Reviews in Cardiovascular Medicine

Rev. Cardiovasc. Med. **2026**; 27(11): 54661
https://doi.org/10.31083/RCM54661

Original Research

Comparative Effectiveness of Tirzepatide Versus Oral Semaglutide in Patients With Diabetes and Heart Failure With Preserved Ejection Fraction

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Academic Editor: Krishnaswami Vijayaraghavan
Submitted: 7 June 2026 Revised: 31 July 2026 Accepted: 18 August 2026 Published: 18 November 2026

Abstract

Background: Heart failure with preserved ejection fraction (HFpEF) among patients with type 2 diabetes mellitus (T2DM) remains associated with substantial mortality and hospitalization risk, and evidence to guide optimal metabolic therapy is limited. Thus, this study aimed to compare real-world outcomes of tirzepatide versus oral semaglutide in this population. **Methods:** We conducted a retrospective study using the TriNetX Research Network from June 2022 to June 2025. Adults with T2DM and HFpEF initiating tirzepatide were propensity score-matched 1:1 with those initiating oral semaglutide based on demographics, comorbidities, medications, and laboratory values (n = 2431 per group). The primary outcome was all-cause mortality at 12 months. Secondary outcomes included heart failure (HF) exacerbation and acute myocardial infarction (MI). Furthermore, traumatic brain injury (TBI) was prespecified as a falsification endpoint. Cox proportional hazards models were used to estimate associations. **Results:** Tirzepatide was not associated with a significant difference in all-cause mortality compared with oral semaglutide (hazard ratio [HR] 0.96, 95% confidence interval [CI] 0.71–1.29). No significant differences were observed in HF exacerbation (HR 1.06, 95% CI 0.90–1.24), acute MI (HR 0.89, 95% CI 0.72–1.11), or TBI (HR 1.32, 95% CI 0.80–2.19). **Conclusions:** In this large, propensity-matched real-world cohort of patients with T2DM and HFpEF, tirzepatide was not associated with significantly different 12-month risks of mortality, HF exacerbation, acute MI, or TBI compared with oral semaglutide. These findings do not establish equivalence or noninferiority and warrant prospective validation.

Keywords: heart failure; tirzepatide; oral semaglutide; type 2 diabetes mellitus; mortality

1. Introduction

Heart failure with preserved ejection fraction (HFpEF) affects more than 3 million adults in the United States, with an average of 1.4 hospitalizations per year per patient and an annual mortality rate of 15% [1]. These outcomes are further worsened in individuals with type 2 diabetes mellitus (T2DM), a condition present in nearly half of all HFpEF cases [2,3]. While management has historically been limited, sodium-glucose cotransporter-2 inhibitors (SGLT2i) have demonstrated the clearest reduction in hospitalization rates and mortality [3]. Recent trials indicate that glucagon-like peptide-1 (GLP-1) based therapies such as semaglutide and tirzepatide can improve symptoms, exercise tolerance, inflammation, and body weight in patients with HFpEF and obesity [4]. Despite their growing use, tirzepatide and semaglutide have not been directly compared in patients who have both HFpEF and T2DM. Previous head-to-head evidence demonstrates greater reductions in HbA1c and body weight with tirzepatide than with semaglutide in patients with T2DM [5]. Separately, semaglutide has demonstrated improvements in heart failure–related symptoms, physical limitations, and body weight in patients with obesity-related HFpEF and T2DM [6]. These findings provide a rationale for investigating whether differences in metabolic efficacy translate into differences in clinical outcomes in this population.

While several randomized head-to-head trials have compared injectable tirzepatide with injectable semaglutide in obesity and glycemic control settings, such as SURPASS-2 and SURMOUNT-5, demonstrating greater metabolic efficacy with tirzepatide, no completed randomized trials have directly compared tirzepatide with oral semaglutide in T2DM or obesity [5,7]. Given the rapid expansion of clinical incretin use in HFpEF and T2DM, real-world evidence providing direct comparisons of these pharmaceutical agents is needed to inform individualized treatment strategies. Accordingly, this study aims to evaluate all-cause mortality, heart failure (HF) exacerbation, and acute myocardial infarction (MI) in patients with HFpEF and T2DM taking tirzepatide or oral semaglutide.

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2. Methods

The present study performed a retrospective analysis using data from TriNetX Research Network, a federated research network that provides access to de-identified electronic medical records from 117 participating healthcare organizations (HCOs). Available data domains included patient demographics, diagnoses, procedures, medication exposures, laboratory measurements, and encounter-level information. The study was designed and reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines and adhered to established TriNetX publication standards [8]. All diagnosis, medication, procedure, and laboratory codes used to define cohorts, covariates, and outcomes are provided in the **Supplemental Material**.

2.1 Study Cohort

Adult patients (age ≥18) with T2DM and HFpEF were eligible for inclusion. Patients were required to meet all cohort-defining criteria between June 1, 2022, and June 1, 2025. The exposure cohort included patients who initiated tirzepatide without prior oral semaglutide use, while the comparator cohort consisted of patients who initiated oral semaglutide during the same period without prior tirzepatide use to minimize treatment crossover and to reflect real-world comparative use of incretin-based therapies. The index date was defined as the earliest date of initiation of the index medication. All inclusion and exclusion criteria were required to occur at least 1 day after documentation of T2DM and HFpEF.

2.2 Outcomes

Patients were followed for up to 1 year following index or until censoring, defined as the date of the last recorded clinical encounter within the TriNetX network. Patients were censored after the last recorded fact in their TriNetX record. The primary outcome investigated was all-cause mortality, with secondary outcomes including HF exacerbation and acute MI. HF exacerbation was defined as a composite electronic health record (EHR)-based outcome consisting of acute pulmonary edema, injectable loop diuretic use, injectable thiazide-related diuretic use, or metolazone use. Traumatic brain injury (TBI) was included as a falsification outcome to assess residual confounding.

2.3 Propensity Matching

To address baseline imbalances between treatment groups, 1:1 propensity score matching (PSM) was performed between the tirzepatide and oral semaglutide cohorts using the TriNetX platform. Matching was conducted using a greedy nearest-neighbor algorithm with a predefined caliper of 0.1 across 49 prespecified covariates. In accordance with TriNetX methodology, patient records were randomized prior to matching to prevent order-dependent bias. Covariates included in the propensity score model were selected a priori based on clinical relevance and encompassed demographic characteristics, baseline comorbidities, medication exposures, and available laboratory parameters, which can be found in the **Supplemental Material**. Covariate balance before and after matching was evaluated using standardized mean differences (SMDs), with values <0.1 considered indicative of adequate balance.

2.4 Statistical Analysis

All analyses were conducted within the TriNetX Compare Outcomes analytic framework. Baseline characteristics were summarized descriptively before and after PSM. Continuous variables were reported as mean and standard deviation or median and interquartile range, as available and appropriate to their distributions, and categorical variables were reported as counts and percentages. Binary outcome comparisons included absolute risk differences, risk ratios, and odds ratios with 95% confidence intervals (CIs). Absolute risk differences were calculated as the risk in the tirzepatide cohort minus the risk in the oral semaglutide cohort.

Time-to-event analyses were performed in the PSM cohorts using Kaplan–Meier methods. Between-group survival distributions were compared using log-rank tests, and hazard ratios (HRs) with 95% CIs were calculated with tirzepatide compared with oral semaglutide. Patients were censored after the last recorded fact in their TriNetX record. The proportional-hazards assumption was assessed using the TriNetX proportionality test. HRs were designated as the primary measures of association; when the proportional-hazards assumption was not satisfied, HRs were interpreted cautiously alongside cumulative risks and log-rank results.

No separate multivariable regression adjustment was performed after PSM. Statistical significance was defined as a two-sided p value < 0.05. No formal adjustment was made for multiple secondary outcomes; secondary and falsification analyses were therefore considered exploratory, with emphasis placed on effect estimates and 95% CIs.

3. Results

3.1 Cohort Identification and Matching

The initial query identified 19,265 adults with T2DM and HFpEF who initiated tirzepatide and 2514 who initiated oral semaglutide. Of these, 18,770 patients in the tirzepatide cohort and 2452 patients in the oral semaglutide cohort were included in PSM. Following 1:1 PSM, 2431 patients remained in each cohort (Fig. 1). Post-matching assessment demonstrated adequate balance across demographic characteristics, baseline comorbidities, medication exposures, and available laboratory measures, with all standardized mean differences below the prespecified threshold of 0.10 (Table 1). The median follow-up was 332 days (interquartile range [IQR], 213 days) in the tirzepatide cohort and 365 days (IQR, 105 days) in the oral semaglutide cohort.

Table 1. Baseline characteristics of tirzepatide and oral semaglutide cohorts pre- and post-PSM.

Characteristic	Pre-PSM			Post-PSM		
	Tirzepatide (N = 18,770)	Oral semaglutide (N = 2452)	SMD	Tirzepatide (N = 2431)	Oral semaglutide (N = 2431)	SMD
Demographics						
Age at index, years (mean ± SD)	65.0 ± 11.0	69.0 ± 11.1	0.368	69.0 ± 10.1	69.0 ± 11.1	0.005
Female, n (%)	10,518 (56.0)	1350 (55.1)	0.020	1340 (55.1)	1339 (55.1)	0.001
White, n (%)	12,771 (68.0)	1492 (60.8)	0.151	1479 (60.8)	1486 (61.1)	0.006
Black or African American, n (%)	4353 (23.2)	677 (27.6)	0.102	690 (28.4)	671 (27.6)	0.017
Asian, n (%)	296 (1.6)	116 (4.7)	0.181	97 (4.0)	107 (4.4)	0.021
Hispanic or Latino, n (%)	1219 (6.5)	106 (4.3)	0.096	128 (5.3)	106 (4.4)	0.042
Diagnoses						
CKD, n (%)	8450 (45.0)	1125 (45.9)	0.017	1167 (48.0)	1114 (45.8)	0.044
Ischemic heart disease, n (%)	9631 (51.3)	1316 (53.7)	0.047	1312 (54.0)	1304 (53.6)	0.007
Hyperlipidemia, n (%)	15,190 (80.9)	1983 (80.9)	0.001	1989 (81.8)	1964 (80.8)	0.026
Atrial fibrillation/flutter, n (%)	6099 (32.5)	817 (33.3)	0.018	803 (33.0)	812 (33.4)	0.008
Hypertension, n (%)	15,765 (84.0)	2054 (83.8)	0.006	2058 (84.7)	2035 (83.7)	0.026
Nicotine dependence, n (%)	2269 (12.1)	313 (12.8)	0.021	327 (13.5)	311 (12.8)	0.019
Old myocardial infarction, n (%)	2295 (12.2)	287 (11.7)	0.016	297 (12.2)	286 (11.8)	0.014
Cardiomyopathy, n (%)	2614 (13.9)	325 (13.3)	0.020	328 (13.5)	323 (13.3)	0.006
Cerebral infarction, n (%)	1203 (6.4)	198 (8.1)	0.064	189 (7.8)	195 (8.0)	0.009
Medications						
Beta blockers, n (%)	11,715 (62.4)	1574 (64.2)	0.037	1594 (65.6)	1557 (64.0)	0.032
Calcium channel blockers, n (%)	7238 (38.6)	1013 (41.3)	0.056	1027 (42.2)	1006 (41.4)	0.018
ACE inhibitors, n (%)	3401 (18.1)	524 (21.4)	0.082	526 (21.6)	518 (21.3)	0.008
Angiotensin receptor blockers, n (%)	7204 (38.4)	916 (37.4)	0.021	943 (38.8)	908 (37.4)	0.030
Insulin therapy, n (%)	10,100 (53.8)	1170 (47.7)	0.122	1206 (49.6)	1161 (47.8)	0.037
DPP-4 inhibitors, n (%)	725 (3.9)	237 (9.7)	0.233	232 (9.5)	224 (9.2)	0.011
SGLT2 inhibitors, n (%)	6731 (35.9)	935 (38.1)	0.047	933 (38.4)	925 (38.1)	0.007
GLP-1 receptor agonists, n (%)	7976 (42.5)	197 (8.0)	0.864	209 (8.6)	197 (8.1)	0.018
Metformin, n (%)	5050 (26.9)	792 (32.3)	0.118	781 (32.1)	781 (32.1)	<0.001
Diuretics, n (%)	12,852 (68.5)	1698 (69.2)	0.017	1682 (69.2)	1683 (69.2)	0.001
Potassium-sparing diuretics, n (%)	4839 (25.8)	509 (20.8)	0.119	510 (21.0)	507 (20.9)	0.003
Statins, n (%)	12,147 (64.7)	1626 (66.3)	0.034	1660 (68.3)	1610 (66.2)	0.044
Anticoagulants, n (%)	9975 (53.1)	1359 (55.4)	0.046	1363 (56.1)	1347 (55.4)	0.013
Laboratory values						
Hemoglobin A1c, %	7.4 ± 1.8	7.8 ± 1.7	0.245	7.7 ± 1.8	7.8 ± 1.7	0.091
6–9%	11,532 (61.4)	1611 (65.7)	0.089	1621 (66.7)	1591 (65.4)	0.026
9–12%	3153 (16.8)	504 (20.6)	0.097	532 (21.9)	494 (20.3)	0.038
≥12%	695 (3.7)	103 (4.2)	0.026	97 (4.0)	100 (4.1)	0.006
BMI, kg/m^2	39.6 ± 8.7	35.8 ± 8.6	0.440	36.5 ± 8.3	35.9 ± 8.6	0.074
25–30	2747 (14.6)	673 (27.4)	0.318	704 (29.0)	661 (27.2)	0.039
30–35	5543 (29.5)	873 (35.6)	0.130	897 (36.9)	867 (35.7)	0.026
35–40	6523 (34.8)	772 (31.5)	0.069	800 (32.9)	769 (31.6)	0.027
≥40	8788 (46.8)	769 (31.4)	0.321	745 (30.6)	769 (31.6)	0.021

Table 1. Continued.

Characteristic	Pre-PSM			Post-PSM		
	Tirzepatide (N = 18,770)	Oral semaglutide (N = 2452)	SMD	Tirzepatide (N = 2431)	Oral semaglutide (N = 2431)	SMD
BNP, pg/mL	359.0 ± 1246.8	516.1 ± 1898.5	0.098	468.4 ± 1892.0	514.3 ± 1912.1	0.024
0–150	2693 (14.3)	416 (17.0)	0.072	396 (16.3)	410 (16.9)	0.015
150–300	1074 (5.7)	195 (8.0)	0.088	190 (7.8)	192 (7.9)	0.003
300–450	544 (2.9)	111 (4.5)	0.086	108 (4.4)	109 (4.5)	0.002
450–600	347 (1.8)	62 (2.5)	0.046	65 (2.7)	60 (2.5)	0.013
≥600	721 (3.8)	151 (6.2)	0.106	155 (6.4)	144 (5.9)	0.019
NT-proBNP, pg/mL	1731.8 ± 5288.4	2377.8 ± 5506.3	0.120	2782.0 ± 8260.0	2373.9 ± 5514.9	0.058
0–300	1968 (10.5)	169 (6.9)	0.128	155 (6.4)	168 (6.9)	0.021
300–600	1086 (5.8)	94 (3.8)	0.091	99 (4.1)	94 (3.9)	0.011
600–900	690 (3.7)	70 (2.9)	0.046	81 (3.3)	70 (2.9)	0.026
900–1200	493 (2.6)	47 (1.9)	0.048	47 (1.9)	47 (1.9)	<0.001
≥1200	1412 (7.5)	180 (7.3)	0.007	205 (8.4)	179 (7.4)	0.040

Abbreviations: ACE, angiotensin-converting enzyme; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BMI, body mass index; BNP, B-type natriuretic peptide; CI, confidence interval; CKD, chronic kidney disease; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; HbA1c, hemoglobin A1c; HF, heart failure; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro–B-type natriuretic peptide; PSM, propensity score matching; SD, standard deviation; SGLT2, sodium–glucose cotransporter 2; SMD, standardized mean difference.

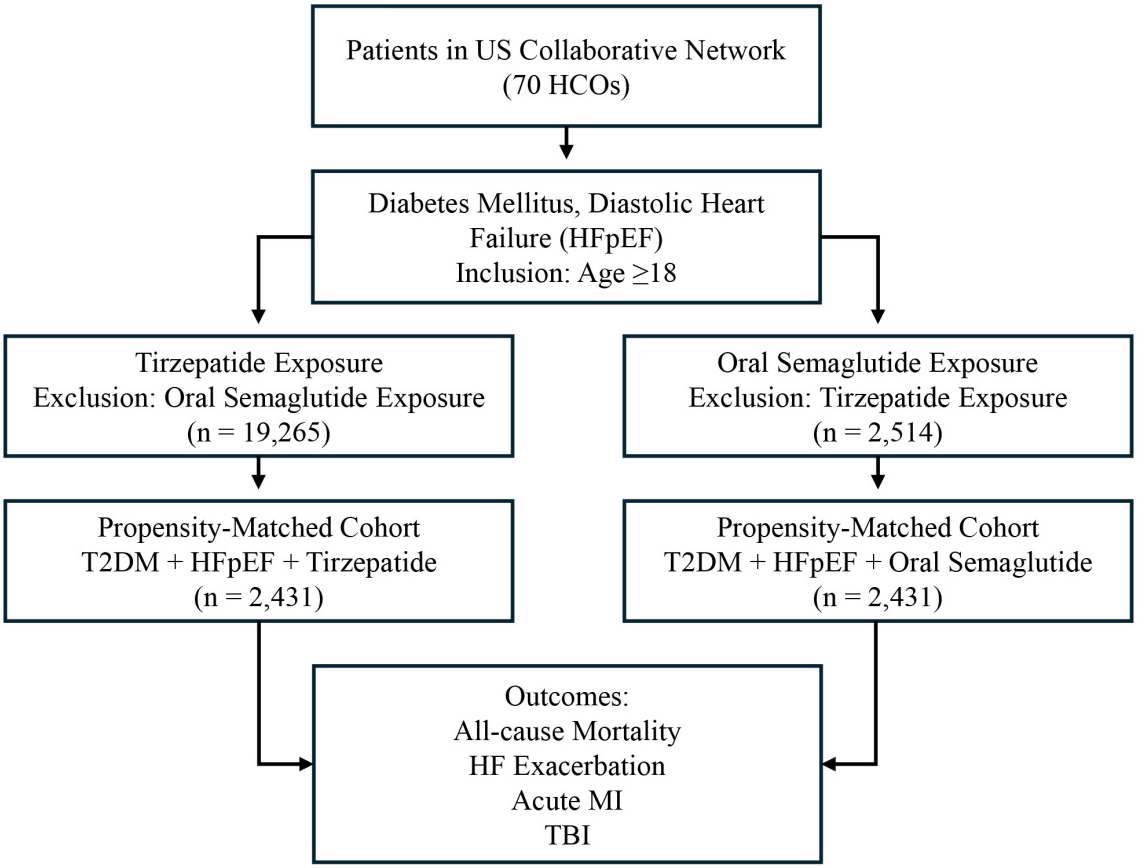


Fig. 1. Cohort selection and propensity score–matched design comparing tirzepatide versus oral semaglutide in patients with T2DM and HFpEF. Abbreviations: HF, heart failure; HFpEF, heart failure with preserved ejection fraction; MI, myocardial infarction; PSM, propensity score matching; T2DM, type 2 diabetes mellitus; TBI, traumatic brain injury; HCOs, healthcare organizations.

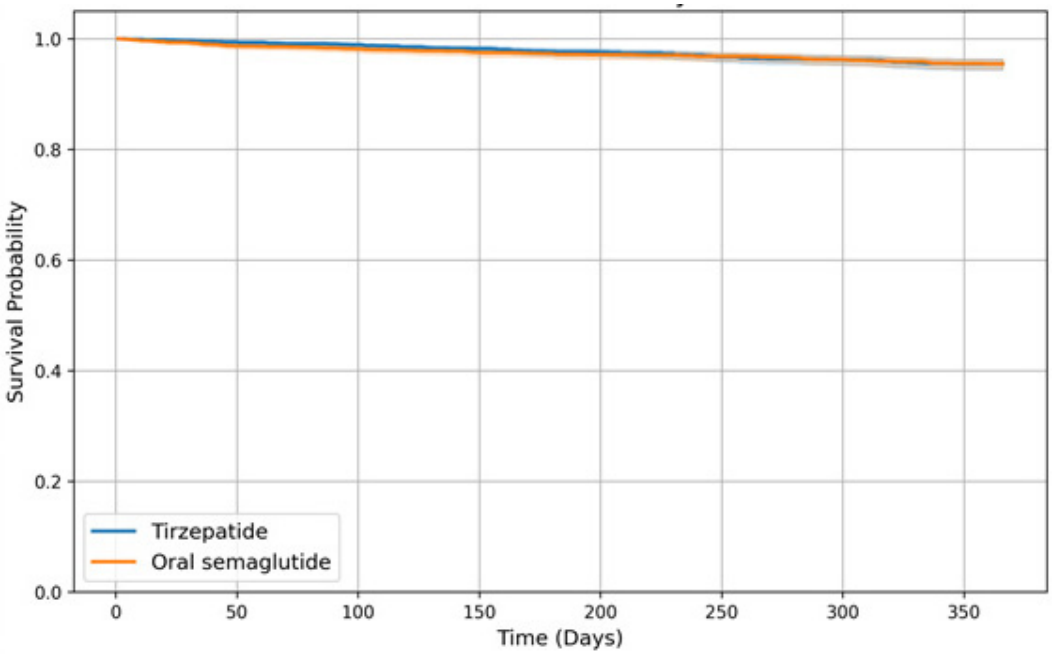


Fig. 2. Kaplan-Meier plot comparing all-cause mortality between the 2 cohorts over 1 year follow-up period.

Table 2. Clinical outcomes comparing tirzepatide vs oral semaglutide post-PSM.

Outcome	Tirzepatide (%), N = 2431	Oral semaglutide (%), N = 2431	ARR	ARD (95% CI)	RR (95% CI)	OR (95% CI)	HR (95% CI)	Log-rank *p*-value
All-cause mortality	80 (3.3%)	93 (3.8%)	0.5%	−0.5% (−1.6%, 0.5%)	0.86 (0.64–1.15)	0.86 (0.63–1.16)	0.96 (0.71–1.29)	0.784
HF exacerbation	302 (12.4%)	312 (12.8%)	0.4%	−0.4% (−2.3%, 1.5%)	0.97 (0.84–1.12)	0.96 (0.81–1.14)	1.06 (0.90–1.24)	0.502
Acute MI	153 (6.3%)	185 (7.6%)	1.3%	−1.3% (−2.7%, 0.1%)	0.83 (0.67–1.02)	0.82 (0.65–1.02)	0.89 (0.72–1.11)	0.305
TBI	33 (1.4%)	28 (1.2%)	−0.2%	0.2% (−0.4%, 0.8%)	1.18 (0.72–1.94)	1.18 (0.71–1.96)	1.32 (0.80–2.19)	0.273

Abbreviations: ARD, absolute risk difference; ARR, absolute risk reduction; CI, confidence interval; HF, heart failure; HR, hazard ratio; MI, myocardial infarction; OR, odds ratio; PSM, propensity score matching; RR, risk ratio; TBI, traumatic brain injury.

3.2 Outcomes

In the propensity-matched cohorts, all-cause mortality occurred in 3.3% of patients receiving tirzepatide and 3.8% receiving oral semaglutide. Survival analysis demonstrated no significant difference in the hazard of all-cause mortality between treatment groups (HR 0.96, 95% CI 0.71–1.29; Table 2; Fig. 2). HF exacerbation occurred in 12.4% of patients receiving tirzepatide and 12.8% receiving oral semaglutide. There was no significant difference in cumulative risk or time-to-event analysis between groups (HR 1.06, 95% CI 0.90–1.24). The proportional-hazards assumption was not satisfied for this outcome; therefore, the HR should be interpreted cautiously. Acute MI occurred in 6.3% of patients receiving tirzepatide and 7.6% receiving oral semaglutide. Although the event rate was numerically lower in the tirzepatide cohort, the difference was not statistically significant in either the cumulative-risk analysis or survival analysis (HR 0.89, 95% CI 0.72–1.11).

As a falsification outcome, TBI was evaluated to assess for residual confounding. Event rates were low and similar between cohorts (1.4% vs 1.2%). No significant difference was observed between groups (risk difference 0.2%, 95% CI −0.4% to 0.8%; HR 1.32, 95% CI 0.80–2.19; log-rank p = 0.273). The confidence interval was wide, and the proportional-hazards assumption was not satisfied; therefore, this finding provides only limited reassurance regarding residual confounding.

4. Discussion

In this large-scale, propensity score–matched real-world cohort of patients with T2DM and HFpEF, tirzepatide was not associated with a significant difference in 12-month all-cause mortality, HF exacerbation, or acute MI compared with oral semaglutide. The falsification outcome of TBI was also not significantly different between treatment groups. These findings suggest that, within the

limitations of this observational analysis, the two treatment groups had broadly similar observed clinical outcomes over 1 year and do not support a survival or HF-related advantage of tirzepatide over oral semaglutide. HFpEF is a heterogeneous syndrome that is associated with substantial morbidity and mortality, particularly among patients with T2DM, obesity, and cardiometabolic diseases [9,10]. Although SGLT2i have demonstrated a reduction in HF hospitalization in HFpEF patients regardless of diabetes status, evidence supporting incretin-based therapies in HFpEF patients has been limited [11,12]. A recent meta-analysis by Albulushi et al. [13] found that both GLP-1 receptor agonists and SGLT2 inhibitors may improve functional, metabolic, and cardiac parameters in patients with T2DM and HFpEF, although evidence regarding comparative long-term clinical outcomes remains limited.

HFpEF is a systemic disorder characterized by adiposity-driven inflammation, myocardial fibrosis, endothelial dysfunction, and impaired ventricular-arterial coupling [9,10]. Tirzepatide is associated with more sustained weight loss than GLP-1 receptor agonists (RAs) alone, which may have a stronger impact on the left ventricular filling pressures, epicardial adipose tissue, and inflammatory cascades [7]. Additionally, the dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptor activation may enhance adipocyte function, insulin sensitivity, and lipid metabolism, which potentially leads to reduced lipotoxicity and microvascular dysfunction in HFpEF patients [14,15]. Prior studies have also shown that tirzepatide was associated with better-controlled blood pressure, blood sugar level, and lipid profiles, which are associated with adverse outcomes in HFpEF patients [16]. Despite these biologically plausible advantages, the present analysis did not identify significantly different mortality, HF exacerbation, or acute MI outcomes between tirzepatide and oral semaglutide over 12 months. Greater improvements in weight or glycemic control therefore may not necessarily translate into detectable differences in clinical events over the follow-up period evaluated in this study.

Recent randomized evidence has established that incretin-based therapies can improve functional status in HFpEF, most notably with injectable semaglutide. The STEP-HFpEF trial (Semaglutide in Patients with Heart Failure with Preserved Ejection Fraction and Obesity) showed that subcutaneous semaglutide significantly improved health-related quality of life, exercise capacity, and weight loss in patients with HFpEF and obesity, but the study was not powered enough to evaluate mortality or HF hospitalization [17]. Improvements in this study were driven primarily by substantial weight loss and reductions in systemic inflammation, reinforcing the concept that cardiometabolic modulation, rather than direct hemodynamic effects, may underlie the observed benefits of GLP-1 receptor agonism in HFpEF [18]. Additionally, other trials of GLP-1 RAs have shown reductions in atherosclerotic events [19,20]. However, improvements in symptoms, functional capacity, and metabolic parameters do not necessarily establish differences in mortality or HF events between individual incretin-based therapies.

Evidence directly comparing tirzepatide and semaglutide in HFpEF has recently emerged. While injectable semaglutide has demonstrated effectiveness in HFpEF, prior randomized trials comparing tirzepatide with semaglutide have shown greater improvements in glycemic control and weight loss with tirzepatide in patients with T2DM, with similar superiority observed in obesity populations; however, such head-to-head comparisons have not been extended to oral formulations in cardiometabolic disease [5,7,21]. Nevertheless, these metabolic head-to-head comparisons were not designed to determine whether such differences result in improved HF or survival outcomes. Oral semaglutide represents the first orally bioavailable GLP-1 RAs approved for clinical use and offers an alternative for patients unwilling or unable to use injectable therapies [22]. However, oral administration is associated with low and highly variable bioavailability, strict fasting requirements, and sensitivity to administration conditions, all of which may attenuate real-world effectiveness compared with injectable formulations [23]. By directly comparing injectable tirzepatide with oral semaglutide, the present study evaluates a clinically relevant question involving agents that differ in receptor activity, route of administration, dosing requirements, adherence considerations, and factors influencing treatment selection. Accordingly, the observed findings cannot be attributed specifically to dual GIP/GLP-1 receptor agonism.

Our neutral findings are consistent with the recently published analysis by Monzo et al. [24], which directly compared semaglutide and tirzepatide in patients with obesity and HFpEF using a global federated EHR network. Following propensity score matching, that study found no significant differences in the composite of mortality and HF hospitalization or in either component individually [24]. The Monzo et al. [24] population differed from the present study because it required obesity, included patients with and without diabetes, evaluated injectable rather than specifically oral semaglutide, and had a shorter median follow-up. Despite these differences, both analyses failed to identify significant differences in mortality or HF-related events between tirzepatide and semaglutide. The present study extends these observations to patients specifically selected for concurrent T2DM and HFpEF and to oral semaglutide as the active comparator.

Several factors may explain the absence of significant between-group differences in the present study. First, although tirzepatide may produce greater average reductions in HbA1c and body weight than GLP-1 receptor agonists alone, the 12-month follow-up period may have been insufficient for differences in metabolic effects to translate into measurable differences in mortality or cardiovascu-

lar events [25]. Second, the analysis could not account for adherence, treatment persistence, dose escalation, medication discontinuation, or administration technique, all of which may be particularly relevant when comparing an injectable medication with an oral medication requiring specific fasting and administration conditions. Third, HFpEF represents a heterogeneous clinical syndrome, and the use of administrative coding did not permit differentiation of obesity-related HFpEF from other phenotypes. Finally, residual differences in treatment selection and healthcare utilization may remain despite propensity score matching.

The present findings differ in emphasis from the SUMMIT trial, in which tirzepatide reduced the composite risk of cardiovascular death or worsening HF compared with placebo among patients with obesity-related HFpEF [26]. This difference may reflect the use of an active incretin-based comparator rather than placebo, as well as differences in cohort eligibility, outcome ascertainment, treatment adherence, and study design. Similarly, prior real-world evidence has reported lower rates of HF exacerbation and mortality among tirzepatide users in other comparator populations [27]. However, those findings do not necessarily indicate superiority over oral semaglutide in patients with both T2DM and HFpEF. Taken together, the available evidence supports potential clinical benefits of incretin-based therapy in appropriately selected patients with HFpEF, but it remains uncertain whether one incretin-based agent provides superior clinical-event reduction over another.

This study has several strengths. It used a large federated EHR network, an active comparator, a common treatment-availability period, and PSM across demographic characteristics, comorbidities, medications, and available laboratory values. Following the revised matching procedure, all included covariates achieved standardized mean differences below 0.10. The inclusion of TBI as a prespecified falsification outcome provided an additional assessment of potential residual confounding [28]. However, the nonsignificant TBI result does not establish the specificity of the clinical findings or eliminate residual confounding. The confidence interval was wide, and TBI may itself be associated with frailty, falls, hypoglycemia, and healthcare utilization. It therefore provides only limited reassurance regarding unmeasured confounding.

5. Limitations

This study has several limitations inherent to its observational design. Despite rigorous 1:1 PSM, residual and unmeasured confounding cannot be excluded, as EHR-based analyses incompletely capture factors such as socioeconomic status, health behaviors, frailty, and clinician or patient preferences that may influence treatment selection and outcomes [28]. Although both cohorts were restricted to a common treatment-availability period beginning in June 2022, residual calendar-time differences in prescribing patterns, HF management, and healthcare delivery may remain. In addition, the analysis did not include a separate adjustment for index year or quarter.

HFpEF diagnoses were based on administrative coding rather than standardized adjudication using imaging or hemodynamic criteria. Given the heterogeneity of HFpEF phenotypes and evolving diagnostic thresholds, misclassification remains possible, particularly in patients with borderline ejection fractions [9,10]. The available data did not require confirmation of preserved left ventricular ejection fraction (LVEF) and did not permit differentiation among obesity-related, hypertensive, ischemic, or other HFpEF phenotypes.

Medication exposure was defined by prescription records rather than confirmed adherence, dose escalation, or treatment persistence, limiting assessment of exposure-response relationships. Additionally, the absence of a formal washout period for prior incretin-based therapies may have attenuated observed associations. Patients were assigned according to their index medication, and the analysis did not censor for treatment discontinuation, switching, or subsequent changes in therapy. Differences in route of administration, dosing requirements, adherence, and treatment selection between injectable tirzepatide and oral semaglutide may therefore have influenced the observed associations.

Outcome ascertainment for HF exacerbation and acute MI relied on diagnosis codes, which are subject to variability in sensitivity and specificity across health systems [29]. The HF exacerbation outcome was an EHR-based composite of acute pulmonary edema or intensified diuretic treatment and did not require a confirmed hospitalization, emergency department encounter, or adjudicated episode of acute HF. Therefore, the outcome may have included outpatient treatment intensification or diuretic use for indications other than acute HF decompensation. Patients with prior documentation of the evaluated outcomes were not excluded, and post-index acute MI and TBI events could represent either incident or recurrent events.

Mortality was identified using the TriNetX demographic designation of deceased. The analytic output did not permit determination of the source used by each contributing HCO to populate mortality status, and deaths not captured in the available records may have been missed. Follow-up was limited to 12 months, which may be insufficient to capture longer-term effects of metabolic therapies on HFpEF progression and outcomes [30]. Observed follow-up was also shorter in the tirzepatide cohort than in the oral semaglutide cohort, although time-to-event analyses incorporated censoring after the last recorded fact in each patient's record.

The proportional-hazards assumption was not satisfied for HF exacerbation or TBI; therefore, the corresponding HRs may not represent constant relative hazards throughout follow-up and should be interpreted alongside

the cumulative-risk and log-rank analyses. No formal adjustment was made for multiple secondary and falsification outcomes, and these analyses should be considered exploratory.

Although TBI was included as a falsification outcome, the absence of a statistically significant association does not eliminate residual confounding. The estimate was imprecise, and TBI may itself be associated with frailty, falls, hypoglycemia, medication use, and healthcare utilization. Accordingly, the TBI analysis provides only limited reassurance regarding unmeasured confounding.

Laboratory data were not available for all patients, and the TriNetX analytic output did not report imputation of missing values. Laboratory covariates therefore reflect patients with available measurements and may be subject to informative missingness. Finally, the federated and de-identified structure of TriNetX precluded assessment of site-level variation and may limit generalizability across healthcare settings and populations not adequately represented in the participating HCOs. Because this analysis was not designed as an equivalence or noninferiority study, the absence of statistically significant differences should not be interpreted as evidence that tirzepatide and oral semaglutide produce equivalent clinical outcomes.

6. Conclusion

In this large, propensity-matched, real-world cohort of patients with T2DM and HFpEF, tirzepatide was not associated with significantly different 12-month risks of all-cause mortality, HF exacerbation, or acute MI compared with oral semaglutide. The falsification outcome of TBI was also not significantly different between groups. These findings do not demonstrate a survival or HF-related advantage of tirzepatide and should not be interpreted as evidence of equivalence or noninferiority. Prospective randomized studies are warranted to determine whether clinically meaningful differences exist between incretin-based therapies in this high-risk population.

Availability of Data and Materials

The data that support the findings of this study were obtained from the TriNetX US Collaborative Network, a federated, multi-institutional clinical research platform that provides access to de-identified electronic health record data. Researchers with appropriate institutional approvals may access the data through the TriNetX platform (https://www.trinetx.com) subject to TriNetX policies and regulatory requirements.

Author Contributions

IM, SM, KC, MS, MB, TB, AA and HJ designed the research study. IM, AL, DB and VQ performed the research. IM analyzed the data. AL, DB and AA wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The University of Texas Medical Branch Institutional Review Board (IRB) determined that informed consent was not required to be obtained from participants for this retrospective study because it involved a secondary analysis of existing, de-identified data obtained from TriNetX. The study did not involve any intervention or direct interaction with human participants. All data met the de-identification standards outlined in Section 164.514(a) of the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule. All analyses were conducted in compliance with applicable ethical and regulatory requirements. The study was conducted in accordance with the Declaration of Helsinki.

Acknowledgment

Not applicable.

Funding

This research was supported by the UTMB Institute for Translational Sciences, supported in part by a Clinical and Translational Science Award (UL1 TR001439) from the National Center for Advancing Translational Sciences at the National Institutes of Health (NIH). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

Conflicts of Interest

The authors declare no conflicts of interest. Hani Jneid is serving as one of the Editorial Board members of this journal. We declare that Hani Jneid had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Krishnaswami Vijayaraghavan.

Declaration of AI and AI-Assisted Technologies in the Writing Process

During the revision of this manuscript, the authors used an AI-assisted language tool solely to improve wording, grammar, and clarity. The tool was not used to generate, analyze, or interpret study data. The authors reviewed and edited all content and take full responsibility for the final manuscript.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/RCM54661.

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