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Review Article

The dual role of SGLT2 inhibitors: glycemic control and cardioprotection in anthracycline-treated cancer patients

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Abstract: Anthracyclines are vital chemotherapy drugs for treating various cancers, including solid tumors and blood cancers; however, they cause dose-dependent cardiotoxicity, manifesting as cardiomyopathy, arrhythmias, and heart failure (HF). Cardiotoxicity, driven by oxidative stress, mitochondrial dysfunction, and other mechanisms, limits its use and affects long-term patient outcomes. Meanwhile, sodium-glucose co-transporter-2 (SGLT2) inhibitors, originally developed for type 2 diabetes, offer cardiovascular benefits beyond glucose control, such as reduced HF hospitalization and mortality. These benefits stem from improved myocardial energetics, reduced fibrosis, and improved regulation of cardiac ion homeostasis. Experimental studies, including animal models, have shown that SGLT2 inhibitors, such as empagliflozin, preserve cardiac function and reduce inflammation in anthracycline-induced cardiotoxicity. Clinical data, although limited to small retrospective studies, suggest lower mortality and fewer cardiovascular events in anthracycline-treated cancer patients using SGLT2 inhibitors. However, variability in the study design highlights the need for a systematic evaluation. This systematic review aimed to critically assess the cardiovascular outcomes associated with SGLT2 inhibitor use in cancer patients treated with anthracyclines, evaluating their dual role in glycemic control and cardioprotection, and to identify evidence gaps to inform therapeutic strategies for optimizing long-term cardiovascular health in this vulnerable population.

Keywords: Heart failure, anthracyclines, sodium-glucose co-transporter-2 inhibitors, cardiotoxicity

Introduction

Anthracyclines are crucial components of chemotherapy protocols for a wide variety of cancers, including solid tumors and blood cancers [1]. Although anthracyclines are well-known for their effectiveness in fighting cancer, they are also associated with dose-dependent cardiotoxicity. This cardiotoxicity can manifest as cardiomyopathy, arrhythmia, and ultimately, heart failure (HF). The heart-related side effects of anthracycline chemotherapy can significantly affect long-term patient outcomes and often limit the ability to administer optimal doses of these powerful anticancer drugs [2]. Several mechanisms have been proposed to explain the cardiac damage caused by anthracyclines. Oxidative stress, which arises from the production of reactive oxygen species (ROS), is a major contributor to this damage. Other factors, including mitochondrial dysfunction, impaired iron metabolism, DNA damage, apoptosis, and autophagy, exacerbate oxidative injury [3, 4]. Together, these pathophysiological processes compromise both the structural and functional integrity of the heart muscle, increasing the risk of HF in cancer patients receiving anthracycline treatment.

Concurrently, sodium-glucose co-transporter-2 (SGLT2) inhibitors, initially developed and approved for managing type 2 diabetes mellitus (T2DM), have attracted significant attention for their cardiovascular benefits that extend beyond glycemic control. SGLT2 inhibitors primarily function by inhibiting glucose reabsorption in the renal proximal tubules, promoting glucosuria, and reducing plasma glucose levels. In addition to their metabolic actions, these agents have been shown to exert direct and indirect cardioprotective effects [5, 6]. Comprehensive clinical trials in HF populations have

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demonstrated that SGLT2 inhibitors reduce the risks of HF-related hospitalizations, cardiovascular death, and overall mortality [7, 8]. These benefits are believed to arise from mechanisms that include improvements in myocardial energetics, reduction in cardiac fibrosis, attenuation of inflammation, and better regulation of intracellular sodium and calcium homeostasis. In experimental models, including animal studies of anthracycline-induced cardiotoxicity, SGLT2 inhibitors, such as empagliflozin, have demonstrated preservation of cardiac function, reduced myocardial fibrosis, and lower levels of pro-inflammatory cytokines, suggesting a potential role in mitigating the deleterious cardiac effects of anthracyclines [9, 10].

Despite promising mechanistic data and evidence from HF and diabetic cohorts, a conspicuous gap remains in the clinical understanding of the benefits of SGLT2 inhibitors in cancer patients receiving anthracycline therapy. Clinical studies exploring this intersection have been limited, with only a few retrospective cohort studies and small-scale investigations reporting on cardiovascular outcomes in this unique patient population. Preliminary data suggest that anthracycline-treated cancer patients receiving SGLT2 inhibitors may experience lower all-cause mortality and potentially reduced cardiovascular events than those not receiving these agents. However, the heterogeneity of the study designs and outcomes underscores the need for a systematic evaluation of the available evidence.

In light of the profound cardiotoxic potential of anthracyclines and the emerging cardioprotective profile of SGLT2 inhibitors, this systematic review aimed to critically assess the cardiovascular outcomes associated with SGLT2 inhibitor use in patients with cancer treated with anthracyclines. By synthesizing data from observational studies and clinical trials, the review seeks to address the current gaps in knowledge and better inform therapeutic strategies to optimize long-term cardiovascular health in this vulnerable population.

Material and methods

Search strategy

For this systematic review, we conducted a comprehensive search to identify relevant studies examining the cardiovascular effects of SGLT2 inhibitors in cancer patients receiving anthracycline therapy. The research was performed in compliance with the PRISMA criteria, Preferred Reporting Items for Systematic Reviews and Meta-Analyses, and the Flow Diagram is shown in **Figure 1**. The research was conducted in the PubMed database until March 2025. It used the Advanced Search Builder, and the keywords were searched in [Title OR Abstract]. We have filtered only research articles published in English language and using the terms (Sodium-Glucose Transporter 2 Inhibitors [Mesh] OR SGLT2 inhibitors OR empagliflozin OR dapagliflozin OR canagliflozin OR ertugliflozin OR sodium glucose cotransporter-2 inhibitors) AND (Anthracyclines [Mesh] OR doxorubicin OR adriamycin OR epirubicin OR idarubicin OR mitoxantrone) AND (Neoplasms [Mesh] OR cancer OR malignancy OR tumor OR oncology) AND (Cardioprotection OR heart protection) AND (Glycemic control [Mesh] OR blood glucose control).

Inclusion and exclusion criteria

We included original articles that followed the following PICO criteria: population (P): adult cancer patients receiving anthracycline-based chemotherapy; intervention (I): use of SGLT2 inhibitors during anthracycline treatment; comparison (C): the comparison group consisted of patients who did not receive SGLT2 inhibitors; outcome (O): primary outcomes of this review were the effects of SGLT-2 inhibitors on all-cause mortality rate and the incidence or exacerbation of HF. The secondary outcomes included cardiac events (HF admissions, new cardiomyopathy, and arrhythmias), preservation of cardiac function (left ventricular ejection fraction [LVEF] and global longitudinal strain [GLS]), cardiac biomarkers (troponin I and B-type natriuretic peptide [BNP]), and specific cardiovascular complications (myocardial infarction and atrial fibrillation/flutter). The inclusion criteria were studies involving patients with cancer who were currently undergoing chemotherapy treatments that included anthracyclines, utilized any SGLT2 inhibitor such as empagliflozin, dapagliflozin, canagliflozin, or ertugliflozin, and assessed cardiovascular function. Preclinical investigations that exclusively used animal models were excluded from this analysis. Individual case reports and small

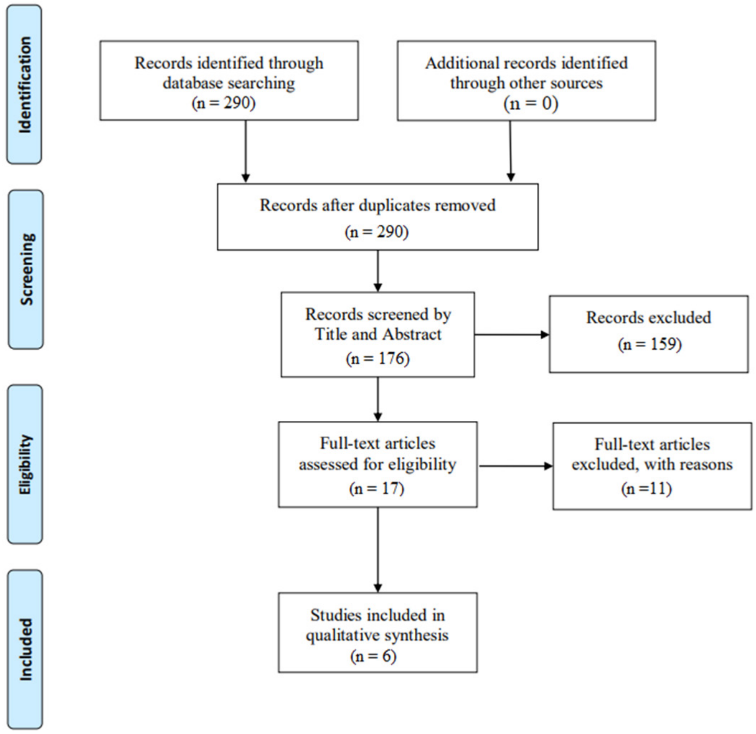

Figure 1. PRISMA flow diagram for enrollment of studies.

case series were excluded owing to their limited sample sizes. Studies primarily focused on cardiotoxicity from non-anthracycline agents were also excluded from the analysis. Furthermore, review articles, meta-analyses, and systematic reviews that did not contain original primary data were excluded from the final analysis.

Data extraction and quality evaluation

Titles and abstracts were reviewed by A.M. After implementing inclusion and exclusion criteria, data from studies were extracted based on the requirements of the survey.

After scanning the references in previously published review articles, any relevant studies were included. We obtained 6 eligible published research articles in their final version. For some of them, we chose to include only the main findings that fit the purpose of this review. Data extraction tables based on the final articles' data are shown in **Table 1**.

Observation indicators and evaluation methods

This review focused on several observational indicators to evaluate the dual role of SGLT2 inhibitors in glycemic control and cardioprotection. Echocardiographic indices, such as LVEF and GLS, were measured using transthoracic echocardiography to assess systolic function and early myocardial dysfunction. Cardiac biomarkers, including troponin I and BNP, were quantified using blood assays to detect myocardial injury and ventricular stress. Adverse cardiovascular events, such as HF exacerbations, myocardial infarction, and atrial fibrillation/flutter, were identified from clinical records or patient follow-ups, and outcomes were reported as incidence rates or odds ratios. Mortality rates, encompassing all-cause and cardiovascular-specific deaths, were assessed using survival analysis, while composite clinical endpoints combined multiple outcomes (e.g., HF hospitalization, myocardial infarction, and mortality) to provide a comprehensive view of cardiovascular risk. Evaluation methods varied across studies, employing statistical approaches such as hazard ratios (HR) and *p*-values. To address heterogeneity, we qualitatively synthesized the findings, noting differences in endpoint definitions and measurement techniques, where applicable.

Results

Search and selection process

After conducting a thorough search, we found 290 articles by March 2025. Following title and abstract screening, 114 articles were excluded, and 176 articles were retained for further analysis. After screening, we excluded 159 studies and were left with 17 to assess their full texts. Ultimately, six studies satisfied all eligibility requirements and were incorporated into the final analysis.

Characteristics of included studies

Table 1 delineates the methodological characteristics of the included studies. The study populations predominantly comprised oncology

Table 1. Summary of studies that evaluated the role of SGLT2 inhibitors on cardiovascular events among cancer patients who treated with anthracyclines

Study	Year	Study type	Study population	Study groups	Type of cancer	Type of SGLT2 inhibitor	Mean of age, year ± SD	Gender, male (%)	Mean follow-up (years/months)
Merry et al.	2025	Retrospective cohort study	112	SGLT2 inhibitor (n = 61) Non-SGLT2 inhibitor (n = 41)	Breast cancer.	Dapagliflozin	49.36	-	3 and 6 months
Avula et al.	2024	Retrospective cohort study	1280	SGLT2 inhibitor (n = 640) Non-SGLT2 inhibitor (n = 640)	Breast, genitourinary, lymphoma, myelodysplastic syndromes, and other cancers.	Dapagliflozin, empagliflozin, and canagliflozin	67.6	748 (58.4)	2 years
Abdel-Qadir et al.	2023	Retrospective cohort study	933	SGLT2 inhibitor (n = 99) Non-SGLT2 inhibitor (n = 834)	Breast, lymph nodes, and other cancers.	Dapagliflozin, empagliflozin, and canagliflozin	71	353 (37.8)	1.6 years
Gongora et al.	2023	Retrospective cohort study	128	SGLT2 inhibitor (n = 32) Non-SGLT2 inhibitor (n = 96)	Lymphoma, breast, genitourinary, gastrointestinal, sarcoma, leukaemia, others.	Dapagliflozin, empagliflozin, and canagliflozin	60	71 (55.4)	1.5 years
Fath et al.	2023	Retrospective cohort study	1412	SGLT2 inhibitor (n = 706) Non-SGLT2 inhibitor (n = 706)	Haematological/lymphatic, gastrointestinal, breast, female genital organs, and other cancers.	Dapagliflozin, empagliflozin, canagliflozin, and ertugliflozin	62.5 ± 11.4	663 (47)	2 years
Hwang et al.	2022	Retrospective cohort study	3117	SGLT2 inhibitor (n = 780) Non-SGLT2 inhibitor (n = 2337)	Lymphoma, breast, genitourinary, and other cancers.	-	56 ± 10	856 (27.4)	3.4 ± 2.3 years

SGLT2: Sodium-glucose cotransporter-2 inhibitors.

patients receiving anthracycline-based chemotherapeutic regimens, with a substantial proportion having comorbid T2DM, including specific cohorts with breast malignancies. The interventions under investigation involved SGLT2 inhibitor administration (specifically dapagliflozin and empagliflozin) compared with conventional antidiabetic therapies, alternative hypoglycemic agents, or non-exposed control groups.

The outcome parameters exhibited heterogeneity across studies but encompassed various echocardiographic indices (including LVEF and GLS), cardiac biomarkers (such as troponin I and BNP), adverse cardiovascular events (including HF exacerbation, myocardial infarction, and atrial fibrillation), mortality rates, composite clinical endpoints, and HF hospitalizations. The mean duration of follow-up ranged from 6 months to 3.4 years. The studies were conducted across diverse geographical regions, including Egypt, the United States, South Korea, and Canada.

The six studies incorporated in this review consistently demonstrated favorable cardiovascular outcomes associated with SGLT2 inhibitor therapy and attenuated anthracycline-induced cardiotoxicity in oncology patients, albeit with variability in the specific endpoints that achieved statistical significance. The following synthesis presents a comprehensive analysis of the individual study findings.

Merry et al. [8] implemented a prospective case-control methodology to evaluate dapagliflozin's cardioprotective effects in anthracycline-treated cancer patients with concomitant T2DM. At both 3-month and 6-month follow-up assessments, the dapagliflozin cohort exhibited significantly attenuated elevation of cardiac biomarkers (troponin I and BNP), superior preservation of myocardial function (as evidenced by maintenance of LVEF and GLS), and markedly reduced incidence of both subclinical and overt cardiotoxicity compared to control subjects ($P < 0.0001$). These observations suggest that SGLT2 inhibition may mitigate early myocardial injury in this vulnerable population.

In a retrospective cohort investigation, Gongora et al. [7] performed a comparative analysis between anthracycline-treated cancer patients with T2DM receiving SGLT2 inhibitor therapy versus those without SGLT2 inhibitor exposure. The SGLT2 inhibitor-treated group demonstrated significantly lower incidence of adverse cardiac events (3% versus 20%, $P = 0.025$) and substantially reduced all-cause mortality (9% versus 43%, $P < 0.001$), highlighting the potential protective effect against both cardiovascular morbidity and overall mortality.

Hwang et al. [11] conducted a large-scale cohort study that corroborated these findings, focusing specifically on T2DM patients undergoing anthracycline chemotherapy. Patients receiving SGLT2 inhibitors demonstrated superior clinical outcomes compared to both non-diabetic subjects and T2DM patients treated with alternative hypoglycemic agents. After multivariate adjustment, the hazard ratio (HR) for a composite endpoint comprising HF hospitalization, myocardial infarction, stroke, and mortality was 0.35 (95% confidence interval [CI]: 0.25-0.51) for T2DM patients on SGLT2 inhibitor therapy and 0.47 (95% CI: 0.32-0.69) for those receiving alternative antidiabetic medications, underscoring the enhanced cardioprotective profile of SGLT2 inhibition.

Abdel-Qadir et al. [12] implemented a population-based cohort study encompassing 933 patients aged > 65 years with pharmacologically-managed diabetes and no prior HF who received anthracycline chemotherapy. Among the 99 patients with SGLT2 inhibitor exposure, no HF hospitalizations were documented, contrasting with 31 such events in the unexposed cohort (HR = 0, $P < 0.001$). However, following a median follow-up duration of 1.6 years, no statistically significant differences were observed regarding the incidence of new-onset HF (HR, 0.55; 95% CI: 0.23-1.31; $P = 0.18$), cardiovascular disease (HR, 0.39; 95% CI: 0.12-1.28; $P = 0.12$), or all-cause mortality (HR, 0.63; 95% CI: 0.36-1.11; $P = 0.11$). These findings suggest a specific benefit in preventing HF exacerbations rather than broader cardiovascular outcomes.

In 2024, Fath et al. [13] examined a large cohort of 82,369 anthracycline-treated cancer patients, with 1,412 subjects included after 1:1 propensity score matching (706 patients per group: SGLT2 inhibitor versus no SGLT2 inhibitor). Over a 2-year surveillance period, patients receiving SGLT2 inhibitors demonstrated reduced risk of all-cause mortality (odds ratio [OR]: 0.7 [95% CI: 0.56-0.88], P = 0.002), acute HF exacerbation (OR: 0.64 [95% CI: 0.41-1.0], P = 0.048), and new-onset atrial fibrillation/flutter (OR: 0.52 [95% CI: 0.33-0.8], P = 0.003) compared to non-recipients. However, no significant inter-group differences were observed regarding the incidence of myocardial infarction, new-onset HF, or all-cause hospitalization. These results reinforce the mortality benefit and HF exacerbation reduction observed in previous studies, while uniquely highlighting a decreased incidence of atrial arrhythmias, an outcome parameter that has received limited attention in prior analyses.

In 2024, Avula et al. [14] investigated the impact of SGLT2 inhibitors in patients who developed cardiac dysfunction following cancer therapy. This research focuses on individuals with type 2 diabetes mellitus who had cancer, exposure to potentially cardiotoxic cancer treatments, and subsequent cardiomyopathy or HF diagnoses. The study population included patients who received various cardiotoxic therapies, with anthracyclines being one of the specifically mentioned treatments. After propensity score matching, 1,280 patients were included in the final analysis, with 640 patients receiving SGLT2 inhibitors plus conventional HF therapy compared to 640 patients receiving only conventional guideline-directed medical therapy. Over the two-year follow-up period, patients treated with SGLT2 inhibitors demonstrated significantly improved outcomes, including a 52% lower risk of acute HF exacerbation (OR: 0.483), 70% reduction in all-cause mortality (OR: 0.296), and 52% fewer all-cause hospitalizations or emergency department visits (OR: 0.479). Additional benefits included a 60% lower risk of atrial fibrillation/flutter, 51% reduction in acute kidney injury, and 60% less need for renal replacement therapy, with all findings showing statistical significance (P < 0.001 for most outcomes).

Discussion

Dual benefits of SGLT2 inhibition: glycemic control and cardiovascular protection

SGLT2 protein is not expressed in the human heart. Consequently, any cardioprotective benefits conferred by SGLT2 inhibitors are likely attributable to indirect mechanisms, potentially mediated through systemic hemodynamic and/or metabolic alterations [15]. SGLT2 inhibitors lower plasma glucose levels by blocking the high-capacity, low-affinity SGLT2 transporter in the proximal renal tubule, preventing the reabsorption of approximately 90% of filtered glucose and causing sustained glycosuria. This insulin-independent mechanism not only reduces fasting and postprandial glucose levels (with typical HbA1c reductions of 0.8-1.2%) but also induces mild osmotic diuresis and natriuresis, promoting calorie loss and modest weight reduction. The resulting negative glucose and sodium balance translates into lower fasting blood sugar, improved glycemic variability, and decreased reliance on exogenous insulin or secretagogues - advantages especially valuable in cancer patients whose appetite and metabolic reserve may be compromised by chemotherapy.

The mechanisms postulated to underpin the cardiorenal protective effects of SGLT2 inhibitors are multifactorial, encompassing both hemodynamic and metabolic dimensions. Specifically, SGLT2 inhibitors induce natriuresis by inhibiting sodium reabsorption within the proximal convoluted tubule. This process enhances tubuloglomerular feedback, thereby reducing intraglomerular pressure and contributing to the maintenance of renal function [16, 17]. In addition to glucosuria, SGLT2 inhibition exerts multifaceted cardioprotective effects. Osmotic diuresis and natriuresis reduce intravascular volume and preload without triggering the reflex sympathetic activation seen with loop diuretics, while modest blood pressure lowering (≈2-5 mmHg systolic) eases afterload. The natriuresis-mediated decrease in extracellular volume leads to reductions in systemic blood pressure and cardiac preload, which collectively represent the proposed hemodynamic pathway through which SGLT2 inhibitors ameliorate HF [18].

The administration of SGLT2 inhibitors has been associated with improvements in myocardial energy metabolism, a phenomenon linked to elevated levels of circulating ketone bodies, particularly beta-hydroxybutyrate [19]. By shifting myocardial substrate use toward ketone bodies, these agents supply the energy-starved anthracycline-injured heart with an alternate "thrifty" fuel, supporting adenosine triphosphate (ATP) production when glucose oxidation is impaired. These inhibitors elicit a metabolic profile that parallels certain aspects of the accelerated starvation response, characterized by increased gluconeogenesis and free fatty acid oxidation. Ketone bodies are frequently described as "super-fuels" due to their enhanced oxygen efficiency compared to fatty acids. By upregulating ketone body production, SGLT2 inhibitors may augment cardiac energy metabolism and enhance cellular function at the mitochondrial level [20]. Moreover, ketone body oxidation occurs independently of the oxidation rates of fatty acids or glucose, providing a supplementary energy substrate for cardiac metabolism [21, 22]. Elevated ketone metabolism has been documented in patients with HF, indicating that the shift toward ketone body utilization may constitute an adaptive response in the failing heart [23]. Accordingly, this metabolic reprogramming induced by SGLT2 inhibitors is regarded as the principal mechanism underlying their cardioprotective effect.

At the cellular level, SGLT2 inhibitors inhibit the cardiomyocyte Na^+/H^+ exchanger, attenuating calcium overload, and activate autophagy pathways that clear damaged mitochondria, thereby reducing oxidative stress and nucleotide-binding oligomerization domain, leucine-rich repeat, and pyrin domain-containing 3 [NLRP3] inflammasome signaling. An additional cardioprotective mechanism attributed to SGLT2 inhibitors involves the attenuation of ROS production, which subsequently reduces cardiomyocyte apoptosis [24]. The phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) signaling pathway is a critical regulator of cardiomyocyte survival [25]. Evidence suggests that SGLT2 inhibitors activate PI3K/AKT signaling in cardiomyoblasts following doxorubicin exposure, thereby mitigating ROS production and preserving mitochondrial integrity [26]. Furthermore, signal transducer and activator of transcription 3 (STAT3) has been implicated in various cardioprotective processes, and dapagliflozin-mediated restoration of STAT3 activity is associated with diminished cardiomyocyte apoptosis [27].

Emerging evidence suggests that SGLT2 inhibitors may mitigate cardiotoxicity by modulating autophagy [28]. In an animal model of doxorubicin-induced cardiotoxicity, empagliflozin enhanced autophagic flux, reduced autolysosome accumulation, and conferred protection against cardiac injury [29]. Concomitant decreases in epicardial fat and sympathetic tone further diminish pro-inflammatory cytokine levels and adverse remodeling. Together, these actions preserve left ventricular function, lower troponin and natriuretic biomarkers, and translate into a 30-35% reduction in heart failure events and cardiovascular deaths, independent of their glucose-lowering effects. Collectively, the reduction of ROS generation, inhibition of apoptosis, preservation of mitochondrial function, and regulation of autophagy position the cardioprotective properties of SGLT2 inhibitors as potential countermeasures to the specific mechanisms driving anthracycline-induced cardiotoxicity [26, 30].

In summary, the application of SGLT2 inhibitors in experimental models of doxorubicin-induced cardiotoxicity has been linked to the preservation of cardiomyocyte morphology, attenuation of myocardial fibrosis, enhancement of cardiac contractility, and reversal of cardiac remodeling. These combined cardioprotective effects culminate in the amelioration of cardiac remodeling, as evidenced by reductions in left ventricular mass and improvements in LVEF.

Scientific evidence of SGLT2 inhibitors among cancer patients treated with anthracycline

A systematic evaluation of research exploring the influence of SGLT2 inhibitors on cardiovascular outcomes in cancer patients subjected to anthracycline therapy has elucidated promising evidence of a potential cardioprotective capacity inherent in these pharmacological agents. This analysis concurrently emphasizes pivotal considerations pertaining to their safety and broader implications for patient health.

A salient point of convergence across the empirical investigations is the substantiated attenuation of adverse cardiovascular events associated with the administration of SGLT2 inhibitors among patients receiving anthracycline treatment. Specifically, Gongora et al. [7] delineated a statistically significant reduction in the incidence of cardiac events (3% versus 20%, $P = 0.025$) within a cohort of 32 patients diagnosed with both diabetes and cancer who were prescribed SGLT2 inhibitors, compared to 96 propensity-matched controls devoid of such therapy, over a median follow-up period of 1.5

years. Their composite endpoint encapsulated HF incidence, HF-related hospitalizations, newly diagnosed cardiomyopathy, and clinically significant arrhythmias, thereby underscoring a comprehensive protective effect. Correspondingly, Abdel-Qadir et al. [12] discerned a robust correlation between SGLT2 inhibitor utilization and a diminished rate of HF hospitalization ($P < 0.001$) within a cohort of 933 diabetic patients aged over 65 years, with no events documented among the SGLT2 inhibitor recipients during a median follow-up of 1.6 years. Nonetheless, their analysis failed to establish a statistically significant decrement in new HF diagnoses ($P = 0.18$) or other cardiovascular disease diagnoses ($P = 0.12$), intimating that the cardioprotective influence may be more pronounced for severe manifestations necessitating inpatient care. These initial studies provide compelling evidence that SGLT2 inhibitors are particularly effective in preventing the most severe cardiovascular complications, suggesting that their primary benefit lies in reducing hospitalizations and acute cardiac events rather than preventing all forms of heart disease.

Bolstering these observations, Fath et al. [13] executed an expansive analysis, which encompassed 82,369 cancer patients treated with anthracyclines. Following the application of 1:1 propensity score matching, their study scrutinized 1,412 patients (706 per group) over a two-year follow-up duration. The results elucidated that individuals receiving SGLT2 inhibitors exhibited significantly diminished rates of all-cause mortality ($P = 0.002$), acute HF exacerbations ($P = 0.048$), and new-onset atrial fibrillation or flutter ($P = 0.003$) relative to their counterparts not administered these agents. However, comparable rates of myocardial infarction, new-onset HF, and all-cause hospitalization were observed between the groups, suggesting a selective impact across diverse cardiac endpoints. This large-scale analysis confirms that SGLT2 inhibitors provide targeted protection against specific cardiovascular complications, with the most significant benefits observed in mortality reduction and rhythm disorders, while having a limited impact on coronary artery disease events.

Enhancing this body of evidence, Hwang et al. [11] conducted an emulated target trial utilizing nationwide cohort data from South Korea, incorporating 81,572 patients who received anthracycline chemotherapy between 2014 and 2021. Post-propensity score matching, their investigation contrasted 779 SGLT2 inhibitor users with 7,800 non-diabetic patients and 2,337 T2DM patients managed with alternative hypoglycemic therapies. The findings revealed that SGLT2 inhibitor users demonstrated significantly superior composite outcomes - including HF hospitalization, acute myocardial infarction, ischemic stroke, and mortality - compared to both non-diabetic patients and non-SGLT2 inhibitor users. Moreover, these individuals exhibited reduced mortality rates relative to both comparator groups. In a parallel vein, Merry et al. [8] contributed further substantiation of the cardioprotective efficacy of SGLT2 inhibitors, documenting a significant reduction in cardiovascular events among anthracycline-treated cancer patients administered these agents, as opposed to those who were not, within a cohort comprising both diabetic and non-diabetic individuals, thereby extending the relevance of antecedent findings. Although Avula et al. [14] refrained from presenting specific quantitative outcomes, their work contextualizes these observations by referencing the extensive literature on the cardioprotective effects of SGLT2 inhibitors in cohorts such as those with chronic kidney disease and T2DM, positing a mechanistic plausibility for comparable benefits in anthracycline-treated patients. Robust evidence from these large-scale, real-world studies establishes that SGLT2 inhibitors provide comprehensive cardiovascular protection that extends beyond diabetic patients, suggesting universal applicability in anthracycline-treated cancer populations, regardless of diabetes status.

Disparities in the statistical significance of outcomes across these studies may be attributable to variations in the methodological design, cohort demographics, or endpoint definitions. For instance, Abdel-Qadir et al. [12] focused on an older population (> 65 years) that may reflect an elevated baseline cardiovascular risk, potentially obscuring less severe outcomes, such as incident HF diagnoses. Conversely, Gongora et al. [7], including a younger median age and smaller sample size, may have accentuated the differences in the composite endpoints. A large-scale network analysis conducted by Fath et al. [13] provides critical insights through its extensive sample size and thorough endpoint evaluation, notably emphasizing the reduction in atrial fibrillation/flutter, an outcome less prominently addressed elsewhere. The discrepancy between the observation by Fath et al. [13] of similar rates of new-onset HF and the reduced HF outcomes reported by other researchers may be attributed to variations in diagnostic criteria, follow-up durations, or characteristics of the populations studied. Hwang et al. robust nationwide cohort, coupled with propensity score matching, lends compelling support to the cardioprotective role of SGLT2 inhibitors, particularly in ameliorating severe cardiovascular events and mortality. Merry et al. [8] incorporated non-diabetic patients into a significant dimension, suggesting that the therapeutic benefits of SGLT2 inhibitors may transcend the conventionally studied diabetic population, a trend corroborated by other empirical studies. This aligns with preclinical evidence referenced by Gongora et al. [7] and Hwang et al. [11], who demonstrated that SGLT2 inhibitors mitigate myocardial dysfunction, fibrosis, and inflammation in animal models of doxorubicin-induced cardiotoxicity. The observed variations in the study outcomes highlight the importance of standardizing research methodologies and endpoint definitions, whereas the consistency of benefits across diverse populations and study designs strengthens the overall evidence base for SGLT2 inhibitor cardioprotection.

Beyond cardiovascular endpoints, these studies illuminate the safety profile and supplementary advantages of SGLT2 inhibitors in this vulnerable population. Gongora et al. [7] reported a markedly reduced overall mortality rate among SGLT2 inhibitor users (9% versus 43%, $P < 0.001$) and a lower incidence of sepsis and neutropenic fever (16% versus 40%, $P = 0.013$), indicative of systemic benefits extending beyond cardioprotection. Similarly, Hwang et al. [11] observed diminished mortality rates among SGLT2 inhibitor users compared to both non-diabetic and non-SGLT2 inhibitor T2DM patients. Abdel-Qadir et al. [12] found no significant increase in mortality ($P = 0.11$), reinforcing the safety of these agents. The findings of Fath et al. [13] regarding reduced all-cause mortality substantiate this evidence, thereby reinforcing the concept of survival advantage. Similarly, Merry et al. [8] corroborated this safety profile by noting the absence of significant adverse events directly linked to the use of SGLT2 inhibitors, although their primary investigation did not specifically target safety outcomes. However, Avula et al. [14] highlights potential risks, such as lower extremity amputation and urinary tract infections, documented in prior meta-analyses. Although these adverse events were not notably prevalent in the anthracycline-treated cohorts examined, they merit cautious consideration in broader clinical contexts and future investigations.

A critical insight from this review is the uniform call, articulated by Fath et al. [13], Merry et al. [8], and others, for randomized controlled trials (RCTs) to validate these observational findings. The retrospective and cohort-based methodologies employed - including the claims-based approach of Hwang et al. [11] and the network-based analysis of Fath et al. [13] - preclude definitive causal inference due to potential confounders, despite mitigation efforts such as propensity score matching and control matching. While the extensive sample of 779 patients utilizing SGLT2 inhibitors in the study by Hwang et al. [11], along with the 706 users examined by Fath et al. [13], offers significant insights, the limitations inherent in claims and network data, such as the lack of detailed laboratory or demographic information, remain a concern. Furthermore, although Gongora et al. [7], Abdel-Qadir et al. [12], and Hwang et al. [11] predominantly studied diabetic patients, the inclusion of non-diabetic individuals by Merry et al. [8] prompts important questions regarding the effectiveness and safety of SGLT2 inhibitors in a broader population treated with anthracyclines. Preclinical evidence cited by Gongora et al. [7] and Hwang et al. [11] suggests direct cardioprotective mechanisms independent of glucose modulation, positing potential benefits for non-diabetic cohorts - an avenue ripe for RCT exploration. While the current observational evidence is compelling, the field urgently requires well-designed RCTs to establish definitive causal relationships and determine optimal patient selection criteria, particularly for non-diabetic cancer patients who may benefit from SGLT2 inhibitor cardioprotection.

The potential mechanisms underpinning these cardioprotective effects constitute another vital discourse. Although not directly assessed in these clinical studies, Gongora et al. [7], Avula et al. [14], and Hwang et al. [11] reference animal models and prior reviews suggesting that SGLT2 inhibitors may counteract anthracycline-induced cardiotoxicity via anti-inflammatory, anti-fibrotic, and antioxidant pathways, alongside enhancements in myocardial energetics. These mechanisms resonate with the established pathophysiology of anthracycline cardiotoxicity, characterized by oxidative stress and mitochondrial dysfunction. The observation of reduced new-onset atrial fibrillation/flutter by Fath et al. [13] prompts speculation regarding possible anti-arrhythmic properties, warranting further investigation. Merry et al. [8] reinforces this mechanistic plausibility, advocating for human studies to delineate these pathways. Such understanding could refine therapeutic strategies and patient selection for SGLT2 inhibitor use in this setting.

In summary, the collective evidence from these studies suggests that SGLT2 inhibitors offer considerable potential for reducing severe cardiovascular events, notably HF hospitalizations, among anthracycline-treated cancer patients, with additional benefits in mortality reduction and systemic protection. Nevertheless, inconsistencies in outcome significance underscore the need for standardized measures and expanded, diverse cohorts. The safety profile appears reassuring, although the long-term risks observed in other populations warrant vigilance. This body of evidence supports the consideration of SGLT2 inhibitors as a promising cardioprotective strategy for cancer patients receiving anthracycline therapy; however, clinical implementation should await confirmation through randomized controlled trials and the development of evidence-based guidelines for patient selection and monitoring.

Conclusion

In conclusion, SGLT2 inhibitors exhibit substantial cardioprotective potential against anthracycline-induced cardiotoxicity by lowering systemic blood pressure, enhancing myocardial energy metabolism through ketone bodies, and improving mitochondrial function. They alleviate oxidative stress and apoptosis, while modulating autophagy, thereby preserving cardiac structure and function. Clinical evidence underscores their capacity to reduce HF hospitalizations, all-cause mortality, and acute cardiovascular events in cancer patients undergoing anthracycline therapy. Nonetheless, the predominance of observational data necessitates randomized controlled trials to confirm causality and elucidate mechanisms, such as anti-inflammatory and antioxidant effects.

Disclosure of conflict of interest

None.

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