

**ORIGINAL ARTICLE**

Association Between Statin Use and Mortality in Adults With Parkinson's Disease: A Nationwide Cohort Study

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ABSTRACT

Objective The impact of statin use on the progression and survival of patients with Parkinson's disease (PD) remains unclear. Moreover, evidence in Asian populations is limited. This study aimed to assess the associations between statin prescription, cumulative dosage, and all-cause mortality in PD patients.

Methods This retrospective cohort study was conducted using sample data obtained from the Korean National Health Insurance Service (KNHIS) claims database. The study included 3,152 adults who were diagnosed with PD and whose history of statin use and cumulative dose information were obtained from claims records. Data were collected from the KNHIS database, and all eligible participants were followed longitudinally to determine all-cause mortality. The primary outcome was all-cause mortality, and the exposures were statin use (yes or no) and cumulative dose. The analysis was conducted using Cox proportional hazards regression adjusted for relevant covariates.

Results Statin use was associated with a lower risk of all-cause mortality (hazard ratio [HR], 0.600; 95% confidence interval [CI], 0.521–0.691). Among statin users, a higher cumulative statin dose was linked to a further reduction in mortality (HR, 0.800; 95% CI, 0.761–0.842).

Conclusion Statin use and increased cumulative exposure were associated with reduced all-cause mortality in patients with PD, and these findings suggest a potential survival benefit and warrant further investigation in diverse populations.

Keywords Parkinson's disease; Statin; Adults; Cohort study.

INTRODUCTION

Parkinson's disease (PD) is the second most common neuro-

degenerative disorder and is characterized by progressive degeneration of the nigrostriatal system and a range of motor and nonmotor symptoms.¹ The specific pathophysiology of PD re-

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mains unknown; however, several pathomechanisms, including abnormal protein homeostasis, oxidative stress, neuroinflammation, and lipid metabolism disturbance, are believed to contribute to the development and progression of PD.^{1,2} Large-scale genome sequencing studies of patients with PD have revealed risk gene loci and several known gene mutations linked to PD, suggesting that lipid homeostasis disturbance may contribute to the development of disease.³ Statins block cholesterol biosynthesis, are widely prescribed for the primary and secondary prevention of cardiovascular and cerebrovascular diseases,^{4,5} and are known for their potential neuroprotective effects through their pleiotropic actions.⁶

Nevertheless, the role of statins in PD remains controversial. Several *in vitro* and *in vivo* studies have shown that statins may have beneficial effects by inhibiting α -synuclein aggregation and protecting against dopaminergic neuronal death via the modulation of oxidative stress and inflammatory processes.⁷⁻⁹ In addition, epidemiological studies have demonstrated that statin therapy is associated with a lower risk of PD,^{10,11} thus supporting the results of previous preclinical studies. Conversely, another observational study suggested that the low incidence of PD may be primarily attributed to high cholesterol levels,¹² given that patients with PD exhibit reduced cholesterol biosynthesis.¹³ Moreover, recent epidemiological studies have suggested that statin use increases the risk of PD in several populations.^{12,14,15}

Notably, the effects of statin therapy on longitudinal outcomes in patients with PD have not been thoroughly examined. Research has suggested that statins have the ability to slow the progression of motor deficits and cognitive impairment^{16,17}; however, a recent study revealed an association between statin use, low baseline dopamine transporter availability, and poor prognosis in drug-naïve patients with PD.¹⁸ Therefore, the effect of statin therapy on the long-term outcomes of patients with PD remains undetermined.

Therefore, we aimed to investigate the association between statin prescription and all-cause mortality in patients with PD using data from a national sample cohort obtained from the Korean National Health Insurance Service (KNHIS). We investigated the longitudinal association between statin use and overall mortality in patients with PD both qualitatively and quantitatively.

MATERIALS & METHODS

Data source

The KNHIS is a comprehensive national claims database that provides various medical information for research purposes,

such as patient demographics, diagnoses, procedures, surgical histories, and prescribed medications.¹⁹ In this study, we selected a study cohort whose medical records were recorded in the Korean National Health Insurance Service–National Sample Cohort (KNIHS-NSC) database from 2007 to 2019. The KNIHS-NSC is a cohort of approximately 1 million individuals and is designed to be representative of the entire South Korean population.¹⁹ For this study, we utilized patient data, including the identification of PD patients, history of comorbidities, and drug prescription data extracted from the period from 2007 to 2019. The data were extracted and analyzed in January 2023. The KNHIS provided deidentified health information. This study was approved by the Institutional Review Board of Wonju Severance Hospital (Ref# CR323356), and informed consent was waived by the institutional review board. The research protocol adhered to the principles of the Declaration of Helsinki and its subsequent revisions.

Study population

The Rare Intractable Disease Registration Program was initiated in South Korea in 2004 for conditions such as PD. In the present study, participants with PD were defined as individuals who satisfied both of the following criteria to ensure diagnostic validity: 1) the G20 code (International Classification of Diseases, 10th Revision [ICD-10]) identified in the type-of-disease table, which contains master diagnostic information, and 2) the V124 code (rare intractable disease registration code for PD) identified in the statement table, which contains claim details generated at each medical visit. By requiring codes from both the master diagnostic records and visit-specific claim details, we aimed to identify PD patients more accurately than by using claim codes alone. We included patients aged >18 years who were newly diagnosed with PD between January 1, 2007, and December 31, 2019. Among those, we excluded patients with duplicate medical records, missing data in health insurance quantiles, and outliers regarding total statin dose (defined as any value >1.5 times the interquartile range of the total dose range). Patients who were subsequently diagnosed with PD before January 1, 2009, were excluded from the analysis. This exclusion was based on the findings of a previous study, which indicated that at least 2 years of prediagnosis prescription data are necessary to define the exposure to statin therapy operationally. Thus, this study enrolled patients who had been diagnosed with PD between 2009 and 2019 ($n=3,219$), and the exclusion of missing covariates and outliers of total statin dose resulted in the inclusion of 3,152 subjects in the analysis. The study cohort selection procedures are presented in Figure 1.

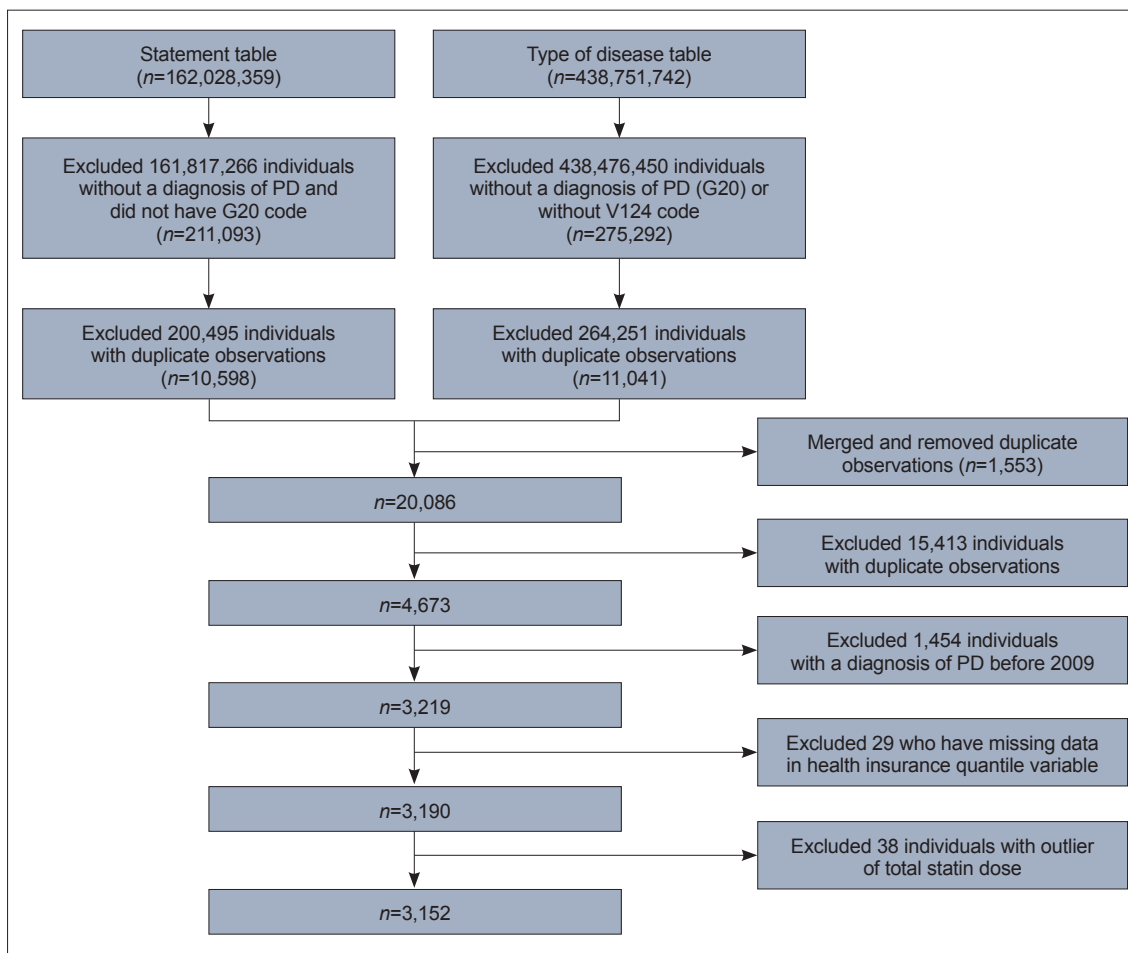


Figure 1. Flowchart of participant enrollment. PD, Parkinson's disease.

Assessment of statin use

Statin use was evaluated by extracting information from the KNHIS database using statin prescription codes (Supplementary Table 1). The participants were divided into two groups, the ever-statin group and the never-statin group, according to their history of statin prescription. The ever-statin group was defined as individuals who had been prescribed statins at least once in the 2 years preceding the date of PD diagnosis or at least once since the date of PD diagnosis. The never-statin group comprised individuals who had never been prescribed statin medication during the study period. The cumulative duration of statin prescription for each individual was computed by aggregating the total number of days for which statins were prescribed throughout the observation period. The formula for calculating total statin use is as follows: total defined daily dose (DDD) = (prescribed daily dose of statin/DDD of the statin) × (number of days prescribed). Since participants received either hydrophilic or lipophilic statins during the observation period, the cumulative doses of hydrophilic statins (atorvastatin, simv-

astatin, pitavastatin, lovastatin, and fluvastatin) and lipophilic statins (rosuvastatin and pravastatin) were calculated separately.

Covariates

The study covariates included age at PD diagnosis, sex, income level, Charlson Comorbidity Index (CCI), hypertension, dyslipidemia, osteoporosis, and levodopa equivalent daily dose (LEDD). Age was calculated on the basis of age at the time of PD diagnosis. Income levels were categorized into three groups using health insurance decile data. The CCI was derived from the number of concomitant diseases for 13 chronic diseases that were disclosed, excluding sensitive information. Hypertension, dyslipidemia, and osteoporosis were classified according to the disease codes in the disease type table (hypertension codes I100, I101, and I109; dyslipidemia code E78; osteoporosis codes M80, M81, and M82). The 13 covariates and three chronic diseases (hypertension, dyslipidemia, and osteoporosis) were coded as 1 if the cases occurred within 1 year before being diagnosed with PD; otherwise, they were coded as 0. The LEDD was cal-

culated at the time of enrollment²⁰ and transformed by obtaining the logarithm of the LEDD to increase normality and obtain accurate values for survival analysis.

Mortality outcomes

The causes of death were determined by comparing the National Health Insurance Service data with the death certificate data. The following causes of death were categorized into eight groups on the basis of the ICD-10 codes: infection (A00-B99), neurological diseases (G00-G99), circulatory diseases (I00-I99), pulmonary diseases (J00-J99), digestive diseases (K00-K93), neoplasms (C00-D48), metabolic diseases (E00-E99), and genitourinary diseases (N00-N99).

Statistical analysis

Population characteristics were analyzed using independent *t*-tests for continuous variables and chi-square tests for categorical variables. Survival time analysis was conducted by comparing the ever-statin and never-statin groups using Kaplan-Meier curves. Univariate and multivariate Cox regression analyses were conducted to investigate the association between statin use and the survival rate of participants with PD in 3 individual models (Model 1: unadjusted; Model 2: age, sex, and income level as covariates; Model 3: age, sex, income level, CCI, presence of hypertension, dyslipidemia and osteoporosis, and initial LEDD as covariates). Survival time was defined as the time from PD diagnosis to death. For individuals who died before January 1, 2020, the year of diagnosis was subtracted from the year of death. For those who died after December 31, 2019, and those who were alive, the date of diagnosis was subtracted from the end date of observation.

In addition to the comparison of ever-statin versus never-statin use, we performed dose-response analyses using the cumulative statin dose as a continuous variable and a categorized variable to quantitatively investigate the longitudinal association between statin use and mortality. We categorized cumulative statin exposure into 3 groups (1–365 DDD, 366–730 DDD, and DDD>730) to facilitate interpretability and to evaluate potential threshold effects. Statistical significance was set at $p<0.05$. All analyses were performed using SAS software version 9.4 (SAS Institute).

Sensitivity analyses

To investigate whether the effects of lipophilic statins and hydrophilic statins differ, we performed a sensitivity analysis of the cumulative dose of hydrophilic statins and lipophilic statins as independent variables using Cox regression analysis adjusted for study covariates, including sex, age, insurance premium quintile, CCI, and LEDD. In addition, as demographic charac-

teristics, including sex, age at diagnosis, CCI, and the incidence of diabetes, hypertension, dyslipidemia, and osteoporosis, significantly differed between the never-statin and ever-statin groups, we performed subgroup analyses using the inverse probability of treatment weighting (IPTW) method to minimize the confounding effects of those variables. Among the matched samples, we investigated the association between statin use and survival rates by adjusting for study covariates, including age, sex, insurance premium quintile, CCI, and LEDD. To mitigate possible immortal time bias, we analyzed the effect of time-dependent statin use on the risk of mortality using time-dependent Cox regression analysis. To elucidate the effects of statin use on cardiovascular and neurological mortality, we performed separate Cox regression analyses for cardiovascular mortality and neurological mortality. To consider the possible association between lipids and mortality, we conducted analyses in a subpopulation whose blood lipid profiles were available at baseline. In these models, baseline low-density lipoprotein (LDL) cholesterol was included as an additional independent variable, and we also constructed models in which LDL cholesterol, high-density lipoprotein (HDL) cholesterol, total cholesterol, and triglycerides were included as additional independent variables.

RESULTS

Baseline characteristics of the study participants

The demographic characteristics of the study participants are presented in Table 1. A total of 3,152 adults with PD were included in the analysis, of which 1,755 (55.68%) were statin users. The cohort included more female patients ($n=1,805$; 57.27%). In the ever-statin group, there were 1,097 female patients (62.51%) and individuals with two or more chronic diseases ($n=1,068$, 60.85%). The initial LEDD values of the ever- and never-statin groups were 366.9 mg (standard deviation [SD]=476.4) and 379.3 mg (SD=583.5), respectively, which were not significantly different. The total person-years of follow-up duration was 15,805 years, with 9,203 person-years in the ever-statin group and 6,602 person-years in the never-statin group. The mean observation period (SD) was longer in the ever-statin group (5.2 [2.9] years) than in the never-statin group (4.7 [2.8] years, $p<0.0001$).

Mortality

During the follow-up period, 956 (30.3%) patients died, with 476 deaths (27.1%) in the ever-statin group and 480 (34.4%) in the never-statin group. The Kaplan-Meier curve revealed significantly higher mortality in the never-statin group than in the ever-statin group (log-rank $p<0.0001$) (Figure 2).

Cox regression analysis

Cox regression analysis revealed that statin use was associated with a lower risk of mortality in Model 1 (hazard ratio [HR]

0.691; 95% confidence interval [CI] 0.608–0.784; $p<0.0001$), Model 2 (HR 0.727; 95% CI 0.640–0.826; $p<0.0001$), and Model 3 (HR 0.600; 95% CI 0.521–0.691; $p<0.0001$) (Table 2). Cox re-

Table 1. Demographic characteristics of study participants

Variables	Total samples (n=3,152)	Statin use		p
		Yes (n=1,755)	No (n=1,397)	
Age at diagnosis (yr)	71.36±9.88	71.87±8.55	70.72±11.31	0.0012
Sex				<0.0001
Male	1,347 (42.73)	658 (37.49)	689 (49.32)	
Female	1,805 (57.27)	1,097 (62.51)	708 (50.68)	
Observation period (yr)	5.0±2.9	5.2±2.9	4.7±2.8	<0.0001
Person-years	15,805	9,203	6,602	
Income levels				0.2823
Q1 (lowest)	787 (24.97)	425 (24.22)	362 (25.91)	
Q2	831 (26.36)	454 (25.87)	377 (26.99)	
Q3 (highest)	1,534 (48.67)	876 (49.91)	658 (47.10)	
CCI				<0.0001
0	912 (28.93)	422 (24.05)	490 (35.08)	
1	585 (18.56)	265 (15.10)	320 (22.91)	
≥2	1,655 (52.51)	1,068 (60.85)	587 (42.02)	
Hypertension (Yes)	1,318 (41.81)	888 (50.60)	430 (30.78)	<0.0001
Diabetes (Yes)	936 (29.70)	648 (36.92)	288 (20.62)	<0.0001
Dyslipidemia (Yes)	1,406 (44.61)	1,097 (62.51)	309 (22.12)	<0.0001
Osteoporosis (Yes)	741 (23.51)	473 (26.95)	268 (19.18)	<0.0001
Initial LEDD (mg)	373.9±539.0	366.9±476.4	379.3±583.5	0.5270
Statin usage				
Statin prescription day		1,213.7±1,057.5	-	
Total DDD		1,681.7±1,363.1	-	

Values are presented as mean±standard deviation or n (%).

CCI, Charlson Comorbidity Index; DDD, defined daily dose; LEDD, levodopa equivalent daily dose.

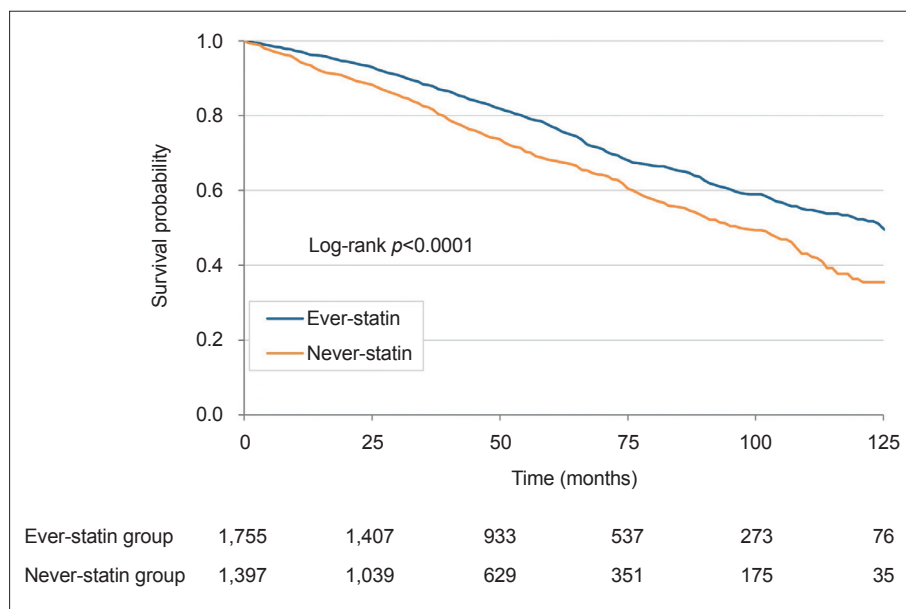


Figure 2. Kaplan–Meier estimates of the probability of survival in the ever-statin group vs. the never-statin group.

gression analysis revealed that a higher total dose of statins (DDD) was associated with reduced mortality in Model 1 (HR 0.855, 95% CI 0.813–0.896; $p<0.0001$), Model 2 (HR 0.860, 95% CI 0.820–0.902; $p<0.0001$), and Model 3 (HR 0.800, 95% CI 0.761–0.842; $p<0.0001$) (Table 3). When cumulative statin DDDs were categorized, participants with >730 DDDs had a lower risk of mortality in Model 1 (HR 0.604, 95% CI 0.524–0.695, $p<0.0001$), Model 2 (HR 0.631, 95% CI 0.547–0.727, $p<0.0001$), and Model 3 (HR 0.487, 95% CI 0.401–0.590, $p<0.0001$) (Table 4). However, those with 1–365 DDDs and 366–730 DDDs had a comparable risk of mortality. Cox regression sensitivity analysis revealed that both a higher total dose of hydrophilic statins (HR 0.904, 95% CI 0.875–0.934; $p<0.0001$) and lipophilic statins (HR 0.912, 95% CI 0.878–0.947; $p<0.0001$) were associated with reduced mortality independent of covariates among the ever-statin group (Supplementary Table 2).

Causes of death

Comparisons of the causes of death between the ever-statin and never-statin groups are shown in Supplementary Figure 1.

A statistically significant difference in the cause of death was observed between the two groups ($p=0.002$). The most common cause of death in the ever-statin group was neurological disease ($n=135$; 28.6%), followed by circulatory disease ($n=87$; 18.4%). The most common cause of death in the never-statin group was neurological disease ($n=170$, 35.6%), similar to that in the ever-statin group. Other diseases ($n=73$, 15.3%) were the second most common cause of death in the never-statin group. Among the 305 neurological deaths, 271 were attributed to PD and 1 to secondary parkinsonism, with the remainder due to various other neurological causes (Supplementary Table 3).

Sensitivity analyses

After propensity score matching using the IPTW method, demographic characteristics, including age at diagnosis, sex, CCI, initial LEDD, income level, and the presence of diabetes, hypertension, dyslipidemia, and osteoporosis, were comparable between the ever-statin and never-statin groups (Supplementary Table 4). The standardized mean differences (SMDs) between the two groups revealed that the data were adequately

Table 2. Cox proportional hazard regression analysis on the risk of all-cause mortality according to the statin use

	PD (n)	Mortality (n)	Person-years	Mortality rate	Model 1		Model 2		Model 3	
					HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
Never-statin	1,397	480	6,602	0.34	1.00		1.00		1.00	
Ever-statin	1,755	476	9,203	0.27	0.691 (0.608–0.784)	<0.0001	0.727 (0.640–0.826)	<0.0001	0.600 (0.521–0.691)	<0.0001

Model 1: Unadjusted. Model 2: Adjusted for age, sex, and income levels. Model 3: Adjusted for age, sex, income levels, CCI, presence of hypertension, dyslipidemia, osteoporosis, and initial LEDD.

PD, Parkinson's disease; HR, hazard ratio; CI, confidence interval; CCI, Charlson Comorbidity Index; LEDD, levodopa equivalent daily dose.

Table 3. Cox proportional hazard regression analysis on the risk of all-cause mortality according to the cumulative statin dose

	PD (n)	Mortality (n)	Person-years	Mortality rate	Model 1		Model 2		Model 3	
					HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
Total dose of statins (DDD)	1,755	476	9,203	0.27	0.855 (0.813–0.896)	<0.0001	0.860 (0.820–0.902)	<0.0001	0.800 (0.761–0.842)	<0.0001

Model 1: Unadjusted. Model 2: Adjusted for age, sex, and income levels. Model 3: Adjusted for age, sex, income levels, CCI, presence of hypertension, dyslipidemia, osteoporosis, and initial LEDD.

PD, Parkinson's disease; HR, hazard ratio; CI, confidence interval; DDD, defined daily dose; CCI, Charlson Comorbidity Index; LEDD, levodopa equivalent daily dose.

Table 4. Cox proportional hazard regression analysis on the risk of all-cause mortality according to the categorized cumulative statin dose

Groups	n	Mortality (n)	Person-years	Mortality rate	Model 1		Model 2		Model 3	
					HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
Never statin	1,397	480	6,602	0.34	Ref.		Ref.		Ref.	
DDD 1–365	289	115	1,520	0.39	0.974 (0.792–1.198)	0.8028	1.077 (0.876–1.326)	0.4808	1.048 (0.807–1.360)	0.7260
DDD 366–730	102	37	516	0.36	0.985 (0.705–1.376)	0.9298	0.974 (0.697–1.361)	0.8767	0.851 (0.549–1.319)	0.4702
DDD >730	1,364	324	7,167	0.23	0.604 (0.524–0.695)	<0.0001	0.631 (0.547–0.727)	<0.0001	0.487 (0.401–0.590)	<0.0001

Model 1: Unadjusted. Model 2: Adjusted for age, sex, and income levels. Model 3: Adjusted for age, sex, income levels, CCI, presence of hypertension, dyslipidemia, osteoporosis, and initial LEDD.

HR, hazard ratio; CI, confidence interval; DDD, defined daily dose; CCI, Charlson Comorbidity Index; LEDD, levodopa equivalent daily dose.

balanced after matching (all SMDs <0.1) (Supplementary Table 5). Cox regression analysis revealed that statin use (HR 0.595, 95% CI 0.520–0.680; $p<0.0001$) was associated with a reduced mortality risk among matched participants (Supplementary Table 6). Time-dependent Cox regression revealed a protective effect of statin use on the risk of mortality (HR 0.591, 95% CI 0.513–0.681; $p<0.0001$) (Supplementary Table 7). Cox regression revealed that the risk of cardiovascular mortality was comparable between the ever-statin group and the never-statin group (Supplementary Table 8). However, the ever-statin group had a lower risk of neurological mortality with and without the covariates in Model 1 (HR 0.551; 95% CI 0.439–0.691; $p<0.0001$), Model 2 (HR 0.575; 95% CI 0.458–0.722; $p<0.0001$), and Model 3 (HR 0.597; 95% CI 0.476–0.749; $p<0.0001$) (Supplementary Table 9). Among those with available health check-up data, triglyceride levels were higher in the ever-statin group than in the never-statin group (134.7 ± 72.2 mg/dL vs. 112.8 ± 61.5 mg/dL, $p<0.0001$) (Supplementary Table 10). With LDL as an additional independent variable, statin DDD remained significantly associated with lower mortality in Model 1 (HR 0.827, 95% CI 0.754–0.907; $p<0.0001$), Model 2 (HR 0.838, 95% CI 0.764–0.918; $p=0.0002$), and Model 3 (HR 0.897, 95% CI 0.862–0.933; $p<0.0001$) (Supplementary Table 11). This association remained significant even after simultaneous adjustment for LDL, HDL, total cholesterol, and triglyceride in Model 1 (HR 0.829; 95% CI 0.756–0.910; $p<0.0001$), Model 2 (HR 0.836; 95% CI 0.762–0.917; $p=0.0001$), and Model 3 (HR 0.898; 95% CI 0.862–0.935; $p<0.0001$) (Supplementary Table 12).

DISCUSSION

In this nationwide population-based study of 3,152 participants with PD, we investigated the association between statin prescription and all-cause mortality in patients with PD. A lower mortality rate was observed in individuals with PD who were prescribed statins than in those who were never prescribed statins. Moreover, the cumulative dose of statins exhibited an inverse dose–response relationship with all-cause mortality in patients with PD. The inverse dose–response relationship was significant for both the hydrophilic statin and lipophilic statin cumulative doses. These results might reflect the possible beneficial effect of statins on mortality in patients with PD.

In addition to their ability to protect against cardiovascular disease, statins have pleiotropic effects, including protective effects against oxidative stress and anti-inflammatory effects.²¹ However, the role of statins in PD is unclear. Several animal studies have revealed multiple protective mechanisms of statins in preclinical studies of PD.^{7,9,22–24} Conversely, the harmful effects

of statins on dopaminergic neurons have been demonstrated in a 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine mouse model of PD.²⁵ Clinical studies have also shown contradicting results. Several epidemiological studies have shown a reduced risk of PD in population cohorts.^{10,11} However, Jeong et al.²⁶ reported a J-shaped association between statins and the incidence of PD, and another study¹⁴ demonstrated an increased risk of PD in those who used statins for more than 12 months. Moreover, Jeong et al.¹⁸ revealed a detrimental effect of statins on dopaminergic depletion and dementia conversion in patients with PD. Considering the lipid-lowering effect of statins and the association between lipids and the risk of PD, the relationship between statin use and PD becomes more complicated.

The effect of statins on the long-term prognosis of PD has rarely been investigated. A recent randomized controlled study revealed less deterioration of dopamine transporter uptake in participants treated with lovastatin.²⁷ In contrast, another randomized controlled trial revealed that participants treated with simvastatin experienced comparable deterioration in motor severity at 24 months.²⁸ However, to the best of our knowledge, the effect of statins on mortality in PD patients has not been investigated.

In our study, we observed that statin use was associated with lower mortality in patients with PD. These findings are consistent with those of previous studies that revealed the possible protective effect of statins on α -synuclein aggregation and associated PD neuropathology.^{7,8,24,29} Patients with PD who were prescribed statins (ever-statin group) had a lower risk of mortality than those who had never been prescribed statins (never-statin group) during the study period. Moreover, in the ever-statin group, the cumulative dosage of statins during the follow-up period was negatively associated with the mortality rate, indicating that patients with PD who were prescribed a higher statin dose had a lower risk of mortality. Interestingly, when cumulative DDDs were categorized, the protective effect of statin use was significant only in the DDD>730 group, indicating that prolonged use of statins may be associated with reduced mortality in PD patients. These findings suggest the possibility of a protective effect of statins on PD prognosis. However, mortality in patients with neurodegenerative diseases is a complex outcome that occurs over a relatively long disease course. Patients with PD are known to have a higher risk of mortality than the general population is,³⁰ and the most common primary cause of death is pneumonia in patients with PD.³¹ With respect to the clinical phenotype, higher mortality is associated with the non-tremulous motor phenotype, with earlier cognitive impairment and the involvement of autonomic dysfunction in PD.³² However, the effects of statins or other medications on mortality in PD patients have not been fully elucidated. Statins are associat-

ed with lower cardiovascular mortality in the general population owing to their lipid-lowering effect,⁴ and cardiovascular mortality is an important cause of death in both the general population and patients with PD. With respect to cardiovascular risk factors, the incidence of hypertension, diabetes, and dyslipidemia was higher in the ever-statin group at baseline, and even after controlling for the CCI, hypertension, diabetes, and dyslipidemia as covariates, statins were still associated with lower mortality. Interestingly, while the prevalence of dyslipidemia was greater in the ever-statin group, their actual lipid levels did not differ significantly from those in the never-statin group. This phenomenon suggests that statin treatment effectively modified the lipid profiles of these high-risk patients. Therefore, it is plausible that such lipid stabilization might have contributed to the observed reduction in all-cause mortality among statin users. Our study revealed comparable causes of cardiovascular death between the ever-statin and never-statin groups. Interestingly, when the contribution of statin use to cardiovascular or neurological mortality was investigated, there was no significant difference in the risk of cardiovascular mortality between the ever-statin group and the never-statin group; however, compared with the never-statin group, the ever-statin group had a lower risk of neurological mortality, with and without covariates. Moreover, among those whose blood lipid profiles were available, those in the ever-statin group had higher triglyceride levels at baseline; however, the effect of statins on overall mortality was significant even when the baseline lipid profiles were controlled. Intriguingly, the occurrence of myocardial infarction, cardiovascular events, and stroke was greater in the ever-statin group during the observation period (Supplementary Table 13). Despite this apparent cardiovascular “penalty,” overall mortality was lower in the ever-statin group, suggesting that the protective effect of statins against mortality may extend beyond their cardiovascular effects. However, the so-called cholesterol paradox remains unresolved. Some studies have suggested that higher serum cholesterol levels may be beneficial,³³⁻³⁵ whereas others have reported that elevated cholesterol levels can be harmful, particularly through its association with vascular comorbidities.^{36,37} In our study, statin use was associated with a protective effect on mortality, and this association persisted after adjustment for baseline lipid profiles, despite a higher incidence of vascular events in the ever-statin group. These findings suggest that the benefit of statins may be at least partially independent of lipid levels. However, as we were unable to assess longitudinal changes in lipid profiles, future studies are warranted to determine whether the mortality benefit observed in our cohort is lipid driven or reflects the effects of statins themselves (e.g., pleiotropic or neuroprotective). Furthermore, there was a tendency toward fewer neurological causes of death in the ever-

statin group, suggesting the possibility of a protective effect of statin use on the progression of PD. However, our study lacks detailed clinical and biomarker features of PD, and further research is necessary to elucidate the underlying biological basis of the mortality-lowering effect of statins in PD.

This study has several limitations. First, selection bias may have occurred, as this study was based on sample cohort data, and not every patient with PD in Korea was investigated. Thus, this sample may not be representative of the entire population of patients with PD in Korea. However, considering the large number of study participants, the beneficial effects of statins on mortality in patients with PD may still be meaningful. Second, the diagnoses of PD and other comorbidities were defined using the diagnostic codes in the claims data. Therefore, the possibility of misclassification cannot be excluded. Third, clinical features, such as the severity of motor symptoms or motor phenotype, degree of dopaminergic depletion, and severity of non-motor symptoms, were unavailable in this study. Since the clinical phenotype is associated with favorable or poor prognosis in PD patients, future studies regarding these clinical characteristics are warranted. Fourth, the baseline characteristics were not balanced between the ever-statin and never-statin groups. The ever-statin group was older and had a higher CCI. Moreover, conditions associated with increased mortality, such as diabetes mellitus, hypertension, dyslipidemia, and osteoporosis, were more frequently observed in the ever-statin group. Despite this higher burden of mortality-related risk factors, the risk of overall mortality was lower in the ever-statin group. Moreover, sensitivity analyses after propensity score matching revealed similar results. Therefore, the protective effect of statins might not be attributable to differences in baseline characteristics. Fifth, the effects of lipid status, such as serum LDL, HDL, and total cholesterol levels, were not available for all study participants because this study was based on claims data. However, we performed sensitivity analyses among those with available health checkup data and serum lipid profiles. The ever-statin group had higher triglyceride levels at baseline; however, the association between statin use and lower mortality was significant after controlling for the lipid profiles. Additionally, as the incidence of cardiovascular events was greater in the ever-statin group, overall cardiovascular mortality was comparable between the two groups. These findings suggest that the association between statin use and reduced mortality involves mechanisms independent of those underlying the cardiovascular or lipid-associated effects of statins. However, as our study did not investigate the trajectory of longitudinal lipid status, future studies are needed to elucidate the complex relationships among statins, lipids, and mortality in patients with PD. Sixth, the cause of death was obtained from death certificate data and may not be accurate. A

recent study revealed that only 66.8% of death certificates of patients from a prospective incident cohort with degenerative/vascular parkinsonian syndromes mentioned any parkinsonian syndrome.³⁸ Moreover, the complications of PD, such as pneumonia or femoral fractures, which can lead to death, might have been misclassified. Therefore, evaluating the specific causes of death in patients with PD in this claims-based study was challenging. Accordingly, our cause-specific mortality analyses (e.g., neurological versus cardiovascular mortality) should be interpreted cautiously and considered exploratory, whereas our primary endpoint—all-cause mortality—is less vulnerable to cause-of-death misclassification.

In this analysis of 3,152 adults with PD, we identified an inverse association between statin use and all-cause mortality. Additionally, an inverse dose–response relationship was observed between cumulative statin dose and mortality, regardless of comorbidities and the lipophilicity of statins. These findings suggest a potential protective effect of statins on PD prognosis, possibly extending beyond their cardiovascular effects to regulate neurodegenerative processes. Despite limitations such as potential selection bias and a lack of detailed clinical data, our results highlight the need for further research to clarify the mechanisms underlying the mortality-lowering effects of statins in PD and to explore their role in disease progression. Future studies are needed to elucidate the underlying mechanism between statin use and mortality in patients with PD.

Supplementary Materials

The Data Supplement is available with this article at <https://doi.org/10.14802/jmd.25240>.

Conflicts of Interest

The authors have no financial conflicts of interest.

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