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Effectiveness of tirzepatide in patients with HFpEF using a target trial emulation retrospective cohort study

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Tirzepatide, a dual agonist of glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptors, has shown promise in improving metabolic and cardiovascular profiles in patients with obesity. However, its potential benefits in patients with heart failure with preserved ejection fraction (HFpEF) remain unclear. We conducted a real-world, retrospective cohort study using the TriNetX global database. A total of 14,154 patients with HFpEF were included after 1:1 propensity score matching. Tirzepatide use was associated with significantly lower risks of the primary composite outcome of heart failure exacerbation and all-cause mortality (HR 0.52), as well as reductions in major adverse cardiovascular events (HR 0.64) and major adverse kidney events (HR 0.44). Subgroup analyses demonstrated consistent benefits across different strata. Sensitivity analyses using alternative exposure definitions confirmed the robustness of the findings. These results support the potential clinical utility of tirzepatide in HFpEF management and warrant further investigation in randomized controlled trials.

Heart failure with preserved ejection fraction (HFpEF) accounts for nearly half of all heart failure cases, yet therapeutic options remain relatively limited[1,2]. Previous treatment recommendations have primarily focused on managing comorbidities and congestion control[3]. However, effective pharmacological treatments targeting the pathophysiological mechanisms of HFpEF, such as visceral adiposity and systemic inflammation, are still lacking[4]. Emerging evidence suggests that GLP-1 receptor agonists (GLP-1 RA) may offer clinical benefits in HFpEF patients through anti-inflammatory and hemodynamic effects[5,6].

Tirzepatide, a dual agonist targeting both glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptors, has demonstrated superior efficacy in metabolic regulation, including significant weight loss and anti-inflammatory properties, compared to GLP-1 RAs alone[7–10]. Recent randomized controlled trial (RCT) has shown that tirzepatide reduces the risk of cardiovascular death and worsening heart failure in patients with HFpEF and obesity. However, this study primarily focused on patients with a body mass index (BMI) > 30 kg/m^2, included a relatively small sample size, and had a shorter follow-up duration[11].

In this work, we use real-world data from the TriNetX global federated health research network to evaluate the association between tirzepatide use and one-year clinical outcomes in a broad HFpEF population, including individuals with and without obesity.

Results

Patient selection

A total of 71,282,114 individuals visited the TriNetX network at least once between January 1, 2022, and November 30, 2024. Of these,

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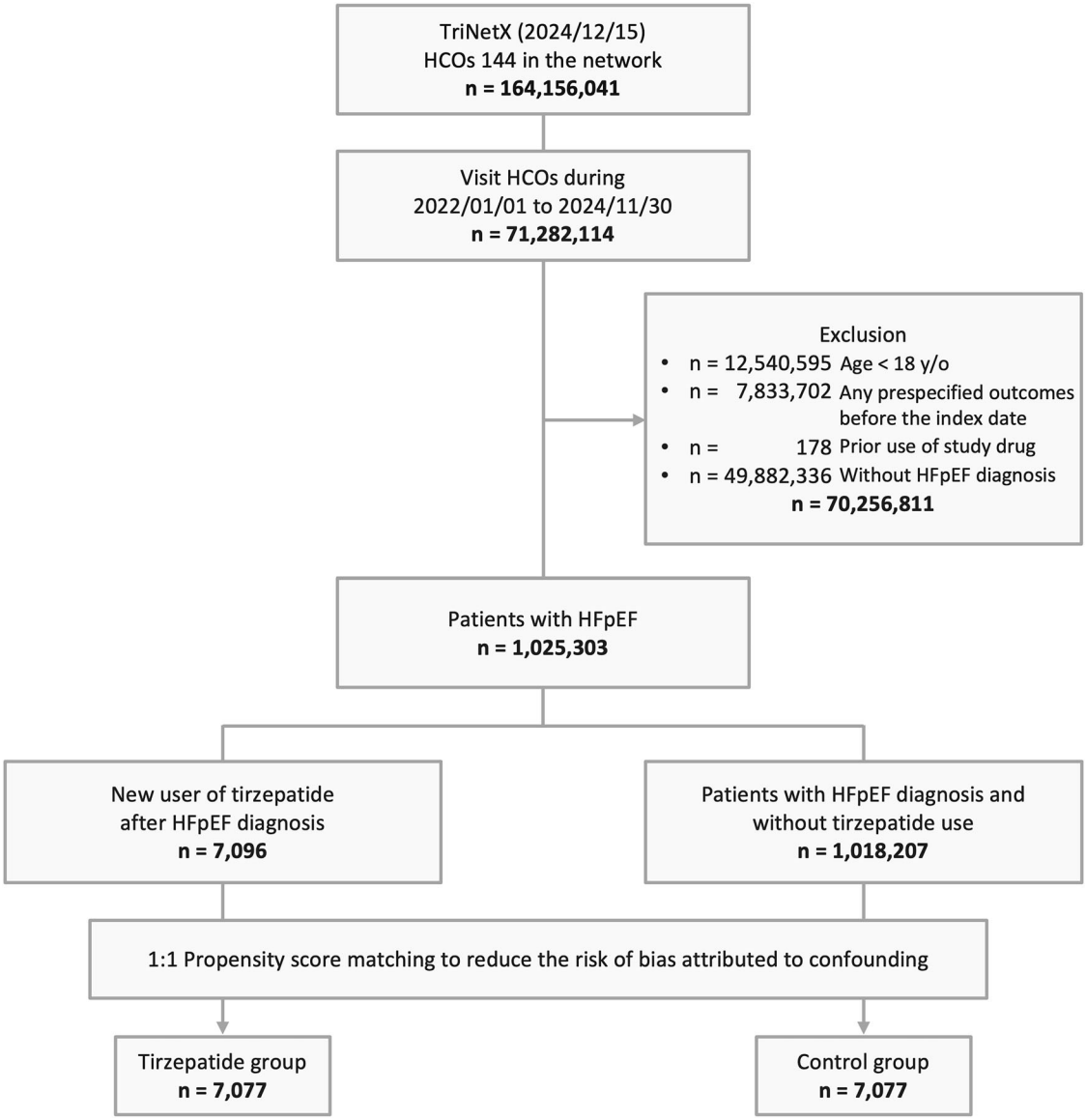

Fig. 1 | Study cohort process. HCOs healthcare organizations, HFpEF Heart failure with preserved ejection fraction, T2D type 2 diabetes, y/o years old.

70,251,811 were excluded for meeting at least one of the following criteria: age < 18 years, presence of any prespecified outcome prior to the index date, prior use of the study drug, or absence of an HFpEF diagnosis. Among the remaining 1,025,303 patients with HFpEF, 7096 were newly treated with tirzepatide and 1,018,207 had not used tirzepatide. After 1:1 propensity score matching (PSM), 7077 matched pairs were included in the final analysis (Fig. 1).

Demographic characteristics

Before PSM, there were significant differences between the tirzepatide group ($n = 7096$) and the control group ($n = 1,018,207$). Participants in the tirzepatide group were younger (63.0 ± 11.4 vs. 69.8 ± 13.7 years) and included a slightly higher proportion of women (54.2% vs. 48.7%). They were more likely to have overweight or obesity (72.7% vs. 17.1%), type 2 diabetes (T2D) (75.6% vs. 26.4%), hypertension, and chronic kidney disease compared with controls. Medications such as HMG-CoA reductase inhibitors and sodium-glucose co-transporter 2 inhibitor (SGLT2i) were also used more frequently in the tirzepatide group (Table 1).

After PSM, the tirzepatide (n = 7,077) and control (n = 7,077) groups were well balanced on baseline characteristics, as shown by standardized differences <0.1. Their mean ages were comparable (63.1 ± 11.3 vs. 63.1 ± 13.1 years), as were sex distributions (54.1% vs. 53.0% women). Comorbidities such as T2D, hypertension, overweight/obesity, and chronic kidney disease, and associated medication use (lipid-lowering agents, antihypertensives, and antiplatelet therapies) were also similar. Hemoglobin A1c and estimated Glomerular filtration rate (eGFR) distributions showed satisfactory balance (standardized differences < 0.1; Table 1).

Primary outcome

For the primary outcome (composite of heart failure exacerbation (HFE) and all-cause mortality), tirzepatide use was associated with a significantly lower cumulative incidence compared with controls (hazard ratios [HR], 0.52; 95% confidence interval [CI], 0.42–0.63; $p < 0.001$), reflecting incidence rates of 3.09 and 6.55 per 100 person-years, respectively (Table 2). The E-value for this association was 3.26 (95% lower confidence limit [LCL], 2.55), indicating that only a relatively large unmeasured confounder could negate tirzepatide's effectiveness against the composite outcome. Consistently, Kaplan-Meier curves demonstrated a lower cumulative incidence of the primary outcome in the tirzepatide group compared with the control

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Table 1 | Baseline characteristics of tirzepatide and control groups before and after matching

Variables	Before matching			After matching		
	Tirzepatide group (*n* = 7096)	Control group (*n* = 1,018,207)	Standardized difference	Tirzepatide group (*n* = 7077)	Control group (*n* = 7077)	Standardized difference
Age at index, years						
Mean (SD)	63.0 (11.4)	69.8 (13.7)	0.536	63.1 (11.3)	63.1 (13.1)	0.005
Sex, *n* (%)						
Female	3845 (54.2)	496,251 (48.7)	0.109	3830 (54.1)	3750 (53)	0.023
Male	3027 (42.7)	476,515 (46.8)	0.083	3023 (42.7)	3098 (43.8)	0.021
Race, *n* (%)						
White	4601 (64.8)	656,056 (64.4)	0.009	4592 (64.9)	4606 (65.1)	0.004
Black or African American	1230 (17.3)	163,081 (16)	0.035	1225 (17.3)	1219 (17.2)	0.002
Asian	112 (1.6)	29,573 (2.9)	0.090	112 (1.6)	112 (1.6)	< 0.001
Other Race	173 (2.4)	23,358 (2.3)	0.009	172 (2.4)	163 (2.3)	0.008
Unknown Race	900 (12.7)	131,484 (12.9)	0.007	896 (12.7)	895 (12.6)	< 0.001
Comorbidities, *n* (%)						
Alcohol related disorders	204 (2.9)	25,927 (2.5)	0.020	204 (2.9)	220 (3.1)	0.013
Nicotine dependence	811 (11.4)	87,465 (8.6)	0.095	811 (11.5)	821 (11.6)	0.004
Hypertension	5701 (80.3)	525,311 (51.6)	0.637	5684 (80.3)	5732 (81.0)	0.017
Dyslipidemia	5486 (77.3)	423,867 (41.6)	0.780	5467 (77.3)	5485 (77.5)	0.006
Type 2 diabetes mellitus	5365 (75.6)	269,107 (26.4)	1.130	5346 (75.5)	5429 (76.7)	0.028
Overweight and obesity	5156 (72.7)	174,600 (17.1)	1.345	5137 (72.6)	5215 (73.7)	0.025
Hypertensive diseases	6304 (88.8)	576,269 (56.6)	0.777	6285 (88.8)	6342 (89.6)	0.026
Cerebrovascular diseases	960 (13.5)	105,674 (10.4)	0.097	955 (13.5)	948 (13.4)	0.003
Ischemic heart diseases	3551 (50.0)	308,634 (30.3)	0.411	3537 (50.0)	3540 (50.0)	0.001
Chronic kidney disease	2843 (40.1)	198,180 (19.5)	0.462	2829 (40.0)	2858 (40.4)	0.008
Chronic lower respiratory diseases	2772 (39.1)	203,675 (20.0)	0.427	2760 (39.0)	2822 (39.9)	0.018
Neoplasms	1739 (24.5)	171,433 (16.8)	0.190	1733 (24.5)	1793 (25.3)	0.020
Systemic connective tissue disorders	285 (4.0)	21,686 (2.1)	0.109	284 (4.0)	281 (4.0)	0.002
T2D complications, *n* (%)						
Kidney complications	2440 (34.4)	84,775 (8.3)	0.671	2424 (34.3)	2474 (35.0)	0.015
Ophthalmic complications	916 (12.9)	26,030 (2.6)	0.395	907 (12.8)	895 (12.6)	0.005
Neurological complications	2165 (30.5)	62,198 (6.1)	0.665	2149 (30.4)	2149 (30.4)	< 0.001
Circulatory complications	1197 (16.9)	34,213 (3.4)	0.460	1186 (16.8)	1206 (17.0)	0.008
Lipid-lowering medications, *n* (%)						
HMG CoA reductase inhibitors	4468 (63.0)	373,395 (36.7)	0.545	4450 (62.9)	4484 (63.4)	0.010
Ezetimibe	580 (8.2)	24,029 (2.4)	0.263	573 (8.1)	561 (7.9)	0.006
Evolocumab	138 (1.9)	2850 (0.3)	0.159	135 (1.9)	127 (1.8)	0.008
Alirocumab	42 (0.6)	1092 (0.1)	0.082	41 (0.6)	35 (0.5)	0.012
Antihypertensives, *n* (%)						
ACEis	1473 (20.8)	185,890 (18.3)	0.063	1471 (20.8)	1502 (21.2)	0.011
ARBs	2889 (40.7)	186,628 (18.3)	0.506	2873 (40.6)	2927 (41.4)	0.016
Beta blockers	4439 (62.6)	431,826 (42.4)	0.412	4426 (62.5)	4433 (62.6)	0.002
Calcium channel blockers	2584 (36.4)	267,609 (26.3)	0.220	2575 (36.4)	2633 (37.2)	0.017
Diuretics	5183 (73.0)	428,288 (42.1)	0.660	5164 (73)	5159 (72.9)	0.002
Furosemide	3588 (50.6)	322,320 (31.7)	0.392	3579 (50.6)	3577 (50.5)	0.001
Anti-anginal/Anti-ischemic drugs, *n* (%)						
Organic nitrates	1783 (25.1)	165,982 (16.3)	0.219	1775 (25.1)	1750 (24.7)	0.008
Ranolazine	155 (2.2)	9215 (0.9)	0.104	154 (2.2)	120 (1.7)	0.035
Heart failure drugs, *n* (%)						
ARNI	877 (12.4)	29,449 (2.9)	0.363	869 (12.3)	850 (12.0)	0.008
Eplerenone	107 (1.5)	3580 (0.4)	0.121	105 (1.5)	103 (1.5)	0.002
Vericiguat	10 (0.1)	174 (0.0)	0.044	10 (0.1)	10 (0.1)	< 0.001
Digitalis glycosides	212 (3.0)	27,448 (2.7)	0.018	209 (3.0)	223 (3.2)	0.012
SGLT-2i	2609 (36.8)	39,133 (3.8)	0.897	2590 (36.6)	2473 (34.9)	0.034
Spironolactone	2024 (28.5)	81,652 (8.0)	0.550	2008 (28.4)	1977 (27.9)	0.010

Table 1 (continued) | Baseline characteristics of tirzepatide and control groups before and after matching

Variables	Before matching			After matching		
	Tirzepatide group (*n* = 7096)	Control group (*n* = 1,018,207)	Standardized difference	Tirzepatide group (*n* = 7077)	Control group (*n* = 7077)	Standardized difference
Ivabradine	33 (0.5)	1386 (0.1)	0.060	33 (0.5)	34 (0.5)	0.002
Antiplatelet agents, *n* (%)						
Aspirin	2445 (34.5)	271,635 (26.7)	0.169	2440 (34.5)	2396 (33.9)	0.013
Clopidogrel	875 (12.3)	87,790 (8.6)	0.121	873 (12.3)	867 (12.3)	0.003
Ticagrelor	114 (1.6)	12,681 (1.2)	0.030	113 (1.6)	107 (1.5)	0.007
Prasugrel	54 (0.8)	3223 (0.3)	0.061	54 (0.8)	49 (0.7)	0.008
Cangrelor	10 (0.1)	564 (0.1)	0.027	10 (0.1)	10 (0.1)	< 0.001
Hemoglobin A1c, %, Mean (SD)	7.4 (1.8)	6.7 (1.7)	0.406	7.4 (1.8)	7.6 (2.0)	0.074
≥ 9, *n* (%)	1283 (18.1)	36,945 (3.6)	0.478	1271 (18.0)	1272 (18.0)	< 0.001
eGFR, *n*(%), mL/min/1.73 m^2, Mean (SD)	62.0 (26.2)	63.1 (29.2)	0.037	62.1 (26.2)	61.8 (28.5)	0.011
< 15, *n* (%)	351 (4.9)	52,518 (5.2)	0.010	349 (4.9)	350 (4.9)	0.001

ACEi angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *ARNI* angiotensin receptor-neprilysin inhibitor, *eGFR* estimated Glomerular filtration rate, *SD* standard deviation, *SGLT-2i* sodium-glucose cotransporter-2 inhibitor,*T2D* type 2 diabetes.

Table 2 | Hazard ratio of outcomes between tirzepatide and control groups

Outcome	Tirzepatide group (*n* = 7077)		Control group (*n* = 7077)		HR (95% CI)	*P*-value	E-value (95% LCL)
	Events (n)	Incidence rate per 100 person-years	Events (n)	Incidence rate per 100 person-years			
Primary outcome							
Composite of HFE and all-cause mortality	129	3.09	371	6.55	0.52 (0.42,0.63)	< 0.001	3.26 (2.55)
Secondary outcomes							
HFE	110	2.64	286	5.05	0.57 (0.46,0.71)	< 0.001	2.90 (2.17)
All-cause mortality	77	1.85	317	5.59	0.33 (0.25,0.42)	< 0.001	5.51 (4.19)
MACEs	122	2.92	260	4.59	0.64 (0.51,0.79)	< 0.001	2.50 (1.85)
MAKEs	55	1.32	164	2.89	0.44 (0.33,0.60)	< 0.001	3.97 (2.72)

CI confidence interval, *MACEs* major adverse cardiovascular events, *MAKEs* major adverse kidney events, *HFE* heart failure exacerbation; *HR* hazard ratio, *LCL* lower confidence limit.
The Cox proportional hazards analysis was used to assess the hazard ratios of outcomes between groups, with significance determined at a two-sided *p*-value < 0.05. No adjustment was made for multiple comparisons.

group during the 30–365 days follow-up period (log-rank $p < 0.001$, Fig. 2).

The lower cumulative incidence of primary outcome remained consistent across stratified analyses by sex (males: HR, 0.54; 95% CI, 0.41–0.71; females: HR, 0.46; 95% CI, 0.35–0.59), age (18–64 years: HR, 0.42; 95% CI, 0.31–0.58; ≥ 65 years: HR, 0.58; 95% CI, 0.45–0.75), SGLT2i use (SGLT2i user: HR, 0.31; 95% CI, 0.19–0.49; non-user: HR, 0.57; 95% CI, 0.46–0.70), mineralocorticoid receptor antagonist (MRA) status (MRA user: HR, 0.56; 95% CI, 0.35–0.90; non-user: HR, 0.51; 95% CI, 0.41–0.64), T2D status (T2D: HR, 0.47; 95% CI, 0.37–0.58; non-T2D: HR, 0.68; 95% CI, 0.47–0.98), BMI category (BMI ≥ 35 kg/m^2: HR, 0.57; 95% CI, 0.45–0.73; BMI < 35 kg/m^2: HR, 0.60; 95% CI, 0.37–0.99), and eGFR (≥ 60 mL/min/1.73 m^2: HR, 0.42; 95% CI, 0.31–0.58; < 60 mL/min/1.73 m^2: HR, 0.60; 95% CI, 0.45–0.80; Fig. 3).

Secondary outcomes

Tirzepatide treatment was associated with significantly lower cumulative incidence rates across all secondary outcomes compared with controls. For HFE, incidence rates were 2.64 versus 5.05 per 100 person-years (HR, 0.57; 95% CI, 0.46–0.71; $p < 0.001$; E-value, 2.90 [95% LCL, 2.17]). All-cause mortality was also lower (1.85 vs. 5.59 per 100 person-years), yielding an HR of 0.33 (95% CI, 0.25–0.42; $p < 0.001$) and an E-value of 5.51 (4.19). The risk of major adverse cardiovascular event (MACE) was significantly lower in the tirzepatide group (HR, 0.64; 95% CI, 0.51–0.79; $p < 0.001$; E-value, 2.50 [1.85]), with incidence rates of 2.92 versus 4.59 per 100 person-years. Similarly, the risk of major adverse kidney events (MAKE) showed a significant lower in the tirzepatide group (HR, 0.44; 95% CI, 0.33–0.60; $p < 0.001$; E-value, 3.97 [2.72]), with incidence rates of 1.32 versus 2.89 per 100 person-years (Table 2).

Negative outcome and active comparator control

Associations between tirzepatide use and the two negative control outcomes: traumatic brain injury (HR, 1.39; 95% CI, 0.72–2.69) and skin cancer (HR, 1.08; 95% CI, 0.65–1.80) were not statistically significant (Supplementary Table 5). When compared to another GLP-1RA (active comparator), tirzepatide remained associated with a lower risk of the composite outcome of HFE and all-cause mortality (HR, 0.80; 95% CI, 0.70–0.92; $p = 0.001$; Supplementary Table 5).

Sensitivity analysis

For the primary outcome, the landmark analysis evaluated outcome across two distinct time periods. The tirzepatide group showed lower risks in the 2-month to 1-year analysis (HR, 0.49; 95% CI, 0.40–0.60; $p < 0.001$), and 3-momth to 1-year analysis (HR, 0.48; 95% CI, 0.38–0.60; $p < 0.001$; Supplementary Table 7). When varying the time window for tirzepatide initiation, the findings remained consistent across all analyses. Specifically, for initiation within 1-month (HR, 0.63;

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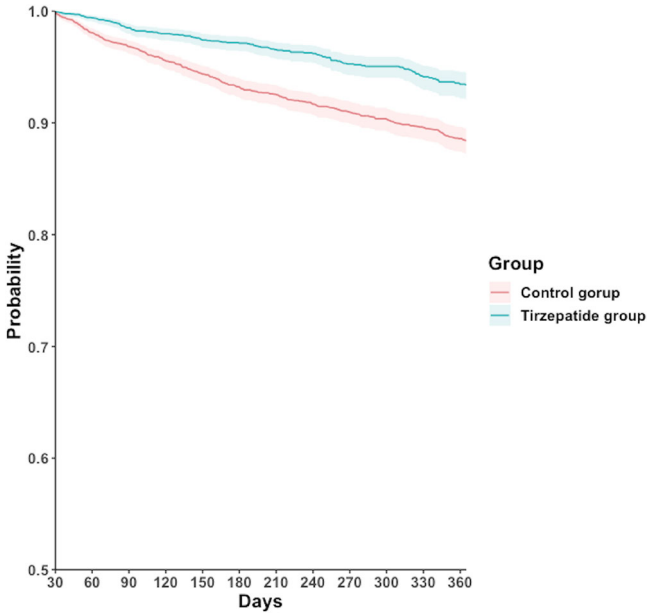

Fig. 2 | Kaplan-Meier time-to-event free curves of the composite outcome including heart failure exacerbation and all-cause mortality comparison to tirzepatide and control groups. Survival probabilities over 1 year are shown for the tirzepatide and control groups. Shaded areas represent 95% confidence intervals.

95% CI, 0.45–0.86; $p = 0.004$), initiation within 3-months (HR, 0.48; 95% CI, 0.37–0.63; $p < 0.001$), and initiation within 6-months (HR, 0.52; 95% CI, 0.42–0.66; $p < 0.001$; Supplementary Table 10). By using HFpEF diagnosis date as index date for both groups, the analysis yielded a HR 0.46 (95% CI, 0.37–0.56; $p < 0.001$; Supplementary Table 11). When diagnosed with HFpEF and left ventricular ejection fraction (LVEF) greater than 50%, showed a result of a HR 0.25 (95% CI, 0.09–0.74; $p = 0.007$; Supplementary Table 12). Finally, when restricted the analysis to patients who received a second prescription between 6-months and 1-year after the index date, the HR was 0.36 (95% CI, 0.24–0.53; $p < 0.001$; Supplementary Table 13).

Discussion

This target trial emulation study including 14,154 patients revealed that in patients with HFpEF, tirzepatide was significantly associated with lower 1-year rates of all-cause mortality or HFE compared to those not using tirzepatide. For secondary outcomes, patients treated with tirzepatide were associated with lower cumulative incidences of all-cause mortality, HFE, MACE, and MAKE. Subgroup analyses demonstrated consistent results across different strata, including sex, age, use of MRA or SGLT2i, presence or absence of T2D, BMI ≥ 35 or <35, and eGFR ≥60 or <60, further supporting its potential role as a therapeutic option for HFpEF. Sensitivity analyses further supported these findings, showing that tirzepatide compared to GLP-1 RA is associated with lower composite outcomes in HFpEF patients. Negative control analysis with traumatic brain injury and skin cancer showed no significant differences between groups. Additionally, we conducted landmark analyses to evaluate time-dependent effects, varied the time window for tirzepatide initiation, and reset the index date to HFpEF diagnosis to minimize potential biases. The results remained consistent across all approaches, reinforcing the robustness of our findings. We also restricted analyses to patients with LVEF > 50% to address potential HFpEF classification heterogeneity and to those with a second tirzepatide prescription, confirming that the observed benefits were attributable to tirzepatide treatment. These findings highlight the robustness of tirzepatide's association with improved outcomes in HFpEF, underscoring its potential as an effective therapeutic option across diverse HFpEF subgroups.

A systematic review of 14 articles demonstrated that GLP-1 RA significantly reduced MACE in T2D patients compared to placebo[12]. Subsequently, two RCTs showed that semaglutide treatment in patients with HFpEF led to significant symptomatic improvement and weight loss, likely through anti-inflammatory and hemodynamic mechanisms[5,6]. hese findings were further supported by a pooled analysis of three RCTs, which revealed that semaglutide reduced both the composite endpoint of cardiovascular death or worsening heart failure events, and worsening heart failure events alone in HFpEF patients[13]. Additional evidence came from an international database retrospective study of 7044 individuals, which found that combining GLP-1 RA with SGLT2i significantly lowered the risk of heart failure hospitalizations in HFpEF patients compared to SGLT2i monotherapy[14]. Tirzepatide, which harnesses both GLP-1 and GIP effects, has shown even greater potential than traditional GLP-1 RAs, demonstrating enhanced weight loss and anti-inflammatory effects[15,16]. This superiority was confirmed in a large retrospective study of 140,308 T2D patients, where tirzepatide showed significantly lower risks of all-cause mortality, MACE, and MAKE compared to GLP-1 RAs[8]. Our study corroborated these benefits, with subgroup analyses demonstrating statistically significant advantages in both diabetic and non-diabetic patients. Building on previous GLP-1 RA research, tirzepatide emerged as a promising therapeutic option for HFpEF. A recent RCT involving 731 HFpEF patients with obesity found that tirzepatide reduced the risk of the composite outcome of cardiovascular death or worsening heart failure compared to placebo (HR 0.62; 95% CI, 0.41–0.95)[11]. While this trial provided promising results, its limitations included a small sample size and exclusive focus on patients with obesity. Our analysis addressed these constraints by including HFpEF populations with and without obesity. By utilizing real-world data, our study complemented the RCT evidence, offering insights that are more generalizable across diverse clinical settings and patient populations, thereby addressing the external validity limitations inherent to controlled trials.

The benefits of tirzepatide in HFpEF patients may be attributed to its ability to target key pathophysiological mechanisms of HFpEF, including inflammation and plasma volume expansion[17,18]. Tirzepatide significantly reduced the infiltration of pro-inflammatory M1 adipose tissue macrophages within adipose tissue and lower levels of inflammatory cytokines, thereby improving insulin sensitivity[19,20]. Its strong anti-inflammatory effects can also be attributed to its modulation of the ERK signaling pathway and the promotion of M1-type macrophage apoptosis[21].

This study utilized a large multicenter database and PSM to enhance statistical power and minimize the impact of measured confounders. Our findings indicate that, in patients with HFpEF, tirzepatide use is significantly associated with reduced all-cause mortality and HFE. Sensitivity analyses further validated these results, showing that tirzepatide demonstrates superior outcomes even when compared to GLP-1 RA. These findings provide promising evidence supporting the clinical application of tirzepatide in HFpEF management. Nevertheless, further studies are essential to confirm these results, evaluate long-term outcomes, and assess tirzepatide's efficacy in a broader HFpEF population.

Limitations

This study has some limitations. First, as the TriNetX data are registry-based, there may be issues with misidentification and under-representation, particularly for milder cases or individuals not actively engaged with the healthcare system, which could impact the results. Additionally, the reliance on diagnostic codes to identify variables and outcomes may lead to misclassification, introducing potential bias. To address this, we conducted a negative control analysis comparing

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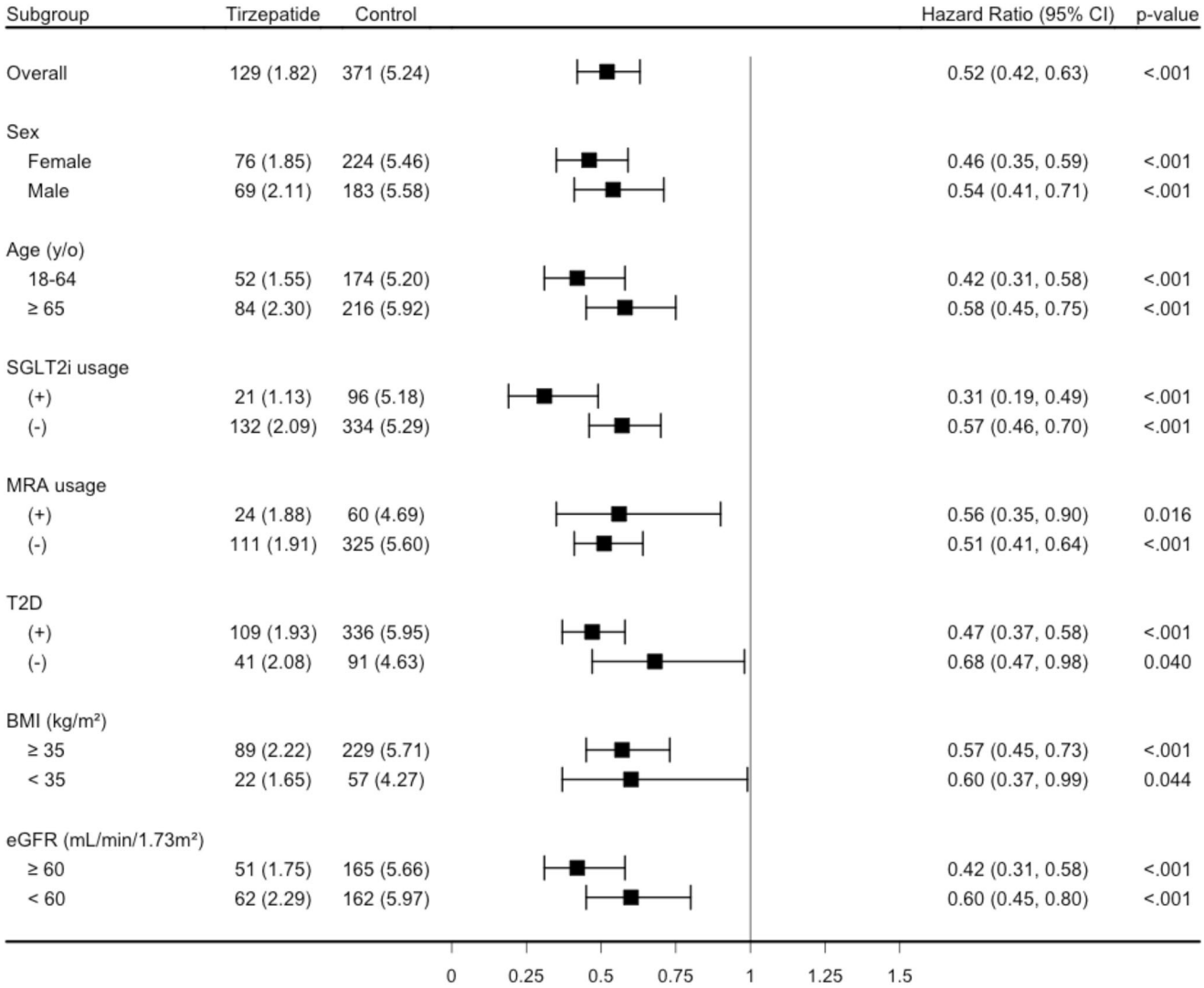

Fig. 3 | Subgroup analysis for the risk of composite outcome of heart failure exacerbation and all-cause mortality comparison to tirzepatide and control groups. BMI body mass index, CI confidence interval, eGFR estimated Glomerular filtration rate, MRA mineralocorticoid receptor antagonist, SGLT2i sodium-glucose co-transporter 2 inhibitors, T2D type 2 diabetes, y/o, years old. HRs and 95% CIs are presented, with the centre defined as the HR and error bars representing the CIs. The vertical line indicates an aHR of 1.0. The Cox proportional hazards analysis was used to assess the hazard ratios of outcomes between groups, with significance determined at a two-sided p-value < 0.05. No adjustment was made for multiple comparisons.

unrelated events with tirzepatide, which showed no significant differences, suggesting minimal registration bias. Second, the treatment duration could not be determined from the database, limiting our ability to assess long-term carryover effects. Third, unmeasured variables may have influenced the outcomes, introducing potential confounding. Thus, despite the matching for baseline characteristics between groups, we further calculated the E-values to quantify the influence of unmeasured confounders. Fourth, as we did not include a placebo group and compared with patients who were not using tirzepatide, there might be immortal time bias. However, sensitivity analyses comparing tirzepatide to GLP-1 RA demonstrated consistent results, strengthening our findings. Fifth, loss to follow-up and right-censoring are inherent limitations of using EHR-based data. In TriNetX, patients are censored at their last recorded encounter within the network, which may result in loss of follow-up if they transition to a non-TriNetX healthcare provider. Since TriNetX does not explicitly track dropout reasons, patients lost to follow-up are treated as administratively censored, potentially introducing informative censoring bias. Sixth, a small number of patients could not be matched during the PSM process, leading to their exclusion from the final analysis. Seventh, we were unable to directly characterize the distribution of time to tirzepatide initiation in the tirzepatide group. Although TriNetX permits individual-level analysis within a secure cloud-based environment, it does not allow access to patient-level data or export of time-to-treatment initiation distributions. As a result, we could not summarize the timing variability of tirzepatide initiation, which may introduce heterogeneity in exposure. However, to mitigate this limitation, we performed Landmark analyses and varied the time window for tirzepatide initiation to evaluate the consistency of the observed associations. At last, due to database limitations, we were unable to define the causes of mortality, which may have introduced additional bias. In conclusion, tirzepatide was significantly associated with lower 1-year all-cause mortality and HFE in patients with HFpEF compared to those not receiving tirzepatide. These findings provide valuable insights into managing HFpEF, a condition with limited therapeutic options despite its increasing prevalence. This study demonstrates the value of real-world data in complementing evidence from the RCT, providing a more comprehensive understanding of tirzepatide's clinical utility. However, the observational nature of this study underscores the need for further trials to validate these findings, explore long-term

outcomes, and assess tirzepatide's efficacy across diverse HFpEF populations.

Methods

Data sources

This retrospective cohort study used data from the TriNetX platform, a global federated health research network. TriNetX curates electronic medical records, including diagnoses, procedures, prescriptions, laboratory results, and genomic information—from approximately 150 healthcare organizations, representing some 140 million patients. While TriNetX provides only aggregated counts and deidentified summaries, it allows researchers to perform individual-level analyses within its secure, cloud-based analytics environment. Researchers define cohorts and apply statistical models such as PSM and Cox proportional hazards regression directly within the platform. The study was conducted using data obtained from the TriNetX global health research network, which operates under a waiver of informed consent granted by the Western Institutional Review Board because all records are de-identified. Nevertheless, the protocol for the present analysis was also reviewed and approved by the Institutional Review Board of Chi Mei Medical Center, Tainan, Taiwan (approval No. 11402-E02, approved on 13 January 2025). Written informed consent was obtained from all participants before enrollment. All procedures complied with the principles of the Declaration of Helsinki. The study was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines[22].

Study design

We employed a target trial design to emulate a RCT using observational data (Supplementary Table 1). Participants aged ≥18 years with a diagnosis of HFpEF documented between January 2022 and November 2024 were eligible to minimize time-related biases. HFpEF was identified using International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) codes I50.3 or I50.4. Patients were then categorized into two groups. Those who received tirzepatide within one year after the date of HFpEF diagnosis formed the tirzepatide group, while those without tirzepatide use were assigned to the control group. The index date was defined as the date of first recorded use of tirzepatide for the tirzepatide group, and the date of HFpEF diagnosis for the control group; the baseline period was the year preceding this index date. To include only incident cases, we excluded individuals who had experienced the outcomes prior to the follow-up period. We also excluded patients who had been treated with tirzepatide before the index date to ensure a new-user design[23]. Detailed coding algorithms for identifying baseline characteristics, clinical diagnoses, procedures, medications, and laboratory parameters appear in Supplementary Table 2.

Covariates

We matched our statistical models for the following covariates: age, sex, T2D complications (kidney, ophthalmic, neurological, and circulatory), comorbidities (alcohol-related disorders, nicotine dependence, hypertension, dyslipidemia, T2D, overweight/obesity, hypertensive disease, cerebrovascular disease, ischemic heart disease, chronic kidney disease, chronic lower respiratory disease, neoplasms, and systemic connective tissue disorders), lipid-lowering agents (HMG-CoA reductase inhibitors, ezetimibe, evolocumab, and alirocumab), antihypertensives (angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, beta-blockers, calcium-channel blockers, diuretics, and furosemide), anti-anginal or anti-ischemic agents (organic nitrates and ranolazine), heart failure medications (angiotensin receptor-neprilysin inhibitors, eplerenone, vericiguat, digitalis glycosides, SGLT2i, spironolactone, and ivabradine), antiplatelet drugs (aspirin, clopidogrel, ticagrelor, prasugrel, and cangrelor), hemoglobin A1c, and eGFR. A full list of covariates and their operational definitions is presented in Supplementary Table 3.

Outcomes and follow-up

The primary outcome was the composite of HFE and all-cause mortality. HFE was defined using ICD-10-CM codes or a requirement for intravenous diuretics or a diagnosis of pulmonary edema in emergency or inpatient settings[24]. Secondary outcomes included HFE alone, all-cause mortality, MACE, and MAKE. MACE included cerebral infarction, acute myocardial infarction, or cardiac arrest; MAKE encompassed end-stage kidney disease or incident dialysis[25]. Further definitions of cardiovascular events—such as acute myocardial infarction, cerebral infarction, cardiac arrest, and atrial fibrillation, are reported in the Appendix. Because the effectiveness of tirzepatide may not be immediate, observation began on day 30 after the index date and continued until the occurrence of an outcome event, final clinical visit, death, or one year after the index date, whichever came first. All diagnostic, procedural, and visit codes used for identifying the outcomes are described in Supplementary Table 4.

Statistical analysis

Continuous variables are reported as mean ± standard deviation, and categorical variables as counts and percentages. PSM was applied to balance baseline covariates between groups prior to primary, subgroup, and sensitivity analyses. In TriNetX, after defining the cohorts, index dates, outcomes, and relevant covariates that could serve as potential confounders, the platform creates a covariate matrix by capturing each variable for individual patients—typically within one year before the index date. A logistic regression model is then used to derive propensity scores, reflecting the probability of assignment to the second cohort based on these covariates. Using a greedy nearest-neighbor matching method with a caliper width of 0.1 pooled standard deviations, patients from the smaller cohort are matched to those in the larger cohort who have similar propensity scores. An absolute standardized mean difference of <0.1 was considered adequate balance[26]. HRs and 95% CIs were calculated using Cox proportional hazards models. Kaplan-Meier curves with log-rank tests were used for survival analysis. All analyses were performed in the TriNetX platform.

Stratified analyses

We conducted stratified subgroup analyses to assess potential heterogeneity in treatment effects across different patient characteristics. Stratified analyses were performed based on sex (male or female), age group (18–64 or ≥ 65 years), SGLT2i use, MRA use, baseline T2D status, BMI (kg/m^2), and eGFR (mL/min/1.73 m^2). For each subgroup, PSM was conducted separately, followed by the estimation of HRs using Cox proportional hazards models within each stratum. This approach ensures that comparisons within each subgroup account for potential confounding while avoiding assumptions of a uniform interaction effect across all groups.

Sensitivity analyses

We performed multiple sensitivity analyses to evaluate potential bias and ensure the robustness of our findings. We selected traumatic brain injury and skin cancer as negative outcomes, anticipating similar incidence rates regardless of tirzepatide treatment[27]. We also used GLP-1RA as an active comparator to test the consistency of tirzepatide's effectiveness[23]. To minimize time-dependent confounding, we conducted landmark analyses in which follow-up began two and three months after the index date, extending to one year[28]. Furthermore, to address concerns related to potential immortal time bias, we performed additional sensitivity analyses, varying the time window for tirzepatide initiation to assess whether different initiation periods influenced the results, and by resetting the index date to the HFpEF

diagnosis date for both groups. Additionally, recognizing the heterogeneity in HFpEF classification using ICD-10-CM codes, we conducted a sensitivity analysis restricted to patients with LVEF ≥ 50% to verify the HFpEF cohort definition. To indirectly evaluate the impact of treatment duration, we conducted a sensitivity analysis restricted to patients who received a second tirzepatide prescription between six months and one year after the index date. Lastly, we calculated E-values to further gauge the impact of potential unmeasured confounders on the primary and secondary outcomes[29].

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

The aggregated datasets analyzed in this study were obtained from the TriNetX platform, which provides access to de-identified electronic health records. Due to TriNetX's data-sharing policies, individual-level data are not accessible to the authors; only aggregated, de-identified results were available for analysis. Access to TriNetX data is restricted as it includes protected health information. Researchers interested in accessing the data may apply through the TriNetX platform by demonstrating appropriate credentials, a defined research purpose, and adherence to applicable privacy regulations. The approval process may take several weeks depending on the proposal and institutional qualifications. Further details on data access can be found at https://trinetx.com, or by contacting TriNetX at support@trinetx.com. Source data are provided with this paper. Data supporting the findings of this study is available in the article, its Supplementary information, the Source Data file and from the corresponding authors upon request. Source data are provided with this paper.

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Y.M.L. and J.Y.W., analyzed the data; Y.M.L., J.Y.W., and C.C.L. contributed to the design and implementation of the research; K.M.L., T.Y., Y.M.L., and J.Y.W. wrote the manuscript in consultation with C.C.L.

Competing interests
The authors declare no competing interests.

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