RESEARCH ARTICLE

Glucagon-Like Peptide-1 Receptor Agonists and Risk of Parkinson's Disease in Patients with Type 2 Diabetes: A Population-Based Cohort Study

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ABSTRACT: Background: Previous studies have suggested that glucagon-like peptide-1 receptor agonists (GLP-1RAs) may have a disease-modifying effect in the development of Parkinson's disease (PD), but population studies yielded inconsistent results.

Objective: The aim was to compare the risk of PD associated with GLP-1RAs compared to dipeptidyl peptidase 4 inhibitors (DPP4i) among older adults with type 2 diabetes (T2D).

Methods: Using U.S. Medicare administrative data from 2016 to 2020, we conducted a population-based cohort study comparing the new use of GLP-1RA with the new use of DPP4i among adults aged ≥66 years with T2D. The primary endpoint was a new diagnosis of PD. A stabilized inverse probability of treatment weighting (sIPTW)–adjusted Cox proportional hazards regression model was employed to estimate the hazard ratio (HR) and 95% confidence intervals (CI) for PD between GLP-1RA and DPP4i users.

Results: This study included 89,074 Medicare beneficiaries who initiated either GLP-1RA (n = 30,091) or DPP4i (n = 58,983). The crude incidence rate of PD was lower among GLP-1RA users than DPP4i users (2.85 vs. 3.92 patients per 1000 person-years). An sIPTW-adjusted Cox model showed that GLP-1RA users were associated with a 23% lower risk of PD than DPP4i users (HR, 0.77; 95% CI, 0.63–0.95). Our findings were largely consistent across different subgroup analyses such as sex, race, and molecular structure of GLP-1RA.

Conclusion: Among Medicare beneficiaries with T2D, the new use of GLP-1RAs was significantly associated with a decreased risk of PD compared to the new use of DPP4i. © 2024 International Parkinson and Movement Disorder Society.

Key Words: glucagon-like peptide-1 receptor agonist (GLP-1RA); dipeptidyl peptidase 4 inhibitor (DPP4i); Parkinson's disease; type 2 diabetes

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Parkinson's disease (PD) is the second-most common neurodegenerative disease, characterized by a wide range of debilitating motor and nonmotor symptoms.[1] PD represents a major public health challenge, affecting nearly 1 million people in the United States alone,[2] with this number projected to double by 2040.[3] Moreover, PD imposes a substantial economic burden on U.S. society, with costs estimated at $51.9 billion in 2017.[2] Nonetheless, there is still no available pharmacologic therapy to cure or slow the progression of PD. Although the exact etiology underlying the development of PD remains unknown, accumulative evidence has suggested linking type 2 diabetes (T2D) to PD.[4] Both conditions share common pathogenic mechanisms, such as insulin dysregulation, mitochondrial dysfunction, and neuroinflammation.[5-7] This raises the intriguing possibility that certain glucose-lowering drugs (GLD) used to treat T2D may also hold the potential for preventing or treating PD.

Glucagon-like peptide-1 receptor agonists (GLP-1RA) are a newer class of GLDs that have gained popularity due to their benefits beyond glycemic control, including cardiovascular, renal, and weight loss benefits.[8] Importantly, preclinical studies have shown neuroprotective effects of GLP-1RAs, including improvements in motor function and cognition, mediated through their ability to ameliorate insulin resistance and inflammation.[9] However, population studies examining the association between GLP-1RAs and risk of PD yielded conflicting results,[10-12] which may be attributable to the selection of a comparator. Dipeptidyl peptidase 4 inhibitors (DPP4i) shared similar mechanisms of action with GLP-1RAs, lowering glucose levels, and both drug classes are recommended as second-line treatments for T2D,[13] making DPP4i an ideal comparator for minimizing confounding by indication. Furthermore, DPP4is are not associated with an increased risk of PD.[14] Given the additional benefits of GLP-1RAs such as cardiovascular, renal, and weight loss benefits,[8] it remains unclear whether GLP-1RAs could confer additional neuroprotective benefits and subsequently reduce the risk of PD to a greater extent compared to DPP4i. Therefore, we conducted a population-based cohort study to assess the risk of PD associated with GLP-1RAs among older individuals with T2D compared to DPP4i.

Patients and Methods

Study Design and Data Source

This study was a retrospective population-based cohort study using an active-comparator, new-user study design to evaluate the risk of PD associated with GLP-1RAs compared to DPP4i in Medicare administrative data (Medicare) (Fig. S1).

Medicare is a federal health insurance program that primarily provides medical coverage for the U.S. population aged ≥65 years, including Part A (inpatient), Part B (outpatient physician services), and Part D (dispensed prescription drugs) coverage. The Medicare database included longitudinal, individual-level data such as demographics, inpatient and outpatient diagnoses and procedures, and pharmacy claims. For this study, we accessed data from a 15% random sample of all Medicare beneficiaries with fee-for-service coverage of Medicare Parts A, B, and D between January 2016 and December 2020. This study was approved by the University of Florida Institutional Review Board.

Study Population

To ensure comprehensive medical records for patients, this study included patients aged ≥66 years who were continuously enrolled in Medicare Parts A, B, and D for at least 1 year before the cohort entry date (index date). The study population consisted of patients diagnosed with T2D who initiated treatment with GLP-1RA or DPP4i between January 1, 2017, and December 31, 2020. The drugs included in GLP-1RA and DPP4i are summarized in Table S1. The index date was the day of the first prescription for GLP-1RA or DPP4i defined as without a previous prescription for either drug within the preceding year. To identify individuals with T2D, we identified those with a diagnosis of diabetes using the Chronic Conditions Warehouse data and excluded those with an International Classification of Diseases (ICD) code of type 1 diabetes.[15] DPP4is were selected as the active comparator due to their similarity in clinical indications and mechanisms of action compared to GLP-1RAs,[13] aiming to minimize potential confounding by indication. Also, previous studies suggest that DPP4i are not associated with an increased risk of PD,[14] making them a suitable comparator for evaluating the potential neuroprotective effects of GLP-1RAs.

Individuals were excluded if they had the following diagnoses and treatments during the baseline period: any form of parkinsonism, Lewy body dementia, end-stage renal disease, and prior exposure to anti-PD medications (eg, levodopa [L-dopa], dopamine agonist, monoamine oxidase inhibitors, and entacapone). The definitions of the aforementioned conditions are summarized in Table S2. The individuals who started treatment with both GLP-1RA and DPP4i on the index date were also excluded.

Study Outcome and Follow-Up

The outcome of interest in this study was a new diagnosis of PD, determined by having at least two diagnosis codes for PD per individual. Using this approach to identify PD patients yielded a sensitivity of 89.6% and

a positive predictive value (PPV) of 79.4%.[16] The first diagnosis date during the follow-up defined the outcome date. The ICD diagnosis codes used for identifying PD are presented in Table S2.

Because PD is an irreversible and chronic disease, we followed the "intention-to-treat" principle of randomized controlled trial analysis, which did not censor data on the discontinuation of the index drug (switching to or addition of the comparator). The individuals were followed up from the day after cohort entry through the first occurrence of the following events: a study outcome; death; disenrollment from Parts A, B, or D; and the end of the study period (December 31, 2020).

Statistical Analysis

We calculated the incidence rate (IR) of PD for GLP-1RA and DPP4i groups and employed a Cox proportional hazards regression model to estimate the hazard ratio (HR) and 95% confidence interval (CI) of PD between the two groups.[17] We included a broad set of baseline covariates as potential confounders, including demographic characteristics, comorbidities, and comedications. These covariates were selected based on clinical experience and literature,[18] and were obtained 1 year before or on the index date (Table 1). To account for the nonrandom allocation of individuals receiving the treatment, a stabilized inverse probability of treatment weighting (sIPTW) was applied to reduce the effects of confounding. The sIPTW created a pseudo-population in that the distribution of measured baseline covariates was independent of treatment selection.[17] sIPTW was derived from propensity score (PS), which was calculated using a multivariable logistic regression model that modeled the probability of each patient initiating a GLP-1RA, including baseline covariates as provided in Table 1. We assessed the balance of baseline covariate before and after weighted cohorts using standardized mean differences (SMD), with a value <0.1 suggesting a negligible imbalance between the two groups.[19] We also plotted the cumulative incidence of PD using an sIPTW-adjusted Kaplan–Meier plot.

We conducted several sensitivity analyses to assess the robustness of our findings. First, we created a 1:1 PS-matched cohort using a nearest-neighbor matching without a replacement approach within a maximum caliper width of 0.05.[20] Second, we applied an "as-treated" analysis that accounted for treatment discontinuation of the index drug (defined as 60 days elapsed after the expiration date of the last prescription's supply without the prescription being refilled) or switching to or addition of the comparator. An additional follow-up up to 1 year after censoring was applied. Third, to address the competing risk of all-cause mortality, we employed a Cox proportional hazards model with the Fine and Gray method to estimate the adjusted subdistribution HR for PD.[21] Fourth, to minimize potential reverse causality bias, where underlying prodromal PD may have influenced treatment selection, we excluded patients who had a PD diagnosis within the first 6 months after the index date. Moreover, we quantified the association between GLP-1RAs and PD and tested the potential interaction in the following subgroups: (1) age (≥75 vs. <75 years); (2) sex (female vs. male); (3) race/ethnicity (non-Hispanic White population vs. non-Hispanic Black population vs. Hispanic population vs. others); (4) GLD use at baseline (insulin vs. no GLD vs. one GLD [excluding insulin] vs. ≥two GLDs [excluding insulin]); (5) obesity at baseline (yes vs. no); (6) chronic kidney disease (CKD) at baseline (yes vs. no); (7) atherosclerotic cardiovascular disease (ASCVD) at baseline (yes vs. no); and (8) molecular structure of GLP-1RA (exenatide vs. dulaglutide vs. liraglutide vs. semaglutide).

In addition, to assess the potential unmeasured confounder between GLP-1RAs and risk of PD, we calculated the *E*-value.[22] The *E*-value provides an assumption-free estimate of an unmeasured confounder that would be necessary to negate the observed results.[22] A *P*-value <0.05 was considered statistically significant. All statistical analyses were performed using SAS, version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Study Population

This study included 89,074 individuals who initiated either GLP-1RA (n = 30,091) or DPP4i (n = 58,983) (Fig. 1). The baseline characteristics of the study population are presented in Table 1. GLP-1RA initiators were younger than DPP4i initiators, with mean ages of 72.7 and 76.3 years, respectively. Additionally, new users of GLP-1RA had a higher proportion of non-Hispanic Whites (77.8% vs. 68.8%), obesity (40.8% vs. 24.7%), insulin use (42.2% vs. 18.2%), diabetic retinopathy (13.0% vs. 9.9%), and diabetic neuropathy (32.2% vs. 27.3%) and a lower proportion of Alzheimer's disease and related dementias (ADRD) (9.6% vs. 18.9%) and stroke/transient ischemic attack (TIA) (12.9% vs. 19.4%) than new users of DPP4i. The median duration of follow-up for PD was 1.54 years (interquartile range, 0.75–2.53) in the GLP-1RA group and 1.75 (interquartile range, 0.83–2.77) in the DPP4i group. After sIPTW (Table 1), all baseline covariates were well balanced with SMDs <0.1.[23]

Risk of PD

Of the study cohort, 143 of 30,091 GLP-1RA users developed PD (IR, 2.85 cases per 1000 person-years), whereas 424 of 58,983 DPP4i users developed PD (IR, 3.92 cases per 1000 person-years), leading to an

TABLE 1 *Baseline characteristics of patients included in the study*

Characteristic	Original cohort			SMD	
	All (n = 89,074)	GLP-1RA (n = 30,091)	DPP4i (n = 58,983)	Before sIPTW	After sIPTW
Age (y), mean (SD)	75.1 (6.8)	72.7 (5.3)	76.3 (7.2)	−0.57	0.004
Female	48,740 (54.7%)	15,868 (52.7%)	32,872 (55.7%)	−0.06	−0.005
Race/ethnicity					
Non-Hispanic Whites	63,984 (71.8%)	23,423 (77.8%)	40,561 (68.8%)	0.21	0.000
Non-Hispanic Black	8755 (9.8%)	2543 (8.5%)	6212 (10.5%)		
Hispanic	9767 (11.0%)	2406 (8.0%)	7361 (12.5%)		
Others	6568 (7.4%)	1719 (5.7%)	4849 (8.2%)		
Medicare and Medicaid dual eligibility	24,826 (27.9%)	6192 (20.6%)	18,634 (31.6%)	−0.253	0.011
Low-income subsidy	27,845 (31.3%)	7167 (23.8%)	20,678 (35.1%)	−0.249	0.012
Diabetes-related conditions					
Diabetes retinopathy	9740 (10.9%)	3905 (13.0%)	5835 (9.9%)	0.097	0.004
Diabetic neuropathy	25,787 (29.0%)	9675 (32.2%)	16,112 (27.3%)	0.106	0.003
Peripheral vascular disease	18,958 (21.3%)	5645 (18.8%)	13,313 (22.6%)	−0.094	0.001
Hypoglycemia	2413 (2.7%)	664 (2.2%)	1749 (3.0%)	−0.048	−0.014
Hyperglycemic emergency	343 (0.4%)	120 (0.4%)	223 (0.4%)	0.003	0.004
Comorbid conditions					
Acute myocardial infarction	6065 (6.8%)	1731 (5.8%)	4334 (7.3%)	−0.065	0.008
Alzheimer's disease and related dementias	14,009 (15.7%)	2878 (9.6%)	11,131 (18.9%)	−0.269	0.013
Atrial fibrillation	15,734 (17.7%)	4375 (14.5%)	11,359 (19.3%)	−0.126	−0.001
Cataract	57,031 (64.0%)	17,445 (58.0%)	39,586 (67.1%)	−0.190	0.008
Chronic kidney disease	63,930 (71.8%)	22,050 (73.3%)	41,880 (71.0%)	0.051	0.007
Chronic obstructive pulmonary disease	26,044 (29.2%)	7707 (25.6%)	18,337 (31.1%)	−0.122	0.012
Chronic heart failure	30,180 (33.9%)	8889 (29.5%)	21,291 (36.1%)	−0.140	0.010
Glaucoma	23,363 (26.2%)	6793 (22.6%)	16,570 (28.1%)	−0.127	−0.010
Hip or pelvic fracture	2284 (2.6%)	417 (1.4%)	1867 (3.2%)	−0.120	0.015
Ischemic heart disease	53,146 (59.7%)	16,802 (55.8%)	36,344 (61.6%)	−0.118	0.000
Depression	34,801 (39.1%)	11,731 (39.0%)	23,070 (39.1%)	−0.003	0.005
Osteoporosis	15,540 (17.4%)	3859 (12.8%)	11,681 (19.8%)	−0.190	−0.001
Rheumatoid arthritis/osteoarthritis	56,390 (63.3%)	18,440 (61.3%)	37,950 (64.3%)	−0.063	0.010
Stroke/TIA	15,310 (17.2%)	3883 (12.9%)	11,427 (19.4%)	−0.177	0.011
Breast cancer	5115 (5.7%)	1528 (5.1%)	3587 (6.1%)	−0.044	0.002
Colorectal cancer	2573 (2.9%)	659 (2.2%)	1914 (3.2%)	−0.065	0.005
Prostate cancer	5250 (5.9%)	1599 (5.3%)	3651 (6.2%)	−0.038	0.004
Lung cancer	1292 (1.5%)	300 (1.0%)	992 (1.7%)	−0.060	−0.006
Endometrial cancer	1110 (1.2%)	352 (1.2%)	758 (1.3%)	−0.011	0.004
Anemia	54,572 (61.3%)	16,357 (54.4%)	38,215 (64.8%)	−0.214	0.007

(Continues)

TABLE 1 *Continued*

Characteristic	Original cohort			SMD	
	All (n = 89,074)	GLP-1RA (n = 30,091)	DPP4i (n = 58,983)	Before sIPTW	After sIPTW
Asthma	15,379 (17.3%)	5049 (16.8%)	10,330 (17.5%)	−0.020	0.002
Hyperlipidemia	84,295 (94.6%)	28,423 (94.5%)	55,872 (94.7%)	−0.012	0.002
Benign prostate hyperplasia	20,363 (22.9%)	6479 (21.5%)	13,884 (23.5%)	−0.048	0.002
Hypertension	85,481 (96.0%)	28,754 (95.6%)	56,727 (96.2%)	−0.031	0.003
Acquired hypothyroidism	29,357 (33.0%)	9615 (32.0%)	19,742 (33.5%)	−0.032	−0.005
Inflammatory bowel disease	1027 (1.2%)	327 (1.1%)	700 (1.2%)	−0.009	−0.001
Obesity	26,827 (30.1%)	12,277 (40.8%)	14,550 (24.7%)	0.349	−0.003
Medications					
Antidepressants	29,845 (33.5%)	10,846 (36.0%)	18,999 (32.2%)	0.349	−0.001
Angiotensin-converting enzyme inhibitors	33,372 (37.5%)	11,239 (37.4%)	22,133 (37.5%)	0.081	0.003
Angiotensin receptor blockers	32,609 (36.6%)	11,520 (38.3%)	21,089 (35.8%)	−0.004	−0.015
β-Blockers	47,230 (53.0%)	15,496 (51.5%)	31,734 (53.8%)	0.052	0.001
Calcium channel blockers	33,747 (37.9%)	10,498 (34.9%)	23,249 (39.4%)	−0.046	−0.003
Diuretics	35,671 (40.0%)	12,133 (40.3%)	23,538 (39.9%)	−0.094	−0.002
Opioids	23,882 (26.8%)	8757 (29.1%)	15,125 (25.6%)	0.009	0.007
Antibiotics	14,447 (16.2%)	4863 (16.2%)	9584 (16.2%)	0.078	−0.006
Statins	70,072 (78.7%)	24,283 (80.7%)	45,789 (77.6%)	−0.002	−0.003
Antipsychotics	1714 (1.9%)	501 (1.7%)	1213 (2.1%)	0.076	0.009
NSAIDs	19,599 (22.0%)	6869 (22.8%)	12,730 (21.6%)	−0.029	−0.008
Oral steroids	35,139 (39.4%)	11,841 (39.4%)	23,298 (39.5%)	0.030	−0.004
Antiplatelets	2132 (2.4%)	723 (2.4%)	1409 (2.4%)	−0.003	0.006
Aldosterone receptor antagonists	5595 (6.3%)	1984 (6.6%)	3611 (6.1%)	0.001	−0.003
Anticoagulants	13,492 (15.1%)	3985 (13.2%)	9507 (16.1%)	0.019	0.002
Immunosuppressants	387 (0.4%)	120 (0.4%)	267 (0.5%)	−0.081	0.002
Tumor necrosis factor inhibitors	218 (0.2%)	71 (0.2%)	147 (0.2%)	−0.008	0.000
Other GLDs					
GLD use at baseline					
Insulin	23,465 (26.3%)	12,709 (42.2%)	10,756 (18.2%)	0.565	0.052
No GLD	8942 (10.0%)	2100 (7.0%)	6842 (11.6%)		
1 GLD (excluding insulin)	30,301 (34.0%)	7173 (23.8%)	23,128 (39.2%)		
≥2 GLDs (excluding insulin)	26,366 (29.6%)	8109 (26.9%)	18,257 (31.0%)		
Metformin	59,119 (66.4%)	20,099 (66.8%)	39,020 (66.2%)	0.014	0.003
Sulfonylureas	37,346 (41.9%)	11,703 (38.9%)	25,643 (43.5%)	−0.093	0.022
SGLT2 inhibitors	8890 (10.0%)	4099 (6.9%)	4791 (15.9%)	0.285	0.004

(Continues)

TABLE 1 *Continued*

Characteristic	Original cohort			SMD	
	All (n = 89,074)	GLP-1RA (n = 30,091)	DPP4i (n = 58,983)	Before sIPTW	After sIPTW
Thiazolidinediones	6746 (7.6%)	2611 (8.7%)	4135 (7.0%)	0.062	0.006
Meglitinides	1695 (1.9%)	525 (1.7%)	1170 (2.0%)	−0.018	0.008
α-Glucosidase inhibitors	460 (0.5%)	139 (0.5%)	321 (0.5%)	−0.012	0.004

Abbreviations: SMD, standardized mean difference; GLP-1RA, glucagon-like peptide-1 receptor agonist; DPP4i, dipeptidyl peptidase 4 inhibitor; sIPTW, stabilized inverse probability of treatment weighting; SD, standard deviation; TIA, transient ischemic attack; NSAID, nonsteroidal anti-inflammatory drugs; GLD, glucose-lowering drug; SGLT2 inhibitors, sodium-glucose cotransporter 2 inhibitors.

unadjusted HR of 0.73 (95% CI, 0.60–0.88) (Table 2). The sIPTW-adjusted Kaplan–Meier plot provided the cumulative incidence of PD over time (Fig. 2), showing a significantly lower risk of PD in the GLP-1RA group compared to the DPP4i group (log-rank test, $P = 0.02$). Within the sIPTW-adjusted Cox proportional hazards model, GLP-1RAs were significantly associated with a lower risk of PD than DPP4i (HR, 0.77; 95% CI, 0.63–0.95).

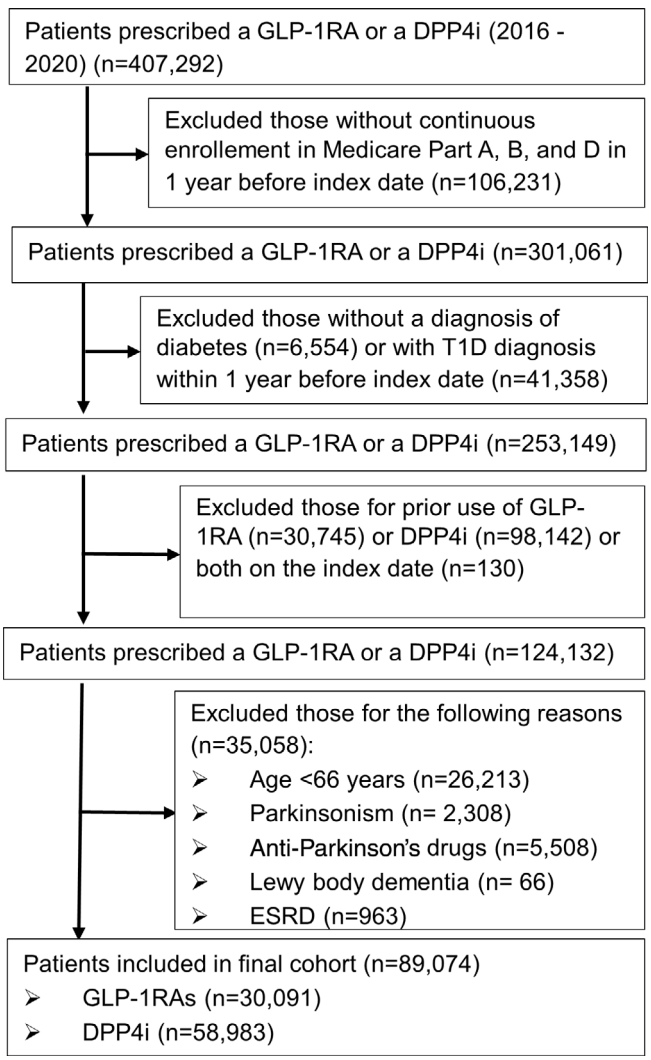

FIG. 1. Flowchart of patient selection. DPP4i, dipeptidyl peptidase 4 inhibitor; ESRD, end-stage renal disease; GLP-1RAs, glucagon-like peptide-1 receptor agonists; T1D, type 1 diabetes.

Sensitivity and Subgroup Analyses

In the sensitivity analyses, the results were consistent when using a 1:1 PS matching Cox model (HR, 0.73; 95% CI, 0.58–0.92), an "as-treated" approach (HR, 0.65; 95% CI, 0.52–0.82), and the Fine and Gray method (HR, 0.80; 95% CI, 0.64–0.98). However, the association between GLP-1RA and decreased risk of PD was attenuated when those with a diagnosis of PD were excluded within the first 6 months after the index date (HR, 0.80; 95% CI, 0.57–1.14).

The results of subgroup analyses are shown in Figure 3. The treatment effects were consistent across the subgroups by factors such as age, sex, race/ethnicity, a diagnosis of obesity at baseline, a diagnosis of CKD at baseline, a diagnosis of ASCVD at baseline, and the molecular structure of GLP-1RA. However, GLD use at baseline appeared to be a potential modifier

TABLE 2 *Association between GLP-1RAs and risk of Parkinson's disease*

Analysis	Parkinson's disease
Number of cases/number of patients at risk (%)	
GLP-1RA	143/30,091 (0.48)
DPP4i	424/58,983 (0.72)
Incidence rate (number of cases/1000 person-years)	
GLP-1RAs	2.85
DPP4i	3.92
Crude HR (95% CI)	0.73 (0.60–0.88)
sIPTW adjusted HR (95% CI)	0.77 (0.63–0.95)

Abbreviations: GLP-1RA, glucagon-like peptide-1 receptor agonist; DPP4i, dipeptidyl peptidase 4 inhibitor; HR, hazard ratio; CI, confidence interval; sIPTW, stabilized inverse probability of treatment weighting.

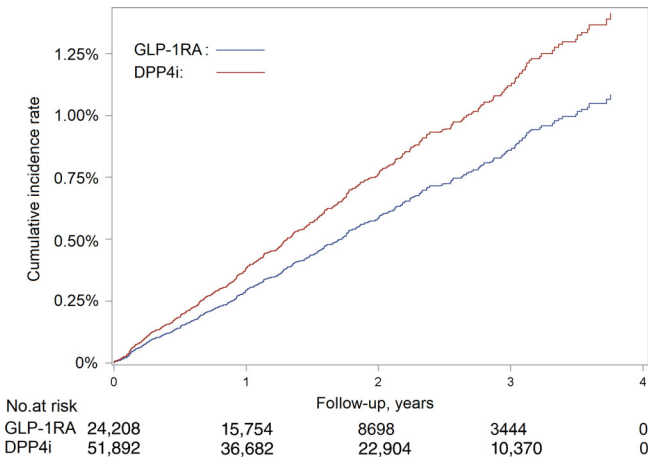

FIG. 2. Cumulative incidence of Parkinson's disease in sIPTW GLP-1RA and DPP4i cohorts. DPP4i, dipeptidyl peptidase 4 inhibitors; GLP-1RAs, glucagon-like peptide-1 receptor agonists; sIPTW, stabilized inverse probability of treatment weighting. [Color figure can be viewed at wileyonlinelibrary.com]

of the association between GLP-1RA and risk of PD ($P = 0.01$ for interaction). Patients using insulin at baseline seemed to derive greater benefits from GLP-1RAs (HR, 0.51; 95% CI, 0.36–0.72) compared to those using one GLD at baseline (excluding insulin) (HR, 1.12; 95% CI, 0.75–1.68).

E-value

The *E*-value for the risk of PD between GLP-1RA and DPP4i was 1.92. This suggests that the observed association could be explained by an unmeasured confounder that was associated with both GLP-1RA use and PD, with at least a risk ratio of 1.92-fold each.

Discussion

In this population-based cohort study of U.S. older adults with T2D, we found that new users of

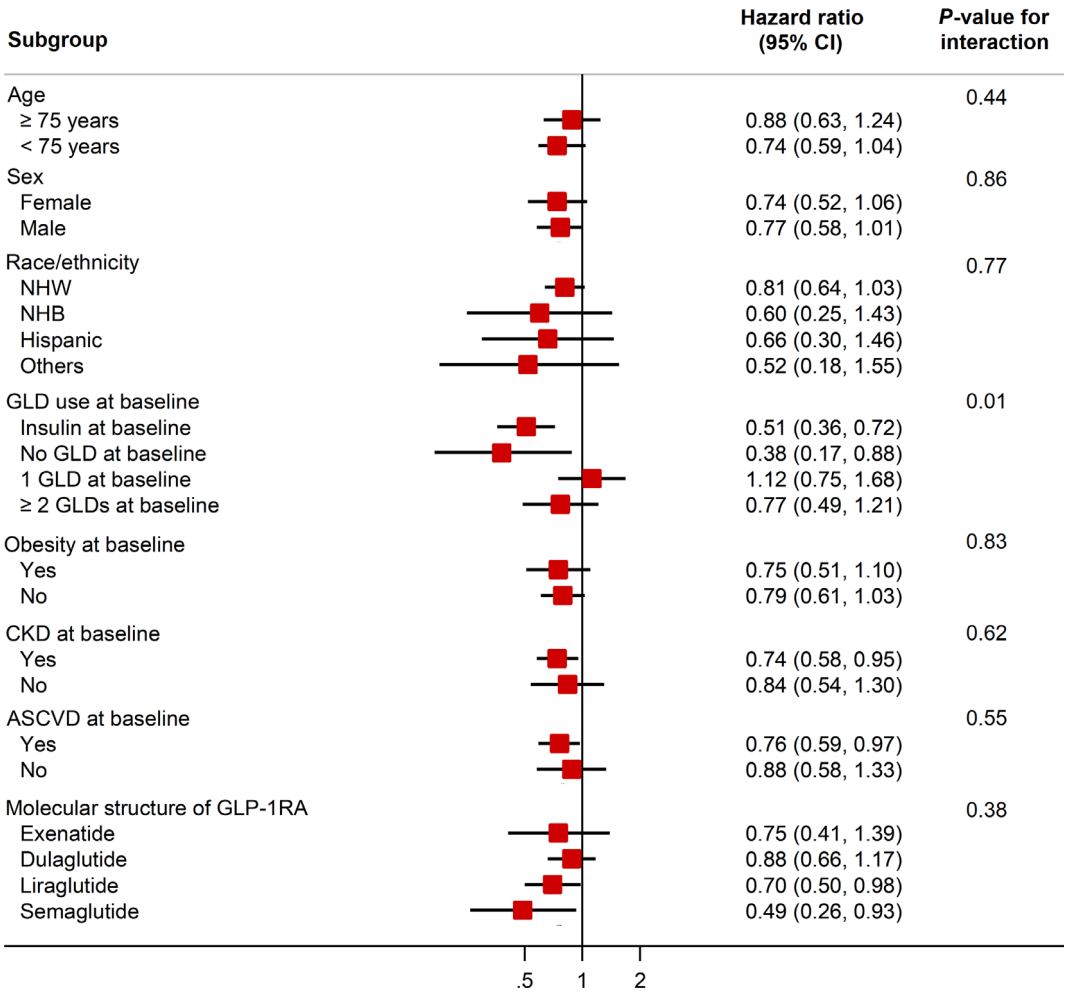

FIG. 3. Subgroup analyses of the association between GLP-1RA and risk of Parkinson's disease in sIPTW (stabilized inverse probability of treatment weighting) GLP-1RA (glucagon-like peptide-1 receptor agonist) and DPP4i (dipeptidyl peptidase 4 inhibitor) cohorts. ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; GLD, glucose-lowering drug; NHB, non-Hispanic Black; NHW, non-Hispanic White. [Color figure can be viewed at wileyonlinelibrary.com]

GLP-1RAs had a significantly decreased risk of new-onset PD compared to new users of DPP4i. However, the association between GLP-1RA and a decreased risk of PD was attenuated in a sensitivity analysis that excluded patients with a diagnosis of PD within the first 6 months after the index date. Our findings were generally consistent across various subgroups stratified by factors such as sex, race, and molecular structure of GLP-1RA. GLD use at baseline appeared to potentially modify the association between GLP-1RA and risk of PD.

Our finding of a lower risk of PD associated with GLP-1RAs is supported by emerging evidence from multiple mechanistic studies.[24-27] In preclinical models of PD, GLP-1RAs manifested neuroprotective effects by improving motor function, rescuing dopaminergic neuronal loss and motor impairment, restoring dopamine synthesis, and increasing cortical activity and energy utilization in the brain.[24-27] Importantly, GLP-1RAs may attenuate dyskinesia, a complication of chronic L-dopa replacement therapy.[28] Early clinical trials showed promising signals of potential disease modification with exenatide (a GLP-1RA) among individuals with PD.[29-32] A trial involving 62 individuals with moderate PD reported positive and sustained improvements in motor function over 12 weeks after the administration of exenatide.[29] Then, a post hoc analysis indicated the potential benefits of exenatide for nonmotor symptoms like mood and emotional well-being, although these effects were transient.[30] However, another trial found no benefits in motor or nonmotor symptoms in individuals with early untreated PD receiving NLY01 (a brain-penetrant, pegylated, long-lasting version of exenatide), though a possible motor benefit was observed in younger individuals (age <60 years).[33] In a phase 2 trial including participants with early PD, lixisenatide therapy resulted in less progression of motor disability at 12 months.[34]

Our observation of a significantly lower risk of PD in GLP-1RA users than in DPP4i users aligns with the enhanced ability of GLP-1RAs to activate GLP-1 receptors, surpassing the effects achieved through increasing endogenous GLP-1 levels with DPP4i.[35] Previous research has indicated that GLP-1RAs can cross the blood–brain barrier and exert their neuroprotective properties.[36] Thus, it is suggested that GLP-1RAs with greater brain penetrance, such as exenatide and lixisenatide, may be more likely to modify the clinical course of PD. However, our subgroup analysis did not detect a statistically significant difference in the risk of PD across different molecular structures of GLP-1RA ($P = 0.38$). These findings add to the growing body of evidence supporting the potential neuroprotective benefits of GLP-1RAs in mitigating PD development and symptom progression. However, our findings must be contextualized with regard to the recent negative clinical trial results for NLY01,[33] and further research is warranted to elucidate the mechanisms and clinical implications of our observations.

We observed an interaction effect between GLP-1RA use and other GLD use on the risk of PD. GLD use at baseline may modify the association between GLP-1RA and risk of PD. Individuals with insulin use at baseline may have greater benefits from GLP-1RAs on reducing risk of PD than those using one GLD at baseline (excluding insulin). Insulin use itself was associated with an increased risk of PD when compared to those not using insulin.[37] This suggests that GLP-1RAs may mitigate any adverse effects associated with insulin use, consequently reducing the risk of PD. Moreover, insulin use and/or number of GLDs has been considered to be proxies for the severity of diabetes.[37,38] Insulin treatment is typically prescribed for individuals with T2D who are insulin deficient and/or have failed other GLDs, and is therefore linked to severe diabetes.[38] Notably, diabetes severity has been identified as a crucial factor that significantly increases the risk of developing PD.[37] Our findings suggest that GLP-1RAs possibly attenuate the risk for PD through improved glycemic control and management of complications of T2D, as well as related deleterious neuroinflammatory effects, though this remains speculative. It is intriguing to find a decreased risk of PD associated with GLP-1RAs among individuals with no GLD use at baseline, indicating that the first-line use of GLP-1RA among individuals with T2D may have beneficial effects on the risk of developing PD, though this required further investigation.

Existing observational studies exploring the association between GLP-1RAs and risk of PD have yielded mixed results.[10-12] Two case–control studies found a nonsignificant difference between GLP-1RAs and risk of PD,[10,12] whereas one population-based cohort study using primary care data from the Health Improvement Network showed an inverse association between GLP-1RAs and onset of PD when compared with other oral GLDs in individuals with diabetes (adjusted IR ratio, 0.38; 95% CI, 0.17–0.60).[11] It should be noted that these studies had several inherent limitations, such as time-related bias,[10-12] residual confounding,[10,12] and potential exposure misclassification.[10,12] Additionally, the nonsignificant findings in the case–control study may be explained by the limited sample size of GLP-1RA users.[10,12]

Our study addressed these limitations using several strategies. First, we applied an active comparator study design using GLP-1RAs versus DPP4i, which mitigates the susceptibility to confounding bias (eg, confounding by indication).[39] The choice of DPP4i as the active comparator was appropriate given their similar mechanisms of action to GLP-1RAs and the clinical practice of using these drug classes at similar stages of

diabetes.[13] Also, previous studies have not associated DPP4i use with an increased risk of PD.[40,41] Our finding of a significantly decreased risk of PD among GLP-1RA users compared to DPP4i users indicates a potential protective role of GLP-1RAs against the development of PD. Second, we defined cohort entry as the first prescription of GLP-1RA or DPP4i and identified newer users based on a 1-year washout period, not only reducing the immortal time bias but also minimizing the influence of pre-exposure on study outcomes. These improvements in study design strengthen our findings and contribute to a more nuanced understanding of the potential relationship between GLP-1RAs and PD risk.

However, our results should be interpreted with caution in light of several important limitations. First, although our analyses adjusted for a comprehensive set of potential confounders, we recognize the inherent limitations of overadjustment in observational studies. Correcting for an extensive number of factors may introduce biases and lead to overcorrection. To provide transparency, we included the crude (unadjusted) HR in addition to the IPTW-adjusted estimates, allowing for the evaluation of the potential impact of the adjustments on the effect estimates. Nevertheless, residual confounding due to unmeasured covariates cannot be entirely ruled out. For instance, certain important confounders, such as the severity of diabetes, HbA1c, and body mass index, were unavailable in the claims data. To address this challenge, we adjusted for GLD use at baseline (eg, insulin use at baseline), a proxy for the severity of diabetes. A previous study indicated that employing an active comparator and a new user design with PS matching to proxies of diabetes severity using claims-based data yielded an enhanced balance in unmeasured baseline covariates.[42] Despite our efforts to balance baseline characteristics through IPTW, there remained a higher proportion of insulin users in the GLP-1RA group (SMD = 0.052). This small imbalance warrants cautious interpretation, as it may indicate poorer baseline glycemic control and cardiovascular outcomes, as well as more severe diabetes in the GLP-1RA group, potentially leading to an underestimation of the association between GLP-1RA and risk of PD. In this study, we also used the *E*-value to assess the potential effect of unmeasured confounding with a value of 1.92, suggesting that a moderately strong unmeasured confounder associated with both treatment and PD could potentially nullify the observed association.[22] Second, there was a potential for misclassification of PD diagnosis in this study. Incident PD was defined as having at least two medical claims with a PD diagnosis code. Although this approach seemed to be a reasonable algorithm with a sensitivity of 89.6% and a PPV of 79.4%,[43] some degree of misclassification is likely. Certain cases may have been missed or falsely classified as noncases. This misclassification could have biased our effect estimates toward or away from the null, potentially underestimating or overestimating the true effect. Third, our study has a relatively short follow-up with a median of 1.54 years for the GLP-1RA group and 1.75 years for the DPP4i group. This limited follow-up period would have impacted our ability to fully capture the long-term effects of GLP-1RAs and DPP4i on risk of PD. Also, a shorter observation window increases the potential for protopathic bias, where prodromal disease symptoms or characteristics could have influenced the initial treatment selection. Individuals with early, undiagnosed PD have a higher likelihood of receiving DPP4i rather than receiving GLP-1RA, as evidenced by the higher prevalence of ADRD and stroke/TIA among the DPP4i group than the GLP-1RA group in the original cohort. This channeling of patients with prodromal disease into the comparator group could systematically bias the results, potentially overestimating the protective association observed with GLP-1RA. Fourth, not all GLP-1RAs were available in Medicare claim data. Lixisenatide, a GLP-1RA with greater brain penetrance, would be more likely to confer neuroprotective benefits. Lixisenatide was one of the exposures of interest, but it was infrequently prescribed in Medicare Part D,[44] and no patients using lixisenatide were included in this study. Although no significant difference across the molecular structures of GLP-1RA was observed in this study, future research is warranted to determine whether the GLP-1RAs with higher brain penetrance could have more substantial benefits on reducing the development of PD. Fifth, this study employed an sIPTW as the primary analysis method to mitigate confounding bias while preserving the sample size. However, this approach has inherent limitations, including the potential for extreme weights and bias amplification. To corroborate our findings, we also performed 1:1 PS matching, which yielded similar results. Finally, this study included older individuals with T2D; thus, the generalizability of our findings to younger individuals or those without T2D remains uncertain.

Conclusions

In summary, this population-based study found that older individuals with T2D who initiated GLP-1RA therapy had a reduced risk of PD compared to those who initiated DPP4i. However, these findings should be interpreted with caution due to several limitations, such as a short follow-up duration, potential unmeasured confounders, and possible misclassification of outcome. Future research with longer follow-up and more diverse real-world populations could further clarify this association.

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Data Availability Statement

The Medicare Administrative data could be obtained through ResDAC (resdac@umn.edu).

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Supporting Data

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H.T.: 1A, 1B, 1C, 2A, 2B, 3A
Y.L.: 1C, 2C, 3B
M.S.O.: 2C, 3B
W.T.D.: 2C, 3B
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