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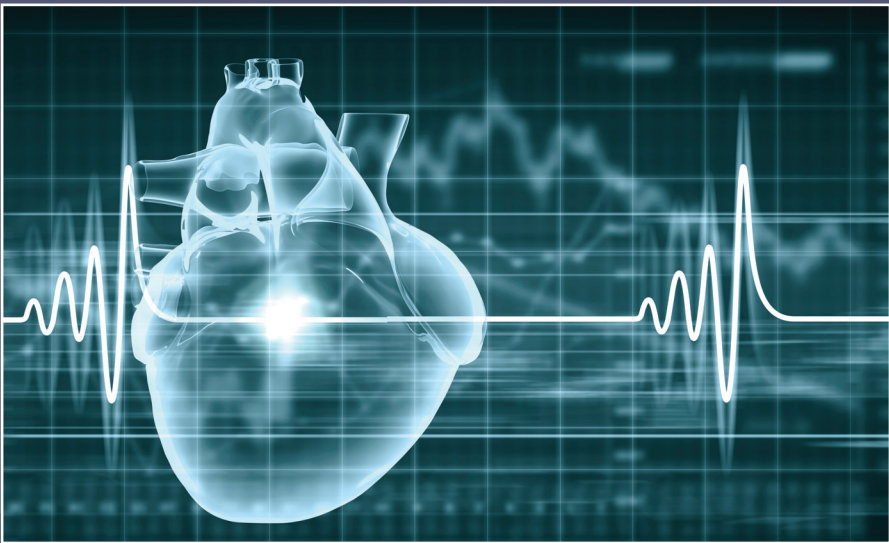
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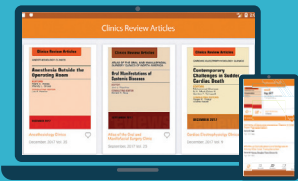


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Omar M. Makram, Priyanshu Nain, Alexi Vasbinder, Neal L. Weintraub, and Avirup Guha

This review goes beyond traditional approaches in cardio-oncology, highlighting often-neglected factors impacting patient care. Social determinants, environment, health care access, and gut microbiome significantly influence patient outcomes. Powerful tools like multi-omics and wearable technologies offer deeper insights into real-world experiences. The future lies in integrating these advancements with established practices to achieve precision cardio-oncology care. By crafting tailored therapies and continuously updating comprehensive management plans based on real-time data, we can unlock the full potential of personalized care for all patients.

Clonal Hematopoiesis of Indeterminate Potential and Cardiovascular Health

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Michael A. Raddatz, Yash Pershad, Alyssa C. Parker, and Alexander G. Bick

Clonal hematopoiesis of indeterminate potential (CHIP) is an age-related phenomenon in which somatic mutations lead to clonal expansion of hematopoietic stem cells without the development of hematologic abnormalities. A growing body of literature demonstrates an association between CHIP and cardiovascular disease. This pathophysiology demonstrates a novel connection between global inflammation and cardiovascular morbidity. While there is limited consensus addressing the cardiovascular care of these patients, risk factor optimization and disease surveillance are advisable. Investigation into possible therapies is ongoing and provides promise for the treatment of inflammation contributing to cardiovascular disease in patients with and without CHIP.

Unique Challenges of Adult Congenital Heart Disease in Cardio-Oncology

25

Gentian Lluri and Prashanth Venkatesh

Adults with congenital heart disease make up most patients with congenital heart disease vastly surpassing the pediatric patients largely because of significant improvements in the medical, interventional, and surgical approaches. An increasing body of evidence highlights the impact of noncardiac morbidity and mortality in these patients. Malignancy is a known major cause of death in adult patients with congenital heart disease. The causes are multifactorial, including genetics, radiation, delayed age-appropriate screening, anatomy variations, and thymectomy. This article provides an overview of the specific risk factors and how health care providers and patient education can mitigate some of these risk factors.

Classes of Antineoplastic Agents Associated with Increased Risk of Cancer Therapy-associated Hypertension and Management Strategies

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Hoda Sayegh, Alexia Zagouras, Joel W. Neal, Ronald M. Witteles, Han Zhu, and Sarah Waliany

Hypertension (HTN) has been found to be the most common comorbidity in patients with cancer. In addition to increased prevalence of baseline HTN, patients with cancer may be at increased risk of HTN as a short-term or long-term adverse event from

cancer therapy. Different classes of cancer therapies have been implicated in the development of HTN, including inhibitors of vascular endothelial growth factor (VEGF), Bruton tyrosine kinase inhibitors, proteasome inhibitors, androgen deprivation therapy, and others. While some of these drugs may lead to increases in blood pressure through on-target effects (eg, with VEGF inhibition), others may be associated with HTN from off-target mechanisms that are not always well understood.

Arrhythmia Challenges in Cardio-Oncology: High-Risk Therapies, Management, and Anticoagulation

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Jonathan C. Wright, Sneha Sharma, and Adam S. Potter

Cardiovascular disease and cancer are the leading cause of mortality in the United States. In 2021, there were 695,547 and 605,213 deaths due to heart disease and cancer, respectively. With novel oncologic and cardiac therapies, survival has improved leading to increased life-expectancy albeit with chronic illness burden. Arrhythmia management in patients with cancer, whether active or in remission, can be quite challenging. In this review, we will discuss high-risk oncological therapies, prevention, and management of Atrial fibrillation, Ventricular Arrhythmias, and Bradyarrhythmias.

Ischemic Heart Disease in the Cancer Population: Trends, Outcomes, Epidemiology, and Challenges in Diagnosis and Treatment

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Dorina-Gabriela Condurache, Zahra Raisi-Estabragh, Arjun K. Ghosh, and Mamas A. Mamas

Patients with cancer are at increased risk of ischemic heart disease (IHD). The increased risk of IHD in these patients is due to the interaction of shared risk factors, cancer type and stage, and immuno/chemotherapy and radiotherapy regimens. Management of IHD in cancer patients is challenging, due to atypical presentation, increased thrombotic and bleeding risk, and worse outcomes compared to patients without cancer. In this review, we will discuss the trends, outcomes, epidemiology and challenges in the diagnosis and treatment of IHD among cancer patients.

Cardiovascular Health in Breast Cancer: Survivorship Care

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Coralea Kappel, Robin Tumlinson, and Susan Dent

Improved screening and treatment have increased breast cancer survival rates, with over 7.8 million women surviving 5 years post-diagnosis globally. However, survivors face heightened cardiovascular morbidity and mortality due to cancer treatment and patient related risk factors. Cardio-oncology has emerged as a discipline to manage cardiovascular health in patients throughout and following cancer treatment. This review focuses on strategies to optimize cardiovascular health in breast cancer survivors, aligning with ASCO’s survivorship principles. Key strategies include risk stratification, primary prevention, lifestyle interventions, pharmacologic management, appropriate cardiovascular monitoring, and tailored exercise programs. Effective cardio-oncology care hinges on collaboration between specialists and patients, underscoring the significance of shared-care models and telemedicine options in survivorship management.

Cardiovascular Risk in Prostate Cancer

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Darryl P. Leong, Filipe Cirne, and Jehonathan H. Pinthus

Cardiovascular disease is common in patients with prostate cancer and is an important cause of death. Cardiovascular risk factors are frequent in this population and are often not addressed to thresholds recommended by cardiovascular practice guidelines. Androgen deprivation therapy (ADT) reduces muscle strength and increases adiposity, thereby increasing the risk of diabetes and hypertension,

although its relationship with adverse cardiovascular events requires confirmation. Androgen receptor signaling inhibitors and CYP17A1 inhibitors may confer incremental risks of hypertension and cardiovascular events to ADT. Lower cardiovascular risk with gonadotropin-releasing hormone antagonists as compared with agonists requires prespecified randomized clinical trial confirmation,

Evolving Strategies in Cardiac Amyloidosis: From Mechanistic Discoveries to Diagnostic and Therapeutic Advances

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Ashley F. Stein-Merlob, Rachel Swier, and Darko Vucicevic

Diagnosis and treatment of cardiac amyloidosis have rapidly evolved over the past decade by harnessing mechanisms of disease pathogenesis. Cardiac amyloidosis is caused by myocardial deposition of fibrils formed by misfolded proteins, namely transthyretin (ATTR) and immunoglobulin light chains (AL). Advances in noninvasive imaging have revolutionized diagnosis of ATTR cardiomyopathy (CM). Novel treatments for ATTR-CM utilize a range of therapeutic techniques, including protein stabilizers, interfering RNA, gene editing, and monoclonal antibodies. AL-CM, primarily driven by plasma cell dyscrasias, requires treatment with chemotherapy and consideration for autologous stem cell transplant. These incredible advances aim to improve patient outcomes in cardiac amyloidosis.

Cardiotoxicity of Anthracyclines

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Elizabeth Balough, Abul Ariza, Aarti Asnani, and Christopher W. Hoeger

Anthracycline chemotherapy is associated with cardiotoxicity, predominantly manifesting as left ventricular systolic dysfunction within the first year of treatment. Early detection is possible through biomarkers and cardiovascular imaging before clinical symptoms develop. Comprehensive cardiovascular risk assessment is essential for all patients prior to anthracycline therapy to stratify their risk of cardiotoxicity. Preventive measures, including cardiovascular risk optimization, as well as anthracycline dose adjustments, the use of liposomal anthracyclines, and dexrazoxane in high-risk patients, are crucial to mitigate the risk of cardiotoxicity. Long-term follow-up and cardiovascular risk optimization are critical for cancer survivors to optimize cardiovascular outcomes.

Cardiac Complications of Radiation Therapy

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Raja Zaghlol, Lauren Pedersen, Syed Qamer, Sang Gune K. Yoo, Daniel A. Ladin, Adeesh Parvathaneni, Carmen Bergom, and Joshua D. Mitchell

Radiation therapy is a critical component in managing many malignancies by improving local control and survival. The benefits of radiation may come at the expense of unintended radiation injury to the surrounding normal tissues, with the heart being one of the most affected organs in thoracic radiation treatments. As cancer survivors live longer, radiation-induced cardiotoxicity (RICT) is now increasingly recognized. In this review, we highlight the spectrum and pathophysiology of RICT. We summarize contemporary recommendations for risk stratification, screening, prevention, and management of RICT. We briefly highlight novel applications for radiation to treat some cardiac conditions such as resistant arrhythmias.

Cardiac Complications of Immune Checkpoint Inhibitors and Chimeric Antigen Receptor T Cell Therapy

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Bhargav Makwana, Aishwarya Malode, Sumanth Khadke, Vahin Patel, Rushin Shah, Manav Patel, Aneri Parikh, Sourbha S. Dani, and Sarju Ganatra

Immune checkpoint inhibitors and chimeric antigen receptor T-cell therapy have revolutionized cancer treatment but can cause life-threatening cardiovascular toxicities through immune-related adverse events. Myocarditis is the most common and

potentially fatal toxicity with immune checkpoint inhibitors. T-cell therapies can potentially lead to cytokine release syndrome. Diagnosis of ICI-myocarditis requires a multimodal approach, including biomarkers, imaging, and endomyocardial biopsy, while CRS is characterized by a clinical syndrome resembling distributive shock. Management involves discontinuing the offending therapy, immunosuppression with corticosteroids for ICI-myocarditis, and interleukin-6 antagonists for CRS. Collaboration between oncologists and cardiologists is crucial for early recognition and prompt treatment.

Cardio-oncology Drug Interactions: A Primer for Clinicians on Select Cardiotoxic Oncologic Therapies

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Craig J. Beavers and Alana M. Ferrari

Cardio-oncology is an emerging multidisciplinary field intended to mitigate and manage cardiovascular side effects and risks associated with cancer therapies. Clinician awareness of drug interaction management among cancer treatments, cardiovascular medications, and supportive care agents is important for optimizing efficacy and safety. Historically, chemotherapies have been associated with pharmacodynamic interactions with few, but important, pharmacokinetic interactions. The advent of oral targeted inhibitors has introduced more complex pharmacokinetic interactions, especially via cytochrome P450 pathways. Given the accelerated development of oncology therapies, clinicians need to be familiar with reviewing multiple sources for interaction information as well as adjusting and monitoring regimens when contending with drug interaction challenges.

Cardio-Oncology Program Building: A Practical Guide

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Michelle Weisfelner Bloom, Alana M. Ferrari, Jadranka Stojanovska, Kathleen Kiernan Harnden, Yaisa Beckford, Kerry Skurka, and Ana Barac

The organization of a cardio-oncology clinic and overall program is designed to provide comprehensive cardiovascular care to patients who are at risk of or have developed cardiovascular sequelae during or following cancer treatments. In this article, we summarize the core components of a contemporary cardio-oncology program, including its core members (cardiologists, oncologists, clinical pharmacists, advanced practice providers, nurses, and coordinators), key services (risk assessment, treatment planning, cardiac imaging, intervention, and management), and practical integration within the health care system.

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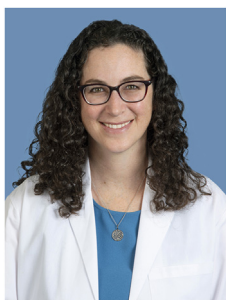
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Preface

Addressing the Growing Intersectionality of Cancer and Heart Disease: The Rise of Cardio-Oncology



Ashley F. Stein-Merlob, MD



Eric H. Yang, MD

Editors

With significant strides in cancer treatment and survivorship, the reach and scope of Cardio-Oncology has extended beyond its traditional, perceived association with chemotherapy-induced heart failure to encompass every facet of the cardiovascular landscape intersecting with an expanding array of anticancer therapies. With over 20 million cancer survivors expected in the United States alone by 2030,¹ understanding, predicting, and treating the cardiovascular health of the growing cancer population is paramount. These patients cannot just be cared for by those who practice cardio-oncology as a so-called niche science—but it is a necessary field of study applicable to all cardiovascular specialists. In this focus issue of *Cardiology Clinics*, we aim to showcase both the breadth and the depth of the growing field of Cardio-Oncology. These articles examine the unique challenges of

the treatment of common cardiovascular conditions in this population, highlight important risk factors relevant to cardio-oncology patients, and delve into the cardiovascular consequences of specific cancer treatments.

Revolutionary advances in cancer therapeutics have transformed many cancers from rapidly fatal to a more chronic disease state, comparable to cardiovascular diseases like heart failure and stable coronary artery disease. Arguably, many cancers—even with advanced or metastatic disease—now have superior survival rates to some cardiovascular diseases, like heart failure.² While cardiovascular specialists celebrate advances in guideline-directed medical therapies prolonging survival in disease states such as coronary artery disease and heart failure, it is dwarfed by the impressive pharmaceutical pipeline of

immunotherapies and targeted therapies. One type of immunotherapy, immune checkpoint inhibitors (ICIs), is now a potential treatment for which more than 50% of all cancer patients are eligible.³ Unfortunately, various forms of short- and long-term cardiotoxic sequelae can manifest, including cardiomyopathy, premature atherosclerosis, myocarditis, arrhythmias, and hypertension—essentially all facets of cardiovascular disease.⁴ State-of-the-art guidelines have been written to help provide guidance for diagnosis, surveillance, and treatment within this overwhelming new world of cardiotoxicities and cardiovascular disease,⁵ but robust evidence driving these recommendations and documents originates from expert opinion—more evidence and studies are needed.⁶ The field remains both exciting and daunting because, despite important steps in recognizing and understanding cardiotoxicities of old and new cancer treatments, we are continuously overwhelmed by the tidal wave of cancer therapeutics that are arriving by the week driving the growing wilderness of cardio-oncology.

An important interplay exists between cancer and cardiovascular disease whereby common risk factors, like smoking or air pollution, predispose to both conditions, and treatment of either condition inextricably affects the management of the other. Makram and colleagues' article, "[Cardiovascular Risk Assessment and Prevention in Cardio oncology: Beyond Traditional Risk Factors](#)," in this issue examine emerging and nontraditional risk factors like air pollution, the gut microbiome, and social determinants of health, which should be considered when caring for cardiology, oncology, and cardio-oncology patients. From a genetics perspective, there is increasing interest in the role of somatic genetic mutations, known as clonal hematopoiesis of indeterminate potential, or CHIP, which predispose to both hematologic malignancies and cardiovascular disease, summarized by Raddatz and colleagues' article, "[Clonal Hematopoiesis of Indeterminate Potential and Cardiovascular Health](#)," in this issue. In patients with adult congenital heart disease, there is an increased risk of malignancy due to linked risk factors (like genetic syndromes) and treatment-related sequelae (like liver damage from Fontan physiology, radiation exposure from interventional procedures, or thymectomy), which are discussed in depth by Lluri and colleagues' article, "[Unique Challenges of Adult Congenital Heart Disease in CardioOncology](#)," in this issue.

Beyond heart failure, the full spectrum of cardiovascular diseases is commonly seen in cardio-oncology due to both preexisting cardiovascular disease in the aging cancer population and direct

toxicity from antineoplastic treatments. The unique challenges of diagnosis, treatment, and prevention in patients on current or prior cancer therapy are addressed in state-of-the-art reviews on hypertension (see Sayegh and colleagues' article, "[Classes of Anti-Neoplastic Agents Associated with Increased Risk of Cancer Therapy-Associated Hypertension and Management Strategies](#)," in this issue), arrhythmia (Wright and colleagues's article, "[Arrhythmia Challenges in Cardio-oncology: High Risk Therapies, Management, and Anticoagulation](#)," in this issue), and ischemic heart disease (Condurache and colleagues' article, "[Ischemic Heart Disease in the Cancer Population: Trends, Outcomes, Epidemiology and Challenges in Diagnosis and Treatment](#)," in this issue).

Breast cancer and prostate cancer are the most commonly diagnosed cancers in women and men, respectively, with excellent survival rates of greater than 90%.⁷ Therefore, these populations represent a large portion of cancer patients and cancer survivors. In an article by Kappel and colleagues's article, "[Cardiovascular Health in Breast Cancer: Survivorship Care](#)," in this issue, the specific cardiotoxicities of breast cancer treatments, including anthracyclines and anti-HER2 treatments, are outlined, and survivorship care is emphasized. The growing concerns about cardiotoxicities associated with treatments for prostate cancer, particularly androgen-deprivation therapy, are detailed by Leong and colleagues' article, "[Cardiovascular Risk in Prostate Cancer](#)," in this issue.

Cardiac amyloidosis is a unique population within cardio-oncology. Misfolded proteins, due to monoclonal plasma cell production of light chains or transthyretin, form fibrils that deposit within the cardiac tissue and disrupt cardiac function. Diagnosis and treatment of both forms of cardiac amyloidosis are summarized in the review by Stein-Merlob and colleagues' article, "[Evolving Strategies in Cardiac Amyloidosis: From Mechanistic Discoveries to Diagnostic and Therapeutic Advances](#)," in this issue to highlight novel targeted therapeutics that can be applied to cardiovascular disease.

Historical regimens, including anthracycline and radiation treatments—still the mainstay therapy in many malignancies, are risk factors for significant cardiotoxicity, and it remains elusive which patients remain at risk for short- and long-term cardiotoxicity. State-of-the-art reviews on mechanisms, risk assessment, and surveillance are provided with these important treatments (see Balough and colleagues' article "[Cardiotoxicity of Anthracyclines](#)," in this issue, see Zaghlool and colleagues' article, "[Cardiac Complications of Radiation Therapy](#)," in this issue). The last decade has seen a proliferation

of immunotherapies, such as ICIs, which harness the immune system to fight tumor cells. As described by Makwana and colleagues' article, "[Cardiac Complications of Immunotherapy: Immune Checkpoint Inhibitors and CAR T Cell Therapy](#)," in this issue, these agents cause cardiotoxicities through overactivation of the immune system via cellular infiltration (ICI-associated myocarditis) or cytokine release (CAR T-cell therapy) and can manifest in a variety of ways, including myocarditis, atherosclerosis, and arrhythmias. With the rapid increase in both oncologic and cardiovascular treatments, it is increasingly important to understand the underlying pharmacology and potential interactions, as summarized by Beavers and colleagues' article, "[Cardio-Oncology Drug Interactions: A Primer for Clinicians on Select Cardiotoxic Oncologic Therapies](#)," in this issue, to ensure safe and effective care for patients.

Our focus section issue in *Cardiology Clinics* hopes to present to the reader the importance of addressing a "new" population that has always been in our backyard but relatively neglected in terms of optimal cardiovascular disease management and risk factor modification—the cancer survivor population. The growing field of cardio-oncology is important to provide specialized care to this unique population (see Bloom and colleagues' article, "[Cardio-Oncology Program Building: A Practical Guide](#)," in this issue). However, the staggeringly growing number of patients with cancer is not something a small band of subspecialists labeled as cardio-oncologists can address—this is a mainstream, multidisciplinary, team sport that requires all hands on deck from our cardiology and cancer colleagues. We hope this issue provides an adequate introduction to readers of all backgrounds to showcase the fascinating developments and unexplored realms of the growing wilderness of cardio-oncology—and an effective argument about its relevance to the entire field of cardiology.

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Cardiovascular Risk Assessment and Prevention in Cardio-Oncology Beyond Traditional Risk Factors



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KEYWORDS

- Cardio-oncology • Precision medicine • Multi-omics • Wearable technology • Real-time data
- Social determinants • Gut microbiome • Machine learning

KEY POINTS

- Cardio-oncology care extends beyond traditional risk factors, encompassing social determinants, environment, and even gut microbiome.
- Multi-omics approaches, wearable technology, and big data analytics offer deeper insights into real-world patient experiences beyond controlled settings.
- Seamless integration of novel tools with established practices is crucial for personalized care strategies.
- Continuous real-time data-driven updates to treatment plans empower true precision medicine. This holistic approach holds great potential for improved patient outcomes and a future of precision cardio-oncology.

INTRODUCTION

Cardio-oncology has emerged as a vital interdisciplinary field addressing cardiovascular complications from cancer treatments, such as chemotherapies, radiotherapy, immunotherapy, and targeted therapies, which may cause adverse effects like cardiomyopathies, heart failure, and hypertension.^{1–8} This field has evolved from treating overt cardiotoxicities to focusing on prevention and early detection of these complications, integrating preventive cardiology into cancer patient care.^{9–11} Moreover, cardiovascular diseases

(CVDs) and cancer share common risk factors, including lifestyle behaviors and genetic predispositions, but broader social, commercial, and environmental determinants impacting patient health are often overlooked in cardio-oncology clinical studies.^{12–15}

Emerging risk factors such as the social determinants of health (SDOH), environmental factors, and microbiome disturbances play a critical role in the risk for both CVDs and cancer (**Fig. 1**). These factors not only disproportionately affect patients with cancer compared with the general population but also create a complex interplay

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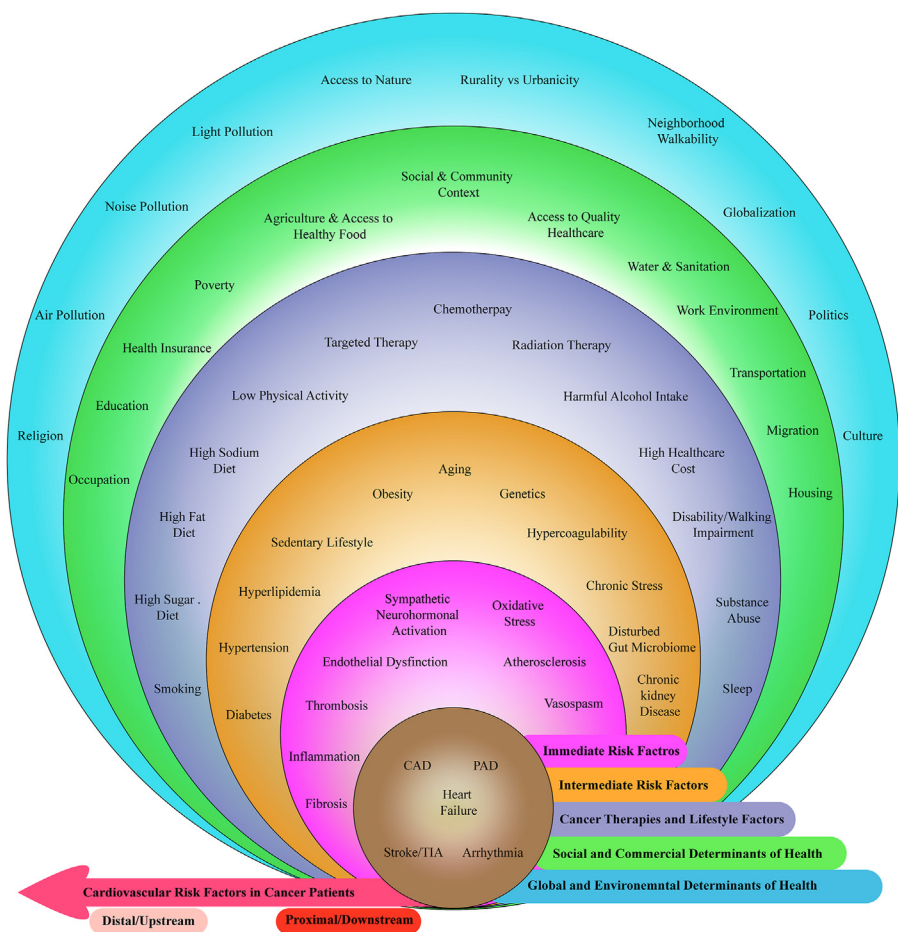


Fig. 1. The web causation of cardiovascular diseases (CVD) in cardio-oncology population. Distal/Upstream risk factors are the factors that have indirect impact on health and are usually more remote, broader, and systemic and have long-term influence; Proximal/Downstream risk factors are the factors that have direct impact on health and usually occur closer in time to the health outcome, specific, and have more immediate effect; Intermediate risk factors are those factors that act as independent cardiovascular risk factors and also as mediating factors for the more distal factors.

of risks that significantly impact these individuals’ health. This vignette-based review aims to enhance cardio-oncology care by examining these factors, understanding their interactions, and exploring strategies to manage and mitigate their impact on patient outcomes.

EMERGING RISK FACTORS
Social Determinants of Health

A 63-year-old male prostate cancer survivor from a rural community who relies on public transportation is facing delays in accessing cardiac care post cancer treatment because of missed appointments and inconsistent follow-up. His low income, educational background, having no health insurance, and limited access to health care

further complicate the situation and exacerbate his cardiovascular risk.

ACCESS TO CARE

SDOH significantly impact cardiovascular health in patients with cancer, with access to care being a critical factor. Economic stability and education level influence disparities in CVD outcomes,^{16–18} where unemployment and low income restrict access to quality health care,^{19–21} essential medications, and nutritious food, exacerbating CVD risk.²² These disparities extend to life-saving procedures such as percutaneous coronary interventions,^{23–26} with affordability and provider discrimination limiting access for low-income and rural individuals, further complicating the cardiovascular health landscape for patients with

cancer.^{12,13,27,28} Similarly, educational attainment is closely related to the risk of CVD, especially in patients with cancer.^{27,29} By recognizing the individual circumstance and providing tailored support, health care providers can empower patients to navigate these challenges and improve their overall health, particularly cardiovascular health.^{30,31}

Coordination between specialists and primary care physicians (PCPs) is also vital in providing comprehensive care for the growing number of cardio-oncology patients, especially in remote and disadvantaged areas.³² With that growth and the shortage of dedicated cardio-oncologists, PCPs and general cardiologists are becoming crucial to bridge that access gap. PCPs especially emerge as central figures in coordinating cardio-oncology care in survivorship owing to their established patient relationships, holistic approach, and the frequent patient interactions allowing closer monitoring.³³

NEIGHBORHOOD

The neighborhood environment plays a significant role in cardiovascular health outcomes. Areas with lower socioeconomic status (SES) often lack healthy food options ("food deserts") and are saturated with unhealthy alternatives ("food swamps"), contributing to risk factors such as diabetes and obesity.^{34–36} Additionally, neighborhood factors, including limited access to nature and transportation, poor walkability, and high crime rates, can increase CVD risks and negatively impact mental health through stress and depression, highlighting the need for interventions tailored to these environmental challenges.^{37–44} Community-based education programs and counseling can empower individuals with the knowledge of health ownership and encourage the adoption of healthy habits like physical activity, with outreach programs such as Walk Your Heart to Health program in Michigan and Houston Bayou Greenways program in Texas.^{45,46}

FINANCIAL TOXICITY

Financial toxicity arises from the adverse economic impacts of cancer treatment costs, leading to cost-cutting behaviors that can affect medication adherence and increase mental health burdens.^{47,48} Key risk factors include demographic characteristics, cancer-related factors, treatment type, and insurance coverage.⁴⁹ The high costs of health care contribute to significant financial hardship, with many patients with cancer depleting their assets or incurring debt.⁵⁰ Another study revealed that

cost concerns led around 20% of patients to under-use prescribed medications, 18% to partially fill prescriptions, and 24% to skip medications entirely.⁵¹ Furthermore, the psychological impact is substantial, with more studies suggesting that 20% to 50% of patients with cancer report financial stress.^{52,53} Multifaceted solutions, including societal and clinic-level strategies, are proposed to mitigate these effects, emphasizing the importance of addressing financial toxicity in cancer care. At the national policy level, broader interventions, such as government price negotiations, aim to align drug prices with evidence-based effectiveness and support clinical trials for more affordable alternatives.^{48,49}

HEALTH INSURANCE COVERAGE

Health insurance coverage is crucial in mitigating financial toxicity and ensuring access to necessary care. The lack of adequate coverage can delay cardiovascular screenings and contribute to higher mortality rates among cancer survivors, particularly those uninsured or on Medicaid.^{54,55} Multidisciplinary teams and initiatives, such as the administration of questionnaires (eg, Comprehensive Score for Financial Toxicity questionnaire) to understand patients' SDOH challenges, are essential in tailoring support and alleviating financial burdens.⁴⁷ At our cardio-oncology clinic at the Medical College of Georgia and Georgia Cancer Center, we have launched an initiative where all our patients are administered the Protocol for Responding to and Assessing Patients' Assets, Risks, and Experiences questionnaire. This tool allows us to gain a deeper understanding of each patient SDOH challenges and tailor the support accordingly.¹³

ENVIRONMENTAL FACTORS AND AIR QUALITY

A 48-year-old colon cancer survivor, who reports living in an urban area with high pollution levels, shows increased heart palpitations during days with poor air quality. Despite completing his cancer treatment, he remains attentive about his health, but the environmental conditions significantly impact his ability to exercise and spend more time in nature and green spaces.

Environmental factors, particularly pollution, play a critical role in cardiovascular health, contributing significantly to morbidity and mortality worldwide.⁵⁶ Notably, pollution is responsible for 21% of CVD deaths globally, with contaminants like lead, arsenic, and cadmium being significant

contributors.^{57,58} The World Health Organization has identified air pollution as the largest environmental health risk, attributing 37% of deaths from ischemic heart disease and stroke to air pollution.⁵⁹

This impact is further compounded by the exacerbation of existing cardiovascular risk factors such as hypertension, diabetes, and atherosclerosis, even below regulatory standards, affecting an estimated 94% of the global population living in areas with unsafe air quality levels.^{14,60–62} Furthermore, the disproportionate impact on lower SES groups and communities of color highlights the inequities in the global impact of air pollution, emphasizing the need for policy changes to reduce exposure.^{14,15,63}

In response to the growing concern over the health risks associated with air pollution, initiatives like the Environmental Protection Agency's Air Quality Index (AQI) have been developed.⁶⁴ The AQI provides daily air quality reports and activity recommendations based on pollution levels, empowering individuals with heart disease to make informed decisions regarding their exposure.⁶⁵ Additionally, technological advancements, such as wearable devices, offer real-time environmental data, revealing significant associations between environmental factors and adverse patient responses, including increased blood pressure due to noise pollution and higher heart rate variability with air pollution exposure.^{66–69} These insights underscore the importance of understanding the impact of environmental factors on cardiovascular health and the potential of policy changes and innovative technologies to mitigate risks and improve cardiovascular outcomes.⁷⁰

MICROBIOME

A 45-year-old lymphoma survivor experiences persistent unexplained digestive issues and cardiovascular symptoms including higher blood pressure and palpitations. On further examination, he is found to have a gut microbiota dysbiosis with elevated levels of trimethylamine N-oxide (TMAO), a metabolite associated with higher risk for CVD and risk factors.

The gut microbiota, a complex community of microbes residing in the human gut, plays a significant role in health and disease, extending its influence beyond mere digestion to act as a secondary endocrine organ.⁷¹ Its composition and function are intricately linked to CVD development and progression, with gut-derived metabolites like TMAO emerging as potent predictors of CVD risk.^{71–77} Factors such as diet, gut age, and renal functions significantly influence TMAO levels,

underscoring the impact of dietary choices, particularly red meat and animal products, on cardiovascular health.^{78–81} Moreover, the interplay between cancer treatments and gut microbiota highlights the complex relationships affecting cardiovascular health.⁸² Promising therapeutic interventions include dietary modifications, such as the Mediterranean diet, and the use of metformin, intermittent fasting, prebiotics, and probiotics to modulate gut microbiota composition, alongside the potential of nanomedicine for targeted interventions.^{76,83–87} With advancements in sequencing technologies and bioinformatics, there is an increasing emphasis on personalized therapies targeting the gut microbiota, offering new avenues for CVD prevention and management.^{88–90}

NOVEL METHODS OF RISK FACTOR DETECTION AND PREVENTION

Wearable Technologies

A 58-year-old lung cancer survivor experiences challenges with frequent palpitations and in maintaining physical activity levels. Despite regular follow-ups, his PCP is struggling with detecting and characterizing these palpitations. Upon using a smartwatch, both the physician and the patient were able to identify the blood pressure, heart rate fluctuation patterns, and irregular sleep patterns. They were also able to associate it with different environmental factors such as air quality, pollution, and noise.

Wearable technologies, exemplified by devices such as the Apple Watch, have transformed cardiovascular care by enabling self-monitoring and early disease detection (Fig. 2). Equipped with advanced sensors for accelerometers, electrocardiography, and photoplethysmography, these devices facilitate continuous health monitoring, improving pulse checks, and enhancing the detection of arrhythmias like atrial fibrillation with notable accuracy.^{91–95} Their adoption has democratized access to health monitoring, bypassing the need for extensive outreach or training programs. Furthermore, they play a pivotal role in managing chronic conditions by promoting physical activity and adherence to medical advice, thus significantly benefiting patients with heart failure and those with complex care needs by monitoring vital signs and activity levels, enhancing rehabilitation, and medication adherence.^{96–98}

In the context of cardio-oncology, wearable devices offer the ability to not only monitor the shared traditional risk factors but also continuously track the various environmental factors

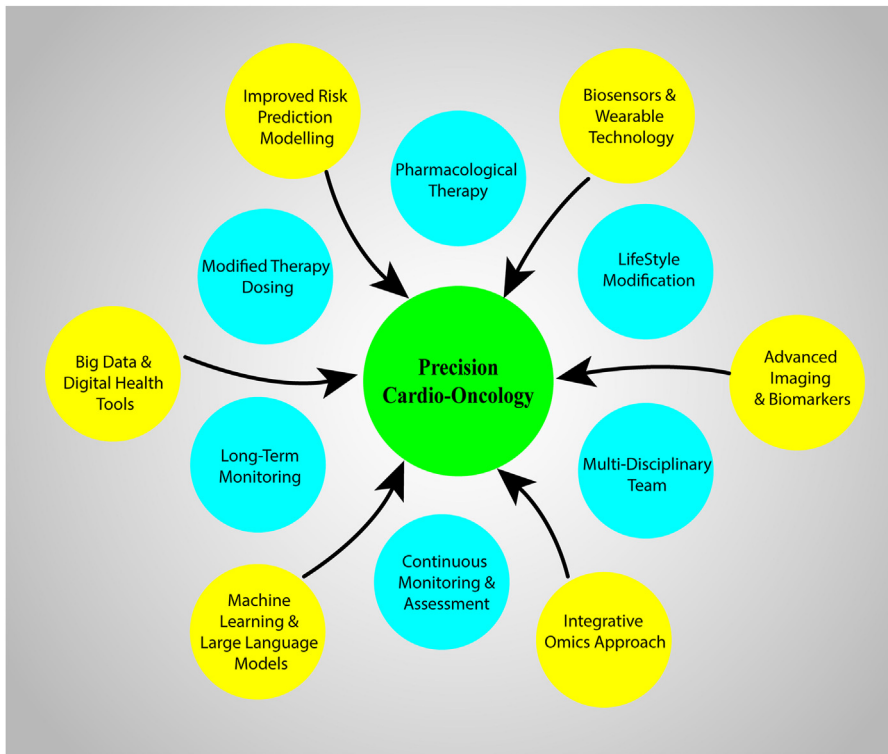


Fig. 2. The toolbox for achieving precision cardio-oncology care. Yellow circles represent the emerging methods to identify risk factors. Blue circles represent the preventative strategies taken to mitigate the risk factors impact.

such as pollution and noise and lifestyle factors like sleep patterns and physical activity levels. These devices can also measure vital signs including blood pressure and heart rate and detect arrhythmias, facilitating earlier detection of cardiotoxicities. This continuous monitoring increases the patients' awareness of their health and environment, encouraging healthier lifestyles and enabling earlier behavioral and lifestyle interventions. When combined with artificial intelligence and telehealth, wearable technology would promote healthy lifestyles and personalized care, marking a shift toward precision health care by analyzing real-time data to provide tailored health recommendations.^{99–101}

MULTI-OMICS APPROACH

A 42-year-old lymphoma patient with a strong family history of heart disease presented with complex medical history that includes several comorbidities. During the cancer treatment, he showed fluctuating biomarkers and varying responses to cancer therapies which further complicated his cardiovascular risk assessment. Utilizing the multi-omics approach, the team was able to integrate the genomic, radiomic, proteomic, and metabolomic data to construct a

detailed cardiovascular health profile, develop a personalized treatment strategy, and monitor for potential cardiotoxicities.

The multi-omics approach represents a systemic strategy to understand the complex interplay between various biological layers (genome, epigenome, transcriptome, proteome, and metabolome) in CVD.^{102,103} This approach transcends traditional single-target investigations, employing tools for disease states such as familial congenital heart diseases,¹⁰⁴ pulmonary arterial hypertension,¹⁰⁵ and coronary artery disease,¹⁰⁶ while enabling novel biomarker discovery. The integration of multi-omics data, utilizing network science tools, offers a holistic understanding of disease mechanisms at multiple levels.^{107–111} This systemic perspective is essential for identifying key pathways, differentiating between disease phenotypes, and guiding personalized treatment strategies, thereby unlocking immense potential for drug discovery and precision medicine in cardio-oncology.^{112,113}

ADVANCED IMAGING STUDIES AND RADIOMICS

A 55-year-old multiple myeloma survivor presents with unexplained shortness of breath on exertion.

Traditional risk factors appear within the normal range. A comprehensive cardiac evaluation, including coronary artery calcium scoring, reveals the presence of subclinical atherosclerosis, and further cardiac MRI suggested cardiac amyloidosis.

Advanced cardiac imaging and radiomics have significantly expanded beyond their traditional diagnostic roles, becoming instrumental in prognostication, risk stratification, and the early detection of cancer therapy-related cardiac dysfunction.¹¹⁴

Techniques such as echocardiography and cardiac magnetic resonance offer detailed assessments of cardiac function and structure (eg, myocardial strain).^{114–118} Recent advancements in deep learning have further enhanced the capabilities of these imaging modalities, enabling accurate detection and risk stratification of various cardiac conditions (eg, point-of-care screening for aortic stenosis).¹¹⁹ Additionally, computed tomography calcium scoring has emerged as a valuable tool for assessing coronary atherosclerosis and predicting major adverse cardiovascular events.^{120–123}

MACHINE LEARNING AND LARGE LANGUAGE MODELS

Machine learning (ML) and large language models (LLMs) are reshaping the landscape of cardiovascular care and research by enabling the analysis and interpretation of vast amounts of medical data. These technologies have demonstrated their potential in improving cardiovascular risk stratification, particularly in patients with cancer undergoing treatment.¹²⁴ By analyzing clinical notes, electronic health records, and leveraging cancer-specific ML algorithms, these models have shown superiority over conventional risk scores in predicting CVD in patients with cancer.^{125,126} In our lab, we were able to leverage ML models to improve risk prediction models for CVD in patients with cancer, for example, breast^{127,128} and prostate cancers.¹²⁹ The application of ML and LLMs in cardio-oncology holds promise for enhancing diagnostic accuracy, personalizing treatment plans, and ultimately improving patient outcomes in the intersection of CVD and cancer.

SUMMARY AND CONCLUDING REMARKS

This review delves into the often-overlooked factors impacting cardio-oncology patient care, highlighting existing tools and emerging approaches to navigate these challenges. In an increasingly complex world, SDOH, environmental influences, access to health care, financial toxicity, and

microbiome disruptions pose significant burdens on patient well-being.

The use of multi-omics approach offers a powerful lens to delve deeper into the intricate relationships between diseases and the interplay of contributing factors. Combining real-time data from wearable technologies with machine learning and big data analytics allows for deeper understanding of daily life experiences beyond controlled research settings.

Besides the advancements in pharmacologic therapies and multidisciplinary teams, our ultimate goal lies in seamlessly integrating innovative approaches with established practices. This synergy will unlock the secrets of complex and heterogeneous CVD in patients with cancer, ushering in an era of precision cardio-oncology. This vision translates to tailored therapies and comprehensive management plans, continuously updated for each patient based on real-world data, empowering us to provide truly personalized care.

CLINICS CARE POINTS

- **Comprehensive Risk Stratification:** Utilize cancer-specific cardiovascular risk assessment tools that integrate traditional risk factors with cancer- and treatment-related characteristics, including cancer type and types of therapies.
- **SDOH and Personalized Risk:** Incorporate social determinants of health (eg, access to care and financial stress) into cardiovascular risk assessments to better tailor management strategies for vulnerable patients.
- **Wearable Technology and Remote Monitoring:** Leverage the real-time data from wearable devices and telehealth to detect early cardiovascular anomalies and adjust care accordingly.
- **Tailored Lifestyle Modifications:** Provide personalized recommendations for exercise, dietary interventions, and stress management based on each patient's cardiovascular risk profile, cancer treatment plan, and gut microbiome health to improve long-term outcomes.

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Clonal Hematopoiesis of Indeterminate Potential and Cardiovascular Health



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KEYWORDS

• Clonal hematopoiesis • Atherosclerosis • Inflammation • Cardiovascular genetics

KEY POINTS

- Clonal hematopoiesis of indeterminate potential (CHIP) is an age-related phenomenon in which somatic mutations lead to clonal expansion of hematopoietic stem cells without the development of hematologic malignancy.
- CHIP is associated with cardiovascular disease, including accelerated atherosclerosis, early-onset myocardial infarction, incident heart failure, and arrhythmias.
- Best practices include serial monitoring and optimization of other cardiovascular risk factors, as no targeted therapies currently exist.
- Anti-inflammatory medications show promise as future therapies for CHIP-related cardiovascular disease.

INTRODUCTION

Clonal hematopoiesis of indeterminate potential (CHIP) is an age-related phenomenon in which somatic mutations lead to clonal expansion of hematopoietic stem cells (HSCs) without the development of hematologic abnormalities. The prevalence of CHIP reaches 5% by the age of 60 years and 10% by the age of 70 years,¹ and while this phenomenon increases the risk of hematologic malignancies, most patients with CHIP never develop such cancers.² CHIP has also been linked to an increased risk of cardiovascular disease, mediated, at least in part, through inflammation.^{2–4} CHIP presents a novel risk factor for cardiovascular disease that cardiologists will soon be asked to integrate into their practice. In this review, the authors discuss the risk factors for CHIP, its clinical associations, mechanisms for cardiovascular morbidity, and potential therapeutic strategies.

CLONAL HEMATOPOIESIS OF INDETERMINATE POTENTIAL

Clonal hematopoiesis arises from acquired, somatic mutations in HSCs. Because HSCs divide frequently, there is increased opportunity for mutational events compared to other cells like cardiomyocytes.^{5,6} When an acquired mutation carries a fitness advantage, the affected HSCs and their progeny give rise to a clone. This clonal expansion can lead to oncogenesis, but landmark studies of clonal hematopoiesis demonstrated that many patients carry oncogenic mutations in hematopoietic clones without ever developing leukemia.²

CHIP is defined by mutations in a set of approximately 75 myeloid cancer-associated genes that lead to clonal hematopoiesis as described above. These mutations may be single nucleotide variants or short insertions and deletions. Larger alterations

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that affect chromosomal regions on the order of megabases are classified not as CHIP but as mosaic chromosomal alterations. As a group, mosaic chromosomal alterations do not have an association with cardiovascular disease,⁷ but their clinical associations vary widely by the specific alteration. For example, mosaic loss of the Y chromosome alone is associated with cardiac fibrosis and cardiovascular mortality.⁸ While ongoing investigations in this area promise to inform future clinical care, forms of clonal hematopoiesis other than CHIP are beyond the scope of this review.

CHIP can be detected with whole genome sequencing, exome sequencing, or targeted sequencing.^{1,9} CHIP is formally defined in sequencing data as the presence of a clone representing greater than 4% of circulating cells (corresponding to a variant allele frequency [VAF] of 2% assuming heterozygosity) in a patient without abnormal cell counts or abnormal cell morphology.¹ Most commonly, this finding occurs in the course of sequencing patients with known cancer, during work-up of an unexplained cytopenia without overt neoplasm, or during surveillance for recurrent hematologic neoplasms after treatment. It is also a possible finding in sequencing healthy patients for research purposes or through direct-to-consumer products. Higher fidelity methods reveal that nearly all middle-aged patients carry mutations in these genes at very low VAF,¹⁰ but increased clone size correlates with risk of cardiovascular disease.²

Even among CHIP clones of the same size and growth rate, the risk of cardiovascular disease varies with driver mutation. Mutations in *DNA methyltransferase 3 alpha (DNMT3A)*, *ten-eleven translocation-2 (TET2)*, and *additional sex combs like transcriptional regulator 1 (ASXL1)* are most common and have been linked to cardiovascular disease.³ Mutations in *Janus kinase 2 (JAK2)* are less common but carry high cardiovascular risk, and mutations in *TP53* and *PPM1D* are most common after chemotherapy treatment, and therefore may be more prevalent in cardio-oncology cohorts.¹¹

While mutations in these genes are known to confer oncogenic risk, transformation into myeloproliferative neoplasms (MPNs) occurs in less than 1% of patients with CHIP per year.^{1,2,12} The risk of MPN can be determined using novel risk scores, including the clonal hematopoiesis risk score (CHRS).¹³ Among the approximately 1% of patients with the highest CHRSs, greater than 20% develop MPNs within 5 years. MPNs carry their own risk of cardiovascular disease that the specific biology of CHIP mutations may complement.¹⁴ For example, patients with CHIP mutations and AML are at increased risk of cardiovascular

disease.¹⁵ However, the vast majority of CHIP clones will never progress to MPNs. Indeed, cardiovascular risk in patients with MPNs is outside the scope of this review and should be managed in collaboration with their oncologist and a cardio-oncologist, if available. In contrast, the population burden of cardiovascular disease in patients with CHIP requires that a general cardiologist workforce is prepared to manage cardiac diagnoses in these patients.

RISK FACTORS FOR CLONAL HEMATOPOIESIS OF INDETERMINATE POTENTIAL

Age is the most significant risk factor for CHIP with an exponential growth curve from a prevalence of less than 1% under the age of 40 years to greater than 20% by the age of 90 years.^{1,16} Other factors that increase risk for CHIP include demographic factors, behavioral and environmental risk factors, and traditional cardiovascular risk factors. Among demographic factors, sex impacts the distribution of driver mutations and therefore downstream disease risk, but has little impact on overall prevalence.¹⁷ Specifically, female individuals have a higher prevalence of *DNMT3A* clones than male, while male individuals have a higher prevalence of *TET2* clones than female.¹⁷ Among patients in the United States, Hispanic and East Asian ancestry is associated with reduced CHIP incidence, aligned with decreased prevalence of myeloid neoplasms in these populations.¹⁸ Along with demographics, behavioral and environmental risk factors can help predict CHIP risk. CHIP is associated with diet,¹⁹ pollution,²⁰ and smoking in a dose-dependent manner.^{17,21,22} Obesity has also been shown to increase CHIP expansion rate through inflammation in humans and mice,^{23,24} while a Mendelian randomization analysis found that genetic predisposition to higher body mass index is associated with CHIP expansion (VAF > 0.1).¹⁷

Additionally, traditional cardiovascular risk factors (ie, the “metabolic syndrome”) also reflect and promulgate an inflammatory milieu and therefore may increase risk of CHIP. The metabolic syndrome is defined by a combination of insulin resistance, elevated waist circumference, elevated triglycerides, reduced high-density lipoprotein (HDL) cholesterol, and hypertension.²⁵ The relationship among metabolic syndrome, inflammation, and cardiovascular disease has led to speculation on how CHIP may play a complementary (rather than entirely separate) role in this pathophysiology. It is important to note that repeated studies have shown that the risk of cardiovascular disease in patients with CHIP is independent of

traditional risk factors. To that end, causal association of traditional risk factors with CHIP has shown largely null or weak associations with hypertension,¹⁷ type 2 diabetes,² and hyperlipidemia.¹⁸ Regarding hyperlipidemia, multiple studies have found lower levels of low-density lipoprotein (LDL) cholesterol and total cholesterol among patients with CHIP^{17,18}; however, Mendelian randomization analyses suggest that genetically predicted apolipoprotein B levels were associated with *TET2* CHIP specifically.¹⁷ While the exact relationship remains opaque, understanding the interplay will inform future therapeutic strategies.

Conversely, inflammation plays a clear role in the development and progression of CHIP. In mice, interleukin (IL)-6,²⁶ IL-1,²⁷ tumor necrosis factor (TNF) α ,²⁸ and STAT3²⁹ promote *TET2* CHIP expansion, while interferon- γ ,³⁰ TNF α ,³¹ and IL-6³² promote *DNMT3A* CHIP expansion. Incident CHIP is also associated with clinical correlates of molecular inflammation in patients. For example, increased CHIP prevalence has been described in patients with systemic sclerosis,³³ rheumatoid arthritis,³⁴ or ulcerative colitis.³⁵ Patients living with HIV also have increased prevalence of CHIP.^{36,37} In sum, clinical inflammatory syndromes should raise suspicion for CHIP and inflammation-associated cardiovascular disease.

CLINICAL ASSOCIATIONS

Patients with CHIP have a 1.4x (95% confidence interval [CI] of 1.1–1.8) relative risk of all-cause mortality.² Early studies demonstrated that cardiovascular disease accounted for a large proportion of this risk,^{2,12} and many cardiovascular diagnoses are found to be increased among patients with CHIP (Table 1).^{38–41} Jaiswal and colleagues² first described the risk of incident coronary artery disease (CAD) in 2014 with a hazard ratio of 2.0 (95% CI: 1.2–3.5), and in 2017, went on to find increased CHIP in patients with early-onset myocardial infarction (MI), defined as an event at less than 50 years of age, with more significant risk among those with non-*DNMT3A* mutations.³ Subsequent studies have demonstrated that CAD risk is isolated to non-*DNMT3A* mutations,⁴¹ with *TET2* and *JAK2* mutations having the highest risk of CAD.⁴ Simultaneous murine studies revealed accelerated atherosclerosis in mice with *TET2* CHIP, corroborating the epidemiologic data.^{3,42} Beyond obstructive coronary disease, there is also increased prevalence of CHIP in those with coronary microvascular dysfunction.⁴³

In addition to the association of CHIP with incident CAD, recent work has shown that among

patients with established atherosclerotic disease, those with CHIP have increased risk of severe disease and adverse outcomes.^{44,45} Indeed, once those with CHIP present with an event, they are at increased risk of mortality. For example, those presenting with ST-elevation MI have increased risk of mortality,⁴⁶ and among those with acute MI complicated by cardiogenic shock, those with CHIP have increased risk of mortality or kidney failure.^{47,48} Furthermore, after patients with CHIP suffer from ischemic events, those with associated cardiomyopathy and chronic heart failure are at increased risk of death or hospitalization.^{49,50} Notably, this association is again driven by those with expanded CHIP clones.⁵¹ These data together suggest that while CHIP certainly increases the risk of CAD and atherosclerotic cardiovascular disease (ASCVD) events, it also contributes to pathophysiologic post-ischemic remodeling.

To that end, regardless of coronary anatomy, CHIP is associated with incident heart failure.³⁸ A recent study demonstrated that *TET2* CHIP was significantly associated with incident heart failure with preserved ejection fraction (HFpEF) but not incident heart failure with reduced ejection fraction (HFrEF).⁴⁰ Nonetheless, among those with HFrEF, CHIP portends a worse prognosis across ischemic and nonischemic etiologies.⁵² Another study found that CHIP is associated with poorer echocardiographic metrics in those with HFpEF.⁵³ Interestingly, patients with CHIP who undergo heart transplant do not have increased risk of posttransplant mortality or cardiac allograft vasculopathy.⁵⁴ Together, these findings suggest that CHIP may affect the pathogenesis of heart failure in ways distinct from atherosclerotic disease.

Along with CAD and heart failure, CHIP is also associated with arrhythmias.^{55,56} Recent cross-sectional studies in the UK Biobank and a cohort of individuals of East Asian descent demonstrate associations between CHIP and incident arrhythmias, including supraventricular arrhythmias, bradyarrhythmias, ventricular arrhythmias, and cardiac arrest.^{39,57} In the UK Biobank, the highest risk of arrhythmia was in individuals with mutations in *TP53* and *PPM1D*, genes often mutated among cancer survivors, whereas in the East Asian cohort, a *DNMT3A* mutation significantly elevated an individual's odds of developing atrial fibrillation. While further work is required to clarify any mutation-specific effects, evidence supports an association between CHIP and cardiac arrhythmias.

Notably, the increased risk of cardiovascular disease is most exaggerated, and in some studies

Table 1
Selected evidence for clinical associations with clonal hematopoiesis of indeterminate potential and cardiovascular disease

Disease	Cohort	N	Phenotype	CHIP mutation(s)	Hazard Ratio	References
Coronary artery disease	UK Biobank	451,180	Incident CAD, ischemic heart disease, MI, PCI, CABG, or death attributed to these causes	All	1.12 [1.05–1.20]	Vlasschaert, et al, 2023 ⁴¹
				<i>DNMT3A</i>	1.04 [0.95–1.13]	
				Non- <i>DNMT3A</i>	1.21 [1.11–1.32]	
Heart Failure	ARIC, CHS, JHS, and WHI	56,597	Incident heart failure	All	1.25 [1.13–1.38]	Yu, et al, 2021 ³⁸
	JHS and WHI	8090	Incident HFpEF Incident HFrEF	<i>TET2</i> <i>TET2</i>	2.35 [1.34–4.11] 1.62 [0.76–3.45]	Schuermans, et al, 2024 ⁴⁰
Arrhythmias	UK Biobank	410,702	Incident arrhythmias	<i>DNMT3A</i> <i>TET2</i>	1.01 [0.94–1.08] 1.22 [1.08–1.38]	Scheurmans, et al, 2023 ³⁹
				<i>ASXL1</i>	1.17 [1.02–1.33]	
			Incident supraventricular arrhythmias	All	1.13 [1.05–1.22]	
			Incident bradyarrhythmias	All	1.09 [1.01–1.19]	
			Incident ventricular arrhythmias	All	1.22 [1.03–1.45]	

Bold entries indicate significant associations.

Abbreviations: ARIC, Atherosclerosis Risk in Communities Study; CABG, coronary artery bypass graft; CAD, coronary artery disease; CHS, cardiovascular health study; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; JHS, Jackson heart study; MI, myocardial infarction; PCI, percutaneous coronary intervention; WHI, Women’s Health Initiative.

strictly limited to patients with “large clones”, defined as VAF greater than 10%.^{2,4} However, using higher specificity in CHIP calls and grouping CHIP mutations into biologically meaningful subtypes has redemonstrated a consistent but smaller magnitude association with increased mortality in patients with low VAF clones.^{1,41} As genetic methods are advanced into the clinic, it will be important to create reliable methods for somatic mutation events with relatively low VAF. Moreover, when defining the clinical relevance of smaller clones, identifying risk factors for clonal expansion will enable prognostication to identify individuals who may develop larger clones and heightened disease risk.¹³

The clinical associations of CHIP also extend to other areas of human disease beyond the heart. As might be expected given the association with ASCVD, there is an increased risk of ischemic stroke and recurrent vascular events.^{58,59} Outside of atherosclerotic disease, CHIP is associated with severe COVID-19 infection,⁶⁰ liver disease,⁶¹ and kidney disease.^{62,63} The wide set of outcomes in

those with CHIP continues to be explored and highlights the multisystem effects of blood-borne inflammation.

MECHANISMS OF CARDIOVASCULAR DISEASE

Since the initial discoveries linking CHIP and cardiovascular disease, the field has begun to gain a mechanistic understanding of how CHIP may cause cardiovascular disease. The pathophysiologies of atherosclerosis, arrhythmia, and heart failure each involve an expanded population of proinflammatory immune cells.

Atherosclerosis

Initial mechanistic studies of *TET2* CHIP and atherosclerosis demonstrated that mice with *TET2*-deficient HSCs had a greater burden of atherosclerosis (ie, 2.7 fold larger atherosclerotic lesion area).^{3,42} The underlying mechanism for this increased atherosclerotic burden is thought to be *nucleotide-binding oligomerization domain*

leucine-rich repeat and pyrin domain-containing protein 3 (NLRP3) inflammasome activation as a result of widespread changes to DNA methylation.⁴² Epigenetic changes to HSCs lead to a bias in hematopoiesis toward monocytes and enhanced IL-6 and IL-1 β secretion.^{3,42,64} Addressing this cascade further, among those with CHIP, a common variant in the IL-6 receptor that causes hypofunction of the receptor (ie, *IL6R* p.Asp358Ala) leads to a significantly decreased risk of MI.⁴¹ In individuals with *JAK2* CHIP, monocytes have a similar proinflammatory phenotype with increased IL-6 and IL-1 β secretion, in addition to an increased risk of thrombosis.^{65,66}

CHIP likely acts to accelerate the previously established pathophysiology of atherosclerosis and vascular disease. Prior evidence in non-CHIP-related atherosclerosis has implicated the *NLRP3* cascade via IL-6 and IL-1 β signaling.⁶⁷ When proinflammatory monocytes transmigrate across the endothelial barrier and move into the tunica intima, they collect cholesterol and become foam cells to form atheromatous plaques at risk of rupture causing an acute thrombotic event.^{68,69} The process of transmigration is driven by cytokine signaling and ligand–receptor interactions between myeloid cells and endothelial cells. Prior work from human peripheral blood mononuclear cells has shown that activated myeloid cells in CHIP have enhanced leukocyte activation, cell adhesion, and migration signaling.^{70,71} Indeed, atheromatous plaques in mice with CHIP mutant HSCs are larger, driven by the accumulation of mutant plaque macrophages.⁷² The aberrant activation of myeloid cells and their increased signaling toward endothelial cells is thought to drive accelerated atherosclerosis in individuals with CHIP (Fig. 1).

Heart Failure

Current literature suggests that CHIP causes infiltration of the cardiac tissue with proinflammatory immune cells that promote pathogenic fibrosis and heart failure. In both ischemic and pressure overload murine models of heart failure, mice transplanted with *TET2* CHIP HSCs had worse cardiac function, increased fibrosis, and higher IL-1 β expression.⁷³ Treatment with selective *NLRP3* inflammasome inhibition was protective against heart failure and rescued the phenotype in *TET2* CHIP mice, implicating the *NLRP3* inflammasome as the mechanistic link between *TET2* CHIP and heart failure.⁷³ Similarly, the angiotensin II model of murine heart failure led to greater cardiac hypertrophy and fibrosis with *TET2* and *DNMT3A* HSC transplants.⁷⁴ The same underlying

mechanism of IL-1 β , IL-6, and *NLRP3* inflammasome activation drives heart failure outcomes in mouse models of *JAK2* and *PPM1D* CHIP.^{75,76} More recent efforts to compare human patients with heart failure and CHIP to those with heart failure without CHIP have recapitulated these findings: IL-1 β , IL-6, and *NLRP3* were differentially expressed in single-cell transcriptomic profiling.⁷⁷ Moreover, these studies demonstrated changes in signaling between monocytes and T cells, which may ultimately lead to infiltration of the cardiac tissue with inflammatory T cells and drive fibrosis. More work is necessary to understand the mutation-specific effects of CHIP on heart failure and further correlate the severity of outcomes to measures of intracardiac inflammation.

Arrhythmias

As studies of large genetic cohorts like the UK Biobank uncovered associations between CHIP and arrhythmias, murine studies have demonstrated that hematopoietic-specific *TET2* inactivation increases atrial fibrillation propensity and is mediated in part by increased *NLRP3* expression.⁷⁸ Increased *Ca²⁺/calmodulin-dependent protein kinase II (CaMKII)* activation and altered calcium handling are thought to be the ultimate arrhythmogenic mechanism, but further work is required to corroborate this new evidence.

THERAPEUTIC STRATEGIES

Due to the associations described above, CHIP has clinical importance for disease surveillance and risk stratification. Unfortunately, the genetic sequencing necessary to diagnose CHIP is only performed in rare clinical circumstances and is not typically obtained in cardiovascular care. This poses a major barrier to appropriate treatment of patients with CHIP. The recent development of low-cost targeted sequencing assays to identify patients with CHIP provides a strategy to reduce this barrier, and testing may eventually become standard of care: for example, in patients presenting with MI.⁹

Once identified, aggressive risk factor modification and short-interval clinical surveillance for progression of cardiovascular comorbidities are the mainstays of current treatment strategies. Some providers recommend empirically initiating statin therapy, lowering LDL goals in patients already on statin therapy, or obtaining coronary artery calcium scores in low risk cases.^{79,80} Providers must also incorporate each patient's specific mutational profile into decision-making. For example, those with non-*DNMT3A* mutations warrant a stronger consideration of statin therapy or intensification.

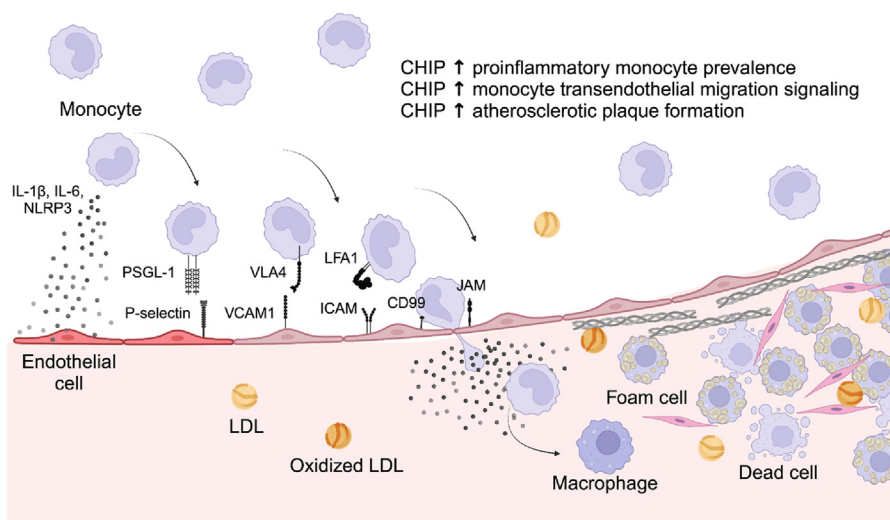


Fig. 1. The pathophysiology of atherosclerosis involves monocytes migrating across the vascular endothelium into the tunica intima to become macrophages. Subsequent phagocytosis of oxidized LDL and accumulation of cells drives expansion of atheromatous plaques. Prior work has shown that individuals with CHIP have (1) increased proinflammatory monocyte prevalence, (2) increased monocyte transmigration signaling, and (3) accelerated plaque expansion in atherosclerosis.

However, there is no clear optimal approach to lipid-lowering therapy. Given (1) the nature of CHIP as a de facto precursor lesion to MPNs and (2) the rapidly changing understanding of this disease, close collaboration with oncologists and referral to cardio-oncology or CHIP clinics is advised when available.⁸¹

As the translational science in this area moves forward toward treatment, individuals who are sequenced and diagnosed with CHIP may derive outsized cardiovascular benefit from anti-inflammatory medications. Accordingly, clinical trials targeting inflammation in cardiovascular disease must now be interpreted through the lens of CHIP. For example, in a non-prespecified post hoc analysis of the Canakinumab Anti-inflammatory Thrombosis Outcomes Study of IL-1 β antibody canakinumab, investigators performed sequencing to ascertain CHIP status (Table 2).⁸² This demonstrated that individuals with *TET2* CHIP had a significantly reduced risk of major cardiovascular events with canakinumab treatment compared to individuals without CHIP.⁸³ No such association was seen among those with *DNMT3A* CHIP. Separately, the Low-dose Colchicine for Secondary Prevention of Cardiovascular Disease 2 trial demonstrated that low-dose colchicine, which inhibits the NLRP3 inflammasome and IL-1 β , reduced cardiovascular events risk.⁸⁴ No analysis of CHIP has been performed in this trial cohort, but an unrelated retrospective analysis showed that a history of

colchicine use abrogated the association between *TET2* CHIP and MI.⁸⁵ Prospective trial data is needed to further assess this relationship.

The above post hoc analyses and mechanistic studies suggest that anti-inflammatory drugs may reduce cardiovascular risk in patients with CHIP, but no randomized controlled trials have been completed. A steady increase in awareness and diagnostic sequencing has accelerated trial development and enrollment,⁹ and two multicenter, blinded, randomized, placebo-controlled trials are currently recruiting patients with CHIP. The first is a Phase II trial of inflammatory biomarker reduction using an oral NLRP3 inhibitor and a bispecific IL-1 β /IL-18 monoclonal antibody among patients with a prior MI and *TET2* or *DNMT3A* CHIP (NCT06097663).⁸⁶ The second trial is a Phase I trial of selnoffast, an oral NLRP3 inhibitor, in individuals with CAD and high C-reactive protein, with a subgroup of individuals with *TET2* CHIP (trial identifier GC43343).⁸⁷ In addition to safety endpoints, this trial also examines plasma C-reactive protein levels and IL-1 β levels. The results of these trials will guide future studies that focus on more clinically meaningful endpoints associated with cardiovascular morbidity and mortality. Given the increasing accessibility of targeted sequencing to diagnose CHIP and these ongoing randomized controlled trials, CHIP has the potential to become a modifiable risk factor for cardiovascular disease in the next decade.

Table 2 Summary of evidence for anti-inflammatory therapies for coronary artery disease in the setting of clonal hematopoiesis of indeterminate potential						
Therapy	Inclusion Criteria	Study Design	CHIP Mutation(s)	Endpoints	Results	References
Canakinumab	Previous MI, elevated CRP, and <i>TET2</i> CHIP	Post hoc analysis of RCT	<i>TET2</i>	Major adverse cardiac events	Hazard ratio: 0.38 (95% CI, 0.15–0.96)	Svensson, et al, 2022 ⁸³
Oral NLRP3 inhibitor and bispecific IL-1 β /IL-18 monoclonal antibody	Previous MI and <i>TET2</i> or <i>DNMT3A</i> CHIP	RCT—Phase II	<i>TET2</i> , <i>DNMT3A</i>	Serum levels of IL-6 and IL-18	Actively recruiting participants	NCT06097663 ⁸⁶
Selnoflast (oral NLRP3 inhibitor)	Previous MI, elevated CRP, and <i>TET2</i> CHIP	RCT—Phase I	<i>TET2</i>	Safety, pharmacokinetics	Actively recruiting participants	Roche/Genentech GC43343 ⁸⁷

Abbreviations: CRP, C-reactive protein; MI, myocardial infarction; RCT, randomized controlled trial.

SUMMARY

CHIP is a novel risk factor for cardiovascular disease. In today’s practice, the presence of CHIP should heighten suspicion for accelerated pathophysiology, with particularly high suspicion among patients with non-*DNMT3A* mutations. In the coming years, diagnosis of CHIP may serve to identify likely responders to anti-inflammatory therapies for cardiovascular disease.

CLINICS CARE POINTS

- Clonal hematopoiesis of indeterminate potential (CHIP) is associated with atherosclerotic cardiovascular disease, incident heart failure, and arrhythmias.
- No evidence-based recommendations for monitoring or addressing CHIP-associated cardiovascular risk currently exist.
- Ongoing randomized controlled trials of patients with CHIP and previous myocardial infarction may offer guidance on clinical strategies.

DISCLOSURE

A.G. Bick reports personal fees and serves on the Scientific Advisory Board of TenSixteen Bio unrelated to the present work. All other authors have nothing to disclose.

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Unique Challenges of Adult Congenital Heart Disease in CardioOncology



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KEYWORDS

• Adult congenital heart disease • Malignancy • Thymectomy • Anatomy variation

KEY POINTS

- Adults with congenital heart disease are at an increased risk of cancer related mortality and morbidity.
- Genetic predisposition, radiation, and timely access to preventative screening are some of the factors that play a role in increased risk of malignancy.
- A better understanding of these risk factors and how to mitigate them can help decrease the risk of malignancy.

INTRODUCTION

Congenital heart disease (CHD) has a prevalence of approximately 1% to 2% of live births, making it the most common congenital malformation in newborns.¹ The last few decades have seen unparalleled advancements in the medical, surgical, and interventional treatments and more than 97% of children with CHD are expected to reach adulthood.² As a result, adults with CHD represent a very heterogenous and growing population that currently comprises most patients with CHD.³ Such increase in survival is associated with an increased risk of acquired diseases such as atherosclerotic disease and neoplastic disease. The incidence of cancer, in particular, has been shown in multiple large population-based studies to be approximately twice that of age and sex-matched controls.^{4,5} This article aims to discuss some of the causes (Fig. 1) for this increased risk and explores the pathophysiologic underpinnings of malignancy in adult CHD.

SYNDROMES ASSOCIATED WITH CONGENITAL HEART DISEASE AND INCREASED RISK OF CANCER

There are certain syndromes strongly associated with CHD as well as malignancy. A recent population-based study from Sweden has demonstrated that these genetic syndromes appear to account for the increased mortality risk in CHD patients with cancer compared to patients without CHD who have cancer.⁵ Among such syndromes, the most common are Down syndrome and 22q11.2 deletion syndrome.

Among individuals with intellectual disability, Down syndrome is the most common genetic abnormality, occurring in 1 out of every 800 to 1000 live births.⁶ The vast majority of patients with Down syndrome have a full trisomy of chromosome 21 with subsequent overexpression of different genes that could explain the increased frequency of CHD.⁷ Approximately 50% of the patients with Down syndrome have CHD.⁸ The most

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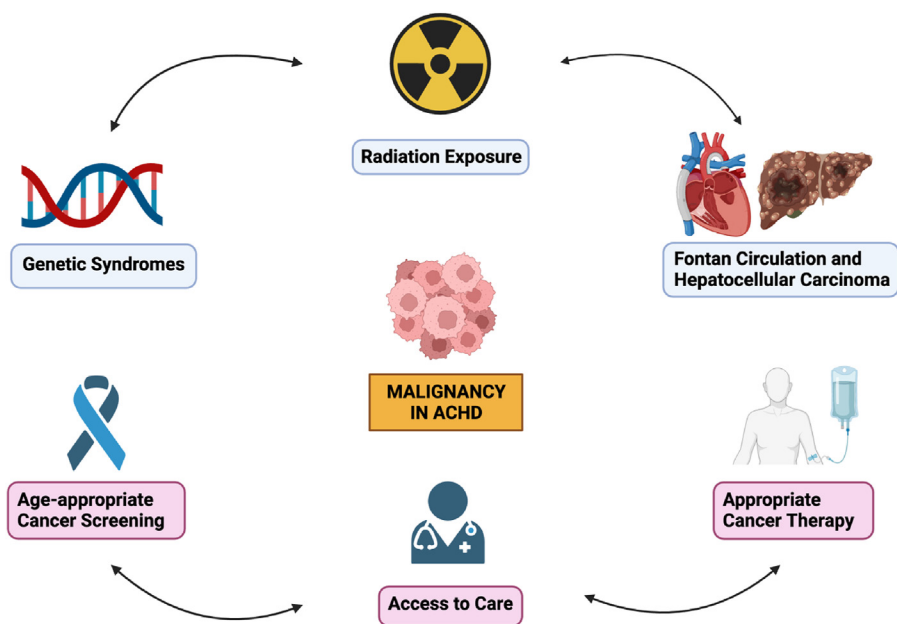


Fig. 1. Several factors play a role in the increased risk of cancer in adult patients with congenital heart disease.

common types of CHD anomalous in Down syndrome patients are endocardial cushion defects, such as atrioventricular canal defects, atrial septal defects (ASD), ventricular septal defects , and Tetralogy of Fallot (TOF).⁹ Additionally, it is also well known that the risk of malignancy, specifically hematologic malignancies, such as acute myeloid leukemia and germ cell tumors is significantly increased in individuals with Down syndrome. Overexpression of chromosome 21 genes, such as RUNX1 could account for this increased risk.^{10,11} In animal studies, some chromosome 21 genes have been found to play a role on DNA stability, mutations, and immune alterations of all the factors that contribute to malignancy development.¹² While genetic predisposition as well as environmental factors play a role in the risk of malignancy development, it is important for providers caring for patients with Down syndrome to be aware regarding the risk of cancer and the sites of cancer and pursue aggressive preventative strategies as well as early detection and treatment.

Another genetic syndrome associated with cardiac congenital defects as well as increased risk of malignancies is the chromosome 22q11.2 deletion syndrome. This deletion occurs in approximately 1 of 4000 to 10000 children.¹³ It is manifested in a multisystem fashion with a broad variety of phenotypical syndromes, the most common one being DiGeorge syndrome. Among the most common cardiac abnormalities are truncus arteriosus, TOF as well as interrupted aortic arch and hematologic disorders.¹⁴ It should be noted that in addition to

alterations in genes for proper cardiac hematologic development, patients with 22q11.2 deletion have thymic hypoplasia, which results in immunodeficiency and subsequent risk of malignancy. While large prospective studies evaluating long-term malignancy risk in these patients are lacking, several case reports of premature malignancy in patients with 22q11.2 deletion syndrome suggest increased malignancy risk with this condition.¹⁵

Given that the patients with these genetic syndromes are reaching adult age, it is extremely important to remain vigilant regarding the appropriate screening and diagnosis of cancer among this special population.

PATIENTS WITH COMPLEX SINGLE VENTRICLE PHYSIOLOGY AND RISK OF HEPATOCELLULAR CARCINOMA

Patients with Fontan circulation are at particularly high risk for developing hepatocellular carcinoma (HCC). The Fontan operation was first described in the early 1970s for patients with tricuspid valve atresia.¹⁶ It has undergone several modifications since its initial description and it is being applied as a third surgical step for pediatric patients with univentricular cardiac physiology where a biventricular repair is not feasible.¹⁷ Before such surgical advancements, children born with univentricular physiology faced an early death during infancy. Following a three-step surgical approach, and preceded by the Glenn procedure where a superior cavopulmonary connection is created, the Fontan

procedure involves the creation of a surgical shunt where the blood from the inferior vena cava is diverted to the pulmonary arteries. As a result, blood from the superior vena cava and inferior vena cava bypasses a subpulmonary ventricle, and drains directly into the pulmonary arteries.

A major characteristic of the Fontan circulation is the absence of a subpulmonary ventricle, which leads to an obligatory high central venous pressure, to allow for the forward flow of the blood into the pulmonary circulation. Diminished cardiac preload for the systemic ventricle leads to a chronic low cardiac output state. These hemodynamic factors as well as mildly decreased arterial blood oxygen saturations lead to chronic multiorgan dysfunction, including chronic liver dysfunction. In the United States, there are more than 900 patients who undergo Fontan operation every year with excellent greater than 97% early survival.¹⁸ The Fontan palliation is usually completed before the age of 5 year; however, the long-term effects of Fontan physiology are noted throughout adult life.¹⁹

Fontan-associated liver disease (FALD) is an example of one such effect of the physiology, particularly in adulthood. FALD encompasses the development of congestive hepatopathy, liver fibrosis, and even cirrhosis over time. Liver neoplasia is found at relatively high rates in patients after the Fontan operation, ranging from 3% to 15% in patients who have had Fontan physiology for 22 years.²⁰ A regenerative liver nodules are fairly common with a prevalence of 20% to 30%, any hepatic lesion warrants a detailed evaluation for HCC.²¹ Although there is a paucity of robust data on the relationship of Fontan hemodynamics and risk of HCC, there are several single-center studies that suggest a relationship of Fontan pressures by cardiac catheterization and progression of FALD.^{22,23} In addition, surveillance cardiac catheterization and transjugular liver biopsy studies show a strong correlation of FALD severity and time since Fontan completion.^{24,25} In general, the American Association for the Study of Liver disease guidelines for HCC surveillance recommend ultrasound and alpha-fetoprotein levels every 6 months in patients at high risk of developing HCC.²⁶ Such guidelines can reasonably be applied to FALD patients until a more specific approach for this patient population is validated.²⁷ Suspicious lesions should be evaluated with advanced imaging, such as contrast magnetic resonance. As such, patients with Fontan circulation should be cared by a multidisciplinary team approach including adult congenital cardiologists, hepatologists, and other subspecialists. Any liver surveillance strategy should be

implemented starting 10 to 15 years after Fontan surgery as the time since Fontan completion remains the most important predictor of advanced FALD.

RISK OF THYMECTOMY AND CANCER

Several studies have attempted to delineate the potential risk factors for malignancy in patients with CHD. One such possible risk factor is thymectomy at a young age.²⁸ For infants with CHD undergoing surgical repair, thymectomy is routinely performed to optimize surgical access. However early thymectomy has been associated with several immunologic changes including T-cell lymphopenia, with a less robust T-cell receptor profile and a skewed autoantibody repertoire.^{29,30} These immunologic alterations could lead to a suboptimal immune surveillance and subsequent increased risk for infections, cancers, and autoimmune diseases. When compared with the general population, the thymectomy group from a major Swedish national registry study, showed an overall risk of cancer significantly increased with a Hazard Ratio of 1.61.²⁸ Because of the observational nature of this study, a causal mechanism cannot be assumed. Nevertheless, it is reasonable that during early cardiac surgery, total thymectomy be avoided if possible.

RADIATION EXPOSURE AND CANCER

A significant number of patients with adult congenital heart disease (ACHD) have undergone cardiac catheterization procedures, either diagnostic or interventional. For some of these patients, such procedure has occurred more than once, including during childhood years. Interventional ACHD cardiac procedures have forever changed the landscape in the care of this patient population. However such procedures are performed using X-rays, which is associated with an increased lifetime risk for cancer (the United Nations Scientific Committee on Atomic Radiation. Sources, effects, and risks of ionizing radiation. Volume II, Annex B: Effects of radiation exposure of children. New York: United Nations, 2013). An understanding of the potential long-term risks of X-ray exposure is critical in optimizing exposure reduction as well as communicating with patients and their families when describing such procedures and obtaining consent. Cancers attributed to X-ray exposure typically can take decades to develop, including cancers of organs receiving the largest dose of radiation, such as the lungs, the esophagus, the breast, the stomach, and the liver. In the general population, many risk projections assume a normal

life expectancy and while the study of risk of cancer due to X-ray exposure is inherently challenging when controlling many confounding factors, such study is particularly challenging in the ACHD population because of the wide variability of survival in such patient population. For many conditions such as pulmonary valve stenosis or ASD, survival approaches that of the general population.³¹ However, for patients with much more complex congenital heart defects (for example, hypoplastic left heart syndrome), survival is significantly reduced despite optimal medical, surgical, and interventional therapies.³² Harbron and colleagues concluded that the adjusted cancer risk of radiation exposure from cardiac catheterizations in children is relatively low and the risk of breast cancer following pulmonary artery angioplasty and valve replacement is of greatest concern.³³ A landmark study from Cohen and colleagues concluded that patients with higher radiation exposure (defined as 6 or more cardiac catheterization procedures) had a 2.4-fold greater risk of developing cancer than the low-exposure group.³⁴ It should be noted that while cardiac catheterization is a source of X-ray exposure, it is not the only source. Patient with CHD undergo different types of diagnostic imaging tests, including computed tomography, which could be another source of radiation exposure. This exposure is heightened particularly in those with complex CHD who often have undergone several surgeries, fluoroscopic procedures, and advanced imaging studies, all of which would increase cumulative lifetime radiation exposure. A unique group of patients, includes patients with complex CHD who have undergone several surgeries and interventions during their lifetime (such as Fontan circulation patients as described above), and despite this, ultimately they will require heart (or heart and liver) transplant evaluation. Although overall transplant patients are at an increased risk of malignancy, this applies also specifically to CHD patients who have undergone transplants.³⁵

INADEQUATE CANCER SCREENING IN ADULT CONGENITAL HEART DISEASE PATIENTS

Cardiac complications including heart failure, valve disease, and arrhythmias can overshadow the need for primary care and preventative screening measures. Among many factors affecting preventative screening, lack of a primary care provider is a major one.³⁶ Many patients with complex chronic conditions rely heavily on subspecialists for their medical care, thus reducing the likelihood to seek and access general preventative care. Not only does this hold particularly true

for ACHD patients, but there are also additional challenges that ACHD patients face— inadequate understanding by patients and their parents, of the importance of life-long medical care, and the challenges in proper transition from pediatric to adult care.^{37,38} Christman and colleagues showed the importance of cancer screening in ACHD patients and emphasize the need for collaboration of ACHD providers and primary care physicians, which not only can save lives but also could transfer the approach to overall care of ACHD patients.³⁹ The median age of cancer diagnosis in ACHD patients at 43.5 years when compared with the general US population at 66 years limits some of the health benefits of age-appropriate screening.⁴⁰ Hence additional research is needed to develop appropriate screening protocols for ACHD patients in general. As ACHD patients are less likely to participate in cancer screening, it leads to the cancer being diagnosed at later stages, which affects their survival rate.⁴⁰ Appropriately so, the importance of increased access to primary care and appropriate transition from pediatric to adult care for ACHD patients have been incorporated in the 2018 American College of Cardiology/American Heart Association ACHD Guidelines.⁴¹

CANCER TREATMENT IN ADULT CONGENITAL HEART DISEASE PATIENTS

Whereas ACHD patients face such additional challenges in proper cancer screening and diagnosis, they can face equally daunting concerns with regard to treatment. It is well established that cancer treatments can lead to various cardiac adverse events, among which heart failure, arrhythmias, blood pressure abnormalities, are not uncommon. Patients with CHD have a higher risk of heart failure and arrhythmias when compared to aged-matched controls.⁴² Not surprisingly, a single-center cohort study of ACHD patients with malignancy found a markedly high rate of major adverse cardiovascular and cerebrovascular events of 59% over a 5-year follow-up period.⁴⁰ This could affect cancer treatments and it requires a close collaboration of hematology–oncology and ACHD providers for proper monitoring and treatment of adverse cardiovascular events. Among those undergoing cancer therapy, a reassuringly low rate of suspected cancer therapy related cardiac effects of 14% was observed in the aforementioned single-center study—only a single patient required temporary cessation of cancer therapy—followed by resumption at the original therapeutic dosing.⁴⁰ Additional data regarding safety and tolerability of cancer therapy in ACHD patients are required.

SUMMARY

With the exponentially increasing number of ACHD patients and concurrent uptrend in cancer diagnosis in these patients, it is only proper to speculate that the new exciting area of ACHD–oncology is taking shape. Among many factors that can affect the risk of cancer in ACHD, some can be modified and some are intrinsic to this patient population; but when it comes to treatment, we can make a difference in helping these patients by ensuring that they benefit from the full range of treatment options. Additional long-term outcome studies are required to further enhance our understanding of pathophysiology and influence treatment decision in this complex patient population.

CLINICS CARE POINTS

- Adult patients with congenital heart disease undergo diagnostic imaging as well as invasive procedures, which can increase lifetime radiation exposure. Such exposure could play a role in the observed increased risk of malignancy that is seen in the adults with congenital heart disease (CHD).
- Patients with single ventricle physiology who have undergone Fontan palliation are at an increased risk of hepatocellular carcinoma. Aggressive periodic screening can lead to early detection and better outcomes in the treatment of hepatocellular carcinoma.
- Certain genetic mutations such as Trisomy 21 and chromosome 22q11.2 deletion are commonly associated with CHD as well as increased risk of malignancy.
- Although increased risk of malignancy is multifactorial, access to preventative care and timely age-appropriate screening should be emphasized by all providers caring for these patients.

DISCLOSURE

The authors have nothing to disclose.

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Classes of Antineoplastic Agents Associated with Increased Risk of Cancer Therapy-associated Hypertension and Management Strategies



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KEYWORDS

• Cancer therapy-associated HTN • Cardiovascular adverse events • Antihypertensive classes

KEY POINTS

- Multiple classes of cancer therapies have been implicated in the development of HTN, including inhibitors of vascular endothelial growth factor (VEGF), Bruton tyrosine kinase inhibitors, proteasome inhibitors, androgen deprivation therapy, and others.
- The mechanisms underlying cancer therapy-associated HTN vary depending on the class of drugs, with some common mechanisms including imbalance between vasoconstrictor and vasodilator levels (eg, with VEGF inhibitors).
- Many of the drug classes associated with HTN also are associated with other cardiotoxicities (eg, cardiomyopathy with V-Raf Murine Sarcoma Viral Oncogene Homolog B [BRAF]/VEGF inhibitors, ischemic cardiovascular disease with androgen deprivation therapy), and the degree of overlap between HTN and other cardiovascular adverse events is not consistently well understood.
- With oncologic therapies improving cancer-related survival, diagnosing and managing cancer therapy-associated HTN are essential although the long-term impacts on cardiovascular morbidity are still not well understood.

INTRODUCTION

A focus on cardiovascular (CV) adverse effects of oncologic treatments has emerged due to rapidly expanding oncologic treatments allowing for longer overall survival and a growing population of cancer survivors. Hypertension (HTN) is a critical concern

in the field of cardio-oncology with multiple different classes of antineoplastic agents implicated in risk of either short-term or long-term HTN. Understanding the underlying mechanisms, appropriately diagnosing, and managing cancer therapy-associated HTN add a layer of complexity to cancer care and survivorship medicine.

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High-grade HTN may result in significant morbidity and may also complicate treatment of cancer by necessitating dose reduction or complete discontinuation. HTN poses an independent risk factor for the development of coronary artery disease, heart failure, arrhythmias, valvular disease, chronic kidney disease, and stroke.^{1,2} Understanding the incidence, risk factors, and underlying mechanisms of cancer therapy-associated HTN is important to allow for prompt identification and management of this adverse event to prevent long-term CV morbidity and mortality.

This article provides a review of different classes of cancer therapies associated with risk of HTN, data on the underlying pathophysiology, and possible management strategies.

WHY DOES CANCER THERAPY-ASSOCIATED HYPERTENSION MATTER?

Patients undergoing treatment of cancer have a higher incidence of HTN compared to the general population. A prior prospective study of more than 17,000 patients with cancer found that HTN was the most common CV comorbidity.³ Patients with cancer may be at increased risk of baseline HTN due to shared risk factors (eg, prior smoking history, obesity). However, many classes of antineoplastic agents are also associated with increased risk of developing new or worsening HTN.

The development of cancer therapy-related HTN has implications both for cancer-related outcomes due to a potential need for dose reduction/discontinuation and for long-term CV outcomes from increased risk of ischemic heart disease and CV mortality. Those long-term sequelae are particularly concerning for cancer survivors who received treatment with curative intent for prior cancer (eg, androgen deprivation therapy [ADT] for prostate cancer) or for patients on cardiotoxic oncologic treatments for prolonged periods (eg, Bruton tyrosine kinase [BTK] inhibitors for chronic lymphocytic leukemia [CLL]).

Among adults followed longitudinally after cancer treatment in childhood (including chest-directed radiation treatment), HTN was associated with a 6 times higher risk for coronary artery disease, 6 times higher risk of arrhythmia, 13 times higher risk of valvular disease, and 19 times higher risk of heart failure. Additionally, by age 50 years or more, prevalence of HTN was 40% in adults who were treated for childhood cancer versus 26% in their healthy siblings.¹

Further, cancer therapy-associated HTN highlights health discrepancies among underrepresented minority populations. Studies in cancer

survivors indicate an increased prevalence of HTN among Black patients.⁴ An extensive registry-focused study revealed that Black patients with breast cancer had twice the risk of hospital admissions due to HTN post-cancer diagnosis compared to other populations⁵; it is unclear whether this disparity is linked to Black patients being at higher risk of poorly controlled HTN on treatment or a higher risk of CV adverse events (CVAEs) in general. The underlying factors contributing to these disparities warrant further investigation.

CLASSES OF CANCER THERAPIES ASSOCIATED WITH HYPERTENSION

Vascular Endothelial Growth Factor Inhibitors

Anticancer treatment with inhibitors of vascular endothelial growth factor (VEGF) has long been known to cause HTN in patients with cancer. VEGF inhibitors include both multi-kinase inhibitors such as sunitinib, sorafenib, pazopanib, axitinib, and cabozantinib; and monoclonal antibodies such as bevacizumab or ramucirumab. These agents are used for a wide range of malignancies including renal cell carcinoma (RCC), thyroid cancer, colorectal cancer, hepatocellular carcinoma (HCC), non-small cell lung cancer, sarcoma including gastrointestinal stromal tumor, and others (Table 1).

Risk of HTN with bevacizumab appears to be dose dependent, with meta-analyses identifying an incidence of 3% to 32% for low-dose and 17.6% to 36% for high-dose bevacizumab.⁶ Analyses of real-world data have shown high incidence of HTN with anti-VEGF tyrosine kinase inhibitor (TKIs), with an incidence of systolic blood pressure (SBP) 140 mm Hg or greater and/or diastolic blood pressure (DBP) 90 mm Hg or greater of 52% with sunitinib, 59% with sorafenib, and 40% with pazopanib; and an incidence of SBP 160 mm Hg or greater and/or DBP 100 mm Hg or greater (or need for ≥ 2 antihypertensives) of 37% with sunitinib, 36% with sorafenib, and 28% with pazopanib.⁷ Data are limited comparing incidence of HTN between different VEGF inhibitors. Prior retrospective analyses have suggested early absolute increases in SBP of 13 mm Hg and in DBP of 8 mm Hg within the first 4 weeks of treatment, with a gradual decline overtime though still remaining elevated above baseline; the mean absolute change overtime was an increase in SBP of 8 to 9 mm Hg and in DBP of 6 to 7 mm Hg, with the greatest increases noted with axitinib.⁸ The increase in blood pressure associated with VEGF inhibitors has been shown to resolve with discontinuation of treatment, suggesting that

Table 1
Classes of antineoplastic agents with association with hypertension and examples of common Food and Drug Administration-approved indications

Drug Class	Examples of Drugs	Examples of FDA-Approved Indications	Incidence of HTN
VEGF Inhibitors ^{80–86}	<i>Multi-kinase inhibitors:</i> sunitinib, sorafenib, pazopanib, axitinib, cabozantinib <i>Monoclonal antibodies:</i> Bevacizumab, ramucirumab	Colorectal carcinoma, RCC, HCC, epithelial ovarian or fallopian tube cancers, thyroid cancer, sarcoma including gastrointestinal stromal tumor	Bevacizumab low-dose, 3%–32% ⁶ Bevacizumab high-dose, 18%–36% ⁶ Sunitinib, 52% ⁷ Sorafenib, 59% ⁷ Pazopanib 40% ⁷
Bruton TKIs ^{87–89}	Ibrutinib, acalabrutinib, zanubrutinib	CLL/SLL, mantle cell lymphoma (MCL), marginal zone lymphoma (MZL), Waldenström's macroglobulinemia	Ibrutinib, 14%–78% ^{19,20,24} Acalabrutinib, 9% ²⁴
Proteasome Inhibitors ^{90–92}	Bortezomib, ixazomib, carfilzomib	Multiple myeloma, mantle cell lymphoma (bortezomib only)	Carfilzomib, 18%–32% ^{29–31} Bortezomib, 10% ²⁹ Ixazomib, no significant risk ³²
BRAF/MEK Inhibitors ^{38,39,93–96}	Dabrafenib/trametinib, vemurafenib/cobimetinib, encorafenib/binimetinib	<i>BRAF V600E or V600K:</i> Melanoma in adjuvant, unresectable or metastatic setting <i>BRAF V600E only:</i> Metastatic NSCLC, locally advanced or metastatic anaplastic thyroid cancer	Dabrafenib/trametinib, 22% ⁴⁵ Dabrafenib, no MEK component, 14% ⁴⁵
Androgen Deprivation Therapy ^{97–99}	<i>GnRH agonist:</i> leuprolide <i>GnRH antagonist:</i> degarelix, relugolix	Prostate cancer	
Androgen Signaling Suppressors ^{100–107}	<i>Androgen receptor inhibitors:</i> Bicalutamide, enzalutamide, apalutamide, darolutamide <i>CYP17 inhibitor:</i> Abiraterone acetate	Prostate cancer	Abiraterone, 3%–37% ⁵⁷
Platinum-based Chemotherapy ^{108–110}	Cisplatin, carboplatin, oxaliplatin	Testicular, urothelial carcinoma, small cell lung cancer, NSCLC, pancreatic, colorectal, gynecologic cancers	Cisplatin, 39% ⁶²
RET Inhibitors ^{65,66}	Pralsetinib, selpercatinib	<i>Pralsetinib:</i> RET fusion-positive metastatic NSCLC <i>Selpercatinib:</i> RET fusion-positive locally advanced or metastatic NSCLC	Pralsetinib, 11% (grade 3–4 HTN) ⁶⁹ Selpercatinib, 7/13% (grade 1–2/grade3) ⁶⁸

HTN secondary to VEGF inhibition is a reversible drug-mediated effect. However, the long-term sequelae of VEGF inhibitor-induced HTN warrant further investigation, with past studies suggesting absence of impact on long-term renal function.⁹ Of note, studies have also found that the development of HTN from anti-VEGF agents is a biomarker of tumor response to treatment, suggesting an on-target effect.

The mechanism underlying increased blood pressure is believed to be multifactorial due to effects on vasoconstrictor and vasodilator levels, vascular rarefaction, and glomerular injury.^{10,11} VEGF plays a role in maintaining homeostasis between levels of vasoconstrictors and vasodilators through transcription of nitric oxide synthase (resulting in increased nitric oxide levels), promoting endothelial cell production of prostacyclin, and decreasing endothelin-1 levels.^{10–13} As a result, inhibiting VEGF leads to increased levels of vasoconstrictors and decreased levels of vasodilators, thereby promoting vascular constriction. As VEGF additionally is vital for survival of endothelial cells, inhibition of VEGF causes endothelial cell apoptosis and reduces capillary bed density.^{10,11}

As VEGF TKIs are also increasingly being combined with other antineoplastic agents such as immune checkpoint inhibitors in the treatment of metastatic RCC, HCC, and other malignancies, further studies will be needed to determine the CV effects of combining VEGF TKIs with other agents.^{14–16}

Bruton Tyrosine Kinase Inhibitors

BTK inhibitors are a class of small molecule anti-neoplastic agents that are used primarily in B-cell malignancies, including CLL/small lymphocytic lymphoma (SLL), mantle cell lymphoma (MCL), marginal zone lymphoma, and Waldenström's macroglobulinemia (see [Table 1](#)). The BTK is a cytoplasmic kinase expressed primarily in B lymphocytes and critically involved in the downstream signaling cascade of the B-cell receptor. BTK activation results in the proliferation, maturation, and survival of B lymphocytes and in cytokine signaling needed for B-cell motility and tissue homing.^{17,18} The discovery of the important role of BTK signaling in B-cell pathways led to the development of BTK inhibitors in treating B-cell malignancies such as CLL/SLL (characterized by progressive accumulation of monoclonal B cells in the blood or lymphoid tissues) and MCL (a type of non-Hodgkin lymphoma). Currently, available BTK inhibitors include the first-generation inhibitor ibrutinib and more selective next-generation inhibitors such as acalabrutinib and zanubrutinib.

Although early trials indicated an incidence of all-grade HTN of 14% and grade 3 HTN of 4% with ibrutinib,¹⁹ subsequent studies have revealed a higher incidence of HTN with ibrutinib. For example, one single-institution study in over 500 patients identified 78% new or worsening HTN with ibrutinib, including 71% in those without baseline HTN.²⁰ Although the mean increase in SBP was 5.2 mm Hg, approximately 10% experienced an increase in SBP of 50 mm Hg, suggesting that there is a subset of patients at risk of severe HTN. Risk factors associated with increased risk of new/worsening HTN included receipt of the BTK inhibitor for CLL (vs other B-cell malignancies) and high baseline SBP.²⁰ Ibrutinib is also known to be associated with increased risk of arrhythmias such as atrial fibrillation^{21,22}; of note, patients with ibrutinib-associated HTN are at especially higher risk of major adverse CV effects (predominantly arrhythmias) compared with those without ibrutinib-associated HTN.²⁰ Other studies have similarly identified increased risk of HTN with ibrutinib, with a meta-analysis of 8 randomized controlled trials (RCTs) involving ibrutinib (with a pooled cohort of 2580 patients) demonstrating 2.8 times increased risk of HTN among patients randomized to ibrutinib therapy.²³

Next-generation BTK inhibitors also have an association with HTN although at a lower incidence compared with ibrutinib. The ELEVATE-RR phase 3 randomized trial that involved a head-to-head comparison of ibrutinib versus acalabrutinib in patients with previously treated CLL demonstrated a 23% incidence of all-grade HTN with ibrutinib (grade 3: 9%) compared with 9% (grade 3: 4%) with acalabrutinib.²⁴

The mechanisms by which BTK inhibitors increase HTN risk are not completely characterized. The development of HTN with both first-generation and next-generation BTK inhibitors, but with higher incidence of HTN with ibrutinib, suggests that there may be both on-target-mediated and off-target-mediated mechanisms of HTN associated with BTK inhibitors. One hypothesis is that the effect may be mediated via decreased production of nitric oxide, leading to increased vascular tone.²⁵ Inhibition of phosphatidylinositol 3-kinase (PI3K) pathways may also play a role via vascular fibrosis, similar to the mechanism underlying BTK inhibitor-associated arrhythmias,^{26,27} although notably other PI3K inhibitors do not have the same association with HTN. Although prior studies have demonstrated an association between BTK inhibitors and atrial fibrillation,²¹ it is unclear to what extent the mechanisms underlying BTK inhibitor-associated HTN and atrial fibrillation are linked.

Proteasome Inhibitors

Proteasome inhibitors (PIs) are a class of anticancer agents used in combination regimens for the treatment of multiple myeloma, light chain amyloidosis (AL amyloidosis), and Waldenström's macroglobulinemia and include bortezomib, carfilzomib, and ixazomib (see [Table 1](#)).²⁸ Carfilzomib in particular has an increased risk of CVAEs, including HTN, with higher risk compared with bortezomib. In ENDEAVOR, a phase 3, multicenter, open-label randomized trial of carfilzomib and dexamethasone (Kd) versus bortezomib and dexamethasone (Vd) for patients with relapsed or refractory multiple myeloma, 32% of patients receiving Kd developed new HTN, compared to 10% receiving Vd.²⁹ An analysis of the CV safety profile of carfilzomib across multiple clinical trials reported an 18% incidence of any-grade HTN, and a 5.9% incidence of HTN considered a grade 3 or higher adverse event.³⁰ Similarly a prior prospective study of CVAE with carfilzomib-based versus bortezomib-based therapy for relapsed multiple myeloma identified higher risk of CVAE with carfilzomib, with HTN representing the second most common event (incidence 23%, all representing grade ≥ 3) after heart failure (HF).³¹ In contrast, the oral PI ixazomib has not been found to have a significant risk of HTN.^{32,33}

PIs function by disrupting the ubiquitin-proteasome pathway, leading to disruption of protein homeostasis and accumulation of intracellular protein, resulting in apoptosis of cancer cells. PIs are thought to increase HTN risk by reducing nitric oxide production in vascular endothelial cells through impaired modulation of endothelial nitric oxide synthetase expression.³⁴ Proteasome inhibition also leads to proteome instability in vascular smooth muscle cells, leading to increased arterial stiffness.³⁵ Of note, thrombotic microangiopathy is known adverse effect of PIs, further implicating vascular endothelial dysfunction in PI-associated toxicity.³⁶ Factors specific to the population of patients who are treated with PIs, such as advanced age and prior treatment with other cardiotoxic agents, may also augment this CV risk.³⁷

BRAF/MEK Inhibitors

The combination of kinase inhibitors of v-raf murine sarcoma viral oncogene homolog B (BRAF) and MEK is used in various malignancies harboring BRAF V600 E mutation, including unresectable or metastatic melanoma, metastatic non-small cell lung cancer (NSCLC), and anaplastic thyroid cancer, with one such combination (dabrafenib/trametinib) even having tumor-agnostic accelerated approval for all metastatic solid malignancies

harboring the BRAF V600 E point mutation (see [Table 1](#)).^{38,39} Other commonly used combinations include encorafenib/binimetinib and vemurafenib/cobimetinib.^{40,41} The rationale for using BRAF inhibitors in combination with MEK inhibitors is from preclinical data that suggest that BRAF inhibition alone may allow for feedback signals that reactivate mitogen-activated protein kinase signaling.^{42–44} Understanding the CVAEs of BRAF/MEK inhibition is increasingly important with the use of these combinations in the adjuvant setting for melanoma.

Studies have identified an increased risk of HTN associated with BRAF/MEK combination relative to BRF inhibition alone. In the COMBI-d phase 3 trial that randomized 423 patients to either dabrafenib/trametinib or dabrafenib/placebo, the combination BRAF/MEK inhibitor group had a greater incidence of all-grade HTN compared with the BRAF inhibitor monotherapy group (22% vs 14%), though with similar rates of grade 3 HTN (4% vs 5%).^{45,46} A systematic review and meta-analysis of 5 RCTs of 2317 patients with melanoma similarly found 1.5 times increased risk of HTN with BRAF/MEK inhibitor combination therapy relative to BRAF inhibitor monotherapy.⁴⁰ Of note, BRAF/MEK inhibitors also have a known association with cardiomyopathy, but the degree of overlap between patients with BRAF/MEK inhibitor-associated HTN and cardiomyopathy is unknown.^{41,42}

The mechanisms underlying HTN secondary to BRAF/MEK inhibition are not well understood. BRAF and MEK signaling has been implicated in carcinogenesis via effects on cell proliferation and survival.^{43,44} However, BRAF/MEK/ERK signaling also plays a role in myocyte and vascular endothelial protection.⁴⁷ BRAF/MEK inhibition has been shown to lead to upregulation of CD47 expression downstream of BRAF/MEK inhibition,^{48,49} which may decrease levels of nitric oxide and the vasodilatory molecule cyclic guanosine monophosphate, potentiating endothelial dysfunction and vasoconstriction.⁵⁰

Androgen Deprivation Therapy

ADT is the foundation of systemic treatment of prostate cancer and is received by about half of the patients with prostate cancer (see [Table 1](#)).⁵¹ Classes of pharmacologic ADT include gonadotropin-releasing hormone (GnRH) agonists (eg, leuprolide) and GnRH antagonists (eg, degarelix, relugolix). Suppression of androgen signaling can also be achieved by androgen receptor inhibitors (eg, bicalutamide, enzalutamide, apalutamide, darolutamide) or the cytochrome P450 17A1 (CYP17) inhibitor abiraterone acetate.⁵²

Overall, these antihormonal therapies are received across varying settings including localized intermediate-risk or high-risk prostate cancer or advanced/metastatic disease.

ADTs have a well-known association with increased risk of CV diseases, including metabolic syndrome, insulin resistance, and ischemic heart disease from accelerated atherosclerosis.^{53–55} The main drugs with a well-established association with HTN in particular are abiraterone and androgen receptor inhibitors, especially enzalutamide. The mechanism driving HTN from androgen receptor inhibitors is not well understood. A meta-analysis of 3 major phase 3 trials (PROSPER, SPARTAN, and ARAMIS) investigating the combination of androgen receptor inhibitors with ADT compared to placebo with ADT for nonmetastatic castrate-resistant prostate cancer identified that adding enzalutamide, apalutamide, or darolutamide to ADT was associated with 1.3 times higher risk of HTN compared to placebo/ADT.⁵⁶

Abiraterone has also been demonstrated to have an increased risk of HTN, with a meta-analysis of 4 phase 3 and 1 phase 2 trial identifying incidence of HTN ranging from 3.3% to 36.7%, with an overall incidence of 21.9% and incidence of grade 3 HTN or greater of 10.2%.⁵⁷ The mechanism underlying HTN from abiraterone may be related to its inhibition of CYP17, including 17 α -hydroxylase and 17,20-lyase, which inhibits production of not only testosterone but also cortisol; even though abiraterone is given with low-dose prednisone to compensate for this, the decrease in cortisol synthesis triggers increased adrenocorticotrophic hormone levels via loss of negative feedback, which leads to mineralocorticoid excess, resulting in increased risk of HTN and hypokalemia.^{58,59}

Platinum-based Chemotherapy

Platinum-based drugs such as cisplatin, carboplatin, and oxaliplatin are used to treat patients with a wide array of malignancies across different stages including testicular, colorectal, ovarian, urothelial, head and neck malignancies, lung cancers, and others; they are often used in combination with other antineoplastic agents (see [Table 1](#)). These alkylating agents exert their antineoplastic effect by cross-linking with purine nucleotides, inhibiting DNA synthesis and leading to apoptosis.⁶⁰

In the short term, platinum-based agents are not associated with HTN and in fact may be associated with lower blood pressure.⁶¹ However, cancer survivors who have been exposed to platinum-based compounds are at increased risk of developing HTN years later compared with

cancer survivors who were not exposed to those agents. For example, a prospective study in long-term survivors of metastatic testicular cancer who were disease free for greater than 10 years found that 39% of patients treated with platinum-based chemotherapy developed HTN compared with 13% of those treated with orchiectomy alone for stage I disease⁶²; although limited by the differences in disease stage between the 2 cohorts, these findings suggest a significant risk of HTN as a long-term sequela from exposure to platinum-based chemotherapy. This is most clinically significant for patients receiving treatment in the curative setting such as germ cell tumors, and the differences in risk of HTN between carboplatin and cisplatin are not known.

Underlying mechanisms likely are linked to vascular endothelial injury and nephrotoxicity. Studies have demonstrated detectable platinum levels in the serum of patients years following treatment with platinum-based chemotherapy, which may lead to chronic vascular endothelial damage⁶³ and may underly the association between high circulating platinum levels and HTN risk.^{63–65}

RET Inhibitors

Tyrosine kinase inhibitors targeting rearranged during transfection receptor (*RET*) have been approved for patients with locally advanced or metastatic solid tumors that harbor *RET* gene rearrangements. The 2 Food and Drug Administration (FDA)-approved *RET* inhibitors are pralsetinib and selpercatinib (see [Table 1](#)).^{66,67} Selpercatinib has accelerated approval in the tumor-agnostic setting based on the open-label basket trial LIBRETTO-001 and has full approval for NSCLC or medullary thyroid carcinomas (MTCs) with *RET* fusions.⁶⁸ Based on the ARROW trial, pralsetinib has regular FDA approval for NSCLC with *RET* fusions and accelerated approval for advanced or *RET* fusion-positive metastatic thyroid cancers that are radioactive iodine refractory.⁶⁹ Approximately 60% of cases of sporadic MTC, nearly all of hereditary MTC, and 1% to 2% of NSCLC have *RET* fusions.^{70,71}

High rates of HTN were observed in the clinical trials that led to the approval of pralsetinib and selpercatinib. In the LIBRETTO-001 open-label basket trial, grade 1 to 2 HTN attributed to selpercatinib was reported in 7% of cases and grade 3 in 13% of cases, with a higher rate of treatment-emergent HTN (grade 3 HTN in 22% of cases and grade 1–2 in 9% of cases).⁶⁸ In the ARROW trial investigating pralsetinib, grade 3 to 4 HTN was observed in 11% of patients.⁶⁹

The mechanism underlying HTN from RET inhibition is poorly understood. Pralsetinib has been found in preclinical models to have low affinity for off-target kinases such as VEGF receptor 2.⁷² However, given that pralsetinib has 88 times greater affinity for RET than VEGFR2,⁷² it is unclear whether such low activity against VEGF would be sufficient to explain the degree of HTN observed with this agent. Further studies are needed to understand whether the HTN observed with these agents is due to on-target activity against RET versus off-target activity against other kinases.

Non-neoplastic Adjunctive or Supportive Therapies

Nonneoplastic adjunctive therapies, such as glucocorticoids or calcineurin inhibitors, also may be implicated in HTN in patients with cancer. Glucocorticoids are often received by patients with cancer either concurrently with chemotherapy for various reasons (eg, to reduce the risk of infusion reactions or other side effects from chemotherapy) or for other reasons unrelated to systemic therapy (eg, reduce edema from brain metastases). Glucocorticoids are known to activate mineralocorticoid receptors, leading to fluid and sodium retention and increased circulating blood volume, which may be implicated in glucocorticoid-induced HTN.⁷³

Allogeneic hematopoietic stem cell transplant (allo-HSCT) is a mainstay of management for many patients with hematologic malignancies. Hematopoietic stem cell transplant (HSCT) itself has been identified as a risk factor for early arterial wall thickening and HTN.⁷⁴ One study of 689 long-term pediatric HCST survivors identified a 17% rate of HTN with average age of onset of 25 years, compared to onset at age 40 years in the general population.⁷⁵ Similar findings have been reported in adult patients, with allo-HSCT associated with greater HTN risk compared to auto-HSCT.⁷⁶ Calcineurin inhibitors, which include tacrolimus and cyclosporine, are used for prophylaxis of graft-versus-host disease in these patients. Calcineurin inhibition is also believed to increase risk of HTN, although the incidence is not well characterized in allo-HSCT recipients. Studies elucidating the pathophysiology of HTN from calcineurin inhibitors largely come from the organ transplant space, identifying increased activation of the renin-angiotensin system, impaired balance between endothelin-1 and nitric oxide, increased oxidative stress, and augmented activity of sodium chloride cotransporters leading to increased renal sodium retention.⁷⁷

DIAGNOSIS AND MANAGEMENT OF CANCER THERAPY-RELATED HYPERTENSION

For the general population, the 2017 American College of Cardiology (ACC)/American Heart Association Hypertension (AHA) Clinical Practice Guidelines suggest initiating antihypertensives for primary prevention in adults with SBP 130 mm Hg or greater or DBP 80 mm Hg or greater who have an estimated 10 year atherosclerotic cardiovascular disease (ASCVD) risk of 10% or higher; for those with 10 year ASCVD risk less than 10% and no history of CV disease, the guidelines recommend a higher SBP and DBP cut-off of 140 and 90 mm Hg.⁷⁸ The data used to support those guidelines are based on the general population, with very limited data for optimal blood pressure (BP) targets in patients with cancer. As a result, most of the guidance for how to define, prevent, and treat cancer therapy-related HTN is derived from consensus statements. The ideal BP goal should likely be based on multiple factors including but not limited to presence of preexisting CV diseases and oncologic treatment setting (eg, treatment with curative intent vs for metastatic disease).

The 2022 International Cardio-Oncology Society (IC-OS) statement is aligned with the 2017 ACC/AHA statement in recommending an HTN diagnostic threshold of SBP greater than 130 mm Hg and/or DBP greater than 80 mm Hg both before and after initiating cancer therapy (Table 2).⁷⁹ Their statement recommends a threshold for initiating antihypertensives of BP greater than 130/80 for patients with pre-existing CV disease, renal disease with proteinuria, or diabetes; and a threshold of BP greater than 140/90 mm Hg in all other patients with cancer. The statement also recommends that for patients with SBP greater than 180 mm Hg or DBP greater than 110 mm Hg, any cancer therapies with a known association with HTN should be withheld until BP can be lowered to less than 160/100 mm Hg. The 2022 European Society of Cardiology (ESC) guidelines recommend different BP thresholds depending on whether patients are receiving treatment with curative intent or for metastatic cancer, with higher thresholds for those with a worse prognosis.⁸⁰ Overall, they similarly recommend a BP target of 140/90 mm Hg for most patients and suggest holding cancer therapy if SBP 180 mm Hg or greater or DBP 110 mm Hg or greater.

Limited data exist evaluating optimal choice of antihypertensive drugs for the management of cancer therapy-associated HTN, with most guidelines extrapolating based on data from the general population. Studies have identified that use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) in patients

Table 2
The International Cardio-Oncology Society consensus statement recommendations⁷⁹

Blood Pressure (mm Hg)	Demographic	Recommendation
>130/80	Patients with cancer and • Preexisting cardiovascular disease, or • Renal disease with protein-uria, or • Diabetes	Initiate antihypertensive treatment
>140/90	Patients with cancer without concomitant risk factor, listed earlier	Initiate antihypertensive treatment
>180/110	Patients with cancer undergoing anticancer therapy	Hold anticancer therapies known to be associated with hypertension until BP is lowered to <160/100 mm Hg

Adapted from Herrmann J, Lenihan D, Armenian S, et al. Defining cardiovascular toxicities of cancer therapies: an International Cardio-Oncology Society (IC-OS) consensus statement. European Heart Journal (2022) 43, 280–299.

with metastatic RCC is associated with improved survival outcomes⁸¹; it is unclear how much of this association may be driven by synergistic anti-neoplastic activity versus improved long-term CV outcomes and renal protection. Dihydropyridine calcium channel blockers (CCBs) have been found to be particularly useful in treating VEGF inhibitor-associated HTN, potentially through vasodilatory effects.^{12,82} The 2022 ESC guidelines recommend using ACE inhibitors or ARBs as first-line hypertensives and dihydropyridine CCBs as second-line hypertensives for cancer therapy-associated HTN.⁸⁰ For antineoplastic agents that are hepatically cleared via the cytochrome P450 3A4 (CYP3A4) pathway (eg, VEGF multi-kinase inhibitors, BTK inhibitors), the non-dihydropyridine CCBs verapamil and diltiazem should be avoided if possible as these drugs inhibit CYP3A4 and may result in increased plasma concentrations of those respective agents.⁸⁰

As in patients without cancer, treatment of HTN in patients undergoing anticancer therapy can include lifestyle modifications, such as reducing salt intake, limiting alcohol and caffeine use, and increasing physical activity as able.^{78–80} The decision for when to dose reduce, hold, or discontinue cancer therapy is complex and warrants multidisciplinary collaboration between oncologists/hematologists and cardiologists with consideration of factors such as the treatment intent and availability/cancer-related outcomes of other anti-neoplastic therapies without risk of HTN.

SUMMARY

With improvements in cancer-related survival due to a rapidly expanding armamentarium of more

effective antineoplastic agents, patients with cancer face increased risk of long-term CV sequelae. Diagnosing and treating cancer therapy-associated HTN is critical not only to avoid significant increases in BP that warrant dose reduction/discontinuation but also to prevent CV diseases such as ischemic heart disease, stroke, and other complications. Further studies are needed to understand the impact of cancer therapy-associated HTN on long-term CV disease in cancer survivors, particularly ones who received cancer therapies with curative intent. Multiple classes of cancer therapies are associated with increased risk of HTN, ranging from targeted therapies such as inhibitors of BRAF/MEK, VEGF, BTK, and RET; monoclonal antibodies (eg, targeting VEGF); hormonal therapies (eg, androgen deprivation therapy); and others. Understanding the incidence of and mechanisms underlying HTN from these agents may allow for more optimal diagnosis and treatment of this adverse event. Further studies are needed to determine appropriate management of HTN in patients with cancer due to the current limitations of extrapolating data derived from the general population.

CLINICS CARE POINTS

- Due to limited studies specifically investigating cancer therapy-associated HTN, most recommendations for management are derived from consensus-based guidelines.
- The 2022 IC-OS statement and the 2022 ESC guidelines have some nuanced differences in recommendations but largely recommend a threshold of BP greater than 140/90 mm

Hg to initiate antihypertensives for patients with cancer.

- IC-OS additionally recommends a lower BP threshold of 130/80 for patients with coexisting CV comorbidities, and ESC recommends consideration of treatment setting (eg, curative intent vs metastatic cancer) with higher BP thresholds for those with a worse prognosis.
- For antineoplastic agents that are hepatically cleared via the CYP3A4 pathway, the non-dihydropyridine CCBs verapamil and diltiazem should be avoided.

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Arrhythmia Challenges in Cardio-Oncology

High-Risk Therapies, Management, and Anticoagulation



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KEY WORDS

- Cardiotoxicity • Arrhythmia • Atrial fibrillation • Ventricular arrhythmia • Bradyarrhythmia
- Anticoagulation • Antiarrhythmics

KEY POINTS

- Cancer therapy-induced atrial fibrillation is a common co-morbidity and a rate control strategy with beta-blockers is the preferred management.
- Cancer patients with atrial fibrillation are both at increased risk of thromboembolic events and bleeding which complicates the use of anticoagulation, therefore, contributing to underutilization.
- Direct oral anticoagulants are the preferred agent in cancer patients.
- Ventricular arrhythmias are rare but life-threatening arrhythmias induced by cancer therapies and select patients may benefit from implantable cardiac defibrillators.
- Bradyarrhythmias from cancer therapies are typically benign and self-limiting but important to recognize as select patients may benefit from permanent pacing.

INTRODUCTION

Cardiovascular disease (CVD) and cancer are the leading cause of mortality in the United States. In 2021, there were 695,547 and 605,213 deaths due to heart disease and cancer, respectively.¹ With novel oncologic and cardiac therapies, survival has improved leading to increased life-expectancy albeit with chronic illness burden. Arrhythmia management in patients with cancer, whether active or in remission, can be quite challenging. In this review, we will discuss high-risk oncological therapies, prevention, and management of Atrial fibrillation (AF), Ventricular Arrhythmias (VA), and Bradyarrhythmias.

ATRIAL FIBRILLATION

Atrial Fibrillation in Cancer

Atrial fibrillation (AF) is the most common cardiac arrhythmia encountered among cancer patients. Patients at highest risk are those suffering from esophageal and lung cancers, as well as hematologic malignancies, such as multiple myeloma (MM), leukemia, and non-Hodgkin's lymphoma.² Breast cancer survivors who are less than 40 years of age appear to have a 2-fold higher risk of AF compared to patients without cancer.³ While cancer is an inherent nidus for AF, cancer therapy-related cardiovascular toxicity (CTR-CVT) is the leading cause of AF in cancer

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populations and has been shown to be a risk factor for AF in breast cancer populations.⁴ The sequelae of cancer including electrolyte derangements, malnutrition, hypoxia, and aging contribute to the development of AF.⁵ AF is often a chronic disease associated with an increased risk of thromboembolism, CVD, renal disease, and death.⁶ Given the rising cancer incidence and improving cancer survivorship, there is a growing need for clinicians to screen and manage AF.⁷

Atrial Fibrillation: High-Risk Therapies

The association of anthracyclines and atrial arrhythmias is well established. AF induced by doxorubicin was first described in a cohort of 256 patients in 1978, and occurred in 2.2% of the treated individuals.⁸ More recent studies have reported an incidence of new AF in 2.9% to 5% of patients, and an even higher incidence in a study by Onoue and colleagues, which reported 40% of the patients with post-anthracycline heart failure developed AF.^{9,10}

Cisplatin is among the most commonly used chemotherapies with CTR-CVT secondary to generation of reactive oxygen species and mitochondrial dysfunction.¹¹ Evidence for cisplatin-induced AF is associated with intrapericardial and intracavitary administration with an incidence up to 32%.¹²

5-fluorouracil (5-FU) and other antimetabolites have the potential to cause CTR-CVT, including AF. Studies have associated 5-FU with AF, especially when administered in combination with cisplatin.¹³ Capecitabine, a 5-FU pro-drug, has an AF incidence of 0.5% to 1.1%.^{14,15} Fludaurabine, when used alongside Busulfan and total body irradiation in hematopoietic stem cell transplantation, induced AF and atrial flutter (AFL) in approximately 8.3% of the patients.¹⁶

Androgen deprivation therapy (ADT) is an oral therapy for metastatic prostate cancer with an AF incidence of 11.1% over 3 years.¹⁷ Abiraterone has the most significant risk of atrial tachyarrhythmias.¹⁸ While prostate cancer patients typically have non-modifiable risk factors for AF (age and sex), abiraterone further increases the risk.⁵

Burton's tyrosine kinase (BTK) inhibitors are most often used to treat chronic lymphocytic leukemia and are perhaps the most pro-arrhythmogenic cancer therapies.¹⁹ Ibrutinib, a first generation BTK inhibitor, likely has the highest risk of AF with a 15-fold increase in risk and a 2 year incidence of 38%.²⁰ Several meta-analyses have confirmed ibrutinib's high-risk association: across 16 studies, the incidence was 5.8 over 100 person-years and

across 8 RCTs, the pooled relative risk of developing AF was 4.69 (95% confidence interval [CI], 2.17–7.64).^{21,22} Left atrial enlargement identified on electrocardiograms and pre-existing heart failure were noted to increase the risk of developing ibrutinib-associated atrial fibrillation.²³

Newer generation BTK inhibitors such as acalabrutinib, zanubrutinib, and pirtobrutinib exhibit higher BTK selectivity with lower risk of off-target effects.²⁴ Acalabrutinib has a lower reported rate of AF and AFL with a cumulative incidence of 5% to 7%.^{25,26} Zanubrutinib has an AF incidence of 1.9% to 4%.^{27,28} Pirtobrutinib appears to have the lowest AF incidence with 1% to 3.8%, thought to be due to its noncovalent mechanism of inhibition.^{29–31}

Other tyrosine kinase inhibitors (TKI) such as sorafenib, ponatinib, and CDK4/6 inhibitors have demonstrated risk of AF. Sorafenib when combined with 5-FU was observed to have an incidence of 5.1%.³² Ponatinib has an advertised risk for AF of 4% per the manufacturer label; however, a randomized open-label study only accounted for 1.5% incidence.^{33,34} CDK4/6 inhibitors were reported to have a 4.9% incidence of AF in a cohort of 1376 patients.³⁵

Immune checkpoint inhibitors (ICI) are known to cause myocarditis; however, their inductive risk of AF is relatively understudied. In a 30-patient case series evaluating ICI cardiotoxicity, 9 patients (30%) had new diagnosis of atrial fibrillation.³⁶ Additionally, in 35 patients with ICI-associated myocarditis, 9 patients (25.7%) developed AF or AFL.³⁷ While risk is demonstrated in myocarditis, studies are needed to fully elucidate the risk of AF with ICI.

Chimeric antigen receptor-T cell (CAR-T) agents are novel therapies administered for refractory and relapsed MM and lymphoma. The incidence of AF in CAR-T has been reported at a range of 2% to 8%.^{38,39} Among the highest are idecabtagene vicleucel with an incidence of 10.3% and axicabtagene ciloleucel with an incidence of 2.4%.^{40–42} Cytokine release syndrome, an adverse event from CAR-T, has been associated with tachyarrhythmias, but its association with AF remains understudied.⁴⁰

Cancer patients with history of radiotherapy exposure are more likely to develop AF and is associated with poor long-term outcomes.^{43,44} Risk factors for radiation-associated AF include targeting the pulmonary veins or sinoatrial node.^{45,46}

Numerous cancer-related therapies demonstrate evidence of inducing AF. Those with the highest risk appear to be BTK inhibitors, CAR-T, ADT, alkylating agents, and ICIs.

Management of Atrial Fibrillation in Cancer

Cardioversion

The acute management of symptomatic AF with hemodynamic instability should be direct current cardioversion (DCCV).⁴⁷ Post DCCV, patients are at increased risk of thrombus formation due to myocardial stunning and require anticoagulation (AC) for at least 4 weeks following cardioversion.⁵ Pharmacologic cardioversion can be considered in cancer patients.⁵ For cancer patients who are hemodynamically stable, cardioversion following transesophageal echocardiogram can be considered.⁵ Cardioversion commits patients to uninterrupted AC which can be challenging in cancer patients who often have pancytopenia, tissue friability, and overall increased bleeding risk. Additionally, the long-term efficacy of cardioversion of AF in cancer populations remains in question.⁴⁸

Rate control

Rate control with beta blockers (BB) is the preferred strategy and supported by the American Heart Association (AHA) and the European Society of Cardiology (ESC).^{47,49} Beta blockers are preferred over non-dihydropyridine calcium channel blockers (NDCCB), as they pose a number of drug interactions due to inhibition of cytochrome p450 (CYP) 3A4 (**Table 1**).^{22,47,49,50} NDCCB can be added to beta-blockers if additional rate control is required.²² Medication reconciliation should be addressed for patients on NDCCB as close monitoring and possibly dose reduction is required depending on drug metabolism (see **Table 1**).²²

Adverse drug interactions between chemotherapies and rate control agents can pose a challenge for AF management. CYP2D6 is inhibited by imatinib and abiraterone which can increase concentrations of metoprolol and carvedilol.⁵¹ Digoxin can be considered in rare cases, but special attention needs to be given to medications with P-glycoprotein inhibition such as ibrutinib.²² Ibrutinib-associated AF is a common yet challenging clinical scenario. Within the authors' institution, a rate control strategy with BB is preferred in these patients, given lower risk for drug interaction and prior demonstrated safety. Complications from the negative chronotropy and inotropy of rate control agents in cancer patients can be exacerbated by concomitant hypotension, dehydration, vasoplegia, and electrolyte derangements from malignancy and cancer therapy.

Rhythm control

Rhythm control is instituted in cases of symptomatic AF with inability to tolerate rate control or maintain sinus rhythm.⁴⁹ Studies have suggested early rhythm control can lower adverse events of

AF; however, this strategy remains understudied. Class IC antiarrhythmics like flecainide and propafenone have no evidence in cancer patients. Class III antiarrhythmics have very limited evidence. A retrospective study of 81 cancer patients found ibutilide safe and effective for acute cardioversion of AF and AFL without serious adverse events.⁵² Within the authors' center, rhythm control, by use of antiarrhythmic drugs, electrical cardioversion, or ablation is considered for ibrutinib-associated AF if the patient fails to have adequate symptom relief despite rate control, and if transitioning to another cancer therapy is not an option.

Ablation

Ablation can be considered for symptomatic persistent AF, albeit with considerations specific to cardio-oncology.⁴⁸ Prior to ESC and AHA cardio-oncology expert consensus, the role of AF ablation in cancer patients was not well studied.^{47,49} One retrospective study compared patients with recent cancer (within 5 years) to those without cancer and found no significant difference in 1-year rate of efficacy or repeat ablation.⁵³ In fact, patients with a history of cancer were less likely to require antiarrhythmics following ablation.⁵³ Finally, a meta-analysis of ablation in cancer survivors found no significant difference in efficacy between cancer and non-cancer patients, but reported an increased risk of bleeding in cancer survivors.⁵⁴

Anticoagulation for Atrial Fibrillation in Cancer

Risk of thromboembolism

Patients with active cancer are prone to thromboembolism (TE) due to a convalescence of inflammation, therapy adverse effects, malignancy pathophysiology, and surgery.⁵⁵ CHA₂DS₂-VASc stratifies risk of TE in AF patients which offers limited application in cancer patients, given malignancy and cancer therapy are not included as risk factors.⁵ Furthermore, cancer onset and stage heavily influence risk of TE especially within the first year of cancer diagnosis.⁵⁶

Despite these considerations, AHA expert consortium recommends a similar CHA₂DS₂-VASc risk profile to the general population: AC is recommended for scores ≥ 2 in men and ≥ 3 in women.⁴⁹ ESC recommends considering AC in those with CHA₂DS₂-VASc scores of 1 or 2 in the context of their cancer phenotype and cancer therapy.⁴⁷ Unfortunately, a recent study found CHA₂DS₂-VASc was not predictive of embolic risk in cancer patients but a score of 0 identified low-risk patients.⁵⁷ AC is under-prescribed in cancer patients with utilization rates of 44% to 57% for patients at risk of

Table 1
Drug interactions between common arrhythmogenic chemotherapies compared with antiarrhythmics

	Metoprolol	Carvedilol	Landiolol	Verapamil	Diltiazem	Digoxin	Flecainide	Propafenone	Amiodarone	Sotalol	Dofetilide	Ibutilide
Melphalan						X ₁ (Abs.)						
Fluorouracil						X ₁ (Abs.)	QTe↑	QTe↑	QTe↑	QTe↑	QTe↑	QTe↑
Capecitabine						X ₁ (Abs.)	QTe↑	QTe↑	QTe↑	QTe↑	QTe↑	QTe↑
Gemcitabine						X ₁ (Abs.)						
Doxorubicin (conventional)		Y↑ (PGP ₁)		Y↑ (PGP ₁)	Y↑ (3A4 ₁)	X ₁ (Abs.)		Y↑ (PGP ₁)	Y↑ (PGP ₁)			
Doxorubicin (liposomal)		Y↑ (PGP ₁)		Y↑ (PGP ₁)	Y↑ (3A4 ₁)	X ₁ (Abs.)		Y↑ (PGP ₁)	Y↑ (PGP ₁)			
Abiraterone	X↑ (2D6 ₁)	X↑ (2D6 ₁)					X↑ (2D6 ₁)					
Enzastamide				X↑ (3A4 ₁)	X↑ (3A4 ₁)	X↑ (PGP ₁)			X↑ (3A4 ₁)			
Aldesleukin	HoTN	HoTN	HoTN	HoTN	HoTN				HoTN		X↑ (CYP-S)	
Lenalidomide						X↑ (PGP-C)						
Ibrutinib				Y↑ (3A4 ₁)	Y↑ (3A4 ₁)	X↑ (PGP-C)						
Acalabrutinib				Y↑ (3A4 ₁)	Y↑ (3A4 ₁)							
Zanubrutinib				Y↑ (3A4 ₁)	Y↑ (3A4 ₁)	X↑ (PGP ₁)						
Pirtobrutinib				Y↑ (3A4 ₁)	Y↑ (3A4 ₁)	X↑ (PGP ₁)						
Sorafenib							QTe↑	QTe↑	QTe↑	QTe↑	X↑ (3A4 ₁)	QTe↑
Ponatinib				Y↑ (3A4 ₁)	Y↑ (3A4 ₁)							
Pazopanib	Y↑ (PGP ₁)			Y↑ (PGP ₁)	Y↑ (PGP ₁)		QTe↑	Y↑ (PGP ₁), QTe↑	Y↑ (PGP ₁), QTe↑	QTe↑	QTe↑	QTe↑
Sumatinib				Y↑ (3A4 ₁)	Y↑ (3A4 ₁)		QTe↑	QTe↑	QTe↑	QTe↑	QTe↑	QTe↑
Imatinib				Y↑ (3A4 ₁)	Y↑ (3A4 ₁)			X↑ (3A4 ₁)	X↑ (3A4 ₁)		X↑ (3A4 ₁)	
Nilotinib				XY↑ (3A4 ₁)	XY↑ (3A4 ₁)		QTe↑	QTe↑	QTe↑	QTe↑	QTe↑	QTe↑
Dasatinib				Y↑ (3A4 ₁)	Y↑ (3A4 ₁)		QTe↑	QTe↑	QTe↑	QTe↑	QTe↑	QTe↑
Crizotinib	Brady	Brady	Brady	Y↑ (3A4 ₁)	Y↑ (3A4 ₁)	Brady	Brady, QTe↑	Brady, QTe↑	QTe↑ (3A4 ₁)	QTe↑ (3A4 ₁)	QTe↑ (3A4 ₁)	QTe↑ (3A4 ₁)
Alectinib	Brady	Brady	Brady	Brady	Brady	Brady	Brady	Brady	Brady	Brady	Brady	
Brigatinib	HTN, Brady	HTN, Brady	Brady	Y↑ (3A4 ₁)	Y↑ (3A4 ₁)	Brady	Brady	Brady	Brady	Brady	Brady	
Lorlatinib				X ₁ (3A4↑)	X ₁ (3A4↑)	X↑ (PGP ₁)		X ₁ (3A4↑)	X ₁ (3A4↑)			
Ceritinib	Brady	Brady	Brady	Brady	Brady	Brady	Brady	Brady, QTe↑	Brady, QTe↑	Brady, QTe↑	QTe↑	QTe↑
Bortezomib	HoTN	HoTN	HoTN	Y↑ (3A4 ₁)	Y↑ (3A4 ₁)				HoTN			
Arsenic Trioxide	HoTN	HoTN	HoTN	HoTN	HoTN		QTe↑	QTe↑	QTe↑	QTe↑	QTe↑	QTe↑
Thalidomide	Brady	Brady	Brady	Brady	Brady	Brady	Brady	Brady	Brady	Brady	Brady	
Docetaxel				Y↑ (3A4 ₁)	Y↑ (3A4 ₁)	X ₁ (Abs.)						
Cabazitaxel				Y↑ (3A4 ₁)	Y↑ (3A4 ₁)	X ₁ (Abs.)						
Paclitaxel (conventional)	HoTN	HoTN	HoTN	Y↑ (3A4 ₁)	Y↑ (3A4 ₁)	X ₁ (Abs.)			HoTN	HoTN		
Paclitaxel (protein bound)				Y↑ (3A4 ₁)	Y↑ (3A4 ₁)	X ₁ (Abs.)						
Cyclophosphamide						X ₁ (Abs.)			X Tex↑			

Interaction Risk		Mechanism		Effects	
Effect	Avoid	(2D6 ₁)	CYP2D6 Inhibition	HTN	Hypertension
Effect	High Risk	(3A4 ₁)	CYP3A4 Inhibition	HoTN	Hypotension
Effect	Moderate Risk	(3A4↑)	CYP3A4 Inducer	Brady	Bradycardia
Effect	Low Risk	(CYP-S)	Cytochrome substrate interaction	QTe↑	QTe prolongation
		(PGP ₁)	P-glycoprotein Inhibition	X↑	Column Variable Drug Increases
		(PGP-C)	P-glycoprotein competition	X↓	Column Variable Drug Decreases
		(Abs.)	Decreased drug absorption	Y↑	Row Variable Drug Variable Increases

If no mechanism is listed, then literature is not available to describe the mechanism. CYP: Cytochrome P450. High-risk therapies should consider alternatives, moderate risk should be monitored, and low-risk therapies should be monitored in select patient populations.
Data from Interaction risk based on Lexicomp, Accessed March 14, 2024.

TE.^{58,59} However, cancer patients with AF pre-scribed AC had better clinical outcomes and reduced risk of all-cause mortality.⁵⁸

Risk of bleeding

Anticoagulation in the oncology population often confers risk of bleeding given complications of cancer therapy, bleeding diathesis, and malnutrition. Initiation of anticoagulation poses a significant challenge to oncologists and cardiologists alike. A meta-analysis by Balomenakis and colleagues suggested cancer patients with AF were at significantly higher risk of bleeding and all-cause mortality.⁶⁰ Conversely, AF patients with cancer have higher risks of all-cause mortality, major bleeding, and intracranial hemorrhage (ICH), but are not at higher risk of ischemic events.^{55,61} While hemorrhagic risk stratification tools are limited, ORBIT performed the best in predicting any risk of bleeding in AF in cancer pateints.⁶² Bleeding risk tools do not take account thrombocytopenia and intracerebral metastasis

which in part could explain the underutilization of AC for AF in cancer patients.⁶³ When recommending anticoagulation to patients on ibrutinib, patients’ medical history, including prior bleeding and TE history, as well as associated risk factors should be considered.

Oral anticoagulation

Warfarin, a vitamin K antagonist (VKA), was the first oral anticoagulant utilized for TE prevention in AF patients. Direct oral anticoagulants (DOACs) and VKAs have similar efficacy in preventing TE in cancer patients.^{61,64,65} However, a study of cancer patients found VKAs, but not DOACs, to be independently predictive of bleeding.⁵⁷ Furthermore, when compared to DOACs, VKAs are associated with higher mortality in cancer patients due to higher risk of bleeding and ICH.^{66–68} In these populations, apixaban and rivaroxaban have superior safety and efficacy profiles with apixaban having the lowest rate of bleeding.⁶⁷ Finally, DOACs are primarily metabolized by CYP3A4,

so it is imperative to consider drug interactions with chemotherapeutics (Table 2).^{50,69} DOACs offer a safer adverse effect profile compared to VKAs and are the preferred AC for AF in cancer patients.

Left atrial appendage occlusion

For patients with high TE risk and contraindications to long-term AC, left-atrial appendage occlusion (LAAO) can be considered.^{5,48} However, patients need to tolerate AC for at least 45 days post-LAAO and dual-antiplatelet therapy for 6 months.⁷⁰ In a small cohort of 55 patients following LAAO, there was no significant difference in ischemic stroke events or bleeding between patients with and without cancer.⁷¹ However, 2 studies reported patients with active cancer who received LAAO had higher odds of peri-procedural complications including TE, pericardial effusion requiring drainage, and major bleeding.^{72,73}

VENTRICULAR ARRHYTHMIAS

Introduction

Ventricular arrhythmias (VA) can often be life threatening leading to hemodynamic collapse. Cancer patients have an increased risk of ventricular tachycardia (VT) and ventricular fibrillation (VF). A study reported 32% of cancer patients with implantable cardiac defibrillators (ICD) experience VT/VF within first 2 years of cancer diagnosis while patients with metastatic disease were at a

significantly higher risk of VA at 41%.⁷⁴ Cancer therapy or drug-induced QTc prolongation increases risk of VA and is an important modifiable risk factor for prevention. Pharmacovigilance studies have raised concern for multiple agents, but those with robust evidence of VA include anthracyclines, arsenic trioxide, 5-FU, TKI, ICI, and CAR-T.

High-Risk Therapies

Anthracyclines are used for numerous cancers and are associated with QTc prolongation. Anthracyclines have a reported VA incidence of 6%, but VA often manifests years after exposure.^{75,76} One study found VA in anthracycline-associated cardiomyopathy (AACM) has a similar prevalence of VA in ischemic cardiomyopathy (ICM).⁷⁷ This suggests anthracycline's arrhythmogenicity is secondary to drug-induced cardiomyopathy, but more studies are needed to establish this association.

5-FU has multiple case reports of inducing VA by inciting premature ventricular contractions.^{78–81} In 1992, De Forni and colleagues reported 5-FU had a VA incidence of 1.1%.⁸² Capecitabine was initially reported to have a slighter higher VA incidence of 2.1%, but a more recent and robust prospective study reported a VA incidence of 7.3%.^{83,84} 5-FU and capecitabine's arrhythmogenicity is likely due to drug-induced coronary artery vasospasm which could subsequently lead to transient ischemia and VA.⁸⁵

Table 2
Drug interactions between arrhythmogenic chemotherapy and anticoagulation

	Warfarin	Enoxaparin	Rivaroxaban	Dabigatran	Apixaban	Edoxaban	
Fluorouracil	X↑ (2C9↓)						Interaction Risk Effect Avoid Effect High Risk Effect Moderate Risk Effect Low Risk
Capecitabine	X↑ (2C9↓)						
Gemcitabine	X↑ (2C9↓)						
Enzalutamide	X↓ (2C9↑)						
Aldesleukin	X↑ (CYP-S)						Mechanism (2C9↓) CYP2C9 Inhibition (2C9↑) CYP2C9 Inducer (3A4↓) CYP3A4 Inhibition (3A4↑) CYP3A4 Inducer (CYP-S) Cytochrome substrate interaction (PGP↓) P-glycoprotein Inhibition (PGP↑) P-glycoprotein Inducer
Ibrutinib	Hem	Hem	Hem	Hem	Hem	Hem	
Acalabrutinib	Hem	Hem	Hem	Hem	Hem	Hem	
Zanubrutinib	Hem	Hem	Hem	Hem	Hem	Hem	
Pirtobrutinib	Hem	Hem	Hem	X↑ (PGP↓)	Hem	X↑ (PGP↓)	Effects Hem Hemorrhage, mechanism unknown X↑ Column Variable Drug Increases X↓ Column Variable Drug Decreases Y↑ Row Variable Drug Variable Increases Y↓ Row Variable Drug Decreases
Sorafenib	INR↑						
Imatinib	X↑		X↑(3A4↓)		X↑(3A4↓)		
Nilotinib			X↑(3A4↓)		X↑(3A4↓)		
Dasatinib	Hem	Hem	Hem	Hem		Hem	
Crizotinib	X↑		X↑(3A4↓)		X↑(3A4↓)		
Alectinib	X↑						
Lorlatinib	X↓ (2C9↑)		X↓ (PGP↑)	X↓ (PGP↑)	X↓ (PGP↑, 3A4↑)	X↓ (PGP↑)	
Ceritinib	X↑ (2C9↓)		X↑(3A4↓)		X↑(3A4↓)		
Paclitaxel (conventional)	INR↓						
Paclitaxel (protein bound)	INR↑						
Cyclophosphamide	X↓						

If no mechanism is listed, then literature is not available to describe the mechanism. CYP: Cytochrome P450, INR: International Normalized Ratio. High-risk therapies should consider alternatives, moderate risk should be monitored, and low-risk therapies should be monitored in select patient populations

Data from Interaction risk based on Lexicomp, Accessed March 14, 2024.

Arsenic trioxide has been speculated to have the highest risk of QTc prolongation.⁸⁶ However, only a few reports of VA associated with arsenic trioxide exist.^{87–89} Tyrosine kinase inhibitors (TKIs) are known to be among the most arrhythmogenic anti-cancer therapies. Ibrutinib in particular has an incidence of VA from 596 to 788 events per 100,000 person-years.^{90,91} Acalabrutinib has a slightly lower rate with 394 events per 100,000 person-years.⁹² A recent study of pazopanib, sunitinib, imatinib, nilotinib, and dasatinib found QTc prolongation in 28.8% of the patients with 14 cases of life-threatening VA.⁹³

ICI-induced VA is speculated to be due to drug-induced myocarditis. Power and colleagues reviewed 147 patients with ICI myocarditis and reported 15% of the patients experienced 1 or more VA.⁹⁴ The most common was VT or VF, and 7.5% of the patients experienced life-threatening VA with complete heart block. Additionally, QRS duration is increased in ICI myocarditis and is associated with adverse cardiovascular outcomes.⁹⁵

Finally, CAR-T therapies have a variable risk of VA depending on the agent. A study found among 1475 hospitalized patients treated with CAR-T, 4.7% experienced VT.⁹⁶ However, a study focused on axicabtagene ciloleucel reported VA in only 0.7% of the patients.⁴⁰ Overall, the rate of VA in CAR-T varies and could be over reported in hospitalized patients. Evidence for VA from CTR-CVT is difficult to elucidate due to the multifocal nature and acuity of the disease.

Management of Ventricular Arrhythmias

QTc monitoring

In cancer populations, Fridericia correction is preferred for QTc calculation while Bazett correction is not recommended.^{97,98} All patients should receive a baseline ECG prior to cancer therapy initiation. An absolute safe QTc interval to start chemotherapy is less than 450 ms in men and less than 460 ms in women.⁹⁹ However, a limit of QTc less than 480 ms can be considered with periodic monitoring.⁴⁷ If initial QTc greater than 480 ms then it is recommended to consider alternative treatment and if initial QTc greater than 500 ms then it is recommended to choose an alternative treatment.⁴⁷

All patients with safe initial QTc intervals should be periodically monitored for electrocardiogram (ECG) changes.¹⁰⁰ Patients who are prescribed high-risk therapies should have QTc monitoring before and after all dose adjustments.¹⁰¹ Therapy can be continued with periodic monitoring as long as the patient is asymptomatic, the QTc is less than 480, the change in QTc remains less than 60 ms, and there have been no VA events.^{47,102} If

the QTc increases to 480 to 500 ms, the authors recommend continuing treatment with weekly ECG after second evaluation for modifiable risk factors, reducing QTc prolonging medications, and correcting electrolyte abnormalities.⁴⁷

Cardioversion and medical management of ventricular arrhythmias

Prior to initiating cancer therapy, baseline ECG should be obtained to assess for QRS and QT prolongation which can be associated with an increased risk of VA.¹⁰³ For patients with asymptomatic non-sustained VA, the best approach is to assess, monitor, and replete electrolytes with specific attention to magnesium, potassium, phosphorus, and calcium.^{49,104} For those with symptomatic non-sustained VT, cancer therapy should be dose reduced or discontinued after multidisciplinary discussions.¹⁰⁵

Patients with recurrent symptoms or life-threatening VA require emergent resuscitation, DCCV, along with discontinuation of their cancer therapy. For patients who are hemodynamically stable, a conservative approach can be taken with IV antiarrhythmics including amiodarone, lidocaine, or procainamide.¹⁰⁴

For prevention of VA, beta-blockers are first-line therapy due to their safer adverse effect and drug interaction profile. Evidence suggests beta-blockers can suppress VA in patients with structurally normal heart, which is common in CTR-CVT.¹⁰⁴ Ablation can be considered for patients with recurrent VA when antiarrhythmics are ineffective or intolerable.¹⁰⁴

Role of devices in cancer therapy-induced ventricular arrhythmias

Given improvement in prognosis and patient life-expectancy in cancer, ICDs could be a viable option when life expectancy is greater than 1 year.⁴⁷ In a study of patients with ICDs, Mazur and colleagues found similar survival rates amongst patients with AACM and ICM.⁷⁷ A study consisting of 149 cancer patients with ICDs implanted for secondary prevention found two-thirds of patients were alive at 3 years.¹⁰⁶

Multicenter Automatic Defibrillator Implantation Trial-Chemotherapy-Induced Cardiomyopathy (MADIT-CHIC) is a trial which investigated cardiac resynchronization therapy (CRT) implantation for CTR-CVT. The trial reported that patients with CTR-CVT with ejection fraction (EF) $\leq$ 35% and QRS greater than 120 ms and on optimized guideline direct medical therapy had a significant benefit in left ventricular (LV) ejection fraction, LV end-systolic volume, and LV end-diastolic volume with CRT.¹⁰⁷

It is vital to consider anatomic challenges in cancer patients who have undergone prior axillary lymph node dissections or concurrent central venous access.¹⁰⁸ It is also important to consider future needs for radiation therapy to areas where ICDs are typically implanted. In select cases, subcutaneous ICDs can be utilized when vascular access is difficult. Subcutaneous ICDs were non-inferior to transvenous ICDs and associated with fewer infectious complications.¹⁰⁹ Subcutaneous ICD implantation could be a more desirable option for cancer patients given cancer's associated risk of TE and infection.

BRADYARRHYTHMIA AND BLOCKS

Introduction

Beyond tachyarrhythmias, cancer therapy-induced bradyarrhythmias and conduction disease (CD) also impact cancer therapy. The most induced bradyarrhythmia reported is sinus bradycardia (SB). Long-term ECG monitoring is often employed to detect bradyarrhythmias. Management is often conservative, but some patients may benefit from permanent pacemakers.

High-Risk Therapies

Ibrutinib has some evidence for bradyarrhythmia. A study reported that 50 out of 2000 patients on ibrutinib developed CD in form of atrioventricular block and bundle branch blocks, with a respective incidence of 1.6% and 0.7%.¹¹⁰

Thalidomide is used to treat myeloma with an incidence of symptomatic SB up to 19%.¹¹¹ These patients sometimes required pacemaker implantation, but typically recovered after thalidomide discontinuation.^{111,112} Overall, there are numerous agents which can elicit bradycardia but the total burden of disease remains understudied.

ALK inhibitors are associated with bradyarrhythmias. These agents include the first generation crizotinib as well as the newer generation agents like alectinib, brigatinib, and lorlatinib.¹¹³ Rate of sinus bradycardia for crizotinib was reported to be 11% to 15%.^{114,115} Alectinib was originally reported to have a rate of sinus bradycardia of 6.6%.¹¹⁴ However, 2 more recent studies demonstrated significantly higher incidence rates of 42% to 51%.^{116,117} Brigatinib was associated with a similar rate of 8.8%, while ceritinib appeared to have the lowest rate of 2.3% to 3%.^{114,118,119} Providers may need to consider ceritinib as the ALK inhibitor of choice in patients with low baseline heart rates.

Reports of taxane-associated sinus bradycardia have not been investigated in the modern era. In the early 1990s, asymptomatic sinus bradycardia

was reported in 10.4% to 30% of patients; hence, patients did not require intervention.^{120–122}

Total body radiation and chest radiation have been associated with bradycardia and conduction disease, demonstrated by 2 case series of 9 total patients.^{123,124} Improvement in radiation targeting has made radiation-induced conduction disease rare. However, a recent study from 2022 showed a trend of breast cancer patients treated with radiotherapy more often required future pacemaker placement compared to those without radiation exposure ($P=.09$).¹²⁵

Management of Cancer Therapy-Induced Bradyarrhythmias and Blocks

Prior to initiating cancer therapy, clinicians must perform baseline ECG and medication reconciliation to minimize risk of drug-induced bradyarrhythmias. Initial evaluation and management of bradycardia secondary to CTR-CVT is largely similar to general populations and cardiology should be involved early in care.¹²⁶

For patients treated with ICIs who develop heart block, steroids may be indicated to address inflammation causing CD. Heart blocks can be the first manifestation of ICI myocarditis and a high index of suspicion should be given to patients who develop blocks on ICIs.³⁷ In a study amongst 42 patients with ICI myocarditis, 36% developed complete heart block.¹²⁷ Attention must be paid to PR intervals in patients on ICI therapy. If PR interval prolongs over 300 milliseconds, patients must be closely monitored, hospitalized, and initiated on IV steroids if there is concern for myocarditis.⁴⁷

Management of symptomatic high-degree blocks or conduction delays centers around multidisciplinary discussion regarding discontinuation or dose reduction of cancer therapy alongside telemetry monitoring.⁴⁷ Furthermore, permanent pacemakers (PPM) can be considered in patients with Class I indication and life expectancy greater than 1 year.¹⁰⁸ Device implantation necessitates a multidisciplinary discussion to consider patient prognosis, anatomy, and burden of disease.⁴⁷ PPMs have been shown to provide benefit even in populations aged greater than 80 years, so discussion regarding cancer prognosis plays a vital role in shared decision-making.¹²⁸ Significant device (PPM or ICD)-related complications during radiotherapy are exceedingly rare, and should not exclude patients who would otherwise benefit.¹²⁹ Finally, if patients experience symptomatic bradycardia and no alternative chemotherapies are available, it is reasonable to consider PPM placement in context of a meaningful prognosis.⁴⁷ However, it is

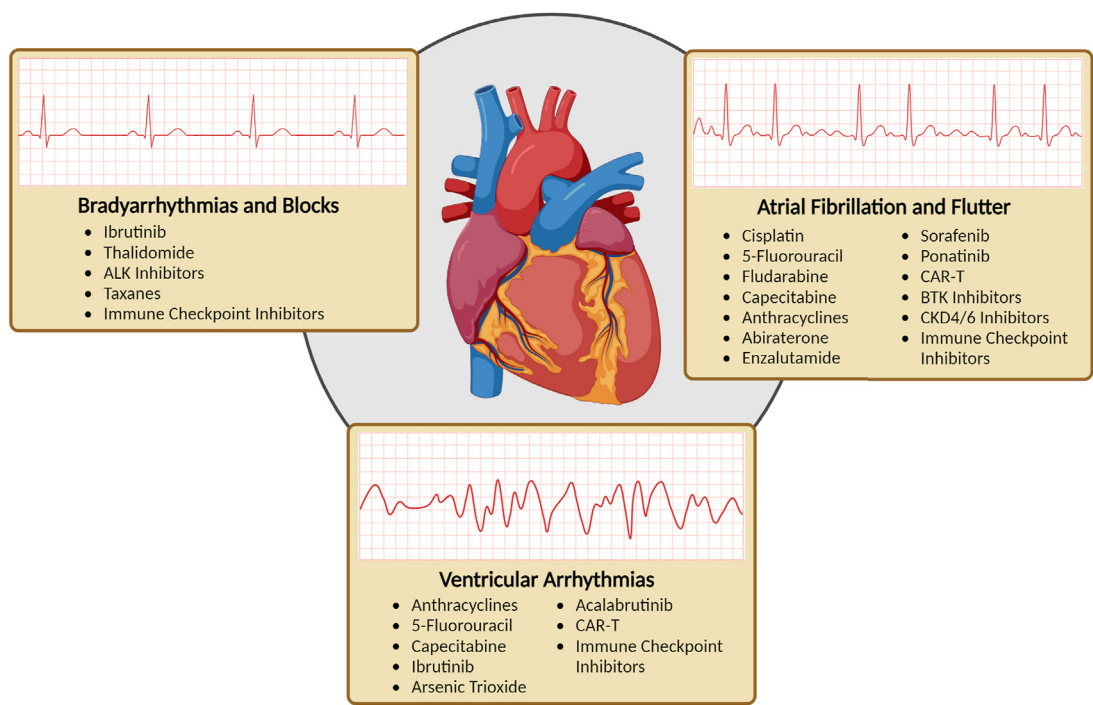


Fig. 1. High-risk arrhythmogenic anti-cancer therapies. (Created with BioRender.com.)

important for clinicians to be able to recognize as early as first-degree atrioventricular (AV) block in patients treated with ICIs, given the risk of transformation into fulminant myocarditis.

SUMMARY

In this review, we have discussed various arrhythmias induced by cancer therapies and their respective challenges and caveats to management (Fig. 1). Due to disease milieu, CTR-CVT, and therapy complications such as pancytopenia, these patients are at higher risk of both TE and bleeding with limited tools for risk stratification. Incidence and severity of arrhythmia depends on patient risk factors, comorbidities, baseline cardiac function, cancer staging, and cancer agents.

Currently, no studies exist evaluating the efficacy and safety of rhythm control agents in arrhythmias induced by cancer therapies. This issue could be addressed with cohort studies of high-risk treatments such as ibrutinib. Furthermore, given the complexity of anticoagulation in cancer patients, studies on AC strategies could elucidate the safest option. Given the limited utility of CHA₂DS₂-VASc in cancer patients, the authors emphasize the need for a thromboembolic risk stratification score for oncology population should be developed. Finally, there are scarce

studies on cancer survivors or while in remission and the long-term impact of arrhythmias.

Anthracyclines, TKIs, and BTKi are among the cancer therapies most likely to cause arrhythmias. Clinicians must closely monitor patients on immunotherapy who develop arrhythmias with consideration of ICI-induced myocarditis. Device therapy should be considered in patients with life expectancy over a year and warrants a multidisciplinary discussion between patients and their providers.

CLINICS CARE POINTS

- Atrial fibrillation thought to be induced by cancer therapy should be treated with a rate control strategy. Beta-blockers are preferred when patients are hemodynamically stable.
- The choice for anticoagulation in atrial fibrillation must be tailored to individual patient scenarios. CHA₂DS₂-VASc and bleeding risk tools have limited evidence for use in cancer patient populations. Direct oral anticoagulants are preferred but warfarin can still be used.
- There is limited evidence for ventricular arrhythmias induced by cancer therapy. However, it is important to pay close attention to QTc and QRS intervals after starting cancer therapy.

- Device therapies including permanent pacemakers and implantable cardiac defibrillators can be utilized in cancer patients, but their use should be tailored to individual patient scenarios and prognosis.

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Ischemic Heart Disease in the Cancer Population

Trends, Outcomes, Epidemiology, and Challenges in Diagnosis and Treatment



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KEYWORDS

• Coronary artery disease • Cancer population • Cardio-oncology • Population heart

KEY POINTS

- Cancer survivors have an increased risk of developing ischemic heart disease (IHD) compared with the general population.
- The population burden of IHD mortality and morbidity is increasing as cancer survivorship increases.
- A cancer diagnosis has also been identified as an independent predictor of all-cause readmissions after an acute myocardial infarction.
- People with IHD and cancer co-morbidity have poorer outcomes compared to those without cancer.

INTRODUCTION

Over recent decades, advances in the detection and treatment of cancer have led to significant improvements in cancer survival rates. In high-income countries, the survival rate for cancer has doubled in the past 40 years, with half of those diagnosed now expected to live at least ten years.¹ Importantly, survival rates in all stages of breast cancer combined and stage III prostate cancer or below exceed 90% at five years.² Longitudinal studies of cancer survivors have consistently reported significant rates of chronic morbidity, including elevated cardiovascular risk and premature mortality, with cardiovascular disease (CVD)

now being recognized as the leading cause of premature non-cancer mortality in this population.^{3,4}

Several factors account for the inter-relationship between these two conditions including the pro-thrombotic and pro-inflammatory states associated with the underlying malignancy.⁵ Secondly, cancer and heart diseases share risk factors, such as diabetes, hypertension, obesity, smoking, and low physical activity.⁶ Moreover, acute and chronic coronary vascular disease can be caused by direct toxicity from chemo-radiotherapy enhancing atherosclerosis, endothelial dysfunction, coronary thrombosis and coronary spasm.^{5,7} (**Fig. 1**).

Management of these patients poses unique challenges because cancer survivors have historically

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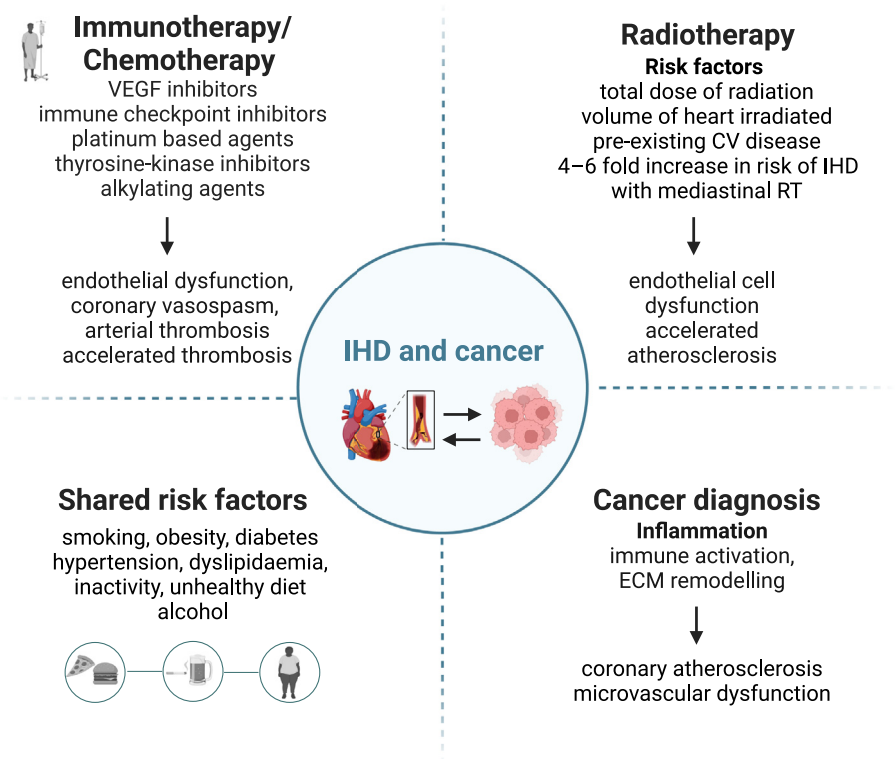


Fig. 1. Mechanisms of the association of cancer and IHD. The occurrence of IHD in cancer patients is due to many factors. CV, cardiovascular; ECM, extracellular matrix; IHD, ischemic heart disease; RT, radiotherapy; VEGF, vascular endothelial growth factor.

been excluded from most randomized control trials (RCT) of pharmacologic and interventional therapy in the treatment of ischemic heart disease (IHD). Therefore, there are limited trial data around treatment of these complex patients, with risk of both undertreatment and treatment complications.

Recognizing IHD in cancer patients is crucial, as it affects the long-term survival outcomes of these individuals and identifies those who are more susceptible to cardiotoxicity from cancer therapies. This ensures that cancer patients can safely undergo treatments for their condition while minimizing the risk of CVD-related complications.

This review therefore aims to provide clinicians with an overview of the following topics: (1) the trends, outcomes and epidemiology of IHD in cancer patients and (2) the challenges in the diagnosis and treatment of IHD among this vulnerable group.

DISCUSSION

Trends and Epidemiology

Prevalence of ischemic heart disease among different cancer types

In 2020, there were 19.3 million incident cancer cases⁸ and 10.6 million incident IHD cases

worldwide.⁹ Compared to the general population, cancer survivors have a 1.3 to 3.6 times greater chance of having IHD and a 1.7 to 18.5 fold higher risk of developing atherosclerosis risk factors.¹⁰ The highest incidence of IHD is observed in the first decade of survival (44%)¹¹ and continues to increase in the second decade.¹²

Survival rates for different cancer types have improved due to advancements in treatment and early detection. For instance, prostate cancer has a 5-year survival rate of over 95% when diagnosed at stages 1 to 3,² whilst lung cancer, has a lower 5-year survival rate of approximately 20% in developed regions.¹³ Using data from the National Cancer Registration Dataset of England, Battisti and colleagues¹⁴ analyzed 634,240 patients to determine the prevalence of CVD, including IHD. Non-small cell lung cancer (NSCLC) patients had the greatest observed prevalence of IHD (22.0%; 95% CI: 21.7%–22.3%), according to the data. Numerous studies have provided evidence of a substantial correlation between lung cancer and IHD, with patients with lung cancer having an 89% higher risk of the disease than those without it.¹⁵

Prostate cancer patients showed a significant risk of IHD in the first six months following diagnosis

(standardized incidence ratio [SIR] 1.41; 95% CI 1.33 to 1.49), with the risk persisting for up to a decade.¹⁶ Among cancer survivors, lung and prostate had the greatest proportion of CV deaths due to IHD (67.8% and 58.3%, respectively).¹⁷

Breast cancer patients generally have a favourable prognosis with a 5-year survival rate exceeding 90% in most countries, largely due to effective screening programs and improvements in therapy,² but this group have an increased risk of developing IHD, especially in the first six months after cancer diagnosis.¹⁶ Current research indicates that women irradiated for left-sided breast cancer receive 2-3 times greater doses to the heart compared to women irradiated for right-sided breast cancer.¹⁸ Furthermore, several studies show a 20% higher risk of IHD after RT in left-sided breast cancer¹⁹ and a higher incidence of stenosis in the left anterior descending artery (LAD) following left-sided RT.²⁰ Newer RT techniques have refined the radiation field with lower cardiac exposure, and the IHD risks associated with RT are expected to reduce in the coming years.

Colorectal cancer has a survival rate of around 65%, varying by stage at diagnosis.²¹ A study conducted in Taiwan showed that the risk of IHD significantly increased for up to nine years following a diagnosis of colorectal cancer.¹⁸ The CHD risk was highest within the first year after diagnosis (SIR 1.73, 95% CI, 1.65–1.81).²²

In a large Swedish registry, patients with leukemia, multiple myeloma (MM) and non-Hodgkin lymphoma (NHL) had a marked risk of IHD in the first six months after diagnosis (SIR 2.81, 2.17 and 1.36, respectively).²³ Therefore, understanding and addressing cancer survivors' cardiovascular health is paramount.

Incidence and outcomes of acute myocardial infarction in cancer

Patients with cancer have an increased risk for arterial thromboembolism, including myocardial infarction (MI) and ischemic stroke,²⁴ particularly immediately after their cancer diagnosis. This elevated risk varies by cancer type and stage. Lung cancer patients experience the highest excess risk, with a six-month cumulative incidence of 8.3%, followed by patients with non-Hodgkin lymphoma, who have a six-month cumulative incidence of 5.4%. Additionally, the risk also correlates with the cancer stage, being higher in advanced stages.²² In the study performed by Navi and colleagues,²⁴ stage 4 cancer patients had a relative hazard of 3.6 for arterial thromboembolism, highlighting the critical interplay between cancer severity and cardiovascular risk. Findings from a large multicentre

diagnostic study indicated that patients with active or past cancer presenting to the emergency department (ED) with acute chest pain had a 1.5 times higher prevalence of acute myocardial infarction (AMI) compared with patients without cancer and required more extended hospitalization.²⁵

The Nationwide Inpatient Sample (NIS) analysis²⁶ which included approximately 6 mil. percutaneous coronary intervention (PCI) procedures among patients with cancer showed that metastatic cancer was independently associated with poorer outcomes, higher mortality and PCI complications. The study underlines that cardiologists should treat cancer patients with ACS using standard care therapies. However, these are challenging, as certain malignancies are associated with worse outcomes. This was particularly evident in patients with lung cancer which had significantly higher in-hospital mortality (OR 2.81) and colon cancer, which carried the highest risk of bleeding (OR 3.65) compared to other cancer types. In the same study, cancer patients undergoing PCI were older and carried a greater burden of comorbidities.

Prior analyses have consistently shown lower rates of invasive evaluation and treatment of AMI in cancer patients compared to those without cancer, including patients presenting with STEMI.²⁷ The rates for invasive coronary angiography (82% vs 90%), PCI (72% vs 81%), or coronary artery bypass grafting (CABG) (0.9% vs 1.5%)²⁵ were all lower in cancer patients.²⁸ Furthermore, the use of evidence-based medications including ACE-inhibitors/angiotensin receptor blockers and high-intensity statins, were also lower in cancer patients. The study concluded that while prior cancer diagnosis impacts the quality of AMI care and survival, these differences are primarily driven by patient age and comorbidities.

Moreover, existing evidence has shown decreased adherence to guideline-recommended treatment, including antiplatelets, statin and neurohormonal blockade in cancer patients with systolic dysfunction, along with higher readmissions for heart failure (HF) after STEMI compared with patients without cancer.²⁹

A major gap in current knowledge is the ability to effectively risk-stratify which types of cancer may derive more harm than benefit from PCI and the subsequent antiplatelet treatments. This gap underscores the need for individualised treatment plans and close collaboration between oncologists and cardiologists to optimise care for this high-risk patient population. To address these challenges, further research and improved guidelines are needed to understand better the complex interplay between cancer types and

cardiovascular treatments, and to develop more refined risk assessment tools for this growing patient population.

Challenges in Diagnosis of Ischemic Heart Disease

The recently published 2022 cardio-oncology guidelines from the European Society of Cardiology (ESC) serve as a fundamental reference for cardiologists who manage cancer patients.²⁸ Yet, numerous points need to be addressed in the future to solidify the empirical support underpinning many of these recommendations. The diagnosis of IHD in patients with cancer should comply with the guidelines on ACS³⁰ and chronic coronary syndrome (CCS)³¹ and it should be based on the same principles as in patients without cancer (Fig. 2).

The clinical presentation of IHD can be atypical in cancer patients,³² often obscured by the effect of cancer and its treatment or by the patients' older age and their co-morbidities. NSTEMI (non-ST-elevation myocardial infarction) is the most common manifestation of an ACS in cancer patients, with the most frequently reported symptom being shortness of breath.³³ About 20% of cancer patients with ACS experience hypotension and heart failure.³⁴ Frequently, the administration of analgesics to alleviate cancer-related pain can obscure the presence of chest pain.³⁵

The diagnosis of IHD is also complicated by the fact that troponin levels in oncological patients are often elevated. There are far greater numbers of potential explanations for troponin elevation in cancer patients compared to individuals without cancer. This includes myocardial ischemia secondary to reduced oxygen supply or increased

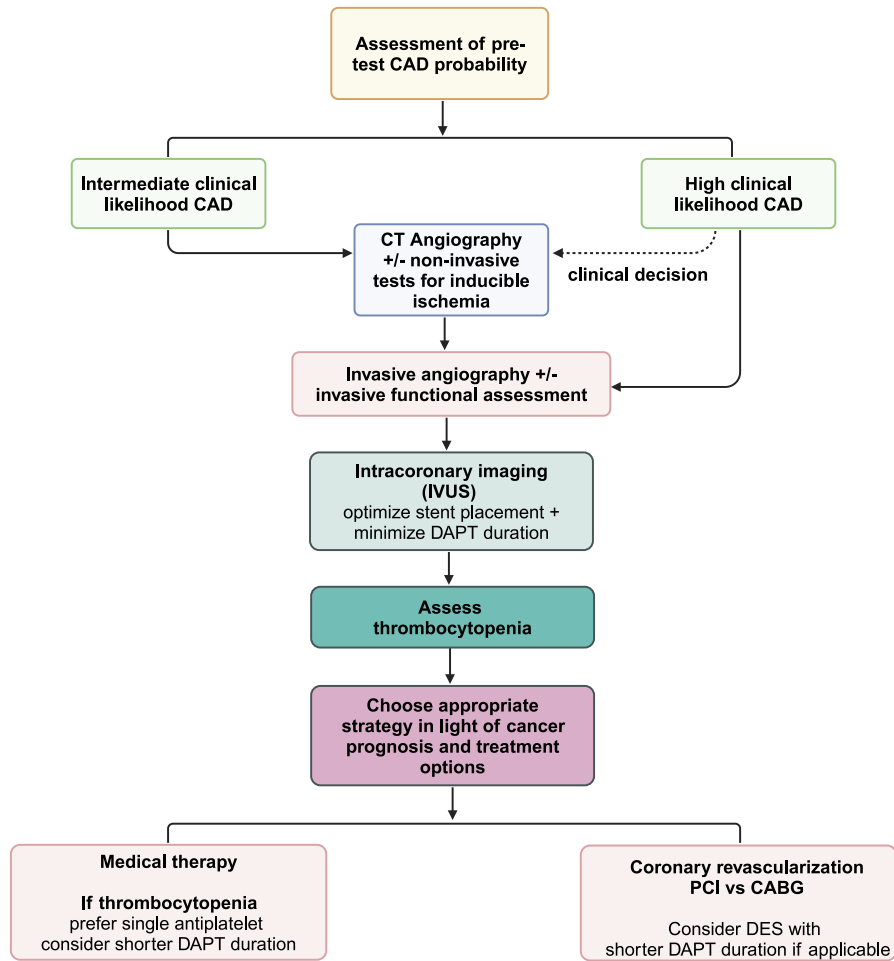


Fig. 2. Diagnosis and treatment of chronic coronary syndromes (CCS) in patients with cancer. CABG, coronary artery bypass graft; CAD, coronary artery disease; DAPT, dual antiplatelet; DES, drug eluting stent; PCI, percutaneous coronary intervention.

oxygen demand or by direct cardiac damage secondary to chemotherapy.³²

Cancer patients with vasospasm due to fluoropyrimidines can be challenging to diagnose because they can present with nontypical chest pain without ECG changes or a rise in cardiac troponin levels.³⁶ The risk of Takotsubo cardiomyopathy is also increased in cancer patients. The potential triggers in cancer patients include emotional stress from the diagnosis and physical stress from various cancer therapies.³⁷

Immune-check inhibitors (ICIs), widely used in various cancer fields, present additional diagnostic challenges. While ICIs improve the outcomes of a variety of hematological and solid tumors, their use is associated with a substantial risk of immune-related adverse effects.³⁸ Myocarditis is a severe complication of ICI with a high mortality rate, which can mimic ACS. Clinical data suggest that whilst the overall incidence of cardiac adverse events is low in patients treated with ICIs, the high mortality rate (24.6%) associated with these events is a significant concern.³⁹ When ICI-associated myocarditis is suspected, TTE and CMR with modified Lake Louise criteria are recommended in all patients.²⁹ If CMR is not available, the guidelines recommend cardiac fluorodeoxyglucose PET or endomyocardial biopsy in suspected cases and non-confirmed invasively.²⁸

Coronary angiography is the gold standard for diagnosing IHD and evaluating coronary vascular status.⁴⁰ Cardiac MRI (CMRI) and coronary computed tomography angiography (CTA) can help diagnose IHD and systolic dysfunction caused by ischemia.²⁸ Coronary CTA should be considered as an alternative to invasive coronary angiography in the context of troponin elevation, particularly in those who are at high risk of bleeding complications.²⁸ It can also improve the accuracy of CAD estimation for asymptomatic patients by utilising the coronary artery calcification score (CAC).⁴⁰

Screening for Ischemic Heart Disease in Cancer Survivors

Atherosclerotic cardiovascular disease risk stratification

Calculation of atherosclerotic cardiovascular disease (ASCVD) risk using a clinical score such as the American College of Cardiology/American Heart Association 10-year risk estimator, the Q-RISK3 algorithm or the European SCORE (Systematic Coronary Risk Evaluation) charts, is recommended.⁴¹ ASCVD risk scores may be used for guiding primary prevention. However they have not been validated in cancer population or cancer

survivors.⁴² Consequently, these scores might underestimate the cardiovascular risk in survivors, potentially resulting in under-treatment for this susceptible group of patients.⁴²

In cancer patients with an intermediate estimated risk of CVD based on clinical scoring, and especially in those with a current or past cancer diagnosis, there may be a need for additional evaluation using screening instruments like CT scans for CAC quantification or other imaging techniques might be necessary for accurate risk stratification.

Role of cardiac computed tomography in risk stratification of cancer patients

Estimation of CAC burden can be obtained from either CT of the chest or ECG-gated cardiac multi-detector CT (MDCT) has emerged as a powerful tool for subclinical CAD in asymptomatic patients, leading to better informed clinical decision-making.⁴²

A significant number of oncology patients undergo non-cardiac, non-gated CT as part of their cancer screening, cancer diagnosis, staging and treatment planning. Pre-treatment coronary artery calcium (CAC) score of more than 0 has been associated with an increased risk of adverse cardiac outcomes among patients undergoing RT and post-chemotherapy for patients with breast⁴³ or lung cancer.⁴⁰

Findings indicate that CAC is prevalent in 69% of patients with early-stage non-small cell lung cancer diagnosis without known atherosclerotic CVD.⁴⁴ Despite the high prevalence, the incidental findings of CAC on NGCCT rarely resulted in the prescription of preventive therapies such as statins or aspirin. Specifically, only 2.1% of statin-naïve patients initiated these therapies after CAC was identified, representing a missed opportunity to modify cardiovascular risk among patients predisposed to adverse cardiovascular events.

Considering the potential implications of pre-treatment CAC scores in cancer patients, a 2022 expert consensus document from the Society of Cardiovascular Computed Tomography (SCCT) provided a strong recommendation for the calculation of a CAC score for all cancer patients using their routine non-gated chest CT or CAC scan before initiation of therapy.⁴⁵

The current recommendation is to incorporate the CAC score as a decision-making tool to reclassify CV risk and guide statin therapy in patients with borderline to intermediate (5%–20%) 10-year ASCVD risk.⁴⁵ For patients with a risk of less than 5%, re-evaluation in 1 year is recommended. For patients with a greater than 20% risk, high-intensity statin and aspirin treatment is

recommended (the latter with caution especially in thrombocytopenic patients).⁴⁵

Other imaging modalities

Screening for coronary heart disease should be considered in high-risk patients who have received chest RT.²⁸ The American Society of Echocardiography (ASE), and European Association of Cardiovascular Imaging (EACVI) recommend screening for radiation-induced heart disease with echocardiography ten years after treatment and then at five-year intervals thereafter in asymptomatic survivors.⁴⁶ In patients deemed high risk for radiation-induced heart disease, the recommendation is to screen with echocardiogram at five years post-treatment followed by non-invasive stress testing every five years.⁴⁶

Challenges and Management of Ischemic Heart Disease

Primary and secondary prevention

Aggressive risk factor modification and implementing healthy behaviors (including smoking cessation, recommended physical activity, a healthy diet, and maintaining a healthy weight) significantly decrease the risk of future CV events.²⁸ Oncologists, cardiologists, and primary care physicians should collaborate to emphasize the importance of preventive measures in this patient group.

Therapeutic management of IHD in cancer patients focuses on cardioprotective medical therapies, PCI and surgical coronary revascularization. The pharmacologic treatment of IHD should not differ from that of the general population. Aspirin, angiotensin-converting enzyme inhibitors (ACEi)/angiotensin-receptor blockers (ARB), beta-blockers, and statins are the primary cardioprotective medications used in cancer survivors with IHD if not contraindicated.^{30,47} Long-term statin use in cancer survivors is associated with a significant decrease in cancer-related mortality.³⁴ In the BleeMACS multicentre registry, beta-blockers, ACEi/ARB, and statins were under-prescribed in patients with cancer, even though these medications were shown to be cardioprotective.⁴⁸

Careful considerations should be taken of the potential drug interactions between cardioprotective medications and chemotherapeutic agents and their potential clinical significance. The combined use of beta-blockers with tyrosine kinase inhibitors (TKI) can cause additive bradycardia. Furthermore, carvedilol could increase chemotherapy drug concentration when used in combination with doxorubicin, paclitaxel, vincristine, and vinblastine due to moderate inhibition of P-glycoprotein.⁴⁹

Coronary revascularization

In patients with active cancer presenting with multivessel or complex CAD, the decision between CABG and PCI presents unique challenges. While CABG may be preferred in cases of critical left main disease, triple vessel disease or complex coronary anatomy due to its potential for improved long-term outcomes, it often requires a significant recovery period. This recovery time can delay critical life-prolonging or life-saving cytotoxic therapies, which is a considerable concern for patients with active cancer.

The ESC guidelines highlight retrospective data that cancer patients have invasive coronary intervention less frequently than non-cancer patients and PCI is associated with reduced in all-cause mortality in patients following ACS compared to medical management alone.²⁸ An early invasive management with coronary angiography and PCI is recommended for patients with cancer and STEMI or high-risk NSTEMI where life expectancy is greater than six months²⁸ or, irrespective of life expectancy if the patient is unstable.²⁷ If patients have acute complications of ACS (pulmonary oedema, cardiogenic shock, ventricular arrhythmias), PCI can be considered as a rescue option.²⁸ When life expectancy is shorter than months, and in NSTEMI without ongoing ischemia or haemodynamic impairment and/or with a high risk of bleeding, a conservative strategy can be considered.

The current ESC guidelines also recommend using third-generation drug-eluting stents (DES) in cancer patients due to their lower risk of restenosis and in-stent thrombosis. DES also allows for a shortened duration of dual antiplatelet therapy (DAPT).²⁸ Thrombocytopenia is a major concern prior to cardiac catheterization in more than 10% to 25% of cancer patients. PCI can be performed with a good haemostatic technique and minimal bleeding risk at counts more than 30,000/mm³.²⁸ Furthermore, the ESC cardiology guidelines²⁸ stress the importance of intravascular imaging, including intravascular ultrasound (IVUS) to ensure appropriate stent expansion. IVUS can assist in determining antiplatelet therapy, especially where there is concern about increased bleeding risk.

For patients with CCS and active cancer, the choice to proceed with invasive versus conservative management in subjects with CCS and active cancer should be carefully planned by an appropriate MDT discussion.³¹ Coronary artery bypass grafting (CABG) is generally indicated in patients with critical left main disease, triple vessel disease, or those with complex coronary anatomy, whose expected survival is more than 12 months following an MDT discussion.²⁸

For oncological patients who have undergone mediastinal radiotherapy, technical difficulties may arise due to the coexistence of mediastinal scarring and internal mammary artery and valvular disease.⁵⁰ In one study, the 5-year post-operative survival rate exceeded 50% in patients with solid tumors and concomitant IHD undergoing CABG.⁵¹ This indicates that cardiac surgery can be considered an option, particularly for individuals with a good cancer prognosis.

In conclusion, the decision-making process for managing multivessel/complex CAD in cancer patients must balance the immediate cardiovascular benefits against the potential delay in critical cancer therapies. While CABG may offer superior long-term cardiovascular outcomes, PCI may be preferred in scenarios where cancer survival or recurrence is the primary concern. Further studies are required to elucidate the optimal strategies across different stages and types of malignancies.

Antithrombotic and medical therapy

While active cancer significantly increases the risk of bleeding, the presence of thrombocytopenia should not preclude the use of antiplatelet therapy in the case of ACS, since treatments with aspirin and/or clopidogrel have been shown to improve outcomes in ACS patients with low platelet counts.⁵² Omission of antiplatelet agents is justified when the platelet count is critically low, that is, less than 10 000/ μ L, less than 30 000/ μ L, and

less than 50 000/ μ L for aspirin, clopidogrel, and prasugrel or ticagrelor, respectively.²⁸

The ESC guidelines advocate DAPT for 1 to 3 months after PCI for ACS in cancer patients with a shorter duration of DAPT in those with very high risk of bleeding. While individual patient factors must be considered, clopidogrel is the preferred P2Y12 antagonist for managing ACS in patients with active cancer, due to its lowest percentage of hemorrhagic complications.²⁸ Additionally, newer P2Y12 antagonists, such as ticagrelor and prasugrel, should be avoided due to their high bleeding risk and the lack of literature on this patient group (**Table 1**).

Studies have shown that aspirin improved overall survival in cancer patients with ACS and thrombocytopenia with a 1-week survival rate close to 90% (6% in patients who did not receive it).⁵³ For patients who require anticoagulation due to atrial fibrillation, the standard treatment approach combines a direct oral anticoagulant with a single antiplatelet medication (ideally clopidogrel). This is after a period of up to 1 week on triple antithrombotic therapy, aiming to reduce the risk of bleeding.²⁸

In cancer patients with CCS, the DAPT duration following PCI should be as short as possible, similar to the DAPT regimen following PCI for ACS. Additionally, for patients with CCS who have confirmed CAD, but no history of AMI or coronary revascularization, the guidelines suggest that using aspirin or clopidogrel may be an option.^{28,30}

Table 1
Evidence gaps on IHD management in cancer and potential solutions

Evidence Gap	Potential Strategies to Address Knowledge Gap
Limited randomized controlled trials evidence addressing the efficacy of antithrombotic therapy in cancer patients with ACS	Randomized controlled trials that include cancer patients to gather specific data on antithrombotic therapy efficacy
Lack of evidence on the use of newer P2Y12 antagonist such as ticagrelor and prasugrel in cancer patients	Randomized controlled trials and multicentre retrospective or prospective studies to evaluate the safety and efficacy of newer P2Y12 antagonists in cancer patients
Lack of evidence on the optimal duration of dual antiplatelet (DAPT) in cancer patients post-PCI	Randomized controlled trials to guide the optimal DAPT duration in cancer patients, considering their high bleeding risk
Lack of clear guidelines for managing CCS in cancer patients, including choice between invasive vs conservative management	Develop and update clinical guidelines specific to cancer patients with input from MDTs
Insufficient data on interactions between cardiovascular and oncological therapies	Conduct pharmacokinetic and pharmacologic studies to understand drug interactions better
Limited information on outcomes of PCI and CABG in cancer patients	Observational studies and meta-analyses to gather more data on PCI and CABG outcomes in cancer patients

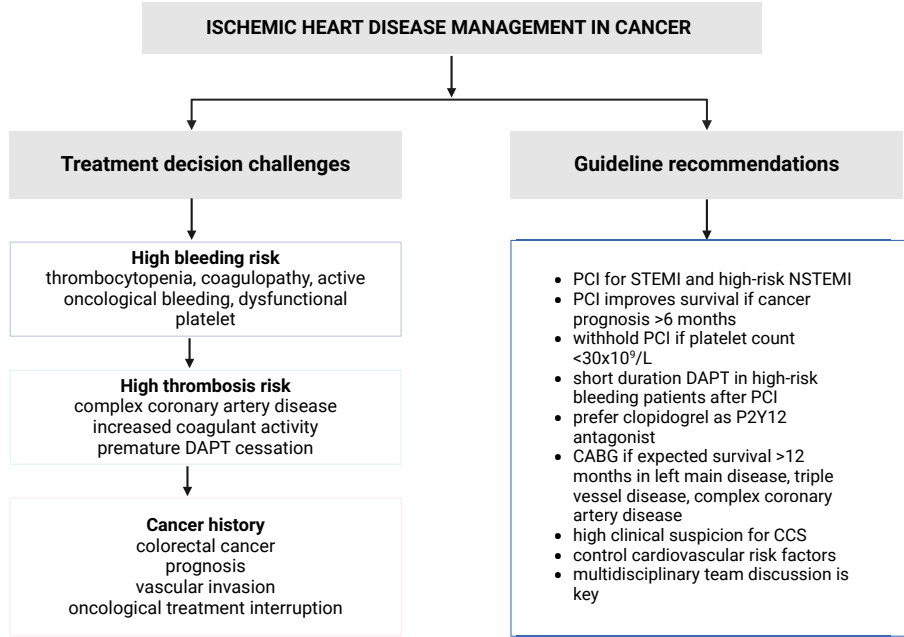


Fig. 3. Management of ischemic heart disease in patients with cancer.CABG, coronary artery bypass grafting; CCS, chronic coronary syndrome; DAPT, dual antiplatelets; NSTEMI, non-ST segment elevation acute coronary syndrome; PCI, percutaneous coronary intervention; STEMI, ST segment elevation myocardial infarction.

Given the complexity of decision-making about antithrombotic therapy after an ACS/CCS with concomitant cancer, MDT discussion is key. This discussion should engage all specialists involved in the patient’s care and meticulously evaluate factors such as life expectancy, additional comorbidities such as thrombocytopenia, increased thrombosis risk, and potential interactions between drugs used in ACS/CCS management and antineoplastic agents.^{28,30–32} If acute ischemia is triggered by cancer therapy, an urgent MDT review should be conducted at the time of ACS diagnosis to consider alternative oncological therapies²⁸ (Fig. 3).

SUMMARY

The number of cancer survivors has grown substantially in the last two decades, in whom IHD is an important source of morbidity and premature death. The diagnosis of IHD in this population is challenging. While standard treatments are recommended for treatment of acute events, many cancer patients and survivors are suboptimally-treated. There is a need for increased awareness of the association of cancer therapies and acute and chronic IHD presentations, with a better understanding of alternative cancer and IHD management strategies in such situations. Furthermore, the decision for revascularization should take a

holistic approach, considering cancer status and treatment plans as well as bleeding and thrombosis risk. Such decisions should take an MDT approach centred on patient preference.

CLINICS CARE POINTS

- As cancer survivorship improves, it becomes increasingly important to tailor the management of ACS to the overall prognosis of the cancer patient.
- Management of IHD in cancer should be based on guidelines with appropriate individualized MDT discussion.
- PCI improves survival in cases of ACS and therefore an invasive strategy should be preferred if survival greater than or equal to 6 months is expected.
- If the expected survival is less than 6 months and/or bleeding risk is very high, a conservative strategy should be considered.
- Retrospective data have reported that over use of PCI in cancer patients with STEMI is associated with higher mortality rates in certain populations.
- Patients who undergo invasive therapies generally have better outcomes, although there is obvious selection bias in these cohorts

depending on overall prognosis and other factors related to cancer treatment, course and comorbidities.

- The preferred P2Y12 inhibitor for ACS patients with active cancer is clopidogrel.
- If acute ischemia is provoked by cancer therapy, alternative cancer therapies should be considered after MDT discussions.

DISCLOSURE

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Cardiovascular Health in Breast Cancer Survivorship Care



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KEYWORDS

• Cardio-oncology • Survivorship • Breast cancer • Cardiac disease

KEY POINTS

- Improved breast cancer treatments have led to higher survival rates, but survivors face an increased risk of cardiovascular morbidity and mortality.
- The field of cardio-oncology has emerged to balance cancer treatment efficacy with cardiovascular health, emphasizing regular monitoring and proactive interventions.
- Effective survivorship care requires collaboration among oncologists, cardiologists, primary care providers, and pharmacists, with shared-care models and telehealth options enhancing coordination and patient outcomes.

INTRODUCTION

Improved screening strategies and advances in breast cancer treatment have led to significant improvements in clinical outcomes for patients with breast cancer. There are now 7.8 million women worldwide alive at least 5 years after a breast cancer diagnosis.¹ Although gains in life expectancy are to be applauded, it should be recognized that cancer survivors are now at increased risk of non-cancer related morbidity and mortality including cardiovascular disease.² The majority of women diagnosed with breast cancer (median age 63 years) have at least one cardiometabolic comorbidity. Post-menopausal women with early-stage breast cancer, several years out from their diagnosis, have a greater risk of mortality from cardiovascular disease than recurrence of their cancer.³ Breast cancer treatment options, including systemic therapy with anthracyclines, HER-2 targeted therapies, immunotherapy, hormonal therapy, and radiation, can exacerbate pre-existing and/or new

cardiovascular risk factors resulting in significant cardiovascular disease⁴ which may occur during, or many years after, completion of cancer treatment. Cardio-oncology is a rapidly developing subspecialty of medicine that has emerged to enhance collaboration across the disciplines of oncology and cardiology to provide optimal cancer care without compromising cardiovascular health (Fig. 1).

Cancer survivorship begins at the time of a cancer diagnosis. The aim of this review is to focus on strategies to optimize cardiovascular health in breast cancer survivors incorporating the American Society of Clinical Oncology (ASCO) eight core tenets of survivorship: (a) facilitate team medicine by connecting oncology, primary care, subspecialists and programs, researchers, and patients and caregivers; (b) educate patients and support them in self-management; (c) mitigate toxicities; (d) manage comorbidities; (e) promote healthy behaviors and wellness; (f) improve health equity; (g) provide clear personalized follow-up;

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Diagnosis

Modifiable CV risk factors



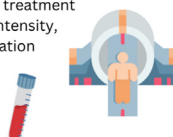
Systemic therapy type, duration, intensity



Non-modifiable CV risk factors

Surveillance

Based on treatment type, intensity, duration



Post

Risk stratification with HFA-ICOS at 12 months and 5 years

Modifiable CV risk factors yearly

Lifestyle counseling



Fig. 1. Breast cancer survivorship.

and (h) provide ongoing opportunities for participation in research as the standard of care.⁵

THE TEAM

- Comprehensive care in breast cancer survivorship necessitates the interaction and collaboration of multiple health care providers and yet there is little evidence in the literature to support the adoption of this approach in clinical practice.
- Survivorship plans advocated by organizations like the American Society of Clinical Oncology (ASCO) focus on early cancer recurrence detection, yet the importance of a holistic approach to cancer care, including cardiovascular health, has been increasingly recognized.
- Initiatives like the ONE TEAM study aims to enhance multidisciplinary collaboration, involving oncologists, cardiologists, endocrinologists, and various allied health professionals to improve comorbidity management and medication adherence in cancer survivors.

The 5-year survival rate for women diagnosed with breast cancer now exceeds 90% due in part to better screening and improvement in cancer treatments.¹ Patients with breast cancer treated with chemotherapy, targeted therapy, radiation and/or endocrine therapy (5–10 years) are at risk of cancer therapy related cardiovascular toxicity (eg, heart failure) which can be exacerbated in the setting of cardiovascular risk factors or pre-existing cardiovascular disease. In order to optimize long term outcomes for patients with cancer, organizations such as ASCO have promoted the development of survivorship plans, which focus on early detection of cancer recurrence, to guide patient's primary care providers. Yet there is now an increasing awareness of the importance of a more holistic approach to

cancer care and survivorship. The presence of other disease states, comorbidities (eg, diabetes), and social determinants of health, may have a negative impact on the overall health and productivity of a cancer survivor. Comprehensive care in breast cancer survivorship necessitates the interaction and collaboration of multiple health care providers and yet there is little evidence in the literature to support the adoption of this approach. To promote a multidisciplinary team-based approach for cancer survivors and those living with chronic cancer, Zullig and al. are currently conducting prospective clinical trial in patients with solid tumors receiving cancer treatment, including breast cancer patients, who have diabetes, dyslipidemia, or hypertension (NCT04258813). The aim of the ONE TEAM study is to move away from siloed care and improve efficient and timely communication to improve CVD comorbidity management and adherence to medications among patients with cancer. The TEAM study aims to include the oncology, cardiology and primary care team in the care of cancer patients with comorbidities.⁵ Its members beyond cardiologists and medical oncologists would also constitute endocrinologists, exercise physiologists, pharmacists, rehabilitation medicine, psychologists, dietician, physical therapy, nurses and other allied health care providers.

EDUCATION OF PATIENTS

- Patient education is integral to cancer care, improving outcomes, and empowering patients to manage their health confidently.
- Transitioning care to primary providers necessitates patient education on cancer treatment and cardiac surveillance, fostering a collaborative approach.
- Virtual tools can address engagement barriers, enhance accessibility, and facilitate

communication between patients and providers, with the goal of improving quality of life.

Patient education, empowerment, and support is a crucial part of quality cancer care. Patient education has not only been found to reduce hospitalizations but also to improve patient and caregiver quality of life.⁶ As patients complete active cancer treatment, their care is often transferred to primary care clinicians and other specialists. Equipping patients with information about their cancer treatment and cardiac surveillance allows them to have greater confidence in their ability to manage their life and health. While several position statements and guidelines have addressed cardiac surveillance strategies for patients at risk of cancer therapy related cardiovascular toxicity (CTRCD) they have focused mainly on education of health care providers. The European Society of Cardiology (ESC) Cardio-Oncology guideline published in 2022 provides guidance to health care providers as well as patient educational resources highlighting the importance of partnership between the patients and their medical team. Education is provided in patient-friendly language on how to self-monitor for signs of heart problems and to discuss new heart symptoms and risk of cardiovascular toxicity with their medical team.⁷

There are multiple factors that may limit engagement in educational opportunities such as out-of-pocket cost related to time off work or travel, feeling unwell, language or geographic barriers.⁸ Virtual patient/caregiver education tools may help address some of these barriers; for example, the Digital Education prescription which was developed for health care providers to tailor a list of multimedia patient education materials.⁸ In cardio-oncology, educational strategies utilized in cardiology such as smartphone based remote monitoring can be explored where patients can report clinical measurements, symptoms, complete education modules, and communicate with specialist nurses as needed. There is evidence that patients reporting their symptoms have an improved quality of life.⁸

Mitigating Toxicity and Managing Comorbidities

- **Risk Stratification:** The HFA-ICOS risk stratification tool offers a comprehensive CV risk assessment, prior to starting cancer therapy, which can guide appropriate referrals and intervention strategies.
- **Primary Prevention:** Focuses on managing modifiable CV risk factors, modifying cancer treatments, and cardioprotective interventions.

- **Modifiable Risk Factors:** Lifestyle changes such as smoking cessation, exercise, and a healthy diet are crucial for reducing cardiovascular risk; structured exercise programs like CORE show promise in attenuating cardiac events among cancer patients.

Clinical guidelines for cancer survivorship in the sphere of cardio-oncology have been developed by several organizations including ASCO, European Society of Medical Oncology (ESMO) and the European Society of Cardiology (ESC). Risk of CV toxicity is a dynamic variable that changes throughout survivorship based on modifiable and non-modifiable conditions, as well as the type, duration, and intensity of cancer therapies.⁹

Risk stratification

While a number of tools have been developed to identify breast cancer patients at risk of cardiovascular toxicity these have not been widely adopted into clinical practice (eg, Ezaz model).¹⁰ The ESC HFA developed a baseline HFA-ICOS risk score, which although not prospectively validated, incorporates the patient's cardiovascular risk factors, cardiovascular disease history, current and past cancer therapies, and social factors (eg, smoking).¹¹ Patients are categorized as low, medium, high and very high risk of cardiovascular toxicity (14.0% low, 16.7% medium, 30.3% high/very high; $P=.002$).⁹ The risk stratification based on the patient's risk profile and planned treatment guides further testing including cardiac biomarkers, such as cardiac Troponin (cTn) and natriuretic peptides, cardiovascular imaging, as well as recommendation's for follow up and referral to a cardio-oncologist.⁹ In the CARDIOTOX study, a prospective multi-center registry of patients treated with potential cardiotoxic cancer therapy, 67% presented at baseline with at least one CV risk factor, highlighting the importance of baseline cardiovascular risk assessment. In this study, a higher Systemic Coronary Risk Estimation (SCORE) was significantly associated with higher rates of severe cardiotoxicity and all-cause mortality (with an HR of 4.90 for SCORE ≥ 10 compared to those with a lower SCORE between 0-4).¹²

Primary Prevention strategies

There are several primary and secondary cancer-therapy related CV toxicity prevention strategies based on risk of cardiovascular toxicity. As highlighted in a review article by Omeland and colleagues, there are three pillars of preventative strategies: general preventative strategies (ie, modifiable cardiovascular risk factors), cancer treatment modifications, and potential cardioprotective interventions. Clinicians should screen for,

and actively manage, modifiable cardiovascular risk factors (ie, smoking, hypertension, diabetes, dyslipidemia, obesity). There is increasing evidence that aggressive control of cardiac risk factors including hypertension, hyperlipidemia and diabetes along with lifestyle modification with diet and exercise may decrease the likelihood of adverse cardiotoxic effects.¹³ Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and beta-blockers are recommended for primary prevention in high and very-high risk BC patients receiving anthracyclines and/or anti-HER2 therapies as per the ESC guideline (Class 2A recommendation) although results from previous studies on the efficacy of this approach has been mixed. In absence of a cardiovascular indication, there currently is no strong evidence to recommend statin therapy in BC patients. The PREVENT clinical trial did not demonstrate attenuation of LVEF decline with statin among patients receiving cardiotoxic cancer therapy and no existing indication for statin therapy.¹⁴ SGLT2i are another class of drug that reduces cardiovascular events, particularly heart failure in patients with and without type II diabetes and may have anticancer effects. Cohort studies demonstrate that initiation of these agents prior to anthracycline based therapy may lower rates of cardiac events, decrease mortality and improve outcomes in patients that have developed CTRCD/HF.^{15–17} RCTs are underway to further elucidate the role of SGLT2i's in mitigating cardiotoxicity for patients undergoing cardiotoxic therapies (EMPACT NCT05271162).

Modifiable Risk Factors

Low-fat diet, high in fruits/vegetables and whole grain, combined with weight loss improves overall CV risk.¹⁸ Tobacco smoking is a well-known cardiovascular risk; smoking cessation was associated with a 36% reduction in the risk of major adverse cardiac events in cancer survivors.¹⁹ Patients with cancer should be referred to a smoking cessation program that rely on both pharmacologic therapy and psychological counseling. Obesity and sedentary lifestyle increase the risk for CVD; exercise and healthy nutrition has a role in prevention of cancer, improvement of cancer-related and all-cause mortality, as well as improving health-related outcomes for cancer survivors.²⁰ Current guidelines recommend patients with cancer and survivors perform moderate-intensity exercise for at least 150 minutes per week and 2 to 3 weekly sessions of strength training.²¹ The AHA has proposed a comprehensive model for structured exercise training in cardiac rehabilitation for patients with cancer called the cardio-oncology rehabilitation (CORE).²⁰ CORE can identify patients at

high risk of CVD and use the multimodality approach to cardiac rehab to prevent or mitigate cardiovascular events. The cardiac rehabilitation staff of CORE is tasked to develop an individualized exercise prescription for each patient that includes aerobic and resistance exercise. In the ONCORE randomized controlled trial, an exercise-based CORE program was shown to be safe and to help attenuate LVEF decline in BC patients receiving cardiotoxic therapy.²² In a prospective study of 55 women with breast cancer and no comorbid CV risk factors, exercise correlated with a decrease in CV events.²³ Rurality is another important cardiovascular risk factor with higher incidence of cardiovascular disease in rural residents compared to their urban counterparts as well as in patients of lower socioeconomic status.²⁴

In the context of a cancer diagnosis, cardio-oncology clinics have emerged to deliver a multidisciplinary approach to the care of patients with cancer to mitigate cardiovascular risks while minimizing interruptions in cancer treatment. Although this has provided an integrative approach, there exists an accessibility gap between urban and rural communities in both oncology and cardio-oncology. However, telehealth and artificial intelligence may provide opportunities to address disparities.²⁵ Beyond routine cardiology care to address modifiable cardiovascular risk factors and to implement CV guideline-based treatment, another important aspect of cardiovascular risk modification in cancer patients lies in the patient's cancer therapy, duration, and intensity. Modifications to minimize the risk of anthracycline induced cardiotoxicity include using infusional versus bolus dosing, slower infusion rate, and use of pegylated liposomal rather than unencapsulated preparations.¹³

Strategies to Mitigate Toxicity During and After Breast Cancer Treatment

- Cardiovascular monitoring is essential throughout cancer treatment and into survivorship, with risk assessment guided by cancer regimen and patient related factors.
- CV imaging and assessment should be based on risk of CTRCD which is driven by cancer therapy and patient risk factors.
- In BC patients who develop asymptomatic moderate CTRCD (LVEF 40%–49%) while on HER2 targeted therapies, there is guidance on continuing treatment while starting cardio-protective medication

Cardiovascular monitoring remains an important part of a patient's treatment plan into survivorship. Cardiotoxicity risk is dependent on the cancer

regimen which together with patient risk factors (ie, hypertension, diabetes, smoking, dyslipidemia, and obesity) guides CV monitoring strategies. The ESC has surveillance recommendations for breast cancer patients receiving endocrine therapy, anthracyclines, HER2 directed therapy, and immunotherapy-based therapy among others.

Endocrine therapy is the cornerstone of treatment for hormone receptor-positive breast cancer. This includes selective estrogen receptor modulators such as tamoxifen or aromatase inhibitors (AI) along with cyclin-dependent kinase (CDK) 4/6 inhibitors in advanced disease and the patients with early-stage breast cancer at high risk of relapse. The use of AIs is associated with dyslipidemia metabolic syndrome, hypertension, heart failure and myocardial infarction.²⁶ A retrospective study of over 5000 patients also found an arrhythmic risk to AI over tamoxifen with a higher rate of new-onset atrial fibrillation HR 2.18.²⁷ The current recommendations are for a baseline CV risk assessment including BP, lipids, fasting glucose, HbA1c, ECG and patient education on healthy lifestyle and thereafter re-assessment and optimization of risk factors while on endocrine therapy with frequency dependant on risk of the individual.²⁸

Anthracyclines have been a mainstay in breast cancer therapy given their ability to improve survival for women with HR + HER2-and triple negative early breast cancer.²⁹ In regimens with anthracycline, dexrazoxane and modification of anthracycline exposure are associated with decreased chemotherapy-induced cardiotoxicity. Not only is it recommended in those with high cumulative doses of anthracyclines, defined as ≥ 250 mg/m² of doxorubicin equivalent, it has also been suggested as a secondary cardioprotective therapy during anthracycline treatment in patients with pre-existing ventricular dysfunction.³⁰ Dexrazoxane is an effective drug for primary prevention of anthracycline-related cardiotoxicity as it is believed to chelate intracellular iron, block iron-assisted oxidative radical production and inhibit the topoisomerase II-beta isoenzyme which is implicated in anthracycline cardiotoxicity³¹ however this approach has not been widely adopted in clinical practice. Regarding imaging, adult survivors at moderate risk should have a TTE every 5 years (Level 2B evidence) and those at high or very high risk should have a TTE 1, 3 and 5 years after therapy (Level 2A evidence). In all adults receiving anthracycline chemotherapy, an echocardiogram is recommended within 12 months after completing treatment (Level 1B evidence).²⁸ In the presence of symptoms or abnormal cardiac imaging, patients should be referred to a cardiologist.

HER2 monoclonal antibodies form the backbone of systemic therapy for early and metastatic HER2 + breast cancer, and HER2 antibody drug conjugates have emerged as an important therapy in both HER2+ and HER2-low breast cancer (defined as HER2 IHC score of 1+ or 2+ without ERBB2 amplification by FISH). All HER2 antibody-based therapy is associated with the risk of cardiac dysfunction, potentially due to the role of neuregulin-1/HER2 signaling in cardiomyocyte survival and maintenance of normal myofibrillar structure.³² Current guidelines recommend evaluation of LVEF every 3 months whilst on neo-adjuvant or adjuvant HER2-targeted therapies and within 12 months after completing treatment (Level 1B evidence)⁹ and monitor for signs of cardiotoxicity to guide treatment interruption.²⁸ However, the utility of this approach, particularly in low-risk patients, is being evaluated. Global longitudinal strain (GLS) can detect subclinical LV dysfunction but has not been shown to guide treatment decisions. The SUCCOR trial showed no difference in change of EF between the GLS- and EF-guided cardio-protection strategies.³³ The use of cardiac serum biomarkers to identify CTRCD can be considered in individuals at higher risk (Level 1C). Although recent meta-analyses in patients receiving anthracycline chemotherapy and HER2-targeted therapies reported that RAS blockers, beta-blockers, and MRAs have a significant benefit in preventing LVEF reduction (mean difference in LVEF improvement of 7.62%, 7.30% and 12.80% respectively), there were no statistical differences in the incidence of overt HF or other clinical outcomes.³⁴

In breast cancer patients who develop asymptomatic moderate CTRCD (LVEF 40%–49%) while on HER2 targeted therapy, there is guidance on continuing treatment while starting cardioprotective medication.⁹ Reduced left ventricular systolic function is independently associated with an adverse prognosis and may necessitate an interruption or cessation of HER2-directed antibody therapy, which precludes patients from achieving the full survival benefit offered by this intervention. The SAFE-HEaRT and SCHOLAR trials provide safety data of continuation of HER2-targeted therapies in asymptomatic patients with below normal LVEF (40%–49%; drop > 15% from baseline).^{35,36}

Fluoropyrimidines are commonly used medications in breast cancer especially in the metastatic setting with 5-FU likely one of the most common chemotherapeutic agents to cause cardiotoxicity, second only to anthracyclines. Clinical manifestations have largely been consistent with angina attributed to coronary vasospasms, however other CV toxicity have been reported.³⁷ Proposed

risk factors for fluoropyrimidine cardiotoxicity include older age, concurrent administration of other cardiotoxic therapies and a history of cardiac disease or presence of CV risk factors. Asymptomatic ECG changes and arrhythmias, as well as an increase in plasma levels of NT-pro-BNP during 5-FU chemotherapy, have been suggested as markers of subclinical cardiotoxicity. However, the clinical significance of these findings remains uncertain and therefore there are no guideline recommendations to screen patients with these investigations. In patients with a history of cardiotoxicity from 5-FU or capecitabine or in those with significant coronary artery disease, raltitrexed is a common substitute. In terms of prevention, testing for DNA variation in the DPD gene (*DPYD*) is recommended in patients planning to receive fluoropyrimidines to detect and determine zygosity of six *DPYD* variants. If present, the reduced activity of dihydropyrimidine dehydrogenase (DPD), which catalyzes the breakdown of over 80% of 5-FU metabolism, results in a reduction of FU clearance and a subsequent increase in systemic drug exposure leading to an increased risk of toxicity.³⁸ Thus, an inadequate activity of DPD plays a significant role in augmented cardiotoxicity.³⁹

NEW BREAST CANCER THERAPIES

- Novel HER2 targeted therapies, including antibody-drug conjugates and tyrosine kinase inhibitors, are associated with a low risk of cardiotoxicity, however experience with these agents in the real world setting is limited.
- Immune checkpoint inhibitors, used in the treatment of high-risk early stage and PDL-1 positive advanced triple negative breast cancer, are associated with cardiovascular toxicity including myocarditis.
- Guidelines recommend pre-treatment cardiac assessment and monitoring during therapy, especially for patients at high/very high risk of cardiovascular toxicity.

Novel HER2 targeted therapies such as selective tyrosine kinase inhibitors (eg, lapatinib) and antibody-drug conjugates (ie, ado-trastuzumab emtansine [T-DM1], trastuzumab deruxtecan [T-DXd]) are associated with a decrease in LVEF; however, the rate of cardiac dysfunction is low (OR of 0.48 and 2.49 respectively) in comparison to anti-HER2 monoclonal antibodies.⁴⁰ While the CLEOPATRA regimen, with dual HER2 blockade with trastuzumab and pertuzumab demonstrated a $\geq$ grade 3 LVD of 5.4%, trials evaluating T-DXd have shown LVEF decline in 2.3% of patients (all

of which were asymptomatic) in DESTINY-Breast03 and in 4.3% (0.3% grade 3) of patients in DESTINY-Breast04.⁴¹ A pooled analysis of 7 trials with T-DM1 revealed a grade 3/4 LVEF drop in 0.71% and grade 1/2 drop in 2.04% of patients with a total cardiac event rate of 3.37%; noting that approximately a quarter of patients received TDM-1 along with pertuzumab.⁴²

Immune checkpoint inhibitors are standard of care in the neoadjuvant/adjuvant setting for patients with high-risk early-stage triple negative breast cancer (TNBC) and in metastatic TNBC with a combined positive score for PDL-1 $\geq 10\%$, which occurs in approximately half of TNBC patients.^{43,44} Cardiovascular toxicities related to the use of immune checkpoint inhibitors (ICIs) include myocarditis, stress cardiomyopathy, vasculitis, arrhythmia, and increased atherosclerosis.⁴⁵ Myocarditis is the most frequently reported cardiovascular irAE associated with ICI therapy. The aim of CV monitoring for patients with breast cancer receiving ICI therapy should be to recognize subclinical or asymptomatic cases of myocarditis as early diagnosis is key to initiation of effective therapy.⁴⁶ Current guidelines (NCCN, ASCO, ESC and SITC) recommend an ECG, cardiac biomarkers, and a CV risk assessment in all patients prior to ICI initiation. An echocardiogram is only recommended in high-risk patients (patients receiving combined ICI treatments, or combination of ICI with other cardiotoxic agents, patients with history of cardiotoxicity, non-cardiovascular irAEs, and patients with cardiovascular diseases), though it can be considered in all patients (Level 1C evidence). Surveillance of ICI therapy with echocardiography to assess LVEF and global longitudinal strain is recommended in patients with increase in cardiac biomarkers or new-onset symptoms.²⁸ There are no current guidelines regarding cardioprotective therapy in primary or secondary prevention of cardiotoxicity associated with ICIs. **Fig. 2** illustrates common breast cancer therapies and their cardiovascular adverse events.

RADIATION THERAPY

- Radiation therapy stands as a cornerstone in breast cancer management, yet it carries an elevated risk of short- and long-term adverse effects on the heart.
- Thoracic radiation therapy heightens the risk of coronary artery disease, heart failure, valvular heart disease, and chronic pericarditis, leading to cardiovascular mortality.
- Radiation therapy guidelines focuses on preventative measures, risk assessment and

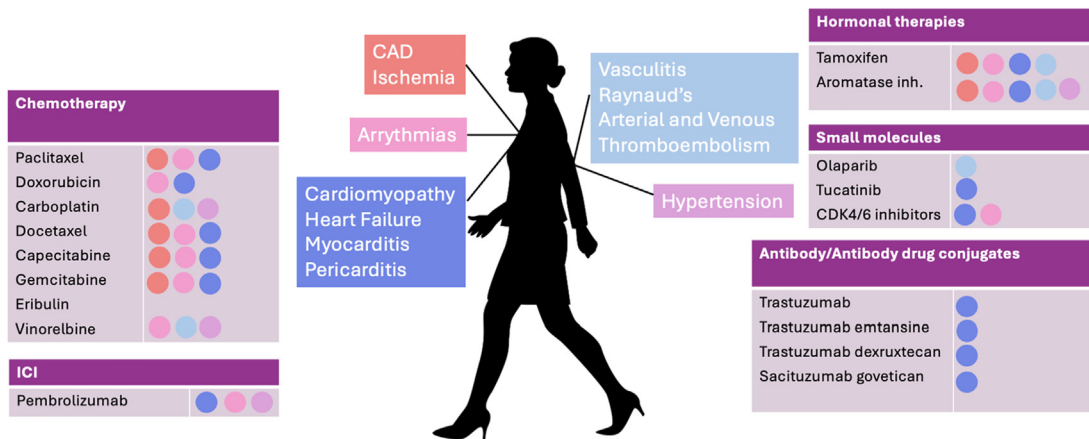


Fig. 2. Cardiovascular toxicity associated with breast cancer treatments.

management of radiation-induced cardiovascular disease favoring percutaneous treatments over surgical options.

- New radiation techniques such as “breath hold” decrease cardiac exposure and risk of long-term CV disease.

Radiation therapy is another important modality of treatment in breast cancer. Despite its positive impacts on cancer outcomes there are both short- and long-term adverse effects on the heart. Thoracic radiation therapy increases the risk of coronary artery disease and subsequent CV mortality. Patients are also at risk for heart failure, cardiomyopathy, valvular heart disease and chronic pericarditis.⁴⁷ A consensus statement by the International Cardio-Oncology Society outlines recommendations for risk assessment, early detection through imaging, and management of radiation-induced cardiovascular diseases, emphasizing the preference for contemporary percutaneous treatments over surgical options. The American Society for Radiation Oncology guidelines for whole breast radiation therapy (RT) recommend minimizing the cardiac dose as much as possible.⁴³ To minimize radiation-induced heart disease (RIHD) there exist maneuvers to separate the heart from the chest wall including having the patient in the prone position and using deep inspiration breath hold.^{44,48} Another technical approach to minimize heart dose during RT includes optimisation of beam angles, using a multileaf collimator shielding, intensity-modulated radiotherapy, proton therapy and partial breast irradiation.⁴⁴

In patients undergoing therapy in the curative setting there are guidelines on post-therapy CV assessment. At 12 months after completing cancer therapy the recommendation is to repeat a CV risk assessment in patients who have a good

long-term prognosis. Patients are stratified by both early and late risk, and symptomatology into very high, high, moderate and low-risk groups based on the HFA-ICOS risk assessment. Patients considered early high risk include those with high or very high pre-treatment risk, recipients of therapies associated with long-term risk of complications, patients that develop CTCVT during treatment, and those with new abnormalities on TTE, biomarkers or symptoms at the end-of-therapy assessment.

From 12 months onwards, annual screening and modifiable CV risk factor management are recommended.⁹ Adult patients should have risk re-stratification at 5-years post-therapy. All patients that have emergent cardiovascular symptoms should have a cardiology assessment. In clinical practice, the question remains, which healthcare provider should be responsible for this and how is this surveillance implemented. Artificial intelligence may be able to facilitate this surveillance in oncology clinics.

An annual CV risk assessment including ECG and NP, and CVRF management is recommended in cancer survivors who received treatment with a potentially cardiotoxic cancer drug or RT (Level 1B evidence).

PROMOTING HEALTHY BEHAVIORS

- CORE recommends tailored aerobic and resistance exercise for all cancer survivors.
- Moderate-intensity and high-intensity interval training (HIIT) exercises are safe and effective in preventing and treating CV morbidity in most BC survivors.
- Exercise, including pre-habilitation, during and after cancer treatment, improves heart health and quality of life.

In 2019, the American Heart Association proposed the CORE, a multidisciplinary approach to cardiovascular rehab for cancer survivors. CORE recommends individualized aerobic and resistance exercise based on American College of Sports Medicine guidelines (ie, 150 min/week of moderate-intensity or 75 min/week of vigorous-intensity aerobic exercise and 2 strength training sessions) for all cancer survivors. Current evidence supports that moderate-intensity continuous exercise and HIIT are effective at preventing and treating cardiovascular disease and are safe and well tolerated in most patients with cancer. HIIT is effective at preventing and treating CVD and its risk factors.⁴⁹ Exercise can also be used as a primary prevention strategy to prevent the development of treatment-induced cardiotoxicity and risk factors. Combined aerobic and resistance exercise studies may attenuate risk of cancer-treatment-induced LVEF and GLS decrease and may prevent substantial treatment-related detrimental changes in cardiac injury biomarkers. In a prospective study of 40,000 BC patients, pre-diagnosis exercise (ie, “prehabilitation”) was associated with a graded reduction in CVAEs.⁵⁰ Exercise can also be safely performed during chemotherapy and has been shown to prevent fatigue and decrease in VO_2 peak (a reflection of cardiorespiratory fitness), and to improve muscle strength and HRQoL.⁵¹ Therefore, an exercise prescription should be incorporated into survivorship from the time of a patient’s diagnosis.

Personalized Follow-Up

- Rising incidence of cardiovascular disease (CVD) in cancer survivors highlights the need for universally adopted survivorship plans and interventions.
- Home-based multimodal interventions encompassing psychological support, physical activity, nutrition, education, lifestyle, and caregiver support are key components of survivorship care.
- Collaboration among oncologists, cardiologists, primary care providers, and pharmacists is crucial for effective management, with proposed models including shared-care, chronic care, risk-stratification, and transition models.

With advancements in cancer treatment prolonging survival, the number of cancer survivors developing cardiovascular disease and heart failure is rising. A recent study suggests a 42% higher risk of developing incident CVD in cancer survivors.⁵² Guidelines and survivorship plans

are being developed but have not yet been adopted universally in clinical practice. Both health practitioner and patient-led interventions are important for prevention of these long-term effects of cancer treatment. Similarly to cancer treatments, survivorship care captures the heterogeneous population of patients, with various diseases, treatments, comorbidities and potential acute and long-term effects. In a recent scoping review of current home-based multimodal, self-management interventions for cancer patients, there were six key modalities identified in survivorship care plans: psychological support, physical activity, nutrition, patient education, lifestyle and caregiver support. For healthcare provider’s various models have been proposed, such as shared-care model, chronic care model, risk-stratification model, and the transition models. In all models, healthcare providers are involved in the care of patients at different time points, and therefore a clear survivorship care plan accompanying the patient is crucial, with a specific recommendation to provide a copy of the care plan for the patient to share with their providers.⁵³ Whereas oncologists typically follow patients for recurrence for 5 years, more emphasis should be placed on managing comorbidities and cardiotoxicity risk. Primary care providers are a pivotal point of care, and although confident with managing many long-term side effects, most were not confident in managing cardiotoxicity and “chemobrain”.⁵⁴ Primary care physicians face the challenge of seamlessly incorporating cancer survivorship-specific diagnostic pathways into their current practices, leveraging pre-existing cancer survivorship plans.⁵⁴

Risk stratification and appropriately referring patients at high risk of cardiotoxicity to a cardio-oncology program is important for primary prevention and/or secondary treatment of new or worsening cardiovascular disease in cancer survivors. The facets of survivorship care include lifestyle education, pharmacotherapy, enhanced cardiovascular surveillance, and support services such as exercise training. Collaboration between cardiologists, oncologists, pharmacists and primary care providers are key. Furthermore, given the emerging evidence of behavioral interventions for patients exposed to cardiotoxic treatments, one proposed discipline that is well-positioned to potentially guide/coordinate this field is cardiac rehabilitation. A proposed survivorship care plans integrates a multidisciplinary care plan and proposed telemedicine as an option to facilitate patient-healthcare provider’s interaction in each phase.⁵³

Table 1
Prevention of Cardiovascular Toxicity–Active/Ongoing trials

Ongoing Studies	Population	Intervention	Main Outcomes
TITAN (NCT01621659)	Patients with confirmed malignancy (breast or lymphoma) scheduled to receive anthracycline and/or trastuzumab-based chemotherapy	Multidisciplinary team interventions with cardiology team, clinical nutrition, pharmacist, exercise physiologist and physiotherapist	Change in LVEF using cardiac MRI, troponin, BNP
REDEEM (NCT04962711)	Prospective study in cancer survivors >65 years old with chemotherapy >10 ys ago.	Heart Failure intervention (pharmacotherapy and exercise intervention)	Change in exercise capacity with VO ₂ peak
NCT02993198	Phase 2 of HER2 + early-stage breast cancer (stages I-III) with a baseline EF >53% and scheduled to receive anthracycline and/or trastuzumab and pertuzumab-based regimens	Carvedilol	Change in global longitudinal strain
FAST-TRACK (NC05799898)	All patient referred to the cardio oncology unit for suspected immune related cardiovascular complication on immune checkpoint inhibitors	None (prospective cohort)	Incidence of MACE
CARTIER (NCT03711110)	Patients ≥ 65 years old with onco-hematological cancers	Primary prevention strategy with intensive cardiovascular monitoring focused on prevention and early diagnosis and treatment of cardiotoxicity based in cardio-onco-hematology teams	All-cause mortality
PRADA II (NCT03760588)	Patients with invasive early breast cancer scheduled for adjuvant therapy with anti-cancer regimens that include anthracyclines	Randomized placebo controlled double blind trial of sacubitril/valsartan (target dose 97/103 mg b.i.d.) and matching placebo in a 1:1 fashion during treatment	Change in left ventricular ejection fraction by cardiovascular magnetic resonance

(continued on next page)

Table 1
(continued)

Ongoing Studies	Population	Intervention	Main Outcomes
CCT Guide Pilot (NCT04023110)	Patients with stage I-III breast cancer with treatment plan to include therapy with anthracyclines and/or trastuzumab in the adjuvant or neoadjuvant setting	Single-center, randomized clinical trial of carvedilol vs placebo during 12 mos or completion of treatment.	Change in LVEF with echocardiography, treatment adherence using pill counts, adverse events.
NTproBNP-Guide	Patients with breast cancer or lymphoma planned to receive an anthracycline based chemotherapy regimen.	NTproBNP monitoring	Change in LVEF, incidence of cardiotoxicity, change in NTproBNP, incidence of heart failure
HER-SAFE (NCT05880160)	Patients with HER2 targeted therapy related cardiac dysfunction who currently receive standard heart failure/cardioprotective medications	Withdrawal of heart failure/ cardioprotective treatments as per TRED-HF study	Relapse in cardiotoxicity Defined based on International Cardio-Oncology Society 2021 Guidelines as (at least one of): a) Asymptomatic LVEF reduction by $\geq 10\%$ to an LVEF of $<50\%$; b) Asymptomatic LVEF reduction by $\geq 5\%$ to an LVEF of $<50\%$ plus new relative decline in global longitudinal strain (GLS) by $>15\%$ from baseline AND/OR new rise in cardiac biomarkers (>2 fold increase in NTproBNP to >400 ng/L, or high sensitivity Troponin >99 th percentile), c) Clinical heart failure (based on symptoms and clinical examination) with at least one of the following: fall in LVEF $\geq 5\%$, increase in cardiac biomarkers (as above), relative fall in GLS $> 15\%$, new arrhythmia (excluding ectopy)

STOP-MED (NCT06183437)	Patients with cancer therapy completed more than 6 mos prior and no plan for further therapy with prior asymptomatic moderated CTRCD with at least one heart failure medication started for CTRCD.	Structured stopping of heart failure medication(s) under supervision of a study team.	CTRCD relapse - comparison at 1 y follow-up one or both of the following (i) left ventricular ejection fraction <50% by CMR (ii) new heart failure signs (at least two physical findings or one physical finding and one laboratory finding) AND symptoms (at least one) with the initiation of qualifying heart failure therapy.
NCT06251401	Breast cancer patient that has previously received an anthracycline and/or trastuzumab.	In-person cardiac rehabilitation compared to virtual home-based rehabilitation.	Change in LVEF, estimated aerobic fitness, GLS
ATOPE (NCT03787966)	Patients with stage I-III breast cancer on waiting list to anticancer medical treatment (at least surgery, chemotherapy and radiotherapy)	Adapted therapeutic exercise program performed before medical treatment	Change in LVEF, cardiovascular events, resting heart rate, heart rate variability, quality of life

FUTURE DIRECTION

Breast cancer clinical trials focused on prevention of cancer therapy related cardiac dysfunction is crucial for gaining deeper insights and minimizing unnecessary harm to patients with breast cancer. Several trials are currently underway to assess prevention and de-escalation of cardiotoxic therapies (Table 1). Referring patients to clinical trials in cardio-oncology offers a pathway to accessing cutting-edge treatments/management/prevention strategies, potentially minimizing cardiotoxicity. Participation by patients not only leads to innovative approaches but also contributes to advancing scientific knowledge, particularly in understanding and mitigating long-term cardiac effects of cancer treatments. In this collective pursuit, we aspire not only to prevent cancer therapy related cardiovascular toxicity but also to enhance cancer care efficacy, all the while protecting the long-term health of our patients’ hearts and quality of life.

CLINICS CARE POINTS

- Clinical trials focused on prevention and de-escalation of potentially cardiotoxic therapies aim to minimize heart-related side effects, improving the overall safety and quality of life for patients with breast cancer.
- These trials will deepen our understanding of the impact of cancer treatment on heart health, leading to more effective, tailored therapies.

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Cardiovascular Risk in Prostate Cancer



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KEYWORDS

- Cardio-oncology • Risk factors • Prostate cancer • Cardiovascular disease
- Androgen deprivation therapy

KEY POINTS

- Patients with prostate cancer have a high burden of cardiovascular risk factors, which are often suboptimally controlled. The best strategy for stratifying and addressing cardiovascular risk in patients with prostate cancer has not been defined.
- Androgen deprivation therapy (ADT), most frequently administered in the form of a gonadotropin-releasing hormone (GnRH) agonist, is a cornerstone of prostate cancer therapy. It leads to increased adiposity and loss of skeletal muscle strength and has been associated with an increase in the risk of developing hypertension and diabetes. ADT has been weakly associated with an increase in the risk of adverse cardiovascular outcomes. However, these data are methodologically limited and the association needs confirmation in prospective studies.
- Androgen receptor signaling inhibitors (eg, enzalutamide, apalutamide, darolutamide) and cytochrome p450 17A1 (CYP17A1) inhibitors (eg, abiraterone) are used in addition to GnRH agonists for metastatic prostate cancer and increasingly for high-risk nonmetastatic disease. They increase hypertension over and above GnRH agonists and have been associated with incremental cardiovascular risk.
- GnRH antagonists have been associated with less adverse cardiovascular outcomes than GnRH agonists. However, this observation has yet to be proven in a prespecified randomized, controlled trial. While GnRH antagonists can be considered in patients at high cardiovascular risk, there is insufficient high-quality evidence to support its routine use in this population for the reduction of cardiovascular events.

INTRODUCTION

Patients with diverse cancers, including prostate cancer (PC), are experiencing progressive improvements in survival owing to advances in cancer therapeutics. This shift alone will leave populations of patients treated for cancer susceptible to the competing risk of cardiovascular disease (CVD). Coupled with the cardiotoxicity of some cancer treatments, many patients with

cancer might be at high risk of developing CVD, and their management complicated by specific treatment and prognostic considerations of both morbidities. These issues have led to the rapid growth of the field of cardio-oncology.

Worldwide, PC is the most common cancer in men.¹ It is projected that the number of new PC cases annually will double between 2020 and 2040, from 1.4 million per year to 2.9 million.² It is estimated that over 3.5 million men in the United

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States have been diagnosed with PC³ and there are approximately 300,000 new cases annually.⁴ Importantly, at least 90% of patients with newly diagnosed PC in contemporary cohorts will have localized disease, and PC mortality in these individuals is infrequent, occurring in less than 1.5% of patients per year.^{5,6} Even in those with de novo metastatic disease, survival rates are generally 4 to 5 years.⁷ Therefore, many patients with PC will be at risk of cardiovascular events for an extended time and the burden of cardio-oncology morbidity in patients treated for PC is large and will likely increase. The purpose of this article is to discuss what is known about the epidemiology of cardiovascular risk factors and disease in the PC population; the role of specific PC treatments in promoting cardiovascular risk factors and disease; strategies to address these challenges; and considerations in the management of severe CVD in patients with PC.

EPIDEMIOLOGY OF CARDIOVASCULAR DISEASE IN PATIENTS WITH PROSTATE CANCER

Most patients with localized disease have excellent long-term cancer-specific survival and for contemporary patients who are diagnosed with metastatic disease, cancer-specific survival is usually over 4 years.^{8,9} The widespread use of screening, especially in high-income countries and settings, has led to increases in PC incidence, including the identification of many patients in the indolent phase. The favorable life-expectancy among these patients with early-stage PC⁵ leaves them at risk of developing comorbid conditions for an extended time. Among such comorbidities, cardiovascular risk factors and disease are particularly relevant if only because of their frequency in men of the same demographic typically affected by PC.

In the subgroup of patients with PC who will develop advanced disease, hormonal therapy represents the cornerstone of cancer control. However, these treatments are well recognized as leading to worsening cardiometabolic complications. Such complications enhance the importance of cardiovascular risk factors and disease in patients with PC.

Among men with nonmetastatic PC in the United States, CVD is a more frequent cause of death than the cancer itself, while even in those with metastatic disease, the standardized cardiovascular mortality ratio is 1.48 (95% confidence interval [CI]: 1.41–1.54), indicating that these patients are at approximately 50% higher risk of cardiovascular death than expected for their age.¹⁰ These

data indicate that CVD may be very important comorbidity in patients with PC.

MECHANISMS UNDERLYING CARDIOVASCULAR DISEASE IN PROSTATE CANCER

Patients with PC may develop CVD frequently because of several potential reasons. These include demographic factors, shared risk factors, and the effects of androgen deprivation therapy (ADT; [Fig. 1](#)).

Demographics and Cardiovascular Risk Factors in Patients with Prostate Cancer

PC most frequently affects older men, a demographic that is inherently characterized by elevated CVD risk. Patients with PC exhibit a high burden of cardiovascular risk factors even at the time of PC diagnosis. In a large Canadian cohort, 58% of individuals with PC were current or former smokers, 45% had hypertension, 16% diabetes, 31% were obese (with body mass index ≥ 30 kg/m²), 24% had low levels of physical activity, and 22% already had established CVD.¹¹ For these reasons, 69% had a Framingham cardiovascular risk score associated with a high risk for future adverse cardiovascular outcomes. While these risk factors are clearly associated with a high burden of CVD,^{12,13} some may also be risk factors for PC (especially more aggressive PC), although epidemiologic patterns are inconsistent. Some prospective cohort data suggest that there is no relationship between cardiovascular risk factors and the incidence of PC.¹⁴ However, other data suggest that every 5 kg/m² increase in body mass index has been associated with a relative risk of advanced PC of 1.12 (95% CI: 1.01–1.23).¹⁵ This contrasts with evidence that diabetes has been associated with a lower incidence of PC,¹⁶ while vigorous physical activity, which is typically associated with a lower risk of diabetes, has been linked with a lower risk of advanced PC.¹⁷ *In summary, while the burden of cardiovascular risk factors in patients with PC is high, it is unclear whether they play a role in promoting the development or progression of PC.*

Androgen Deprivation Therapy

ADT is a fundamental part of the therapeutic armamentarium against advanced PC ([Fig. 2](#)). Ever since the seminal discovery of the effects of orchiectomy in patients with metastatic PC,¹⁸ ADT, now more frequently administered in the form of gonadotropin-releasing hormone (GnRH)

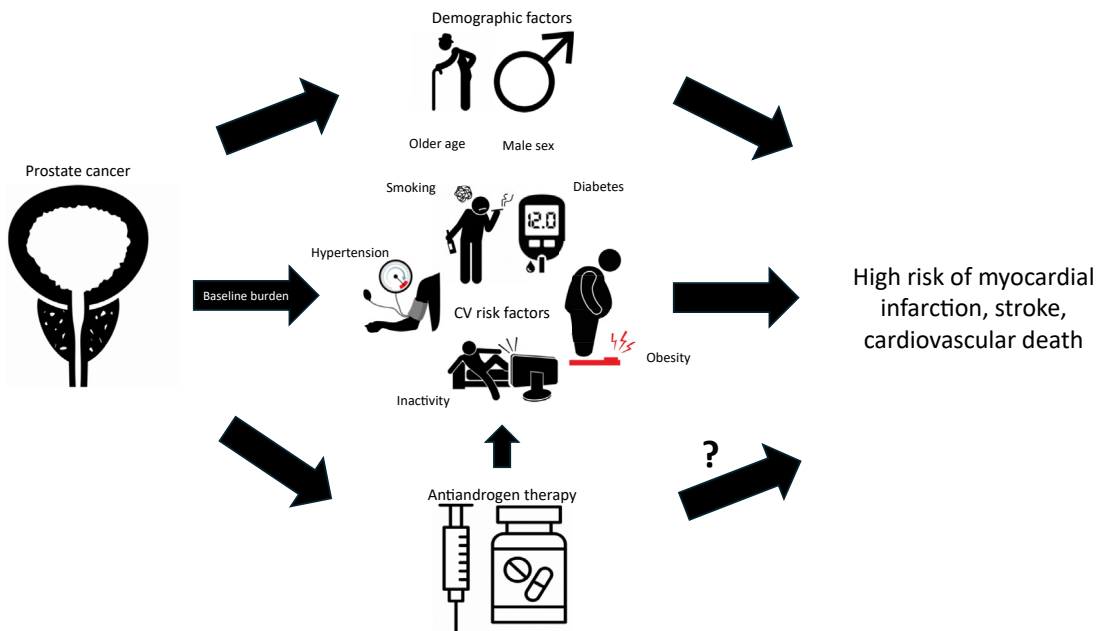


Fig. 1. Factors that may account for high cardiovascular risk in patients with prostate cancer. These include age and a high burden of conventional cardiovascular risk actors, which may be exacerbated by androgen deprivation therapy.

agonists together with new generation androgen receptor axis inhibitors, is standard-of-care for metastatic disease. ADT is also often used as adjuvant therapy with radiotherapy or in patients with evidence of biochemical relapse after previous definitive PC therapy. In this population, ADT reduces PC-specific mortality and overall mortality, with respective relative risks (95% CIs) of 0.69 (0.56–0.84) and 0.86 (0.80–0.93).¹⁹

The most common contemporary means of delivering ADT is as subcutaneous or depot GnRH agonist injection, which can be administered at intervals of 1, 3, 4, or 6 months. These drugs continuously stimulate the anterior pituitary, resulting in an initial surge of luteinizing hormone, and thus, testosterone. However, continuous (rather than physiologic pulsatile) stimulation of the anterior pituitary rapidly leads to marked reductions in luteinizing hormone, and thus testicular testosterone synthesis.

Gonadotropin-releasing hormone agonists and cardiovascular risk

GnRH agonists lead to weight gain, mostly through inducing an increase in fat mass, which increases by approximately 11%²⁰ (Table 1). Given the close relationship among adiposity, diabetes, and hypertension, it is an unsurprising consequence of weight gain that GnRH agonist use has been associated with an increased risk of diabetes and hypertension. In a large retrospective analysis, ADT

use was associated with a 60% increase in the risk of developing diabetes among patients with localized PC.²¹ In another large, retrospective Taiwanese study, ADT use was associated with an 80% higher risk of developing hypertension.²²

GnRH agonists are also well known to cause loss of skeletal muscle strength.²³ Muscle strength is an underappreciated risk factor for adverse cardiovascular outcomes, including myocardial infarction, stroke, heart failure, and cardiovascular death.^{13,24}

A meta-analysis of retrospective studies found that GnRH agonist use was associated with nonfatal cardiovascular events, with relative risk (95% CI) 1.38 (1.29–1.48).²⁵ In a retrospective analysis of patients with localized PC, ADT was associated with an approximately 2 fold higher risk of cardiovascular death in men aged 65 years or more who had undergone prostatectomy, with 5 year cumulative incidence rates of 5.5% (95% CI 1.2%–9.8%) as compared with 2.0% (95% CI 1.1%–3.0%) in those not receiving ADT.²⁶ This finding contrasts with those of a meta-analysis of randomized trials in which up-front ADT was compared with a control arm of delayed or no ADT.¹⁹ In this study, no difference in the risk of cardiovascular death was observed.

Given the metabolic effects of ADT, it is plausible that ADT is a risk factor for subsequent CVD. However, the association between ADT and adverse cardiovascular events has been poorly characterized because most data are from

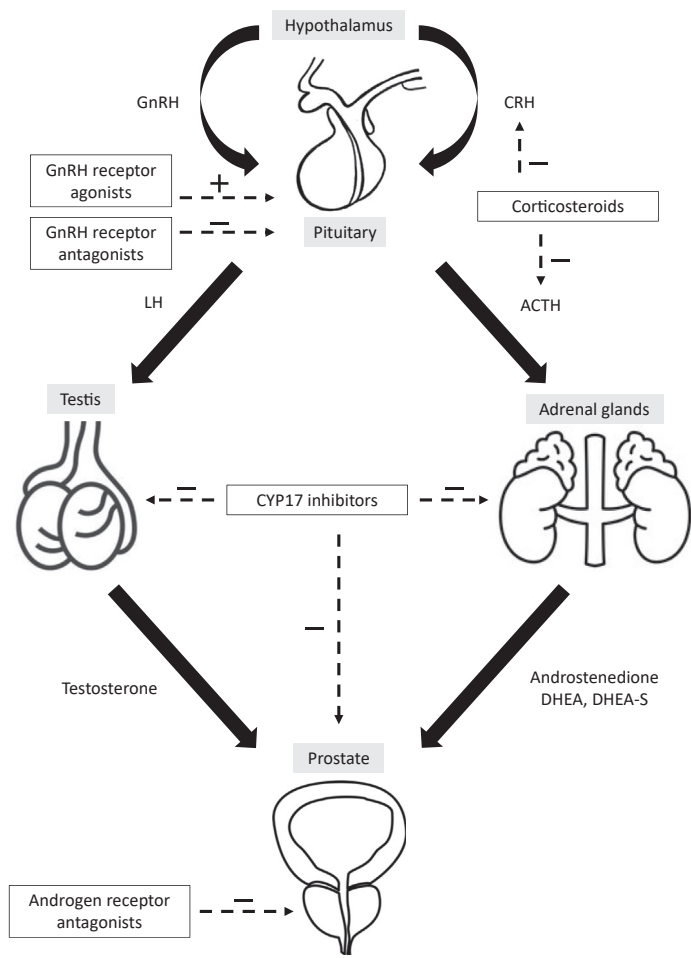


Fig. 2. Mechanisms of action of pharmacologic approaches to inhibiting androgen effects on prostate cancer. ACTH, adrenocorticotrophic hormone; CRH, corticotropin-releasing hormone; DHEA, dehydroepiandrosterone; DHEA-S, dehydroepiandrosterone sulfate; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone.

retrospective studies—mostly using administrative sources—where the ability to account for confounding factors is limited.

GnRH antagonists represent another means of inhibiting anterior pituitary gland stimulation of

testicular testosterone synthesis. The relationship between this drug class and cardiovascular outcomes is described subsequently, given the promising but inconclusive evidence that GnRH antagonists may lead to fewer adverse cardiovascular events than GnRH agonists.

Table 1 Likely effects of androgen deprivation therapy on cardiovascular risk factors	
Cardiovascular Risk Factor	ADT Effect
Adiposity	
Weight	
Waist Circumference	
Waist-hip Ratio	
Hypertension/Blood Pressure	
Diabetes/Blood Glucose	
Muscle Strength	
Lipids	
Triglycerides	

Other androgen pathways inhibitors
Castrate-resistant PC develops when the cancer acquires mutations that enable disease progression despite castrate levels of testosterone. It is recognized, however, that castrate-resistant PC is still frequently driven by androgens, but that the responsible mutations enhance the tumor’s ability to proliferate under conditions of low-circulating testosterone and de novo intra-tumoral synthesis of androgens. Mechanisms include amplification or augmented sensitivity of androgen receptors, and responsiveness to non-testosterone androgens. Understanding of these pathophysiologic pathways has led to the development of classes of drugs, such as androgen receptor signaling

inhibitors (eg, enzalutamide, apalutamide, darolutamide) and CYP17A1 inhibitors (eg, abiraterone), which inhibit adrenal synthesis of androgen precursors, such as dehydroepiandrosterone. Importantly, abiraterone, enzalutamide, darolutamide, and apalutamide prolong overall survival in patients with metastatic PC.^{9,27–29}

As compared to placebo, abiraterone and, to a greater extent, enzalutamide are associated with an increased risk of hypertension, with respective relative risks (95% CI): 1.46 (1.20–1.78) and 2.66 (1.93–3.66).³⁰ Population-based research from Sweden demonstrated that these 2 drugs are associated with a higher risk of incident CVD than their nonuse, with respective hazard ratios (95% CI) for abiraterone and enzalutamide of 1.19 (1.03–1.38) and 1.10 (1.01–1.20).³¹ Importantly, the increase in cardiovascular risk associated with these newer androgen pathway inhibitors is incremental to GnRH agonists, with which these drugs are used in combination. A further consideration is a potential for drug–drug interactions between these drugs and cardiovascular medications through cytochrome P450 and p-glycoprotein inhibition.

ADDRESSING CARDIOVASCULAR RISK IN PATIENTS WITH PROSTATE CANCER ***Gaps in Cardiovascular Risk Factor Control***

Data from both administrative sources and a prospective cohort study suggest that cardiovascular risk factor control is suboptimal in patients with PC. Among US veterans with PC, 36% did not have blood pressure below a threshold of 140/90 mm Hg, 22% had elevated cholesterol levels as identified by low-density lipoprotein cholesterol of 130 mg/dL or greater or total cholesterol 240 mg/dL or greater, and 17% had glycated hemoglobin (HbA1c) 7% or greater or fasting glucose levels 126 mg/dL or greater.³² The thresholds referenced in this analysis were not refined according to patient's past history of CVD or cardiovascular risk. However, general cardiology guidelines recommend risk factor targets that vary, with more aggressive goals in those with established CVD or risk factors, such as diabetes. In 2811 patients with PC from 4 countries, risk factor targets were specified according to these participant characteristics. With these more stringent thresholds, 51% had suboptimal control of 3 of 5 or greater modifiable cardiovascular risk factors.³³ Ten percent were current smokers, 20% were considered physically inactive, 51% had low-density lipoprotein cholesterol levels above target, 75% had suboptimal blood pressure, and 91% had an elevated waist–hip

ratio (>0.90). These data indicate that many patients with PC have suboptimal control of cardiovascular risk factors, highlighting an important care gap.

The optimal strategy to address this gap in care is unclear. Many uro-oncologists' scope of practice may not extend to requesting and interpreting blood glucose and lipid results. While primary care may be considered the appropriate setting for managing cardiovascular risk factors, especially in patients receiving ADT, the data presented earlier indicate that risk factor targets are frequently unmet in these cohorts, despite most having had access to primary health care. Tools have been developed to help uro-oncologists identify patients with CVD, address cardiovascular risk factors, and refer suitable patients to a cardio-oncologist.³⁴ However, the extent to which clinicians will have the capacity to implement these recommendations, and their effectiveness at reducing cardiovascular risk, is unknown.

The implementation of cardiovascular risk scores may represent one way of identifying patients with PC who are at high cardiovascular risk. There are limited data about the validity of risk scores in PC populations that have been developed in the general population. The New Zealand cardiovascular risk prediction equation predicts 5 year cardiovascular event rates in New Zealand patients with PC.³⁵ The generalizability of this finding to other countries, and whether the inclusion of ADT use or PC characteristics in the risk score would add incremental information, is not known.

The Speculative Role of Gonadotropin-Releasing Hormone Antagonists

Unlike GnRH agonists, which achieve testosterone suppression by continual stimulation of the anterior pituitary, GnRH antagonists block the effects of GnRH on the pituitary. This leads to a more rapid and persistent suppression of luteinizing hormone, as well as testosterone release.

Degarelix was the first GnRH antagonist to achieve widespread availability. A post hoc analysis of early-phase randomized, controlled trials demonstrated that degarelix may be associated with fewer cardiovascular events than a GnRH agonist.³⁶ In addition, there are complementary data from animal models that raise the hypothesis that GnRH antagonists might differ from GnRH agonists with respect to their atherogenic effects. In *in vivo* studies in low-density lipoprotein (LDL) receptor (LDLR) knockout mice, the GnRH receptor antagonist, degarelix, led to less atherosclerotic aortic disease than a GnRH agonist.³⁷ In a more

recent *in vivo* study using a double-knockout (LDLR^{-/-}/follicle-stimulating hormone [FSH]-) mouse model,³⁸ we demonstrated that FSH facilitates the atherogenic effects of testosterone deprivation. Specifically, FSHβ^{-/-}: LDLR^{-/-} mice, untreated or castrated (orchiectomy, GnRH agonist, or antagonist), demonstrated significantly less atherogenesis compared with similarly treated LDLR^{-/-} mice. Delivery of exogenous FSH in FSHβ^{-/-}:LDLR^{-/-} mice restored the significant atherosclerotic changes seen in untreated LDLR^{-/-} mice. Smaller plaque burden in LDLR^{-/-} mice receiving GnRH antagonists versus agonists was nullified in FSHβ^{-/-}:LDLR^{-/-} mice. Importantly, these data should be considered hypothesis generating only because they relate to atherogenesis and characteristics of atherosclerotic plaque vulnerability in a murine model and not to clinical cardiovascular events.

Interest in this potential protective effect of GnRH antagonists was renewed when the HERO trial found a lower incidence of cardiovascular events in patients randomized to receive the oral GnRH antagonist, relugolix, as compared with the GnRH agonist, leuprolide.³⁹ When these data were included in a systematic review of randomized trials of GnRH antagonists, the pooled risk ratios (95% CIs) for adverse cardiovascular events, cardiovascular death, and all-cause mortality were respectively 0.57 (0.39–0.81), 0.49 (0.25–0.96), and 0.48 (0.28–0.83) as compared with GnRH agonists.⁴⁰ However, an important caveat to these data was the high risk of bias in the trials identified.

The PRONOUNCE trial was the first prospective trial to compare a GnRH antagonist (degarelix) with a GnRH agonist (leuprolide) with respect to a primary cardiovascular endpoint.⁴¹ However, the trial was terminated prematurely by the sponsor when only 545 of the planned 900 participants had been enrolled. Owing to the reduced sample size, as well as a lower outcome event rate than anticipated (which may have been partly related to the requirement that all participants be managed by a cardiologist), the trial was not powered to be able to draw inference about the cardiovascular effects of degarelix.⁴² When the findings from this trial were incorporated into an updated meta-analysis, the odds ratios (95% credible interval) for the composite of major adverse cardiovascular events and overall mortality were respectively 0.57 (0.37–0.86) and 0.58 (0.32–1.08).⁴³ However, as with the prior meta-analysis, confidence in these findings is low owing to the open-label nature of the trials and other potential biases and methodological limitations. Currently, it remains unclear whether GnRH antagonists offer cardiovascular benefits over

GnRH agonists. Further, there are clinical limitations to the current commercially available GnRH antagonists. Degarelix, which requires monthly injections, leads to a higher rate of skin adverse effects than GnRH agonists that can be administered less frequently. Relugolix is an oral agent, which requires adherence to a daily-dosing regimen. Research is ongoing into teverelix, a GnRH antagonist that can be administered every 6 weeks.

MANAGEMENT OF SEVERE CARDIOVASCULAR DISEASE IN PATIENTS WITH METASTATIC PROSTATE CANCER

Administrative data suggest that survival with metastatic PC is increasing. Between 2008 and 2020, 5 year survival in patients with metastatic castrate-sensitive disease in Sweden increased from 26% to 35%.⁴⁴ In the United States, from the years 2000 to 2004 to 2015 to 2019, among patients with *de novo* metastatic PC, median survival increased from 23 months to 30 months in the SEER registry and from 26 months to 31 months in the Veterans Health Administration registry.⁴⁵ The progressive improvement in overall survival in patients with metastatic PC exposes this population to the risk of developing severe CVD for a longer time, which is especially pertinent given the cardiovascular risks described previously.

There are numerous ongoing developments in the treatment of advanced PC, including the addition of androgen receptor signaling inhibitors to a GnRH agonist; PARP inhibitors; the promise of prolonged disease control with the use of radiotherapy for oligometastases; and prostate-specific membrane antigen-targeted therapies. These strategies have delivered or are expected to deliver even longer survival for patients with metastatic PC.

Historically (and to some extent currently), a cancer diagnosis has been associated with less invasive treatment of coronary artery disease.⁴⁶ Given the improving survival and rapid advances in metastatic PC treatment, the role of invasive cardiovascular interventions in patients with metastatic disease needs to be carefully considered. Factors that contribute to the decision-making process include characteristics of both the PC and the cardiovascular comorbidity; non-PC, non-cardiovascular comorbidities, including the risk of bleeding; and patient goals-of-care.⁴⁷ In general, cardiovascular interventions that confer substantial benefit (including symptomatic benefit) rapidly, such as primary percutaneous coronary intervention for ST-elevation myocardial infarction, transcatheter aortic valve implantation (TAVI), a routine invasive approach for non-ST elevation myocardial

infarction with ongoing symptoms, and cardiac resynchronization therapy for severe symptomatic heart failure, are compelling in many patients with metastatic PC. In contrast, invasive strategies like primary prevention implantable cardioverter-defibrillators that confer little symptomatic benefit and whose survival benefits are only observed after a longer lag are generally not indicated in those with metastatic cancer. The most challenging of decisions relates to the role of coronary revascularization (and in particular coronary artery bypass surgery) for minimally symptomatic multivessel coronary disease because the survival advantage over medical therapy is more modest, because of the front-loaded procedural risks and because net benefit may only be apparent years after intervention.

As localized PC has a low risk of 10 year PC-specific mortality, most invasive cardiovascular interventions that are otherwise indicated should be adopted in these patients. Among cardiac interventions, cardiac transplantation arguably demands the largest commitment on the part of the patient, health care providers, and health systems. At present, cardiac transplantation in patients with localized PC is only considered in a minority of intuitions in the United States.⁴⁸ Further research on outcomes in patients with localized PC may inform cardiac transplantation policies given their generally favorable cancer prognosis.

In some instances, PC may be diagnosed during the work-up of patients for invasive cardiac interventions. In one series of 414 German patients who underwent imaging in preparation for TAVI, 36 (9%) had incidental findings consistent with malignancy with a potential impact on life expectancy, including 3 (0.7%) with advanced PC.⁴⁹ While this research is methodologically limited, there was no evidence that such findings changed patient management or outcomes in these patients with an indication for TAVI.

In summary, the decision to undertake an invasive cardiovascular intervention in a patient with metastatic PC should be informed by a multidisciplinary team, with the patient and their caregivers at the center of the decision-making process, so that their goals-of-care are prioritized.

SUMMARY

CVD is common in patients with PC and is an important cause of death. Cardiovascular risk factors are frequent in this population and are often not addressed to thresholds recommended by cardiovascular practice guidelines. Further research is needed to understand the reasons for these treatment gaps and to examine the role of low

education, racial inequities, disparities in access to care, patient perceptions of health priorities, and the impact of anxiety and depression.

ADT reduces muscle strength and increases adiposity, thereby increasing the risk of diabetes and hypertension, although its relationship with adverse cardiovascular events requires confirmation. Androgen receptor signaling inhibitors and CYP17A1 inhibitors may confer incremental risks of hypertension and cardiovascular events to ADT, so these patients may require particularly close clinical attention.

GnRH antagonists have been linked with a lower cardiovascular risk as compared with GnRH agonists. However, this association has yet to be confirmed in a randomized clinical trial that has implemented the appropriate measures to mitigate bias. Until such data are available, it is reasonable to consider GnRH antagonists in individuals at high cardiovascular risk who are likely to comply with GnRH antagonist regimens.

CLINICS CARE POINTS

- Clinicians should be aware that patients with prostate cancer frequently have a high burden of cardiovascular risk factors and disease, which may be undertreated.
- Androgen deprivation therapy increases adiposity and decreases muscle strength. Strategies for monitoring blood pressure, blood glucose levels and lipid levels should be developed.
- Prescribers should be aware of the potential for pharmacokinetic drug-drug interactions related to androgen receptor signaling inhibitors and abiraterone. These drugs also increase the risk of hypertension and fluid retention.
- It is uncertain whether GnRH antagonists, such as degarelix and relugolix, offer cardiovascular benefits over GnRH agonist androgen deprivation therapy regimens.

DISCLOSURE

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Evolving Strategies in Cardiac Amyloidosis

From Mechanistic Discoveries to Diagnostic and Therapeutic Advances



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KEYWORDS

• Amyloidosis • Amyloid cardiomyopathy • Transthyretin • AL • TTR • Fibril • Misfolded

KEY POINTS

- Cardiac amyloidosis is caused by the self-aggregation of misfolded proteins, transthyretin amyloid (ATTR) monomers or light chains, into amyloid fibrils that deposit into the myocardium.
- Diagnosis of cardiac amyloidosis requires a high index of suspicion due to the nonspecific initial clinical findings, followed by a diagnostic pathway that utilizes a combination of biomarkers, noninvasive cardiac imaging (bone scintigraphy), and biopsy of affected organs to differentiate the type of cardiac amyloidosis.
- The treatment of ATTR cardiac amyloidosis is rapidly evolving with multiple new treatments that target specific steps in the pathogenesis of disease, including ATTR tetramer stabilizers, interfering RNA, gene editing, and monoclonal antibodies.
- Treatment of immunoglobulin light chain cardiac amyloidosis requires chemotherapy to reduce monoclonal plasma cell light chain production, sometimes followed by autologous stem cell transplant.

INTRODUCTION

Cardiac amyloidosis is an underrecognized cause of heart failure with a rapidly evolving armamentarium of novel, targeted diagnostic tools and therapeutics. Systemic amyloidosis occurs due to self-aggregation of abnormally misfolded precursor proteins into stereotyped insoluble β -sheet fibrils. These fibrils deposit into the extracellular space and disrupt the normal function of multiple organs, including kidney, brain, nerves, liver, and heart.¹ Over 30 precursor proteins have been

identified, each of which has specific predispositions toward different organ involvement. Cardiac amyloidosis is primarily caused by misfolding of either transthyretin (TTR) or immunoglobulin light chains (LC), leading to amyloid transthyretin (ATTR) and light chain (AL) cardiomyopathy (CM), respectively (Fig. 1A, B). Deposition of amyloid fibrils in the myocardium disrupts the normal cardiac structure and function, causing progressive myocardial dysfunction through both mechanical and electrophysiological changes. Typically, there is a latent asymptomatic phase followed by early

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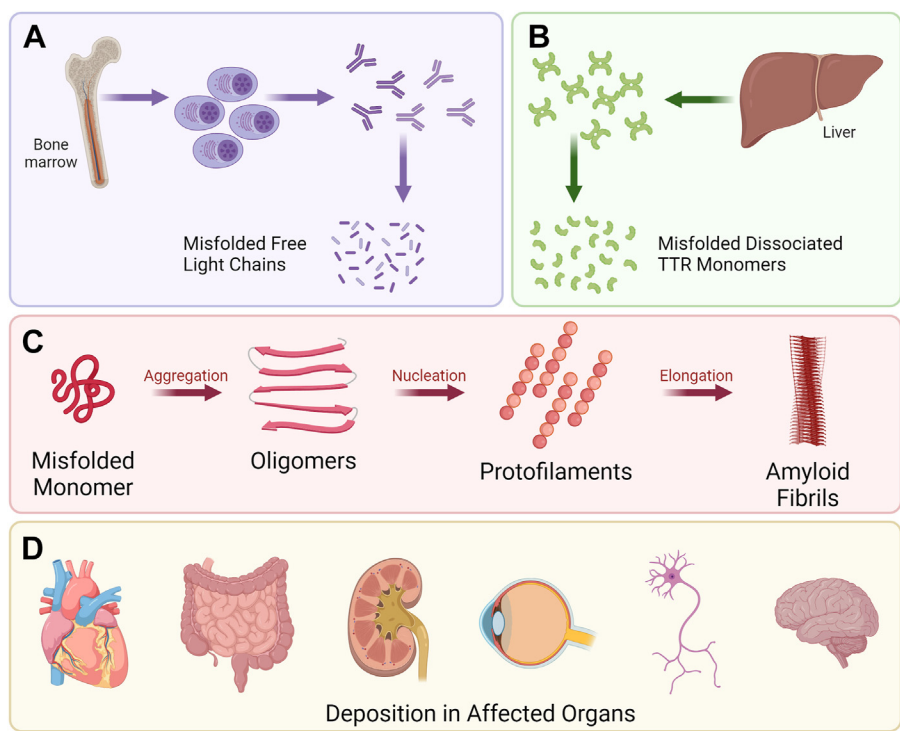


Fig. 1. Mechanism of Cardiac Amyloidosis. (A) Proliferation of monoclonal plasma cells in the bone marrow produces excess free light chains (LC). (B) Transthyretin (TTR), a tetramer protein, is produced primarily in the liver. Destabilization of the tetramer structure leads to misfolded monomers. (C) The conserved mechanism of amyloid fibril formation. Misfolded precursor proteins, TTR and LC in cardiac amyloidosis, self-aggregate to form oligomers with an intermediate cross-β sheet structure. These form protofilaments, which form a nucleus on which monomers can preferentially bind to form fibrils. (D) Amyloidosis is a systemic disease, and fibrils can deposit in organs throughout the body, including heart, gastrointestinal tract, kidney, eye, and peripheral and central nervous system. (Created in BioRender. Stein-merlob, A. (2024) BioRender.com/e62c872.)

diastolic dysfunction, then a restrictive CM and, in some patients, eventual development of left ventricular (LV) dilation and reduced left ventricular ejection fraction (LVEF).² In this review, the authors explore recent advances in our understanding of cardiac amyloidosis, focusing on the underlying mechanisms of disease pathogenesis, improvements in diagnostic approaches, and the development of innovative, targeted treatments.

EPIDEMIOLOGY OF CARDIAC AMYLOIDOSIS

Once considered a rare disease, cardiac amyloidosis is now recognized as a significant cause of heart failure. Breakthroughs in noninvasive imaging techniques for ATTR-CM have reshaped our diagnosis of the disease, and there is growing evidence to suggest it is more prevalent than previously believed. Prevalence estimates for ATTR-CM in Sweden, for example, have increased from 1.0 to 5.0 per 100,000 person years from 2008 to 2018.³ Moreover, ATTR-CM is thought to be the underlying etiology in 20% of elderly patients

with heart failure and increased LV wall thickness.⁴ AL amyloidosis is the most common form of systemic amyloidosis and cardiac manifestations occur in about 70% of patients. AL amyloidosis has an estimated incidence of about 12 per 1 million per year and an estimated prevalence of 40 to 58 individuals per million person years.⁵ Improved survival has increased the prevalence, with estimates rising by 12% annually from 2007 to 2015.^{5,6}

Despite recent improvements in treatment, the prognosis of cardiac amyloidosis is poor. For ATTR-CM, even with early presymptomatic diagnosis, one-third of patients die or require orthotopic heart transplant (OHT) at 3 years follow-up. When diagnosis is made after the development of clinical signs of heart failure, median survival is 3 years.^{7,8} The prognosis for AL-CM is particularly poor and is dependent on the degree of cardiac involvement. AL-CM patients with abnormal cardiac biomarkers (N-terminal-pro B-type natriuretic peptide and troponin), with thresholds based on the well-validated Mayo Clinic staging system,

have historically had a median survival of 7 to 8 months.¹ However, with current advances in targeted therapeutics for both ATTR-CM and AL-CM, the landscape of disease management is constantly evolving to improve patient outcomes through early detection and personalized treatment.

PATHOPHYSIOLOGY OF CARDIAC AMYLOIDOSIS

Production of Amyloid Precursors

AL amyloidosis is caused by proliferation of monoclonal plasma cells in the bone marrow that produce an excess of free light chains, either lambda LC (75%–80%) or kappa LC (20%–25%; see **Fig. 1A**). These light chains are kinetically or thermodynamically unstable and can self-aggregate into soluble prefibrillar oligomers followed by amyloid fibrils. In AL amyloidosis in particular, these oligomers have been found to be particularly cytotoxic leading to mitochondrial damage and myocyte death.⁵

TTR, also called prealbumin, is a tetramer protein primarily synthesized in the liver (>95%) with a normal function of transporting thyroxine (T₄) and retinol (vitamin A). When the tetramer structure destabilizes, monomer subunits have the propensity to misfold and self-aggregate into ATTR fibrils that deposit within the myocardium (see **Fig. 1B**). In addition to spontaneous destabilization, vascular clots containing plasminogen, tissue plasminogen activator, and urokinase have been hypothesized to cleave TTR into monomers and accelerate perivascular ATTR deposition.⁹ TTR is produced by a single gene. Most of the 130 known mutations destabilize the ATTR tetramer and promote the production of free monomers. These pathogenic variants cause hereditary transthyretin amyloidosis (hATTR).¹⁰ Even in the absence of known genetic mutations, wild-type transthyretin amyloid (wtATTR) causes an age-dependent systemic amyloidosis, previously called senile systemic amyloidosis. In fact, up to a quarter of individuals aged over 80 years had evidence of myocardial ATTR deposition on autopsy.² The mechanism is not yet fully understood, but hypotheses include oxidation-induced destabilization of TTR or reduced ATTR clearance with age.

Conserved Mechanism of Amyloid Fibril Formation

Amyloid fibrils form via stereotyped kinetics (**Fig. 1C**) that have been well established in vitro. There is a sigmoidal growth curve and 3 distinct phases: (1) lag phase, (2) elongation phase, and (3) equilibrium phase.^{11–13} For ATTR, the rate-limiting

step is the dissociation of circulating TTR tetramers into misfolded monomers and dimers. After dissociation, monomers self-aggregate to form intermediate cross- β sheets oligomers followed by stable amyloid fibrils. After the formation of critical-sized nuclei and fibrils, monomers preferentially bind to the ends of fibrils in the elongation phase until an equilibrium is reached. Importantly, when preformed amyloid fibrils or seeds are present, the initial lag phase is bypassed. This is seen clinically with ongoing ATTR fibril formation even after orthotopic liver transplant (OLT) stops production of hATTR tetramers due to ongoing production of wtATTR.¹⁴

In vitro amyloid fibrils demonstrate significant mechanical anisotropy, or direction-dependent mechanical properties. There is increased stiffness in the axial direction, due to hydrogen bonding of the β -sheet backbone, compared to the tangential stiffness, which is determined by the interactions of protein side chains.¹⁵ Amyloid fibrils typically have a diameter of 7.5 to 10.0 nm.⁵ In the axial direction, fibrils are linearly elastic with Young's modulus of about 1 GPa, similar to collagen and silk.¹⁶ Greater fibril diameter increases axial stiffness of the amyloid fibril and decreases radial stiffness.¹⁷ Due to their unique mechanical properties, synthetic amyloid fibrils have been investigated for their use as nanomaterials.¹⁷

Deposition and Clearance of Myocardial Amyloid Fibrils

The progression and pattern of amyloid fibril deposition in the myocardium have been more extensively studied in ATTR-CM. A comprehensive histologic analysis of myocardial tissue from autopsy in wtATTR and hATTR elucidated 2 key patterns of ATTR deposition.¹⁸ In wtATTR, there were predominantly large, discrete nodules with histologically weak congophilic birefringence with short, randomly oriented ATTR fibrils on electron microscopy (EM). These findings were theorized to occur due to differences in local fragmentation and clearance of fibrils in wtATTR.¹⁸ In hATTR, there was patchy subendocardial and subepicardial ATTR deposition without distinct nodules. Histologically, the ATTR was strongly congophilic and birefringent with long, straight, and parallel amyloid fibrils surrounding myocytes on EM. Comprehensive EM in 11 patients with hATTR detailed the progression of amyloid deposition in the myocardium. Early stages of deposition occur on the subendocardial surface and then progressively penetrate the myocardium, encasing myocytes. In advanced stages, amyloid fibrils surround and project into apoptotic myocytes.¹⁹ With increased

ATTR fibril deposition, the diameter of amyloid fibrils increased to greater than 10 nm.¹⁹ It was found that the basement membrane on the subendocardial surface can act as a seed for amyloid fibril formation, likely playing a role in the subendocardial predominance.¹⁹

The accumulation of amyloid fibrils within the myocardium occurs due to a loss of balance in protein homeostasis (called proteostasis), which is maintained by removal of misfolded proteins from the extracellular space. There are over 1600 molecules involved in preserving proteostasis, but a specific extracellular chaperone, clusterin, has been particularly implicated in the pathogenesis of ATTR-CM and AL-CM.²⁰ Clusterin, also known as apolipoprotein J, is a highly conserved extracellular chaperone found in the extracellular space in multiple organs including the myocardium. Clusterin binds to misfolded proteins to inhibit fibril formation and forms a soluble complex capable of endocytosis.²¹ Expression of clusterin is upregulated by cellular stress, growth, differentiation and aging, and it is also induced by the presence of amyloid monomers and fibrils. Immunohistochemistry in V30M transgenic mice has shown colocalization with fibrillar and non-fibrillar ATTR. In vitro, ATTR oligomers induce clusterin overexpression, and clusterin depletion leads to increased extracellular ATTR aggregation.²² In addition to clusterin, there are likely additional mechanisms for ATTR clearance utilizing both fibroblasts and macrophages.²³ A similar process occurs in AL amyloidosis.⁵ Loss of efficacy of proteostasis overtime may contribute to the increased risk of the ATTR and AL-CM with advanced age.

DIAGNOSIS OF CARDIAC AMYLOIDOSIS

Amyloid deposition into the cardiac muscle, conduction system, and valves has variable effects on cardiac function. The effects of this systemic disease on other organ systems can be diverse as well, as evident by the widely varied phenotypes seen between and even within subtypes. Unsurprisingly, the range of clinical manifestations leads to difficulties and delays in diagnosis, likely contributing to its underestimated prevalence.²⁴ Moreover, the need for diagnostic accuracy and timeliness was historically less clinically relevant than it is today, as recent innovations in noninvasive diagnostic imaging and targeted treatment modalities have transformed the landscape of cardiac amyloidosis.

Clinical Presentation

Early recognition of cardiac amyloidosis requires a thorough clinical evaluation and a high index of

suspicion. Familiarity with risk factors and clinical manifestations of AL and ATTR amyloidosis are particularly important as the majority (98%) of cardiac amyloidosis cases are caused by these subtypes.²⁵

Advanced age is a common risk factor for both subtypes. This association is especially true for ATTR-CM, which typically presents in patients aged 60 years or more and most commonly greater than 70 years. A family history of amyloidosis is another important risk factor given the genetic etiology of some ATTR subtypes. While hATTR-CM can occur in patients of all races, ethnicities, and geographic backgrounds, genetic variants known to cause hATTR appear disproportionately in certain populations. For example, the Val122Ile variant is seen more frequently in individuals of West African ancestry, who most often identify as Black or Hispanic. Other variants are more prevalent in those claiming Portuguese, Japanese, or Swedish nationality (Val30Met) and in those of Irish ancestry (Thr60Ala).²⁶

The risk of AL amyloidosis also increases with age, as is seen with other types of plasma cell dyscrasias. The median age at diagnosis of 64 years, and presentations before the age of 40 years are exceedingly rare. A previous diagnosis of monoclonal gammopathy of unknown significance (MGUS) is an important historic clue. Individuals with a history of another plasma cell dyscrasia, like multiple myeloma or Waldenström's, also appear to be at increased risk of developing AL amyloidosis.

Cardiac manifestations

Cardiac involvement is a predominate feature of both AL and ATTR amyloidosis and a leading cause of morbidity and mortality. The natural history of ATTR-CM has a long latent, asymptomatic period with progressive ventricular wall thickening, followed by diastolic dysfunction and a restrictive CM. Patients most commonly present with signs and symptoms of heart failure including dyspnea, fatigue, lower extremity edema, congestive hepatopathy, and an elevated jugular venous pressure. Elevations in natriuretic peptides (BNP, NT-proBNP) and cardiac troponins may occur from long-standing progressive cardiac strain and myocyte damage. Rarely, severe progressive disease can present with decreased cardiac output and cardiogenic shock.

Conduction disease and arrhythmias are also common in ATTR-CM. Changes in atrial contractility from myocardial infiltration can alter sinus node and conduction system function, as can direct effects of amyloid fibril deposition into the conduction system. This process may manifest

as sick sinus syndrome, heart blocks, or tachyarrhythmias, which may produce symptoms (ie, palpitations, presyncope, syncope) or present asymptotically. Atrial fibrillation is seen in an estimated 40% to 70% of patients with cardiac amyloidosis and is especially common in wtATTR-CM.^{27–30} Cardiac amyloidosis is also associated with an increased risk of arterial thromboembolic events, a known complication of atrial fibrillation and other arrhythmias, with studies suggesting an increased risk of thromboembolism risk in sinus rhythm as well.³¹

Valvular disease has also been associated with cardiac amyloidosis, especially aortic stenosis (AS). Advanced age is a known risk factor for both diseases, and numerous studies have described a high prevalence of cardiac amyloidosis in patients with severe AS. A study by Castaño and colleagues³⁰, for example, found that 16% of study participants (n = 156) undergoing transcatheter aortic valve replacement (TAVR) for severe AS also had ATTR-CM on bone scintigraphy. Other studies evaluating patients undergoing SAVR or TAVR found similar findings, with concomitant ATTR-CM in 5.6% to 33% of participants.^{32–37} The prognosis of concomitant disease appears to be worse than either AS or ATTR-CM alone, suggesting a possible bidirectional relationship in the pathophysiology of these 2 diseases.

The range of clinical manifestations of AL-CM is similar to ATTR-CM, though patients with AL-CM tend to have more severe and symptomatic disease. Based on such observations as well as in vitro studies, it is postulated that some amyloid deposits associated with AL may cause direct myocyte toxicity in addition to their infiltrative properties.^{38,39} AS and other valvular disease are less frequently associated with AL-CM than with ATTR, possibly related to discrepancies in age, duration of disease, or distribution of amyloid fibril deposition.³²

Extracardiac symptoms

Evaluation for extracardiac disease can provide clues into the diagnosis of amyloidosis (Fig. 1D). Signs and symptoms of neuropathy are frequently seen in with both ATTR and AL amyloidosis. Patients may experience peripheral neuropathy, with complaints of pain or thermal sensitivity in the hands and feet. Focal neuropathy such as carpal tunnel syndrome is a common early symptom of ATTR and often bilateral. Autonomic neuropathy may occur, which can present as orthostatic/postural hypotension (light headedness, presyncope, or even syncope), genitourinary complaints (bladder dysfunction, erectile dysfunction), or

gastrointestinal symptoms (early satiety; diarrhea, constipation, or both).⁴⁰

Other extracardiac symptoms are more subtype specific. A history of musculoskeletal complaints (ie, lumbar spinal stenosis, biceps tendon rupture, tendinopathy, joint pain, history of orthopedic surgery) is often reported in patients with ATTR amyloidosis.^{24,41} Soft tissue involvement including macroglossia and submandibular gland enlargement is seen almost exclusively in AL amyloidosis. Periorbital purpura from capillary fragility and acquired Factor x deficiency, presumably due to adsorption of Factor x to amyloid fibrils, is an uncommon but pathognomonic findings of AL amyloidosis.^{40,41} Proteinuria from renal involvement is often seen in AL amyloidosis, as well as other less common subtypes (AA, fibrinogen A a-chain, ALect, AApoA1, Alys).¹ AL fibril deposition may lead to hepatic dysfunction and hypothyroidism as well.^{1,41}

Routine Cardiac Imaging

Electrocardiogram (ECG) and echocardiograms provide key information and should be collected in all patients undergoing evaluation for possible cardiac amyloidosis. ECG may show evidence of conduction dysfunction or arrhythmias as noted earlier. Low QRS complex voltage is a widely known characteristic finding but has low sensitivity.²⁴ On echocardiogram, moderate-to-severe LV wall thickness (≥ 14 mm), particularly in the absence of a history of hypertension, and/or a QRS voltage on EKG that is discordant to the degree of wall thickness should raise suspicion for cardiac amyloidosis. Evidence of diastolic dysfunction with a preserved LVEF is typically seen, though up to 30% to 40% of patients will have a reduced LVEF.⁴² Evaluation of myocardial global longitudinal strain (GLS) by speckle tracking echocardiogram can be useful for identifying myocardial dysfunction before a reduction in EF and for distinguishing between other etiologies causing LV hypertrophy. Cardiac amyloid has a characteristic “apical sparing” pattern of GLS, whereby strain is relatively preserved in the apex. Although this pattern increases the likelihood of diagnosis of cardiac amyloidosis, it has only moderate sensitivity and specificity for diagnosis.^{43,44} The mechanism by which apical sparing occurs is still not fully elucidated, though hypotheses include relative differences in amyloid deposition from apex to base, myocyte and myofiber orientation changes due to amyloid deposition, and differential apoptosis due to wall stress.⁴⁵

Cardiac MRI (CMR) can be useful in the initial workup in some clinical scenarios, particularly in

differentiating between other forms of CM that may present similarly. Characteristic findings in cardiac amyloidosis include elevated native T1, increased extracellular volume (ECV) fraction, late gadolinium enhancement (LGE), and abnormal gadolinium kinetics.²⁴ Cardiac amyloid typically presents with diffuse subendocardial LGE. ECV has been shown to be an accurate marker of extracellular cardiac amyloid infiltration and correlates well with disease severity.⁴⁶ The absence of these findings can help rule out cardiac amyloidosis in patients with low pretest probability. In contrast, CMR may be unnecessary in patients with a high-pretest probability of cardiac amyloidosis. In select patients, a diagnosis of cardiac amyloidosis may be inferred from a positive extracardiac biopsy and characteristic CMR findings. In most cases, however, CMR is insufficient for definitive diagnosis of cardiac amyloidosis.

Risk stratification tools

With recent and ongoing therapeutic advances, there has been an understandable push to increase earlier diagnosis of ATTR-CM. Numerous risk scores have been developed, incorporating clinical, ECG, and/or echocardiography data. Tools using advanced artificial intelligence (AI) have also been devised as well with promising preliminary results.^{47–49} For example, a novel AI algorithm that integrates ECG and echocardiogram was developed with a positive predictive value of 74% to 77%.⁴⁷ Similarly, an automated deep learning algorithm analyzing LV hypertrophy on echocardiogram imaging was able to detect cardiac amyloidosis with an area under the curve of 0.79.⁵⁰ While more studies are needed for validation in larger and more diverse populations, risk stratification tools, particularly those that harness the power of AI, may prove useful in the future.

Evaluation for Cardiac Amyloidosis

In patients with suspected cardiac amyloidosis based on clinical presentation and initial cardiac evaluation, we propose a diagnostic algorithm (Fig. 2) that can be used for definitive diagnosis and typing of cardiac amyloidosis.²⁶ First, a monoclonal protein screen should be performed to identify patients at risk for AL amyloidosis. Three laboratory studies are recommended for the evaluation of monoclonal protein expansion: serum-free light chain (sFLC) assay, serum immunofixation electrophoresis (SIFE), and urine immunofixation electrophoresis (UIFE). The sFLC measures the relative proportions of kappa and lambda light chains, with normal ratios ranging from 0.26 to 1.65.²⁶ Of note, light chains are cleared in part by the kidney, and renal clearance of kappa light

chains occurs more efficiently than lambda under normal conditions. As such, higher ratios (ie, up to 3.30) may be considered normal in patients with chronic kidney disease.²⁶ A proposed adjustment to the “normal” ratio range is 0.50 to 2.00 for glomerular filtration rate (GFR) 40 to 60 and 0.7 to 2.25 for GFR less than 40.⁵¹ SIFE and UIFE assess for the presence of a monoclonal protein using electrophoresis followed by immunofixation. It is important to recognize that electrophoresis alone without immunofixation has decreased sensitivity with very small proteins like amyloid fibrils and cannot determine heavy or light chain classes. Therefore, serum/urine protein electrophoresis is less accurate compared to SIFE/UIFE for AL amyloidosis and is not recommended.

An abnormal kappa/lambda ratio on sFLC (ie, <0.26 or >1.65) or detection of a monoclonal protein on SIFE or UIFE is considered a positive monoclonal protein screen and raises concern for AL-CM. Alternatively, if the screen is negative, AL amyloidosis can be excluded with a negative predictive value of approximately 99%,^{26,52,53} and patients should undergo evaluation for ATTR-CM.

Evaluation for AL amyloidosis

Abnormalities on sFLC, SIFE, or UIFE can indicate a variety of diseases, including multiple myeloma, MGUS, or AL amyloidosis. In the setting of an abnormal monoclonal protein evaluation, confirmation of amyloid fibril deposition via tissue biopsy is required to confirm the diagnosis of AL amyloid. If there is a concern for extracardiac manifestations, biopsy of the involved tissue is preferred. Alternatively, biopsy of the abdominal fat pad is low risk with high sensitivity. Endomyocardial biopsy is rarely performed but can be done if there is ongoing diagnostic uncertainty despite exploration of alternative sites. On biopsy samples, Congo red staining with birefringence on polarized light microscopy is still the gold standard for diagnosis. Immunohistochemistry and mass spectrometry can then be performed to specifically phenotype the amyloid fibrils to confirm the diagnosis of AL-CM or ATTR-CM. All patients should be referred to an oncologist for a bone marrow biopsy and further evaluation for plasma cell malignancies, as well as comanagement of AL amyloidosis if confirmed.

Evaluation for ATTR amyloidosis

In patients in whom AL-CM has been excluded, the next step in the diagnostic pathway is a Technetium-99m pyrophosphate (PYP) single-photon emission computed tomography (SPECT) scan (also referred to as Tc-99m PYP or bone scintigraphy scan).

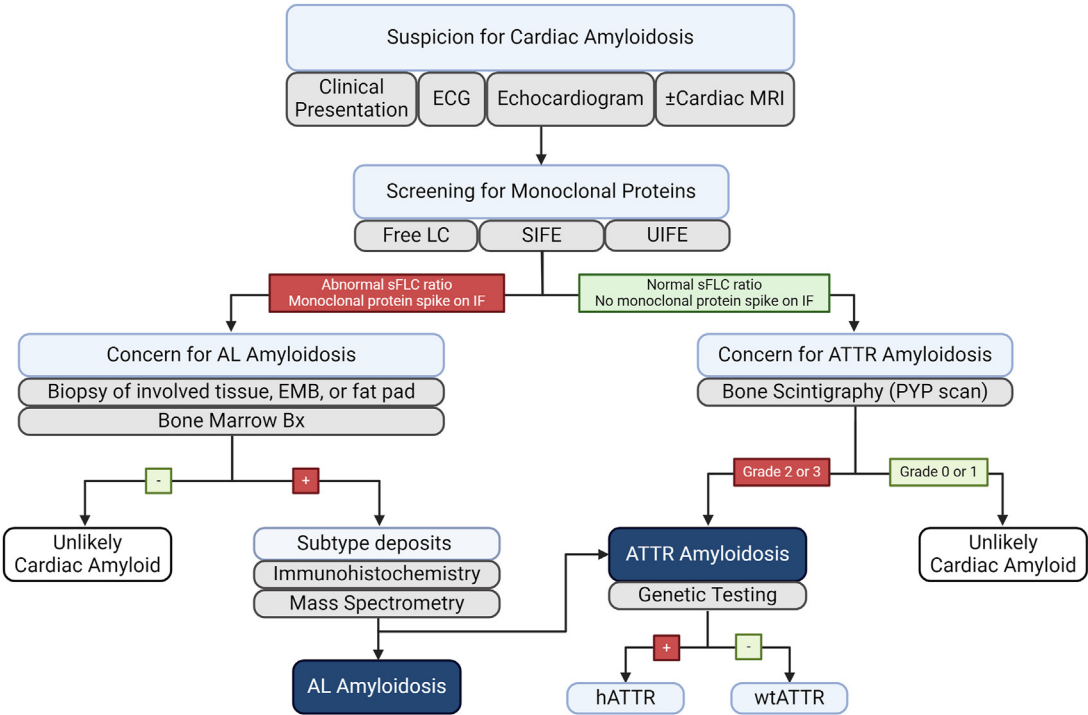


Fig. 2. Diagnostic algorithm for treatment of cardiac amyloidosis. ATTR, amyloid transthyretin; ECG, electrocardiogram; EMB, endomyocardial biopsy; hATTR, hereditary transthyretin amyloidosis; LC, light chain; PYP, pyrophosphate; SIFE, serum immunofixation electrophoresis; UIFE, urine immunofixation electrophoresis; wtATTR, wild-type transthyretin amyloidosis. (Created in BioRender. Stein-merlob, A. (2024) BioRender.com/h30n772.)

Recent studies have shown that in the context of a negative monoclonal screen, bone scintigraphy can diagnose ATTR-CM with high sensitivity and specificity,^{46,54,55} a revolutionary discovery in the diagnosis of ATTR-CM. In a landmark study by Gillmore and colleagues⁵⁶, bone scintigraphy was greater than 99% sensitive for identifying ATTR-CM, with a positive predictive value of 86%. False positives were almost exclusively due to cases of AL-CM, highlighting the importance of the monoclonal screening test. It is thought that Tc-99m PYP binds to amyloid deposits due to microcalcifications that are evident more in ATTR than AL amyloidosis.⁵⁷

The Tc-99m PYP scan starts with an injection of the bone avid tracer, PYP. Tracer uptake in cardiac muscle is compared to uptake in the ribs at 1 and 3 hours after tracer injection and graded on a scale of 0 to 3 per the Perugi staging system (grade 0 no cardiac uptake, grade 1 mild uptake less than the rib, grade 2 moderate uptake equal to the rib, grade 3 high uptake greater than the rib).⁵⁸ The ratio of tracer uptake in the heart compared to lungs is also evaluated. The presence of grade 2 or 3 using the cardiac-to-rib uptake grading system or a heart-to-lung uptake ratio greater than 1.5 is considered a positive test and is diagnostic for

ATTR-CM in the setting of a negative monoclonal protein screen.^{46,54,55} SPECT allows for the additional benefit of 3 dimensional analysis, which is used to evaluate positive cases for any blood pooling that may be misidentified as cardiac uptake.

In addition to the Tc-99m PYP scan, there are multiple novel targeted imaging tracers currently being developed for cardiac amyloidosis but are not yet in clinical use.⁵⁷ The amyloid-specific probes that have been developed target both AL and ATTR amyloid deposits. For example, the PET tracers [¹¹C]-Pittsburgh compound B ([¹¹C]-C-PiB) and [¹⁸F]-florbetapir bind to any β -amyloid structure and were initially developed for the diagnosis of Alzheimer disease. Both agents show significant uptake in the presence of all types of cardiac amyloidosis, and [¹¹C]-C-PiB shows promise for measuring response to treatment in AL-CM. Large studies to evaluate the diagnostic accuracy of these novel agents are needed before application to clinical use.

Once ATTR-CM is confirmed, genetic sequencing of the TTR gene is recommended in all patients. This additional testing is needed to differentiate between hATTR and wtATTR forms, as there are important management considerations for patients with hATTR. First, family members of these patients

may be at increased risk of cardiac amyloidosis, and genetic counseling and screening of family members may be indicated. Second are therapeutic implications, as certain treatments have only been approved for variant subtypes.²⁴ Third, patients with high-risk mutations associated with more progressive cardiac disease (ie, Val122Ile) or neurologic and other extracardiac manifestations (ie, Val30Met, Thr60Ala) may prompt consideration for closer follow-up or specialist referrals.^{24,26}

TREATMENT OF ATTR-CARDIOMYOPATHY

Recently developed targeted treatments have revolutionized the care of ATTR-CM. Treatments have been developed to target almost every step of ATTR fibril formation and clearance (Fig. 3). These mechanisms range from modification of hATTR mutations, reduced synthesis of ATTR, and disruption of ATTR fibrils, to direct clearance

of fibrils. Next, we discuss the current investigational and approved treatments for ATTR-CM, and the pivotal clinical trials are summarized in Table 1.

Modification of Transthyretin Mutations

Liver transplant

As over 95% of TTR is produced in the liver, the first specific treatment of hATTR was OLT, first performed in 1990.^{30,59} However, because of the kinetics of amyloid fibril seeding, preexisting ATTR fibrils within the myocardium can serve as substrate for ongoing deposition of wtATTR that may be produced posttransplant, leading to progressive cardiac dysfunction.⁶⁰ Nevertheless, long-term survival after OLT for patients with hATTR, particularly for early onset patients, has been good, with 20 year survival post-OLT of 55.3%.⁶¹ In select cases of severe cardiac

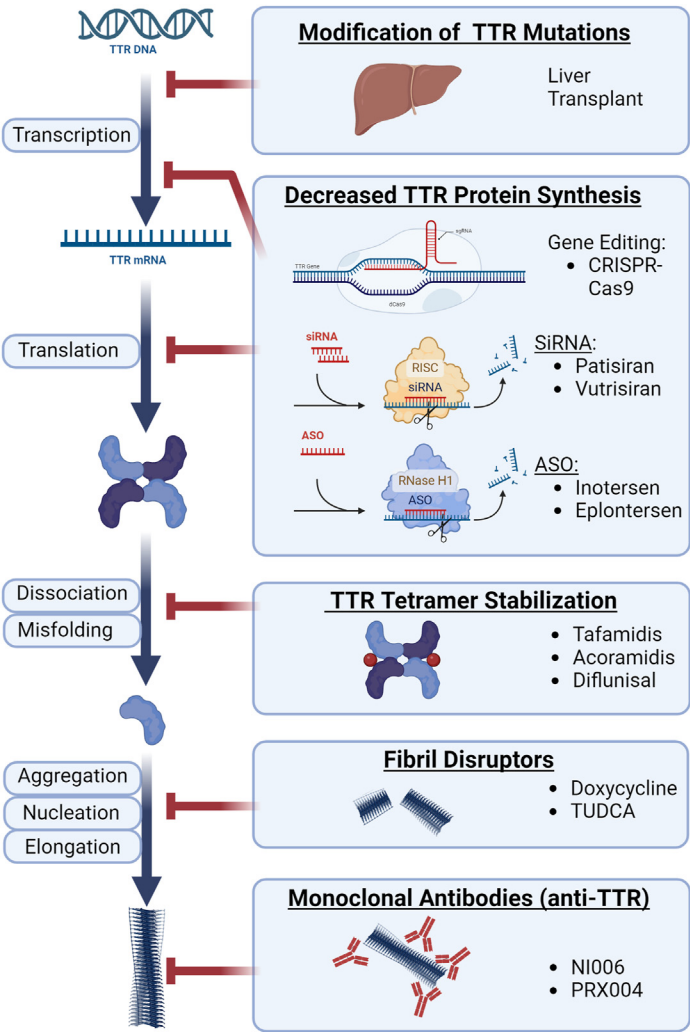


Fig. 3. Treatment mechanisms in transthyretin cardiac amyloidosis. Mechanisms of current investigational and clinical treatments for transthyretin cardiac amyloidosis. ASO, antisense oligonucleotides; CRISPR-Cas9, clustered regularly interspaced short palindromic repeats and associated Cas9 endonuclease; siRNA, small interfering ribonucleic acid; TTR, transthyretin; TUDCA, tauro-ursodeoxycholic acid. (Created in BioRender. Stein-merlob, A. (2024) BioRender.com/v57s149.)

Table 1
Major clinical trial for treatments of transthyretin amyloidosis

Study	Treatment	Trial Type	Population	Primary Outcome	Secondary Findings
Decreased TTR Protein Synthesis					
Small Interfering RNA (siRNA)					
APOLLO, Adams et al, ⁶² 2018	Patisiran	Phase 3, randomized placebo-controlled (2:1) trial for 18 mo	225 patients with hATTR-PN	Slowed progression of neuropathy	Subgroup analysis ATTR-CM (n = 126): reduced LV wall thickness, improved GLS, improved CO, reduced NT-pro-BNP ²
APOLLO-B, Maurer et al, ⁶³ 2023	Patisiran	Phase 3, double-blind, randomized placebo-controlled (1:1) trial for 12 mo	360 patients with hATTR-CM and wtATTR-CM	Decline in 6MWT decreased	Secondary endpoints negative: KCCQ-OS, composite (mortality, CV events, 6MWT), (mortality, hospitalization and HF)
ENDEAVOR, Judge et al, ⁶⁵ 2020	Revusiran	Phase 3, randomized, double-blind placebo-controlled (2:1) trial for 18 mo	206 patients with hATTR-CM	6MWT; Stopped early due to increased mortality	
HELIOS-A, Adams et al, ¹⁰⁸ 2023	Vutrisiran	Phase 3, randomized, open-label, patisiran, and placebo-controlled (3:1) trial for 18 mo	164 patients with hATTR-PN	Improvement in mNIS+7(neuropathy score)	Non-inferiority to patisiran. Improvement in QOL, 10-m walk test, modified BMI.
HELIOS-B, Fontana et al, ⁶⁶ 2024	Vutrisiran	Phase 3, randomized placebo-controlled trial (1:1) for 30–36 mo	655 patients with hATTR- and wtATTR-CM	Reduced mortality Reduced CV events	Less decline in 6MWT, less decline in KCCQ-OS score
Antisense Oligonucleotides (ASO)					
NEURO-TTR, Benson et al, ⁶⁷ 2018	Inotersen	Phase 3, randomized, double-blind, placebo-controlled (2:1) trial for 15 mo	172 patients with hATTR-PN	Reduced neurologic progression (mNIS+7, QOL-DN), improved QOL	Increased risk of thrombocytopenia and glomerulonephritis
Gene Editing – CRISPR-Cas9					
Gillmore et al, ⁶⁹ 2021	NTLA-2001	Phase 1, open-label dosing trial	6 patients with hATTR-PN	No serious adverse events	87% reduction in serum TTR at 28 d at high dose (continued on next page)

Table 1
(continued)

Study	Treatment	Trial Type	Population	Primary Outcome	Secondary Findings
TTR Stabilizers					
Castano et al, ⁷³ 2012	Diflunisal	Single arm, open label study for 12 mo	13 patients with hATTR-CM or wtATTR-CM	No adverse events; No change in LV mass, LVEF, or biomarkers	6% decline in estimated GFR
ATTR-ACT, Maurer et al, ¹⁰⁹ 2018	Tafamidis	Phase 3, randomized double-blind, placebo-controlled (2:1:2) trial for 30 mo	341 patients with wtATTR-CM or hATTR-CM	Decreased hierarchical outcome of mortality and hospitalization	Lower rate of decline in 6MWT and KCCQ-OS. Similar adverse events
ATTRIBUTE-CM, ⁸⁰ Gillmore et al, 2024	Acoramidis	Phase 3, randomized, double-blind, placebo-controlled (2:1) trial for 30 mo	632 patients with hATTR-CM or wtATTR-CM	Improved hierarchical outcome of mortality, morbidity and function	No increased adverse events
ATTR Fibril Disruption					
Wixner et al, ⁸² 2017	Doxycycline and TUDCA	Phase II, open-label prospective study for 18 mo	28 patients with hATTR-CM and wtATTR-CM	Increased pro-BNP, no change LV wall, increased QOL	High drop out rate (only 36% completed 12 mo of treatment)
Karlstedt et al, ⁸³ 2019	Doxycycline and TUDCA	Retrospective study, follow-up median 22 mo	53 patients with hATTR-CM and wtATTR-CM	No change functional class, biomarkers or imaging	GLS improved in 16 patients (38%) with less advanced disease
Monoclonal Antibodies					
Garcia-Pavia et al, ⁸⁵ 2023	NI006/NI301A	Phase 1, randomized, double-blind, placebo-controlled (2:1) trial for 12 mo	40 patients with hATTR-CM and wtATTR-CM	No drug-related serious adverse events	Reduced tracer uptake on scintigraphy, reduced ECV on CMR, reduced NT pro-BNP, tnT

Abbreviations: BNP, brain natriuretic peptide; CM, cardiomyopathy; CO, cardiac output; ECV, extracellular volume; GLS, global longitudinal strain; hATTR, hereditary transthyretin amyloidosis; HF, heart failure KCCQ-OS, Kansas City cardiomyopathy questionnaire-overall summary; LV, left ventricle; LVEF, left ventricular ejection fraction; mNIS+7, modified neuropathy impairment score +7; PN, polyneuropathy; QOL, quality of life; QOL-DN, Norfolk quality-of-life diabetic neuropathy; TUDCA, tauro-ursodeoxycholic acid; wtATTR, wild-type transthyretin amyloidosis.

dysfunction, combined OHT and OLT could be considered.

Reduction in Transthyretin Protein Synthesis

Small interfering RNA

Small interfering RNAs (siRNAs) are small double-stranded RNA molecules that lead to cleavage of the target mRNA after binding to the RNA-induced silencing complex. This effectively prevents expression of the target gene, in this case TTR. Patisiran is an intravenously delivered liver-targeted siRNA that reduces both hATTR and wtATTR synthesis. The APOLLO trial was a Phase 3 randomized placebo-controlled trial of patisiran in patients with ATTR polyneuropathy (PN) with and without cardiac involvement; it met the primary endpoint of improvement in multiple measures of PN progression.⁶² A secondary, predefined analysis of the subgroup with preexisting cardiac involvement showed improvement in markers of myocardial involvement including decreased LV wall thickness, decreased GLS, and increased cardiac output compared to placebo at 18 months. Additionally, there was a reduction in rates of cardiac hospitalizations and all-cause mortality compared to placebo.⁶³ A second Phase 3 trial, APOLLO-B, investigated patients with hATTR and wtATTR cardiac amyloidosis and showed a reduction in the decline of functional capacity as measured by the 6 minute walk test (MWT; median difference 14.69 m, 95% confidence interval [CI] 0.69–28.69, $P = .02$) and quality of life as measured by the Kansas City Cardiomyopathy Questionnaire Overall Summary Score (KCCQ-OS) score at 12 months. Serum TTR levels decreased by a mean of 80%.⁶⁴ A similar siRNA drug, Revusiran, was similarly tested in a Phase 3 trial, ENDEAVOR, of patients with hATTR-CM but was stopped early due to observed increase mortality.⁶⁵ No clear causative mechanism was determined to explain the increased mortality compared to patisiran. Cardiovascular outcomes for a longer acting siRNA therapy, vutrisiran, injected subcutaneously every 3 months, were recently investigated in the HELIOS-B trial of patients with both wtATTR-CM and hATTR-CM. This study showed reduced mortality (hazard ratio [HR] 0.65, 95% CI 0.46–0.90, $P = .01$) and reduced cardiovascular events HR 0.72 (95% CI 0.49–0.93, $P = .02$), compared to placebo.⁶⁶ Patisiran and vutrisiran are currently Food and Drug Administration (FDA) approved for patients with ATTR-PN.

Antisense oligonucleotide inhibitors

Inotersen, a weekly SQ injection, is a 2'-O-methoxyethyl-modified antisense oligonucleotide (ASO)

inhibitor that binds TTR mRNA and triggers cleavage of the mRNA by ribonuclease H1. NEURO-TTR, the largest Phase 3 study of Inotersen, evaluated neurologic outcomes in patients with hATTR-PN and showed improved neurologic outcomes and quality of life. No cardiac outcomes were evaluated. There was an increased risk of adverse events compared to placebo, particularly glomerulonephritis and thrombocytopenia.⁶⁷ This trial led to FDA approval for hATTR-PN. A Phase 3 study of eplonteresens, an ASO-injected subcutaneously every 4 weeks, is currently enrolling to specifically evaluate patients with hATTR-CM (CARDIO-TTRransform, NCT04136171).⁶⁸

Gene editing (clustered regularly interspaced short palindromic repeats and associated Cas9 endonuclease)

In contrast to mRNA-targeted gene silencing techniques earlier, clustered regularly interspaced short palindromic repeats and associated Cas9 endonuclease (CRISPR-Cas9) techniques are a promising alternative for sustained reduction in synthesis of TTR. NTLA-2001 is an intravenous medication composed of a lipid nanoparticle (LNP) delivery system that encapsulates a single guide RNA targeted to the gene that encodes TTR and mRNA encoding *Streptococcus pyogenes* Cas9 protein. The LNP is specifically designed to transport its cargo to the liver via low-density lipoprotein receptor-mediated endocytosis. This functionally knocks down gene expression by introducing a frameshift mutation to prevent TTR synthesis. In preclinical studies, TTR mRNA expression was decreased by 91% and TTR protein synthesis by 95%.⁶⁹ In phase 1 study of NTLA-2001 in patients with hereditary hATTR-PN, there were 52% and 87% reduction in serum TTR protein concentration at doses of 0.1 mg per kilogram and 0.3 mg per kilogram, respectively. The MAGNITUDE trial is a Phase 3 clinical trial of NTLA-2001 that is currently recruiting (NCT06128629).⁷⁰

Transthyretin Tetramer Stabilization

Diflunisal

Diflunisal is a nonsteroidal anti-inflammatory drug (NSAID) that binds to the T₄ binding site in the TTR tetramer for stabilization.⁷¹ Diflunisal also potentiates clusterin-mediated clearance of high molecular weight ATTR oligomers.⁷² In a single-arm, open-label study of diflunisal for ATTR-CM, there was no change in cardiac endpoints, but there was evidence of increased renal dysfunction.⁷³ A larger randomized study of neurologic changes in ATTR-PN demonstrated reduced progression of neurologic disease.⁷⁴ Use of diflunisal

has been limited by the NSAID-associated risks of renal dysfunction, volume overload, and gastrointestinal bleeding, as well as limited cardiac efficacy.

Tafamidis

The first and most widely used targeted treatment of ATTR-CM is the TTR stabilizer tafamidis. Development was based on the protective mutation Thr119→Met119 (T119M), which stabilizes a tetramer with a V30 M ATTR mutation.⁷⁵ The landmark ATTR-ACT phase 3 study demonstrated lower all-cause mortality (29.5% vs 42.9%, HR 0.70, 95% CI 0.51–0.96) and decreased hospitalizations (relative risk ratio 0.68, 95% CI 0.56–0.81). Rates of decline of cardiac function, as measured by quality of life score and 6MWT, were also reduced with tafamidis treatment compared to placebo.⁷⁶ Early treatment with tafamidis has been shown to produce improved cardiac outcomes, indicating that timing of treatment is important.⁷⁷

Acoramidis

Acoramidis (AG10) is a small molecule TTR stabilizer designed to mimic the protective genetic variant T119M.⁷⁸ In vitro stabilization studies demonstrated over 90% stabilization of ATTR tetramers in both wtATTR and hATTR.⁷⁹ This is due to stronger bonding through hydrogen bonds compared to tafamidis, which relies on hydrophobic binding. ATTRIBUTE-CM was a phase 3 randomized, placebo-controlled trial of acoramidis and it demonstrated significant improvement in a combination endpoint of all-cause mortality, cardiovascular hospitalizations, NT-proBNP, and 6 MWT.⁸⁰ Acoramidis has submitted for FDA approval on the basis of the ATTRIBUTE-CM study.⁷⁶

Fibril Disruption

The antibiotic doxycycline causes fibril destruction in Val30Met mutant mice.⁸¹ By disrupting the amyloid fibril structure, there is increased clearance of the fibrils from the myocardium. Because the main mechanism of doxycycline effects occurs in the disease process, it has clinically been combined with tauro-ursodeoxycholic acid (TUDCA), which has been shown to decrease cardiotoxic ATTR oligomers and reduce cytotoxicity of these oligomers due to its role as an antioxidant.⁸¹ Clinical trials of combined doxycycline/TUDCA have shown limited clinical efficacy. One small prospective open-label study⁸² and a larger retrospective study⁸³ showed no significant improvement in functional status, biomarkers, or LV wall thickness. There was a signal toward improvement in GLS in patients with less advanced disease.

Anti-transthyretin Monoclonal Antibody Clearance

The majority of current ATTR treatments focus on reducing the production of ATTR fibrils in an effort to regain the balance of proteostasis and encourage ATTR fibril clearance. However, these mechanisms are slow. Newer agents aim to directly clear fibrils from the myocardium via antibody-mediated activation of phagocytosis. NI006/ALXN2220 (NI301A) is a recombinant human monoclonal immunoglobulin G1(IgG1) that, in preclinical studies, was shown to bind selectively to disease-associated ATTR aggregates of both wtATTR and hATTR, but not to physiologic TTR.⁸⁴ A Phase 1 study of this agent was recently completed, and, while it was only powered to demonstrate drug safety, at doses greater than 10 mg/kg, there was evidence of myocardial ATTR fibril depletion as measured by PYP uptake on scintigraphy and reductions of ECV on CMR at 12 months without significant adverse side effects of the treatment.⁸⁵ ALXN2220 is currently enrolling for a Phase 3 trial (DepleteTTR-CM).⁸⁶ Similarly, NNC6019/PRX004 is a humanized monoclonal antibody that targets an epitope, only expressed on misfolded ATTR monomers and aggregates, to facilitate clearance from the myocardium. A Phase 1 study has been completed and a Phase 2 study is currently underway.⁸⁷ In addition to the ATTR-specific monoclonal antibodies, a new pan-amyloid anti-fibril antibody, called AT-02, is currently in development. This antibody can bind multiple types of amyloid fibrils via peptide interactions. In preclinical studies, it was found to bind with high affinity to amyloid fibrils and stimulates an immune response to promote clearance.⁸⁸ Currently, there is an ongoing Phase 1 study (NCT05521022).

TREATMENT OF AL-CARDIOMYOPATHY

Treatment of AL amyloidosis primarily aims to treat the underlying plasma cell dyscrasia to prevent further LC production. The current first-line therapy for treatment of AL amyloidosis is a 4 drug combination of daratumumab, cyclophosphamide, bortezomib and dexamethasone (daratumumab-CyBorD).⁸⁹ Daratumumab is a human IgG-κ monoclonal antibody targeting CD38, expressed on all human plasma cells, and previously used in multiple myeloma. This combination therapy with daratumumab was evaluated in the Phase 3 ANDROMEDA trial, demonstrating increased complete hematologic response (53% vs 18.1%, relative risk ratio 2.9; 95% CI 2.1–4.1, $P < .001$) and improved survival free from major

organ deterioration or hematologic progression (HR 0.58; 95% CI 0.36–0.93, $P = .02$) compared to CyBorD plus placebo. From a cardiac perspective, there was improved cardiac response (41.5% vs 22.2%).⁹⁰ This treatment involves 6 cycles of daratumumab-CyBorD followed by up to 2 years of single-agent daratumumab maintenance therapy. Options for second-line therapy for relapsed disease are beyond the scope of this review.

Patients are commonly evaluated for autologous stem cell transplant (AutoSCT), a field that has continued to evolve with emerging up-front treatments. Whether or not to proceed with AutoSCT is a nuanced decision, but commonly AutoSCT is reserved for patients who do not achieve adequate response after daratumumab-CyBorD or as consolidation therapy in young, healthy patients. The limited AutoSCT clinical trials were done prior to the era of daratumumab treatment, but key improvements in patient selection have significantly improved survival. Patients at highest risk of mortality were identified as those with advanced cardiac involvement as measured by clinical status, LVEF, cardiac biomarkers, GLS, and hypotension.⁸⁹ For example, in a large retrospective study of 410 AutoSCT between 1996 and 2011, NT-proBNP greater than 5000 and serum troponin T were markers for increased mortality with mortality rates of 25% in those patients.⁹¹ This has led to increasing exclusion of these patients from AutoSCT candidacy and increased emphasis on close cardiovascular monitoring during the pretransplant and posttransplant period.

Given the poor prognosis outcomes in AutoSCT in advanced AL-CM, there is increasing evidence for OHT followed by maintenance chemotherapy or AutoSCT.⁹² Multiple single-center retrospective studies have shown that this approach is safe and has similar short-term and long-term survival compared to the population with nonamyloid OHT.^{93–96} In general, evidence of hematologic response to upfront chemotherapy is needed prior to consideration for OHT. Commonly cited contraindications to OHT in AL-CM include significant gastrointestinal involvement, proteinuria, GFR less than 30, advanced multiple myeloma, or severely limiting PN. In 2018, United Network for Organ Sharing updated the OHT listing criteria to allow higher listing status for patients with restrictive cardiomyopathies, which includes AL-CM, requiring invasive hemodynamics and inotropic support. This has led to decreased mortality on the wait list, which had previously been increased compared to other populations.⁹⁶ With increased hematologic response to chemotherapy, particularly in the era of daratumumab, the future role of

AutoSCT versus maintenance chemotherapy after OHT needs to be further studied.

Like ATTR-CM, there are multiple targeted treatments for AL amyloidosis that are currently being investigated. In addition to AT-02 discussed earlier, there are 2 AL antiamyloid fibril antibodies currently in development, CAEL0191, and birtamimab (NEOD001). CAEL-101, a chimeric monoclonal IgG1 antibody that binds to kappa and lambda LC misfolded proteins,⁹⁷ has been investigated in a Phase II trial of 25 patients with AL amyloidosis in conjunction with CyBorD with or without daratumumab. This study showed long-term safety and, in a subgroup analysis, early signs of improved cardiac function as measured by improved (30%) or stable (60%) NT-proBNP.⁹⁸ Birtamimab, a humanized IgG1 monoclonal antibody that also binds to kappa and lambda misfolded proteins, has completed the Phase 3 clinical trial. This trial, called VITAL, was discontinued early due to futility. A trend toward the primary composite endpoint of all-cause mortality or cardiac hospitalization in patients with advanced cardiac AL amyloidosis (Mayo Stage IV) led to a post hoc analysis showing improved survival at 9 months in the group receiving birtamimab (74% vs 49%).⁹⁹ A Phase 3 trial of patients with Mayo Stage IV AL amyloidosis is currently enrolling (AFFIRM-AL; NCT04973137).¹⁰⁰

RACIAL, GENDER, AND SOCIOECONOMIC DISPARITIES IN CARDIAC AMYLOIDOSIS

As diagnosis and treatment of cardiac amyloidosis rapidly advance, it is critical that attention is paid to racial, gender, and socioeconomic disparities in this field. Cardiac amyloidosis is significantly underdiagnosed, but it has become clear that the rates of underdiagnosis are not equal in all communities. For example, all counties with the highest cardiac amyloid-related mortality rates were located less than 400 km from a major amyloidosis referral center, indicating areas of reduced diagnosis due to access to care.¹⁰¹ Low rates of amyloidosis-related mortality also occur in regions with the highest proportions of Black patients.¹⁰² Despite this underdiagnosis, between 1999 and 2015, Black men had the highest mortality from ATTR-CM (12.36 per 1 million) followed by Black women (6.48 per 1 million).¹⁰¹

Cardiac amyloidosis, particularly hATTR-CM, disproportionately affects Black patients, and yet they are underrepresented in clinical trials. For example, in the ATTR-ACT trial of tafamidis, only 14% ($n = 63$) of patients were Black and there were no sites on the African continent.¹⁰² Additionally, most drugs were initially studied in the

ATTR-PN cohort, generally excluding diverse patients with V122I mutations. To determine the true prevalence of ATTR-CM in this population, the ongoing SCAN-MP trial (NCT03812172) is a prospective study that aims to enroll 800 patients who self-identify as Black or Caribbean Hispanic and are greater than 60 years old with a diagnosis of heart failure and increased LV wall thickness (>12 mm).¹⁰³ All patients will undergo evaluation for ATTR-CM with noninvasive nuclear imaging. It is critical to improve diagnosis in this population and ensure inclusion in all future clinical trials.

ATTR-CM has traditionally been thought to be less common among women; however, the data have been mixed, signaling potential underdiagnosis. In a meta-analysis of 69 studies, the overall proportion of women was 17% with a prevalence of only 9% in wtATTR-CM studies.¹⁰⁴ Women with ATTR-CM were found to have lower LV wall thickness and higher LVEF. This suggests that there may be underdiagnosis due to decreased wall thickness, which is generally the trigger for further evaluation. Future studies are needed to characterize the prevalence of ATTR-CM among women to understand whether the disparity is due to underdiagnosis or a biologically protective mechanism.

Disparities in AL amyloidosis have not been well studied. In a large cohort of patients with AL amyloidosis from 1990 to 2020, 14% of patients were minorities with non-Hispanic Black patients making up 8% of patients. These patients were younger at diagnosis with more aggressive disease. Notably, there were lower rates of AutoSCT in Hispanic patients compared to non-Hispanic White patients. Race and ethnicity were not associated with increased mortality after controlling for disease severity.¹⁰⁵

A major limitation to equitable expansion of novel therapeutics is high drug costs, particularly for the uninsured or underinsured. When tafamidis was initially developed, it was given orphan drug designation because the prevalence of disease was thought to be very low ($<200,000$ cases per year).¹⁰⁶ Therefore, the high pricing, initially around \$225,000 per year, was based on the projected low demand for these drugs. However, with increased diagnosis, it has been estimated that if tafamidis were prescribed to all patients with ATTR-CM, US health care spending could increase by \$32.3 billion.¹⁰ It was estimated that a 93% price reduction would be needed for it to be considered cost-effective.¹⁰⁷ The cost of newer therapeutics has only continued to increase, and, given the potential for improved mortality and quality of life, it is vital to ensure fair access to these treatments.

SUMMARY

The field of cardiac amyloidosis is rapidly evolving, with a recent surge of novel, cutting-edge diagnostic tools and innovative-targeted treatments. An improved understanding of the pathophysiology of both ATTR and AL amyloidosis has provided mechanistic insights that facilitated the development of these treatments, which range from small molecules, siRNA, monoclonal antibodies, and CRISPR-Cas9 gene editing. A multitude of ongoing clinical trials are set to transform the treatment of cardiac amyloidosis. However, there are still many unanswered questions in the field regarding the pathogenesis of disease, as well as optimal patient treatment timing and choice of treatments. Cardiac amyloidosis is poised to enter an era of precision medicine; with the broad range of future treatment options, there is great potential to improve patient outcomes for this complex disease.

CLINICS CARE POINTS

- The prevalence of cardiac amyloidosis, including both transthyretin cardiac amyloidosis (ATTR-CM) and amyloid light chain cardiac amyloidosis (AL-CM), is higher than previously believed and recognition requires a high index of suspicion in high-risk patients.
- Diagnostic pathway for diagnosis of ATTR-CM requires first evaluating for AL-CM by screening for monoclonal proteins, followed by noninvasive imaging with nuclear bone scintigraphy.
- The treatment landscape for ATTR-CM and AL-CM is constantly changing with multiple novel treatment options currently under investigation.

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Cardiotoxicity of Anthracyclines



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KEYWORDS

• Cardiotoxicity • Anthracyclines • Cardioprotection • Doxorubicin • Dexrazoxane • CTRCD

KEY POINTS

- Anthracycline cardiotoxicity commonly manifests as left ventricular systolic dysfunction, with early detection possible through biomarkers and cardiovascular imaging before clinical symptoms develop.
- Comprehensive cardiovascular risk assessment is essential for all patients prior to anthracycline therapy to stratify their risk of cardiotoxicity.
- Preventive measures, including cardiovascular risk optimization, as well as anthracycline dose adjustments, the use of liposomal anthracyclines, and dexrazoxane in high-risk patients are crucial to mitigate the risk of cardiotoxicity. Evidence supporting the use of cardioprotective medications is mixed.
- Patients should be monitored during and after anthracycline treatment with the goal of early detection and treatment of cardiotoxicity, though the optimal monitoring strategy remains unknown.
- Long-term follow-up and cardiovascular risk optimization are critical for cancer survivors to optimize cardiovascular outcomes.

INTRODUCTION

In recent decades, the number of cancer survivors in the United States has steadily increased with figures reaching about 18 million in 2022, and projections show continued growth due to an aging demographic burdened with higher prevalence of cancer.¹ Even in the era of targeted cancer therapies, anthracyclines, which include doxorubicin, daunorubicin, epirubicin, idarubicin, and the similar anthraquinone mitoxantrone, remain essential for treating many types of cancer, including leukemias, lymphomas, and breast cancers. Since the time of the initial studies of anthracycline treatment of cancer in the 1960s, the dose-dependent myocardial toxicity of anthracyclines has been well

documented.^{2,3} As both life expectancy and cardiovascular vulnerability of the aging population continue to increase,⁴ it becomes imperative to balance the years gained through contemporary cancer treatment with the risks of cardiac morbidity and mortality associated with those treatments. Effective strategies for the prevention, screening, monitoring, and treatment of anthracycline cardiotoxicity are needed.

CLINICAL MANIFESTATIONS

Anthracycline cardiotoxicity typically manifests as left ventricular (LV) systolic dysfunction ultimately resulting in heart failure (HF), though other reported manifestations include changes in LV

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geometry, diastolic dysfunction, right ventricular (RV) dysfunction, and rarely, an initial presentation with arrhythmia or sudden death.^{5–9} The diagnosis is supported histologically by the finding of vacuolization of cardiomyocytes and myofibrillar loss on endomyocardial biopsy, though this is rarely performed in the clinical setting as the diagnosis is typically ascertained through history, physical, and imaging data alone.^{10,11}

Traditionally, anthracycline cardiotoxicity was classified into acute toxicity and chronic toxicity based on retrospective analyses of small case series, many of which focused on childhood cancer survivors.¹² However, more recent prospective studies demonstrate that the vast majority of LV systolic dysfunction develops within the first year after anthracycline treatment, often preceded by an elevation in cardiac troponin (cTn), suggesting that subclinical myocardial injury at the time of anthracycline exposure leads to later systolic dysfunction and eventually, in a subset of cases, to clinical HF.^{5,13–15} These findings challenge the traditional distinction between acute and chronic toxicity and suggest that preclinical and late cardiotoxicity exist as a continuum of the same disease.

LV systolic dysfunction due to anthracycline toxicity is included within a broader entity referred to in the literature and society guidelines as *cancer therapy-related cardiac dysfunction* (CTRCD). Over time, markers used in the definition of CTRCD have evolved from LV contractile dysfunction and clinical HF alone to the incorporation of blood biomarkers¹³ and, more recently, global longitudinal strain (GLS).^{5,16} A unified definition of CTRCD has not yet been adopted across society guidelines and clinical trials, leading to confusion among clinicians and difficulty in comparing study endpoints.^{17,18} Efforts to standardize the definition of CTRCD by the International Cardio-Oncology Society (ICOS) have led to a consensus definition incorporating left ventricular ejection fraction (LVEF), cTn, natriuretic peptides (NPs), and GLS, and this definition has been adopted by the European Society of Cardiology (ESC; **Table 1**).¹⁷ However, it remains to be seen if other societies and future clinical trials will adopt this common definition.

PATHOGENESIS

While the mechanism of anthracycline cardiotoxicity remains incompletely understood, it is thought that the molecular effects of anthracyclines in cardiac tissue differ in several respects from their behavior in malignant tissue, suggesting that it should be possible to mitigate cardiotoxicity without compromising entirely antitumor efficacy.¹⁹ Several

potential mechanisms of toxicity have been identified, including oxidative stress, intracellular iron overload, mitochondrial dysfunction, and activation of cellular death pathways.

Historically, oxidative stress was considered the primary mechanism of anthracycline-induced cardiotoxicity.²⁰ Reactive oxygen species (ROS) are generated in cardiomyocytes via multiple mechanisms upon anthracycline exposure. Anthracyclines undergo redox cycling of their quinone moieties via a nonenzymatic pathway that leads to the production of superoxide anions, which are subsequently metabolized to toxic radicals, particularly in the presence of heavy metals including iron.^{7,21,22} The formation of anthracycline–iron complexes in mitochondria leads to superoxide and hydrogen peroxide formation.²³ Additionally, a metabolite of doxorubicin, doxorubicinol, increases free intracellular iron content in cardiomyocytes through the inactivation of iron regulatory protein 1 (IRP1), leading to inhibition of ferritin synthesis and disruption of iron homeostasis.²⁴ The combination of excess free iron and the presence of hydrogen peroxide further leads to the production of ROS through the Fenton reaction.²⁵ Cardiomyocytes may be particularly vulnerable to ROS due to low concentration of antioxidant enzymes, which are hypothesized to be further reduced upon exposure to anthracyclines due to suppression of glutathione oxidase activity.²⁶

However, trials of coadministration of antioxidants and ROS scavengers including N-acetylcysteine have failed to prevent anthracycline cardiotoxicity,²⁷ suggesting that either the oxidative stress hypothesis is insufficient to fully explain observed outcomes or the antioxidants studied may not be sufficiently targeted to the myocardium.²⁸ Iron chelators have also been investigated, but the data for these remain mixed, with the exception of dexrazoxane.^{29,30}

Several potential mechanisms of anthracycline cardiotoxicity localize to the mitochondria, which exist in high density in cardiomyocytes. Proposed mechanisms of mitochondrial-mediated cardiotoxicity include apoptosis through the formation of anthracycline–cardiolipin complexes, ferroptosis, and apoptosis through the release of cytochrome C from mitochondria.^{31–35} In addition to direct stimulation of apoptotic pathways through interactions with the mitochondria, anthracyclines may also cause cellular stress through the depletion of mitochondrial DNA (mtDNA).^{36,37} Anthracyclines alter the activity of several enzymes involved directly and indirectly in the transcription and maintenance of mtDNA.^{38–40} Among other potential pathways, anthracyclines bind to topoisomerase 2 β (Top2 β), which is highly expressed in

Table 1
Definition of cancer therapeutics-related cardiac dysfunction^a

	Symptomatic CTRCD^b	Asymptomatic CTRCD
Mild	Mild HF symptoms not requiring intensification of medical therapy	LVEF $\geq 50\%$ plus either new relative decline in GLS by $>15\%$ or a new rise in cardiac biomarkers ^c
Moderate	HF symptoms warranting outpatient intensification of diuretics or GDMT	New decline in LVEF by $\geq 10\%$ to an LVEF 40%–49% or New decline in LVEF by $<10\%$ to an LVEF 40%–49% plus either new relative decline of GLS by $>15\%$ or a new rise in cardiac biomarkers ^c
Severe	HF symptoms warranting hospitalization	New reduction of LVEF to $<40\%$
Very severe	HF requiring inotropic support, mechanical circulatory support, or advanced therapies including transplant	—

Abbreviations: GDMT, goal-directed medical therapy, LVEF, left ventricular ejection fraction, GLS, global longitudinal strain.

^a Based on the International Cardio-Oncology Society (IC-OS) 2021 Consensus.

^b Symptomatic CTRCD is equivalent to clinical HF and implies the presence of supportive imaging and biomarkers. However, the severity classification is independent of LVEF.

^c cTnI or cTnT greater than 99th percentile, BNP ≥ 35 pg/mL, NT-proBNP ≥ 125 pg/mL, or new significant change from baseline.

Adapted from Eur Heart J 2022 Jan 31;43(4):280 to 299.

cardiomyocytes and normally maintains nuclear genes important for mitochondrial regulation, leading to diminished mitochondrial biogenesis and impaired bioenergetics of cardiomyocytes. Animal models with cardiomyocyte-specific knockout of Top2 β are protected against doxorubicin-induced cardiomyopathy, arguing for an important role in the pathway of anthracycline cardiotoxicity.³⁹

Notably, dexrazoxane, in addition to being an iron chelator, is an inhibitor of Top2 β .^{22,41} It is not clear whether the effectivity of this agent in preventing anthracycline cardiotoxicity is primarily mediated through iron chelation, Top2 β inhibition, or a combination of both mechanisms.

INCIDENCE

The incidence of anthracycline cardiotoxicity is difficult to estimate owing to heterogeneous patient populations and variable definitions of cardiotoxicity. One large meta-analysis including 22,815 adults and children treated with anthracyclines found a 6.3% incidence of overt clinical cardiotoxicity and a 17.9% incidence of subclinical cardiotoxicity over a median follow-up of 9 years.⁴² However, this analysis was limited by a reliance on retrospective data from institutional databases. One large, prospective cohort study of women with breast cancer within a single health care system that defined cardiotoxicity as a diagnosis of HF or cardiomyopathy based on International

Classification of Diseases (ICD) diagnostic codes and Current Procedural Terminology (CPT) codes within the medical record found an incidence of 4.1% in patients treated with anthracyclines without trastuzumab at 120 months of follow-up compared with a cumulative incidence of 2.3% among age-matched and ethnicity-matched controls.⁴³ In contrast, a prospective study of 2671 adults with a variety of solid and hematologic cancers, which was performed to establish the time course of anthracycline-induced cardiotoxicity using a predefined schedule of monitoring with echocardiograms, found that cardiotoxicity, defined as a reduction in LVEF of 10% or greater to an absolute value of less than 50%, occurred in 9% of the population studied.⁵ Other studies using even more sensitive markers of myocardial injury appearing before LV dysfunction occurs such as elevation of cTn⁴⁴ or reduction in GLS⁴⁵ have found even higher estimates of the incidence of cardiotoxicity.

RISK ASSESSMENT

All patients planning to undergo treatment with anthracyclines should have a clinical cardiovascular risk assessment and baseline cardiac imaging to determine appropriate surveillance and prevention strategies. While risk calculators for pretreatment patient-related factors exist, including a tool created by the Heart Failure Association of

the European Society of Cardiology (HFA) in collaboration with the ICOS, they are not commonly used in clinical practice in the United States due to lack of adequate validation.^{46,47} In practice, an understanding of relevant factors and the magnitude of risk associated with each allows for individualized patient risk stratification into low, moderate, and high-risk groups (Fig. 1).

Patient-related Factors

The extremes of age are associated with higher risk of anthracycline cardiotoxicity. Patients aged at least 60 years are considered at increased risk, with patients aged 80 years or more considered to be at high risk of cardiotoxicity.^{48,49} The risk of cardiotoxicity is also increased among patients treated before the age of 5 years.^{50,51} The data for an association between sex and risk of anthracycline cardiotoxicity are mixed. While there is evidence of an increased risk of cardiotoxicity in female survivors of pediatric cancers, a sex-specific difference in the risk of cardiotoxicity has not been demonstrated consistently in adult patients.⁵²

The presence of traditional cardiovascular risk factors, including hypertension, diabetes mellitus, and obesity, as well as established coronary artery disease and peripheral vascular disease, has been found to increase the risk of cardiotoxicity.^{53–55} Additionally, a pre-existing cardiomyopathy is

associated with a 5 fold increase in the risk of cardiovascular events with anthracycline therapy.^{56,57} Atrial fibrillation, whether diagnosed before or after anthracycline exposure, is also a significant risk factor for anthracycline cardiotoxicity.⁵⁸

Treatment-related Factors

Anthracycline cardiotoxicity is well known to be dose-dependent. While an exponential increase in the incidence of clinical HF after exposure to a cumulative doxorubicin dose of 400 mg/m² was initially described, more recent data show significant rates of cardiotoxicity at a dose threshold of 250 mg/m² (Table 2).^{48,59,60} Radiation therapy, especially with significant cardiac radiation exposure and doses over 30 Gy, is an important risk factor for toxicity.^{61,62} Additionally, combination therapy with anthracyclines and concurrent human epidermal growth factor receptor 2 (HER2)-directed treatments such as trastuzumab has been found to confer a significantly increased risk of cardiotoxicity.¹⁶ Consequently, practice has changed such that trastuzumab and anthracyclines are almost always given in sequence rather than concurrently.

PRETREATMENT IMAGING

Patients with one or more risk factors are referred for pretreatment cardiac imaging, most commonly

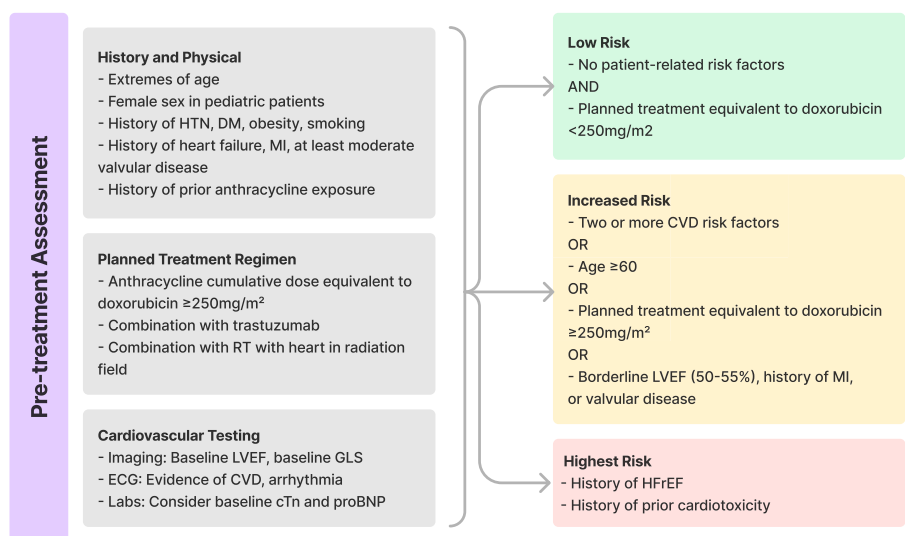


Fig. 1. Cardiovascular risk assessment prior to anthracycline treatment. The risk of anthracycline cardiotoxicity should be determined prior to treatment through an assessment of the patient's clinical history, planned oncologic treatment regimen, and baseline cardiovascular testing. Patients can be stratified into low, increased, and high risk based on these data. CVD, cardiovascular disease; DM, diabetes mellitus; ECG, electrocardiogram; GLS, global longitudinal strain; H&P, history and physical; HFrEF, heart failure with reduced ejection fraction; HTN, hypertension; LVEF, left ventricular ejection fraction; MI, myocardial infarction; RT, radiation therapy; TTE, transthoracic echocardiogram.

Table 2
Anthracycline dose equivalence for risk of cardiotoxicity

Anthracycline	Conversion Factor	Cumulative Dose Associated with Clinical HF in >10% of Patients (mg/m²)
Doxorubicin	1	400–450
Epirubicin	0.8	900
Daunorubicin	0.6	400–550
Idarubicin	5	90
Mitoxantrone	10.5	120

Dose equivalence of anthracyclines for cardiotoxicity and cumulative dose typically associated with significant rates of left ventricular dysfunction.^{13,135,136}

transthoracic echocardiogram (TTE), though cardiac MRI (CMR) and radionuclide multigated acquisition (MUGA) scans are reasonable alternatives. The choice of cardiac imaging technique depends on local expertise and accessibility as consistency in imaging modality throughout the treatment course is paramount to minimize variability.

LVEF should be quantified on a TTE by either a 3-dimensional (3D)-derived LVEF or with Simpson's 2 dimensional (2D) biplane method. Additionally, a pretreatment TTE should include the assessment of RV function and GLS if available.⁶³ Because treatment decisions may be made on the results of serial studies, images should be obtained simultaneously while maintaining consistent frame and imaging depth and that the TTE report should include details on the timing of echocardiography in relation to therapy administration and patient vital signs. The same vendor of the ultrasound machine and analysis software for strain measurements should be used for serial assessment to maximize reproducibility.⁶⁴

CMR is an alternative to TTE when TTE is non-diagnostic, challenging due to difficult sonographic windows, or in select cases with abnormal or borderline LVEF.⁶⁵ MUGA scans may be superior to 2D echocardiography for quantification of LVEF in cases with suboptimal echocardiographic windows due to its high accuracy and low interobserver variability.^{66,67} Although less commonly used in clinical practice, MUGA should be considered in patients with challenging echocardiographic acoustic windows or contraindications to CMR, or when CMR and 3D echocardiography are not available.

PREVENTIVE STRATEGIES

Cardiac Medications

Beta blockers, angiotensin converting enzyme inhibitors, and angiotensin receptor blockers

Beta blockers, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARBs) have been studied in patients undergoing anthracycline treatment alone and in combination as primary prevention strategies.

The beta blocker carvedilol has been shown to impact oxidative stress and mitochondrial function in preclinical models of anthracycline cardiotoxicity.²² In the Carvedilol Effect in Preventing Chemotherapy-Induced Cardiotoxicity (CECCY) trial, patients with HER-2-negative breast cancer were randomized to receive carvedilol or placebo concurrent with anthracycline treatment of primary prevention. While was no difference between the 2 groups in the primary endpoint of a decrease in LVEF of 10% or greater at 6 months, the study power was limited by a lower-than-expected rate of cardiotoxicity in the placebo group.⁶⁸

The Prevention of Cardiac Dysfunction During Adjuvant Breast Cancer Therapy (PRADA) trial used a 2 × 2 factorial design to examine both the beta blocker metoprolol and ARB candesartan for primary prevention in a population of patients with breast cancer undergoing adjuvant anthracycline-containing regimens with or without trastuzumab. Candesartan protected against an early decline in global LV function (early decline in LVEF 0.8% in the candesartan vs 2.6% in the placebo groups; $P = .026$), whereas metoprolol did not affect decline in LVEF. However, in the extended follow-up study of these patients at 2 years, neither candesartan nor metoprolol differed from placebo in the prevention of a reduction in LVEF. Candesartan was associated with preserved GLS at 2 years, though the clinical significance of this remains to be understood. The study lacked adequate statistical power to detect any interaction between candesartan and metoprolol in combination.^{69,70}

The OVERCOME (prevention of left Ventricular dysfunction with Enalapril and carvedilol in patients submitted to intensive Chemotherapy for the treatment of Malignant Hemopathies) trial evaluated the combination of the ACE inhibitor enalapril and carvedilol for primary prevention of anthracycline cardiotoxicity in patients treated for hematologic malignancies. Combination therapy was associated with the preservation of LVEF at 6 months compared with a mean decline in LVEF of −3.1% in the control group. Further, the incidence of the composite outcome of death or HF was significantly lower in the treatment group (6.7% vs 22%, $P = .036$).⁷¹ This study was limited by its small sample size,

lack of blinding, and high rate of noncardiac death, but its results call for further investigation of combination therapy for primary prevention.

Regarding angiotensin receptor/neprilysin inhibitors, while there is preclinical evidence to suggest they may be efficacious in preventing or treating anthracycline cardiotoxicity, clinical data remain sparse.⁷² The PRADAIL trial, a randomized controlled trial of sacubitril/valsartan in women with breast cancer undergoing treatment with anthracyclines, is currently under way with initial results expected in 2025.⁷³

Mineralocorticoid receptor antagonists

The evidence in support of mineralocorticoid receptor antagonist use to prevent cardiotoxicity is limited. One randomized, controlled trial of spironolactone for primary prevention in 83 female patients with breast cancer undergoing anthracycline therapy demonstrated a significant protective effect with respect to decline in LVEF.⁷⁴ However, larger studies are needed to support the routine use of spironolactone in this population.

Statins

Statins were investigated for primary prevention in patients undergoing anthracycline therapy in the Statins to Prevent the Cardiotoxicity of Anthracyclines (STOP-CA) trial, a randomized, placebo-controlled trial of high-intensity atorvastatin in a population of patients with lymphoma. At 12 months' follow-up, 9% of patients in the atorvastatin arm met the primary endpoint of a 10% or greater reduction in LVEF from baseline to a final value of less than 55% in comparison with 22% of patients in the placebo arm.⁷⁵ However, the absolute decline in LVEF in both groups was mild, and the study was not powered to detect an effect on the risk of overt HF.

In contrast, another multicenter, double-blind, placebo-controlled trial of atorvastatin in 112 patients with cancer at increased risk of anthracycline cardiotoxicity did not find a difference in LVEF between patients treated with atorvastatin versus placebo at 2 to 4 weeks after completion of chemotherapy. However, the mean posttherapy LVEF was normal in both groups, suggesting that the study was insufficiently powered to detect a benefit of atorvastatin.⁷⁶

Overall, the existing evidence is insufficient to recommend statin initiation in all patients undergoing anthracycline treatment, though if a patient otherwise has an indication for statin therapy, it should be started or continued during anthracycline treatment in absence of a contraindication.

Sodium-glucose cotransporter-2 inhibitors

While the cardiovascular benefits of sodium-glucose cotransporter-2 (SGLT2) inhibitors in

patients with HF, including decreased HF hospitalizations, lower cardiac mortality, and lower all-cause mortality, have been established in multiple studies, patients with cancer were specifically excluded from these trials.^{77–79}

Preclinical studies show a protective effect of SGLT2 inhibitors against doxorubicin-induced HF in animal models.^{80,81} A recent retrospective cohort study of 1280 patients with CTRCD due to any cancer therapy, not limited to anthracyclines, and type 2 diabetes demonstrated that SGLT2 inhibitors, in conjunction with other contemporary guideline-directed medical therapy (GDMT), significantly reduced HF exacerbations and all-cause mortality over a 2 year follow-up period.⁸² Prospective studies investigating the potential use of SGLT2 inhibitors for primary prevention of anthracycline cardiotoxicity are currently underway.^{83,84}

Modifications to Cancer Therapy

In addition to preventive strategies harnessing traditional cardiac medications, alterations to oncologic therapies can be considered in a multidisciplinary approach balancing the risks of anthracycline therapy with the risks of reduced potency of cancer treatment.

Infusion versus bolus dosing of anthracyclines

Administration of anthracyclines as an infusion rather than with bolus dosing decreases the likelihood of cardiotoxicity. Several small randomized clinical trials performed in the 1980s and 1990s comparing bolus dosing to prolonged infusion over periods ranging from 6 to 96 hours established that infusion-based approaches were noninferior to bolus dosing and were better tolerated.^{85–88} The dose of anthracyclines administered in these studies was considerably above the 250 mg/m² doxorubicin dose equivalent considered the inflection point for cardiotoxicity. However, most of the studies excluded patients with prior anthracycline exposure or known cardiac risk factors, and the definition of cardiotoxicity was heterogeneous. A meta-analysis pooling the data from these studies found a 4 fold increase in overt cardiotoxicity and a 3 fold increase in subclinical cardiotoxicity with bolus dosing, with no difference in oncologic outcomes between the 2 groups.⁸⁹ The drawbacks to continuous infusion strategies are the need for central access and the costs associated with longer infusions. It is important to note that there are no data to support the use of extended infusion therapy in patients receiving lower doses of anthracyclines.⁴⁸

Liposomal anthracyclines

For patients receiving high doses of anthracyclines (≥ 250 mg/m² doxorubicin dose equivalent), there

is evidence to support the use of pegylated liposome-encapsulated doxorubicin (PLD) to mitigate cardiotoxicity. Encapsulating doxorubicin in liposomes is thought to promote entry and retention of the drug in tumor tissue due to its permeable vasculature and impaired lymphatic drainage, theoretically leading to enhanced anti-tumor activity; in contrast, it is thought to prevent entry into the heart through the tighter cardiac endothelium, lowering the local concentration of doxorubicin and its propensity for cardiotoxicity.⁹⁰ A meta-analysis of 3 trials in women with breast cancer and 1 trial in patients with multiple myeloma comparing liposomal doxorubicin with conventional doxorubicin showed a reduced risk of both clinical (odds ratio [OR] 0.18, 95% confidence interval [CI] 0.08–0.38) and subclinical cardiotoxicities (relative risk [RR] 0.31, CI 0.20–0.48).⁸⁹ Tumor responses were comparable in the doxorubicin versus PLD groups. However, PLD is associated with more frequent noncardiac adverse outcomes including stomatitis, mucositis, and hand-foot syndrome.^{91,92}

Dexrazoxane

A third strategy to mitigate cardiotoxicity of anthracyclines is coadministration of dexrazoxane, an iron chelator and inhibitor of topoisomerase II, which is the only Food and Drug Administration-approved medication for the prevention of doxorubicin cardiotoxicity.²² The efficacy of dexrazoxane in the prevention of anthracycline cardiotoxicity has been well established with randomized controlled trials and subsequent meta-analyses. Three meta-analyses of 4 overlapping clinical trials including predominantly patients with breast cancer or sarcoma, some of whom had treatment-related risk factors for anthracycline cardiotoxicity, including previous treatment with anthracyclines and radiation therapy and none of whom had pre-existing LV dysfunction, consistently found a reduction of both clinical cardiotoxicity subclinical cardiotoxicity with coadministration of dexrazoxane with approximate risk reduction around 70% to 80%.^{89,93} A meta-analysis incorporating many of the same studies along with studies in pediatric populations confirmed a similar magnitude of benefit with dexrazoxane.⁹⁴

Despite its promise as a cardio-protectant, dexrazoxane remains underutilized, likely due to concerns regarding interference with antitumor efficacy and increased risk of secondary malignancy. However, a substantial body of evidence suggests that dexrazoxane does not reduce the efficacy of anthracyclines. A large meta-analysis including both adult and pediatric patients identified no difference in tumor response, progression

free survival, or overall survival between patients randomized to receive anthracyclines with dexrazoxane versus anthracyclines alone.⁹⁴ A study of about 500 children treated with doxorubicin, bleomycin, vincristine, and etoposide (ABVE) and low-dose radiation for Hodgkin lymphoma, of whom half were randomly assigned to receive dexrazoxane with chemotherapy, reported the occurrence of 10 secondary malignancies with 8 cases in the dexrazoxane group (6 with acute myelogenous leukemia [AML] or myelodysplastic syndrome [MDS] and 2 with solid tumors) and 2 secondary malignancies in the control group (AML/MDS), representing a nonsignificant difference in the incidence of secondary malignancies.⁹⁵ While this study initially prompted the European Medicines Agency to list dexrazoxane as contraindicated in children, the restriction was lifted in 2017 after review of newer trials redemonstrated the efficacy and safety of dexrazoxane.⁹⁶ Currently, the American Society of Clinical Oncology endorses the use of dexrazoxane in patients planning to receive high-dose anthracycline therapy equivalent to doxorubicin 250 mg/m² or greater.⁴⁸

SURVEILLANCE AND DIAGNOSIS

Surveillance During Therapy

Strategies for echocardiographic surveillance during treatment are largely based on expert opinion. Echocardiography can be considered at a cumulative doxorubicin dose of 250 mg/m² in moderate risk patients (see Fig. 1 for risk assessment). In patients at high risk of cardiotoxicity, surveillance imaging can be performed every 2 cycles during anthracycline chemotherapy and within 3 months after therapy completion.⁴⁹ For patients receiving high doses of anthracyclines, echocardiography should be considered when the cumulative dose reaches or exceeds 300 mg/m² doxorubicin equivalent, with a repeat TTE with every additional dose of 50 mg/m², especially in patients at elevated risk of chemotherapy-related cardiotoxicity.

Imaging Markers of Cardiotoxicity

Left ventricular ejection fraction

Assessment of LVEF is a key component of the diagnosis of anthracycline cardiotoxicity. However, while LVEF is a reliable predictor of morbidity and mortality in most populations and has been shown to be inversely associated with subsequent cardiac events in patients undergoing anthracycline therapy,⁹⁷ there are limitations for its use in the detection of anthracycline cardiotoxicity owing largely to its high temporal variability, low interobserver and intraobserver reliabilities, and low

sensitivity to detect small changes in contractile function.^{63,98,99} The high temporal variability is likely related to the inherent dependence of LVEF on fluctuations in volume status and other physiologic states such as adrenergic tone that are likely to shift during cancer therapy.^{63,100} LVEF may also lack sensitivity to detect subclinical LV dysfunction at a stage when it can be intervened upon with greatest efficacy.¹⁰¹ In general, LVEF as measured by 3D echocardiography is preferred over Simpson's 2D-biplane or 2D-triplane methods owing to a variability of 5% to 6% as compared to 10% to 13% for 2D methods in patients undergoing serial imaging during cancer treatment.⁹⁸

Global longitudinal strain

GLS has shown promise as an imaging parameter that can detect anthracycline cardiotoxicity at an earlier stage than LVEF. A relative change in GLS of 10% to 15% has a sensitivity of 65% to 80% and a specificity of 80% to 99% for the detection of anthracycline cardiotoxicity.^{16,56,102–104}

However, it remains unclear whether utilization of GLS in the diagnosis of anthracycline cardiotoxicity improves clinical outcomes. The SUCCOUR trial compared an LVEF-guided versus a GLS-guided strategy of cardioprotective therapy initiation in patients with breast cancer undergoing anthracycline and trastuzumab therapy. While the rate of cardioprotective therapy initiation was higher in the GLS-guided group (31% in the GLS-guided group vs 14.6% in the LVEF-guided group), no significant difference in the primary end point of change in LVEF at 3 years was seen.¹⁰⁵ Additionally, the study was not powered to detect differences in the risk of HF.

Diastolic function

The use of diastolic dysfunction in screening for anthracycline cardiotoxicity is controversial. While diastolic dysfunction may occur before a reduction in LVEF,⁵ diastolic parameters have not been shown to predict cardiotoxicity conclusively.¹⁰⁶

Newer metrics of subclinical LV dysfunction may hold promise in the prediction of clinical cardiotoxicity. Left atrial reservoir strain decreases in a greater proportion of patients receiving anthracyclines as compared to GLS, though it remains unclear whether those patients would go on to develop overt cardiotoxicity and HF.¹⁰⁷ Quantification of myocardial work through pressure-strain loop (PSL) analysis is an emerging method to identify subclinical myocardial dysfunction. PSL analysis combines data from speckle-tracking strain imaging with noninvasive estimations of LV pressure.¹⁰⁸ The clinical utility of PSL analysis in the

detection of anthracycline cardiotoxicity remains the subject of active investigation.^{109–112}

Serum biomarkers

While a variety of blood biomarkers have been the subject of study for the prediction and monitoring of cardiotoxicity, markers currently in clinical use include cTn and NPs. cTn is particularly effective at detecting early myocardial injury, while NPs are more sensitive in identifying late-presenting cardiotoxicity and HF.¹¹³

Several studies and meta-analyses have provided evidence supporting the notion that monitoring cTn levels can serve as an effective method for surveillance of adverse cardiovascular events in patients undergoing cancer therapy. Furthermore, the use of NPs can assist in identifying individuals at higher risk for subsequent cardiac events early in their chemotherapy course. Changes in N-terminal prohormone of brain natriuretic peptide (NT-proBNP) levels have been found to correlate temporally with alterations in imaging parameters indicative of cardiac dysfunction, offering predictive value for cardiotoxicity, particularly in patients receiving sequential anthracycline and trastuzumab therapy.^{114–116} The ESC guidelines recommend obtaining a baseline cTn and brain natriuretic peptide (BNP) levels and monitoring these levels after each cycle of anthracycline-based chemotherapy as well as 3 and 12 months posttreatment for patients at high risk and very high risk of cardiotoxicity as well as cTn and BNP at baseline and after every other cycle as well as 3 months posttreatment in patients at low or moderate risk of cardiotoxicity.⁴⁹

However, numerous observational studies have demonstrated that conventional troponin I (TnI), high-sensitivity TnI, or high-sensitivity troponin T levels are not significantly associated with cardiovascular outcomes following anthracycline therapy. Similar results have been observed in studies examining the relationship between baseline BNP or NT-proBNP levels and cardiovascular outcomes.^{116–120} The inconsistency in the association between biomarkers and anthracycline-induced cardiotoxicity could be due to the relatively low baseline cardiovascular risk observed in some of the studied patient populations, their inherent heterogeneity, and differences in follow-up durations.¹²¹ Standardized cutoffs and reference values for cardiovascular biomarkers are yet to be established for patients with cancer or those undergoing anthracycline chemotherapy.⁴⁹ Clinically, abnormal biomarker results need to be evaluated within the patient's clinical context, considering factors such as the timing of cancer treatment and existing comorbidities, and many centers do

not routinely screen for toxicity with these biomarkers given the low quality of evidence.

MANAGEMENT OF ANTHRACYCLINE CARDIOTOXICITY

The management of anthracycline cardiotoxicity requires collaborative decision-making between cardiology and oncology regarding modification of cancer therapy, initiation of GDMT for HF, and surveillance planning. These decisions depend on the severity of cardiac dysfunction as well as the presence or absence of symptoms of clinical HF. Notably contemporary management is based on expert opinion and small, single-arm studies given the dearth of randomized trials conducted in this population. The following approach is largely in line with the ESC guidelines (Fig. 2).⁴⁹

For asymptomatic patients with mild LV dysfunction, anthracycline therapy may be continued. A referral to cardio-oncology is warranted for the evaluation and management of cardiovascular risk factors. If patients have comorbidities for which GDMT or statins are indicated, these medications may be initiated.^{5,17,101,122} At present, the data supporting the use of GDMT for patients with LV dysfunction are limited. While 1 cohort study conducted in patients with breast cancer saw improvement in LVEF at 4 years posttreatment in most patients who were started on a beta blocker and ACE inhibitor or ARB, including full recovery in 11% of patients, it remains unclear whether GDMT would have an impact on hard outcomes such as mortality and development of clinical HF.⁵

For patients with mild LV dysfunction who are experiencing symptoms of HF, the decision whether to continue anthracycline therapy is made through a collaborative, multidisciplinary approach while further cardiovascular evaluation is performed. GDMT should be initiated according to LVEF as with any other HF syndrome. After initiation and titration of GDMT, oncologic plans may be revisited based on symptom improvement and reassessment of cardiac function.^{5,101,122}

In the presence of moderate LV dysfunction with or without symptoms or severe LV dysfunction without symptoms, anthracycline therapy is interrupted for further cardiac evaluation. Reversible causes of cardiomyopathy should be ruled out through appropriate ischemic evaluation, serologic studies, and, in cases where the LVEF cannot be accurately estimated on TTE or there remains uncertainty regarding the etiology, CMR. GDMT should be initiated or intensified as tolerated.^{17,122}

Following the initial evaluation and GDMT initiation, the LVEF is reassessed after 2 to 4 weeks. If

symptoms improve and LVEF is 40% or greater, a multidisciplinary team weighing the oncologic and cardiovascular risks for an individual patient may recommend reinitiating anthracycline therapy with modification using dose reduction, liposomal anthracycline formulations, or dexrazoxane. Alternatively, nonanthracycline-containing cancer treatments could be considered. If anthracyclines are resumed, the evaluation of LVEF should be repeated prior to each treatment cycle. For patient who remains symptomatic or LVEF is less than 40% after optimal medical management, anthracycline therapy should be discontinued in most cases.¹²³

Symptomatic patients with severe LV dysfunction require discontinuation of anthracyclines, assessment for other causes of cardiomyopathy, and when stable, introduction and titration of GDMT. Some of these patients may require inotropic support, mechanical circulatory support, or evaluation for heart transplantation if their malignancy is in remission.^{122,123}

Additionally, Cardio-Oncology Rehabilitation (CORE) is recommended in society guidelines and statements for patients with who develop cardiotoxicity, though evidence demonstrating a benefit of CORE on cardiac-specific outcomes is limited.^{49,124}

LONG-TERM SURVEILLANCE IN SURVIVORS OF ADULT CANCERS

There remains a gap in determining the most effective modalities for screening long-term survivor populations for complications arising from anthracycline chemotherapy. The majority of LV dysfunction due to anthracycline toxicity manifests within the year after completion of anthracycline therapy,⁵ and while later presentations occur, they represent a diagnosis of exclusion. Focusing cardiac screening in the 12 months after treatment in most patients, with close follow-up in those at the highest risk, is a cost-effective strategy that significantly benefits patients at risk.¹²⁵

In low-to-moderate-risk survivors of adult cancers, a TTE can be conducted 6 to 12 months after treatment to screen for cardiac dysfunction. Cancer survivors with new or persistent cardiac abnormalities at their end-of-therapy assessment are at high risk of future cardiovascular events. Asymptomatic but high-risk patients without evidence of cardiotoxicity in the initial posttreatment assessment may be evaluated with echocardiography at 1, 3, and 5 years after anthracycline therapy followed by every 5 years thereafter.⁴⁹ Regardless of risk, long-term surveillance includes patient education and cardiovascular risk factor optimization,

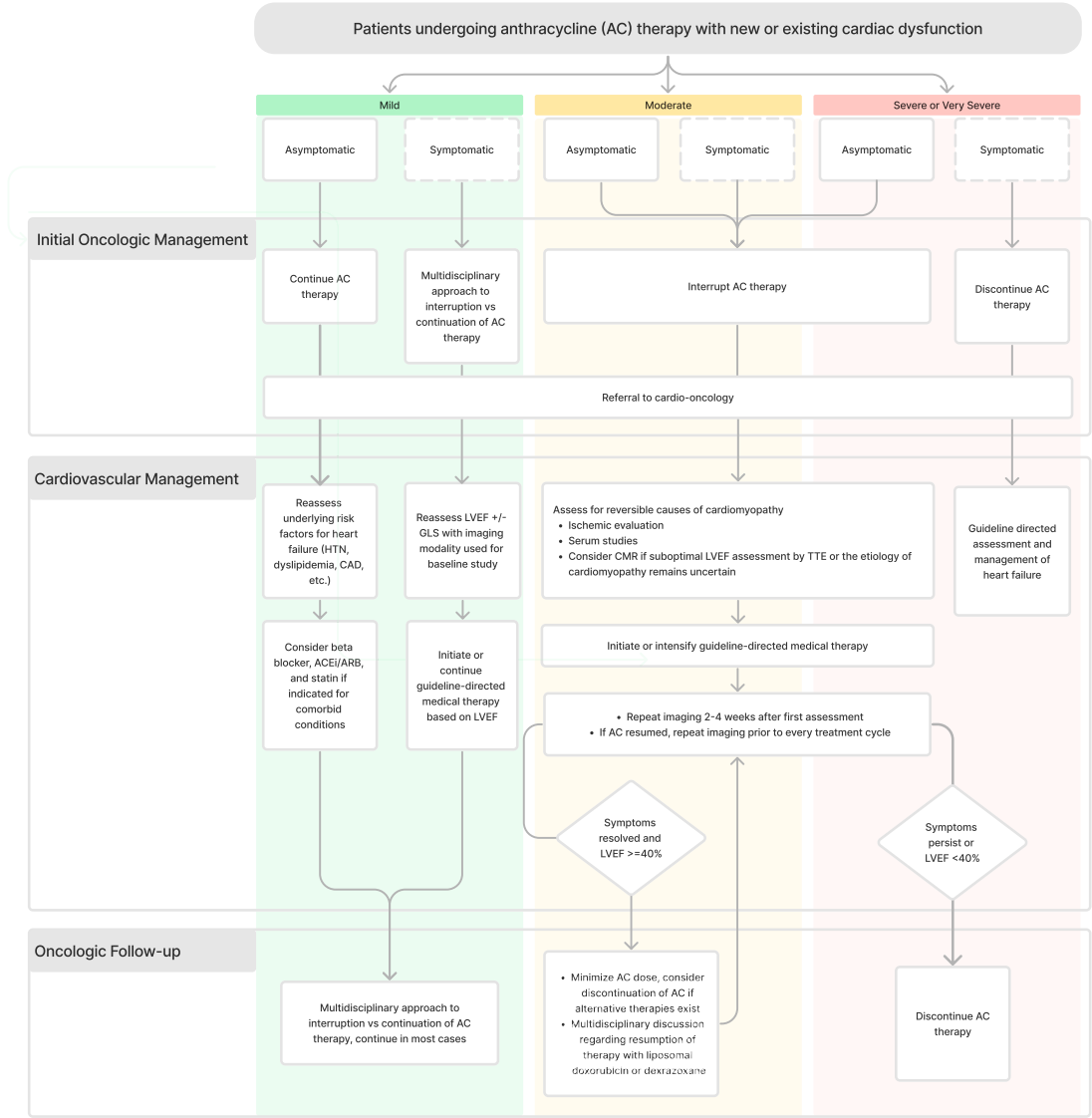


Fig. 2. Management of anthracycline cardiotoxicity. A suggested approach to the oncologic and cardiovascular management of cardiac dysfunction during treatment with anthracyclines. This approach is largely in line with guidelines published by the European Society of Cardiology.⁴⁹ See **Table 1** for definitions of cardiotoxicity. AC, anthracycline; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CAD, coronary artery disease; GLS, global longitudinal strain; HTN, hypertension; LVEF, left ventricular ejection fraction; MR, magnetic resonance; TTE, transthoracic echo.

with repeat cardiac imaging indicated when patients present with new cardiac symptoms.

ADULT SURVIVORS OF CHILDHOOD CANCER

Adult patients who were treated for childhood and adolescent cancers represent a population warranting additional consideration as exposure to anthracyclines during development is associated with substantial morbidity and noncancer-related mortality during adulthood.¹²⁶ The incidence of

anthracycline cardiotoxicity in this population ranges from 4.8% to 10.6% by the age of 40 to 45 years with a frequency of clinical HF of up to 16%.¹²⁷ Like patients treated in adulthood, the risk increases with cumulative anthracycline dose and mean heart radiation dose for patients who underwent radiation therapy.

The frequency of cardiovascular surveillance of adult survivors of childhood cancer is a topic of ongoing research, but it generally depends on the level of risk. High-risk patients are those who

receive anthracycline doses equal to or exceeding doxorubicin 250 mg/m², chest radiation doses equal to or exceeding 35 Gy, or a combination of anthracycline doses equal to or exceeding 100 mg/m² along with chest radiation doses equal to or exceeding 15 Gy.¹²⁸ Patients who received doses ranging from doxorubicin 100 to 250 mg/m² or chest radiation doses of 15 to 35 Gy are classified as moderate risk, while other patients are classified as low risk.

Among all survivors, annual cardiovascular risk factor assessment and lifestyle education is recommended. The International Late Effects of Childhood Cancer Guideline Harmonization Group recommends cardiomyopathy surveillance within 2 years of cessation of anthracycline therapy and at 5 years from the time of cancer diagnosis and every 5 years thereafter for all childhood cancer survivors, though this is a strong recommendation for high-risk patients but only a moderate recommendation for lower risk patients.¹²⁸ The ESC recommends surveillance with TTE every 2 years in adult survivors of childhood cancer at high risk for cardiotoxicity and every 5 years for survivors at moderate risk.⁴⁹ More nuanced risk stratification through the incorporation of surveillance LVEF data may help target surveillance at populations that are most likely to benefit from regular imaging in the near future.¹²⁹ Cardiac biomarkers including NT-proBNP and troponins lack adequate sensitivity to detect LV dysfunction in asymptomatic childhood cancer survivors and are not recommended for surveillance purposes.^{128,129}

FUTURE DIRECTIONS

While there has been substantial improvement in the understanding and management of anthracycline cardiotoxicity over the last 5 decades, much research remains to be done to improve outcomes in this vulnerable patient population.

Risk-stratification is essential for guiding subsequent surveillance and prevention strategies, but tools for systematic risk assessment are lacking. Although a risk calculator has been proposed by HFA-ICOS, further validation is needed. In addition to the demographic and clinical characteristics that typically support risk assessment, there is also considerable research underway to identify genetic variants associated with enhanced risk of anthracycline cardiotoxicity, which could establish more refined, individualized risk assessment to inform treatment planning.¹³⁰

Efforts continue to identify screening tests that would allow for earlier diagnosis and treatment of

anthracycline cardiotoxicity while cardiac remodeling remains reversible. Several novel biomarkers have been identified in recent years, including metabolites associated with nucleoside metabolism and the citric acid cycle,¹³¹ circulating miRNAs,¹³² inflammatory markers including myeloperoxidase and soluble tumorigenicity 2 protein (ST2),^{133,134} and the heme-scavenging protein hemopexin³⁴; validation of these biomarkers in a variety of populations is needed. Multiomics approaches to detect the transcriptomic, proteomic, and metabolomic signatures associated with cardiotoxicity also show promise for early detection.¹³⁵ Additionally, artificial intelligence-enabled electrocardiograms have shown promise in not only detection of anthracycline cardiotoxicity but also prediction of who may be at risk prior to treatment.^{136,137}

Identification and refined implementation of imaging biomarkers in the early detection of cardiotoxicity is needed. The impact of early diagnosis using biomarkers in clinical practice, such as GLS, on the risk of clinical HF and mortality remains to be demonstrated in a prospective manner. Other promising imaging parameters under investigation include myocardial work and left atrial strain, and further investigation is needed to verify their clinical utility and effect on outcomes.

Research into genetic variants associated with the development of cardiotoxicity and overlap with variants predisposing to other cardiomyopathies, such as peripartum cardiomyopathy, is an exciting area of investigation, with implications for both risk stratification and identification of therapeutic targets.¹³⁸ Finally, evidence is needed to define the role of emerging cardioprotective therapies, including SGLT2 inhibitors. Further research is also needed to guide clinical use of dexrazoxane, particularly characterizing its impact on antineoplastic efficacy of anthracyclines, as well as novel, less cardiotoxic anthracyclines.

CLINICS CARE POINTS

- Anthracycline cardiotoxicity often manifests as LV systolic dysfunction within the first year after chemotherapy. Abnormalities in cTn, NPs, and GLS can precede the onset of systolic dysfunction.

Pretreatment assessment

- All patients being considered for anthracycline therapy should undergo a thorough cardiovascular risk assessment to categorize them as low, moderate, or high risk of cardiotoxicity.

Prevention

- While there is no evidence supporting the use of cardioprotective medications in all patients receiving anthracyclines, those with established cardiovascular risk factors or cardiovascular disease should receive guideline-based therapy for these conditions.
- Anthracycline cardiotoxicity is dose-dependent. Consider dose reduction, infusion administration, or liposomal anthracycline formulations to minimize the risk of cardiotoxicity.
- High-risk patients can be administered dexrazoxane to reduce the risk of cardiotoxicity without compromising the efficacy of cancer treatment.

Monitoring

- Patients should be monitored for cardiotoxicity during treatment through a combination of clinical assessment, echocardiography, and biomarkers based on their risk level.

Treatment

- Management of anthracycline cardiotoxicity ranges from continued clinical assessment to discontinuation of anthracycline therapy, in addition to treating HF, depending on the severity of toxicity. A multidisciplinary approach to management is essential.

Cancer survivors

- Cancer survivors who have completed treatment should undergo a risk assessment for cardiotoxicity and require risk-based clinical and imaging follow-up.
- Optimization of cardiovascular risk factors is crucial for improving long-term cardiac outcomes in cancer survivors.

DISCLOSURE

A. Asnani serves on the Board of Directors for Corventum, Inc. The authors have no other disclosures.

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Cardiac Complications of Radiation Therapy



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KEYWORDS

• Radiation • Cardiotoxicity • Cardio-oncology • Radiotherapy

KEY POINTS

- Radiation-induced cardiotoxicity (RICT) can include ischemic heart disease, pericardial disease, myocardial injury and heart failure, arrhythmias and conduction system abnormalities, and valvular disorders.
- Despite advances in radiation therapy to reduce the risk of unintended cardiac injury, RICT still occurs with both early and late cardiovascular (CV) complications.
- Prevention of RICT relies on minimizing cardiac radiation dose and managing underlying modifiable CV risk factors.
- Cardiac biomarkers and CV imaging modalities are recommended for screening to detect early changes of injury and allow for earlier intervention.
- Management of RICT follows standard cardiac guidelines, nevertheless, providers' awareness of unique features and complexities of RICT is important to improve outcomes.

INTRODUCTION

The landscape of cancer treatment has evolved rapidly over the years, with radiation therapy (RT) emerging as a cornerstone in the management of greater than 50% of adult cancers.¹ RT significantly improves cancer-specific survival in thoracic malignancies such as lymphomas, breast, lung, and esophageal cancers. As these patients live longer, both early and late treatment complications of radiation have been recognized. While advancements in the contemporary practice of RT have reduced this risk, radiation-induced cardiac toxicities (RICTs) continue to be among the most common causes of morbidity and mortality in cancer survivors.^{2–4}

As radiation remains a pillar of cancer treatment, it is imperative to recognize the risk of RICT in cancer survivors and implement mitigation strategies. In this review, we summarize the clinical spectrum and pathophysiology of RICT, while highlighting contemporary tools for risk stratification, risk reduction, screening, and management. We also discuss emerging concepts in cardiac radiobiology, such as the therapeutic use of cardiac radiation for treating refractory ventricular arrhythmias and cardiac dysfunction. While extracardiac vascular complications of RT also occur, they are out of the scope of this review, and we will only briefly touch on carotid vascular disease and autonomic neuropathy.

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SUMMARY OF RADIATION PRINCIPLES

Traditionally, therapeutic ionizing RT is delivered as high-energy photons that are generated by a linear accelerator or radioactive source and interact with patients' tissue through a number of mechanisms, predominantly Compton scattering.⁵ In recent decades, particle therapy, which involves the delivery of high-energy protons or carbon ions, has emerged as a treatment option. The interaction of high-energy particles with patients' tissues differs from that of photon irradiation due to the Bragg peak, a phenomenon in which energy deposition rapidly declines after the velocity of a radiation particle reaches zero.⁵ The goal of RT in any form is to deliver a radiation dose with optimal therapeutic ratio, which is the balance between normal tissue tolerance and tumor control. The amount of energy deposited to a tissue during RT is described in gray units, which are defined as joules per kilogram.⁵ Despite the clinical utility of the standard gray unit, the biological effects of a single gray may vary due to a variety of factors, including the radiosensitivity of the tissue being irradiated. Tissue radiosensitivity is frequently discussed in terms of the alpha/beta ratio, in which the probable fraction of surviving cells after irradiation is calculated using a linear-quadratic formula. Fractionation of radiation dose, which involves the segmenting of a radiation treatment into larger, less frequent (hypofraction) or smaller, more frequent (hyperfractionation) schedules, may be chosen based on normal tissue versus tumor alpha/beta ratio in order to optimize the treatment's therapeutic ratio.^{5,6} In weighing such decisions, the clinician compares the biologically effective dose of treatment schedules, which takes into consideration a tissue's alpha and beta radiosensitivity values.⁷

RADIATION-INDUCED CARDIOVASCULAR DISEASE: CLINICAL TRIALS AND COHORT STUDIES

Thoracic radiation can damage any component of the heart in the radiation field including the pericardium, coronary vessels, myocardium, heart valves, capillaries, and the conduction system. Clinical evidence for RICT has largely derived from patients with breast cancer and lymphomas where expected survival has been long enough to observe delayed effects. With improved survival of patients with upper gastrointestinal and lung cancers, RICT in those patients has also been recognized.^{2,8} In this section, we summarize a number of studies providing evidence for various forms of RICT citing some representative studies

(**Table 1**). As there have been increasing efforts to reduce radiation to the heart in radiation treatment planning over the years, the risk of RICT should be interpreted in the context of the radiation delivery in that time period.

Ischemic Heart Disease

Ischemic heart disease (IHD) due to intimal injury, atherosclerosis, and/or coronary luminal narrowing leading to coronary artery disease (CAD) is the most described form of RICT.³ Older radiation techniques delivered relatively high doses to large volumes of the heart and were associated with an increased risk of adverse cardiovascular (CV) outcomes. In a study of 1461 patients with breast cancer between 1949 and 1955 randomized to either early RT or delayed RT only if there was a recurrence, the early radiation group had 43% increased mortality during greater than 15 years follow-up, mostly due to increased death from IHD.⁹ In a meta-analysis that included a combination of older and newer RCTs of approximately 1.2 million patients with breast cancer, RT remained associated with increased CAD (relative risk [RR] 1.3 [95% confidence interval (CI) 1.13–1.49]) and cardiac mortality (RR 1.38 [95% CI 1.18–1.62]). However, the absolute risk was relatively low (76 and 126 cases per 100,000 person-years, respectively).¹⁶

As RT became the standard of care for many patients with breast cancer, studying the contemporary risk of RT on IHD in clinical trials setting became challenging due to the lack of an adequate control arm. Nevertheless, observational data suggest that, despite attempts to reduce IHD, a residual risk still remains. In a population-based Swedish cohort study of around 60,000 patients with breast cancer treated between 1992 and 2012, when 3 dimensional (3D) conformal RT planning started to become widely available, there was an increased incidence of IHD in women receiving left-sided RT compared to right-sided RT.¹⁹ This elevated risk started within a few years after RT and was sustained through longer follow-up.¹⁹ Darby and colleagues³ in 2013 questioned the presence of a "safe dose" of RT, reporting a linear dose-dependent relationship between radiation and the incidence of IHD, starting a few years after RT and continuing for at least 20 years. There was residual risk even in patients who received less than 2 Gy mean heart dose (MHD),³ though the absolute increase in risk was small.

Data regarding IHD in patients with lung cancer receiving RT are also consistent with a dose-related increase in CV events with increasing heart dose.¹⁷ These reports show a relatively early onset

Table 1
Representative studies of radiation-induced cardiovascular toxicities

Author, Year of Publication	Period	Patient Population	Main Findings
Jones et al, ⁹ 1989	1949–1955	• 1461 patients with BC • Randomized to immediate postoperative RT or delayed RT on recurrence • Median follow-up of 15 y	• Early radiation group had 43% increased mortality, mostly due to increased death from IHD • No significant difference in cancer mortality
Hull et al, ¹⁰ 2003	1962–1998	• 415 HL survivors who underwent RT • Median follow-up of 11 y	• CAD in 10%, carotid/subclavian artery disease in 7.4%, and VHD in 6.2% of patients • Aortic stenosis was the most common lesion in patients with VHD • Increased observed-to-expected ratio of CABG/PCI (1.63) and valve surgery (8.42) • Prior CV risk factors and radiation dose were independent predictors of CAD
Heidenreich et al, ¹¹ 2003	RT received before enrollment (1994–1998)	• 294 asymptomatic HL survivors treated with at least 35 Gy to the mediastinum	• In patients who received RT >20 y ago: ◦ Mild or greater aortic regurgitation (60%) ◦ Moderate or greater aortic stenosis (16%) ◦ Moderate or greater tricuspid regurgitation (4%) • Authors suggest considering echocardiographic screening following RT
Aleman et al, ⁴ 2006	1965–1995	• 1474 HL survivors <41 y old at treatment • Median follow-up of 19 y	• Mediastinal RT was associated with increased risk of IHD, HF, and VHD (2–7 folds)
Maraldo et al, ¹² 2012	2006–2010	• 29 young adults receiving contemporary RT for HL	• Reduced MHD using contemporary involved node RT compared to historic mantle field RT • Although risk was lower than historic cohorts with older RT techniques, there was still a residual absolute excess risk of cardiac events (5% at 25 y follow-up)
Darby et al, ³ 2013	1958–2011	• Swedish + Danish cohort • 2168 women underwent RT for BC	• Linear increase in major coronary adverse events with increasing MHD (7.4% per Gray) • Risk starts within few years of RT and continues to >20 y

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Table 1
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Author, Year of Publication	Period	Patient Population	Main Findings
			• Residual risk even in patients who received <2 Gy questioning the concept of “safe dose” • Greater absolute increases in risk in women with prior CV risk factors
Armstrong et al, ¹³ 2013	1970–1986	• Retrospective review of 10,724 survivors in the Childhood Cancer Survivor Study • Median follow-up of 26 y	• Cumulative incidence of CV events among patients receiving RT: ◦ CAD ~9% ◦ VHD ~3% ◦ Arrhythmias ~1%–2% ◦ HF ■ With anthracyclines ~13% ■ Without anthracyclines ~4% • The combined effect of RT plus hypertension resulted in multiplicative potentiation of risk
Groarke et al, ¹⁴ 2015	2003–2013	• 263 HL survivors • Exercise treadmill testing at a median of 19 y following RT • 526 age, gender, and CV risk-matched controls	• RT associated with increased resting HR (OR 3.9), slower HR recovery (OR 5.3), and reduced exercise capacity • Abnormal HR recovery was associated with increase mortality (AHR 4.6)
Van Nimwegen et al. ¹⁵	1965–1995	• Dutch cohort of 2524 patients diagnosed with HL <the age of 51 y • Median follow-up of 20 y	• Mediastinal RT was associated with increased risk of IHD (HR 2.7), VHD (6.6), and HF (HR 2.7) • Risk persisted even after 35 y of follow-up • Additive rather than multiplicative effect when RT was combined with anthracyclines or smoking • Relatively low anthracycline dose (median ~210 mg/m²) • Highest risk among young patients receiving RT (<25 y of age)
Cheng et al, ¹⁶ 2015	Studies published between 1980 and 2015	• Meta-analysis of 39 studies • 1,191,371 patients with BC	• Higher risk of CAD (RR 1.29) and cardiac mortality (RR 1.22) in left-sided vs right-sided breast radiation • Higher risk of CAD (RR 1.3) and cardiac mortality (RR 1.38) in patients receiving radiation

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Table 1
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Author, Year of Publication	Period	Patient Population	Main Findings
			Relatively small absolute risk increase of 76.4 cases of CAD and 125.5 cases of cardiac death per 100,000 person-years
Wang et al, ¹⁷ 2017	1996–2009	127 patients with stage III non-small-cell lung cancer receiving RT	- At a median follow-up of around 9 y, adverse cardiac events in 23% of patients, mostly IHD and arrhythmias - Risk increased with increase MHD and baseline CV risk factors - Earlier onset of IHD compared to younger cohorts with BC
Saiki et al, ¹⁸ 2017	1998–2013	- Case-control study 59 female individuals undergoing RT for BC who developed HF - Matched control of 111 patients undergoing RT for BC who without HF	89% of HF cases had preserved LVEF (HFpEF) - Mean time from RT to HF ~6 y - Each increase in the log of the MHD was associated with significantly increased risk of HFpEF (odds ratio [OR] 16.9) and a nonsignificant increased risk of HFrEF (OR 3.2 [95% CI 0.8–13])
Wennstig et al, ¹⁹ 2020	1992–2012	- Swedish BC registry 60,217 women - Contemporary cohort with modern RT planning	- Increased risk of IHD in left-sided compared to right-sided BC (HR 1.18) - Increased risk with concomitant systemic therapy
Seth et al, ²⁰ 2024	- Studies published between 1999 and 2022 - Institutional cohort 2010–2022	- Meta-analysis of studies comparing left-sided vs right-sided RT in patients with BC - Institutional cohort of patients with BC receiving RT between 2010 and 2022	- Historic trend of increased risk of CAD in patients with BC receiving left-sided RT (10% increased risk) - Subgroup analysis of more recent cohorts (patients diagnosed after 1980) showed no effect of BC laterality on CAD - Institutional cohort also found no significant difference in CAD between left-sided vs right-sided BC

Abbreviations: AHR, adjusted hazard ratio; BC, breast cancer; CAD, coronary artery disease; CV, cardiovascular; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HL, Hodgkin lymphoma; HR, heart rate; IHD, ischemic heart disease; LVEF, left ventricular ejection fraction; MHD, mean heart dose; OR, odds ratio; RR, relative risk; RT, radiation therapy; VHD, vascular heart disease.

of ischemic events after RT, perhaps related to a population with higher burden of baseline CV risk factors and a higher cardiac radiation dose compared to younger women with breast cancer.¹⁷

Patients with Hodgkin lymphoma (HL) have also been shown to have an increased risk of IHD associated with mediastinal radiation.⁴ In a seminal publication studying 1474 survivors of HL aged

younger than 41 years at treatment, patients who received mediastinal RT had a significantly higher risk for myocardial infarction (hazard ratio [HR] 2.42) and angina (HR 4.85) during a median follow up of 18.7 years.⁴

Another study investigating a cohort of HL survivors who received RT in a similar era (1960s–1990s) reported an incidence rate of CAD around 10% at a median of 9 years after treatment.¹⁰ That increased risk was translated into an increased observed-to-expected ratio for coronary artery bypass graft (CABG) surgery or percutaneous coronary intervention (PCI) of 1.63. Also, extracardiac atherosclerotic disease occurred in the carotid and subclavian arteries in around 7% of survivors at a median of 17 years after treatment.¹⁰ These observations were further supported by van Nimwegen and colleagues¹⁵ reporting a 4 to 6 fold increased standardized incidence ratio of IHD or HF compared with the general population. That risk persisted even after 35 years of RT and was highest among younger patients who received RT (<25 years of age). Fortunately, radiation doses and field sizes for patients with HL have decreased over time, leading to decreases in the risk of RICT.^{21,12}

Pericardial Disease

The effect of radiation on the pericardium remains minimally studied despite being long recognized.²² The spectrum of pericardial disease following radiation ranges from rare early complications in the form of acute pericarditis to more commonly encountered delayed complications such as pericardial effusion, chronic pericarditis, and constrictive pericarditis (CP) from pericardial thickening and fibrosis. The incidence of radiation-associated pericardial complications is variable between different cancers and radiation protocols but has been reported to range from 10% to 50% of patients undergoing thoracic radiation.²² Risk factors for radiation-induced pericardial disease are older radiation protocols, a total cardiac dose of greater than 30 Gy, radiation fraction of greater than 2 Gy per day, and heart volume in the treatment field greater than 45%.²²

Arrhythmias and Autonomic Dysfunction

Thoracic radiation has been linked with an increased risk of arrhythmias including tachyarrhythmias such as atrial fibrillation and atrial flutter, bradyarrhythmias including heart blocks, permanent pacemaker placement, and autonomic dysfunction.²³ These observations may be mechanistically related to radiation-induced injury and fibrosis of the conduction system, valvular calcification of the tricuspid and mitral annuli causing direct compression on

the AV node and the proximal His bundles, and/or atrial fibrosis acting as a substrate for atrial fibrillation and flutter.^{23,24}

Autonomic dysfunction following radiation remains poorly understood with limited mechanistic data. In a study by Groarke and colleagues,¹⁴ 263 patients with HL treated with mediastinal radiation were compared to age-matched and gender-matched control subjects with exercise testing at a median 19 years after initial therapy. RT had a dose-dependent association with elevated resting heart rate, abnormal heart rate recovery after exercise, and increased all-cause mortality in patients exhibiting autonomic dysfunction compared to controls. This is further supported by Noor and colleagues,²⁵ where they observed a high prevalence of prior chest and neck radiation in about two-thirds of patients referred for autonomic dysfunction to an academic cardio-oncology program.

Cardiologists should also be aware that radiation can also interfere with the programming and function of cardiac implantable electronic devices (CIEDs) such as pacemakers and defibrillators, especially with treatments involving neutron-producing high-energy photon beam therapies. Current expert consensus recommendations include CIED evaluation prior to and weekly during neutron-producing RT.²⁶

Valvular Heart Disease

Valvular heart disease (VHD) is often encountered decades after RT and can be confounded by aging-related valvular degeneration making it challenging to accurately establish the true effect of RT. Valvular regurgitation was reported to be more common than stenosis and most often involves the aortic valve.¹¹ In 294 asymptomatic patients who received mediastinal radiation for HL, the prevalence of aortic regurgitation was 60%, tricuspid regurgitation was 4%, and aortic stenosis was 16% in patients who received RT more than 20 years prior versus 4%, 0%, and 0%, respectively, among those who received radiation less than 10 years prior.¹¹ In contrast, another cohort of HL survivors who received RT in the 1960s to 1990s reported significant incidence of valvular disease in 6% of patients at a median of 22 years following RT, with aortic stenosis being the most common lesion.¹⁰ Interestingly, most studies suggest higher incidence of left-sided as opposed to right-sided valvular disease despite the more anterior position of right-sided structures in the chest. It is theorized that the high pressure-flow across the left-sided valves acts as a secondary mechanism in the degeneration of those valves.²⁷

Cardiomyopathy and Myocardial Disease

Patients are at increased risk for heart failure (HF) after RT secondary to radiation-induced ischemic, valvular, or pericardial disease, or directly from radiation-induced myocardial injury, fibrosis, and scarring. The incidence of HF with preserved ejection fraction (HFpEF) after RT is higher than HF with reduced ejection fraction (HFrEF).¹⁸ Among 170 female individuals undergoing contemporary breast cancer RT, each increase in the log of the MHD was associated with significantly increased risk of HFpEF (odds ratio [OR] 16.9 [95% CI 3.9–73.7]) and a nonsignificant increased risk of HFrEF (OR 3.2 [95% CI 0.8–13]).¹⁸ These patients commonly present with diastolic dysfunction and a restrictive cardiomyopathy phenotype, thus a clinical evaluation for diastolic HF is important during their follow-up and screening even in patients with preserved ejection fraction.

PATHOPHYSIOLOGY OF RADIATION-INDUCED CARDIAC TOXICITY

RICT results from the interplay of reactive oxygen species (ROS) generation, cellular and organelle DNA damage, macromolecule alteration, and/or signaling cascades related to inflammation and tissue remodeling (Fig. 1). Radiation ionizes water within cardiac tissue creating ROS and reactive nitrogen species that directly damage organelles and DNA in the nucleus and mitochondria.²⁸ This DNA damage can then result in additional organelle dysfunction, apoptosis, or cell death.²⁸ Reactive species also lead to chemical alteration of cellular macromolecules (eg, lipid peroxidation and protein nitration) and induction of signaling cascades associated with inflammation and tissue remodeling.

The latter is mediated by the release of soluble factors, such as cytokines (such as tumor necrosis factor [TNF]- α , interleukin-1 beta [IL-1 β], IL-6, transforming growth factor beta, and platelet-derived growth factor) and chemokine (C-C motif) ligand 2 (CCL2), and enacted through upregulation of transcriptional pathways (Nuclear factor kappa-light-chain-enhancer of activated B cells [NF- κ B] and NLRP).^{28,29}

The myocardium contains different cell types with varying sensitivities to radiation. Adult cardiomyocytes are relatively radioresistant, owing to their limited ability for mitosis and replication.³⁰ Conversely, endothelial cells are highly radiosensitive, and their activation and/or destruction is a critical step in radiation toxicity.³¹ Consequences of endothelial damage include increased vascular permeability and intimal immune cell infiltration (via upregulation of adhesion molecules and integrins), decreased capillary density and devascularization of cardiac tissue, dysfunctional coagulation, and altered platelet activation.³¹ Although sparse in a healthy heart, radiation can promote infiltration of immune cells into the myocardium.³² Response of immune cells to radiation may also vary by dose; while high doses are cytotoxic, low-dose radiation has been found to provoke both proinflammatory and anti-inflammatory responses.³³

Apart from direct injury to the heart and the vasculature, RT may be associated with autonomic dysfunction that can indirectly affect the CV system. While mechanistic data are still lacking, several theories have been proposed.³⁴ Head and neck RT may cause direct nerve damage and fibrosis of the vagal nerve and the baroreflex of the carotid sinus.³⁵ Also, the proinflammatory state following RT may be associated with dampened vagal activity due the excess production of

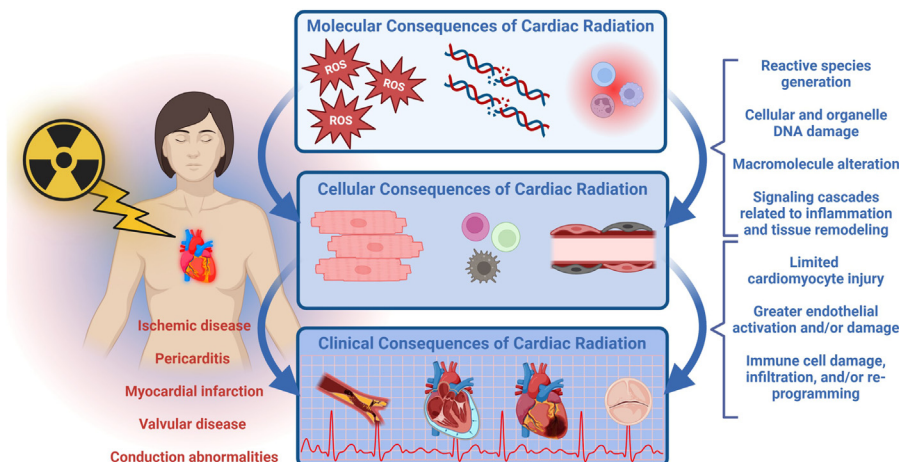


Fig. 1. Pathophysiology of radiation-induced cardiac toxicity.

inflammatory cytokines such as IL-1, IL-6, and TNF- α leading to a sympathetic overdrive.³⁶ These inflammatory cascades may also result in increased oxidative stress and ROS release that can lead to autonomic nerve damage, axonal injury, and demyelination.³⁴ Finally, in cases of radiation-induced left ventricle (LV) dysfunction, HF and tissue hypoperfusion can lead to increases in sympathetic drive and parasympathetic withdrawal, which can manifest as signs of autonomic dysfunction.³⁷

RISK FACTORS OF RADIATION-INDUCED CARDIOTOXICITY

Several patient and therapy related factors have been associated with increased risk of RICT (Fig. 2).

Therapy-related Factors

Concomitant antineoplastic therapies

RT is often administered with other systemic cancer therapies including chemotherapy, hormonal therapy, and/or immunotherapy. These combinations improve cancer-related survival, but some may also increase the risk of RICT. In 10,724 pediatric cancer survivors in the Childhood Cancer Survivor Study, RT + anthracyclines was associated with significantly increased HF compared to either alone.¹³ Another European study of 36,205 childhood cancer survivors similarly found anthracycline + RT was associated with increased and earlier incidence of IHD when compared with either alone.³⁸ In the previously mentioned Dutch cohort of around 2500 patients treated for HL in the 1960s to 1990s, mediastinal radiation was associated with an increased risk of IHD (HR 2.7) and HF (HR 2.7) during a 40 year follow-up.¹⁵ Anthracycline use was also associated with an increased risk of valvular disease and HF but not IHD. The combination of RT and anthracyclines showed additive

rather than multiplicative risk; however, the median anthracyclines dose used in that population was relatively low (210 mg/m²).¹⁵

Over the last decade, immunotherapy with immune checkpoint inhibitors (ICIs) has become a highly utilized class of antitumor agents. Effective immunotherapy relies on tumor antigenicity, with “cold” tumors (eg, those accompanied by low T-cell infiltration, programmed death-ligand 1 (PD-L1) expression, and tumor mutational load) responding less favorably to ICIs.³⁹ Radiation may promote tumor antigenicity prior to ICI treatment, thereby priming the tumor to a more effective ICI response.⁴⁰ The CV effects of combining RT with ICIs remain unknown due to the recent introduction of this class of therapy, with limited available follow-up. Due to shared mechanistic pathways of cardiotoxicity between ICI and RT that include accelerated atherosclerosis and enhanced cardiac inflammation, the combination may be associated with increased risk over individual therapy. However, real-world data are still limited.

In 194 patients with locally advanced and metastatic lung cancer, concurrent immunotherapy and RT did not significantly impact the incidence of cardiotoxicity compared to immunotherapy alone.⁴¹ However, the patients who received combination therapy nonconcurrently had a greater incidence of cardiotoxicity compared to immunotherapy alone, suggesting that the temporal relationship between immunotherapy and RT may impact cardiotoxicity risk. In a cohort study of greater than 5000 patients with various cancers who received ICIs, prior radiation was not a predictor of major adverse cardiac events (MACE) within 1 year of treatment, using a broad definition of MACE including arrhythmia and pericarditis.⁴² Given the heterogeneity of the studied populations, varying outcomes analyzed, and short follow-up time, further study is needed.

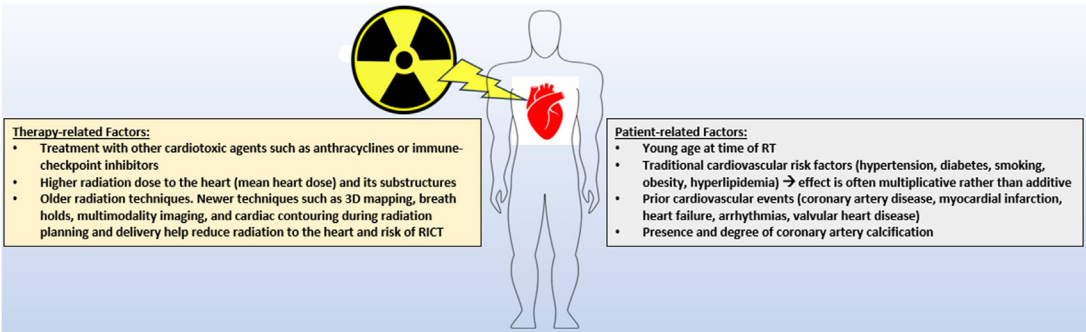


Fig. 2. Risk factors of radiation-induced cardiotoxicity. Several patient-related and therapy-related factors increase the risk of RICT. Close collaboration among medical oncologists, radiation oncologists, and cardio-oncologists is important to implement early screening, prevention, and management strategies to mitigate the risk of RICT.

Radiation Dose to the Heart and Its Substructures

Traditionally, guidelines have recommended minimizing radiation dose to the heart as a whole (ie, MHD), rather than specific cardiac substructures.⁴³ Advancements in radiation planning and delivery have made it possible to both visualize and avoid cardiac substructures, raising the question of whether cardiac substructure doses may be better predictors of RICT than MHD. Recent evidence suggests that MHD is not a surrogate for substructure dose, particularly in the setting of new radiation techniques that deliver heterogeneous doses across the heart.^{21,44,45} In addition, cardiac substructures may not be uniform in their sensitivity to radiation,⁴³ further underlining the need to evaluate dose to specific substructures. To date, several substructures have been implicated in RICT. Left ventricular radiation dose has been found to be an important prognostic parameter of acute coronary events in patients with breast cancer⁴⁶ and acute (<1 year) alterations in left ventricular ejection fraction (LVEF) and LV strain in patients with lymphoma and thoracic cancers.⁴⁷ Recent reports also suggest that dose to the left anterior descending artery (LAD) correlates with MACE in patients with breast cancer⁴⁸ and with all-cause mortality and MACE in patients with non-small cell lung cancer.⁴⁹

Radiation Therapy Planning

Advancements in RT planning and delivery have dramatically reduced heart dose and subsequent risk for RICT in many contemporary patients.²¹ The 3D or 4 dimensional (4D/3D + respiratory motion) computed tomography (CT) radiation planning scans can now delineate the heart and other organs-at-risk. Manual contouring of the heart and its substructures, however, represents an additional challenge in radiation planning, as it is a time-consuming process with high rates of intraobserver variability. Cardiac atlases, such as by the Radiation Therapy Oncology Group,⁵⁰ help to standardize manual segmentation of the heart. More recently, technological advancements in deep learning and artificial intelligence have led to experimental use of automated segmentation, in which cardiac substructures are delineated by algorithms based on imported CT scans.⁵¹ Such tools may allow clinicians to determine cardiac substructure dosing during RT planning more quickly and accurately.

Notably, radiation dose calculations are further complicated by cardiac and respiratory motion, which can be partially addressed by respiratory gating deep-inspiratory breath hold (DIBH). DIBH is a common technique used during imaging or

treatment that flattens the diaphragm, expands the lungs, and moves the heart away from the chest wall while also minimizing cardiac motion.⁵² Other advanced imaging modalities, such as MRI, can be utilized to better capture heart motion, although they are used infrequently.

Radiation Delivery

Fractionation, the separation of radiation delivery into multiple daily fractions, was first conceptualized in the 1920s and is still a mainstay of RT, owing to its ability to balance tumor control with sparing of normal tissue.⁵³ In the 1990s, 3D conformal radiation therapy (3DCRT) replaced 2 dimensional radiation field arrangements, which was made possible by the integration of CT imaging (Fig. 3).⁵³ By the early 2000s, intensity-modulated radiation therapy (IMRT) became available, which leveraged multileaf collimators to allow for nonuniform beam intensities.⁵³ By passing lower intensity x-rays through organs-at-risk versus targeted tumors, IMRT improves upon the normal tissue-sparing capacity of 3DCRT, yet necessitates a longer treatment duration.⁵⁴ Volumetric modulated arc therapy (VMAT), a form of IMRT introduced in the mid-2000s, helped to solve this problem by delivering an entire radiation dose in a single gantry arc.⁵⁴ Stereotactic body radiation therapy (SBRT) is also a hallmark of current RT. In contrast to fractionated RT, SBRT's goal is to deliver high-intensity, conformal radiation doses to small areas in a single or low number of fractions, leading to tissue ablation.⁵⁵ Proton particle therapy is also becoming more common, as the physical properties of protons allow a sharp peak (the Bragg peak) with a rapid drop-off of dose, thus minimizing lower dose spill to organs at risk. While these contemporary techniques have improved radiation delivery to minimize unintended RICT, they are still not uniformly available, and their use varies among different centers.

Overall, recent evidence supports the notion of improved CV safety with contemporary RT techniques in breast cancer. In a meta-analysis of 9 studies comparing left-sided and right-sided RT for breast cancer, Seth and colleagues²⁰ reported a historic trend of increased risk of CAD in left versus right breast radiation; however, that association was not observed in a subgroup analysis of 6 studies that included patients diagnosed after 1980. The authors also reported no increased risk of CAD among 2692 patients with breast cancer in their center who received left-sided versus right-sided radiation in a contemporary period between 2010 and 2022.²⁰ These results are very promising but should not be extrapolated to other

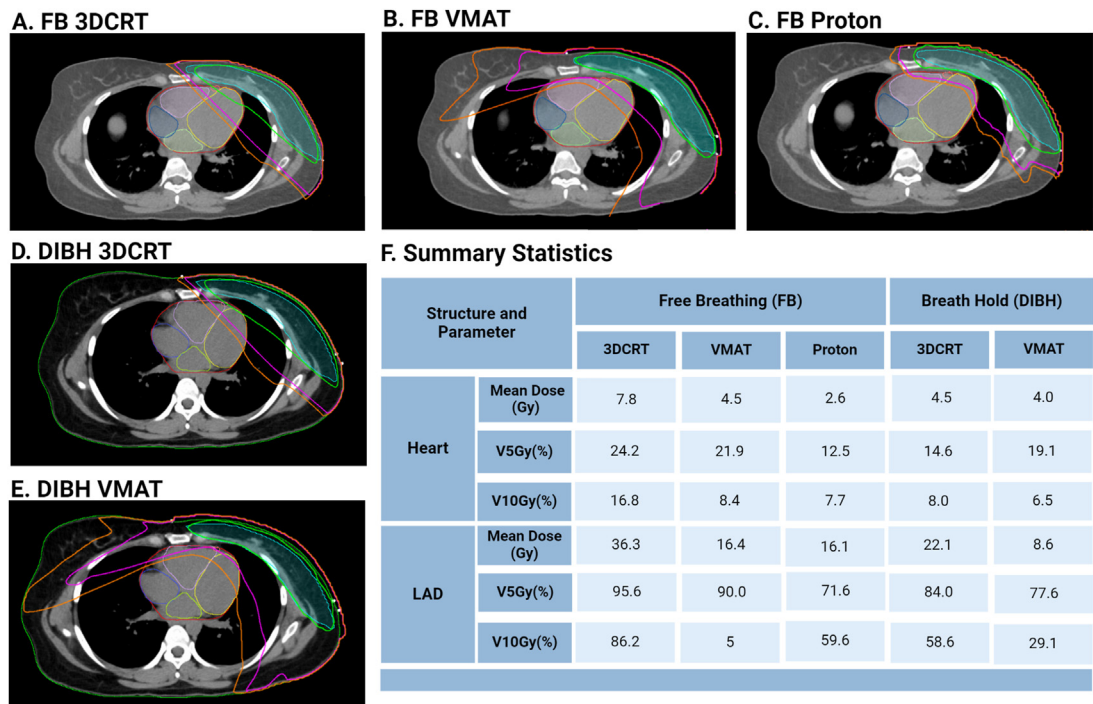


Fig. 3. How contemporary radiation treatment planning and delivery can influence radiation doses to the heart and cardiac substrctions. Panels A through E show the radiation contour lines for five different contemporary techniques of radiation planning and delivery used in a young patient with breast cancer treated definitively to the left chest wall and regional lymph nodes. Axial CT slices from the approximate same levels are shown for the following plans: (A) free breathing (FB) 3DCRT (3-dimensional conformal radiation therapy); (B) FB volumetric modulated arc therapy (VMAT), a type of intensity modulated radiation therapy (IMRT); (C) FB proton therapy; (D) deep inspiration breath hold (DIBH) 3DCRT; and (E) DIBH VMAT. The table in Panel F illustrates the effect of these different techniques on the estimated radiation dose to the heart and the left anterior descending artery. 3DCRT, 3 dimensional conformal radiation therapy; DIBH, deep inspiratory breath hold; FB, free breathing; LAD, left anterior descending coronary artery; VMAT, volumetric modulated arc therapy.

cancers, such as esophageal cancer, which have more limited available techniques to reduce heart irradiation.

Patient Factors

The risk for RICT is also increased by patient factors including a younger age (variably defined as <25 years to <50 years) at the time of RT and the presence of traditional CV risk factors.²⁷ In a case–control study of female individuals undergoing thoracic radiation for breast cancer, CV risk factors such as diabetes, smoking, and obesity were associated with 3.2, 1.9, and 1.5 fold increased risk of adverse cardiac events, respectively.³ The increased risk conferred by these factors may be multiplicative rather than additive. In a study of 4414 breast cancer survivors, smoking and RT together were associated with a more than additive effect on the risk of future myocardial infarction (HR of 3.04, *P* for departure from additivity of .04).⁵⁶ Another study reported a synergistic, multiplicative

effect of hypertension to potentiate the risk of RICT.¹³

Over the last few decades, coronary artery calcifications (CAC) detection and quantification evolved as a powerful tool to predict CV events beyond the prognostic ability of traditional risk factors both in the general population and in cancer cohorts.^{57,58} CAC identifies patients who have already developed underlying CAD, representing the integrated result of their genetic risk and prior environmental exposures. While CAC was originally studied using gated coronary CT scans, investigations demonstrated that CAC assessment on non-gated scans, including radiation planning scans, correlate well with gated CAC scans and have a strong predictive value for adverse events.⁵⁹ In a study of 939 female individuals with breast cancer treated with RT, the presence of pretreatment CAC strongly correlated with acute coronary events over 9 year follow-up even after correction for traditional risk factors and MHD.⁵⁸ Thus, International Cardio-Oncology Society (ICOS) recommends

that CT scans for radiation survivors be assessed for the presence of CAC in order to institute appropriate preventive therapy.⁶⁰

Management of Modifiable Risk Factors

It is imperative that cancer survivors undergo regular screening for modifiable CV risk factors. Optimal lifestyle and medical preventative therapy should be employed early as appropriate. Cardiac rehabilitation reduces CV mortality in patients with CAD in the general population. While cardiac rehabilitation is less studied in cancer survivors, it is generally perceived to improve cardiorespiratory fitness and quality of life and is thus encouraged.⁶¹ The use of traditional CV medications for the specific prevention of RICT remains unproven. Early evidence of the use of statins and angiotensin-converting enzyme inhibitors to counteract the development of radiation-induced vascular disease is promising; however, its benefit in humans is still unproven.⁶⁰ In the absence of specific preventive trials, patients should be treated as per existing current guidelines for optimal treatment of CV risk factors and primary and secondary prevention of CV disease.⁶⁰

SCREENING FOR RADIATION-INDUCED CARDIOTOXICITY

The goal of screening is to improve earlier detection of disease to enable prompt medical treatment and mitigate further decline. CV screening for RICT utilizes a combination of imaging modalities such as transthoracic echocardiography (TTE), CT, and cardiac magnetic resonance imaging (CMR) alongside potential use of cardiac biomarkers, aiming to detect early signs of cardiac dysfunction and/or CAD.⁶² Screening intervals are loosely based on exposure history, cardiac doses, and the structures involved. Although higher radiation exposure has been shown to be associated with increased cardiac events, the optimal screening interval for a particular radiation treatment and dosing is unknown. Often expert consensus recommendations are relied upon rather than evidence-based approaches, and there is a paucity of data comparing the diagnostic performance of different modalities in detecting and predicting RICT. An optimal screening approach is best obtained by understanding the advantages and disadvantages of each modality as it relates to the patient's symptoms and specific risk for RICT (**Table 2**).

Multiple European and American oncology and cardiology societies have proposed testing for those deemed at higher risk, including those with a heart dose greater than 30 Gy with the heart in the treatment field, history of anthracycline exposure,

young age at exposure, and/or CV risk factors. The European Society of Cardiology (ESC) more conservatively deems those with greater than 15 Gy MHD or those with greater than 5 Gy MHD and 100 mg/m² or greater anthracycline exposure as high risk.⁶⁵ Screening for RICT frequently involves TTE starting as early as 12 months after the completion of treatment and at various intervals depending on risk (see **Table 2**). In regard to screening for IHD, both the The European Association of Cardiovascular Imaging (EACI) and American Society of Echocardiography (ASE) recommend periodic stress testing.²⁷ ICOS recommendations emphasize an early initiation of preventive therapy after the identification of CAC on imaging, with no clear benefit for additional empiric stress testing given the lack of evidence for revascularization in an asymptomatic individual.⁶⁰

The use of advanced imaging in screening for RICT is still under investigation. CMR may play an important role in evaluating pericardial and myocardial effects from RT including radiation-induced pericarditis and restrictive cardiomyopathy. However, small studies have yet to correlate RT to changes in quantitative CMR evaluations such as late gadolinium enhancement and myocardial tissue characterization.⁶⁶ Similarly, small studies evaluating the use of PET in patients with left-sided breast cancer receiving radiation showed mixed results regarding changes in coronary flow reserve and fluorodeoxyglucose uptake in the myocardium.⁶²

It is unclear at this time what, if any, role that cardiac biomarkers such as N-terminal pro-B-type natriuretic peptide (NT-proBNP) and high-sensitivity troponin (hs-troponin) play in screening for RICT.⁶⁷ In a small study, there were no differences in NT-proBNP and hs-troponin between patients with cancer before and after RT.⁶⁸ In another small prospective cohort study of patients with left breast cancer receiving RT without chemotherapy, 21% of patients had an increase in hs-troponin correlating with higher MHD. Follow-up of this same cohort study found elevation of NT-proBNP at 3 years correlating with higher MHD.⁶⁹ ICOS supports the use of NT-proBNP to screen for HF after RT given its value in screening for HF in the general population.⁶⁰ Natriuretic peptide screening likely provides the most benefit in patients with prior anthracycline exposure who are at the highest risk for developing HF. Screening can be considered on an annual basis using accepted age-based cutoffs for chronic HF.

Given the close proximity of the carotid artery with the lymphatic targets in head and neck RT, it is prone to radiation-induced vascular disease. Several studies have linked head and neck RT

Table 2
Recommendations for screening for radiation-induced cardiotoxicity with key characteristics of available modalities

Screening Modality	Strengths	Weaknesses	EACI/ASE ²⁷	ASCO ⁶³	ESMO ⁶⁴	ICOS ⁶⁰	ESC ⁶⁵
TTE	• Safe and widely available • Estimation of LVEF • Estimation of GLS • Tissue Doppler to assess valvular abnormalities and diastolic function • No radiation risk	• Operator dependent • Some patients with poor acoustic windows • Reduced tissue characterization • Limited evaluation of the pericardium	• Average risk: baseline, at 10 y then every 5 y • High risk: at 5 y then every 5 y	6–12 mo after potential cardiotoxic therapies (including RT) in high-risk patients	Starting 5 y after mediastinal radiation and then at least every 3–5 y thereafter	• High risk: within 6–12 mo of RT and then every 5 y • Average risk: within 5 y of RT and then every 5 y	• Baseline prior to RT in those at high risk • Every 2–5 y after RT depending on CV risk in childhood survivors • At 1, 3, and 5 y in adult survivors at very high risk • At 5 y and every 5 y in adults at moderate to high risk
Stress testing	• Different modalities with variable performance and limitations • Relatively cheap and widely available • Evaluation of ischemia • Can also evaluate cardiac structure and function	• Does not offer anatomic evaluation of CAD • False positives and false negatives occur	Every 5 y in high-risk patients	N/A	Consider evaluation for ischemia 5 y after mediastinal radiation and then at least every 3–5 y thereafter	• Focus on identifying subclinical CAD (eg, CAC) to start preventive therapy. • In patients without known CAD, screening every 5 y can be useful	High-risk patients: every 5–10 y starting 5 y after RT

Cardiac MRI	• Excellent quantification of cardiac function and chambers volumes • Excellent tissue characterization • Late gadolinium enhancement to detect scarring and fibrosis • Parametric mapping to detect early tissue changes • Excellent pericardial evaluation	• High cost • Not readily available • Requires additional training and expertise to perform and interpret • May not be feasible/possible in patients with claustrophobia, breast spacers, or some cardiac devices	• Can be considered when TTE results are equivocal or suboptimal	Can be considered when available to replace or supplement TTE	Can be considered when available to replace or supplement TTE	• Can be used as an alternative to TTE • Can be especially useful in patients with poor acoustic windows on TTE, or concern for constriction	Can be considered when available to replace or supplement TTE
Noncontrast CT including radiation planning CT scans	• Excellent risk predictor for CV events • No additional testing or exposure needed if CT has already been done for other indications • Identifies subclinical atherosclerosis	• Cannot evaluate the degree of luminal obstruction • Nongated CTs can have 9% false-negative rate	N/A	N/A	N/A	• Baseline evaluation for CV risk • Screening at 5 y can be useful in patients without prior documented CAC	Baseline evaluation for CV risk
[18F]FDG-PET/CT scans	• Can assess myocardial inflammation, viability, and perfusion, and microvascular dysfunction	• High cost • Not readily available • Requires additional training and expertise to perform and interpret • Limited anatomic assessment	N/A	N/A	N/A	N/A	N/A

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Table 2
(continued)

Screening Modality	Strengths	Weaknesses	EACI/ASE ²⁷	ASCO ⁶³	ESMO ⁶⁴	ICOS ⁶⁰	ESC ⁶⁵
NT-proBNP	• Easy to obtain and relatively cheap • A marker of myocardial stretch/injury • Can be useful to detect early toxicity and augment physical examination	• Mixed evidence regarding utility to screen for RICT • False normal or elevated values from other noncardiac conditions such as obesity, renal disease, and sepsis	N/A	• May be helpful in patients with clinical signs/symptoms concerning for cardiac dysfunction • No recommendations for screening after RT	• May be considered at baseline in high-risk patients receiving cardiotoxic therapies, repeat if there is a change in symptoms during follow up • No specific recommendations after RT	• May be considered at baseline in patients at risk for HF • Every 5 y can be useful to screen for HF after RT	• No specific recommendations for RT • May be recommended if receiving other cardiotoxic cancer therapy
Hs-troponin	• Easy to obtain and relatively cheap • A marker of myocardial injury • Can potentially be useful to detect early toxicity/myocardial injury	• Mixed evidence regarding utility to screen for RICT • Can be elevated from other noncardiac conditions such as renal disease and sepsis	N/A	• May be helpful in patients with clinical signs/symptoms concerning for cardiac dysfunction • No recommendations for screening after RT	• May be considered at baseline in high-risk patients receiving cardiotoxic therapies, repeat if there is a change in symptoms during follow up. • No recommendations for screening after RT	• No specific recommendations for RT	• No specific recommendations for RT • May be recommended if receiving other cardiotoxic cancer therapy

Expert society recommendations for screening modalities and intervals. Strengths and weaknesses for each modality are presented.

Abbreviations: CAC, coronary artery calcifications; CAD, coronary artery disease; CT, computed tomography; CVD, cardiovascular disease; GLS, global longitudinal strain; HF, heart failure; Hs, high sensitivity; LVEF, left ventricular ejection fraction; N/A, not available; NT-proBNP, N terminal probrain natriuretic peptide; RICT, radiation-induced cardiotoxicity; RT, radiation therapy; TTE, transthoracic echocardiogram.

with an increased risk of transient ischemic attacks and strokes.⁷⁰ While detailed discussion of the spectrum of extracardiac vascular effects of RT is out of the scope of this study, it is worth noting that screening for carotid artery disease should be considered in patients with prior neck RT. In these patients, ICOS recommends auscultation for carotid bruits during routine physical examinations and reviewing available CT scans for carotid calcification to help in risk stratification. They also recommend screening for asymptomatic atherosclerotic plaques starting as early as 1 year after RT in high-risk patients with consideration of repeated testing every 3 to 5 years.⁶⁰ Further study is required, though, to guide the optimal patient selection (such as radiation dosing), screening modalities, and screening intervals.

Together, the balance of radiation exposure and CV risk profiles present a platform for which patients should be evaluated for radiation treatment effects. The myriad proposals from various societies paint a broad picture based on available data (see [Table 2](#)), most of which is retrospective in nature. Thus, individualized risk profiling remains key in tailoring screening and preventative strategies to each patient. Close multidisciplinary collaboration among oncologists, cardio-oncologists, and radiation oncologists is crucial to balance adequate disease control while minimizing unintended RICT ([Fig. 4](#)).

MANAGEMENT OF RADIATION-INDUCED CARDIOTOXICITIES

Due to their unique pathophysiology, the management of RICT requires distinct considerations. However, the scarcity of robust treatment evidence

necessitates a multidisciplinary team approach with an emphasis on treatment personalization and shared decision-making. Decisions on risk versus benefit of percutaneous versus surgical management of CV disease are affected by the potential concerns of a “hostile chest” with prior radiation-induced scarring, adhesions, and calcifications of the aorta.

Management of Radiation-induced Coronary Artery Disease

Radiation-induced coronary artery disease (RICAD) is primarily characterized by accelerated atherosclerosis and premature CAD. Unique to RICAD, many affected coronary arteries exhibit a distribution associated with the radiation exposure site. For example, mediastinal radiation predominantly affects the LAD and right coronary arteries. Additionally, evaluating the patency of the internal mammary artery prior to CABG surgery is important in patients receiving RT for breast cancer given its inclusion in the target volume to treat the internal mammary lymph nodes.²¹ RICAD overall tends to be more severe and diffuse when compared to CAD in individuals without a prior history of radiation.

Preventive therapy should be considered early in the atherosclerotic disease process, consistent with traditional guidelines for primary and secondary prevention in the general population.^{71,72} While there are no clinical trials specifically in patients with RICAD for low-density lipoprotein (LDL) lowering therapy such as statins, there is no biologically plausible reason to suspect these therapies would not provide benefit in accordance with basic science and clinical studies conducted

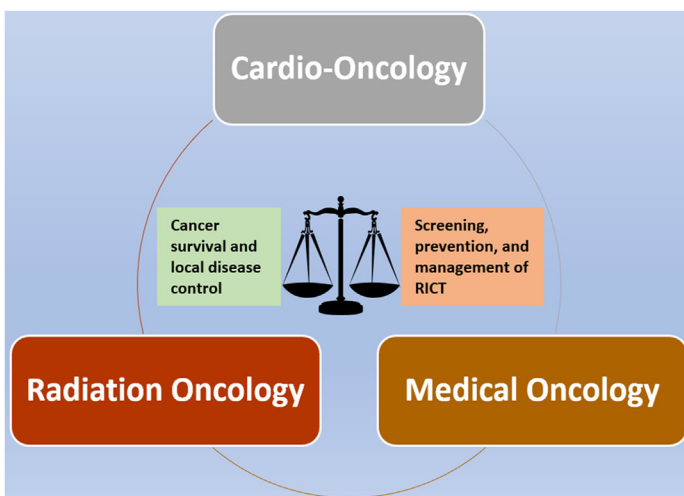


Fig. 4. Multidisciplinary collaboration to provide optimal care in cancer survivors after radiation therapy.

to date. Indeed, trials in patients with documented RICAD are unlikely given lack of current equipoise (ie, randomizing patients with RICAD to no treatment). There is interest in investigating the benefit of statins in preventing radiation-induced vascular injury with early support from basic science studies. A study by Ait-Aissa and colleagues⁷³ demonstrated that short-term treatment with pravastatin-reduced radiation-induced vascular injury in a mouse model, while long-term treatment completely reversed it. Additionally, Gaugler and colleagues⁷⁴ found that pravastatin decreased inflammation and endothelial activation in irradiated human microvascular endothelial cells. These studies suggest that LDL-lowering therapies may hold promise to specifically prevent the onset of RICAD; however, targeted clinical trials would be needed to evaluate their efficacy in humans.

In patients with obstructive CAD, the optimal revascularization strategy (ie, CABG or PCI) remains unknown given a lack of randomized trials. In a retrospective cohort of 478 patients undergoing cardiac surgery, patients with RICT had increased mortality compared to age-matched and sex-matched controls.⁷⁵ Worse outcomes in patients with RICT may be due to radiation-induced fibrosis as well as atresia of possible surgical grafts, though at least some of the increased mortality in the retrospective study was likely due to residual confounding. Nonetheless, in many cases, PCI will be preferred over CABG, while patients with concomitant structural heart disease may still benefit from, and even do very well with, cardiac surgery.⁶⁰ Notably, the risk of a hostile chest will vary greatly with radiation dosing parameters in a given individual.

Management of Radiation-induced Valvular Disease

Radiation can cause progressive valve thickening and shortening with or without calcification. Given the possibility of multiple valve involvement, a collaborative heart team approach is highly recommended. For aortic valve disease, transcatheter aortic valve replacement (TAVR) is often favored over surgical aortic valve replacement (SAVR) due to the latter's association with worse outcomes in retrospective analysis.⁶⁰ However, the decision to pursue SAVR may be influenced by the presence of other dysfunctional valves (ie, mitral valve), the need for CABG, or the expected need for reintervention in the future in younger patients. Patient undergoing TAVR after RT may be at an increased risk for complete heart block and the need for pacemaker, especially if they have pre-existing conduction disease. In the setting of mitral and

tricuspid valvular disease, transcatheter edge-to-edge repair (TEER) and transcatheter mitral valve replacement or tricuspid valve replacement (TTVR) are emerging as possible options. While TEER to treat significant functional mitral regurgitation has been extensively investigated and used in the general population,⁷⁶ it remains minimally studied among patients with cancer. A study conducted by Khan and colleagues⁷⁷ assessed TEER in cancer survivors in an administrative database and found comparable overall outcomes to the general population; however, only 2.7% of the study population had a history of RT. Truong and colleagues⁷⁸ reported their experience and hemodynamics associated with a case of radiation-induced tricuspid regurgitation and pericardial constriction undergoing TTVR. Overall, the use of percutaneous valvular interventions in patients with cancer remains an important gap of knowledge that warrants further study.

Management of Radiation-induced Pericardial Disease

The spectrum of pericardial diseases induced by radiation encompasses pericarditis, pericardial effusion, tamponade. Diagnosing CP can be challenging as patients may have concurrent restrictive physiology due to underlying cardiomyopathy from myocardial scarring and fibrosis. Invasive hemodynamics with heart catheterization may be required to accurately differentiate between the 2 given potential differences in management approaches. While management of both restrictive CM and CP will focus on symptom control and volume optimization, there are unique considerations in CP. Although not studied in radiation specifically, early stages of CP may respond to conservative management with anti-inflammatory agents such as colchicine and nonsteroidal anti-inflammatory drugs to reduce inflammation and halt progression to surgical disease in patients with elevated inflammatory markers and evidence of pericardial inflammation on cardiac MRI.⁷⁹ Pericardiectomy is reserved for patients who fail to respond to conservative measures and was historically associated with high surgical mortality that often exceeds pericardiectomy for other causes of CP.^{60,80,81} In patients who do require pericardiectomy, outcomes appear to be better when surgery is performed earlier in the course.^{60,82}

NOVEL THERAPEUTIC APPLICATIONS OF RADIATION THERAPY IN CARDIAC CONDITIONS

Emerging evidence suggests that RT may have therapeutic potential in the setting of specific

cardiac conditions. For instance, SBRT (with doses typically of 25 Gy to scar) is being pioneered to treat patients with treatment-refractory ventricular tachycardia (VT), a novel therapy also referred to as stereotactic arrhythmia radioablation (STAR).^{83–85} Preclinical models suggest that the mechanism through which cardiac SBRT reduces VT burden is not through scar formation (as is the case with catheter ablation); instead, cardiac SBRT may beneficially reprogram the myocardium to reduce arrhythmic events.⁸⁵ Moving beyond VT, Pedersen and colleagues⁸⁶ recently demonstrated that patients with VT and HF who were treated with STAR had an MHD of approximately 5 Gy outside of the planning target volume, and in a subset of patients who had CMR preradiation and postradiation, there was a rapid improvement of measurements of heart function (eg, LVEF and end-diastolic volume) prior to appreciable reductions in VT burden. Furthermore, the authors showed that 5 Gy cardiac radiation attenuated cardiac dysfunction in multiple murine models of HF, which was associated with the reduction in adverse myocardial remodeling and inflammation.⁸⁶ Taken together, these findings highlight the potential of radiation to be used therapeutically in patients with certain cardiac dysfunctions.

SUMMARY

Despite tremendous strides in the practice of radiation oncology to improve cancer survival and reduce the unintended adverse effects of RT, RICT remains an important concern after RT. Providers' awareness and understanding of the intricacies of this unique patient population are crucial to provide optimal care and support future research initiatives to advance the field. Multidisciplinary collaborations among medical, radiation, and cardio-oncologists are growing and becoming vital to provide adequate cancer control, mitigate the risk of RICT, and appropriately manage RICT when it occurs. Management of RICT begins with prevention including minimizing radiation to the heart without sacrificing tumor efficacy and optimizing CV risk factors. In patients requiring invasive procedures for RICAD or valvular disease, percutaneous approaches appear beneficial given the increased risk of surgical complications. Further study, however, is still needed.

CLINICS CARE POINTS

- In patients with radiation therapy to the chest and/or neck, clinicians should recognize

the potential early or late onset of ischemic heart disease, pericardial disease, heart failure, arrhythmias, conduction abnormalities, valvular disease, and extracardiac vascular complications, including carotid and subclavian atherosclerosis.

- Risk factors for radiation-induced cardiovascular toxicity (RICT) include higher radiation doses, older radiation techniques, younger age at the time of treatment, concurrent use of cardiotoxic antineoplastic agents, and the presence of traditional cardiovascular risk factors.
- Risk of RICT varies significantly based on radiation dose and is generally lower with improved radiation delivery techniques; though there is no safe dose of radiation, and some patients still receive high radiation doses to the heart or its substructures in the modern era.
- Radiation delivery plans should minimize radiation to the heart and its substructures as able without reducing tumor efficacy.
- The optimal screening interval for RICT after radiation therapy is unknown, but patients should receive yearly cardiovascular histories and exams with consideration for cardiac testing every few years, especially in patients at higher levels of risk.
- Prevention of atherosclerotic disease and management of RICT generally follows established guidelines for non-radiation patients, with a strong consideration for percutaneous revascularization or valve procedures over cardiac surgery when feasible.

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Cardiac Complications of Immune Checkpoint Inhibitors and Chimeric Antigen Receptor T Cell Therapy



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KEYWORDS

- CAR T-cell therapy • Immune checkpoint inhibitors • Cardiotoxicity
- Cytokine release syndrome (CRS) • Myocarditis • Pericarditis

KEY POINTS

- Immune checkpoint inhibitors (ICIs) and chimeric antigen receptor (CAR) T-cell therapy, despite their groundbreaking success in treating refractory malignancies, can cause life-threatening cardiovascular toxicities through immune-related adverse events, necessitating close monitoring and prompt management by a multidisciplinary team.
- Myocarditis is the most common and potentially fatal cardiovascular immune-related adverse event associated with ICIs. At the same time, other cardiotoxicities include pericardial diseases, Takotsubo cardiomyopathy, atherosclerotic cardiovascular disease, vasculitis, arrhythmias, and conduction disorders.
- High-dose corticosteroids are the primary treatment for ICI-related myocarditis, while additional immunosuppressive therapies (eg, mycophenolate mofetil, infliximab, anti-thymocyte globulin, abatacept) may be considered in steroid-refractory cases.
- Cytokine release syndrome (CRS) is the most common acute toxicity following CAR T-cell therapy, characterized by a systemic inflammatory response that can lead to cardiovascular manifestations such as arrhythmias, heart failure, and cardiogenic shock.
- Management of CRS depends on the severity grade and includes supportive care for grade 1, tocilizumab (IL-6 receptor antagonist) for grade 2 or higher, with the addition of corticosteroids if unresponsive, and aggressive supportive care with fluids, vasopressors, and ventilatory support for grade 3 or 4.

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INTRODUCTION

Cancer immunotherapies, particularly immune checkpoint inhibitors (ICIs) and T-cell therapies, have revolutionized the treatment landscape for various advanced malignancies in recent years. By enhancing the activity of the body's immune cells against cancer cells, ICIs have demonstrated remarkable efficacy in improving progression-free and overall survival in patients with previously minimally responsive cancers.¹ However, along with their widespread therapeutic use, there is growing recognition of immune-related adverse events (irAEs) affecting various organ systems, including the cardiovascular system.²

ICIs block specific proteins like programmed cell death-1 (PD-1), programmed cell death ligand 1 (PD-L1), and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), among others, present on the surface of immune and tumor cells, acting as the negative regulators of immune activation, thereby enabling the immune system to recognize and attack cancer cells effectively, leading to tumor regression.²⁻⁴ Cardiovascular adverse events (CVAEs) associated with ICIs, although infrequent, are increasingly being reported in the literature and are emerging as a serious concern.⁵ These toxicities can range from myocarditis and cardiomyopathy to potentially life-threatening arrhythmias, pericardial diseases, and vasculitis.⁵

On the other hand, chimeric antigen receptor (CAR) T-cell therapy has emerged as a novel immunotherapy in which autologous cells or allogenic T cells are genetically engineered to express a synthetic receptor that targets specific antigens on the surface of cancer cells. CAR T-cell therapy is a type of adoptive cell therapy, along with other modalities such as bispecific T-cell engager (BiTE) and tumor-infiltrating lymphocyte (TIL) therapies. BiTE consists of 2 linked variable fragments arranged on a single chain, thus forming 2 antigen-binding sites—1 for tumor-specific antigen and 1 for a native T-cell.⁶ TIL therapy uses T-cells from within the tumor, which can potentially recognize and target the tumor cells.³ By combining the antigen specificity of antibodies with the cytotoxic effector functions of T-cells, CAR T-cell therapy has achieved remarkable success in the treatment of certain hematological malignancies, particularly B-cell acute lymphoblastic leukemia and diffuse large B-cell lymphoma (DLBCL).⁷ T-cell therapies are, however, frequently associated with a pathophysiological syndrome resembling distributive shock due to the widespread activation of the immune system, termed cytokine release syndrome (CRS).^{2,6}

This review summarizes the mechanisms and most updated preclinical and clinical data on

cardiovascular toxicities associated with ICIs. We also highlight the recent practice guidelines from different cancer network associations on the diagnosis and management of ICI-related CVAEs, with a focus on myocarditis.

MECHANISMS OF CARDIOTOXICITY

Immune Checkpoint Inhibitors

The precise mechanisms of ICI-induced cardiotoxicity are not fully elucidated. Still, evidence suggests a central role for the robust proliferation and activation of T-cells expressing common, high-frequency receptors against antigens shared by the tumor and affected cardiac tissue.^{6,8} Under physiologic conditions, immune checkpoints like PD-1/PD-L1 and CTLA-4 maintain cardiac immune homeostasis and prevent autoimmunity. The PD-1/PD-L1 axis is crucial in regulating T-cell activity in the heart, as PD-L1 is constitutively expressed on rodent and human cardiomyocytes and can be upregulated in response to inflammatory stimuli.^{3,7,9} ICI therapy disrupts these cardioprotective signaling pathways, making cardiac cells vulnerable to immune-mediated injury.¹⁰

Animal models have demonstrated that genetic deletion of CTLA-4, PD-1, or PD-L1 can cause autoimmune myocarditis and dilated cardiomyopathy.¹⁰⁻¹² Mechanistically, ICI therapy may induce the clonal expansion of T-cells targeting antigens present in the myocardium, leading to cardiac inflammation.⁸ Axelrod and colleagues used homozygous PD-1 and heterozygous CTLA-4 knockout mice as a proxy to create the immunopathologic phenotype of ICI-associated myocarditis. Recipients of immune cells from these mice developed fulminant myocarditis, predominantly due to CD8 + T-cells recognizing α -myosin—a peptide encoded by the MYH6 gene found in cardiac tissues and some tumor cells. The MYH6 gene is not necessarily expressed in all tumor cells, as reported in an analysis of the cancer genome atlas melanoma cohort showing 250 out of 363 tumors with detectable MYH6 expression.¹³ This antigenic cross-reactivity between tumor and cardiac tissue is supported by the discovery of identical T-cell clones from ICI-treated patients in myocardial and tumor samples.⁸

ICI-associated pericardial disease likely stems from a similar cytotoxic T-cell activation mechanism against pericardial antigens.⁴ The pathogenesis of ICI-related Takotsubo cardiomyopathy is less clear but may involve catecholamine-induced myocardial stunning secondary to extreme physical or emotional stress in the setting of ICI treatment.^{14,15} Several mechanisms for ICI-associated myocardial

infarction have been proposed, including atherosclerotic plaque destabilization by activated T-cells, coronary vasculitis, and ICI-induced systemic inflammation leading to coronary vasospasm.^{15,16} Conduction disease and ventricular arrhythmias likely result from direct inflammatory infiltration of the conduction system and myocardium, respectively.¹⁵ Fig. 1 briefly shows the mechanism of cardiotoxicity due to ICIs.

T-cell Therapies

The mechanisms underlying immune-mediated cardiotoxicity induced by T-cell therapies, such as CAR T-cells, can be divided into 3 broad categories.

- i. On-target, on-tumor effects that lead to CRS: The activation of large numbers of T-cells can trigger a massive release of inflammatory cytokines, leading to a systemic inflammatory response and potentially causing cardiac dysfunction, arrhythmias, and circulatory collapse.¹⁷
- ii. On-target, off-tumor effects, resulting in direct toxicity: CAR T-cells may directly target

antigens expressed on cardiomyocytes, leading to cardiac cell death and dysfunction.¹⁷ This was observed in a preclinical study by Cameron and colleagues, in which they identified a peptide sequence from the muscle protein titin as a cross-reactive target for engineered MAGE A3-directed T-cells.¹⁸

- iii. Off-target, off-tumor effects involve unexpected T-cell-mediated autoimmunity instead of the intended immune response against the tumor antigen. In this scenario, the engineered T-cells recognize and attack cardiac antigens unrelated to the intended tumor target, leading to autoimmune myocarditis.¹⁷

While direct (on-target, off-tumor) and autoimmune-mediated effects (off-target, off-tumor) do contribute to a fraction of cases, the primary driver of cardiotoxicity mediated by T-cell therapies appears to be associated with the on-target, on-tumor effects that lead to CRS.¹⁹

Hence, while both-ICIs and T-cell therapies—cause cardiotoxicity, the primary mechanism of cardiotoxicity with ICIs is related to T-cell-mediated injury to cardiac cells expressing shared tumor antigens or unintended targets. In contrast, T-cell

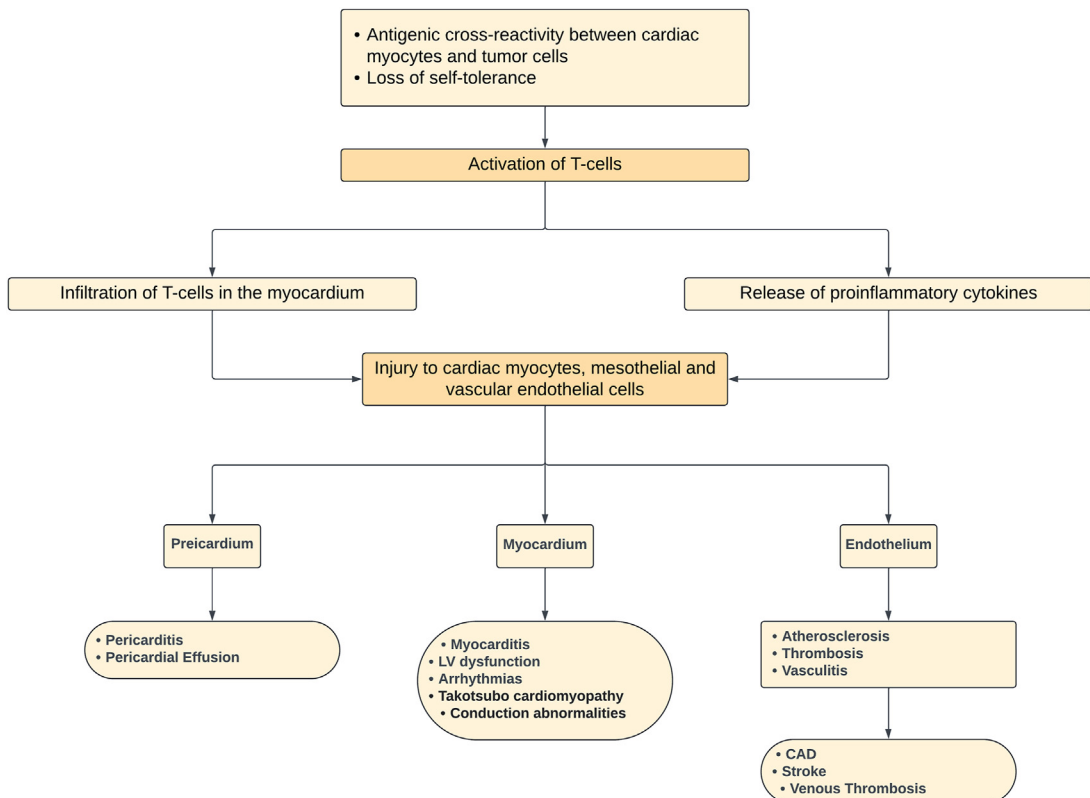


Fig. 1. A simplified flowchart showing the predominant mechanism and manifestations of cardiotoxicity due to immune checkpoint inhibitors. CAD, coronary artery disease; LV, Left Ventricle.

therapies predominantly lead to cardiotoxicity due to CRS. A deeper understanding of the immunologic basis of immunotherapy-related cardiotoxicity will enable the development of predictive biomarkers and novel cardioprotective strategies.

EPIDEMIOLOGY, MANIFESTATIONS, AND CLINICAL FEATURES

Incidence of Immune Checkpoint Inhibitors-Mediated Cardiotoxicity

The reported incidence of ICI-related CVAEs varies across studies, likely due to differences in patient populations, treatment regimens, and diagnostic criteria. In a recent observational study of 2606 patients treated with ICIs, the cumulative incidence of myocarditis was 1.0%, or 0.14 cases per 10,000 person-years.²⁰ This incidence is consistent with previous estimates ranging from 0.04% to 1.14%.²¹ Notably, the incidence of myocarditis appears to be higher with combination ICI therapy compared to monotherapy. In a multicenter registry, the incidence of myocarditis was 2.4% among patients receiving combination therapy versus 1.14% in the overall cohort.²²

The incidence of other CVAEs, such as pericardial disease, Takotsubo cardiomyopathy, and acute coronary syndromes (ACSs), is less well-defined but appears to be lower than that of myocarditis. In a meta-analysis of 22 ICI trials in patients with lung cancer, the incidence of heart failure and myocardial infarction was 2% and 1%, respectively.²³ A pharmacovigilance study using Vigibase, the World Health Organization's global database of individual case safety reports (ICSRs), found that pericardial diseases accounted for 13.6% of all reported ICI-related CVAEs.²⁴ A meta-analysis of 51 randomized clinical trials (n = 12,518) showed a significantly higher rate of cardiovascular irAEs with ICI therapy (monotherapy: 3.1%, combination: 5.8%) compared to chemotherapy (2.5%). Moreover, cardiac irAEs were associated with a high case fatality rate (24.6%).²⁵

Despite its relatively low incidence, ICI-related myocarditis is associated with a high fatality rate, with estimates ranging from 25% to 50%.²¹ This underscores the importance of early recognition and prompt management of this potentially life-threatening complication.

Incidence of Chimeric Antigen Receptor T-cell Therapy-Mediated Cardiotoxicity

The incidence of CVAEs associated with CAR T-cell therapy is less well-characterized than ICIs. CRS is the most common acute toxicity following CAR T-cell therapy, with a reported incidence between 37% and 93% across different

studies.²⁶ Cardiovascular manifestations of CRS may include arrhythmias, heart failure, and cardiogenic shock.²⁷ CAR T-cell therapy mediated cardiotoxicity was more frequently reported with axicabtagene-ciloleucel (57.3%) compared with tisagenlecleucel-T (42.7%).²⁸

Other CVAEs, such as left ventricular dysfunction, elevated troponin, and arrhythmias, have also been reported following CAR T-cell therapy. In a study leveraging the Food and Drug Administration Adverse Events Reporting System (FAERS), approximately 20% of all adverse events related to CAR T-cell therapy involved the cardiovascular system, with arrhythmia (77.6%), heart failure (14.3%), and myocardial infarction (0.5%) being the most common.²⁹ The mortality rate associated with these events was reported to be 30%.²⁹ Interestingly, retrospective studies have shown that around 10% to 20% of adverse cardiovascular events (including cardiomyopathy, heart failure, myocardial infarction, arrhythmias, atrial fibrillation, cardiac arrest, or cardiovascular death) following T-cell therapies occur following the development of high-grade CRS (particularly ≥ 3 grade).¹⁹

Further research is needed to define better the incidence and spectrum of CVAEs associated with CAR T-cell therapy and to identify risk factors for their development. As the use of CAR T-cell therapy expands, it will be crucial for clinicians to maintain a high index of suspicion for these potentially serious complications.

Spectrum of Cardiovascular Toxicities with Immune Checkpoint Inhibitors

ICIs can lead to a broad spectrum of cardiovascular toxicities, ranging from asymptomatic biomarker elevations to life-threatening conditions such as fulminant myocarditis, pericardial disease, arrhythmias, Takotsubo cardiomyopathy, ACSs, and CRS.¹⁵

Myocarditis

Myocarditis is the most well-characterized and potentially fatal ICI-related CVAE, with a reported prevalence of 1.14% in patients receiving combination ICI therapy.²² The median time to onset is 34 to 65 days after treatment initiation, with most cases occurring within the first 3 months.²² Clinical manifestations range from asymptomatic cardiac biomarker elevations to fatigue, chest pain, dyspnea, arrhythmias, heart failure, cardiogenic shock, and sudden cardiac death.³⁰ Notably, a normal left ventricular ejection fraction does not exclude the diagnosis, as preserved cardiac function has been reported in up to 50% of cases.^{22,31}

Takotsubo cardiomyopathy

Takotsubo cardiomyopathy syndrome (TTS), characterized by transient left ventricular apical ballooning and systolic dysfunction, can present with chest pain, dyspnea, and electrocardiographic (ECG) changes mimicking ACS.³² A history of malignancy appears to be an independent risk factor for TTS, possibly due to intense physical and emotional stress experienced by cancer patients. However, in patients on ICI therapy with an acute MI-like presentation, TTS should be considered only after ruling out ACS and myocarditis.

Pericardial diseases

Pericardial diseases, including pericarditis and pericardial effusion, are the second most common ICI-related CVAEs, with a reported incidence of 13.6% in one study.²⁴ Clinical symptoms may include chest pain, shortness of breath, and signs of hemodynamic compromise in the setting of large pericardial effusions or cardiac tamponade.³³ In a large retrospective cohort study, there was a more than 4 fold increase in the risk of pericarditis or a pericardial effusion among patients on an ICI compared with those not treated with ICI.¹² Pericardial disease occurring with ICI therapy has a high mortality, with a case fatality rate of 21%.²⁴

Atherosclerotic cardiovascular disease

Atherosclerotic cardiovascular disease (CVD) and vasculitis have been associated with ICI therapy. In a retrospective study, patients treated with ICIs had a 3-fold higher risk of atherosclerotic cardiovascular events, including myocardial infarction, coronary revascularization, and ischemic stroke.¹⁶ Vasculitis, particularly large vessel vasculitis and vasculitis of the central and peripheral nervous systems, has been reported in case series of patients receiving ICIs.³⁴ The rate of progression of total plaque volume was 2.1% per year before the initiation of ICI and 6.7% per year after the initiation of ICI, suggesting that treatment with ICIs may accelerate atherosclerotic plaque progression.¹⁶ In another case-control study (cases: individuals with lung cancer receiving ICI; controls: individuals with lung cancer receiving alternate chemotherapy) investigating the aortic plaque progression using sequential contrast-enhanced chest computed tomography (CT) scans, the relative change in total plaque volume per year was 10.1% in individuals receiving ICI and 5.95% in individuals receiving other antineoplastic therapy. While the annual progression rate for non-calcified plaque volume was 7 times higher in the ICI group

compared with the controls (11.2% vs 1.6% per year, $P = .001$), the controls showed a greater progression in calcified plaque volume compared with the ICI group (25% vs 2% per year, $P = .017$).³⁵ These findings indicate that ICIs may promote the progression of atherosclerotic plaque and make the plaques unstable and prone to rupture.

Vascular and endothelial injury

ICIs, particularly those targeting PD-1, have been shown to mediate blood vessel inflammation.²⁷ In a case series consisting of 20 cases of vasculitis, the most commonly reported types of vasculitis were large vessel vasculitis (giant cell arteritis, isolated aortitis) and vasculitis of the nervous system (primary angiitis of the central nervous system and isolated vasculitis of the peripheral nervous system) with a median duration of 3 months following the initiation of immunotherapy.³⁴ A pharmacovigilance study reported a median onset of 55 days for the development of vasculitis, with a fatality rate of 6%.²⁴ In a retrospective study comprising 2854 patients receiving ICI therapy at Massachusetts General Hospital, the risk of venous thromboembolism events, defined as a composite of deep vein thrombosis or pulmonary embolism, was 7.4% at 6 months after starting an ICI, increasing to 13.8% at 1 year of its initiation.³⁶

Cardiovascular Toxicities Associated with T-cell Therapies

The toxicities associated with CAR T-cell therapy can broadly be divided into systemic and organ-specific toxicities.

CRS is a clinical syndrome resulting from generalized immune activation following the expansion of reinfused CAR T-cells and marked elevations of serum inflammatory markers and cytokines. Its presentation ranges from mild flu-like symptoms, including fever, myalgias, and fatigue, to life-threatening complications like hypotension, shock, and multiorgan failure.³⁷ CRS occurs within 1 to 14 days after infusion, depending on the type of product and population being treated. The duration of CRS is variable and dependent on intervention, with complete resolution typically by 2 to 3 weeks after CAR T infusion.³⁸ Given the range of symptoms associated with CRS, a standardized grading for CRS based on clinical signs and symptoms is necessary to assess its severity objectively. Although different grading systems are used for estimating the severity of CRS, one of the most commonly used symptom-based grading systems was provided by the National

Cancer Institute’s Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (Table 1).

While many classification systems for CRS have been developed, the American Society for Transplantation and Cellular Therapy has developed a consensus grading system for CRS severity. Grade 1 CRS is characterized by fever greater than or equal to 38°C with or without constitutional symptoms such as myalgia, arthralgia, and malaise. Grade 2 CRS involves the presence of fever with hypotension not requiring vasopressors and/or hypoxia requiring low-flow nasal cannula or blow-by. Grade 3 CRS consists of fever with hypotension requiring a vasopressor (with or without vasopressin) and/or hypoxia requiring a high-flow nasal cannula, facemask, non-rebreather mask, or Venturi mask. Grade 4 CRS is defined by fever with hypotension requiring multiple vasopressors (excluding vasopressin) and/or hypoxia requiring positive pressure ventilation (CPAP, BiPAP, intubation, or mechanical ventilation).¹⁹

Apart from the acute mortality risk posed, CRS is also associated with adverse cardiovascular events. In a retrospective study of 145 patients receiving CAR T-cell therapy for a variety of hematologic malignancies, with a median follow-up of 456 days, Lefebvre and colleagues studied the incidence of major adverse cardiovascular events (MACE), which included symptomatic heart failure, de novo cardiac arrhythmia, ACS, ischemic stroke, and cardiovascular death. Of the 41 MACE that occurred, there were 22 heart failure events, 12 episodes of atrial fibrillation, 2 events of other arrhythmias (supraventricular tachycardia, non-sustained ventricular tachycardia), 2 episodes of ACS, and 2 cardiac deaths.³⁹ According to an analysis of

CAR T-cell therapy-related ICSRs submitted to VigiBase, the World Health Organization’s pharmacovigilance database, 13% of ICSRs were related to cardiotoxicity, including cardiac arrhythmias, pericardial effusion, stress cardiomyopathy, left ventricular dysfunction, and cardiac arrest. Cardiotoxicity-related ICSRs were higher with axicabtagene-ciloleucel (57.3%) compared with tisagenlecleucel-T (42.7%).²⁸

Fig. 2 summarizes the mechanism and manifestations of CAR T-cell therapy-related cardiotoxicity.

DIAGNOSTIC STUDIES
Immune Checkpoint Inhibitors

Diagnosing ICI-related myocarditis can be challenging, partly due to the lack of definitive guidelines and significant overlap of non-specific cancer-related symptoms, which may blur the clinical presentation. Myocarditis should be considered only after ruling out ACS in a patient receiving ICI therapy, as it is the most common acute cardiovascular irAE and has a very high case fatality rate. Investigations for suspected patients should include ECG, serum cardiac biomarkers, transthoracic echocardiography, cardiac magnetic resonance (CMR) imaging, coronary imaging, and possibly endomyocardial biopsy (EMB). Table 2 summarizes findings in the above-mentioned diagnostic studies that suggest a diagnosis of ICI-related myocarditis.

Electrocardiogram

Electrocardiographic abnormalities are common in ICI-related myocarditis, with changes reported in up to 89% of patients.²² Findings may include elevated heart rate, prolonged QRS interval, prolonged QT corrected for heart rate, decreased Sokolow-Lyon index (sum of S wave in V1 and R wave in V5 or V6), increased incidence of left bundle branch block and other repolarization abnormalities, including, but not limited to a composite of diffuse or regional ST-segment depression and T-wave inversion. Notably, a normal ECG does not rule out myocarditis due to the lack of sensitivity and specificity. Moreover, Power J and colleagues cited a prognostic implication, reporting that pathologic Q-waves and a decreased Sokolow-Lyon index were independently associated with all-cause mortality.^{40,41}

Cardiac and non-cardiac biomarkers

Troponin and natriuretic peptides (NPs) are sensitive markers of myocardial injury and ventricular wall stress, respectively. Troponin I elevation has been reported in up to 94% of patients with ICI-related myocarditis, with higher levels associated with an increased risk of MACE.²² However,

Table 1 CTCAE version 5.0 grading criteria for CRS	
Grading	Symptoms
Grade 1	Fever, with or without constitutional symptoms
Grade 2	Hypotension responding to fluids. Hypoxia responding to <40% Fio ₂
Grade 3	Hypotension managed with one pressor. Hypoxia requiring ≥40% Fio ₂
Grade 4	Life-threatening consequences; urgent intervention needed

Abbreviations: CRS, cytokine release syndrome; CTCAE, common terminology criteria for adverse events.

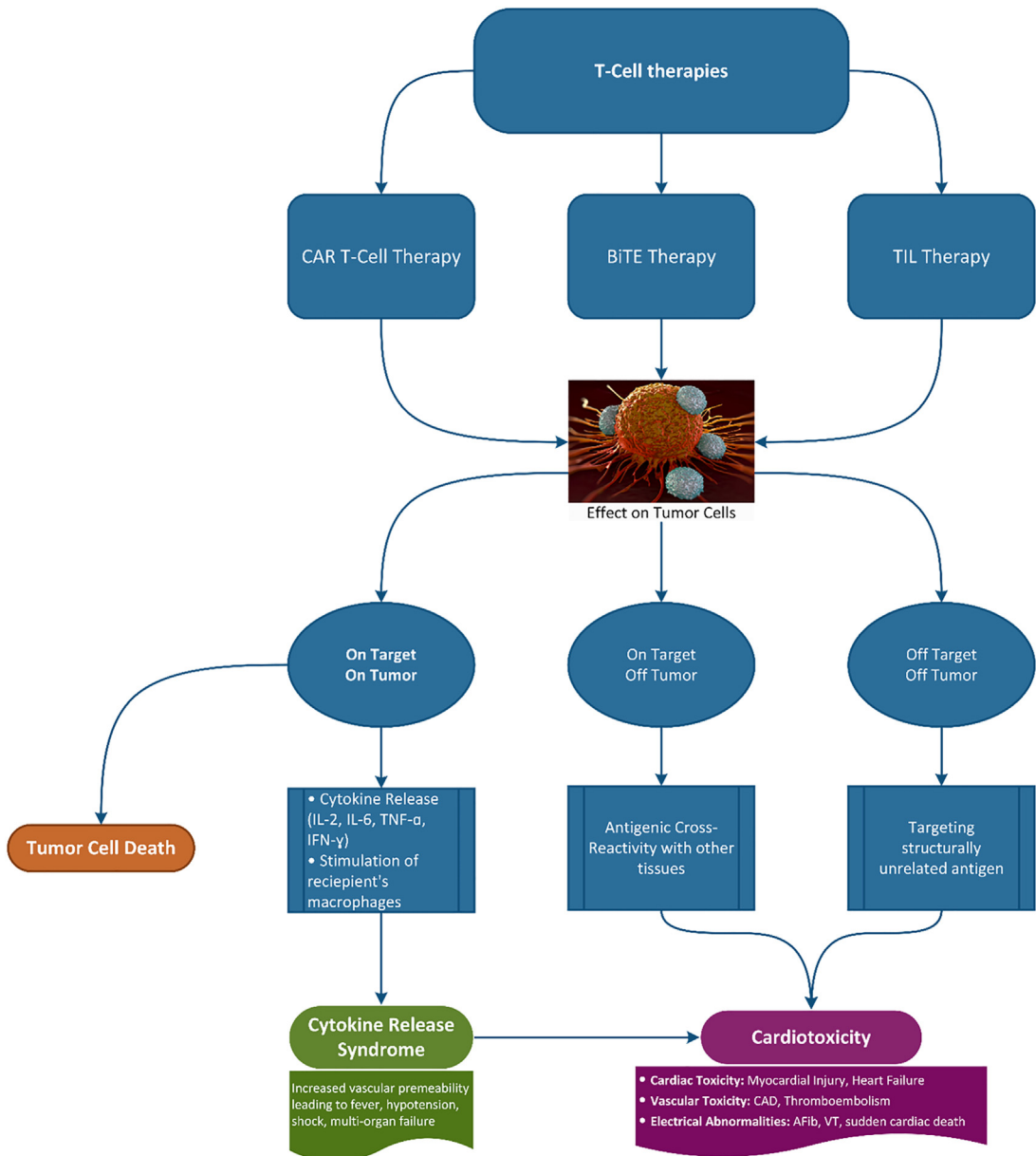


Fig. 2. Mechanism and manifestations of CAR T cytotoxicity. AFib, Atrial Fibrillation; CAD, coronary artery disease; VT, Ventricular Tachyarrhythmia.

troponin elevation alone is not specific to myocarditis and should be interpreted in the context of the clinical presentation and other diagnostic findings. A recent study found that NPs, such as brain natriuretic peptide (BNP) or NT-proBNP, are elevated in approximately 66% of patients with ICI-related myocarditis but do not appear to predict MACE.²² In a recent prospective cohort study that included 60 patients admitted for ICI-related myocarditis, Lehmann and colleagues found that a cardiac troponin T (cTnT) level greater than 32

times the upper reference limit within 3 days of an ICI myocarditis diagnosis was associated with a 11-fold increased risk of MACE.⁴² Moreover, there was a faster decline in median cardiac troponin I and creatine kinase (CK) levels among these patients within the first 4 weeks of ICI-myocarditis diagnosis compared to cTnT, making cTnT a more reliable test in a suspected case of ICI myocarditis.⁴² In a recent study, noncardiac biomarkers such as aspartate aminotransferase, alanine transaminase, creatine kinase (CK), and

Table 2 Diagnostic findings in ICI-associated myocarditis		
Diagnostic Study	Finding(s) Suggestive of ICI-Related Myocarditis	Additional Comments (including Prognostic Information, if Any)
ECG	• Elevated heart rate • Prolonged QRS interval • Prolonged QT corrected for heart rate • Decreased Sokolow-Lyon Index^a • Increased incidence of left bundle-branch block • Repolarization abnormalities^b	• A prolonged QRS duration is associated with poorer prognosis and adverse cardiac events
Serum Cardiac Biomarkers	• Elevated troponin noted in 94% of patients with ICI-associated myocarditis	• Sensitive, but not specific; higher admission, peak, and discharge/final troponin T value associated with cardiac adverse events • ICI-associated myositis, a reasonably common occurrence, may also lead to a rise in troponin T. In such cases, high-sensitivity troponin I should be considered
Echocardiography	• Reduced Global Longitudinal Strain, regardless of LVEF • Reduced LVEF is a less consistent finding. Of note, Awadulla and colleagues noted that LVEF was usually preserved in >60% of patients and rarely severely reduced • Wall Motion Abnormalities may be seen	• Lower GLS is strongly associated with major adverse cardiac events
Cardiac MRI	• LGE with involvement of septum and mid-wall • Higher z score for global native T1, ECV, and T2	• LGE in ICI-associated myocarditis occurs less frequently as compared to viral myocarditis (82% vs 100%) • Septal LGE was associated with a higher risk of MACE
PET-CT	• Limited to no role	• Myocardial FDG-PET signal between biopsy-confirmed myocarditis patients and those without myocarditis on biopsy showed no difference
Endomyocardial biopsy	• Gold standard test • T-Lymphocyte rich infiltrate with myocardial necrosis • Histopathologic appearance similar to cardiac transplant rejection	• Less sensitive • Risk of complication, including perforation • Performed only when diagnosis uncertain after other non-invasive techniques

ECV, extracellular volume fraction; LGE, late gadolinium enhancement.
^a Sum of S wave in V1 and R wave in V5 or V6.
^b a composite of diffuse or regional ST-segment depression and T-wave inversion.

lactate dehydrogenase were found to be elevated in most patients with ICI-related myocarditis, often indicating the need for workup of concurrent non-cardiac IRAEs.²²

Echocardiography

Echocardiography is a widely available, noninvasive imaging modality that plays a key role in

evaluating patients with suspected ICI-related cardiotoxicity. Findings may include left ventricular systolic dysfunction, regional wall motion abnormalities, diastolic dysfunction, or pericardial effusion.²² However, it is essential to note that a normal left ventricular ejection fraction does not exclude the diagnosis of myocarditis, as up to 51% of patients may have preserved systolic

function at presentation.²² Novel echocardiographic techniques, such as global longitudinal strain (GLS), may provide additional diagnostic and prognostic information.⁴³

Cardiac MRI

CMR imaging is considered the noninvasive gold standard for diagnosing myocarditis.⁴⁴ CMR findings in ICI-related myocarditis may include myocardial edema (T2-weighted imaging), late gadolinium enhancement (LGE), and altered myocardial mapping parameters (T1, T2, and extracellular volume fraction).⁴⁵ LGE is reported in approximately 48% of patients with ICI-related myocarditis and may be associated with an increased risk of MACE.⁴⁶ However, the absence of LGE does not exclude the diagnosis, mainly if CMR is performed early in the disease course. In patients with a high clinical suspicion of myocarditis but inconclusive CMR findings, repeat imaging or EMB may be considered. LGE is commonly seen in the mid-wall and septal regions. Moreover, ICI-associated myocarditis is also associated with a higher z-score for global native T1, ECV, and T2 on cardiac MRI.⁴⁶

Endomyocardial biopsy

EMB remains the gold standard for the definitive diagnosis of myocarditis.⁸ Histopathological findings in ICI-related myocarditis include lymphocytic infiltration (predominantly CD4+ and CD8+ T-cells) and variable degrees of myocyte necrosis.⁸ Immunohistochemical staining may demonstrate PD-L1 expression on injured cardiomyocytes and infiltrating T-cells.⁸ However, due to its invasive nature and potential complications, EMB is typically reserved for cases with diagnostic uncertainty or when the results may impact management decisions.

Other investigations

Additional imaging modalities such as PET, CT, or magnetic resonance angiography may be considered based on the clinical presentation and suspected vessel involvement in patients with suspected ICI-related vasculitis.³⁴ Coronary angiography may be indicated in patients presenting with ACS or to exclude obstructive coronary artery disease as a cause of the clinical presentation.

Chimeric Antigen Receptor T-Cell Therapy

CRS and CAR T-cell therapy-induced cardiotoxicity diagnosis is primarily based on clinical features. A pretherapy evaluation of patients is essential for all patients, regardless of history or presence of CVD, before starting treatment. A cardiology or cardio-oncology consult should be obtained. A

detailed assessment and evaluation with a medical history, clinical examination, ECG, echocardiography including the assessment of GLS, and cardiac biomarkers [cardiac troponin and (N-terminal pro-) brain natriuretic peptide (NT-pro) BNP] should be obtained to establish baseline cardiovascular dynamics.^{19,45} After each successful CAR T-cell infusion, cardiac biomarkers, electrocardiogram, and echocardiography should be repeated to monitor for the development of cardiotoxicity. Close attention should be paid to possible clinical deterioration with the development of new-onset profound hypotension, heart failure, or abnormal electrical activity, as the presence of one or more of these features potentially indicates cardiotoxicity and requires prompt inpatient admission.

MANAGEMENT

Immune Checkpoint Inhibitor-related Cardiotoxicity

The management of ICI-related cardiotoxicity involves a multidisciplinary approach, with close collaboration between oncologists, cardiologists, and other specialists. The primary goals of management are to minimize myocardial damage, prevent further deterioration of cardiac function, and reduce the risk of life-threatening complications while optimizing cancer treatment outcomes.

Identifying and evaluating the type and severity of cardiotoxicity

The first step in managing ICI-related cardiotoxicity is to promptly identify and assess the severity of the cardiac adverse event. The American Society of Clinical Oncology (ASCO) guidelines classify the severity of ICI-related myocarditis into 4 grades based on clinical presentation, biomarker elevations, and imaging findings.^{47,48} This grading system can help guide management decisions, including the need for hospitalization, immunosuppressive therapy, and temporary or permanent discontinuation of ICI treatment.

Withholding and restarting immune checkpoint inhibitor therapy

The decision to withhold or permanently discontinue ICI therapy depends on the severity of the cardiotoxicity and the risk-benefit assessment of continuing cancer treatment. For grade 1 toxicity (asymptomatic biomarker elevations), ICI therapy may be temporarily held and resumed if abnormalities resolve or are deemed unrelated to the ICI.^{45,47} For grade 2 or higher toxicity, ICI therapy should be discontinued, and the patient should be closely monitored with serial assessments of cardiac biomarkers and imaging studies. In cases

of severe or life-threatening cardiotoxicity (grade 3–4), permanent discontinuation of ICI therapy is generally recommended.^{45,47} The decision to restart ICI therapy after an episode of cardiotoxicity should be made on a case-by-case basis, considering the severity of the initial event, the response to treatment, and the overall risk-benefit profile of continuing ICI therapy.⁴⁵ In general, rechallenge with ICIs is not recommended in patients who experienced severe or life-threatening cardiotoxicity (grade 3–4). For patients with less severe toxicity (grade 1–2) who have achieved clinical stability and resolution of cardiotoxicity, cautious rechallenge with ICIs may be considered, ideally using a different agent than the one associated with the initial event.⁴⁹ Close monitoring with serial biomarkers and imaging studies is essential to detect early signs of recurrent cardiotoxicity. **Fig. 3** shows an overview of management of cardiotoxicity due to ICIs.

Initiating steroid and immunosuppressive therapy

Immunosuppression with high-dose corticosteroids is the mainstay of treatment for ICI-related myocarditis.^{33,45} Initial therapy typically consists of intravenous methylprednisolone (500–1000 mg daily) for 3 to 5 days, followed by a gradual taper to oral prednisone (1–2 mg/kg/day) over 4 to 6 weeks.^{22,45} Early initiation of high-dose corticosteroids has been associated with improved outcomes and reduced risk of MACE.⁵⁰ In cases of steroid-refractory myocarditis or severe/fulminant presentation, additional immunosuppressive agents such as mycophenolate mofetil, infliximab, or anti-thymocyte globulin may be considered.⁴⁵ More recently, abatacept (a CTLA-4 agonist) has shown promise in the treatment of steroid-refractory ICI-related myocarditis.⁵¹

Starting conventional cardiac treatment

In addition to immunosuppressive therapy, patients with ICI-related cardiotoxicity should receive standard guideline-directed medical treatment for the management of heart failure, arrhythmias, or other cardiovascular complications.⁴⁵ This may include using beta-blockers, ACE inhibitors, diuretics, antiarrhythmic agents, or mechanical circulatory support as clinically indicated. Close monitoring and follow-up with a cardiologist are essential to optimize cardiac treatment and assess response to therapy.

Chimeric Antigen Receptor T-cell Therapy-Mediated Cytokine Release Syndrome

Before initiating CAR T-cell therapy, medical treatment for pre-existing CVDs, including heart failure

therapy, antihypertensive treatment, and anti-thrombotic treatment, must be optimized, and the conditions should be adequately controlled. A standardized cardio-oncology follow-up on day 7 following CAR T-cell transfusion, including ECG, echocardiography, and biomarkers, may be beneficial to look for the early occurrence of symptoms.

The management of CRS depends on the grade of severity. Grade 1 CRS can often be managed with supportive care alone. For grade 2 CRS or higher, tocilizumab, an IL-6 receptor antagonist, is considered first-line therapy. If the response to tocilizumab is inadequate, the addition of corticosteroids is recommended as a second-line treatment. In cases of grade 3 or 4 CRS, patients require hospitalization for close monitoring and aggressive supportive care, which may include fluid resuscitation, vasopressors, supplemental oxygen, and ventilatory support as needed based on the severity of the hemodynamic instability and respiratory distress.¹⁹

Abnormal surveillance results or clinical features of hypotension should prompt an immediate cardio-oncology consult with hospitalization if required. Patients with other manifestations of cardiotoxicity, such as arterial hypotension unrelated to CRS, arrhythmias, or heart failure, must be managed supportively using fluids and vasopressors, anti-arrhythmic medications, or electric cardioversion and inotropes/mechanical circulatory support with modalities like extracorporeal membrane oxygenation, respectively.¹⁹

Early use of tocilizumab has been associated with a lower risk of adverse cardiac outcomes.⁵² Persistent hemodynamic instability warrants the use of a second dose of tocilizumab. Corticosteroids can be added if and when needed. However, whenever clinically feasible, corticosteroids should be used at the lowest dose and for the shortest duration while managing CAR T-cell therapy-associated toxicities, as they are associated with decreased survival in patients with relapsed or refractory large B-cell Lymphoma.⁵³ Siltuximab can be an alternative to tocilizumab; however, its efficacy and safety, specifically for CAR T-cell therapy-related CRS, have yet to be studied extensively. However, Patel S and colleagues reported it as effective as tocilizumab.⁵⁴

Esmolol is shown to alleviate the harmful cardiac consequences arising from a hyperadrenergic state, leading to sustained tachycardia in septic shock.⁵⁵ Since the CRS development mechanism also resembles systemic inflammatory response syndrome (SIRS) and septic shock, additional studies are required to evaluate the role of esmolol for adrenergic excess in CRS. **Fig. 4** describes the overview of managing CRS.

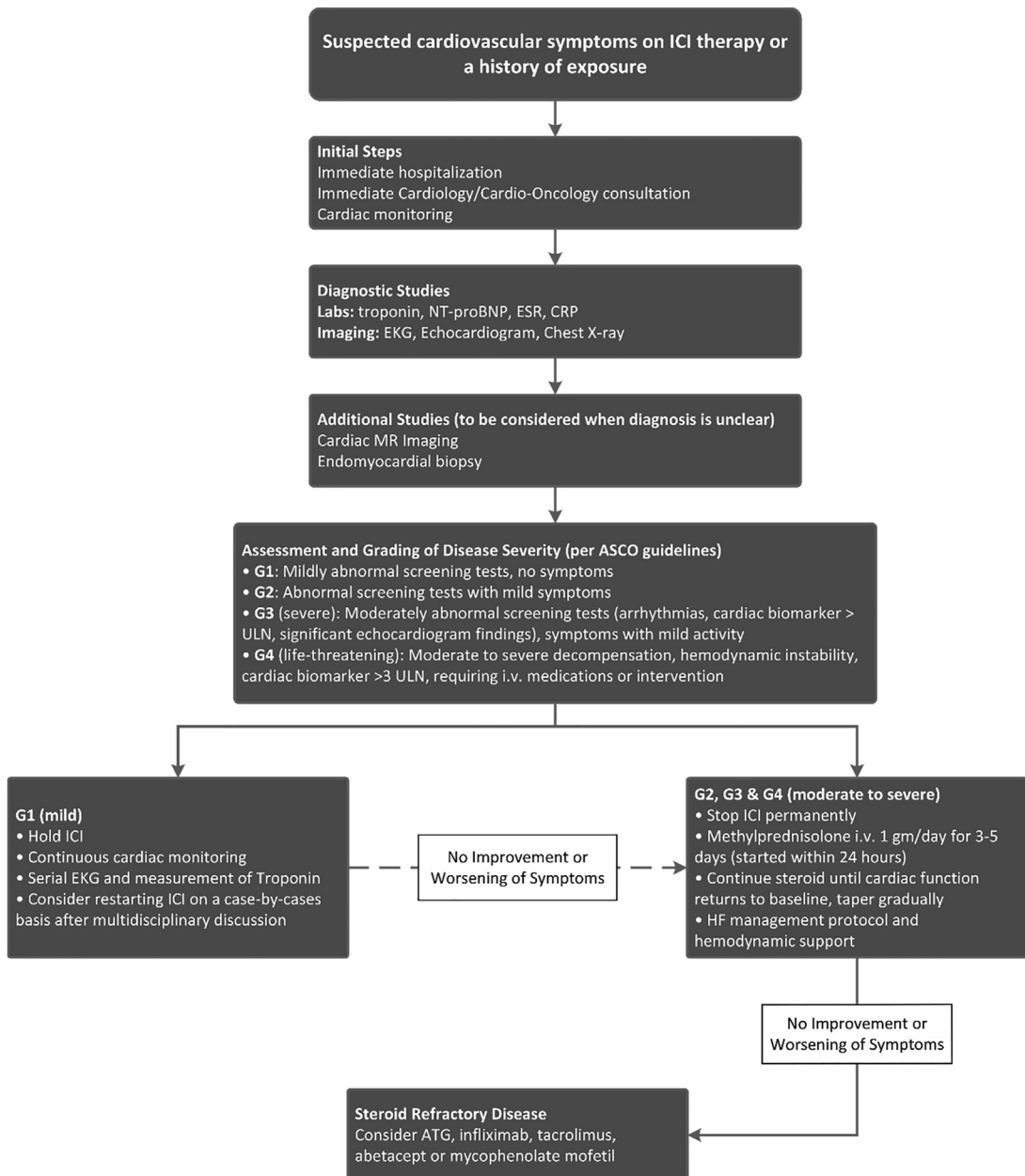


Fig. 3. A simplified management algorithm for a patient presenting with signs and symptoms of suspected ICI-related cardiotoxicity. ATG, Anti-Thymocyte Globulin; ULN, Upper Limit of Normal.

PROGNOSIS AND SURVEILLANCE

Immune Checkpoint Inhibitors

ICI-related myocarditis is associated with a significantly worse prognosis compared to other types of myocarditis, with mortality rates ranging from 25% to 50% over a short follow-up period.⁵⁶ Non-fatal MACE, including heart failure, cardiogenic shock, cardiac arrest, ventricular arrhythmias, and complete heart block, have also been

reported in approximately 50% of cases.⁵⁷ Moreover, patients who developed pericardial disease while on an ICI had a trend for increased all-cause mortality compared with patients who did not create a pericardial event.⁴ In addition, steroid-refractory ICI-myocarditis requiring the administration of immunosuppressants is also associated with a poorer prognosis.⁵⁸

The ASCO's Clinical Practice Guideline recommends a screening ECG and consideration of

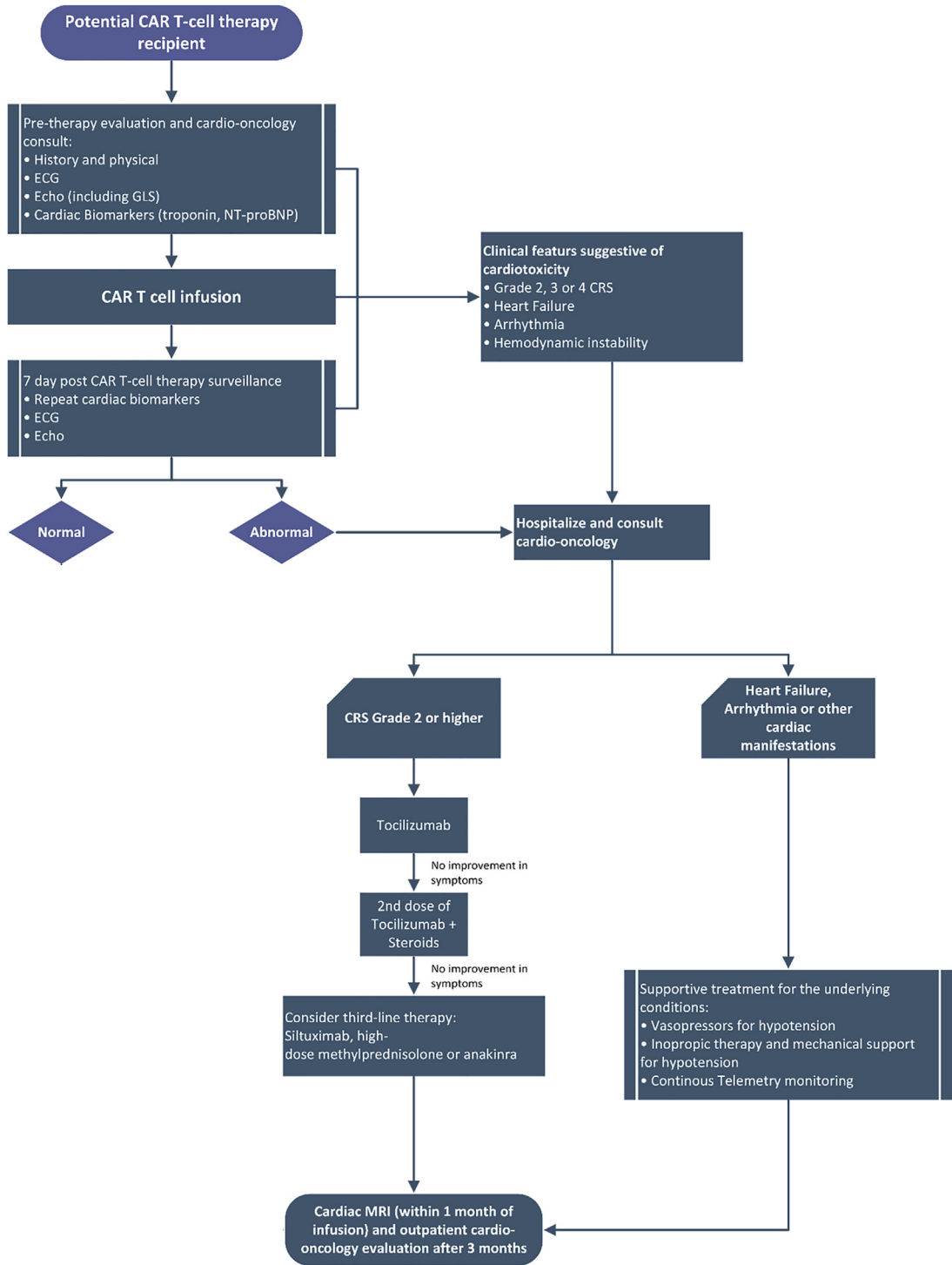


Fig. 4. Screening, Monitoring, and Management of CAR T-cell therapy-associated cardiotoxicity. CRS, Cytokine Release Syndrome.

troponin measurement for patients before initiating ICI, particularly in patients receiving dual ICI therapy.⁴⁸ Echocardiography showing baseline LVEF and GLS is not usually required because the baseline values are not consistently correlated with the

risk of myocarditis.⁴³ However, screening echocardiography may be considered if patients have an underlying history of CVD. A routine surveillance strategy combining ECG and troponin during ICI treatment would have the advantage of higher

sensitivity. Although it may lead to unnecessary interruptions of cancer therapy, especially among patients with a modestly asymptomatic (isolated) troponin elevation, medical professionals providing services in cardiovascular and oncology domains should be educated about the importance of routine surveillance and in the context of cancer therapeutics and their effects on the cardiovascular system.

Chimeric Antigen Receptor T-Cell Therapy Induced Cytokine Release Syndrome

Patients experiencing CVAEs following CAR T therapy have a reported all-cause mortality rate of 30%, compared to 21% in those without such events.²⁹ Furthermore, high-grade CRS grade 2 or higher have significantly higher risk of developing cardiomyopathy.³⁷ Additionally, half of these patients exhibited persistent cardiac dysfunction even after 6 months of follow-up.

The case fatality rate associated with specific cardiovascular complications is also concerning. A pharmacovigilance study by Goldman and colleagues (2020) reported a high case fatality rate of 36.5% and 36.9% for tachyarrhythmias and cardiomyopathy, respectively, following CAR T therapy.⁵⁹

Limited data exist on the long-term consequences of CAR T therapy. However, the persistent activation of the immune system and resulting inflammation raise concerns about the potential development of metabolic syndrome, hypertension, vascular disease, and even future cases of cardiomyopathy after a latent period.

IMPACT OF CARDIOMETABOLIC, SOCIO-ECONOMIC AND ENVIRONMENTAL FACTORS ON IMMUNOTHERAPY INDUCED CARDIOTOXICITY

It is well established that age, pre-existing CVD, genetic predisposition, socioeconomic disparities, environmental injustice, obesity, and metabolic dysfunction are potential contributors to the complex interplay between cancer, cardiovascular health, and immunotherapy-induced toxicities.^{60,61} A multitude of factors like cardiometabolic, socioeconomic, and environmental factors can influence the development and progression of ICI-mediated cardiotoxicity. Recent studies have established that increased socioeconomic vulnerabilities, including, but not limited to, racial and ethnic disparities, lack of health care affordability and accessibility, are associated with increased cardio-oncology mortality and poorer cardiovascular health outcomes.⁶² Moreover, environmental injustice conferred upon a community also significantly determines its cardiovascular health.⁶³ Other

shared risk factors, such as obesity and metabolic dysfunction, inflammation, and poor diet, contribute to the bidirectional relationship between cancer and CVD.⁶⁴ Based on these results, it can be hypothesized that these factors may indirectly accentuate the progression of cardiovascular irAEs. Further studies are required to definitively identify the association and complex interaction of metabolic, socio-economic, and environmental factors with the incidence and progression of cardiac irAEs.

FUTURE DIRECTIONS IN THE MANAGEMENT OF CARDIAC IMMUNE-RELATED ADVERSE EVENTS

The expanding use of ICIs in oncology necessitates a deeper understanding of the potential for cardiovascular toxicity. Although relatively rare, ICI-associated cardiotoxicity can lead to life-threatening complications. Close collaboration between oncologists and cardiologists is crucial for the early recognition and optimal management of these adverse events. Several vital areas warrant further investigation to advance our knowledge and clinical approach to ICI-related cardiotoxicity.

1. Elucidating the pathophysiological mechanisms: The exact mechanisms underlying the development of ICI-induced cardiotoxicity remain poorly understood. Preclinical studies suggest that robust proliferation and activation of T-cells expressing high-frequency receptors against shared antigens between tumor and myocardial cells may play a role. However, further research is needed to characterize the complex immunologic processes driving these toxicities entirely.
2. Identifying predictive biomarkers and imaging findings: Currently available biomarkers for ICI-associated cardiac irAEs lack specificity and extensive validation. The development of novel biomarkers that are appropriately sensitive and specific to ICI-induced cardiac injury could facilitate earlier detection and risk stratification. Additionally, standardized criteria for the histopathologic grading of ICI-related myocarditis on EMB and specific patterns on advanced cardiac imaging could provide prognostic insights.
3. Developing targeted therapeutic strategies: Management of ICI-related cardiotoxicity primarily relies on immunosuppression with high-dose corticosteroids. However, a subset of patients may have steroid-refractory disease. Several immunomodulatory agents, such as abatacept, are being explored as potential therapies, but their safety and efficacy need to be established in more extensive studies. Moreover, the optimal

- dosing and duration of immunosuppressive regimens have yet to be determined.
4. Establishing evidence-based surveillance protocols: The timing and frequency of cardiovascular monitoring in patients receiving ICIs remain controversial. Prospective studies are needed to evaluate the clinical utility and cost-effectiveness of different surveillance strategies, including cardiac biomarkers, electrocardiography, and imaging modalities. Risk-adapted approaches based on pre-existing CVD or concomitant cardiotoxic therapies may help guide personalized monitoring.
 5. Harnessing multidisciplinary collaborations: Given the complexities in diagnosing and treating ICI-related cardiotoxicity, a multidisciplinary approach involving oncologists, cardiologists, and immunologists is paramount. Establishing dedicated cardio-oncology teams and tumor boards can facilitate prompt referrals, optimize management decisions, and improve patient outcomes. Furthermore, creating multi-institutional registries and databases can enable robust data sharing and analysis to inform clinical practice.
 6. Designing prospective clinical trials: Future clinical trials of ICIs should incorporate standardized definitions and grading systems for cardiac irAEs, as well as detailed cardiovascular efficacy and safety endpoints. Dedicated studies are essential to characterize the incidence, risk factors, and long-term outcomes of ICI-related cardiotoxicity. Moreover, trials evaluating the effectiveness of novel preventive or therapeutic strategies are needed to guide evidence-based management.

As the indications for ICI therapy continue to expand, clinicians across disciplines must collaborate to unravel the mechanisms, optimize prevention and surveillance strategies, and develop targeted treatments for ICI-related cardiotoxicity. Ongoing research efforts and multidisciplinary initiatives hold promise in enhancing our understanding and management of these critical cardiovascular complications while harnessing the life-saving potential of cancer immunotherapy.⁶⁵

SUMMARY

While ICIs and CAR T-cell therapy have transformed the landscape of cancer treatment, their potential for severe cardiovascular toxicities necessitates a proactive, multidisciplinary approach to patient care. Early recognition and prompt management of ICI-related cardiotoxicity are crucial to improve patient outcomes. An interdisciplinary

approach involving collaboration between oncologists, cardiologists, and cardio-oncologists is essential for the optimal management of patients with ICI-related cardiotoxicity. With current evidence, the optimal management strategy appears to be appropriate risk stratification prior to immunotherapy, close follow-up of patients during treatment with multi-disciplinary collaboration, and post-therapy surveillance.

CLINICS CARE POINTS

- Individuals receiving immune checkpoint inhibitors should be assessed for impending signs of ICI-associated myocarditis including development chest pain, fatigue, ECG abnormalities and cardiac biomarker elevation, especially withing the first three months of starting the therapy, which should be further investigated using echocardiography and cardiac MRI.
- Discontinuation of offending ICI and initiation of high-dose corticosteroids preferably should be considered as early as possible following the diagnosis of myocarditis. Immunosuppressive therapies may be added in steroid refractory cases.
- Development of fever, hypotension, tachycardia, and hemodynamic instability in individuals following T cell infusion should raise concern for the development of high-grade CRS, and should prompt the initiation of tocilizumab, an IL-6 antagonist.

DISCLOSURE

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Cardio-oncology Drug Interactions

A Primer for Clinicians on Select Cardiotoxic Oncologic Therapies



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KEYWORDS

- Cardio-oncology • Drug interactions • Pharmacokinetics • Pharmacodynamics • Chemotherapy
- Tyrosine kinase inhibitors • BRAF/MEK inhibitors • PARP Inhibitors

KEY POINTS

- Recognition and appropriate management of oncology drug interactions minimizes toxicities, improves tolerability, and ensures that regimens are safe for the patient with cardio-oncology.
- Novel targeted inhibitors, chemotherapies, and hormonal treatments have complex pharmacologic properties with drug interactions most commonly via the metabolic cytochrome 450 pathways.
- Pharmacokinetic studies and physiologically based pharmacokinetic modeling are needed to assess common therapeutics in combination with oncology treatments to better inform management strategies for drug interactions.

INTRODUCTION

Cancer and cardiovascular disease are linked through common risk factors, coexisting disease states, and the cardiotoxic effects of cancer treatments.¹ Over the past 15 years, cancer therapies providing progression-free and overall survival benefits have substantially expanded. Many new agents are oral targeted inhibitors that are greatly impacted by absorption, metabolism, and elimination pathways. These medications have diverse and complex drug interactions (DIs), especially related to altered drug disposition. The nature of these interactions can impact efficacy and safety of both antineoplastic and cardiovascular agents. Thus, a proficient understanding of these interactions is essential to optimizing pharmacotherapy regimens for the cardio-oncology patient.

A DI is defined as the “pharmacologic or clinical response to the coadministration of a medication with another substance that modifies a patient’s response to the medication in either a beneficial or detrimental manner.”² DIs are primarily classified as either pharmacodynamic or pharmacokinetic.² A pharmacodynamic interaction occurs when one drug alters the sensitivity or responsiveness of another agent without impacting kinetics. For example, the concomitant use of sunitinib, a vascular endothelial growth factor (VEGF) inhibitor, with an anticoagulant may compound bleeding risk. A pharmacokinetic interaction involves one medication altering absorption, distribution, metabolism, or elimination of another agent. For example, there is a metabolic interaction between zanubrutinib, a Bruton’s tyrosine kinase (BTK) inhibitor, and diltiazem. Zanubrutinib

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is extensively metabolized by cytochrome P450 3A4 (CYP3A4). Diltiazem is a moderate CYP3A4 inhibitor. Concomitant use of diltiazem with zanubrutinib requires a 50% decrease in the zanubrutinib dose to account for the impact diltiazem will have on the function of CYP3A4 enzymes and subsequently zanubrutinib blood concentrations and exposure.^{3,4} Metabolic and transport interactions are the most common type of pharmacokinetic interactions. Historically, these metabolism-based interactions have been identified by testing new compounds with known enzymatic inhibitors and inducers. With recent advances using novel physiologically based pharmacokinetic (PBPK) modeling, the impact of DIs can be more readily quantified and qualified.⁵

Many agents used to manage both cancer and cardiovascular diseases have complex pharmacologic profiles, including intra-patient and inter-patient variability, narrow therapeutic indices, and steep dose-toxicity curves. Thus, it is important for both cardiology and hematology/oncology clinicians to be aware of DIs. Due to the dynamic and multifaceted nature of cardio-oncology, it is imperative that a team-based approach be applied to help manage these complex patients.⁶ Since there is considerable variability in DI screening and management information for cancer therapies, clinicians are encouraged to check multiple sources for additional information and guidance.^{7,8}

The purpose of this review is to provide a discussion of common DIs in cardio-oncology based on cancer therapy class and to complement several of the thematic topics found within this journal edition. Select classes of oncologic medications associated with cardiotoxicity chosen for this review include the anthracyclines, human epidermal growth receptor 2 (HER2) antagonists, poly(ADP-ribose) polymerase (PARP) inhibitors, select hormonal therapies used in the treatment of breast cancer, rapidly accelerated fibrosarcoma B-type proto-oncogene and mitogen-activated extracellular signal-regulated kinase (BRAF/MEK) inhibitors, BTK inhibitors, VEGF inhibitors, epidermal growth factor receptor (EGFR) inhibitors, fluorouracil and capecitabine, and breakpoint cluster region-Abelson (BCR-ABL) inhibitors. Given the complexity of DIs and the multitude of agents in the cancer and cardiovascular space, this article is not intended to be an all-encompassing review but rather provide a foundational overview of considerations. Clinicians are encouraged to review multiple sources pertaining to drug interactions and consult a clinical pharmacist for patient-specific treatment decisions. It should also be noted that DIs between cancer

agents that are not germane to a cardio-oncology focus are beyond the scope of this article.

DISCUSSION

Anthracyclines

As a class, the anthracyclines are effective for the treatment of diverse malignancies including breast cancer, small cell lung cancer, bladder cancer, leukemias, lymphomas, and sarcomas.⁹ Conventional anthracyclines predispose patients to cardiomyopathy and subsequent heart failure risk. The mechanism of toxicity is related to the inhibition of topoisomerase 2 β that is expressed in cardiomyocytes. The development of cardiomyopathy and heart failure is related to cumulative lifetime anthracycline exposure.⁹ Doxorubicin, one of the most commonly used anthracyclines, is unique compared to other agents in the class as it is metabolized by cytochrome P450 2D6 (CYP2D6) and CYP3A4 and transported by P-glycoprotein (P-gp).^{10,11} Thus, drugs that inhibit CYP2D6, CYP3A4, or P-gp are often listed as contraindicated in many DI databases due to the potential pharmacokinetic interactions that may increase doxorubicin exposure (**Table 1**). This risk is enhanced when inhibitor agents are chronically used, like oral diltiazem or amiodarone for atrial fibrillation, rather than short-term acute use.¹⁰ Thus, agents such as diltiazem, verapamil, amiodarone, and dronedrone should be avoided during treatment with doxorubicin.

Doxorubicin alone carries a potential to reduce the absorption of digoxin tablets, but not other formulations, by up to 50%.^{2,11} This interaction is most likely mediated by both an upregulation of P-gp and intestinal epithelial toxicity.² It has been noted that the liposomal doxorubicin formulation is associated with a lower cardiotoxicity profile and may also have less impact on P-gp induction. Thus, digoxin levels should be monitored with initiation, dose changes, or discontinuing of doxorubicin-based regimens.²

Human Epidermal Growth Factor 2 (HER2) Antagonists

Approximately 20% of breast cancers overexpress the HER2 cell surface tyrosine kinase receptor.¹² HER2-positive breast cancer is associated with more aggressive disease, higher risk of recurrence, and lower survival rates.¹³ Efforts to develop agents targeting this receptor have led to therapies associated with improved progression free and overall survival such as trastuzumab. In terms of cardiotoxicity, most HER2-targeted therapies increase the risk of

Table 1
Anthracyclines ^{11,84–92}

Agent	Doxorubicin	Daunorubicin	Idarubicin	Epirubicin	Mitoxantrone
Key Cardiovascular Toxicities	• Cardiomyopathy • Arrhythmia • Myocardial damage • Heart failure				
Metabolic/Transport Pharmacokinetic Drug–Drug interactions	• Major: CYP3A4 substrate • CYP2D6 substrate • P-gp substrate	• Minor: P-gp substrate	• Minor: P-gp substrate • In vitro: CYP2D6 substrate • CYP2C9 substrate • CYP2D6 inhibitor	• In vitro: P-gp substrate • P-gp inducer	• Minor: BCRP substrate • P-gp weak substrate
Additional Pharmacokinetic Drug–Drug interactions	• Avoid concomitant use of moderate and strong CYP3A4 inhibitors and inducers • Avoid concomitant use of moderate and strong CYP2D6 inhibitors and inducers • Avoid concomitant use of moderate and strong P-gp inhibitors and inducers • Grapefruit juice, Seville oranges, star fruit	• Avoid concomitant use of moderate and strong P-gp inhibitors and inducers	• Avoid concomitant use of moderate and strong P-gp inhibitors and inducers	• none	• Avoid concomitant use of moderate and strong P-gp inhibitors and inducers
Pharmacodynamic Considerations	• Additive cardiotoxicity risk if used in combination with trastuzumab, fam-trastuzumab deruxtecan, ado-trastuzumab emtansine, margetuximab, and likely pertuzumab • Coadministration with bevacizumab may enhance cardiotoxic effects				
Cardiovascular Drug Interaction Clinical Pearls	• Amiodarone, diltiazem, dronedarone, verapamil, carvedilol may increase serum	• Amiodarone, dronedarone, verapamil, carvedilol may	• Amiodarone, dronedarone, verapamil, carvedilol may	• Caution with digoxin as damage to mucosal membrane	• Amiodarone, dronedarone, verapamil, carvedilol may

(continued on next page)

Table 1
(continued)

Agent	Doxorubicin	Daunorubicin	Idarubicin	Epirubicin	Mitoxantrone
	concentration of doxorubicin • Bosentan may decrease doxorubicin concentrations • Caution with digoxin tablets as damage to mucosal membrane impacts P-gp and inhibits absorption.	increase daunorubicin concentrations. • Caution with digoxin as damage to mucosal membrane impacts P-gp and inhibits absorption.	increase idarubicin concentrations. • Caution with digoxin as damage to mucosal membrane impacts P-gp and inhibits absorption.	impacts P-gp and inhibits absorption.	increase mitoxantrone concentrations. • Caution with digoxin as damage to mucosal membrane impacts P-gp and inhibits absorption.

cardiomyopathy. A clinical trial in metastatic HER2-positive breast cancer demonstrated that the combination of anthracyclines with trastuzumab resulted in over 20% of patients developing reductions in left ventricular ejection fraction due to pharmacodynamic interactions.¹² Due to this additive cardiotoxic effect, current treatment paradigms do not simultaneously combine HER2-targeted therapy with anthracyclines. Furthermore, the HER2 tyrosine kinase inhibitor (TKI) lapatinib has the potential to prolong the QT interval and use with other agents that prolong the QT interval should be limited or avoided.^{14,15} The HER2-targeted monoclonal antibodies have limited pharmacokinetic DIs, but cardiotoxicity effects can create additive pharmacodynamic interactions when used in combination with other therapies that are toxic to the cardiac myocyte.² **Table 2** provides a comparison of the HER2 agents.

Alternatively, HER2 oral TKIs may impact the metabolism of other agents. In terms of pharmacokinetic interactions, both lapatinib and neratinib are major substrates of CYP3A4 and exposure may be increased with strong or moderate CYP3A4 inhibitors, such as amiodarone, diltiazem, verapamil, or dronedarone.^{2,15,16} Use of these agents should be avoided or monitoring and dosing modification of the TKI enacted. All HER2-targeted TKIs are inhibitors of P-gp.¹⁵⁻¹⁷ Thus, concomitant use of P-gp substrates, such as edoxaban and dabigatran, should be avoided. If concomitant use with P-gp substrates is unavoidable, a dose reduction of the P-gp substrate will likely need to be made and a monitoring plan for adverse effects of the P-gp substrate created. Lastly, absorption of the oral HER2 TKIs lapatinib and neratinib is pH dependent and gastric acid suppression may reduce blood concentrations and potentially efficacy.^{2,15,16}

Poly(ADP-ribose) Polymerase (PARP) Inhibitors

The PARP inhibitors target enzymes with a role in DNA repair and are effective in treating malignancies with genetic deficiencies in the homologous recombination pathway.¹⁸ Malignancies with demonstrated efficacy and Food and Drug Administration (FDA)-approved indications include ovarian, breast, prostate, and pancreatic cancers.¹⁹ PARP inhibitors have diverse pharmacokinetic profiles, including varying degrees of hepatic metabolism (**Table 3**) that can cause potential pharmacokinetic interactions. Olaparib is primarily metabolized by CYP3A4.²⁰ Rucaparib is a minor substrate of CYP2D6, CYP1A2, and CYP3A4.²¹ Talazoparib is minimally metabolized by hepatic

enzymes and has the lowest potential for metabolic DIs among the PARP inhibitors.²² Due to the extensive dependency of olaparib on CYP3A4 metabolism, concomitant use of moderate and strong CYP3A4 inhibitors, such as verapamil, amiodarone, diltiazem, and dronedarone, should be avoided or an olaparib dose adjustment be implemented.^{2,20} Rucaparib has weak and moderate inhibitory activity on several hepatic enzymes. Thus, rucaparib has the potential to increase concentrations of agents such as simvastatin, rosuvastatin, and warfarin. Additional monitoring and selection of alternative agents are recommended strategies for management. Lastly, talazoparib is a major substrate of P-gp transporters and dose reductions are recommended in the FDA label when used in conjunction with P-gp inhibitors.^{2,22}

Breast Cancer Hormonal Agents

The recommendations for estrogen receptor-positive and/or progesterone receptor-positive breast cancer include the use of endocrine therapy in the neoadjuvant, adjuvant, and advanced or metastatic setting. The two main categories of agents for treatment include the aromatase inhibitors and the selective estrogen receptor modulator tamoxifen. Aromatase inhibitors include anastrozole, letrozole, and exemestane. The aromatase inhibitors do not have any major pharmacokinetic DIs. However, tamoxifen is extensively metabolized via CYP3A4 and CYP2D6 to the important and potent metabolite, endoxifen.²³ Thus, to preserve efficacy of tamoxifen, CYP3A4 and CYP2D6 inhibitors or inducers should be avoided. Such agents include the non-dihydropyridine calcium channel blockers verapamil and diltiazem, quinidine, bosentan, amiodarone, propafenone, dronedarone, and the weak inhibitor labetalol.²

Rapidly Accelerated Fibrosarcoma B-type Proto-oncogene (BRAF) and Mitogen-activated Extracellular Signal-regulated Kinase (MEK) Inhibitors

BRAF and MEK inhibitors are key agents in the management of melanoma as well as certain recurrent and metastatic solid tumors. BRAF inhibitors are also important in the treatment of BRAF-mutated hairy cell leukemia. Medications in the BRAF and MEK inhibitor drug classes have unique interaction profiles²⁴ (**Table 4**). BRAF inhibitors include dabrafenib, vemurafenib, and encorafenib. Dabrafenib is a major substrate of CYP2C8 and CYP3A4.²⁵ Strong inducers of these enzymes are likely to reduce dabrafenib concentrations and should be avoided or efficacy should be

Table 2
Human epidermal growth factor 2 antagonists ^{15–17,93–99}

Agent	Monoclonal Antibodies: Trastuzumab; Trastuzumab/ Hyaluronidase Pertuzumab Pertuzumab/ Trastuzumab/ Hyaluronidase Margetuximab					
	Ado-Trastuzumab Emtansine	Fam-Trastuzumab Deruxtecan	Lapatinib	Neratinib	Tucatinib	
Key Cardiovascular Toxicities	• Cardiomyopathy	• Myocardial damage	• Heart failure		• Not associated with cardiotoxicity	• Not associated with cardiotoxicity
Metabolic/Transport Pharmacokinetic Drug–Drug interactions	• Not applicable	• Minor: CYP3A4 substrate	• Minor: BCRP substrate CYP3A4 substrate OATP1B1	• Major: CYP3A4 substrate • Minor: BCRP substrate CYP3A4 weak inhibitor P-gp substrate, inhibitor	• Major: CYP3A4 substrate • Minor: P-gp substrate P-gp inhibitor	• Major: CYP2C8 substrate CYP3A4 inhibitor • Minor: BCRP substrate CYP3A4 substrate CYP2C8 inhibitor OCT2 inhibitor P-gp inhibitor
Additional Pharmacokinetic Drug–Drug interactions	• Not applicable	• Avoid concomitant use of strong CYP3A4 inhibitors	• Avoid concomitant use of strong CYP3A4 inhibitors	• Antacids • Caution with narrow therapeutic index drugs that are P-gp substrates • Grapefruit juice, Seville oranges, star fruit	• Proton pump inhibitors • Histamine 2R antagonists • Antacids	• None
Pharmacodynamic Considerations	• Additive cardiotoxicity risk if used in combination with anthracycline			• Avoid coadministration of medications that can prolong QTc	• None	• None

Cardiovascular Drug Interaction Clinical Pearls	• Not applicable	• Amiodarone, dronedarone, verapamil, diltiazem may increase deruxtecan concentrations.	• Amiodarone, dronedarone, verapamil, diltiazem may increase DMI concentrations.	• Amiodarone, diltiazem, dronedarone, verapamil may increase lapatinib concentrations • Lapatinib may increase edoxaban, dabigatran, simvastatin, atorvastatin, ranolazine concentrations • Caution with digoxin	• Amiodarone, dronedarone, verapamil, carvedilol may increase neratinib concentrations. • Neratinib may increase concentrations of edoxaban, dabigatran, ranolazine • Caution with digoxin	• Tucatinib may increase amiodarone, verapamil, diltiazem, atorvastatin, cilostazol, dofetilide concentrations. • Tucatinib may increase apixaban, rivaroxaban concentrations; consider dose decrease of apixaban or rivaroxaban • Gemfibrozil may increase concentration of tucatinib
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Table 3
Poly(ADP-ribose) polymerase Inhibitors^{20–22}

Agent	Olaparib	Rucaparib	Talazoparib
Key Cardiovascular Toxicities	• Venous thromboembolism	• Peripheral edema	• Not associated with cardiotoxicity
Metabolic/Transport Pharmacokinetic Drug–Drug interactions	• Major: CYP3A4 substrate	• Major: CYP1A2 moderate inhibitor • Minor: CYP2C9 weak inhibitor CYP2C19 weak inhibitor CYP3A4 weak inhibitor	• Major: P-gp substrate • Minor: BCRP substrate
Additional Pharmacokinetic Drug–Drug interactions	• Avoid concomitant use of moderate and strong CYP3A4 inhibitors and inducers • Grapefruit juice, Seville oranges, star fruit	• Caution with CYP1A2, CYP2C9, CYP3A4 narrow therapeutic drugs	• Avoid concomitant use of moderate and strong P-gp inhibitors and inducers
Pharmacodynamic Considerations	• Caution with agents that can increase risk of clot such as estrogen-based hormonal therapies	• None	• None
Cardiovascular Drug Interaction Clinical Pearls	• Amiodarone, diltiazem, dronedarone, and verapamil may increase serum concentration of olaparib • Bosentan may decrease olaparib concentration and avoid combination	• Monitor therapy with finerenone, propranolol, simvastatin, rosuvastatin • Caution with warfarin. • Consider therapy modification with concurrent use of mavacamten	• Amiodarone and verapamil may increase serum concentration of talazoparib; consider therapy modification • Atorvastatin, diltiazem, felodipine may increase serum concentration of talazoparib • Carvedilol and diltiazem may increase serum concentration of talazoparib, consider therapy modification

Table 4
Rapidly accelerated fibrosarcoma B-type and mitogen-activated extracellular signal-regulated kinase inhibitors^{25–27,100–103}

Class	MEK Inhibitors			BRAF Inhibitors		
Agent	Binimetinib	Trametinib	Cobimetinib	Dabrafenib	Encorafenib	Vemurafenib
Key Cardiovascular Toxicity	• Cardiomyopathy • Hypertension • Edema • Venous thromboembolism • Hemorrhage	• Cardiomyopathy • Hypertension • Edema • Venous thromboembolism • Hemorrhage	• Cardiomyopathy • Hypertension • Hemorrhage	• Cardiomyopathy • Venous thromboembolism • Hemorrhage • QTc prolongation	• Cardiomyopathy • Hypertension • Edema • Hemorrhage • QTc prolongation	• Hypertension • Edema • Hemorrhage • QTc prolongation
Metabolic/ Transport Pharmacokinetic Drug–Drug Interactions	• Minor: CYP1A2 substrate CYP2C19 substate P-gp substrate BCRP substrate UGT1A1 substrate	• None	• Major: CYP3A4 substrate • Minor: P-gp substrate	• Major: CYP2C8 substrate CYP3A4 substrate • Minor: P-gp substrate CYP2C9 weak inducer CYP3A4 moderate inducer BCRP substrate	• Major: CYP3A4 substrate CYP3A4 inducer • Minor: CYP2C19 substrate CYP2D6 substrate P-gp substrate CYP1A2 weak inhibitor CYP2B6 weak inducer	• Major: CYP3A4 substrate CYP1A2 moderate inhibitor • Minor: P-gp substrate P-gp inhibitor CYP2D6 weak inhibitor CYP2C9 weak inhibitor CYP3A4 weak inducer • In vitro: CYP2C8 inhibitor CYP2A6 inhibitor

(continued on next page)

Table 4 (continued)						
Class	MEK Inhibitors			BRAF Inhibitors		
Agent	Binimetinib	Trametinib	Cobimetinib	Dabrafenib	Encorafenib	Vemurafenib
Additional Pharmacokinetic Drug–Drug Interactions	None	None	Caution with coadministration of CYP3A4 inhibitors and inducers	CYP3A4 and CYP2C8 inducers may decrease the serum concentration of dabrafenib	- CYP3A4 inducers may decrease the serum concentration of substrates - Strong and moderate CYP3A4 inhibitors may increase serum concentration of encorafenib	- Strong CYP3A4 inhibitors may increase vemurafenib and strong CYP3A4 inducers may decrease vemurafenib - Vemurafenib may increase concentrations of P-gp substrates such as digoxin
Pharmacodynamic Considerations	- Enhanced risk of cardiotoxicity when used with other agents with same toxicity. - Caution with agents that can increase bleed risk such as antiplatelets, anticoagulants, or medications with antiplatelet or anticoagulant effects such as aspirin, NSAIDs, vitamin E, fish oil, ginseng, omega 3, and omega 6 fatty acids. - Caution with androgen hormonal agents can increase hypertensive effect. - Avoid coadministration of medications that can prolong QTc interval.					
Cardiovascular Drug Interaction Clinical Pearls	None	None	Avoid use with amiodarone, diltiazem, dronedarone, and verapamil	Concentrations of amlodipine, atorvastatin, diltiazem, finerenone, ivabradine, lovastatin, macitentan, nifedipine, ranolazine, sildenafil, ticagrelor, verapamil, and warfarin concentration may be decreased with use of dabrafenib	Encorafenib may decrease concentrations of apixaban, amlodipine, bisoprolol, felodipine, finerenone, ivabradine, lovastatin, nicardipine	- Avoid use with amiodarone, diltiazem, dronedarone, verapamil - Dabigatran digoxin, edoxaban, ranolazine, warfarin may be increased with vemurafenib

Abbreviations: BCRP, breast cancer resistance protein; NSAID, non-steroidal anti-inflammatory drugs.

monitored. Similarly, CYP3A4 inhibitors will likely increase BRAF inhibitor concentrations as all BRAF inhibitors are CYP3A4 substrates. There are limited cardiovascular management agents that would be of impact based on enzyme induction, but amiodarone and dronedarone as well as diltiazem and verapamil are likely to be of impact based on their inhibitory potential on CYP3A4. Additionally, dabrafenib is a moderate inducer of CYP3A4 and a weak inducer of cytochrome P450 2C9 (CYP2C9).²⁵ Thus, apixaban, amlodipine, bisoprolol, felodipine, finerenone, ivabradine, lovastatin, and nicardipine may be decreased by dabrafenib. These combinations should be avoided or efficacy monitored. Encorafenib is both a substrate of CYP3A4 and a strong inducer of CYP3A4. Thus, encorafenib is likely to decrease blood concentrations of agents that are CYP3A4 substrates such as apixaban, rivaroxaban, ivabradine, and finerenone. Concomitant use of these agents with encorafenib should be avoided. Vemurafenib is metabolized by CYP3A4 and has similar considerations with CYP3A4 inducers and inhibitors as dabrafenib.²⁶ Vemurafenib has demonstrated inhibitory effects on CYP1A2, CYP2D6, CYP2C9, as well as P-gp. Thus, combining substrates of these enzymes with vemurafenib may likely increase substrate concentrations and should be avoided or the risk of adverse events be monitored. Agents such as lidocaine, mexiletine, dabigatran, digoxin, edoxaban, ranolazine, and warfarin could be affected. In terms of the MEK inhibitors, DI concerns exist with cobimetinib as a major CYP3A4 substrate and use with CYP3A4 inhibitors or inducers should be avoided or efficacy monitored.^{2,24,27}

Bruton's Tyrosine Kinase (BTK) Inhibitors

The development of the BTK inhibitor class led to a paradigm shift in treatment for small lymphocytic lymphoma/chronic lymphocytic leukemia, mantle cell lymphoma, Waldenström's macroglobulinemia, and marginal zone lymphoma.^{3,28–30} BTK is a non-receptor tyrosine kinase critical to mediating downstream proliferation and survival in the B-cell receptor signaling pathway.^{31,32} While BTK is an effective target as demonstrated from benefits in response rates and progression-free survival, key limitations of BTK inhibitors include off-target effects and cardiotoxicity.^{33–36} This is most broadly experienced with ibrutinib, an irreversible inhibitor of BTK. Proposed affinities for TEC and Src, HER2 and HER4 in cardiomyocytes, as well as BMX in endothelial cells, may explain some cardiotoxicities experienced with ibrutinib including atrial fibrillation, hypertension, and

increased bleed risk due to an inhibition of BTK-mediated platelet adhesion.^{37–39}

Acalabrutinib and zanubrutinib are also irreversible BTK inhibitors but are more selective for BTK than ibrutinib. From clinical trial data, both acalabrutinib and zanubrutinib are associated with lower incidence of atrial fibrillation and bleeding events compared to ibrutinib.^{35,36} Additionally, acalabrutinib is associated with lower rates of treatment-emergent hypertension.³⁵ Pirtobrutinib is the newest agent in this drug class. Unlike the others, pirtobrutinib is a reversible inhibitor of BTK. As pirtobrutinib was FDA approved via the accelerated approval pathway, information regarding pirtobrutinib's side effect profile is still being evaluated, but pirtobrutinib appears to have similar side effects as the others in this class.⁴⁰

Pharmacokinetic interactions with BTK inhibitors can be abundant as all BTK inhibitors are primarily metabolized by CYP3A4 (**Table 5**). In a DI study of ibrutinib with the strong CYP3A4 inhibitor posaconazole, ibrutinib peak plasma concentrations were increased 8.2 to 8.5 fold and total ibrutinib exposure was increased 9.5 to 10.3 fold, raising concern for increased ibrutinib-related toxicities such as arrhythmias, hypertension, bleeding, and infections, among others.⁴¹ Ideally, concomitant use of CYP3A4 inhibitors such as the non-dihydropyridine calcium channel blockers verapamil and diltiazem, as well as amiodarone and dronedarone should be avoided or an appropriate BTK inhibitor dose reduction implemented.^{3,28–30,42} Similarly, CYP3A4 inducers, such as bosentan, should be avoided or an appropriate BTK inhibitor dose increase implemented.^{3,28–30,43} Acalabrutinib is considered a P-gp weak substrate.²⁹ Thus, verapamil or dronedarone may increase acalabrutinib concentrations via both P-gp inhibition and CYP3A4 inhibition, potentially further increasing risk of atrial fibrillation, bleeding, hypertension, and infection. Thus, concomitant use with acalabrutinib should be avoided.²

Additionally, attributed to off-target effects at TEC, and presumably the additive activity of ibrutinib on Src kinases, the BTK inhibitors can increase the risk of bleeding.^{38,44} Importantly, if a patient necessitates an anticoagulant or antiplatelet agent, it is important to weigh the benefit with the risk of bleed and to monitor for signs and symptoms of bleeding. Pirtobrutinib has demonstrated P-gp inhibitory activity and could increase serum concentrations of dabigatran or edoxaban, further increasing bleeding risk. Caution with use and increased monitoring is advised.^{2,30} Supplements that can influence the coagulation cascade and increase the risk of bleeding such as fish oil or vitamin E should also be avoided or used with caution.

Table 5
Bruton's tyrosine kinase inhibitors^{3,28–30,104–106}

Agent	Ibrutinib	Acalabrutinib	Zanubrutinib	Pirtobrutinib
Key Cardiovascular Toxicities	• Atrial fibrillation, atrial flutter • Bleed risk, hemorrhage • Hypertension (19%)	• Atrial fibrillation, atrial flutter • Bleed risk, hemorrhage • Hypertension (<10%)	• Atrial fibrillation, atrial flutter • Bleed risk, hemorrhage • Hypertension	• Atrial fibrillation, atrial flutter • Bleed risk, hemorrhage • Hypertension (<10%)
Metabolic Pharmacokinetic Drug–Drug Interactions	• Major: CYP3A4 substrate • Minor: CYP2D6 substrate • In vitro: P-gp inhibitor, BCRP inhibitor	• Major: CYP3A4 substrate • Minor: P-gp substrate^a, BCRP substrate^a • In vitro: BCRP inhibitor, CYP3A4 weak inhibitor, inducer, CYP3A5 weak inhibitor, CYP2C8 weak inhibitor^a, CYP2C9 weak inhibitor^a, CYP2B6 weak inducer, CYP1A2 weak inducer	• Major: CYP3A4 substrate • Minor: CYP3A4 weak inducer, CYP2C19 weak inducer, P-gp inhibitor • In vitro: P-gp substrate, CYP2B6 inducer, CYP2C8 inducer	• Major: CYP3A4 substrate, P-gp inhibitor • Minor: P-gp substrate, BCRP moderate inhibitor, CYP2C8 moderate inhibitor, UGT1A8 substrate, UGT1A9 substrate, CYP3A4 weak inhibitor, CYP2C19 weak inhibitor
Additional Pharmacokinetic Drug–Drug Interactions	• Grapefruit juice, Seville oranges, star fruit	• Grapefruit juice, Seville oranges, star fruit • Proton pump inhibitors • Histamine 2R antagonists • Antacids	• Grapefruit juice, Seville oranges, star fruit	• Grapefruit juice, Seville oranges, star fruit • May increase concentrations of sensitive CYP substrates of 2C8, 2C19, 3A4, P-gp, and BCRP
Pharmacodynamic Considerations	• Caution with agents that can increase bleed risk such as antiplatelets, anticoagulants, or medications with antiplatelet or anticoagulant effects such as aspirin, NSAIDs, vitamin E, fish oil, ginseng, omega 3, and omega 6 fatty acids.			
Cardiovascular Drug Interaction Clinical Pearls	• Caution with digoxin • Ibrutinib may increase concentrations of dabigatran, edoxaban	• Carvedilol, diltiazem, verapamil may increase concentrations of acalabrutinib	• Caution with digoxin • Diltiazem, verapamil may increase concentrations of zanubrutinib	• Pirtobrutinib may increase concentrations of dabigatran, edoxaban • Diltiazem, verapamil may increase concentrations of pirtobrutinib

^a Active metabolite of acalabrutinib reported to exhibit this in vitro PK effect as well as acalabrutinib parent drug.

Vascular Endothelial Growth Factor (VEGF) Inhibitors

The VEGF inhibitor class is comprised of both monoclonal antibodies such as bevacizumab, ziv-aflibercept, and ramucirumab, as well as oral targeted TKIs. VEGF inhibitors are used as monotherapy or in combination with chemotherapy or immunotherapy to treat a myriad of diseases such as central nervous system tumors, lung cancer, gynecologic cancers, gastrointestinal cancers, and renal cell carcinoma.^{45–53} VEGF inhibitors prevent angiogenesis to restrict vascularization at tumor sites. This disrupts vessel growth and initiates an imbalance between vasoconstrictors and vasodilators that modulate vascular tone.⁵⁴ Consequently, these agents are associated with a side effect profile of hypertension, arterial thromboembolic events, increased risk of cardiomyopathy or heart failure, and increased bleed risk.

Pharmacokinetic interactions with oral VEGF inhibitors can be abundant as all oral VEGF inhibitors are CYP3A4 substrates, but they are differentially affected by CYP3A4 inhibitors (**Table 6**). In pharmacokinetic studies with the strong CYP3A4 inhibitor, ketoconazole, axitinib, pazopanib, and sunitinib demonstrated the largest increases in area under the curve exposure.^{45,48,53} Overall, best practice is to avoid concomitant use of CYP3A4 inhibitors with these agents; however, if use is unavoidable, dose reductions are necessitated.^{45,52–54} Thus, in the management of VEGF inhibitor-induced hypertension, agents such as the non-dihydropyridine calcium channel blockers verapamil and diltiazem should be avoided in favor of alternative antihypertensives with less interaction potential.⁵⁵

Due to CYP2D6 inhibitory potential of pazopanib, the M-2 metabolite of regorafenib, and lenvatinib, monitoring and dose titration of CYP2D6 substrates such as carvedilol, metoprolol, and nebivolol are advised.^{2,47,48,51} Due to the P-gp inhibitory potential of sorafenib and sunitinib, titration of P-gp substrates such as losartan, labetalol, and propranolol is advised and either alternative therapy chosen or close monitoring for bleeding with concomitant dabigatran or edoxaban is warranted.^{2,56,57} Vandetanib and tivozanib concentrations were more affected by concomitant CYP3A4 inducers than by CYP3A4 inhibitors.^{49,50} Thus, CYP3A4 inducers should be avoided with these agents. Due to pharmacodynamic interactions, balancing the treatment of thrombosis with bleeding can be challenging in patients on VEGF inhibitors that intrinsically carry their own risk of bleeding.⁵⁵ Patients on concomitant anticoagulants or antiplatelet agents should

be closely monitored for signs and symptoms of bleeding.

Importantly, QTc prolongation is a concern for many of the oral VEGF inhibitors.¹⁴ Electrocardiogram (ECG) should be performed prior to initiation of oral VEGF TKIs. In fact, vandetanib carries a boxed warning for QTc prolongation.⁴⁹ Concomitant use of amiodarone, dronedarone, sotalol, or dofetilide should be avoided along with other medications that may prolong the QT interval.

Epidermal Growth Factor Receptor (EGFR) Inhibitors

EGFR inhibitors are TKIs FDA approved for treating EGFR-mutated non-small cell lung cancer and pancreatic cancer. Gefitinib and erlotinib are reversible EGFR inhibitors. Afatinib, dacomitinib, mobocertinib, and osimertinib, are irreversible inhibitors.⁵⁸ There have been several case reports associating use of EGFR inhibitors to the development of cardiomyopathy.⁵⁹ A review of the FDA Adverse Event Reporting System database identified a greater incidence of cardiotoxicities, including heart failure, atrial fibrillation, QTc prolongation, myocardial infarction, and pericardial effusion with osimertinib compared to other EGFR inhibitors.⁶⁰ The exact mechanism underlying the development of cardiomyopathy among the EGFR inhibitor class is not well elucidated but is hypothesized to be due to activity at HER2 receptors that may disrupt myocardial homeostasis and is reversible.⁶¹

There are many pharmacokinetic interactions that may affect the drug disposition of EGFR inhibitors. Erlotinib, gefitinib, mobocertinib, and osimertinib are all CYP3A4 substrates, so the use of the non-dihydropyridine calcium channel blockers diltiazem and verapamil, as well as medications like dronedarone, should be avoided to mitigate interaction risk^{62–65} (**Table 7**). Interestingly, an osimertinib pharmacokinetic study with the strong CYP3A4 inhibitor itraconazole only demonstrated a 24% increase in area under the curve exposure, suggesting that use of strong CYP3A4 inhibitors may not necessitate a dose change but would require monitoring for increased osimertinib side effects.⁶⁵ Strong CYP3A4 inducers should be avoided, and if they cannot be avoided, dose adjustments are needed for gefitinib and osimertinib.^{63,65} Of note, gefitinib and erlotinib have been reported to increase international normalized ratio (INR) and may enhance the anticoagulant effect of warfarin.^{62,63} Afatinib is a P-gp substrate and use of P-gp inhibitors such as verapamil, dronedarone, carvedilol,

Table 6
Vascular endothelial growth receptor inhibitors^{1,33,45–53,56,57,106–111}

Monoclonal Antibodies: Ziv-Aflibercept Bevacizumab Ramucirumab										
Agent	Axitinib	Cabozantinib	Lenvatinib	Pazopanib	Regorafenib	Sorafenib	Sunitinib	Vandetanib	Tivozanib	
Key Cardiovascular Toxicities	• Cardiomyopathy and/or heart failure • Arterial Thromboembolic Events • Hypertension • Hemorrhage, bleed risk									
			• Venous thrombotic events	• QTc prolongation	• QTc prolongation		• QTc prolongation	• QTc prolongation	• QTc prolongation, sudden death	• Venous thrombotic events
					• Venous thrombotic events			• Cerebrovascular Events	• Ischemic cerebrovascular Events	
Metabolic Pharmacokinetic Drug–Drug interactions	• Not applicable	• Major: CYP3A4 substrate • Minor: CYP1A2 substrate • In vitro: CYP1A2 inhibitor	• Major: CYP3A4 substrate • Minor: CYP2C9 substrate • In vitro: CYP2C8 inhibitor	• Minor: CYP3A4 substrate • In vitro: BCRP substrate • In vitro: UGT1A1 inhibitor	• Major: CYP3A4 substrate • Minor: BCRP substrate • In vitro: CYP1A2 substrate • In vitro: CYP2C8 weak inhibitor • In vitro: UGT1A1 inhibitor	• Major: CYP3A4 substrate • Minor: UGT1A1 inhibitor • In vitro: CYP2C8 inhibitor • In vitro: CYP2C9 inhibitor • In vitro: CYP3A4 inhibitor • In vitro: UGT1A1 inhibitor • In vitro: CYP2C19 inhibitor • In vitro: UGT1A1 inhibitor • In vitro: CYP2D6 inhibitor	• Major: CYP3A4 substrate • Minor: P-gp inhibitor	• Major: CYP3A4 substrate • Minor: OCT2 inhibitor • In vitro: MATE1/2- K inhibitor	• Major: CYP3A4 substrate • In vitro: BCRP inhibitor	
Additional Pharmacokinetic Drug–Drug interactions	• Not applicable	• Grapefruit juice, Seville oranges, star fruit	• Grapefruit juice, Seville oranges, star fruit		• Proton pump inhibitors	• Caution with BCRP substrates with narrow therapeutic window	• Grapefruit juice, Seville oranges, star fruit	• Avoid dual CYP3A4 and P-gp inducers/inhibitors	• Grapefruit juice, Seville oranges, star fruit	• Grapefruit juice, Seville oranges, star fruit

					• Caution with CYP2D6, CYP2C8 or CYP3A4 substrates with a narrow therapeutic index. • Grapefruit juice, Seville oranges, star fruit	• Grapefruit juice, Seville oranges, star fruit		• Grapefruit juice, Seville oranges, star fruit		
Pharmacodynamic Considerations	• Caution with agents that can increase bleed risk such as antiplatelets, anticoagulants, or medications with antiplatelet or anticoagulant effects such as aspirin, NSAIDs, vitamin E, fish oil, ginseng, omega 3 and omega 6 fatty acids. • Caution with agents that can increase risk of clot such as estrogen-based hormonal therapies. • Caution with androgen hormonal agents can increase hypertensive effect.									
				• Avoid coadministration of medications that prolong QTc	• Avoid coadministration of medications that prolong QTc		• Avoid coadministration of medications that prolong QTc • Increased bleed risk with warfarin	• Avoid coadministration of medications that prolong QTc	• Avoid coadministration of medications that prolong QTc	
Cardiovascular Drug Interaction Clinical Pearls	• Not applicable	• Diltiazem, verapamil, dronedarone may increase concentration of axitinib	• Diltiazem, verapamil, dronedarone may increase concentration of cabozantinib	• Lenvatinib may increase INR. Caution with warfarin	• Pazopanib may increase concentration of simvastatin, dofetilide • Clopidogrel may increase concentration of pazopanib • Carvedilol, dronedarone, verapamil, diltiazem may increase concentrations of pazopanib	• Regorafenib may increase Fluvastatin, rosuvastatin, atorvastatin concentrations • Regorafenib may increase warfarin concentration	• Diltiazem, verapamil, dronedarone may increase concentration of sorafenib • Sorafenib may increase warfarin concentration and INR. • Sorafenib may increase concentration of edoxaban, dabigatran.	• Diltiazem, verapamil, dronedarone may increase concentration of sunitinib • Sunitinib may increase concentration of edoxaban, dabigatran.	• Diltiazem, verapamil, dronedarone may increase concentration of vandetanib • Vandetanib may increase dofetilide concentration • Caution with digoxin • Vandetanib may increase concentrations of edoxaban, dabigatran	• Diltiazem, verapamil, dronedarone may increase concentration of tivozanib

^a M-2 metabolite of regorafenib.

Table 7
Epidermal growth factor receptor inhibitors^{62–67,112–114}

Agent	Afatinib	Dacomitinib	Erlotinib	Gefitinib	Mobocertinib	Osimertinib
Key Cardiovascular Toxicities	[case reports of cardiotoxicity]	[case reports of cardiotoxicity]	• Hemorrhage	[case reports of cardiotoxicity]	• Cardiomyopathy • QTc prolongation	• Cardiomyopathy • QTc prolongation
Metabolic Pharmacokinetic Drug–Drug Interactions	• Major: P-gp substrate • In vitro: BCRP substrate • BCRP inhibitor • P-gp inhibitor	• Major: CYP2D6 inhibitor • Minor: CYP2D6 substrate • In vitro: UGT1A1 inhibitor • BCRP substrate, inhibitor • P-gp substrate, inhibitor • OCT1 inhibitor	• Major: CYP3A4 substrate • CYP1A2 substrate • Minor: CYP3A4 weak inducer	• Major: CYP3A4 substrate • BCRP substrate • Minor: CYP2D6 substrate	• Major: CYP3A4 substrate • Minor: P-gp substrate • CYP3A4 weak inducer • In vitro: P-gp inhibitor • BCRP inhibitor	• Major: CYP3A4 substrate • Minor: BCRP substrate, inhibitor • P-gp substrate, inhibitor • In vitro: CYP1A2 inducer
Additional Pharmacokinetic Drug–Drug Interactions	• None	• Proton pump inhibitors • Histamine 2R antagonists	• Proton pump inhibitors • Histamine 2R antagonists • Antacids • Cigarette smoking can induce CYP1A2 and lower erlotinib concentrations	• Proton pump inhibitors • Histamine 2R antagonists • Antacids • Caution with CYP2D6 inhibitors	• None	• None
Pharmacodynamic Considerations	• None	• None	• Erlotinib can increase INR. In combination with warfarin increase bleed risk • Fenofibrate may decrease erlotinib concentrations	• Gefitinib can increase INR. In combination with warfarin increase bleed risk	• Avoid use of narrow therapeutic window CYP3A4 substrates • Avoid coadministration of medications that can prolong QTc	• Avoid coadministration of medications that can prolong QTc

Cardiovascular Drug Interaction Clinical Pearls	• Carvedilol, verapamil, amiodarone, dronedarone may increase concentrations of afatinib	• Dacomitinib may increase carvedilol, flecainide, metoprolol, nebivolol, propafenone, propranolol concentrations	• Amiodarone may increase erlotinib concentrations • Erlotinib may decrease concentration of nimodipine	• Quinidine may increase gefitinib concentration • Diltiazem, verapamil, dronedarone may increase gefitinib concentration	• Available through compassionate use only post March 2024 • Diltiazem, verapamil, dronedarone may increase mobocertinib concentration	• Diltiazem, verapamil, dronedarone may increase osimertinib concentration • Osimertinib may increase concentrations of rosuvastatin • Caution with digoxin • Osimertinib may increase concentrations of edoxaban and dabigatran
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and amiodarone should be avoided.⁶⁶ Dacomitinib is a strong CYP2D6 inhibitor.⁶⁷ Thus, initiations of flecainide and propafenone should be avoided, and initiations of the CYP2D6 substrates metoprolol, nebivolol, carvedilol, and propranolol should be started at low doses and titrated based on a patient’s tolerability.² Due to the risk of QTc prolongation, patients initiating osimertinib or mobocertinib should have an ECG performed at baseline and medications that can contribute to additive QT interval prolongation risk should be minimized.^{64,65}

Antimetabolites: Fluorouracil and Capecitabine

Fluorouracil is a pyrimidine analog that incorporates into DNA and disrupts mitosis of rapidly dividing cells.⁶⁸ Capecitabine is an oral prodrug of fluorouracil. Both agents have multiple FDA-approved indications including, but not limited to, gastrointestinal malignancies, urologic cancers, gynecologic malignancies, and breast cancer.^{68,69} Cardiotoxicity of these agents can present as angina, coronary vasospasm, ischemia, arrhythmia, and potentially cardiomyopathy.^{68–70} In terms of pharmacokinetic interactions, both fluorouracil and capecitabine are weak inhibitors of CYP2C9^{68,69} (Table 8). This is important for narrow therapeutic drugs such as warfarin that rely on CYP2C9 for proper metabolism. The effect on INR may be delayed and last a few weeks after initiation of fluorouracil-based treatment.⁷¹ Due to this DI, the FDA has placed a boxed warning in the capecitabine label.⁶⁹ Ideally warfarin alternatives would be used. If unable to avoid the DI, then patients should have INR checked more frequently with appropriate adjustments made to their warfarin regimen.⁷¹

Breakpoint Cluster Region-Abelson (BCR-ABL) Inhibitors

The BCR-ABL inhibitors are TKIs FDA approved to treat chronic myeloid leukemia and some are also used to treat Philadelphia chromosome-positive acute lymphoblastic leukemia.⁷² Each BCR-ABL inhibitor has multiple off-target affinities that are hypothesized to be the cause of their diverse toxicities.⁷³ Cardiotoxic manifestations vary between agents within this class and include arterial thromboembolic events, ischemia, arrhythmias, hemorrhage, pericardial and pleural effusions, hypertension, pulmonary hypertension, and heart failure.^{1,73}

Imatinib is primarily metabolized by CYP3A4; however, a pharmacokinetic study performed with a strong CYP3A4 inhibitor demonstrated a 40% increase in area under the curve⁷⁴ (Table 9). Thus, concomitant use of CYP3A4 inhibitors should be used with caution and monitored for imatinib-associated toxicities. Imatinib exhibits autoinhibition of CYP3A4 and has the potential to increase blood concentrations of CYP3A4 substrates. This may be significant for some CYP3A4 substrates as simvastatin concentrations were increased 3.5-fold when administered with imatinib.⁷⁴ Caution and monitoring should be utilized for therapy initiations of CYP3A4 substrates such as ticagrelor, amiodarone, sildenafil, and atorvastatin, among others.² Imatinib also acts as a CYP2C9 and CYP2D6 inhibitor.⁷⁴ Thus, alternatives to warfarin, which is metabolized by CYP3A4 and CYP2C9, are recommended. Caution and increased monitoring should be utilized when initiating CYP2D6 substrates such as flecainide, propafenone, metoprolol, carvedilol, or nebivolol.²

Table 8 Antimetabolites ^{68,69,115–117}		
Agent	Fluorouracil (5-FU)	Capecitabine
Key Cardiovascular Toxicities	• Angina • Heart failure • QTc prolongation • Ischemic events • Arrhythmias	
Metabolic Pharmacokinetic Drug–Drug interactions	• CYP2C9 weak inhibitor	
Additional Pharmacokinetic Drug–Drug interactions	• Dihydropyrimidine dehydrogenase (DPD) deficiency can increase in fluorouracil and capecitabine concentrations	
Pharmacodynamic Considerations	• Leucovorin inhibits thymidylate synthase	
Cardiovascular Drug Interaction Clinical Pearls	• Caution with warfarin	

Table 9
Breakpoint cluster region-Abselson tyrosine kinase inhibitors^{74–80,106,118–122}

Agent	Imatinib	Dasatinib	Nilotinib	Bosutinib	Ponatinib	Asciminib
Key Cardiovascular Toxicities	- Heart failure - Fluid retention: pericardial, pleural effusions - Bleed risk, hemorrhage	- Arterial thrombo-embolic events - Heart failure - Fluid retention: pericardial, pleural effusions - Pulmonary arterial hypertension - QTc prolongation - Bleed risk, hemorrhage, particularly GI bleed	- QTc prolongation, sudden death - Arterial thrombo-embolic events - Fluid retention: pericardial, pleural effusions - Bleed risk, hemorrhage	- Ischemic events - Heart failure - Fluid retention: pericardial, pleural effusions	- Arterial thrombo-embolic events - Venous thrombo-embolic events - Heart failure - Arrhythmias - Fluid retention - Hypertension - Bleed risk, hemorrhage	- Arterial thrombo-embolic events - Venous thrombo-embolic events - Hypertension - Heart failure - QTc prolongation
Metabolic Pharmacokinetic Drug–Drug interactions	- Major: CYP3A4 substrate, CYP3A4 inhibitor - Minor: CYP2C9 substrate, CYP2C9 inhibitor, CYP2D6 substrate, CYP2D6 inhibitor, CYP3A5 inhibitor, P-gp substrate	- Major: CYP3A4 substrate, P-gp substrate, BCRP substrate - Minor: CYP3A4 inhibitor, time dependent	- Major: CYP3A4 substrate, CYP3A4 moderate inhibitor - Minor: P-gp substrate, CYP2C8 substrate <i>In vitro</i>: CYP2C8 inhibitor, CYP2D6 inhibitor, CYP2B6 inducer, CYP2C8 inducer, UGT1A1 inhibitor, P-gp inhibitor	- Major: CYP3A4 substrate, P-gp Sub <i>In vitro</i>: Intestinal BCRP inhibitor	- Major: CYP3A4 substrate - Minor: CYP2D6 substrate, CYP2C8 substrate <i>In vitro</i>: P-gp substrate, inhibitor, BCRP substrate, inhibitor, BSEP inhibitor	- Major: CYP3A4 substrate, CYP3A4 inhibitor, CYP2C9 inhibitor, P-gp inhibitor - Minor: OATP1B inhibitor, BCRP inhibitor <i>In vitro</i>: UGT1A1 inhibitor, CYP2C19 inhibitor, concentration dependent

(continued on next page)

Table 9
(continued)

Agent	Imatinib	Dasatinib	Nilotinib	Bosutinib	Ponatinib	Asciminib
Additional Pharmacokinetic Drug–Drug interactions	- Caution and monitoring with CYP2D6 or CYP2C9 substrates that are narrow therapeutic index drugs - Grapefruit juice, Seville oranges, star fruit	- Proton pump inhibitors - Histamine 2R antagonists - Antacids - Grapefruit juice, Seville oranges, star fruit	- Proton pump inhibitors - Histamine 2R antagonists - Antacids - Grapefruit juice, Seville oranges, star fruit	- Proton pump inhibitors - Histamine 2R antagonists - Grapefruit juice, Seville oranges, star fruit	- Monitor if co-administered with P-gp or BCRP substrates - Avoid use of strong inhibitors or inducers of P-gp or BCRP - Grapefruit juice, Seville oranges, star fruit	Avoid coadministration with medications that include cyclodextrin excipient as can decrease plasma concentrations of asciminib Grapefruit juice, Seville oranges, star fruit
Pharmacodynamic Considerations	- Caution with agents that can increase bleed risk such as antiplatelets, anticoagulants, or medications with antiplatelet or anticoagulant effects such as aspirin, NSAIDs, vitamin E, fish oil, ginseng, omega 3, and omega 6 fatty acids. - Caution with agents that can increase risk of clot such as estrogen-based hormonal therapies					
		Avoid concomitant QTc prolonging medications	Avoid concomitant QTc prolonging medications			Avoid concomitant QTc prolonging medications
Cardiovascular Drug Interaction Clinical Pearls	- Warfarin should be avoided - Imatinib may increase amiodarone, dronedarone, lovastatin, amlodipine, atorvastatin, diltiazem, verapamil, dofetilide, ivabradine, eplerenone, ticagrelor concentrations - Imatinib may decrease ticagrelor metabolite concentration	Diltiazem, verapamil, dronedarone may increase dasatinib concentration. Dronedarone should be avoided due to QTc prolongation risk	- Nilotinib may increase concentration of amiodarone, dronedarone, lovastatin, amlodipine, atorvastatin, diltiazem, verapamil, dofetilide, ivabradine, eplerenone, ticagrelor concentrations - Nilotinib may decrease ticagrelor metabolite concentration	Diltiazem, verapamil, dronedarone may increase bosutinib concentration.	Diltiazem, verapamil, dronedarone may increase ponatinib concentration.	- Warfarin should be avoided - Asciminib may increase concentrations of atorvastatin, rosuvastatin, fluvastatin, simvastatin, carvedilol, dofetilide, Co-administration of asciminib with either rosuvastatin or atorvastatin should be avoided

- Imatinib may increase concentration of apixaban, rivaroxaban. Consider adjustment if in combination with P-gp inhibitor

- Nilotinib may increase concentration of apixaban and rivaroxaban. Consider adjustment if in combination with P-gp inhibitor

Dasatinib, nilotinib, and ponatinib are all metabolized by CYP3A4 and are significantly affected by CYP3A4 inhibitors.^{75–77} CYP3A4 inhibitors such as dronedarone and the non-dihydropyridine calcium channel blockers verapamil and diltiazem should be either avoided or doses of BCR-ABL inhibitor reduced.^{2,75–77} Additionally, it is important to avoid the concomitant use of QTc prolonging medications such as amiodarone, dronedarone, sotalol, or dofetilide with dasatinib and nilotinib. Due to the sudden deaths that have been reported, the FDA has designated a boxed warning for QTc prolongation for nilotinib.⁷⁶ All patients should have an ECG performed prior to nilotinib initiation and periodically monitored throughout therapy. Similar to imatinib, nilotinib also has the potential to inhibit CYP3A4 as well.⁷⁶ Caution is advised with CYP3A4 substrates like atorvastatin, diltiazem, and ivabradine, among others that may be increased when used concomitantly with nilotinib.

Asciminib is a major CYP3A4 substrate, but concomitant therapy with strong CYP3A4 inhibitors may not have clinically meaningful effects on drug concentration.^{78,79} Thus, monitoring should be utilized for patients who necessitate concomitant therapy. Asciminib also has the potential to inhibit CYP3A4 and is a CYP2C9 inhibitor. Thus, medications with narrow therapeutic indices, such as warfarin, that require either CYP3A4 or CYP2C9 or both for metabolism should be avoided.⁷⁸ Caution and monitoring are advised with CYP2C9 substrates such as losartan, irbesartan, and candesartan.² Asciminib may also increase concentrations of rosuvastatin and atorvastatin, and thus, their combination is recommended to be avoided.⁷⁸ Additionally, absorption of the BCR-ABL TKIs is pH dependent and gastric acid suppression may have a large impact on serum concentrations and potentially efficacy.^{75,76,80}

SUMMARY

The growth of targeted therapies has expanded treatment options for patients with cancer but has added complexity of DIs and side effects that may increase cardiovascular risk. This review highlights a sample of medications and their potential for pharmacokinetic and pharmacodynamic interactions commonly seen in the cardio-oncology clinic. The importance of identifying and managing these interactions is essential to safe and efficacious care. A study by van Leeuwen and colleagues⁸¹ found that at least 27% of patients with cancer had at least one clinically meaningful DI that necessitated either a physician or pharmacist intervention. Another

assessment by Wolf and colleagues⁸² estimated that over 60% of patients with cancer had at least one major DI between cancer therapies and medications for comorbidities. Most prominent DIs identified included additive risk of QTc prolongation, CYP3A4 DIs, and additive bleed risk.⁸² These reports underscore the need for appropriate dosing and monitoring in the setting of potential DIs and complex patient medication management.

Most DI information is extrapolated from *in vitro* and *in vivo* assessments of known enzymatic inhibitors and inducers. Thus, unless an exact combination of agents has been tested, it is difficult to predict how a combination may impact exact pharmacokinetic or pharmacodynamic relationships. PBPK modeling is currently used to account for the complexity of metabolism, organ function, and transport systems that may affect drug disposition. PBPK models may allow for more combination of agents to be assessed and better inform interaction potential.⁵

For the multidisciplinary clinic, DI evaluations can be incorporated into daily practice.^{1,83} Across the spectrum of care for the patient with cardio-oncology, it is important to ensure that a pharmacist can be engaged as a member of the care team. The pharmacists, especially those with expertise in oncology and cardiology, have the training and scope to be able to identify, rationalize, and address pharmacodynamic and pharmacokinetic DIs for patient-specific needs. The pharmacist can provide recommendations for appropriate dose modifications, agents to avoid, how and how often to monitor, and develop alternative therapy plans. Synthesizing data available from multiple drug resources and primary literature will help providers efficiently recognize DIs. Use of drug tertiary resources, such as UpToDate®/Lexidrug™ (formerly Lexicomp®) or Micromedex®, and the package insert can be a starting point to determine any known DIs. However, given the evolving nature of clinical science, clinicians should also do a quick search through the primary literature via PubMed to assess any pharmacokinetic studies completed as well as DI management specified in clinical trials. This can be helpful as patients may be on an oncologic therapy chronically and new drug interactions can be identified after approval.

Multidisciplinary clinics can offer patient-specific recommendations and develop individualized monitoring plans by considering concomitant medications, patient comorbidities, organ function, and goals of care. If appropriate, medication changes should be made to avoid major or potentially harmful DIs and minimize cardiotoxicity.

Checklists can be incorporated into each visit to ensure medications are being reviewed frequently and adjusted when needed. As clinics create and implement strategies to minimize DIs and cardiotoxic risk within a multidisciplinary structure, it will be important to share successful experiences and measure the outcomes of such initiatives.

CLINICS CARE POINTS

- Having familiarity with and a proficient understanding of pertinent drug interactions is essential to optimizing pharmacotherapy regimens and minimizing potential cardiotoxic adverse effects for the cardio-oncology patient.
- When assessing for drug-drug interactions, check multiple sources to help guide dosing decisions. These sources include tertiary resources, FDA package inserts, clinical trial protocols, and primary literature for published PK or PD studies or case reports.
- In your assessment, include considerations for patient specific factors such as past medical history when optimizing drug regimens and creating monitoring plans.

DISCLOSURE

The authors have nothing to disclose.

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Cardio-Oncology Program Building: A Practical Guide



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KEYWORDS

- Cardio-oncology program • Cardio-oncology clinic • Integrated care • Health care system
- Chemotherapy • Cardiovascular toxicity • Prevention • Cardiac imaging

KEY POINTS

- Building a multidisciplinary program can be a challenging and complicated endeavor owing to the complexity of integration across disciplines and the significant investment in infrastructure, personnel, and funding.
- Organizing a cardio-oncology program and clinic involves careful planning and coordination to address the complex needs of patients who are dealing with 2 of the most serious health issues: cancer and heart disease.
- All components of cardio-oncology programs are patient-centered with attention to individual needs and clear communication of care plans with patients and their families.
- The emphasis is on delivering multidisciplinary, tailored care that recognizes and treats the cardiovascular side effects of cancer treatments without compromising oncological efficacy.

The organization of a cardio-oncology clinic and building of an overall program focus on providing comprehensive cardiovascular care to patients who are at risk of or have developed cardiovascular sequelae during or following cancer treatments. With the growth and evolution of the field of cardio-oncology, the traditional model of a single cardio-oncology clinic may no longer be adequate to meet patients' needs¹ (Fig. 1). In a contemporary setting cardio-oncology represents a component of overall cancer care, requires cardiovascular expertise along the spectrum of the cancer continuum, from diagnosis through survivorship, and must be integrative and collaborative with oncology.

Over 2 million new cancer cases are expected to be diagnosed in the United States in 2024, with cancer as the second leading cause of death behind cardiovascular disease.² As of 2022, there were an estimated 18 million survivors of cancer in the United States, expected to grow to 26 million by 2040.³ At the same time, growing cardiovascular disease burden in the aging population may act in synergy and result in a higher risk of treatment-related adverse effects.^{4,5} The prevalence of cancer, aging, and higher risk population of patients receiving cancer therapies, highlight the burgeoning need for expertise in cardiovascular care of these patients.

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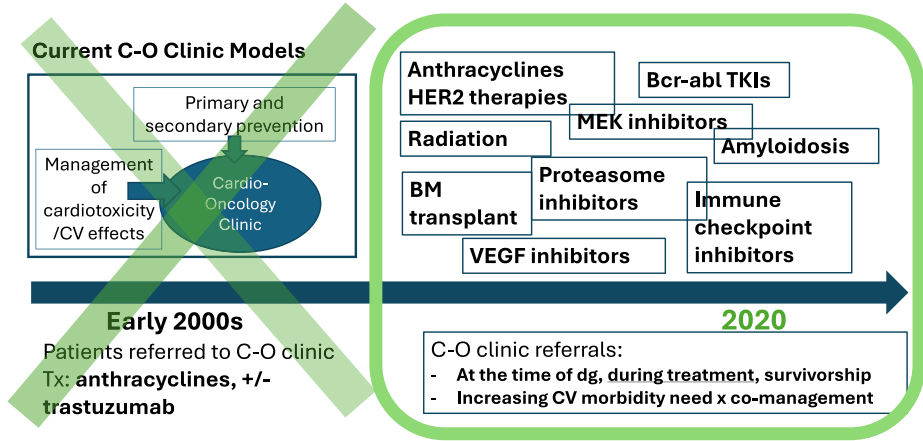


Fig. 1. Increased complexities of cardiovascular effects of cancer treatment in contemporary cardio-oncology program.

Modern oncology practice is characterized by multitudes of oncology therapeutics, from conventional chemotherapy to agents targeting kinases, proteasomes, and the immune system, all of which may be given in combination and with other treatment modalities such as radiation.⁶ The historical concept of cardiac toxicity, mainly involving anthracycline- and radiation-related cardiac injury, is now in many ways overshadowed by a wide array of newer, targeted therapies as well as the need for the treatment of older patients with significant preexisting cardiovascular morbidity. In turn, we face a growing diversity and complexity of cardiovascular toxicities presenting in a larger and higher risk population of patients.

Therefore, the premise of providing comprehensive cardiovascular care before, during, and after cancer treatment, increasingly requires the creation of integrated programs linking oncology and cardiovascular specialists and subspecialists and, in health care systems, dedicated service lines (Fig. 2). In this article, we summarize the core components of a contemporary cardio-oncology program, including its core members (cardiologists, oncologists, clinical pharmacists, advanced practice providers, nurses, and coordinators), key

services (risk assessment, treatment planning, cardiac imaging, intervention, and management), and practical integration within the health care system.

CORE PEOPLE AND TEAMS: THE BUILDING BLOCKS OF A CARDIO-ONCOLOGY PROGRAM

Multidisciplinary collaboration and a team-based approach are at the core of cardio-oncology. The cardiologists, oncologists (medical, radiation, and surgical), hematologists, pharmacists, nurses, and advanced practice providers all play critical roles to ensure a coordinated approach to the overall care of patients with cancer. In addition, specialized teams, such as heart failure, palliative care, structural heart, and others, often have representation in patient management.

Cardiologists in the cardio-oncology program have expertise and often specialized training in the acute and chronic cardiovascular effects of oncologic therapies and provide guidance throughout the trajectory of cancer care, including pretreatment evaluation with a comprehensive cardiovascular risk assessment, optimization of pre-existing cardiovascular conditions, management,

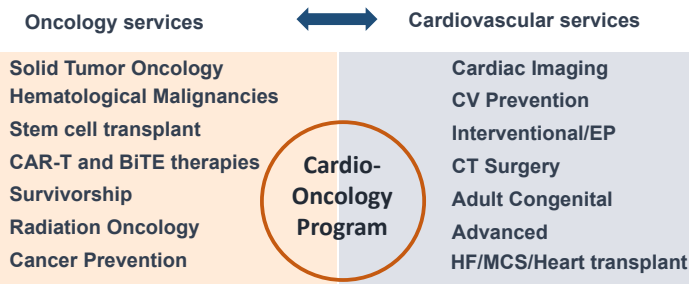


Fig. 2. Integrated model of cardio-oncology program in a center with cardiovascular and oncology service lines. BiTE, bispecific T-cell engager therapy; CAR-T, chimeric antigen receptor T-cell therapy; CV, cardiovascular; EP, electrophysiology; HF, heart failure; MCS, mechanical circulatory support.

and ongoing risk monitoring. In this article, we utilize the term cardiologist and cardio-oncologist (referring to a cardiovascular specialist with expertise in the cardiovascular care of oncology patients) interchangeably, recognizing their primary focus on cardiovascular health. They participate in multidisciplinary decision making and provide cardiovascular input regarding continuation, alteration, or cessation of cancer therapies based on risk.

Referrals to cardio-oncology clinic include a diverse group of patients throughout the spectrum of cancer care with a vast array of potential cardiovascular toxicities, including cardiomyopathy and heart failure, arrhythmias and QT-prolongation, coronary artery disease, valvular heart disease, pericardial disease, hypertension (HTN), and arterial and venous thromboembolism.⁶ Specialists in cardio-oncology may serve as or work with other cardiology subspecialists (cardiac imaging, advanced heart failure, electrophysiology, and interventional cardiology specialists as well as cardiothoracic surgeons) in managing patients and in establishing subspecialized cardio-oncology protocols for patient care. Examples include creation of echocardiographic, cardiac magnetic resonance (CMR), and cardiac computed tomography (CCT) imaging protocols focused on diagnosis of cardiovascular toxicities and blood pressure management protocols for patients receiving vascular endothelial growth factor (VEGF) inhibitors. In addition to pharmacotherapy, cardiologists advise patients on lifestyle modifications to mitigate cardiovascular risks. Cardiologists work closely with the patient's oncology team in choosing or modifying cancer treatments to minimize cardiotoxicity and in balancing the effectiveness of cancer treatment with cardiovascular safety. They participate and lead clinical trials aimed at finding more effective ways to prevent or treat cardiotoxicity. Cardiologists participate in multidisciplinary case conferences including tumor boards to discuss complex patient cases involving cardiovascular pathology and develop comprehensive care plans with oncology. During survivorship, they provide a long-term cardiovascular care and assure monitoring for late-onset cardiovascular effects of cancer treatment. Finally, cardiologists lead cardiovascular disease prevention and health promotion in the cancer survivor population as well as in patients living with cancer.

Oncology care delivery might vary based on setting. For example, in private practice models or outside of academic centers, oncologists might care for patients across broader facets of hematology and oncology, whereas in tertiary centers, practice is often highly subspecialized. This is

relevant for cardiovascular care as clinical flows may differ and referrals and communication pathways need to be developed with the local oncology practice type in mind. Medical oncologists play a primary role in shared decision making with a patient regarding the choice of anticancer therapy and the balance of cancer survival with toxicity risks. This includes a plan for cardiac function monitoring for select therapies such as anthracyclines and Human Epidermal Growth Factor 2 (HER-2) targeted agents, and discussion of different toxicities that occur with immunotherapies and targeted agents.

When choosing a cancer treatment plan with a patient, the medical oncologist determines the goal of treatment (cure/eradication of cancer or control/prolongation of life) as well as the estimated benefit of the different treatment options. It is important to note that definitions of cure continue to evolve and in addition to statistical cure (when risk of dying or relapsing has become equal to the mortality of age-matched population), personal cure (a patient dying of a disease other than their cancer), and psychological cure (a patient feeling the chances of their disease returning is sufficiently low to consider themselves effectively cured) are being used.⁷ Further, targeted treatments are increasingly given in a chronic fashion and new and emerging treatment options across many cancers rapidly change prognosis and survival estimates in many cancers. The central role of the oncologist on the multidisciplinary team is to develop an individualized cancer treatment plan taking into account any preexisting comorbidities as well as patient preferences after discussion of the risks and benefits of the treatment.

The oncologists also inform and educate the entire team about the goals of therapy, its expected benefit, and the approach to adverse events. Given the vast array of potential toxicities with modern cancer treatments, oncologists work closely with many specialists to prevent and manage short- and long-term adverse effects. In the setting of a cardio-oncology program, this often includes providing input into creation and guiding implementation of cardiovascular risk stratification and cardiac toxicity monitoring protocols (eg, echocardiographic screening, blood pressure monitoring, and managing patients with manifest toxicities).

Pharmacists are well positioned to be members of the interdisciplinary cardio-oncology clinical team. As medication experts, pharmacists have a comprehensive understanding of both the complex pharmacology of cancer therapies and the mechanisms of cardiovascular medications

used to manage cardiovascular conditions. The involvement of cardiology pharmacists improves guideline-directed medication therapy use and adherence for patients with heart failure and coronary artery disease. Their involvement has been shown to improve patient outcomes and reduce cardiovascular readmission rates.^{8–10} For the care of patients with cancer, oncology pharmacists improve supportive care and side effect management, patient education, selection and dosing of appropriate treatment regimens, toxicity monitoring and management, and patient adherence to oral regimens.^{11,12} Despite the value added within these specialties, the role of pharmacists within a cardio-oncology clinic is not well-defined. In a Canadian survey of eight pharmacists in varied specialties who care for patients at risk for cancer associated cardiac toxicity, the majority of respondents endorsed a lack of role recognition for pharmacists within the cardio-oncology space.¹³ The authors suggested the creation of a community of practice for pharmacists with cardio-oncology interests to share approaches to care and promote collaboration.¹³ In fact, the 2022 European Society of Cardiology Consensus Guideline highlights the need for research on practice models to help define and support the role of a pharmacist in the cardio-oncology clinic.¹⁴

In 2022, Yaseen and colleagues published their one-year experience working collaboratively with an embedded cardiology clinical pharmacist in a cardio-oncology clinic in Iraq.¹⁵ In this model, past medical and medication history, cardiac labs, and imaging were collected at an initial visit. The cardiology pharmacist then recommended appropriate pharmacologic interventions including identifying and modifying medications to account for drug–drug interactions, avoidance of duplicative therapies, and tailoring of cardiovascular therapies for patient-specific needs. The pharmacist also utilized telemedicine interventions to provide education, medication management, and follow-up monitoring for patients at home. Their data demonstrated that 75% of the clinical interventions were made by the pharmacist.¹⁵ The most prevalent type of intervention was initiating guideline-directed and evidence-based therapies, most commonly for hypertension or chemotherapy-related cardiac dysfunction. In a follow-up report, the authors describe three patients for whom the pharmacist recognized new signs and symptoms of cancer therapy-induced cardiotoxicity and appropriately triaged their care to the cardiologist for evaluation.¹⁶

While limited, available data underscore the value a cardio-oncology clinical pharmacist can provide to a multidisciplinary cardio-oncology

program. Pharmacists can provide evidence-based recommendations for medication initiation or optimization, ensure safety of dosing, identify toxicities, and identify drug–drug interactions, such as ones between non-dihydropyridine calcium channel blockers and VEGF inhibitors or FLT3 inhibitors and QTc prolonging medications. In addition, pharmacists develop individualized monitoring plans for patients such as those necessitating concomitant use of anticoagulants and Bruton's Tyrosine Kinase (BTK) inhibitors. In addition to drug interaction identification and monitoring plan creation, pharmacist input is integral for developing management guidelines and protocols within the cardio-oncology clinic. Some examples could include, but are not limited to, considerations for dexrazoxane administration or cardioprotective agents in patients receiving anthracyclines, creation of regimens to help prevent recurrent vasospasms in patients necessitating fluorouracil, and protocols for baseline cardiovascular risk evaluation for patients starting Breakpoint Cluster Region-Abelson (BCR-ABL) or Bruton kinase (BTK) inhibitors. Pharmacists can leverage the electronic medical record for remote monitoring to improve medication adherence and to facilitate patient counseling (**Box 1**)¹⁷ They can also ensure patients are receiving appropriate monitoring with cardiac laboratory testing and imaging. Cardio-oncology clinical pharmacists can be involved in clinical research and quality improvement initiatives that lead to improved outcomes and success of the cardio-oncology clinic. Active involvement will help to mend the evidence gap, support a community of cardio-oncology pharmacists, and establish the role of a pharmacist in dedicated cardio-oncology clinics.

Nurse navigators play an integral role within a cardio-oncology program. They contribute to patient care throughout the entire journey by mitigating the complexities of clinical care navigation, identifying gaps in patient care, and empowering patients through resources and education relevant to their care. Whether termed “nurse navigator” or “nurse coordinator,” a nurse in a cardio-oncology program works to ensure patient access, facilitate care navigation, and shared opportunities for informed decision making with the patient care team. Serving as a bridge between patients, oncology, and cardiology providers, nurse navigators enhance the quality of care and health outcomes in a cardio-oncology clinic.^{18–20}

As a valuable resource, a nurse navigator understands the flow of the patient care path which enables them to address the patient's individual needs while providing timely care coordination. As an advocate, the navigator amplifies the desires

Box 1**Tools within the electronic medical record****Remote Monitoring and Patient Engagement**

- Telemedicine virtual visits can allow more frequent contact with clinic team
- Patient portal for communication, patient education, and remote monitoring
- Secure portal for uploading of patient's home monitoring records including biometric data devices

Clinical Decision Support

- Smart sets for easy order retrieval
- Triggered passive or active alerts for reminders of upcoming ECHO, ECG laboratory needs
- Integrating advanced order groups cardio-oncology monitoring into the patient's oncology treatment plan

Care Pathways

- Establish cardio-oncology referral paradigm
- Integrate guidance for cardiovascular monitoring
- Embed links to open clinical trials and automated screening for eligibility criteria

Customized Dashboard Generation

- Generate customized informational or monitoring reports
- Coordinate routine cardiovascular monitoring reminders and appointments

Adapted from recommendations in Kao DP, Trinkley KE, Lin CT. Heart failure management innovation enabled by electronic health records. JACC: Heart Failure. 2020;8(3):223–233. <https://doi.org/10.1016/j.jchf.2019.09.008>.

of the patient and caregivers, addressing their psychosocial needs. The involvement of nurse navigators within a cardio-oncology program helps advance the priorities of early identification and stratification of high-risk patients, the streamlining of referrals to cardio-oncology providers, ensuring timely and appropriate testing, and fostering effective communication between patients and providers.^{21–23} With these roles in mind, nurse navigators assist in advancing the mission of cardio-oncology, including minimizing interruption of discontinuation of cancer therapies and improving quality of life and overall cancer and cardiac survival.

In a practical sense, a nurse navigator might be physically located within the oncology practices,

to best facilitate patient identification, streamline cardiac testing, provide timely and onsite education to oncology providers and patients, and resolve clinical dilemmas that might interfere with clinical care. This includes access barriers, such as understanding the burden of financial toxicity and constraints related to travel and loss of work, for the patient as well as for their support team. A knowledgeable nurse trained in cardio-oncology can assist in developing order sets, protocols, and algorithms that support cardio-oncology care pathways. The success of the cardio-oncology navigator is multifaceted and has proven to be a value role in improving patient satisfaction and clinical outcomes. Examples of nurse navigator roles can be found in **Table 1**.

Advanced Practice Providers

The involvement of advance practice providers (APPs) enhances the quality and delivery of care both in oncology^{21,23} and cardiology.²² Within cardiology practices, APPs can improve outcomes by utilizing a team-based approach in primary prevention and by increasing access and timeliness of care delivery in advanced heart failure.²⁴ With the complexity of care navigation and need for delivery of timely and specialized cardiac care to patients with cancer, APPs are increasingly becoming key members of the cardio-oncology programs.

APPs provide a strong support system for physicians and their role involves delivery of patient care throughout the continuum of cancer care before, during, and after cancer therapy (see **Table 1**). Pre-therapy, they assist in cardiovascular risk assessment and implementation of primary prevention strategies including management of uncontrolled risk factors and recommendations for cardiac testing. APPs often follow the results of the surveillance strategies and initiate cardioprotective pharmacotherapy. During cancer therapy, APPs assist with diagnosis and symptoms management, assuring appropriate and timely follow-up, particularly in higher risk cases where more frequent visits might be beneficial (ie, acute heart failure, myocarditis). Examples of APP leadership roles in cardio-oncology clinic include hypertension clinics (VEGF/hypertension), prevention and weight management clinic, as well as in pre-hematopoietic and post-hematopoietic stem cell transplant evaluation, etc. APPs provide education to patients and caregivers and, with their counterparts in oncology, play a major role in optimizing cardio-oncology clinic flow aligned with cancer care.

Table 1 Nursing and advanced practice providers' roles in a cardio-oncology clinic		
Tasks	Nurse Navigators	Advanced Practice Providers
Clinical Patient Care Tasks	• Participate in identification of patients at high risk (eg, identifying patients with CV burden, decreased cardiac function) via chart reviews • Coordinate timely service delivery including diagnostic and surveillance testing • Assist with social economic needs and services within patients' community	• Participate and lead subspecialty cardio-oncology clinics (eg, hypertension monitoring, prevention, weight management, CHIP) • Assist with titration of meds to ensure optimization of GDMT • Enhance access including utilization of tele-visits and rounding visits when the patient is receiving treatments
Provider Education	• Work with oncology nurses, oncology nurse navigators, and infusion nurses on implementation of cardio-oncology protocols • Educate cardiology diagnostic and cardiac care staff about cancer care and treatments	• Conduct new and follow-up clinical patient visits (thus increasing bandwidth for emergency visits) • Partner with oncology APP to facilitate bidirectional knowledge and collaboration in care delivery
Patient Education	• Participate in patient/family caregiver education regarding signs/symptoms of cardiac toxicity tailored to individual cancer therapy (eg, give instructions to patients on when/what to call for) • Provide educational material based on their identified learning needs. • Identify local socioeconomic support services and connect them with the patients in need	• Follow-up on the results of testing (eg, imaging, event monitoring, biomarkers) • Plan the continued care based on results, including the need for surveillance testing • Provide guidance to patients about monitoring (eg, blood pressure, weight monitoring, symptoms) and reporting
Partnership	• Partner with clinical teams to assure timely and appropriate CO scheduling triage • Collect data about the program performance and assist in planning growth and sustainability • Work with CO committee to identify gaps and solutions to improve coordination and delivery of services	• Create and implement interdepartmental workflow protocols • Collaborate with oncology team members in patient management • Partner and communicate with the ED and inpatient teams to assure continuity of care and coordinate management plan
Identification of Clinical Needs	• Assist with scheduling of cardiac diagnostic testing (eg, ECG, ECHO, CMR/CCT) • Identify the need for ongoing surveillance and facilitate timely planning and scheduling close to home (eg, cardiac imaging and/or laboratory testing)	• Follow-up on testing results (imaging/biomarkers) and identify potential need for changes in monitoring or intervention • Communicate the plan with the patient and the oncology team
Assistance with Workflow	• Assist with creation and dissemination of interdepartmental work-flow protocols • Participate in the CO committee with other key members of the care team	• Assist with implementation of interdepartmental work-flow protocols across services • Participate in the CO committee and assist in creation of workflow protocols

Abbreviations: APP, advance practice providers; CCT, cardiac computed tomography; CHIP, clonal hematopoiesis of indeterminate potential; CMR, cardiac magnetic resonance; CO, cardio-oncology; CV, cardiovascular; ECG, electrocardiogram; ECHO, echocardiogram; ED, emergency department; GDMT, guideline directed medical therapy.

KEY SERVICES, WORKFLOW, AND INTEGRATION WITHIN HEALTH CARE SYSTEM

Risk Assessment: Defining the Cardio-Oncology Patient Population and Building Referral Pathways

The identification of individuals who would benefit from screening, surveillance, diagnostics, and therapy of cardiac-related disorders as they intersect with cancer is essential to the success of developing a cardio-oncology program. Cardio-oncology involvement will be beneficial for a wide range of patients, including those who have established cardiovascular disease or preexisting risk factors during active cancer treatment or into survivorship; those who have cardiovascular complications because of cancer therapies; those who have cardiovascular symptoms during or after cancer therapy; and survivors of cancers that occurred in childhood or early adulthood. Risk stratification, which takes into account criteria related to both patients and treatments, is the essential component of the referral algorithm. Older age, a larger load of cardiovascular (CV) risk factors (eg, Type II Diabetes Mellitus, HTN, vascular disease, cardiomyopathy, etc.), or a history of cardiovascular disease (CVD) are all associated with higher risk. High risk treatment-related characteristics may be linked to the use of a range of medications, including anthracyclines, anti-HER2 therapies, VEGF inhibitors, proteasome inhibitors, Epidermal Growth Factor Receptor (EGFR) inhibitors, radiation therapy, and in certain situations, immunotherapy.

The European Society of Cardiology has published proformas for several cancer therapy agents that can be used to risk stratify patients and inform referral decisions.²⁵ There is considerable variation in referral needs and patterns within oncology practices. For example, patients in a breast cancer practice might benefit from referral when planned for anthracycline/trastuzumab $\pm$ immunotherapy at otherwise elevated cardiovascular risk. Breast cancer patients with decrement in left ventricular function during treatment are considered at risk and should be referred immediately, as early identification and management can avoid interruptions in cancer therapy. Thoracic oncology patients may be high risk owing to preexisting CV disease or risk factors, certain agents including osimertinib,²⁶ and the use of thoracic radiation. Patients with hematologic malignancies often receive high doses of anthracycline chemotherapy, and patients undergoing stem cell transplantation are at high risk for arrhythmia and heart failure. Patients receiving hormonal modulating therapies, such as those with genitourinary and breast malignancies might

benefit from early referral to preventive cardiology for risk factor modification including lipid management and hypertension control. Being mindful of bandwidth and clinic availability, referrals should be tailored with respect to urgency, being mindful of the importance of avoiding treatment interruption and oncology outcomes. Importantly, effective referral pathways to a cardio-oncology program should tailor to the specific needs of individual oncology practices, and availability of providers should take into account the urgency of referral and cardiac imaging.

In summary, the effectiveness of cardio-oncology program is dependent on (1) identification of patients who are at high risk (through appropriate screening or surveillance) and (2) timely referral, diagnosis, and treatment of cardiovascular issues, with ongoing oncology treatment. The keystone of the referral algorithm is risk stratification, which considers factors pertaining to both patients and therapies (Fig. 3). Patients who have established cardiovascular disease or preexisting risk factors during active cancer treatment or into survivorship, as well as those who experience cardiovascular complications from cancer therapies, cardiovascular symptoms during or after cancer therapy, and survivors of childhood or early adult cancers, will all benefit from cardio-oncology involvement. Cardio-oncology should be consulted as soon as possible for patients whose cardiovascular risks are deemed to be moderate to high.

Cardiovascular Imaging in Cardio-Oncology Program

Early diagnosis and monitoring of structural changes in cardiac function, structure, perfusion, and tissue is important in assuring safe and uninterrupted use of cancer therapeutics. Cardiovascular imaging including transthoracic echocardiography (TTE), CCT, CMR, and nuclear imaging represent the cornerstone of imaging necessary for a cardio-oncology program. Within a cardio-oncology practice, the goals of CV imaging include the diagnosis, risk stratification, and monitoring for cardiovascular complications.^{27,28}

TTE remains the initial imaging modality of choice for the assessment of cardiovascular structure and function in patients with cancer and is also the preferred modality for serial cardiac function testing in majority of patients. The change in left ventricular systolic function remains the key parameter of safety with certain oncology therapies and defines the presence of cardiotoxicity,⁶ therefore, rigorous approach to quality echocardiographic imaging is of paramount importance.

Table 2
The utility of cardiac CT and MR in diagnosing commonly encountered cardiac conditions in cardio-oncology patients

	CAD	Myocardial Inflammation	Stress Cardiomyopathy	Cardiac Tumors & Thrombus
Cardiac CT	+	–	+/–	+/–
Cardiac MR	–			
1. Cine imaging		+	+	+/–
2. T2 properties (T2WI or T2 mapping)		+	+	+
3. T1 properties (pre- and post-gadolinium T1 mapping, LGE)		+	–	+
4. Fat saturation technique		–	–	+
5. First pass perfusion		–	–	+
6. Diffusion weighted		–	–	+

Abbreviation: CAD, coronary artery disease.

Imaging modalities and their built-in tailored protocols to diagnose these conditions. + refers proven utility, +/- refers to utility to some extent, and – refers to no proven utility.

Note that patients with stress cardiomyopathy demonstrate wall motion abnormality and may demonstrate positive myocardial edema (T2 properties) but negative late gadolinium enhancement whereas patients with myocardial inflammation may demonstrate myocardial edema in addition to one positive T1 property such as increased native T1 (diffuse fibrosis), increased extracellular volume, or post-gadolinium T1 mapping or late gadolinium enhancement. The diagnosis is made in reference to Lake Louise criteria. Cardiac tumor and thrombus protocol harnesses the advantages of sequences used for tissue characterization such as first pass perfusion to assess for tissue vascularity, fat saturation technique to rule in or out the presence of adipose tissue, and diffusion weighted imaging to evaluate for restricted diffusion within the mass as seen in lymphoma.

multiparametric imaging including cine imaging, tagging, T1 and T2 mapping, as well as late gadolinium enhancement. The challenges with CMR examination are long test duration which can reach 1 hour for comprehensive testing (eg, ischemia, parametric mapping, and tissue characterization), claustrophobia as well as the presence of tissue expanders used in reconstructive which often have ferromagnetic components. In contrast, breast implants do not represent a contraindication and do not create artifact with screening. Tailoring of CMR protocols, implementation of workflow strategies, and consistency and timeliness with reporting of results that answer the specific clinical questions all improve patient throughput and allow for a more streamlined and “patient-centric” imaging experience for patients with cancer. **Table 2** lists CMR findings and sequences tailored to different clinical scenarios.

Undoubtfully, establishing patient and physician-centered CV imaging as an integral part of the cardio-oncology program requires a conceptual framework that builds on several key pillars (**Fig. 4**). The first step includes the proactive assessment of the current needs and barriers to cardiac imaging. This will allow for the prediction of future imaging needs based on projected growth of imaging volume, current infrastructure, and expertise within institution including identifying gaps for improvement.

Components of the Conceptual Framework for the Integration of Comprehensive Cardiac Imaging in a Cardio-Oncology Program

- Transdisciplinary collaborative team of cardiologists, cardiac imaging physicians,



Fig. 4. Conceptual framework for the integration of comprehensive cardiac imaging in a cardio-oncology program.

Cardio-Oncology Consult Referral Form:

Oncology Dx:

Oncology Tx:

Reason for Consult:

Referral Priority:

Class:

Dept Specialty:

Provider Specialty:

Ref to Department:

Scheduling Instructions:

Comments:

Oncology Dx (Choose from List): ☐ Breast cancer ☐ Cardiac tumor

Oncology Tx (Choose from List): ☐ Immune checkpoint inhibitor ☐ Anthracycline ☐ Investigational agent

Reason for Consult: ☐ Concern for symptomatic cardiovascular event/toxicity ☐ Referral for prevention ☒ Other

Additional Order Details

Next Required:

☐ Concern for symptomatic cardiovascular event/toxicity ☒ Referral for prevention and CV risk

☒ Other

History of present heart failure or cardiomyopathy Severe valvular heart disease

History of myocardial infarction, PCI of CABG or known CAD History of prior anthracycline therapy

History of prior chest radiation Two of the following risks factors: HTN, DMII, CKD, Age >65, current smoker, BMI >30

Fig. 5. An example of a specialized electronic referral to cardio-oncology designed with guidance from Dr Michael Fradley from the University of Pennsylvania³⁵ and developed with support of the Epic information technology team at Inova Health. The referral form designed within electronic health record and containing the information about the type of malignancy, treatment, and cardiovascular risk factors. The goal of the specialized referral is to facilitate communication between referring the teams and cardio-oncology specialists and to assure appropriate assignment and scheduling.

- oncologists, surgeons, technologists, scientists including patients' involvement to provide holistic approach for the benefit of cardio-oncology patients. The patient and physician-centered CV imaging approach ensures patient access to imaging, education of patients about the utility of imaging in assessing cardiovascular health. Structured reporting that addresses referring physicians' questions including information about the diagnosis, risk stratification, and prognostication builds on physician centeredness.
- State-of-the-art imaging technology including scanners and cardiac postprocessing software to provide image quality for accurate assessment of the cardiovascular state in oncology patients.
 - Standardized and tailored CMR and CCT protocols and guidelines to efficiently scan oncology patients and provide timely and accurate reads.
 - Establish quality assurance plan and performance metrics including peer-review process

to assess adherence to the protocols and quality.

- Foster culture of inclusivity and lifelong learning and education to adopt new technologies to improve workflow efficiency and diagnostic accuracy in addition to training the new leaders in the field.
- New advances in cardiac imaging are only enabled by research and innovation. Collaborative approach to develop imaging tools to improve current challenges to monitor therapeutic efficacy is paramount to move this field forward.

Leveraging the Relationships with Other Services

When feasible, a cardio-oncology program can leverage experience resources in the subspecialty arenas of cardiac preventive, electrophysiology, advanced heart failure cardiology, vascular medicine, interventional and structural cardiology, and other related fields. Occasionally, direct

Table 3
Top 10 initial strategies for building a successful cardio-oncology program

Establish Need	Number of patients in system with diagnosis of invasive cancer? Breakdown of cancer by diagnosis? Gaps in care and timely referral? Map out locations of cancer care across system? Main site? Off sites or locations?
Understand Institution Cancer and Cardiovascular Landscape	Are there existing alliances between cancer care and CVD (eg, With cardiac prevention? With cancer survivorship? With CV imaging?)
Create a Mission Statement and Vision for Program	Define core values and purpose of program Build projected timeline with goals for implementation
Secure Institutional Support and Funding	Build business plan with projections Assure support from administrative leaders in cardiology and cancer to ensure adequate resources, staffing, and infrastructure
Establish Multidisciplinary Collaboration and Integrate Expertise in both CVD and Cancer	Meet with system/hospital administration (cancer and cardiovascular) Identify interested leaders/"champions" within difference cancer disciplines (breast, lung, etc)
Identify Key Leaders and Partnerships Across CV Disciplines	Identify "Champion" to co-lead program from oncology side Establish partnerships across disciplines Examples: Cardiac Prevention Group Electrophysiology (arrhythmia care/QTc abnormalities/screening, etc) Onco-Rehabilitation Cardiac Rehabilitation Cancer Survivorship Program Cardiac Imaging
Raise Awareness within the Institution	<i>Be Available!</i> Participate in: Oncology Case Conference Tumor Board Regular Oncology Leadership Meetings Outreach and Patient Education
Develop Specialized Clinical Pathways	Establish protocols for referrals and screening Identify types of patients for referral based on: Type of cancer/cancer therapy Level of CV risk Spectrum of CV toxicity Educate oncology providers about need and types of referrals Standardize care protocols for management of cancer therapy-related cardiac toxicity (eg, protocol for ICI myocarditis)
Leverage Technology for Coordination of Care	Work with IT for integration of program through electronic medical record (for referral, risk identification, imaging) Utilize telemedicine especially for patients in remote areas or for follow-up of testing/plans
Develop and Implement CV Imaging Protocols	Cardio-oncology imaging protocols (echo, MRI, cardiac CT, nuclear) Identify "champions" within imaging disciplines to serve as liaisons
Invest in Education and Training	Create opportunities for training in cardio-oncology (ie, lectures for cardiology and hematology oncology fellows, residents, and students, clinical elective)

Abbreviations: CV, cardiovascular; CVD, cardiovascular disease; ICI immune checkpoint inhibitors.

referrals to these practices may enhance bandwidth and enable quicker access to specialized care (see [Fig. 3](#); [Fig. 5](#)) To facilitate direct referrals, a cardio-oncology program should ideally have

recognized "champions" within each cardiovascular discipline. More practically, though, the cardio-oncology program can take referrals and assign the appropriate level of triage. The identification

and management of cardiovascular risk factors including cardiac prevention and primary care will help a sizable population of patients with cancer. Programs should create and offer referral algorithms for appropriate referral to general and preventive cardiology, with pathways, given the shortage of cardio-oncology specialist doctors. This can be done by education and through the electronic medical record.

STRATEGIES FOR BUILDING A SUCCESSFUL CARDIO-ONCOLOGY PROGRAM

Building a multidisciplinary program can be a challenging and complicated endeavor owing to the complexity of integration across disciplines and the significant investment in infrastructure, personnel, and funding. In Table 3, we summarize the key strategies to consider when starting a cardio-oncology program.

In summary, organizing a cardio-oncology program and clinic involves careful planning and coordination to address the complex needs of patients who are dealing with 2 of the most serious health issues: cancer and heart disease. All components of cardio-oncology program are patient-centered with attention to individual needs and clear communication of care plans with patients and their families. The emphasis is on delivering multidisciplinary, tailored care that recognizes and treats the cardiovascular side effects of cancer treatments without compromising oncological efficacy

CLINICS CARE POINTS

- Step 1: Identify needs (oncology) and resources (cardiology and oncology).
- Step 2: Create multidisciplinary team(s).
- Step 3: Create pathways for referral and communication between services.
- Step 4: Integrate cardio-oncology services within health care system.
- Step 5: Assure access and set quality metrics.

DISCLOSURE

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