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RESEARCH ARTICLE

Increased atrial fibrillation risk in Parkinson's disease: A nationwide population-based study

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Abstract

Objective: Parkinson's disease (PD) is the second most common neurodegenerative disorder associated with various morbidities. Although the relationship between cardiovascular disease and PD has been studied, a paucity of information on PD and atrial fibrillation (AF) association exists. Thus, we aimed to investigate whether patients with PD have an increased risk of AF. **Methods**: This study included 57,585 patients with newly diagnosed PD (≥40-year-old, mean age 69.7 years, men 40.2%) and without a history of AF from the Korean National Health Insurance Service (NHIS) database between 2010 and 2015. Furthermore, an equal number of age- and sex-matched subjects without PD were selected for comparison. The primary outcome was new-onset AF. **Results**: During the mean follow-up period of 3.4 ± 1.8 years, AF was newly diagnosed in 3,665 patients. A significantly higher incidence rate of AF was noted among patients with PD than among patients without PD (10.75 and 7.86 per 1000 person-year, respectively). Multivariate Cox-regression analysis revealed that PD was an independent risk factor for AF (hazard ratio [HR]: 1.27, 95% confidence interval [CI]: 1.18–1.36). Furthermore, subgroup analyses revealed that AF risk was higher in the younger age subgroups, and compared with the non-PD group, the youngest PD group (age: 40–49 years) had a three-fold increased risk of AF (HR: 3.06, 95% CI: 1.20–7.77). **Interpretation**: Patients with PD, especially the younger age subgroups, have an increased risk of AF. Active surveillance and management of AF should be considered to prevent further complications.

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder affecting approximately 2% of the population aged more than 40 years.[1] Cardinal motor symptoms such as bradykinesia, tremor, and rigidity are essential in diagnosis, but several non-motor symptoms such as orthostatic hypotension, anosmia, constipation, and depression are also frequently involved and are often recognized as premotor symptoms of PD.[2,3] Autonomic nervous system (ANS) dysfunction is thought to be one of the common causes of non-motor symptoms,[2] and regardless of clinical symptoms and clinical stages, PD patients frequently have coexisting autonomic, neurocardiological abnormalities.[4-6]

Traditionally, PD patients were considered to be at low risk of cerebrovascular and cardiovascular diseases because they had fewer risk factors of vascular disease.[7] However, this belief is recently being questioned because of the emerging evidence from recent studies stating that PD patients have a higher risk of cardiovascular disease.[8] Cerebrovascular and cardiovascular diseases were found to be major causes of death in patients with PD.[9] Additionally, sudden death is not uncommon among patients with PD, and cardiac death, including arrhythmia, has been suggested as a potential mechanism.[10] However, data

suggesting the relationship between PD and arrhythmia, including atrial fibrillation (AF), are lacking.

As ANS is strongly involved in the pathogenesis of AF, patients with PD might be exposed to the risk of AF development. Owing to an increase in the prevalence and extensive healthcare burden of AF, [11-13] a study with a larger population size and longer study duration validating the incidence of AF among patients with PD is required. Moreover, identifying subgroups at high risk of developing AF is crucial in the clinical context. Therefore, we investigated whether patients with PD have an increased risk of AF development compared with the general population using a nationwide population database.

Methods

Data source and study population

Our study used the national claims data established by the National Health Insurance Service (NHIS) of Korea. The NHIS database has access to the medical records of the entire Korean population. It includes information regarding diagnoses, procedures performed, prescription records, demographics, and mortality data of patients.[14,15] Diagnoses in the database are provided as the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) codes. In addition, the NHIS in Korea has a registration system for Rare Intractable Diseases (RID) that provides support to patients with rare and intractable diseases. The database is open to all researchers who have approval for the study protocol from the official review committee. This study was exempted from review by the Seoul National University Hospital Institutional Review Board (E-1811-070-984).

Patients (age $\geq$ 40 years) with newly diagnosed PD between January 1, 2010, and December 31, 2015 were identified using ICD-10-CM codes (G20) and RID codes (V124). The Korean RID program diagnostic criteria for PD, similar to the UK PD Society Brain Bank criteria,[16] are as follows: (1) diagnosis of a parkinsonian syndrome —bradykinesia and at least one other finding among muscular rigidity, rest tremor, and postural instability; (2) exclusion of secondary causes of a parkinsonian syndrome such as stroke, exposure to neurotoxic agents, head trauma, encephalitis, and hypoxia; and (3) three or more supporting features for PD—unilateral onset, rest tremor, progressive disorder, persistent asymmetry, excellent response to levodopa (70%–100%), severe levodopa-induced chorea, response to levodopa for 5 years or more, or a clinical course of 10 years or more. We excluded the subjects with a prior diagnosis of AF during the 1-year washout period (n = 6763) and those with a previous history of AF (n = 8716). A total of 57 585 patients with PD were identified. Then, for the control group, we recruited 1:1 age- and sex-matched subjects (n = 57 585) without PD (Figure 1).

Defining the comorbidities and outcome

Comorbidities were defined using ICD-10-CM codes: hypertension (ICD-10-CM codes: I10–13, and I15), diabetes mellitus (DM; ICD-10-CM codes: E11–14), dyslipidemia (ICD-10-CM code: E78), congestive heart failure (CHF; ICD-10-CM code: I50), peripheral artery disease (PAD; ICD-10-CM codes: I70 and I73), previous history of myocardial infarction (MI; ICD-10-CM codes: I21 and I22) and ischemic stroke (ICD-10-CM codes: I63 and I64), chronic obstructive pulmonary disease (COPD; ICD-10-CM codes: J43 and J44), and end-stage renal disease (ESRD; ICD-10-CM codes: N18, N19, Z49, Z905, Z94, and Z992). The primary outcome was the development of non-valvular AF (ICD-10-CM code: I48). We regarded the AF with rheumatic mitral stenosis (ICD-10-CM codes: I05.0, I05.2, and I05.9) and mechanical heart valves (ICD-10-CM codes: Z95.2–Z95.4) as valvular AF and excluded as in our previous study.[17] We used the same definition of AF reported in previous studies.[18,19] This operational definition of AF was validated, and the positive predictive value was 94.1% compared with electrocardiogram.[20] Definitions of comorbidities, medications, and outcomes are described in detail in Supplementary Table S1.

Statistical analysis

Categorical and continuous variables are presented as numbers and percentages and mean $\pm$ standard deviation, respectively. The chi-square test was used to compare the PD and control groups and Student's t-test was used to analyze continuous variables. Annual event rates are described as the number of events per 1000 person-years (PY). The Kaplan–Meier curves were used for demonstrating the cumulative events in both the groups and were compared using the log-rank test. Hazard ratios (HR) and the corresponding 95% confidence intervals (CI) were calculated using Cox proportional hazard models for analyzing the association between PD and AF. Cox proportional hazard models were adjusted for age, sex, hypertension, DM, dyslipidemia, CHF, PAD, history of MI and ischemic stroke, COPD, and ESRD. The study cohort presented an imbalance in baseline characteristics; hence, we performed the sensitivity analysis using a propensity score-matched cohort. The probable confounding factors for outcome were selected, and absolute standardized differences (ASD) of each factor were corrected to less than 0.1. Furthermore, groups were divided

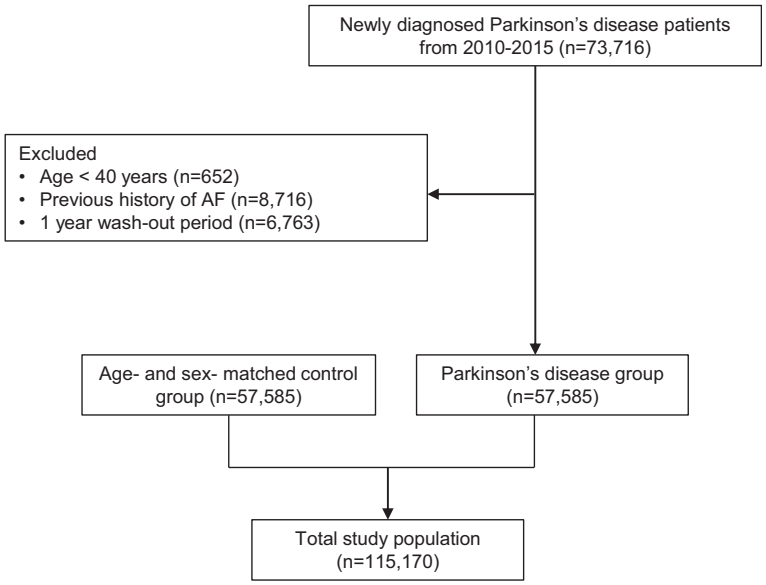

Figure 1. Flowchart of the study population.Abbreviations: AF, Atrial fibrillation.

by multiple cardiovascular risk factors and subgroups analyses were performed. Sensitivity analysis was performed, excluding patients with comorbidities that might affect the risk of AF, such as hypertension, diabetes, previous myocardial infarction, previous stroke, and thyroid disease. All P-values were two-sided, and a value of less than 0.05 was considered statistically significant. Statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC, USA).

Results

Baseline characteristics of the cohort

Study participants were followed up until December 31, 2017, and the mean follow-up duration was 3.35 ± 1.8 years. The baseline characteristics of the study population are summarized in Table 1. The mean age of all the participants was approximately 70 years and 40.2% of them were men. The proportion of patients with low income was higher in the PD group than in the control group (26.3% vs 25%, respectively). Compared with patients without PD, the patients with PD had greater number of comorbidities, including hypertension, DM, dyslipidemia, CHF, previous MI, stroke, PAD, COPD, and ESRD.

Table 1. Baseline characteristics of the cohort.

	Parkinson's disease		
Variables	No 57585	Yes 57585	*P*
Male	23165 (40.2)	23165 (40.2)	1
Age	70.0 ± 9.6	70.0 ± 9.6	1
40-49	2006 (3.5)	2006 (3.5)	1
50-59	7076 (12.3)	7076 (12.3)	
60-69	15281 (26.5)	15281 (26.5)	
70-79	25603 (44.5)	25603 (44.5)	
80-89	7619 (13.2)	7619 (13.2)	
Low income	14416 (25.0)	15116 (26.3)	<0.0001
Hypertension	26770 (46.5)	29531 (51.3)	<0.0001
Diabetes mellitus	9976 (17.3)	13506 (23.5)	<0.0001
Dyslipidemia	14772 (25.7)	19768 (34.3)	<0.0001
Congestive heart failure	1632 (2.8)	3058 (5.3)	<0.0001
Previous MI	703 (1.2)	1245 (2.2)	<0.0001
Previous stroke	4235 (7.4)	15444 (26.8)	<0.0001
Peripheral artery disease	8947 (15.5)	13825 (24.0)	<0.0001
COPD	6444 (11.2)	8242 (14.3)	<0.0001
ESRD	154 (0.3)	490 (0.9)	<0.0001

Values presents by mean ± standard deviation or number (%).
Abbreviation: COPD, chronic obstructive pulmonary disease; ESRD, end-stage renal disease; MI, myocardial infarction

Incidence rates and relative risks of AF

Among a total of 115 170 patients in the cohort, new-onset AF was diagnosed in 3,565 patients (3.1%, PD group: 1,973 and control group: 1,592). The incidence of AF was higher among patients with PD than among patients without PD (log-rank test $P < 0.0001$) and these results were consistent among male and female patients (Figure 2). The incidence rate of AF was higher among PD patients than among controls (10.75 vs 7.86 per 1000 PY; Table 2). Multivariable Cox proportional hazard models revealed that patients with PD had an increased relative

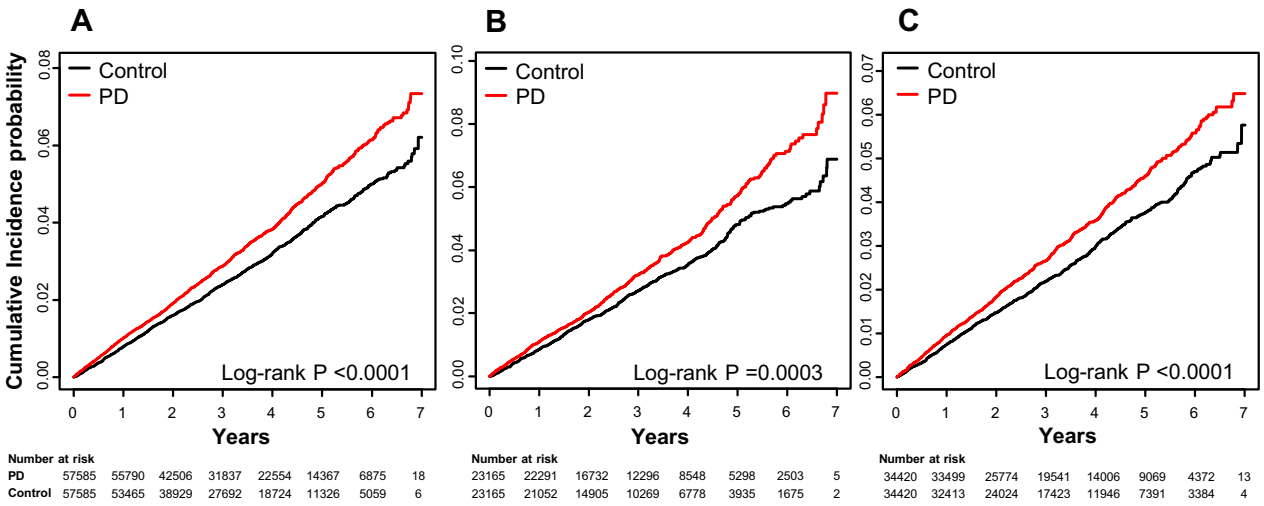

Figure 2. Comparison of Cumulative Incidence of Atrial Fibrillation Events Depending on the Presence or Absence of Parkinson's disease. A. Total cohort, B. Male, C. Female. Abbreviations: PD, Parkinson's disease.

Table 2. The risk of atrial fibrillation according to Parkinson's disease

	N	AF event	Duration (years)	Incidence Rate*	Hazard Ratio	
					Crude	Adjusted†
Parkinson's disease						
No	57585	1592	202569.31	7.86	1 (reference)	1 (reference)
Yes	57585	1973	183535.58	10.75	1.37 (1.28,1.47)	1.27 (1.18, 1.36)
Propensity score-matched population						
Parkinson's disease						Hazard Ratio
No	44772	1302	156851.24	8.30		1 (reference)
Yes	44772	1450	142704.01	10.16		1.23 (1.14, 1.33)

Abbreviation: AF, atrial fibrillation.

*Incidence rate presented by per 1,000 person-year.

†Model adjusted with age, sex, low income, hypertension, diabetes mellitus, dyslipidemia, congestive heart failure, previous myocardial infarction, previous stroke, peripheral artery disease, chronic obstructive pulmonary disease, and end-stage renal disease.

risk of AF development compared with those without PD (adjusted HR: 1.27, 95% CI: 1.18–1.36). In the sensitivity analysis excluding patients with AF-related comorbidities, the incidence of AF was higher in the PD group compared to the control group (7.71 vs 5.11 per 1000 PY, Supplementary Table S2). The hazard ratio was calculated by multivariable Cox proportional hazard analysis, showing an increased risk of AF (adjusted HR: 1.56, 95% CI: 1.37-1.78).

Subgroup analyses

Subgroup analyses revealed that compared with the control group, the PD group was consistently associated with a higher AF risk in most of the subgroups (Figure 3). The risk of AF in the male and female subgroups was significantly higher in the PD group than in the control group. A significant interaction was observed in the age subgroups (P for interaction < 0.001). Although AF incidence gradually increased with age in both the groups, the relative risk of AF in the PD group was considerably higher in the younger age subgroup than in the older subgroup (age 40s, HR: 3.06, 95% CI: 1.20–7.77 vs age 80s, HR: 1.07, 95% CI: 0.91–1.25). In addition, the absolute incidence rates were higher among those with cardiovascular risk factors. Among subgroups with cardiovascular risk factors, hypertension and previous stroke presented significant interaction. The effect of PD on AF risk disappeared in subgroups with previous stroke but was maintained in those without previous stroke.

Propensity score matching results

After propensity score matching, the baseline characteristics between the PD and control groups became equivalent (Supplementary Table S3). The distribution of the

Incidence rate by subgroups	Control (n=57858)	PD (n=57858)	Absolute Difference	HR (95% CI)	$P_{interaction}$
Total	7.86	10.75	2.89	1.27 (1.18,1.36)	
Male	8.74	12.03	3.29	1.31 (1.18,1.46)	0.894
Female	7.29	9.96	2.67	1.24 (1.13,1.36)	
Age 40-49	0.78	2.84	2.06	3.06 (1.20, 7.77)	
50-59	1.80	4.67	2.87	2.16 (1.51, 3.08)	
60-69	5.61	9.79	2.84	1.35 (1.16, 1.57)	<0.001
70-79	9.79	13.10	3.31	1.26 (1.14, 1.38)	
≥80	15.58	18.13	2.55	1.07 (0.91, 1.25)	
Hypertension	10.59	13.02	2.43	1.16 (1.06, 1.26)	0.002
Without hypertension	5.55	8.38	2.82	1.46 (1.30, 1.63)	
DM	9.87	11.96	2.09	1.16 (1.00, 1.34)	0.096
Without DM	7.46	10.39	2.93	1.30 (1.20, 1.40)	
Dyslipidemia	9.35	11.96	2.61	1.21 (1.07, 1.37)	0.604
Without dyslipidemia	7.38	10.13	2.75	1.29 (1.19, 1.41)	
Congestive heart failure	19.73	23.02	3.29	1.22 (0.95, 1.57)	0.473
Without congestive heart failure	7.56	10.14	2.57	1.27 (1.18, 1.36)	
Previous stroke	13.72	12.96	-0.77	1.03 (0.87, 1.21)	0.008
Without previous stroke	7.42	9.95	2.52	1.32 (1.22, 1.43)	
Previous MI	14.56	16.82	2.26	1.34 (0.86, 2.07)	0.698
Without previous MI	7.78	10.63	2.26	1.27 (1.18, 1.36)	
With ≥ 1 of CV risk factors*	13.85	13.20	-0.65	1.06 (0.90, 1.23)	0.014
Without any CV risk factors*	7.35	9.80	2.45	1.32 (1.22, 1.42)	

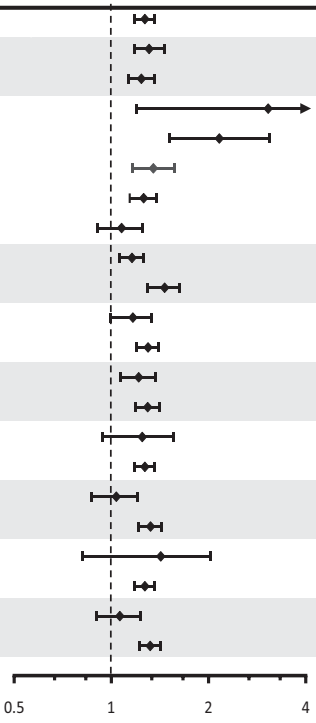

Figure 3. Subgroup analyses for Risk of Atrial Fibrillation in Parkinson's Disease Patients. All subgroup analyses were adjusted with age, sex, low income, hypertension, diabetes mellitus, dyslipidemia, congestive heart failure, previous myocardial infarction, previous stroke, peripheral artery disease, chronic obstructive pulmonary disease, and end-stage renal disease. Incidence rate presented by per 1,000 person-year. *Cardiovascular risk factors included hypertension, DM and dyslipidemia. Abbreviations: PD, Parkinson's disease; HR, hazard ratio; CI, confidence interval; DM, diabetes mellitus; MI, myocardial infarction; CV, cardiovascular.

propensity score after matching was well-balanced and assessed by standardized differences of baseline characteristics (Supplementary Figure S1). In line with our main results, the risk of AF was significantly higher in the PD group than in the control group (HR: 1.23, 95% CI: 1.14–1.33; Table 2). Subgroup analyses were performed using the propensity score-matched population (Supplementary Table S4). Significant interaction was consistently observed in the subgroup of patients with hypertension after propensity score matching. The subgroup with diabetes showed significant interaction after matching. However, subgroups with previous stroke and one or more cardiovascular risk factors did not show significant interaction after propensity score matching.

Discussion

Our study aimed to discover the risk of AF among patients with PD by using the Korean NHIS database. To the best of our knowledge, this is the largest population-based study to identify the risk of AF using a nationwide cohort of patients with PD. The main result of the study is that PD was found to be associated with a higher risk of AF even after detailed adjustment of risk factors such as age, sex, underlying diseases, and socioeconomic status. Interestingly, in the subgroup analyses, the relative risk of AF increased in the younger age subgroup. Although the absolute incidence of AF was higher in the older age subgroups, patients with PD (age in 40s) had a threefold increased risk of AF compared with their matched controls after meticulous adjustment of potential confounders.

Risk of AF in patients with PD

A previous epidemiological study conducted by Hong et al. indicated that patients with newly diagnosed PD were more likely comorbid with AF (odds ratio: 1.12), but patients with PD and without AF had a lower AF risk when compared with the control group (subdistribution

HR: 0.92).[21] The authors concluded that AF might be one of the premotor symptoms of PD, and caudal-rostral spreading of α-synuclein pathology may play a role in this relationship. Compared with this study, our study differed on several points. We presented that AF risk increased in newly diagnosed patients with PD and without AF history, using a larger database comprising nearly four times the number of patients with PD. To ensure the inclusion of definite patients with PD and minimize misclassification bias, we used the ICD-10-CM diagnosis codes for classifying PD and the Korean RID diagnostic codes, respectively. As PD has been classified as a RID by the Korean NHIS, a detailed history and physical examination fulfilling of adequate criteria (described in the methods section), which is similar to the UK PD Society Brain Bank criteria, is required for diagnosing and registering a patient as a patient with PD. PD patients with comorbidities that might affect the risk of AF, such as adrenal disease, history of stroke, thyroid disease, and heart disease were excluded in the previous study[21]. However, to offer a larger cohort for improved generalizability, we included such patients in our study. To exclude potential bias caused by AF-related comorbidities, we performed a sensitivity analysis excluding patients with comorbidities that might increase AF risks, such as a history of hypertension, diabetes mellitus, myocardial infarction, stroke, and thyroid disease. Similar to the main result, AF risk was significantly increased in the sensitivity analysis, supporting our assumption that PD is independently associated with a higher risk of AF.

ANS dysfunction in the aspect of association between AF and PD

According to numerous neuroimaging studies, autonomic dysfunction is a common non-motor symptom of PD.[22,23] Cardiac noradrenergic denervation is one of the pathophysiological basis for this phenomenon.[24] Studies have presented that cardiac noradrenergic denervation is a widespread phenomenon in PD regardless of clinical ANS dysfunction.[5,23,25] In addition, atrial conduction time was prolonged in newly diagnosed patients with PD, and it had a positive correlation with PD severity and duration.[26] Although the pathogenesis of AF is very complex and not fully understood, ANS has an important role in triggering and maintaining AF.[27] Both the sympathetic and parasympathetic nervous systems carry out different roles in the regulation of atrial electrophysiological properties, and the concept of autonomic nervous imbalance has been proposed to explain the atrial electrical instability and AF occurrence in the aspect of cardiac ANS.[28] Furthermore, frequent atrial ectopic beats and atrial conduction time prolongation are well-known predictors of paroxysmal AF.[29,30] Putting these findings together, cardiac sympathetic denervation and ANS dysfunction are plausible mechanisms of the increased risk of AF in patients with PD.

Clinical implication

Our findings are vital in the clinical context for several reasons. A significant proportion of patients with PD die from cerebrovascular diseases, but sufficient explanation for the underlying cause and management for the problem are lacking. Determining a modifiable cause of the cerebrovascular disease in PD could provide further insights for improving outcomes in patients with PD. Furthermore, PD at a young age has a substantial impact on an individual patient's socioeconomic function,[31] but AF may add to functional and social burden through associated complications. Therefore, active surveillance and monitoring for AF, such as electrocardiography and 24-hours Holter monitoring, should be considered in patients with PD, to prevent further complications and consequences.

Study limitations

Our study has several limitations. First, despite using a large cohort with high-quality data, our study was a retrospective study using claims data that might generate concerns regarding misclassification or selection bias. However, we used detailed multivariable analysis and sophisticated operational definition, including the Korean RID diagnostic codes, to overcome such limitations. Also, frequent hospital visits in PD patients might have the possibility of detection bias, augmenting the risk of AF in the PD group. However, the majority of AF is symptomatic, and the first diagnosis of AF is usually established in symptomatic episodes regardless of a routine examination. Also, diagnosis methods of AF were not a routine examination of PD. To decrease the possibility of AF detection in the PD group, we used a one-year washout period for the primary endpoint from the initial diagnosis of PD, so AF patients who were diagnosed as AF within 1 year were excluded. Second, we did not adjust the potential confounding effect of concurrent PD medication, which has a potential risk for cardiovascular events. Numerous drugs used in PD, including levodopa, have a potential concern on cardiovascular side effects,[32,33] but no direct evidence on increased tachyarrhythmia or cardiovascular events due to PD drugs exists. Moreover, the use of these drugs is often unavoidable and polypharmacy frequently occurs due to uncontrolled symptoms and complex nature of the disease.[34,35] Moreover, the results of this study suggest that clinicians

should be aware of AF risk and appropriate diagnostic tests when using drugs with arrhythmogenic potential in patients with PD. Therefore, although there are some concerns regarding an increased risk of AF due to PD drugs, concomitant drug use should be considered as a part of the whole disease process that increases the risk of AF, leaving our key message insisting increased AF risk among patients with PD still valid. Third, we could not include clinical manifestations of PD and clinical staging such as the Hoehn and Yahr scale in this study. Since patient symptoms and clinical manifestation are not included in the Korean NHIS database, we could not adjust the individual patient's clinical factors. Future prospective studies are warranted to overcome these limitations.

In conclusion, our findings suggest that patients with PD are at an increased risk of AF, and the relative risk of AF is greater among young patients. Therefore, the potential impact of AF and associated complication risk should not be overlooked, and adequate management should be provided to young patients. Future prospective studies are warranted for investigating appropriate surveillance and treatment methods for AF in patients with PD.

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Conflict of Interest

All authors declare that there is no conflict of interest.

Author Contributions

S.H., and I.M. participated in the conception and design of the study, literature search, data interpretation, and drafting the article. K.-D.H participated in the conception and design of the study, performed the statistical analysis and data interpretation and review of the manuscript. E.-K.C. participated in the conception and design of the study, data interpretation, and critical revision of the manuscript. H.-C.C., S.-Y.L., S.Y., S.K., Y.-J.C., H.-J.L., E.L, S.-R.L., M.-J.C., and S.O. participated in the study design, data interpretation, and review of the manuscript. All authors reviewed the study's findings and read and approved the final manuscript.

References

1. Ascherio A, Schwarzschild MA. The epidemiology of Parkinson's disease: risk factors and prevention. Lancet Neurol 2016;15(12):1257–1272.
2. Poewe W. Non-motor symptoms in Parkinson's disease. Eur J Neurol 2008;15(Suppl 1):14–20.
3. Pont-Sunyer C, Hotter A, Gaig C, et al. The onset of nonmotor symptoms in Parkinson's disease (the ONSET PD study). Mov Disord 2015;30(2):229–237.
4. Goldstein DS. Orthostatic hypotension as an early finding in Parkinson's disease. Clin Auton Res 2006;16 (1):46–54.
5. Courbon F, Brefel-Courbon C, Thalamas C, et al. Cardiac MIBG scintigraphy is a sensitive tool for detecting cardiac sympathetic denervation in Parkinson's disease. Mov Disord 2003;18(8):890–897.
6. Palma JA, Kaufmann H. Autonomic disorders predicting Parkinson's disease. Parkinsonism Relat Disord 2014;20 (Suppl 1):S94–S98.
7. Scigliano G, Musicco M, Soliveri P, et al. Reduced risk factors for vascular disorders in Parkinson disease patients: a case-control study. Stroke 2006;37(5):1184–1188.
8. Alves M, Caldeira D, Ferro JM, Ferreira JJ. Does Parkinson's disease increase the risk of cardiovascular events? A systematic review and meta-analysis. Eur J Neurol 2020;27(2):288–296.
9. Pinter B, Diem-Zangerl A, Wenning GK, et al. Mortality in Parkinson's disease: a 38-year follow-up study. Mov Disord 2015;30(2):266–269.
10. Matsumoto H, Sengoku R, Saito Y, et al. Sudden death in Parkinson's disease: a retrospective autopsy study. J Neurol Sci 2014;343(1–2):149–152.
11. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/ HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol 2014;64(21):e1–76.
12. Lee SR, Choi EK, Han KD, et al. Trends in the incidence and prevalence of atrial fibrillation and estimated thromboembolic risk using the CHA2DS2-VASc score in the entire Korean population. Int J Cardiol 2017;1 (236):226–231.
13. Li YG, Lee SR, Choi EK, Lip GY. Stroke prevention in atrial fibrillation: focus on asian patients. Korean Circ J 2018;48(8):665–684.
14. Song SO, Jung CH, Song YD, et al. Background and data configuration process of a nationwide population-based study using the korean national health insurance system. Diabet Metabol J 2014;38(5):395–403.
15. Choi E-K. Cardiovascular research using the Korean National Health Information Database. Korean Circ J. 2020;50.
16. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry 1992;55(3):181–184.

17. Moon I, Choi EK, Jung JH, et al. Ankylosing spondylitis: a novel risk factor for atrial fibrillation - A nationwide population-based study. Int J Cardiol 2019;15(275):77–82.
18. Lee SR, Choi EK, Rhee TM, et al. Evaluation of the association between diabetic retinopathy and the incidence of atrial fibrillation: a nationwide population-based study. Int J Cardiol 2016;15(223):953–957.
19. Choi Y-J, Choi E-K, Han K-D, et al. Increased risk of atrial fibrillation in patients with inflammatory bowel disease: a nationwide population-based study. World J Gastroenterol 2019;25(22):2788–2798.
20. Lee SS, Ae Kong K, Kim D, et al. Clinical implication of an impaired fasting glucose and prehypertension related to new onset atrial fibrillation in a healthy Asian population without underlying disease: a nationwide cohort study in Korea. Eur Heart J 2017;38(34):2599–2607.
21. Hong CT, Chan L, Wu D, et al. Association between Parkinson's disease and atrial fibrillation: a population-based study. Front Neurol 2019;10:22.
22. Goldstein DS, Holmes C, Cannon RO 3rd, et al. Sympathetic cardioneuropathy in dysautonomias. N Engl J Med 1997;336(10):696–702.
23. Sakakibara R, Tateno F, Kishi M, et al. MIBG myocardial scintigraphy in pre-motor Parkinson's disease: a review. Parkinsonism Relat Disord 2014;20(3):267–273.
24. Jain S, Goldstein DS. Cardiovascular dysautonomia in Parkinson disease: from pathophysiology to pathogenesis. Neurobiol Dis 2012;46(3):572–580.
25. Goldstein DS. Dysautonomia in Parkinson disease. Compr Physiol 2014;4(2):805–826.
26. Canga Y, Emre A, Yuksel GA, et al. Assessment of atrial conduction times in patients with newly diagnosed Parkinson's disease. Parkinsons Dis 2018;2018:2916905.
27. Coumel P. Autonomic influences in atrial tachyarrhythmias. J Cardiovasc Electrophysiol 1996;7 (10):999–1007.
28. Shen MJ, Choi EK, Tan AY, et al. Neural mechanisms of atrial arrhythmias. Nat Rev Cardiol 2011;9(1):30–39.
29. Dewland TA, Vittinghoff E, Mandyam MC, et al. Atrial ectopy as a predictor of incident atrial fibrillation: a cohort study. Ann Intern Med 2013;159(11):721–728.
30. Lalani GG, Schricker A, Gibson M, et al. Atrial conduction slows immediately before the onset of human atrial fibrillation: a bi-atrial contact mapping study of transitions to atrial fibrillation. J Am Coll Cardiol 2012;59 (6):595–606.
31. Schrag A, Hovris A, Morley D, et al. Young- versus older-onset Parkinson's disease: impact of disease and psychosocial consequences. Mov Disord 2003;18(11):1250–1256.
32. Noack C, Schroeder C, Heusser K, Lipp A. Cardiovascular effects of levodopa in Parkinson's disease. Parkinsonism Relat Disord 2014;20(8):815–818.
33. Malek NM, Grosset KA, Stewart D, et al. Prescription of drugs with potential adverse effects on cardiac conduction in Parkinson's disease. Parkinsonism Relat Disord 2013;19 (6):586–589.
34. McLean G, Hindle JV, Guthrie B, Mercer SW. Co-morbidity and polypharmacy in Parkinson's disease: insights from a large Scottish primary care database. BMC Neurol 2017;17(1):126.
35. Leoni O, Martignoni E, Cosentino M, et al. Drug prescribing patterns in Parkinson's disease: a pharmacoepidemiological survey in a cohort of ambulatory patients. Pharmacoepidemiol Drug Saf 2002;11 (2):149–157.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Supplementary Figure S1. Distribution of Propensity Score and Balance Assessment before and after Matching. A. Propensity Score Distribution before and after Matching, B. Balance Assessment after Matching. Abbreviations: CHF, congestive heart failure; PAD, peripheral artery disease; COPD, chronic obstructive pulmonary disease; ESRD end-stage renal disease; MI, myocardial infarction.

Supplementary Table S1. The definitions of Parkinson disease, baseline comorbidities, and outcome. Abbreviations: AF, atrial fibrillation; COPD, chronic obstructive pulmonary disease; ICD, international classification of disease; MI, myocardial infarction.

Supplementary Table S2. Results of sensitivity analysis: The risk of atrial fibrillation in Parkinson's disease patients without previous history of comorbidities that may affect the risk‡. *Incidence rate presented by per 1,000 person-year. †Model adjusted with age, sex, low income, dyslipidemia, congestive heart failure, peripheral artery disease, chronic obstructive pulmonary disease, and end-stage renal disease. ‡Comorbidities include hypertension, diabetes mellitus, previous myocardial infarction, thyroid disease, previous stroke. Abbreviation: AF, atrial fibrillation.

Supplementary Table S3. Baseline characteristics of the Propensity score-matched population. Values presents by mean ± standard deviation or number (%). Abbreviation: ASD, absolute standardized difference; COPD, chronic obstructive pulmonary disease; ESRD, end-stage renal disease; MI, myocardial infarction.

Supplementary Table S4. Subgroup analyses for Risk of Atrial Fibrillation in propensity score-matched population. All subgroup analyses were adjusted with age, sex, low income, hypertension, diabetes mellitus, dyslipidemia,

congestive heart failure, previous myocardial infarction, previous stroke, peripheral artery disease, chronic obstructive pulmonary disease, and end-stage renal disease. Incidence rate presented by per 1,000 person-year. *Cardiovascular risk factors included hypertension, DM, and dyslipidemia. Abbreviations: PD, Parkinson's disease; HR, hazard ratio; CI, confidence interval; DM, diabetes mellitus; MI, myocardial infarction; CV, cardiovascular.

