Cardio-Oncology

REVIEW

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Anthracycline- and HER2-induced cardiotoxicity: mechanisms, current strategies, and the emerging role of dapagliflozin as a targeted cardioprotective agent

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Abstract

Chemotherapy-induced cardiotoxicity (CIC) is a well-recognized and potentially severe complication of cancer treatment, particularly with anthracyclines and HER2-targeted therapies. As cancer survival improves, long-term cardiovascular outcomes have become increasingly important, yet current preventive strategies—such as dose reduction, dexrazoxane, neurohormonal blockers, and statins—offer only limited protection and are underutilized in routine clinical practice. There is a growing need for novel interventions that are safe, effective, and mechanistically targeted.

Dapagliflozin, a SGLT2 inhibitor initially developed for type 2 diabetes, has demonstrated substantial cardioprotective effects in patients with heart failure, regardless of glycemic status. Its mechanisms—including improved cardiac metabolism, mitochondrial preservation, anti-inflammatory and antioxidant effects, and inhibition of fibrosis—align closely with the known pathways of chemotherapy-induced myocardial injury. Preclinical models have shown that dapagliflozin can preserve left ventricular function, reduce biomarker elevation, and prevent structural remodeling in hearts exposed to doxorubicin.

Building on this evidence, a randomized, double-blind, placebo-controlled clinical trial (NCT06888505) is currently underway to evaluate dapagliflozin in cancer patients receiving anthracycline-based chemotherapy, with or without trastuzumab. The study incorporates serial biomarker assessments and cardiac function monitoring to assess its preventive potential.

Dapagliflozin represents a promising therapeutic candidate in cardio-oncology. Its pleiotropic cardioprotective effects, oral route of administration, and established safety profile make it a strong contender for integration into future preventive strategies aimed at reducing the cardiovascular burden of cancer therapy.

Keywords Chemotherapy-induced cardiotoxicity, HER2-targeted therapies, Dapagliflozin, Cardio-oncology, SGLT2 inhibitors, Anthracyclines

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Background

Chemotherapy remains an essential cornerstone of cancer treatment, significantly enhancing survival rates across numerous malignancies. However, the benefits of chemotherapy are often compromised by severe adverse effects, notably cardiac toxicity, which can substantially impact patient quality of life and long-term outcomes. Chemotherapy-induced cardiotoxicity (CIC) encompasses a spectrum of cardiovascular complications ranging from asymptomatic myocardial injury to overt heart failure (HF), and its incidence is rising as cancer survival improves, posing a significant clinical challenge [1].

Anthracyclines, such as doxorubicin, and targeted therapies like trastuzumab and pertuzumab are well-known agents causing significant cardiac damage. There are several mechanisms by which doxorubicin cardiotoxicity is produced that involve oxidative stress, mitochondrial dysfunction, iron regulatory protein alteration, deregulation of Ca2 + homeostasis, and defective apoptosis that ultimately leads to defective cardiac function and enhanced morbidity [2, 3]. Early detection, prevention, and management of CIC are essential for optimizing cancer therapy outcomes and preserving cardiac function [4].

Current preventive and therapeutic strategies primarily focus on dose adjustments, use of less cardiotoxic chemotherapy agents, and pharmacological interventions, including angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), beta-blockers, and statins [5]. Despite these measures, the incidence and clinical impact of CIC remain substantial, indicating an unmet need for novel preventive and therapeutic approaches [6].

Sodium-glucose cotransporter-2 (SGLT2) inhibitors, particularly dapagliflozin, have recently emerged as promising agents in cardiovascular medicine, demonstrating significant cardioprotective properties in patients with HF, irrespective of diabetes status [7, 8]. Preclinical studies and emerging clinical evidence suggest that dapagliflozin might attenuate chemotherapy-induced cardiac damage through mechanisms including improved myocardial metabolism, reduced inflammation, oxidative stress, and fibrosis [1, 9].

This review aims to comprehensively discuss the current understanding of chemotherapy-induced cardiac toxicity, critically evaluate existing diagnostic and management strategies, and highlight the emerging evidence supporting the potential cardioprotective role of dapagliflozin. Finally, we outline critical research gaps and introduce an ongoing clinical investigation exploring dapagliflozin's efficacy in mitigating CIC, which may substantially impact clinical practice and patient outcomes.

Mechanisms of chemotherapy-induced cardiac toxicity

Chemotherapy-induced cardiotoxicity (CIC) encompasses a diverse array of pathophysiological processes that impair cardiac structure and function. The underlying mechanisms differ significantly depending on the type of chemotherapeutic agent used. Broadly, CIC can be classified into two categories: irreversible myocardial injury, most often associated with anthracyclines such as doxorubicin, and reversible functional impairment, typically seen with HER2-targeted therapies like trastuzumab and pertuzumab [2]. Recent mechanistic studies, including several seminal papers, have clarified these distinct pathways, which are essential for optimizing surveillance strategies and guiding cardioprotective interventions tailored to the molecular signature of each agent..

Topoisomerase IIβ-Mediated DNA damage

One of the earliest and most critical events in anthracycline-induced cardiotoxicity involves the interaction between doxorubicin and topoisomerase IIβ (Top2β), an isoform predominantly expressed in mature cardiomyocytes. Doxorubicin forms stable ternary complexes with Top2β and DNA, resulting in double-strand breaks that activate the p53-dependent apoptotic pathway. Beyond direct genotoxicity, this interaction also represses the transcription of key genes involved in mitochondrial biogenesis and oxidative defense, including PGC-1α, NRF1, and TFAM. The suppression of these mitochondrial regulators leads to compromised energy production and increased vulnerability to oxidative injury, ultimately promoting cardiomyocyte apoptosis and irreversible structural damage [10, 11].

Oxidative Stress and Reactive Oxygen Species (ROS)

Oxidative stress is a central and well-characterized mechanism in anthracycline-induced cardiotoxicity. Doxorubicin undergoes redox cycling in the presence of NADPH, generating excessive reactive oxygen species (ROS) such as superoxide anions, hydrogen peroxide, and hydroxyl radicals. These ROS overwhelm the heart's antioxidant defenses—including glutathione peroxidase, superoxide dismutase (SOD), and catalase—resulting in widespread lipid peroxidation, DNA fragmentation, and protein oxidation.

A key contributor to this process is doxorubicin's high affinity for cardiolipin, a phospholipid in the inner mitochondrial membrane that anchors components of the electron transport chain. This interaction impairs mitochondrial respiration and amplifies ROS production.

Over time, the sustained oxidative damage leads to mitochondrial dysfunction, activation of apoptotic signaling, and irreversible myocardial injury [3, 12, 13].

Mitochondrial dysfunction and quality control impairment

Mitochondrial damage is a hallmark of anthracycline-induced cardiotoxicity and plays a central role in disease progression. Doxorubicin accumulates in mitochondria and binds to cardiolipin, disrupting the structure of the inner mitochondrial membrane and impairing the electron transport chain (ETC). This interference reduces ATP production, increases electron leakage, and further enhances ROS generation [13].

One major consequence is the opening of the mitochondrial permeability transition pore (mPTP), which leads to loss of membrane potential, mitochondrial swelling, and cytochrome c release, ultimately triggering intrinsic apoptosis [14].

Beyond direct structural damage, doxorubicin impairs mitochondrial quality control (MQC) — the system responsible for maintaining mitochondrial health — by disrupting:

Mitophagy, through downregulation of PINK1 and Parkin
Fission–fusion dynamics, via imbalance of Drp1 and OPA1
Biogenesis, by suppressing SIRT3, PGC-1α, and TFAM expression

These maladaptations lead to an accumulation of dysfunctional mitochondria, amplifying oxidative stress and compromising cardiomyocyte survival [15].

Iron overload and ferroptosis

Anthracyclines disrupt cardiac iron metabolism, creating a pro-oxidative environment that contributes to cardiomyocyte death. Doxorubicin increases cellular iron uptake by upregulating transferrin receptor 1 (TfR1) and simultaneously downregulates ferroportin, reducing iron export. This leads to iron accumulation within cardiomyocytes, especially in mitochondria, where it catalyzes Fenton reactions that generate highly reactive hydroxyl radicals [14].

This iron overload promotes a specific, non-apoptotic form of regulated cell death known as ferroptosis, which is characterized by lipid peroxidation, mitochondrial membrane shrinkage, and loss of glutathione peroxidase 4 (GPX4) activity. Doxorubicin enhances this process by depleting GSH, increasing ACSL4 and lipoxygenase expression, and impairing antioxidant defenses [15].

In addition, anthracycline exposure upregulates heme oxygenase-1 (HO-1) and inhibits heme biosynthesis enzymes, further aggravating iron misdistribution and oxidative stress [13]. These overlapping insults lead to mitochondrial collapse and irreversible myocardial injury.

Calcium homeostasis disruption

Doxorubicin disrupts intracellular calcium balance, contributing to both systolic and diastolic cardiac dysfunction. It impairs the activity of sodium–calcium exchangers (NCX) and sarcoplasmic reticulum calcium ATPases (SERCA2a), leading to elevated cytosolic calcium levels during diastole [13].

The resulting calcium overload activates calpain, a calcium-dependent cysteine protease, which cleaves structural and regulatory proteins such as titin and troponin I, weakening cardiomyocyte contractility and accelerating cellular apoptosis [15].

Moreover, the excess mitochondrial calcium uptake leads to mitochondrial swelling, membrane rupture, and further amplification of ROS production, creating a feedback loop that exacerbates energy failure and cardiac cell death [14].

Epigenetic alterations and MicroRNA dysregulation

Doxorubicin induces lasting epigenetic changes in cardiomyocytes, including DNA methylation, histone modifications, and altered microRNA (miRNA) profiles [10]. These changes impair cardioprotective signaling and promote cell death.

Key survival genes such as GATA-4 and Bcl-2 are downregulated, shifting the balance toward apoptosis [15]. At the same time, dysregulation of miRNAs like miR-34a and miR-146a contributes to oxidative stress, impaired mitochondrial function, and early cardiac remodeling [10].

These epigenetic alterations may persist beyond treatment, particularly in aging or at-risk hearts, leading to progressive dysfunction.

Reversible cardiotoxicity (HER2-Targeted Therapies)

Inhibition of HER2/Neuregulin-1 survival signaling

Unlike anthracyclines, trastuzumab and pertuzumab typically cause reversible cardiac dysfunction without structural injury. Their cardiotoxic effects arise from blocking the HER2/HER4–neuregulin-1 pathway, which is critical for cardiomyocyte survival, repair, and stress response [16].

Under normal conditions, HER2 activation stimulates PI3K/Akt and ERK1/2 signaling, protecting the heart

from oxidative and mechanical stress. Inhibition of HER2 interferes with these prosurvival signals, leading to contractile dysfunction, particularly in patients with reduced cardiac reserve [11].

Importantly, this mechanism is functional rather than structural, and cardiac function often recovers after discontinuation of the drug.

Mitochondrial stress and ferroptosis sensitization

HER2-targeted therapies may increase mitochondrial vulnerability by impairing the cardiomyocyte's ability to manage oxidative stress. HER2 signaling supports mitochondrial function and antioxidant responses; thus, its inhibition reduces the cell's defense against ROS and metabolic strain [11].

Recent evidence also shows that trastuzumab can sensitize cardiomyocytes to ferroptosis, an iron-dependent form of cell death. This occurs through altered lipid metabolism, downregulation of protective enzymes like GPX4, and increased mitochondrial lipid peroxidation [17].

These effects are often exacerbated in patients previously exposed to anthracyclines, creating a two-hit model of cardiotoxicity.

Risk factors for irreversibility

Although HER2-targeted cardiotoxicity is typically reversible, certain factors increase the risk of persistent dysfunction. These include prior anthracycline exposure, older age, hypertension, diabetes, and pre-existing cardiac disease [18].

In such cases, the loss of HER2-mediated protective signaling may expose subclinical myocardial vulnerabilities, especially when combined with mitochondrial or oxidative stress. Patients with.

these risk factors may experience delayed or incomplete recovery, underscoring the need for early detection and individualized cardioprotective strategies [19].

Diagnostic tools and biomarkers for chemotherapy-induced cardiotoxicity

Detecting CIC early is essential to prevent irreversible cardiac damage and guide timely interventions. Clinicians now rely on a combination of imaging techniques and cardiac biomarkers to assess both structural and functional changes in the heart during and after cancer treatment. Each tool offers unique advantages and limitations in terms of sensitivity, specificity, and clinical utility.

Cardiac imaging modalities

Echocardiography

Echocardiography is often the first tool used to evaluate cardiac function during chemotherapy. It's non-invasive, widely available, and cost-effective. While traditional echocardiography provides valuable measurements like LVEF, newer techniques such as speckle-tracking echocardiography (STE) offer enhanced sensitivity. STE enables the measurement of global longitudinal strain (GLS), which can detect subclinical cardiac dysfunction before a drop in LVEF occurs [20].

Despite its strengths, echocardiography has some drawbacks. Image quality can be poor in certain patients (e.g., obese or post-mastectomy), and results may vary depending on the operator's skill, potentially limiting its reproducibility.

Cardiac Magnetic Resonance Imaging (CMR)

Cardiac MRI is considered the gold standard for assessing cardiac volumes, function, and tissue characterization. It is particularly useful when echocardiographic images are inconclusive. CMR can identify myocardial edema, fibrosis, or inflammation using advanced techniques such as late gadolinium enhancement (LGE) and T1/T2 mapping [21].

However, CMR has its limitations—it's expensive, time-consuming, and not always available. Patients with claustrophobia or implanted metallic devices may also find it challenging to undergo MRI scans.

As emphasized by Christian et al., combining echocardiography and CMR within a standardized, multimodal imaging framework enhances diagnostic accuracy and allows for earlier detection of drug-induced myocardial dysfunction [22]. Their work underscores the importance of consistency in imaging protocols to improve longitudinal monitoring, particularly in patients undergoing cardiotoxic cancer therapies.

Cardiac biomarkers

Troponins

Cardiac troponins (especially high-sensitivity troponin I and T) are among the most sensitive and specific biomarkers of myocardial injury. Elevations in troponin levels during chemotherapy—particularly with anthracyclines or HER2-targeted therapies—can serve as early indicators of cardiotoxicity, even before symptoms or imaging abnormalities appear [23]. However, elevations may also occur in other conditions (e.g., renal failure) [24], which can reduce specificity.

Natriuretic peptides (BNP and NT-proBNP)

B-type natriuretic peptide (BNP) and its inactive fragment, NT-proBNP, are released in response to ventricular wall stress and volume overload. They are commonly used to assess HF risk and have shown value in predicting CIC [25]. NT-proBNP, with its longer half-life and

stability, is often preferred in clinical settings. However, like troponins, these markers may also be elevated due to other non-cardiac conditions, including renal dysfunction [26].

Galectin-3

Galectin-3, a β-galactoside-binding lectin involved in inflammation and fibrosis, has been studied as a potential biomarker for CIC. Some studies have found correlations between elevated Galectin-3 levels and cardiac remodeling in cancer patients, particularly in relation to fibrosis and oxidative stress [27, 28]. However, others—including a meta-analysis by Wu et al. and a cohort study by van den Berg et al.—reported no consistent association, with limited predictive value and possible sex-specific differences [29, 30]. These mixed findings suggest that Galectin-3's role remains uncertain and requires further validation in larger prospective studies.

Myeloperoxidase (MPO)

MPO is an oxidative enzyme released by activated immune cells during inflammation, where it contributes to endothelial injury and promotes oxidative stress [31]. In the context of cancer therapy—particularly with anthracyclines and HER2-targeted agents—MPO has emerged as a promising early biomarker for detecting subclinical cardiotoxicity. Elevated MPO levels may precede measurable declines in cardiac function, offering a valuable window for early risk stratification and intervention [32]. Although further prospective validation is needed, current evidence supports its potential role in cardio-oncology surveillance.

While each diagnostic modality offers valuable insights into CIC, they also have inherent limitations. Therefore, integrating imaging techniques with sensitive circulating biomarkers remains essential for accurate early detection, risk stratification, and timely intervention. As emphasized by Murtagh et al., standardizing the use of biomarkers such as troponins, natriuretic peptides, and galectin-3—alongside imaging tools—could significantly enhance surveillance strategies and improve clinical outcomes in cardio-oncology [33].

Risk factors and clinical predictors of chemotherapy-induced cardiotoxicity

CIC arises from a complex interplay of patient-related vulnerabilities and therapy-specific characteristics. Recognizing these risk factors is essential for guiding risk stratification, optimizing treatment decisions, and implementing preventive strategies in cardio-oncology.

Patient-related factors

A range of individual characteristics may predispose patients to CIC:

- Age**:** Age is a well-established determinant of cardiotoxicity risk. According to a review by Screever et al., children may exhibit heightened vulnerability due to increased apoptotic priming of cardiac cells, whereas elderly patients are more affected by age-related cardiac senescence and telomere dysfunction [34]. These distinct age-related mechanisms highlight the need for tailored preventive approaches across the lifespan.
- Pre-existing Cardiovascular Disease: Patients with underlying cardiovascular conditions—including hypertension, diabetes, or coronary artery disease—face a markedly increased risk of cardiotoxic complications, particularly with anthracycline-based regimens. Raisi et al. emphasized the necessity of comprehensive baseline cardiovascular assessment and individualized monitoring protocols for this high-risk group [35].
- Genetic and Epigenetic Susceptibility: Genetic variation also contributes significantly to differential susceptibility. Polymorphisms in genes regulating drug metabolism, oxidative stress responses, and myocardial function can influence cardiotoxic outcomes. Moreover, emerging evidence suggests that epigenetic mechanisms may further modify individual risk [36].
- Lifestyle Factors: Modifiable factors such as smoking, obesity, sedentary behavior, and poorly controlled diabetes exacerbate cardiovascular vulnerability during cancer therapy. These risks underscore the importance of lifestyle optimization as part of a comprehensive cardio-oncology care plan [37].

Cancer therapy–related factors

Therapy-related variables are equally critical in determining cardiotoxicity risk:

- Drug Type: Different classes of cancer therapies exert cardiotoxic effects through diverse mechanisms. Anthracyclines, such as doxorubicin, are known for causing dose-dependent and often irreversible myocardial injury [3]. In contrast, HER2-targeted agents like trastuzumab typically induce reversible cardiac dysfunction [19]. Other therapies—including VEGF inhibitors, immune checkpoint inhibitors, and tyrosine kinase inhibitors—have been implicated in a

range of cardiovascular events such as hypertension, arrhythmias, myocarditis, and HF [38].

- Cumulative Dose: Among all chemotherapeutic agents, anthracyclines carry the most pronounced dose-dependent cardiotoxic risk. The incidence of HF rises substantially when the cumulative dose of doxorubicin exceeds 400 mg/m^2, underscoring the need for strict dose surveillance throughout treatment [39].
- Combination Therapies: The combined use of multiple cardiotoxic modalities—such as anthracyclines, HER2 inhibitors, and mediastinal radiotherapy—significantly amplifies the risk of cardiac injury. These agents may exert synergistic effects on myocardial tissue, necessitating careful regimen design and intensified cardiovascular monitoring in patients receiving multimodal cancer therapy [40].

Preventive strategies for chemotherapy-induced cardiotoxicity

As cancer survival rates improve, preventing CIC has become essential in cardio-oncology. Cardiac complications can disrupt treatment and impact long-term outcomes. Recent evidence supports a range of pharmacological and non-pharmacological strategies, particularly for high-risk patients receiving anthracyclines or HER2-targeted therapies. This section summarizes current preventive approaches and key clinical trial findings while addressing ongoing challenges.

Dexrazoxane: targeted cardioprotection for anthracycline therapy

Dexrazoxane remains the only FDA-approved cardioprotective agent specifically indicated for use alongside anthracycline chemotherapy. Its dual mechanism—chelating intracellular iron and inhibiting topoisomerase IIβ in cardiomyocytes—attenuates the formation of anthracycline–iron complexes and subsequent oxidative stress [41]. Clinical trials and meta-analyses have consistently demonstrated its efficacy in reducing the incidence of left ventricular dysfunction and HF in adult patients receiving anthracyclines [41, 42]. A recent consensus and guideline statement by Lyon et al. confirmed that dexrazoxane significantly reduces anthracycline-induced cardiotoxicity without compromising anticancer efficacy [43]. These guidelines recommend its use in high-risk patients, particularly those approaching or exceeding a cumulative doxorubicin dose of 300–400 mg/m^2. Although initial regulatory concerns—such as potential interference with chemotherapy efficacy, increased risk of secondary malignancies, and myelosuppression—led the EMA to temporarily contraindicate dexrazoxane in children in 2011, these restrictions were partially lifted in 2017 following evidence from adult studies that did not substantiate these risks [44, 45]. Nevertheless, its use remains limited in clinical practice, particularly in pediatric settings, due to persistent caution and a lack of long-term safety data. Broader clinical adoption will require clearer guideline recommendations, enhanced clinician awareness, and improved access—especially for high-risk patients receiving cumulative anthracycline doses.

Neurohormonal blockers (ACEIs, ARBs, Beta-Blockers)

ACEIs, ARBs and beta-blockers have been investigated for preventing CIC due to their roles in reducing myocardial fibrosis, oxidative stress, and ventricular remodeling [46]. The CECCY trial found that carvedilol did not significantly prevent LVEF decline in low-risk patients but reduced troponin elevation [47]. Similarly, the PRADA trial showed a modest benefit of candesartan in preserving LVEF, with no significant effect from metoprolol [48].

A 2023 meta-analysis pooling 15 RCTs confirmed that ACEIs/ARBs and beta-blockers significantly preserved LVEF in patients receiving anthracyclines or trastuzumab, especially those with elevated cardiac risk [46]. The ESC 2022 guidelines support prophylactic use of these agents in selected high-risk patients [43].

Although not universally recommended, neurohormonal blockers—including β-blockers and RAAS inhibitors—are increasingly used in patients with cardiovascular comorbidities or early subclinical myocardial injury during chemotherapy due to their favorable safety profile and potential cardioprotective effects [2]. However, their benefits remain modest and variable. Most randomized trials and meta-analyses report small improvements in LVEF, typically ranging from 2 to 4%, with unclear long-term impact on clinical outcomes such as mortality or sustained HF prevention [6, 46].

Statins

Statins (e.g., atorvastatin) are known for their anti-inflammatory and antioxidant effects beyond lipid-lowering. Retrospective cohort studies and the 2023 STOP-CA randomized controlled trial showed that atorvastatin significantly reduced LVEF decline in patients receiving high-dose anthracyclines, particularly in lymphoma patients [49]. A 2024 umbrella review further supported statins' cardioprotective potential, especially in patients receiving trastuzumab [50]. However, the PREVENT trial, which included mostly lower-risk breast cancer patients receiving lower anthracycline doses (~ 240 mg/

Table 1 Summarizes key preventive strategies for CIC, highlighting their mechanisms, evidence levels, and limitations

Strategy	Mechanism of Action	Evidence Level	Limitations	Key References
Dexrazoxane	Iron chelation and inhibition of topoisomerase IIβ	High (RCTs, Guidelines)	Limited use in pediatrics; concerns about long-term safety; underutilized	[42, 43]
ACEIs / ARBs	Inhibition of RAAS; reduces remodeling and fibrosis	Moderate (RCTs, Meta-analyses)	Modest effect on LVEF; variability in trial outcomes	[46, 47]
Beta-blockers	Reduces sympathetic tone and oxidative stress	Moderate	Some studies report no significant benefit in LVEF preservation	[48]
Statins	Antioxidant and anti-inflammatory actions beyond lipid-lowering	Moderate (Cohorts, RCTs)	No benefit in low-risk settings; efficacy may depend on baseline risk	[49, 51]
Dapagliflozin (SGLT2i)	Enhances myocardial metabolism; reduces oxidative stress, inflammation, fibrosis	Emerging (Preclinical, RCTs)	Lacks large-scale cardio-oncology trials; long-term data pending	[7, 9]

m^2), found no significant LVEF benefit from atorvastatin over 24 months [51]. This suggests statin efficacy may depend on baseline cardiovascular risk and chemotherapy intensity. While statins show promise in high-risk patients, they are not yet recommended for routine use in all cancer patients. More research is needed to define ideal candidates and timing (Table 1).

Limitations of current preventive approaches

While pharmacological agents show promise, their modest efficacy, limited eligibility, and unresolved safety concerns—such as the debated risk of secondary malignancies with dexrazoxane—reflect broader systemic challenges. Despite increasing focus on CIC, preventive strategies remain limited by clinical, structural, and research-related gaps that hinder consistent use and real-world effectiveness.

System-level barriers continue to limit the success of cardiotoxicity prevention. Current risk models based on age or anthracycline dose lack precision—some patients develop toxicity at low doses, while others remain unaffected [52]. Most interventions are reactive, initiated only after biomarker changes like troponin rise or GLS decline, which may miss the optimal window for prevention [32].

Care is often fragmented, with cardiology input delayed until symptoms appear. Inconsistent access to cardio-oncology services and unclear monitoring protocols contribute to underdiagnosis [2, 43]. Trials frequently exclude high-risk patients, and most focus on short-term outcomes like LVEF, offering limited insight into long-term risks or cost-effectiveness [39].

Emerging cardioprotective agents: the role of SGLT2 inhibitors

Given the limited efficacy of current strategies for preventing CIC, there is growing interest in repurposing agents with established cardiovascular benefits. Sodium-glucose cotransporter 2 (SGLT2) inhibitors—originally developed for type 2 diabetes—have emerged as particularly promising candidates. These agents have demonstrated significant cardioprotective effects across a wide range of patient populations, including those without diabetes. The landmark DAPA-HF and EMPEROR-Reduced trials established dapagliflozin and empagliflozin, respectively, as effective treatments for HF with reduced ejection fraction (HFrEF), reducing both cardiovascular mortality and HF hospitalizations irrespective of glycemic status [7, 8]. Their success has expanded their indication to include HF with preserved ejection fraction (HFpEF) and has led to their adoption as cornerstone therapies in HF management.

The mechanisms underlying these cardioprotective effects are multifactorial. SGLT2 inhibitors promote natriuresis and osmotic diuresis, thereby reducing preload and ventricular wall stress. They improve myocardial energetics by shifting substrate utilization toward ketone bodies—an efficient fuel source for the failing heart—and enhance mitochondrial function and ATP production [53]. Additionally, they exert potent anti-inflammatory and antioxidant effects, reducing systemic cytokine levels and mitigating oxidative stress, both of which are key contributors to chemotherapy-induced myocardial injury [54].

These pleiotropic actions suggest a mechanistic overlap with the pathogenesis of CIC, particularly in the context of anthracycline- or trastuzumab-induced cardiac dysfunction.

Implications for chemotherapy-induced cardiotoxicity

Given their efficacy in HF and their favorable safety profile, SGLT2 inhibitors have become attractive candidates for repurposing in cardio-oncology. Preclinical studies have begun exploring their potential role in preventing CIC, with encouraging results in animal models showing reduced oxidative damage, fibrosis, and apoptosis in doxorubicin-treated hearts [1, 9].

These findings support the rationale for evaluating SGLT2 inhibitors as novel cardioprotective agents in cancer patients undergoing high-risk chemotherapy. Among them, dapagliflozin stands out due to its extensive cardiovascular safety data and favorable tolerability, making it a prime candidate for clinical trials in cardio-oncology.

While dapagliflozin is the primary focus of this review, it is important to acknowledge that other SGLT2 inhibitors—such as empagliflozin and canagliflozin—have also demonstrated significant cardioprotective benefits in heart failure populations. Both dapagliflozin (DAPA-HF) and empagliflozin (EMPEROR-Reduced) have shown reductions in cardiovascular mortality and heart failure hospitalizations, regardless of glycemic status [7, 8]. Mechanistically, these agents share similar pathways involving improvements in myocardial energetics, reductions in inflammation and oxidative stress, and attenuation of fibrosis [55, 56]. However, dapagliflozin was chosen as the focus of this review based on its superior availability in our clinical setting, robust safety profile, and its selection as the investigational agent in our ongoing randomized trial (NCT06888505) evaluating cardioprotection in patients receiving anthracyclines with or without HER2-targeted therapies.

Dapagliflozin as a potential cardioprotective agent in oncology

Building on the established cardioprotective profile of SGLT2 inhibitors, dapagliflozin has emerged as a particularly promising candidate for application in cardio-oncology. Its efficacy in reducing cardiovascular mortality and HF hospitalizations—demonstrated in both diabetic and non-diabetic patients—has positioned it as a leading agent among this class, with extensive safety data supporting its use in vulnerable populations [7].

What distinguishes dapagliflozin in the context of CIC is the overlap between its mechanistic benefits and the pathophysiology of cancer therapy–related cardiac injury. Chemotherapeutic agents such as anthracyclines and HER2-targeted therapies promote cardiotoxicity via oxidative stress, mitochondrial dysfunction, inflammation, and fibrosis—precisely the pathways modulated by dapagliflozin.

Modulation of cardiac metabolism and mitochondrial integrity

Dapagliflozin improves cardiac metabolic efficiency by shifting myocardial substrate utilization toward ketone bodies, which generate more ATP per molecule of oxygen than glucose or fatty acids. This metabolic adaptation is particularly beneficial under stress conditions such as those induced by chemotherapy, where energy demand increases and mitochondrial function is often compromised [53]. In addition to enhancing energy production, dapagliflozin helps preserve mitochondrial structure by reducing swelling and maintaining membrane integrity. It also inhibits the opening of the mitochondrial permeability transition pore (mPTP), a key trigger of apoptosis, thereby supporting cardiomyocyte survival during exposure to cardiotoxic agents like doxorubicin [1].

Anti-inflammatory and antioxidant actions

Inflammation and oxidative stress are central to the pathogenesis of CIC, contributing to cardiomyocyte injury and fibrosis. Dapagliflozin exerts protective effects by downregulating key pro-inflammatory cytokines, including TNF-α and IL-6, thereby dampening the inflammatory cascade [54]. Recent evidence also implicates SGK1 (serum- and glucocorticoid-regulated kinase 1) as a key upstream mediator of inflammation and apoptosis in doxorubicin-induced cardiotoxicity. SGK1 enhances NF-κB activity, thereby promoting pro-inflammatory signaling and cell death [57]. Dapagliflozin has been shown to suppress SGK1 expression, contributing to reduced myocardial inflammation and improved mitochondrial functionc [58]. In parallel, the drug enhances antioxidant defenses by upregulating enzymes such as superoxide dismutase and glutathione peroxidase, limiting oxidative damage and supporting cardiomyocyte survival during chemotherapy [9].

Antifibrotic and remodeling effects

Myocardial fibrosis and adverse ventricular remodeling are major contributors to long-term cardiac dysfunction in patients receiving chemotherapy. Dapagliflozin has demonstrated antifibrotic effects in preclinical models, primarily through inhibition of the TGF-β1/Smad signaling pathway, leading to reduced collagen deposition and improved ventricular structure [59]. Additionally, it enhances SIRT6 expression, which mitigates oxidative stress and suppresses fibroblast activation [55]. Recent studies have also identified SGK1 as a key regulator of fibrosis in doxorubicin-induced cardiotoxicity. Dapagliflozin appears to downregulate SGK1 expression, thereby attenuating profibrotic signaling and extracellular matrix accumulation [57, 58]. These mechanisms are consistent with findings from Ulusan et al., who observed reduced

myocardial injury and structural remodeling with dapagliflozin in a rat model of anthracycline exposure [9]. Clinically, its capacity to reduce cardiac stiffness and improve diastolic function further supports its potential for cardioprotection in oncology settings [56]. These mechanistic pathways are summarized in Fig. 1.

Preclinical evidence and ongoing clinical translation

Dapagliflozin has demonstrated consistent cardioprotective effects in multiple preclinical models of CIC. These include preservation of left ventricular function, reduction of myocardial fibrosis, and protection of mitochondrial structure and function [1, 9]. The mechanisms underlying these effects include attenuation of oxidative stress, inhibition of apoptosis, and modulation of fibrosis-related signaling pathways—such as TGF-β1/Smad and SIRT6-mediated remodeling [55, 59]. Collectively, these preclinical findings provide a strong rationale for investigating dapagliflozin in patients undergoing anthracycline-based chemotherapy.

To explore its clinical relevance, our group is conducting a randomized, double-blind, placebo-controlled clinical trial evaluating the cardioprotective effect of dapagliflozin in adult cancer patients receiving anthracycline-based chemotherapy, with or without trastuzumab. The trial aims to assess whether dapagliflozin can reduce the incidence and severity of chemotherapy-induced cardiac dysfunction. Participants are randomized to receive either dapagliflozin 10 mg daily or placebo during chemotherapy, with serial monitoring of cardiac function and biomarkers throughout the study period.

The primary outcomes include changes in LVEF and circulating biomarkers such as high-sensitivity troponin I, NT-proBNP, and galectin-3—markers with established utility in detecting early myocardial injury, neurohormonal stress, and fibrotic remodeling [33]. The study design aligns with contemporary cardio-oncology recommendations advocating for biomarker-guided surveillance to facilitate early detection and intervention.

If successful, these investigations—including our ongoing trial—could establish dapagliflozin as a novel cardioprotective strategy in patients receiving potentially cardiotoxic cancer therapies. With several studies currently underway, this growing body of evidence may collectively position SGLT2 inhibitors as part of standard supportive care in oncology. Given its oral administration, favorable safety profile, and multitargeted mechanisms, dapagliflozin offers a practical and promising approach to mitigating cardiovascular complications during cancer treatment. *Our study is registered at ClinicalTrials.gov (Identifier: NCT06888505).*

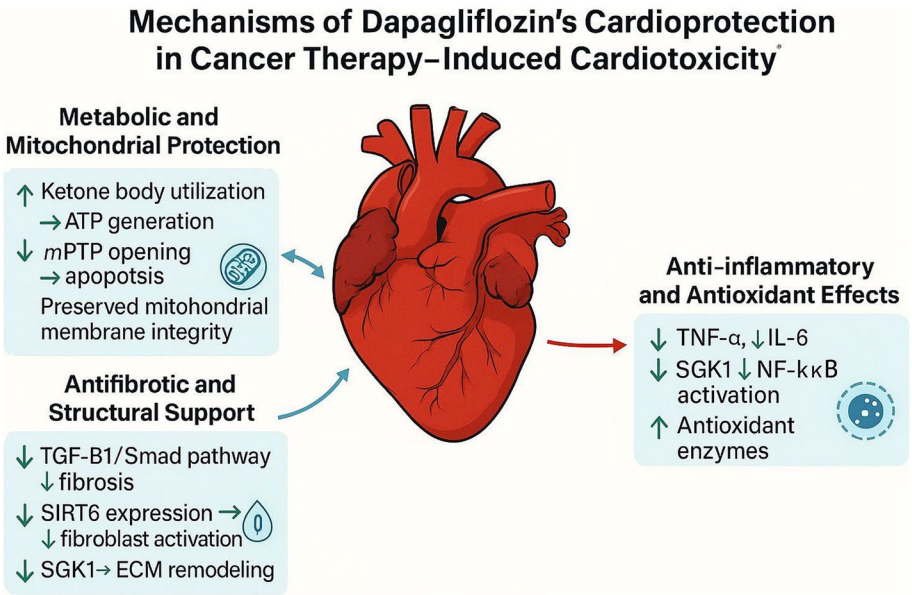

Fig. 1 Proposed mechanisms of dapagliflozin's cardioprotection in cancer-therapy–induced cardiotoxicity. Dapagliflozin may confer (A) metabolic/mitochondrial protection—enhanced ketone utilization and ATP generation, reduced mPTP opening, and preservation of mitochondrial membrane integrity; (B) anti-inflammatory/antioxidant effects—lower TNF-α/IL-6 levels, decreased SGK1/NF-κB signalling, and increased antioxidant enzymes; and (C) antifibrotic/structural support—attenuation of TGF-β1/Smad signalling, reduced fibroblast activation (via SIRT6), and modulation of SGK1-dependent ECM remodelling. Abbreviations: ATP, adenosine triphosphate; ECM, extracellular matrix; IL-6, interleukin-6; mPTP, mitochondrial permeability transition pore; NF-κB, nuclear factor-κB; SGK1, serum/glucocorticoid-regulated kinase 1; SIRT6, sirtuin-6; TGF-β1, transforming growth factor-β1

Conclusion

CIC remains a major limitation in cancer care, with significant implications for survivorship. While current preventive strategies offer only modest benefits, emerging evidence suggests that SGLT2 inhibitors—particularly dapagliflozin—may offer a novel, mechanistically aligned approach to cardioprotection. Through improvements in mitochondrial function, reductions in oxidative stress, and antifibrotic actions, dapagliflozin directly addresses the key pathophysiological drivers of CIC. Preclinical models have demonstrated consistent benefits, and ongoing clinical trials, including our own, aim to validate its role in cancer patients receiving anthracycline-based chemotherapy. If confirmed, dapagliflozin could become a cornerstone of cardio-oncology care, offering a practical, evidence-based solution to preserve cardiac health during and after cancer treatment.

Abbreviations

ACEI	Angiotensin-Converting Enzyme Inhibitor
ARB	Angiotensin II Receptor Blocker
CIC	Chemotherapy-Induced Cardiotoxicity
CMR	Cardiac Magnetic Resonance
HF	Heart Failure
LVEF	Left Ventricular Ejection Fraction
NT-proBNP	N-terminal pro-B-type Natriuretic Peptide
SGLT2i	Sodium-Glucose Cotransporter-2 Inhibitor

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Authors' contributions

H.A.S. conceptualized the review topic, conducted the literature search, and drafted the manuscript. N.A.M.A. provided critical revisions, contributed to the interpretation of cardiotoxicity mechanisms, and supervised the scientific direction. R.T.O. reviewed clinical evidence, refined the sections on emerging therapies, and contributed to manuscript editing. All authors read and approved the final manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

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Competing interests

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