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REVIEW

Risk Assessment Prior to Cardiotoxic Anticancer Therapies in 7 Steps

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Abstract

The burdens of cardiovascular (CV) diseases and cardiotoxic side effects of cancer treatment in oncology patients are increasing in parallel. The European Society of Cardiology (ESC) 2022 Cardio-Oncology guidelines recommend the use of standardized risk stratification tools to determine the risk of cardiotoxicity associated with different anticancer treatment modalities and the severity of their complications. The use of the Heart Failure Association-International Cardio-Oncology Society (HFA-ICOS) is essential for assessing risk prior to starting cancer treatment, and validation of these methods has been performed in patients receiving anthracyclines, human epidermal receptor 2 (HER2)-targeted therapies and breakpoint cluster region-abelson oncogene locus (BCR-ABL) inhibitors. The benefits of performing baseline CV risk assessment and stratification include early recognition of cardiotoxicities, personalisation of cancer treatment and monitoring strategies, and allocation of cardioprotection to those at the highest risk. This review summarizes the key points of risk stratification in these patients. The steps include identifying the target population, assessing nonmodifiable and modifiable CV risk factors, reviewing previous oncologic therapies and CV histories, and performing baseline investigations. In summary, this review aims to provide general physicians with a simple 7-step guide that will help steer and navigate them through cardiac risk evaluation of potentially cardiotoxic oncologic treatment strategies.

Key words: cardio-oncology; risk stratification; cardiotoxicity; anti-cancer therapy; guide

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Introduction

New anti-cancer therapies have led to improved mortality rates and survival for cancer patients (Miller et al, 2022; Michaeli et al, 2023). However, the burden of cardiovascular (CV) disease (CVD) and the side effects of potentially cardiotoxic anti-cancer therapy have also increased in parallel (Bohdan et al, 2021). The aim of cardio-oncology is to allow cancer patients to receive appropriate cancer treatment safely, with the fewest interruptions and CV side effects (Lancellotti et al, 2019).

CV risk assessment and stratification performed before starting anti-cancer therapy allow for the personalisation of cardioprotective treatment and monitoring. The baseline CV risk can be divided into two components, the likelihood of cardiotoxicity occurring and the severity of this complication.

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High-risk patients can be identified and monitored more closely during and after cancer therapy, with a subgroup offering cardioprotective medication. This review provides a framework and an approach to assess the risk of patients starting with potentially cardiotoxic anti-cancer therapy for general physicians.

Baseline CV Risk Assessment

Step 1: Who to Assess Risk?

All patients should undergo a risk assessment before receiving potentially cardiotoxic anti-cancer medications to guide the prevention and surveillance of CV complications during and after therapy.

Anti-cancer therapies can be divided into the following groups (Roy and Ahmed, 2024; Shuel, 2022):

(a) Traditional cytotoxic chemotherapy

(b) Molecular targeted therapy

(c) Immunotherapy

(d) Radiotherapy

(e) Haematopoietic stem cell transplantation and chimeric antigen receptor (CAR)-T-cell therapy

(f) Hormone therapy

Each category of treatment has its own unique signature of CV toxicity. The 4 classes of commonly used therapies and associated cardiotoxicities are listed in Table 1. The type of cardiotoxicity will determine the investigations required for surveillance and guide prevention strategies while supporting the patient during the course of their cancer treatment.

Step 2: Reviewing the Biodata and Comorbidities of the Patient

There are shared risk factors for the development of CVD and cancer and between CVD and cancer therapy-related cardiac dysfunction (CTRCD) (Koene et al, 2016). Recently, a study identified several cancers (lung, blood, brain, oral) as contributing to CV risk when added to a CV risk score, the QRESEARCH cardiovascular risk algorithm (QRISK3) calculator (Hippisley-Cox et al, 2024). Postulated mechanisms include inflammation (Meijers and de Boer, 2019) and reactive oxygen species-induced oxidative stress (Mauro et al, 2023).

Modifiable CV risk factors are important to recognise, as they are actionable. Obesity is an independent risk factor for the development of CVD, cancer and cancer therapy-related CV toxicity (Beasley and Towbin, 2021). Smoking and excessive alcohol use can lead to similar developments due to the increased incidence of heart disease and cancer complications (Agmon Nardi and Iakobishvili, 2018). Important comorbidities are hyperlipidaemia, diabetes mellitus and hypertension, which, when present, increase the risk of cardiotoxicity during cancer therapies (Lyon et al, 2022; Szalda et al, 2017). Poor control of these CV risk factors is likely to amplify the absolute risk imparted, and the presence of two or more modifiable risk factors also increases the incidence of cardiotoxicity during chemotherapy

Table 1. 4 classes of potentially cardiotoxic anti-cancer therapies.

Group	Class	Names	Cardiotoxicity
(A) Traditional chemotherapy	Anthracyclines	Doxorubicin, Daunorubicin, Epirubicin, Idarubicin, Valrubicin, and Mitoxantrone	Heart failure Asymptomatic LVSD Atrial and ventricular arrhythmias
(B) Targeted therapy	1. HER2-targeted therapies	Trastuzumab, Pertuzumab, Lapatinib and Trastuzumab emtansine (T-DM1), neratinib, tucatinib	Heart failure Asymptomatic LVSD Hypertension
	2. VEGF inhibitors		
	2.1. Tyrosine kinase inhibitors	Sunitinib, pazopanib, sorafenib, axitinib, tivozanib, cabozantinib, regorafenib, lenvatinib, vandetinib	Hypertension Heart failure Asymptomatic LVSD Myocardial ischaemia and infarction QTc prolongation
	2.2. Monoclonal antibodies	Bevacizumab, ramucirumab	Hypertension Cardiomyopathy Arterial and venous thrombosis Bleeding
	3. EGFR inhibitors	Osimertinib	Heart failure Venous thrombosis Atrial fibrillation QTc prolongation
	4. ALK inhibitors	Crizotinib, alectinib, ceritinib	Bradyarrhythmias QTcprolongation Arterial, venous thrombosis

Table 1. Continued.

Group	Class	Names	Cardiotoxicity
	5. FLT3 inhibitors	Gilteritinib, midostaurin	QTc prolongation
	6. PI3K inhibitors	Idelalisib, copanlisib	Hypertension Hyperglycemia Peripheral oedema
	7. BCR-ABL multitargeted tyrosine kinase inhibitors (2nd & 3rd generation)	Ponatinib, nilotinib, dasatinib, bosutinib	Hypertension Heart failure Asymptomatic LVSD QTc prolongation Atherosclerosis Pulmonary hypertension Arterial and venous thrombosis
	8. Proteasome inhibitors	Bortezomib, carfilzomib, and ixazomib	Hypertension Heart failure Asymptomatic LVSD Myocardial ischaemia and infarction Atrial and ventricular arrhythmias Venous and arterial thrombosis
	9. Combination RAF & MEK inhibitors	Dabrafenib & trametinib, vemurafenib & cobimetinib, encorafenib & binimetinib	Heart failure Asymptomatic LVSD Hypertension QTc prolongation

Table 1. Continued.

Group	Class	Names	Cardiotoxicity
	10. BTK inhibitors	Ibrutinib, acalabrutinib	Heart failure Atrial fibrillation Hypertension Ventricular arrhythmias Bleeding
	11. CDK 4/6 inhibitors	Ribociclib	QTC prolongation
(C) Hormonal therapy	1. Anti-androgen therapy	Abiraterone	Atherosclerosis
	2. GnRH agonists	Goserelin, Leuprorelin	Myocardial ischaemia and infarction Diabetes mellitus Hypertension
(D) Radiotherapy			Coronary disease Pericardial effusion or constriction Valvular heart disease Cardiomyopathy Arrhythmias

LVSD, left ventricular systolic dysfunction; HER2, human epidermal receptor 2; VEGF, vascular endothelial growth factor; EGFR, epidermal growth factor; ALK, anaplastic lymphoma kinase; FLT3, FMS-like tyrosine kinase 3; PI3K, phosphoinositide 3-kinase; BCR-ABL, breakpoint cluster region-abelson oncogene locus; RAF, rapidly accelerated fibrosarcoma; MEK, mitogen-activated extracellular signal-regulated kinase; BTK, Bruton tyrosine kinase; CDK, cyclin-dependent kinase; GnRH, gonadotropin-releasing hormone.

(Armenian et al, 2008). Controlling these risk factors through smoking cessation, weight loss, physical activity and pharmacological interventions can improve overall cardiac health and reduce the development of cardiotoxicity (Zamorano et al, 2016).

Nonmodifiable CV risk factors such as age, sex and family history have been shown to significantly increase both the incidence of CVD and cancer (Koene et al, 2016; Lyon et al, 2022). Older patients are more likely to develop more frequent and more severe cardiac complications than younger patients. Older females are at greater risk for CVD than are age-matched men (Rodgers et al, 2019). Genetic variation has been shown to contribute to the development of some CV toxicities, such as anthracycline chemotherapy-related cardiac dysfunction (Linschoten et al, 2018).

The use of ten-year CV risk calculators for vascular disease in the general population, such as QRISK3 and Joint British Societies 3 (JBS3) is recommended when coronary artery disease or vascular risk assessment is relevant and when there is no prior history of coronary artery or peripheral vascular disease (JBS3 Board, 2014; Hippisley-Cox et al, 2017). This includes cancer patients planning for radiotherapy to a field including the heart or major blood vessels and men diagnosed with prostate cancer who require androgen deprivation therapy (Lyon et al, 2022). If the ten-year CV risk is elevated >10%, then addressing the modifiable factors contributing to the elevated risk is advised.

Therefore, high-risk patients from the CV perspective also face significant risks of developing CTRCD during the course of cancer treatment. The use of CV risk calculators such as the QRISK3 or JBS3 helps to highlight this group so that good control of modifiable risk factors and closer monitoring of those with nonmodifiable risk factors can be performed to potentially reduce the risk of cardiotoxicity with cancer treatment.

Step 3: Looking for Previous CVD

As mentioned previously, cancer patients have more CV risk factors than noncancer patients do (Caro-Codón et al, 2022). In addition, diseased hearts are a substrate for cardiotoxicity and have an additive effect on the risk of developing CTRCD (Perez et al, 2019). This is observed among those receiving tyrosine kinase inhibitors and those treated with anthracycline chemotherapy or trastuzumab (Blaes et al, 2020; Camilli et al, 2024; Perez et al, 2019; Vo et al, 2024).

The following cardiac conditions greatly increase the risk of CTRCD (Lyon et al, 2020).

- Heart failure or cardiomyopathy
- Severe valvular heart disease
- Significant coronary artery disease, including myocardial infarction or previous coronary revascularization with percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG)
- Atrial or ventricular arrhythmias (atrial fibrillation and/or flutter, ventricular tachycardia or fibrillation)

There is increasing evidence to suggest that genetic predisposition leads to the development of CTRCD. In a study of 213 patients with CTRCD, there was an increased incidence of pathogenic variants in genes associated with the development of cardiomyopathies, such as the Titin-truncating variants (TTNtvs), compared with healthy volunteers or the reference population. The affected patients had more heart failure, atrial fibrillation and impaired cardiac recovery than did those without the variant. The same study investigated the effects of anthracycline on mice with the TTNtv variant and reported that there was sustained myocardial contractile dysfunction in this group compared with that in those with the same variant but who did not receive anthracyclines (Garcia-Pavia et al, 2019). In another cohort of 46 patients with CTRCD, all of the identified pathogenic variants were truncating variants of Titin (Boen et al, 2024). Other genes, such as myosin heavy chain7 (*MYH7*), BAG Cochaperone 3 (*BAG3*), titin-cap (*TCAP*), lamin A/C (*LMNA*) and troponin T2 cardiac type (*TNNT2*), have also been identified among those with CTRCD (Garcia-Pavia et al, 2019). There are case reports that also suggest that pathogenic variants of the *TNNT2* gene predispose one to the development of CTRCD (Lee et al, 2024; Moghadasi et al, 2021).

According to current guidelines, preexisting valvular heart disease increases the risk of CTRCD (Lyon et al, 2020; Lyon et al, 2022). It has been postulated that valvular heart disease may lead to increased wall stress and myocardial damage, thus potentially increasing the risk of cardiotoxicity during cancer treatment (Płońska-Gościniak et al, 2023). There are also certain chemotherapy regimens that require large amounts of fluid intake, which may lead to heart failure in patients with significant valvular heart disease. For example, cisplatin carries a risk of nephrotoxicity, and rapid short-term hydration over a period of a few hours is recommended during its administration to prevent renal dysfunction (Sikking et al, 2024).

Underlying ischaemic heart disease and cardiac arrhythmias provide a substrate for future chemotherapy-related cardiotoxicity through likely similar mechanisms of myocardial injury and damage. Certain chemotherapeutic agents, such as capecitabine and 5-fluorouracil, can induce myocardial ischaemia through coronary vasospasm (Jensen et al, 2010; Mosseri et al, 1993), which may be aggravated by the presence of underlying significant coronary artery disease. Electrolyte disturbances can occur during the administration of chemotherapy, leading to QT interval disturbances and arrhythmias. Direct cardiotoxic effects from anti-cancer therapy can also result in arrhythmias. For example, Bruton tyrosine kinase inhibitors such as ibrutinib and acalabrutinib are known to confer an increased risk of atrial fibrillation (Byrd et al, 2021; Xiao et al, 2020).

In summary, preexisting CVD is a significant risk factor for the development of CTRCD. These patients will require closer follow-up and monitoring. Optimising guideline-directed medical therapy prior to starting anti-cancer treatment can potentially attenuate this risk.

Table 2. Risk categories for asymptomatic adults who are childhood and adolescent cancer survivors.

Risk category	RT dose[a] (Gy MHD)	Total cumulative doxorubicin[b] dose (mg/m^2)	Combination therapy	
			RT dose[a] (Gy MHD)	Total cumulative doxorubicin[b] dose (mg/m^2)
Very high risk	>25[c]	≥400	>15[c]	≥100
High risk	>15 to 25[c]	250–399	5–15[d]	≥100
Moderate risk	5–15[d]	100–249	<5[e]	≥100
Low risk	<5[e]	<100	-	

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[a]RT risk categorization on the basis of MHD is recommended over categorization on the basis of the prescribed dose, which may not accurately reflect cardiac radiation exposure. Depending on the dose distribution and exposure of specific cardiac substructures (as well as clinical risk factors), the treatment team may judge the patient to belong to a higher risk category. In addition, a patient may be judged to belong to a lower risk category if only a small part of the heart is exposed to a relatively high prescribed dose.

[b]Or doxorubicin equivalent.

[c]Or prescribed RT ≥35 Gy to a volume exposing the heart if MHD is not available. Note that in this case, the limited information about cardiac exposure does not allow one to distinguish between high- and very high-risk categories.

[d]Or prescribed RT 15–34 Gy to a volume exposing the heart if MHD is not available.

[e]Or prescribed RT, 15 Gy to expose the heart if MHD is not available.

Gy, grey; MHD, mean heart dose; RT, radiotherapy.

Step 4: History of Previous Cardiotoxic Oncology Treatments

Previous cancer history and therapies used are important in CV risk assessment, as some can impart a legacy for future CV complications. Knowledge of the type of cancer therapy that the patient previously received and any CV complications at the time is important in determining the risk of future cancer therapy-related cardiotoxicities.

Mitochondrial dysfunction resulting from anthracycline use can lead to cardiomyocyte destruction, progressive deterioration of cardiac function and clinical heart failure. The incidence of this phenomenon increases exponentially at higher dosages (3–5% at 400 mg/m^2 and 18–48% at 700 mg/m^2) (Cardinale et al, 2020; Curigliano et al, 2016). Past and present anthracycline exposure increases the risk of future cardiotoxicity with anti-cancer therapy (Kaboré et al, 2023; Lyon et al, 2020). In a study of 222 patients, a greater decrease in the left ventricular ejection fraction after anthracycline use was shown to lead to a nearly 8-fold increase in the incidence of trastuzumab-related cardiotoxicity (Goel et al, 2019).

Similarly, previous trastuzumab cardiotoxicity also increases the likelihood of recurrence (Lyon et al, 2020). Patients with trastuzumab cardiotoxicity often present with an asymptomatic drop in left ventricular systolic function or clinical heart failure (Mohan et al, 2018). Real-world data suggest a much higher incidence

of trastuzumab cardiotoxicity than results from meta-analyses (21% versus less than 5%) (Tang et al, 2017). Interruption and subsequent resumption of trastuzumab may be necessary if cardiotoxicity occurs with a subsequent improvement in left ventricular ejection fraction (LVEF). While most patients are able to complete trastuzumab therapy with preserved cardiac function, the risk of persistent cardiac dysfunction is the highest among those who have resumed trastuzumab therapy without cardio-oncology care (Fabiani et al, 2020).

A history of previous radiation to the chest is also important in the risk prediction of cardiotoxicity, as radiation-induced cardiac disease can develop years after exposure (Bergom et al, 2021). Conduction abnormalities and cardiomyopathies often develop as early as 2 months and up to 5 years after radiation therapy, whereas conditions such as coronary artery disease, valvular heart disease and chronic pericardial syndrome may take decades to manifest (Siaravas et al, 2023). A higher mean heart dose places the patient at increased risk of radiation-induced cardiotoxicity (Koutroumpakis et al, 2020). According to pooled analyses of 6 trials in patients with non-small cell lung cancer, those who received more than 20 grey (Gy) of radiation were 5 times more likely to develop radiation cardiotoxicity than those who received less than 10 Gy of radiation (Wang et al, 2017).

Likewise, for patients planning to receive tyrosine kinase or proteasome inhibitors, a previous history of cardiotoxicity with these medications places them at a much higher risk for subsequent cardiotoxicity (Lyon et al, 2020). Various types of tyrosine kinase inhibitors (TKIs) exhibit different cardiotoxic profiles: atrial and ventricular arrhythmias such as atrial fibrillation or ventricular tachycardia are seen with Bruton TKIs, and vascular endothelial growth factor (VEGF) TKIs result in hypertension and arterial thromboembolism, whereas epidermal growth factor (EGFR) TKIs can lead to a decline in cardiac function, heart failure and QT prolongation (Sayegh et al, 2023). Proteasome inhibitors can lead to hypertension, heart failure and even acute coronary syndrome (Georgiopoulos et al, 2023).

In addition to additive effects from older age, CV risk factors and previous cardiac disease, the European Society of Cardiology (ESC) 2022 Cardio-Oncology guidelines further classify and stratify patients according to previous cancer therapies received (Lyon et al, 2022). This will determine the risk of developing CV complications after cancer treatment and the direct intensity of monitoring for CVD in survivors.

Among childhood and adolescent cancer survivors, those who received more than 15 Gy of radiotherapy, 250 mg/m^2 total cumulative doxorubicin, or a combination of more than 5 Gy of radiotherapy and at least 100 mg/m^2 total cumulative doxorubicin, are at significant risk of developing cardiotoxicity (Table 2).

Among adult cancer survivors, pretreatment CV toxicity risk is taken into consideration, along with the dose received during radiotherapy and doxorubicin treatments. Previous high-risk haematopoietic stem cell transplantation increases the risk of CV complications in the first 5 years after therapy (Table 3).

The risk of CTRCD increases with the historical and current use of cardiotoxic anti-cancer treatment. There is also a legacy effect on the CV risk profile of cancer survivors who will benefit from closer surveillance and monitoring.

Table 3. Risk categories for asymptomatic adult cancer survivors.

Risk category	Baseline CV toxicity risk pretreatment	Additional details		RT dose[a] (Gy MHD)	Total cumulative doxorubicin[b] dose (mg/m^2)	Combination therapy	
						RT dose[a] (Gy MHD)	Total cumulative doxorubicin[b] dose (mg/m^2)
Very high risk	Very high			>25 Gy MHD[c]	≥400	>15–25 Gy MHD[c]	≥100
Early high risk (<5 years after therapy)	High	Symptomatic or asymptomatic moderate-to-severe CTRCD during treatment	High-risk HSCT[d]		250–399		
Late high risk	High	Poorly controlled CVRF		>15–25 Gy MHD[c]		5–15 Gy MHD[e]	≥100
Moderate risk	Moderate			5–15 Gy MHD[e]	100–249	<5 Gy MHD[f]	≥100
Low risk	Low	Normal end-of-therapy cardiac assessment	Recovered mild CTRCD	<5 Gy MHD[f]	<100		

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[a]RT risk categorization on the basis of MHD is recommended over categorization on the basis of the prescribed dose, which may not accurately reflect cardiac radiation exposure. Depending on the dose distribution and exposure of specific cardiac substructures (as well as clinical risk factors), the treatment team may judge the patient to belong to a higher risk category. In addition, a patient may be judged to belong to a lower risk category if only a small part of the heart is exposed to a relatively high prescribed dose.

[b]Or equivalent.

[c]Or prescribed RT ≥35 Gy to a volume exposing the heart if MHD is not available. Note that in this case, the limited information about cardiac exposure does not allow one to distinguish between high- and very high-risk categories.

[d]High-risk HSCT patients: allogenic HSCT; preexisting CVD or multiple uncontrolled CVRFs; cancer treatment history (mediastinal or mantle field radiation, alkylating agents, >250 mg/m^2 doxorubicin or equivalent); conditioning schemes (total body irradiation, alkylating agents); development of GVHD.

[e]Or prescribed RT 15–34 Gy to a volume exposing the heart if MHD is not available.

[f]Or prescribed RT, 15 Gy to expose the heart if MHD is not available.

CTRCD, cancer therapy-related cardiac dysfunction; CV, cardiovascular; CVD, cardiovascular disease; CVRF, cardiovascular risk factor; GVHD, graft vs. host disease; Gy, grey; HSCT, haematopoietic stem cell transplantation; MHD, mean heart dose; RT, radiotherapy.

Step 5: Cardiac Biomarkers

There are no precise and validated biomarker models available to date that can accurately predict and risk stratify patients starting cancer treatment.

Taking the lead from heart failure guidelines, there are strong recommendations for the use of natriuretic peptides in the diagnosis, treatment monitoring and guidance of the prognosis of heart failure patients (Heidenreich et al, 2022; McDonagh et al, 2023). In CTRCD, multiple trials have shown the utility of natriuretic peptides in the early detection of cardiotoxicity in patients receiving radiation therapy, anthracyclines, proteasome inhibitors and tyrosine kinase inhibitors (Catino et al, 2018; Cornell et al, 2019; Lenihan et al, 2016; Palumbo et al, 2016). Elevated natriuretic peptide levels have also been shown in several studies to predict the risk of adverse cardiac events and mortality. In a study with 555 cancer patients receiving different types of anti-cancer treatment, elevated levels of the precancer treatment N-terminal pro-B-type natriuretic peptide (NT-proBNP) increased the risk of mortality by 1.5 times compared with those with normal pretreatment levels (Pavo et al, 2015). Natriuretic peptide use before therapy has been shown to predict the risk of future CV events (Cornell et al, 2019; Demissei et al, 2020).

Cardiac troponins (troponin I and T) are excellent markers of cardiac myocyte injury and damage. Persistent elevations in troponin I have been shown to result in greater left ventricular cardiac dysfunction and adverse cardiac events (Cardinale et al, 2010). Trials have also shown that patients with elevated baseline troponin levels are more likely to have impaired cardiac function and demonstrate poorer recovery despite optimal guideline-directed medical therapy (Michel et al, 2018; Zardavas et al, 2017). However, owing to the sensitive nature of cardiac troponins, an increase in their levels can occur even in the absence of cardiotoxicity (Cardinale et al, 2018).

Recent publications have encouraged the use of cardiac troponin (cTn) and natriuretic peptides such as B-type natriuretic peptide (BNP) or NT-proBNP to assist in risk stratification of patients planning to receive certain cancer therapies (Lyon et al, 2020; Pudil et al, 2020). This study identified patients who may benefit from early cardioprotective strategies when receiving cardiotoxic cancer treatment. In addition, baseline measurement of these serum cardiac biomarkers is essential for monitoring the development of early CTRCD.

Step 6: Baseline Cardiology Investigations

An electrocardiogram (ECG) performed at baseline is recommended. It is simple, inexpensive and widely available, and it can indicate the presence of CVD, including undiagnosed arrhythmia. It serves as a baseline for comparison. In selected cancer patients, the baseline ECG is essential for the measurement of the QTc, with the Fridericia correction, when the patient is to start receiving a cancer therapy that may prolong the QTc intervals (Richardson et al, 2022)

Transthoracic echocardiography has been recommended by guidelines for the initial assessment of cardiac function in selected oncology patients (Lyon et al, 2022). Baseline assessment of the LVEF through 2D and 3D echocardiography and global longitudinal strain (GLS) before starting cancer therapy allows for risk

stratification and identification of changes in cardiac function during and after therapy. Current guidelines have used echocardiographic LVEF and changes in GLS to define different grades of CTRCD (Lyon et al, 2022). They also advise that these investigations be performed in patients who are planning to receive anthracycline chemotherapy, human epidermal receptor 2 (HER2)-targeted cancer therapies, those with preexisting structural heart disease who are planning to receive radiotherapy to the left chest, and high-risk patients scheduled to receive cancer therapies associated with an increased risk of CTRCD and heart failure. The challenge is access to echocardiography for many cancer patients depending upon availability and pressure on current echocardiography services. Fig. 1 summarises the guideline screening recommendations of cardiac biomarkers (natriuretic peptides and cardiac troponins), cardiac imaging (transthoracic echocardiogram), and the level of evidence for each investigation according to different risk profiles prior to starting potentially cardiotoxic cancer treatment.

Step 7: How to Deliver the Baseline CV Risk Assessment

Fig. 2 summarises the general approach one should take in managing a patient who is planning for potentially cardiotoxic therapy and helps guide the intensity of monitoring and treatment strategies for the different risk profiles.

Baseline CV risk stratification prior to starting cardiotoxic cancer therapies allows for the individualization of surveillance and cancer treatment strategies, which is a class 1 recommendation in the 2022 ESC guidelines on cardio-oncology (see Fig. 2). One method involves the use of baseline CV risk data from the 2020 position paper written by the Cardio-Oncology study group of the Heart Failure Association (HFA) of the ESC and the International Cardio-Oncology Society (ICOS), which allows oncologists and haematologists to stratify their patients into low-, moderate-, high- and very high-risk groups for developing cancer treatment-related cardiovascular toxicity (CTR-CVT) (Lyon et al, 2020). Risk assessment will identify patients at high risk of CV complications and select patients at moderate risk who will benefit from a cardio-oncology review prior to starting their cancer treatment. In addition, this process also identifies cancer patients at high or very high risk of cardiotoxicity who may benefit from cardioprotective medical therapy prior to commencing cancer treatment (Lyon et al, 2022). The individual procedures designed for each class of cancer therapy are available in the ESC Pocket Guideline App.

These risk scores have been validated in different population groups and proven to be useful in predicting the risk of CTRCD. In HER2-positive breast cancer patients, the Heart Failure Association-International Cardio-Oncology Society (HFA-ICOS) HER2-targeted therapy platform was able to identify patients at the highest risk of developing trastuzumab-related cardiac dysfunction in women with early invasive HER2+ breast cancer (Suntheralingam et al, 2022). The same protocol was validated in another cohort of HER2-positive early breast cancer patients (Battisti et al, 2021). The proforma identified 43% of the 931 patients to be at low risk, 49% to be at medium risk, 8% to be at high risk and 1% to be at very high risk of developing trastuzumab-related cardiotoxicity. Cardiotoxicity (defined as

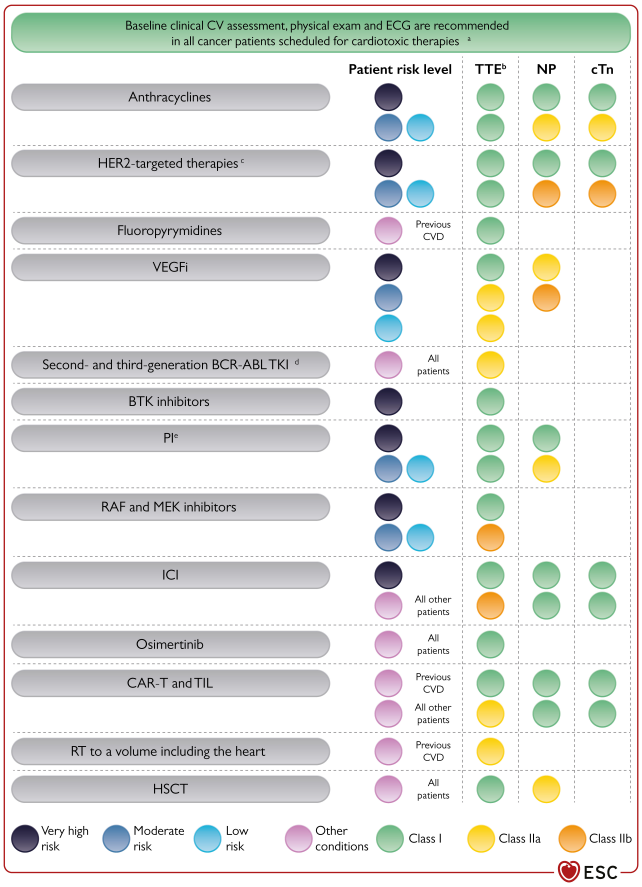

Fig. 1. Baseline screening recommendations before starting cardiotoxic drugs. Reproduced with permission from Lyon et al (2022), European Heart Journal 43, 4229–4361 (2022); published by Oxford University Press 2022. [a]Patients scheduled to receive ADT for prostate cancer, CDK4/6 inhibitors, endocrine hormone therapy for BC and anaplastic lymphoma kinase inhibitors. [b]TTE is recommended as the first-line modality for the assessment of cardiac function. Three-dimensional echocardiography is recommended for measuring LVEF. GLS is recommended for all patients with cancer who undergo echocardiography, if available. CMR should be considered when echocardiography is unavailable or not diagnostic. [c]Baseline cTn measurement should be considered (class IIa, level A) in low- and moderate-risk patients post anthracycline chemotherapy but prior to starting HER2-targeted therapies. Baseline NP and cTn measurements may be considered (class IIb, level C) in low- and moderate-risk patients. [d]Baseline echocardiography is recommended for patients scheduled to receive dasatinib (class I, level C). [e]NP and cTn measurements are recommended at baseline in patients with AL-CA (class I, level B). 3D, three-dimensional; ADT, androgen deprivation therapy; AL-CA, amyloid light-chain cardiac amyloidosis; BC, breast cancer; BCR-ABL, breakpoint cluster region-abelson oncogene locus; BNP, B-type natriuretic peptide; BTK, Bruton tyrosine kinase; CAR-T, chimeric antigen receptor T cell; CDK, cyclin-dependent kinase; CMR, cardiac magnetic resonance; cTn, cardiac troponin; CV, cardiovascular; CVD, cardiovascular disease; ECG, electrocardiogram; GLS, global longitudinal strain; HER2, human epidermal receptor 2; HSCT, haematopoietic stem cell transplantation; ICI, immune checkpoint inhibitor; LVEF, left ventricular ejection fraction; MEK, mitogen-activated extracellular signal-regulated kinase; NP, natriuretic peptide (including BNP and NT-proBNP); NT-proBNP, N-terminal pro-B-type natriuretic peptide; PI, proteasome inhibitor; RAF, rapidly accelerated fibrosarcoma; RT, radiotherapy; TIL, tumour-infiltrating lymphocyte; TKI, tyrosine kinase inhibitor; TTE, transthoracic echocardiography; VEGFi, vascular endothelial growth factor inhibitor.

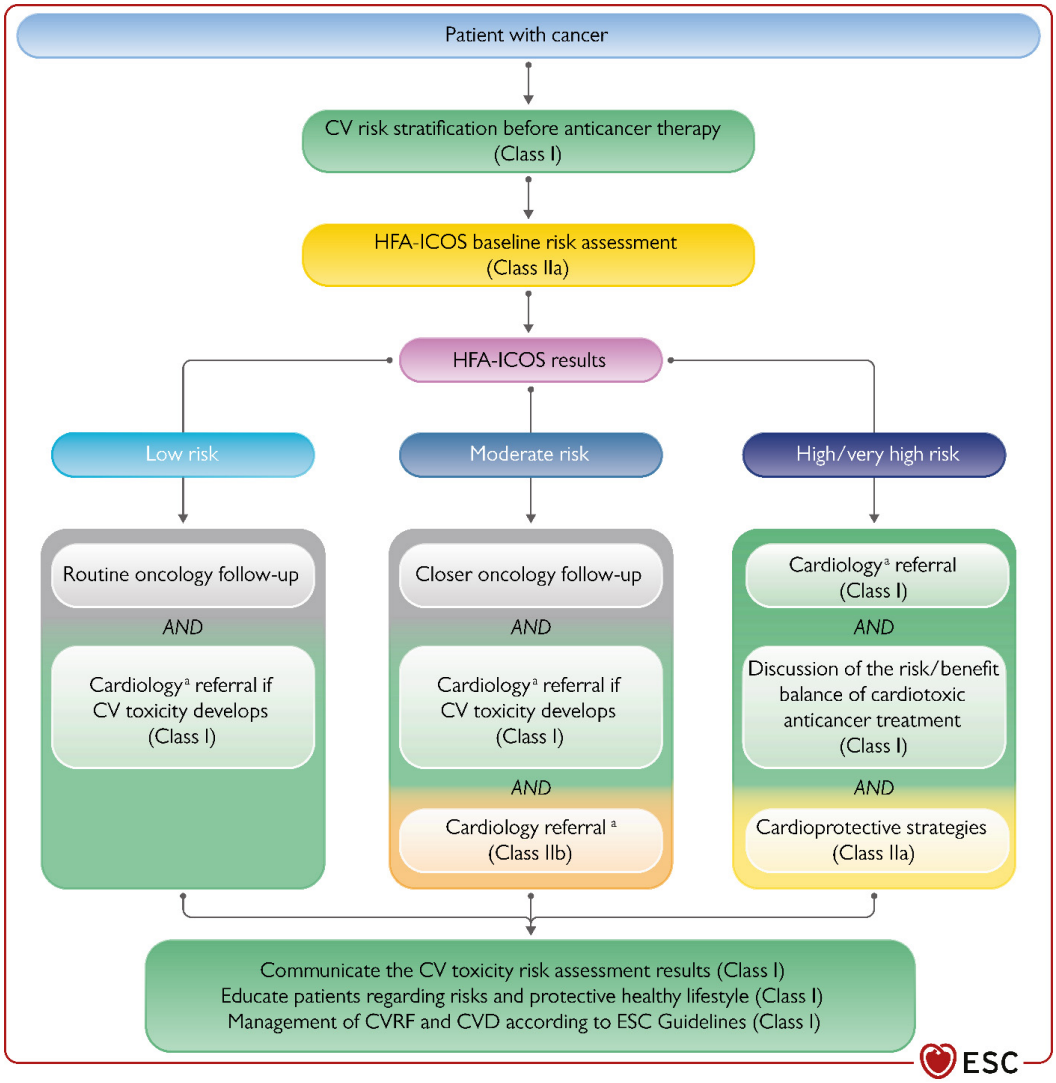

Fig. 2. General cardio-oncology approach after Heart Failure Association–International Cardio-Oncology Society toxicity risk assessment. Reproduced with permission from Lyon et al (2022), European Heart Journal 43, 4229–4361 (2022); published by Oxford University Press 2022. [a]Cardio-oncology referral is recommended when available; alternatively, patients should be referred to a specialized cardiologist with expertise in managing CVD in patients with cancer. CV, cardiovascular; CVD, CV disease; CVRF, CV risk factor; ESC, European Society of Cardiology; HFA, Heart Failure Association; ICOS, International Cardio-Oncology Society.

an asymptomatic ≥10% decline in LVEF, LVEF <50%, New York Heart Association (NYHA) Class II to IV heart failure or discontinuation of trastuzumab for cardiac reasons) was observed in 17% of the patients. The incidence of cardiotoxicity increased with increasing severity of baseline risk assessed with the HFA-ICOS HER2-targeted therapy protocol. Among patients in the low-risk group, 14% had cardiotoxicity, whereas the incidence of cardiotoxicity increased significantly to 30% in patients in the high- or very high-risk groups. This proves that the risk assessment platform was able to correctly identify patients at significant risk of developing CTRCD.

Among patients receiving anthracyclines for the treatment of different cancers, the HFA-ICOS is able to stratify patients by risk and has a good ability to predict cardiotoxicity and all-cause mortality (Rivero Santana et al, 2022; Rivero-Santana et al, 2024). One of the studies included 1066 patients from the CARDIOTOX registry who had received anthracycline therapy. The HFA-ICOS risk stratification tool was able to adequately predict symptomatic, severe, or moderate asymptomatic CTRCD at 1 year (Rivero-Santana et al, 2024).

Most recently, the HFA-ICOS risk stratification tool was found to be predictive in patients with chronic myeloid leukaemia (CML) undergoing treatment with the tyrosine kinase inhibitor (TKI) nilotinib. The proforma was able to categorize patients into low-, medium-, high- or very high-risk groups and showed that the latter group of patients had higher rates of CV events (Fernando et al, 2024).

Uncertainty remains for other agents. When the proforma was used in a small study of patients with rapidly accelerated fibrosarcoma B-type (BRAF)-mutated melanoma treated with BRAF and mitogen-activated extracellular signal-regulated kinase (MEK) inhibitors, a large proportion of low- and medium-risk patients developed CTRCD; hence, the utility of the risk stratification tool was limited (Glen et al, 2023). However, further studies are needed to validate the results of therapies other than anthracyclines, HER2-targeted therapies, BCR-ABL inhibitors and nilotinib.

Gaps in Knowledge and Future Directions

There are significant gaps in knowledge in the following areas: (a) mechanisms of cardiotoxicity in newer anti-cancer therapies, (b) cost-effectiveness of cardiotoxicity screening in the low-risk population, (c) lack of risk stratification tools for patients receiving immunotherapy and radiation treatment, and (d) external validation of the HFA-ICOS risk stratification tool. More research will be needed to improve the understanding of the pathophysiology of cardiotoxicity in newer anti-cancer therapeutic agents, as well as to explore other biochemical and imaging tools to improve baseline assessment and monitoring of cardiotoxicity. Additionally, more studies are needed to validate the HFA-ICOS risk scoring system, such that its use can be widely implemented.

Conclusion

All cancer patients scheduled to receive cardiotoxic cancer therapies should undergo baseline CV risk assessment. This is especially true for patients planning to start cancer therapies that cause CTRCD. It is also relevant for all potential CV toxicities, including hypertension, QTc prolongation and arrhythmias. This baseline assessment should be performed in the oncology and haematology departments, where the diagnosis is initially made and the nature of cancer treatment is decided. It is the type of cancer therapy that guides the need for baseline CV risk assessment, which in turn affects the degree and frequency of CV monitoring during cancer treatment and the need for cardioprotection. The HFA-ICOS is a tool that helps deliver CV risk assessment via a practical and user-friendly method, guides personalisation

of cancer therapy and the intensity of monitoring to prevent CTRCD, and guides the use of medical therapies in secondary prevention cases. The 7 steps in this review provide a general framework and explain the purpose of risk stratification. Further research is needed to improve the risk stratification process and identify new risk factors in specific cancer patient groups.

Key Points

- The personalisation of cardioprotection and monitoring strategies increases the chance of completing cancer treatment.
- Risk assessment and stratification allow for improved resource allocation for monitoring purposes and the initiation of cardioprotective treatment if needed.
- A 7-step algorithm provides the general physician with a framework to perform risk stratification before the commencement of cardiotoxic anti-cancer treatment.
- Important variables include the target population, nonmodifiable and modifiable cardiovascular risk factors, and previous oncologic and cardiovascular history. Baseline cardiac investigations are essential in risk assessment.

Availability of Data and Materials

The datasets generated and/or analysed during the current study are not publicly available due patient confidentiality but are available from the corresponding author on reasonable request.

Author Contributions

JT, IS, SR and ARL were contributors in the conception and analysis of this review. JT and AL were major contributors with drafting of the manuscript, while IS and SR assisted with the revision of this article. All authors contributed to the important editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

References

Agmon Nardi I, Iakobishvili Z. Cardiovascular Risk in Cancer Survivors. Current Treatment Options in Cardiovascular Medicine. 2018; 20: 47. https://doi.org/10.1007/s11936-018-0645-8

Armenian SH, Sun CL, Francisco L, Steinberger J, Kurian S, Wong FL, et al. Late congestive heart failure after hematopoietic cell transplantation. Journal of Clinical Oncology. 2008; 26: 5537–5543. https://doi.org/10.1200/JCO.2008.17.7428

Battisti NML, Andres MS, Lee KA, Ramalingam S, Nash T, Mappouridou S, et al. Incidence of cardiotoxicity and validation of the Heart Failure Association-International Cardio-Oncology Society risk stratification tool in patients treated with trastuzumab for HER2-positive early breast cancer. Breast Cancer Research and Treatment. 2021; 188: 149–163. https://doi.org/10.1007/s10549-021-06192-w

Beasley GS, Towbin JA. Acquired and modifiable cardiovascular risk factors in patients treated for cancer. Journal of Thrombosis and Thrombolysis. 2021; 51: 846–853. https://doi.org/10.1007/s11239-020-02273-7

Bergom C, Bradley JA, Ng AK, Samson P, Robinson C, Lopez-Mattei J, et al. Past, Present, and Future of Radiation-Induced Cardiotoxicity: Refinements in Targeting, Surveillance, and Risk Stratification. JACC. CardioOncology. 2021; 3: 343–359. https://doi.org/10.1016/j.jaccao.2021.06.007

Blaes A, Manisty C, Barac A. How to Follow, Manage and Treat Cardiac Dysfunction in Patients With Her2+ Breast Cancer. JACC. CardioOncology. 2020; 2: 661–665. https://doi.org/10.1016/j.jaccao.2020.08.010

Boen HM, Alaerts M, Goovaerts I, Saenen JB, Franssen C, Vorlat A, et al. Variants in structural cardiac genes in patients with cancer therapy-related cardiac dysfunction after anthracycline chemotherapy: a case control study. Cardio-Oncology. 2024; 10: 26. https://doi.org/10.1186/s40959-024-00231-3

Bohdan M, Kowalczys A, Mickiewicz A, Gruchała M, Lewicka E. Cancer Therapy-Related Cardiovascular Complications in Clinical Practice: Current Perspectives. Journal of Clinical Medicine. 2021; 10: 1647. https://doi.org/10.3390/jcm10081647

Byrd JC, Hillmen P, Ghia P, Kater AP, Chanan-Khan A, Furman RR, et al. Acalabrutinib Versus Ibrutinib in Previously Treated Chronic Lymphocytic Leukemia: Results of the First Randomized Phase III Trial. Journal of Clinical Oncology. 2021; 39: 3441–3452. https://doi.org/10.1200/JCO.21.01210

Camilli M, Cipolla CM, Dent S, Minotti G, Cardinale DM. Anthracycline Cardiotoxicity in Adult Cancer Patients: *JACC: CardioOncology* State-of-the-Art Review. JACC. CardioOncology. 2024; 6: 655–677. https://doi.org/10.1016/j.jaccao.2024.07.016

Cardinale D, Ciceri F, Latini R, Franzosi MG, Sandri MT, Civelli M, et al. Anthracycline-induced cardiotoxicity: A multicenter randomised trial comparing two strategies for guiding prevention with enalapril: The International CardioOncology Society-one trial. European Journal of Cancer. 2018; 94: 126–137. https://doi.org/10.1016/j.ejca.2018.02.005

Cardinale D, Colombo A, Torrisi R, Sandri MT, Civelli M, Salvatici M, et al. Trastuzumab-induced cardiotoxicity: clinical and prognostic implications of troponin I evaluation. Journal of Clinical Oncology. 2010; 28: 3910–3916. https://doi.org/10.1200/JCO.2009.27.3615

Cardinale D, Iacopo F, Cipolla CM. Cardiotoxicity of Anthracyclines. Frontiers in Cardiovascular Medicine. 2020; 7: 26. https://doi.org/10.3389/fcvm.2020.00026

Caro-Codón J, López-Fernández T, Álvarez-Ortega C, Zamora Auñón P, Rodríguez IR, Gómez Prieto P, et al. Cardiovascular risk factors during cancer treatment. Prevalence and prognostic relevance: insights from the CARDIOTOX registry. European Journal of Preventive Cardiology. 2022; 29: 859–868. https://doi.org/10.1093/eurjpc/zwaa034

Catino AB, Hubbard RA, Chirinos JA, Townsend R, Keefe S, Haas NB, et al. Longitudinal Assessment of Vascular Function With Sunitinib in Patients With Metastatic Renal Cell Carcinoma. Circulation. Heart Failure. 2018; 11: e004408. https://doi.org/10.1161/CIRCHEARTFAILURE.117.004408

Cornell RF, Ky B, Weiss BM, Dahm CN, Gupta DK, Du L, et al. Prospective Study of Cardiac Events During Proteasome Inhibitor Therapy for Relapsed Multiple Myeloma. Journal of Clinical Oncology. 2019; 37: 1946–1955. https://doi.org/10.1200/JCO.19.00231

Curigliano G, Cardinale D, Dent S, Criscitiello C, Aseyev O, Lenihan D, et al. Cardiotoxicity of anticancer treatments: Epidemiology, detection, and management. CA: a Cancer Journal for Clinicians. 2016; 66: 309–325. https://doi.org/10.3322/caac.21341

Demissei BG, Hubbard RA, Zhang L, Smith AM, Sheline K, McDonald C, et al. Changes in Cardiovascular Biomarkers With Breast Cancer Therapy and Associations With Cardiac Dysfunction. Journal of the American Heart Association. 2020; 9: e014708. https://doi.org/10.1161/JAHA.119.014708

Fabiani I, Cipolla CM, Colombo N, Cardinale D. Cardioncological Approach for Trastuzumab Therapy in Breast Cancer Patients With Cardiotoxicity: Impact on Adherence and Clinical Outcome. Frontiers in Pharmacology. 2020; 11: 1190. https://doi.org/10.3389/fphar.2020.01190

Fernando F, Andres MS, Claudiani S, Kermani NZ, Ceccarelli G, Innes AJ, et al. Cardiovascular events in CML patients treated with Nilotinib: validation of the HFA-ICOS baseline risk score. Cardio-Oncology. 2024; 10: 42. https://doi.org/10.1186/s40959-024-00245-x

Garcia-Pavia P, Kim Y, Restrepo-Cordoba MA, Lunde IG, Wakimoto H, Smith AM, et al. Genetic Variants Associated With Cancer Therapy-Induced Cardiomyopathy. Circulation. 2019; 140: 31–41. https://doi.org/10.1161/CIRCULATIONAHA.118.037934

Georgiopoulos G, Makris N, Laina A, Theodorakakou F, Briasoulis A, Trougakos IP, et al. Cardiovascular Toxicity of Proteasome Inhibitors: Underlying Mechanisms and Management Strategies: *JACC: CardioOncology* State-of-the-Art Review. JACC. CardioOncology. 2023; 5: 1–21. https://doi.org/10.1016/j.jaccao.2022.12.005

Glen C, Adam S, McDowell K, Waterston A, Tan YY, Petrie MC, et al. Cardiotoxicity of BRAF/MEK Inhibitors: A Longitudinal Study Incorporating Contemporary Definitions and Risk Scores. JACC. CardioOncology. 2023; 5: 628–637. https://doi.org/10.1016/j.jaccao.2023.04.004

Goel S, Liu J, Guo H, Barry W, Bell R, Murray B, et al. Decline in Left Ventricular Ejection Fraction Following Anthracyclines Predicts Trastuzumab Cardiotoxicity. JACC. Heart Failure. 2019; 7: 795–804. https://doi.org/10.1016/j.jchf.2019.04.014

Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2022; 145: e895–e1032. https://doi.org/10.1161/CIR.0000000000001063

Hippisley-Cox J, Coupland C, Brindle P. Development and validation of QRISK3 risk prediction algorithms to estimate future risk of cardiovascular disease: prospective cohort study. BMJ (Clinical Research Ed.). 2017; 357: j2099. https://doi.org/10.1136/bmj.j2099

Hippisley-Cox J, Coupland CAC, Bafadhel M, Russell REK, Sheikh A, Brindle P, et al. Development and validation of a new algorithm for improved cardiovascular risk prediction. Nature Medicine. 2024; 30: 1440–1447. https://doi.org/10.1038/s41591-024-02905-y

JBS3 Board. Joint British Societies' consensus recommendations for the prevention of cardiovascular disease (JBS3). Heart. 2014; 100: ii1–ii67. https://doi.org/10.1136/heartjnl-2014-305693

Jensen SA, Hasbak P, Mortensen J, Sørensen JB. Fluorouracil induces myocardial ischemia with increases of plasma brain natriuretic peptide and lactic acid but without dysfunction of left ventricle. Journal of Clinical Oncology. 2010; 28: 5280–5286. https://doi.org/10.1200/JCO.2009.27.3953

Kaboré EG, Macdonald C, Kaboré A, Didier R, Arveux P, Meda N, et al. Risk Prediction Models for Cardiotoxicity of Chemotherapy Among Patients With Breast Cancer: A Systematic Review. JAMA Network Open. 2023; 6: e230569. https://doi.org/10.1001/jamanetworkopen.2023.0569

Koene RJ, Prizment AE, Blaes A, Konety SH. Shared Risk Factors in Cardiovascular Disease and Cancer. Circulation. 2016; 133: 1104–1114. https://doi.org/10.1161/CIRCULATIONAHA.115.020406

Koutroumpakis E, Palaskas NL, Lin SH, Abe JI, Liao Z, Banchs J, et al. Modern Radiotherapy and Risk of Cardiotoxicity. Chemotherapy. 2020; 65: 65–76. https://doi.org/10.1159/000510573

Lancellotti P, Suter TM, López-Fernández T, Galderisi M, Lyon AR, Van der Meer P, et al. Cardio-Oncology Services: rationale, organization, and implementation: A report from the ESC Cardio-Oncology council. European Heart Journal. 2019; 40: 1756–1763. https://doi.org/10.1093/eurheartj/ehy453

Lee SY, Kim HS, Jung MH, Chang S, Kim M, Youn JC, et al. Genetic predisposition in chemotherapy-induced cardiomyopathy in a 65-year-old female with metastatic breast cancer. ESC Heart Failure. 2024; 11: 2410–2414. https://doi.org/10.1002/ehf2.14803

Lenihan DJ, Stevens PL, Massey M, Plana JC, Araujo DM, Fanale MA, et al. The Utility of Point-of-Care Biomarkers to Detect Cardiotoxicity During Anthracycline Chemotherapy: A Feasibility Study. Journal of Cardiac Failure. 2016; 22: 433–438. https://doi.org/10.1016/j.cardfail.2016.04.003

Linschoten M, Teske AJ, Cramer MJ, van der Wall E, Asselbergs FW. Chemotherapy-Related Cardiac Dysfunction: A Systematic Review of Genetic Variants Modulating Individual Risk. Circulation. Genomic and Precision Medicine. 2018; 11: e001753. https://doi.org/10.1161/CIRCGEN.117.001753

Lyon AR, Dent S, Stanway S, Earl H, Brezden-Masley C, Cohen-Solal A, 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. European Journal of Heart Failure. 2020; 22: 1945–1960. https://doi.org/10.1002/ejhf.1920

Lyon AR, López-Fernández T, Couch LS, Asteggiano R, Aznar MC, Bergler-Klein J, 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). European Heart Journal. 2022; 43: 4229–4361. https://doi.org/10.1093/eurheartj/ehac244

Mauro AG, Mezzaroma E, Toldo S, Melendez GC, Franco RL, Lesnefsky EJ, et al. NLRP3-mediated inflammation in cardio-oncology: sterile yet harmful. Translational Research. 2023; 252: 9–20. https://doi.org/10.1016/j.trsl.2022.08.004

McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, ESC Scientific Document Group, et al. 2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) With the special contribution of the Heart Failure Association (HFA) of the ESC. European Heart Journal. 2023; 44: 3627–3639. https://doi.org/10.1093/eurheartj/ehad195

Meijers WC, de Boer RA. Common risk factors for heart failure and cancer. Cardiovascular Research. 2019; 115: 844–853. https://doi.org/10.1093/cvr/cvz035

Michaeli DT, Michaeli JC, Michaeli T. Advances in cancer therapy: clinical benefit of new cancer drugs. Aging. 2023; 15: 5232–5234. https://doi.org/10.18632/aging.204839

Michel L, Rassaf T, Totzeck M. Biomarkers for the detection of apparent and subclinical cancer therapy-related cardiotoxicity. Journal of Thoracic Disease. 2018; 10: S4282–S4295. https://doi.org/10.21037/jtd.2018.08.15

Miller KD, Nogueira L, Devasia T, Mariotto AB, Yabroff KR, Jemal A, et al. 2022. Cancer treatment and survivorship statistics, 2022. CA: A Cancer Journal for Clinicians. 2022; 72: 409–436. https://doi.org/10.3322/caac.21731

Moghadasi S, Fijn R, Beeres SLMA, Bikker H, Jongbloed JDH, Josephus Jitta D, et al. Case series, chemotherapy-induced cardiomyopathy: mind the family history! European Heart Journal. Case Reports. 2021; 5: ytab333. https://doi.org/10.1093/ehjcr/ytab333

Mohan N, Jiang J, Dokmanovic M, Wu WJ. Trastuzumab-mediated cardiotoxicity: current understanding, challenges, and frontiers. Antibody Therapeutics. 2018; 1: 13–17. https://doi.org/10.1093/abt/tby003

Mosseri M, Fingert HJ, Varticovski L, Chokshi S, Isner JM. In vitro evidence that myocardial ischemia resulting from 5-fluorouracil chemotherapy is due to protein kinase C-mediated vasoconstriction of vascular smooth muscle. Cancer Research. 1993; 53: 3028–3033.

Palumbo I, Palumbo B, Fravolini ML, Marcantonini M, Perrucci E, Latini ME, et al. Brain natriuretic peptide as a cardiac marker of transient radiotherapy-related damage in left-sided breast cancer patients: A prospective study. Breast. 2016; 25: 45–50. https://doi.org/10.1016/j.breast.2015.10.004

Pavo N, Raderer M, Hülsmann M, Neuhold S, Adlbrecht C, Strunk G, et al. Cardiovascular biomarkers in patients with cancer and their association with all-cause mortality. Heart. 2015; 101: 1874–1880. https://doi.org/10.1136/heartjnl-2015-307848

Perez IE, Taveras Alam S, Hernandez GA, Sancassani R. Cancer Therapy-Related Cardiac Dysfunction: An Overview for the Clinician. Clinical Medicine Insights. Cardiology. 2019; 13: 1179546819866445. https://doi.org/10.1177/1179546819866445

Płońska-Gościniak E, Piotrowski G, Wojakowski W, Gościniak P, Olszowska M, Lesiak M, et al. Management of valvular heart disease in patients with cancer: Multidisciplinary team, cancer-therapy related cardiotoxicity, diagnosis, transcatheter intervention, and cardiac surgery. Expert opinion of the Association on Valvular Heart Disease, Association of Cardiovascular Interventions, and Working Group on Cardiac Surgery of the Polish Cardiac Society. Kardiologia Polska. 2023; 81: 82–101. https://doi.org/10.33963/KP.a2023.0023

Pudil R, Mueller C, Čelutkienė J, Henriksen PA, Lenihan D, Dent S, et al. Role of serum biomarkers in cancer patients receiving cardiotoxic cancer therapies: a position statement from the Cardio-Oncology Study Group of the Heart Failure Association and the Cardio-Oncology Council of the European Society of Cardiology. European Journal of Heart Failure. 2020; 22: 1966–1983. https://doi.org/10.1002/ejhf.2017

Richardson DR, Parish PC, Tan X, Fabricio J, Andreini CL, Hicks CH, et al. Association of QTc Formula With the Clinical Management of Patients With Cancer. JAMA Oncology. 2022; 8: 1616–1623. https://doi.org/10.1001/jamaoncol.2022.4194

Rivero Santana B, Caro Codon J, Juarez Olmos V, Martinez Monzonis A, Zatarain-Nicolas E, Moliner P, et al. HFA-ICOS cardiovascular toxicity risk score validation in CARDIOTOX registry. European Heart Journal. 2022; 43: ehac544.2591. https://doi.org/10.1093/eurheartj/ehac544.2591

Rivero-Santana B, Saldaña-García J, Caro-Codón J, Zamora P, Moliner P, Martínez Monzonis A, et al. Anthracycline-induced cardiovascular toxicity: validation of the Heart Failure Association and International Cardio-Oncology Society risk score. European Heart Journal. 2024; ehae496. https://doi.org/10.1093/eurheartj/ehae496

Rodgers JL, Jones J, Bolleddu SI, Vanthenapalli S, Rodgers LE, Shah K, et al. Cardiovascular Risks Associated with Gender and Aging. Journal of Cardiovascular Development and Disease. 2019; 6: 19. https://doi.org/10.3390/jcdd6020019

Roy D, Ahmed S. Principles of systemic anticancer therapy (SACT). Surgery. 2024; 42: 164–169. https://doi.org/10.1016/j.mpsur.2023.12.015

Sayegh N, Yirerong J, Agarwal N, Addison D, Fradley M, Cortes J, et al. Cardiovascular Toxicities Associated with Tyrosine Kinase Inhibitors. Current Cardiology Reports. 2023; 25: 269–280. https://doi.org/10.1007/s11886-023-01845-2

Shuel SL. Targeted cancer therapies. Canadian Family Physician. 2022; 68: 515–518. https://doi.org/10.46747/cfp.6807515

Siaravas KC, Katsouras CS, Sioka C. Radiation Treatment Mechanisms of Cardiotoxicity: A Systematic Review. International Journal of Molecular Sciences. 2023; 24: 6272. https://doi.org/10.3390/ijms24076272

Sikking C, Niggebrugge-Mentink KL, van der Sman ASE, Smit RHP, Bouman-Wammes EW, Beex-Oosterhuis MM, et al. Hydration Methods for Cisplatin Containing Chemotherapy: A Systematic Review. The Oncologist. 2024; 29: e173–e186. https://doi.org/10.1093/oncolo/oyad297

Suntheralingam S, Fan CPS, Calvillo-Argüelles O, Abdel-Qadir H, Amir E, Thavendiranathan P. Evaluation of Risk Prediction Models to Identify Cancer Therapeutics Related Cardiac Dysfunction in Women with HER2+ Breast Cancer. Journal of Clinical Medicine. 2022; 11: 847. https://doi.org/10.3390/jcm11030847

Szalda D, Ahluwalia M, Carver JR. Cardiac Toxic Chemotherapy and Cancer Survivorship. In Kimmick GG, Lenihan DJ, Sawyer DB, Mayer EL, Hershman DL, (eds.), Cardio-Oncology: The Clinical Overlap of Cancer and Heart Disease (pp. 253–280). Springer International Publishing: Cham. 2017. https://doi.org/10.1007/978-3-319-43096-6_11

Tang GH, Acuna SA, Sevick L, Yan AT, Brezden-Masley C. Incidence and identification of risk factors for trastuzumab-induced cardiotoxicity in breast cancer patients: an audit of a single "real-world" setting. Medical Oncology. 2017; 34: 154. https://doi.org/10.1007/s12032-017-1018-y

Vo JB, Ramin C, Veiga LHS, Brandt C, Curtis RE, Bodelon C, et al. Long-term cardiovascular disease risk after anthracycline and trastuzumab treatments in US breast cancer survivors. Journal of the National Cancer Institute. 2024; 116: 1384–1394. https://doi.org/10.1093/jnci/djae107

Wang K, Eblan MJ, Deal AM, Lipner M, Zagar TM, Wang Y, et al. Cardiac Toxicity After Radiotherapy for Stage III Non-Small-Cell Lung Cancer: Pooled Analysis of Dose-Escalation Trials Delivering 70 to 90 Gy. Journal of Clinical Oncology. 2017; 35: 1387–1394. https://doi.org/10.1200/JCO.2016.70.0229

Xiao L, Salem JE, Clauss S, Hanley A, Bapat A, Hulsmans M, et al. Ibrutinib-Mediated Atrial Fibrillation Attributable to Inhibition of C-Terminal Src Kinase. Circulation. 2020; 142: 2443–2455. https://doi.org/10.1161/CIRCULATIONAHA.120.049210

Zamorano JL, Lancellotti P, Rodriguez Muñoz D, Aboyans V, Asteggiano R, Galderisi M, et al. 2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC). European Heart Journal. 2016; 37: 2768–2801. https://doi.org/10.1093/eurheartj/ehw211

Zardavas D, Suter TM, Van Veldhuisen DJ, Steinseifer J, Noe J, Lauer S, et al. Role of Troponins I and T and N-Terminal Prohormone of Brain Natriuretic Peptide in Monitoring Cardiac Safety of Patients With Early-Stage Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer Receiving Trastuzumab: A Herceptin Adjuvant Study Cardiac Marker Substudy. Journal of Clinical Oncology. 2017; 35: 878–884. https://doi.org/10.1200/JCO.2015.65.7916