Two-Year Persistent Glucagon-Like Peptide-1 Agonist Obesity Without Diabetes Treatment: Clinical Outcomes Among Commercially Insured

L.Z. Marshall, PharmD, PhD[1]; B.Y. Urick, PharmD, PhD[1]; N. Friedlander, PharmD[1]; Y. Qiu, MS[1]; R.S. Leslie, PhD, MPH[1]; P.P. Gleason, PharmD[1,2]. [1]Prime Therapeutics LLC, Eagan, MN, United States. [2]University of Minnesota College of Pharmacy, Minneapolis, MN, United States.

Background

- Glucagon-like peptide-1 (GLP-1) receptor agonists have demonstrated significant weight reduction benefits and efficacy in reducing major adverse cardiovascular events (MACE) such as non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death in clinical trials.[1,2]
- Additionally, while weight loss may reduce the need for bariatric surgery and joint replacement, evidence also suggests improved clinical outcomes among patients combining GLP-1 with endoscopic bariatric therapy or bariatric surgeries and when used concomitantly in joint replacement.[3-5]
- While GLP-1s are efficacious for weight management, these medications are associated with gastrointestinal side effects such as nausea, vomiting, and diarrhea. Long-term safety concerns include potential risks of pancreatitis, gastroparesis, cholecystitis, intestinal obstruction, acute kidney failure, nonarteritic ischemic optic neuropathy, and thyroid cancer.[6]
- The impact of GLP-1 obesity treatment initiation on clinical outcomes in members without diabetes in the real-world setting has not been fully elucidated.

Objective

The objective is to describe changes in clinical outcomes 1 year before and 2 years after GLP-1 obesity treatment initiation among commercially insured obese members without diabetes mellitus (DM) who were persistent to GLP-1 therapy compared to a matched control group.

4085-D 04/25

2900 Ames Crossing Road,
Eagan, MN 55121

Academy of Managed Care Pharmacy (AMCP) Annual Meeting, March 31-April 3, 2025, Houston, TX

Patrick Gleason:
PGleason@PrimeTherapeutics.com

Methods

- This retrospective, observational cohort study analyzed Prime Therapeutics' integrated pharmacy and medical claims data from 16 million commercially insured members covering all regions of the United States across the 4-year period of January 1, 2020, to December 31, 2023.
- Study inclusion was limited to members newly initiating a GLP-1 (index date in calendar year 2021), defined as no GLP-1 use in prior year, i.e., the identification period, with member continuous enrollment 1 year before (pre-period) and 2 years after (post-period) the index date required.
- Members were required to have a pre-period medical claim, including a diagnosis code for obesity or Z code for body mass index (BMI) ≥30.
- Members were excluded if they had a DM diagnosis medical claim or a pharmacy DM drug therapy claim during the pre-period, or medical claim diagnosis in pre-period for HIV/AIDS, hemophilia, sickle cell disease, malignant cancer, or end-stage renal disease.
- Using the same inclusion and exclusion criteria, a control group was identified using 13.5 million members with at least 1 pharmacy claim for any drug during 2021 and without a GLP-1 claim in calendar year 2021 and 1 year prior to study index date.
- A 2-step matching approach with direct matching followed by propensity score matching was used to identify the control group.
  - **Step 1:** Direct matching on gender, health plan, line of business (i.e., fully insured, health insurance marketplace, self-insured), BMI group, prediabetes, pregnancy, and use of statin, renin-angiotensin system antagonist (RASA), and/or antidepressants at index date.
  - **Step 2:** After the direct match, GLP-1 utilizers were matched using propensity scores on 5-year age bands, month of index study date, Charlson Comorbidity Index score and conditions,[7] and pre-period drug utilization of non-GLP-1 weight loss drug therapy by class (e.g. phentermine, topiramate, naltrexone, etc).
- After matching, the cohort was limited to persistent GLP-1 users who did not have a 60-day gap in GLP-1 therapy during the 2-year post-period and their matched controls.
- Clinical outcomes included: bariatric surgery, joint replacement, major adverse cardiovascular event (MACE) (a composite of acute myocardial infarction, stroke, transient ischemic attack, coronary artery bypass graft, and percutaneous transluminal coronary angioplasty), RASA and statin medication use change, and negative clinical events.

Outcome Event	Outcome Definition
Acute kidney failure	ICD-10-CM in any position: N17.x
Acute myocardial infarction	ICD-10-CM in any position: I21.x, I22.x
Acute pancreatitis	ICD-10-CM in any position: K85.x
Bariatric surgery	CPT in any position: 43644, 43645, 43770, 43775, 43842, 43843, 43845, 43846, 43847
Cholecystitis	ICD-10-CM in any position: K81.9x
Coronary artery bypass graft	CPT in any position: 33510 to 33523, 33533 to 33536
Gastroparesis	ICD-10-CM in any position: K31.84
Intestinal obstruction	ICD-10-CM in any position: K56.x
Joint (hip or knee) replacement	CPT in any position: 27440, 27442, 27443, 27445, 27446, 27447, 27120, 27125, 27130, 27132
Nonarteritic ischemic optic neuropathy	ICD-10-CM in any position: H47.01
Percutaneous transluminal coronary angioplasty	CPT in any position: 92920 to 92944, C9600 to C9608
Renin-angiotensin system antagonists (RASA) medication	Generic Product Identifier: 3610x, 3615x, 3617x, 3699x
Statin medication	Generic Product Identifier: 279930x, 3940x, 399940x, 409925x
Stroke	ICD-10-CM in any position: I60.x to I64.x
Thyroid cancer	ICD-10-CM in any position: C73.x
Transient ischemic attack	ICD-10-CM in any position: G45.x

- Negative clinical events included: acute kidney injury or failure, acute pancreatitis, cholecystitis, gastroparesis, intestinal obstruction, nonarteritic ischemic optic neuropathy, and thyroid cancer. Severe negative events were limited to acute kidney failure, acute pancreatitis, intestinal obstruction, nonarteritic ischemic optic neuropathy, and thyroid cancer.
- All study outcomes were measured as annual percent of members with the outcome of interest.
- Annual percent change between groups and across periods (pre-period vs. year 1 post-period, pre-period vs. year 2 post-period) were statistically analyzed using difference-in-difference (DID) regression.

Table 1a

Pre-Post Year 1 Clinical Outcome Change, Among New Start GLP-1 Persistent Members to Treat Obesity Without Diabetes and Matched Controls*

Clinical Event	GLP-1 Persistent Pre-Year	GLP-1 Persistent Year 1	Year 1-Pre Difference (% change)	Matched Controls Pre-Year	Matched Controls Year 1	Year 1-Pre Difference (% change)	Annual Difference-in-Difference (95% CI)††	P-value
	N = 436			N = 1,249				
Bariatric surgery	0.2%	0.2%	0.0%	1.2%	0.6%	-0.6%	0.6% (-0.4 to 1.6)	0.2646
Joint replacement	**0.5%**	**1.4%**	**0.9%**	**1.6%**	**0.6%**	**-1.0%**	**1.9% (0.4 to 3.4)**	**0.0151**
MACE	**2.1%**	**0.7%**	**-1.4%**	**0.8%**	**1.0%**	**0.2%**	**-1.5% (-3.0 to -0.1)**	**0.0374**
RASA medication initiation‡	29.6%	29.8%	0.2%	33.7%	34.1%	0.4%	-0.2% (-2.6 to 2.3)	0.8920
Statin medication initiation‡	20.4%	22.3%	1.9%	20.6%	23.0%	2.4%	-0.6% (-2.9 to 1.8)	0.6362
Acute kidney injury	0.9%	0.2%	-0.7%	0.6%	0.6%	0.0%	-0.6% (-1.6 to 0.4)	0.2146
Acute pancreatitis	0.2%	0.2%	0.0%	0.4%	1.0%	0.6%	-0.6% (-1.4 to 0.3)	0.1963
Cholecystitis	0.2%	0.0%	-0.2%	0.2%	0.2%	0.0%	-0.3% (-0.9 to 0.3)	0.2872
Gastroparesis	0.0%	0.2%	0.2%	0.2%	0.4%	0.2%	0.0% (-0.6 to 0.6)	0.9703
Intestinal obstruction	0.2%	0.2%	0.0%	0.7%	0.5%	-0.2%	0.2% (-0.6 to 1.1)	0.5801
Nonarteritic ischemic optic neuropathy	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0% (0.0 to 0.0)	0.7228
Thyroid cancer	0.0%	0.0%	0.0%	0.0%	0.1%	0.1%	-0.1% (-0.2 to 0.1)	0.3171
≥1 negative event§	1.4%	0.7%	-0.7%	1.9%	2.6%	0.7%	-1.3% (-2.9 to 0.3)	0.0990
≥1 severe negative event¶	1.1%	0.7%	-0.5%	1.7%	2.0%	0.3%	-0.8% (-2.2 to 0.7)	0.2917

Table 1b

Pre-Post Year 2 Clinical Outcome Change, Among New Start GLP-1 Persistent Members to Treat Obesity Without Diabetes and Matched Controls*

Clinical Event	GLP-1 Persistent Pre-Year	GLP-1 Persistent Year 2	Year 2-Pre Difference (% change)	Matched Controls Pre-Year	Matched Controls Year 2	Year 2-Pre Difference (% change)	Annual Difference-in-Difference (95% CI)††	P-value
	N = 436			N = 1,249				
Bariatric surgery	0.2%	0.5%	0.3%	1.2%	0.4%	-0.8%	1.0% (0.0 to 2.1)	0.0538
Joint replacement	**0.5%**	**1.4%**	**0.9%**	**1.6%**	**0.8%**	**-0.8%**	**1.7% (0.2 to 3.2)**	**0.0231**
MACE	2.1%	2.5%	0.4%	0.8%	1.4%	0.6%	-0.1% (-1.6 to 1.4)	0.8938
RASA medication initiation‡	29.6%	29.4%	-0.2%	33.7%	35.7%	2.0%	-2.2% (-5.5 to 1.0)	0.1799
Statin medication initiation‡	20.4%	23.2%	2.8%	20.6%	25.9%	5.3%	-2.6% (-5.5 to 0.2)	0.0717
Acute kidney injury	0.9%	0.5%	-0.4%	0.6%	1.2%	0.6%	-1.0% (-2.4 to 0.3)	0.1392
Acute pancreatitis	0.2%	0.2%	0.0%	0.4%	0.5%	0.1%	-0.1% (-0.9 to 0.7)	0.8428
Cholecystitis	0.2%	0.5%	0.3%	0.2%	0.2%	0.0%	0.2% (-0.6 to 1.1)	0.5922
Gastroparesis	0.0%	0.5%	0.5%	0.2%	0.2%	0.0%	0.5% (-0.2 to 1.1)	0.1809
Intestinal obstruction	0.2%	1.4%	1.2%	0.7%	0.8%	0.1%	1.1% (-0.3 to 2.4)	0.1163
Nonarteritic ischemic optic neuropathy	0.0%	0.0%	0.0%	0.0%	0.1%	0.1%	-0.1% (-0.2 to 0.1)	0.3171
Thyroid cancer	0.0%	0.0%	0.0%	0.0%	0.1%	0.1%	-0.1% (-0.2 to 0.1)	0.3171
≥1 negative event§	1.4%	2.8%	1.4%	1.9%	2.9%	1.0%	0.4% (-1.7 to 2.5)	0.7009
≥1 severe negative event¶	1.1%	2.1%	0.9%	1.7%	2.6%	0.9%	0.0% (-2.0 to 2.0)	0.9712

CI = Confidence Interval, MACE = major adverse cardiovascular event; RASA = renin-angiotensin system antagonist (antihypertensive)
†Eligible control group members were matched to GLP-1 treatment members on characteristics and conditions using a combined exact and propensity score matching approach.
††Difference between GLP-1 post-pre difference and control post-pre difference
‡Medication supply at day 365 (year 1) or day 730 (year 2) post-GLP-1a initiation or control group members' index date
§Negative event defined as any of the following: acute kidney injury, acute pancreatitis, cholecystitis, gastroparesis, intestinal obstruction, nonarteritic ischemic optic neuropathy, or thyroid cancer
¶Severe negative event defined as any of the following: acute kidney failure, acute pancreatitis, intestinal obstruction, nonarteritic ischemic optic neuropathy, or thyroid cancer

Results

- A total of 3,346 commercially insured members newly initiating GLP-1 therapy, and 384,309 control group members, met all initial study criteria.
- After matching, 3,046 GLP-1 therapy members met all study criteria; 436 (14.3%) were persistent at the end of year 2 with 1,249 members matched as controls. Characteristics were well-matched between groups, with standardized mean differences (SMD) less than 0.1 for all comparisons, except for age group with a standardized mean difference (SMD) of 0.1703.
- Mean age for both GLP-1 utilizers and control group members was 48.2 years; 84.3% were women, 16.3% had prediabetes, and <1% had a history of myocardial infarction.
- Across pre-year and year 1, DID statistical comparison found the GLP-1 persistent group had significantly higher annual rate of joint replacement (annual DID: 1.9% (0.4 to 3.4) and significantly lower rate of MACE (annual DID: -1.5%, p=0.0374) compared to controls.
- Across pre-year and year 2, DID statistical comparison found the GLP-1 persistent group had significantly higher annual rates of joint replacement (annual DID 1.7%, p=0.0231) compared to controls.
- No other statistically significant changes in annual clinical outcomes were observed.

Limitations

- While the full GLP-1 sample was well-matched to controls with a 3:1 ratio, balance cannot be assured among this GLP-1 persistent subgroup representing 15% of the full sample. For example, pre-period MACE rates were 3-fold higher in the GLP-1 persistent subgroup compared to matched controls.
- While groups were well-balanced, 9% of identified new start GLP-1 obesity without DM treated members were not matched to a control, potentially resulting in an external validity threat.
- Control group members may have initiated GLP-1 weight loss therapy after 2021, resulting in a potential misclassification bias.
- Data were sourced from administrative health care claims; therefore, misclassification bias may have occurred due to using medical and pharmacy claims to exclude individuals without diabetes and to identify those with obesity.
- Our study examined a commercially insured membership and therefore is not generalizable to Medicare or Medicaid populations.
- The impact of an individual's cost sharing, other diagnoses, social determinants of health, or other member characteristics are outside the scope of this analysis and are worthy of future consideration.

Conclusions

- The first year observed statistical reduction in MACE rates was likely the result of a substantially higher pre-period event rate among treatment group members compared to controls, and the difference was not seen in year 2. Differences in bariatric surgery and joint replacement outcomes may also be due to balance and selection-related concerns.
- No difference in negative GLP-1 events in this 2-year real-world study of persistent GLP-1 obesity treated commercially insured members is a positive finding. However, clinical event rates for MACE, bariatric surgery, and joint replacement were not lower compared to controls, tempering expectations for substantial benefits during the first 2 years of GLP-1 obesity treatment.

References

1. Wong HJ, Sim B, Teo YH, et al. Efficacy of GLP-1 receptor agonists on weight loss, BMI, and waist circumference for patients with obesity or overweight: A systematic review, meta-analysis, and meta-regression of 47 randomized controlled trials. *Diabetes Care.* 2025;48(2):292-300. doi:10.2337/dc24-1678
2. Drucker DJ. Efficacy and safety of GLP-1 medicines for type 2 diabetes and obesity. *Diabetes Care.* 2024;47(11):1873-1888. doi:10.2337/dci24-0003
3. Imam A, Alim H, Binhussein M, et al. Weight loss effect of GLP-1 RAs with endoscopic bariatric therapy and bariatric surgeries. *J Endocr Soc.* 2023;7(12):bvad129. doi:10.1210/jendso/bvad129
4. GLP-1 drugs found to improve joint replacement outcomes. Maimonides Medical Center. Published 2024. Accessed February 6, 2025. https://maimo.org/glp-1-drugs-found-to-improve-joint-replacement-outcomes/
5. Pre-operative use of GLP-1s may reduce complications after metabolic and bariatric surgery in patients with extreme obesity. American Society for Metabolic and Bariatric Surgery. Published June 13, 2024. Accessed February 6, 2025. https://asmbs.org/news_releases/pre-operative-use-of-glp-1s-may-reduce-complications-after-metabolic-and-bariatric-surgery-in-patients-with-extreme-obesity/
6. Gao X, Hua X, Wang X, Xu W, Zhang Y, Shi C, Gu M. Efficacy and safety of semaglutide on weight loss in obese or overweight patients without diabetes: A systematic review and meta-analysis of randomized controlled trials. *Front Pharmacol.* 2022;13:935823. doi: 10.3389/fphar.2022.935823.
7. Glasheen WP, Cordier T, Gumpina R, Haugh G, Davis J, Renda A. Charlson Comorbidity Index: ICD-9 update and ICD-10 translation. *Am Health Drug Benefits.* 2019;12(4):188-197. https://pmc.ncbi.nlm.nih.gov/articles/PMC6684052/pdf/ahdb-12-188.pdf