

CARDIOPROTECTIVE EFFECTS OF SGLT2 INHIBITORS ON CARDIAC DYSFUNCTION IN CANCER PATIENTS RECEIVING ANTHRACYCLINE CHEMOTHERAPY: A SYSTEMATIC REVIEW

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КАРДИОПРОТЕКТИВНИ ЕФЕКТИ НА SGLT2 ИНХИБИТОРИТЕ ВЪРХУ СЪРДЕЧНАТА ДИСФУНКЦИЯ ПРИ ПАЦИЕНТИ С РАК, ПОЛУЧАВАЩИ ХИМИОТЕРАПИЯ С АНТРАЦИКЛИНИ: СИСТЕМАТИЧЕН ПРЕГЛЕД

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Abstract.

Background: Anthracyclines have been associated with cancer-therapy related cardiac dysfunction (CTRCD). Sodium-glucose co-transporter 2 (SGLT2) inhibitors are potential cardioprotective agents that could reduce cardiotoxicity in cancer patients receiving anthracyclines. This review aims to report the cardioprotective effects of SGLT2 inhibitors on CTRCD in cancer patients receiving anthracycline chemotherapy. **Methods:** This study is a systematic review written according to PRISMA guidelines. We searched PubMed, Scopus, and DOAJ on July 24th, 2024, for studies that compared heart failure (HF) hospitalisations and overall mortality between cancer patients with a history of anthracycline therapy who received SGLT2 inhibitor treatment and those without. **Results:** Three studies included in our review found that subjects in the SGLT2 inhibitor treatment group had fewer hospitalisations due to HF and lower overall mortality than those in the non-SGLT2 inhibitor treatment group. The cardioprotective effects of SGLT2 inhibitors are achievable mainly through their ability to attenuate oxidative stress, mitochondrial dysfunction, apoptosis, and inflammation induced by anthracycline toxicity. **Conclusions:** Cohort studies have shown that SGLT2 inhibitors exhibit cardioprotective effects in cancer patients receiving anthracycline chemotherapy through their extensive pharmacodynamics. However, available studies are limited to cancer patients with preexisting type 2 diabetes mellitus (T2DM). Hence, future trials tailored to the general population are highly needed to yield results with greater validity.

Key words:

Sodium-glucose cotransporter-2 inhibitor; cardiac dysfunction; anthracycline; chemotherapy; systematic review

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Резюме.

Въведение: Антрациклините се свързват със сърдечна дисфункция вследствие на онкологичното лечение. Инхибиторите на натриево-глюкозния котранспортер 2 (SGLT2) са потенциални кардиопротективни средства, които биха могли да намалят кардиотоксичността при онкологични пациенти, получаващи антрациклини. Настоящият обзор цели да се представят кардиопротективните ефекти на инхибиторите на SGLT2 при сърдечна дисфункция вследствие на онкологично лечение при болни на химиотерапия с антрациклини. **Методи:** Настоящото проучване представлява систематичен преглед, изготвен в съответствие с насоките PRISMA. На 24 юли 2024 г. извършихме търсене в PubMed, Scopus и DOAJ за проучвания, сравняващи хоспитализациите поради сърдечна недостатъчност (СН) и общата смъртност при пациенти с рак, в чиято анамнеза е описана терапия с антрациклини, които са лекувани с инхибитори на SGLT2, и болни, които не са получавали такова лечение. **Резултати:** Три проучвания,

включени в нашия преглед, установиха, че субектите в групата, на терапия със SGLT2 инхибитори, са с по-малко хоспитализации поради СН и по-ниска обща смъртност в сравнение с тези в групата, не получаваха SGLT2 инхибитори. Кардиопротективните ефекти на SGLT2 инхибиторите се постигат главно чрез способността им да намаляват оксидативния стрес, митохондриалната дисфункция, апоптозата и възпалението, предизвикани от токсичността на антрациклините. **Заключение:** Кохортните проучвания показват, че инхибиторите на SGLT2 проявяват кардиопротективни ефекти при раковоболни, получаващи химиотерапия с антрациклини, благодарение на обширна си фармакодинамика. Наличните проучвания обаче са ограничени до раковоболни с вече съществуващ захарен диабет тип 2 (ЗДТ2). Поради това има голяма нужда от бъдещи проучвания, насочени към общата популация, за да се получат резултати с по-голяма валидност.

Ключови думи: инхибитор на натриево-глюкозния котранспортер-2; сърдечна дисфункция; антрациклин; химиотерапия; систематичен преглед

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INTRODUCTION

Research on cancer treatment has made extraordinary advances over the past decade. Currently, a wide range of chemotherapeutic agents is available, each with distinct pharmacokinetic and pharmacodynamic characteristics. Despite the tremendous benefits that chemotherapeutic agents have to offer, research has shown that they induce numerous acute and chronic cardiotoxic effects [1, 2]. These cardiotoxic outcomes include cancer therapy-related heart failure (HF), arrhythmia, thromboembolism, myocardial ischemia, and alterations in blood pressure [2, 3].

Anthracyclines are among the most potent chemotherapeutic agents available to date. They are considered the base treatment for most solid and hematologic cancer cases [4, 5]. Doxorubicin, daunorubicin, and epirubicin are currently three of the most common and active anthracycline agents used to treat various cancers [2]. However, many studies have reported a correlation between the use of anthracyclines and cancer-therapy related cardiac dysfunction (CTRCD), with cardiomyopathy being the most common adverse effect [6-8]. Several hypotheses regarding its mechanism of toxicity have emerged over the decades. Studies have discussed free radical formation, lipid peroxidation, cellular apoptosis, reduction of specific mRNA expression, alterations in ATP production in cardiac myocytes, depression in cardiac glutathione peroxidase activity, damage to the mitochondrial DNA, and interference with topoisomerase II beta as the mechanisms of anthracycline-induced cardiotoxicity [9-11].

The question of how to prevent cardiotoxicity while preserving the antineoplastic benefits of anthracycline administration has prompted researchers and clinicians to strive for novel modalities. Several strategies have been implemented to prevent CTRCD, including modifying anthracyclines to produce analogues with lower cardiotoxicity [11], developing novel drug-delivery techniques that minimise cardiac absorption [12], and

administering cardioprotective agents [12]. Thousands of anthracycline analogues have been developed over the decades, but only a few have been approved. However, studies have reported that cardiotoxicity persists to some extent among these approved analogues, especially in higher cumulative doses [5, 10, 12]. Liposomal formulations are among the current drug delivery systems being developed to reduce CTRCD. Studies reported that this method was generally safer and exhibited lesser cardiotoxicity than anthracycline analogues, but still poses some risks for various hypersensitivity reactions [10, 12, 13].

The use of cardioprotective agents has been particularly prioritised over other strategies [10, 12]. Sodium-glucose co-transporter 2 (SGLT2) inhibitors are a class of drugs commonly used to treat type 2 diabetes mellitus (T2DM). However, several studies have found that these drugs also demonstrate cardioprotective effects on patients with and without diabetes [14, 15]. Several recent *in vivo* studies have further advocated these findings, showing that administering SGLT2 inhibitors could reduce anthracycline-induced cardiotoxicity via various mechanisms [16-20]. This review aims to report the cardioprotective effects of SGLT2 inhibitors on CTRCD in cancer patients receiving anthracycline chemotherapy.

METHODS

This systematic review is written by adhering to PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) guidelines. We searched online databases such as PubMed, Scopus, and Directory of Open Access Journals (DOAJ) on July 24th, 2024, for studies that compared HF hospitalisations and overall mortality between cancer patients with a history of anthracycline therapy who received SGLT2 inhibitor treatment and those without. We did not limit the studies' year of publication on all databases. Studies that

reported additional interventions in combination with the predetermined intervention were excluded. We also excluded studies that were duplicates, irretrievable, not written in English, not peer-reviewed, had fewer than five subjects, not conducted on the appropriate population, did not include SGLT2 inhibitors as treatment, or did not report the predetermined outcomes.

Acquired search query results from all databases were inserted into a Microsoft Excel® worksheet. Two independent authors (GBB and IGNASD) manually screened the titles and abstracts of the studies and excluded duplicates. Subsequent to the exclusion of duplicates, the two authors manually screened the acquired studies' titles and abstracts for study eligibility. Suitable studies were then retrieved for the full-text screening. The study profiles, study designs, population characteristics, and relevant outcomes from studies that met the inclusion criteria were manually extracted by the two authors. The primary outcomes assessed include hospitalisation with HF as the primary cause, overall mortality, and, where available, any significant differences in outcomes between treatment groups. The extracted data were then recorded in a separate, preformatted Microsoft Excel® worksheet. Any disagreements and uncertainties at each step were resolved through discussions with a third author (RCS).

Each retrieved study's quality of evidence and risk of bias were assessed using the Risk of Bias in

Non-randomised Studies – of Interventions (ROBINS-I) tool for non-randomised cohort studies and visualised using the ROBVIS tool. Extracted data were independently recorded in a separate standardised Microsoft Excel® worksheet for risk-of-bias assessment. This study is registered on PROSPERO under the ID CRD42024531387.

RESULTS

Study Screening and Selection Process

A total of 708 studies were identified in the databases searched, of which 599 were from PubMed, 108 from Scopus, and 1 from DOAJ. We manually excluded 41 duplicate studies and then screened the titles and abstracts of the remaining 667 studies. We further excluded 662 studies using the predetermined exclusion criteria and sought to retrieve five suitable studies. One study was excluded because it was irretrievable. We screened four retrieved full-text studies and removed one as it did not report HF hospitalisation and overall mortality. The study results from the remaining three studies were synthesised. The studies' screening and selection process is shown in the PRISMA flow diagram (Fig. 1).

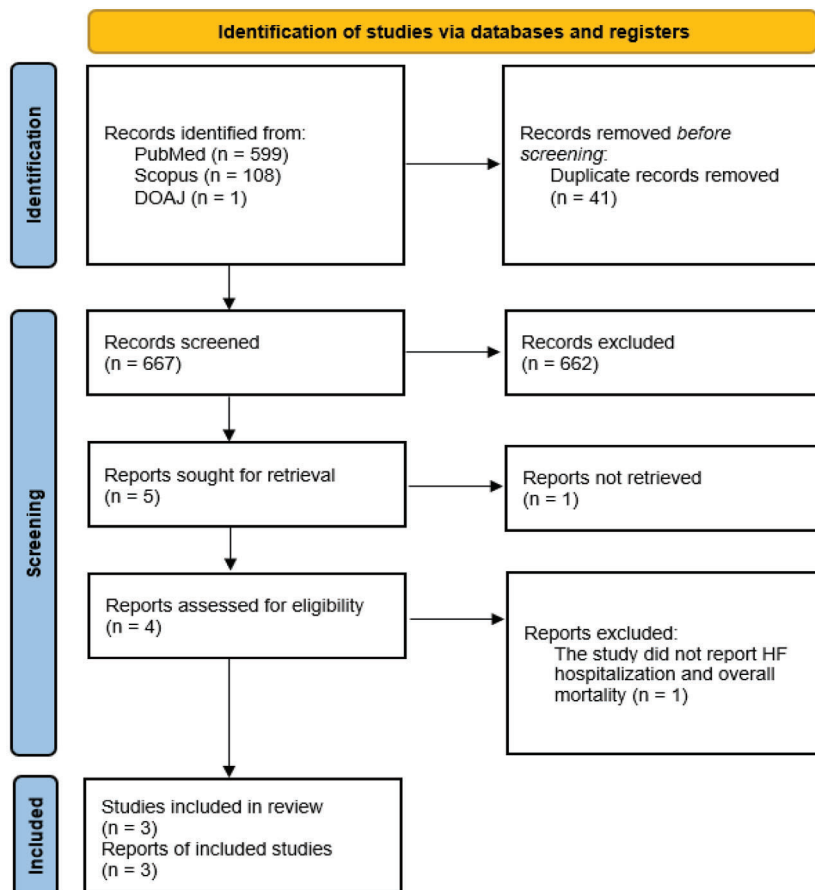


Fig. 1. PRISMA Flow Diagram on Article Selection

Study Characteristics

Two studies were published in 2023, and one was published in 2022. All studies were retrospective cohorts, and the main intervention group was subjects with pre-existing T2DM receiving SGLT2 inhibitors before anthracycline therapy. Abdel-Qadir et al. [21] and Gongora et al. [22] compared subjects in the intervention group to T2DM subjects not receiving SGLT2 inhibitor. The other study by Hwang et al. [23] compared the treatment group to an additional non-T2DM group. The complete extracted study characteristics are presented in Table 1.

Abdel-Qadir et al. [21] included 933 Ontarian subjects with treated diabetes and no prior history of HF in their study population, consisting of 99 subjects in the T2DM with SGLT2 inhibitor group (intervention) and 834 subjects in the T2DM without SGLT2 inhibitor group (comparison). The median age of the subjects

in the intervention group was 70 years old (Q1-Q3: 67-73), while the median age in the comparison group was 71 years old (Q1-Q3: 68-76). The majority of subjects from both groups were females. The intervention group presented with a significantly younger median age, longer diabetes duration, more recent cancer diagnoses, and higher frequency of breast-originated cancer compared to the comparison group ($p < 0.05$). There were no significant differences in comorbidities ($p > 0.05$).

Gongora et al. [22] included 128 subjects in their study population, consisting of 32 subjects in the T2DM with SGLT2 inhibitor group (intervention) and 96 subjects in the T2DM without SGLT2 inhibitor group (comparison). The mean age of the subjects in the intervention group was 60 ± 11 years, with a balanced sex distribution (50%). The mean age of the subjects in the comparison group was 56 ± 10 years, and the sex distribution was predominantly male (57%). There were no significant differences ($p > 0.05$) in terms of ethnic or

Table 1. Study Characteristics

Author (year)	Study Type	Treatment Groups	Number of Subjects	Demographics	Comorbidities	Cancer Type
Hwang et al. (2023)	Retrospective cohort	T2DM with SGLT2 inhibitor	779	Age: 56 ± 10 Sex: M (29%), F (71%)	Hypertension: 48% Dyslipidemia: 48% Coronary artery disease: 4%	Lymphoma: 61% Breast: 61% Genitourinary: 7% Others: 21%
		T2DM without SGLT2 inhibitor	2337	Age: 56 ± 10 Sex: M (27%), F (73%)	Hypertension: 46% Dyslipidemia: 47% Coronary artery disease: 2%	Lymphoma: 12% Breast: 63% Genitourinary: 7% Others: 19%
		Non-DM without SGLT2 inhibitor	7800	Age: 58 ± 11 Sex: M (30%), F (70%)	Hypertension: 53% Dyslipidemia: 47% Coronary artery disease: 3%	Lymphoma: 60% Breast: 60% Genitourinary: 7% Others: 22%
Gongora et al. (2022)	Retrospective cohort	T2DM with SGLT2 inhibitor	32	Age: 60 ± 11 Sex: M (50%), F (50%)	Hypertension: 66% Hyperlipidemia: 59% Obesity: 53% Obstructive sleep apnea: 34% Coronary artery disease: 6% Prior heart failure: 6% Prior myocardial infarction: 0% Chronic kidney disease: 0%	Lymphoma: 34% Breast: 28% Genitourinary: 9% Gastrointestinal: 16% Sarcoma: 6% Leukemia: 3% Others: 3%
		T2DM without SGLT2 inhibitor	96	Age: 56 ± 10 Sex: M (57%), F (43%)	Hypertension: 60% Hyperlipidemia: 55% Obesity: 38% Obstructive sleep apnea: 18% Coronary artery disease: 10% Prior heart failure: 7% Prior myocardial infarction: 3% Chronic kidney disease: 3%	Lymphoma: 34% Breast: 23% Genitourinary: 19% Gastrointestinal: 7% Sarcoma: 7% Leukemia: 3% Others: 6%
Abdel-Qadir et al. (2023)	Retrospective cohort	T2DM with SGLT2 inhibitor	99	Age: 70 (67-73) Sex: M (35%), F (65%)	Hypertension: < 6% Ischemic heart disease: 12% Atrial fibrillation: 6% Chronic obstructive pulmonary disease: 7%	Lymphoma: 24% Breast: 50% Others: 26%
		T2DM without SGLT2 inhibitor	834	Age: 71 (68-76) Sex: M (38%), F (62%)	Hypertension: 10% Ischemic heart disease: 10% Atrial fibrillation: 9% Chronic obstructive pulmonary disease: 5%	Lymphoma: 29% Breast: 33% Others: 39%

Abbreviations: F, Female; M, Male; SGLT2, Sodium-glucose co-transporter 2; T2DM, type 2 diabetes mellitus

race proportions, cancer types and stages, prevalence of cardiac risk factors (smoking history, hypertension, and hyperlipidemia), use of cardiac medications, and incidence of prior HF between the groups. The subjects in both groups were primarily White. The most common cancer type was lymphoma, followed by breast cancer in both groups.

Hwang et al. [23] had the largest study population, using a nationwide database of South Korea. After propensity score matching, the study included 10916 subjects, consisting of 779 subjects in the T2DM with SGLT2 inhibitor group (intervention), 2337 subjects in the T2DM without SGLT2 inhibitor group (comparison 1), and 7800 subjects in the non-DM group (comparison 2). The mean age for the T2DM with SGLT2 inhibitor and the T2DM without SGLT2 inhibitor groups was 56 ± 10 years, whereas the non-DM group was slightly older at 58 ± 11 years. All groups consisted primarily of females. There were no significant differences (standardised mean difference < 0.1) between groups regarding T2DM duration, comorbidities, cardiac medications, and cancer types.

Study Results

The full study outcomes are presented in Table 2. Abdel-Qadir et al.[21] reported a median follow-up duration of 1.6 years (Q1-Q3: 0.8-2.9 years) for the subjects in their cohort. During this period, the incidence rate of hospitalisation with HF as the most responsible diagnosis was 0 per 100 person-years in the SGLT2 inhibitor group, compared with 2.1 (1.4-2.9) per 100 person-years in the non-SGLT2 inhibitor group. Since there were no HF hospitalisations in the SGLT2 inhibitor group, the pooled cumulative incidence function curves from weighted samples in the study showed a hazard ratio (HR) of 0 ($p < 0.001$) for HF hospitalisation. Despite being a significant difference, this finding became one of the study's limitations as it hindered the calculation of the effect size of a potential protective ef-

fect on this outcome. The overall mortality rate was 8.9 (5.3-15.1) per 100 person-years in the SGLT2 inhibitor group and 16.6 (14.7-18.8) per 100 person-years in the non-SGLT2 inhibitor group. However, the overall survival rate analysis using the Pooled Kaplan-Meier estimate showed no significant difference ($p = 0.32$).

Gongora et al.[22] reported a median follow-up duration of 1.5 years for the subjects in their cohort. During this period, there was only 1 (3%) HF hospitalisation in the SGLT2 inhibitor group, compared with 12 (12%) in the non-SGLT2 inhibitor group. However, there was no statistical analysis to conclude whether this difference was significant. Overall mortality was lower in the SGLT2 inhibitor group, with 3 deaths (9%) compared with 41 (43%) in the non-SGLT2 inhibitor group. The Kaplan-Meier survival analysis showed a significantly higher survival rate in the SGLT2 inhibitor group, with an HR of 4.7 ($p = 0.005$).

Hwang et al.[23] reported a mean follow-up duration of 3.4 ± 2.3 years for the clinical outcomes of the subjects in their cohorts. After propensity score matching by adjusting covariates, the incidence rate of HF hospitalisation was 0.10 in the SGLT2 inhibitor and non-SGLT2 inhibitor groups and 0.26 in the non-DM group. The comparison of HF hospitalisation in cohort 1 (SGLT2 inhibitor vs non-DM) showed an adjusted HR of 0.35, whereas cohort 2 (SGLT2 inhibitor vs non-SGLT2 inhibitor) showed an adjusted HR of 2.04. However, neither result was significant ($p > 0.05$). The overall mortality rate was the lowest in the SGLT2 inhibitor group, with an incidence rate of 1.26. The adjusted HR for overall mortality in both cohorts showed significant differences, where the results were 0.33 in cohort 1 ($p < 0.05$) and 0.42 in cohort 2 ($p < 0.05$).

Risk of Bias

Three studies included in this study were analysed for their risk of bias using the ROBINS-I tool—the studies by Abdel-Qadir et al.[21] and Hwang et al.[23] were

Table 2. Study Results

Author (year)	Follow Up Duration	Outcome Measured	Study Results
Hwang et al. (2023)	3.4 ± 2.3 years (mean)	HF hospitalisation	T2DM SGLT2 inhibitor < Non-DM (IR 0.10 vs 0.26, HR 0.35, $p > 0.05$) T2DM SGLT2 inhibitor < T2DM Non-SGLT2 inhibitor (IR 0.10 vs 0.10, HR 2.04, $p > 0.05$)
		Overall mortality	T2DM SGLT2 inhibitor < Non-DM (IR 1.26 vs 3.37, HR 0.33, $p < 0.05$) T2DM SGLT2 inhibitor < T2DM Non-SGLT2 inhibitor (IR 1.26 vs 2.72, HR 0.42, $p < 0.05$)
Gongora et al. (2022)	1.5 years (median)	HF hospitalisation	T2DM SGLT2 inhibitor < T2DM Non-SGLT2 inhibitor (incidence 3% vs 12%)
		Overall mortality	T2DM SGLT2 inhibitor < T2DM Non-SGLT2 inhibitor (incidence 9% vs 43%, HR 4.7, $p < 0.05$)
Abdel-Qadir et al. (2023)	1.6 years (median)	HF hospitalisation	T2DM SGLT2 inhibitor < T2DM Non-SGLT2 inhibitor (IR 0 vs 2.1, HR 0, $p < 0.001$)
		Overall mortality	T2DM SGLT2 inhibitor < T2DM Non-SGLT2 inhibitor (IR 8.9 vs 16.6, $p > 0.05$)

Abbreviations: HF, Heart Failure; HR, Hazard Ratio; IR, Incidence Rate; SGLT2, Sodium-glucose co-transporter 2; T2DM, type 2 diabetes mellitus

considered to have a moderate risk of bias, whereas Gongora et al.[22] was deemed to have a serious risk of bias due to potential confounding variables that had not been accounted for. The specific risk of bias for each domain is shown in the traffic light plot (Fig. 2) and the summary plot (Fig. 3) below.

DISCUSSION

Over the past two decades, SGLT2 inhibitors have been an approved choice in the treatment of T2DM, and several trials have been trying to evaluate their effects on HF over the last five years. All these trials have demonstrated favourable results across the full spectrum of ejection fraction in HF, regardless of patients' T2DM status. The most widely recognized trials evaluating the protective effects of SGLT2 inhibitors were EMPA-REG OUTCOME, DAPA-HF, EMPEROR-Reduced, EMPEROR-Preserved, and DELIVER. These trials specifically evaluated two SGLT2 inhibitor drugs – empagliflozin and dapagliflozin[24,25]. The EMPA-REG OUTCOME trial was the oldest and the starting point for the following trials. This study as-

sessed the effect of empagliflozin on cardiovascular outcomes in T2DM patients and unexpectedly found that it significantly reduced the incidence of HF hospitalisations[26]. Following publication of the EMPA-REG OUTCOME results in patients with T2DM, subsequent studies were designed to assess the effect of SGLT2 inhibitors on HF, not only in subjects with T2DM but also in those without.

The DAPA-HF and EMPEROR-Reduced trials evaluated the effect of SGLT2 inhibitors on subjects with HF with reduced ejection fraction (HFrEF)[27,28]. In contrast, the EMPEROR-Preserved and DELIVER trials assessed the effect on HF with mildly reduced ejection fraction (HFmrEF) and preserved ejection fraction (HFpEF)[29,30]. HFpEF and HFmrEF represent more intricate forms of HF, featuring diastolic dysfunction typically found in geriatric populations presenting with cardio-renal-metabolic comorbidities. These variants also have fewer treatment options than HFrEF[24]. However, all trials evaluating the effects of SGLT2 inhibitors across the full spectrum of HF ejection fractions, regardless of T2DM status, have consis-

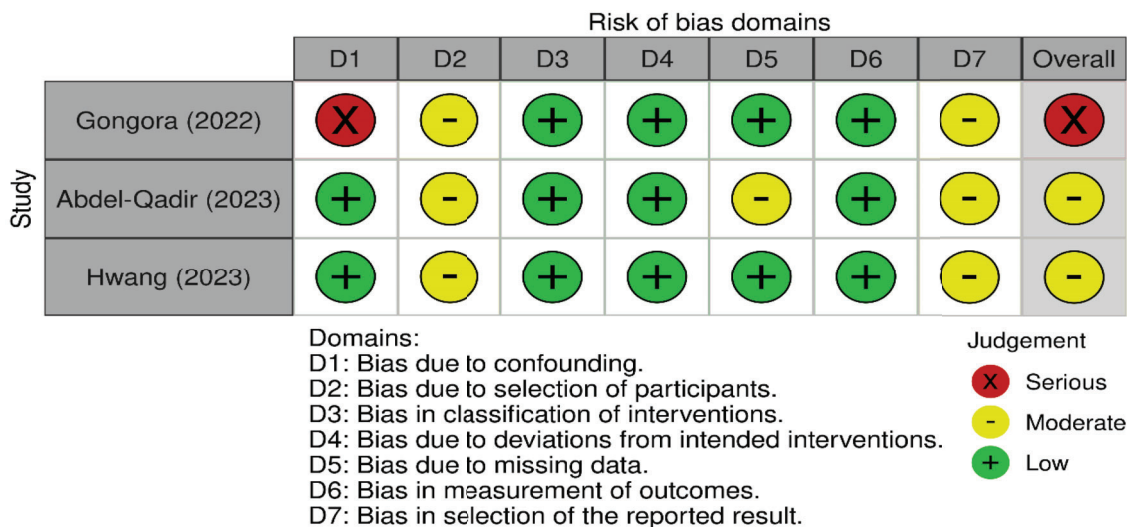


Fig. 2. ROBINS-I Risk of Bias Traffic Light Plot

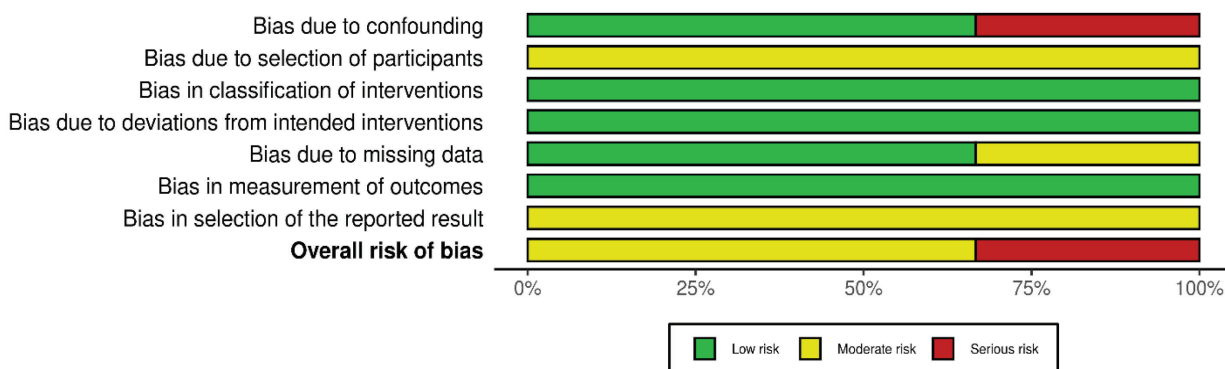


Fig. 3. ROBINS-I Risk of Bias Summary Plot

tently demonstrated that they significantly reduce the incidence of HF hospitalisations [27-30].

The general cardioprotective effects of SGLT2 inhibitors may be explained by various mechanisms [31]. They have been shown to improve ventricular loading by reducing preload through osmotic diuresis and natriuresis and by reducing afterload, possibly through reduced arterial pressure and arterial stiffness [32-35]. SGLT2 inhibitors could also provide an alternative energy source for the heart via the cardiac ketone β -hydroxybutyrate [36]. SGLT2 inhibitors have also been shown to reduce and reverse hypertrophy, fibrosis, remodelling, and systolic dysfunction by inhibiting the sodium-hydrogen (Na^+/H) exchanger in cardiac muscle [37]. Reducing cardiac fibrosis could further reduce left ventricular mass and improve diastolic function [38-40]. Other effects, such as improving endothelial function and stimulating glucagon secretion, also contribute to the overall cardioprotective effects of SGLT2 inhibitors [41, 42]. In the setting of anthracycline-induced cardiotoxicity, HF might not follow the typical pathophysiology, as it is drug-induced and has its own mechanisms of toxicity. However, recent studies by Hwang et al. [23], Gongora et al. [22], and Abdel-Qadir et al. [21] have found that SGLT2 inhibitors could also reduce the number of HF hospitalisations in anthracycline-induced cardiotoxicity. Many experimental studies have then elucidated the mechanisms by which SGLT2 inhibitors can attenuate the cardiotoxic effects of anthracycline therapy.

Anthracycline cardiotoxicity has been attributed to multiple pathways, but the specific mechanisms remain incompletely understood. Major research findings on anthracycline-induced cardiotoxicity indicate that potential mechanisms include the production of reactive oxygen species (ROS), mitochondrial dysfunction, disruption of DNA synthesis, and deviations in iron metabolism [10, 43]. The study by Volkova and Russel [1] reported that doxorubicin-induced cardiotoxicity arises from ROS production during doxorubicin metabolism. Anthracyclines have complex chemical structures and can generate highly reactive species via reductive and oxidative biotransformation [2]. For instance, when doxorubicin is reduced by NADH dehydrogenase in mitochondrial respiratory complex I, it can trigger the generation of ROS. This process of redox cycling results in the formation of hydrogen peroxide and hydroxyl radicals [1].

The reductive metabolism of anthracyclines could also induce cardiac toxicity and cell damage via an alternative iron-dependent mechanism. One pathway linking iron metabolism to anthracycline metabolism also involves redox cycling, during which free radicals are generated. These molecules possess a sufficiently low one-electron redox potential to reduce ferric iron

(Fe (III)) to ferrous iron (Fe (II)), thereby releasing Fe (II) from ferritin. Doxorubicin can also directly interact with iron, undergoing a redox cycle between Fe(III) and Fe(II) states in the presence of oxygen. These drug-iron complexes can lead to an increase in ROS within cells [1, 2].

A separate study revealed that doxorubicin increases mitochondrial permeability by interfering with the association of inner mitochondrial membrane proteins via direct binding to the mitochondrial phospholipid cardiolipin. This could then lead to mitochondrial dysfunction and induce cell death. Anthracycline's high affinity towards cardiolipin in the inner mitochondrial membrane also results in the accumulation of anthracycline in cardiomyocytes. Cardiomyocytes have high oxidative metabolism and relatively less antioxidant protection from radicals than other organ cells [10].

The accumulation of ROS and mitochondrial dysfunction is implicated in numerous adverse cardiovascular effects, including hypertrophy and fibrosis [44, 45]. The study by Hsieh et al. [46] demonstrated that dapagliflozin could attenuate oxidative stress and mitochondrial dysfunction due to anthracycline therapy through the P13K/AKT/Nrf2 axis. Administration of dapagliflozin has been shown to upregulate phosphorylated AKT expression in cardiac cells [46]. Previous studies have shown that the phosphatidylinositol 3-kinase (PI3K)/AKT pathway plays a crucial role in activating nuclear factor erythroid 2-related factor 2 (Nrf2), which suppresses anthracycline-related cardiotoxicity [47, 48]. Through the activation of this suppressor, the antioxidant genes of heme oxygenase-1 (HO-1) and NAD(P)H: quinone oxidoreductase (NQO1) are upregulated [49]. In addition to antioxidant genes, an essential antioxidant enzyme crucial in the role of cardioprotection – superoxide dismutase (SOD) – is also regulated by Nrf2. The increased activity of SOD will, in turn, suppress ROS production [50].

Another subsequent effect of ROS accumulation that also plays a crucial role in cardiotoxicity is inflammation. The inflammation of the heart cells that occurs during anthracycline therapy is mediated by the p38 mitogen-activated protein kinase (MAPK)/nuclear factor- κ B (NF- κ B) pathway [51]. Furthermore, NF- κ B activation can induce interleukin-8 (IL-8), and elevated IL-8 levels have been linked to HF exacerbations [52, 53]. The administration of dapagliflozin has demonstrated the ability to suppress the regulation of phosphorylated p38, NF- κ B, and IL-8 via the P13K/AKT/Nrf2 signalling pathway [46].

Anthracyclines also inhibit the synthesis of DNA, RNA, and proteins, as well as key transcription factors that regulate cardiac-specific genes [54]. This reduction in protein expression, combined with myofibril breakdown, disrupts sarcomeric proteins such as titin

in cardiac cells, ultimately causing cardiac sarcopenia. Anthracyclines inhibit topoisomerase II, which uncoils DNA, thereby disrupting DNA synthesis. This dysfunction arrests the G1 and G2 phases, triggering apoptotic pathways and increased ROS accumulation. Several studies demonstrated that anthracycline could also induce apoptosis in cardiac muscle cells through oxidative stress-mediated endoplasmic reticulum (ER) stress [55, 56].

The experimental study by Chang et al. [57] demonstrated that doxorubicin administration increased the apoptosis-associated proteins Bax and cleaved caspase-3, whereas the levels of the anti-apoptotic protein Bcl-2 were reduced. However, pre-treatment with dapagliflozin suppressed Bax and cleaved caspase-3 expression, whereas Bcl-2 expression was upregulated. Doxorubicin was also shown to increase the expression of ER stress-associated proteins GRP78, p-PERK, eIF-2 α , ATF4, and CHOP. In contrast, pre-treatment with dapagliflozin could significantly suppress the expression of p-PERK, eIF-2 α , ATF4, and CHOP [57].

Continuous apoptosis in myocytes reduces the number of myocardial cells, which have limited regeneration capacity. This could lead to histological changes especially in the ventricles. The left ventricle wall eventually becomes thinner with reduced myocardial mass and reduced compliance. These anthracycline-induced changes eventually lead to adverse remodelling and decreased contractility [2, 10]. It was shown that the administration of dapagliflozin could reduce adverse cardiac remodelling by suppressing atrial natriuretic peptide (ANP), brain (B-type) natriuretic peptide (BNP), type I collagen, fibronectin, and α -smooth muscle actin (α -SMA) that are typically elevated by anthracyclines [46].

The study by Chen [58] demonstrated that empagliflozin administration activated the AMPK/SIRT-1/PGC-1 α signalling pathway, which is typically suppressed by doxorubicin. AMPK is an enzyme that regulates mitochondrial biogenesis, function, autophagy, and fibrosis [58]. SIRT-1 is an essential protein that regulates the autophagy activity in cardiomyocytes, reduces apoptosis, and protects against cardiac injuries [59]. PGC-1 α is another protein that also contributes to mitochondrial biogenesis through mtDNA transcription and replication. It also plays a role in mitochondrial oxidative phosphorylation via regulation of NRF-1 and -2, and in fatty acid oxidation via regulation of peroxisome proliferator-activated receptor expression [60]. In general, the AMPK/SIRT-1/PGC-1 α signalling pathway functions as an energy-sensing system that regulates mitochondrial biogenesis, energy metabolism, and oxidative stress [61].

It was also found that empagliflozin modulates energy metabolism by increasing ATP and decreasing

ADP. Increased ATP levels in the heart muscle have been associated with improved cardiac function and energy metabolism [62]. Another study by Barış et al. [19] found that empagliflozin could reduce hydropic degeneration, karyorrhexis, karyolysis, and inflammation by reducing sarcoplasmic reticulum degradation [19]. It was also shown that empagliflozin could reduce prolonged QT intervals induced by doxorubicin, possibly via intracellular calcium regulation by increasing L-type Ca channel activation, sodium-calcium (Na⁺/Ca²⁺) exchanger activity, SERCA2a, and ryanodine receptor 2 (RyR2) protein expression. The regulation is further enhanced by reducing late sodium channel activation and RyR2-pS2808 protein levels [63].

The recent studies by Hwang et al. [23], Gongora et al. [22], and Abdel-Qadir et al. [21] showed that SGLT2 inhibitors could improve the overall mortality in patients receiving anthracycline therapy. This improvement in mortality rates may be attributed to reduced cardiovascular adverse events and partially due to the additional antineoplastic effects of SGLT2 inhibitors. SGLT2 inhibitors have been shown to inhibit breast cancer proliferation and growth. These drugs induce AMPK-mediated cell cycle arrest in the G1/G0 phase and apoptosis [64].

SGLT2 was found to be highly expressed in pancreatic cancer, prostate cancer, renal cancer, and lung cancer during their early stages [65-67]. SGLT2 inhibitors have been shown to slow cancer cell growth and improve survival in patients by inhibiting SGLT2 expression, which is required for metabolically active cancer cells to obtain glucose and proliferate [66]. Dapagliflozin, in particular, was shown to have a high cytotoxic effect on human renal cancer cells. It regulated the cell cycle, induced apoptosis, and reduced SGLT2 expression in CaKi-1 cells, a human renal cancer cell line [65].

Hyperinsulinemia is a crucial factor in promoting the progression of obesity-associated cancers. Dapagliflozin demonstrated cancer growth-inhibitory effects through its glucose- and insulin-lowering properties. SGLT2 inhibitors also have a secondary effect of reducing body weight through glycosuria [68]. The reduction of body weight further complements the inhibitory effect on cancer development, as several studies have found that weight loss is associated with a lower risk of breast and colon cancers [69, 70]. These findings are further supported when dapagliflozin was demonstrated to suppress the development of breast and colon cancer in mouse models [68].

CONCLUSION

We concluded that SGLT2 inhibitors have demonstrated cardioprotective effects by attenuating the development of CTRCD, particularly HF, in cancer

patients receiving anthracyclines. This is achievable through the drugs' extensive pharmacodynamic profiles, which primarily contribute to the control of ROS production, mitochondrial dysfunction, inflammation, and apoptosis. In addition, SGLT2 inhibitors exhibited antineoplastic effects by disrupting cancer proliferation and reducing body weight, resulting in lower overall mortality. However, currently available studies were only conducted in populations of T2DM patients with cancer. This is a limitation of the study, as the results may not fully represent the general population. Future trials addressing this issue are advised to follow the progression of past SGLT2 inhibitor trials in HF, such as EMPA-REG OUTCOME, in which subsequent studies were continually tailored to address the general population and not only those with T2DM.

No conflict of interest was declared

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