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Antihypertensive drugs may not delay the symptom progression of Parkinson's disease: A 2-year follow-up study

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ABSTRACT

Background: Parkinson's disease (PD) is one of the most common neurodegenerative disease, and half of PD patients have hypertension as well. The effect of antihypertensive drugs on the progression of PD has been less studied. The focus of this study was on the changes in dopamine transporter (DAT) levels to assess the effect of antihypertensive drugs on the progression of PD.
Methods: Data from 321 drug-naïve patients from the Parkinson's Disease Progression Marker Initiative (PPMI) were collected over a 2-year period. Patients were divided into the PD with arterial hypertension (AH) group (102 cases) with antihypertensive drugs, the PD with other cardiovascular risk factors (CVRFs) group (60 cases) with antidiabetic and/or lipid-lowering drugs, and the pure PD group (159 cases) without CVRFs. The Movement Disorder Society Sponsored Revision Unified Parkinson's Disease Rating Scale (MDS-UPDRS) and Hoehn-Yahr (H&Y) stage were used to assess progression. DAT semiquantitative values were used to evaluate damage to dopaminergic neurons in the substantia nigra, including the contralateral and ipsilateral count density ratio and asymmetry index.
Results: There were no significant differences among the three groups in MDS-UPDRS score and H&Y stage. Changes in DAT levels among the three groups were without distinct differences in the first year and second year. In each group, DAT decreased more in the first year than in the second year. There was no decrease in DAT uptake in the PD with AH group compared with the other groups during the follow-up period.
Conclusions: There is no evidence that antihypertensive drugs can delay PD progression within 2 years.

1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease in old age after Alzheimer's disease (AD). The prevalence, disability and death rates are rapidly increasing worldwide [1]. Arterial hypertension (AH) is the most common

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cardiovascular risk factor (CVRF) in PD patients [2]. PD and AP frequently coexist in older populations [3]. Studies have shown that more than 60% of PD patients are diagnosed with AP by office blood pressure (BP) measurements or outpatient monitoring [3,4]. Therefore, the role of antihypertensive drugs in the progression of PD is worth exploring.

The following therapeutic drugs are mainly selected for the treatment of middle-to old-age hypertension patients: angiotensin converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs) and calcium channel blockers (CCBs) [5]. The current study noted that ACEIs [6], ARBs [7] and CCBs [8] can reduce the incidence of PD. However, there have been few studies on the effect of antihypertensive drugs on PD progression, and the conclusions are not unanimous [9–11]. ACEIs are the most commonly used antihypertensive drugs in middle-aged and elderly people. Among these studies, a double-blind placebo-controlled study in seven moderately severe PD patients suggested that after a four-week treatment period, the ACEI perindopril may have a place in the management of motor symptoms in PD patients without AP [9]. In addition, a study from PPMI revealed that ARB reduced the MDS-UPDRS total score during the first year in newly diagnosed PD patients who were exposed to this drug, but ACEI did not [11]. The research included 423 samples, and approximately 10 patients with or without AP used ARB medication at least 2 years before entering the study and were exposed to ARB during the 5-year follow-up. Another phase 2, randomized, double-blind, parallel group trial was undertaken in 99 drug-naïve, early PD subjects without AP treated with isradipine (a CCB) and showed that 10 mg of isradipine daily can delay the progression of PD disability [12]; however, 336 early-stage patients who used isradipine did not show lowered total UPDRS scores compared with placebo recipients over 36 months [13]. Therefore, based on the current studies, we do not know the exact effect of antihypertensive drugs on the progression of PD [14].

With the development of molecular imaging, DAT uptake levels have become a reliable indicator for evaluating PD progression [15]. This is a more objective approach than the UPDRS score and is rarely used to assess the effects of antihypertensive drugs on PD [7, 16]. In our study, UPDRS III score, H&Y stage and DAT uptake level were used to assess the development of PD. The focus was on evaluating the effect of antihypertensive drugs in PD using DAT uptake levels from PPMI.

2. Methods

2.1. Study design

Data used in the preparation of this article were obtained from the Parkinson's Progression Markers Initiative (PPMI) database (https://www.ppmi-info.org/access-data-specimens/download-data). For up-to-date information on the study, visit www.ppmi-info.org. The subjects in this study were selected from the sporadic PD group. Each patient required the following [17]: (1) An asymmetric resting tremor and bradykinesia or two of bradykinesia, resting tremor and rigidity. (2) PD diagnosed within two years. (3) Drug-naïve for PD. (4) A DAT deficit. (5) Patients entered the sporadic PD group between February 2011 and February 2015. The detailed protocol of participant selection, clinical evaluation and data collection has been described previously [18]. PPMI data were downloaded for use in the present investigation on February 10, 2022. Study was approved by the institutional review boards of 49 clinical sites (https://www.ppmi-info.org/about-ppmi/ppmi-clinical-sites) [17]. Participants provided written informed consent. The study is registered in clinicaltrials.gov as NCT01141023.

For this study, PD patients were eligible if they met the following criteria: (1) follow-up of more than 2 years; (2) patients with or without AP, hyperlipidemia (HLP) and type 2 diabetes mellitus (DM) who had detailed medication records; and (3) complete DAT data and UPDRS data. The exclusion criteria were as follows: (1) complicated with another central nervous system (CNS) disease; (2) interruption of follow-up or incomplete data; (3) patients with AP, HLP or DM who changed the dosage regimen, took drugs irregularly or interrupted medication at the follow-up; (4) patients with AH, HLP or DM who took drugs less than 2 years or were dissatisfied with drug control; and (5) patients with serious heart, lung, liver and kidney dysfunction.

These patients were divided into three groups. The PD with AH group (102 patients) using antihypertensive drugs, the PD with other CVRFs group (60 patients) using antidiabetic and/or lipid-lowering drugs, and the pure PD group (159 patients) without CVRFs. The above information was determined by collecting medical history and medication records in the PPMI database.

The clinical characteristics of enrolled patients in the PPMI study were collected, including demographics, severity of motor and nonmotor symptoms and imaging features. We extracted the MDS-UPDRS and Hoehn & Yahr (H&Y) scores as measures of impairment. The level of DAT was semiquantitatively analyzed by single photon emission computed tomography (SPECT). A standardized process was used for imaging data collection and analysis [18].

2.2. Statistical analysis

All statistical analyses were performed with IBM SPSS Statistics (ver. 26.0; IBM Corp., Armonk, NY, USA). According to the data distribution, a χ^2 test was applied to compare classified variables, and one-way ANOVA was used to compare continuous variables. Other data were analyzed by the statistical description method. Analyses of covariance (ANCOVAs) were used to eliminate potential confounding effects of age. Although our subjects differed in gender, studies showed that DAT is not affected by gender [19,20]. $p < 0.05$ was taken to indicate statistical significance.

3. Results

3.1. The demographic characteristics of PD patients

The data were obtained from a document entitled "PPMI Original Cohort from Baseline to 5 Years". A total of 423 sporadic PD subjects were included. To observe the progress of the disease, 71 subjects with imperfect DAT or UPDRS data at baseline or 2 years later were excluded. Five patients with a lack of medication information and 4 patients with central nervous system problems were also eliminated. Individual drug subjects were excluded. After that, these subjects were divided into the PD with AH group (102 cases) with antihypertensive drugs, the PD with other CVRFs group (60 cases) with lipid-lowering and/or antidiabetic drugs, and the pure PD group (159 cases), which was without CVRFs or cardiovascular drugs (Supplementary Table 1). A total of 31.78% of patients had AH. A total of 95.33% of patients were white. Detailed data are shown in Table 1. There were more men than women in the three groups of PD patients. Patients in the Pure PD group were younger. Due to the limitations of the inclusion and exclusion criteria, less than half of the PD subjects in our study had hypertension.

3.2. Analysis of baseline condition in PD patients

Compared with the Pure PD group, the UPDRS I score was significantly higher in the PD with other CVRFs group after adjusting for age ($p = 0.004$). There was no significant difference ($p > 0.05$) in each part of the UPDRS score in the other groups. Depression and anxiety scores were similar between the groups (Table 1). After adjusting for age, there were no significant differences in the DAT uptake ratio among the three groups (Table 2).

3.3. Analysis of scale assessment and DAT changes each year

The number of PD patients without levodopa medication showed a decreasing trend every year among these groups. At the first year follow-up, the PD with AH group had the highest levodopa measurement ($p = 0.037$) (Table 3). The number of people whose UPDRS III score, H&Y stage and levodopa drug-naïve status did not change at each follow-up visit gradually decreased, and no significant changes were observed in each group (Fig. 1A–C).

In the three groups, there were no distinct differences in the mean uptake level, contralateral and ipsilateral striatum uptake level and asymmetry index in the change level in the first and second years (Table 4 and Table 5). However, comparing the changes in DAT

Table 1
Characteristics of patients for the baseline condition of motor, nonmotor syndrome.

	Overall situation (n = 321)	A: Pure PD Group (n = 159)	B: PD with AH Group (n = 102)	C: PD with other CVRFs group (n = 60)	p value	F	Adjusted for age p value
Sex (%)					0.000		
Male	209 (65.1)	86 (54.1)	78 (76.5)	45 (75.0)			
Female	112 (34.9)	73 (45.9)	24 (23.5)	15 (25.0)			
Age, y	61.35 ± 9.65	58.48 ± 9.77	64.65 ± 8.19	63.33 ± 9.50	**0.000**		
Race							
Asian	6 (1.87)	2 (1.26)	1 (0.98)	3 (0.05)	0.285		
African American	4 (1.25)	0 (0)	3 (2.94)	1 (1.67)	0.107		
White	306 (95.33)	154 (96.86)	97 (95.10)	55 (91.67)	0.085		
OFF THE TOTAL	5 (1.56)	3 (1.89)	1 (0.98)	1 (1.67)			
Age at diagnosis of PD, y	6.74 ± 6.78	7.23 ± 7.50	6.49 ± 6.17	5.88 ± 5.66	0.382		
Education, y	15.64 ± 2.77	15.67 ± 2.78	15.44 ± 2.96	15.90 ± 2.44	0.588		
CVRF							
AH	102 (31.78)	0 (0)	102 (100.00)	0 (0)			
HLP	106 (33.02)	0 (0)	54 (52.90)	52 (92.90)			
DM	15 (4.67)	0 (0)	8 (7.80)	7 (12.50)			
HY Stage (%)					0.717		
Stage I	153 (47.7)	76 (47.8)	48 (47.1)	29 (48.3)			
Stage II	166 (51.7)	81 (50.9)	54 (52.9)	31 (51.7)			
Stage III	2 (0.6)	2 (1.3)	0 (0)	0 (0)			
UPDRS I score	5.51 ± 4.181	5.23 ± 3.978	5.64 ± 4.452	6.05 ± 4.240	0.402	2.642	0.073 **A vs. C:0.04**
UPDRS II score	5.76 ± 4.165	5.60 ± 4.109	5.96 ± 4.293	5.83 ± 4.142	0.788	0.481	0.618
UPDRS III score	20.73 ± 8.693	20.47 ± 9.253	21.79 ± 8.083	19.58 ± 8.081	0.258	0.633	0.532
UPDRS total score	32.00 ± 13.137	31.30 ± 13.379	33.39 ± 13.311	31.47 ± 12.180	0.430	0.521	0.594

#: Compared with the PD Group. *: Compared with the PD with AH group.
Abbreviation: AH: High blood pressure. HY: Hoehn-Yahr. UPDRS: Unified Parkinson Disease Rating Scale. BJLOT: Benton Judgment of Line Orientation Score. DAT: Dopamine transporters. GDS: Geriatric depression score. STAI: State Trait Anxiery Inventory. MoCA: Montreal Cognitive Assessment. SFT: semantic fluency total score. HVLT: Hopkins Verbal Learning Test. Rdly: Delayed recall. Trec: delayed recognition. Fprl: False alarms. LNS: Letter Number Sequencing Score.

Table 2
The Baseline condition of DAT.

	Overall situation (n = 321)	Pure PD Group (n = 159)	PD with AH Group (n = 102)	PD with other CVRFs group (n = 60)	p value	F	Adjusted for age p value
Count density ratio							
mean caudate	1.80 ± 0.495	1.84 ± 0.501	1.81 ± 0.515	1.69 ± 0.428	0.112	1.725	0.180
mean putamen	0.71 ± 0.242	0.72 ± 0.224	0.71 ± 0.259	0.68 ± 0.258	0.668	0.305	0.737
mean striatum	1.26 ± 0.347	1.28 ± 0.345	1.26 ± 0.366	1.18 ± 0.311	0.195	1.269	0.283
Contralateral							
caudate	1.65 ± 0.492	1.67 ± 0.484	1.67 ± 0.538	1.57 ± 0.426	0.385	0.661	0.517
putamen	0.61 ± 0.288	0.61 ± 0.199	0.62 ± 0.258	0.60 ± 0.246	0.760	0.168	0.845
striatum	2.26 ± 0.661	2.28 ± 0.626	2.29 ± 0.745	2.17 ± 0.596	0.484	0.521	0.595
caudate/putamen	2.86 ± 0.809	2.88 ± 0.798	2.82 ± 0.761	2.88 ± 0.918	0.848	0.136	0.873
Ipsilateral							
caudate	1.95 ± 0.544	2.01 ± 0.563	1.95 ± 0.540	1.80 ± 0.475	0.036	2.801	0.062
putamen	0.80 ± 0.303	0.82 ± 0.300	0.79 ± 0.309	0.77 ± 0.302	0.446	0.615	0.541
striatum	2.76 ± 0.799	2.83 ± 0.824	2.75 ± 0.796	2.57 ± 0.710	0.086	1.985	0.139
caudate/putamen	2.56 ± 0.633	2.56 ± 0.593	2.61 ± 0.666	2.50 ± 0.680	0.530	0.654	0.521
Asymmetry Index							
caudate	19.75 ± 14.929	20.34 ± 13.720	20.03 ± 17.713	17.70 ± 12.742	0.496	0.846	0.430
putamen	32.67 ± 21.536	33.61 ± 21.685	32.52 ± 21.618	30.45 ± 21.183	0.624	0.249	0.779
striatum	22.10 ± 14.754	23.02 ± 13.266	22.16 ± 17.289	19.57 ± 13.743	0.306	1.075	0.343

Table 3
Changes in DAT levels.

	Overall situation (n = 321)	A: Pure PD Group (n = 159)	B: PD with AH Group (n = 102)	C: PD with other CVRFs group (n = 60)	p value	F	Adjusted for age p value
first year							
Change of HY Stage (%)–off					0.621		
0	225 (70.09)	115 (72.33)	73 (71.57)	37 (61.67)			
1	1 (0.31)	1 (0.63)	0 (0)	0 (0)			
UPDRS I score	0 ± 0	0 ± 0	0 ± 0	0 ± 0			
UPDRS II score	0 ± 0	0 ± 0	0 ± 0	0 ± 0			
UPDRS III score–off	0 ± 0	0 ± 0	0 ± 0	0 ± 0			
OFF THE TOTAL	98 (30.53)	45 (28.30)	29 (28.43)	24 (40.00)			
LEDD	291.15 ± 216.43	252.85 ± 169.59	356.23 ± 273.50	275.58 ± 188.36	0.010	3.345	**0.037**
OFF THE TOTAL	123 (38.32)	64 (40.25)	37 (36.27)	22 (36.67)			
second year							
Change of HY Stage (%)–off					0.094		
−1	12 (3.74)	8 (5.03)	3 (2.94)	1 (1.67)			
0	124 (38.63)	61 (38.36)	35 (34.31)	28 (46.67)			
1	15 (4.67)	6 (3.77)	9 (8.82)	0 (0.00)			
2	2 (0.62)	1 (0.63)	0 (0)	1 (1.67)			
3	1 (0.31)	0 (0)	1 (0.98)	0 (0.00)			
UPDRS I score	1.00 ± 3.72	1.42 ± 3.52	0.68 ± 3.95	0.43 ± 3.79	0.126	2.886	0.057
UPDRS II score	0.55 ± 3.25	0.68 ± 2.95	0.57 ± 3.55	0.15 ± 3.50	0.561	0.678	0.508
UPDRS III score–off	1.93 ± 9.14	1.55 ± 8.43	2.76 ± 9.48	1.52 ± 10.50	0.748	0.245	0.783
OFF THE TOTAL	167 (52.02)	83 (52.20)	53 (51.96)	31 (51.67)			
LEDD	221.05 ± 243.72	216.17 ± 243.29	221.06 ± 284.49	234.40 ± 169.13	0.926	0.046	0.955
OFF THE TOTAL	119 (37.07)	55 (34.59)	42 (41.18)	22 (36.67)			

uptake levels, each group had their own characteristics in these two years. In the PD with AH group, the decrease in the ipsilateral putamen uptake level was slower in the second follow-up year than in the first year (Fig. 2A). The uptake levels of the ipsilateral caudate and striatum in the PD with other CVRFs group were decreased in the second year compared with the first year (Fig. 2B and C).

3.4. Changes in DAT between the groups of antihypertensive drugs

Antihypertensive drugs are mainly used alone (CCB or ACEI/ARB drugs) or in combination (CCB + ARB/ACEI drugs [8]) in middle-old-age AH patients. We only described the use of one drug regimen. Due to sample size limitations, we only performed statistical analysis on ACEI/ARB drugs. A total of 53.92% of patients in the PD with AH group received antihypertensive treatment with

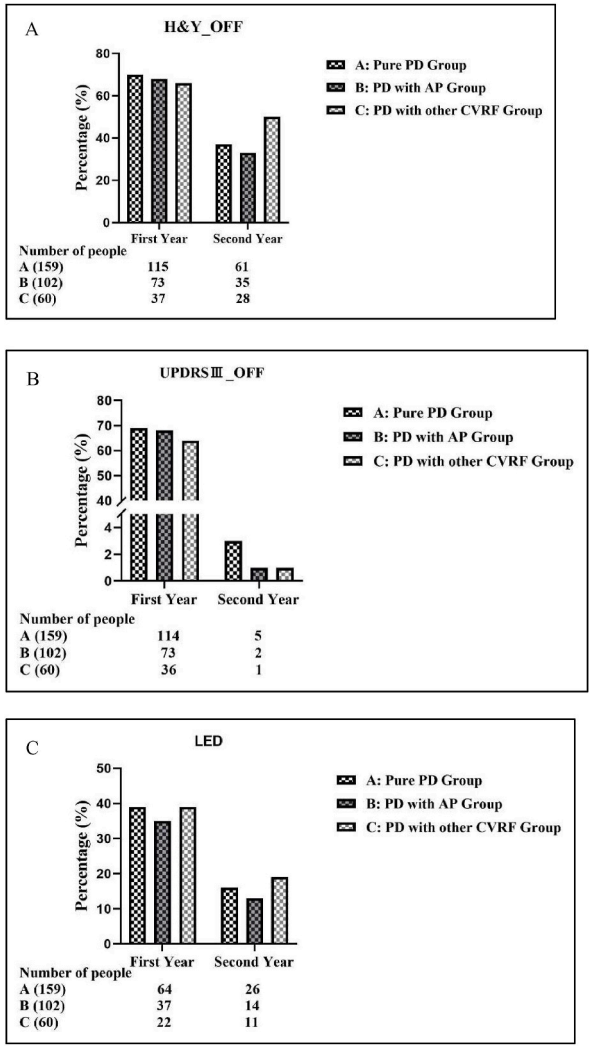

Fig. 1. Number of people without progression at each follow-up visit
A. The number of people whose H&Y_off scores remained unchanged gradually decreased.
B. There was a significant decrease in the number of UPDRSIII_off scores that remained unchanged.
C. The number of people who did not use LED decreased.
Abbreviations H&Y= Hoehn-Yahr, UPDRS=Movement Disorder Society Sponsored Revision Unified Parkinson's Disease Rating Scale, LED = Levodopa equivalent dose.

ACEIs/ARBs. There was no difference in the change in DAT level among the pure PD group, ACEI group and ARB group (Table 6).

4. Discussion

The main purpose of this study was to observe the modification effect of different antihypertensive agents on the progression of. Antihypertensive drugs are the most commonly used drugs for PD patients. The clinical data of PD patients were collected to explore the effects of different antihypertensive drugs on the progression of PD using functional imaging changes in dopaminergic neurons. Our study showed that antihypertensive drugs did not delay the decrease in each striatal subfield of DAT uptake level in patients, at least not in the 2-year follow-up period.

DAT scans were used to judge the relationship between antihypertensive drugs and dopamine neurons (DN) injury, which increased the objectivity of the assessment of PD progression [21]. The use of DAT scans to evaluate DN changes in PD progression is one of the characteristics of this research. A deficiency of DN is one of the main features of PD. The activity of DN in the brain can be directly shown by the uptake of DAT in SPECT [22]. However, previous research has not used DAT scans to evaluate the effect of antihypertensive drugs on PD patients, and it is difficult to directly assess the activity of DN. In this study, there was no significant difference in DAT uptake among the groups in the follow-up period. The use of antihypertensive drugs may not delay DN damage. After the

Table 4
Changes in 1 year of DAT.

	Overall situation (n = 321)	Pure PD Group (n = 159)	PD with AH Group (n = 102)	PD with other CVRFs group (n = 60)	p Value	F	Adjusted for age P value
Count density ratio							
mean caudate	−0.2033 ± 0.291	−0.2055 ± 0.319	−0.1884 ± 0.226	−0.223 ± 0.313	0.759	0.194	0.824
mean putamen	−0.1161 ± 0.166	−0.1168 ± 0.162	−0.1153 ± 0.160	−0.1153 ± 0.187	0.997	0.045	0.956
mean striatum	−0.1597 ± 0.201	−0.1611 ± 0.215	−0.1519 ± 0.163	−0.1692 ± 0.226	0.864	0.157	0.855
Contralateral							
caudate	−0.1858 ± 0.311	−0.1931 ± 0.244	−0.1696 ± 0.257	−0.1937 ± 0.305	0.818	0.095	0.909
putamen	−0.0739 ± 0.189	−0.0688 ± 0.189	−0.0757 ± 0.193	−0.0842 ± 0.187	0.861	0.174	0.840
striatum	−0.2596 ± 0.414	−0.2619 ± 0.441	−0.2453 ± 0.361	−0.2778 ± 0.430	0.886	0.855	0.426
caudate/ putamen	0.0163 ± 0.984	−0.013 ± 0.938	0.025 ± 1.073	0.0791 ± 0.957	0.822	0.226	0.798
Ipsilateral							
caudate	−0.2209 ± 0.343	−0.2178 ± 0.360	−0.2072 ± 0.279	−0.2523 ± 0.397	0.713	0.296	0.744
putamen	−0.1583 ± 0.225	−0.1648 ± 0.226	−0.155 ± 0.198	−0.1465 ± 0.265	0.853	0.250	0.779
striatum	−0.3791 ± 0.490	−0.3826 ± 0.516	−0.3622 ± 0.401	−0.3988 ± 0.560	0.893	0.199	0.819
caudate/ putamen	0.1465 ± 0.692	0.1795 ± 0.642	0.1684 ± 0.686	0.0216 ± 0.819	0.300	0.940	0.392
Asymmetry Index							
caudate	0.4733 ± 13.823	0.5856 ± 13.658	0.8451 ± 14.684	−0.4567 ± 12.903	0.838	0.425	0.654
putamen	−6.0742 ± 26.901	−7.3537 ± 27.021	−2.5987 ± 27.490	−8.5916 ± 25.386	0.275	1.489	0.227
striatum	−1.7475 ± 13.559	−2.0412 ± 12.930	−0.7707 ± 14.432	−2.6297 ± 13.792	0.653	0.855	0.426

Table 5
Changes in DAT levels over 2 years.

	Overall situation (n = 321)	Pure PD Group (n = 159)	PD with AH Group (n = 102)	PD with other CVRFs group (n = 60)	p value	F	Adjusted for age p value
Count density ratio							
mean caudate	−0.116 ± 0.284	−0.120 ± 0.304	−0.117 ± 0.252	−0.103 ± 0.284	0.929	0.253	0.776
mean putamen	−0.051 ± 0.154	−0.054 ± 0.159	−0.038 ± 0.147	−0.064 ± 0.155	0.522	0.418	0.659
mean striatum	−0.083 ± 0.198	−0.087 ± 0.213	−0.077 ± 0.171	−0.084 ± 0.201	0.926	0.224	0.800
Contralateral							
caudate	−0.112 ± 0.287	−0.109 ± 0.311	−0.106 ± 0.270	−0.131 ± 0.251	0.853	0.147	0.863
putamen	−0.044 ± 0.168	−0.043 ± 0.176	−0.034 ± 0.164	−0.061 ± 0.153	0.618	0.333	0.717
striatum	−0.156 ± 0.388	−0.152 ± 0.419	−0.141 ± 0.356	−0.192 ± 0.356	0.706	0.276	0.759
caudate/ putamen	0.101 ± 1.644	0.030 ± 0.897	0.056 ± 1.275	0.369 ± 3.104	0.374	0.870	0.420
Ipsilateral							
caudate	−0.120 ± 0.342	−0.131 ± 0.351	−0.128 ± 0.304	−0.076 ± 0.379	0.548	0.777	0.461
putamen	−0.058 ± 0.216	−0.066 ± 0.218	−0.041 ± 0.213	−0.068 ± 0.218	0.615	0.337	0.714
striatum	−0.178 ± 0.0.489	−0.196 ± 0.512	−0.169 ± 0.429	−0.143 ± 0.525	0.756	0.512	0.600
caudate/ putamen	0.061 ± 0.744	0.084 ± 0.675	0.024 ± 0.857	0.065 ± 0.721	0.820	0.112	0.894
Asymmetry Index							
caudate	1.179 ± 13.650	0.561 ± 13.545	0.913 ± 14.231	3.270 ± 12.922	0.414	0.725	0.485
putamen	−0.153 ± 28.501	−0.060 ± 27.942	−0.552 ± 27.868	0.277 ± 31.384	0.983	0.040	0.960
striatum	0.163 ± 13.439	−0.060 ± 13.321	−0.462 ± 14.432	1.817 ± 12.010	0.558	0.496	0.610

subgroup analysis of the antihypertensive drugs used, ACEIs and ARBs had similar effects. Other research has shown that ARBs may have a beneficial effect on PD [11]. This result was presented with some theoretical support. Dopamine depletion and age-related declines in dopaminergic activity lead to overactivation of the local renin angiotensin system (RAS), which may cause DN degeneration and α-syn aggregation [23]. Therefore, cutting off the RAS pathway may be an effective neuroprotective strategy for the brain. However, the UPDRS scale and the small number of patients may bias the study results. Therefore, increased sample size and long-term follow-up of patients using ACEI/ARB drugs and simultaneous evaluation using DAT would be required to generate more convincing results.

PD patients may have AH and BP pattern can be shifted towards nocturnal hypertension during the PD course [4]. And even BP may go to orthostatic hypotension (OH) over time. OH occurs as a result of defect in the release of norepinephrine from sympathetic terminals during standing and is now considered an important marker in PD progression [24]. None of the patients suffered from OH during the 2-year follow-up period in this study. Patient medication records showed that 7 patients developed OH after more than 2 years of follow-up (mean 3.5 years) (Results are not presented in the text). Patients in the PD with AH group were not included in these seven patients. It is speculated that the use of antihypertensive drugs may have a protective effect on autonomic nerves in PD patients.

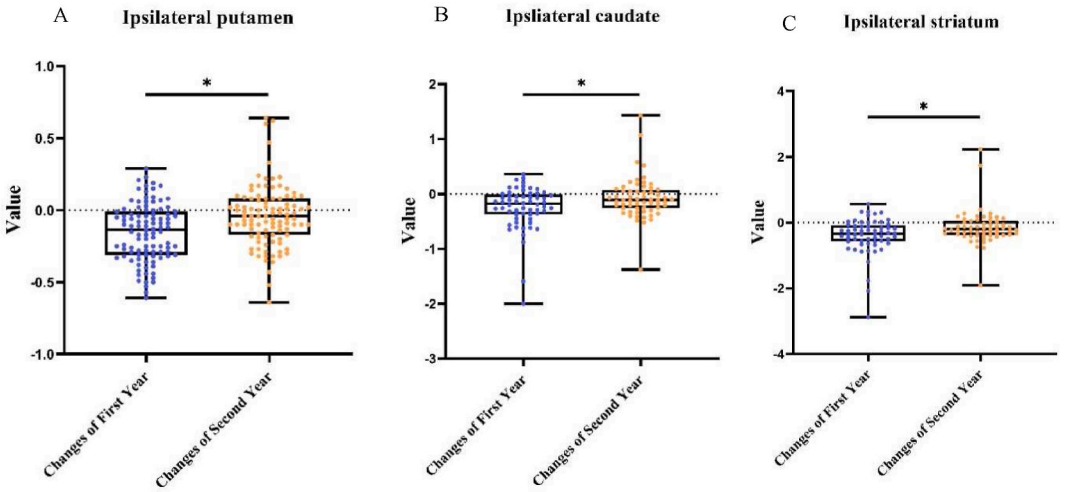

Fig. 2. Brain regions with significant differences in levels of DAT annual change
A. There were significant differences in uptake rate changes in the ipsilateral putamen each year in PD with AH Group.
B. There were significant differences in uptake rate changes in the ipsilateral putamen each year in PD with other CVRF Group.
C. There were significant differences in uptake rate changes in the ipsilateral striatum each year in PD with other CVRF Group.
*$p < 0.05$.

Table 6
Changes in DAT levels.

	Pure PD Group (n = 159)	ACEI (n = 35)	ARB (n = 19)	p Value	F	Adjusted for age P value
first year						
Count density ratio						
mean caudate	−0.2033 ± 0.291	−0.17 ± 0.255	−0.18 ± 0.174	0.782	0.161	0.852
mean putamen	−0.1161 ± 0.166	−0.10 ± 0.159	−0.10 ± 0.186	0.728	0.276	0.759
mean striatum	−0.1597 ± 0.201	−0.13 ± 0.184	−0.14 ± 0.153	0.712	0.252	0.778
Contralateral						
caudate	−0.1858 ± 0.311	−0.17 ± 0.285	−0.12 ± 0.192	0.643	0.335	0.716
putamen	−0.0739 ± 0.189	−0.04 ± 0.176	−0.09 ± 0.208	0.669	0.394	0.675
striatum	−0.2596 ± 0.414	−0.21 ± 0.386	−0.21 ± 0.334	0.755	0.181	0.834
caudate/putamen	0.0163 ± 0.984	−0.15 ± 0.674	0.22 ± 1.146	0.373	1.030	0.359
Ipsilateral						
caudate	−0.2209 ± 0.343	−0.17 ± 0.317	−0.23 ± 0.209	0.761	0.167	0.846
putamen	−0.1583 ± 0.225	−0.15 ± 0.202	−0.10 ± 0.195	0.472	0.792	0.454
striatum	−0.3791 ± 0.490	−0.32 ± 0.444	−0.33 ± 0.335	0.763	0.228	0.796
caudate/putamen	0.1465 ± 0.692	0.16 ± 0.552	−0.10 ± 0.891	0.203	1.673	0.190
Asymmetry Index						
caudate	0.4733 ± 13.823	4.17 ± 15.685	−3.43 ± 12.087	0.147	1.813	0.166
putamen	−6.0742 ± 26.901	−4.52 ± 22.851	0.87 ± 23.154	0.398	0.973	0.380
striatum	−1.7475 ± 13.559	1.47 ± 14.823	−2.23 ± 12.664	0.353	0.925	0.398
second year						
Count density ratio						
mean caudate	−0.116 ± 0.284	−0.11 ± 0.26	−0.09 ± 0.21	0.888	0.271	0.763
mean putamen	−0.051 ± 0.154	−0.05 ± 0.17	−0.05 ± 0.15	0.959	0.066	0.937
mean striatum	−0.083 ± 0.198	−0.08 ± 0.19	−0.07 ± 0.15	0.924	0.192	0.826
Contralateral						
caudate	−0.112 ± 0.287	−0.10 ± 0.28	−0.10 ± 0.26	0.979	0.104	0.901
putamen	−0.044 ± 0.168	−0.05 ± 0.13	−0.05 ± 0.17	0.978	0.012	0.988
striatum	−0.156 ± 0.388	−0.15 ± 0.36	−0.15 ± 0.35	0.998	0.038	0.963
caudate/putamen	0.101 ± 1.644	−0.09 ± 0.61	0.47 ± 2.35	0.241	1.403	0.248
Ipsilateral						
caudate	−0.120 ± 0.342	−0.12 ± 0.34	−0.07 ± 0.24	0.789	0.366	0.694
putamen	−0.058 ± 0.216	−0.04 ± 0.27	−0.06 ± 0.18	0.864	0.190	0.827
striatum	−0.178 ± 0.0.489	−0.16 ± 0.54	−0.13 ± 0.35	0.835	0.305	0.738
caudate/putamen	0.061 ± 0.744	0.11 ± 1.00	0.21 ± 0.81	0.771	0.259	0.772
Asymmetry Index						
caudate	1.179 ± 13.650	−1.61 ± 26.67	3.66 ± 16.08	0.432	0.849	0.429
putamen	−0.153 ± 28.501	1.29 ± 18.85	2.94 ± 35.88	0.886	0.079	0.924
striatum	0.163 ± 13.439	−2.12 ± 14.14	3.62 ± 17.09	0.348	1.003	0.369

OH impacts on activity of daily living and cognitive dysfunction [25]. So it also deserves attention. Autonomic dysfunction results in OH and/or supine hypertension. And then white matter may be damaged and subsequent cognitive decline may arise. Therefore, early adjustment of dopaminergic therapy and intervention of CVRF are effective ways to prevent OH in PD patients. Because both are related to cardiovascular autonomic and cognitive condition dysfunction [25]. Unfortunately, this was not explored further due to objective limitations of the database in this research.

Our study found that the DAT uptake decreased less in the ipsilateral striatal region in the PD with AH group and the PD with other CVRFs group in the second year compared to the first year. Similar changes were not observed in the pure PD group. However, no intergroup differences were observed in the lateral comparison of the three groups. This phenomenon may be related to the use of cardiovascular-related drugs that may exert some protective effect on dopaminergic neurons in the ipsilateral striatum region or to factors such as reducing the accumulation of reactive oxygen species in vascular tissue. The reasons for this phenomenon deserve further investigation.

However, the use of any single indicator is insufficient for assessing the overall PD progression. At present, the clinical markers used to evaluate the progression of PD are mainly included motor symptom scores (MDS-UPDRS, H&Y, falls) and the occurrence of non-motor symptoms (clinical definition of dementia and hallucinations, autonomic tests) [26]. The evaluation of the scale is easy to be doped with subjective factors. The aforementioned clinical tests are not applicable to all patients. PD is a group of disorders which related by neurodegeneration, genetic characteristics, biological and molecular abnormal condition with multiple related disease stages [27]. The detection of biomarkers are considered to be the most commonly used in clinical practice. However, an accurate and stable method for diagnosing sporadic PD has not yet been developed.

Several limitations of our study should be addressed. The medical records of PD patients with complete 2-year data were collected from the PPMI database; however, there were partially missing UPDRS-OFF data during the follow-up period, which made it difficult to analyze the UPDRS scores and H&Y stage changes during the follow-up period for all samples. Moreover, OH and horizontal hypertension in PD patients also deserve attention, especially in PD patients with AP. Unfortunately, the detailed follow-up record of blood pressure was not recorded in the PPMI database, which is also a deficiency of this study. Although the PPMI database is the largest PD database, sample size problems were inevitable after we excluded patients who did not regularly take antihypertensive medication or did not complete the DAT. With more patients, we can conduct a more comprehensive study.

5. Conclusion

In summary, this study showed that antihypertensive drugs may have no positive effect on retarding dopamine neuron damage in PD.

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All participation centers were approved by respective institutional review boards. Informed consent forms were signed by all patients. (All the data were obtained from the PPMI database.)

The statement that all authors have approved the final article is true and included in the disclosure.

Author contribution statement

Zhaoying Dong: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Rui Zuo: Analyzed and interpreted the data; Wrote the paper.

Changhong Zhang, Xiaoni Zhong: Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.

Xiaoya Zou: Analyzed and interpreted the data.

Yuan Tian: Contributed reagents, materials, analysis tools or data.

Hongzhou Zuo, Xinyi Du, Qian Yu: Performed the experiments.

Oumei Cheng: Conceived and designed the experiments; Wrote the paper.

Data availability statement

The data were collected from the Parkinson's Disease Progression Marker Initiative (PPMI) database. The subgroup is People with untreated PD.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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