

Combination therapy with sodium-glucose cotransporter 2 inhibitors and glucagon-like peptide-1 receptor agonists in heart failure patients with type 2 diabetes

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ABSTRACT

Introduction Sodium-glucose cotransporter 2 inhibitors (SGLT2i) and glucagon-like peptide-1 receptor agonists (GLP-1 RAs) improve cardiovascular outcomes in type 2 diabetes (T2D), and SGLT2i reduces events in heart failure (HF). However, the benefit of their combination in patients with both conditions remains unclear. This study assessed the risk of all-cause death and hospitalization with combination therapy versus SGLT2i monotherapy.

Research design and methods This multicenter, retrospective, observational study used the TriNetX database between January 1, 2018, and December 31, 2021. We identified 928,981 patients aged ≥ 18 years with HF and T2D. Of these, 168,422 received an SGLT2i. The exposure group comprised patients who initiated a GLP-1 RA within 6 months of SGLT2i initiation, while the control group included those who did not receive a GLP-1 RA after SGLT2i initiation. The index date was defined as 6 months after SGLT2i. 25,989 patients received SGLT2i and GLP-1 RA and 54,619 received SGLT2i monotherapy. Following propensity score matching, each group comprised 23,240 patients.

Results Over 1 year, the risk of all-cause death in patients who received SGLT2i and GLP-1 RA relative to those who received SGLT2i monotherapy was significantly lower (2.8% vs 6.3%, $p < 0.001$; HR 0.43; 95% CI 0.39 to 0.48). Similarly, the risk of hospitalization in patients who received SGLT2i and GLP-1 RA was also lower (32.9% vs 36.4%, $p < 0.001$; HR, 0.87; 95% CI 0.84 to 0.90).

Conclusions The risk of all-cause death and hospitalization in patients who received combination therapy with SGLT2i and GLP-1 RA relative to those who received SGLT2i monotherapy was significantly lower in patients with HF and T2D.

INTRODUCTION

Heart failure (HF) is a major public health problem worldwide.^{1–3} Type 2 diabetes (T2D) is a major risk factor for cardiovascular diseases including HF, and patients with T2D have worse outcomes than those without diabetes.^{4–7} Sodium-glucose cotransporter

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Sodium-glucose cotransporter 2 inhibitors (SGLT2i) reduce heart failure (HF) events and glucagon-like peptide-1 receptor agonists (GLP-1 RAs) lower cardiovascular risk in type 2 diabetes (T2D), but robust evidence for their combined use specifically in patients with both HF and T2D has been limited, warranting dedicated evaluation.

WHAT THIS STUDY ADDS

⇒ In a large propensity score-matched cohort of patients with HF and T2D, adding a GLP-1 RA to SGLT2i therapy was associated with lower 1-year all-cause death (HR 0.43) and hospitalization (HR 0.87) than SGLT2i monotherapy.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These findings support earlier consideration of dual therapy in appropriate patients and underscore the need for randomized trials to confirm causal benefit.

2 inhibitors (SGLT2i) reduce glucose and sodium reabsorption in the kidney, which helps reduce the cardiac workload and protect renal function.⁸ Clinical trials have shown that SGLT2i improve cardiovascular outcomes in patients with HF, with or without diabetes.^{9–12} These results have been confirmed in both HF with reduced left ventricular ejection fraction (HFrEF) and HF with preserved left ventricular ejection fraction (HFpEF).^{9–11} Based on these findings, SGLT2i is highly recommended in clinical guidelines for HF.^{1–3}

Glucagon-like peptide-1 receptor agonists (GLP-1 RA) act primarily by enhancing insulin secretion in a glucose-dependent manner, which means that they help increase

insulin only when blood sugar levels are elevated.¹³ Additionally, these drugs slow gastric emptying, which contributes to reduced appetite and aids weight loss.¹³ GLP-1 RA have been shown to reduce cardiovascular events in cardiovascular outcome trials in patients with T2D.^{14 15} The effectiveness of GLP-1 RA in patients with HF is controversial; however, it has recently been shown that GLP-1 RA improve HF-related symptoms, physical limitations, body weight, and exercise function, and reduce the elevated levels of N-terminal pro-B-type natriuretic peptide and C-reactive protein in patients with HF non-rEF and obesity.^{16–18} The findings of these clinical trials suggest that GLP-1 RA may have additional benefits for patients with HF.^{18 19}

Although previous studies have tested the effectiveness of SGLT2i and GLP-1 RA individually in patients with HF or T2D, the effectiveness of combination therapy with SGLT2i and GLP-1 RA in patients with HF and T2D remains unknown. This study aimed to evaluate the risk of combination therapy with SGLT2i and GLP-1 RA compared with SGLT2i monotherapy in all-cause death and hospitalization for patients with HF and T2D using a global healthcare research network.

METHODS

Study population

We conducted a multicenter, retrospective observational study using TriNetX (TriNetX, Cambridge, Massachusetts, USA), a global healthcare data and analytics platform. The TriNetX platform provides real-world data analysis using electronic health records (EHR) for more than 250 million patients from 130 healthcare organizations across North America, South America, Europe, the Middle East, Africa, and the Asia-Pacific region. The TriNetX database aggregates de-identified longitudinal health data from millions of patients across multiple healthcare settings, including hospitals, outpatient centers, and primary care clinics. Each healthcare organization maintains local control of its data, whereas TriNetX securely accesses and aggregates de-identified data across institutions. By only aggregating the results of the analysis, TriNetX enhances privacy. Available data included patient demographics (such as age, sex, race, and ethnicity), diagnoses (standardized by the International Statistical Classification of Diseases and related Health Problems (ICD)-10 codes), procedures (using Current Procedural Terminology codes), laboratory results, prescribed medications, and clinical outcomes. Because the TriNetX platform collects data from the EHR, disease diagnosis is not based on diagnostic criteria but rather on the recording of disease names in the EHR; therefore, we identified disease and health problems from the ICD-10 code. We included patients aged ≥18 years with HF (ICD-10 code: I50) and T2D (ICD-10: E11) between January 1, 2018, and December 31, 2022. The exposure group was defined as patients who initiated combination therapy with an SGLT2i and a GLP-1

RA. Combination therapy was defined as the initiation of a GLP-1 RA within 6 months after starting SGLT2i therapy. The control group was administered an SGLT2i monotherapy. Patients who received a first-time prescription for a GLP-1 receptor agonist or an SGLT2 inhibitor were included. To minimize immortal time bias, patients who underwent laboratory examinations approximately 6 months after initiating SGLT2i therapy were included according to this additional criterion. The date of the laboratory examination was defined as the index date for the observation period.

Outcome measures

The primary outcome measure was all-cause death during the 1-year follow-up period. The 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 considered confounding factors for exposure and outcome were extracted from the database with reference to previous studies.^{20 21} Each factor was extracted from 1 month before day 0 of the index date. Comorbidities were defined as conditions with a recorded diagnosis within 1-month prior to the index date. Diseases recorded in the EHR during the observation period were included as comorbidities, whereas previously recorded diseases that were discontinued at the beginning of the observation period were not included as comorbidities. In addition, conditions documented more than 1 month before the index date were also considered comorbidities if they remained active during the 1-month period following the index date. Diagnoses that had been previously recorded but were deleted more than 1 month before the index date were not considered comorbidities. We extracted the following 43 factors: age, sex, body mass index (BMI), race (Asian, American Indian or Alaska Native, black or African American, 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, ACE inhibitors, angiotensin II receptor blockers, sacubitril, mineralocorticoid receptor antagonists, diuretics, loop diuretics, thiazides, calcium channel blockers, platelet aggregation inhibitors, anti-coagulants, biguanides, sulfonylureas, dipeptidyl peptidase 4 (DPP-4) inhibitors, insulins, statins), laboratory assay data (sodium, potassium, glomerular filtration rate (GFR), hemoglobin, albumin, low-density lipoprotein (LDL) cholesterol, hemoglobin A1c (HbA1c), B-type natriuretic peptide (BNP), N-terminal pro-B type natriuretic peptide (NT-proBNP), and systolic blood pressure, diastolic blood pressure, heart rate, left ventricular ejection fraction (LVEF). A list of definitions of the covariates is provided in online supplemental table 1.

Ethics approval

This study was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology Reporting Guidelines. This study used TriNetX and did not require ethical review, primarily because it deals only with anonymized data; the results available for reference are representative of the study population and do not deal with individual patient-level data.^{22 23} This study was approved by the Ethics Committee of the Omi Medical Center (local identifier: 2024-0044) because it included patient data from our institution, although the data were completely anonymized, as mentioned above.

Statistical analysis

Covariates were compared between patients who received SGLT2i and GLP-1 RA and those who received SGLT2i monotherapy. Categorical variables are presented as numbers (%), and continuous variables are presented as means with SD. To reduce the potential confounding effects in the comparison between patients who received SGLT2i and GLP-1 RA and those who received SGLT2i monotherapy, we estimated a propensity score (PS) using a logistic regression model that adjusted for all covariates. One-to-one pair matching between patients who received SGLT2i and GLP-1 RA and those who received SGLT2i monotherapy was performed using greedy nearest neighbor matching without replacement, using calipers of width equal to 0.1 SD of the logit of the PS. To measure the covariate balance, we checked the standardized mean difference (SMD) of before and after

matching. When the SMD was <0.10 ,^{24 25} there was negligible imbalance between the two groups. The cumulative incidence of the outcome measures that occurred during the 1-year follow-up period was estimated using the Kaplan-Meier method, with intergroup differences assessed using the log-rank test. Patients are censored on the day after the last recorded clinical event within the analysis time window. Person-time at risk was calculated from the index date until the earliest occurrence of the outcome, loss to follow-up, or the end of the study period. Incidence rates were expressed as events per 100 person-years, calculated by dividing the number of events by the total person-years of follow-up. These analyses were conducted for both all-cause death and hospitalization. The risks for patients who received SGLT2i and GLP-1 RA relative to those who received SGLT2i monotherapy for the outcome measures were estimated by calculating crude HRs and their 95% CIs. To assess the potential impact of unmeasured confounding, we calculated E values based on HRs and their corresponding 95% CIs for outcome measures.^{26 27}

To measure the differences in treatment effects, subgroup analyses were performed for HF (HFrEF (ICD-10 code: I50.2 or I50.4), HFpEF (ICD-10 code: I50.3 or I50.4)), age (18–64 years, 65–74 years, over 75 years), sex (female, male), BMI ($<30 \text{ kg/m}^2$, $30 \text{ kg/m}^2 \leq$), HbA1c ($<7.0\%$, $7.0\text{--}7.9\%$, $8.0\% \leq$), GFR ($<60 \text{ mL/min/1.73 m}^2$, $60 \text{ mL/min/1.73 m}^2 \leq$), ischemic heart disease, and hypertension. The TriNetX platform

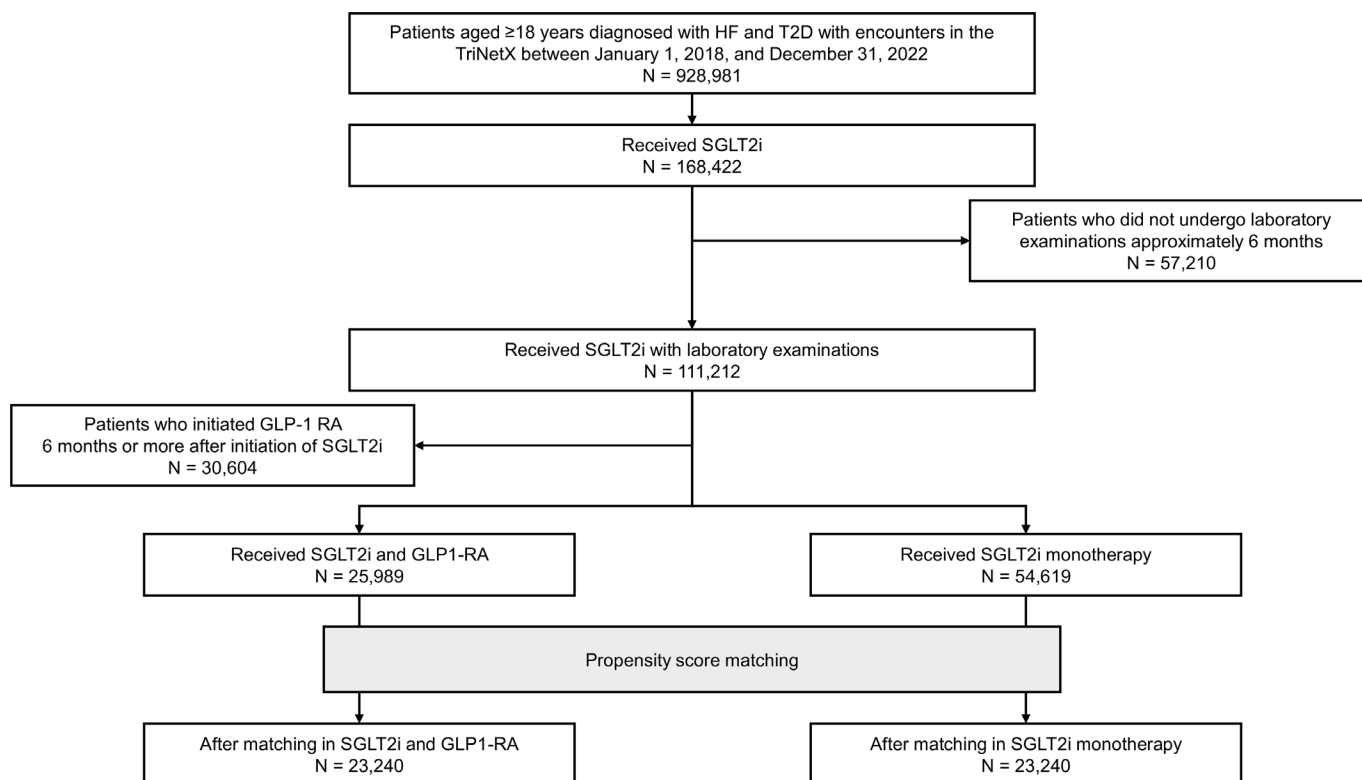


Figure 1 Patient flow. GLP-1 RA, glucagon-like peptide-1 receptor agonists; HF, heart failure; SGLT2i, sodium-glucose cotransporter 2 inhibitors; T2D, type 2 diabetes.

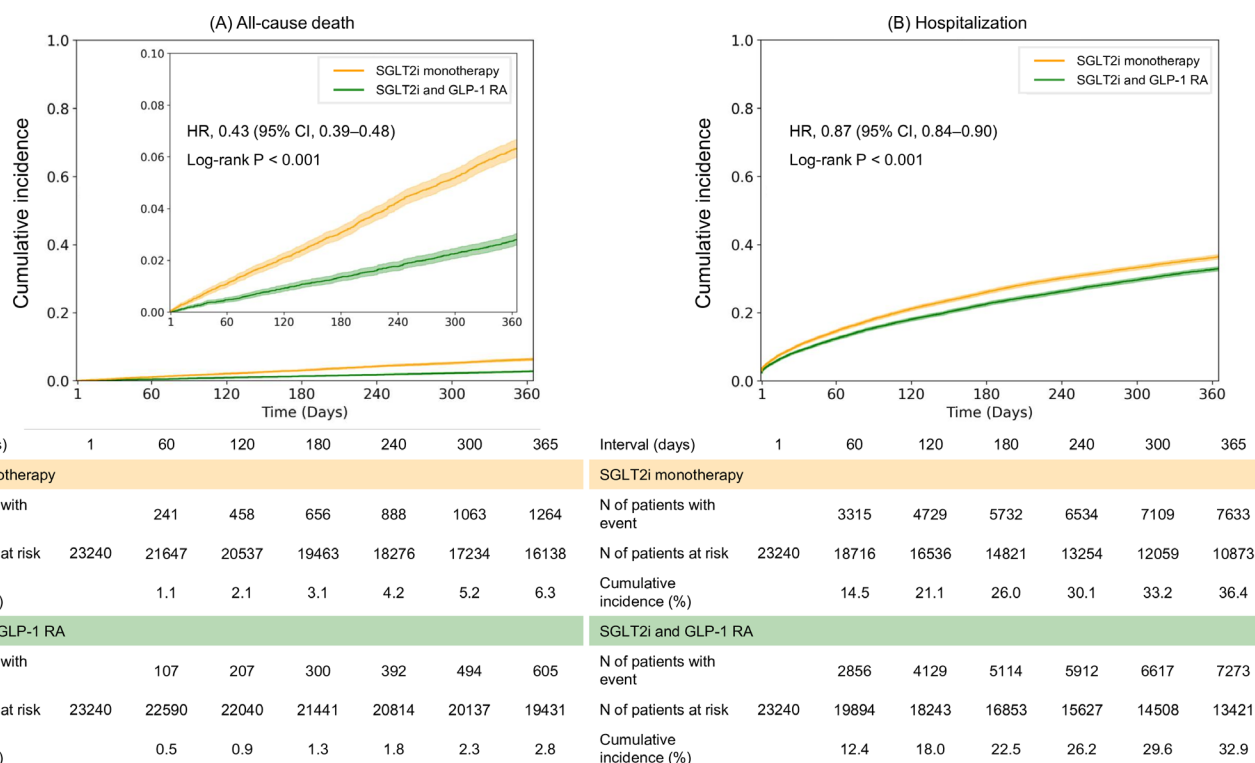


Figure 2 Kaplan-Meier curves for the primary and secondary outcome measures: SGLT2i and GLP-1 RA versus SGLT2i monotherapy. Shaded area indicates 95% CI. (A) All-cause death, (B) hospitalization. GLP-1 RA, glucagon-like peptide-1 receptor agonists; SGLT2i, sodium-glucose cotransporter 2 inhibitors.

required the creation of additional cohorts for subgroup analysis. After PS matching, the difference in treatment effects between patients who received SGLT2i and GLP-1 RA and those who received SGLT2i monotherapy on all-cause death was evaluated within each subgroup. Crude HRs with the corresponding 95% CIs were calculated. Similarly, a subgroup analysis was conducted for hospitalization.

Cohort definitions and statistical analyses were performed on May 14, 2025, using the Query Builder and Analytics Functions on the TriNetX platform. All tests were two-tailed, and differences were considered statistically significant at $p < 0.05$.

RESULTS

Study population

From January 1, 2018, to December 31, 2022, 928,981 patients aged ≥ 18 years with HF and T2D were identified from the TriNetX platform. Among these, 168,422 patients received SGLT2i, of whom 111,212 had laboratory data available within approximately 6 months of treatment initiation. Patients without relevant laboratory data during this period ($n=57,210$) were excluded.

Of the 111,212 patients with available laboratory data, those who initiated a GLP-1 RA more than 6 months after SGLT2i initiation ($n=30,604$) were excluded. As a result, 25,989 received combination therapy with SGLT2i and GLP-1 RA, while 54,619 received SGLT2i monotherapy.

After PS matching, each group included 23,240 patients (figure 1).

Baseline clinical characteristics

The characteristics of patients ≥ 18 years with HF and T2D according to the SGLT2i and GLP-1 RA group and the SGLT2i monotherapy group were summarized in online supplemental table 2.

Before PS matching, patients who received SGLT2i and GLP-1 RA were younger, more likely to be female, more frequently of unknown race, and had a higher BMI compared with those who received SGLT2i monotherapy. These patients were less likely to have ischemic heart disease, cardiomyopathy, and atrial fibrillation/flutter, and more likely to have hypertension. Additionally, they were less likely to receive anticoagulants, and more likely to receive ACE inhibitors, biguanides, and insulin. They also had higher diastolic blood pressure, heart rate, GFR, hemoglobin, albumin, HbA1c, and LVEF levels, and lower BNP and NT-proBNP levels. After PS matching, the covariate balance between the groups improved substantially (online supplemental table 2).

Clinical outcomes

The 1-year cumulative incidence of all-cause death was significantly lower in patients who received SGLT2i and GLP-1 RA than in those who received SGLT2i monotherapy (2.8% (605/23,240) vs 6.3% (1,264/23,240), log-rank $p < 0.001$). The risk for all-cause death in patients

Table 1 Primary and secondary outcomes: the SGLT2i and GLP-1 RA group versus the SGLT2i monotherapy group

Outcome	SGLT2i and GLP-1 RA (N=23,240)		SGLT2i monotherapy (N=23,240)		HR (95% CI)
	N of patients with event (Cumulative 1-year incidence)	N/100 person-year	N of patients with event (Cumulative 1-year incidence)	N/100 person-year	
All-cause death	605 (2.8%)	2.8	1264 (6.3%)	6.5	0.43 (0.39 to 0.48)
Hospitalization	7273 (32.9%)	42.5	7633 (36.4%)	50.1	0.87 (0.84 to 0.90)

GLP1-RA, glucagon-like peptide-1 receptor agonists; SGLT2i, sodium glucose cotransporter 2 inhibitor.

who received SGLT2i and GLP-1 RA relative to those who received SGLT2i monotherapy remained significant (HR, 0.43; 95% CI 0.39 to 0.48; E value=3.60) (figure 2A and table 1). Similarly, patients who received SGLT2i and GLP-1 RA were less likely to be hospitalized (32.9% (7,273/23,240) vs 36.4% (7,633/23,240); HR, 0.87; 95% CI 0.84 to 0.90; log-rank $p<0.001$; E value=1.36) (figure 2B and table 1).

Subgroup analyses

Figure 3 showed the results of the subgroup analyses for HF, age, sex, BMI, HbA1c, GFR, ischemic heart disease, and hypertension. The 1-year cumulative incidence of all-cause death was significantly lower in patients receiving SGLT2i and GLP-1 RA compared with those receiving SGLT2i monotherapy across all subgroups. A similar

trend was observed in the subgroup analysis of hospitalization (online supplemental figure 1).

DISCUSSION

In this multicenter, retrospective, observational study using a global healthcare research network, combination therapy with SGLT2i and GLP-1 RA in patients with HF and T2D was associated with a lower 1-year risk of all-cause death and hospitalization compared with SGLT2i monotherapy. This association was consistent across the spectrum of LVEF. These findings support the potential utility of combination therapy as a treatment strategy in patients with HF and coexisting T2D.

Previous studies have shown that SGLT2i improve cardiovascular outcomes in patients with HF, with

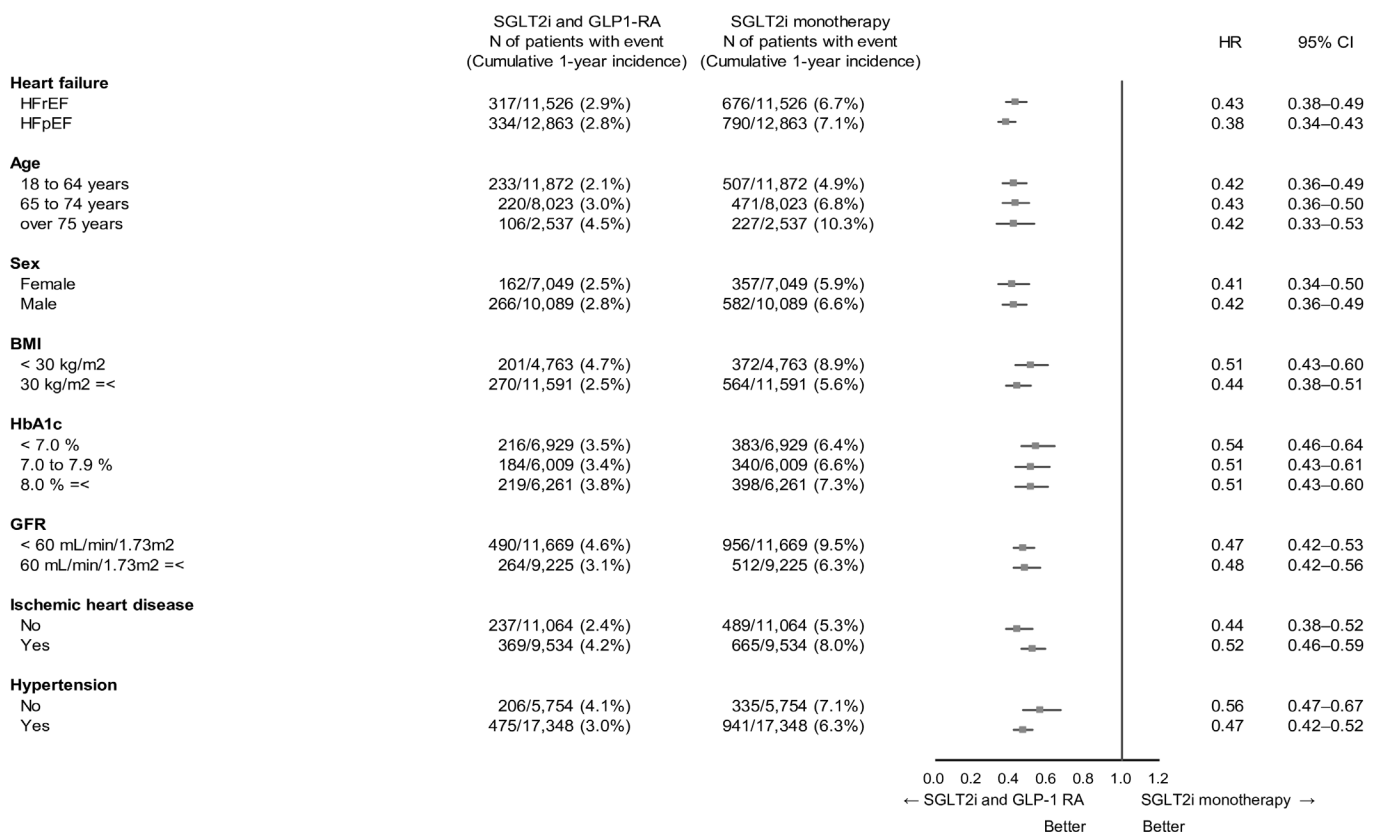


Figure 3 Subgroup analyses for all-cause death: SGLT2i and GLP-1 RA versus SGLT2i monotherapy. BMI, body mass index; GFR, glomerular filtration rate; GLP-1 RA, glucagon-like peptide-1 receptor agonists; HbA1c, hemoglobin A1c; HFpEF, heart failure with preserved left ventricular ejection fraction; HFrEF, heart failure with reduced left ventricular ejection fraction; SGLT2i, sodium-glucose cotransporter 2 inhibitors.

or without T2D.^{9–12} Several mechanisms have been proposed for the cardioprotective effect of SGLT2i; diuretic effects, blood pressure reduction, improved glycemic control, improvement of myocardial energy metabolism, anti-inflammatory effects, and renal protection.^{8 28–31} SGLT2i increases diuretic volume through osmotic effects by increasing glycosuria and natriuretic effects,³² as confirmed in clinical trials.^{9–11} Clinical trials have also confirmed that SGLT2i have a renal protective effect compared with placebo.^{33 34} GLP-1 RA has a beneficial effect on patients with T2D and cardiovascular risk.^{14 15} The proposed mechanisms underlying the effects of GLP-1 RA in T2D include improved glycemic control, weight loss,³⁵ blood pressure reduction,¹⁵ anti-inflammatory effects,³⁶ and direct protection of the heart.³⁷ In addition, other effects of GLP-1 RA have been observed, including lowering of LDL cholesterol and greater weight loss than for SGLT2i.^{9 10 38 39} However, the cardioprotective mechanisms of SGLT2i and GLP-1 RA may differ. Further research into these mechanistic differences is needed to explain the observed reduction in all-cause death with combination therapy using SGLT2i and GLP-1 RA, as demonstrated in this study.

HF classification based on LVEF

Since SGLT2i have demonstrated good cardioprotective effects in all categories of LVEF,^{9–11 40} SGLT2i are a class 1 recommendation for patients with HFrEF or HFpEF.^{1–3 41} However, the effectiveness of GLP-1 RA in HFrEF and HFpEF remains controversial. Exenatide, a GLP-1 RA, increased HF hospitalizations in patients with HFrEF, and there was an interaction with other LVEF subgroups.^{42 43} A meta-analysis of two clinical trials of liraglutide, the LIVE and FIGHT trials, showed that liraglutide did not improve cardiovascular outcomes in patients with HFrEF compared with placebo.^{44–46} A recent observational study has shown that GLP-1 RAs are associated with a reduction in all-cause death and hospitalization at 1-year compared with DPP-4 inhibitors in patients with HFrEF and T2D,²⁵ consistent with our present study. Although the effectiveness of GLP-1 RA in HFrEF has not yet been determined, the favorable result of the combination therapy with SGLT2i and GLP-1 RA in our study is hypothesis-generating and needed to be confirmed by the clinical trials.

Evidence for GLP-1 RA in HFpEF is accumulating, particularly in patients with obesity.¹⁸ The STEP-HFpEF and STEP-HFpEF DM trials, which enrolled patients with a BMI of at least 30 kg/m² and an LVEF of at least 45%, with or without T2D, demonstrated that semaglutide significantly improved the Kansas City Cardiomyopathy Questionnaire clinical summary score compared with placebo.^{16 17} The SELECT trial, which included overweight or obese adults aged 45 years or older with a history of cardiovascular disease and no history of diabetes, found a reduction of approximately 20% in composite endpoints, including worsening HF and all-cause mortality.⁴⁷ However, at the time of these clinical

trials, the proportion of patients receiving concomitant SGLT2 inhibitors was low; in the pooled analysis of the STEP-HFpEF and STEP-HFpEF-DM trials, only 20% of patients were receiving SGLT2 inhibitors.¹⁸ Moreover, subgroup analyses stratified by SGLT2 inhibitor use were not conducted. In contrast, SGLT2i is now recognized as standard therapy in contemporary HF guidelines.^{1–3} Accordingly, our study—which evaluated the incremental benefit of GLP-1 RAs added to SGLT2i in patients with HFpEF, a population in which these agents have shown efficacy—provides important real-world evidence despite its observational design.

Limitations

The present study has several limitations. First, this study collected information from electronic healthcare records, and the diagnoses were based on ICD-10 codes. Thus, it is not a definitional diagnosis, such as using the modified Framingham criteria to diagnose HF. Alternatively, a diagnosis of diabetes can be made in order to administer certain HF medications, such as SGLT2i, to a patient. Second, this study did not assess cause-specific outcomes such as cardiovascular death or hospitalization for HF, which are clinically important for addressing the research question. The TriNetX platform does not provide information on the cause of death or hospitalization; therefore, we selected all-cause death as the primary outcome and all-cause hospitalization as the secondary outcome. Third, each factor, collected as a confounding factor and presented in patient characteristics, was data from 1 month before the index day-to-day 0. Because of the difference of up to 1 month, the data may not reflect the patient's condition on the index day. Fourth, the TriNetX platform did not provide access to information on socioeconomic status, insurance coverage, lifestyle factors, or medication adherence. We acknowledge that these factors can influence patient outcomes; however, they are often difficult to extract from EHRs. Fifth, there are limitations in the handling of patient censoring in survival analysis. In this study, patients were censored the day after their last recorded clinical event within the analysis time window, at which point they no longer contributed meaningful information to the analysis. We acknowledge the difficulty in determining subsequent clinical outcomes for patients who initially received care at TriNetX-affiliated facilities but later transitioned to non-participating institutions. Although the prevalence of such patients within the cohort is an important consideration, accurately identifying these cases remains challenging. Sixth, this study did not include information on medication dosage or adherence. These factors are particularly relevant for GLP-1 receptor agonists. For example, semaglutide has demonstrated dose-dependent effects on glycemic control and weight loss.¹⁵ Additionally, differences in drug formulation may influence patient adherence.^{48 49} Finally, there was a limitation regarding the PS matching used in the outcome analysis. Although we included as many confounders as

possible in PS matching, we did not adjust for unknown or unmeasured confounders. To enhance the robustness of our findings, we assessed the potential impact of unmeasured confounding by calculating the E value. For the significant association between combination therapy with SGLT2i and GLP-1 RA versus SGLT2i monotherapy in relation to all-cause death, the E value for the lower limit of the CI of the HR was 3.60. For the significant association between hospitalization risk and combination therapy versus SGLT2i monotherapy, the corresponding E value was 1.36. If unmeasured confounders with effect sizes exceeding these E values were present, the observed associations could be rendered non-significant. Therefore, the results of this study must be confirmed in clinical trials or observational studies designed to thoroughly exclude bias.

CONCLUSION

In this multicenter, retrospective, observational study, the risk of all-cause death and hospitalization in patients who received combination therapy with SGLT2i and GLP-1 RA relative to those who received SGLT2i monotherapy was significantly lower in patients with HF and T2D. Additional prospective observational studies and randomized controlled trials are required to validate these findings.

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Data availability statement Data are available upon reasonable request. Researchers can request access to data from the TriNetX research network using the TriNetX platform (<https://live.trinetx.com>). However, this may involve associated costs and require a data-sharing agreement, and no patient-identifiable information is available.

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