use, n = 719

Additional analysis, 46 Excluded

Prescription of both lipophilic and hydrophilic statin

AD with early statin use, n = 678

Lipophilic (n = 581) vs. hydrophilic (n = 97)
mechanisms of anti-inflammatory, antioxidant, and antithrombotic actions, and thus the decrease of amyloid-beta production.\textsuperscript{18,19} However, in human studies, although most observational studies have found a significantly lower risk of dementia or incident AD in statin users, the subsequent randomized controlled trials did not show the beneficial effect of statin on dementia patients who were already treated by AChEIs.\textsuperscript{20–23} The discrepancy in findings were attributed to the optimal timing of starting statin therapy in dementia patients, suggesting statins may exert any beneficial effects only before the presence of obvious deterioration of neurodegenerative diseases.

The findings in our cohort study, designed to examine the effect of statin use 1 year before the definite diagnosis of mild-to-moderate AD that was confirmed by the starting prescription of AChEIs from Taiwan NHI catastrophic illness registry file, further agreed with the importance of choosing the optimal timing to start statin therapy on AD patients. Indeed, 1 recent longitudinal observational study showed that early use of statin was beneficial for cognitive decline in normal cognitive

![Kaplan-Meier survival estimates](image1.png)

**FIGURE 2.** Rate of AD progression in mild-to-moderate AD patients categorized by early statin use: (A) with early statin use versus without early statin use; (B) with early lipophilic statin use or early hydrophilic statin use versus without early statin use. AD = Alzheimer diseases.
subjects but not in patients with mild cognitive impairment. However, the limitations of that observational study were (1) self-reported use of statin, and (2) other existing comorbid conditions such as ischemic heart disease, congestive heart failure, and stroke and other medication use such as aspirin, anticoagulant, and benzodiazepine were not considered.

We found that the use of lipophilic statin, but not hydrophilic statin, could ameliorate mild-to-moderate AD progression, probably because lipophilic statin can cross the blood–brain barrier (BBB) to produce its beneficial effect. Riekse and colleagues measured the levels of 1 AD biomarker, phospho-tau-181 (p-tau181) in cerebrospinal fluid (CSF) after a 14-week treatment with simvastatin (a BBB permeant statin; n = 10) at 40 mg/day or pravastatin (a BBB impermeant statin; n = 13) at 80 mg/day in hypercholesterolemic subjects without dementia. They found simvastatin, but not pravastatin, reduced CSF p-tau181 levels in all subjects. Another similar experimental study, conducted by Vuletic and co-workers, used the same statins, same dosage, and same number of adults with intact cognition and modest hypercholesterolemia as the study from Riekse et al and found simvastatin, but not pravastatin, significantly increased CSF phospholipid transfer protein (PLTP) activity (P = 0.005), which can decrease p-tau181 levels in AD patients. These studies concluded that lipophilic statin, but not hydrophilic statin, can penetrate BBB to affect several important pathological biomarkers related to AD in CSF. However, in human observational studies, the evidence for lipophilic and hydrophilic statins on dementia or AD have been inconsistent. Some studies showed the equal beneficial effect of lipophilic and hydrophilic statins on neurodegenerative diseases, whereas others found that lipophilic statin reduced the risk of the occurrence of dementia or AD than did hydrophilic statin. Our findings were more consistent with the latter results.

This study also found that diabetes and congestive heart failure (CHF) are the risk factors of AD progression which are consistent with previous studies. The pathophysiology of developing or aggravating AD by diabetes were proposed from (1) the increase of β-amyloid peptide levels and deposition in the brain, (2) the cause of cerebrovascular dysregulation, and (3) the alteration of insulin signaling in the brain, which affects neuronal functions. For CHF, brain hypoperfusion is probably the main contributor for the onset of neurodegenerative diseases such as dementia and AD. Although this study covered almost all mild-to-moderate AD patients in the entire Taiwan area and spanned >10 years (1997–2008), this is still observational data which is inferior to a randomized trial design. To minimize the inherent bias of the observational study, we identified the study drug exposure before the index date and matched this by using the propensity score to increase the comparability of 2 study groups. However, even well-designed observational studies cannot be guaranteed to avoid all potential sources of moderate bias. Consequently, large randomized trials would be needed to reliably confirm (or refute) the associations reported in this paper. Another limitation is that the information about personal lifestyle habits such as smoking, alcohol consumption, and physical activity is not well recorded in the database.
as smoking and biochemical laboratory data such as blood sugar, cholesterol, and apolipoprotein E was not considered.

In conclusion, early statin use is significantly associated with a reduction in AD progression in mild-to-moderate AD patients and the beneficial effect is probably from lipophilic statin. Future studies could implement multiarmed randomized trials to compare the statin effect before and after AD aggravation and the beneficial effect between lipophilic and hydrophilic statins.27

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