Discontinuation of statin therapy associates with Parkinson disease

A population-based study

Yen-Chieh Lee, MD*
Chin-Hsien Lin, MD, PhD*
Ruey-Meei Wu, MD, PhD
Min-Shung Lin, MD
Jou-Wei Lin, MD, PhD
Chia-Hsuin Chang, MD, PhD
Mei-Shu Lai, PhD

Correspondence to Dr. Lin: jouweilin@yahoo.com.tw or Dr. Chang: chiahsuin123@yahoo.com.tw

ABSTRACT

Objective: To evaluate the effect of discontinuing statin therapy on incidence of Parkinson disease (PD) in statin users.

Methods: Participants who were free of PD and initiated statin therapy were recruited between 2001 and 2008. We examined the association between discontinuing use of statins with different lipophilicity and the incidence of PD using the Cox regression model with time-varying statin use.

Results: Among the 43,810 statin initiators, the incidence rate for PD was 1.68 and 3.52 per 1,000,000 person-days for lipophilic and hydrophilic statins, respectively. Continuation of lipophilic statins was associated with a decreased risk of PD (hazard ratio [HR] 0.42 [95% confidence interval 0.27–0.64]) as compared with statin discontinuation, which was not modified by comorbidities or medications. There was no association between hydrophilic statins and occurrence of PD. Among lipophilic statins, a significant association was observed for simvastatin (HR 0.23 [0.07–0.73]) and atorvastatin (HR 0.33 [0.17–0.65]), especially in female users (HR 0.11 [0.02–0.80] for simvastatin; HR 0.24 [0.09–0.64] for atorvastatin). As for atorvastatin users, the beneficial effect was seen in the elderly subgroup (HR 0.42 [0.21–0.87]). However, long-term use of statins, either lipophilic or hydrophilic, was not significantly associated with PD in a dose/duration-response relation.

Conclusions: Continuation of lipophilic statin therapy was associated with a decreased incidence of PD as compared to discontinuation in statin users, especially in subgroups of women and elderly. Long-term follow-up study is needed to clarify the potential beneficial role of lipophilic statins in PD. ***Neurology***® **2013;81:410–416**

GLOSSARY

ATC = anatomical therapeutic chemical; **CI** = confidence interval; **COPD** = chronic obstructive lung disease; **CoQ10** = coenzyme Q10; **HMG-CoA** = 3-hydroxy-3-methylglutaryl coenzyme A; **HR** = hazard ratio; ***ICD-9-CM*** = *International Classification of Diseases*, ninth revision, clinical modification; **LDL** = low-density lipoprotein; **NHI** = National Health Insurance; **NHIRD** = National Health Insurance Research Database; **NSAID** = nonsteroidal anti-inflammatory drugs; **PD** = Parkinson disease.

Parkinson disease (PD) is a common neurodegenerative disorder[1] for which causes are diverse and that involves neuroinflammation cascade.[2–5] Given that there is no mechanism-based treatment to ameliorate dopaminergic neuron loss, agents that can attenuate neuroinflammatory processes may play a role in halting the degeneration process of PD.

Statins, which are inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase,[6] have been shown to have potent anti-inflammatory effects.[7–10] Additionally, statins could reduce intraneuronal α-synuclein aggregations in animal models of PD.[11] These observations led to the hypothesis that statins may have a protective role for PD. However, given that HMG-CoA reductase is also involved in the synthesis of coenzyme Q10 (CoQ10),[12] the possible favorable effects of statins could be offset by their potential detrimental effects on lowering the level of plasma CoQ10.[13]

Editorial, page 406

Supplemental data at www.neurology.org

Studies have been conducted to examine the association between statin use and PD risk with inconsistent results.[14–21] Most of these studies depend on self-reported questionnaires to gather

*These authors contributed equally to this work.

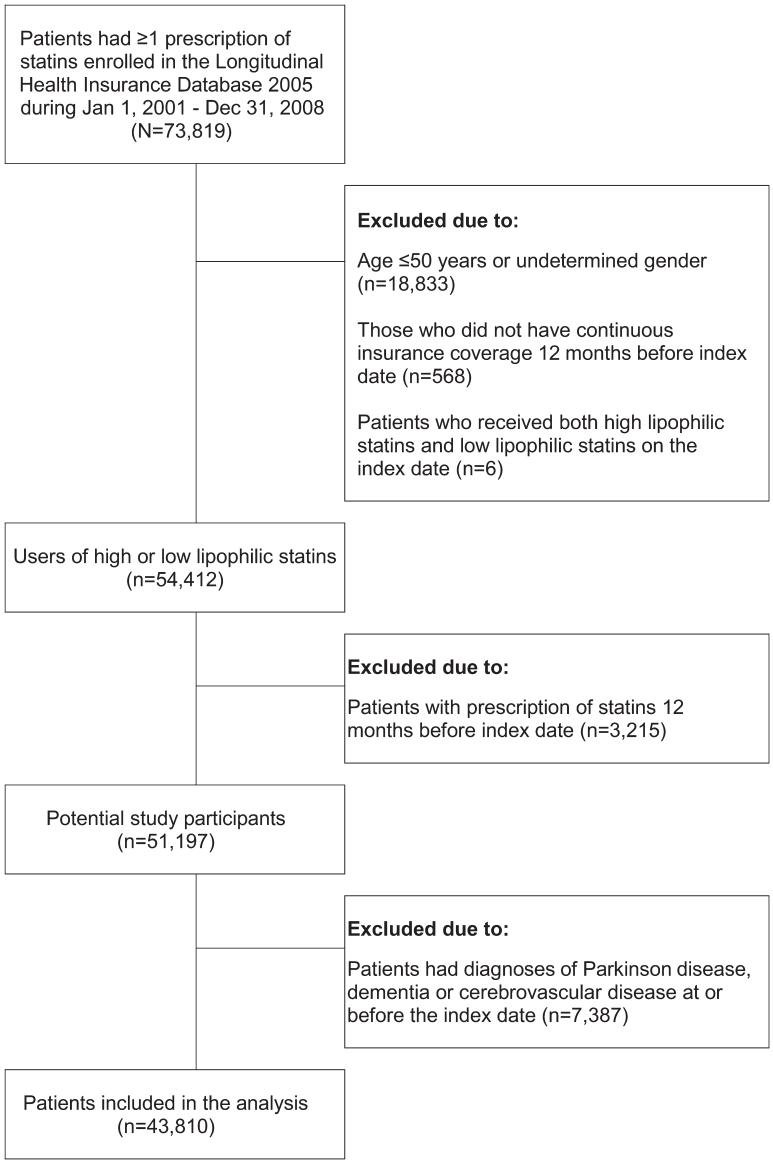
From the Department of Family Medicine (Y.-C.L., M.-S.L), Cathay General Hospital, Taipei; the Departments of Neurology (C.-H.L., R.-M.W.) and Medicine (C.-H.C.), National Taiwan University Hospital, Taipei; Department of Medicine, College of Medicine (J.-W.L., C.-H.C.), and Institute of Preventive Medicine, College of Public Health (C.-H.C., M.-S.L.), National Taiwan University, Taipei; and Cardiovascular Center (J.-W.L.), National Taiwan University Hospital Yun-Lin Branch, Dou-Liou City, Yun-Lin County, Taiwan.

Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

the information on statin use and some studies failed to control several important confounders such as comorbidity of diabetes mellitus[22] and use of nonsteroidal anti-inflammatory drugs (NSAID),[23] antidiabetics,[24] and calcium channel blockers,[25] which have been shown to modulate the risk of PD and are medications frequently used by statin users.

Given that Taiwan's National Health Insurance Reimbursement Policy requested physicians to discontinue statin therapy once low-density lipoprotein (LDL) cholesterol levels reached treatment goal (less than 100 mg/dL), this allowed us to evaluate the effect of discontinuing statins on risk of PD in statin users.

Figure **Flow chart of the study cohort assembly from prescriptions in Taiwan's National Health Insurance Research Database**



METHODS **Data source.** A single-payer and compulsory National Health Insurance program was implemented in Taiwan in 1995. Enrollment rate was 98.4% in 2007. The National Health Insurance Research Database (NHIRD) is a research database developed at the National Health Research Institute, with linked data from the demographic and enrollment records, hospital claims, ambulatory care visits, and pharmacy dispensing claims from hospitals, outpatient clinics, and community pharmacies. The Longitudinal Health Insurance Database 2005 comprises a random sample of 1 million subjects from the NHIRD with longitudinally linked data available from 1997 through 2009. Our source population comprised all beneficiaries from the Longitudinal Health Insurance Database 2005 who were at least 50 years of age on January 1, 2001.

Standard protocol approvals. The study was approved by the National Taiwan University Hospital Research Ethics Committee (study ID: 201210066RIC) and informed consent was waived due to analyzing the previously stored de-identified medical information from the National Health Insurance (NHI) database.

Study population. From the source population, we identified patients who initiated simvastatin, fluvastatin, lovastatin, atorvastatin, pravastatin, and rosuvastatin (anatomical therapeutic chemical [ATC] classification system codes are provided in table e-1 on the *Neurology*® Web site at www.neurology.org) between January 1, 2001, and December 31, 2008. Initiation was defined as free of any prescription of statin therapy 12 months prior to the first prescription (index date). Exclusion criteria were 1) age more than 100 years, 2) patients who did not have continuous insurance coverage 12 months before the index date, 3) patients who received lipophilic and hydrophilic statins on the index date, and 4) patients who had ever had the inpatient or outpatient diagnoses of PD before the index date.

Use of study drugs. We collected information on prescribed drug types, dosage, date of prescription, supply days, and total number of pills dispensed from the outpatient pharmacy prescription database. Every person-day during the study period was classified into current statin use and nonuse. Current use was defined as use during the period between the prescription start date and the end of the days of supply. Statin use was further classified according to the pharmacokinetic characteristics of the various statins: simvastatin, lovastatin, fluvastatin, and atorvastatin are lipophilic molecules, whereas pravastatin and rosuvastatin are more hydrophilic.[26] We defined discontinuation of statin therapy if no medication refill was available. Due to highly variable treatment patterns during the follow-up period, a given patient was allowed to contribute person-days into both "continuing use" and "discontinuation" categories in case of no endpoint occurrence.

Ascertainment of PD. The outcome of interest was defined as having any hospital discharge diagnosis or any outpatient diagnosis of PD by neurologists (*ICD-9-CM* code 332). Because it is possible that patients with atypical or secondary parkinsonism may be misdiagnosed with idiopathic PD, we also excluded patients who had ever had the diagnoses of dementia or cerebrovascular diseases at or 1 year before the index date. A previous validation study using a hospital administrative database reported a positive predictive value more than 90% using this definition.[27] A patient would be considered as an incident case of PD if the diagnosis was made after statin initiation. To minimize the influence of false-positive cases, we conducted a sensitivity analysis and used a more stringent definition of PD: *ICD-9-CM* code of 332.0 and received medical treatment for PD (i.e., levodopa, carbidopa, bromocriptine mesylate, pergolide mesylate, amantadine, selegiline, cabergoline, ropinirole, pramipexole). Patients were followed from the index date to the earliest

Table 1 Demographic data, comorbidities, medication use, and resource utilization of the study population and risk factors associated with Parkinson disease (n = 43,810)

	Total population (n = 43,810)	OR (95% CI)
Patient characteristics		
Age at statin initiation, y, mean (SD)	63.2 (8.91)	1.10 (1.08–1.11)
Male, %	41.1	0.82 (0.66–1.03)
Initiation year, %		
2001	8.10	1.07 (1.00–1.14)
2002	10.6	
2003	13.2	
2004	15.0	
2005	12.6	
2006	13.3	
2007	13.3	
2008	14.0	
Cormorbidities, %		
Hypertension	51.0	1.43 (1.15–1.78)
Diabetes mellitus	40.5	1.02 (0.82–1.27)
Ischemic heart disease	20.5	1.81 (1.44–2.29)
Heart failure	4.59	1.53 (0.97–2.40)
Migraine	1.89	1.28 (0.64–2.59)
Gout	16.1	1.06 (0.80–1.41)
Peripheral vascular disease	1.83	1.28 (0.60–2.70)
Chronic liver disease	15.7	0.96 (0.71–1.29)
Chronic obstructive pulmonary disease	14.2	1.44 (1.09–1.89)
Chronic kidney disease	10.7	1.55 (1.15–2.09)
Seizure	0.49	1.49 (0.37–5.95)
Rheumatoid arthritis	3.49	1.06 (0.59–1.88)
Osteoarthritis	21.9	1.54 (1.22–1.96)
Osteoporosis	7.17	1.44 (1.02–2.03)
Depression	3.89	2.40 (1.62–3.56)
Anxiety disorder	14.9	1.53 (1.17–2.01)
Bipolar disorder	0.34	1.80 (0.45–7.24)
Psychotic disorder	0.49	2.17 (0.70–6.76)
Upper gastrointestinal bleeding	33.2	1.67 (1.34–2.08)
Peptic ulcer disease	18.5	1.77 (1.40–2.25)
Cancer	3.88	1.21 (0.71–2.06)
Medication use, %		
COX-2 nonselective NSAIDs	76.6	1.26 (0.95–1.65)
COX-2 selective NSAIDs	6.73	2.50 (1.83–3.41)
Antiplatelet agents	38.6	1.75 (1.41–2.17)
Warfarin	0.89	0.77 (0.19–3.09)
ACE inhibitors/angiotensin receptor blockers	40.6	1.22 (0.98–1.52)
β-Blockers	39.7	1.64 (1.32–2.03)
Calcium channel blockers	45.8	1.81 (1.45–2.26)

Continued

of outcome occurrence, last hospital discharge date or date of last outpatient visit, or December 31, 2009.

To evaluate the accuracy of the PD diagnostic criteria in our study, we performed a validation study using the medical records of patients who were consecutively diagnosed with PD and received long-term follow up at the National Taiwan University Hospital, a tertiary referral center in Taiwan, during 2002 to 2010. A movement disorder specialist (C.H.L.) evaluated the medical records of these subjects. A total of 1,985 patients with PD were confirmed by critical medical record review. Among these clinically confirmed patients, 1,883 (94.8%) were identified using the diagnostic criteria in our main study (based on *ICD-9-CM* code), suggesting a good diagnostic accuracy of our study criteria.

Covariate ascertainment and adjustment. We used inpatient and outpatient diagnosis files and prescription files during the 12-month period before the index date to ascertain patients' history of hypertension; diabetes mellitus; cardiovascular, peripheral vascular, cerebrovascular, chronic kidney, and liver disease; neurologic and psychiatric disorders; musculoskeletal and gastrointestinal diseases; cancer (*ICD-9-CM* codes provided in table e-1); and use of cyclooxygenase-2 selective and nonselective NSAID, antiplatelet agents, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, β-blockers, calcium channel blockers, other antihypertensive agents, nitrates, insulin, oral antidiabetics, fibrates, diuretics, antiarrhythmic agents, antipsychotics, antidepressants, antiepileptics, thyroid therapy drugs, and antigout preparations (ATC codes provided in table e-1). Of note, we use the diagnosis of chronic obstructive lung disease (COPD) as a proxy for heavy smoking. We also collected patient information on age, sex, and resource utilization (number of outpatient visits, number of hospitalizations, number of laboratory test measurements) 12 months prior to the index date.

Statistical analysis. Baseline characteristics, comorbidities, medication use, and resource utilization among overall study population were presented. For all cohort members, we computed their person-days of follow-up in each statin use category. We estimated the incidence rates and their 95% confidence interval (CIs) of PD on a Poisson distribution.

Because laboratory results were not available in the claims database and patients with hypercholesterolemia who did not receive statin treatment could not be identified, the comparison of statin users with nonusers is susceptible to confounding by indication. Due to Taiwan's National Health Insurance Reimbursement Policy request, statin discontinuation was most likely because patients' serum LDL cholesterol had reached appropriate levels. Therefore, we examined the effect of statin therapy on risk of PD by comparing the occurrence of PD during continuation of statin therapy with that during statin discontinuation among statin initiators. Cox regression model with time-varying statin use was used to calculate the hazard ratios (HRs) and their 95% CIs. We also examined potential dose- or duration-response relation of statin use on incidence of PD between statin users and another control group of nonusers. We hypothesized that subjects with highest cumulative use of statin would be associated with a lower PD incidence as compared with those without use or lowest cumulative statin users.

Because the number of PD cases was small in comparison to the number of covariates that reflected participants' baseline characteristics, we included disease risk score deciles as summary measures of all these covariates in the regression model to adjust for baseline imbalance. With a logistic regression model, we estimated the disease risk score, i.e., the probability of developing

Table 1 Continued

	Total population (n = 43,810)	OR (95% CI)
Other antihypertensive agents	10.6	1.26 (0.72–1.74)
Nitrates	15.7	2.09 (1.64–2.66)
Antidiabetic agents	34.8	1.07 (0.85–1.34)
Insulin	4.04	1.56 (0.97–2.50)
Fibrates	13.2	1.03 (0.76–1.39)
Diuretics	25.9	2.16 (1.73–2.69)
Antiarrhythmic agents	2.33	1.88 (1.08–3.28)
Estrogen	5.75	1.01 (0.67–1.53)
Digoxin	2.78	1.27 (0.70–2.32)
Antipsychotics	10.6	1.53 (1.13–2.07)
Antidepressants	9.05	1.58 (1.14–2.18)
Antiepileptics	6.02	2.95 (2.17–4.01)
Thyroid therapy	2.22	1.20 (0.62–2.32)
Antigout preparations	16.9	1.30 (1.00–1.69)

Abbreviations: ACE = angiotensin-converting enzyme; CI = confidence interval; COX = cyclooxygenase; NSAID = nonsteroidal anti-inflammatory drugs; OR = odds ratio.

PD, using indicators for individual statin use, as well as age, sex, initiation year, underlying diseases, and concomitant medications, 12 months prior to the index date.[28] In addition, time-varying medication use including other group of statins, antihypertensives, antidiabetes, antiplatelets, NSAID, and antipsychotics were also adjusted in the outcome model as these drugs were reported to be associated with PD occurrence.

In the sensitivity analyses, we investigated whether effect estimates would change by using traditional multivariable regression model or by more strict definition of outcome (PD diagnosis and treatment). Additionally, stratified analyses were performed to evaluate potential effect modification. Participants were further stratified according to 1) age (<65, ≥65 years) and 2) sex (men, women). A test of interaction was performed using likelihood ratio test. Two-sided p value <0.05 was considered to be statistically significant. All statistical analyses were performed with SAS 9.2 (SAS Institute, Cary, NC).

RESULTS After excluding subjects who did not meet our study criteria, a total of 43,810 statin initiators were included in the analysis (figure). Among the statin initiators enrolled in our study, several baseline characteristics were associated with increased incidence of PD, including age, hypertension, ischemic heart disease, COPD and chronic kidney disease, osteoarthritis, osteoporosis, depression, anxiety disorder, upper gastrointestinal bleeding, and peptic ulcer disease (table 1). Meanwhile, uses of cyclooxygenase-2-selective NSAID, antiplatelet agents, β-blockers, calcium channel blockers, nitrates, diuretics, antiarrhythmic agents, antipsychotics, antidepressants, and antiepileptics were also associated with higher incidence of PD (table 1).

Table 2 Person-days, number of events, and crude incidence rates for Parkinson disease associated with lipophilic and hydrophilic statin use

	Lipophilic statins	Hydrophilic statins
Exposed person-days	14,870,157	3,982,188
Number of events	25	14
Crude incidence rate per 1,000,000 person-days (95% CI)	1.68 (1.02–2.34)	3.52 (1.67–5.36)

Abbreviation: CI = confidence interval.

The incidence rate for PD was 1.68 and 3.52 per 1,000,000 person-days for lipophilic and hydrophilic statins, respectively (table 2). As compared with statin discontinuation, continuing use of lipophilic statins was associated with a decreased risk of PD with the adjusted HR of 0.42 (95% CI 0.27–0.64). The protective association of continuing lipophilic statin therapy persisted in the sensitivity analysis while using traditional multivariable regression model or using stricter outcome definition (table 3). The reduced risk seemed to be nonsignificantly more obvious in women than in men, but without obvious difference between different age groups (table 4). Of note, among lipophilic statins, a significantly reduced risk effect for PD was observed for simvastatin and atorvastatin, with only a trend toward decreased risk of PD in lovastatin and fluvastatin (table e-2). Similarly, the protective effect was more obvious in female users of simvastatin and atorvastatin (table e-3). As for atorvastatin users, the beneficial effect was also seen in the elderly subgroup with age more than 65 years. In contrast, there was no association between PD and use of hydrophilic statins, with neither age nor sex difference (tables 3 and 4).

With regard to the concerns that patients who continued on the statins would have higher levels of LDL cholesterol than those who discontinued and hence may have a higher mortality that resulted in a lower incidence of PD, we examined the mortality rate in statin continuation and discontinuation. We observed that in the status of statin discontinuation, there were 869 deaths/51,085,753 person-days. For statin continuation, there were 39 deaths/16,448,171 person-days for lipophilic statin use and 18 deaths/4,484,067 person-days for hydrophilic statin use. There was a significantly decreased risk of death for continuing lipophilic statin use as compared to discontinuation (HR 0.31; 95% CI 0.18–0.54), and only a trend for hydrophilic statin use (HR 0.48; 95% CI 0.23–1.00). These results showed that statin continuation, especially lipophilic statins, results in lowered chance of dying as compared to statin discontinuation.

In the context that PD is a progressive neurodegenerative disorder, we also examined the chronic cumulative effect of statin use on risk of PD, especially lipophilic ones. We did not find any association between higher cumulative dose of lipophilic statins as compared with nonusers or lowest cumulative use (data not shown). There was also no dose or

Table 3 Hazard ratios for Parkinson disease associated with lipophilic and hydrophilic statin use

	Lipophilic statins, HR (95% CI)		Hydrophilic statins, HR (95% CI)	
	Crude HR	Adjusted HR[a]	Crude HR	Adjusted HR[a]
Statin discontinuation	Reference	Reference	Reference	Reference
Main analysis	0.48 (0.32–0.73)	0.42 (0.27–0.64)	1.20 (0.70–2.05)	0.95 (0.55–1.65)
Sensitivity analysis 1[b]		0.46 (0.30–0.71)		0.98 (0.56–1.69)
Sensitivity analysis 2[c]	0.48 (0.32–0.72)	0.44 (0.29–0.66)	1.11 (0.65–1.90)	0.91 (0.53–1.58)

Abbreviations: CI = confidence interval; HR = hazard ratio.
[a] Adjusted for baseline disease risk score, time-varying comorbidities, and medication use (lipophilic or hydrophilic statins, antihypertensives, antidiabetes, antiplatelets, nonsteroidal anti-inflammatory drugs, antipsychotics, ischemic heart disease, heart failure, chronic kidney disease, and chronic obstructive pulmonary disease).
[b] Multivariable analysis, adjusted for baseline demographic data (age, sex, index year of first statin prescribed), comorbidities (hypertension, diabetes mellitus, ischemic heart disease, myocardial infarction, angina, heart failure, migraine, chronic kidney disease, chronic liver disease, chronic obstructive pulmonary disease, rheumatoid arthritis, osteoarthritis, upper gastrointestinal bleeding, peptic ulcer disease, cancer, thyroid disease, gout, seizure disorder, depressive disorder, anxiety disorder, psychotic disorder, bipolar disorder, peripheral vascular disease, and osteoporosis), medication use (nonsteroidal anti-inflammatory drugs, selective and nonselective, antiplatelet, anticoagulant, vasodilators, calcium channel blocker, fibrates, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, antiarrhythmics, β-blockers, diuretics, oral hyperglycemic agents, insulin, antihypertensives, estrogen, digoxin, antipsychotics, antidepressants, antiepileptics, thyroid-therapy medications, uric acid–lowering agent), and time-varying comorbidities and medication use (lipophilic or hydrophilic statins, antihypertensives, antidiabetes, antiplatelets, nonsteroidal anti-inflammatory drugs, antipsychotics, ischemic heart disease, heart failure, chronic kidney disease, and chronic lung disease).
[c] Outcome defined as having diagnosis and treatment for Parkinson disease.

duration response relation between use of lipophilic statins and incidence of PD for the subgroups of men or women and those aged <65 or ≥65 years.

DISCUSSION Our study demonstrated that continuing use of lipophilic statins has a decreased association with PD as compared to statin discontinuation in statin users, especially for simvastatin and atorvastatin, after adjusting for age, sex, comorbidities, and other potential confounder medications. The potential beneficial effect was not observed in users of hydrophilic statins. Chronic cumulative use of lipophilic statins did not reveal significant association with PD as compared to the nonstatin users or users with the lowest cumulative dose.

Due to the amphiphilic side chain in their molecular structures, lipophilic statins are able to cross the blood–brain barrier more readily than hydrophilic statins.[26] These good penetration abilities into the neuronal and glial cells could be associated with more antioxidant and anti-inflammatory effects than the hydrophilic statins. Among the individual type of lipophilic statins, the strength of the inverse association with PD risk was most significant in simvastatin and atorvastatin. Lovastatin and fluvastatin also showed a trend toward reduced risk of PD. Two prospective studies showed that simvastatin use was associated with a lower PD risk as compared to nonusers,[16,19] which suggested that all statins may not be the same in terms of PD protection. Animal studies have shown that oral administration of simvastatin attenuated the percentage of dopamine depletion in striatum caused by neurotoxin in a dose-dependent manner.[29] The combination

Table 4 Disease modification effect associated with lipophilic and hydrophilic statin use on Parkinson disease incidence among patients stratified by sex and age

	Lipophilic statins		Hydrophilic statins	
	Crude HR	Adjusted HR[a]	Crude HR	Adjusted HR[a]
Sex				
Female (n = 25,811)	0.37 (0.21–0.67)	0.33 (0.18–0.58)	0.80 (0.36–1.81)	0.63 (0.27–1.42)
Male (n = 17,999)	0.47 (0.23–0.97)	0.45 (0.21–0.94)	0.94 (0.35–2.55)	0.80 (0.29–2.21)
Age, y				
≥65 (n = 17,625)	0.43 (0.26–0.71)	0.40 (0.24–0.67)	1.10 (0.56–2.14)	0.92 (0.47–1.82)
<65 (n = 26,185)	0.40 (0.16–0.99)	0.39 (0.16–0.98)	0.92 (0.29–2.92)	0.83 (0.24–2.64)

Abbreviation: HR = hazard ratio. Data are presented as hazard ratio (95% confidence interval).
[a] Adjusted for baseline disease risk score, time-varying comorbidities, and medication use (lipophilic or hydrophilic statins, antihypertensives, antidiabetes, antiplatelets, nonsteroidal anti-inflammatory drugs, antipsychotics, ischemic heart disease, heart failure, chronic kidney disease, and chronic obstructive pulmonary disease).

of its strong efficacy and high lipid permeability gives simvastatin unique pharmacologic properties as compared with the other statins, which could explain the strongest association with the decreased risk of PD in our findings.

Since PD is a neurodegenerative disorder with a long presymptomatic period,[30] there may be a window of opportunity for modification of the disease process before onset of motor symptoms. In this context, we speculated that lipophilic statins may act through modifying the level or sensitivity of dopamine receptors in striatum, rather than holding the neuronal degeneration process. Supportively, previous animal study has demonstrated that simvastatin reversed the downregulation of dopamine D1 and D2 receptor expression in 6-hydroxydopamine-induced parkinsonian rats, with normalized dopamine receptors in striatum.[30] These enhancing effects on striatal dopamine receptors caused by simvastatin were significant when given for 4 weeks, which was a short time period.[31] Notably, one recent study showed that simvastatin treatment could regulate the expression of NMDA receptor through anti-inflammatory mechanisms within 3 weeks in experimental parkinsonian models.[32] Based on these findings, it is pharmacologically reasonable that the observed protective effect of lipophilic statins may be due to the regulation of expression of dopamine or nondopamine receptors, rather than decreasing the dopaminergic neuron cell death. Further experimental studies are needed to confirm our findings.

We observed that the protective effect of continuing use of lipophilic statins might be different for women and men. Numerous observations have suggested that PD seems to occur less commonly in women than men. One recent meta-analysis has confirmed a significantly higher incidence rate of PD among men with the relative risk being 1.5 times greater in men than women.[33] One of the possible reasons comes from the neuroprotective effect by estrogen.[33] Further research is needed to explore the potential sex difference in PD risk.

The strength of our study is the enrollment of a nationally representative cohort of a large sample size. We analyzed the effects of individual type of statins according to their lipophilicity. The information regarding statin use is obtained by linking to the NHI pharmacy database rather than self-reported questionnaires to reduce exposure misclassification. Furthermore, covariates including underlying diseases (especially diabetes mellitus),[22] medication use, and health care utilization prior to statin initiation were taken into consideration. We also adjusted the use of medications that potentially may affect PD risk such as NSAID,[23] antidiabetic agents,[24] calcium channel blockers,[25] and neuroleptic agents. However, there are several limitations. First, although we analyzed health care records from a national representative dataset of 1 million people, there were still few PD cases to allow us to have a precise estimation. Second, smoking is well known for its negative association with PD. We were unable to directly control for smoking due to lack of data. Instead, we adjusted for COPD, since it may serve as a proxy for heavy smoking. Other PD risk factors, such as consumption of tea or coffee, pesticide exposure, and other lifestyle-related factors, were not included in the study. However, residual confounding by smoking and other factors cannot fully explain the observed protective association because they were not likely to be related to statin discontinuation. Third, our diagnosis of PD was based on the diagnosis code from the NHI database; therefore, we were not able to distinguish primary and secondary parkinsonism. Nonetheless, we tried to validate our diagnosis by using a more stringent definition of PD (*ICD-9-CM* code and medical treatment for PD) in the sensitivity analysis and reviewing large-scale medical records in the validation assay. However, given that all the medical information from the NHI database was de-identified due to ethical privacy concern, we could not recognize all the PD-diagnosed subjects in our study and therefore did not have the opportunity to review all their medical charts. Fourth, we could not exclude the possibility that the observed association was due to sick-stopper effect (nonadherence to medication due to higher risk) or protopathic bias (early PD symptoms leading to statin discontinuation). However, in that case, continuing use of both lipophilic and hydrophilic statin would be associated with lower risks, not just lipophilic statins. Finally, information regarding the serum level of lipid metabolism, such as cholesterol and LDL, which has been shown to be associated with risk of PD,[20,34,35] was not available in the claims dataset. Further longitudinal study including measures of cholesterol levels over time is needed to clarify the interrelated roles of LDL cholesterol, statin use, and PD.

We observed that continuation of lipophilic statin therapy had a decreased association with PD as compared with discontinuation among statin users. Further long-term follow-up study is needed to confirm the potential beneficial role of lipophilic statins in PD.

AUTHOR CONTRIBUTIONS

Study concept and design: Y.-C. Lee, C.-H. Chang, J.-W. Lin. Acquisition of data: M.-S. Lai. Analysis and interpretation of data: C.-H. Lin, Y.-C. Lee, C.-H. Chang, J.-W. Lin. Drafting of the manuscript: C.-H. Lin, Y.-C. Lee. Critical revision of the manuscript for important intellectual content: C.-H. Lin, M.-S. Lin, J.-W. Lin, C.-H. Chang, R.-M. Wu. Statistical analysis: Y.-C. Lee. Obtained funding: M.-S. Lai. Study supervision: M.-S. Lai.

STUDY FUNDING

Supported in part by Taiwan Ministry of Education grant 98HP0021, which did not play any role in the study design, collection, analysis,

and interpretation of data, in report writing, or in the decision to submit the paper for publication.

DISCLOSURE

The authors report no disclosures relevant to the article. This study is based in part on data from the National Health Insurance Research Database provided by the Bureau of National Health Insurance, Department of Health, and managed by National Health Research Institutes. The interpretation and conclusions contained herein do not represent those of the Bureau of National Health Insurance, Department of Health, or National Health Research Institutes. Go to Neurology.org for full disclosures.

Received December 16, 2012. Accepted in final form April 1, 2013.

REFERENCES

1. Forno LS. Neuropathology of Parkinson's disease. J Neuropathol Exp Neurol 1996;55:259–272.
2. Schapira AH, Gu M, Taanman JW, et al. Mitochondria in the etiology and pathogenesis of Parkinson's disease. Ann Neurol 1998;44:S89–S98.
3. Jenner P. Oxidative stress in Parkinson's disease. Ann Neurol 2003;53(suppl 3):S26–S36.
4. Hirsch EC, Hunot S. Neuroinflammation in Parkinson's disease: a target for neuroprotection? Lancet Neurol 2009; 8:382–397.
5. Mogi M, Kondo T, Mizuno Y, Nagatsu T. p53 protein, interferon-gamma, and NF-kappaB levels are elevated in the parkinsonian brain. Neurosci Lett 2007;414:94–97.
6. Mann D, Reynolds K, Smith D, Muntner P. Trends in statin use and low-density lipoprotein cholesterol levels among US adults: impact of the 2001 National Cholesterol Education Program guidelines. Ann Pharmacother 2008;42:1208–1215.
7. Cucchiara B, Kasner SE. Use of statins in CNS disorders. J Neurol Sci 2001;187:81–89.
8. Wang Q, Yan J, Chen X, et al. Statins: multiple neuroprotective mechanisms in neurodegenerative diseases. Exp Neurol 2011;230:27–34.
9. Wood WG, Eckert GP, Igbavboa U, Muller WE. Statins and neuroprotection: a prescription to move the field forward. Ann NY Acad Sci 2010;1199:69–76.
10. Devaraj S, Chan E, Jialal I. Direct demonstration of an antiinflammatory effect of simvastatin in subjects with the metabolic syndrome. J Clin Endocrinol Metab 2006;91:4489–4496.
11. Bar-On P, Crews L, Koob AO, et al. Statins reduce neuronal alpha-synuclein aggregation in in vitro models of Parkinson's disease. J Neurochem 2008;105:1656–1667.
12. Shults CW, Oakes D, Kieburtz K, et al. Effects of coenzyme Q10 in early Parkinson disease: evidence of slowing of the functional decline. Arch Neurol 2002;59:1541–1550.
13. Mortensen SA, Leth A, Agner E, Rohde M. Dose-related decrease of serum coenzyme Q10 during treatment with HMG-CoA reductase inhibitors. Mol Aspects Med 1997; 18(suppl):S137–S144.
14. Becker C, Jick SS, Meier CR. Use of statins and the risk of Parkinson's disease: a retrospective case-control study in the UK. Drug Saf 2008;31:399–407.
15. Gao X, Simon KC, Schwarzschild MA, Ascherio A. Prospective study of statin use and risk of Parkinson disease. Arch Neurol 2012;69:380–384.
16. Hippisley-Cox J, Coupland C. Unintended effects of statins in men and women in England and Wales: population based cohort study using the QResearch database. BMJ 2010;340:c2197.
17. Ritz B, Manthripragada AD, Qian L, et al. Statin use and Parkinson's disease in Denmark. Mov Disord 2010;25:1210–1216.
18. Wahner AD, Bronstein JM, Bordelon YM, Ritz B. Statin use and the risk of Parkinson disease. Neurology 2008;70: 1418–1422.
19. Wolozin B, Wang SW, Li NC, Lee A, Lee TA, Kazis LE. Simvastatin is associated with a reduced incidence of dementia and Parkinson's disease. BMC Med 2007;5:20.
20. Huang X, Chen H, Miller WC, et al. Lower low-density lipoprotein cholesterol levels are associated with Parkinson's disease. Mov Disord 2007;22:377–381.
21. Samii A, Carleton BC, Etminan M. Statin use and the risk of Parkinson disease: a nested case control study. J Clin Neurosci 2008;15:1272–1273.
22. Schernhammer E, Hansen J, Rugbjerg K, Wermuth L, Ritz B. Diabetes and the risk of developing Parkinson's disease in Denmark. Diabetes Care 2011;34:1102–1108.
23. Driver JA, Logroscino G, Lu L, Gaziano JM, Kurth T. Use of non-steroidal anti-inflammatory drugs and risk of Parkinson's disease: nested case-control study. BMJ 2011;342:d198.
24. Wahlqvist ML, Lee MS, Hsu CC, Chuang SY, Lee JT, Tsai HN. Metformin-inclusive sulfonylurea therapy reduces the risk of Parkinson's disease occurring with type 2 diabetes in a Taiwanese population cohort. Parkinsonism Relat Disord 2012;18:753–758.
25. Marras C, Gruneir A, Rochon P, et al. Dihydropyridine calcium channel blockers and the progression of parkinsonism. Ann Neurol 2012;71:362–369.
26. Schachter M. Chemical, pharmacokinetic and pharmacodynamic properties of statins: an update. Fundam Clin Pharmacol 2005;19:117–125.
27. Hernan MA, Logroscino G, Rodriguez LA. A prospective study of alcoholism and the risk of Parkinson's disease. J Neurol 2004;251(suppl 7):vII14–17.
28. Zhou Z, Rahme E, Pilote L. Are statins created equal? Evidence from randomized trials of pravastatin, simvastatin, and atorvastatin for cardiovascular disease prevention. Am Heart J 2006;151:273–281.
29. Selley ML. Simvastatin prevents 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced striatal dopamine depletion and protein tyrosine nitration in mice. Brain Res 2005;1037:1–6.
30. Hawkes CH, Del Tredici K, Braak H. A timeline for Parkinson's disease. Parkinsonism Relat Disord 2010 Feb;16:79–84.
31. Wang Q, Wang PH, McLachlan C, Wong PT. Simvastatin reverses the downregulation of dopamine D1 and D2 receptor expression in the prefrontal cortex of 6-hydroxydopamine-induced parkinsonian rats. Brain Res 2005;1045: 229–233.
32. Wang Q, Ting WL, Yang H, Wong PT. High doses of simvastatin upregulate dopamine D1 and D2 receptor expression in the rat prefrontal cortex: possible involvement of endothelial nitric oxide synthase. Br J Pharmacol 2005;144:933–939.
33. Yan J, Xu Y, Zhu C, et al. Simvastatin prevents dopaminergic neurodegeneration in experimental parkinsonian models: the association with anti-inflammatory responses. PLoS One 2011;6:e20945.
34. Wooten GF, Currie LJ, Bovbjerg VE, Lee JK, Patrie J. Are men at greater risk for Parkinson's disease than women? J Neurol Neurosurg Psychiatry 2004;75:637–639.
35. de Lau LM, Koudstaal PJ, Hofman A, Breteler MM. Serum cholesterol levels and the risk of Parkinson's disease. Am J Epidemiol 2006;164:998–1002.