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ORIGINAL RESEARCH

Comparative Outcomes of Glucagon-Like Peptide-1 Receptor Agonists to Dipeptidyl Peptidase 4 Inhibitors in Patients With Heart Failure and Type 2 Diabetes

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BACKGROUND: Clinical trials showed that glucagon-like peptide-1 receptor agonist (GLP1-RA) significantly improved the control of diabetes and reduced body weight compared with dipeptidyl peptidase 4 inhibitor (DPP-4i). However, it is unclear whether GLP1-RA is effective compared with DPP-4i in patients with heart failure (HF) with type 2 diabetes (T2D). The purpose of this study was to evaluate the risk of GLP1-RA compared with DPP-4i in all-cause death and hospitalization in patients with HF and T2D.

METHODS: This multicenter retrospective observational study using TriNetX, a global health care data and analytics platform, included patients with HF and T2D who had received GLP1-RA or DPP-4i from January 1, 2018, to December 31, 2022. Primary outcome was 12-month incidence of all-cause death. Secondary outcome was hospitalization. We used odds ratios (ORs) and 95% CIs to evaluate outcome measures.

RESULTS: Among 1 005 097 patients with HF and T2D, 57 965 initiated GLP1-RA and 77 098 initiated DPP-4i. After propensity score matching, the number of participants in both the GLP1-RA group and the DPP-4i group was 36 557. The proportion of 12-month incidence of all-cause death was lower in the GLP1-RA group than in the DPP-4i group (5.9% [2140/36 557] versus 8.5% [3103/36 557]; OR, 0.67 [95% CI, 0.63–0.71]).The proportion of 12-month incidence of hospitalization was also lower in the GLP1-RA group than in the DPP-4i group (42.3% [15 455/36 557] versus 48.5% [17 733/36 557]; OR, 0.78 [95% CI, 0.76–0.80]).

CONCLUSIONS: Use of GLP1-RA for patients with HF and T2D was associated with reduced 12-month incidence of all-cause death and hospitalization compared with DPP-4i.

Key Words: dipeptidyl peptidase 4 inhibitor ■ glucagon-like peptide-1 receptor agonist ■ heart failure ■ type 2 diabetes

Heart failure (HF) is a major public health issue worldwide.[1–3] Type 2 diabetes (T2D) is one of the most important risk factors for cardiovascular diseases, including HF, and patients with T2D are more likely to develop HF and have worse outcomes compared with those without diabetes.[4–7]

Dipeptidyl peptidase 4 inhibitors (DPP-4i) are promising antihyperglycemic agents because they improve blood glucose levels without causing hypoglycemia or weight gain and are well tolerated.[8] Despite the supposed cardioprotective effects of DPP-4i for HF not only through their hypoglycemic effects but also

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CLINICAL PERSPECTIVE

What Is New?

- This study is one of the first to evaluate the comparative effects of glucagon-like peptide-1 receptor agonist (GLP1-RA) and dipeptidyl peptidase 4 inhibitor specifically in patients with heart failure (HF) and type 2 diabetes (T2D). The findings suggest that GLP1-RA therapy is associated with a significantly lower risk of all-cause death and hospitalization compared with dipeptidyl peptidase 4 inhibitor in this high-risk population over a 12-month period.
- This highlights the potential of GLP1-RA beyond its established role in glycemic control and weight loss, particularly in patients with HF.

What Are the Clinical Implications?

- In terms of clinical management, GLP1-RA could be considered as a preferred treatment for patients with HF and T2D, particularly for those at high risk of adverse cardiovascular outcomes; this could lead to a change in prescribing patterns and improve patient outcomes in both diabetes and HF management.
- Further studies are needed to assess the long-term safety and efficacy of GLP1-RA in this population, particularly in patients with more advanced stages of HF or those with other comorbidities.

Nonstandard Abbreviations and Acronyms

DPP-4i	dipeptidyl peptidase 4 inhibitor
GLP1-RA	glucagon-like peptide-1 receptor agonist
HFnon-rEF	HF with nonreduced ejection fraction
HFrEF	HF with reduced ejection fraction

through a glucagon-like peptide 1-dependent mechanism, many clinical trials have failed to demonstrate the cardioprotective effect of DPP-4i.[8] The SAVOR-TIMI 53 (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients With Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53) trial showed that DPP-4 inhibitors did not reduce the risk of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke but increased the risk of HF hospitalization.[9] The EXAMINE (Cardiovascular Outcomes Study of Alogliptin in Patients With Type 2 Diabetes and Acute Coronary Syndrome), TECOS (Trial Evaluating Cardiovascular Outcomes With Sitagliptin), CARMELINA (Cardiovascular and Renal Microvascular Outcome Study With Linagliptin in Patients With Type 2 Diabetes Mellitus), and CAROLINA (Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Patients With Type 2 Diabetes) trials reported neutral effect for the risk of HF hospitalization with DPP-4i.[10–13] However, some observational studies have shown that DPP-4i is safe to use in patients with diabetes or HF complicated by diabetes and reduces the risk of cardiovascular death and HF hospitalization.[14–16]

Glucagon-like peptide-1 receptor agonists (GLP1-RA) act primarily by enhancing insulin secretion in a glucose-dependent manner, which means they help increase insulin only when blood sugar levels are elevated.[17] Additionally, these drugs slow down gastric emptying, which contributes to a reduced appetite and can aid in weight loss.[17] Findings from the LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) trial indicate that GLP1-RA reduces cardiovascular events in patients with T2D.[18] These results were confirmed in the SUSTAIN-6 (Trial to Evaluate Cardiovascular and Other Long-Term Outcomes With Semaglutide in Subjects With Type 2 Diabetes) study.[19]

In a clinical trial comparing GLP1-RA and DPP-4i, both the SUSTAIN-2 (Efficacy and Safety of Semaglutide Once-Weekly Versus Sitagliptin Once-Daily as Add-On to Metformin and/or TZD in Subjects With Type 2 Diabetes) and PIONEER-3 (Efficacy and Long-Term Safety of Oral Semaglutide Versus Sitagliptin in Subjects With Type 2 Diabetes) trials demonstrated that semaglutide significantly improved glycemic control and promoted weight loss compared with sitagliptin in patients with T2D.[20,21] Thus, clinical trials directly comparing GLP1-RA and DPP-4i have shown that GLP1-RA significantly improved the control of diabetes and reduced body weight compared with DPP-4i.[22] However, there is insufficient evidence to directly compare GLP1-RA and DPP-4i for reducing the risk of all-cause death and hospitalization in patients with HF and T2D. The purpose of this study was to evaluate the risk of GLP1-RA compared with DPP-4i in all-cause death and hospitalization in patients with HF and T2D, using a global health care research network.

METHODS

Data Access and Responsibility

Researchers can request access to data from the TriNetX research network through the TriNetX platform (https://live.trinetx.com). However, this may involve associated costs and require a data-sharing agreement, and no patient-identifiable information can be accessible.

Study Population

We conducted a multicenter retrospective observational study using TriNetX (TriNetX, LLC, Cambridge,

MA), a global health care data and analytics platform. The TriNetX platform provides real-world data analysis using electronic health records for more than 250 million patients from 120 health care organizations across North America, South America, Europe, the Middle East, Africa, and Asia Pacific. We identified disease and health problems from *International Classification of Diseases, Tenth Revision* (*ICD-10*) code. We included patients aged ≥18 years with HF (*ICD-10* code: I50) and T2D (*ICD-10*: E11) from January 1, 2018, to December 31, 2022. The exposure group was defined as the initiation of GLP1-RA. The control group was defined as initiation of DPP-4i. The start day of the observation period was defined as the day of the respective drug initiation.

Outcome Measures

The primary outcome measure was 12-month incidence of all-cause death. Secondary outcome measure was hospitalization. As one of the limitations for the TriNetX platform, it is not allowed to determine cause-specific death or hospitalizations.

Data Collection and Definitions

Covariates that were considered confounding factors for exposure and outcome were extracted from the database with reference to previous studies.[20,21,23,24] Each factor was extracted for the period from 6 months before the index event to day 0. We extracted the following 43 factors: age, sex, body mass index (BMI), race (Asian, American Indian or Alaska Native, Black, Native Hawaiian or Other Pacific Islander, White, Other race, unknown), diagnosis (hypertensive heart disease, ischemic heart diseases, old myocardial infarction, cardiomyopathy, atrial fibrillation and flutter, peripheral artery disease, hypertension, hyperlipidemia, chronic kidney disease, cerebral infarction), medication (beta blockers, angiotensin-converting enzyme inhibitors, angiotensin II inhibitors, sacubitril, diuretics, calcium channel blockers, platelet aggregation inhibitors, biguanides, sulfonylureas, thiazolidinediones, alpha glucosidase inhibitors, SGLT2 [sodium-glucose cotransporter 2] inhibitors, repaglinide, insulins), laboratory (sodium, potassium, creatinine, glomerular filtration rate, hemoglobin, hemoglobin A1c, BNP [B-type natriuretic peptide], NT-proBNP [N-terminal pro-B-type natriuretic peptide]), and left ventricular ejection fraction [LVEF]. A list including definitions of covariates is reported in Table S1.

BMI was categorized as <25 kg/m^2, 25 to <30 kg/m^2, 30 to <35 kg/m^2, 35 to <40 kg/m^2, 40 kg/m^2 or higher. Glomerular filtration rate was categorized as <30 mL/min per 1.73 m^2, 30 to <45 mL/min per 1.73 m^2, 45 to <60 mL/min per 1.73 m^2, 60 to <90 mL/min per 1.73 m^2, 90 mL/min per 1.73 m^2 or higher. Hemoglobin was categorized as <11 g/dL, and 11 g/dL or higher. Hemoglobin A1c was categorized as <6%, 6% to <8%, 8% to <10%, and 10% or higher. BNP was categorized as <100 pg/mL, 100 to <300 pg/mL, 300 to <600 pg/mL, and 600 pg/mL to higher. NT-proBNP was categorized as <400 pg/mL, 400 to <800 pg/mL, 800 to <1200 pg/mL, and 1200 pg/mL or higher. HF was divided into HF with reduced LVEF (HFrEF [LVEF <40%]) and HF with nonreduced LVEF (HFnon-rEF [LVEF 40%≤]).

Ethics Approval

We conducted this study following the Strengthening the Reporting of Observational Studies in Epidemiology reporting guidelines. This study using TriNetX does not require ethical review primarily because it deals only with anonymized data; the results available for reference are representative of the study population, and it does not deal with individual patient-level data.[25,26] This study was approved by the Ethics Committee of Omi Medical Center (local identifiers: 2024-0038) because it included patient data from our institution, although the data were completely anonymized as mentioned.

Statistical Analysis

Covariates were evaluated between the GLP1-RA group and the DPP-4i group. Categorical variables were presented as numbers (%) and continuous variables were presented as mean±SD. To reduce the potential confounding effects in the comparison between the GLP1-RA and the DPP-4i, we estimated a propensity score (PS) by using a logistic regression model that adjusted for all covariates. One-to-one pair matching between the GLP1-RA group and the DPP-4i group was performed using greedy nearest neighbor matching using calipers of width equal to 0.1 of the SD of the logit of the PS. To measure covariate balance, we checked density curves of the PS and the standardized mean difference (SMD) of before and after matching. When the SMD is <0.10,[27,28] it means that there is a negligible imbalance between the 2 groups. To investigate the association between the GLP1-RA group or the DPP-4i group and the outcome measures, we calculated the crude odds ratio (OR) and their 95% CIs.

In order to measure the differences in treatment effects between HFrEF and HFnon-rEF, we added the condition of LVEF <40% or LVEF 40%≤ in the Query Builder for the GLP1-RA group and the DPP-4i group. To prepare for comparison between the 2 groups in HFrEF or HFnon-rEF, PS matching was performed for each of the covariates using 42 factors, excluding LVEF. In investigating treatment effects, we calculated the crude OR with the corresponding 95% CI. In the same way, subgroup analyses were performed for BMI and NT-proBNP. Regarding BMI, subgroups were

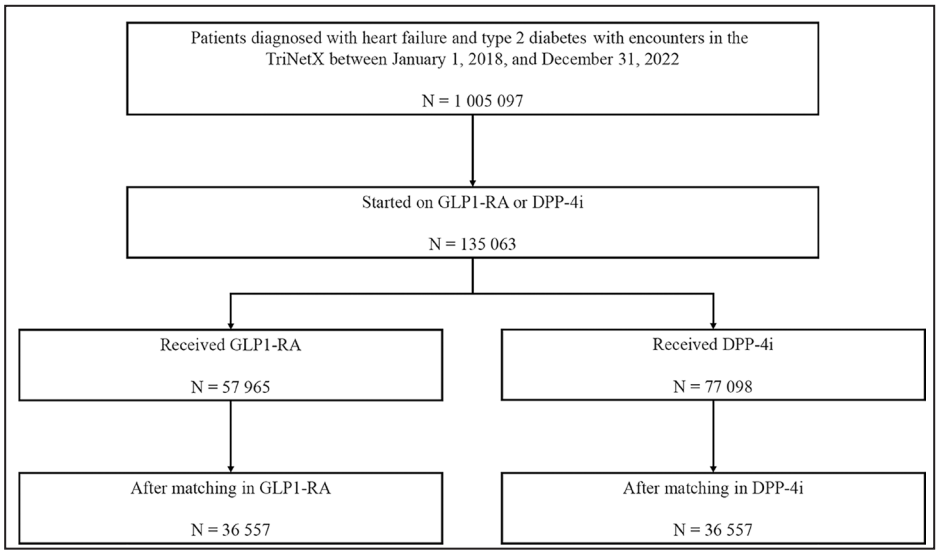

Figure 1. Patient flow.
DPP-4i indicates dipeptidyl peptidase 4 inhibitor; and GLP1-RA, glucagon-like peptide-1 receptor agonist.

defined as <25 kg/m^2, 25 to <30 kg/m^2, 30 to <35 kg/m^2, 35 to <40 kg/m^2, 40 kg/m^2 or higher. Regarding NT-proBNP, subgroups were defined as <400 pg/mL, 400 to <800 pg/mL, 800 to <1200 pg/mL, and 1200 pg/mL or higher. The difference in treatment effects between the GLP1-RA group and the DPP-4i group on all-cause death among the subgroups was analyzed and calculated the crude OR with the corresponding 95% CI, after PS matching.

Cohort definition and statistical analysis were performed on May 27, 2024, using the Query Builder and Analytics Functions on the TriNetX platform. All tests were 2 tailed, and differences with $P<0.05$ were considered to be statistically significant.

RESULTS

Study Population

Among 1 005 097 patients with HF and T2D, 57 965 initiated GLP1-RA and 77 098 initiated DPP-4i. After PS matching, the number of patients in both the GLP1-RA group and the DPP-4i group was 36 557 (Figure 1).

Baseline Clinical Characteristics: The GLP1-RA Group Versus the DPP-4i Group

The characteristics of patients with HF and T2D according to the GLP1-RA group and the DPP-4i group were summarized in Table 1.

In before-PS matched patients, patients in the GLP1-RA group compared with those in the DPP-4i group were younger, had higher BMI, were more likely to be unknown race, received SGLT2 inhibitors, and had lower hemoglobin and higher hemoglobin A1c. After PS matching, the covariate balance between the groups was well improved. The density curves of the PS before and after matching are shown in Figure S1.

Clinical Outcomes: The GLP1-RA Group Versus the DPP-4i Group

The proportion of 12-month incidence of all-cause death was lower in the GLP1-RA group than in the DPP-4i group (5.9% [2140/36 557] versus 8.5% [3103/36 557]; OR, 0.67 [95% CI, 0.63–0.71]). The proportion of 12-month incidence of hospitalization was also lower in the GLP1-RA group than in the DPP-4i group (42.3% [15 455/36 557] versus 48.5% [17 733/36 557]; OR, 0.78 [95% CI, 0.76–0.80]) (Table 2).

Analyses in HFrEF

Among patients with HFrEF and T2D, the GLP1-RA group had 3793 patients and the DPP-4i group had 4079 patients (Figure S2). After PS matching, the number of patients in both groups was 2249, with all SMDs <0.25, indicating a covariate balance between the 2 groups Table S2.

The proportion of 12-month incidence of all-cause death was lower in the GLP1-RA group than in the DPP-4i group (9.6% [216/2249] versus 13.5% [303/2249]; OR, [0.68]; [95% CI, 0.57–0.82]). Similarly, the proportion of 12-month incidence of hospitalization was also lower in the GLP1-RA group than in the DPP-4i group (59.4% [1336/2249] versus 65.3% [1469/2249]; OR, 0.78 [95% CI, 0.69–0.88]) (Table 3).

Table 1. Baseline Clinical Characteristics: The GLP1-RA Group Versus the DPP-4i Group

	Patients before matching					Propensity score matched patients				
	GLP1-RA (N=57 965)		DPP-4i (N=77 098)		SMD	GLP1-RA (N=36 557)		DPP-4i (N=36 557)		SMD
Age, y, mean±SD	62.2	(11.8)	71.4	(11.7)	0.784	66.0	(10.5)	65.9	(11.6)	0.009
Female sex, n (%)	27 255	(47.0)	34 571	(44.8)	0.044	16 517	(45.2)	16 331	(44.7)	0.010
Body mass index, kg/m^2, mean±SD	37.7	(35.9)	32.0	(145.4)	0.054	35.0	(8.6)	34.8	(65.1)	0.005
0 to <25, n (%)	2830	(4.9)	11 564	(15.0)	0.343	2473	(6.8)	2461	(6.7)	0.001
25 to <30, n (%)	6718	(11.6)	15 684	(20.3)	0.241	5488	(15.0)	5502	(15.1)	0.001
30 to <35, n (%)	11 418	(19.7)	14 159	(18.4)	0.034	7679	(21.0)	7771	(21.3)	0.006
35 to <40, n (%)	11 025	(19.0)	7959	(10.3)	0.248	5793	(15.8)	5784	(15.8)	0.001
40≤, n (%)	14 327	(24.7)	6381	(8.3)	0.454	5638	(15.4)	5455	(14.9)	0.014
Race, n (%)										
Asian	1125	(1.9)	5192	(6.7)	0.237	980	(2.7)	985	(2.7)	0.001
American Indian or Alaska Native	220	(0.4)	188	(0.2)	0.024	119	(0.3)	110	(0.3)	0.004
Black	10 848	(18.7)	10 919	(14.2)	0.123	6159	(16.8)	6148	(16.8)	0.001
Native Hawaiian or Pacific Islander	428	(0.7)	651	(0.8)	0.012	272	(0.7)	318	(0.9)	0.014
White	37 760	(65.1)	42 723	(55.4)	0.200	23 297	(63.7)	23 409	(64.0)	0.006
Other race	1236	(2.1)	1696	(2.2)	0.005	801	(2.2)	777	(2.1)	0.005
Unknown	6348	(11.0)	15 729	(20.4)	0.262	4929	(13.5)	4810	(13.2)	0.010
Diagnosis, n (%)										
Hypertensive heart disease	9185	(15.8)	13 399	(17.4)	0.041	5923	(16.2)	6002	(16.4)	0.006
Ischemic heart diseases	22 152	(38.2)	33 410	(43.3)	0.104	14 634	(40.0)	14 741	(40.3)	0.006
Old myocardial infarction	4337	(7.5)	6990	(9.1)	0.058	2987	(8.2)	3046	(8.3)	0.006
Cardiomyopathy	6436	(11.1)	7465	(9.7)	0.047	3804	(10.4)	3805	(10.4)	<0.001
Atrial fibrillation and flutter	10 927	(18.9)	19 820	(25.7)	0.165	7829	(21.4)	7868	(21.5)	0.003
Peripheral artery disease	1195	(2.1)	2388	(3.1)	0.065	880	(2.4)	911	(2.5)	0.005
Hypertension	38 753	(66.9)	44 909	(58.2)	0.179	23 021	(63.0)	22 986	(62.9)	0.002
Hyperlipidemia	25 166	(43.4)	30 564	(39.6)	0.077	15 200	(41.6)	15 279	(41.8)	0.004
Chronic kidney disease	15 920	(27.5)	29 568	(38.4)	0.233	11 466	(31.4)	11 487	(31.4)	0.001
Cerebral infarction	4447	(7.7)	5879	(7.6)	0.002	2781	(7.6)	2811	(7.7)	0.003
Medication, n (%)										
Beta blockers	30 802	(53.1)	47 727	(61.9)	0.178	20 749	(56.8)	20 913	(57.2)	0.009
Angiotensin-converting enzyme inhibitors	16 796	(29.0)	20 788	(27.0)	0.045	10 495	(28.7)	10 573	(28.9)	0.005
Angiotensin II inhibitors	16 135	(27.8)	22 113	(28.7)	0.019	10 143	(27.7)	10 119	(27.7)	0.001
Sacubitril	2922	(5.0)	2905	(3.8)	0.062	1577	(4.3)	1605	(4.4)	0.004
Diuretics	32 381	(55.9)	46 178	(59.9)	0.082	20 847	(57.0)	20 846	(57.0)	<0.001
Calcium channel blockers	16 697	(28.8)	28 783	(37.3)	0.182	11 685	(32.0)	11 595	(31.7)	0.005
Platelet aggregation inhibitors	22 914	(39.5)	37 705	(48.9)	0.190	15 838	(43.3)	15 953	(43.6)	0.006
Biguanides	23 408	(40.4)	29 324	(38.0)	0.048	14 521	(39.7)	14 552	(39.8)	0.002

(*Continued*)

Table 1. Continued

	Patients before matching					Propensity score matched patients				
	GLP1-RA (N=57965)		DPP-4i (N=77098)		SMD	GLP1-RA (N=36557)		DPP-4i (N=36557)		SMD
Sulfonylureas	9162	(15.8)	18984	(24.6)	0.221	7051	(19.3)	7102	(19.4)	0.004
Thiazolidinediones	1708	(2.9)	2727	(3.5)	0.033	1163	(3.2)	1215	(3.3)	0.008
Alpha glucosidase inhibitors	121	(0.2)	536	(0.7)	0.073	105	(0.3)	98	(0.3)	0.004
Sodium-glucose cotransporter 2 inhibitors	9063	(15.6)	5026	(6.5)	0.294	3934	(10.8)	3841	(10.5)	0.008
Repaglinide	359	(0.6)	1444	(1.9)	0.113	315	(0.9)	310	(0.8)	0.001
Insulins	33735	(58.2)	39987	(51.9)	0.128	20215	(55.3)	20179	(55.2)	0.002
Laboratory										
Sodium, mEq/L, mean±SD	138.2	(3.4)	137.9	(4.0)	0.092	138.3	(3.5)	137.9	(3.8)	0.105
Potassium, mEq/L, mean±SD	4.3	(0.5)	4.3	(0.6)	0.008	4.3	(0.5)	4.2	(0.6)	0.058
Creatinine, mg/dL, mean±SD	1.3	(2.5)	1.7	(1.9)	0.197	1.4	(2.5)	1.5	(1.7)	0.052
Glomerular filtration rate, mL/min per 1.73 m^2, mean ±SD	64.6	(28.6)	53.1	(29.9)	0.394	60.0	(28.0)	59.6	(30.4)	0.011
0 to <30, n (%)	7038	(12.1)	16912	(21.9)	0.263	5572	(15.2)	5547	(15.2)	0.002
30 to <45, n (%)	10908	(18.8)	19977	(25.9)	0.171	7825	(21.4)	7816	(21.4)	0.001
45 to <60, n (%)	14811	(25.6)	21597	(28.0)	0.056	9751	(26.7)	9825	(26.9)	0.005
60 to <90, n (%)	20655	(35.6)	21951	(28.5)	0.154	11906	(32.6)	11907	(32.6)	<0.001
≤90, n (%)	10549	(18.2)	9647	(12.5)	0.158	5562	(15.2)	5486	(15.0)	0.006
Hemoglobin, g/dL, mean±SD	12.6	(2.2)	11.5	(2.3)	0.470	12.3	(2.2)	12.1	(2.3)	0.073
0 to <11, n (%)	9474	(16.3)	23349	(30.3)	0.334	7489	(20.5)	7422	(20.3)	0.005
≤11, n (%)	29798	(51.4)	38358	(49.8)	0.033	18424	(50.4)	18405	(50.3)	0.001
Hemoglobin A1c, %, mean±SD	8.4	(2.1)	7.8	(1.9)	0.304	8.2	(2.0)	8.1	(2.0)	0.013
0 to <6, n (%)	4267	(7.4)	5825	(7.6)	0.007	2471	(6.8)	2418	(6.6)	0.006
6 to <8, n (%)	16811	(29.0)	22963	(29.8)	0.017	10560	(28.9)	10600	(29.0)	0.002
8 to <10, n (%)	12764	(22.0)	11148	(14.5)	0.197	6822	(18.7)	6889	(18.8)	0.005
≤10, n (%)	8482	(14.6)	5222	(6.8)	0.256	3799	(10.4)	3714	(10.2)	0.008
BNP, pg/mL, mean±SD	831.8	(10794.7)	1286.8	(6250.9)	0.052	1095.2	(13124.8)	874.1	(3780.3)	0.023
0 to <100, n (%)	3408	(5.9)	3082	(4.0)	0.087	1877	(5.1)	1877	(5.1)	<0.001
100 to <300, n (%)	2522	(4.4)	3866	(5.0)	0.031	1759	(4.8)	1780	(4.9)	0.003
300 to <600, n (%)	1420	(2.4)	3115	(4.0)	0.090	1114	(3.0)	1121	(3.1)	0.001
≤600, n (%)	1825	(3.1)	5150	(6.7)	0.164	1504	(4.1)	1550	(4.2)	0.006
N-terminal proBNP, pg/mL, mean±SD	2049.7	(4743.5)	5628.8	(9470.7)	0.478	2759.1	(5583.9)	3608.3	(7438.1)	0.129
0 to <400, n (%)	2515	(4.3)	1730	(2.2)	0.118	1162	(3.2)	1122	(3.1)	0.006
400 to <800, n (%)	995	(1.7)	1295	(1.7)	0.003	630	(1.7)	635	(1.7)	0.001
800 to <1200, n (%)	683	(1.2)	1041	(1.4)	0.015	471	(1.3)	481	(1.3)	0.002
≤1200, n (%)	1991	(3.4)	6063	(7.9)	0.193	1638	(4.5)	1658	(4.5)	0.003

(*Continued*)

Table 1. Continued

	Patients before matching					Propensity score matched patients				
	GLP1-RA (N=57 965)		DPP-4i (N=77 098)		SMD	GLP1-RA (N=36 557)		DPP-4i (N=36 557)		SMD
Left ventricular ejection fraction, %, mean±SD	49.0	(17.0)	48.6	(17.5)	0.025	48.8	(17.3)	49.1	(17.3)	0.020
0 to <40, n (%)	1261	(2.2)	1656	(2.1)	0.002	782	(2.1)	791	(2.2)	0.002
≤40, n (%)	3900	(6.7)	4416	(5.7)	0.041	2305	(6.3)	2304	(6.3)	<0.001

BNP indicates B-type natriuretic peptide; DPP-4i, dipeptidyl peptidase 4 inhibitor; GLP1-RA, glucagon-like peptide-1 receptor agonist; and SMD, standardized mean difference.

Analyses in HFnon-rEF

Among patients with HFnon-rEF and T2D, the GLP1-RA group had 11 017 patients and the DPP-4i group had 10 048 patients (Figure S3). After PS matching, the number of patients in both groups was 5930, with all SMDs <0.25, indicating a covariate balance between the 2 groups (Table S3).

The proportion of 12-month incidence of all-cause death was lower in the GLP1-RA group than in the DPP-4i group (7.2% [429/5930] versus 10.0% [592/5930]; OR, 0.70 [95% CI, 0.62–0.80]). Likewise, the proportion of 12-month incidence of hospitalization was also lower in the GLP1-RA group than in the DPP-4i group (58.2% [3449/5930] versus 64.2% [3809/5930]; OR, 0.77 [95% CI, 0.72–0.83]) (Table 4).

Subgroup Analyses in BMI and NT-proBNP

Figure 2 showed the results of the subgroup analyses for BMI and NT-proBNP. In both subgroups, GLP1-RA significantly reduced the proportion of 12-month incidence of all-cause death compared with DPP-4i.

DISCUSSION

In this multicenter retrospective observational study, using a global health care research network, use of GLP1-RA for patients with HF and T2D was associated with reduced 12-month incidence of all-cause death and hospitalization compared with use of DPP-4i. This result was also confirmed by the analyses in the subgroups with HFrEF or HFnon-rEF, thus demonstrating the robustness of our present study. Our findings provide important evidence for the selection of antidiabetic medications in patients with HF and T2D.

Previous studies have shown that GLP1-RA provides better diabetes control in patients with diabetes compared with DPP-4i.[20,21] Cardiovascular outcome trials of GLP1-RA in patients with T2D have also shown that GLP1-RA reduces the risk of cardiovascular events in patients with T2D with cardiovascular high-risk compared with placebo.[18,19] Mechanisms for this cardioprotective effect of GLP1-RA include not only improved glycemic control and weight loss[29] but also blood pressure reduction,[19] anti-inflammatory effects,[30] and direct cardioprotection.[31] In the SUSTAIN-6 trial, semaglutide showed a mean systolic blood pressure 2.6 mm Hg lower at week 104 compared with the placebo.[19] GLP1-RA were reported to affect atherosclerosis via an anti-inflammatory mechanism by in vivo experiment using ApoE−/− (apolipoprotein E-deficient) mice and low-density lipoprotein receptor-deficient mice.[30] Another basic experiment suggests that liraglutide increases cyclic AMP formation in a GLP1-R-dependent manner and may have a direct cardioprotective effect.[31] To reduce cardiovascular events, current diabetes guidelines recommend the use of GLP1-RA in patients who are high risk for cardiovascular issues with T2D and recommend the use of SGLT2i in patients with HF and T2D.[32,33] Our study found that GLP1-RA reduced the 12-month incidence of all-cause death and hospitalization compared with DPP-4i in patients with HF and T2D. Our findings suggest that the cardioprotective effect of GLP1-RA can be extended to patients with HF as well as T2D.

Meanwhile, our findings in the subgroup analyses suggest a more effective patient population for GLP1-RA among patients with HF and T2D. The results of the subgroup analysis of BMI indicated that the higher the weight, the more likely it was that the treatment effect of GLP1-RA would be enhanced. In addition, the results

Table 2. Clinical Outcomes: The GLP1-RA Group Versus the DPP-4i Group

	Number of events in GLP1-RA group (N=36 557)		Number of events in DPP-4i group (N=36 557)		OR	95% CI
All-cause death	2140	(5.9%)	3103	(8.5%)	0.67	0.63–0.71
Hospitalization	15 455	(42.3%)	17 733	(48.5%)	0.78	0.76–0.80

DPP-4i indicates dipeptidyl peptidase 4 inhibitor; GLP1-RA, glucagon-like peptide-1 receptor agonist; and OR, odds ratio.

Table 3. Clinical Outcomes: The GLP1-RA Group Versus the DPP-4i Group in HFrEF

	Number of events in GLP1-RA group (N=2249)		Number of events in DPP-4i group (N=2249)		OR	95% CI
All-cause death	216	(9.6%)	303	(13.5%)	0.68	0.57–0.82
Hospitalization	1336	(59.4%)	1469	(65.3%)	0.78	0.69–0.88

DPP-4i indicates dipeptidyl peptidase 4 inhibitor; GLP1-RA, glucagon-like peptide-1 receptor agonist; HFrEF, heart failure with reduced ejection fraction; and OR, odds ratio.

of the subgroup analysis of NT-proBNP indicated that the milder the HF, the more likely the treatment effect of GLP1-RA would be enhanced. These findings suggest that GLP1-RA is more likely to be effective in patients who are more overweight or in patients with milder HF. The STEP-HFpEF (Effect of Semaglutide 2.4 mg Once Weekly on Function and Symptoms in Subjects With Obesity-related Heart Failure With Preserved Ejection Fraction) trial, including patients without diabetes, with BMI of at least 30 kg/m^2 and LVEF of at least 45%, showed that semaglutide, a GLP1-RA, improved the Kansas City Cardiomyopathy Questionnaire clinical summary score from baseline compared with placebo.[34] Similarly, the STEP-HFpEF DM (Effect of Semaglutide 2.4 mg Once-Weekly on Function and Symptoms in Subjects With Obesity-Related Heart Failure With Preserved Ejection Fraction, and Type 2 Diabetes) trial, including patients with T2D, BMI of at least 30 kg/m^2, and LVEF of at least 45%, showed that semaglutide also improved Kansas City Cardiomyopathy Questionnaire clinical summary score from baseline compared with placebo.[35] The SELECT (Semaglutide Effects on Cardiovascular Outcomes in People With Overweight or Obesity) trial, which included adults 45 years or older with overweight or obesity, history of cardiovascular disease, and no history of diabetes and compared the effectiveness of semaglutide to placebo for up to 5 years, found a reduction of approximately 20% in composite end points, including worsening HF and all-cause mortality.[36] Our findings confirmed the results of these clinical trials. Although these trials were conducted in patients with HF with preserved LVEF, the results of future trials in patients with HF with reduced LVEF are promising.

HF Classification Based on LVEF

In a previous study investigating mortality in patients with HF with different LVEF, diabetes increased mortality in patients with HF with LVEF <40% (HFrEF), and a similar trend was observed in patients with HF with LVEF >40% (HFnon-rEF).[37] In patients with HF with LVEF at least 50% among HFnon-rEF, a high prevalence of T2D and the presence of T2D has been shown to increase mortality by 30% to 50%, even after adjusting for age, sex, hospital factors, and other patient characteristics.[38] DPP4is are widely used worldwide as diabetes medications that considerably lower hyperglycemia without increasing the risk of hypoglycemia.[39] DPP-4i inhibits the enzymatic activity of the proteolytic enzyme DPP-4, resulting in an increase in glucagon-like peptide 1 and a reduction in blood glucose.[14,40] An animal study using knockout mice showed that inhibition of DPP-4 may have a direct protective effect on the heart after myocardial infarction by inducing an antiapoptotic effect.[41] Another animal study demonstrated in a mouse model that DPP-4i inhibits cardiac hypertrophy by suppressing oxidative stress.[42] Clinical trials have shown that DPP-4i treatment of patients with T2D does not increase cardiovascular events and may increase some HF hospitalization.[9–13] However, these clinical trials have not confirmed the efficacy of DPP-4i in patients with already established HF. In a multicenter retrospective observational study, DPP-4i use was associated with a lower incidence of a composite outcome of cardiovascular death or HF hospitalization in patients with HF and LVEF of ≥50%.[14] In a subgroup analysis divided by LVEF of a previous study investigating the effectiveness of DPP-4i in patients with HF and T2D, there was no association between DPP-4i use and all-cause death in patients with HF and LVEF <45%, whereas DPP-4i use significantly reduced all-cause death in patients with HF and LVEF of ≥45%.[15] Thus, there are a few positive studies of DPP-4i in patients with HF and preserved LVEF, but the evidence is limited. Although the previous studies mentioned might suggest the effectiveness of GLP1-RA compared

Table 4. Clinical Outcomes: The GLP1-RA Group Versus the DPP-4i Group in HFnon-rEF

	Number of events in GLP1-RA group (N=5930)		Number of events in DPP-4i group (N=5930)		OR	95% CI
All-cause death	429	(7.2%)	592	(10.0%)	0.70	0.62–0.80
Hospitalization	3449	(58.2%)	3809	(64.2%)	0.77	0.72–0.83

DPP-4i indicates dipeptidyl peptidase 4 inhibitor; GLP1-RA, glucagon-like peptide-1 receptor agonist; HFnon-rEF, heart failure with nonreduced ejection fraction; and OR, odds ratio.

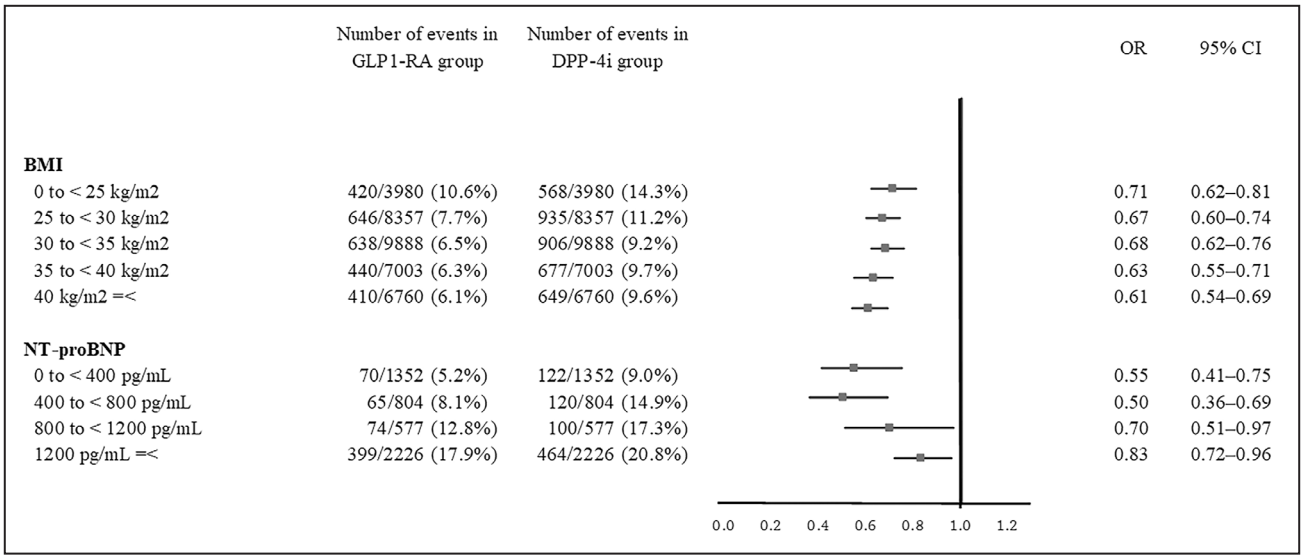

Figure 2. Subgroup analyses for all-cause death: the GLP1-RA group versus the DPP-4i group.
BMI indicates body mass index; DPP-4i, dipeptidyl peptidase 4 inhibitor; GLP1-RA, glucagon-like peptide-1 receptor agonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; and OR, odds ratio.

with DPP-4i, there are no clinical trials that have directly compared GLP1-RA and DPP-4i in patients with diabetes and HFpEF. Our finding that GLP1-RA compared with DPP-4i reduced the 12-month incidence of all-cause death and hospitalization in patients with HFnon-rEF and T2D represents a new possibility for preferable diabetes treatment in patients with HF without reduced LVEF. It is also consistent with the results of the STEP-HFpEF, STEP-HFpEF DM, and SELECT trials, because our study included a large number of patients with overweight or obesity.

As for HFrEF, there is a lack of evidence investigating the effectiveness of GLP-RA or DPP-4i on cardiovascular outcomes in patients with HFrEF and T2D. In a multicenter retrospective observational study, there was no association between DPP-4i use and a composite outcome of cardiovascular death or HF hospitalization in patients with LVEF <50%.[14] A retrospective cohort study, comparing SGLT2i and DPP-4i with a composite outcome of all-cause death and worsening HF in patients with HF and T2D, showed consistent effectiveness of SGLT2i against DPP-4i in a subgroup analysis of HFpEF or HFrEF.[43] These results indicate that DPP-4i might not reduce cardiovascular events in patients with HFrEF and T2D. Our findings in this study show that GLP1-RA reduces the 12-month incidence of all-cause death and hospitalization compared with DPP-4i in patients with HFrEF and T2D. Although these results suggest that GLP1-RA is effective for cardiovascular events in patients with HFrEF, the strength of the evidence is limited by the fact that the control drug, DPP-4i, was not shown to be effective for cardiovascular events in patients with HFrEF. To confirm the effectiveness of GLP1-RA on patients with HFnon-rEF and HFrEF and T2D, further studies are needed directly comparing them to other diabetes drugs or weight-loss strategies, such as NCT05371496 and NCT06423599 as ClinicalTrials.gov number, that have already been shown to be effective for patients with HF.

LIMITATION

The present study had several limitations. First, this study collected information from electronic health care records, and the diagnosis was based on *ICD-10* codes. Thus, it is not a definitional diagnosis, for example, using modified Framingham criteria to diagnose HF. Alternatively, a diagnosis of T2D could be made in order to administer certain HF medications, such as SGLT2i, to a patient. Second, there were some missing data in this study. In particular, the results of blood tests and echocardiography are often missing. There is a concern about the existence of selection bias, such as not tested because of a mild state or tested because of a severe state. Third, each factor, collected as a confounding factor and presented in patient characteristics, is data from 6 months before index day to day 0. Because of the difference of up to 6 months, the data may not reflect the patient's condition on the index day. Fourth, there were covariates with SMDs >0.1, indicating imbalance after PS matching. The mean sodium levels of the 2 groups after matching are very similar and are considered clinically acceptable in terms of balance. NT-proBNP is not balanced in terms of its mean value, as the SMD exceeds

0.1. However, it is balanced across categories and is considered clinically acceptable overall. Finally, there is a limitation regarding the PS matching used in the outcome analysis of this study. Although we included as many confounders as possible in the PS matching, we did not adjust for unknown or unmeasured confounders. Therefore, the results of this study need to be reconfirmed in clinical trials or observational studies designed to thoroughly exclude bias.

CONCLUSIONS

GLP1-RA use for patients with HF and T2D was associated with reduced 12-month incidence of all-cause death and hospitalization compared with DPP-4i, irrespective of LVEF.

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None.

Supplemental Material

Data S1–S3
Figures S1–S3

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