AUCTORES
Globalize your Research

Journal of Clinical Cardiology and Cardiovascular Interventions
Macit Kalcik *

Open Access

Review Article

Molecular Mechanisms, Diagnosis, and Management of Chemotherapy Related Cardiotoxicity

Ahmed Şefik Begoğlu [1], Macit Kalçık [2]*, Mucahit Yetim [2], Muhammet Cihat Çelik [1], Lütfü Bekar [2], Yusuf Karavelioğlu [2]

[1]Department of Cardiology, Hitit University Erol Olçok Education and Research Hospital, Corum, Turkey.

[2]Department of Cardiology, Facult of Medicine, Hitit University, Corum, Turkey

***Corresponding Author:** Macit Kalcik, Department of Cardiology, Facult of Medicine, Hitit University, Corum, Turkey.

Received date: September 30, 2025; Accepted date: October 24, 2025; Published date: November 06, 2025

Citation: Ahmed Şefik Begoğlu , Macit Kalçık , Mucahit Yetim , Muhammet Cihat Çelik, Lütfü Bekar, , et al, (2025), Molecular Mechanisms, Diagnosis, and Management of Chemotherapy Related Cardiotoxicity, *J Clinical Cardiology and Cardiovascular Interventions*, 8(15); **DOI:10.31579/2641-0419/522**

Abstract

Cardiotoxicity remains a major limitation of contemporary cancer therapy, affecting both traditional cytotoxic agents and novel targeted and immunotherapeutic drugs. This review summarizes current understanding of the molecular and clinical mechanisms underlying therapy-induced cardiac injury and highlights strategies for prevention, early detection, and management. Classical antineoplastic agents such as anthracyclines, cyclophosphamide, and platinum compounds induce myocardial damage primarily through oxidative stress, mitochondrial dysfunction, calcium handling abnormalities, and apoptotic signaling. Targeted therapies, including HER2 inhibitors and tyrosine kinase inhibitors, cause cardiac dysfunction via interference with survival pathways and endothelial injury, while immune checkpoint inhibitors can trigger fulminant myocarditis through T-cell–mediated inflammation. Despite their diverse mechanisms, these treatments converge on shared molecular pathways involving reactive oxygen species generation, mitochondrial impairment, and inflammasome activation. Advances in biomarkers (troponins, natriuretic peptides) and imaging techniques (strain echocardiography, cardiac magnetic resonance) have enabled earlier recognition of subclinical dysfunction. Preventive interventions, such as dose optimization, liposomal anthracyclines, ACE inhibitors, beta-blockers, and dexrazoxane, reduce risk, while structured cardio-oncology collaboration facilitates safe continuation of oncologic therapy. Emerging approaches, including artificial intelligence–based risk modeling, digital health monitoring, and precision pharmacogenomics, promise to individualize care and integrate cardiac protection into cancer treatment planning. Cardio-oncology is evolving toward a precision-based discipline focused on preserving both life expectancy and long-term cardiovascular health in cancer survivors.

Key Words: cardiotoxicity; cancer therapy; anthracyclines; immune checkpoint inhibitors; cardio-oncology

Introduction

Over the past few decades, remarkable progress in cancer therapy has substantially improved survival rates across many malignancies. However, this therapeutic success has unveiled a new challenge: the growing burden of cardiovascular complications among cancer survivors. Cardiotoxicity induced by cancer treatment has emerged as a leading cause of morbidity and mortality in this population, sometimes surpassing the risk of tumor recurrence itself [1,2].

In clinical practice, the term *cardiotoxicity* encompasses a broad spectrum of adverse cardiovascular outcomes related to cancer therapies. These range from asymptomatic myocardial injury and declines in left ventricular ejection fraction (LVEF) to overt heart failure, arrhythmias, hypertension, ischemic heart disease, and thromboembolic events [3]. The onset of cardiotoxicity can be acute, occurring during or immediately after treatment; early, within the first year, or delayed, developing years after therapy completion [4]. Importantly, while certain agents, such as anthracyclines, induce irreversible myocardial damage, others, like HER2 inhibitors, typically cause reversible dysfunction if recognized early and managed appropriately (5).

The molecular mechanisms underlying treatment-related cardiotoxicity are multifactorial. Oxidative stress and excessive reactive oxygen species generation, mitochondrial dysfunction, calcium handling abnormalities, DNA damage, endothelial injury, and activation of inflammatory and apoptotic signaling cascades are key contributors [6]. These processes ultimately impair cardiomyocyte viability, promote fibrosis, and compromise contractile performance. Furthermore, the combination or sequential use of different anticancer modalities can amplify cardiac injury through additive or synergistic mechanisms [7].

Understanding these pathways is fundamental to developing effective cardioprotective strategies. This review will first examine the classical antineoplastic drugs, particularly anthracyclines and other cytotoxic agents, whose cardiotoxic effects have been studied for decades and remain clinically relevant. Subsequently, it will discuss the molecular and clinical mechanisms of newer targeted and immunotherapeutic agents,

which, despite their selectivity, also impose significant cardiac risks. By integrating mechanistic insights across traditional and modern therapies, this work aims to highlight the biological convergence of cardiotoxic injury and provide a framework for improving cardiac surveillance and prevention in oncology patients.

Classical Antineoplastic Agents and Cardiotoxicity

Anthracyclines, particularly doxorubicin, remain among the most effective and widely used antineoplastic drugs, yet they are also the prototypical cause of chemotherapy-induced cardiotoxicity. Their cardiac effects are dose-dependent and cumulative, with risk increasing sharply above total lifetime exposures of 400–550 mg/m². Despite their clinical efficacy, the mechanisms by which these drugs damage the myocardium are multifactorial and tightly interlinked [8].

A dominant hypothesis attributes anthracycline cardiotoxicity to excessive production of reactive oxygen species (ROS). Doxorubicin undergoes redox cycling through its quinone moiety in the presence of NADPH, generating superoxide anions and hydrogen peroxide. The high mitochondrial density and low antioxidant capacity of cardiomyocytes make them uniquely susceptible to oxidative injury. This ROS surge disrupts mitochondrial membranes, oxidizes lipids and proteins, and triggers DNA damage, ultimately impairing ATP synthesis and leading to necrotic or apoptotic cell death [9].

Another pivotal mechanism involves topoisomerase IIβ (Top2β). In cardiomyocytes, doxorubicin binds to Top2β-DNA complexes, inducing double-strand DNA breaks and transcriptional repression of mitochondrial biogenesis regulators such as PGC-1α and NRF-1. This impairs mitochondrial renewal and accelerates energy failure and apoptosis [10].

Mitochondrial dysfunction represents a convergent endpoint of these pathways. Structural abnormalities, including mitochondrial swelling, cristae loss, and disruption of oxidative phosphorylation, have been documented in both experimental and clinical settings (11). These defects lead to further ROS accumulation, calcium overload, and activation of intrinsic apoptotic signaling via cytochrome c release and caspase-3 activation.

Calcium dysregulation also contributes significantly to cardiomyocyte injury. Doxorubicin alters sarcoplasmic reticulum Ca^{2+} handling by inhibiting SERCA2a and sensitizing ryanodine receptors, causing diastolic calcium leak, contractile dysfunction, and arrhythmogenicity. In parallel, impairment of nitric oxide signaling and direct endothelial toxicity reduce coronary microvascular perfusion, compounding ischemic stress [12].

Inflammatory signaling and maladaptive remodeling further amplify chronic injury. ROS and damaged mitochondria activate NF-κB and NLRP3 inflammasome pathways, promoting cytokine release, fibrosis, and progressive left ventricular remodeling. This molecular cascade explains the delayed onset of anthracycline cardiomyopathy that may emerge years after completion of chemotherapy [13].

Beyond anthracyclines, other cytotoxic agents such as cyclophosphamide and cisplatin also exert cardiotoxic effects through distinct but related mechanisms. Cyclophosphamide metabolites, notably acrolein, provoke endothelial injury, oxidative stress, and hemorrhagic myocarditis, whereas platinum-based drugs induce endothelial dysfunction, increased vascular stiffness, and accelerated atherosclerosis. Although their clinical presentations vary, from acute heart failure to delayed ischemic disease, the underlying mechanisms often converge on oxidative stress and mitochondrial injury [14].

Taken together, classical antineoplastic agents compromise cardiac structure and function through an intricate web of oxidative, mitochondrial, inflammatory, and apoptotic pathways. These foundational insights have guided the development of early detection and cardioprotective strategies discussed in later sections (Table 1).

Drug Class	Representative Agents	Primary Cardiac Effects	Mechanistic Basis	Typical Onset
Anthracyclines	Doxorubicin, Daunorubicin	LV systolic dysfunction, heart failure	ROS generation, Top2β inhibition, mitochondrial injury	Dose-dependent, cumulative
Alkylating agents	Cyclophosphamide, Ifosfamide	Myocarditis, pericarditis, heart failure	Endothelial injury, oxidative stress, acrolein toxicity	Early (within days)
Platinum compounds	Cisplatin, Carboplatin	Hypertension, ischemia, endothelial dysfunction	Oxidative stress, vascular stiffness	Subacute to chronic
HER2 inhibitors	Trastuzumab, Pertuzumab	LV dysfunction (often reversible)	ErbB2 signaling inhibition	During therapy
VEGF inhibitors / TKIs	Bevacizumab, Sunitinib, Sorafenib	Hypertension, heart failure, ischemia	VEGF blockade, microvascular rarefaction	Variable
Immune checkpoint inhibitors	Nivolumab, Pembrolizumab, Ipilimumab	Myocarditis, arrhythmias	T-cell–mediated inflammation	Early (first 2 months)

Table 1: Major Classes of Antineoplastic Agents and Their Principal Cardiotoxic Effects

Abbreviations: *LV: left ventricle; ROS: reactive oxygen species; SR: sarcoplasmic reticulum; VEGF: vascular endothelial growth factor; TKI: tyrosine kinase inhibitor; ICI: immune checkpoint inhibitor.*

Targeted Cancer Therapies and Cardiotoxicity

The shift from broad chemotherapeutics to targeted therapies promised greater specificity and fewer off-target toxicities. In practice, this optimism has been tempered by the recognition that even highly selective agents can provoke cardiovascular injury via on-target or off-target mechanisms. These mechanisms frequently overlap with those triggered by classical agents, but also introduce unique pathways specific to growth factor signaling, receptor inhibition, and kinase cross-reactivity.

HER2-targeted Agents (Trastuzumab, Pertuzumab, ADCs)

HER2 (ErbB2) signaling is essential not only in oncogenesis but also in cardiomyocyte survival and stress response. Inhibiting HER2 disrupts neuregulin–ErbB4/ErbB2 axis, compromising cell survival signals under stress, especially in synergy with anthracyclines (15). Trastuzumab cardiotoxicity typically presents as a decline in LVEF, often reversible if managed promptly (16). Real-world and trial data show that patients with prior anthracycline exposure, older age, hypertension, or borderline

cardiac reserve are at higher risk [17]. A meta-analysis of trials combining trastuzumab with chemotherapy demonstrated that the incidence of cardiac adverse events was roughly 10–14%, with higher rates when anthracyclines were included [18]. Emerging HER2-directed agents (antibody–drug conjugates, small molecules) appear to have lower cardiotoxic rates, but long-term surveillance remains limited [19].

VEGF / Angiogenesis Inhibitors (Bevacizumab, Sunitinib, Sorafenib, etc.)

VEGF inhibitors cause a spectrum of cardiovascular toxicities, most commonly hypertension, but also myocardial ischemia, left ventricular dysfunction, thromboembolism, and vascular rarefaction [20]. The pathophysiology is multifactorial: endothelial dysfunction from VEGF blockade reduces nitric oxide bioavailability and impairs microvascular integrity; microvascular rarefaction increases peripheral resistance; and interference with repair pathways predisposes to ischemic injury in susceptible myocardium [21]. A network meta-analysis of VEGF-TKIs in cancer patients found that less selective agents (e.g. sorafenib, sunitinib) were associated with significantly higher risk of major adverse cardiovascular events and heart failure [22]. Animal models have confirmed that anti-VEGF therapy reduces capillary density and worsens pressure overload stress tolerance in the heart.

Other Kinase Inhibitors (BRAF/MEK, mTOR, EGFR, multitarget TKIs)

Beyond VEGF, many small-molecule inhibitors target multiple kinases and can exert unintended cardiac effects. BRAF/MEK inhibitors may alter cardiomyocyte metabolism and increase oxidative stress due to dysregulation of MAPK/ERK signaling. mTOR inhibitors impair mitochondrial biogenesis and stress adaptation. Some agents inhibit kinases involved in ion channel regulation, promoting QT prolongation or arrhythmia. A review summarizing targeted agents noted that many share downstream mechanisms: ROS generation, mitochondrial injury, impaired autophagy, and microvascular rarefaction [23].

Immunotherapy-Induced Cardiotoxicity

Immune checkpoint inhibitors (ICIs) have revolutionized oncology by enabling durable tumor control through T-cell activation. However, this immune re-engagement may also trigger autoimmune reactions against cardiac tissue, leading to potentially fatal myocarditis and other cardiovascular complications [24]. Although the reported incidence of ICI-related myocarditis is low, generally under 1%, its case-fatality rate may exceed 25% in severe presentations [25].

ICI-associated myocarditis typically occurs early, often within the first two months of therapy, and is more frequent when PD-1 and CTLA-4 inhibitors are administered in combination. The clinical presentation varies widely, ranging from asymptomatic troponin elevation to fulminant heart failure or malignant arrhythmias [26]. Endomyocardial biopsy findings reveal dense infiltration of $CD4^+$ and $CD8^+$ T lymphocytes with myocyte necrosis, indicating a T-cell–mediated cytotoxic process (27). Experimental studies confirm that loss of PD-1 signaling predisposes to spontaneous myocarditis and dilated cardiomyopathy, supporting an autoimmune pathogenesis [28].

Beyond myocarditis, other cardiovascular toxicities of immunotherapy include pericarditis, vasculitis, Takotsubo-like cardiomyopathy, and conduction abnormalities. Cytokine release syndrome associated with chimeric antigen receptor T-cell (CAR-T) therapy also contributes indirectly to cardiac dysfunction by causing systemic inflammation, endothelial activation, and myocardial depression.

Early recognition of ICI-related cardiac toxicity is critical. Cardiac biomarkers such as troponin and natriuretic peptides, electrocardiographic surveillance, and echocardiography are recommended at baseline and during therapy in high-risk patients [29]. Management generally involves prompt discontinuation of immunotherapy and initiation of high-dose corticosteroids; in steroid-refractory cases, additional immunosuppressive agents such as mycophenolate mofetil, infliximab, or abatacept may be required [30].

Although rare, ICI-induced cardiotoxicity underscores the delicate balance between immune activation and self-tolerance. Ongoing research aims to identify genetic, immunologic, and biomarker-based predictors to individualize therapy and reduce the risk of cardiovascular complications.

Shared Molecular Pathways of Cardiotoxicity

Although the clinical manifestations of cardiotoxicity vary across drug classes, multiple molecular and cellular mechanisms converge on common pathogenic pathways. These shared processes, oxidative stress, mitochondrial dysfunction, calcium handling abnormalities, endothelial injury, inflammation, and apoptosis, form the biological foundation of treatment-induced cardiac injury across both classical and targeted cancer therapies [31] (Table 2).

Pathophysiologic Process	Key Molecular Events	Cellular Consequence	Representative Agents
Oxidative stress	Excess ROS, lipid peroxidation	DNA and membrane damage	Anthracyclines, Cisplatin
Mitochondrial dysfunction	ETC disruption, cytochrome c release	ATP depletion, apoptosis	Anthracyclines, TKIs
Calcium dysregulation	SERCA2a inhibition, RyR sensitization	Ca^{2+} overload, arrhythmia	Anthracyclines
Endothelial injury	NO depletion, inflammation	Microvascular ischemia	VEGF inhibitors, Cyclophosphamide
Immune activation	T-cell infiltration, NLRP3 inflammasome	Myocarditis, fibrosis	ICIs

Table 2: Shared Molecular Mechanisms of Cancer Therapy–Induced Cardiotoxicity

Abbreviations: *ROS: reactive oxygen species; ETC: electron transport chain; SERCA2a: sarco/endoplasmic reticulum Ca^{2+}-ATPase 2a; RyR: ryanodine receptor; NO: nitric oxide; NLRP3: NOD-like receptor pyrin domain containing 3; ICI: immune checkpoint inhibitor; DNA: deoxyribonucleic acid.*

Oxidative stress is among the most universal mechanisms. Many anticancer agents, including anthracyclines, tyrosine kinase inhibitors (TKIs), and immune checkpoint inhibitors (ICIs), increase the generation of reactive oxygen species (ROS) in cardiomyocytes. Excess ROS impairs mitochondrial respiration, oxidizes lipids and contractile proteins, and damages DNA, leading to functional deterioration and cell death (11). Persistent oxidative imbalance also triggers maladaptive activation of nuclear factor-κB (NF-κB) and mitogen-activated protein kinase (MAPK) signaling, amplifying inflammation and apoptosis [8].

Mitochondrial dysfunction plays a pivotal role in both acute and chronic cardiotoxicity. Mitochondria are not only the main ROS source but also the primary target of oxidative injury. Doxorubicin and other chemotherapeutics disrupt the electron transport chain and promote mitochondrial permeability transition pore opening, resulting in cytochrome c release and caspase activation. In targeted therapy, inhibition of kinases such as mTOR and AMPK interferes with mitochondrial biogenesis and metabolic homeostasis, reducing cardiomyocyte resilience to stress [32].

Calcium dysregulation is another unifying feature. Dysregulated sarcoplasmic reticulum (SR) calcium cycling due to SERCA2a inhibition or ryanodine receptor sensitization leads to intracellular Ca^{2+} overload, contractile dysfunction, and arrhythmogenesis. Mitochondrial Ca^{2+} accumulation further exacerbates ROS generation and apoptotic signaling [33].

Endothelial dysfunction bridges vascular and myocardial injury. Antiangiogenic drugs such as VEGF inhibitors diminish nitric oxide (NO) bioavailability, promote vascular stiffness, and impair myocardial microcirculation. Similarly, cyclophosphamide and cisplatin damage endothelial cells directly through oxidative and inflammatory mechanisms, compromising coronary perfusion and promoting ischemic injury [14].

Finally, **inflammatory and apoptotic signaling** are central amplifiers of injury. Damaged mitochondria release damage-associated molecular patterns (DAMPs), activating pattern recognition receptors and inflammasomes such as NLRP3. This initiates cytokine release, leukocyte infiltration, and fibrosis, leading to chronic myocardial remodeling. These inflammatory processes are further intensified in immune checkpoint inhibitor–associated myocarditis, where T-cell–mediated cytotoxicity parallels the molecular cascades observed in chemotherapy-induced cardiomyopathy [34].

Overall, these interconnected mechanisms underscore the concept that cancer therapy–related cardiac injury is not agent-specific but the product of converging molecular stress pathways. Understanding these shared targets provides a mechanistic basis for future cardio-protective interventions, such as antioxidant modulation, mitochondrial stabilizers, or anti-inflammatory therapies.

Diagnostic and Monitoring Strategies

Early identification of cardiotoxicity is fundamental to prevent irreversible cardiac injury and to maintain oncologic treatment continuity. Current cardio-oncology practice emphasizes a multimodal surveillance approach combining circulating biomarkers, cardiac imaging, and clinical risk assessment [35] (Table 3).

Modality	Diagnostic Marker/Technique	Diagnostic Role	Sensitivity for Early Detection	Limitations
Biomarkers	Troponin I/T, NT-proBNP, ST2	Early detection of injury	High	Limited specificity
Echocardiography	LVEF, Global Longitudinal Strain (GLS)	Functional monitoring	High	Operator-dependent
Cardiac MRI	LGE, T1/T2 mapping, ECV	Tissue characterization	Very high	Limited availability
ECG / Holter	QT prolongation, arrhythmia	Rhythm assessment	Moderate	Nonspecific
Nuclear imaging	MUGA scan	LVEF quantification	Moderate	Radiation exposure

Table 3: Diagnostic Modalities for Cardiotoxicity Surveillance

Abbreviations: *LVEF: left ventricular ejection fraction; GLS: global longitudinal strain; LGE: late gadolinium enhancement; CMR: cardiac magnetic resonance; ECV: extracellular volume; ECG: electrocardiogram; MUGA: multigated acquisition scan; NT-proBNP: N-terminal pro–B-type natriuretic peptide; ST2: suppression of tumorigenicity 2.*

Cardiac biomarkers are the most sensitive indicators of early myocardial injury. Elevations in cardiac troponins (I or T) reflect direct cardiomyocyte damage, while increases in natriuretic peptides (BNP, NT-proBNP) signal myocardial strain or subclinical dysfunction [36]. Prospective studies have shown that patients developing chemotherapy-related troponin elevation are at significantly higher risk for later LVEF reduction and symptomatic heart failure. Novel biomarkers such as soluble ST2 and galectin-3 are under evaluation for their potential to detect early fibrosis and inflammation [37].

Echocardiography remains the cornerstone of cardiac monitoring because of its accessibility, safety, and reproducibility. Traditional assessment based on LVEF is complemented by strain imaging, particularly global longitudinal strain (GLS), which detects subclinical systolic dysfunction before overt ejection fraction decline. A relative GLS reduction of ≥15% from baseline reliably predicts subsequent cardiotoxicity [38].

Cardiac magnetic resonance imaging (CMR) provides high-resolution tissue characterization and is invaluable for diagnosing myocarditis, fibrosis, or diffuse myocardial edema. Quantitative mapping techniques (T1, T2, extracellular volume fraction) allow noninvasive detection of early structural injury. CMR has proven especially useful in confirming immune checkpoint inhibitor-associated myocarditis and anthracycline-induced fibrosis, even when LVEF remains preserved [39].

Electrocardiography (ECG) and rhythm monitoring are necessary adjuncts for detecting arrhythmic and repolarization abnormalities, particularly with tyrosine kinase inhibitors and immune therapies that prolong QT intervals or induce conduction block [40].

Finally, **integrated risk stratification**, incorporating demographic, clinical, therapeutic, and imaging variables, forms the basis of modern cardio-oncology protocols. Both the European Society of Cardiology (ESC) and the American Society of Clinical Oncology (ASCO) recommend baseline cardiovascular assessment before initiation of potentially cardiotoxic regimens and structured follow-up during and after therapy [7]. Machine learning–assisted predictive models that combine biomarker trends and imaging data are being developed to improve individualized monitoring and minimize treatment interruptions.

Cardioprotective and Management Strategies

Preventing and mitigating cardiotoxicity have become integral components of cancer care. The current approach combines pharmacologic cardioprotection, careful treatment planning, and multidisciplinary collaboration between oncologists and cardiologists [7]

Pharmacologic prevention remains the cornerstone of cardioprotection. Angiotensin-converting enzyme (ACE) inhibitors and beta-blockers have consistently demonstrated benefit in attenuating chemotherapy-induced cardiac dysfunction. Randomized studies have shown that agents such as enalapril and carvedilol reduce both troponin elevation and left ventricular ejection fraction (LVEF) decline during anthracycline-based therapy [41]. Dexrazoxane, an iron-chelating agent, remains the only drug specifically approved for preventing anthracycline-induced cardiotoxicity, primarily by limiting free radical formation [42].

Treatment modification is another critical preventive strategy. Using lower cumulative anthracycline doses, liposomal drug formulations, or prolonged infusion regimens significantly reduces cardiac risk. In targeted therapy, sequential rather than concurrent administration of anthracyclines and HER2 inhibitors minimizes additive toxicity. For tyrosine kinase inhibitors and immune checkpoint inhibitors, dose adjustment and temporary suspension are often effective when early cardiac dysfunction or myocarditis occurs [7].

Lifestyle and risk factor management, including strict blood pressure control, avoidance of smoking, and correction of dyslipidemia, complement pharmacologic measures. In survivors, exercise-based cardiac rehabilitation programs have shown improvement in cardiorespiratory fitness and endothelial function [43].

Multidisciplinary care is essential. Cardio-oncology teams coordinate surveillance and intervention, ensuring that cancer therapy continues safely without compromising cardiovascular health. This team-based model allows individualized balancing of oncologic efficacy and cardiac safety (Table 4).

Strategy	Mechanism / Rationale	Evidence Level	Clinical Outcome
Dexrazoxane	Iron chelation, limits ROS	High	Reduces anthracycline-induced HF
ACE inhibitors / ARBs	Neurohormonal blockade	High	Prevents LVEF decline
Beta-blockers	Sympathetic inhibition	High	Preserves LV function
Liposomal anthracyclines	Reduced myocardial exposure	Moderate	Lower incidence of HF
Sequential HER2 therapy	Avoids synergistic toxicity	Moderate	Reduces cardiac events
Cardiac rehabilitation	Improves endothelial and exercise function	Moderate	Enhances survivorship quality

Table 4: Evidence-Based Strategies for Prevention and Management of Cardiotoxicity

Abbreviations: *ACE: angiotensin-converting enzyme; ARB: angiotensin II receptor blocker; HF: heart failure; LVEF: left ventricular ejection fraction; LV: left ventricle; HER2: human epidermal growth factor receptor 2.*

Emerging cardioprotective approaches include statins, sodium-glucose cotransporter-2 (SGLT2) inhibitors, and mitochondrial-targeted antioxidants, which are currently under investigation. These novel strategies aim to preserve cardiac energetics and reduce oxidative stress during therapy.

Future Directions and Emerging Concepts

Rapid advances in both oncology and cardiovascular science are redefining the landscape of cardio-oncology. Future progress depends on translating mechanistic knowledge into precise, individualized strategies for early detection and prevention of cardiotoxicity [44].

Artificial intelligence (AI) and machine learning (ML) are emerging as powerful tools for risk prediction. By integrating data from imaging, biomarkers, electrocardiography, and clinical variables, AI-based algorithms can detect subtle patterns predictive of future cardiac dysfunction long before symptoms or measurable LVEF decline occur [45]. These models are being trained to identify high-risk patients who may benefit from intensified surveillance or prophylactic cardioprotective therapy.

Omics-based approaches, including genomics, transcriptomics, proteomics, and metabolomics, are uncovering patient-specific susceptibility to cardiotoxicity. Genetic polymorphisms in drug transporters, oxidative stress pathways, and mitochondrial enzymes influence individual risk profiles for anthracycline and tyrosine kinase inhibitor–induced cardiomyopathy. Integration of these molecular insights with clinical data could enable truly personalized cardio-oncology care [46].

Digital health and remote monitoring technologies are also transforming survivorship management. Wearable sensors and mobile platforms capable of tracking heart rate variability, physical activity, and early signs of heart failure are being validated for real-time detection of cardiac stress during cancer treatment. Such systems can allow timely clinical intervention while reducing hospital visits [47].

Finally, **novel therapeutic strategies** targeting oxidative stress, mitochondrial dysfunction, and inflammation are under active investigation. Agents such as mitochondrial-targeted antioxidants, sodium-glucose cotransporter-2 (SGLT2) inhibitors, and modulators of the NLRP3 inflammasome show potential for cardioprotection in both preclinical and early clinical studies [48].

The long-term vision of cardio-oncology is to transition from reactive management to *precision prevention*—a model where individual cardiovascular risk is predicted, monitored, and mitigated dynamically alongside cancer therapy. Achieving this will require close collaboration between oncologists, cardiologists, data scientists, and basic researchers to harmonize personalized medicine with compassionate, evidence-based care (Table 5).

Research Area	Emerging Approach	Clinical Potential	Current Challenges
Artificial intelligence	Risk prediction models integrating biomarkers and imaging	Early individualized prevention	Data standardization, validation
Omics-based precision medicine	Pharmacogenomics, proteomics	Tailored cardioprotection	Cost, accessibility
Digital health	Wearable monitoring, tele-cardiology	Real-time detection	Regulatory and privacy issues
Novel pharmacotherapy	SGLT2 inhibitors, mitochondrial antioxidants	Mechanistic cardioprotection	Limited clinical data
Multidisciplinary care	Cardio-oncology teams, survivorship clinics	Integrated long-term management	Implementation in practice

Table 5. Future Perspectives in Cardio-Oncology

Abbreviations: *AI: artificial intelligence; SGLT2: sodium–glucose cotransporter 2; HF: heart failure; ROS: reactive oxygen species; ECG: electrocardiogram; LV: left ventricle; TKI: tyrosine kinase inhibitor.*

Conclusion

Cancer therapy–related cardiotoxicity represents one of the most significant challenges of modern oncology. As therapeutic efficacy and patient survival continue to improve, cardiovascular complications increasingly determine long-term outcomes and quality of life. The interplay between anticancer efficacy and cardiac safety demands a paradigm shift—from reactive management of symptomatic heart failure to proactive prevention and early detection of subclinical injury.

Over the past two decades, substantial progress has been made in elucidating the molecular and cellular mechanisms of cardiotoxicity. Shared pathways involving oxidative stress, mitochondrial dysfunction, calcium dysregulation, endothelial injury, and immune-mediated inflammation have emerged as central mediators of cardiac damage across drug classes. These insights have enabled the development of more sophisticated surveillance methods, such as biomarker-based monitoring and strain imaging, that allow detection of early myocardial injury long before irreversible remodeling occurs.

The integration of cardioprotective strategies, including pharmacologic interventions, treatment modification, and lifestyle optimization, has already shown clear benefits in high-risk populations. However, the future of cardio-oncology will depend on the successful translation of novel scientific and technological advances into personalized prevention programs. Artificial intelligence, digital health tools, and molecular profiling promise to identify patients most vulnerable to cardiac injury and tailor therapy intensity accordingly

Ultimately, the success of cardio-oncology hinges on interdisciplinary collaboration. Effective partnership between oncologists, cardiologists, and primary care physicians ensures that treatment decisions are both life-saving and heart-preserving. The goal is not merely to cure cancer but to safeguard cardiovascular health throughout survivorship.

Contributorship: All of the authors contributed planning, conduct, and reporting of the work. All authors had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Funding: No financial funding was received for this study.

Competing interests: All of the authors have no conflict of interest.

References

1. Camilli M, Cipolla CM, Dent S, Minotti G, Cardinale DM.(2024).Anthracycline Cardiotoxicity in Adult Cancer Patients: JACC: CardioOncology State-of-the-Art Review. JACC CardioOncol.;6(5):655-677.
2. Booth LK, Redgrave RE, Folaranmi O, Gill JH, Richardson GD.(2022). Anthracycline-induced cardiotoxicity and senescence. Front Aging.;3:1058435.
3. Alexandre J, Cautela J, Ederhy S, et al. (2020).Cardiovascular Toxicity Related to Cancer Treatment: A Pragmatic Approach to the American and European Cardio-Oncology Guidelines. J Am Heart Assoc.;9(18):e018403.
4. Lyon AR, Dent S, Stanway S, et al.(2020). Baseline cardiovascular risk assessment in cancer patients scheduled to receive cardiotoxic cancer therapies: a position statement and new risk assessment tools from the Cardio-Oncology Study Group of the Heart Failure Association of the European Society of Cardiology in collaboration with the International Cardio-Oncology Society. Eur J Heart Fail.;22(11):1945-1960.
5. Cardinale D, Ciceri F, Latini R, et al.(2018). Anthracycline-induced cardiotoxicity: A multicenter randomised trial comparing two strategies for guiding prevention with enalapril: The International CardioOncology Society-one trial. Eur J Cancer.;94:126-137.
6. Gao F, Xu T, Zang F, Luo Y, Pan D.(2024). Cardiotoxicity of Anticancer Drugs: Molecular Mechanisms, Clinical Management and Innovative Treatment. Drug Des Devel Ther.;18:4089-4116.
7. Lyon AR, López-Fernández T, Couch LS, et al. (2022). ESC Guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS). Eur Heart J. 2022;43(41):4229-4361.
8. Zhang S, Liu X, Bawa-Khalfe T, et al. (2012).Identification of the molecular basis of doxorubicin-induced cardiotoxicity. Nat Med.;18(11):1639-1642.
9. Tadokoro T, Ikeda M, Ide T, et al. (2020).Mitochondria-dependent ferroptosis plays a pivotal role in doxorubicin cardiotoxicity. JCI Insight.;5(9):e132747.
10. Lebrecht D, Setzer B, Ketelsen UP, Haberstroh J, Walker UA. (2003).Time-dependent and tissue-specific accumulation of mtDNA and respiratory chain defects in chronic doxorubicin cardiomyopathy. Circulation.;108(19):2423-2429.
11. Wallace KB, Sardão VA, Oliveira PJ. (2020).Mitochondrial Determinants of Doxorubicin-Induced Cardiomyopathy. Circ Res.;126(7):926-941.
12. Shinlapawittayatorn K, Chattipakorn SC, Chattipakorn N. (2022).The effects of doxorubicin on cardiac calcium homeostasis and contractile function. J Cardiol.;80(2):125-132.
13. Zhao XP, Duan L, Zhao QR, et al.(2025). NLRP3 inflammasome as a therapeutic target in doxorubicin-induced cardiotoxicity: role of phytochemicals. Front Pharmacol.;16:1567312.
14. Herrmann J. Vascular toxic effects of cancer therapies. Nat Rev Cardiol. 2020;17(8):503-522.
15. Zhang X, Yin Y, Yu Q, Chen X, Cheng Y. (2025).Review of the clinical status of cardiotoxicity of HER-2 positive breast cancer targeted therapeutic drugs. Front Oncol.;14:1492203.
16. Copeland-Halperin RS, Liu JE, Yu AF. (2019).Cardiotoxicity of HER2-targeted therapies. Curr Opin Cardiol.;34(4):451-458.
17. Dempsey N, Rosenthal A, Dabas N, Kropotova Y, Lippman M,(2021). Bishopric NH. Trastuzumab-induced cardiotoxicity: a review of clinical risk factors, pharmacologic prevention, and cardiotoxicity of other HER2-directed therapies. Breast Cancer Res Treat.;188(1):21-36.
18. Liu J, Meng Z, Yidan X. (2024).Cardiotoxicity of HER2-Targeted Drugs When Combined with Other Drugs: A Systematic and Meta-analysis of Randomized Controlled Trials. Cardiovasc Toxicol.;24(8):757-765.
19. Dent SF, Morse A, Burnette S, Guha A, Moore H. (2021).Cardiovascular Toxicity of Novel HER2-Targeted Therapies in the Treatment of Breast Cancer. Curr Oncol Rep.;23(11):128.
20. Mihalcea D, Memis H, Mihaila S, Vinereanu D. (2023).Cardiovascular Toxicity Induced by Vascular Endothelial Growth Factor Inhibitors. Life (Basel).;13(2):366.
21. le Noble FAC, Mourad JJ, Levy BI, Struijker-Boudier HAJ. (2023).VEGF (Vascular Endothelial Growth Factor) Inhibition and Hypertension: Does Microvascular Rarefaction Play a Role?. Hypertension.;80(5):901-911.
22. Chen YC, Chen JH, Hsieh FI. (2024).Major adverse cardiovascular events of vascular endothelial growth factor tyrosine kinase inhibitors among patients with different malignancy: A systemic review and network meta-analysis. J Chin Med Assoc.;87(1):48-57.

23. Wu Q, Bai B, Tian C, et al. (2022).The Molecular Mechanisms of Cardiotoxicity Induced by HER2, VEGF, and Tyrosine Kinase Inhibitors: an Updated Review. Cardiovasc Drugs Ther.;36(3):511-524.
24. Lyon AR, Yousaf N, Battisti NML, Moslehi J, Larkin J. (2018).Immune checkpoint inhibitors and cardiovascular toxicity. Lancet Oncol.;19(9):e447-e458.
25. Salem JE, Manouchehri A, Moey M, et al. (2018).Cardiovascular toxicities associated with immune checkpoint inhibitors: an observational, retrospective, pharmacovigilance study. Lancet Oncol.;19(12):1579-1589.
26. Mahmood SS, Fradley MG, Cohen JV, et al. (2018).Myocarditis in Patients Treated With Immune Checkpoint Inhibitors. J Am Coll Cardiol.;71(16):1755-1764.
27. Johnson DB, Balko JM, Compton ML, et al. (2016).Fulminant Myocarditis with Combination Immune Checkpoint Blockade. N Engl J Med.;375(18):1749-1755.
28. Nishimura H, Okazaki T, Tanaka Y, et al. Autoimmune dilated cardiomyopathy in PD-1 receptor-deficient mice. Science. 2001;291(5502):319-322.
29. Brahmer JR, Lacchetti C, Schneider BJ, et al.(2018). Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol.;36(17):1714-1768.
30. Zhang L, Jones-O'Connor M, Awadalla M, et al.(2019). Cardiotoxicity of Immune Checkpoint Inhibitors. Curr Treat Options Cardiovasc Med.;21(7):32.
31. Octavia Y, Tocchetti CG, Gabrielson KL, Janssens S, Crijns HJ, Moens AL. (2012).Doxorubicin-induced cardiomyopathy: from molecular mechanisms to therapeutic strategies. J Mol Cell Cardiol.;52(6):1213-1225.
32. Chen MH, Kerkelä R, Force T.(2008). Mechanisms of cardiac dysfunction associated with tyrosine kinase inhibitor cancer therapeutics. Circulation.;118(1):84-95.
33. Tokarska-Schlattner M, Zaugg M, Zuppinger C, Wallimann T, Schlattner U. New insights into doxorubicin-induced cardiotoxicity: the critical role of cellular energetics. J Mol Cell Cardiol. 2006;41(3):389-405.
34. Toldo S, Abbate A. The NLRP3 inflammasome in acute myocardial infarction. Nat Rev Cardiol. 2018;15(4):203-214.
35. Cardinale D, Sandri MT, Colombo A, et al. (2004).Prognostic value of troponin I in cardiac risk stratification of cancer patients undergoing high-dose chemotherapy. Circulation.;109(22):2749-2754.
36. Ky B, Putt M, Sawaya H, et al.(2014). Early increases in multiple biomarkers predict subsequent cardiotoxicity in patients with breast cancer treated with doxorubicin, taxanes, and trastuzumab. J Am Coll Cardiol.;63(8):809-816.
37. Armenian SH, Hudson MM, Mulder RL, et al. (2015).Recommendations for cardiomyopathy surveillance for survivors of childhood cancer: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group. Lancet Oncol.;16(3):e123-e136.
38. Thavendiranathan P, Poulin F, Lim KD, Plana JC, Woo A, Marwick TH. (2014).Use of myocardial strain imaging by echocardiography for the early detection of cardiotoxicity in patients during and after cancer chemotherapy: a systematic review. J Am Coll Cardiol. 63(25 Pt A):2751-2768.
39. Neilan TG, Coelho-Filho OR, Shah RV, et al.(2013). Myocardial extracellular volume by cardiac magnetic resonance imaging in patients treated with anthracycline-based chemotherapy. Am J Cardiol.;111(5):717-722.
40. Narayan HK, Finkelman B, French B, et al. (2017).Detailed Echocardiographic Phenotyping in Breast Cancer Patients: Associations With Ejection Fraction Decline, Recovery, and Heart Failure Symptoms Over 3 Years of Follow-Up. Circulation;135(15):1397-1412.
41. Bosch X, Rovira M, Sitges M, et al. (2013).Enalapril and carvedilol for preventing chemotherapy-induced left ventricular systolic dysfunction in patients with malignant hemopathies: the OVERCOME trial (preventiOn of left Ventricular dysfunction with Enalapril and caRvedilol in patients submitted to intensive ChemOtherapy for the treatment of Malignant hEmopathies). J Am Coll Cardiol.;61(23):2355-2362.
42. Swain SM, Whaley FS, Ewer MS.(2003). Congestive heart failure in patients treated with doxorubicin: a retrospective analysis of three trials. Cancer.;97(11):2869-2879.
43. Armenian SH, Lacchetti C, Barac A, et al. (2017).Prevention and Monitoring of Cardiac Dysfunction in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol.;35(8):893-911.
44. Herrmann J, Lerman A, Sandhu NP, Villarraga HR, Mulvagh SL, Kohli M (2014).. Evaluation and management of patients with heart disease and cancer: cardio-oncology. Mayo Clin Proc. 89(9):1287-1306.
45. Guha A, Shah V, Nahle T, et al. (2025).Artificial Intelligence Applications in Cardio-Oncology: A Comprehensive Review. Curr Cardiol Rep. 27(1):56.
46. Hansson P, Blacker C, Uvdal H, Wadelius M, Green H, Ljungman G. (2025).Pharmacogenomics in pediatric oncology patients with solid tumors related to chemotherapy-induced toxicity: A systematic review. Crit Rev Oncol Hematol.;211:104720.
47. Echefu G, Batalik L, Lukan A, et al. (2025).The Digital Revolution in Medicine: Applications in Cardio-Oncology. Curr Treat Options Cardiovasc Med.;27(1):2.
48. Liu X, Ding R, Zhang A. (2025).Pharmacological interventions to prevent cardiotoxicity in patients undergoing anthracycline-based chemotherapy: a network meta-analysis. Front Cardiovasc Med.;12:1612060.

DOI:10.31579/2641-0419/522