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ORIGINAL RESEARCH

Glucagon-Like Peptide 1 Receptor Agonist Is Associated With Improved Survival in Overweight Heart Failure Patients

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ABSTRACT

BACKGROUND Glucagon-like peptide 1 receptor agonists (GLP-1RAs) have shown improved symptomatic relieving and functional capacity in patients with heart failure (HF) with preserved ejection fraction and obesity.

OBJECTIVES The purpose of this study was to evaluate the effect of GLP-1RA on outcome in patients with HF.

METHODS A retrospective analysis was performed based on the Swedish HF Registry since 2007 among patients with a body mass index (BMI) >25 kg/m^2 to assess whether GLP-1RA treatment was associated with reduced mortality in patients with HF.

RESULTS In the overall cohort, 34,247 patients were not treated with GLP-1RA, and 808 patients were. In patients treated with GLP-1RA, 96.3% had diabetes mellitus. Treatment with GLP-1RA showed a statistically significant association with reduced all-cause (adjusted HR [aHR]: 0.75 [95% CI: 0.60-0.94]; $P = 0.013$) and cardiovascular (CV) mortality (aHR: 0.52 [95% CI: 0.35-0.77]; $P = 0.0010$) compared with those not receiving GLP-1RA within 2 years after index registration. In a 1:1 propensity score matched cohort, there was no significant association between GLP-1RA and all-cause mortality (aHR: 0.79 [95% CI: 0.59-1.06]; $P = 0.11$), but there was with CV mortality (aHR: 0.53 [95% CI: 0.32-0.87]; $P = 0.012$). GLP-1RA–associated risk reduction in CV death was more pronounced in patients with a BMI >30 kg/m^2 and appears to be greater in individuals with an ejection fraction ≤40% compared with >40%.

CONCLUSIONS This nationwide real-world study shows that patients with HF who received GLP-1RA have a significant reduction in CV mortality, which is particularly pronounced in overweight and obese patients with reduced ejection fraction. (JACC Heart Fail. 2025;■:■-■) © 2025 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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ABBREVIATIONS AND ACRONYMS

ARNI = angiotensin receptor-neprilysin inhibitor

BMI = body mass index

CV = cardiovascular

GLP-1RA = glucagon-like peptide 1 receptor agonist

HF = heart failure

HFmrEF = heart failure with mildly reduced ejection fraction

HFpEF = heart failure with preserved ejection fraction

HFrEF = heart failure with reduced ejection fraction

LVEF = left ventricular ejection fraction

SGLT2i = sodium-glucose cotransporter 2 inhibitor

T2DM = type 2 diabetes mellitus

In parallel with increasing heart failure (HF) the prevalence of obesity is also increasing. Among patients with heart failure with preserved ejection fraction (HFpEF), the majority of patients are overweight or obese. Obesity is known not only as a risk factor and driver of HF, but also to be associated with worse outcomes in patients with HF.[1] In a pooled analysis from STEP-HFpEF (Semaglutide in Patients with Heart Failure with Preserved Ejection Fraction and Obesity; NCT04788511) and STEP-HFpEF DM (Semaglutide in Patients with Obesity-Related Heart Failure and Type 2 Diabetes; NCT04916470) trials, glucagon-like peptide 1 receptor agonist (GLP-1RA) improved symptoms, physical limitations, and exercise function in people with obesity-HFpEF phenotype.[2] However, to date, no clinical trial has adequately evaluated the efficacy of GLP-1RA on mortality in either HFpEF or heart failure with reduced ejection fraction (HFrEF).

In the FIGHT (Functional Impact of GLP-1RA for Heart Failure Treatment; NCT01800968) trial liraglutide did not improve the primary endpoint (time to mortality/hospitalization and change in N-terminal pro-B-type natriuretic peptide (NT-proBNP).[3] In the LIVE (Effect of Liraglutide on Left Ventricular Function in Stable Chronic Heart Failure Patients With and Without Diabetes; NCT01472640) trial liraglutide did not affect left ventricular systolic function in HFrEF patients with or without diabetes mellitus.[4] In both trials, there was a trend to increase the risk of adverse effects of GLP-1RA treatment.[3,4]

Although randomized controlled trials are considered to be the criterion standard for evaluating treatment efficacy, real-world data extracted from registries are not only useful for generating evidence for designing confirmatory trials, but also easily expandable to real-life populations. Given the granularity and coverage of the Swedish Heart Failure Registry (SwedeHF) linked to 3 additional Swedish national administrative health registries (Swedish National Patient Register, the Cause of Death Register, and the National Prescribed Drug Register) our data provide one of the most reliable real-world observations. Although several GLP-1RAs have Class IA recommendations in patients with type 2 diabetes mellitus (T2DM) by reducing cardiovascular (CV) events in high risk individuals, their possible effects on outcome have not yet been prospectively determined in HF population. Very recently in a post hoc pooled analysis of participants with HFpEF, semaglutide reduced the risk of the combined endpoint of CV death or worsening heart failure events with more pronounced effect in greater severity of obesity.[5] Therefore it is assumed that GLP-1RA might be a disease-modifying therapy and therefore improve survival in patients with obesity-phenotype HF, because GLP-1RAs are able to effectively target obesity. In the present study we sought to assess whether GLP-1RAs are associated with reduced mortality (all cause- and CV) in our real-life database containing patients with overweight-HF phenotype with or without GLP-1RA treatment.

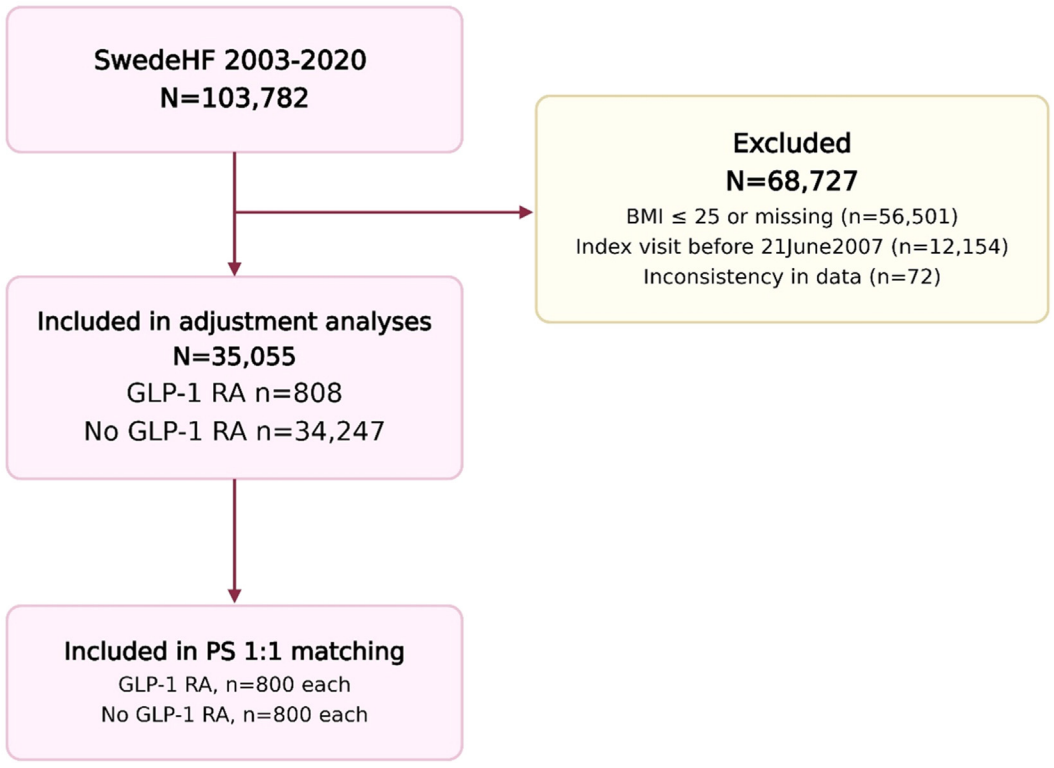
METHODS

STUDY MATERIAL. The data for this retrospective observational study were extracted from SwedeHF, as previously described.[6] Patients have been included in SwedeHF since 2003. The only inclusion criterion was clinician-judged HF up to 2017 and defined since 2017 by the following International Classification of Diseases-10th Revision (ICD-10) codes: I11.0, I13.0, I13.2, I25.5, I42.0, I42.6, I42.7, I50.0, I50.1, and I50.9. In 2020, approximately 31% of the prevalent HF population in Sweden was registered in the SwedeHF. About 80 variables are registered after hospital discharge or at an outpatient clinic visit and are entered into a database managed by the Uppsala Clinical Research Center, Uppsala, Sweden. To access diverse information (eg, comorbidities, dates of death, and causes thereof) and medication dispensation from pharmacies, SwedeHF was linked to the Swedish National Patient Registry, including both inpatient and outpatient visits, the Cause of Death Registry, and the National Prescribed Drug Registry, respectively, by means of the unique personal identification number assigned to all Swedish permanent residents. The extracted comorbidities and reason for death were identified through the ICD-10 codes, and medications through the Anatomical Therapeutic Chemical classification (Supplemental Table 1).

The study and the linking of SwedeHF and the other registries were approved by the Swedish Ethical Review Authority (Dnr 308-17). The study complied with the Declaration of Helsinki.

STUDY DESIGN AND STATISTICAL ANALYSIS. The study population comprised patients whose index date fell between June 21, 2007, the date of the first dispensation of GLP-1RA, and December 31, 2020. The exclusion criteria were patients with a body mass index (BMI) of ≤25 kg/m^2 or those with missing BMI data (n = 56,501; 61.7%) and patients with inconsistent dates (n = 72; 0.08%). We applied the intention-to-treat approach, assigning patients to the respective

FIGURE 1 Flowchart of Patient Inclusion and Exclusion



BMI = body mass index; GLP-1RA = glucagon-like peptide 1 receptor agonist; PS = propensity score; SwedeHF = Swedish Heart Failure Registry.

treatment groups based on medication data in SwedeHF and medication dispensation records. This included information on GLP-1RA medication prescribed from 3 months before to 12 months after the index date. A sensitivity analysis was performed by studying patients who had dispensed GLP-1RA 3 months before and 6 months before the index date.

Studied endpoints were all-cause and CV mortality, followed up from the index date until censoring or event. Owing to bias in the follow-up time between the HF therapy groups, endpoints were also studied within 2 years from the index date.

Continuous variables were described using mean ± SD, median (Q1-Q3), and categoric variables were expressed as frequency and percentage. For the test between the GLP-1RA and non-GLP-1RA groups, Fisher test was used for dichotomous variables, the Mantel-Haenszel chi-square trend test for ordered categoric variables, and the Mann-Whitney U test for continuous variables. Event rates were calculated as the number of events divided by the total number of follow-up years, expressed by 100 person-years. Lower and upper 95% confidence limits were estimated with the use of exact Poisson limits.

Time-to-events analyses were performed with the use of multivariable Cox proportional hazard models. Adjustment was made for the known confounders and variables differing statistically between the patients with and without GLP-1RA: age, sex, BMI, NYHA functional class, left ventricular ejection fraction (LVEF), NT-proBNP, estimated glomerular filtration rate (eGFR), ischemic heart disease, any valve surgery or disease, hypertension, atrial fibrillation, diabetes, implantable cardioverter-defibrillator, cardiac resynchronization therapy, and medications, including angiotensin receptor-neprilysin inhibitor (ARNI) and sodium-glucose cotransporter 2 inhibitor (SGLT2i). HRs were presented along with their corresponding 95% CIs. The assumption of proportional hazards was checked by studying the interaction between the treatment group variable and the log(follow-up time) in the Cox regression models. Overall unadjusted cumulative incidence curves were presented for the treatment groups as well as by the 2

TABLE 1 Patient Demographics, Clinical Data, and Comorbidities at the Index Visit in SwedeHF Comparing Patients With and Without GLP-1RA Treatment

	GLP-1RA (n = 808)	No GLP-1RA (n = 34,247)	*P* Value
Patient demographics			
Male	587 (72.6)	22,228 (64.9)	<0.0001
Age, y	67.2 ± 9.6	72.8 ± 12.0	<0.0001
Age ≥70 y	356 (44.1)	22,083 (64.5)	<0.001
Clinical data at index visit			
Heart failure duration ≥6 mo	392 (49.9)	15,121 (45.7)	0.018
Body mass index, kg/m^2	34.5 ± 5.9	30.4 ± 4.7	<0.0001
Body mass index category, kg/m^2			<0.0001
>25-30	187 (23.1)	19,785 (57.8)	
>30-35	279 (34.5)	9,454 (27.6)	
>35	342 (42.3)	5,008 (14.6)	
Systolic blood pressure, mm Hg	126.3 ± 19.4	128.6 ± 19.8	0.024
Diastolic blood pressure, mm Hg	73.9 ± 10.6	75.2 ± 11.8	0.012
Heart rate, beats/min	76.8 ± 13.4	72.2 ± 14.8	<0.0001
NYHA functional class			0.0010
I	54 (8.8)	2,709 (11.1)	
II	280 (45.8)	12,300 (50.5)	
III	262 (42.9)	8,776 (36.0)	
IV	15 (2.5)	578 (2.4)	
LVEF, %			0.0028
≥50	154 (20.1)	7,456 (23.8)	
40-49	173 (22.5)	7,627 (24.3)	
30-39	237 (30.9)	8,826 (28.1)	
<30	204 (26.6)	7,466 (23.8)	
Missing	40	2,872	
NT-proBNP, pg/mL	2,451.2 ± 3,429.3	3,758.4 ± 5,791.5	<0.0001
NT-proBNP category, pg/mL			<0.0001
≤900	242 (39.2)	5,768 (25.8)	
>900-2,500	194 (31.4)	7,374 (33.0)	
>2,500-5,000	99 (16.0)	4,653 (20.8)	
>5,000	83 (13.4)	4,549 (20.4)	
Missing	190	11,903	
eGFR, mL/min/1.73 m^2	67.8 ± 23.5	66.8 ± 21.9	0.36
<60	220 (40.3)	7,851 (38.7)	0.45
Missing	262	13,936	
CKD stage			0.23
1 (eGFR ≥90 mL/min/1.73 m^2, normal and high)	109 (20.0)	3,066 (15.1)	
2 (eGFR 60 to <90 mL/min/1.73 m^2, mild reduction, normal range for young adult)	217 (39.7)	9,394 (46.3)	
3 (eGFR 30 to <60 mL/min/1.73 m^2, moderate reduction)	200 (36.6)	6,946 (34.2)	
4 (eGFR 15 to <30 mL/min/1.73 m^2, severe reduction)	18 (3.3)	818 (4.0)	
5 (eGFR <15 mL/min/1.73 m^2, kidney failure)	2 (0.4)	87 (0.4)	

Continued on the next page

subgrouping variables, BMI (<30, ≥30 kg/m^2) and LVEF (≤40%, >40%). Cumulative incidence curves of CV mortality handled other death as competing risk.

For robustness, all analyses were repeated on 1:1 propensity score (PS)-matched groups, including the same variables as in the aforementioned adjustments. As a matching algorithm, a 1:1 nearest neighbor matching with the optimal caliper width of 0.2 of the SD of the logit of the PS was used. Unadjusted cumulative incidence curves were presented for pairwise 1:1 PS matched groups of GLP-1RA treatment.

All tests were 2-tailed, and values of $P < 0.05$ were considered to be significant. All analyses were performed with the use of SAS Software v9.4 (SAS Institute Inc).

The study adhered to the principles of the Declaration of Helsinki, and ethical approval was granted by the Swedish Ethical Review

TABLE 1 Continued

	GLP-1RA (n = 808)	No GLP-1RA (n = 34,247)	*P* Value
Medical history at the index visit			
Ischemic heart disease	474 (58.7)	16,560 (48.4)	<0.0001
Valve disease or surgery	97 (12.0)	5,772 (16.9)	0.0002
Hypertension	737 (91.2)	25,493 (74.4)	<0.0001
Atrial fibrillation	382 (47.3)	19,651 (57.4)	<0.0001
Chronic obstructive lung disease	158 (19.6)	6,637 (19.4)	0.89
Diabetes mellitus	778 (96.3)	11,053 (32.3)	
Stroke/TIA	117 (14.5)	4,887 (14.3)	0.88
Psychiatric diagnosis past 3 y	105 (13.0)	4,400 (12.8)	0.87
Musculoskeletal disease past 3 y	155 (19.2)	6,707 (19.6)	0.82
Malignant cancer past 3 y	73 (9.0)	3,440 (10.0)	0.37
ICD	80 (10.0)	1,643 (4.9)	<0.0001
CRT	43 (5.4)	1,070 (3.2)	0.0016
Medications			
ARNI dispensed 3 mo before to 6 mo after index	141 (17.5)	1,925 (5.6)	<0.0001
ACEI/ARB dispensed 3 mo before to 6 mo after index	730 (90.3)	30,738 (89.8)	0.64
SGLT2i dispensed 3 mo before to 6 mo after index	176 (21.8)	582 (1.7)	<0.0001
Diuretic agents	568 (80.2)	18,577 (78.6)	0.31

Values are n (%) or mean ± SD, unless otherwise indicated. Fisher test was used to test the dichotomous variables between the 2 groups, the Mantel-Haenszel chi-square trend test for ordered categoric variables, and the Mann-Whitney U test for continuous variables.

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor–neprilysin inhibitor; CRT = cardiac resynchronization therapy; eGFR = estimated glomerular filtration rate; GLP-1RA = glucagon-like peptide-1 receptor agonist; ICD = implantable cardioverter-defibrillator; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide; SGLT2i = sodium-glucose cotransporter 2 inhibitor; SwedeHF = Swedish Heart Failure Registry; TIA = transient ischemic attack.

Authority. Although individual patient consent was not required, all patients were informed about their inclusion in SwedeHF and were given the choice to decline participation or withdraw from the trial at any time.

RESULTS

PATIENT POPULATION. From the SwedeHF data set covering 2007 and onward, 35,055 patients were identified, comprising 808 patients receiving GLP-1RA and 34,247 patients not receiving GLP-1RA.

The flowchart outlining this study is depicted in Figure 1. In patients treated with GLP-1RA, 20.1% had an LVEF ≥50%, 22.5% LVEF 40%-49%, and 26.6% LVEF <40%, and 23.1% had BMI 25-30 kg/m^2, 34.5% BMI 30-35 kg/m^2, and 42.3% BMI >35 kg/m^2; 96.3% had diabetes mellitus. In addition, the 1:1 PS-matched population with (n = 800) and without (n = 800) GLP-1RA was created by comparing patients with and without GLP-1RA in demographics, clinical data, and comorbidities at the index visit from 2007 onwards (Supplemental Table 2).

BASELINE CHARACTERISTICS. As presented in Table 1, patients treated with GLP-1RA were younger, were predominantly male, had higher BMI, were more symptomatic, had lower LVEF, decreased NT-proBNP levels, more hypertension, and less atrial fibrillation, more were treated with ARNI and SGLT2i, and more had implantable cardioverter-defibrillators and cardiac resynchronization therapy. In patients who received GLP-1RA and had a BMI of 25-30 kg/m^2, 69.1% exhibited an LVEF ≤40%. Conversely, in patients with a BMI >30 kg/m^2, only 53.8% had an LVEF ≤40%. Among patients who received GLP-1RA treatment and had a BMI of 25-30 kg/m^2, 69.1% exhibited an LVEF ≤40%. In patients with LVEF ≤40% treated with GLP-1RA, 33.6% had a BMI of 30-35 kg/m^2 and 38.1% had a BMI >35 kg/m^2, whereas in patients with LVEF >40% treated with GLP-1RA, 36.7% had a BMI of 30-35 kg/m^2 and 46.2% had a BMI >35 kg/m^2.

ALL-CAUSE MORTALITY WITH GLP-1RA VS WITHOUT GLP-1RA IN THE OVERALL COHORT. During complete follow-up, all-cause mortality occurred in 19.8% of patients treated with GLP-1RA and in 39.9% of those without GLP-1RA (Table 2). Within the first 2 years of index registration, all-cause mortality occurred in 9.8% of patients with GLP-1RA and 18.0% in patients without GLP-1RA. GLP-1RA was associated with a 12% risk reduction in all-cause mortality (adjusted HR [aHR]: 0.88 [95% CI: 0.75-1.04]; *P* = 0.13) during complete follow-up and a significant risk reduction by 25% within 2 years after index

TABLE 2 Event Rates, Number of Events, Follow-Up Time, and Fully Adjusted HRs (Cox Regression) Comparing Patients With vs Without GLP-1RA Treatment

	GLP-1RA			No GLP-1RA				
	Events	Follow-Up, y	Events per 100 PY	Events	Follow-Up, y	Events per 100 PY	GLP-1RA vs No GLP-1RA, HR (95% CI)[a]	*P* Value
All patients								
All-cause death	160/808 (19.8)	2.09 (1.08-3.32) Sum = 2,027	7.9 (6.7-9.2)	13,649/34,247 (39.9)	2.98 (1.35-5.50) Sum = 129,689	10.5 (10.3-10.7)	0.88 (0.75-1.04)	0.13
All-cause death within 2 y	79/808 (9.8)	2.00 (1.08-2.00) Sum = 1,249	6.3 (5.0-7.9)	6,163/34,247 (18.0)	2.00 (1.35-2.00) Sum = 55,988	11.0 (10.7-11.3)	0.75 (0.60-0.94)	0.013
CV death	54/808 (6.7)	2.09 (1.08-3.32) Sum = 2,027	2.7 (2.0-3.5)	6,886/34,247 (20.1)	2.98 (1.35-5.50) Sum = 129,689	5.3 (5.2-5.4)	0.66 (0.50-0.86)	0.0024
CV death within 2 y	26/808 (3.2)	2.00 (1.08-2.00) Sum = 1,249	2.1 (1.4-3.0)	3,475/34,247 (10.1)	2.00 (1.35-2.00) Sum = 55,988	6.2 (6.0-6.4)	0.52 (0.35-0.77)	0.0010
BMI 25-30 kg/m^2								
All-cause death	36/187 (19.3)	1.95 (1.04-3.16) Sum = 426	8.4 (5.9-11.7)	8,103/19,785 (41.0)	2.90 (1.30-5.43) Sum = 74,092	10.9 (10.7-11.2)	0.91 (0.65-1.27)	0.57
All-cause death within 2 y	18/187 (9.6)	1.95 (1.04-2.00) Sum = 280	6.4 (3.8-10.2)	3,763/19,785 (19.0)	2.00 (1.30-2.00) Sum = 32,090	11.7 (11.4-12.1)	0.70 (0.44-1.12)	0.14
CV death	17/187 (9.1)	1.95 (1.04-3.16) Sum = 426	4.0 (2.3-6.4)	4,212/19,785 (21.3)	2.90 (1.30-5.43) Sum = 74,092	5.7 (5.5-5.9)	0.85 (0.52-1.37)	0.50
CV death within 2 y	8/187 (4.3)	1.95 (1.04-2.00) Sum = 280	2.9 (1.2-5.6)	2,150/19,785 (10.9)	2.00 (1.30-2.00) Sum = 32,090	6.7 (6.4-7.0)	0.63 (0.31-1.26)	0.19
BMI >30 kg/m^2								
All-cause death	124/621 (20.0)	2.13 (1.10-3.40) Sum = 1,600	7.7 (6.4-9.2)	5,546/14,462 (38.3)	3.11 (1.41-5.56) Sum = 55,597	10.0 (9.7-10.2)	0.85 (0.71-1.02)	0.08
All-cause death within 2 y	61/621 (9.8)	2.00 (1.10-2.00) Sum = 969	6.3 (4.8-8.1)	2,400/14,462 (16.6)	2.00 (1.41-2.00) Sum = 23,898	10.0 (9.6-10.5)	0.74 (0.57-0.97)	0.026
CV death	37/621 (6.0)	2.13 (1.10-3.40) Sum = 1,600	2.3 (1.6-3.2)	2,674/14,462 (18.5)	3.11 (1.41-5.56) Sum = 55,597	4.8 (4.6-5.0)	0.57 (0.41-0.80)	0.0009
CV death within 2 y	18/621 (2.9)	2.00 (1.10-2.00) Sum = 969	1.9 (1.1-2.9)	1,325/14,462 (9.2)	2.00 (1.41-2.00) Sum = 23,898	5.5 (5.2-5.9)	0.46 (0.29-0.74)	0.0013
LVEF ≤40%								
All-cause death	67/441 (15.2)	2.10 (1.06-3.46) Sum = 1,134	5.9 (4.6-7.5)	5,607/16,292 (34.4)	3.19 (1.44-5.81) Sum = 65,030	8.6 (8.4-8.9)	0.76 (0.60-0.98)	0.032
All-cause death within 2 y	34/441 (7.7)	2.00 (1.06-2.00) Sum = 680	5.0 (3.5-7.0)	2,454/16,292 (15.1)	2.00 (1.44-2.00) Sum = 26,989	9.1 (8.7-9.5)	0.67 (0.47-0.94)	0.022
CV death	26/441 (5.9)	2.10 (1.06-3.46) Sum = 1,134	2.3 (1.5-3.4)	2,987/16,292 (18.3)	3.19 (1.44-5.81) Sum = 65,030	4.6 (4.4-4.8)	0.62 (0.42-0.91)	0.015
CV death within 2 y	11/441 (2.5)	2.00 (1.06-2.00) Sum = 680	1.6 (0.8-2.9)	1,477/16,292 (9.1)	2.00 (1.44-2.00) Sum = 26,989	5.5 (5.2-5.8)	0.43 (0.24-0.79)	0.0059
LVEF >40%								
All-cause death	82/327 (25.1)	1.98 (1.08-3.15) Sum = 777	10.6 (8.4-13.1)	6,318/15,083 (41.9)	2.84 (1.33-5.18) Sum = 54,559	11.6 (11.3-11.9)	1.05 (0.84-1.31)	0.66
All-cause death within 2 y	42/327 (12.8)	1.98 (1.08-2.00) Sum = 503	8.3 (6.0-11.3)	2,856/15,083 (18.9)	2.00 (1.33-2.00) Sum = 24,589	11.6 (11.2-12.0)	0.91 (0.67-1.25)	0.58
CV death	22/327 (6.7)	1.98 (1.08-3.15) Sum = 777	2.8 (1.8-4.3)	2,978/15,083 (19.7)	2.84 (1.33-5.18) Sum = 54,559	5.5 (5.3-5.7)	0.67 (0.44-1.03)	0.07
CV death within 2 y	14/327 (4.3)	1.98 (1.08-2.00) Sum = 503	2.8 (1.5-4.7)	1,484/15,083 (9.8)	2.00 (1.33-2.00) Sum = 24,589	6.0 (5.7-6.4)	0.70 (0.41-1.20)	0.19

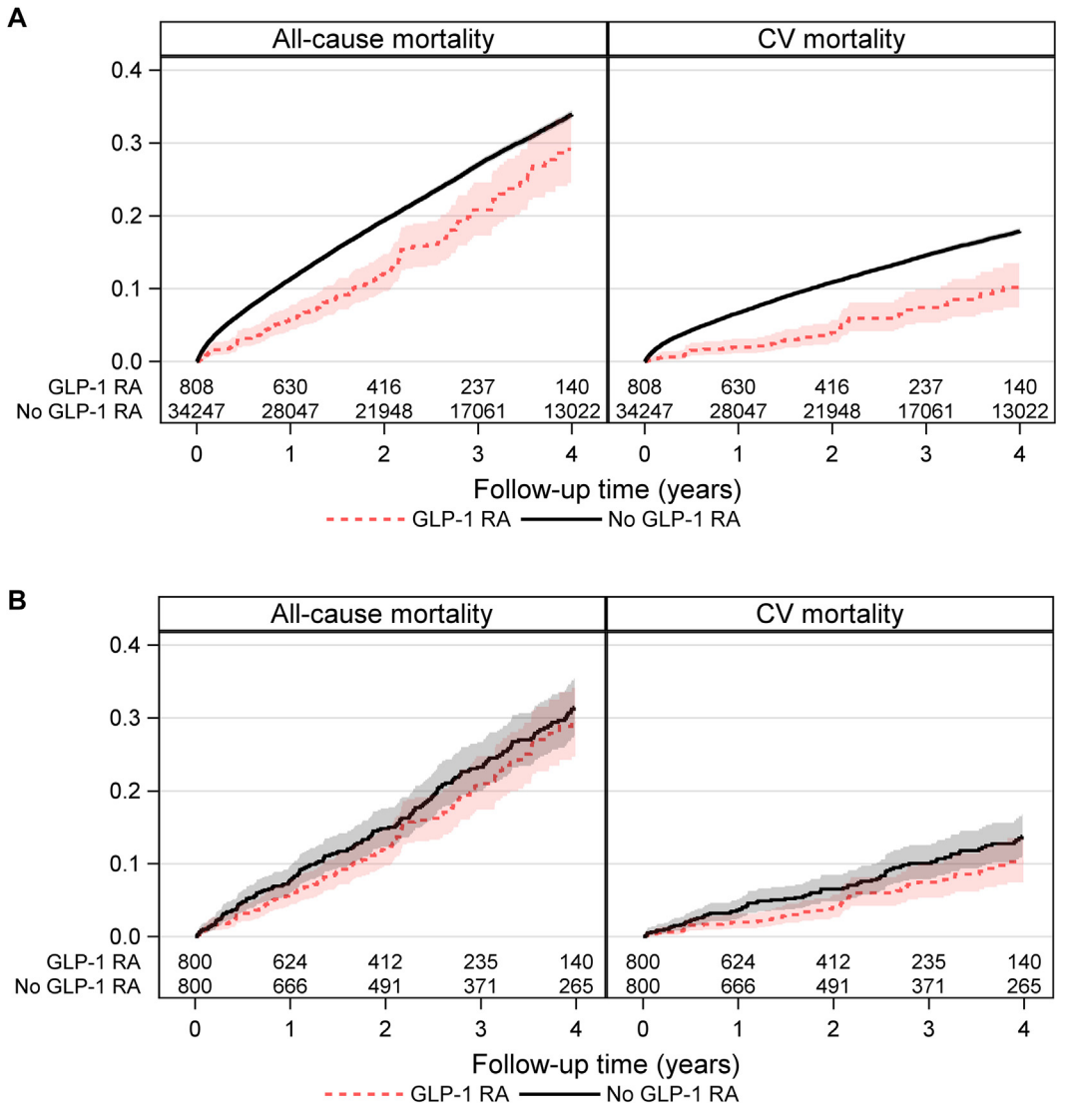
Values are n/n (%) or median (Q1-Q3), unless otherwise indicated. CIs for unadjusted event rates per 100 person-years were obtained from exact Poisson confidence limits. Cox regression was used to measure the time of any event presented by HR. [a]Adjusted for age, sex, BMI category, NYHA, LVEF, NT-proBNP category, eGFR category, ischemic heart disease, any valve surgery or disease, hypertension, atrial fibrillation, diabetes, ICD, CRT, ARNI, SGLT2i.

CV = cardiovascular; PY = person-years; other abbreviations as in Table 1.

registration compared with patients who did not receive GLP-1RA (aHR: 0.75 [95% CI: 0.60-0.94]; $P = 0.013$). GLP-1RA-associated risk reduction in mortality was more pronounced in patients with BMI >30 kg/m^2 (aHR: 0.74 [95% CI: 0.57-0.97]; $P = 0.026$) than those with lower BMI. Similarly, patients with LVEF ≤40% (aHR: 0.67 [95% CI: 0.47-0.94]; $P = 0.022$) had greater risk reduction in mortality than those with an LVEF >40% (Table 2, Figure 2A).

CV DEATH WITH GLP-1RA VS WITHOUT GLP-1RA IN THE OVERALL COHORT. During complete follow-up, CV mortality occurred in 6.7% of patients treated

FIGURE 2 Cumulative Incidence Curves for All-Cause and Cardiovascular Mortality Rates for GLP-1RA vs No GLP-1RA



Time-to-event curves for all-cause and CV mortality in the overall cohort (A) and the 1:1 propensity score-matched cohort (B).
CV = cardiovascular; GLP-1RA = glucagon-like peptide 1 receptor agonist.

with GLP-1RA and 20.1% without GLP-1RA (Table 2). Within 2 years of index registration, CV mortality occurred in 3.2% of patients with GLP-1RA and in 10.1% of those without GLP-1RA. GLP-1RA was associated with a significant risk reduction of 34% in CV mortality (aHR: 0.66 [95% CI: 0.50-0.86]; $P = 0.0024$) during complete follow-up, and an even greater risk reduction by 48% (aHR: 0.52 [95% CI: 0.35-0.77]; $P = 0.0010$) within 2 years after index registration compared with patients not treated with GLP-1RA (Figure 2A).

FURTHER OUTCOME ANALYSIS IN A PS-MATCHED COHORT. A PS analysis revealed that in a 1:1 matched cohort, treatment with GLP-1RA was not associated with significant risk reduction in all-cause mortality, regardless of BMI and LVEF, despite numeric risk reduction, compared with treatment without GLP-1RA. However, for CV death within 2 years of index registration, there was a significant risk reduction associated with the use of GLP-1RA (aHR: 0.53 [95% CI: 0.32-0.87]; $P = 0.012$) (Table 3, Figure 2B).

TABLE 3 Event Rates, Number of Events, Follow-Up Time, and Unadjusted HRs (Cox Regression) Comparing Patients With vs Without GLP-1RA Treatment in a 1:1 Propensity Score–Matched Cohort

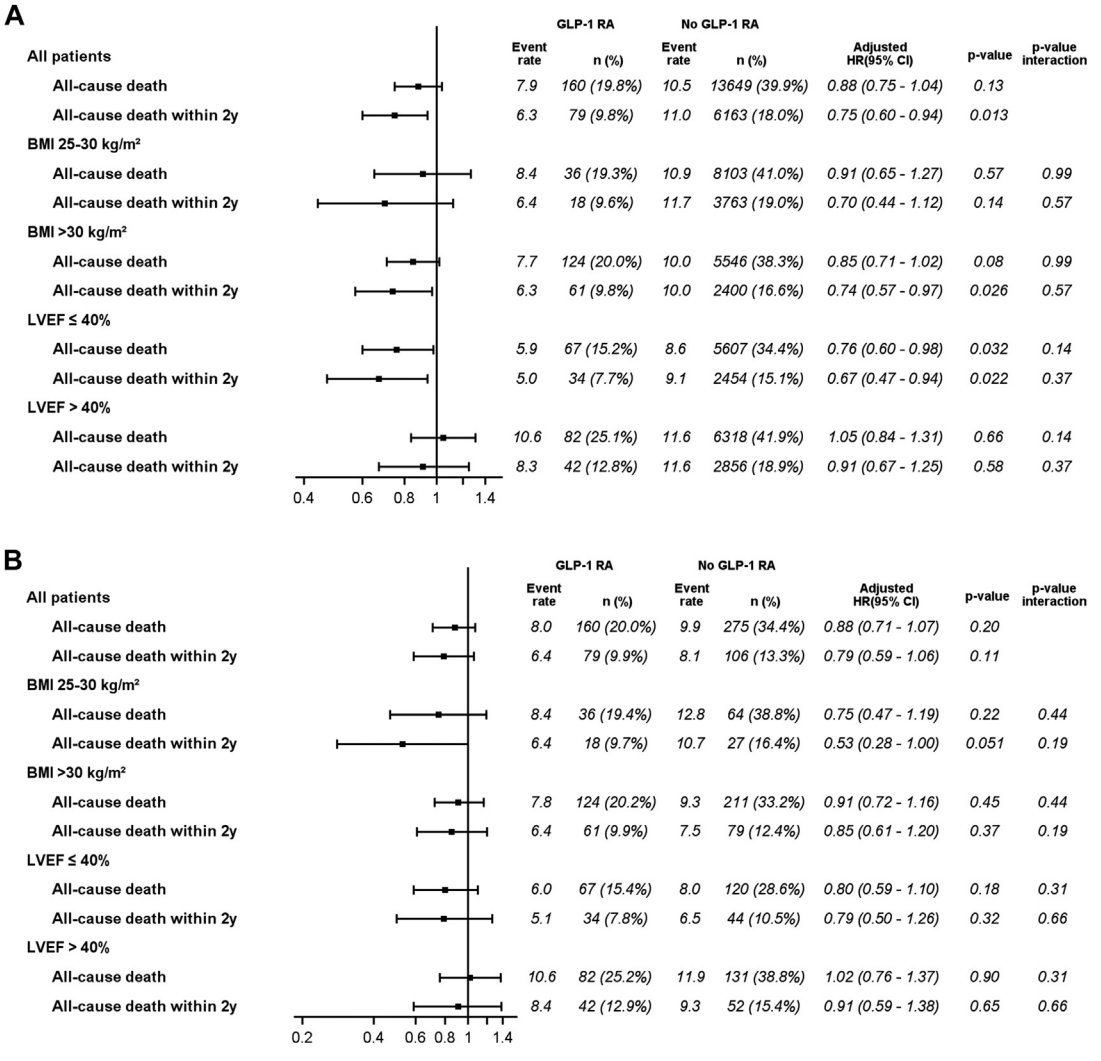
	GLP-1RA			No GLP-1RA			GLP-1RA vs No GLP-1RA, HR (95% CI)	*P* Value
	Events	Follow-Up, y	Events per 100 PY	Events	Follow-Up, y	Events per 100 PY		
All patients								
All-cause death	160/800 (20.0)	2.09 (1.08-3.32) Sum = 2,010	8.0 (6.8-9.3)	275/800 (34.4)	2.74 (1.28-4.88) Sum = 2,770	9.9 (8.8-11.2)	0.88 (0.71-1.07)	0.20
All-cause death within 2 y	79/800 (9.9)	2.00 (1.08-2.00) Sum = 1,237	6.4 (5.1-8.0)	106/800 (13.3)	2.00 (1.28-2.00) Sum = 1,307	8.1 (6.6-9.8)	0.79 (0.59-1.06)	0.11
CV death	54/800 (6.8)	2.09 (1.08-3.32) Sum = 2,010	2.7 (2.0-3.5)	112/800 (14.0)	2.74 (1.28-4.88) Sum = 2,770	4.0 (3.3-4.9)	0.61 (0.43-0.86)	0.0049
CV death within 2 y	26/800 (3.3)	2.00 (1.08-2.00) Sum = 1,237	2.1 (1.4-3.1)	47/800 (5.9)	2.00 (1.28-2.00) Sum = 1,307	3.6 (2.6-4.8)	0.53 (0.32-0.87)	0.012
BMI 25-30 kg/m^2								
All-cause death	36/186 (19.4)	1.96 (1.05-3.16) Sum = 426	8.4 (5.9-11.7)	64/165 (38.8)	2.25 (1.01-4.56) Sum = 499	12.8 (9.9-16.4)	0.75 (0.47-1.19)	0.22
All-cause death within 2 y	18/186 (9.7)	1.96 (1.05-2.00) Sum = 280	6.4 (3.8-10.2)	27/165 (16.4)	2.00 (1.01-2.00) Sum = 251	10.7 (7.1-15.6)	0.53 (0.28-1.00)	0.051
CV death	17/186 (9.1)	1.96 (1.05-3.16) Sum = 426	4.0 (2.3-6.4)	32/165 (19.4)	2.25 (1.01-4.56) Sum = 499	6.4 (4.4-9.1)	0.68 (0.34-1.33)	0.26
CV death within 2 y	8/186 (4.3)	1.96 (1.05-2.00) Sum = 280	2.9 (1.2-5.6)	15/165 (9.1)	2.00 (1.01-2.00) Sum = 251	6.0 (3.3-9.8)	0.33 (0.12-0.91)	0.031
BMI >30 kg/m^2								
All-cause death	124/614 (20.2)	2.12 (1.10-3.46) Sum = 1,584	7.8 (6.5-9.3)	211/635 (33.2)	2.89 (1.36-4.99) Sum = 2,272	9.3 (8.1-10.6)	0.91 (0.72-1.16)	0.45
All-cause death within 2 y	61/614 (9.9)	2.00 (1.10-2.00) Sum = 958	6.4 (4.9-8.2)	79/635 (12.4)	2.00 (1.36-2.00) Sum = 1,055	7.5 (5.9-9.3)	0.85 (0.61-1.20)	0.37
CV death	37/614 (6.0)	2.12 (1.10-3.46) Sum = 1,584	2.3 (1.6-3.2)	80/635 (12.6)	2.89 (1.36-4.99) Sum = 2,272	3.5 (2.8-4.4)	0.60 (0.40-0.91)	0.016
CV death within 2 y	18/614 (2.9)	2.00 (1.10-2.00) Sum = 958	1.9 (1.1-3.0)	32/635 (5.0)	2.00 (1.36-2.00) Sum = 1,055	3.0 (2.1-4.3)	0.61 (0.33-1.11)	0.10
LVEF ≤40%								
All-cause death	67/434 (15.4)	2.11 (1.06-3.46) Sum = 1,121	6.0 (4.6-7.6)	120/420 (28.6)	2.82 (1.23-5.17) Sum = 1,506	8.0 (6.6-9.5)	0.80 (0.59-1.10)	0.18
All-cause death within 2 y	34/434 (7.8)	2.00 (1.06-2.00) Sum = 670	5.1 (3.5-7.1)	44/420 (10.5)	2.00 (1.23-2.00) Sum = 678	6.5 (4.7-8.7)	0.79 (0.50-1.26)	0.32
CV death	26/434 (6.0)	2.11 (1.06-3.46) Sum = 1,121	2.3 (1.5-3.4)	58/420 (13.8)	2.82 (1.23-5.17) Sum = 1,506	3.9 (2.9-5.0)	0.50 (0.30-0.82)	0.0064
CV death within 2 y	11/434 (2.5)	2.00 (1.06-2.00) Sum = 670	1.6 (0.8-2.9)	23/420 (5.5)	2.00 (1.23-2.00) Sum = 678	3.4 (2.1-5.1)	0.37 (0.17-0.80)	0.012
LVEF >40%								
All-cause death	82/326 (25.2)	1.98 (1.08-3.15) Sum = 775	10.6 (8.4-13.1)	131/338 (38.8)	2.70 (1.39-4.53) Sum = 1,105	11.9 (9.9-14.1)	1.02 (0.76-1.37)	0.90
All-cause death within 2 y	42/326 (12.9)	1.98 (1.08-2.00) Sum = 501	8.4 (6.0-11.3)	52/338 (15.4)	2.00 (1.39-2.00) Sum = 560	9.3 (6.9-12.2)	0.91 (0.59-1.38)	0.65
CV death	22/326 (6.7)	1.98 (1.08-3.15) Sum = 775	2.8 (1.8-4.3)	42/338 (12.4)	2.70 (1.39-4.53) Sum = 1,105	3.8 (2.7-5.1)	0.75 (0.43-1.32)	0.32
CV death within 2 y	14/326 (4.3)	1.98 (1.08-2.00) Sum = 501	2.8 (1.5-4.7)	19/338 (5.6)	2.00 (1.39-2.00) Sum = 560	3.4 (2.0-5.3)	0.77 (0.36-1.62)	0.49

Values are n/n (%) or median (Q1-Q3), unless otherwise indicated. CIs for unadjusted event rates per 100 person-years were obtained from exact Poisson confidence limits. Cox regression was used to measure the time of any event presented by HR. 1:1 propensity score matching was made for: age, sex, BMI category, NYHA, LVEF, NT-proBNP category, eGFR category, ischemic heart disease, any valve surgery or disease, hypertension, atrial fibrillation, diabetes, ICD, CRT, ARNI, SGLT2i.

Abbreviations as in Tables 1 and 2.

SUBGROUP ANALYSIS ASSESSING THE ASSOCIATION BETWEEN GLP-1RA AND OUTCOME. In the overall cohort, risk reduction of all-cause mortality within 2 years in patients treated with GLP-1RA vs without GLP-1RA appeared more pronounced in those with LVEF ≤40% (aHR: 0.67 [95% CI: 0.47-0.94]; $P = 0.022$) compared with LVEF >40% (Figure 3A). However, no significant association of risk reduction was found

FIGURE 3 Forest Plots for All-Cause and CV Mortality for GLP-1RA vs No GLP-1RA



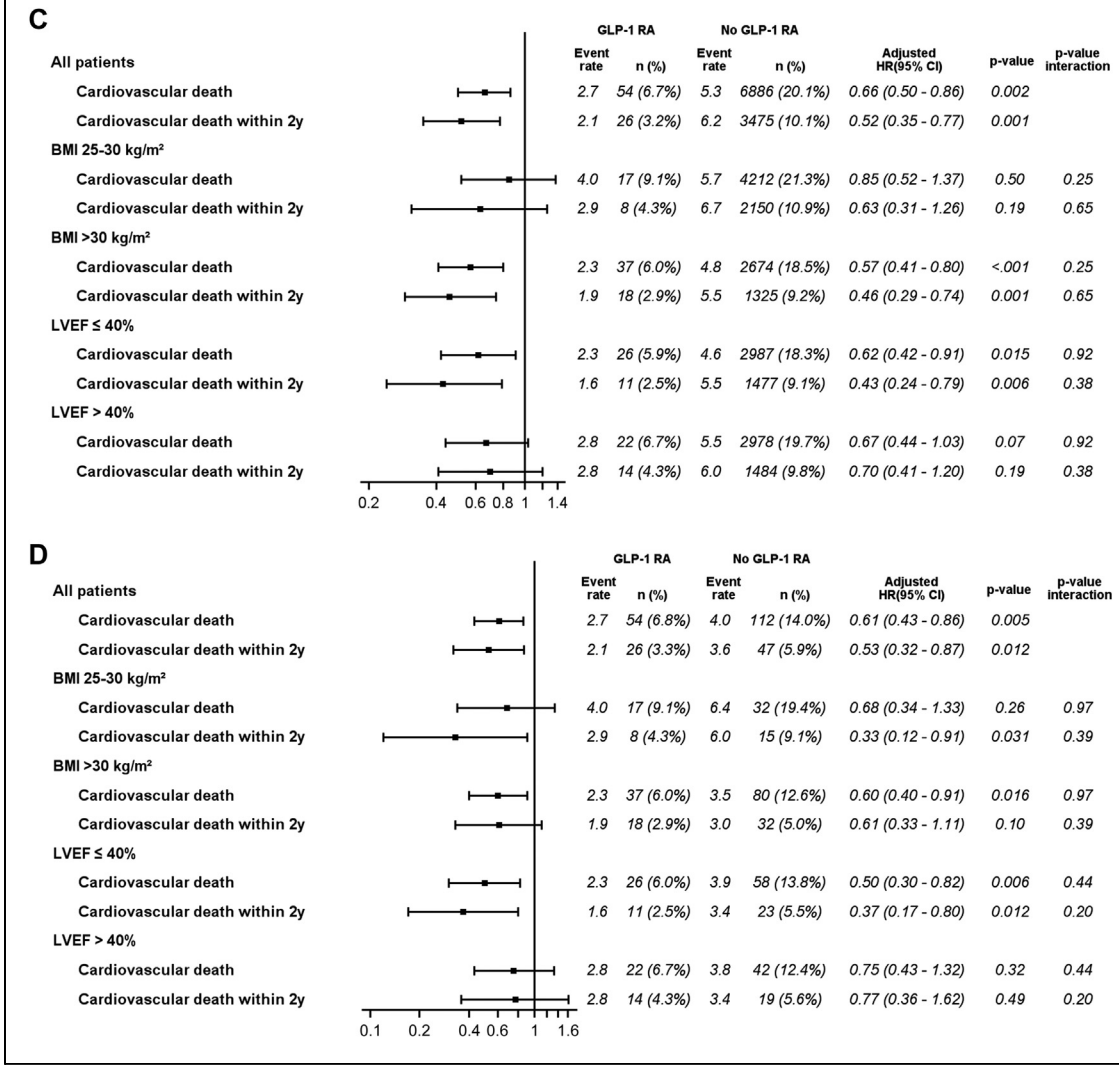
All-cause (A,B) and CV mortality (C,D) in the overall cohort (A,C) and the 1:1 propensity score–matched cohort (B,D) according to subgroups BMI 25-30 kg/m^2 or >30 kg/m^2 and LVEF ≤40% or >40%. LVEF = left ventricular ejection fraction; other abbreviations as in Figures 1 and 2.

Continued on the next page

after PS matching regardless of BMI and LVEF (Figure 3B). For CV mortality, in the overall cohort there was a significant risk reduction associated with the use of GLP-1RA in patients with BMI >30 kg/m^2 (aHR: 0.46 [95% CI: 0.29-0.74]; $P = 0.0013$) but not BMI 25-30 kg/m^2, and only in those with LVEF ≤40% (aHR: 0.43 [95% CI: 0.24-0.79]; $P = 0.0059$) and not with LVEF >40% (Figure 3C). After PS matching, there was still a significant risk reduction in patients treated with GLP-1RA with LVEF ≤40% (Figure 3D, Central Illustration).

SENSITIVITY ANALYSES WITH GLP-1RA DISPENSED 3 MONTHS BEFORE AND 6 MONTHS AFTER THE INDEX DATE. Similar results were derived from the sensitivity analyses that evaluated GLP-1RA

FIGURE 3 Continued



dispensation 3 months before and 6 months after the index date (Supplemental Table 3).

DISCUSSION

In this real-world study, GLP-1RA treatment in the Swedish HF population was associated with a significant risk reduction in CV mortality. This study represents the first nationwide analysis reporting the real-world efficacy of GLP-1RA in HF, predominantly in overweight individuals with HFrEF.

It remains ambiguous whether GLP-1RA is beneficial in HFrEF. In the LIVE trial involving 241 patients with HFrEF, regardless of diabetes status, no discernible effect on LVEF or functional class was observed between placebo and liraglutide during a 6-month treatment period. However, in the liraglutide-treated arm, increased serious cardiac adverse events (including sustained ventricular tachycardia, atrial fibrillation requiring intervention, aggravation of ischemic heart disease, and worsening of HF) were observed.[4] Likewise, in the FIGHT trial, including 300 patients diagnosed with HFrEF and experiencing recent decompensation, a numerically increased risk was seen for the composite outcome of death or HF hospitalization in those with diabetes who were treated with liraglutide.[3]

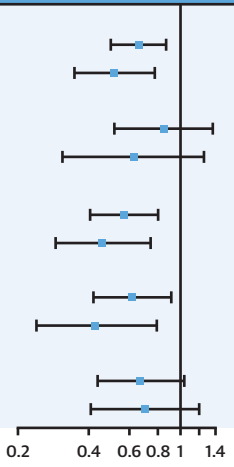
However, in STEP-HFpEF and STEP-HFpEF-DM, semaglutide was convincingly demonstrated to improve symptoms, physical capacity, and exercise

CENTRAL ILLUSTRATION **Treatment With or Without GLP-1RA and Cardiovascular Mortality, Also Divided by BMI and LVEF**

Use of GLP-1RA vs No GLP-1RA Real-Life Data 2007-2020

GLP-1RA: N = 808 No GLP-1RA: N = 34.247
Methods: adjusted Cox regression, and propensity score 1:1 matching

	GLP-1RA Event Rate	GLP-1RA n (%)	No GLP-1RA Event Rate	No GLP-1RA n (%)	Adjusted HR (95% CI)	*P* Value	*P* Value Interaction
All Patients							
Cardiovascular Death	2.7	54 (6.7)	5.3	6,886 (20.1)	0.66 (0.50-0.86)	0.002	
Cardiovascular Death Within 2 y	2.1	26 (3.2)	6.2	3,475 (10.1)	0.52 (0.35-0.77)	0.001	
BMI 25-30 kg/m^2							
Cardiovascular Death	4.0	17 (9.1)	5.7	4,212 (21.3)	0.85 (0.52-1.37)	0.50	0.25
Cardiovascular Death Within 2 y	2.9	8 (4.3)	6.7	2,150 (10.9)	0.63 (0.31-1.26)	0.19	0.65
BMI >30 kg/m^2							
Cardiovascular Death	2.3	37 (6.0)	4.8	2,674 (18.5)	0.57 (0.41-0.80)	<0.001	0.25
Cardiovascular Death Within 2 y	1.9	18 (2.9)	5.5	1,325 (9.2)	0.46 (0.29-0.74)	0.001	0.65
LVEF ≤40%							
Cardiovascular Death	2.3	26 (5.9)	4.6	2,987 (18.3)	0.62 (0.42-0.91)	0.015	0.92
Cardiovascular Death Within 2 y	1.6	11 (2.5)	5.5	1,477 (9.1)	0.43 (0.24-0.79)	0.006	0.38
LVEF >40%							
Cardiovascular Death	2.8	22 (6.7)	5.5	2,978 (19.7)	0.67 (0.44-1.03)	0.07	0.92
Cardiovascular Death Within 2 y	2.8	14 (4.3)	6.0	1,484 (9.8)	0.70 (0.41-1.20)	0.19	0.38



Karlström P, et al. JACC Heart Fail. 2025;■(■):■-■.

BMI = body mass index; GLP-1RA = glucagon-like peptide 1 receptor agonist; LVEF = left ventricular ejection fraction.

function while greatly reducing body weight compared with placebo, and thus provided important reassurance regarding the use of the GLP-1RA in obese patients with an LVEF >45%.[7,8] Given that obesity is an important risk factor in the progression of HF, including HFrEF, it is assumed that the GLP-1RA may also benefit people with HFrEF and obesity. To our knowledge, no outcome study with the GLP-1RA is available in HF, including HFrEF, HFmrEF, or HFpEF.

In this study, we sought to evaluate the real-world effectiveness of GLP-1RA in the survival of patients with HF with the use of SwedeHF. It was expected that nearly all patients enrolled in this study from 2017 to 2020 and treated with GLP-1RA had diabetes mellitus. This is because GLP-1RA is not indicated for HF, and patients with HF received GLP-1RA because of their diabetes condition. Consequently, approximately 20% of patients treated with GLP-1RA also were on treatment with SGLT2i after the publication of the EMPA-REG OUTCOME study (BI 10773 [Empagliflozin] Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients; NCT01131676),[9] which showed significantly lower risks of death from any cause and hospitalization for HF. Data for the current analysis were retrieved from the Swedish Prescribed Drug Register linked to the SwedeHF.

This observational study is arguably the most comprehensive in assessing the real-world effectiveness of GLP-1RA in HF with the following important features. First, we evaluated the association of outcome with GLP-1RAs (semaglutide, liraglutide, dulaglutide) in all HF patients regardless of LVEF. Second, our patients were from a real-world setting without exclusions except for lower body weight (BMI <25 kg/m^2), implying a significantly higher event rate. Third, all described outcome associations of the GLP-1RA were after adjustment for other HF medications, including ARNI and SGLT2i. Fourth, 98% of our HF patients treated with GLP-1RA had coexisting diabetes mellitus. Fifth, in those treated with GLP-1RA, 20% had LVEF ≥50%, 23% LVEF

40%-49%, and 57% LVEF <40%. Finally, we included normal body weight as comparison with overweight and obesity. We excluded BMI <25 kg/m^2 because there are few patients with HF and BMI <25 kg/m^2 who have received GLP-1RA.

Our results show a significant reduction in CV mortality, as well as a numeric risk reduction in all-cause mortality in HF, observed in both the overall and the PS-matched cohorts. It is striking that this association with the outcome of GLP-1RA is more pronounced in those with LVEF <40% and BMI >30 kg/m^2. Our data support the hypothesis that GLP-1RA might be a disease-modifying therapy and therefore improve survival in patients with obesity-phenotype HF because GLP-1RA is effective to modify obesity. Our results may also provide explanations to previous failed studies in HFrEF. For example, the median BMI was 31 kg/m^2 in FIGHT trial.

This finding may not be surprising when we compare it with SGLT2i in HF, in which SGLT2i effectively reduces mortality risk in HFrEF but not in individuals with LVEF >40%. Given that obesity is an important risk factor in the progression of HF, including HFrEF, it is not surprising that GLP-1RA could potentially exhibit greater efficacy in individuals with HFrEF and obesity. Our results are only hypothesis-generating, however, because our study design cannot determine causal relationships.

STUDY STRENGTHS AND LIMITATIONS. The strength of this study is access to several large high-quality linked national registries, as well as the identification of clinical data, data on drug dispensation, and mortality.

One major limitation is the small sample size of people treated with GLP-1RA, with only 808 patients, which does not permit subgroup analysis for LVEF 41%-49% and LVEF ≥50%. Patients treated with GLP-1RA were predominantly male, 73% in the GLP-1RA arm and 65% in no GLP-1RA arm, and among women in the GLP-1RA arm there were only 24 all-cause deaths and only 10 CV deaths within 2 years. Considering the small sample size of GLP-1RA treatment, the results would be questionable if we further diluted this limited sample size by sex. We excluded BMI <25 kg/m^2 because there are extremely few patients (n = 59) with HF and BMI <25 kg/m^2 who have received GLP-1RA. To include them would create imbalance of GLP-1RA treatment between different BMI categories. For comparison with overweight and obesity, which are the focus of this study group, normal body weight was included. Another limitation is that our data do not come from a randomized clinical trial rather than registry-based observation, and therefore they remain hypothesis generating for future clinical trials. In addition, the verification of individual diagnoses was not feasible. For example, there was undoubtedly erroneous coding between type 1 diabetes mellitus and T2DM. Still, T2DM was the most common form in our patient cohort with HF. However, this possibility should not affect our results. Not all patients with HF-initiated GLP-1RA were reported to SwedeHF. To address this issue, we limited patients to those who received GLP-1RA <3 months before and 12 months after the index date. Moreover, similar results were obtained when we limited patients to those who received GLP-1RA <3 months before and 6 months after the index date. In addition, we cannot be sure that patients continuously took medications throughout the study. In the current data set we are unable to distinguish the first-generation GLP-1RAs vs the second-generation GLP-1RAs. Because of limited sample sizes, 1:1 matching was chosen because it is more efficient, preserving statistical power without adding unnecessary variance. Higher ratios, such as 1:3-5, can introduce covariate imbalance, and lead to selection bias if not all patients have got 3-5 matches. This would be a problem for this study if too many patients were to be excluded from the GLP1-RA group. It is noteworthy to point out that the 95% CIs should be interpreted with caution due to lack of control for family-wise error rate.

As in many observational studies, socioeconomic data were not included. Although SwedeHF collects data from multiple variables, enabling comprehensive adjustments, the possibility of residual and unmeasured confounding cannot be disregarded. As mentioned, observational studies can assess only associations, not causal relationships. Previous studies have also shown that fewer sick patients, a higher representation of men, and younger and better-treated patients are enrolled in SwedeHF,[10] thereby limiting the generalizability of our results.

CONCLUSIONS

In this nationwide real-world study we demonstrated a statistically significant relative risk reduction in CV mortality associated with GLP-1RA in patients with

HF, particularly those with HFrEF and BMI >30 kg/m².

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr Karlström has received lecture fees from AstraZeneca and Boehringer Ingelheim; and has been a member of advisory boards for Pharmacosmos, Novartis, and AstraZeneca. Dr Fu has received research grants from the Swedish Heart-Lung Foundation and AstraZeneca; has received fees for lectures and as advisory board member from Boehringer Ingelheim, AstraZeneca, and Novo Nordisk; and is the Swedish National Coordinator for the multicenter study EMPULSE, sponsored by Boehringer Ingelheim, and the Swedish National Coordinator for the multicenter study STEP-HFPEF-DM, sponsored by Novo Nordisk. Dr Pivodic has reported that she has no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In this retrospective cohort analysis with data from SwedeHF, which included 34,247 HF patients and 808 overweight patient with HF who were treated with GLP-1RA, We evaluated the beneficial effect of GLP-1RA on all-cause and CV mortality across the range of ejection fraction. Patients treated with GLP-1RA had a significant reduction in CV mortality and a nominal risk reduction in all-cause mortality, which was particularly pronounced in those who were overweight with HFrEF.

TRANSLATIONAL OUTLOOK: These findings provide evidence that GLP-1RA could potentially exhibit greater efficacy in individuals with HFrEF and obesity. The results are only hypothesis generating because the study design cannot determine causal relationships.

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KEY WORDS effectiveness, glucagon-like peptide 1 receptor agonist, heart failure, overweight, real world

APPENDIX For supplemental tables, please see the online version of this paper.