From unidirectional toxicity to bidirectional systemic interplay in Cardio-Oncology

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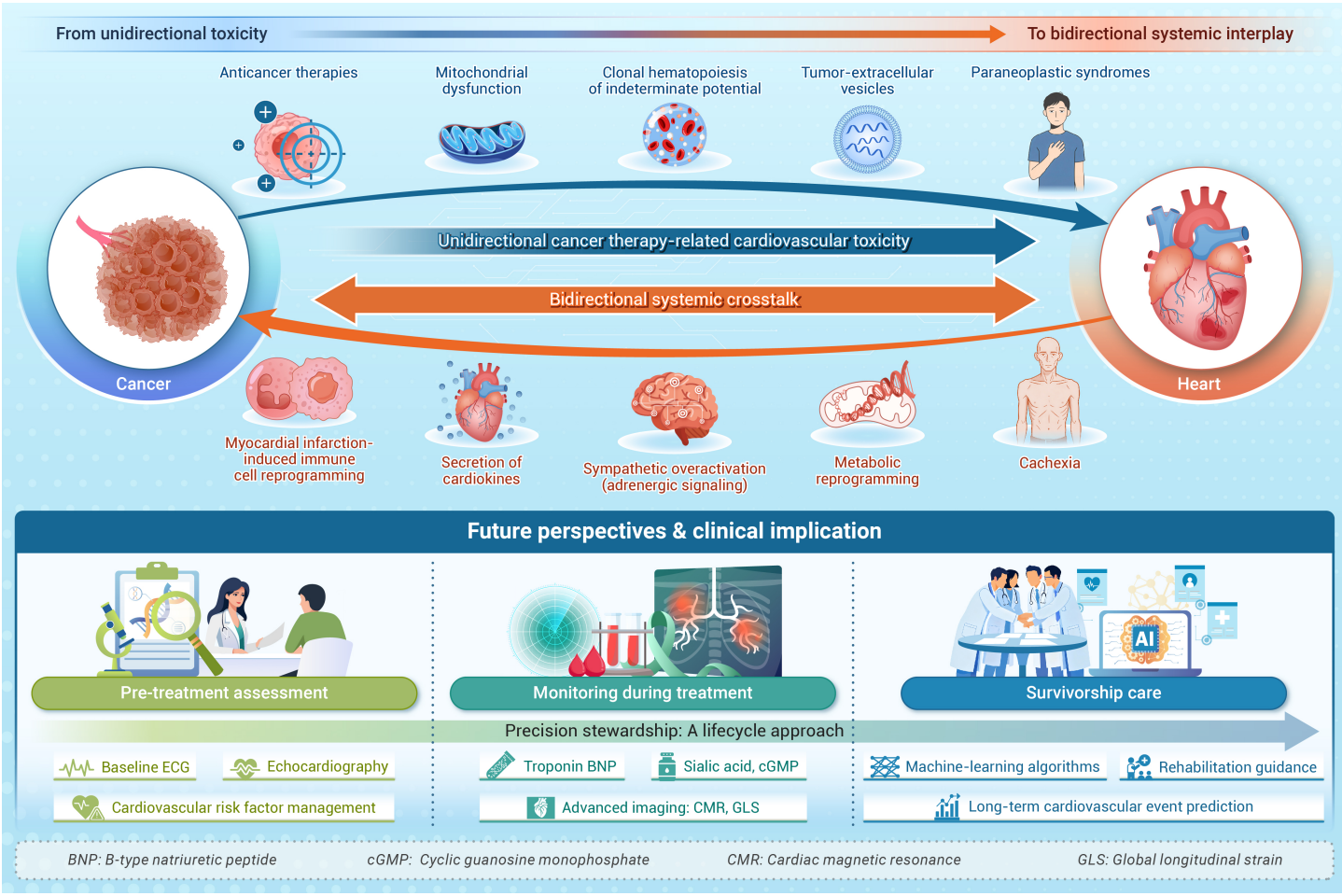
GRAPHICAL ABSTRACT



PUBLIC SUMMARY

- Cancer treatment can damage the heart and blood vessels in many different ways.
- This field now extends beyond toxicity to include two-way interactions between cancer and the heart.
- Heart disease may also influence tumor progression through immune, metabolic, and systemic signals.
- Better imaging, biomarkers, and artificial intelligence may improve earlier detection of risk.
- Closer integration of oncology and cardiology may support safer and more precise patient care.

REVIEW CancerX: Interdisciplinary Cancer Research

From unidirectional toxicity to bidirectional systemic interplay in Cardio-Oncology

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Cardio-oncology has expanded beyond the traditional focus on cancer therapy-related cardiovascular toxicity (CTR-CVT) to encompass the broader and increasingly recognized interplay between cancer and the cardiovascular system. Although advances in anticancer therapy have markedly improved survival, cardiovascular complications have become a major determinant of long-term morbidity and mortality in patients with cancer. At the same time, emerging evidence suggests that the relationship between cancer and cardiovascular disease is bidirectional: malignancy itself may impair cardiac structure and function, whereas pre-existing cardiovascular disease may contribute to tumor progression through immune, metabolic, neuroendocrine, and secretory mechanisms. In this review, we summarize the evolving clinical spectrum of CTR-CVT, discuss its pathophysiological basis within a multi-hit framework linking baseline cardiovascular vulnerability, tumor-derived signals, treatment-related injury, and review recent advances in multi-modal imaging, biomarker surveillance, artificial intelligence-assisted risk assessment, and real-world data integration. We further propose a multi-dimensional stewardship framework spanning pre-therapy risk stratification, intra-therapy surveillance and cardio protection, and long-term survivorship care. Finally, we highlight the emerging concept of reverse cardio-oncology, in which the diseased cardiovascular system may act as a systemic driver of malignancy, thereby reinforcing a reciprocal relationship between cancer and the heart. Together, these advances support a shift from a unidirectional toxicity model toward a systems-based framework for precision surveillance, mechanism-informed intervention, and integrated cardio-oncology care.

INTRODUCTION

Driven by major advances in cancer therapeutics and improvements in patient survival, cardio-oncology has become an essential component of contemporary cancer care.[1,2] Although these therapeutic gains have substantially improved oncologic outcomes, they have also increased long-term exposure to cardiovascular complications among cancer survivors. Cardiovascular disease (CVD) now rivals, and in some cohorts exceeds, malignancy itself as a leading cause of long-term morbidity and mortality in this population.[3,4] This shift underscores the need for cardiovascular stewardship across the cancer continuum, from the management of anthracycline-related injury to surveillance for toxicities associated with targeted therapies and immune checkpoint inhibitors.[5-7]

The relationship between CVD and cancer is no longer viewed solely through the lens of treatment-related toxicity. Instead, growing evidence supports a bidirectional interaction shaped by shared risk factors and overlapping biological mechanisms.[8] Obesity, chronic inflammation, and microbial dysbiosis, among other factors, may create a common pathophysiological background that predisposes patients to both malignancies and cardiac dysfunction.[9] In parallel, emerging evidence from reverse cardio-oncology suggests that cardiovascular disease may contribute to tumor progression, whereas tumors themselves can impair cardiac metabolism and function through systemic inflammatory and paracrine signaling.[10]

Accordingly, the conceptual framework of cardio-oncology is shifting from a predominantly unidirectional model of cancer therapy-related cardiovascular toxicity (CTR-CVT) to a broader view of reciprocal crosstalk between the tumor and the cardiovascular system.[11-13] This evolving framework has expanded current research priorities to include reverse cardio-oncology, the systemic consequences of malignancy itself, and new strategies for precision surveillance and prevention.[14] At the same time, multi-modal imaging, liquid biopsies, and artificial intelligence (AI)-assisted analytics are reshaping cardiovascular risk stratification in oncology.[15,16] Cardioprotective strategies are also moving beyond conventional neurohormonal blockade toward mechanism-informed interventions, including sodium-glucose cotransporter 2 (SGLT2) inhibitors and other targeted approaches.[17-20]

In this review, we summarize recent advances in cardio-oncology, focusing on the bidirectional interplay between cancer and CVD, the evolving spectrum of CTR-CVT, and emerging strategies for prevention, surveillance, and management. By integrating mechanistic insights with clinical perspectives, we aim to clarify current challenges, identify key knowledge gaps, and highlight future directions for research and practice.

CLINICAL MANIFESTATIONS AND MECHANISTIC LANDSCAPES OF CTR-CVT

Clinical phenotypes and systemic drivers

CTR-CVT represents a broad and heterogeneous spectrum of cardiovascular complications, including cancer therapy-related cardiac dysfunction (CTRCD), coronary artery disease (CAD), valvular heart disease, arrhythmias, hypertension, thromboembolism, peripheral arterial disease, hemorrhagic complications, pulmonary arterial hypertension (PAH), and pericardial diseases.[21] Epidemiological studies indicate that cancer survivors have a 1.55-fold higher risk of cardiovascular morbidity than the general population.[22] This burden is shaped by multiple interacting systemic drivers, which can be broadly categorized as cardiac-specific risk factors, such as hypertension, diabetes, and history of heart failure; cancer-specific risk factors, such as anthracyclines, anti-human epidermal growth factor receptor 2 (HER2) therapies, and history of chest radiotherapy; and shared risk factors, such as age, smoking, obesity, and inflammatory status (Table 1).[11,21,23]

Pathophysiological foundations: From cellular stress to systemic remodeling in the multi-hit model

The pathophysiology of CTR-CVT can be understood within a multi-hit framework, in which myocardial injury arises from the combined effects of pre-existing cardiovascular risk, the systemic burden of malignancy, and the direct insults of anticancer therapies.[12,24] Rather than representing a single toxic event, this process reflects a continuum from early cellular stress to progressive systemic remodeling. Importantly, cancer-induced cardiac dysfunction (CICD) may develop even before anticancer treatment is initiated, highlighting the contribution of the malignancy itself to cardiovascular vulnerability.[25]

Within this framework, the tumor may act as an initial hit through the tumor-heart axis. Recent studies have identified tumor-derived small extracellular vesicles (sEVs) as mediators of this crosstalk. Specifically, sEVs secreted by breast cancer cells can induce cardiomyocyte apoptosis and worsen mitochondrial bioenergetic dysfunction.[26] In lung cancer models, exosomal miR-216a-5p promotes cardiomyocyte pyroptosis by targeting the silent information regulator 1/nuclear factor kappa B (SIRT1/NF-κB) signaling axis.[27] These tumor-derived signals may also sensitize the myocardium to subsequent treatment-related injury by promoting lipid peroxidation and genomic instability, thereby amplifying the cardiovascular effects of chemotherapy, targeted therapy, immunotherapy, and radiotherapy.[28]

Oxidative stress represents another central component of the multi-hit process. Tumor-derived factors increase systemic reactive oxygen species

Table 1. Integrated classification of cardiovascular risk factors in cancer patients.

Classification	Core determinants and systemic drivers
Cardiac-specific risk factors	
Pre-existing cardiovascular substrate	Coronary artery disease (CAD), heart failure (HF), cardiomyopathy, and arrhythmias.
Metabolic precursors	Hypertension, diabetes mellitus, and dyslipidemia.
Organ reserve & subclinical injury	Chronic kidney disease (CKD) and baseline elevation of cardiac biomarkers (e.g., cTn, BNP/NT-proBNP).
Cancer-specific risk factors	
Therapeutic exposure	High-risk regimens include anthracyclines, anti-HER2 agents, immune checkpoint inhibitors (ICIs), tyrosine kinase inhibitors (TKIs), and alkylating agents.
Radiotherapy	Current or prior exposure to chest, mediastinal, or left-sided breast radiation.
Tumor-driven systemic effects	Pro-inflammatory tumor microenvironment, tumor-derived small extracellular vesicles (sEVs), and malignancy-associated metabolic reprogramming.
Shared risk factors	
Demographic & genetic architecture	Advanced age (geriatric) or extreme youth (pediatric), biological sex, and genetic susceptibility (e.g., TOP2B polymorphisms).
Lifestyle & behavioral factors	Tobacco use, physical inactivity, pro-inflammatory diets, and excessive alcohol consumption.
Systemic biological drivers	Obesity, chronic systemic inflammation, and Clonal Hematopoiesis of Indeterminate Potential (CHIP).
Social determinants of health (SDOH)	Socioeconomic status, psychosocial stressors, and disparities in healthcare accessibility.

(ROS), which can promote cardiac atrophy by activating the ubiquitin-proteasome system and promoting myofibrillar proteolysis.[29] Sustained oxidative stress further activates inflammatory and apoptotic pathways, contributing to cardiomyocyte loss and pathological myocardial remodeling.[24] Concurrently, endothelial and microvascular injury disrupt vascular homeostasis, creating a pro-thrombotic environment and accelerating atherosclerosis. These structural and functional abnormalities may manifest clinically as CAD, arrhythmias, and sudden cardiac death.[30] Collectively, these changes support a model in which genetic, metabolic, and signaling disturbances converge to drive systemic remodeling across the cancer continuum (Figure 1).

Clinical spectra and mechanistic divergence in CTR-CVT

Advances in anticancer therapies have substantially improved patient survival. However, chemotherapy, targeted therapies, immunotherapies, and radiotherapy are also associated with a broad spectrum of cardiovascular complications that increasingly influence long-term outcomes.[31,32] These toxicities differ substantially in their molecular mechanisms, clinical phenotypes, and temporal patterns (Table S1).

Chemotherapy: Programmed cell death and metabolic interference. Anthracyclines (e.g., doxorubicin) remain a major cause of CTRCD, inducing cardiotoxicity through DNA topoisomerase II beta (TOP2B)-mediated DNA double-strand breaks and ferroptosis.[33] At high cumulative doses, anthracyclines may also remodel the topologically associating domains (TADs), contributing to persistent cardiac dysfunction.[34] By contrast, antimetabolites are more commonly associated with acute endothelial dysfunction and vasospasm, whereas alkylating agents (e.g., cyclophosphamide) may cause heart failure through microcirculatory injury and capillary leak.[27,35,36] Antimitotic agents (e.g., taxanes) may further contribute through cytoskeletal disruption and autonomic dysfunction.[37,38]

Chemotherapy-associated injury also involves multiple programmed cell death pathways. Ferroptosis is driven by iron overload and glutathione peroxidase 4 (GPX4) inactivation, whereas cuproptosis involves copper-dependent aggregation of lipoylated tricarboxylic acid cycle (TCA) proteins. These processes may intersect in PANoptosis, a hybrid inflammatory cell death orchestrated by the PANoptosome complex.[39] In acute myeloid leukemia, necrotic tumor cells may further impair cardiac energetics through interleukin-1 alpha (IL-1α)-mediated suppression of peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) via NF-κB signaling, thereby disrupting glucose and fatty acid oxidation.[40] Additionally, sEVs may further aggravate injury by promoting mitochondrial DNA damage and pro-apoptotic signaling.[26]

Targeted therapies: Pathway disruption and microvascular dysfunction. Targeted therapies improve cancer outcomes by inhibiting oncogenic signaling pathways, but they may also disrupt myocardial and vascular homeostasis through "on-target, off-tumor" effects (Figure 2). Their cardiovascular toxicity is highly pathway-dependent. Breakpoint cluster region-abelson (BCR-ABL) and multi-target tyrosine kinase inhibitors (TKIs), such as imatinib and sorafenib, impair physiological angiogenesis, endothelial integrity, and mitochondrial bioenergetics by inhibiting kinases, including vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), and rapidly accelerated fibrosarcoma (RAF). These effects may result in hypertension, PAH, and myocardial ischemia, with sorafenib-related heart failure reported in approximately 2%-4% of cases.[31,41,42] Targeted agents also interfere with pathways involved in myocardial adaptation and repair. Vascular endothelial growth factor (VEGF) inhibitors reduce nitric oxide bioavailability, leading to hypertension and coronary vasospasm, and may cause early, potentially reversible impairment of contractile function.[43,44] HER2 inhibitors (e.g., trastuzumab) impair the neuregulin-1 (NRG-1)/ErbB4 repair pathway and increase susceptibility to subsequent cardiac stress.[45] The spectrum of toxicity continues to broaden with novel agents. Mitogen-activated protein kinase kinase 1/2 (MEK1/2) inhibitors may cause bradycardia and a reduction in the left ventricular ejection fraction (LVEF), whereas cyclin-dependent kinase 4/6 (CDK4/6) inhibitors have been implicated in corrected QT (QTc) prolongation (3%-5%) and heart failure (1.5%-3%), potentially through cardiomyocyte cell-cycle arrest, endothelial injury, and cellular senescence.[46] Proteasome inhibitors (PIs) add another dimension of injury by disrupting proteostasis and promoting apoptosis through dysregulation of the ubiquitin-proteasome system.[47]

Immunotherapies: Immune hyperactivation and cytokine cascades. Cardiovascular toxicities associated with immunotherapies, primarily ICIs and other T-cell-based therapies, represent a paradigm shift from direct biochemical injury to immune-mediated toxicity. Although the incidence is relatively low (1%-2%), these events may be fulminant and carry high mortality.[48,49] These toxicities arise through three main mechanisms: direct myocardial infiltration by autoreactive T cells, systemic injury mediated by cytokine release syndrome (CRS), and vascular injury related to immune-mediated endothelial dysfunction.[50,51] Immunotherapy-induced cardiotoxicity (IIC) is characterized by enhanced T-cell activation and immune-mediated inflammatory injury. ICIs may trigger cross-reactivity against shared myocarditis antigens, leading to T-cell infiltration and myocarditis.[52] Conversely, adoptive cell therapies (ACT) and bi-specific T-cell engagers (BiTEs) more commonly cause toxicity through CRS. Excessive release of IL-6, TNF-α, and interferon

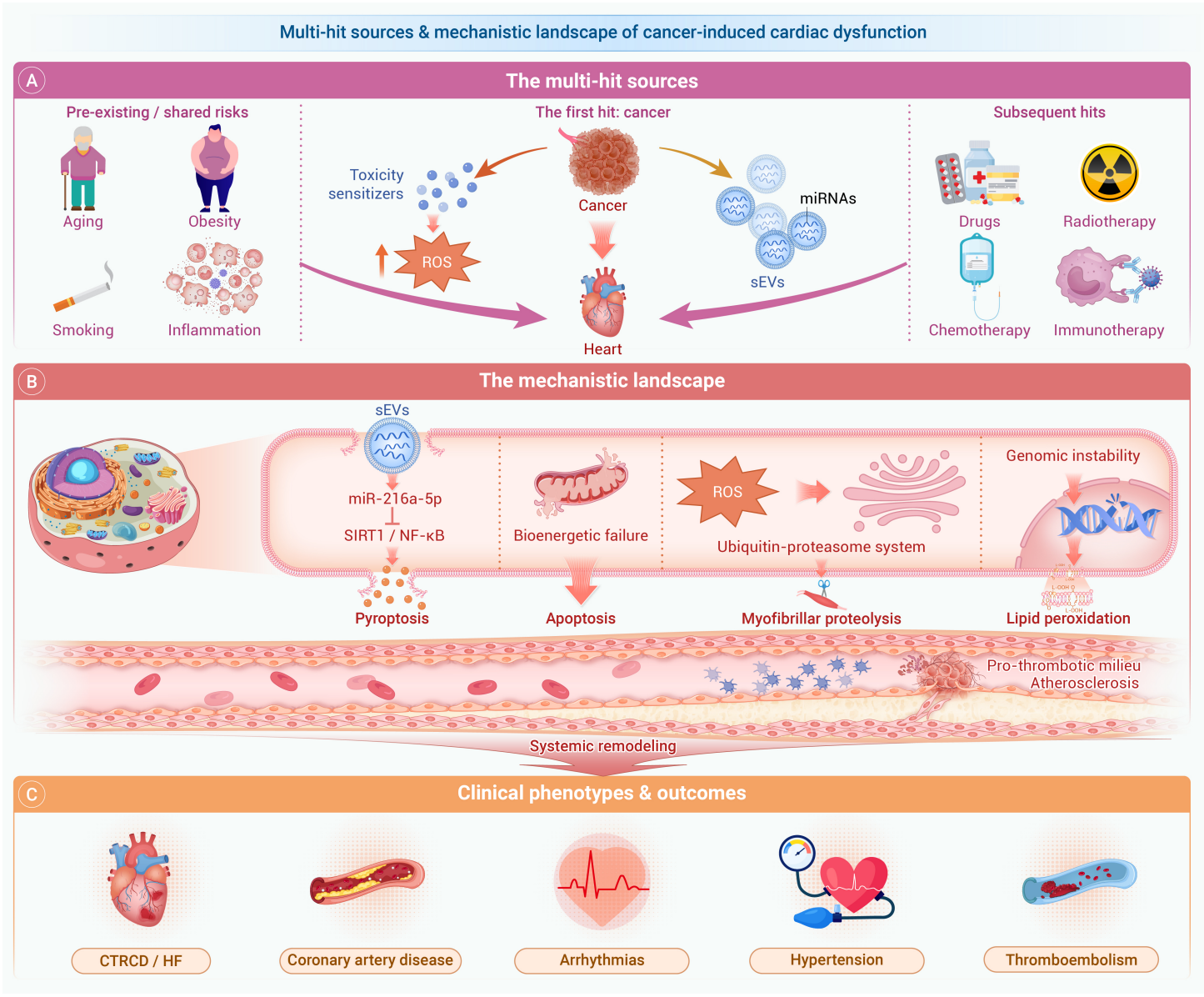

Figure 1. Multi-hit sources and mechanistic landscape of cancer-induced cardiac dysfunction (A) The upper panel summarizes the major multi-hit sources contributing to cardiac injury, including pre-existing/shared risks, the malignancy itself as the first hit, and subsequent treatment-related hits. Aging, obesity, smoking, and inflammation are illustrated as representative baseline risk factors. The tumor acts as a primary stressor and releases microRNAs (miRNAs), sEVs, and ROS, which may function as toxicity sensitizers linking cancer to cardiac injury. Subsequent hits include drugs, chemotherapy, immunotherapy, and radiotherapy. (B) The middle panel depicts the mechanistic landscape of cancer-induced cardiac dysfunction. Tumor-derived sEVs and exosomal microRNA-216a-5p (miR-216a-5p) are shown to promote pyroptosis through the SIRT1/NF-κB axis. In parallel, bioenergetic failure, ROS accumulation, activation of the ubiquitin-proteasome system, genomic instability, myofibrillar proteolysis, lipid peroxidation, and apoptosis collectively drive systemic remodeling and contribute to a pro-thrombotic milieu and atherosclerosis. (C) The lower panel summarizes the major clinical phenotypes and outcomes, including CTRCD/ heart failure (HF), coronary artery disease, arrhythmias, hypertension, and thromboembolism.

gamma (IFN-γ) may result in myocardial depression, vascular leak, and arrhythmias.[50] This inflammatory state may be amplified in cardiovascular-kidney-metabolic (CKM) syndrome, in which pre-existing metabolic abnormalities increase vulnerability to immunotherapy-related toxicity.[45] Immunomodulatory drugs, such as thalidomide and lenalidomide, may further exacerbate endothelial dysfunction and thrombosis, thereby increasing the risk of arterial and venous thromboembolic events.[53]

Other therapeutic modalities: Endocrine interventions and radiotherapy. In addition to chemotherapy, targeted agents, and immunotherapies, endocrine therapy and radiotherapy also confer important cardiovascular risks. Endocrine therapies, including anti-estrogens, gonadotropin-releasing hormone (GnRH) agonists, and anti-androgens, primarily affect cardiovascular health through adverse metabolic remodeling. These agents may promote lipid dysregulation, insulin resistance, direct myocardial injury, and endothelial dysfunction, thereby contributing to hypertension, heart failure, and arrhythmias.[54-56]

Radiotherapy-related cardiovascular injury results from the combined effects of direct ionizing damage and sustained inflammation. This process induces genomic instability, mitochondrial dysfunction, and endothelial apoptosis. Over time, these molecular alterations may lead to microvascular rarefaction and interstitial fibrosis, manifesting clinically as accelerated coronary atherosclerosis, valvular dysfunction, and pericardial disease.[57] Radiotherapy may also exert selective pressure that promotes the expansion of CHIP. Radiation-induced genotoxic stress favors the survival of hematopoietic stem cell clones harboring mutations in epigenetic regulators, such as DNA methyltransferase 3A (DNMT3A) and ten-eleven translocation 2 (TET2). These mutant-derived leukocytes exhibit a hyperinflammatory phenotype, with increased IL-1β and IL-6 levels driven by NLRP3 inflammasome activation.[58] This inflammatory priming may further accelerate atherosclerosis, coronary artery disease, and heart failure in cancer survivors exposed to mediastinal radiation.

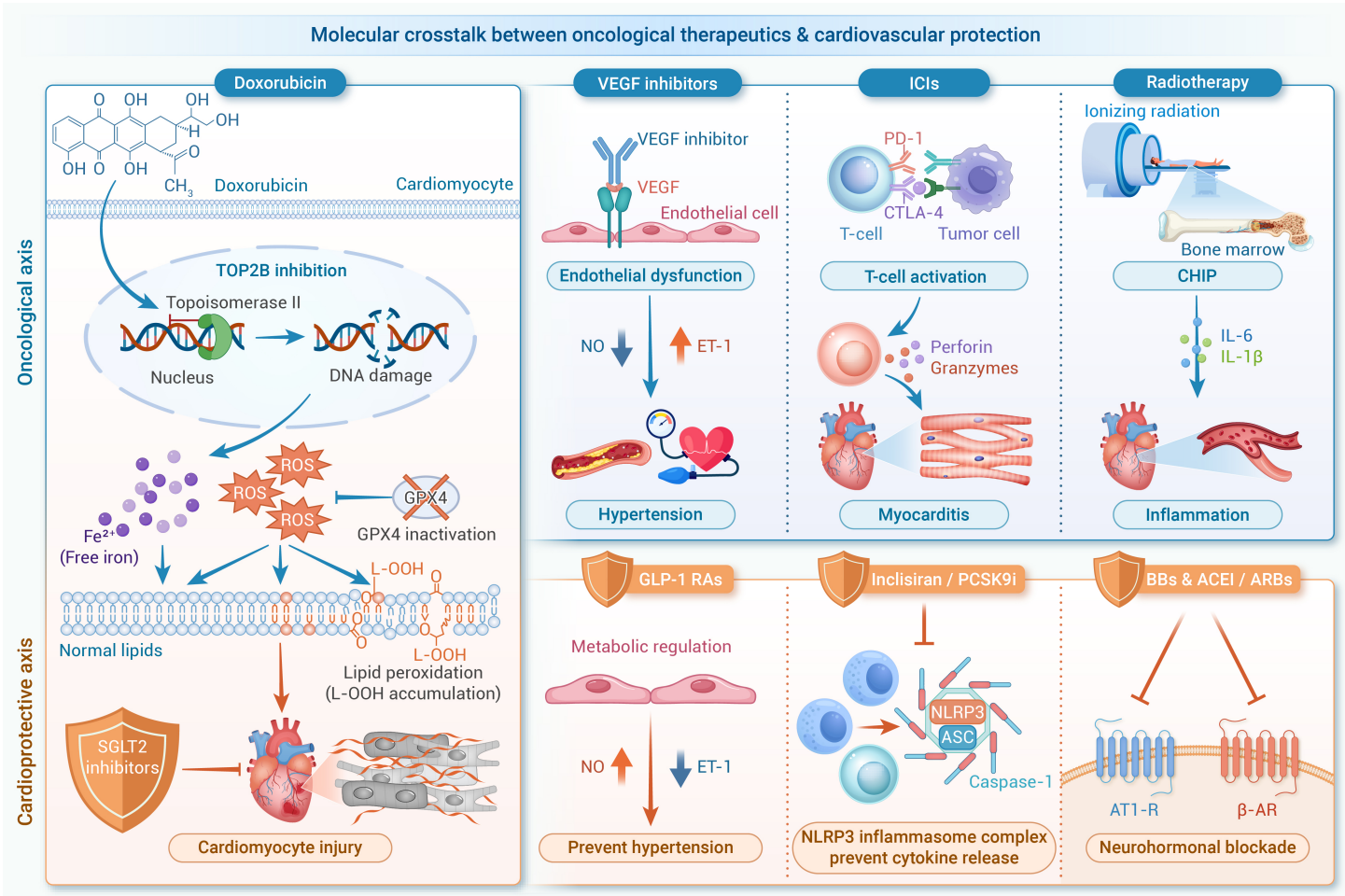

Figure 2. Molecular crosstalk between oncological therapeutics and cardiovascular protection This schematic diagram illustrates the crosstalk between representative anticancer therapies (oncological axis) and their corresponding cardioprotective strategies (cardioprotective axis). In the oncological axis, anthracyclines (e.g., doxorubicin) induce cardiomyocyte injury through TOP2B-related DNA damage and GPX4-dependent ferroptosis, characterized by iron (Fe^{2+}) accumulation and lipid peroxidation. VEGF inhibitors promote endothelial dysfunction, with reduced nitric oxide (NO) bioavailability and elevated endothelin-1 (ET-1) levels, contributing to clinical hypertension. Immune checkpoint inhibitors (ICIs) induce T-cell-mediated myocarditis by releasing perforin and granzymes. Radiotherapy acts on the bone marrow niche to promote clonal hematopoiesis of indeterminate potential (CHIP), which amplifies systemic inflammation through the interleukin-6 (IL-6) and interleukin-1β (IL-1β) signaling. In the cardioprotective axis, SGLT2 inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1 RAs) mitigate toxicity by regulating metabolism, reducing mitochondrial ROS, and improving endothelial homeostasis, including enhanced NO bioavailability. Inclisiran and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors counter cytokine-driven injury by inhibiting assembly of the NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) inflammasome complex, including NLRP3, apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC), and caspase-1. Beta-blockers, together with angiotensin-converting enzyme inhibitors (ACEIs) or angiotesin II receptor blockers (ARBs), provide neurohormonal protection by inhibiting β-adrenergic receptor (β-AR) and angiotensin II type 1 receptor (AT1-R) signaling, thereby attenuating therapy-related myocardial remodeling.

NEXT-GENERATION DIAGNOSTICS: FROM CONVENTIONAL SCORING TO INTELLIGENT EARLY WARNING

Current risk stratification frameworks: Clinical application and limitations

The integration of medical history, clinical assessment, and structured risk-stratification tools is central to individualized cardiovascular surveillance and prevention in cardio-oncology. However, a universally accepted standard for CTR-CVT risk stratification remains lacking. Current scoring systems for CTR-CVT assessment (Table S2) have several limitations, including that many models have not been validated in large, multicenter, prospective cohorts and that the models' predictive scope remains largely focused on cytotoxic regimens, with limited performance in patients receiving immunotherapy, radiotherapy, or new targeted agents. In addition, cancer and cardiovascular disease share several pathogenic drivers, and the tumor milieu itself may contribute to cardiovascular vulnerability. Accordingly, conventional cardiovascular risk calculators, such as Second Manifestations of Arterial Disease (SMART),[59] Action in Diabetes and Vascular Disease: Preterax and Diamicron-MR Controlled Evaluation (ADVANCE),[60] Systematic Coronary Risk Evaluation 2 (SCORE2)[61]/Systematic Coronary Risk Estimation 2-Older Persons (SCORE2-OP),[62] may also be considered at baseline to complement cardiovascular risk assessment, particularly given that cancer itself may increase the likelihood of cardiovascular disease.

Innovations in multi-modal imaging: From static metrics to dynamic phenotyping

Since the 2014 American Society of Echocardiography/European Association of Cardiovascular Imaging (ASE/EACVI) expert consensus statement, cardiac imaging for cardiotoxicity surveillance has advanced substantially (Table S3). However, important challenges remain in achieving early diagnosis and reliable risk prediction. These challenges reflect both the mechanistic heterogeneity of myocardial injury across anticancer therapies and the limited ability of static single-parameter indices, such as LVEF or a single global longitudinal strain (GLS) measurement, to detect subclinical change. Current research is shifting from static assessment toward longitudinal and reproducible quantitative phenotyping. By integrating serial biomarkers, treatment exposure, and temporal patterns, investigators are developing iterative risk models to improve early detection of potentially reversible injury and support more efficient clinical decision-making. Endomyocardial biopsy (EMB) remains the diagnostic gold standard because of its high sensitivity and specificity, but its invasive nature and procedural risks limit its use to selected, complex cases, particularly when the diagnosis is uncertain or mechanistic clarification is clinically necessary.

Emerging biomarkers: Shifting from necrotic markers to multi-pathway integrative surveillance

Traditional biomarkers, such as cardiac troponins (cTn) and natriuretic peptides (BNP/NT-proBNP), remain the cornerstones for screening high-risk patients. However, their sensitivity for early subclinical injury and temporal consistency may be limited.[63] Accordingly, current efforts are shifting toward a multi-pathway, phenotype-oriented biomarker strategy that incorporates inflammatory, oxidative stress, and remodeling signals, in addition to markers of injury and wall stress (Table S4). Several emerging candidates reflecting distinct pathological dimensions have attracted increasing interest, including markers of inflammation, such as high-sensitivity c-reactive protein (hsCRP), IL-6, neutrophil-to-lymphocyte ratio (NLR); oxidative stress, such as myeloperoxidase (MPO) and growth differentiation factor-15 (GDF-15); and myocardial fibrosis, such as galectin-3 (Gal-3) and soluble suppression of tumorigenicity 2 (sST2). Evidence suggests that multi-marker combinations, such as sST2 paired with NT-proBNP, may improve the sensitivity of early CTR-CVT risk stratification.[64] Circulating and exosomal microRNAs, including let-7f, miR-1, miR-126, and miR-210, have also emerged as sensitive indicators of myocardial stress and may provide an earlier molecular signal of injury.[65] Additional candidates, including endothelin-1, NRG-1, and adrenomedullin, further support a shift from markers of overt injury toward broader multi-pathway surveillance.[66,67]

Synergy of artificial intelligence and real-world evidence: Towards an intelligent cardio-oncology ecosystem

Artificial intelligence (AI) is increasingly applied in cardio-oncology, moving from proof-of-concept studies toward early clinical implementation.[16] Current applications can be broadly grouped into four primary domains: (1) Utilizing machine learning models, such as random forests (RF) and artificial neural networks (ANN), to predict cardiotoxicity risk across the therapeutic continuum.[68] (2) Integrating wearable biosensors with remote monitoring platforms for early detection of physiological aberrations.[69] (3) Applying AI-based decision support systems to treatment selection and dose optimization to reduce therapy-related cardiac injury.[70,71] (4) Using multi-modal deep learning to identify subtle structural and functional myocardial signatures.[72,73]

Future work should focus on large, multicenter, prospective studies and real-world validation to determine the clinical utility of AI-integrated workflows, alongside the development of international standards for technical, ethical, and legal governance. In addition, integrating blockchain for data integrity and augmented reality (AR) for real-time procedural or bedside guidance may warrant exploration. Global initiatives such as the Global Cardio-Oncology Registry (G-COR) also provide important real-world data on the incidence, patterns, and outcomes of CTR-CVT. Such registries may help identify key risk factors, harmonize monitoring strategies across regions, and evaluate the influence of socioeconomic and demographic factors on access, equity, and long-term outcomes.[74]

A MULTI-DIMENSIONAL STEWARDSHIP FRAMEWORK ACROSS THE CANCER CONTINUUM

Risk stratification and primordial prevention in the pre-therapy phase

Baseline risk stratification using validated tools, such as the Heart Failure Association-International Cardio-Oncology Society (HFA-ICOS) risk assessment tool, is central to pre-therapy cardiovascular stewardship and transition from reactive monitoring to proactive primordial prevention.[21] In high-risk patients, nutritional counseling and lifestyle intervention are key components of this phase. Evidence suggests that sodium restriction may be particularly beneficial for patients with heart failure or cardiac congestion, especially those for whom a daily sodium intake of ≤2.5 g should be considered.[75] Structured exercise also helps preserve functional capacity, may reduce the risk of CTR-CVT, and improves quality of life. When feasible, high-risk individuals should be encouraged to engage in at least 150 minutes of moderate-intensity exercise per week.[76]

These strategies should be individualized for vulnerable populations based on physiological reserves and comorbidities. In older adults, the mortality burden associated with CTR-CVT may exceed that of the primary malignancy. The risk of cardiovascular death in patients aged ≥80 years has been reported to be approximately 45-fold higher than in those under 39 years.[77,78] Recent evidence indicates that cardiovascular mortality may exceed cancer-related mortality as early as 1.9 years after diagnosis. These patients often present with significant comorbidities and polypharmacy, further complicated by age-related changes in pharmacokinetics, underscoring the need for individualized, risk-stratified decision-making.[79,80] Similarly, pregnancy also requires careful balancing of maternal treatment efficacy and fetal safety. In patients with pre-existing myocardial injury, pregnancy represents a major hemodynamic stressor and has been associated with a markedly increased risk of cardiotoxic events.[81,82] Physiological hemodynamic changes during pregnancy may mask early signs of cardiac dysfunction, requiring clinical vigilance to avoid diagnostic delay.[83-85]

Active surveillance and therapeutic interventions in the intra-therapy phase

Clinical management and multidisciplinary stewardship. During active treatment, cardiovascular stewardship should emphasize careful selection of anticancer regimens, dose optimization, formulation refinement, attention to routes of administration, and close monitoring.[86] This strategy is particularly important in older patients, whose reduced physiological reserve and greater comorbidity burden require individualized, risk-stratified decision-making.[79,80] In life-threatening presentations such as fulminant myocarditis, the cardio-oncology multidisciplinary team (MDT) should be engaged promptly, in accordance with the standardized principles summarized in Table 2.[87,88] Recent advances have also moved the management of ICI myocarditis toward mechanism-based therapy, with abatacept and ruxolitinib emerging as promising options that may improve outcomes compared with conventional high-dose corticosteroid boluses. [52]

Targeted cardioprotection and vulnerable populations. For intermediate- to high-risk patients, targeted cardioprotection represents an important component of intra-therapy management. Dexrazoxane remains the only U.S. Food and Drug Administration (FDA)-approved agent for the prevention of anthracycline-induced cardiotoxicity and is particularly relevant in pediatric, adolescent, and young adult patients.[106,107] Long-term follow-up data suggest that it substantially reduces the risk of left ventricular dysfunction by up to 80% without compromising oncological efficacy. Pregnancy also requires careful balancing of maternal treatment efficacy and fetal safety, and in high-risk patients, serial monitoring may help detect subclinical injury at an early stage.[83-85]

Emerging "two-birds-one-stone" therapies and future directions. Cardio-oncology is increasingly moving toward dual-benefit strategies that aim to inhibit tumor progression while preserving cardiovascular function. Although conventional neurohormonal prophylaxis, including ACEIs/ARBs and beta-blockers, has shown variable efficacy in low-risk populations, statins and emerging metabolic modulators have shown promise as more targeted preventive strategies (Table 3).[108,109] Evidence from the Statins to Prevent the Cardiotoxicity of Anthracyclines (STOP-CA) trial suggests that atorvastatin (40 mg/day) reduces the decline in LVEF in lymphoma patients receiving anthracycline therapy.[105] Beyond statins, SGLT2 inhibitors, such as empagliflozin, have shown cardioprotective potential in preclinical models by modulating inflammatory signaling, preserving mitochondrial energetics, and improving ketone body utilization.[72-74] Similarly, PCSK9 inhibitors, including inclisiran, may exert anti-inflammatory effects through inhibition of NLRP3- and myeloid differentiation primary response 88 (MyD88)-related pathways, thereby stabilizing calcium homeostasis and preserving mitochondrial integrity.[110] GLP-1 RAs may also provide cardioprotective effects beyond glucose lowering by improving myocardial energy metabolism, enhancing endothelial NO bioavailability, and modulating autonomic tone through the vagal-cholinergic signaling.[111-113]

Additional attention should be directed toward shared signaling mechanisms linking tumor-derived factors and cardiovascular injury, as these pathways may offer opportunities for dual-benefit therapy. For example, pharmacological inhibition of the NLRP3 inflammasome, such as MCC950, has been shown in preclinical studies to attenuate immune-mediated cardiac injury associated with ICIs while potentially enhancing antitumor efficacy.[119,120] IL-1 blockade also represents a promising approach, with evidence suggesting benefit in cancer-associated inflammation and chemotherapy-related cardiotoxicity, while also affecting tumor invasion and immune evasion.[121,122]

Table 2. Management strategies and pharmacological interventions for CTR-CVT.

Condition	Therapeutic interventions / agents	Key mechanistic pathways	Guideline recommendations & strength of evidence
Cardiac dysfunction / HF	ACEIs/ARBs/ARNI, beta-blockers, SGLT2 inhibitors, MRAs.	RAAS inhibition; reduction of cardiac afterload; optimization of myocardial metabolic substrate.	ESC 2022: I; CSCO 2025: 2A; ACC/AHA 2022: 2A.
	Regimen modification: Discontinuation, dose reduction, or switch (e.g., to liposomal anthracyclines).[89-91]	Elimination or mitigation of the primary cardiotoxic etiology.	ESC 2022: I/IIa; CSCO 2025: 1A/2A.
	Dexrazoxane	Iron ion chelation; sequestration of topoisomerase IIβ; reduction of ROS-mediated injury.	ESC 2022: IIb; CSCO 2025: 2A.
Coronary artery disease (CAD)	Antiplatelets, statins, beta-blockers, ACEIs/ARBs/ARNI.	Platelet inhibition; plaque stabilization; reduction of myocardial oxygen demand.	CSCO 2025: 1A; ACC/AHA 2025: I.
	Urgent PCI, thrombolysis, and dual antiplatelet therapy (DAPT).[21,92-98]	Revascularization of culprit arteries; acute inhibition of thrombus propagation.	ESC 2022: I; CSCO 2025: 2A; ACC/AHA 2025: I.
Hypertension	ACEIs/ARBs, DHP-CCBs, ARNI.	RAAS blockade; peripheral vasodilation; natriuresis and volume control.	ESC 2022: I; CSCO 2025: First-line; ACC/AHA 2017: First-line.
	Thiazide diuretics, beta-blockers, MRAs.	Diuresis; heart rate modulation; electrolyte homeostasis (K^+ sparing/Na^+ excretion).	ESC 2022: IIA; CSCO 2025: Use with caution; ACC/AHA 2017: Second-line.
Arrhythmias / AF	Beta-blockers.	Ventricular rate control via sympathetic inhibition.	ESC 2022: I; ACC/AHA 2023: Preferred.
	Non-DHP CCBs, anticoagulants (DOACs/VKAs), anti-arrhythmic agents, and pacemaker implantation.[99,100]	Rate/rhythm control; stroke prevention via thromboembolism prophylaxis; stabilization of cardiac electrophysiology.	ESC 2022: I; ACC/AHA 2023: 2A.
Venous thromboembolism (VTE)	UFH, LMWH, DOACs, warfarin.[101,102]	Anticoagulation; inhibition of coagulation cascade factors.	ESC 2022: I; CSCO 2025: 1A/2A; ASCO 2023: Strong.
Immune-related myocarditis	Methylprednisolone, prednisone.[21]	Immunosuppression; attenuation of myocardial inflammatory infiltration.	ESC 2022: I/IIa; CSCO 2025: 2A; ASCO 2018: Recommended.
	Immunosuppressants (e.g., mycophenolate mofetil, tocilizumab, abatacept).[103]	Advanced immunological blockade for refractory cases.	(N/A)
	Discontinuation of ICIs.	Removal of the inciting immunological trigger.	(N/A)
Dyslipidemia	Statins, ezetimibe, probucol, fibrates, niacin, omega-3 fatty acids, PCSK9 inhibitors.[104,105]	Inhibition of cholesterol biosynthesis; enhancement of biliary excretion; reduction of TG and LDL-C levels.	ESC 2022: I; CSCO 2025: 1A/2B.

Abbreviation & Grading Notes: Organizational Full Names. ESC 2022: European Society of Cardiology Guidelines on Cardio-Oncology. CSCO 2025: Chinese Society of Clinical Oncology Practice Guidelines on Cardio-Oncology. ACC/AHA 2022/23/25: American College of Cardiology/American Heart Association Joint Guidelines. ASCO 2018/23: American Society of Clinical Oncology Clinical Practice Guidelines.Standardized Grading Systems. ESC/ACC/AHA Recommendation Classes: Class I (Strongly recommended, benefit >>> risk); Class IIa (Should be considered, benefit >> risk); Class IIb (May be considered, benefit ≥ risk).CSCO Evidence Levels: 1A/1B (High level: Meta-analyses or large RCTs); 2A/2B (Moderate level: Smaller RCTs or high-quality retrospective studies). ASCO Strength: Strong (High-quality evidence, consistent results); Moderate (Good evidence, expert consensus).

In atherosclerosis, dysregulated immune cell infiltration and chronic vascular inflammation contribute to plaque initiation, progression, and destabilization.[123] In acute myeloid leukemia models, IL-1α blockade may alleviate cardiac energetic failure through the NF-κB/PGC-1α axis. Therapeutic modulation of IL-13 signaling may also be relevant, given its dual roles in promoting M2 polarization of tumor-associated macrophages (TAMs) and regulating cardiomyocyte regeneration and extracellular matrix remodeling.[124-127]

Interventions targeting shared metabolic pathways may offer additional therapeutic opportunities. 5-Oxoproline supplementation has been reported to ameliorate doxorubicin-induced cardiotoxicity by restoring glutathione homeostasis and suppressing tumor growth through selective inhibition of γ-glutamyl cyclotransferase (GGCT) in malignant cells.[128] 2-Methoxyestradiol (2-ME), an endogenous estrogen metabolite, has also been reported to suppress tumor growth through anti-microtubule activity while protecting the heart against pathological remodeling and oxidative stress.[129] Highly selective A_3 adenosine receptor agonists, such as MRS1898, have shown multi-modal potential in preclinical studies, including neuroprotection, cardioprotection, and antitumor effects.[130]

Long-term survivorship and health equity in the post-therapy phase

The management of cancer survivors focuses on the early detection of late toxicities and on promoting health equity through structured long-term stewardship. Current guidelines support a multi-stage monitoring strategy in which follow-up intensity is tailored according to baseline risk and evolving clinical and biomarker findings, thereby facilitating the transition to standardized long-term survivorship plans. Digital health technologies are reshaping cardiotoxicity surveillance in survivorship care. AI-enabled decision-support tools, including automated electrocardiogram (ECG) interpretation and quantitative echocardiographic assessment, are increasingly integrated with wearable sensors, such as ECG patches and smartwatches, and remote symptom-reporting platforms. These technologies enable near-real-time collection of physiological data and patient-reported outcomes (PROs), which may improve early detection of arrhythmias, hemodynamic decompensation, and functional decline.[131] For example, the CardioAI platform integrates wearable devices with large language model (LLM)-based assistants for continuous multi-modal monitoring, providing explainable risk-prediction scores to support clinical decision-making.[132] In addition, AI-ECG screening has shown

Table 3. Clinical trials evaluating pharmacological cardioprotection in oncology.

Trial / NCT ID	Phase / design	Population (n)	Intervention	Primary findings / clinical implications	Trial status
NCT02053974[114]	Phase 4	Breast cancer (n=90)	Spironolactone	Simultaneous administration with anthracyclines preserved both systolic and diastolic myocardial functions.	Completed
NCT01434134[115]	Phase 2	Early breast cancer (n=130)	Candesartan / metoprolol	Candesartan attenuated the early decline in LVEF; metoprolol showed no significant protective effect on overall LVEF preservation.	Completed
NCT01724450[116]	Phase 3	HER2-negative breast cancer (n=200)	Carvedilol	Failed to prevent early LVEF reduction but significantly mitigated troponin elevation and diastolic dysfunction.	Completed
NCT01708798[117]	Phase 2/3	Stage I-III breast cancer (n=44)	Eplerenone	Six-month eplerenone administration yielded no significant benefit in preserving systolic or diastolic parameters during anthracycline therapy.	Terminated
NCT04434404	Phase 4	Breast cancer (n=83)	L-Carnitine & silymarin	Data pending / outcome analysis currently under peer review.	Completed
NCT04435028	Observational	Breast cancer (n=111)	Ketotifen	Investigative assessment of mast cell stabilization in cardiotoxicity; outcome data pending.	Completed
NCT06341842[118]	Phase 2	Stage I-III Breast Cancer (n=316)	Dapagliflozin	Evaluating the efficacy of SGLT2 inhibitors in mitigating anthracycline- and/or trastuzumab-induced cardiotoxicity.	Recruiting

utility in detecting LVEF impairment in survivors previously exposed to anthracyclines, offering a cost-effective surveillance strategy for vulnerable populations in resource-limited settings.[133,134]

Implementation of these strategies also depends on effective coordination with a cardio-oncology multidisciplinary team. By integrating expertise from oncology, cardiology, imaging, pathology, and pharmacy, and by using an electronic health record (EHR)-embedded pathway together with shared decision-making, the MDT can support comprehensive risk assessment and timely therapeutic adjustments. This is particularly important for pediatric survivors, whose risk of cardiovascular death has been reported to be approximately eightfold higher than that of the general population, supporting a development-conscious strategy and lifelong surveillance, especially after exposure to anthracyclines and radiotherapy.[135,136] Notably, bridging the healthcare gap through such inclusive clinical frameworks and AI-driven telemedicine will be important for improving global health equity. A comprehensive set of patient empowerment strategies, including psycho-oncological support (e.g., breathing exercises and music therapy) and self-monitoring education, is also essential for optimizing long-term patient adherence to these complex, multi-dimensional management regimens.[137,138]

REVERSE CARDIO-ONCOLOGY: THE HEART AS A SYSTEMIC DRIVER OF MALIGNANCY

Epidemiological evidence linking cardiovascular disease to cancer risk

Reverse cardio-oncology describes a bidirectional relationship in which pre-existing CVD may contribute to oncogenesis, tumor progression, and metastatic dissemination.[13,139,140] Epidemiological studies suggest that patients with chronic heart failure, atherosclerosis, hypertension, and atrial fibrillation exhibit a higher overall incidence of cancer than the general population.[141] Younger patients with atrial fibrillation appear to be at increased risk of several malignancies, including colorectal, breast, lung, hepatobiliary, renal, and thyroid cancers, as well as non-Hodgkin lymphoma (NHL) and leukemia.[142] Patients with hypertension also have an increased risk of kidney, colorectal, breast, endometrial, squamous cell, esophageal adenocarcinoma, and liver cancers.[143] Patients with heart failure have also been reported to be at increased risk of new-onset colorectal cancer, lung cancer, and multiple myeloma.[144] Additionally, individuals with a history of acute myocardial infarction have been reported to have a 49% higher risk of hematologic malignancies than those without such a history.[145] Collectively, these findings support an epidemiological association between cardiovascular disease and subsequent cancer risk, although the extent to which this relationship is causal rather than driven by shared risk factors remains an important question.

Mechanistic insights: Cardiovascular disease as an independent driver of malignancy

A critical challenge in this field is whether the association between cardiovascular disease and cancer is causal or merely reflects shared risk factors. Current evidence suggests that myocardial infarction and heart failure remain associated with increased tumor risk, even after adjustment for potential confounders, including age, sex, body mass index (BMI), alcohol use, smoking, prior cancer history, cholesterol levels, diabetes mellitus, and other comorbidities.[146,147] These findings support the possibility that underlying cardiac pathology may contribute to tumor promotion independently of shared risk factors. Beyond shared risk factors, the diseased heart may act as a systemic driver through cardiokine secretion and immune reprogramming.[14,148-150] For example, myocardial infarction can induce epigenetic reprogramming of bone marrow hematopoietic stem cells through systemic inflammatory signaling, leading to myeloid skewing and the emergence of monocytes with a persistently immunosuppressive phenotype. These cells may then be recruited to tumors, where they promote an immune-evasion microenvironment by suppressing $CD8^+$ T cell function and expanding regulatory T cells, thereby facilitating breast cancer progression.[151]

In addition to immune reprogramming, myocardial infarction may also influence tumor progression through extracellular vesicle-mediated signaling. After myocardial infarction, small extracellular vesicles released from failing hearts may carry protumorigenic signals that enhance cancer cell proliferation and migration and promote macrophage polarization toward a tumor-associated phenotype. In preclinical models, adoptive transfer of post-myocardial infarction cardiac mesenchymal stromal cell-derived small extracellular vesicles (post-MI cMSC-sEVs) accelerates tumor growth, whereas systemic vesicle depletion attenuates this effect.[152] Beyond these heart-derived mechanisms, adrenergic signaling may contribute to cancer progression. Catecholamines activating the β2 adrenergic receptor (β2-AR) can engage cyclic adenosine monophosphate/protein kinase A (cAMP/PKA) and mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) pathways, thereby promoting malignant cell survival, suppressing antitumor immunity, and enhancing angiogenesis.[153]

The dual role of cardiovascular agents in oncology: Anticancer potential and carcinogenic risk

The role of cardiovascular agents in oncology is increasingly recognized, both for their potential antitumor effects and for potential carcinogenic concerns.[141] Recent evidence suggests that statins inhibit the mevalonate pathway, blocking GTPase prenylation, thereby suppressing tumor growth and potentially enhancing the effects of conventional anticancer therapy.[154] Beta-blockers may also inhibit β-adrenergic signaling, suppressing tumor progression and counteracting stress-induced immunosuppression by restoring natural killer (NK) cell and $CD8^+$ T cell cytotoxicity, thereby enhancing antitumor immunity and potentially improving therapeutic response.[155] SGLT2 inhibitors have also been reported to activate AMP-activated protein kinase (AMPK), partly by inhibiting mitochondrial complex I, thereby modulating the mammalian target of rapamycin/phosphoinositide 3-kinase-protein kinase B (mTOR/PI3K-AKT) axis and glucose uptake. They may also promote

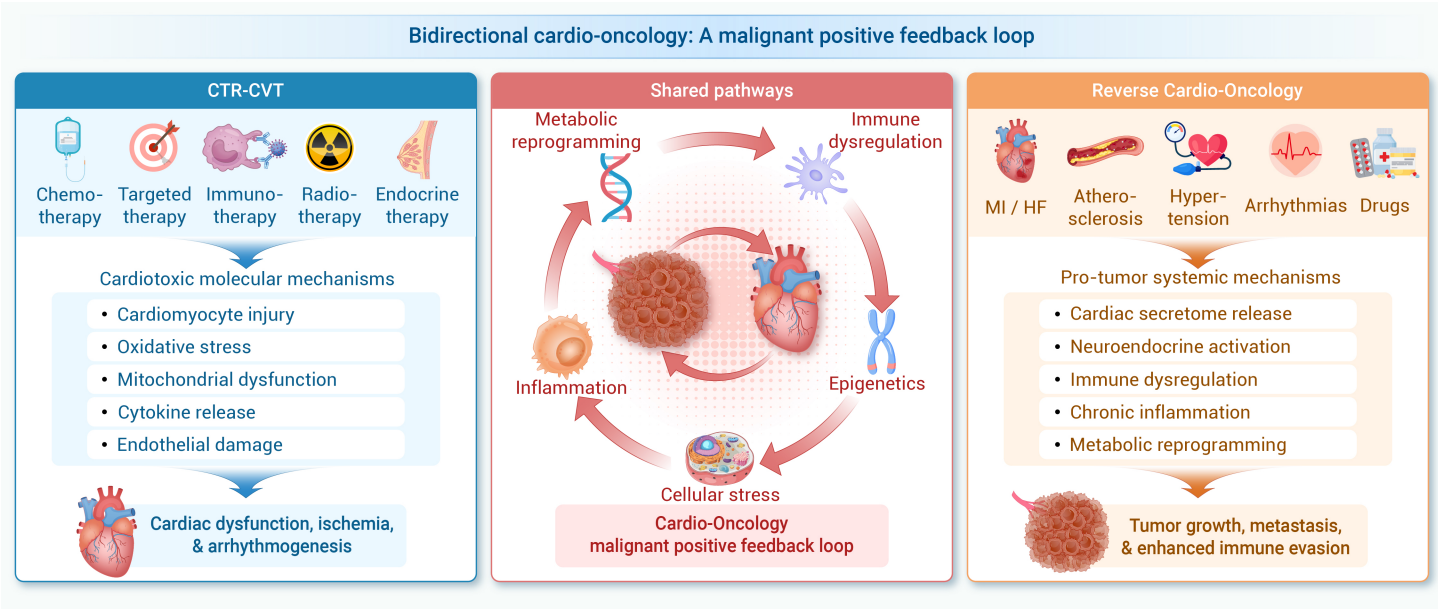

Figure 3. Bidirectional cardio-oncology as a malignant positive feedback loop This figure summarizes the reciprocal relationship between cancer-related cardiovascular toxicity and reverse cardio-oncology. CTR-CVT arises from chemotherapy, targeted therapy, immunotherapy, radiotherapy, and endocrine therapy, leading to cardiomyocyte injury, oxidative stress, mitochondrial dysfunction, cytokine release, and endothelial damage, resulting in cardiac dysfunction, ischemia, and arrhythmogenesis. These effects intersect with shared pathways, including metabolic reprogramming, immune dysregulation, inflammation, epigenetic alterations, and cellular stress. In turn, cardiovascular conditions such as myocardial infarction/heart failure (MI/HF), atherosclerosis, hypertension, arrhythmias, and cardiovascular drug exposure promote pro-tumor systemic mechanisms, including cardiac secretome release, neuroendocrine activation, immune dysregulation, chronic inflammation, and metabolic reprogramming, thereby facilitating tumor growth, metastasis, and immune evasion. Together, these processes establish a self-reinforcing malignant positive feedback loop between cancer and the heart.

programmed cell death and enhance antitumor immunity by degrading programmed death-ligand 1 (PD-L1) and activating the stimulator of interferon genes (STING) pathway.[17] Beyond these agents, warfarin has been reported to exert antitumor effects by potentially inhibiting vitamin K epoxide reductase complex subunit 1-like 1 (VKORC1L1) and disrupting the vitamin K reduction cycle, thereby promoting programmed cell death and ferroptosis in tumor cells.[156]

In patients with atrial fibrillation, emerging evidence suggests that oral anticoagulation, including both warfarin and direct oral anticoagulants, may not directly increase cancer risk but may instead unmask previously occult malignancies through bleeding events that promote earlier cancer diagnosis.[157] Hydrochlorothiazide has been demonstrated to be associated with increased risk of non-melanoma skin cancer, possibly through UVA-dependent photosensitivity mechanisms involving dysregulation of the p53-MDM2 axis, oxidative DNA damage, chronic inflammation, and downregulation of the tumor suppressor receptors vitamin D receptor (VDR) and P2X purinoceptor 7 (P2RX7).[158] For other agents, such as chlorthalidone, amlodipine, lisinopril, and candesartan, the association with cancer risk remains uncertain, and the available evidence is inconsistent.[141]

The malignant positive feedback loop between cancer and the heart: Bidirectional drive and reciprocal causation

Within the framework of bidirectional cardio-oncology, the relationship between cancer and the heart can be understood as a reciprocally reinforcing pathological loop (Figure 3). Cancer and its therapies, including chemotherapy, targeted therapy, immunotherapy, radiotherapy, and endocrine therapy, can cause cardiac dysfunction, myocardial ischemia, and arrhythmias by inducing cardiomyocyte injury, oxidative stress, mitochondrial dysfunction, cytokine release, and endothelial damage, thereby activating the classical cardiotoxicity pathway. Conversely, the diseased cardiovascular system, shaped by heart failure, myocardial infarction, hypertension, atherosclerosis, arrhythmias, or exposure to cardiovascular drugs, may promote tumor growth, metastasis, and immune evasion through systemic mechanisms, including cardiac secretome release, neuroendocrine activation, immune dysregulation, chronic inflammation, and metabolic reprogramming. These two pathways are linked by chronic inflammation, metabolic remodeling, epigenetic modifications, and shared signaling cascades, together forming a malignant positive feedback loop in which cancer and its therapies aggravate cardiovascular injury. In parallel, the injured heart may further facilitate tumor progression. This bidirectional interplay supports a model of amplification between cancer and cardiovascular disease.

CONCLUSIONS AND FUTURE PERSPECTIVES: BRIDGING THE KNOWLEDGE GAPS

Personalized risk prediction integrating oncology and cardiology

The 2022 European Society of Cardiology (ESC) Guidelines on Cardio-Oncology recommend baseline cardiovascular risk assessment for patients scheduled to receive potentially cardiotoxic antitumor therapies, including the use of the HFA-ICOS risk assessment tool. This framework supports individualized decisions regarding surveillance intensity, cardioprotective therapy, and potential modifications of anticancer treatment strategies.[159] In parallel, a multicenter, prospective cohort study developed the PrevCardioOncAI model, an interpretable algorithm trained on 89 clinical, laboratory, and echocardiographic variables from a multiethnic cohort of 3,835 cancer survivors to estimate the 5-year risk of major adverse cardiovascular events (MACE) and support risk-stratified management.[160]

Biomarker discovery for integrated surveillance

Emerging evidence has identified several shared biomarkers, including total sialic acid (TSA), bound sialic acid (BSA), and free sialic acid (FSA), that may reflect convergent pathobiological mechanisms in both malignancy and cardiovascular disease and therefore have value for integrated risk stratification and longitudinal monitoring.[161] Similarly, circulating and urinary cyclic guanosine monophosphate (cGMP) concentrations are elevated in selected cardiovascular conditions and malignancies and may serve as a longitudinal marker of treatment trajectories and pharmacodynamic response.[162] Accordingly, identification of tumor-associated cardiac biomarkers may improve risk stratification, facilitate early detection of cardiotoxicity, and support more personalized therapeutic decision-making in patients with cancer.

Tumor microenvironment-heart interactions and dual-purpose therapeutic strategies

Accumulating evidence suggests that tumor pathobiology extends beyond the local tumor microenvironment (TME). The emerging concept of the tumor systemic organoid environment highlights that malignancies can exert organ-specific effects on distant physiological systems, including the cardiovascular

system, through circulating factors, exosomes, and immune-mediated crosstalk. An exclusive focus on TME-centric models may overlook systemic drivers of comorbidity, including cancer-associated cardiotoxicity and broader cardio-oncologic syndromes, thereby limiting the identification of more integrated therapeutic targets.[163] Investigation of bidirectional crosstalk between the TME and the cardiovascular system is becoming an important multidisciplinary area in cardio-oncology. Key future research priorities include: (1) use of single-cell and spatial multi-omics approaches to characterize changes in cardiac immune cell subsets, stromal phenotypes, and intercellular communication networks in patients with cancer relative to appropriately matched controls; (2) integrated preclinical evaluation in physiologically relevant murine or humanized models to assess antitumor efficacy together with cardiotoxic and cardioprotective outcomes, including myocardial structure, systolic and diastolic function, and electrophysiological stability; and (3) development of targeted interventions directed at TME-related components, such as cancer-associated fibroblasts or tumor-derived exosomes, with the goal of suppressing oncogenic signaling while preserving cardiac homeostasis and adaptive capacity.[164,165]

Integration of digital health into cardio-oncology care

Integration of digital health technologies into cardio-oncology practice is currently focused on two major areas: remote surveillance and management of immune checkpoint inhibitor-associated cardiotoxicity, and the delivery of evidence-based, remotely supervised pulmonary and cardiac rehabilitation for cancer survivors. Digital health technologies, including remote physiological monitoring platforms and wearable-enabled rehabilitation programs aligned with guideline recommendations, may provide a feasible approach to two important challenges in cardio-oncology: immune checkpoint inhibitor-associated cardiotoxicity and post-treatment cardiorespiratory deconditioning.[166] This direction aligns with the broader integration of digital health into comprehensive supportive care frameworks in oncology and cardio-oncology. These developments support a shift from a cancer-centric to a more patient-centered lifecycle management model. Future care models should integrate novel therapeutics, digital health tools, and structured multidisciplinary collaboration to optimize oncologic outcomes while preserving long-term cardiovascular health.

DECLARATION OF GENERATIVE AI AND AI-ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

During the preparation of this work, the authors used AI-assisted language editing to improve clarity and readability. After using this tool, the author(s) reviewed and edited the content as needed and took full responsibility for the content of the publication.

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J.W. conceived and designed the research, prepared the figures, co-wrote the paper, supervised the review, and revised the manuscript. R.W., L.Y. and X.L. prepared the figures and co-wrote the paper. W.F. and Y.W. supervised the review and revised the manuscript. All authors contributed to the manuscript and approved the final version.

DECLARATION OF INTERESTS

The authors declare no competing interests.

DATA AND CODE AVAILABILITY

No new data were created or analyzed in this study.

SUPPLEMENTAL INFORMATION

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