International Journal of Current Pharmaceutical Research

ISSN- 0975-7066 Vol 17, Issue 5, 2025

Review Article

VARIOUS REASONS FOR CARDIOTOXICITY: AN UPDATED REVIEW

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Received: 05 Jun 2025, Revised and Accepted: 25 Jul 2025

ABSTRACT

Injury to the heart muscle caused by exposure to toxins is called cardiotoxicity and it weakens cardiac function. Cardiotoxicity is one of the most severe adverse effects of cancer treatment and significantly adds to morbidity and mortality. Ventricular systolic dysfunction-induced heart failure is the most frequent and lethal side effect of chemotherapy drugs on the cardiovascular system. Arrhythmias, myocardial ischemia, pericardial disease, hypertension, and thromboembolic disease are additional deleterious consequences. It is a critical problem in environmental health, cancer, and clinical pharmacology. Drug-induced cardiotoxicity (DICT) is a serious problem with drug safety in both clinical use and drug development. The primary reasons for cardiotoxicity are discussed in this research with a focus on drug-induced mechanisms, environmental exposures, genetic susceptibility, and clinical conditions posing threats to cardiac well-being.

Keywords: Cardiotoxicity, Anthracyclines, Drug-induced cardiotoxicity, Pharmacogenomics, Heart diseases, Prevention

DOI: https://dx.doi.org/10.22159/ijcpr.2025v17i5.7022 Journal homepage: https://innovareacademics.in/journals/index.php/ijcpr

INTRODUCTION

"Cardiotoxicity" is defined by the National Cancer Institute as "toxicity that results in damage to the heart." It includes both the direct affect by the drug to the heart, and indirectly, through thrombotic events or by altering hemodynamic flow changes. As cancer treatments improve around the globe, leading to enhanced survival, since side effects from these treatments can have a significant impact on the outcomes of the patients, cardiotoxicity continues to have relevance and importance. Cardiotoxicity from drugs is a complex process. Drug-induced cardiotoxicity (DICT) cannot be fully explained by traditional cardiovascular risk factors (age, sex, renal impairment, iron accumulation, drug-drug interactions, existing cardiac disease). Patient monitoring indicators used in clinical practice usually lack specificity to diagnose DICT. The importance of genetic factors that predispose some people to DICT is being increasingly supported with evidence. Numerous risk genes have been identified, and some have been utilized in clinical practice for programming drug schedules [1, 2].

Various reasons for cardiotoxicity is discussed as

Drug-induced cardiotoxicity (DICT)

Drug-induced cardiotoxicity (DICT) is a significant adverse drug reaction that alters the normal physiological actions of the circulatory system. Various clinical manifestations of DICT can may include cardiomyopathy, arrhythmia, damage to the valves, myocarditis, pericarditis, cardiac dysfunction (also commonly called insufficiency), and myocardial ischemia. Drug-induced QT prolongation has the potential to result in sudden death and significant ventricular tachycardia [3].

Table 1: Drug-induced cardiotoxicity (DICT)

Common drugs	Cardiotoxic manifestations	Types	References
Salbutamol	Arrhythmia (atrial fibrillation, sinus tachycardia, etc.)	Bronchodilators	[4]
Domperidone, cisapride	Q-T interval prolongation and arrhythmia	Gastrointestinal motility promoting drugs	[5]
Thiazide antipsychotics, tricyclic antidepressants	Arrhythmia	Psychotropic drugs	[6]
Probucol	QT interval prolongation, ventricular tachycardia	Lipid-lowering drugs	[7]
Benamin, cetirizine, loratadine, desloratadine, levocetirizine,	Q-T interval prolongation, palpitations, arrhythmias, sinus bradycardia, supraventricular tachycardia, ventricular tachycardia, torsade de pointe, atrial fibrillation, etc.	Antihistamines	[8]
Amiodarone, Digitalis	QT interval prolongation Atrioventricular block, ventricular arrhythmia	Antiarrhythmic drugs	[9]
Macrolides: clarithromycin, azithromycin	Torsade de pointe, QT interval prolongation	Anti-infection drugs	[10]
β Lactams: penicillin	Arrhythmia, myocarditis, heart failure		
Lincomrades: lincomycin and clindamycin	QT interval prolongation, ventricular tachycardia		
Quinolone: ciprofloxacin, levofloxacin, moxifloxacin, etc.	QT interval prolongation, ventricular tachycardia, occasionally develops to severe arrhythmias such as torsade de pointe		
Antifungal: imidazole antifungal agents (Itraconazole)	QT interval prolongation, ventricular tachycardia		
Antiparasitic: chloroquine	Heart block, congestive heart failure, cardiomyopathy		
Antiviral: α-Interferon (IFN-α)	Myocarditis, atrioventricular block, bradycardia		
Anthracyclines: adriamycin, aunorubicin, epirubicin	Arrhythmia, cardiomyopathy, heart failure	Antineoplastic drugs	[11]
Alkylating agent: cyclophosphamide	Hemorrhagic necrotizing pericardial myocarditis, heart failure, arrhythmia		
Proteasome inhibitor: kafezomib	Heart failure		

Table 2: Cardiotoxicity of the main classes of cancer drugs used in clinical practice [12]

Class	Examples	Cancer treated	Cardiotoxicity	Mechanism
Anthracyclines	Epirubicin, daunorubicin	Acute leukemias, Hodgkin's and non-Hodgkin's lymphomas,	Acute: HF, arrhythmias, QT interval changes, ventricular repolarization abnormalities Chronic (dose-dependent): LV dysfunction (non-reversible)	Damage to cardiomyocytes:- Oxidative stress (ROS production) – Apoptosis
Antimetabolites	Capecitabine	Solid tumors, including lung, colon and breast	Myocardial ischemia, MI, arrhythmias	Coronary spasm
Vinca alkaloids	Vincristine, vinblastine and vinorelbine	Leukemias and lymphomas	Myocardial ischemia	
Tyrosine kinase inhibiting antibodies	Rituximab	Lymphomas, leukemias, transplant rejection, some autoimmune disorders	Orthostatic hypotension	Associated with allergies and angioedema

Non-oncology drugs

Antipsychotics are an important and crucial aspect of mental health treatment that frequently lasts a lifetime. The two main classifications of antipsychotics used to treat schizophrenia and other psychotic disorders are first-generation antipsychotics (also known as typical antipsychotics or FGAs) and second-generation antipsychotics (often referred to as atypical antipsychotics or SGAs). A third-generation antipsychotic (TGA) is a still-emerging and newly positioned classification of antipsychotic drug strategies that is new to the market or going through clinical research for the treatment of mental illnesses.

The clinical applications of antipsychotic medications are limited because of their problematic and sometimes fatal cardiotoxicity. In this review, we will summarize the pathological changes and clinical consequences of cardiotoxicity and recent advances in our understanding of the molecular and subcellular organelle mechanisms with antipsychotic development [13].

Environmental and occupational exposures

Environmental contaminants such as heavy metals, insecticides, petrochemical byproducts, and other hazardous substances are persistent and difficult to degrade in the environment, with long half-lives. They can also bioaccumulate in humans through the food chain and bioconcentration, which may have adverse health effects. Heavy metals are inorganic elements that possess a density of greater than 5 g/cm3, and they can be grouped into two classes according to their toxicity, essential and non-essential heavy metals. 1) Essential heavy metals are harmless or relatively less harmful at low concentration (Zn, Cu, Fe, and Co). 2) Even at low concentration, non-essential metals (Cd, Hg, As, and Cr) are highly toxic [14].

- **Arsenic-induced cardiotoxicity**

Arsenic, the twentieth most abundant element in the earth's crust, is a naturally occurring element that comes from its minerals. The recommended maximum levels of arsenic in water are lost due to excretory products, including human excreta. Humans are exposed to arsenic directly from the food chain and indirectly from drinking water. Arsenic is a metalloid element that is plentiful in the earth's crust and biosphere [15].

- **Natural products**

One of the ingredients in Terminaliaarjuna (Roxb. ex DC.) Wight and Arn.'s bark, arjunolic acid, has been shown to provide substantial cardioprotection against isoproterenol-induced myocardial necrosis. Arsenic poisoning (10 mg/kg bm, p. o., 2 d) produces extreme oxidative damage in heart tissue in mice, but treatment with arjunolic acid (20 mg/kg bm, 4 d) was able to prevent this. Arjunolic acid's overall prevention effect may be attributed to its free radical scavenging and chelating metal action, which reduces the arsenic burden in the cells [15].

- **Mercury**

Humans have been exposed to many metal agents, including mercury because of environmental contamination. Furthermore, while new studies show that even small amounts of mercury can adversely affect the heart, kidneys, neurologic system, immune system, and even cancer, it is likely that the global burden of disease accounted for by chemical pollution is greatly underestimated. Mercury (Hg) is a known global pollutant with negative health consequences.

- **Cadmium**

Cadmium is a toxic metal distributed throughout the world. It accumulates in the tissues of organisms and damages a variety of organs, primarily through oxidative stress. Endothelial dysfunction, mainly caused by oxidative stress, is usually associated with cardiovascular diseases. Although cadmium (Cd) is a chemical element which can be and is used in industrial manufacturing, it is detrimental to human health. This article will discuss the connection between cadmium and heart disorders.

- **Pesticide-induced cardiotoxicity**

Pesticides are one of the most common and frequently used types of agricultural chemicals. Pesticides are important for increasing agricultural production and addressing human food issues. However, because pesticides are toxic organisms, they will unavoidably cause environmental pollution and negative effects in humans and other living organisms. Although numerous epidemiological and experimental studies have shown links of pesticide exposure and the occurrence of various human diseases [16].

Mechanisms of cardiotoxicity

Oxidative Stress: Reactive oxygen species (ROS) are extremely reactive oxygen-containing chemical species that biology regulates by both enzymatic and nonenzymatic antioxidant defense systems. ROS generated in the heart and primarily produced by the mitochondria are part of cell homeostasis through their effects on cell division, proliferation, and excitation-contraction coupling. When the quantity of ROS exceeds the buffering capacity of the antioxidant defense systems, oxidative stress occurs, leading to cellular and molecular dysfunction that ultimately culminates in heart failure. This review will highlight the physiological origins of ROS in the heart and the mechanisms of myocardial injury related to oxidative stress as well as the implications of clinical trials and experimental studies of antioxidant therapy in cardiovascular disease [17]. The pathophysiology of chronic illnesses like cancer, diabetes, cardiovascular disease, and neurological diseases is significantly influenced by oxidative stress. In addition to functional changes in various enzymes and cellular structures that result in abnormalities in gene expression, prolonged exposure to elevated amounts of pro-oxidant substances can result in structural defects at the mitochondrial DNA level. Oxidative stress induction is largely caused by the modern lifestyle, which includes processed foods, exposure to a variety of toxins, and inactivity. However, because of their potential to treat or prevent a number of human diseases where oxidative stress appears to be a contributing factor, medicinal plants with antioxidant qualities have been used extensively. The diseases that are triggered by oxidative stress are covered in this review, along with plant-derived antioxidant chemicals and their antioxidant defense mechanisms that can aid in disease prevention [18].

Mitochondrial dysfunction

Oxidative stress is a pathogenic process initiated through an imbalance of free radical generation and antioxidant mechanisms, and it primarily

originates in the mitochondrion, which is the major organelle eliminated throughout the process. Chronically elevated glucose levels lead to an impaired electron transport chain in the mitochondria and generate ROS, which contributes to leakage and impaired mitochondrial membrane potential (MMP). This leakage leads to cytochrome c (cyt-c) release and stimulation of apoptosis. None of which is good, as they create a self-promoting cycle of aberrant mitochondrial DNA (mtDNA) transcription and protein synthesis (which codes for mitochondrial proteins), impaired clearance by the antioxidant system endogenous to the body, and impaired DNA repair systems. All these factors eventually contribute to mitochondrial dysfunction. This study investigates mitochondrial dysfunction in oxidative stress within the context of high glucose-induced oxidative stress in the DM model, and attempts to provide a novel therapy strategy for oxidative stress that considers mitochondrial failure [19].

Inflammation

Individuals exposed to ionizing radiation (IR) have a significantly increased risk of developing heart disease. One of the deleterious effects that may present in people exposed to ionizing radiation is radiation-induced heart disease (RIHD). IR can come from many different sources, such as catastrophes, nuclear accidents, cancer treatment with radiation therapy, and imaging diagnostics. Cancer treatment with radiation therapy, especially in the case of malignant chest tumors like left breast cancer, was the most significant manner of RIHD. Radiation therapy (RT) is one of the principal forms of treatment for all cancers, and the goal of RT is to improve patient survival and lower the risk of cancer recurrence. Although the specific mechanism for radiation-induced cardiotoxicity remains unclear, it may have a pathophysiology related to oxidative stress. Oxidative stress occurs when there is an accumulation of reactive oxygen species (ROS), which can damage proteins, lipids, and DNA, and chemically interfere with intracellular homeostasis, thus causing a cascade of related pathophysiological changes. The goals of this review were to provide preventative and treatment strategies to minimize heart harm and also to summarize the literature on oxidative stress relative to radiotherapy-induced cardiotoxicity [20].

Strategies for prevention and monitoring [21]

The early identification of the existence of cardiotoxicity can involve cardiac imaging and cardiac biomarkers (e. g., troponin and BNP) and imaging modalities (e. g., echocardiography and MRI).

Cardiovascular imaging

• **Echocardiography:** this ultrasound-based modality can assess heart function (LVEF and myocardial strain), which can vary in response to cardiotoxicity,

• **MRI:** cardiac MRI is able to provide high-quality images of left ventricular ejection fraction, myocardial strain and imaging results about tissue (T1/T2 mapping), allowing us to greater assess cardiotoxicity.

Biomarkers

• BNP (heart-type natriuretic peptide): A peptide released by the heart in response to stress or injury. Increased BNP has been associated with heart failure and can be used to assess the degree of heart dysfunction.

• Troponin: A protein that is released into the blood when heart muscle is damaged with increased troponin being representative of an acute myocardial infarction, or myocarditis, which may be associated with certain cancer treatments.

Cardioprotective agents

The risk of cardiotoxicity, a serious side effect of treatments for many types of cancers can be greatly reduced with guidelines to reduce cardiac toxicity by the use of cardioprotective medications (instrument such as Dexrazoxane) and other lifestyle modifications. The risk of cardiotoxicity from anthracycline therapy can be mitigated especially with dexrazoxane; however, lifestyle modifications such as smoking cessation, exercise, and weight loss can help minimize cardiovascular risk factors which can increase the risk of cardiotoxicity.

Agents that protect the heart: dexrazoxane

Dexrazoxane has been shown to be a unique cardioprotective agent that appears to reduce the risk of cardiotoxicity, particularly when used in anthracycline chemotherapy. Chemotherapy agents, particularly anthracyclines, can cause damage to the heart muscle and lead to heart failure and other cardiovascular complications. Dexrazoxane seems to ameliorate the risk of cardiotoxicity by altering the series of activities that alter the heart by anthracyclines.

Other cardiac protectants

Though dexrazoxane consistently emerges as the focus of ways to prevent anthracycline-induced cardiotoxicity, there are other agents that may also be considered to protect the heart and reduce the risk of cardiotoxicity, particularly in individuals with established cardiovascular disease or persons at high risk of cardiovascular disease. These agents include beta-blockers, ACE inhibitors, ARBs, and statins. They all work to decrease blood pressures, decrease cholesterol, improve cardiac function, and all effectively prevent damage to the heart.

Lifestyle modifications [23]

Stop Smoking: Smoking can worsen the cardiac responses to chemotherapy and greatly increases the risk of cardiovascular disease. One of the most important lifestyle changes a patient can make to protect their heart is to stop smoking.

Weight loss

Losing weight can greatly improve heart health. Obesity is a significant risk factor for cardiovascular disease, thus, losing extra weight leads to improved cholesterol levels, decreased blood pressure, and decreased risk of heart failure.

Exercise

Regular physical activity, such as swimming, jogging, or walking, can help lower the risk of heart disease and improve overall cardiovascular health. Other risk factors for cardiovascular disease can also improve with physical activity, such as high blood pressure and high cholesterol.

Healthy eating

Eating a healthy diet, consisting of more fruits, vegetables, whole grains, and lean protein, can lower the risk of getting heart disease and improve overall cardiovascular health.

Stress management

Chronic stress can negatively affect heart health. Learning effective, healthy methods to manage stress, such as meditation, relaxation techniques, or spending time in nature, can be helpful.

CONCLUSION

Cardiotoxicity is increasingly significant due to advances in cancer therapy globally, which maximize survival. Consequentially, treatment-related side effects have significant implications for outcomes in patients. A multifactorial interaction between systemic, genetic, environmental, and pharmacologic elements causes cardiotoxicity. To determine high-risk individuals, instill preventive strategies, and tailor therapies to minimize cardiac injury, multidisciplinary strategies are needed in daily practice. One significant strategy for reducing cardiotoxicity with antineoplastic drugs is to determine individuals at increased risk and better understand the potential cardiac adverse effects of these drugs.

ACKNOWLEDGMENT

It's our privilege to express the profound sense of gratitude and cordial thanks to our respected chairman Mr. Anil Chopra and Vice Chairperson Ms. Sangeeta Chopra, St. Soldier Educational Society, Jalandhar for providing the necessary facilities to complete this review work.

FUNDING

Nil

AUTHORS CONTRIBUTIONS

All authors have contributed equally

CONFLICT OF INTERESTS

Declared none

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