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ORIGINAL RESEARCH

# SGLT2i and Primary Prevention of Cancer Therapy–Related Cardiac Dysfunction in Patients With Diabetes

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## ABSTRACT

**BACKGROUND** Specific cancer treatments can lead to cancer therapy–related cardiac dysfunction (CTRCD). Sodium glucose cotransporter-2 inhibitors (SGLT2is) can potentially prevent these cardiotoxic effects.

**OBJECTIVES** This study sought to determine whether SGLT2i use is associated with a lower incidence of CTRCD in patients with type 2 diabetes mellitus (T2DM) and cancer, exposed to potentially cardiotoxic antineoplastic agents, and without a prior documented history of cardiomyopathy or heart failure.

**METHODS** We conducted a retrospective analysis of patients aged ≥18 years within the TriNetX database with T2DM, cancer, exposure to cardiotoxic therapies, and no prior documented history of cardiomyopathy or heart failure. Patients were categorized by SGLT2i use. After propensity score matching, outcomes were compared over 12 months using Cox proportional HRs. Subgroup analyses focusing on different cancer therapy classes were performed.

**RESULTS** The study included 8,675 propensity-matched patients in each cohort (mean age = ∼65 years, 42% females, 71% White, ∼19% gastrointestinal malignancy, and ∼25% anthracyclines). Patients prescribed SGLT2is had a lower risk of developing CTRCD (HR: 0.76: 95% CI: 0.69-0.84). SGLT2is also reduced heart failure exacerbations (HR: 0.81; 95% CI: 0.72-0.90), all-cause mortality (HR: 0.67; 95% CI: 0.61-0.74), and all-cause hospitalizations/emergency department visits (HR: 0.93; 95% CI: 0.89-0.97). Subgroup analyses also demonstrated reduced CTRCD risk across various classes of cancer therapies in patients prescribed SGLT2is.

**CONCLUSIONS** SGLT2i administration was associated with a significantly decreased risk of developing CTRCD in patients with T2DM and cancer. (JACC CardioOncol. 2024;6:863-875) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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**ABBREVIATIONS AND ACRONYMS**

**CTRCD** = cancer therapy-related cardiac dysfunction

**ED** = emergency department

**EHR** = electronic health record

**GDMT** = guideline-directed medical therapy

**HF** = heart failure

**ICD-10** = International Classification of Diseases-10th Revision

**PSM** = propensity score matching

**SGLT2** = sodium glucose co-transporter 2

**SGLT2i** = sodium glucose co-transporter 2 inhibitor

**T2DM** = type 2 diabetes mellitus

**TKI** = tyrosine kinase inhibitor

Sodium glucose co-transporter 2 inhibitors (SGLT2is), initially developed for type 2 diabetes mellitus (T2DM), have proven effective in reducing heart failure (HF) hospitalization and cardiovascular death independent of T2DM status or degree of left ventricular dysfunction.[1,2] These benefits extend beyond glucose lowering, encompassing cardiac metabolism improvements, cardiac preload reduction, and attenuation of oxidative stress and inflammation.[3,4]

Asymptomatic cardiac dysfunction or symptomatic HF can develop secondary to various antineoplastic therapies, a constellation referred to as cancer therapy-related dysfunction (CTRCD).[5-11] The clinical implications of this entity can be substantial, including premature termination of cancer therapy and disease-related morbidity and mortality.[11-14] Interest has henceforth mounted to effectively target cancer cells while minimizing adverse effects on the cardiovascular system.[12] In keeping with this interest, "cardioprotective" effects have been reported for SGLT2is in patients with anthracycline-associated CTRCD,[15] including a reduction in HF hospitalizations and cardiac events.[4,16] Furthermore, there is evidence that SGLT2is may offer more significant benefits than other conventional 3-agent guideline-directed medical therapy (GDMT) in patients with CTRCD, leading to a lower rate of acute HF exacerbations and all-cause mortality.[17-20]

CTRCD can arise from various mechanisms depending on the specific agents involved. Anthracyclines, which have been shown to have a ~10% incidence of CTRCD,[21] predominantly induce cardiac damage by instigating the production of reactive oxygen species, disrupting mitochondrial function, and causing direct cardiomyocyte injury.[15] Conversely, targeted therapies interfere with signaling pathways necessary for cardioprotection, resulting in dysfunction.[20] Additionally, these therapies can induce electrolyte imbalances, predisposing individuals to arrhythmias.[16]

Given the established cardiovascular benefits of SGLT2is in HF and the shared pathways of cardiovascular dysfunction in T2DM and CTRCD, exploring the potential of SGLT2i use as a primary prevention strategy against CTRCD induced by cardiotoxic cancer therapies is important.[20,22] Leveraging an extensive electronic health record (EHR) database, this retrospective study aimed to examine the association of SGLT2i as a preventive measure against CTRCD in patients with T2DM undergoing potentially cardiotoxic cancer therapies, expanding our understanding of their association in cardioprotection beyond T2DM and HF. This study also aimed to examine a number of secondary outcomes including HF exacerbations, all-cause mortality, all-cause hospitalization or emergency department (ED) visit, new onset atrial fibrillation/flutter, new onset metastatic cancer, and need for further systemic anticancer therapy.

## METHODOLOGY

**DATA SOURCE.** We conducted a retrospective observational cohort study using the TriNetX research network database from January 1, 2013, to October 31, 2022. The TriNetX network offers access to EHRs of approximately 110 million patients from diverse U.S. health care institutions. This network provides aggregate, deidentified data per the deidentification standards defined in section §164.514(a) of the Health Insurance Portability and Accountability Act Privacy Rule. Because this study used deidentified aggregate data, it was determined to be

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

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exempt by the Institutional Review Board of Lahey Hospital and Medical Center.

**PATIENT POPULATION.** We identified adult patients (≥18 years old) with T2DM and cancer, exposed to potentially cardiotoxic antineoplastic medications, and without a prior documented history of cardiomyopathy or HF using International Classification of Diseases-10th Revision (ICD-10) codes. Patients were further categorized into 2 cohorts based on baseline (preantineoplastic therapy) exposure to SGLT2i (empagliflozin, dapagliflozin, or canagliflozin) use using RxNorm codes and EHR curated data. The study cohort included patients exposed to a variety of potentially cardiotoxic antineoplastic agents such as anthracyclines, alkylating agents, antimetabolites, monoclonal antibodies, tyrosine kinase inhibitors (TKIs), and proteasome inhibitors.[18] Various antineoplastic therapies with potential cardiotoxicity in our study were included based on the 2020 European Society of Medical Oncology consensus recommendations.[23] The Supplemental Appendix describes the Current Procedural Terminology and ICD-10 codes used for cohort identification and study window definitions. Additionally, subgroup analyses were conducted to assess the impact of baseline SGLT2i use on incident CTRCD based on the class of antineoplastic therapy received. Data analysis was performed on October 31, 2023. This study was reported per the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.

**STUDY ENDPOINTS.** The index date was the initiation of potentially cardiotoxic antineoplastic therapy. All outcomes were based on a 12-month follow-up period. A 12-month follow-up period was chosen to exclude patients outside of this window given that cardiomyopathy outside of 12 months may not be caused by exposure to cancer therapy.[21,24] The primary outcome of interest was incident CTRCD, defined using ICD-10 codes for new onset cardiomyopathy or HF or requiring intravenous loop diuretic agents at any time within 12 months from the index event after excluding ischemic heart disease as an etiology. To further validate CTRCD diagnosis, we analyzed rates of GDMT use, including angiotensin-converting enzyme inhibitors/angiotensin receptor blockers/angiotensin receptor neprilysin inhibitors, beta-blockers, or mineralocorticoid receptor antagonists. Notably, 93.6% of patients with CTRCD received at least 1 of these GDMT medications. Secondary endpoints included the following additional outcomes: HF exacerbations, all-cause mortality, all-cause hospitalization or ED visit, new onset atrial fibrillation/flutter, new onset metastatic cancer, and the need for further systemic antineoplastic therapy. The Supplemental Appendix elaborates on outcome definitions, with CTRCD further analyzed in the subgroup analyses mentioned previously (class of antineoplastic therapy).

**STATISTICAL ANALYSIS.** Continuous variables are presented as mean ± SD, whereas categoric variables are presented as number (%) as appropriate. Baseline characteristics were compared between SGLT2i users and nonusers using independent samples Student's *t*-tests for continuous variables and chi-square tests for categoric variables. To mitigate baseline differences between cohorts, 1:1 propensity score matching was conducted using greedy nearest neighbor matching with a caliper of 0.1 times the pooled SD of the linear propensity scores. The standardized mean difference represents the difference between the means of 2 groups in terms of SD units, assessing balance in measured variables in the sample weighted by the inverse probability of treatment. The variables were selected based on their potential impact on overall and cardiovascular outcomes.

Post-PSM, adjusted outcomes were compared between cohorts using HRs. Survival analysis was conducted using Kaplan-Meier curves and Cox proportional hazards models, with statistical significance set at $P$ value $<0.05$. Statistical analyses were executed using integrated R (The R Foundation) for statistical computing on the TriNetX platform.

Sensitivity analysis included calculating the E value to assess robustness against bias from unmeasured confounding or omitted covariates for primary and secondary outcomes. A high E value indicates a stronger unmeasured confounder would be required to nullify the observed association between the exposure and the outcome. Furthermore, falsification outcomes such as pneumonia and gastrointestinal bleeding were assessed.

## RESULTS

**STUDY POPULATION.** We identified a total of 95,203 patients with T2DM and cancer, exposed to potentially cardiotoxic antineoplastic agents, and without a prior documented history of cardiomyopathy or HF. Among these, 9,403 patients were on SGLT2is, and 85,800 patients were not on SGLT2is. After PSM, 8,675 patients in each cohort were included in this analysis.

**PATIENT CHARACTERISTICS.** The baseline characteristics of the study patients, before and after PSM, are shown in **Table 1**. In the unmatched cohort, patients on SGLT2is were less likely to be female (41.6% vs 46.0%; $P < 0.001$) and Hispanic (7.5% vs

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**TABLE 1 Baseline Characteristics of the Study Cohort Before and After Propensity Score Matching Based on SGLT2i Treatment**

| | Before Propensity Matching | | | After Propensity Matching | | |
|---|---|---|---|---|---|---|
| | SGLT2i Cohort (n = 9,403) | No SGLT2i Cohort (n = 85,800) | SMD | SGLT2i Cohort (n = 8,675) | No SGLT2i Cohort (n = 8,675) | SMD |
| Demographics | | | | | | |
| Mean age, y | 65.5 ± 10.5 | 65.0 ± 12.5 | 0.039 | 65.5 ± 10.5 | 65.7 ± 11.6 | 0.018 |
| Female | 3,910 (41.6) | 39,429 (46.0) | 0.088 | 3,602 (41.5) | 3,648 (42.1) | 0.011 |
| White | 6,638 (70.6) | 60,006 (69.9) | 0.014 | 6,133 (70.7) | 6,197 (71.4) | 0.016 |
| Black or African American | 1,089 (11.6) | 9,850 (11.5) | 0.003 | 983 (11.3) | 966 (11.1) | 0.006 |
| Hispanic or Latino | 708 (7.5) | 7,307 (8.5) | 0.036 | 665 (7.7) | 619 (7.1) | 0.020 |
| Non-Hispanic/Latino | 6,713 (71.4) | 61,840 (72.1) | 0.015 | 6,160 (71.0) | 6,109 (70.4) | 0.013 |
| Comorbidities | | | | | | |
| Hypertension | 6,938 (73.8) | 49,189 (57.3) | 0.352 | 6,320 (72.9) | 6,251 (72.1) | 0.018 |
| Hyperlipidemia | 6,111 (65.0) | 37,042 (43.2) | 0.449 | 5,530 (63.7) | 5,535 (63.8) | 0.001 |
| Overweight and obesity | 2,638 (28.1) | 14,646 (17.1) | 0.265 | 2,356 (27.2) | 2,026 (23.4) | 0.088 |
| Ischemic heart disease | 2,226 (23.7) | 12,864 (15.0) | 0.221 | 1,979 (22.8) | 1,990 (22.9) | 0.003 |
| Atrial fibrillation/flutter | 888 (9.4) | 5,473 (6.4) | 0.114 | 774 (8.9) | 771 (8.9) | 0.001 |
| Medications | | | | | | |
| Beta-blockers | 3,749 (39.9) | 25,098 (29.3) | 0.225 | 3,382 (39.0) | 3,388 (39.1) | 0.001 |
| ACE inhibitors | 2,733 (29.1) | 16,693 (19.5) | 0.226 | 2,492 (28.7) | 2,522 (29.1) | 0.008 |
| Angiotensin receptor blocker | 2,429 (25.8) | 11,004 (12.8) | 0.334 | 2,089 (24.1) | 2,149 (24.8) | 0.016 |
| Sacubitril/valsartan | 148 (1.6) | 46 (0.1) | 0.170 | 49 (0.6) | 43 (0.5) | 0.010 |
| Statin | 5,714 (60.8) | 29,860 (34.8) | 0.538 | 5,141 (59.3) | 5,136 (59.2) | 0.001 |
| Insulin | 4,417 (47.0) | 25,105 (29.3) | 0.371 | 3,989 (46.0) | 4,039 (46.6) | 0.012 |
| Exenatide | 159 (1.7) | 215 (0.3) | 0.147 | 127 (1.5) | 128 (1.5) | 0.001 |
| Metformin | 4,616 (49.1) | 18,164 (21.2) | 0.612 | 4,108 (47.4) | 4,165 (48.0) | 0.013 |
| Glipizide | 1,227 (13.0) | 4,317 (5.0) | 0.282 | 1,094 (12.6) | 1,159 (13.4) | 0.022 |
| Type of malignancy | | | | | | |
| Breast | 2,472 (26.3) | 22,136 (25.8) | 0.017 | 2,273 (26.2) | 2,220 (25.6) | 0.061 |
| Lymphomas | 1,956 (20.8) | 17,332 (20.2) | 0.097 | 1,813 (20.9) | 1,683 (19.4) | 0.045 |
| Multiple myeloma and myelodysplastic syndromes | 1,202 (12.8) | 10,639 (12.4) | 0.018 | 1,084 (12.5) | 1,224 (14.1) | 0.048 |
| Genitourinary | 446 (4.7) | 4,612 (5.4) | 0.052 | 390 (4.5) | 399 (4.6) | 0.006 |
| Gastrointestinal | 1,775 (18.9) | 15,701 (18.3) | 0.03 | 1,683 (19.4) | 1,691 (19.5) | 0.002 |
| Gynecologic | 649 (6.9) | 7,036 (8.2) | 0.083 | 599 (6.9) | 642 (7.4) | 0.034 |
| Respiratory and intrathoracic organs | 348 (3.7) | 3,775 (4.4) | 0.056 | 312 (3.6) | 304 (3.5) | 0.004 |
| Mesothelial and soft tissue | 555 (5.9) | 4,569 (5.3) | 0.046 | 521 (6.0) | 512 (5.9) | 0.008 |
| Metastatic malignancy | 1,539 (16.4) | 20,793 (24.2) | 0.197 | 1,440 (16.6) | 1,349 (15.6) | 0.029 |
| Laboratory tests | | | | | | |
| HbA1c ≥7% | 5,315 (56.5) | 16,456 (19.2) | 0.834 | 4,702 (54.2) | 4,814 (55.5) | 0.026 |
| Creatinine, mg/dL | 1.0 ± 0.5 | 1.1 ± 1.3 | 0.058 | 1.0 ± 0.5 | 1.2 ± 1.2 | 0.019 |
| LDL cholesterol ≥130, mg/dL | 660 (7.0) | 4,262 (5.0) | 0.087 | 598 (6.9) | 634 (7.3) | 0.016 |
| CRP ≥5, mg/L | 668 (7.1) | 5,738 (6.7) | 0.016 | 606 (7.0) | 567 (6.5) | 0.018 |
| Health care use | | | | | | |
| Outpatient visits | 7,760 (82.5) | 62,633 (73.0) | 0.231 | 7,102 (81.9) | 7,011 (80.8) | 0.027 |
| Hospitalizations | 1,672 (17.8) | 17,314 (20.2) | 0.061 | 1,520 (17.5) | 1,495 (17.2) | 0.008 |
| ED visits | 2,510 (26.7) | 20,106 (23.4) | 0.075 | 2,264 (26.1) | 2,233 (25.7) | 0.008 |

Values are mean ± SD or n (%).

ACE = angiotensin-converting enzyme; CRP = C-reactive protein; ED = emergency department; HbA1C = glycosylated hemoglobin; LDL = low-density lipoprotein; SGLT2i = sodium glucose co-transporter 2 inhibitor; SMD = standardized mean difference.

8.5%; $P = 0.001$) compared to patients who were not on SGLT2is (Table 1). Additionally, before PSM, patients treated with SGLT2is had a higher prevalence of hypertension, ischemic heart disease, overweight/obesity, chronic kidney disease, and atrial fibrillation/flutter. After PSM, the 2 cohorts were well matched for demographics, comorbidities, medication use at baseline, and various laboratory values.

Concerning patients' oncologic characteristics, breast malignancies were most common followed by lymphomas and gastrointestinal malignancies

**TABLE 2 Characteristics of Antineoplastic Therapies**

| Antineoplastic Therapy (After Propensity Matching) | SGLT2i Cohort (N = 8,675) | No SGLT2i Cohort (N = 8,675) | SMD |
|---|---|---|---|
| Anthracyclines | 2,126 (24.5) | 2,135 (24.6) | 0.003 |
| Antimetabolites | 1,648 (19) | 1,690 (19.5) | 0.010 |
| Monoclonal antibodies | 1,834 (21.1) | 1,763 (20.3) | 0.040 |
| Small-molecule TKIs | 1,465 (16.9) | 1,490 (17.2) | 0.020 |
| Proteasome Inhibitors | 720 (8.3) | 722 (8.3) | <0.001 |
| Alkylating agents | 622 (7.2) | 620 (7.1) | 0.001 |
| Aromatase inhibitor | 260 (3.0) | 255 (2.9) | 0.020 |

Values are n (%).
TKI = tyrosine kinase inhibitor; other abbreviations as in Table 1.

(Table 1). The most common class of antineoplastic therapy was anthracyclines followed by anticancer monoclonal antibodies (Table 2).

**PRIMARY OUTCOMES.** After matching, within a 12-month follow-up period, there was a total of 646 patients (7.45%) on SGLT2is that developed CTRCD compared to 948 patients (10.9%) who were not on SGLT2is (HR: 0.76; 95% CI: 0.69-0.84; $P < 0.001$) (Table 3). In the subgroup analysis on different classes of antineoplastic therapies (Figure 1), SGLT2i use was associated with a significantly lower risk of developing CTRCD in patients exposed to anthracyclines (HR: 0.70; 95% CI: 0.58-0.85; $P < 0.001$), monoclonal antibodies (HR: 0.81; 95% CI: 0.66-0.98; $P = 0.03$), antimetabolites (HR: 0.75; 95% CI: 0.65-0.86; $P < 0.001$), small-molecule TKIs (HR: 0.67; 95% CI: 0.54-0.83; $P < 0.001$), and alkylating agents (HR: 0.63; 95% CI: 0.53-0.76; $P < 0.001$). In subgroup analysis focused on individual SGLT2i therapies, empagliflozin was associated with a significantly lower risk of developing CTRCD (HR: 0.78; 95% CI: 0.70-0.87; $P < 0.001$) compared with dapagliflozin (HR: 0.93; 95% CI: 0.79-1.11; $P = 0.45$) and canagliflozin (HR: 0.92; 95% CI: 0.77-1.11; $P = 0.41$).

**SECONDARY OUTCOMES.** The secondary outcomes of HF exacerbations (Figure 2) (HR: 0.81; 95% CI: 0.72-0.90; $P < 0.001$), all-cause mortality (HR: 0.67; 95% CI: 0.61-0.74; $P < 0.001$), hospitalization or ED visit (HR: 0.93; 95% CI: 0.89-0.97; $P < 0.001$), new onset atrial fibrillation/flutter (HR: 0.74; 95% CI: 0.62-0.89; $P = 0.001$), new onset metastatic cancer (HR: 0.66; 95% CI: 0.58-0.75; $P < 0.001$), and systemic antineoplastic therapy (HR: 0.67; 95% CI: 0.64-0.69; $P < 0.001$) were significantly lower in patients on SGLT2is compared to patients who were not on SGLT2is (Table 3). Falsification analysis of gastrointestinal bleeding and pneumonia outcomes led to insignificant event rates as shown in Table 4.

## DISCUSSION

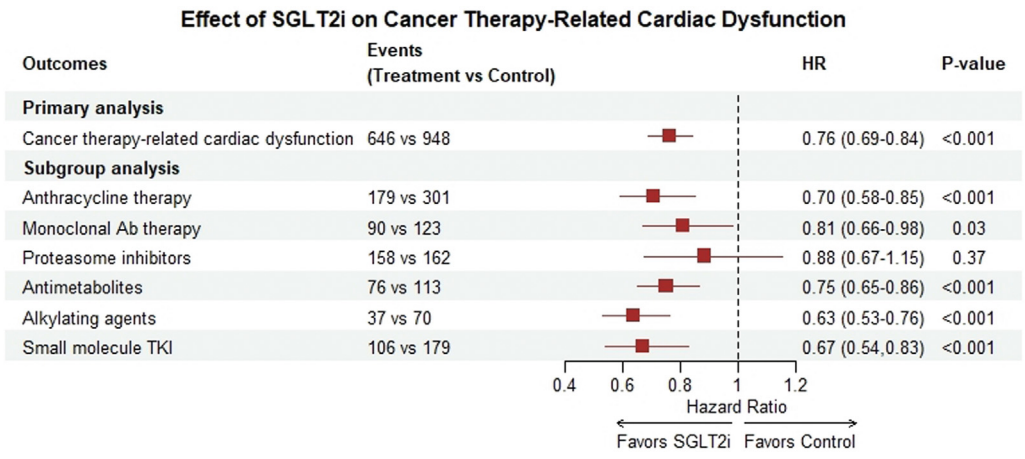
In this retrospective cohort analysis of patients with T2DM and cancer, exposure to potentially cardiotoxic antineoplastic therapies, and no prior documented history of cardiomyopathy or HF, the use of SGLT2is at baseline was associated with a significantly reduced risk of CTRCD during a 12-month follow-up period (Figure 3, Central Illustration). We previously demonstrated the benefits of SGLT2is in patients with T2DM and prevalent CTRCD who were on contemporary GDMT.[19] This study adds to the literature by demonstrating the efficacy of SGLT2is as a preventative strategy to reduce the risk of CTRCD in patients with cancer and T2DM receiving potentially cardiotoxic antineoplastic therapies. In addition, we also demonstrated that the prescription of SGLT2is in this population was associated with a significantly decreased risk of HF exacerbations, all-cause mortality, all-cause hospitalizations/ED visits, new onset

**TABLE 3 Comparison of Outcomes With and Without SGLT2is in Patients Receiving Antineoplastic Therapy**

| | SGLT2i Cohort (N = 8,675)[a] | No SGLT2i Cohort (N = 8,675) | HR (95% CI) | *P* Value | E Value for HR | E Value for Lower CI of HR |
|---|---|---|---|---|---|---|
| Primary outcome | | | | | | |
| CTRCD | 646 (7.45) | 948 (10.9) | 0.76 (0.69-0.84) | <0.001 | 1.96 | 2.26 |
| Secondary outcomes | | | | | | |
| HF exacerbation | 576 (6.6) | 744 (8.6) | 0.81 (0.72-0.90) | <0.001 | 1.81 | 2.11 |
| All-cause mortality | 657 (7.6) | 1,033 (11.9) | 0.67 (0.61-0.74) | <0.001 | 2.34 | 2.66 |
| Hospitalization or ED visit | 3,537 (40.8) | 3,893 (44.9) | 0.93 (0.89-0.97) | <0.001 | 1.39 | 1.51 |
| New onset Afib/flutter | 203 (2.34) | 290 (3.34) | 0.74 (0.62-0.89) | 0.001 | 2.08 | 2.62 |
| New onset metastatic cancer | 394 (4.54) | 656 (7.56) | 0.66 (0.58-0.75) | <0.001 | 2.45 | 2.84 |
| Systemic antineoplastic therapy | 3,991 (46.0) | 5,336 (61.5) | 0.67 (0.64-0.69) | <0.001 | 2.40 | 2.51 |

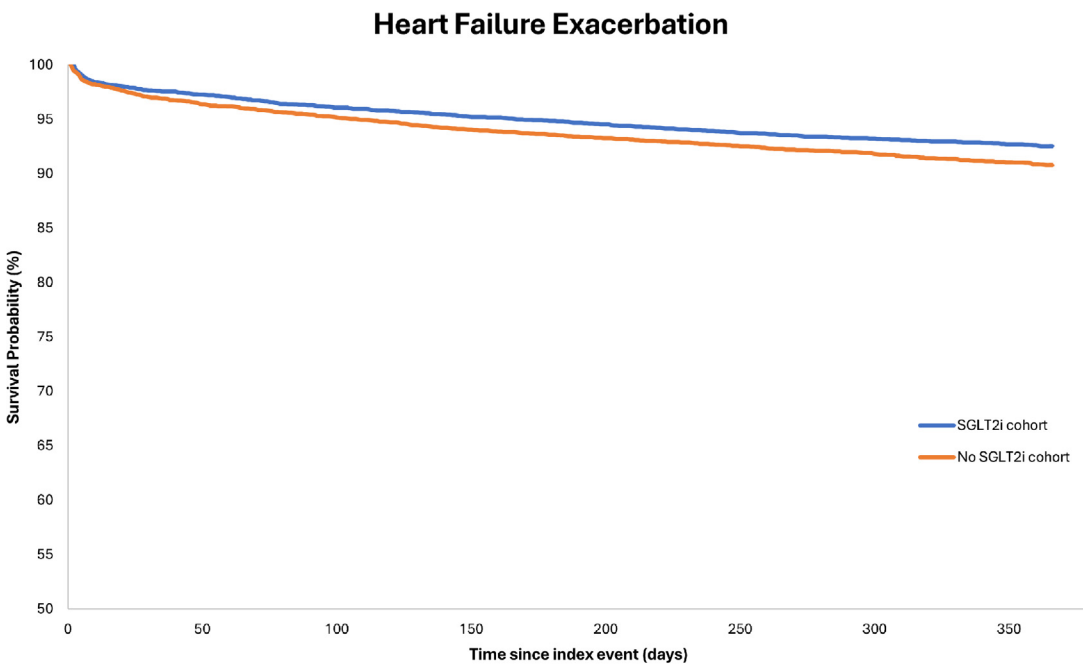
Values are n (%). [a]Raw % noted.
Afib = atrial fibrillation; CTRCD = cancer therapy–related cardiac dysfunction; HF = heart failure; other abbreviations as in Table 1.

**FIGURE 1 Forest Plot for Subgroup Analysis**




Forest plot showing HRs and their corresponding 95% CIs for a subgroup analysis of the class of antineoplastic therapy and the risk of developing cancer therapy-related cardiac dysfunction while on sodium glucose co-transporter 2 inhibitor (SGLT2i). Ab = antibody; SGLT2 = sodium glucose co-transporter 2; TKI = tyrosine kinase inhibitor.

**FIGURE 2 Kaplan-Meier Curve for Heart Failure Exacerbation**




A graph depicting the Kaplan-Meier curve for heart failure exacerbations for patients on sodium glucose co-transporter 2 inhibitor (SGLT2i) vs no SGLT2i.

**TABLE 4 Falsification Outcomes**

| | SGLT2i Cohort (n = 8,675) | No SGLT2i Cohort (n = 8,675) | *P* Value |
|---|---|---|---|
| Gastrointestinal bleeding | 59 (0.68) | 101 (1.16) | 0.47 |
| Pneumonia | 545 (6.28) | 705 (8.13) | 0.56 |

Values are n (%).
SGLT2i = sodium glucose co-transporter 2 inhibitor.

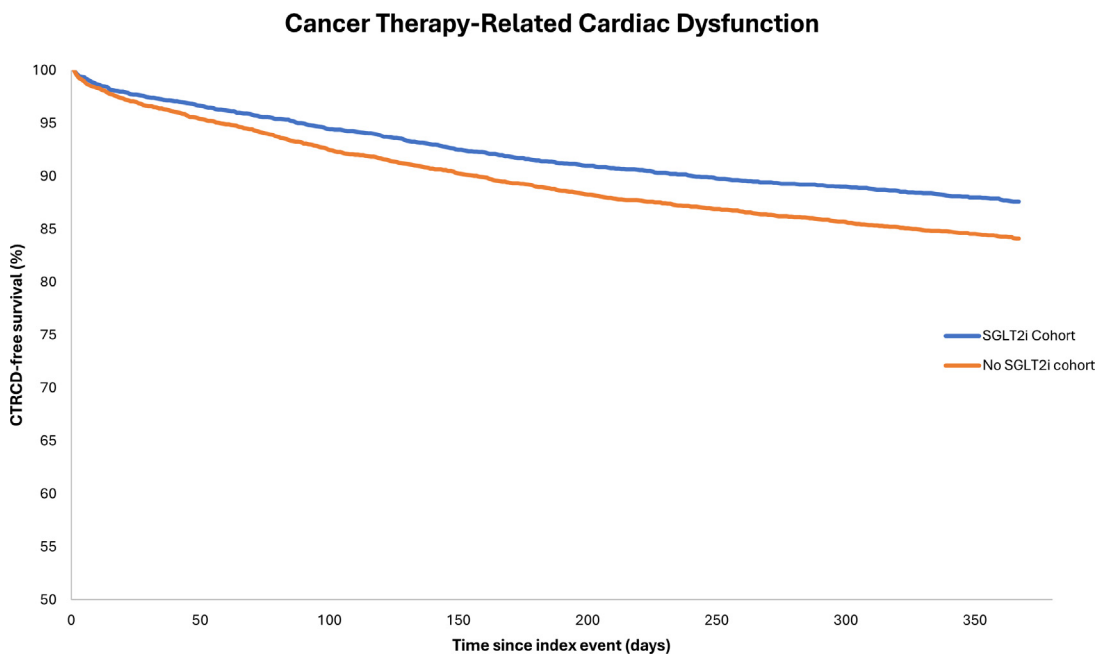
atrial fibrillation/flutter, new onset metastatic cancer, and the need for systemic neoplastic therapy. Furthermore, we also performed a subgroup analysis based on various classes of antineoplastic treatments and found a consistent beneficial association between baseline use of SGLT2is and decreased risk of CTRCD.

Although the role of several agents commonly used in the treatment of HF, such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, and mineralocorticoid receptor antagonists, has been examined for primary prevention of CTRCD,[25-31] the data remain conflicting with marginal benefits at best.[32,33] More recently, the STOP-CA (Atorvastatin for Anthracycline-Associated Cardiac Dysfunction) trial demonstrated that initiating statins before starting higher doses of anthracycline-based therapy reduced the incidence of CTRCD.[34]

Our study builds on the findings of a previous smaller study, which showed the potential role of SGLT2is in the primary prevention of CTRCD in patients with cancer and T2DM.[18] However, the study was limited to patients receiving anthracycline only, with <100 patients in the SGLT2i cohort, and the assessed outcome was HF hospitalization only rather than any CTRCD. To our knowledge, our study is the largest study, albeit observational, to demonstrate the use of SGLT2is at baseline among patients with a history of T2DM and cancer who are exposed to potentially cardiotoxic antineoplastic therapies is associated with a lower incidence of CTRCD and associated adverse cardiovascular outcomes and health care use. Ours is also the first to demonstrate this in antineoplastic therapies, including but not limited to anthracycline-based therapies.

The mechanisms through which SGLT2is may offer cardioprotection in patients with T2DM in the context of cardiotoxic cancer therapies are still not fully understood. Although limited access to granular-level data precluded stratification of the analysis by

**FIGURE 3 Kaplan-Meier Curve for CTRCD**




A graph depicting the Kaplan-Meier curve for cancer therapy–related cardiac dysfunction–free survival for patients on sodium glucose co-transporter 2 inhibitor (SGLT2i) vs no SGLT2i.

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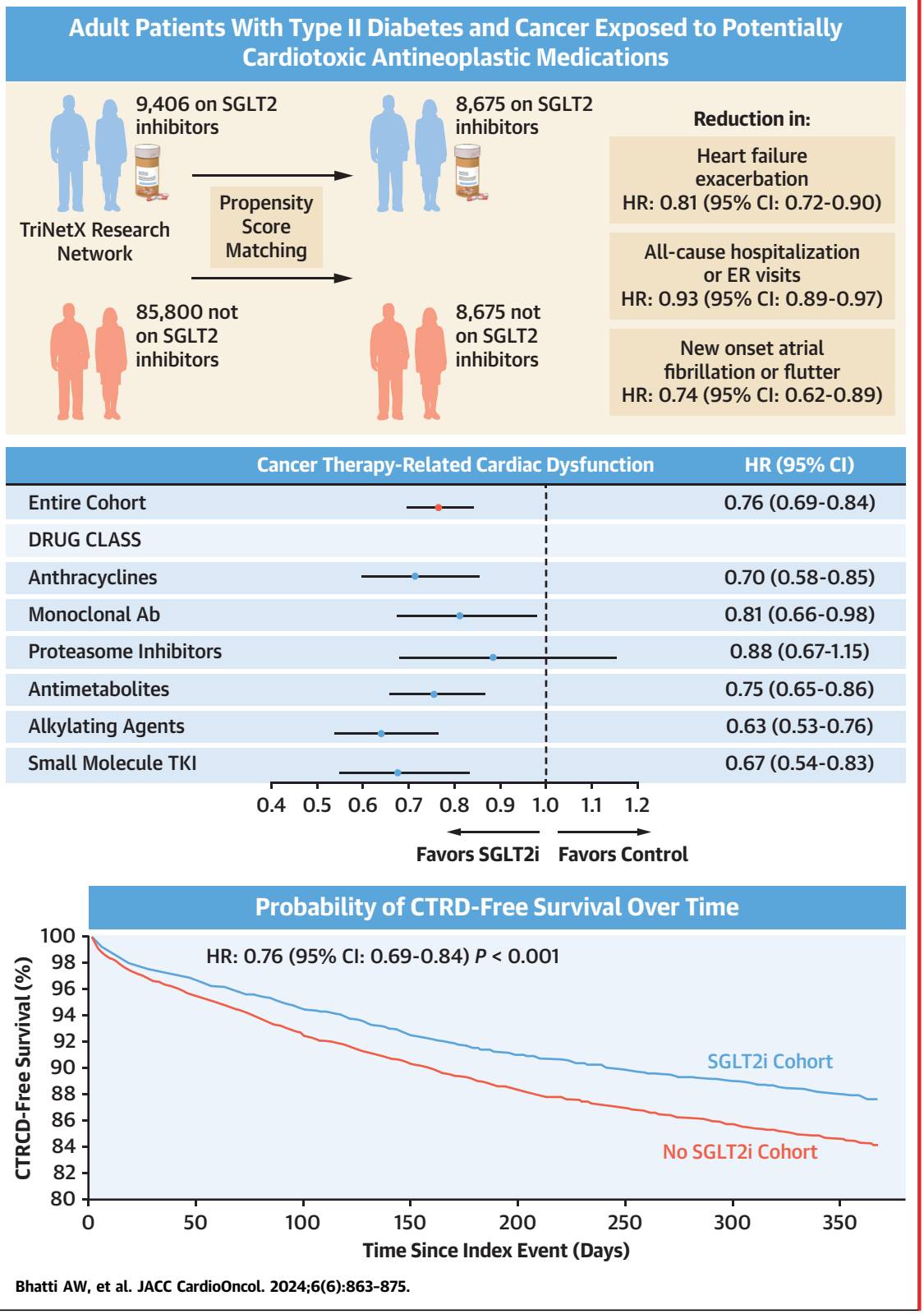
**CENTRAL ILLUSTRATION** **Sodium Glucose Co-Transporter 2 Inhibitors in the Prevention of Cancer Therapy-Related Cardiac Dysfunction**

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cancer subtype, the cardioprotective mechanisms of SGLT2i in CTRCD and its potential for cancer progression inhibition exhibit remarkable concordance.[3,4] These mechanisms involve modulation of cellular metabolism, attenuation of oxidative stress, and dampening of inflammatory responses.[3,4] Dabour et al[20] reviewed evidence from preclinical and clinical studies suggesting that SGLT2is can mitigate systemic inflammation and oxidative stress, which are well-established contributors to both cardiovascular dysfunction and cancer progression. The anticancer effects of SGLT2is were associated with up-regulation of adenosine monophosphate-activated protein kinase and down-regulation of glucose uptake, mitochondrial complex I, phosphoinositide 3-kinase/AKT[35] signaling, and the Hippo pathway.[20] Conversely, the cardioprotective effects were attributed to enhanced energy metabolism, mitochondrial biogenesis, autophagy, and ketone body use alongside a reduction in endoplasmic reticulum stress and ferroptosis, ultimately leading to diminished oxidative stress and inflammation.[20] Additionally, Packer et al[36] demonstrated that SGLT2is can modulate key signaling pathways like adenosine monophosphate-activated protein kinase and mammalian target of rapamycin, which are implicated in both cardiovascular and cancer biology. Translational research in mice following intraperitoneal doxorubicin injection has provided valuable insights.[37] Using cardiac magnetic resonance, this study found that mice treated with empagliflozin exhibited reduced hypertrophy, reduced ventricular remodeling, and enhanced fractional shortening compared to untreated mice. Interestingly, the study also revealed that sodium glucose co-transporter 1 expression was more prevalent than sodium glucose co-transporter 2 (SGLT2) in mouse cardiac myocytes, particularly in the left ventricle. Treatment with SGLT2is led to elevated beta-hydroxybutyrate levels, which protected mice against doxorubicin-induced suppression of antioxidative gene expression, thus mitigating oxidative stress. Additionally, dapagliflozin treatment has been demonstrated to reduce intracellular calcium and proinflammatory cytokine expression in HL-1 adult cardiomyocytes exposed to doxorubicin and trastuzumab.[38] These findings collectively suggest that SGLT2is may confer cardioprotection in the setting of cardiotoxic cancer therapies by reducing hypertrophy, improving cardiac function, and mitigating oxidative stress and inflammation. In our study, this could explain the decreased risk of HF exacerbations and all-cause hospitalizations/ED visits in patients treated with SGLT2is.

We also found a lower rate of all-cause mortality in the SGLT2i group aligning with the results of prior studies.[17] This finding can be partly because of the reduced number of cardiac events and the promotion of a fasting-like state mitigating hyperinsulinemia, which closely mimic antineoplastic effects and slow tumor growth in breast and colon cancers along with gastrointestinal cancers, lung cancer, and liver tumors in mouse models.[17]

Our study also revealed a significant decrease in the incidence of new onset atrial arrhythmias with SGLT2i use, which could potentially avert the development of cardiomyopathy secondary to cancer-mediated atrial arrhythmias.[39-42] Several other studies have demonstrated the beneficial effects of SGLT2is on atrial arrhythmias in patients with T2DM, HF, or chronic kidney disease.[43,44] These effects are believed to be mediated via increased natriuresis and anti-inflammatory and metabolic pathways.[45]

Although CTRCD has been primarily discussed with anthracycline therapies, it is also associated with proteasome inhibitors, small-molecule TKIs, alkylating agents, human epidermal growth factor receptor 2 inhibitors, and antimetabolites.[46,47] Our subgroup analysis highlighted the association of SGLT2is with a reduced risk of CTRCD across different classes of antineoplastic therapy in patients with T2DM and cancer. Specifically, we observed a significant reduction in the risk of CTRCD with anthracyclines, monoclonal antibodies, antimetabolites, small-molecule TKIs, and alkylating agents. Although lower risk with proteasome inhibitors was found, this was not statistically significant, possibly because of the small sample size, as shown in **Figure 1**. Individual agents within different classes of antineoplastic therapies such as TKIs, antimetabolites, and monoclonal antibodies may have varying propensities of inducing cardiac dysfunction, whether it be directly or indirectly via mechanisms such as inducing

**CENTRAL ILLUSTRATION Continued**

This figure presents the results of a propensity score–matched analysis involving adults with cancer and type 2 diabetes mellitus who did not have a previous history of cardiomyopathy or heart failure. It examines their exposure to potentially cardiotoxic antineoplastic therapies and the incidence of cancer therapy–related cardiac dysfunction (CTRCD) based on whether or not patients were taking sodium glucose co-transporter 2 inhibitor (SGLT2i). Ab = antibody; SGLT2 = sodium glucose co-transporter 2; TKI = tyrosine kinase inhibitor.

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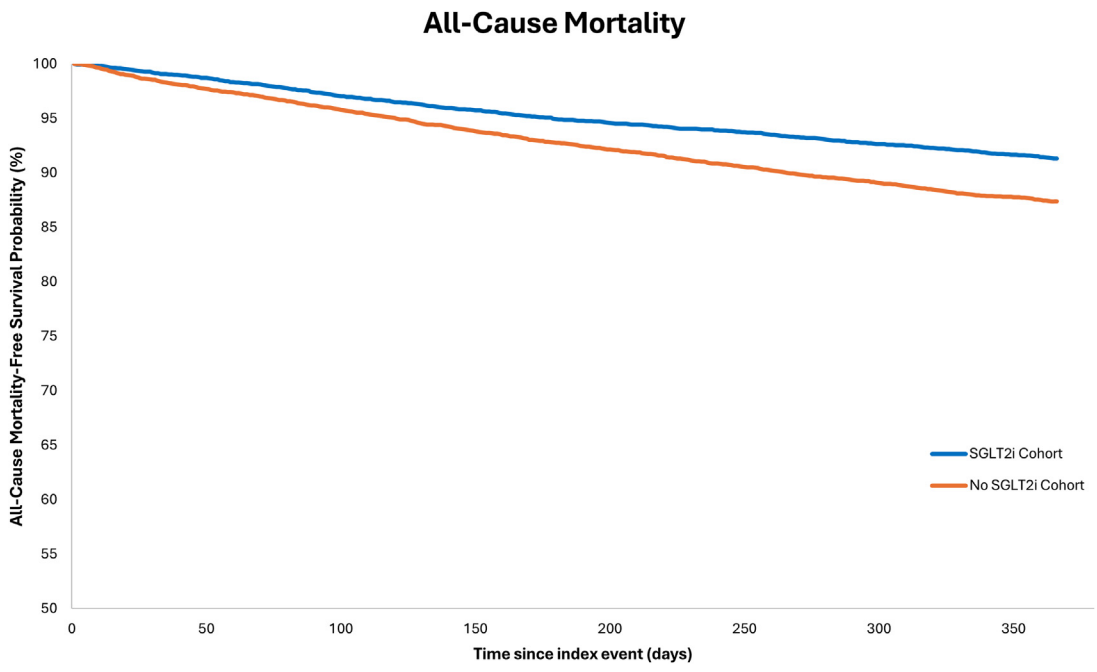
**FIGURE 4** Kaplan-Meier Curve for All-Cause Mortality




A graph depicting the Kaplan-Meier curve for all-cause mortality for patients on sodium glucose co-transporter 2 inhibitor (SGLT2i) vs no SGLT2i.

arrhythmias.[23] However, small sample size restrictions limited our ability to perform cancer-based and individual cancer therapy-based stratified analysis. Furthermore, although mechanisms through which various antineoplastic therapy agents exert cardiotoxicity differ, there are potential commonalities through shared cellular-level metabolic pathways including but not limited to oxidative stress and inflammatory response.[3,4,20] Given the ability of SGLT2is to modulate this pathway favorably, it is plausible that they may provide cardioprotective effects against a broad range of antineoplastic agents. This could begin to explain why our study showed that the effect on anthracyclines had a similar magnitude of risk as other agents such as antimetabolites and TKIs. Future studies capable of obtaining details such as antineoplastic dosing, timing, and combinations could help further clarify this.

Interestingly, in addition to cardiovascular benefits, our study found a significant decrease in all-cause mortality (**Figure 4**), the risk of new onset metastatic cancer, and the need for systemic antineoplastic therapy in the SGLT2i cohort. Although these measures are not equivalent to progression-free survival or overall survival, they can be used as surrogates for such.[48,49] Various studies suggest that SGLT2is may inhibit cancer cell proliferation by impeding glucose uptake. For instance, Komatsu et al[50] demonstrated that human breast cancer MCF-7 cells express SGLT2 receptors, and treatment with ipragliflozin significantly suppressed cell growth through membrane hyperpolarization and mitochondrial membrane instability. Functional SGLT2 receptors have also been identified in human pancreatic, prostate, and lung cancer cells, indicating their potential as early diagnostic and therapeutic targets.[51,52] Villani et al[53] showed that canagliflozin inhibits cellular proliferation in mouse lung and prostate cancer cell models. Additionally, Lawler et al[54] observed an increased risk of colorectal cancer in diabetic patients, suggesting a potential role for SGLT2is in reducing this risk through effective diabetic control.

Additionally, our subgroup analysis on individual SGLT2i therapies showed that empagliflozin was associated with a significantly lower risk of developing CTRCD compared to dapagliflozin and canagliflozin. Empagliflozin improves cardiac energy metabolism, anti-inflammatory and antioxidative effects, and antifibrotic effects,[20] although direct

comparisons of individual SGLT2i propensity for these cardioprotective mechanisms in patients with CTRCD remains unknown. There have been other retrospective studies that have shown that in patients with HF, empagliflozin was associated with improved outcomes compared to dapagliflozin and or canagliflozin.[55,56] Although the findings of our subgroup analysis are similar to other real-world data studies,[55,56] there are both preclinical and prospective studies demonstrating that all SGLT2is can be effective, and the reason as to why our data showed only significance with empagliflozin may be because of the small sample size.[20] However, when interpreting these results, it should be noted that granular-level details such as dose and frequency were not obtainable. Although our findings are hypothesis generating and congruent with other retrospective studies, prospective studies are needed; as a result, our findings should be interpreted with caution.

**STUDY LIMITATIONS.** This study has several limitations. First, we used data from the TriNetX EHR database, which relies on International Classification of Diseases codes. This method is susceptible to coding errors and inherent biases within real-world databases. Additionally, the database limitations prevented the extraction of detailed medication information, including dosage, duration, route of administration, and specific combinations of cardiotoxic therapies. Although these factors likely impacted both cohorts equally, our analysis could not quantify their influence.

Second, our study population exclusively comprised patients with T2DM. Therefore, we cannot generalize these findings to assess SGLT2i as a primary preventative strategy for CTRCD in patients with cancer but without pre-existing T2DM receiving cardiotoxic therapies. Third, although the chosen 12-month follow-up period aligns with the most common timeframe for cardiotoxicity manifestation,[21] the long-term effects of SGLT2is on CTRCD prevention beyond this period remain unknown. Fourth, the lack of individual-level data including specific event times and types prohibited us from performing competing risk analysis. Aggregate data sources provided summary statistics rather than patient-level information, making it challenging to accurately model competing risks. In addition, calculating cumulative incidence functions and cause-specific hazards was not possible because of the lack of time-to-event information. Aggregate data may not have allowed for detailed subgroup analysis identifying different effects across various patient populations.

Finally, despite PSM to reduce confounding bias, the possibility of residual confounding caused by unmeasured factors persists. To assess the robustness of our findings, we conducted sensitivity analyses and calculated E values. High E values suggest minimal influence of unmeasured confounding on observed effects. However, unmeasured socioeconomic factors, known to influence cardiovascular disease prevalence,[57] could still bias the results. These factors might limit access to SGLT2is in socioeconomically disadvantaged populations. We partially addressed this limitation by incorporating a prior health care use analysis into the matching process (details in **Table 1**). Additionally, we evaluated falsification outcomes (gastrointestinal bleeding and pneumonia) and observed similar rates between the cohorts, further supporting the validity of our approach.

## CONCLUSIONS

In summary, our retrospective cohort analysis suggests that in patients with cancer and T2DM, without a prior documented history of cardiomyopathy or HF, and who received potentially cardiotoxic antineoplastic therapies, the baseline use of SGLT2is was safe and associated with a significantly reduced risk of CTRCD, HF exacerbations, all-cause mortality, all-cause hospitalizations/ED visits, new onset atrial fibrillation/flutter, new onset metastatic cancer, and the need for systemic antineoplastic therapy. More extensive prospective randomized trials are warranted to validate the role of SGLT2is as a viable primary prevention strategy for patients exposed to cancer treatment with the potential for cardiotoxicity.

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## PERSPECTIVES

**COMPETENCY IN MEDICAL KNOWLEDGE:** In our retrospective analysis, SGLT2i use at baseline was associated with a significantly decreased risk of developing CTRCD in patients with T2DM and cancer who were exposed to potentially cardiotoxic antineoplastic therapies. SGLT2is were also associated with a lower risk of heart failure exacerbations and all-cause hospitalizations/ED visits.

**TRANSLATIONAL OUTLOOK:** The role of SGLT2is and other cardiometabolic modulators in the primary prevention of CTRCD needs to be further studied in a prospective clinical trial.

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