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SGLT2 Inhibitor Use and Risk of Clinical Events in Patients With Cancer Therapy–Related Cardiac Dysfunction

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ABSTRACT

BACKGROUND Certain antineoplastic therapies are associated with an increased risk of cardiomyopathy and heart failure (HF). Sodium glucose co-transporter 2 (SGLT2) inhibitors improve outcomes in patients with HF.

OBJECTIVES This study aims to examine the efficacy of SGLT2 inhibitors in patients with cancer therapy–related cardiac dysfunction (CTRCD) or HF.

METHODS The authors conducted a retrospective cohort analysis of deidentified, aggregate patient data from the TriNetX research network. Patients aged ≥18 years with a history of type 2 diabetes mellitus, cancer, and exposure to potentially cardiotoxic antineoplastic therapies, with a subsequent diagnosis of cardiomyopathy or HF between January 1, 2013, and April 30, 2020, were identified. Patients with ischemic heart disease were excluded. Patients receiving guideline-directed medical therapy were divided into 2 groups based on SGLT2 inhibitor use. After propensity score matching, odds ratios (ORs) and Cox proportional HRs were used to compare outcomes over a 2-year follow-up period.

RESULTS The study cohort included 1,280 patients with CTRCD/HF (n = 640 per group; mean age: 67.6 years; 41.6% female; 68% White). Patients on SGLT2 inhibitors in addition to conventional guideline-directed medical therapy had a lower risk of acute HF exacerbation (OR: 0.483 [95% CI: 0.36-0.65]; $P < 0.001$) and all-cause mortality (OR: 0.296 [95% CI: 0.22-0.40]; $P = 0.001$). All-cause hospitalizations or emergency department visits (OR: 0.479; 95% CI: 0.383-0.599; $P < 0.001$), atrial fibrillation/flutter (OR: 0.397 [95% CI: 0.213-0.737]; $P = 0.003$), acute kidney injury (OR: 0.486 [95% CI: 0.382-0.619]; $P < 0.001$), and need for renal replacement therapy (OR: 0.398 [95% CI: 0.189-0.839]; $P = 0.012$) were also less frequent in patients on SGLT2 inhibitors.

CONCLUSIONS SGLT2 inhibitor use is associated with improved outcomes in patients with CTRCD/HF.
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ABBREVIATIONS AND ACRONYMS

CTRCD = cancer therapy-related cardiac dysfunction

CV = cardiovascular

ED = emergency department

GDMT = guideline-directed medical therapy

HF = heart failure

LV = left ventricular

LVEF = left ventricular ejection fraction

PSM = propensity score matching

SGLT2 = sodium glucose co-transporter 2

T2DM = type 2 diabetes mellitus

Sodium glucose co-transporter 2 (SGLT2) inhibitors have been shown to be beneficial in patients with heart failure (HF), independent of diabetes status and left ventricular ejection fraction (LVEF).[1] DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) and EMPEROR-Reduced (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction) demonstrated that SGLT2 inhibitors reduce the risk of cardiovascular (CV) death or hospitalization for heart failure in patients with heart failure with reduced ejection fraction (HFrEF).[2,3] Subsequently, data from EMPEROR-Preserved (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction) and DELIVER (Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure) have suggested that SGLT2 inhibitors are also beneficial in patients with heart failure with preserved ejection fraction (HFpEF).[4,5] As a result, the updated 2022 American College of Cardiology, American Heart Association, and Heart Failure Society of America clinical practice guidelines and the 2021 European Society of Cardiology recommend the use of SGLT2 inhibitors as part of guideline-directed medical therapy (GDMT) for HFrEF, heart failure with midrange ejection fraction (HFmrEF), and HFpEF.[6,7] In addition, SGLT2 inhibitors have also been shown to have significant renal protective effects, which may contribute to their efficacy in patients with HF.[8]

HF is a significant and common cardiotoxicity among patients receiving certain antineoplastic therapies.[9,10] For example, low-dose anthracyclines have been associated with a 2% to 4% incidence of clinical HF decompensation, 9% to 11% subclinical change identified on cardiac imaging, and 30% to 35% for cardiac injury defined as biomarker increase.[11] Although SGLT2 inhibitors have demonstrated efficacy in the treatment of patients with ischemic and nonischemic cardiomyopathy and HF, patients with cancer are usually excluded from pivotal clinical trials. Hence, the efficacy of SGLT2 inhibitors remains understudied in patients with cancer therapy-related cardiac dysfunction (CTRCD)/HF.

Recent animal and in vitro studies have shown the cardioprotective effects of SGLT2 inhibitors in the setting of cancer therapy-induced cardiotoxicity. For example, dapagliflozin significantly increased cardiomyocyte viability in a study of HL-1 adult cardiomyocytes exposed to subclinical concentrations of doxorubicin and trastuzumab.[12] In a nondiabetic mouse model, empagliflozin increased systolic and diastolic LV function and decreased myocardial fibrosis by 50% in mice with doxorubicin cardiotoxicity.[13] Empagliflozin was also shown to ameliorate sunitinib-induced cardiac dysfunction by reducing systolic blood pressure and improving LVEF via regulation of adenosine 5′-monophosphate-activated protein kinase-mammalian target of rapamycin (AMPK-mTOR) signaling-mediated autophagy.[14,15] However, whether the benefits observed in animal and in vitro studies are seen in clinical practice remains unclear.

This retrospective cohort study aimed to examine the efficacy of SGLT2 inhibitors in patients with CTRCD/HF.

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METHODS

STUDY OVERSIGHT. Data were analyzed and interpreted by the authors. All authors reviewed the manuscript and affirmed the accuracy and completeness of the data. Institutional Review Board approval was exempted by the Lahey Clinic Institutional Review Board, given that aggregate deidentified data were used from a research network database. These study findings are reported per the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline for cohort studies.

DATA SOURCE. The data analyzed in this study were obtained from the TriNetX research network, which contains data from the electronic health records of approximately 90 million patients from 72 health care organizations, primarily in the United States. This platform only has aggregate, deidentified data per the deidentification standard defined in section §164.514(a) of the Health Insurance Portability and Accountability Act Privacy Rule.

STUDY POPULATION AND DESIGN. Patients aged ≥18 years with type 2 diabetes mellitus (T2DM) with a history of cancer and exposure to potentially cardiotoxic antineoplastic therapies and with a

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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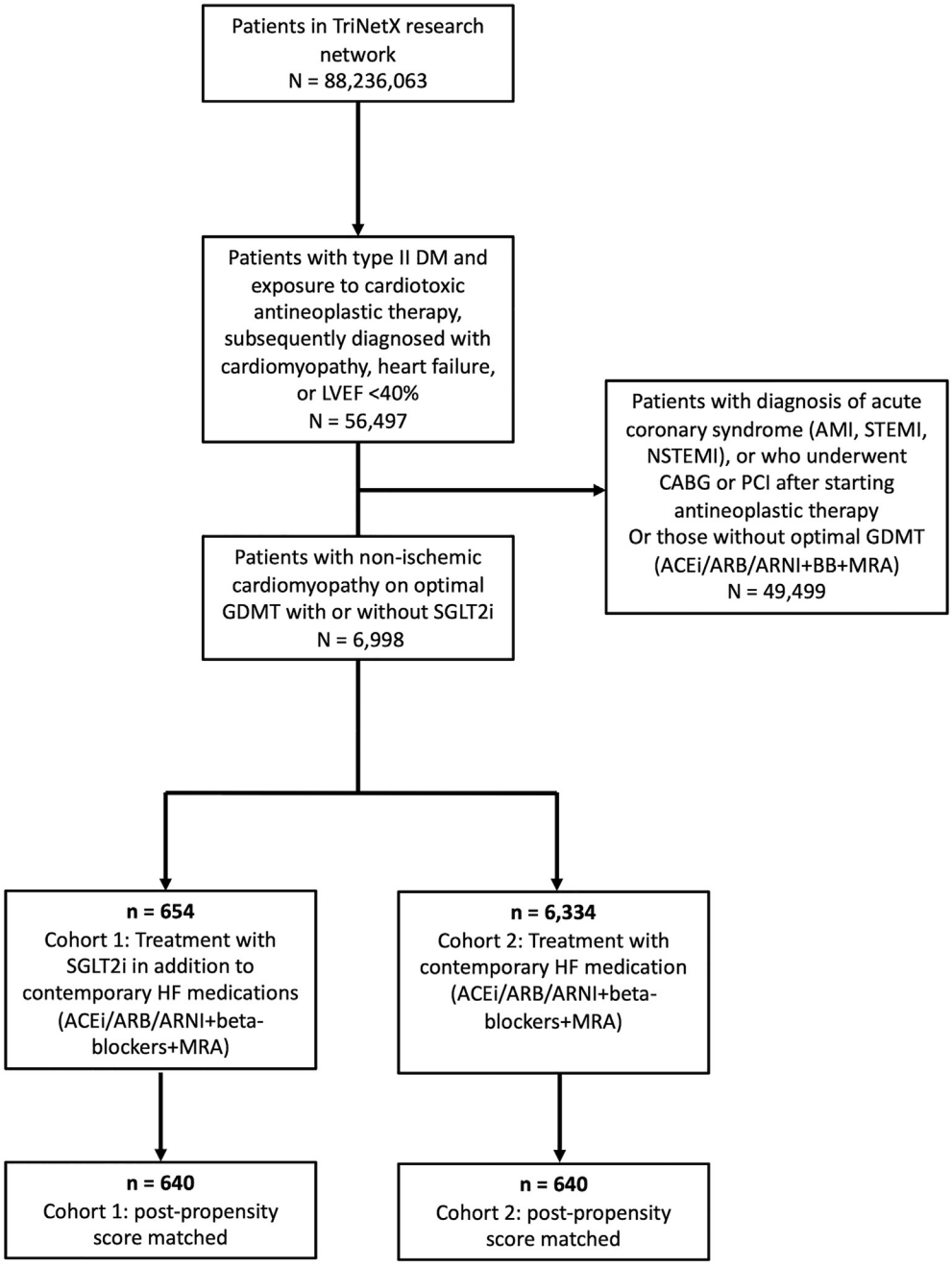
FIGURE 1 Study Consort Diagram



Consort diagram depicting inclusion and exclusion criteria. ACEi = angiotensin-converting enzyme inhibitor; AMI = acute myocardial infarction; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; BB = beta-blocker; CABG = coronary artery bypass graft; DM = diabetes mellitus; GDMT = guideline-directed medical therapy; HF = heart failure; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; NSTEMI = non-ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; SGLT2i = sodium glucose co-transporter 2 inhibitor; STEMI = ST-segment elevation myocardial infarction.

TABLE 1 Baseline Characteristics of the Study Cohort Before and After Propensity Score Matching Based on SGLT2 Inhibitor Treatment

	Before Propensity Score Matching			After Propensity Score Matching		
	SGLT2 Inhibitor			SGLT2 Inhibitor		
	Yes (n = 654)	No (n = 6,334)	Standardized Mean Difference	Yes (n = 640)	No (n = 640)	Standardized Mean Difference
Demographics						
Age, y	67.5 ± 10.8	68.9 ± 13.0	0.116	67.6 ± 10.8	67.6 ± 11.6	0.006
Female	271 (41.4)	2,966 (46.8)	0.109	266 (41.6)	266 (41.6)	0
White	448 (68.5)	4,469 (70.6)	0.045	438 (68.4)	432 (67.5)	0.020
Hispanic	57 (8.7)	320 (5.1)	0.145	57 (8.9)	67 (10.5)	0.053
Comorbidities						
Hypertension	625 (95.6)	5,709 (90.1)	0.212	611 (95.5)	604 (94.4)	0.050
Hyperlipidemia	570 (87.2)	4,536 (71.6)	0.391	556 (86.9)	552 (86.3)	0.018
Atrial fibrillation/flutter	304 (46.5)	2,948 (46.5)	0.001	299 (46.7)	284 (44.4)	0.047
Chronic kidney disease	359 (54.9)	2,861 (45.2)	0.195	346 (54.1)	317 (49.5)	0.091
Medications						
Antiarrhythmics	579 (88.5)	5,252 (82.9)	0.161	565 (88.3)	567 (88.6)	0.010
Antilipemic agents	574 (87.8)	4,612 (72.8)	0.383	560 (87.5)	551 (86.1)	0.042
Insulin	465 (71.1)	2,936 (46.4)	0.519	451 (70.5)	459 (71.7)	0.028
Exenatide	53 (8.1)	56 (0.9)	0.354	41 (6.6)	41 (6.4)	0.006
Metformin	384 (58.7)	1,526 (23.9)	0.755	370 (57.8)	370 (57.8)	<0.001
Glipizide	148 (22.6)	592 (9.3)	0.369	140 (21.9)	153 (23.9)	0.048
Type of malignancy						
Breast	100 (15.3)	1,027 (16.2)	0.025	96 (15)	103 (16.1)	0.30
Lymphomas	164 (24.3)	1,729 (27.3)	0.055	158 (24.7)	156 (24.4)	0.004
Myelodysplastic syndromes	256 (39.1)	2,351 (37.1)	0.042	254 (39.7)	220 (34.4)	0.110
Genitourinary	40 (6.1)	498 (7.9)	0.069	40 (6.3)	35 (5.5)	0.033
Gastrointestinal	117 (17.9)	1,365 (21.6)	0.092	114 (17.8)	139 (21.7)	0.098
Gynecologic	23 (3.5)	210 (3.3)	0.011	21 (3.3)	20 (3.1)	0.009
Respiratory and intrathoracic organs	35 (5.4)	364 (5.7)	0.017	35 (5.5)	31 (4.8)	0.028
Mesothelial and soft tissue	13 (2.0)	217 (3.4)	0.089	13 (2.0)	15 (2.3)	0.021
Neoplasms of unspecified behavior	139 (21.3)	1,249 (19.7)	0.038	138 (21.6)	141 (22.0)	0.011
Metastatic malignancy	197 (30.1)	2,228 (35.2)	0.108	192 (30)	190 (29.7)	0.007

Continued on the next page

subsequent diagnosis of cardiomyopathy or HF between January 1, 2013, and April 30, 2020, were identified. Patients on antineoplastic therapies consisting of either anthracyclines, alkylating agents, antimetabolites, monoclonal antibodies, small-molecule tyrosine kinase inhibitors, or proteasome inhibitors were included (Supplemental Table 1). These medications were selected based on prior studies demonstrating their potential for cardiotoxicity.[16] Patients with a diagnosis of an acute coronary syndrome (acute myocardial infarction, ST-segment elevation myocardial infarction, or non-ST-segment elevation myocardial infarction), coronary artery bypass graft, or percutaneous coronary intervention after starting antineoplastic therapy were excluded. Identification of a history of cancer was made using International Classification of Diseases-9th Revision (ICD-9) and International Classification of Diseases-10th Revision (ICD-10) codes (Supplemental Methods). HF was defined as an ICD-10 code of either HF or cardiomyopathy or an LVEF of ≤40%. Patients were further divided into 2 groups based on whether they were prescribed SGLT2 inhibitors (dapagliflozin, empagliflozin, or canagliflozin) or not. The non-SGLT2 inhibitor group was defined as those who received contemporary HF medications, one from each class of: 1) angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or angiotensin receptor-neprilysin inhibitors; 2) beta-blockers; and 3) mineralocorticoid receptor antagonists. The SGLT2 inhibitor group was defined as those who received SGLT2 inhibitors in addition to other contemporary HF medications. Propensity score matching (PSM) was performed to reduce bias caused by unequal distribution of baseline characteristics, treatment effect bias, and confounding.

STUDY ENDPOINTS. Primary and secondary outcomes were analyzed over a 2-year follow-up period. The primary outcomes of interest included HF exacerbations (defined by ICD-10 codes or the need for intravenous loop diuretics) and all-cause mortality.

TABLE 1 Continued

	Before Propensity Score Matching			After Propensity Score Matching		
	SGLT2 Inhibitor			SGLT2 Inhibitor		
	Yes (n = 654)	No (n = 6,334)	Standardized Mean Difference	Yes (n = 640)	No (n = 640)	Standardized Mean Difference
Antineoplastic therapy						
Alkylating agents						
Ifosfamide	10 (1.5)	35 (0.6)	0.096	10 (1.6)	10 (1.6)	<0.001
Cyclophosphamide	142 (21.7)	1,470 (23.2)	0.036	135 (21.2)	143 (22.3)	0.030
Mitomycin	28 (4.3)	333 (5.3)	0.046	27 (4.2)	21 (3.3)	0.049
Carboplatin	20 (3.1)	273 (4.3)	0.066	20 (3.1)	13 (2.0)	0.069
Cisplatin	13 (2.0)	144 (2.3)	0.020	13 (2.0)	12 (1.9)	0.011
Anthracenediones						
Mitoxantrone	10 (1.5)	35 (0.6)	0.096	10 (1.6)	10 (1.6)	<0.001
Anthracyclines						
Idarubicin	10 (1.5)	74 (1.2)	0.031	10 (1.6)	10 (1.6)	<0.001
Doxorubicin	98 (15.0)	915 (14.4)	0.015	92 (14.4)	103 (16.1)	0.048
Doxorubicin liposomal	10 (1.5)	56 (0.9)	0.059	10 (1.6)	10 (1.6)	<0.001
Daunorubicin	10 (1.5)	93 (1.5)	0.005	10 (1.6)	10 (1.6)	<0.001
Antimetabolites						
Fluorouracil	231 (35.3)	2,129 (33.6)	0.036	227 (35.5)	225 (35.2)	0.007
Capecitabine	36 (5.5)	200 (6.3)	0.034	36 (5.6)	28 (4.4)	0.057
Aromatase inhibitor						
Anastrozole	46 (7.0)	292 (4.6)	0.104	44 (6.9)	48 (7.5)	0.024
Monoclonal antibodies						
Pertuzumab	12 (1.8)	126 (2.0)	0.011	11 (1.7)	12 (1.9)	0.012
Trastuzumab	20 (3.1)	297 (4.7)	0.085	19 (3.0)	18 (2.8)	0.009
Bevacizumab	134 (20.5)	782 (12.3)	0.221	131 (20.5)	136 (21.3)	0.019
Rituximab	51 (7.8)	475 (7.5)	0.011	48 (7.5)	54 (8.4)	0.035
Alemtuzumab	10 (1.5)	22 (0.3)	0.123	10 (1.6)	10 (1.6)	<0.001
Proteosome inhibitors						
Carfilzomib	10 (1.5)	97 (1.5)	<0.001	10 (1.6)	10 (1.6)	<0.001
Bortezomib	34 (5.2)	508 (8.0)	0.114	34 (5.3)	31 (4.8)	0.021
Small-molecule TKIs						
Cabozantinib	10 (1.5)	39 (0.6)	0.089	10 (1.6)	10 (1.6)	<0.001
Nilotinib	10 (1.5)	56 (0.9)	0.059	10 (1.6)	11 (1.7)	0.012
Sorafenib	10 (1.5)	130 (2.1)	0.039	10 (1.6)	10 (1.6)	<0.001
Imatinib	24 (3.7)	162 (2.6)	0.064	23 (3.6)	20 (3.1)	0.026
Osimertinib	10 (1.5)	26 (0.4)	0.114	10 (1.6)	10 (1.6)	<0.001
Ibrutinib	15 (2.3)	187 (3.0)	0.041	15 (2.3)	16 (2.5)	0.010
Trametinib	10 (1.5)	52 (0.8)	0.066	10 (1.6)	10 (1.6)	<0.001
Pazopanib	10 (1.5)	85 (1.3)	0.016	10 (1.6)	10 (1.6)	<0.001
Ponatinib	10 (1.5)	22 (0.3)	0.123	10 (1.6)	10 (1.6)	<0.001
Lapatinib	10 (1.5)	25 (0.4)	0.116	10 (1.6)	10 (1.6)	<0.001
Radiation therapy	77 (11.8)	523 (8.3)	0.117	72 (11.3)	74 (11.6)	0.010
Laboratory data						
Creatinine, mg/dL	1.4 ± 3.7	1.4 ± 1.9	0.009	1.4 ± 3.7	1.4 ± 1.6	0.012
BMI, kg/m^2	32.9 ± 7.6	30.1 ± 7.1	0.385	32.7 ± 7.5	32.0 ± 7.5	0.099
LVEF ≤ 40%	144 (22.0)	758 (12.0)	0.270	138 (21.6)	127 (19.8)	0.042
HbA_{1c} ≥7%	244 (37.3)	950 (15)	0.525	226 (35.3)	229 (35.8)	0.011
Health care use in the prior year						
Hospitalization	225 (34.4)	2,732 (43)	0.176	224 (35)	219 (34.3)	0.013
Emergency department visit	278 (42.5)	2,869 (45.3)	0.058	271 (42.3)	263 (41.1)	0.023

Values are mean ± SD or n (%).

BMI = body mass index; HbA_{1c} = glycosylated hemoglobin; LVEF = left ventricular ejection fraction; SGLT2 = sodium glucose co-transporter 2; TKI = tyrosine kinase inhibitor.

Other secondary outcomes included all-cause hospitalizations or emergency department (ED) visits, atrial fibrillation and flutter, acute kidney injury, and the need for renal replacement therapy. In addition, gastrointestinal bleeding was used as a falsification outcome.

STATISTICAL ANALYSIS. The patient population was divided into 2 groups according to their use of SGLT2 inhibitors. Continuous variables are represented as mean ± SD and were compared between the groups using independent-samples Student's *t*-tests. Categorical variables are reported as count (percentage) and were compared between the groups using the chi-square test. Covariates were matched extensively by 1:1 PSM using the greedy nearest-neighbor algorithm with a caliper of 0.1 pooled standardized mean difference (SMD). The standardized mean difference is a quantitative method used to represent the difference between the means of 2 groups in terms of SD units to assess the balance in measured variables in the sample weighted by the inverse probability of treatment. Any characteristic with a between cohorts lower than 0.1 was considered well matched. The measures of association included risk differences, risk ratios, and odds ratios (ORs) on the matched population for primary and secondary outcomes. Survival analyses were performed for each outcome by plotting Kaplan-Meier curves with log-rank tests; additionally, Cox proportional hazard models were used to calculate the HR to compare the 2 groups. Death was treated as a censoring event. Statistical significance was set at a 2-sided value of $P < 0.05$. *E* values were calculated for the primary and secondary outcomes to address the unmeasured confounders. Statistical analyses were completed using the TriNetX online platform using R for statistical computing.

RESULTS

STUDY POPULATION. We identified a total of 6,988 patients who had developed cardiomyopathy or HF after receiving antineoplastic therapy for cancer; 654 patients were on SGLT2 inhibitors, and 6,334 patients were not on SGLT2 inhibitors (Figure 1). After PSM, 640 matched patients remained in each cohort and were included in this analysis (Figure 1).

PATIENT CHARACTERISTICS. Baseline patient characteristics are summarized in Table 1. In the unmatched cohort, patients treated with SGLT2 inhibitors were more likely to be male (58.6 vs 53.2%; $P < 0.05$) and Hispanic (8.77 vs 5.1%; $P < 0.05$) compared to those not on SGLT2 inhibitors. Furthermore, patients on SGLT2 inhibitors had a higher prevalence of hypertension, diabetes mellitus, chronic kidney disease, and ischemic heart disease. However, after PSM, the baseline characteristics of the 2 groups were similar. Additionally, we balanced the population based on health care use, ie, all-cause hospitalization and ED visits in the prior year of the index event of HF/cardiomyopathy. We found no residual imbalance (standard difference: <0.1 for all covariates) (Figure 2).

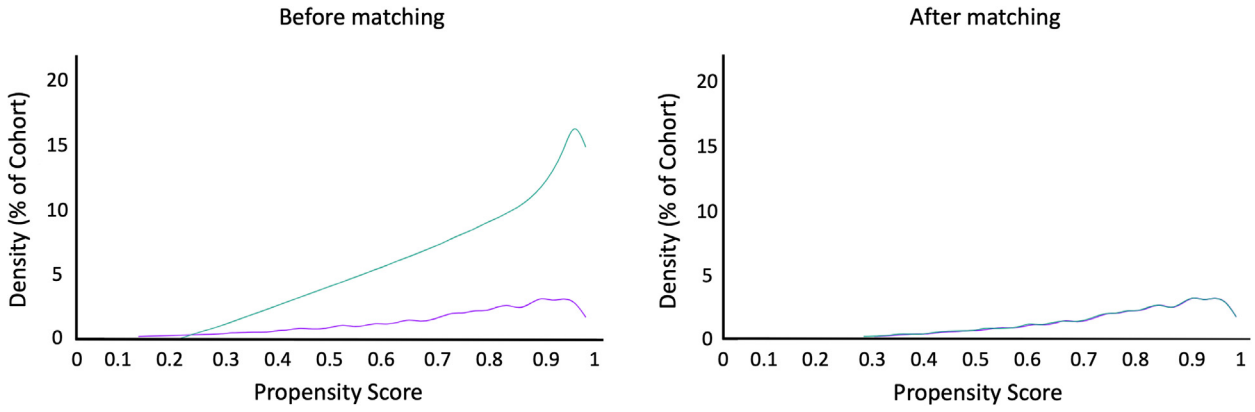
Hematologic cancer was most common, followed by the gastrointestinal system and breast cancer. Of the total, 30% of patients had metastatic disease. Fluorouracil was the most commonly used antineoplastic therapy, followed by bevacizumab and cyclophosphamide. Anthracyclines were used in ~19% of patients. Radiation therapy was given to 11% of patients. Many patients may have received combination therapies. The timeline of cancer diagnosis to cardiomyopathy or HF development and the cancer status are poorly understood.

MAIN OUTCOMES. A total of 85 patients in the SGLT2 inhibitor group experienced an HF exacerbation compared to 154 patients in the non-SGLT2 inhibitor group (OR: 0.483 [95% CI: 0.361-0.647]; $P = 0.001$) (Table 2, Figure 2). In addition, there were 73 deaths in the SGLT2 inhibitor group compared to 194 deaths in the non-SGLT2 inhibitor group (OR: 0.296 [95% CI: 0.220-0.398]; $P < 0.001$) (Table 2). The time-to-event analysis also demonstrated the benefits of SGLT2 inhibitor therapy in patients with CTRCD (Table 3, Figure 3).

SECONDARY OUTCOMES. The secondary outcomes of all-cause hospitalizations or ED visits (OR: 0.479 [95% CI: 0.383-0.599]; $P < 0.001$), atrial fibrillation and flutter (OR: 0.397 [95% CI: 0.213-0.737]; $P = 0.003$), acute kidney injury (OR: 0.486 [95% CI: 0.382-0.619]; $P < 0.001$), and renal replacement therapy (OR: 0.398 [95% CI: 0.189-0.839]; $P = 0.012$) all occurred less frequently among patients on SGLT2 inhibitors (Table 2). There was also a decreased instantaneous risk of adverse outcomes based on time-to-event survival analysis (Table 3). Additionally, for safety outcomes, urinary tract infections were less frequent among patients on SGLT2 inhibitors (OR: 0.517 [95% CI: 0.368-0.727]; $P < 0.001$), and the frequency of lower extremity amputations was similar in both groups (OR: 1.000 [95% CI: 0.413-2.419]; $P > 0.999$) (Table 4).

FALSIFICATION OUTCOME AND SENSITIVITY ANALYSIS. The incidence of gastrointestinal bleeding in patients with and without SGLT2 inhibitors is 8 and 12, respectively (OR: 0.527 [95% CI: 0.22-1.253]; $P = 0.15$). Furthermore, sensitivity analysis using the

FIGURE 2 Propensity Score Matching



This figure demonstrates the cohorts before and after propensity matching.

measurement of the *E* value for primary and secondary outcomes (Tables 2 to 4) ruled out significant confounding.

DISCUSSION

Our study demonstrates that in patients with T2DM and CTRCD, the use of SGLT2 inhibitors, in addition to other contemporary GDMT, reduced HF exacerbations and all-cause mortality during a 2-year follow-up period (Central Illustration). Supported by the recent guidelines recommending SGLT2 inhibitors as GDMT for HF, this study demonstrates that SGLT2 inhibitors should be considered for patients with CTRCD.[6] This study also demonstrates that all-cause hospitalizations or ED visits, atrial fibrillation and flutter, acute kidney injury, and the need for renal replacement therapy occurred less frequently among patients with CTRCD treated with SGLT2 inhibitors.

The results of the present study built upon a recent smaller study evaluating CV events in patients with diabetes and cancer who were on an SGLT2 inhibitor (n = 32) while receiving anthracyclines compared to control individuals (n = 96).[15] Gongora et al[15] found that the incidence of CV events, including new cardiomyopathy, HF hospitalizations, and significant arrhythmias, was significantly reduced in patients treated with SGLT2 inhibitors compared to those who were not (3% vs 20%; $P = 0.025$). These 2 studies suggest that SGLT2 inhibitors may have a cardioprotective role in patients receiving potentially

TABLE 2 Comparison of Outcomes With and Without SGLT2 Inhibitors in Patients With Cancer Therapy-Related Cardiac Dysfunction/Heart Failure

	SGLT2 Inhibitor						
	Yes	No	Risk Difference (%)	OR (95% CI)	*P* Value	*E* Value for OR	*E* Value for Lower Bound of 95% CI of OR
Primary outcomes							
Acute heart failure exacerbation	85 (13.3)	154 (24.1)	−10.8	0.483 (0.361-0.647)	<0.001	3.56	4.98
All-cause mortality	73 (11.4)	194 (30.3)	−18.9	0.296 (0.220-0.398)	<0.001	6.21	8.56
Secondary outcomes							
All-cause hospitalizations or emergency department visits	279 (43.6)	395 (61.7)	−18.1	0.479 (0.383-0.599)	<0.001	2.25	2.61
Atrial fibrillation/flutter	15 (4.5)	37 (10.6)	−6.1	0.397 (0.213-0.737)	0.003	4.47	8.86
Acute kidney injury	152 (23.8)	250 (39.1)	−15.3	0.486 (0.382-0.619)	<0.001	2.22	2.62
Renal replacement therapy	10 (1.7)	24 (4.1)	−2.4	0.398 (0.189-0.839)	0.012	4.46	10.06
Falsification outcome							
Gastrointestinal bleeding	8 (1.3)	15 (2.4)	−1.1	0.5274 (0.222-1.253)	0.148	3.2	8.48

Values are n (%) unless otherwise indicated.
Abbreviation as in Table 1.

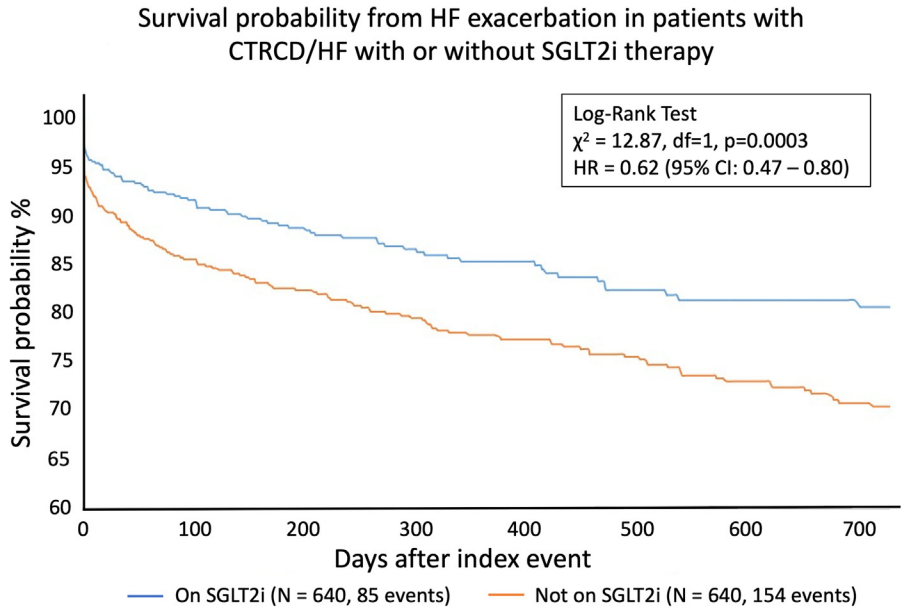
TABLE 3 Survival Analysis of Primary and Secondary Outcomes

	Log-Rank Test					
	Chi-Square	HR	95% CI	*P* Value	*E* Value for HR	*E* Value for Lower Bound of 95% CI of HR
Primary outcomes						
Acute heart failure exacerbation	12.878	0.618	(0.474-0.806)	<0.001	2.62	3.64
All-cause mortality	30.414	0.476	(0.363-0.623)	<0.001	3.62	4.95
Secondary outcomes						
All-cause hospitalizations or emergency department visits	17.703	0.720	(0.618-0.840)	<0.001	1.82	2.14
Atrial fibrillation and flutter	4.734	0.518	(0.284-0.947)	0.030	3.27	6.5
Acute kidney injury	17.156	0.654	(0.534-0.801)	<0.001	2.02	2.46
Renal replacement therapy	2.537	0.552	(0.263-1.159)	0.111	3.02	7.07
Falsification outcome						
Gastrointestinal bleeding	1.594	0.533	(0.225-1.267)	0.206	3.16	8.36

cardiotoxic therapies and may also improve outcomes in patients with established CTRCD and HF. Together, these results set the stage for larger randomized clinical trials to investigate the efficacy of SGLT2 inhibitors in patients treated with potentially cardiotoxic cancer therapies.

The reduction in atrial fibrillation and flutter after SGLT2 inhibitor use suggests that SGLT2 inhibitors may effectively reduce the burden of arrhythmias in this patient population. Clinically, this is important because arrhythmias may exacerbate HF symptoms and progression and are commonly seen in patients with CTRCD.[17-19] Furthermore, several studies have shown the efficacy of SGLT2 inhibitors in reducing the risk of cardiac arrhythmias. For example, in a meta-analysis of 34 randomized controlled trials in patients with T2DM or HF, SGLT2 inhibitor therapy was associated with a 0.81-fold reduction in the odds

FIGURE 3 Acute HF Exacerbations in Patients Treated With and Without SGLT2 Inhibitors



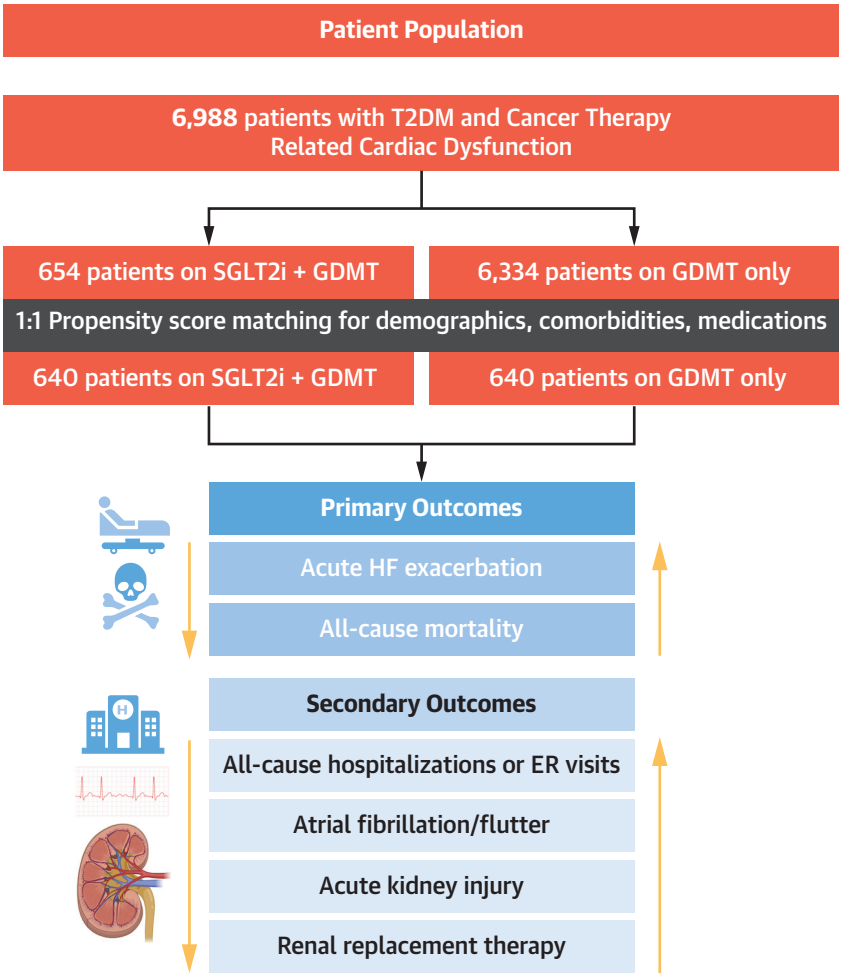
Kaplan-Meier survival curves were used to depict acute heart failure exacerbations in patients with CTRCD/HF treated with or without SGLT2 inhibitors. Log-rank tests were used to compare outcomes between the 2 groups over a 2-year follow-up. CTRCD = cancer therapy–related cardiac dysfunction; other abbreviations as in Figure 1.

TABLE 4 Comparison of Safety Outcomes With and Without SGLT2 Inhibitors in Patients With Cancer Therapy-Related Cardiac Dysfunction

Adverse Outcomes	Risk		Risk Difference, %	OR (95% CI)	*P* Value	*E* Value for OR	*E* Value for Lower Bound of 95% CI for OR
	On SGLT2i	Not on SGLT2i					
Urinary tract infection	59 (9.2)	105 (16.4)	-7.2	0.517 (0.368-0.727)	<0.001	3.28	4.88
Lower extremity amputation	10 (1.6)	10 (1.6)	0.0	1.000 (0.413-2.419)	>0.999	1.00	4.28

Values are n (%), unless otherwise indicated.
Abbreviation as in Table 1.

CENTRAL ILLUSTRATION Study Design and Key Results



Avula V, et al. J Am Coll Cardiol HF. 2024;12(1):67–78.

Diagram of the patient population and main findings. Propensity score matching was conducted to create 2 cohorts of patients with cancer therapy-related cardiac dysfunction based on SGLT2i use. Primary and secondary outcomes were demonstrated to be favorable in the cohort on SGLT2is using odds ratios and log-rank tests. ER = emergency room; GDMT = guideline-directed medical therapy; HF = heart failure; SGLT2i = sodium glucose co-transporter 2 inhibitor; T2DM = type 2 diabetes mellitus.

of incident atrial arrhythmias (95% CI: 0.69-0.95; $P = 0.008$).[20] Another meta-analysis reported similar results in patients with T2DM, HF, or chronic kidney disease; SGLT2 inhibitor therapy was associated with a lower risk of atrial fibrillation (relative risk [RR]: 0.93; 95% CI: 0.70-0.96) and ventricular tachycardia (RR: 0.73; 95% CI: 0.53-0.99).[21] The mechanisms of these effects are thought to be the cardioprotective mechanisms of SGLT2, such as increased natriuresis and metabolic and pleiotropic effects.[22]

The observed reduction in acute kidney injury and the need for renal replacement therapy suggests that SGLT2 inhibitors may have significant renal protective effects in this patient population. Renal dysfunction is often associated with antineoplastic therapy and may contribute to or be exacerbated by HF.[23] Previous studies have shown the benefit of SGLT2 inhibitors (dapagliflozin, empagliflozin, and canagliflozin) on renal function in patients with diabetes and increased CV risk.[24-26] In the EMPA-REG OUTCOME (Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients), empagliflozin improved renal outcomes, as defined by reduced risk of incident or worsening nephropathy, reduced progression to macroalbuminuria, reduced incidence of renal replacement therapies, and reduced occurrence of doubling of serum creatinine in patients with T2DM and an estimated glomerular filtration rate of 30 mL/min/1.73 m^2, when compared to placebo.[25] In the CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation) trial, canagliflozin reduced the primary composite renal outcome of doubling serum creatinine, end-stage kidney disease, renal death, or CV death by 30% in patients with T2DM and albuminuric chronic kidney disease.[26] Following this trial, regulations for canagliflozin were modified to include the use of this agent for renal protective therapy in appropriate patients.[27] The mechanisms behind the renal protective effects of SGLT2 inhibitors are likely multifactorial. They are postulated to include vasoconstriction of afferent arterioles via tubuloglomerular feedback, lowering of filtered albumin, renal transport work, and oxygen consumption, all of which help preserve the glomerular filtration rate and long-term kidney function.[8]

From a safety perspective, SGLT2 inhibitors have been associated with an increased risk of urinary tract infections, specifically fungal genital infections, and canagliflozin has been associated with an increased risk of lower extremity amputations.[28,29] These risks, particularly urinary tract infections, are expected to be higher in patients with cancer undergoing antineoplastic therapy.[30,31] However, this study shows that SGLT2 inhibitor use is safe in patients with CTRCD.[32,33]

Although evidence for SGLT2 inhibitor use in this specific patient population is still emerging, this study, combined with in vitro and animal and human data, prompts further research and consideration of SGLT2 inhibitor use for CTRCD.

STUDY LIMITATIONS. Data in this study were extracted from an aggregate electronic health record database (TriNetX) and, therefore, may not contain accurately reported health conditions and do not capture outcomes occurring outside this database. In addition, cardiotoxic drug exposures and their combinations were not well quantified, including dose/durations of treatments. The database did not allow for the extraction of dosage information, so we could not quantify how many patients in each group achieved the target dose of GDMT. However, these factors likely affect both cohorts equally. We selected patients based on a temporal association between exposure to potentially cardiotoxic antineoplastic therapies and the development of cardiomyopathy/HF, but we cannot accurately attribute causation to antineoplastic therapies in all cases. The timeline of cancer diagnosis to cardiomyopathy or HF development, the status of cancer, and the exact timing of SGLT2 inhibitor use after cardiomyopathy or HF development are not well understood in this database. However, we excluded any patients with acute coronary syndrome or revascularization after the cancer diagnosis, making it more likely that reported cardiomyopathy or HF is related to antineoplastic therapy.

Furthermore, all patients in our study had T2DM; hence, the role of SGLT2 inhibitors in patients with CTRCD without T2DM is not assessed. This study could not differentiate between the effects of the different types of SGLT2 inhibitors (dapagliflozin, empagliflozin, canagliflozin, and ertugliflozin) or between different durations and doses of SGLT2 inhibitor use.

Despite our best efforts, a significant limitation of this study is a potential selection bias attributable to unmeasured confounding factors despite robust propensity matching at baseline. However, to overcome this limitation, we determined baseline health care use in the form of all-cause hospitalizations and ED visits in the prior 12 months for better matching of the population. Additionally, we assessed a falsification outcome in the form of gastrointestinal bleeding, which was similar between both the cohorts, and performed the *E* value

calculation as a sensitivity analysis, a measure to check for robustness against bias from unmeasured confounding or omitted covariates in the observational studies for both primary and secondary outcomes. A high E value implies that a stronger unmeasured confounder would be needed to negate the covariate effect estimate and increase the likelihood of causality.

CONCLUSIONS

In summary, our data suggest that patients with CTRCD and HF treated with SGLT2 inhibitors in addition to other GDMTs, are associated with a lower rate of acute HF exacerbation, all-cause mortality, hospitalizations or ED visits, atrial fibrillation or flutter, acute kidney injury, and renal replacement therapy when compared with patients on contemporary GDMT except for SGLT2 inhibitors. However, larger prospective studies are needed to confirm these findings.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In patients with CTRCD or HF, treatment with SGLT2 inhibitors may reduce the risk of mortality, acute HF exacerbation, atrial arrhythmias, and adverse renal outcomes. SGLT2 inhibitors should be considered for managing CTRCD/HF in addition to traditional HF medications.

TRANSLATIONAL OUTLOOK: Further prospective studies are needed to evaluate the efficacy of SGLT2 inhibitors in managing CTRCD or HF.

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KEY WORDS antineoplastic therapy, cardiomyopathy, outcomes, SGLT2 inhibitors

APPENDIX For an expanded Methods section as well as a supplemental table, please see the online version of this paper.