GLP-1 Receptor Agonist Exposure and Longitudinal Outcomes in Incident Peritoneal Dialysis Patients With Type 2 Diabetes

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Introduction and Objective

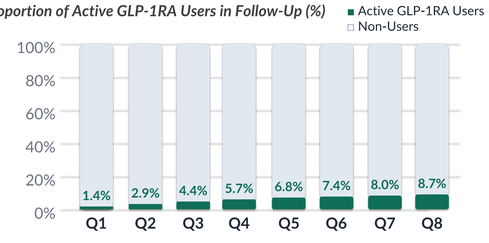
- Peritoneal dialysis (PD) patients with type 2 diabetes (T2D) experience cardiovascular risk and substantial metabolic burden from dialysate glucose exposure and progressive loss of residual kidney function.
- A recent clinical trial showed that the glucagon-like peptide-1 receptor agonist (GLP-1RA) semaglutide reduced the risk of death from cardiovascular causes in patients with T2D and chronic kidney disease (CKD).
- Evidence regarding GLP-1RA use in PD populations remains limited.
- In this study, we sought to determine if GLP-1RA exposure among incident PD patients is associated with better longitudinal outcomes after accounting for time-varying confounding and informative censoring.

Methods

- **Study Design & Population**: Retrospective cohort study of 5,897 adults with T2D initiating PD between April 2021 and September 2024. All patients were GLP-1RA-naive prior to PD initiation. Cohort entry was anchored at day 90 after PD initiation, establishing a common landmark for longitudinal follow-up.
- **Time-Varying Exposure**: GLP-1RA use was assessed every 90 days based on active prescription orders. Across 39,975 person-quarters, 2,146 active-use person-quarters were contributed by 516 ever-users (mean 4.2 active quarters/user).
- **Longitudinal Weighting Approach:** A Marginal Structural Model (MSM) was used to account for time-varying confounding and informative censoring, with weights re-estimated at each 90-day quarter via an LSTM+GBM ensemble capturing evolving exposure trajectories ($\mathbf{W_{it} = ATO_{it} \times IPCW_{it}}$). Overlap weighting (ATO) targeted patients in clinical equipoise. The resulting weighted cohort achieved balance across 40 of 41 measured baseline covariates (SMD < 0.10; max residual SMD = 0.101 for peripheral vascular disease, down from 0.135 unadjusted).
- **Outcomes & Models**: Primary outcome was relative weight change; secondary outcome was all-cause hospitalization. Associations were evaluated using three complementary exposure specifications: (1) primary time-varying exposure (active use vs. non-use), (2) new-user restriction (initiation ≤2 quarters), and (3) cumulative exposure-response based on quarters of sustained use.

Results

Figure 1. Proportion of Active GLP-1RA Users in Follow-Up (%)



	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8
GLP-1RA Users (n):	84	167	238	293	330	334	345	355
Total (N):	5,897	5,727	5,460	5,160	4,830	4,533	4,292	4,076

Figure 1: Values reflect the proportion of active GLP-1RA users among patients remaining in follow-up in each 90-day quarter (n/N). Active use increased from 1.4% (84/5,897) at Q1 to 8.7% (355/4,076) at Q8, demonstrating progressive post-landmark uptake (2,146 total active person-quarters contributed by 516 ever-users).

Figure 2. Love Plot- Baseline Covariates Balance

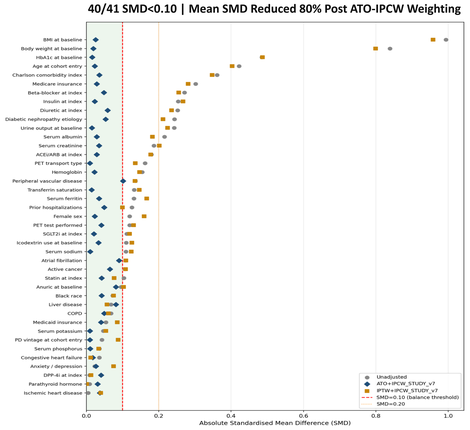


Figure 2: There was no evidence this residual imbalance of PVD (SMD 0.101) is influential. In contrast, standard IPTW left 27 of 41 covariates imbalanced (SMD ≥ 0.10).

Table 1. Selected Key Patient Characteristics Post Covariate Balance

Baseline Characteristic	GLP-1RA Ever-Users (n=516)	Non-Users (n=5,381)	Post-ATO SMD
Age, years	57.5	62.9	0.023
Female, %	45.5%	39.7%	0.023
Primary ESKD: Diabetes, %	61.4%	47.8%	0.053
Medicare Insurance, %	46.1%	60.8%	0.029
BMI, kg/m²	35.7	29.2	0.026
Charlson index, mean	5.2	5.7	0.035
HbA1c, %	7.7	6.9	0.016

Figure 3. Hospitalization Benefit Accrues with Sustained GLP-1RA Use

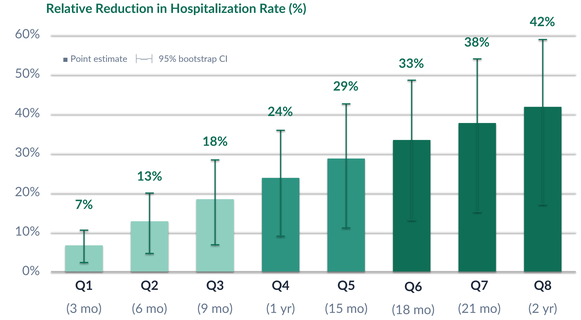


Figure 3: Values represent the marginal counterfactual reduction in hospitalization rate estimated via doubly robust G-computation (combining ATO x IPCW weights and multivariable baseline covariate adjustment with 1,000 patient-cluster bootstrap iterations). Sustained GLP-1RA use was associated with an estimated 23.6% lower rate of hospitalization at 1 year (IRR = 0.764, 95% CI: 0.642–0.910) and a 41.6% reduction at 2 years (IRR = 0.584, 95% CI: 0.412–0.829), compared to 6.5% at Q1 (IRR = 0.935, 95% CI: 0.895–0.977).

Table 2. Longitudinal MSM Estimates of GLP-1RA Exposure on Clinical Outcomes

Outcome	Primary Specification (Active Use vs Non-Use)	New-User Restriction (Initiation ≤ 2 Qtrs)	Cumulative Exposure-Response (Per Quarter)
Relative Weight Change (Percentage points, 95% CI)	-1.19 (-1.97 to -0.42) p = 0.003	-1.69 (-2.53 to -0.85) p <0.001	-0.73 (-0.98 to -0.48) p < 0.001
Hospitalization Burden (IRR, 95% CI)	0.86 (0.63 to 1.18) *p* = 0.35 (NS)	0.77 (0.53 to 1.10) *p* = 0.146 (NS)	0.94 (0.89 to 0.98) p = 0.004

Table 1: All estimates derived from ATO-IPCW weighted MSMs. Weight change estimates represent percentage-point change in relative weight from baseline.

Conclusions

In incident PD patients with T2D, increasing cumulative GLP-1RA exposure was associated with progressive weight reduction and lower hospitalization burden under longitudinal MSM and doubly robust G-computation frameworks. Prospective studies are needed to confirm long-term effects in PD populations.

Limitations

- Observational design: residual unmeasured confounding remains possible despite weighting and sensitivity checks.
- Exposure based on active medication orders, not verified adherence or dispensing of GLP-1RAs.
- Single-provider cohort; external generalizability should be tested in other dialysis networks.

References & Acknowledgments

1. Perkovic V, et al. Effects of Semaglutide on Chronic Kidney Disease in Patients with Type 2 Diabetes. N Engl J Med. 2024;391(2):109-121.

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