Movement Disorders
CLINICAL PRACTICE

BRIEF REPORT

Meta-analysis of Association between Newer Glucose-Lowering Drugs and Risk of Parkinson's Disease

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ABSTRACT: Background: The association between newer classes of glucose-lowering drugs (GLDs) and the risk of Parkinson's disease (PD) remains unclear.
Objective: The aim was to examine the effect of newer GLDs on the risk of PD through a meta-analysis of randomized outcome trials.
Methods: The methods included randomized placebo-controlled outcome trials that reported PD events associated with three newer classes of GLDs (ie, dipeptidyl peptidase-4 inhibitors, glucagon-like peptide-1 receptor agonists, and sodium-glucose co-transporter-2 inhibitors) in participants with or without type 2 diabetes. The pooled odds ratio (OR) and 95% confidence interval (CI) were estimated using Peto's method.
Results: The study included 24 trials involving 33 PD cases among 185,305 participants during a median follow-up of 2.2 years. Newer GLDs were significantly associated with a lower PD risk (OR: 0.50; 95% CI: 0.25–0.98) than placebo.
Conclusion: Newer GLDs may possibly be associated with a decreased risk of PD; however, larger datasets are required to confirm or refute this notion.

Parkinson's disease (PD), the fastest-growing neurological disorder, affects over 1 million persons in the United States.[1,2] With increases in the aging population, the number of PD cases is expected to increase to 1.2 million by 2030.[1] PD contributes to a large US economic burden, with an estimated cost of $51.9 billion in 2017.[3] There is currently no cure for PD, and the existing treatments primarily focus on alleviating symptoms and enhancing or preserving the quality of life of patients.[4]

Newer classes of glucose-lowering drugs (GLDs) (Table S1), including dipeptidyl peptidase-4 (DPP4) inhibitors, glucagon-like peptide-1 receptor agonists (GLP-1RAs), and sodium-glucose co-transporter-2 (SGLT2) inhibitors, have been increasingly used for treating type 2 diabetes (T2D) due to their cardiovascular and renal benefits. T2D and PD both share some common parts of signaling pathways such as insulin resistance.[5] Newer GLDs have been shown to improve insulin resistance and mediate other pathways (eg, mitochondrial dysfunction); thus, they may be potential therapeutic strategies for preventing or treating PD.[5,6] Cardiovascular outcome trials of the newer GLDs, as in T2D,[7] recommended by the U.S. Food and Food Administration to evaluate the cardiovascular outcomes of all newer GLDs, enable us to evaluate the impact of newer GLDs on the risk of PD. However, PD was not the prespecified outcome, which may lead to insufficient statistical power from individual trials. To address this, we conducted a meta-analysis of randomized outcome trials to examine the association between newer GLDs

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(eg, DPP4 inhibitors, GLP-1RAs, and SGLT2 inhibitors) and the risk of PD among individuals with or without T2D.

Methods

We used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement to conduct this analysis.

Search Strategy and Study Selection

Following the previously reported search strategy,[8] we updated the search of PubMed, Embase, and Cochrane Central Register of Controlled Trials (CENTRAL) until December 2022. Additionally, we performed a manual search to identify any other eligible publications by examining the references of relevant reviews.

Two reviewers (H.T. and Y.L.) independently selected the studies based on the following inclusion criteria: (1) randomized placebo-controlled cardiovascular and renal outcome trials; (2) trials enrolled adults (≥18 years) with or without T2D; (3) trials compared newer GLDs, including DPP-4 inhibitors, GLP-1RAs, and SGLT2 inhibitors, with placebo; and (4) trials reported the events of PD. PD was identified using one preferred term—"Parkinson's disease"—using the Medical Dictionary for Regulatory Activities (MedDRA). Because PD was not the prespecified outcome, it was more likely to be reported as an adverse event by patients and confirmed by physicians.

Data Extraction and Quality Assessment

We extracted the following data from each study: first author, publication year, baseline participant characteristics, inclusion criteria, study drug and control treatments, follow-up duration, and the number of PD cases (extracted from trial results published on www.clinicaltrials.gov). We also assessed the quality of each included study using the Cochrane risk of bias assessment tool.[9]

Statistical Analysis

We calculated a pooled odds ratio (OR) and 95% confidence interval (CI) for risk of PD using Peto's method, the least biased and most powerful method for assessing rare events (<1%).[10] We conducted the following two subgroup analyses: (1) based on the class of newer GLDs (DPP4 inhibitors, GLP-1RAs, and SGLT2 inhibitors vs. placebo) and (2) based on the type of participants included (among participants with T2D only and those with or without T2D). We assessed heterogeneity between studies and the interaction between subgroups using χ^2 test. Sensitivity analyses using the Mantel–Haenszel method and a 0.5 continuity correction for zero events in both arms were conducted to test the robustness of the results. Potential publication bias was assessed using a funnel plot, Begg's test, or Egger's test. A two-sided P-value <0.05 was considered statistically significant. The statistical analyses were performed using Stata (version 16; Stata Corp., College Station, TX).

Results

Twenty-four trials met our inclusion criteria and were included in this meta-analysis (Figure S1).[11–34] The baseline characteristics of studies are presented in Table 1. A total of 185,305 participants with a mean age of 65.1 years were randomly allocated to either a newer GLD or placebo group. Twenty trials included T2D participants only,[11–28,33,34] whereas four trials included participants with or without T2D (enrolling patients with heart failure or chronic kidney disease).[29–32] There were five trials for DPP-4 inhibitors,[11–15] eight trials for GLP-1RAs,[16–23] and 11 trials for SGLT2 inhibitors.[24–34] Across the trials, there were 33 PD cases during a median follow-up of 2.2 years (range: 0.8–5.4 years). The risk of bias for the selective reporting domain was determined as unclear because PD was not the prespecified outcome, whereas the other five domains were determined as low risk of bias (Table S2).

Our meta-analysis of 24 trials showed that there was an association between newer GLDs and a lower risk of PD compared to placebo (OR: 0.50; 95% CI: 0.25–0.98) (Fig. 1). Meta-analysis of 11 trials showed that there was weak evidence of an association between SGLT2 inhibitors and a decreased risk of PD (OR: 0.37; 95% CI: 0.13–1.01). However, there was a lack of evidence regarding the association between GLP-1RAs and a decrease in PD risk (OR: 0.51; 95% CI: 0.10–2.55) and between DPP-4 inhibitors and a decrease in PD risk (OR: 0.71; 95% CI: 0.23–2.22). Further subgroup analyses by type of participants found similar effects between trials including participants with T2D only (OR: 0.60; 95% CI: 0.29–1.23) and trials including participants with and without T2D (OR: 0.14; 95% CI: 0.02–0.96), with a P for interaction of 0.16 (Figure S2).

Our sensitivity analyses using the Mantel–Haenszel method (OR: 0.55; 95% CI: 0.29–1.04) (Figure S3) and a 0.5 continuity correction for zero events in both arms (OR: 0.57; 95% CI: 0.31–1.03) (Figure S4) further confirm our primary results. No evidence of statistical heterogeneity was observed in meta-analyses (all $P > 0.05$). Also, there was no evidence of publication bias based on Begg's test ($P = 0.91$), Egger's test ($P = 0.71$), or funnel plot (Figure S5).

Discussion

The results of this meta-analysis showed an association between newer classes of GLDs and a reduced risk of PD. In the subgroup analyses by drug class, there was weak evidence regarding the association between SGLT2 inhibitors and a reduced risk of PD. However, lack of evidence supported the association between GLP-1RAs and DPP-4 inhibitors and a decrease in PD

TABLE 1 *Basic characteristics of 24 randomized placebo-controlled cardiovascular and renal outcome trials*

Study	Trial Name	N	Population	Age (y)	Men (%)	White (%)	Treatment	Follow-up (y)
Scirica et al. (2013)[11]	SAVOR-TIMI 53	16,492	T2D patients with a history of, or at risk for, CVD	65	67	75	Saxagliptin	2.1
White et al. (2013)[12]	EXAMINE	5380	T2D patients with CVD	61	68	73	Alogliptin	1.5
Green et al. (2015)[13]	TECOS	14,671	T2D patients with CVD	66	71	68	Sitagliptin	3
Gantz et al. (2017)[14]	OMNEON	4192	T2D patients with CVD	64	70	81	Omarigliptin	1.8
Rosenstock et al. (2019)[15]	CARMELINA	6979	T2D patients with high cardiovascular risk	66	63	80	Linagliptin	2.2
Pfeffer et al. (2015)[16]	ELIXA	6068	T2D patients with CVD	60	70	75	Lixisenatide	2.1
Marso et al. (2016)[17]	SUSTAIN-6	3297	T2D patients with established CVD or high cardiovascular risk	65	61	83	Semaglutide	2.1
Marso et al. (2016)[18]	LEADER	9340	T2D patients with high cardiovascular risk	64	64	78	Liraglutide	3.8
Holman et al. (2017)[19]	EXSCEL	14,752	T2D patients with or without previous CVD	62	62	76	Exenatide	3.2
Hernandez et al. (2018)[20]	HARMONY	9432	T2D patients with CVD	64	70	70	Albiglutid	1.6
Gerstein et al. (2019)[21]	REWIND	9901	T2D patients with previous CVD or at high cardiovascular risk	66	54	76	Dulaglutide	5.4
Husain et al. (2019)[22]	PIONEER-6	3183	T2D patients at high cardiovascular risk	66	68	72	Semaglutide	1.3
Gerstein et al. (2021)[23]	AMPLITUDE-O	4076	T2D patients with CVD or CKD at high cardiovascular risk	72	55	76	Efpeglenatide	2.2
Zinman et al. (2015)[24]	EMPA-REG OUTCOME	7020	T2D patients with CVD	63	72	72	Empagliflozin	3.1
Neal et al. (2017)[25]	CANVAS Program	10,142	T2D patients with high CV risk	63	64	78	Canagliflozin	2.4
Wiviott et al. (2019)[26]	DECLARE–TIMI 58	17,161	T2D patients had or were at risk for atherosclerotic CVD	64	63	80	Dapagliflozin	4.2
Perkovic et al. (2019)[27]	CREDENCE	4401	T2D patients with albuminuric CKD	63	66	67	Canagliflozin	2.6
Cannon et al. (2020)[28]	VERTIS-CV	8246	T2D patients with atherosclerotic CVD	64	70	88	Ertugliflozin	3.5
McMurray et al. (2019)[29]	DAPA-HF	4744	Patients with HFrEF, regardless of the presence or absence of T2D	66	77	70	Dapagliflozin	1.5
Heerspink et al. (2020)[30]	DAPA-CKD	4304	Patients with CKD	62	67	53	Dapagliflozin	2.4
Packer et al. (2020)[31]	EMPEROR-Reduced	3730	Patients with HFrEF	67	76	70	Empagliflozin	1.3
Anker et al. (2021)[32]	EMPEROR-Preserved	5988	Patients with HFpEF	72	55	76	Empagliflozin	2.2
Bhatt et al. (2021)[33]	SCORED	10,584	T2D patients with CKD and risks for CVD	69	55	83	Sotagliflozin	1.3
Bhatt et al. (2021)[34]	SOLOIST-WHF	1222	T2D patients hospitalized for worsening heart failure	69	66	93	Sotagliflozin	0.75

Abbreviations: CKD, chronic kidney disease; CVD, cardiovascular disease; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; N, number of population; T2D, type 2 diabetes.

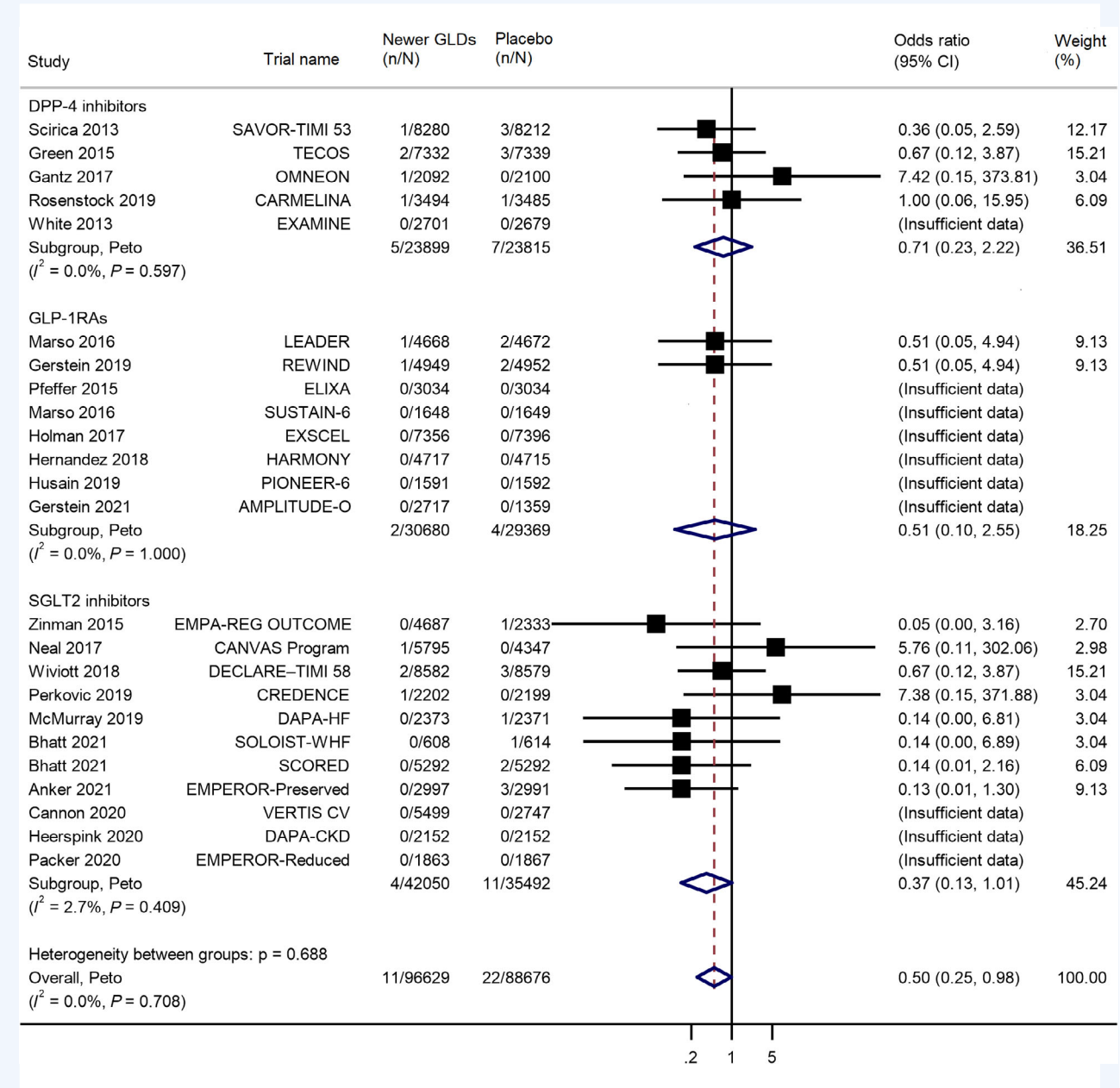

FIG. 1. Meta-analysis of the effects of newer glucose-lowering drugs on the risk of Parkinson's disease in participants with or without type 2 diabetes, subgroup by type of newer GLDs (glucose-lowering drug). CI, confidence interval; DPP-4 inhibitors, dipeptidyl peptidase-4 inhibitors; GLP-1RAs, glucagon-like peptide-1 receptor agonists; SGLT2 inhibitors, sodium-glucose co-transporter-2 inhibitors.

risk. It should be noted that the findings should be interpreted with caution due to the low number of events and short duration of follow-up of trials included.

This study found a decreased risk of PD associated with newer GLDs; however, the underlying mechanism of this effect is not completely clear.[5] Previous studies have reported T2D to be an independent risk factor for PD development,[5,35] and both conditions share similar pathophysiological pathways, such as impaired insulin signaling, mitochondrial dysfunction, oxidative damage, and inflammation.[5] Newer GLDs have generated significant interest in their neuroprotective effects by improving insulin resistance and reducing oxidative damage and inflammation, which make them promising therapeutic options for the management of PD.[6]

The results of this study indicated a potential benefit of SGLT2 inhibitors in reducing the risk of PD, which aligns with previous research findings.[36,37] A recently published population-based cohort study involving people with T2D

found a significant association between SGLT2 inhibitors and a lower risk of PD compared to DPP-4 inhibitors (hazard ratio [HR]: 0.28; 95% CI: 0.09–0.91).[36] Cumulative studies have also shown the neuroprotective effects of GLP-1RAs.[5] One clinical trial showed that exenatide, a specific GLP-1RA, exhibited the ability to alleviate cognitive, motor, and non-motor symptoms in patients with PD.[38] One meta-analysis of two observational studies showed that GLP-1RAs were significantly associated with a 59% decrease in the risk of PD compared to no use (HR: 0.41; 95% CI: 0.19–0.87).[39] However, our study found a nonsignificant decrease in PD risk (OR: 0.51; 95% CI: 0.10–2.55), which could potentially be attributed to the limited number of PD cases (6 of 60,049 participants), resulting in insufficient statistical power to detect a significant difference. In our study, DPP-4 inhibitors were not significantly associated with a decreased risk of PD, which was consistent with results from a meta-analysis of three observational studies (HR: 0.69; 95% CI: 0.35–1.38).[39] Recent population studies have provided encouraging and inspiring insights into the potential benefits of newer GLDs in reducing PD risk. However, current evidence on the matter is still limited, and it needs to be further explored.

Our study findings must be interpreted with caution considering the following limitations. First, PD was not the prespecified outcome in these trials and primarily relied on patient-report/physician confirmation; thus, PD events may not be completely reported during follow-up, resulting in missed cases. The underreporting of PD cases might explain the neutral effects observed in each class of newer GLDs and the results of sensitivity analyses. It is important to note that we cannot completely rule out a significant reduction in PD risk associated with each class of newer GLD. Second, due to the unavailability of individual participant data from the trials, we were unable to determine the PD status of participants at baseline. Furthermore, a clinical diagnosis of PD typically takes 3 to 10 years to confirm.[40] Thus, PD recorded in these trials might be prevalent cases rather than incident events. Third, further analyses (eg, the association between change in glucose levels and PD risk) were not possible because individual participant data from these trials were unavailable.

In conclusion, our meta-analysis of randomized outcome trials suggests that there may be a potential association between newer GLDs and a reduced risk of developing PD. Our findings also highlight the possibility of repurposing newer GLDs for the treatment of PD. However, further studies using real-world data are required to confirm or refute this notion.

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Author Roles

(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript: A. Writing of the First Draft, B. Review and Critique.

H.T.: 1A, 1B, 1C, 2A, 2B, 3A
Y.L.: 1B, 1C, 3B
M.S.O.: 2C, 3B
W.T.D: 2C, 3B
A.R-Z.: 2C, 3B
F.W.: 2C, 3B
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W-H.C.: 2C, 3B
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J.B.: 1A, 1B, 2C, 3B
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Disclosures

Ethical Compliance Statement: Institutional review board approval and informed patient consent were not necessary for this work. We confirm we have read the journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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Supporting Information

Supporting information may be found in the online version of this article.

Table S1. Classes of glucose-lowering drugs (excluding insulin) available for treating type 2 diabetes.

Table S2. Risk of bias of each domain for each study.

Figure S1. Flowchart of the study selection. CENTRAL, Cochrane Central Register of Controlled Trials; DPP-4 inhibitors, dipeptidyl peptidase-4 inhibitors; GLP-1RAs, glucagon-like peptide-1 receptor agonists; SGLT2 inhibitors, sodium-glucose co-transporter-2 inhibitors.

Figure S2. Meta-analysis of the effects of newer glucose-lowering drugs (GLDs) on the risk of Parkinson's disease in participants with or without type 2 diabetes (T2D), subgroup by type of participants included. CI, confidence interval; OR, odds ratio.

Figure S3. Meta-analysis of the effects of newer glucose-lowering drugs (GLDs) on the risk of Parkinson's disease in participants with or without type 2 diabetes using Mantel–Haenszel method. CI, confidence interval; DPP-4 inhibitors, dipeptidyl peptidase-4 inhibitors; GLP-1RAs, glucagon-like peptide-1 receptor agonists; OR, odds ratio; SGLT2 inhibitors, sodium-glucose co-transporter-2 inhibitors.

Figure S4. Meta-analysis of the effects of newer glucose-lowering drugs (GLDs) on the risk of Parkinson's disease in participants with or without type 2 diabetes using a 0.5 continuity correction for zero events in both arms. CI, confidence interval;

DPP-4 inhibitors, dipeptidyl peptidase-4 inhibitors; GLP-1RAs, glucagon-like peptide-1 receptor agonists; OR, odds ratio; SGLT2 inhibitors, sodium-glucose co-transporter-2 inhibitors.

Figure S5. Funnel plot of the effects of newer glucose-lowering drugs on the risk of Parkinson's disease in participants with or without type 2 diabetes. OR, odds ratio.