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CONTEMPORARY REVIEW

Permissive Cardiotoxicity: An Evolving Paradigm

David L. Madnick , MD; Elizabeth Hutchins , MD, PhD; Ashley F. Stein-Merlob , MD, PhD; Eric H. Yang , MD

ABSTRACT: Permissive cardiotoxicity is an evolving clinical practice pattern that balances the management of cancer treatment-associated cardiotoxicities with the risk of interrupting lifesaving or life-extending cancer treatments. This paradigm shift has been catalyzed by advancements in the diagnostic and therapeutic tools available to treating clinicians, as well as a recognition of the consequences of withholding or delaying cancer therapy. Permissive cardiotoxicity has become a central tenet in the practice of cardio-oncologists; however, recognition and confidence in managing cardiotoxicity is also crucial for the general cardiologist and oncologist due to the growing population of patients with cancer. This review aims to (1) highlight the philosophy of permissive cardiotoxicity, (2) provide a framework for risk stratification of cardiovascular toxicities, (3) describe systems of care considerations for successful implementation of permissive cardiotoxicity, and (4) review the existing literature and guideline recommendations for specific cardiovascular toxicity mitigation.

Key Words: cardio-oncology ■ cardioprotective therapies ■ chemotherapy-induced cardiac injury ■ permissive cardiotoxicity

Permissive cardiotoxicity (PC) is an evolving clinical practice paradigm that balances the management of cancer treatment-associated cardiotoxicities with the risk of interrupting effective cancer treatment. A relatively new term in the cardio-oncology lexicon, PC was first officially described in 2022 by Porter et al.¹ and has become a central tenet in the practice of cardio-oncology. Historically, development of cardiotoxicity would trigger immediate discontinuation of the offending oncologic therapy. However, interruption of cancer treatment may compromise oncologic outcomes, including increased risk of disease progression, recurrence, and mortality. Rather than viewing cardiotoxicity as an absolute indication to discontinue therapy, PC emphasizes the early recognition, comprehensive evaluation, and treatment of cardiovascular toxicities to optimize cardiovascular outcomes while allowing patients to continue cancer therapy whenever it can be done safely. This approach relies on individualized cardiovascular risk assessment, cardioprotective interventions, close surveillance, and multidisciplinary collaboration (Figure 1).

The first described cardiotoxicity was anthracycline-induced cardiomyopathy (AIC) in 1967; since then, AIC has been the prototypical cause of cancer therapy-related cardiac dysfunction (CTRCD).² However, with the rapid expansion of new targeted therapies, immunotherapies, and other novel anticancer agents, there is increased recognition that the diverse manifestations of cardiotoxicity span the full-spectrum of cardiovascular disease.³ Simultaneously, cardiovascular care has evolved with improved methods of monitoring, such as quantitative echocardiography and high-sensitivity cardiac biomarkers, and therapeutic advances, such as guideline-directed medical therapies (GDMT). Collectively, these developments have made the practice of PC increasingly feasible and have shifted the focus from treatment discontinuation toward toxicity mitigation and cardiovascular optimization.

Cardiovascular disease has emerged as a leading cause of morbidity and mortality among survivors of cancer as advancements in cancer diagnosis and therapeutics have substantially improved survival in this population.⁴ Clinicians are increasingly challenged to balance the cardiovascular risks of treatment against

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Nonstandard Abbreviations and Acronyms

5-FU	5-fluorouracil
AIC	anthracycline-induced cardiomyopathy
BB	beta blocker
Bcr-abl	breakpoint cluster region-Abelson
BTKi	Bruton tyrosine kinase inhibitor
CPT	cardioprotective therapies
CTRCD	cancer therapy-related cardiac dysfunction
ESC	European Society of Cardiology
GDMT	guideline directed medical therapies
HER2	human epidermal growth factor receptor 2
ICI	immune checkpoint inhibitor
ICI-M	immune checkpoint inhibitor-associated myocarditis
ICOS	International Cardio-Oncology Society
irAE	immune-related adverse event
PC	permissive cardiotoxicity
QTcF	corrected QT interval using the Fridericia formula
TKI	tyrosine kinase inhibitor
VEGF	vascular endothelial growth factor
VSPI	vascular endothelial growth factor signaling pathway inhibitor

the oncologic consequences of interrupting potentially life-saving or life-extending cancer therapies. Recognition and comfort in managing cardiotoxicity are crucial not only for the clinical cardio-oncologist but also for the general cardiologist and oncologist. This review expands upon the conceptual PC framework proposed by Porter et al. by providing a comprehensive evaluation of the major domains of cardiotoxicity through the lens of PC. We discuss principles of risk stratification for cardiovascular toxicities, describe systems of care considerations for successful implementation of PC, and review existing literature and guideline recommendations for specific cardiovascular toxicity mitigation.

THE CONTINUUM OF CARDIOTOXICITY

Cardiotoxicity exists along a continuum of clinical manifestations spanning the full range of cardiovascular syndromes including heart failure (HF), arrhythmia, hypertension, and myocardial infarction. Additionally, the severity varies significantly from asymptomatic hypertension, left ventricular (LV) dysfunction, or biomarker

elevation to life-threatening ventricular arrhythmias and cardiogenic shock. One primary difficulty in cardio-oncology has been lack of uniformity in research clinical end points, as well as variation in what constitutes clinically significant toxicity. In 2021, the International Cardio-Oncology Society (ICOS) authored a consensus statement on cardiovascular adverse events during cancer treatment to standardize the definitions of cardiovascular toxicity for the improvement of interdisciplinary communication in clinical care and research endeavors. The statement categorizes cardiovascular toxicity into 6 domains: CTRCD/HF, myocarditis, vascular toxicities, hypertension, arrhythmias, and QT prolongation.³ The distinction is made between symptomatic and asymptomatic cardiotoxicity, and specific criteria for assessing severity are provided for each domain (Table).

THE EFFECTS OF CANCER THERAPY DISRUPTION

Cancer treatment interruption, premature discontinuation, or dose reduction can lead to both medical and psychosocial consequences.^{5,6} Interruptions to cancer therapy are associated with higher rates of cancer-related mortality in patients with breast and colorectal cancers.^{7,8} Delayed adjuvant therapy is associated with higher rates of local recurrence in breast and head and neck cancers.⁹ Even a 4-week delay in systemic treatment has been associated with increased mortality among a variety of cancers.¹⁰ In early-stage breast cancer, anthracycline dose reduction was associated with a 3.17-fold higher risk of death at 5 years compared with patients who did not experience dose alterations.⁵ Disruptions in cancer care can also lead to significant psychosocial distress for patients. Fear of cancer progression is a common experience for those who experience treatment delay.¹¹ Treatment disruptions have been associated with mental health issues including increased rates of depression, anxiety, and insomnia.⁶

Data describing the effects of cancer therapy disruption specifically due to cardiotoxicity are sparse. In a study of patients with nonmetastatic HER2 (human epidermal growth factor receptor 2)-positive breast cancer, treatment interruptions of >2 weeks or early discontinuation of trastuzumab occurred in 40% of patients. Treatment disruption was primarily due to the development of cardiomyopathy and was associated with worse disease-free survival and worse overall survival.¹²

SYSTEMS OF CARE IN CARDIO-ONCOLOGY

PC creates a unique set of challenges that require a multidisciplinary team; close communication between cardiology, oncology, and pharmacy teams

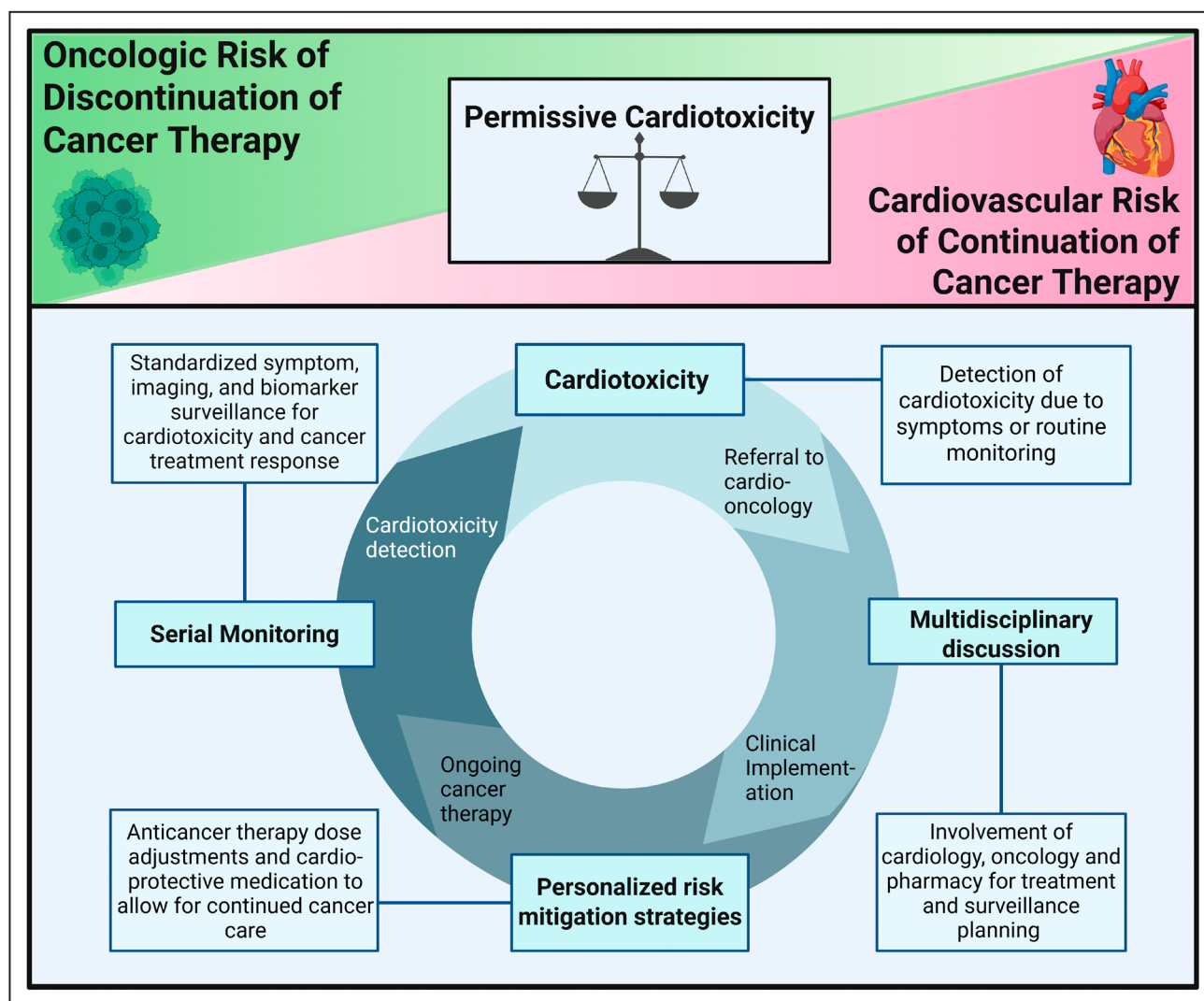


Figure 1. Clinical framework for the practice of permissive cardiotoxicity.

This figure depicts the iterative process underlying permissive cardiotoxicity, including baseline cardiovascular risk assessment and screening, multidisciplinary shared decision-making, implementation of cardioprotective therapies and other risk-mitigation strategies, and serial cardiovascular monitoring. This cyclical approach allows for ongoing reassessment of both cardiovascular status and oncologic priorities, enabling individualized treatment decisions throughout the course of cancer therapy. Figure created with BioRender.com.

is paramount. Cardiologists should provide prompt patient evaluation when cardiotoxicity is suspected to maximize the possibility of PC and minimize treatment interruption. This involves standard processes for timely patient referral and evaluation.

Outlines of cardio-oncology service models suggest that clinical visits should be available within 10 business days of referral, and noninvasive imaging appointments within 5 business days.¹³ Streamlining referrals might entail reserved slots for urgent oncology referrals or accommodating additional patients to an already full schedule. An open line of communication with treating oncologists and pharmacists to discuss alternative therapies or dose adjustments is critical to allow a unified approach for treatment regimens, surveillance

strategies, and contingency plans. Changes in a patient's clinical status or new evidence of progression of cardiovascular or oncologic issues should prompt repeat multidisciplinary discussions.

PERMISSIVE CARDIOTOXICITY STRATEGIES FOR THE CLINICAL CARDIO-ONCOLOGIST

The clinical cardio-oncologist must accurately classify and grade the severity of cardiovascular toxicity to determine whether continuation of cancer treatment is possible. There is a lack of robust data to guide risk-mitigation strategies once cardiotoxicity has occurred;

Table. Cancer Therapy-Related Cardiovascular Toxicity Definitions

Cardiotoxicity domain	Clinic significance/categories		Definitions
Cancer therapy-related cardiac dysfunction	Asymptomatic	Mild	LVEF $\geq 50\%$, and • EITHER a new relative decline in GLS by $>15\%$ from baseline • OR new rise in cardiac biomarkers
		Moderate	New LVEF reduction by $\geq 10\%$ to an LVEF of $40\%–49\%$
			New LVEF reduction by $<10\%$ to an LVEF of $40\%–49\%$, and • EITHER a new relative decline in GLS by $>15\%$ from baseline • OR new rise in cardiac biomarkers
		Severe	New LVEF reduction to $<40\%$
	Symptomatic	Mild	Mild heart failure symptoms, no intensification of therapy required
		Moderate	Requires outpatient intensification of diuretic and heart failure therapy
		Severe	Heart failure hospitalization
		Very Severe	Requiring inotropic support, mechanical circulatory support or consideration for transplantation
Vascular toxicities	Asymptomatic	Nonobstructive vascular disease	Atherosclerosis
			Abnormal vasoreactivity
			Thrombosis
	Symptomatic	Cerebral ischemia	Stroke/transient ischemic attack
		Coronary ischemia	Myocardial infarction
			Acute coronary syndromes
			Chronic coronary syndromes
			Vasospastic angina
			Microvascular angina
		Peripheral Arterial Ischemia	Peripheral arterial disease
Hypertension	Asymptomatic	BP threshold: ASCVD risk $\geq 10\%$	≥ 130 mmHg SBP or ≥ 80 mmHg DBP
		BP threshold: ASCVD risk $\leq 10\%$	≥ 140 mmHg SBP or ≥ 90 mmHg DBP
		BP threshold for cancer therapy disruption	≥ 180 mmHg SBP or ≥ 110 mmHg DBP
	Symptomatic	Hypertensive emergency	Very high BP elevations associated with acute hypertension-mediated organ damage (heart, retina, brain, kidneys, and large arteries), requiring immediate BP reduction
Myocarditis	Asymptomatic	Smoldering/subclinical	Incidentally diagnosed myocarditis without any clinical signs or symptoms
	Symptomatic	Nonsevere	Symptomatic but hemodynamically and electrically stable, may have reduced LVEF, no features of severe disease
		Severe	Hemodynamic instability, heart failure requiring noninvasive or invasive ventilation, complete or high-grade heart block, or significant ventricular arrhythmia
		Steroid refractory	Nonresolving or worsening myocarditis (clinical worsening or persistent troponin elevation after exclusion of other causes) despite high dose methylprednisolone
QT prolongation	Asymptomatic	Acceptable	QTcF <480 ms
		Prolonging	QTcF $480–500$ ms
		Prolonged	QTcF >500 ms
	Symptomatic	Polymorphic ventricular tachycardia/ventricular fibrillation	Torsades de pointes

Definitions and classification of the domains of cancer therapy-related cardiovascular toxicity, which have been derived from the 2021 International Cardio-Oncology Society consensus statement on cardiotoxicity and the 2022 European Society of Cardiology Cardio-Oncology Guidelines.⁴

ASCVD indicates atherosclerotic cardiovascular disease; BP, blood pressure; DBP, diastolic blood pressure; GLS, global longitudinal strain; LVEF, left ventricular ejection fraction; ms, milliseconds; QTcF, corrected QT interval (Fridericia); and SBP, systolic blood pressure.

therefore, cardioprotective therapies (CPT) and monitoring approaches should be individualized using shared decision-making. Several clinical risk calculators, including the Heart Failure Association and ICOS

risk assessment tool, provide clinicians with practical, evidence-based methods for baseline cardiovascular risk stratification. The Heart Failure Association and ICOS tool integrates traditional cardiovascular risk

Cardiotoxicity Type	Cancer-Therapy Related Cardiac Dysfunction	Vascular Toxicities	Hypertension	Myocarditis	Arrhythmia	QTc Prolongation
Representative Drug Classes	Anthracyclines Anti-HER2 agents	Fluoropyrimidines Alkylating agents Bcr-abl TKIs	VEGF inhibitors BTK inhibitors	Immune checkpoint inhibitors (ICI)	BTK inhibitors Bcr-abl TKIs Alkylating agents	Arsenic trioxide CDK 4/6 inhibitors Bcr-abl TKIs
Permissive Cardiotoxicity Strategies	Frequent monitoring of cardiac function Heart failure guideline directed medical therapy Dexrazoxane	Antispasmodic medications Treatments for accelerated atherosclerosis Slowing chemotherapy administration rate	Blood pressure monitoring Antihypertensive medication Temporary cessation of anti-cancer therapy	Frequent biomarker monitoring Serial imaging Rechallenge with single agent or alternate ICI	Pharmacologic rate and rhythm control Anticoagulation strategies Alternative, less arrhythmogenic chemotherapy	Correction of electrolyte abnormalities Close ECG surveillance Cessation of other QTc prolonging medications
Prohibitive Risk Situations*	Moderate to severe symptomatic CTRCD; Severe asymptomatic CTRCD	Coronary vasospasm despite maximal tolerated antispasmodic therapy; life threatening arrhythmia; critical limb ischemia	Severe, medication resistant hypertension; hypertensive emergency	Fulminant myocarditis	Uncontrolled atrial or ventricular arrhythmia, despite attempted rate or rhythm control	TdP or sustained ventricular arrhythmias

Figure 2. Permissive cardiotoxicity strategies by cardiotoxicity type.

This figure summarizes cardiotoxicities caused by cancer therapies, the representative anticancer drugs associated with each cardiotoxicity type, and the corresponding permissive cardiotoxicity strategies. *Examples of prohibitive risk situations, which are not inclusive of all possible scenarios. These situations require a multidisciplinary risk/benefit discussion. Bcr-abl TKI indicates breakpoint cluster region-Abelson tyrosine kinase inhibitor; BTK, Bruton tyrosine kinase; CDK, cyclin-dependent kinase; CTRCD, cancer therapy related cardiac dysfunction; HER2, human epidermal growth factor receptor 2; ICI, immune checkpoint inhibitor; QTc, corrected QT interval; TdP, torsades de pointes; and VEGF, vascular endothelial growth factor. Figure created with [BioRender.com](https://www.biorender.com).

factors with cancer-specific variables, including prior anthracycline exposure and mediastinal radiation, to identify patients at increased risk for cancer therapy-related cardiovascular toxicity. This individualized risk assessment facilitates tailored surveillance strategies and early implementation of CPT.¹⁴ It should be noted that the Heart Failure Association and ICOS risk assessment tool was developed and validated for primary prevention by estimating cardiotoxicity risk before the initiation of potentially cardiotoxic cancer therapies. It has not been validated for secondary risk assessment following the development of treatment-related cardiotoxicity, as encountered in PC. Nevertheless, it may still provide a useful framework for estimating the cardiovascular risk associated with subsequent cancer therapies after cardiotoxicity has occurred. When considering a PC strategy, careful consideration should be given to the cancer and cardiovascular symptom burden, overall cancer prognosis, alternative therapeutic agents, and patient preferences.

This section reviews consensus guideline classifications of several cardiovascular toxicities, as well as summarizes the existing literature for PC strategies using prototypical cancer therapies in each domain of cardiotoxicity (Figure 2).

Cancer Therapy-Related Cardiac Dysfunction

CTRCD encompasses a class of cardiotoxicities that adversely affect myocardial structure and function, typically manifesting as LV dysfunction. Table summarizes the 2022 European Society of Cardiology (ESC) cardio-oncology guidelines, which subdivide CTRCD into either symptomatic or asymptomatic CTRCD.¹⁵ Common cancer therapies associated with CTRCD include anthracyclines, HER2-inhibitors, small molecule tyrosine kinase inhibitors (TKIs) such as those targeting VEGF (vascular endothelial growth factor) receptor, epidermal growth factor receptor, or breakpoint cluster region-Abelson (Bcr-abl),

and proteasome inhibitors.^{2,16,17,18} Notably there is a lower threshold for the initiation of GDMT in CTRCD compared with other forms of nonischemic cardiomyopathy. In patients with mild asymptomatic CTRCD, there is a Class IIa recommendation to start GDMT when the LV ejection fraction (LVEF) is $\geq 50\%$ if there is a relative decrease $>15\%$ in global longitudinal strain, and a Class IIb recommendation to start GDMT if there is an increase in natriuretic peptides.¹⁵

Anthracyclines

Anthracyclines are a central component of treatment in various hematologic and solid malignancies. Their cardiovascular effects are dose dependent and cumulative.² In cases of AIC, continuation of anthracycline can be considered in asymptomatic and mild–moderate symptomatic cases. The ESC guidelines give a Class I recommendation to temporarily interrupt chemotherapy in moderate–severe asymptomatic or moderate symptomatic CTRCD until either HF therapies can be initiated, or symptoms improve.¹⁵ The guidelines also give a Class I recommendation for discontinuation of anthracycline in severe symptomatic CTRCD.¹⁵ AIC is generally considered to be irreversible due to myocyte apoptosis and necrosis that occurs, thus PC should be pursued with particular caution given the potential permanent nature of cardiac damage compared with other cardiotoxic agents with more reversible mechanisms. However, in cases where the oncologic benefit is high there are strategies to mitigate this damage in the appropriate patients.

Treatment of AIC is largely based on observational data and adaptation of existing HF guidelines due to lack of representation in randomized controlled trials. In an observational study of patients with AIC, administration of angiotensin-converting enzyme inhibitors (ACEis) and beta-blockers (BBs) led to complete or partial LVEF recovery in 55% of patients. LVEF recovery was associated with a lower incidence of major adverse cardiac events.¹⁹ Sacubitril/valsartan, an angiotensin receptor-neprilysin inhibitor, has been examined only in a small study but was associated with improvement in LVEF, New York Heart Association functional class, and 6-minute walk test.²⁰ A recent systematic review and meta-analysis of 5 studies (4 observational and 1 case–control) assessing SGLT2 (sodium-glucose cotransporter-2) inhibitors use in patients with AIC revealed lower odds of all-cause mortality, new-onset HF, HF hospitalization, and arrhythmia.²¹ Therefore, initiation of the 4 pillars of HF therapy, including ACEis/angiotensin II receptor blockers/angiotensin receptor-neprilysin inhibitor, BBs, mineralocorticoid receptor antagonists, and SGLT2 inhibitors should be considered in patients without an absolute contraindication. In the STOP-CA (Statins to Prevent the Cardiotoxicity of Anthracyclines) trial, initiation of atorvastatin before anthracycline-based chemotherapy

regimens for lymphoma reduced the incidence of AIC.²² Although this study demonstrated promise for primary prevention of AIC, no studies have evaluated the secondary preventative role of statins in PC among patients who continue anthracycline therapy.

Following cardiovascular optimization, several oncologic strategies can be employed to mitigate the risks associated with ongoing anthracycline exposure. Altering anthracycline dosing schedule from bolus to an extended infusion is thought to reduce AIC through a reduced peak anthracycline exposure. Anthracycline infusion durations of ≥ 6 hours have been shown to reduce the rates of symptomatic and asymptomatic HF, compared with shorter durations.²³ Modifying treatment with another potentially less cardiotoxic anthracycline formulation can also be considered. Pegylated liposomal doxorubicin is associated with significantly lower risk of HF compared with nonliposomal doxorubicin, in part due to its favorable pharmacokinetic profile and biodistribution away from normal tissues, including the myocardium.^{24,25} Finally, off-label use of dexrazoxane has been a successful cardioprotective strategy in a small case series of patients with preexisting asymptomatic cardiomyopathy undergoing anthracycline therapy²⁶; this strategy allowed for completion of planned anthracycline course in all 5 patients without progression to symptomatic CTRCD.²⁶ Dexrazoxane is currently approved by the Food and Drug Administration only for adult patients with metastatic breast cancer who have received a cumulative doxorubicin dose $>300\text{mg/m}^2$ and are continuing anthracycline therapy.²⁷ These limitations are due to concerns that dexrazoxane use has been associated with secondary hematologic malignancies and also may influence cancer therapy efficacy.^{28,29} However, in later studies these concerns have not been replicated.^{30,31}

Human Epidermal Growth Factor Receptor 2 Targeted Therapies

Trastuzumab is a targeted monoclonal antibody directed against the HER2 receptor and has been a mainstay in the treatment of HER2-positive breast cancer since its Food and Drug Administration approval in 1998. More recently, newer generation monoclonal antibodies, antibody-drug conjugates, and TKIs targeting HER2 have been approved to treat other HER2-overexpressing solid malignancies.³² Trastuzumab cardiotoxicity typically manifests as asymptomatic LV dysfunction, and in contrast to anthracycline CTRCD it is typically reversible.³³

There have been several prospective trials investigating the feasibility of continuing HER2-targeted treatments in patients who develop CTRCD. The SAFE-HEART (Cardiac Safety Study in Patients With HER2 + Breast Cancer) trial first explored whether these therapies could be safely administered without treatment interruption. The trial enrolled patients with stage I to IV HER2-positive

breast cancer receiving HER2-targeted therapies who developed asymptomatic CTRCD with LVEF between 40% and 49%. Patients were treated with ACEi and BB and closely followed with in-person visits and serial echocardiograms. The majority (90%) of patients completed HER2-targeted therapy without the development of further significant decline in LVEF or symptomatic HF.³⁴ Similarly, the SCHOLAR (Safety of Continuing Chemotherapy in Overt Left Ventricular Dysfunction Using Antibodies to HER-2) trial was a prospective, phase 1, single-arm study of 20 women receiving trastuzumab (with prior anthracycline exposure) for early-stage breast cancer who subsequently developed mild asymptomatic CTRCD.³⁵ Patients were treated with either ACEi or BB and followed with serial echocardiograms. Only 2 patients (10%) had dose-limiting cardiotoxicity, though both symptoms and LVEF improved after permanent discontinuation of trastuzumab.³⁵ SCHOLAR-2 (Safety of Continuing HER-2 Directed Therapy in Overt Left Ventricular Dysfunction; NCT04680442) is a follow-up phase 2 randomized controlled trial that will compare current standard of care—holding HER2 treatments until LVEF improves—to a more proactive approach with continuation of HER2 treatments similar to that investigated in SCHOLAR.³⁶

The data from SAFE-HEART and SCHOLAR form the basis of the Class I ESC guideline recommendation to continue HER2-targeted therapy in patients with mild asymptomatic CTRCD, with frequent cardiac surveillance and initiation of HF GDMT. In cases of severe asymptomatic or moderate–severe symptomatic CTRCD, there is a Class I recommendation to interrupt treatment and initiate medical therapies for HF. If either symptoms do not resolve or the LVEF remains <40%, HER2-targeted therapy resumption can still be considered in select patients if there are no equally efficacious therapeutic options. Echocardiogram and biomarker surveillance is recommended every 2 cycles for the first 4 cycles after treatment resumption, with further monitoring frequency guided by stability in LVEF and biomarkers.¹⁵

Vascular Toxicities

Vascular toxicities encompass a diverse set of cardiotoxicities, with varying clinical presentations depending on the vascular bed involved. The ESC guidelines subdivide vascular toxicity into asymptomatic and symptomatic toxicity (Table). Asymptomatic toxicities include atherosclerosis, abnormal vasoreactivity, and venous or arterial thrombosis.¹⁵ Symptomatic vascular toxicities include stroke, transient ischemic attack, acute coronary syndromes, chronic coronary syndromes, vasospastic angina, and Raynaud's phenomenon.¹⁵ Chemotherapeutic agents with prominent vascular toxicity profiles include fluoropyrimidines, alkylating agents such as cisplatin or cyclophosphamide, anti-VEGF monoclonal antibodies, TKIs targeting Bcr-Abl or

VEGF, and more traditional chemotherapeutic agents such as taxanes or vinca alkaloids.³⁷

In addition to direct vascular toxicities, hormonal therapies used in cancer treatment such as androgen deprivation therapies, have been shown to worsen cardiometabolic risk factors that contribute to atherosclerotic cardiovascular disease.³⁸ Retrospective studies have demonstrated an association between gonadotropin-releasing hormone agonist therapy and an increased risk of coronary artery disease, myocardial infarction, and cardiovascular mortality among patients with prostate cancer.^{39,40} Regular monitoring of lipids, blood pressure (BP), and hemoglobin A1c levels with uptitration of appropriate medical therapy may be required to mitigate these increased risks.

Fluoropyrimidines

Two common fluoropyrimidines essential in the treatment of colorectal cancers are 5-fluorouracil (5-FU) and capecitabine; they also have efficacy in other solid malignancies including breast, pancreatic, and head and neck cancers.⁴¹ The first, 5-FU, has a well-established vascular toxicity profile, with adverse events that can include coronary vasospasm, coronary thrombosis, and sudden cardiac death. Development of atrial fibrillation (AF), stress cardiomyopathy, and myocarditis have also been described, but are less common.

The cardiovascular toxicity of 5-FU manifests as typical or atypical chest pain. The median time to symptom initiation is 12 hours; however, late presentation of symptoms has been described up to 72 hours following drug infusion.⁴² Prospective studies estimate the incidence of 5-FU-induced chest pain to be between 1% and 13%, depending on drug formulation, concomitant chemotherapies administered, and reporting criteria.⁴³ ECG changes, including ST-segment elevations, and elevated biomarkers may raise concern for acute coronary syndromes at the time of presentation. Coronary vasospasm leading to myocardial ischemia is principally implicated as the cause of chest pain in 5-FU vascular toxicity. Only after severe obstructive coronary artery disease has been ruled out with an appropriate anatomic evaluation (either by invasive or noninvasive coronary angiography depending on the clinical scenario) can the diagnosis of coronary vasospasm be formally established.

Following an episode of 5-FU-induced coronary vasospasm, rechallenge may be considered in a closely monitored setting in the absence of alternative therapies. Several strategies can be employed to optimize patients before 5-FU rechallenge to prevent recurrent vasospasm. Case reports and small case series have described the efficacy and safety of pretreatment with a combination of antispasmodic agents including calcium channel blockers and long-acting nitrates.^{44–46} Additionally, switching from infusion to bolus dosing 5-FU has been proposed

as a method to prevent recurrent vasospasm, as toxicity is thought to result from accumulation of metabolites instead of through a peak-dose effect.^{47,48} A single-center case series of 5-FU rechallenged patients used a protocol that included pretreatment with CPT, as well as bolus dosing of 5-FU. All 11 patients were able to safely continue outpatient cancer therapy with fluoropyrimidines without cardiac events or recurrent coronary vasospasm.⁴⁵ This center's protocol included pretreatment with 30 to 60mg of extended-release nifedipine and 30 to 60mg of isosorbide mononitrate administered 3 to 4 hours before chemotherapy.⁴³ Additionally, they recommend 30mg of short-acting diltiazem administered at the time of infusion, followed by 90 minutes of close monitoring before discharge. Inability to tolerate this regimen due to BP concerns precluded consideration of 5-FU rechallenge.⁴³

Hypertension

Arterial hypertension is one of the most common side effects in patients undergoing cancer treatment. Therapies associated with hypertension include VEGF signaling pathway inhibitors (VSPIs), TKIs, proteasome inhibitors, and traditional chemotherapeutics such as platinum-based compounds and alkylating agents.⁴⁹ The 2021 ICOS consensus statement proposed a treatment threshold for systolic blood pressure (SBP) of ≥ 130 mmHg or diastolic blood pressure of ≥ 80 mmHg in patients with preexisting cardiovascular disease or a 10-year atherosclerotic cardiovascular disease risk of $\geq 10\%$ who develop treatment-related hypertension. In all other patients, the threshold for initiation of antihypertensive treatments is SBP ≥ 140 mmHg or diastolic BP ≥ 90 mmHg.³ The ESC guidelines state that treatment targets should be determined in the context of the cancer and prognosis, with more lenient thresholds in advanced disease.¹⁵ Asymptomatic hypertension is delineated from a hypertensive emergency response, which is characterized by very high BP elevations with acute hypertension-mediated end-organ damage that requires immediate BP reduction (Table).³

Vascular Endothelial Growth Factor Signaling Pathway Inhibitors

VSPIs are a class of targeted chemotherapies that exert their anticancer effects through the antiangiogenic effects of either direct VEGF inhibition or inhibition of downstream tyrosine kinase receptors. These therapies are indicated in a variety of solid malignancies including nonsquamous non-small cell lung cancer, metastatic renal cell carcinoma, metastatic colorectal cancer, and recurrent glioblastoma. The incidence of VSPI-associated hypertension is estimated to be between 30% and 80% and is typically reversible with discontinuation of therapy.³⁷ Interestingly, VSPI-associated hypertension has been found to be a prognostic indicator of cancer treatment efficacy. In a

meta-analysis of 7 studies involving patients with metastatic colorectal cancer, bevacizumab-induced hypertension was associated with improved progression-free survival and overall survival when compared with VSPI-treated patients without hypertension.⁵⁰ Similar prognostic findings have been described in patients treated with sunitinib for metastatic renal cell carcinoma.⁵¹

The positive cancer prognostic implications of VSPI-associated hypertension highlight the importance of the PC paradigm. Prompt recognition of cancer therapy-associated hypertension using guideline thresholds should trigger the initiation of antihypertensive treatments. In cases of asymptomatic hypertension, therapies can be continued while antihypertensives are titrated under close outpatient monitoring. Home BP monitoring is of particular utility, as worsening hypertension can be abrupt in onset and lead to hypertensive emergencies.⁴⁹ At least weekly BP monitoring should be performed during the first 1 to 2 months after initiating an agent known to cause hypertension. Optimal antihypertensive therapy is not yet known, but the ESC guidelines recommend first-line ACEis or angiotensin II receptor blockers followed by a dihydropyridine calcium channel blocker in patients who meet criteria for treatment initiation. Concomitant initiation should be considered in patients with SBP ≥ 160 mmHg and diastolic BP ≥ 100 mmHg.¹⁵ If there is resistant hypertension then BB, mineralocorticoid receptor antagonists, or combination nitrates/hydralazine can be considered (Class IIa). In cases of very high BPs (ie, SBP ≥ 180 mmHg) or hypertensive emergencies, cancer treatment should be temporarily withheld until SBP < 160 mmHg and diastolic BP < 100 mmHg (Class I).¹⁵ Information regarding optimal antihypertensive regimens in patients with cancer is lacking, as most clinical trials exclude patients with cancer.

Myocarditis

Cancer therapy-associated myocarditis can result either from cytotoxic damage by conventional chemotherapeutic agents, such as cyclophosphamide, or increasingly by immune-mediated damage following immunotherapies such as immune checkpoint inhibitors (ICI). ICI-associated myocarditis (ICI-M) is a relatively uncommon immune-related adverse event (irAE), with registry and clinical trial data estimating an incidence of 0.27% to 1.70%.^{52,53} ICOS grades ICI-M cases as either asymptomatic (smoldering or subclinical) or symptomatic nonsevere versus symptomatic severe, a distinction based on the presence of hemodynamic or electrical instability (Table).³

Immune Checkpoint Inhibitors

The indications for ICIs have significantly expanded over the past decade, now with indications in >20

tumor types.⁵⁴ Although ICI-M occurs infrequently, it carries a significant mortality rate ranging from 25% to 50%.⁵² Thus, its prompt recognition and treatment are of paramount importance. There is a Class I indication for ICI treatment interruption after confirmation of ICI-M.¹⁵ High-dose intravenous steroids followed by a prolonged steroid taper form the standard treatment regimen. Complete recovery is defined by resolution of symptoms, and normalization of biomarkers and LVEF following steroid weaning.¹⁵

Data regarding ICI rechallenge after cardiac irAEs (and noncardiac irAEs) are scarce, limited to case reports and small retrospective studies. One notable cohort study followed patients who developed grade 2 or higher noncardiac irAE for a variety of cancer types following ICI therapy and were subsequently rechallenged with ICI.⁵⁵ The most common irAEs included hepatitis, pneumonitis, colitis, and skin toxicity.⁵⁵ Over half of rechallenged patients experienced a recurrent event; the second irAE was not found to be more severe than the first.⁵⁵ ICI-M has a significantly higher morbidity and mortality than the irAEs investigated in this study, thus results should not necessarily be extrapolated to ICI rechallenge after myocarditis. More recently, a single-center retrospective cohort study of 160 patients with suspected ICI-M was published, in which a total of 14 patients with ICI-M (12 nonsevere, 2 severe) were rechallenged with ICI.⁵⁶ Half of the rechallenged patients subsequently developed elevated troponins; however, no patients showed clinical evidence of recurrent myocarditis.⁵⁶ Another cross-sectional study of ICI rechallenge following irAE demonstrated 0 out of 3 patients experiencing recurrent ICI-M after rechallenge.⁵⁷

Extreme caution should be exercised when considering ICI rechallenge after ICI-M. Patient-specific factors should be considered, including severity of myocarditis at presentation, degree of recovery from ICI-M, alternative oncologic treatments, and cancer prognosis.¹⁵ In cases of uncomplicated ICI-M, such as those with asymptomatic biomarker elevations, suggestive imaging findings, or LV dysfunction, the risk-benefit of rechallenge may be acceptable. Close monitoring through regular in-person visits and frequent biomarker measurement are advised, although there are no validated protocols to determine frequency of monitoring or when to reinstitute immunosuppressive therapies for myocarditis recurrence. In cases of ICI-M attributable to combination ICI therapy, deescalation to single-agent ICI can be considered, as the rates of irAEs are significantly lower.⁵⁸

Arrhythmias

The full spectrum of electrophysiologic abnormalities can be appreciated in patients undergoing cancer therapy, ranging from sinus bradycardia/tachycardia to

atrial/ventricular arrhythmias, sick sinus syndrome, and atrioventricular block. These conditions may be directly related to cardiovascular toxicity of cancer therapeutics, predisposing risk factors present in the population of patients with cancer (ie, age, electrolyte disturbances from poor oral intake or medication effects, vomiting, diarrhea or fever, and direct cardiac involvement of cancer), or a combination of the two.⁵⁹

AF is the most common cardiac arrhythmia and is associated with significant morbidity and mortality. Studies have shown an increased incidence of AF in patients with cancer when compared with patients without cancer, with significant variability among cancer subtypes and stage.^{60–62} Cancer has been shown to be an independent risk factor for new onset AF. Cancer subtypes with the highest risk of AF include multiple myeloma, esophageal cancer, and leukemia.⁶² The pathophysiology of cancer-associated AF is thought to be related to numerous factors including underlying cardiovascular and metabolic comorbidities, inflammation, and the direct arrhythmogenic effects of cancer therapies.⁵⁹ Medical therapies that have been implicated in the development or recurrence of AF include alkylating agents, hematopoietic stem-cell transplantation, Bcr-Abl TKIs, and BTK (Bruton tyrosine kinase) inhibitors (BTKis).

Bruton Tyrosine Kinase Inhibitors

BTKis are a class of targeted anticancer therapies essential for treating various B-cell malignancies. They exert their anticancer effect through inhibition of signaling pathways vital to B-cell proliferation, differentiation, and survival.⁶³ Ibrutinib was the first-in-class BTKi. Its use is associated with increased risk of developing AF, with incidence rates ranging from 4% to 16%.⁶⁴ A retrospective case-control study of patients with B-cell malignancies showed a 5-fold increase of incident AF in the ibrutinib-treated group compared with cytotoxic chemotherapy.⁶⁵ Acalabrutinib is a next-generation BTKi that has demonstrated a lower incidence of AF and noninferior cancer outcomes compared with ibrutinib in patients being treated for chronic lymphocytic leukemia.⁶⁶

PC strategies for patients who develop AF during BTKi treatment necessitate careful evaluation for hemodynamic stability and symptoms, assessment of thromboembolic and bleeding risks, review of drug-drug interactions, and shared decision-making conversations with the patient. In the acute setting, hemodynamically unstable patients should undergo cardioversion whereas stable patients may be considered for either rate control or rhythm control using the same principles that influence AF management in the general population. In asymptomatic or mildly symptomatic patients without clinical signs of HF, a rate control strategy of <110 beats per minute is reasonable.⁶⁷ BB are preferred while actively receiving cancer treatment;

nondihydropyridine calcium channel blockers should be used with caution due to CYP3A4 (cytochrome P450 3A4) inhibition, which may lead to interaction with cancer treatments.^{15,64} Successful rate control may be limited by baseline hypotension, in part due to high rates of autonomic dysfunction in patients with cancer.⁶⁸

In those who remain symptomatic or are unable to achieve rate control, rhythm control is reasonable. A thorough medication reconciliation and interval QT monitoring is advisable if pursuing rhythm control with medications. Amiodarone is a commonly used antiarrhythmic agent and is associated with QT prolongation; it can also lead to drug–drug interactions due to inhibition of P-gp (permeability glycoprotein transporters) and CYP3A4 leading to supratherapeutic drug levels.⁶⁹ Flecainide and propafenone may also be considered in those without underlying structural heart disease. There are no robust prospective trials assessing the safety and efficacy of AF catheter ablation specifically in the population of patients with cancer; however, small retrospective studies have shown similar outcomes for AF ablation in patients with and without cancer.⁷⁰ Therefore, catheter ablation can be considered in patients with coexistent HF or for those with symptomatic AF who have failed or are unable to tolerate antiarrhythmic drugs.⁷¹ From an oncologic standpoint, transitioning from ibrutinib to acalabrutinib, which has greater BTK selectivity and carries less risk for AF, may be considered after multidisciplinary discussions, although cost/insurance-related issues may limit access to newer-generation BTKi.

One unique challenge of AF management in the population of patients with cancer is an accurate assessment of thromboembolic risk. Patients with cancer are at elevated risk for both thrombotic and major bleeding events and commonly used risk calculators have not been well validated in this population.^{72,73} Choice of anticoagulant should also specifically consider drug–drug interactions with anticancer or supportive therapies. Notably direct oral anticoagulants are metabolized by P-gp and CYP3A4, which may lead to supratherapeutic levels if there is concomitant use of medications that inhibit these systems or subtherapeutic levels with concomitant use of medications that induce these systems.⁷⁴ Ibrutinib is an inhibitor of the P-gp system and leads to impaired collagen-induced platelet aggregation⁷⁵; an increased rate of major and minor bleeding has been observed in ibrutinib-treated patients with B-cell malignancies.⁷⁶ To mitigate this increased bleeding risk, some centers have recommended initiating a dose-reduced direct oral anticoagulant in select ibrutinib-treated patients who develop AF (ie, those with HAS-BLED scores ≥ 3).^{75,77} These patients should be closely monitored for 10 to 14 days before increasing to full-dose anticoagulation. For patients at extremely high risk of bleeding, continuation of dose-reduced direct oral anticoagulant therapy can be considered until clinical stabilization.

Based on the possible underestimation of thromboembolic risk, the ESC guidelines give a Class IIa recommendation to consider thromboprophylaxis in men with $\text{CHA}_2\text{DS}_2\text{-VASC}=0$ and women with $\text{CHA}_2\text{DS}_2\text{-VASC}=1$.¹⁵ Data evaluating the efficacy of left atrial appendage occlusion in this population are limited; however, small studies have shown similar stroke rates, bleeding risks, and mortality in patients with cancer compared with patients without cancer.^{78,79} In the face of these uncertainties, a multidisciplinary approach that incorporates shared decision-making with patients is essential to tailor safe and effective treatment plans.

QT Prolongation

Cancer therapies have also been recognized to affect cardiac myocyte repolarization, represented on ECG by prolongation of the QT interval. QT prolongation is of particular clinical importance due to its association with torsades de pointes and an increased risk of sudden cardiac death.⁸⁰ Noncancer QT-prolonging medications, such as antiemetics or antidepressants, are often used for symptom palliation during cancer therapy, thereby heightening arrhythmogenic risk. Common QT-prolonging cancer therapies include histone deacetylase inhibitors, cyclin-dependent kinase 4/6 inhibitors, arsenic trioxide, TKIs targeting Bcr-Abl (eg, nilotinib, dasatinib, bosutinib), and VSPis.⁸¹ Use of the Fridericia formula to measure corrected QT interval (QTcF) is recommended due to its more accurate performance at tachycardic and bradycardic heart rates [$\text{QTcF} = \text{QT} \times (\text{R-R interval})^{-1/3}$].⁸² Manual calculation of QTcF is suggested, especially when the QRS complex is prolonged due to ventricular pacing or bundle-branch blocks. There is a 2- to 3-fold increased risk of torsades de pointes with QTcF >500 ms, whereas the risk of torsades de pointes is exceptionally low with QTcF <500 ms.⁸³

ICOS defines a prolonging QTcF as 480 to 500 ms, and a prolonged QTcF as >500 ms³ (Table). Cardiology consultation is recommended for patients with a prolonged or prolonging QTcF to screen for symptoms including palpitations, dizziness, and syncope that may raise concern for malignant arrhythmia. Alternative causes for QT prolongation should be identified and addressed such as electrolyte abnormalities (ie, hypomagnesemia, hypokalemia, and hypocalcemia) and concomitant use of noncancer QT-prolonging medications. There is a Class I recommendation to temporarily interrupt QT-prolonging cancer therapies in those who develop asymptomatic QTcF >500 ms, with daily ECGs until QTcF improves.¹⁵ A multidisciplinary discussion is recommended when PC is being considered. Specific PC strategies include drug dose reduction and weekly ECG monitoring after restarting cancer therapy. Permanent discontinuation of QTcF prolonging cancer therapy is recommended in those

who develop torsades de pointes or sustained ventricular arrhythmia during treatment.¹⁵

END-OF-CANCER THERAPY MANAGEMENT CONSIDERATIONS IN PC

One clinical question that arises for patients managed through PC strategies is whether to continue CPT once cancer treatment is complete. Cancer treatment-associated hypertension is typically reversible (often within a few days), so deescalation of antihypertensives may be necessary to avoid hypotension.⁴⁹ Home BP monitoring can be used to guide titration. Regarding CPT for CTRCD, the ESC guidelines suggest that CPT discontinuation may be considered in patients with asymptomatic mild–moderate CTRCD who have fully recovered their LV function.¹⁵ Before weaning, a multidisciplinary discussion is recommended for risk stratification based on preexisting cardiovascular comorbidities, magnitude and duration of CTRCD before recovery, and family history of cardiomyopathy. CPT should be continued in high-risk patients (Class I), with consideration of weaning in low-moderate risk patients (Class IIa).¹⁵ Notably, these recommendations are based on expert consensus, without any supporting evidence; further study is warranted regarding the safety of long-term discontinuation strategies.

CONCLUSIONS

PC is a concept that reflects a new management paradigm for patients undergoing cancer therapy who develop cardiovascular side effects. It encompasses a change in mindset that focuses on the creation of individualized cardioprotective treatment plans under close multidisciplinary monitoring to allow continuation of lifesaving and life-extending cancer treatments. Improvements in the diagnostic and therapeutic tools available to cardio-oncologists, as well as a recognition of the negative effects of cancer treatment disruption have catalyzed the field of cardio-oncology and made PC strategies possible. However, frequent assessment and consideration of competing risks of cardiotoxicity and benefits of cancer therapy is required. A multidisciplinary team-based approach between cardiologists, oncologists, and pharmacists is essential to safely treat this patient population in a timely and coordinated manner. Although there remains a lack of robust data guiding PC treatment and monitoring, cardio-oncology society guidelines and consensus statements continue to provide a growing framework for clinicians to follow. Future research into the optimal CPT and surveillance strategies is needed to fill current gaps in knowledge surrounding the growing applications of PC.

ARTICLE INFORMATION

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REFERENCES

- Porter C, Azam TU, Mohananey D, Kumar R, Chu J, Lenihan D, Dent S, Ganatra S, Beasley GS, Okwuosa T. Permissive cardiotoxicity. *JACC: CardioOncology*. 2022;4:302–312. doi: [10.1016/j.jacc.2022.07.005](https://doi.org/10.1016/j.jacc.2022.07.005)
- Cardinale D, Iacopo F, Cipolla CM. Cardiotoxicity of anthracyclines. *Front Cardiovasc Med*. 2020;7:26. doi: [10.3389/fcvm.2020.00026](https://doi.org/10.3389/fcvm.2020.00026)
- Herrmann J, Lenihan D, Armenian S, Barac A, Blaes A, Cardinale D, Carver J, Dent S, Ky B, Lyon AR, et al. Defining cardiovascular toxicities of cancer therapies: an International Cardio-Oncology Society (IC-OS) consensus statement. *Eur Heart J*. 2022;43:280–299. doi: [10.1093/eurheartj/ehab674](https://doi.org/10.1093/eurheartj/ehab674)
- Miller KD, Nogueira L, Devasia T, Mariotto AB, Yabroff KR, Jemal A, Kramer J, Siegel RL. Cancer treatment and survivorship statistics, 2022. *CA A Cancer J Clinicians*. 2022;72:409–436. doi: [10.3322/caac.21731](https://doi.org/10.3322/caac.21731)
- Liutkauskienė S, Grizas S, Jureniene K, Suipyte J, Statnickaitė A, Juozaityte E. Retrospective analysis of the impact of anthracycline dose reduction and chemotherapy delays on the outcomes of early breast cancer molecular subtypes. *BMC Cancer*. 2018;18:453. doi: [10.1186/s12885-018-4365-y](https://doi.org/10.1186/s12885-018-4365-y)
- Soriano EC, Perndorfer C, Otto AK, Fenech AL, Siegel SD, Dickson-Witmer D, Clements L, Laurenceau JP. Psychosocial impact of cancer care disruptions in women with breast cancer during the COVID-19 pandemic. *Front Psychol*. 2021;12:662339. doi: [10.3389/fpsyg.2021.662339](https://doi.org/10.3389/fpsyg.2021.662339)
- Raphael MJ, Biagi JJ, Kong W, Mates M, Booth CM, Mackillop WJ. The relationship between time to initiation of adjuvant chemotherapy and survival in breast cancer: a systematic review and meta-analysis. *Breast Cancer Res Treat*. 2016;160:17–28. doi: [10.1007/s10549-016-3960-3](https://doi.org/10.1007/s10549-016-3960-3)
- Biagi JJ, Raphael MJ, Mackillop WJ, Kong W, King WD, Booth CM. Association between time to initiation of adjuvant chemotherapy and survival in colorectal cancer: a systematic review and meta-analysis. *JAMA*. 2011;305:2335. doi: [10.1001/jama.2011.749](https://doi.org/10.1001/jama.2011.749)
- Chen Z, King W, Pearcey R, Kerba M, Mackillop WJ. The relationship between waiting time for radiotherapy and clinical outcomes: a systematic review of the literature. *Radiother Oncol*. 2008;87:3–16. doi: [10.1016/j.radonc.2007.11.016](https://doi.org/10.1016/j.radonc.2007.11.016)
- Hanna TP, King WD, Thibodeau S, Jalink M, Paulin GA, Harvey-Jones E, O'Sullivan DE, Booth CM, Sullivan R, Aggarwal A. Mortality due to cancer treatment delay: systematic review and meta-analysis. *BMJ*. 2020;371:m4087. doi: [10.1136/bmj.m4087](https://doi.org/10.1136/bmj.m4087)
- Lebel S, Ozakinci G, Humphris G, Mutsaers B, Thewes B, Prins J, Dinkel A, Butow P. From normal response to clinical problem: definition and clinical features of fear of cancer recurrence. *Support Care Cancer*. 2016;24:3265–3268. doi: [10.1007/s00520-016-3272-5](https://doi.org/10.1007/s00520-016-3272-5)
- Sardesai S, Sukumar J, Kassem M, Palettas M, Stephens J, Morgan E, Addison D, Baliga R, Stover DG, VanDeusen J, et al. Clinical impact of interruption in adjuvant trastuzumab therapy in patients with operable HER-2 positive breast cancer. *Cardio-Oncology*. 2020;6:26. doi: [10.1186/s40959-020-00081-9](https://doi.org/10.1186/s40959-020-00081-9)
- Liu Y. A novel cardio-oncology service line model in optimizing care access, quality and equity for large, multi-hospital health systems. *Cardio-Oncology*. 2023;9:16. doi: [10.1186/s40959-023-00167-0](https://doi.org/10.1186/s40959-023-00167-0)
- Lyon AR, Dent S, Stanway S, Earl H, Brezden-Masley C, Cohen-Solal A, Tocchetti CG, Moslehi JJ, Groarke JD, Bergler-Klein J, et al. Baseline cardiovascular risk assessment in cancer patients scheduled to receive cardiotoxic cancer therapies: a position statement and new risk

- assessment tools from the cardio-oncology study Group of the Heart Failure Association of the European Society of Cardiology in collaboration with the International Cardio-Oncology Society. *Eur J Heart Fail*. 2020;22:1945–1960. doi: [10.1002/ehf.1920](https://doi.org/10.1002/ehf.1920)
15. Lyon AR, López-Fernández T, Couch LS, Asteggiano R, Aznar MC, Bergler-Klein J, Boriani G, Cardinale D, Cordoba R, Cosyns B, et al. 2022 ESC guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS). *Eur Heart J*. 2022;43:4229–4361. doi: [10.1093/eurheartj/ehac244](https://doi.org/10.1093/eurheartj/ehac244)
 16. Georgiopoulos G, Makris N, Laina A, Theodorakakou F, Briasoulis A, Trougakos IP, Dimopoulos MA, Kastritis E, Stamatelopoulos K. Cardiovascular toxicity of proteasome inhibitors: underlying mechanisms and management strategies. *JACC: CardioOncology*. 2023;5:1–21. doi: [10.1016/j.jacc.2022.12.005](https://doi.org/10.1016/j.jacc.2022.12.005)
 17. Rao VU, Reeves DJ, Chugh AR, O'Quinn R, Fradley MG, Raghavendra M, Dent S, Barac A, Lenihan D. Clinical approach to cardiovascular toxicity of oral antineoplastic agents. *J Am Coll Cardiol*. 2021;77:2693–2716. doi: [10.1016/j.jacc.2021.04.009](https://doi.org/10.1016/j.jacc.2021.04.009)
 18. Franquiz MJ, Waliany S, Xu AY, Hnatiuk A, Wu SM, Cheng P, Wakelee HA, Neal J, Witteles R, Zhu H. Osimertinib-associated cardiomyopathy in patients with non-small cell lung cancer. *JACC: CardioOncology*. 2023;5:839–841. doi: [10.1016/j.jacc.2023.07.006](https://doi.org/10.1016/j.jacc.2023.07.006)
 19. Cardinale D, Colombo A, Lamantia G, Colombo N, Civelli M, de Giacomi G, Rubino M, Veglia F, Fiorentini C, Cipolla CM. Anthracycline-induced cardiomyopathy. *J Am Coll Cardiol*. 2010;55:213–220. doi: [10.1016/j.jacc.2009.03.095](https://doi.org/10.1016/j.jacc.2009.03.095)
 20. Gregoriotti V, Fernandez TL, Costa D, Chahla EO, Daniele AJ. Use of sacubitril/valsartan in patients with cardio toxicity and heart failure due to chemotherapy. *Cardio-Oncology*. 2020;6:24. doi: [10.1186/s40959-020-00078-4](https://doi.org/10.1186/s40959-020-00078-4)
 21. Dilli Babu A, Ali A, Gaddipati G, Ruturaj Jadhav R, Reddy Tallapalli J, Sainatham C, A. Iliescu C, Chatila K, Deswal A, Khalife W. Cardiovascular impacts of SGLT2 inhibitors on the mitigation of anthracycline-induced cardiomyopathy: a comprehensive systematic review and meta-analysis. *Journal of Cardiac Failure - Intersections*. 2026;2:219–229. doi: [10.1016/j.jcf.2026.02.015](https://doi.org/10.1016/j.jcf.2026.02.015)
 22. Neilan TG, Quinaglia T, Onoue T, Mahmood SS, Drobni ZD, Gilman HK, Smith A, Heemelaar JC, Brahmabhatt P, Ho JS, et al. Atorvastatin for anthracycline-associated cardiac dysfunction: the STOP-CA randomized clinical trial. *JAMA*. 2023;330:528–536. doi: [10.1001/jama.2023.11887](https://doi.org/10.1001/jama.2023.11887)
 23. Van Dalen EC, Van Der Pal HJ, Kremer LC. Different dosage schedules for reducing cardiotoxicity in people with cancer receiving anthracycline chemotherapy. *Cochrane Gynaecological, neuro-oncology and orphan cancer group, ed. Cochrane Database Syst Rev*. 2016;6:1–62. doi: [10.1002/14651858.CD005008.pub4](https://doi.org/10.1002/14651858.CD005008.pub4)
 24. Smith LA, Cornelius VR, Plummer CJ, Levitt G, Verrill M, Canney P, Jones A. Cardiotoxicity of anthracycline agents for the treatment of cancer: Systematic review and meta-analysis of randomised controlled trials. *BMC Cancer*. 2010;10:337. doi: [10.1186/1471-2407-10-337](https://doi.org/10.1186/1471-2407-10-337)
 25. Rahman AM, Yusuf SW, Ewer MS. Anthracycline-induced cardiotoxicity and the cardiac-sparing effect of liposomal formulation. *Int J Nanomedicine*. 2007;2:567–583.
 26. Ganatra S, Nohria A, Shah S, Groarke JD, Sharma A, Venesky D, Patten R, Gunturu K, Zarwan C, Neilan TG, et al. Upfront dexrazoxane for the reduction of anthracycline-induced cardiotoxicity in adults with preexisting cardiomyopathy and cancer: a consecutive case series. *Cardio-Oncology*. 2019;5:1. doi: [10.1186/s40959-019-0036-7](https://doi.org/10.1186/s40959-019-0036-7)
 27. ZINECARD® (dexrazoxane) for injection.
 28. Swain SM, Whaley FS, Gerber MC, Weisberg S, York M, Spicer D, Jones SE, Wadler S, Desai A, Vogel C, et al. Cardioprotection with dexrazoxane for doxorubicin-containing therapy in advanced breast cancer. *JCO*. 1997;15:1318–1332. doi: [10.1200/JCO.1997.15.4.1318](https://doi.org/10.1200/JCO.1997.15.4.1318)
 29. Tebbi CK, London WB, Friedman D, Villaluna D, de Alarcon PA, Constine LS, Mendenhall NP, Spoto R, Chauvenet A, Schwartz CL. Dexrazoxane-associated risk for acute myeloid leukemia/myelodysplastic syndrome and other secondary malignancies in pediatric Hodgkin's disease. *JCO*. 2007;25:493–500. doi: [10.1200/JCO.2005.02.3879](https://doi.org/10.1200/JCO.2005.02.3879)
 30. Kopp LM, Womer RB, Schwartz CL, Ebb DH, Franco VI, Hall D, Barkauskas DA, Krailo MD, Grier HE, Meyers PA, et al. Children's Oncology Group. Effects of dexrazoxane on doxorubicin-related cardiotoxicity and second malignant neoplasms in children with osteosarcoma: a report from the Children's Oncology Group. *Cardio-Oncology*. 2019;5:15. doi: [10.1186/s40959-019-0050-9](https://doi.org/10.1186/s40959-019-0050-9)
 31. Reichardt P, Tabone MD, Mora J, Morland B, Jones RL. Risk-benefit of dexrazoxane for preventing anthracycline-related cardiotoxicity: Re-evaluating the European labeling. *Future Oncol*. 2018;14:2663–2676. doi: [10.2217/fon-2018-0210](https://doi.org/10.2217/fon-2018-0210)
 32. Swain SM, Shastry M, Hamilton E. Targeting HER2-positive breast cancer: advances and future directions. *Nat Rev Drug Discov*. 2023;22:101–126. doi: [10.1038/s41573-022-00579-0](https://doi.org/10.1038/s41573-022-00579-0)
 33. Ewer MS, Vooletich MT, Durand JB, Woods ML, Davis JR, Valero V, Lenihan DJ. Reversibility of trastuzumab-related cardiotoxicity: new insights based on clinical course and response to medical treatment. *JCO*. 2005;23:7820–7826. doi: [10.1200/JCO.2005.13.300](https://doi.org/10.1200/JCO.2005.13.300)
 34. Lynce F, Barac A, Geng X, Dang C, Yu AF, Smith KL, Gallagher C, Pohlmann PR, Nunes R, Herbolzheimer P, et al. Prospective evaluation of the cardiac safety of HER2-targeted therapies in patients with HER2-positive breast cancer and compromised heart function: the SAFE-HEaRt study. *Breast Cancer Res Treat*. 2019;175:595–603. doi: [10.1007/s10549-019-05191-2](https://doi.org/10.1007/s10549-019-05191-2)
 35. Leong DP, Cosman T, Alhussein MM, Kumar Tyagi N, Karampatos S, Barron CC, Wright D, Tandon V, Magloire P, Joseph P, et al. Safety of continuing trastuzumab despite mild cardiotoxicity. *JACC: CardioOncology*. 2019;1:1–10. doi: [10.1016/j.jacc.2019.06.004](https://doi.org/10.1016/j.jacc.2019.06.004)
 36. Safety of Continuing HER-2 Directed Therapy in Overt Left Ventricular Dysfunction: A Randomized, Controlled Trial. Published online December 17 2020 Accessed July 1, 2021. <https://clinicaltrials.gov/study/NCT04680442>
 37. Touyz RM, Herrmann SMS, Herrmann J. Vascular toxicities with VEGF inhibitor therapies—focus on hypertension and arterial thrombotic events. *J Am Soc Hypertens*. 2018;12:409–425. doi: [10.1016/j.jash.2018.03.008](https://doi.org/10.1016/j.jash.2018.03.008)
 38. Leong DP, Guha A, Morgans AK, Niaz T, Pinthus JH. Cardiovascular risk in prostate cancer. *JACC: CardioOncology*. 2024;6:835–846. doi: [10.1016/j.jacc.2024.09.012](https://doi.org/10.1016/j.jacc.2024.09.012)
 39. Zhao J, Zhu S, Sun L, Meng F, Zhao L, Zhao Y, Tian H, Li P, Niu Y. Androgen deprivation therapy for prostate cancer is associated with cardiovascular morbidity and mortality: a meta-analysis of population-based observational studies. Kyprianou N, ed. *PLoS One*. 2014;9:e107516. doi: [10.1371/journal.pone.0107516](https://doi.org/10.1371/journal.pone.0107516)
 40. Tsai HK, D'Amico AV, Sadetsky N, Chen MH, Carroll PR. Androgen deprivation therapy for localized prostate cancer and the risk of cardiovascular mortality. *JNCI J Natl Cancer Inst*. 2007;99:1516–1524. doi: [10.1093/jnci/djml168](https://doi.org/10.1093/jnci/djml168)
 41. Sorrentino MF, Kim J, Foderaro AE, Truesdell AG. 5-fluorouracil induced cardiotoxicity: review of the literature. *Cardiol J*. 2012;19:453–457. doi: [10.5603/CJ.2012.0084](https://doi.org/10.5603/CJ.2012.0084)
 42. Sara JD, Kaur J, Khodadadi R, Rehman M, Lobo R, Chakrabarti S, Herrmann J, Lerman A, Grothey A. 5-fluorouracil and cardiotoxicity: a review. *Ther Adv Med Oncol*. 2018;10:1758835918780140. doi: [10.1177/1758835918780140](https://doi.org/10.1177/1758835918780140)
 43. Padegimas A, Carver JR. How to diagnose and manage patients with fluoropyrimidine-induced chest pain. *JACC: CardioOncology*. 2020;2:650–654. doi: [10.1016/j.jacc.2020.06.012](https://doi.org/10.1016/j.jacc.2020.06.012)
 44. Desai A, Mohammed T, Patel KN, Almnajam M, Kim AS. 5-fluorouracil Rechallenge after cardiotoxicity. *Am J Case Rep*. 2020;21. doi: [10.12659/AJCR.924446](https://doi.org/10.12659/AJCR.924446)
 45. Clasen SC, Ky BX, O'Quinn R, Giantonio B, Teitelbaum U, Carver JR. Fluoropyrimidine-induced cardiac toxicity: challenging the current paradigm. *J Gastrointest Oncol*. 2017;8:970–979. doi: [10.21037/jgo.2017.09.07](https://doi.org/10.21037/jgo.2017.09.07)
 46. Zafar A, Drobni ZD, Lei M, Gongora CA, Quinaglia T, Lou UY, Mosarla R, Murphy SP, Jones-O'Connor M, Mahmood A, et al. The efficacy and safety of cardio-protective therapy in patients with 5-FU (fluorouracil)-associated coronary vasospasm. Taniyama Y, ed. *PLoS One*. 2022;17:e0265767. doi: [10.1371/journal.pone.0265767](https://doi.org/10.1371/journal.pone.0265767)
 47. Shaib W, Lee V, Saif MW. Bolus 5-fluorouracil as an alternative modality to infusion 5-fluorouracil in a patient with rectal cancer and capecitabine-induced cardiotoxicity. *In Vivo* 2009;23:821–826.
 48. Chakrabarti S, Sara J, Lobo R, Eiring R, Finnes H, Mitchell J, Hartgers M, Okano A, Halfdanarson T, Grothey A. Bolus 5-fluorouracil (5-FU) in combination with oxaliplatin is safe and well tolerated in patients who experienced coronary vasospasm with Infusional 5-FU or capecitabine. *Clin Colorectal Cancer*. 2019;18:52–57. doi: [10.1016/j.clcc.2018.09.006](https://doi.org/10.1016/j.clcc.2018.09.006)
 49. Cohen JB, Brown NJ, Brown SA, Dent S, Dorst DCH, Herrmann SM, Lang NN, Oudit GY, Touyz RM. Cancer therapy-related hypertension: a

- scientific statement from the American Heart Association. *Hypertension*. 2023;80:e46–e57. doi: [10.1161/HYP.0000000000000224](https://doi.org/10.1161/HYP.0000000000000224)
50. Cai J, Ma H, Huang F, Zhu D, Bi J, Ke Y, Zhang T. Correlation of bevacizumab-induced hypertension and outcomes of metastatic colorectal cancer patients treated with bevacizumab: a systematic review and meta-analysis. *World J Surg Oncol*. 2013;11:306. doi: [10.1186/1477-7819-11-306](https://doi.org/10.1186/1477-7819-11-306)
 51. Izzedine HA, Derosa L, Le Teuff G, Albiges L, Escudier B. Hypertension and angiotensin system inhibitors: impact on outcome in sunitinib-treated patients for metastatic renal cell carcinoma. *Ann Oncol*. 2015;26:1128–1133. doi: [10.1093/annonc/mdv147](https://doi.org/10.1093/annonc/mdv147)
 52. Mahmood SS, Fradley MG, Cohen JV, Nohria A, Reynolds KL, Heinzerling LM, Sullivan RJ, Damrongwatanasuk R, Chen CL, Gupta D, et al. Myocarditis in patients treated with immune checkpoint inhibitors. *J Am Coll Cardiol*. 2018;71:1755–1764. doi: [10.1016/j.jacc.2018.02.037](https://doi.org/10.1016/j.jacc.2018.02.037)
 53. Tawbi HA, Schadendorf D, Lipson EJ, Ascierto PA, Matamala L, Castillo Gutiérrez E, Rutkowski P, Gogas HJ, Lao CD, de Menezes JJ, et al. Relatlimab and nivolumab versus nivolumab in untreated advanced melanoma. *N Engl J Med*. 2022;386:24–34. doi: [10.1056/NEJMoa2109970](https://doi.org/10.1056/NEJMoa2109970)
 54. Tan S, Day D, Nicholls SJ, Segelov E. Immune checkpoint inhibitor therapy in oncology. *JACC: CardioOncology*. 2022;4:579–597. doi: [10.1016/j.jacc.2022.09.004](https://doi.org/10.1016/j.jacc.2022.09.004)
 55. Simonaggio A, Michot JM, Voisin AL, le Pavec J, Collins M, Lallart A, Cengizalp G, Vozy A, Laparra A, Varga A, et al. Evaluation of Readministration of immune checkpoint inhibitors after immune-related adverse events in patients with cancer. *JAMA Oncol*. 2019;5:1310–1317. doi: [10.1001/jamaoncol.2019.1022](https://doi.org/10.1001/jamaoncol.2019.1022)
 56. Itzhaki Ben Zadok O, Levi A, Divakaran S, Nohria A. Severe vs nonsevere immune checkpoint inhibitor-induced myocarditis: contemporary 1-year outcomes. *JACC CardioOncol*. 2023;5:732–744. doi: [10.1016/j.jacc.2023.09.004](https://doi.org/10.1016/j.jacc.2023.09.004)
 57. Dolladille C, Ederhy S, Sassier M, Cautela J, Thuny F, Cohen AA, Fedrizzi S, Chrétien B, da-Silva A, Plane AF, et al. Immune checkpoint inhibitor rechallenge after immune-related adverse events in patients with cancer. *JAMA Oncol*. 2020;6:865–871. doi: [10.1001/jamaoncol.2020.0726](https://doi.org/10.1001/jamaoncol.2020.0726)
 58. Schneider BJ, Naidoo J, Santomaso BD, Lacchetti C, Adkins S, Anadkat M, Atkins MB, Brassil KJ, Caterino JM, Chau I, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: ASCO guideline update. *JCO*. 2021;39:4073–4126. doi: [10.1200/JCO.21.01440](https://doi.org/10.1200/JCO.21.01440)
 59. Buza V, Rajagopalan B, Curtis AB. Cancer treatment-induced arrhythmias: focus on chemotherapy and targeted therapies. *Circ Arrhythm Electrophysiol*. 2017;10:e005443. doi: [10.1161/CIRCEP.117.005443](https://doi.org/10.1161/CIRCEP.117.005443)
 60. Guha A, Fradley MG, Dent SF, Weintraub NL, Lustberg MB, Alonso A, Addison D. Incidence, risk factors, and mortality of atrial fibrillation in breast cancer: a SEER-Medicare analysis. *Eur Heart J*. 2022;43:300–312. doi: [10.1093/eurheartj/ehab745](https://doi.org/10.1093/eurheartj/ehab745)
 61. Madnick DL, Fradley MG. Atrial fibrillation and cancer patients: mechanisms and management. *Curr Cardiol Rep*. 2022;24:1517–1527. doi: [10.1007/s11886-022-01769-3](https://doi.org/10.1007/s11886-022-01769-3)
 62. Yun JP, Choi EK, Han KD, Park SH, Jung JH, Park SH, Ahn HJ, Lim JH, Lee SR, Oh S. Risk of atrial fibrillation according to cancer type. *JACC: CardioOncology*. 2021;3:221–232. doi: [10.1016/j.jacc.2021.03.006](https://doi.org/10.1016/j.jacc.2021.03.006)
 63. Alu A, Lei H, Han X, Wei Y, Wei X. BTK inhibitors in the treatment of hematological malignancies and inflammatory diseases: mechanisms and clinical studies. *J Hematol Oncol*. 2022;15:138. doi: [10.1186/s13045-022-01353-w](https://doi.org/10.1186/s13045-022-01353-w)
 64. Ganatra S, Sharma A, Shah S, Chaudhry GM, Martin DT, Neilan TG, Mahmood SS, Barac A, Groarke JD, Hayek SS, et al. Ibrutinib-associated atrial fibrillation. *JACC: Clinical Electrophysiology*. 2018;4:1491–1500. doi: [10.1016/j.jacep.2018.06.004](https://doi.org/10.1016/j.jacep.2018.06.004)
 65. Fradley MG, Gilksman M, Emole J, Viganego F, Rhea I, Welter-Frost A, Armanious M, Lee DH, Walko C, Shah B, et al. Rates and risk of atrial arrhythmias in patients treated with ibrutinib compared with cytotoxic chemotherapy. *Am J Cardiol*. 2019;124:539–544. doi: [10.1016/j.amjcard.2019.05.029](https://doi.org/10.1016/j.amjcard.2019.05.029)
 66. Byrd JC, Hillmen P, Ghia P, Kater AP, Chanan-Khan A, Furman RR, O'Brien S, Yenerel MN, Illés A, Kay N, et al. Acalabrutinib versus ibrutinib in previously treated chronic lymphocytic leukemia: results of the first randomized phase III trial. *JCO*. 2021;39:3441–3452. doi: [10.1200/JCO.21.01210](https://doi.org/10.1200/JCO.21.01210)
 67. Van Gelder IC, Groenveld HF, Crijns HJGM, Tuininga YS, Tijssen JG, Alings AM, Hillege HL, Bergsma-Kadijk JA, Cornel JH, Kamp O, et al. Lenient versus strict rate control in patients with atrial fibrillation. *N Engl J Med*. 2010;362:1363–1373. doi: [10.1056/NEJMoa1001337](https://doi.org/10.1056/NEJMoa1001337)
 68. Fradley MG, Beckie TM, Brown SA, Cheng RK, Dent SF, Nohria A, Patton KK, Singh JP, Olshansky B. Recognition, prevention, and management of arrhythmias and autonomic disorders in cardio-oncology: a scientific statement from the American Heart Association. *Circulation*. 2021;144:e41–e55. doi: [10.1161/CIR.0000000000000986](https://doi.org/10.1161/CIR.0000000000000986)
 69. McDonald MG, Au NT, Rettie AE. P450-based drug-drug interactions of amiodarone and its metabolites: diversity of inhibitory mechanisms. *Drug Metab Dispos*. 2015;43:1661–1669. doi: [10.1124/dmd.115.065623](https://doi.org/10.1124/dmd.115.065623)
 70. Ganatra S, Abraham S, Parikh R, Kamenetsky D, Patel R, Dani S, Chaudhry G, Resnic F, Shah S, Venes D, et al. Efficacy and safety of catheter ablation for atrial fibrillation in patients with cancer. *Eur Heart J*. 2020;41(Supplement_2):ehaa946.3278. doi: [10.1093/ehjci/ehaa946.3278](https://doi.org/10.1093/ehjci/ehaa946.3278)
 71. Joglar JA, Chung MK, Armbruster AL, Benjamin EJ, Chyou JY, Cronin EM, Deswal A, Eckhardt LL, Goldberger ZD, Gopinathannair R, et al. 2023 ACC/AHA/ACCP/HRS guideline for the diagnosis and management of atrial fibrillation: a report of the American College of Cardiology/American Heart Association joint committee on clinical practice guidelines. *Circulation*. 2024;149:e1–e156. doi: [10.1161/CIR.0000000000001193](https://doi.org/10.1161/CIR.0000000000001193)
 72. D'Souza M, Carlson N, Fosbøl E, Lamberts M, Smedegaard L, Nielsen D, Torp-Pedersen C, Gislason G, Schou M et al. CHA₂DS₂-VASc score and risk of thromboembolism and bleeding in patients with atrial fibrillation and recent cancer. *Eur J Prev Cardiol*. 2018;25:651–658. doi: [10.1177/2047487318759858](https://doi.org/10.1177/2047487318759858)
 73. Leader A, Mendelson Cohen N, Afek S, Jaschek R, Frajman A, Itzhaki Ben Zadok O, Raanani P, Lishner M, Spectre G. Arterial thromboembolism in patients with AF and CHA₂DS₂-VASc score 0-2 with and without cancer. *JACC: CardioOncology*. 2023;5:174–185. doi: [10.1016/j.jacc.2022.08.014](https://doi.org/10.1016/j.jacc.2022.08.014)
 74. Chen A, Stecker EA, Warden B. Direct Oral anticoagulant use: a practical guide to common clinical challenges. *JAHA*. 2020;9:e017559. doi: [10.1161/JAHA.120.017559](https://doi.org/10.1161/JAHA.120.017559)
 75. Essa H, Lodhi T, Dobson R, Wright D, Lip GYH. How to manage atrial fibrillation secondary to ibrutinib. *JACC: CardioOncology*. 2021;3:140–144. doi: [10.1016/j.jacc.2020.11.016](https://doi.org/10.1016/j.jacc.2020.11.016)
 76. Wang J, Zhao A, Zhou H, Zhu J, Niu T. Risk of bleeding associated with ibrutinib in patients with B-cell malignancies: a systematic review and meta-analysis of randomized controlled trials. *Front Pharmacol*. 2020;11:580622. doi: [10.3389/fphar.2020.580622](https://doi.org/10.3389/fphar.2020.580622)
 77. Boriani G, Corradini P, Cuneo A, Falanga A, Foà R, Gaidano G, Ghia PP, Martelli M, Marasca R, Massaia M, et al. Practical management of ibrutinib in the real life: focus on atrial fibrillation and bleeding. *Hematol Oncol*. 2018;36:624–632. doi: [10.1002/hon.2503](https://doi.org/10.1002/hon.2503)
 78. Shabtaie SA, Tan NY, Ward RC, Lewis BR, Yang EH, Holmes DR Jr, Herrmann J. Left atrial appendage occlusion in patients with atrial fibrillation and cancer. *JACC: CardioOncology*. 2023;5:203–212. doi: [10.1016/j.jacc.2022.10.016](https://doi.org/10.1016/j.jacc.2022.10.016)
 79. Davis NE, Shabtaie SA, Tan NY. Left atrial appendage occlusion in patients with cancer. *J Thromb Thrombolysis*. 2025;58:1045–1057. doi: [10.1007/s12399-025-03098-y](https://doi.org/10.1007/s12399-025-03098-y)
 80. Straus SMJM, Kors JA, De Bruin ML, van der Hooft CS, Hofman A, Heeringa J, Deckers JW, Kingma JH, Sturkenboom MC, Stricker BH, et al. Prolonged QTc interval and risk of sudden cardiac death in a population of older adults. *J Am Coll Cardiol*. 2006;47:362–367. doi: [10.1016/j.jacc.2005.08.067](https://doi.org/10.1016/j.jacc.2005.08.067)
 81. Porta-Sánchez A, Gilbert C, Spears D, Amir E, Chan J, Nanthakumar K, Thavendiranathan P. Incidence, diagnosis, and management of QT prolongation induced by cancer therapies: a systematic review. *JAHA*. 2017;6:e007724. doi: [10.1161/JAHA.117.007724](https://doi.org/10.1161/JAHA.117.007724)
 82. Viganego F, Singh R, Fradley MG. Arrhythmias and other electrophysiology issues in cancer patients receiving chemotherapy or radiation. *Curr Cardiol Rep*. 2016;18:52. doi: [10.1007/s11886-016-0730-0](https://doi.org/10.1007/s11886-016-0730-0)
 83. Zeppenfeld K, Tfelt-Hansen J, De Riva M, Winkler BG, Behr ER, Blom NA, Charron P, Corrado D, Dagres N, de Chillou C, et al; ESC Scientific Document Group. 2022 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur Heart J*. 2022;43:3997–4126. doi: [10.1093/eurheartj/ehac262](https://doi.org/10.1093/eurheartj/ehac262)