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Can Ozempic help you sleep better? Comparing Long-Term Adverse Outcomes in Obstructive Sleep Apnea managed With CPAP Alone Vs CPAP Plus GLP-1 Agonists: A Real-World TriNetX Study

Chibuzor V Nwachukwu

chnwachukwu@huhosp.org

Howard University

Rawan Elkomi

Howard University

Mrinalini Deverapalli

Howard University

Shahzad Zafar

Howard University

Julia Gorman

Howard University

Nicholas Azinge

Howard University

Miriam Michael

Howard University

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Can Ozempic help you sleep better? Comparing Long-Term Adverse Outcomes in Obstructive Sleep Apnea managed With CPAP Alone Vs CPAP Plus GLP-1 Agonists: A Real-World TriNetX Study

Chibuzor V Nwachukwu[1], Rawan Elkomi[1], Mrinalini Deverapalli[1], Nicholas Azinge[1], Miriam Michael[1,2]

[1]Department of Internal Medicine, Howard University, Washington, DC, USA

[2]Department of Internal Medicine, University of Maryland School of Medicine, Baltimore, USA

Corresponding Author
Chibuzor Nwachukwu
chnwachukwu@huhosp.org
ORCID: 0009000245224406

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Abstract

Purpose

Obstructive sleep apnea (OSA) is associated with elevated cardiometabolic risk, and continuous positive airway pressure (CPAP) remains the standard therapy. Glucagon-like peptide-1 receptor agonists (GLP-1RAs) have demonstrated cardiovascular benefits, but their combined impact with CPAP in patients with OSA is not well characterized. In view of this, a retrospective cohort study was conducted using the TriNetX Network to compare risks of myocardial infarction (MI), stroke and mortality in CPAP treated OSA patients who did and did not receive GLP-1's. To evaluate whether adding GLP-1 receptor agonists to CPAP therapy reduces cardiovascular events and mortality compared with CPAP alone in adults with OSA.

Methods

Using the TriNetX Network, adults (≥18 years) with OSA treated with CPAP were identified. After exclusion criteria and propensity score matching, patients who received a GLP-1RA within one year of CPAP initiation formed the exposure cohort; controls were similar CPAP users who never received a GLP-1RA (CPAP+GLP1 vs CPAP only). 6,777 patients remained in each cohort. Outcomes up to 10 years including MI, stroke, and all-cause mortality, were analyzed using risk ratios and Kaplan–Meier survival estimates.

Results

Compared with CPAP-only controls, the exposure cohort experienced significantly reduced risks of MI (0.5% vs 1.0%), stroke (0.4% vs 1.0%), and all-cause mortality (4.0% vs 13.9%).

Conclusion

In patients with OSA treated with CPAP, adjunctive GLP-1RA therapy is associated with markedly lower cardiovascular events and substantially improved survival. These findings highlight a potential synergistic cardioprotective effect of combining GLP-1RAs with CPAP in this high-risk population.

Main manuscript:

Introduction

Obstructive sleep apnea (OSA) is a common sleep related breathing disorder that is associated with elevated cardiometabolic risk with increased risk of cardiovascular adverse outcomes, and continuous positive airway pressure (CPAP) remains the standard therapy and has shown to help reduce adverse cardiopulmonary outcomes [1]. OSA is typically associated with obesity and many patients with OSA have overlapping comorbidities that may affect cardiovascular risk. The SURMOUNT-OSA trial found that Tirzepatide was associated with reduced AHI, hsCRP concentration, and systolic blood pressure [2].

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are increasingly being used in managing weight, diabetes and other metabolic disorders that may overlap with OSA. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have demonstrated cardiovascular benefits, but their combined impact with CPAP in patients with OSA has not yet been fully characterized. In view of this, a retrospective cohort study was conducted using the TriNetX Global Collaborative Network [3] to compare risks of myocardial infarction, stroke and mortality in CPAP treated OSA patients who did and did not receive GLP-1's.

Since the SURMOUNT trial showed improved AHI with Tirzapetide which is associated with improved cardiovascular complications and death [4], it warrants further exploration of GLP-1 RAs as adjunctive therapies to OSA. Large federated electronic health record networks allow for real-world comparative effectiveness analyses across diverse healthcare organizations.

Using the TriNetX Global Collaborative Network, we performed a retrospective compare-outcomes analysis evaluating cardiovascular and mortality outcomes among adult patients with OSA treated with CPAP who were prescribed GLP-1 receptor agonists within one year of CPAP initiation compared with CPAP-treated controls without GLP-1 exposure.

Methods

Study Design and Data Source

We conducted a retrospective cohort study using the TriNetX Global Collaborative Network, a federated electronic health record research platform comprising data from 161 participating healthcare organizations [3]. The database contains deidentified longitudinal patient data, including demographics, diagnoses, procedures, medications, and clinical encounters derived from institutional electronic medical records. All analyses were performed using the TriNetX

Compare Outcomes analytic function. Because the data are deidentified and aggregated, institutional review board approval was not required.

Cohort Selection

Two cohorts were constructed from adult patients aged 18 years or older at the most recent recorded encounter with a documented diagnosis of obstructive sleep apnea and evidence of continuous positive airway pressure therapy initiation or management. Obstructive sleep apnea was identified using ICD-10-CM code G47.33, and CPAP initiation or management was identified using CPT code 94660. Patients were required to have both codes present in the electronic health record to meet inclusion criteria.

The exposure cohort included patients who met the above inclusion criteria and had documented exposure to a glucagon-like peptide-1 receptor agonist within one year on or after CPAP initiation. GLP-1 receptor agonist exposure was identified using RxNorm codes for liraglutide (475968), semaglutide (1991302), exenatide (60548), dulaglutide (1551291), and lixisenatide (1440051). For this cohort, at least one GLP-1 prescription had to occur within 365 days following the CPAP initiation date.

The control cohort included patients who met inclusion criteria for obstructive sleep apnea and CPAP initiation but had no documented exposure at any time to the GLP-1 receptor agonists listed above.

Patients were excluded from both cohorts if they had evidence prior to the index date of bariatric surgery, identified using CPT codes 43644 (laparoscopic gastric restrictive procedure with Roux-en-Y reconstruction) or 43645 (gastric restrictive procedure with small intestine reconstruction), heart failure (ICD-10 I50), cerebral infarction (ICD-10 I63), or ischemic heart disease (ICD-10 I20–I25).

The index date was defined as the first date on which both obstructive sleep apnea (G47.33) and CPAP initiation or management (CPT 94660) were recorded. For patients in the exposure cohort, GLP-1 receptor agonist exposure was required to occur within one year following this index date. Patients whose index event occurred 20 years or more before the data extraction date were excluded; no patients met this exclusion criterion.

Matching and Covariate Adjustment

To reduce confounding, 1:1 propensity score matching was performed using TriNetX built-in nearest-neighbor matching algorithms. The propensity model incorporated demographic and

clinical variables selected a priori based on relevance to cardiometabolic risk and treatment selection.

Demographic variables included age, sex, and race. Clinical covariates included type 1 diabetes mellitus (ICD-10 E10), type 2 diabetes mellitus (ICD-10 E11), hypertension (ICD-10 I10), neoplasms (ICD-10 C00–D49), acute and chronic kidney disease (ICD-10 N17–N19), body mass index categories (ICD-10 Z68.1, Z68.2, Z68.3, Z68.4), lipid disorders (ICD-10 E78), alcohol use disorders (ICD-10 F10), tobacco use (ICD-10 Z72.0), and device dependence or long-term use of medical devices (ICD-10 Z99.89).

Before matching, 6,828 patients were identified in the CPAP plus GLP-1 cohort and 113,907 patients in the CPAP-only cohort. After propensity score matching, 6,777 patients remained in each cohort with adequate covariate balance as assessed by standardized mean differences generated by the TriNetX platform.

Follow-Up Periods and Outcomes

Patients were followed beginning one day after the index date and continuing for up to 3,650 days, corresponding to a maximum follow-up of 10 years. Follow-up ended at the earliest occurrence of the outcome of interest, the last documented clinical encounter, or the end of the available observation window.

The primary cardiovascular outcomes included myocardial infarction and stroke. Myocardial infarction was identified using ICD-10 codes I21 (acute myocardial infarction) and I22 (subsequent myocardial infarction). Stroke was identified using ICD-10 code I63 (cerebral infarction). Mortality was assessed using a combination of ICD-10 code Z86.74 (history of sudden cardiac arrest) and the TriNetX deceased status indicator. Patients with documented outcomes occurring before the start of the follow-up window were excluded from the corresponding outcome analyses.

Statistical Analysis

All analyses were conducted within the TriNetX Analytics Platform. Cumulative risk estimates were calculated for each outcome, and measures of association included risk difference, risk ratio, and odds ratio with corresponding 95% confidence intervals. Time-to-event analyses were performed using Kaplan–Meier survival curves, with between-group comparisons assessed using the log-rank test. Cox proportional hazards regression models were used to estimate hazard ratios with 95% confidence intervals, and proportional hazards assumptions were evaluated within the platform.

A number-of-instances analysis was performed to evaluate the frequency of outcome-related encounters among patients who experienced each outcome. This analysis excluded patients with zero outcome instances by design and compared mean visit-grouped counts between cohorts using two-sample t tests. Censoring occurred at the last recorded clinical encounter. Statistical significance was determined using platform-generated z-tests, chi-square tests, and t-tests, with a two-sided p value less than 0.05 considered statistically significant.

Results

In this large real-world analysis, a total of 6,828 patients with obstructive sleep apnea (OSA) treated with CPAP who were prescribed a GLP-1 receptor agonist within one year of CPAP initiation met inclusion criteria. The control cohort consisted of 113,907 patients with OSA treated with CPAP and no GLP-1 exposure. After 1:1 propensity score matching, 6,777 patients remained in each cohort, with well-balanced baseline demographic and clinical characteristics.

Outcomes were assessed beginning 1 day after the index event through a maximum of 3,650 days of follow-up, consistent with the predefined TriNetX analytic window. In the matched analysis, GLP-1 receptor agonist therapy was associated with significantly lower risks of major adverse cardiovascular outcomes. The risk of myocardial infarction was reduced (0.5% vs 1.0%; HR 0.535, 95% CI 0.348–0.823, $p = 0.010$), as was the risk of stroke (0.4% vs 1.0%; HR 0.551, 95% CI 0.356–0.853, $p = 0.003$). Mortality was also significantly lower in the GLP-1 cohort (4.0% vs 13.9%; HR 0.304, 95% CI 0.266–0.349, $p < 0.001$), with higher survival probability at the end of follow-up compared to controls.

These findings suggest that the addition of GLP-1 receptor agonist therapy to CPAP treatment in patients with OSA is associated with meaningful reductions in cardiovascular events and all-cause mortality. Although causality cannot be established due to the observational design, the consistency and magnitude of risk reduction across outcomes support further prospective and randomized investigation to determine whether combined CPAP and GLP-1 therapy confers additive cardiometabolic benefit in this high-risk population.

Follow-Up (After Matching)

- GLP-1 cohort:
  Mean: 935.961 days
  Median: 756 days

- Control cohort:
  Mean: 1140.881 days
  Median: 870 days

Myocardial Infarction

Risk analysis:

Survival: Log-rank p = 0.004
Hazard ratio: 0.535 (95% CI 0.348–0.823)

Instances:

Mean: 0.009 vs 0.023
p = 0.022
Within the follow-up window of 1 day to 3,650 days after index:

- Risk of myocardial infarction in the GLP-1 cohort: **0.5%**
- Risk of myocardial infarction in the control cohort: **1.0%**
- p-value: **0.000**

The difference between cohorts was statistically significant.

Stroke

Risk analysis:
Survival:

- Log-rank p = 0.007
- Hazard ratio: 0.551 (95% CI 0.356–0.853)

Instances:

- Mean: 0.012 vs 0.040
- p = 0.008

Within the same follow-up interval:

- Risk of stroke in the GLP-1 cohort: **0.4%**
- Risk of stroke in the control cohort: **1.0%**
- p-value: **0.000**

The difference between cohorts was statistically significant.

Mortality

Risk analysis:

- GLP-1: 271 / 6,752 (4.0%)
- Control: 931 / 6,715 (13.9%)
- `Risk difference: −0.099 (95% CI −0.108 to −0.089)`
- p = 0.000

Survival:

- Log-rank p = 0.000
- Hazard ratio: 0.304 (95% CI 0.266–0.349)

Instances:

- Mean: 0.003 vs 0.026
- p = 0.000

All-cause mortality during follow-up demonstrated:

- Risk in the GLP-1 cohort: **4.0%**
- Risk in the control cohort: **13.9%**
- p-value: **0.000**

The difference between cohorts was statistically significant.

Cardiovascular and Mortality Outcomes in OSA Patients Treated with CPAP ± GLP-1 Receptor Agonist

Propensity score–matched analysis (n = 6,777 per group)

Table 1. Cohort sizes before and after propensity score matching.

Cohort	*Before matching, n*	*After matching, n*
GLP-1	*6,828*	*6,777*
Control	*113,907*	*6,777*

Comprehensive cardiovascular and mortality outcomes in matched cohorts. Outcomes assessed from 1 day after the index event through 3,650 days.

Outcome	*GLP-1 events, n/N (%)*	*Control events, n/N (%)*	*Risk difference (95% CI)*	*Risk ratio*	*Odds ratio*	*p-value*
Myocardial infarction	*31/6,727 (0.5%)*	*66/6,695 (1.0%)*	*-0.005 (-0.008 to -0.002)*	*0.467*	*0.465*	*<0.001*
Stroke	*30/6,750 (0.4%)*	*66/6,726 (1.0%)*	*-0.005 (-0.008 to -0.003)*	*0.453*	*0.450*	*<0.001*
All-cause mortality	*271/6,752 (4.0%)*	*931/6,715 (13.9%)*	*-0.099 (-0.108 to -0.089)*	*0.289*	*0.260*	*<0.001*

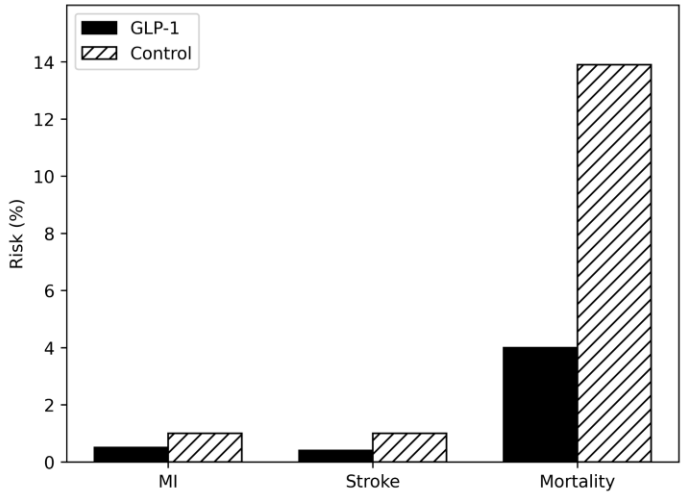
Table 3. Summary of primary outcomes (risk comparison).

Outcome	*GLP-1 risk, %*	*Control risk, %*	*p-value*
Myocardial infarction	*0.5*	*1.0*	*<0.001*
Stroke	*0.4*	*1.0*	*<0.001*
All-cause mortality	*4.0*	*13.9*	*<0.001*

Abbreviations: CI, confidence interval. Risk difference represents absolute risk difference. Percentages calculated using at-risk populations after exclusion of prior events. Two-sided p-values reported as p < 0.001 where applicable.

Combined Bar Chart: GLP-1 vs Control (Matched Cohorts)

Outcomes: Myocardial infarction, stroke, and all-cause mortality.



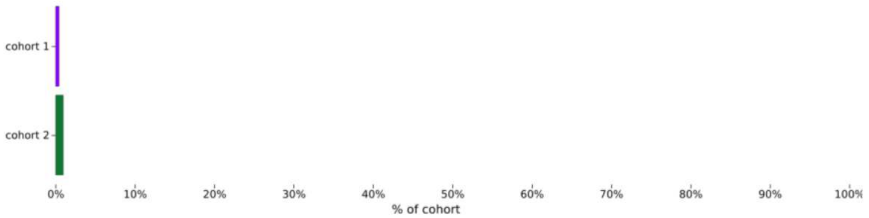
GLP-1 = solid black; Control = striped. Values are cumulative risks within the analytic window.

Figure 1A. Myocardial Infarction

Risk analysis excluding patients with outcome prior to the time window

Cohort	Patients in cohort	Patients with outcome	Risk
1 glp1 1 year	6,727	31	0.005
2 control	6,695	66	0.010

		95% CI	z	p
Risk Difference	-0.005	(-0.008, -0.002)	-3.590	0.000
Risk Ratio	0.467	(0.305, 0.715)	N/A	N/A
Odds Ratio	0.465	(0.303, 0.713)	N/A	N/A



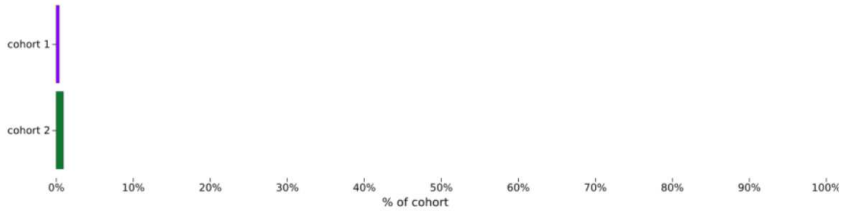
HR 0.535 (95% CI 0.348–0.823); Log-rank p=0.004

Figure 1B. Stroke

Risk analysis excluding patients with outcome prior to the time window

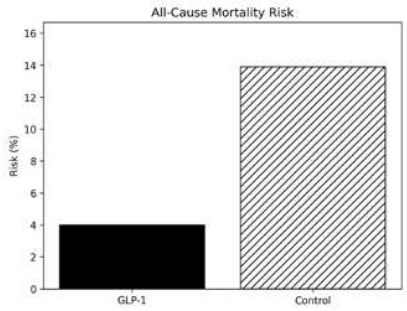
Cohort	Patients in cohort	Patients with outcome	Risk
1 glp1 1 year	6,750	30	0.004
2 control	6,726	66	0.010

		95% CI	z	p
Risk Difference	-0.005	(-0.008, -0.003)	-3.705	0.000
Risk Ratio	0.453	(0.295, 0.696)	N/A	N/A
Odds Ratio	0.450	(0.292, 0.695)	N/A	N/A

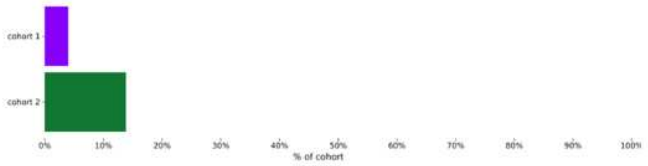


HR 0.551 (95% CI 0.356–0.853); Log-rank p=0.007

Figure 1C. All-Cause Mortality



Risk Difference	-0.099	(-0.108, -0.089)	-20.048	0.000
Risk Ratio	0.289	(0.254, 0.330)	N/A	N/A
Odds Ratio	0.260	(0.226, 0.299)	N/A	N/A



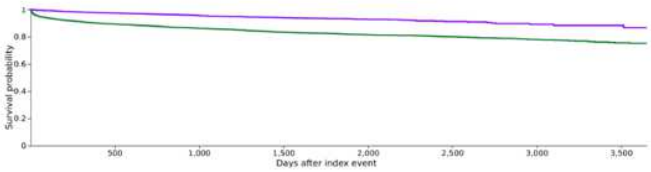
25 patients in Cohort 1 and 62 patients in Cohort 2 were excluded from results because they had the outcome prior to the time window.

Kaplan - Meier survival analysis excluding patients with outcome prior to the time window

Cohort	Patients in cohort	Patients with outcome	Median survival (days)	Survival probability at end of time window
1 glp1 1 year	6,752	271	--	86.68%
2 control	6,715	931	--	75.22%

	χ^2	df	p
Log-Rank Test	329.465	1	0.000

	Hazard Ratio	95% CI	χ^2	df	p
Hazard Ratio and Proportionality	0.304	(0.266, 0.349)	72.685	1	0.000



25 patients in Cohort 1 and 62 patients in Cohort 2 were excluded from results because they had the outcome prior to the time window.

Number of instances excluding patients with outcome prior to the time window

Cohort	Patients in cohort	Patients with outcome	Mean	Standard Deviation	Median	Median (1+ instances)
1 glp1 1 year	6,752	19	0.003	0.053	0	1
2 control	6,715	85	0.026	0.534	0	1

HR 0.304 (95% CI 0.266–0.349); Log-rank p<0.001

GLP-1 represented by solid black bars; Control represented by striped bars. Kaplan–Meier analyses excluded patients with outcome prior to the time window (1 day to 3,650 days post-index).

Discussion

OSA as a Driver of Cardiovascular Risk and the Limitations of CPAP Alone

Obstructive sleep apnea is a recognized independent risk factor for serious cardiovascular events, caused by repeated episodes of intermittent hypoxia, sympathetic nervous system activation, oxidative stress, and widespread inflammation. [5,6,7]. The main pathophysiological model suggests that intermittent hypoxia acts as the key mediator, leading to oxidative stress, endothelial dysfunction, and rapid atherosclerosis, which ultimately result in hypertension, stroke, and myocardial infarction. [5,8]. Cyclical hypoxemia and reoxygenation increase reactive oxygen species, harm endothelial cells, and trigger hypoxia-inducible factor signaling pathways, which enhance atherogenesis and systemic vascular inflammation. [6,9]. although CPAP is the primary standard of care, large randomized controlled trials have consistently not shown a significant reduction in major cardiovascular events when using CPAP alone, mainly due to poor adherence. [10,11]. The ISAACC trial, involving non-sleepy OSA patients with acute coronary syndrome and a median follow-up of 3.35 years, observed similar cardiovascular event rates between the CPAP group (16%) and the usual-care group (17%). The average CPAP use was just 2.78 hours per night. [10]. A 2024 systematic review of randomized controlled trials confirmed that CPAP has no significant impact on cardiovascular death, stroke, or myocardial infarction. The null results are attributed to poor adherence, short follow-up periods, and major methodological limitations. [11,12]. the current study's results show significantly reduced rates of myocardial infarction (RR 0.47), stroke (RR 0.45), and overall mortality (RR 0.29) in the group receiving GLP-1 RA combined with CPAP. This indicates that addressing the core cardiometabolic issues through medication offers additional cardiovascular benefits beyond merely improving airway mechanics [13,14]

GLP-1 RA Cardiovascular Benefits: Evidence from Landmark Trials

The cardioprotective signal from our study is convincingly supported by landmark cardiovascular outcome trials, which demonstrated the MACE reduction effectiveness of GLP-1 receptor agonists in various high-risk groups. [15,16]. The SUSTAIN-6 trial showed that semaglutide significantly lowered the combined risk of cardiovascular death, nonfatal heart attack, or nonfatal stroke in patients with high-risk type 2 diabetes (6.6% vs. 8.9%; HR 0.74), demonstrating both noninferiority and superiority compared to placebo. [15]. post-hoc analyses of the LEADER trial confirmed that liraglutide lowered MACE in patients with previous myocardial infarction or stroke, as well as in those with diagnosed atherosclerotic cardiovascular disease without prior ischemic events. [16,17]. Most notably, the SELECT trial demonstrated that semaglutide 2.4 mg lowered the combined risk of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke, even in patients without diabetes — a group that closely overlaps

with the OSA phenotype analyzed in this study. [18]. A meta-analysis of semaglutide randomized controlled trials confirmed a significant 19% reduction in MACE risk (RR 0.81; 95% CI 0.74–0.88), with specific benefits seen in cardiovascular death and nonfatal myocardial infarction. [19]. The reduction in mortality observed in our cohort (RR 0.29) significantly surpasses what has been reported in previous CVOTs. This may be due to the additional benefit of treating both metabolic factors and sleep-disordered breathing at the same time—a combination not yet tested in any randomized trial. [20,21].

Mechanistic Rationale for GLP-1 RA Cardioprotection in OSA

The significant cardiovascular risk reductions seen in this OSA-specific cohort are biologically plausible, as GLP-1 RAs target many of the same inflammatory, hypoxic, and atherogenic pathways that are triggered by intermittent hypoxia. [22,23]. GLP-1 receptors found in cardiomyocytes and vascular endothelial cells facilitate myocardial glucose absorption, decrease oxidative stress, and inhibit cardiomyocyte apoptosis. These processes collectively provide cardioprotection and prevent harmful cardiac remodeling, all independent of blood sugar reduction [22,24]. GLP-1 RAs also reduce monocyte recruitment to the vascular endothelium by lowering VCAM-1 and E-selectin levels, and they exhibit anti-pyroptotic effects by inhibiting NLRP3 inflammasome formation—pathways that are abnormally activated in OSA due to repeated episodes of hypoxia and reoxygenation. [23,25]. GLP-1 RAs, through coordinated multi-pathway vascular regulation, decrease reactive oxygen species, restore mitochondrial function, and offer direct protection to endothelial cells. These effects provide clear vascular benefits, as supported by both preclinical and clinical evidence. [26]. these agents also exhibit pleiotropic effects such as notable weight loss, blood pressure decrease, and improvements in endothelial dysfunction and arterial stiffness — all of which are independently significant for OSA patients with obesity and cardiometabolic conditions. [13,27]. the way these mechanisms target the same inflammatory and atherogenic pathways triggered by OSA-related intermittent hypoxia offers a strong biological explanation for the enhanced cardioprotection seen when combining GLP-1 RAs with CPAP therapy. [28,29].

GLP-1 RAs and OSA Severity: Emerging Evidence for Combination Therapy

In addition to their systemic cardiovascular benefits, GLP-1 receptor agonists are increasingly acknowledged for their ability to directly lessen OSA severity. This effect is mainly due to weight loss–induced reduction of fat around the upper airway and may also involve direct respiratory mechanisms, which makes them particularly suitable for combined use with CPAP. [4,30]. The SURMOUNT-OSA phase 3 trials showed that tirzepatide — a dual GLP-1/GIP receptor agonist — significantly lowered the apnea-hypopnea index, hypoxic burden, high-

sensitivity C-reactive protein, and systolic blood pressure in adults with moderate-to-severe OSA and obesity over 52 weeks. Additional improvements were seen among PAP therapy users in Trial 2. [2]. A prospective cohort study of patients with heart failure with preserved ejection fraction, OSA, obesity, and type 2 diabetes showed that GLP-1 RA therapy significantly reduced sleep apnea severity, improved heart failure symptoms, lowered pulmonary pressures, and enhanced right ventricular function, highlighting their potential benefits in cardiometabolic health within multi-morbid OSA populations. [30]. A randomized study comparing CPAP, liraglutide, and their combination in patients with moderate-to-severe OSA found that CPAP-based treatments more effectively reduced the apnea-hypopnea index, while liraglutide achieved significant weight loss. This indicates that the two approaches have complementary mechanisms rather than overlapping ones when used together. [31]. Analyses of the SURMOUNT-OSA trials indicate that the decrease in hypoxic burden from GLP-1/GIP agonism could lead to a significant reduction in cardiovascular mortality, as hypoxic burden is an independent predictor of cardiovascular death across sleep cohorts. [4,32]. These combined data support a model where CPAP mechanically eliminates airway obstruction, while GLP-1 RA therapy reduces the systemic metabolic, inflammatory, and atherogenic effects that CPAP alone cannot sufficiently manage. [33,34].

Limitations and Future Directions

Although the findings of this study are clinically important, it is essential to acknowledge several key limitations due to its retrospective, observational nature. Studies that leverage real-world databases like TriNetX are naturally prone to selection bias and residual confounding because exposure and outcome data are pre-existing and cannot be controlled. The inability to randomly assign subjects further limits causal inference when compared to randomized controlled trials [35]. While propensity score matching helps to reduce confounding by balancing observed covariates, residual confounding from unmeasured factors—such as OSA severity indices, medication adherence, CPAP usage hours, and patient-reported outcomes—remains a notable limitation of analyses based on TriNetX. [35]. Additionally, since the TriNetX data source mainly consists of insured populations receiving care at academic and acute care institutions, the findings may not fully apply to underserved communities and patients managed in community or non-academic settings. [35]. The significant mortality reduction (RR 0.29) seen in this cohort, although consistent with previous CVOTs, suggests there might be residual confounding by indication — patients prescribed GLP-1 RAs could have received more intensive cardiometabolic monitoring and overall pharmacological optimization. [20]. future research should focus on prospective randomized trials that systematically explore the combination of GLP-1 RA therapy and CPAP in populations with OSA. These studies should stratify participants based on OSA severity, obesity phenotype, and diabetic status to establish causality,

identify the best combination strategies, and assess whether the cardioprotective benefits are consistent in non-diabetic OSA patients. The recent FDA approval of tirzepatide for OSA makes this an urgent and actionable research priority. [2,34].

Conclusion

In this large real-world analysis of CPAP-treated patients with obstructive sleep apnea, adjunctive therapy with GLP-1 receptor agonists was associated with significantly lower risks of myocardial infarction, stroke, and all-cause mortality over long-term follow-up compared with CPAP therapy alone. These associations were consistent across risk-based, survival, and instance-level analyses in well-matched cohorts.

The findings highlight the potential importance of addressing metabolic disease alongside airway obstruction in patients with OSA and suggest that integrated therapeutic strategies may yield meaningful cardiovascular benefit. While prospective studies are needed to confirm causality and define optimal patient selection, this study provides real-world evidence supporting further investigation of GLP-1 receptor agonists as adjunctive therapy in the long-term management of obstructive sleep apnea.

References

1. Veasey SC, Rosen IM. Obstructive Sleep Apnea in Adults. *N Engl J Med*. 2019;380(15):1442-1449. doi:10.1056/NEJMcp1816152
2. Malhotra A, Grunstein RR, Fietze I, et al.; SURMOUNT-OSA Investigators. Tirzepatide for the treatment of obstructive sleep apnea and obesity. *N Engl J Med.* 2024;391(13):1193–1205. PMID: 38912654
3. TriNetX, LLC. TriNetX Global Collaborative Network [database on the Internet]; c2016–2025. Available from: https://live.trinetx.com
4. Azarbarzin A, Sands SA, Stone KL, et al. The hypoxic burden of sleep apnoea predicts cardiovascular disease-related mortality: the Osteoporotic Fractures in Men Study and the Sleep Heart Health Study. *Eur Heart J.* 2019;40(14):1149–1157. PMID: 30165388
5. Lavie L. Intermittent hypoxia and vascular function: implications for obstructive sleep apnoea. *Exp Physiol.* 2006;92(1):51–55. PMID: 17124276
6. Javaheri S, Barbe F, Campos-Rodriguez F, et al. Sleep apnea: types, mechanisms, and clinical cardiovascular consequences. *J Am Coll Cardiol.* 2017;69(7):841–858. PMID: 28209226
7. Somers VK, White DP, Amin R, et al. Sleep apnea and cardiovascular disease: An American Heart Association/American College of Cardiology Foundation Scientific Statement. *Circulation.* 2008;118(10):1080–1111. PMID: 18725495
8. Drager LF, Togeiro SM, Polotsky VY, Lorenzi-Filho G. Obstructive sleep apnea: a cardiometabolic risk in obesity and the metabolic syndrome. *J Am Coll Cardiol.* 2013;62(7):569–576. PMID: 23770180
9. Kohler M, Stradling JR. Mechanisms of vascular damage in obstructive sleep apnea. *Nat Rev Cardiol.* 2010;7(12):677–685. PMID: 20924369
10. Sánchez-de-la-Torre A, Campos-Rodriguez F, Barbé F; ISAACC Study Investigators. Effect of obstructive sleep apnoea and its treatment with CPAP on the prevalence of cardiovascular events in patients with acute coronary syndrome (ISAACC study): a randomised controlled trial. *Lancet Respir Med.* 2020;8(4):359–367. PMID: 31839558
11. Balk EM, Adam GP, Cao W, et al. Long-term effects on clinical event, mental health, and related outcomes of CPAP for obstructive sleep apnea: a systematic review. *J Clin Sleep Med.* 2024;20(6):895–909. PMID: 38300818
12. McEvoy RD, Antic NA, Heeley E, et al.; SAVE Investigators. CPAP for prevention of cardiovascular events in obstructive sleep apnea. *N Engl J Med.* 2016;375(10):919–931. PMID: 27571048
13. Karakasis P, Sagris M, Patoulias D, et al. Mitigating increased cardiovascular risk in patients with obstructive sleep apnea using GLP-1 receptor agonists and

SGLT2 inhibitors: Hype or hope? *Biomedicines.* 2024;12(11):2503. PMID: 39595069

14. Sánchez-de-la-Torre M, Gracia-Lavedan E, Benitez ID, et al. Adherence to CPAP treatment and the risk of recurrent cardiovascular events: A meta-analysis. *JAMA.* 2023;330(13):1255–1265. PMID: 37787793
15. Marso SP, Bain SC, Consoli A, et al.; SUSTAIN-6 Investigators. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med.* 2016;375(19):1834–1844. PMID: 27633186
16. Marso SP, Daniels GH, Brown-Frandsen K, et al.; LEADER Steering Committee; LEADER Trial Investigators. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med.* 2016;375(4):311–322. PMID: 27295427
17. Verma S, Bhatt DL, Bain SC, et al. Effect of liraglutide on cardiovascular events in patients with type 2 diabetes mellitus with or without history of myocardial infarction or stroke. *Circulation.* 2018;138(25):2884–2894. PMID: 30566004
18. Lincoff AM, Brown-Frandsen K, Colhoun HM, et al.; SELECT Trial Investigators. Semaglutide and cardiovascular outcomes in obesity without diabetes. *N Engl J Med.* 2023;389(24):2221–2232. PMID: 37952131
19. Hassan N, Awan AT, Ansari A, et al. Cardiovascular benefits of semaglutide: a systematic review and meta-analysis of randomized controlled trials. *J Pharm Pharmacol.* 2025;77(3):112–121. PMID: 41272444
20. Sattar N, Lee MMY, Kristensen SL, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of randomised trials. *Lancet Diabetes Endocrinol.* 2021;9(10):653–662. PMID: 34425093
21. Drucker DJ. The cardiovascular biology of glucagon-like peptide-1. *Cell Metab.* 2016;24(1):15–30. PMID: 27411009
22. Ferrannini E, DeFronzo RA. Impact of glucose-lowering drugs on cardiovascular disease in type 2 diabetes. *Eur Heart J.* 2015;36(34):2288–2296. PMID: 26063450
23. Rakipovski G, Rolin B, Nøhr J, et al. The GLP-1 analogs liraglutide and semaglutide reduce atherosclerosis in ApoE−/− and LDLr−/− mice by a mechanism that includes inflammatory pathways. *JACC Basic Transl Sci.* 2018;3(6):844–857. PMID: 30623148
24. Bruen R, Curley S, Kajani S, et al. Cardiovascular protective properties of GLP-1 receptor agonists: more than just diabetic and weight loss drugs. *J Clin Med.* 2024;13(16):4674. PMID: 39200815
25. Rizzo M, Nikolic D, Patti AM, et al. GLP-1 receptor agonists and reduction of cardiometabolic risk: potential underlying mechanisms. *Biochim Biophys Acta Mol Basis Dis.* 2018;1864(9):2814–2821. PMID: 29660352

26. Sposito AC, Rocha VZ, Kimura-Medorima ST, et al. GLP-1 receptor agonists and SGLT2 inhibitors: mechanisms of cardiovascular protection. *Arch Med Sci.* 2023;19(6):1569–1593. PMID: 37835019
27. Apovian CM, Aronne LJ, Bessesen DH, et al. Pharmacological management of obesity: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab.* 2015;100(2):342–362. PMID: 25590212
28. Dempsey JA, Veasna Veasna S, Morgan BJ, O'Donnell CP. Pathophysiology of sleep apnea. *Physiol Rev.* 2010;90(1):47–112. PMID: 20086074
29. Pépin JL, Tamisier R, Lévy P. Obstructive sleep apnoea and metabolic syndrome: put CPAP efficacy in a more realistic perspective. *Thorax.* 2012;67(12):1025–1027. PMID: 22522561
30. Beccuti G, Bioletto F, Parasiliti-Caprino M, et al. Estimating cardiovascular benefits of tirzepatide in sleep apnea and obesity: insight from the SURMOUNT-OSA trials. *Curr Obes Rep.* 2024;13(4):721–731. PMID: 39382796
31. O'Donnell CP, Hogan JL, Bhatt DL. GLP-1 analogs with CPAP for OSA: additive effects on cardiovascular disease risk? *Am J Respir Crit Care Med.* 2014;190(9):970–972. PMID: 25358041
32. Punjabi NM. The epidemiology of adult obstructive sleep apnea. *Proc Am Thorac Soc.* 2008;5(2):136–143. PMID: 18250205
33. Reutrakul S, Mokhlesi B. Obstructive sleep apnea and diabetes: a state of the art review. *Chest.* 2017;152(5):1070–1086. PMID: 28527878
34. Joosten SA, Hamilton GS, Naughton MT. Impact of weight loss management in OSA. *Chest.* 2017;152(1):194–203. PMID: 27569339
35. Baraka BA, Nassar M, Azzam AY, et al. TriNetX and real-world evidence: a critical review of its strengths, limitations, and bias considerations in clinical research. *ASIDE Intern Med.* 2025;1(1). PMID: 40697879