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STATE OF THE ART REVIEW
Cardio-oncology

Breast cancer and cardiovascular health

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Abstract

Modern cancer therapies greatly improve clinical outcomes for both early and advanced breast cancer patients. However, these advances have raised concerns about potential short- and long-term toxicities, including cardiovascular toxicities. Therefore, understanding the common risk factors and underlying pathophysiological mechanisms contributing to cardiovascular toxicity is essential to ensure best breast cancer outcomes. While cardio-oncology has emerged as a sub-speciality to address these challenges, it is essential that all cardiologists recognize and understand the cardiovascular consequences of cancer therapy. This review aims to provide a comprehensive overview of the potential adverse cardiovascular effects associated with modern breast cancer therapies. A preventive, diagnostic, and therapeutic workflow to minimize the impact of cardiovascular toxicity on patient outcomes is presented. Key aspects of this workflow include regular monitoring of cardiovascular function, early detection and management of cancer therapy-related cardiovascular toxicities, and optimization of cardiovascular risk factor control. By highlighting the gaps in knowledge in some areas, this review aims to emphasize the critical role of cardio-oncology research in ensuring the holistic well-being of patients with breast cancer.

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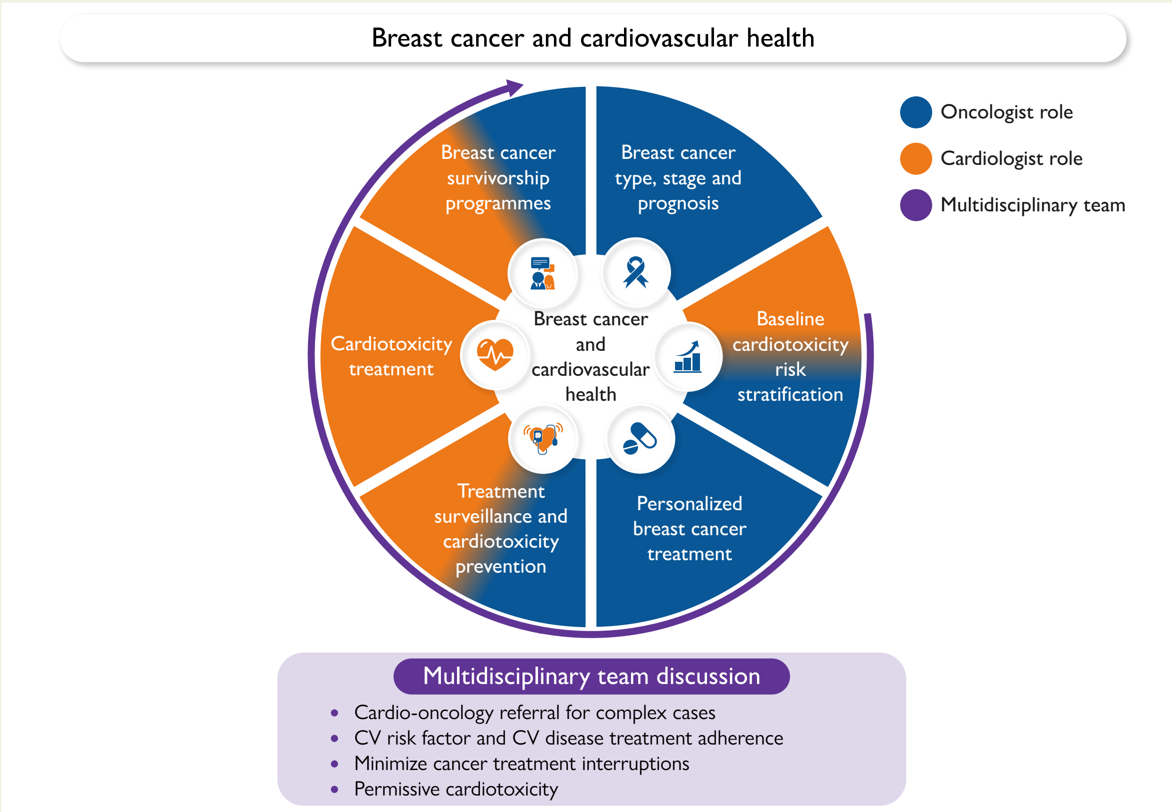
Graphical Abstract



Improved survival rates and the increasing complexity of modern cancer treatments require a comprehensive understanding of the risk factors and underlying pathophysiological mechanisms that contribute to cardiovascular toxicity. The oncologist is usually responsible for baseline risk assessment and the cardiologist for monitoring cardiovascular risks and managing cardiotoxicity. However, for optimal outcomes in breast cancer patients, all cardiologists must understand the cardiovascular implications of cancer therapy and emphasize collaboration with the oncology team during and after cancer treatment. A multidisciplinary approach, particularly in patients with pre-existing cardiovascular risk factors and/or cardiovascular disease, is needed to ensure adherence to optimal cardiovascular therapy and to minimize the risk of interruptions in breast cancer treatment.

Keywords Breast cancer • Cardiotoxicity • Chemotherapy • Radiotherapy • Prevention • Cardio-oncology • Women health • Exercise

Scope of the problem

Breast cancer (BC) is a major public health challenge. It is estimated that over 2 million new cases of BC are diagnosed each year worldwide, accounting for 25% of all cancer cases and 16% of cancer-related deaths among women.[1] The prognosis varies according to the cancer stage, with a 5-year survival rate of 99% for localized BC, 86% for locally advanced BC, and 30% for metastatic disease.[2] Contemporary BC treatment integrates surgery, radiation therapy, and systemic treatments (chemotherapy, endocrine therapy, targeted therapies, and immunotherapy) tailored according to tumour type and stage (see Supplementary data online, *Table S1*).[3,4] The aim is to cure patients with early-stage BC and improve survival and quality of life in those with metastatic disease, while considering the risk of treatment-related toxicities including cardiovascular (CV) toxicity.

Integration of multidisciplinary cardio-oncology team discussions is essential for balanced clinical decision-making on cancer treatment efficacy and potential cancer therapy-related CV toxicity (CTR-CVT) (*Graphical Abstract*).[5] An overly cautious approach may limit the administration of effective cancer therapies, while underestimating the risks of CTR-CVT may lead to major adverse cardiac events (*Figure 1*),[6–8] which are associated with a high personal, social, and economic impact.[9,10] All cardiologists, including those not involved in specialized cardio-oncology programmes, should be able to recognize and understand the CV effects of BC therapy.[11,12] Furthermore, they must be able to implement general preventive measures, including the optimization of CV risk factors (CVRFs) in BC patients.[13,14] Therefore, the European Society of Cardiology (ESC) Core Curriculum for Cardio-Oncology promotes proactive CV care for patients with cancer and cancer survivors.[15]

This review addresses CV toxicities associated with BC therapy, proposing a comprehensive workflow for risk stratification, prevention, diagnosis, and management of CTR-CVT, based on current evidence and the 2022 ESC guidelines on cardio-oncology.[5]

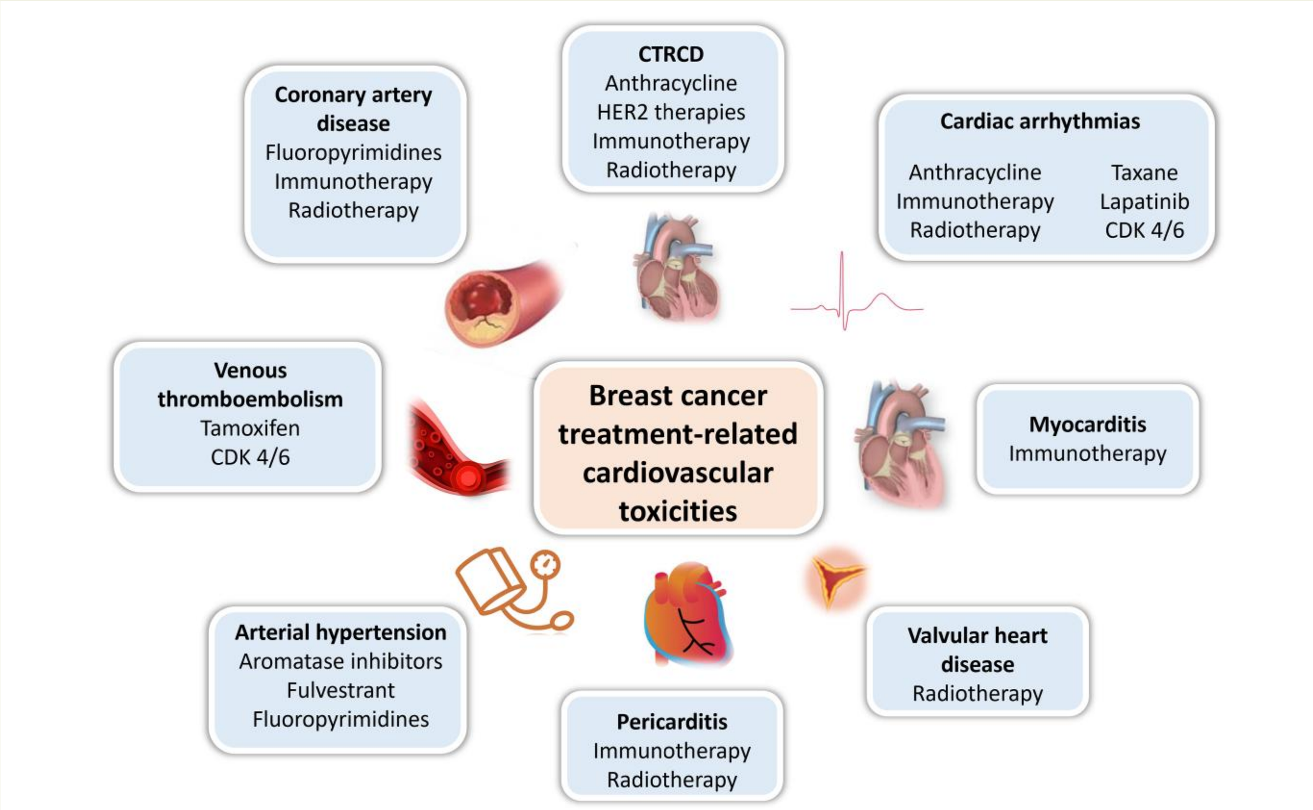


Figure 1 Cardiovascular toxicities associated with breast cancer treatment. CTRCD, cancer therapy-related cardiac dysfunction; CDK 4/6, cyclin-dependent kinase 4/6 inhibitors; HER2, human epidermal growth factor receptor 2

Cardiovascular toxicities related to breast cancer therapy

Systemic cancer therapies can be delivered before (neoadjuvant) or after (adjuvant) BC surgery. Chemotherapy is essential in the treatment of triple negative BC [oestrogen receptor (ER) negative, progesterone receptor negative, and human epidermal growth factor receptor 2 (HER2) protein negative], HER2 positive (*HER2+*), and high-risk luminal breast tumours (ER positive/HER2 negative), traditionally employing anthracyclines combined with cyclophosphamide and taxanes.[3,4] Non-anthracycline-based chemotherapy regimens (taxanes, cyclophosphamide, carboplatin, methotrexate, or fluoropyrimidines) are reasonable alternatives for patients at high risk of CV toxicity.[16,17] *Table 1* describes the primary therapies used in patients with BC, along with their associated CV toxicities (*Figure 1*; Supplementary data online, *Table S2*).

Cardiovascular toxicities related to anthracycline chemotherapy include heart failure (HF), left ventricular dysfunction, and cardiac arrhythmias.[5,18,19] *Cyclophosphamide* seldom causes HF, atrial fibrillation, or myocarditis in patients with BC due to the use of low doses (≤140 mg/kg).[5] *Taxanes* may cause sinus bradycardia, atrioventricular block, ventricular tachycardia, and, rarely, coronary vasospasm.[5,20,21] *Fluoropyrimidines* can cause coronary vasospasm or angina, myocardial infarction, arterial hypertension, and takotsubo syndrome.[5,20]

Patients with high-risk triple negative BC (tumour size > 2 cm or lymph node positive) standardly receive anthracycline chemotherapy combined with carboplatin/paclitaxel and the immune checkpoint inhibitor (ICI) pembrolizumab.[22] Immune checkpoint inhibitors may cause myocarditis in up to 1.4% of patients and are also associated with arrhythmias, non-inflammatory HF, and accelerated atherosclerosis, leading to a three-fold increase in atherosclerosis-related CV events during follow-up.[23,24]

Human epidermal growth factor receptor 2-targeted therapies include monoclonal antibodies (trastuzumab and pertuzumab), tyrosine kinase inhibitors, and antibody–drug conjugates. Human epidermal growth factor receptor 2 overexpression occurs in 20%–30% of BC cases and is associated with more aggressive disease.[3,4] Trastuzumab is a recombinant humanized monoclonal antibody that binds to the extracellular domain of the HER2 receptor. However, HER2 receptors are highly expressed in cardiomyocytes and play a role in several cardioprotective mechanisms in response to cell stressors.[25,26] Consequently, trastuzumab use can lead to left ventricular dysfunction and an increased risk of HF during treatment.[27,28] A combined analysis of the HER2 trials in women treated for early-stage BC revealed that 8.7% of patients experienced mild left ventricular dysfunction, while 2.3% developed HF.[29] Most cardiac events occurred in women over 65 years old or when trastuzumab was administered after anthracyclines.[28]

Although early studies suggested that pertuzumab might be associated with low risk of cardiac events, real-world data have documented higher rates of cardiac dysfunction.[30,31] Dual HER2 blockade with trastuzumab and pertuzumab is currently the gold standard for patients with high-risk HER2+ disease.[3,4] This dual therapy may increase the risk of cardiac dysfunction in patients with coronary artery disease (CAD) or those who have previously received anthracyclines.[32]

Tyrosine kinase inhibitors (lapatinib, neratinib, and tucatinib) are approved for treatment of high-risk early-stage and metastatic

Table 1 Breast cancer treatment cardiovascular toxicity and recommended surveillance strategies

Cancer therapy	CTR-CVT type	Mechanism of CTR-CVT	Incidence	Cardiovascular surveillance strategy *(recommendation class and level of evidence)*
Chemotherapy				
Anthracycline chemotherapy[5,16,17]	Heart failure, left ventricular dysfunction, arrhythmias	Mitochondrial dysfunction, increase oxidative stress, Topoisomerase IIb Inhibition, cellular apoptosis, endothelial damage, DNA damage-induced senescence, clonal haematopoiesis, iron metabolism dysregulation.	RCT: 5%–26% Population-based studies: 2.2%–11.4%	• **Baseline** o ECG for all patients *(I-C)* o TTE for all patients *(I-B)* o NP/cTn in high-risk patients *(I-B)* • **During treatment** • **High risk patients:** o TTE every 2 cycles *(I-C)* o NP/cTn before each cycle *(I-B)* • **All patients** o TTE after ≥250 mg/m^2 of doxorubicin (IIa (for moderate risk) and IIb (for low risk)-C) o NP/cTn every 2 cycles (IIa-C) • **After treatment and 1-year follow-up.** o **All patients**: TTE 12 m after treatment *(I-B)*
Taxanes[5,18,19]	Conduction abnormalities. Rarely myocardial ischemia and left ventricular dysfunction	Possible vasospasm	Retrospective registries: 3%–20% (mild cardiovascular toxicity)	**Clinical follow-up[a]**
Fluoropyrimidines[5,18]	Vascular toxicity, hypertension, takotsubo syndrome	Coronary vasospasm, myocardial toxicity, increased sympathetic stimulation	Meta-analysis 1.2%–4.3%	• **Baseline** o TTE if pre-existing CVD *(I-C)* • **During treatment** Clinical follow-up[a]
HER2-targeted agents				
Monoclonal antibodies Trastuzumab Pertuzumab[11,12,20–29]	Heart failure, left ventricular dysfunction	Direct blockage of HER2 receptor: Disruption of neuregulin-1 growth factor pathway, a protective pathway against myocardial stress)	RCT Tratuzumab 0%–3.9% Pertuzumab 1%–7% Population-based studies: Tratuzumab 12.1%–26.7% Pertuzumab 3.9%–17.9%	• **Baseline** o ECG for all patients *(I-C)* o TTE for all patients *(I-B)* o cTn post-anthracycline prior to anti Her2 *(IIa-A)* NP/cTn in high-risk patients *(I-C)* • **During treatment** • **All patients** o TTE every 3 months (for the first year) *(I-B)* o NP/cTn every 3 cycles *(IIb-C)* • **High risk patients** o NP/cTn every 2–3 cycles *(IIa-C)* • **After treatment and 1-year follow-up.** o **All patients**: TTE 12 m after treatment *(I-B)*

Continued

Table 1 ***Continued***

Cancer therapy	CTR-CVT type	Mechanism of CTR-CVT	Incidence	Cardiovascular surveillance strategy *(recommendation class and level of evidence)*
HER2 targeted KI Lapatinib[29,30]	Left ventricular dysfunction, QTc prolongation	Unknown Rare cardiotoxicity, more frequent when combined with trastuzumab	**Left ventricular dysfunction** RCT: 1.6%–7%. **QT prolongation** RCT: 3.9%	• **Baseline** o QTc assessment and TTE for all patients • **Consider TTE surveillance if pre-existing CVD**
HER2 targeted KI Tucatinib[29]	Left ventricular dysfunction	Unknown	RCT 2.2% vs. 2.5% placebo	• **Baseline** o TTE for all patients • **Consider TTE surveillance if pre-existing CVD**
Antibody-drug conjugates*				
Trastuzumab deruxtecan Trastuzumab emtansine Sacituzumab govitecan[31–34]	CTRCD	Combination of monoclonal antibodies with cytotoxic agents allowing precise drug delivery and reduced toxicity	RCT Trastuzumab-emtansine: 0.4%–1.7% Trastuzumab-deruxtecan: 1.6%–2.3% Sacituzumab-govitecan: 0%	• **Baseline** o TTE for all patients • **Consider TTE surveillance if pre-existing CVD**
Cyclin-dependent kinase 4/6 inhibitors				
Ribociclib Palbociclib Abemaciclib[35,36]	QTc prolongation, VTE	Down-regulation of KCNH2 expression and up-regulation of SCN5A and SNTA1, three genes associated with long QT	**QT prolongation** RCT Ribociclib 6.5% **VTE** Population-based studies: 9%	Ribociclib • **Baseline** o QTcF assessment *(I-A)* • ***QTc monitoring*** at 14 and 28 days and if any dose increase *(I-B)* Palbociclib, abemaciclib: • **Baseline** o QTcF assessment • ***QTc monitoring*** **if** baseline QTcF >480 ms *(IIa-C)*
Immune check-point inhibitors				
Pembrolizumab Atezolizumab[37,38]	Myocarditis, Pericarditis, CTRCD, Arrhythmias, coronary artery disease	Activation of T-cells against non-cancer tissues leading to immune-related adverse events	**Myocarditis** RCT: 0%–0.5%; population-based studies: 1.1%–1.4%	• **Baseline** o TTE for high-risk patients *(I-B)* o ECG, NP/cTn in all patients *(I-B)* • **Serial monitoring** o ECG and cTn before C1-C4 and every 3 cycles the 1st year *(IIa-B)* o Cardiovascular assessment every 6–12 months in high-risk patients *(I-C)*

Continued

Table 1 ***Continued***

Cancer therapy	CTR-CVT type	Mechanism of CTR-CVT	Incidence	Cardiovascular surveillance strategy ***(recommendation class and level of evidence)***
Endocrine therapy				
Tamoxifen[39,40]	VTE	Oestrogenic effects in selected tissues	Population-based studies: 1.2%–7.6%	• **Serial monitoring** o Annual CV risk assessment *(I-C)*
Aromatase inhibitors (anastrozole, letrozole, exemestane)[39–41]	Dyslipidaemia, hypertension, vascular toxicity	Reduction of androgens conversion to oestrogens	**Hypertension** RCT: 9%	
Fulvestrant[41]	Hypertension	Anti-oestrogenic effects	RCT: 7%	
Radiotherapy				
Radiotherapy to a volume including the heart[42]	Valvular heart disease, arrhythmias, coronary artery disease, pericardial disease, CTRCD	Inflammation, oxidative stress, mitochondrial dysfunction, and micro/macro vascular injury Acute (rare) or late (over 5 years post-therapy)	Linear increase of coronary events of 7.4% per grey of mean heart dose	• **Baseline** o TTE in patients with pre-existing CVD *(IIa-C)* • **Serial monitoring** o Annual CV risk assessment *(I-B)*

CTR-CVT, cancer therapy-related cardiovascular toxicity; cTn, cardiac troponin; CV, cardiovascular; CVD, cardiovascular disease; ER, oestrogen receptor; ECG, electrocardiogram; HER2, human epidermal growth factor receptor; KI, kinase inhibitors; m, month; NP, natriuretic peptides; QTcF, QT interval corrected with the Fridericia formula; TE, thromboembolism; TTE, transthoracic echocardiogram; VEGFi, vascular endothelial growth factor inhibitors.

[a]ECG and TTE if new cardiovascular symptoms.

HER2+ BC.[3,4,33] Lapatinib increases the risk of HF and QTc prolongation, particularly in combination with trastuzumab.[35] In contrast, randomized clinical trials have not proven an increase in the risk of cardiotoxicity with tucatinib or neratinib.[35]

Antibody drug conjugates (trastuzumab deruxtecan and ado-trastuzumab emtansine and sacituzumab govitecan) are monoclonal antibodies linked to a cytotoxic agent. They are approved for use in high-risk early and advanced *HER2*+ BC. The incidence of left ventricular dysfunction with these drugs is low (1%–2%) in patients without CVD in the pivotal clinical trials.[36–39]

Endocrine therapy is essential in patients with both early and advanced ER+ BC. Aromatase inhibitors are typically prescribed for postmenopausal women and premenopausal women with high-risk early BC, while tamoxifen is prescribed for premenopausal women with low-risk BC and postmenopausal women who cannot tolerate aromatase inhibitors.[3,4] Tamoxifen increases the risk of venous thromboembolism and modestly reduces LDL cholesterol, while aromatase inhibitors have been associated with a slight increase in CV events through their adverse effects on lipids and blood pressure.[40,41] Fulvestrant, an ER down-regulator, is approved for the treatment of metastatic BC and is associated with a moderate risk of hypertension, when used in combination with alpelisib.[42]

Cyclin-dependent kinase 4/6 inhibitors (ribociclib, palbociclib, and abemaciclib) improve the clinical efficacy of endocrine therapy in the treatment of advanced BC and in high-risk early-stage disease (abemaciclib).[3,4,43] Ribociclib is associated with an increased risk of QTc prolongation, requiring close monitoring of QT interval corrected with the Fridericia formula (QTcF) during the first month of therapy.[5] Tamoxifen is known to prolong the QT interval and should not be co-administered with ribociclib.[5] As patients with cancer are likely to be taking concomitant QT-prolonging medication, a review of concomitant medication is strongly recommended.[5] QT monitoring should also be considered in patients treated with palbociclib or abemaciclib who have a baseline QTcF above the normal range or other conditions that may prolong the QT interval.[5] Venous thromboembolism is an emerging risk in clinical practice not reported in early clinical trials.[44]

Radiotherapy-induced CV toxicity may occur years after completion of cancer therapy, especially in patients with left-side BC and those treated with older radiation therapy techniques.[45] The most common manifestations of late radiation-induced heart disease include CAD, valvular heart disease, pericardial disease, conduction abnormalities, and HF with preserved left ventricular ejection fraction (LVEF).[5,46] The risk is influenced by the radiation dose (mean heart dose and radiation dose to cardiac substructures) and is modulated by patient age, the time elapsed since the course of radiotherapy, and the presence of dyslipidaemia, chronic kidney disease, and CAD.[47–51] Modern radiotherapy techniques, like intensity-modulated radiation therapy and deep inspiration breath hold, have significantly reduced the mean heart dose.[52] A recent meta-analysis confirmed these techniques improve survival in patients with early BC vs. older radiation therapy methods.[53] De-escalation strategies and alternative treatment approaches, such as partial breast irradiation, effectively lower radiation-induced heart disease risk,[54–56] emphasizing the importance of a multidisciplinary team approach.[5,57,58]

Cardiovascular toxicity risk stratification

Cardiotoxicity risk assessment, prior to initiation of cancer therapy, is important to identify pre-existing CV conditions and to discuss implementation of prevention strategies, if appropriate, during and after BC treatment (Class I-B).[5] Several studies have investigated factors that influence the risk of CTR-CVT in women with BC including age, sex, CVRF, pre-existing CVD, baseline LVEF, cancer history, and the intensity and duration of cancer therapy.[5,59,60] Generally, these models are effective in identifying patients at high risk who should be referred to a cardio-oncology clinic; however, their ability to discriminate between mild and moderate risk of CTR-CVT is limited.[61] This may be explained by an inadequate understanding of the mechanisms involved in CRT-CVT across different classes of drugs,[19] exclusion of patients with CVD in oncology trials,[62] and the lack of prospective real-world data.

The ESC guidelines recommend using the Heart Failure Association and International Cardio-oncology Society (HFA-ICOS) risk proforma (Class IIa-C) to assess the risk of CTR-CVT prior to anthracycline and HER2-targeted therapies[5,63] (*Table 2* and *Figure 2*). The HFA-ICOS score effectively stratifies the baseline risk of anthracycline-induced CV toxicity in the CardioTox registry[64] and identifies patients at high risk of trastuzumab-related cardiac dysfunction in retrospective series.[65,66] The SCORE2/SCORE2-OP is recommended to assess CV risk prior to administration of fluoropyrimidines (Class I-C), endocrine therapy (Class I-C), and radiotherapy (Class I-B).[5] For patients receiving other classes of cancer therapy, high-risk conditions are listed in *Table 2*.

Cardiovascular toxicity prevention

Cardiovascular toxicity is associated with a worse prognosis in patients with BC. Severe forms of CTR-CVT lead to early discontinuation of BC treatment, increasing the risk of cancer recurrence and all-cause mortality.[67,68] Therefore, preventing CTR-CVT is essential to improve both CV and oncological outcomes.[5] The goal of secondary prevention strategies is to optimize pre-existing CVD, while primary prevention measures focus on reducing the risk of CTR-CVT and optimizing uncontrolled CVRF.[5,69,70] To ensure a tailored approach, a multidisciplinary team discussion should consider cancer-specific conditions that might increase the risk of CVD (i.e. psychosocial stress, ethnicity, and frailty) or correlate with a poorer cancer prognosis.

The use of SCORE2/SCORE2-OP to guide CVFR management is recommended, despite its lack of validation for patients with cancer.[5] Non-cardiac tests, such as staging computed tomography scans and mammography, can play a crucial role in enhancing CV risk assessment in patients with BC. The Coronary Artery Calcium Data and Reporting System score quantifies coronary artery calcium burden from non-cardiac computed tomography.[71] Additionally, routine mammography can detect breast arterial calcifications, which have been associated with a higher risk of CAD.[72]

Liposomal anthracycline or dexrazoxane should be considered as primary preventive strategies in patients at high risk of cancer therapy-related cardiac dysfunction (CTRCD) (Class IIa-B) when anthracyclines are part of the treatment plan.[5,73,74] However, regulatory authorities such as the European Medicines Agency and the Food and Drug Administration, currently restrict their use to patients with metastatic BC who have already received a high cumulative anthracycline dose if further anthracycline treatment is planned.

Several studies have investigated the use of HF drugs and statins for primary prevention of CTRCD in patients with BC receiving anthracyclines and/or trastuzumab, with mixed results.[5] These studies have been biased by different definitions of CTR-CVT,[18] younger patients with few comorbidities, and short follow-up periods[5] (see Supplementary data online, *Table S3*). A recent meta-analysis found that angiotensin-

Table 2 **Baseline predictors of cancer therapy related cardiovascular toxicity risk**

Cancer treatment	HFA-ICOS risk score[a]			
	Very-high risk	**High risk**	**Moderate risk (M2 = 2 points)**	**Moderate risk (M1 = 1 point)**
Anthracycline chemotherapy	• Heart failure	≥80 years • Coronary artery disease • Severe valvular heart disease • LVEF < 50% • Previous anthracycline • Radiotherapy	• 65–79 years • LVEF 50%–54%	• ↑ baseline cTn/NP • Hypertension • Chronic kidney disease • Diabetes Mellitus • Current smoker • Obesity • Previous cardiotoxic treatments
HER2-targeted therapies	• Heart Failure • Previous trastuzumab exposure	≥80 years • Coronary artery disease • Severe valvular heart disease • LVEF < 50%	• 65–79 years • LVEF 50%–54% • Cardiac arrhythmia • ↑ baseline cTn/NP • Previous anthracycline • Radiotherapy[b]	• Hypertension • Chronic kidney disease • Diabetes Mellitus • Current smoker • Obesity • Current anthracycline
Other conditions that increase the risk of cancer therapy-related cardiac dysfunction				
Antibody-drug conjugates	• Pre-existing CVD (including CTR-CVT)			
Endocrine therapy	• Pre-existing coronary artery disease or heart failure (aromatase inhibitors) • Venous thromboembolism (tamoxifen)			
CDK4/6i	• Baseline QTcF ≥480 ms			
ICI	• Pre-existing CVD ((including other cancer therapy related cardiovascular toxicities) • Dual ICI or combination ICI-cardiotoxic therapy • Non- cardiovascular ICI-related events			
Radiotherapy to a volume including the heart	• Pre-existing CVD (including other cancer therapy related cardiovascular toxicities) • Dyslipidaemia • ≥60 years • Prior anthracycline exposure • Mean heart dose: o **Very high risk** o >25 Gy mean heart dose or >15 Gy mean heart dose + cumulative doxorubicin ≥100 mg/m^2 o **High risk** o >15–25 Gy MHD or 5–15 Gy MHD + cumulative doxorubicin ≥100 mg/m^2			

CDK 4/6i, Cyclin-dependent kinase 4/6 inhibitors; cTn, cardiac troponin; CVD, cardiovascular disease; Gy, grey; HFA-ICOS, Heart Failure Association and International Cardio-Oncology Society; ICI, immune check-point inhibitors; LVEF, left ventricular ejection fraction; NP, natriuretic peptide; QTcF, QT interval corrected with the Fridericia formulae.

[a]An extended version of the HFA-ICOS proforma is available in Cronin *et al.*[66] The HFA-ICOS risk is categorized as low if no risk factors or 1 M1, moderate for patients with 2–4 points, high for ≥5 points, or any high-risk factor and very high for any very high-risk factor.

converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), and/or beta-blockers conferred greater protection in terms of LVEF preservation in patients receiving trastuzumab, with statistically significant effects observed only for beta-blockers.[75] Sodium-glucose cotransporter-2 inhibitors, while promising for cardioprotection in retrospective analyses,[76,77] require validation in prospective trials.

The STOP-CA trial indicated a cardioprotective effect of atorvastatin in patients with lymphoma on high-dose anthracycline treatment, with a number needed to treat of 7.[78] However, the evidence in patients with BC is still controversial. Observational studies suggest that ongoing statin use might lower HF risk during anthracycline treatment.[79] Conversely, the PREVENT trial[80] and the SPARE-HF trail[81] showed no advantage of atorvastatin in preventing left ventricular dysfunction in patients with BC.

Regular physical activity substantially reduces the incidence of cancer[82,83] and CVD.[84–86] A growing number of studies have investigated the association between physical activity and CV outcomes in patients with cancer.[87,88] Pre-treatment physical activity exposure of ∼18 metabolic equivalent hours per week (MET-h/week) decreases the risk of any CV event [37% lower risk; 95% confidence interval (CI): 0.45–0.88] and CAD death (31% lower risk; 95% CI: 0.46–1.04) compared with <2 MET-h/week in 4015 BC patients after 13 years of follow-up.[88] Post-treatment physical activity in BC patients correlates with longer overall survival[89] by reducing CV deaths.[90]

Exercise therapy improves cardiorespiratory fitness in a wide range of cancer patients.[91,92] In women starting treatment for BC, exercise therapy during and/or after chemotherapy is associated with superior improvements in cardiorespiratory fitness compared with a control

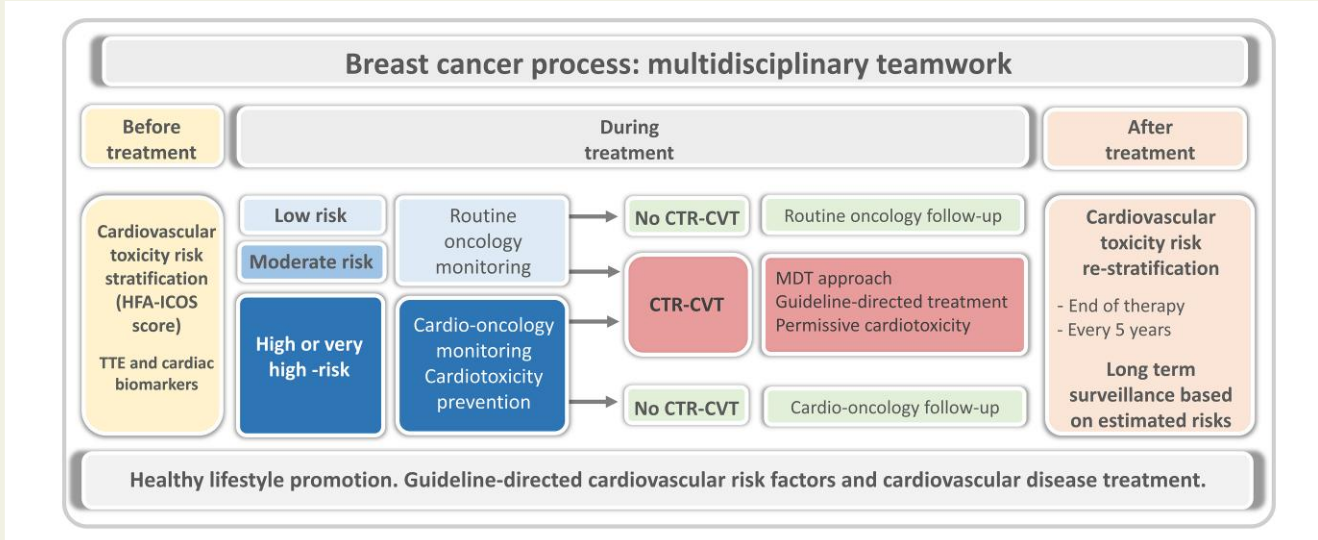


Figure 2 Cardiovascular surveillance along the continuum of the breast cancer process. CTR-CVT, cancer therapy-related cardiovascular toxicities; HFA-ICOS, Heart Failure Association-International Cardio-Oncology Society; MDT, multidisciplinary team; TTE, transthoracic echocardiography

group.[93–96] Therefore, exercise therapy should be initiated early during treatment and continued afterward to mitigate and reverse therapy-related declines in cardiorespiratory fitness. Few studies have evaluated the effects of exercise therapy beyond cardiorespiratory fitness, with conflicting results on its effects on LVEF and natriuretic peptide levels.[94,97,98] These mixed results may be due to differences in regimens (e.g. taxane or non-taxane) or exercise therapy prescription approaches (e.g. 2 or 4 weeks).[96,98] To date, few studies have evaluated the role of exercise therapy in patients who have developed CTRCD (i.e. secondary prevention). Two trials reported that home- or clinic-based exercise therapy was associated with improved cardiorespiratory fitness[99,100] but no change in LVEF.[100]

In conclusion, the current evidence supports exercise therapy to restore impaired cardiorespiratory fitness, but further studies are needed to assess its impact on additional CV endpoints. Nevertheless, exercise therapy is an important feature to include in the comprehensive care of cancer patients, given its benefits in other clinical populations.

Cardiovascular monitoring during breast cancer treatment

Cardiovascular surveillance during cancer treatment should adhere to three fundamental principles. Firstly, it must not unnecessarily hinder or postpone cancer treatment. Secondly, it should align with the expected CTR-CVT type (i.e. echocardiography surveillance is not necessary if the expected CTR-CVT is hypertension) and the patient's projected life expectancy. Historically, oncology clinical trials have linked cardiotoxicity to the direct effects on LVEF[101,102]; however, recognition of new forms of CV toxicity such as immune-related adverse events, arrhythmias, and vascular toxicities is increasing.[103–105] Finally, it should leverage local healthcare resources and foster collaborations with other centres for managing complex cases.[5,14] For patients with low or intermediate risk of CTR-CVT, it is essential to promptly initiate BC treatment while ensuring that oncologists oversee CV monitoring. However, for those at high or very high risk, or patients experiencing CTR-CVT, referral to a cardio-oncology specialist is advisable (*Figure 2*).[5]

Current surveillance protocols for CTRCD are based on expert consensus or clinical trial protocols due to the lack of comprehensive data on their impact on cancer and CV outcomes, patient-reported experience measures, and economic implications. These protocols include cardiac imaging and cardiac biomarker evaluations at various intervals during and after cancer treatment. The timing of these assessments depends on the estimated baseline risk and the likelihood of CTRCD.[106,107] Discussing cardiac imaging methods and cardiac biomarkers assessments in detail falls beyond the scope of this review (see Supplementary data online, *Figure S1*).[106,107] *Table 1* provides an overview of the ESC recommendations for BC treatment surveillance, differentiating between expert-consensus and evidence-based recommendations.[5] Baseline transthoracic echocardiography and cardiac biomarker assessment are advised in patients at high-risk of CTR-CVT or those about to start BC therapies with a known risk of CTRCD. This approach helps identify those who require close surveillance.[5,66,106,107] Elevated baseline biomarkers or a LVEF below 50% (or in the lower normal range, 50%–54%) are indicators of increased CTRCD risk.[66]

The frequency of surveillance for echocardiography and biomarkers during treatment varies depending on the initial risk, the specific cancer therapy, and the likelihood of CTRCD (*Table 1*).[5,106,107] For patients with metastatic BC, cardiac monitoring intervals should be guided by weighing the risks of CV toxicity vs. the benefits of cancer therapy. Cardiac biomarkers play a crucial role in monitoring patients undergoing anthracycline, HER2-targeted. A recent meta-analysis demonstrated that elevated troponin levels in patients receiving anthracycline or HER2-targeted therapies correlated with a higher risk of CTRCD (odds ratio 11.9).[108] However, the utility of natriuretic peptides in predicting CTRCD in BC patients without pre-existing HF is uncertain.

The best CV monitoring strategy during ICI therapy is still under investigation. Baseline assessment should include electrocardiogram (ECG), cardiac troponins, N-terminal pro-B-type natriuretic peptide (NT-proBNP), creatine phosphokinase (CPK), and liver and thyroid function studies. Echocardiography is recommended for patients with pre-existing CVD or abnormal biomarkers or ECG findings. Electrocardiogram and biomarker monitoring during the first 12 weeks (Class IIa-B) may help in

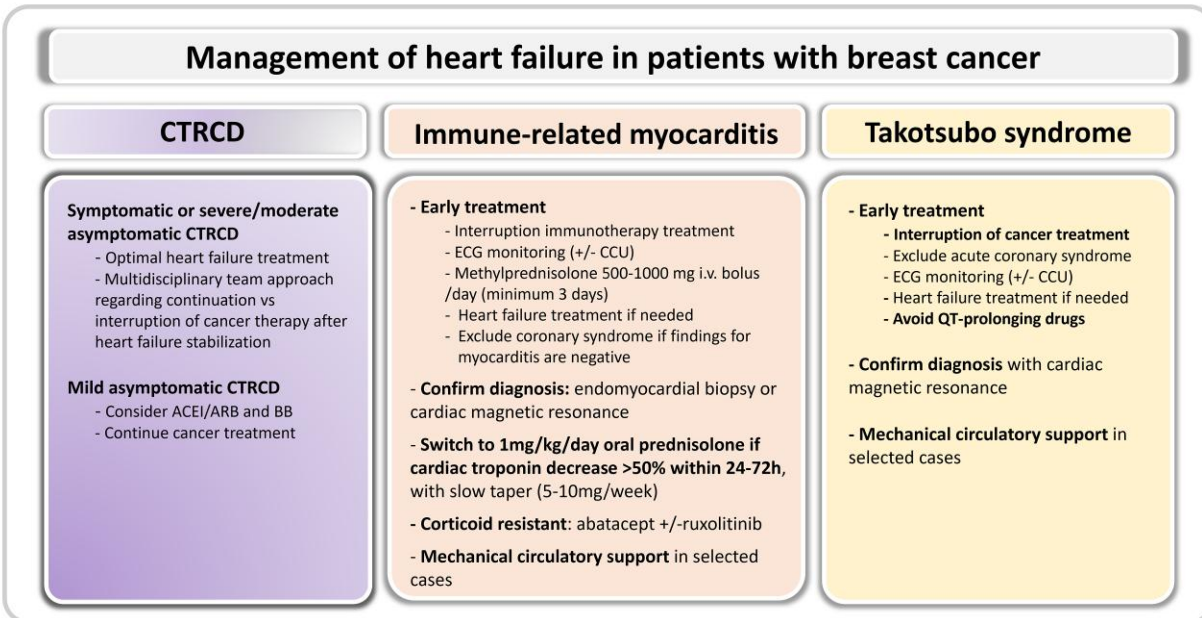


Figure 3 Management of heart failure in patients with breast cancer. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta-blockers; CCU, critical care unit; CTRCD, cancer therapy-related cardiac dysfunction

the early detection of subclinical myocarditis.[5,109,110] However, the therapeutic implications of asymptomatic elevations in cardiac troponins are unclear, and a multidisciplinary team approach is recommended to avoid inappropriate treatment interruptions.[5] The available evidence indicates that cardiac troponin I is more specific for myocardial damage,[111,112] while troponin T may offer superior prognostic value due to its sensitivity in detecting myotoxicity.[109,113]

Monitoring of BC survivors should focus on management of CVRFs. Annual assessment of NT-proBNP may help identify those at higher risk of CV events.[114] Recommendations for echocardiography assessment in asymptomatic BC survivors are based on expert consensus[5] and should be guided by local protocols.

Management of cancer therapy-related cardiovascular toxicity in patients with breast cancer

The 2022 ESC guidelines on cardio-oncology provide precise definitions for CTR-CVT.[5,18] The most common CV toxicities in patients undergoing BC treatment include CTRCD, CAD, stroke, venous thromboembolism, and atrial fibrillation (*Figure 1*).[46,104,115–117] A recent meta-analysis revealed the following observed incidence rates, expressed per 1000 person-years: CV death 1.73, HF 4.44, CAD 4.29, myocardial infarction 1.98, and stroke of any type 4.33.[116]

For many years, patients diagnosed with cancer who had CVDs were managed conservatively resulting in worse clinical outcomes, particularly in patients with acute CV events.[118,119] In the absence of robust evidence-based guidance, the treatment decisions on the management of CTR-CVT in patients with BC should be made through a multidisciplinary approach, integrating clinical practice guidelines.[5,15,120] To minimize the number of unnecessary interruptions of cancer treatment, clinicians should follow the principle of permissive cardiotoxicity and balance cancer treatment and prognosis with CTR-CVT burden.[121]

Cancer therapy-related cardiac dysfunction

In patients with BC, the clinical presentation of CTRCD can vary from asymptomatic mild cardiac dysfunction to severe symptomatic HF (*Figure 3* and Supplementary data online, *Table S4*).[5]

Trastuzumab-related cardiac dysfunction is often asymptomatic and most commonly occurs during treatment.[122] Continuation of trastuzumab therapy with CV surveillance is recommended for patients with *mild asymptomatic CTRCD* (Class I-C). Cardioprotective therapy with ACEI/ARB and/or BB should be considered in these patients (Class IIa-B).[5] Two small prospective studies, SCHOLAR[123] and SAFE-HEART,[124] showed that HER2 therapy can be continued in patients with *moderate asymptomatic CTRCD* (LVEF 40%–49%) if they receive concomitant HF therapy with ongoing cardiac monitoring (Class IIa-B). When patients develop *symptomatic HF or severe* asymptomatic CTRCD (LVEF < 40%), a temporary discontinuation of HER2-targeted treatments is suggested (Class I-C) and guideline-directed HF treatment should be started and carefully titrated.[125] A collaborative, multidisciplinary approach is necessary to decide whether to restart HER2-targeted therapy taking into consideration, response to HF treatment, the availability of alternative cancer therapies, and the overall benefit of cancer therapy.[5]

Patients who develop *symptomatic HF or moderate-to-severe asymptomatic CTRCD* during anthracycline-based chemotherapy require treatment interruption and initiation of HF treatment (Class I-B).[5] Neurohormonal agents are considered safe in patients with BC. There is a hypothetical concern that iron replacement in patients with BC and LVEF < 40% may promote tumour growth and increase anthracycline-related cardiotoxicity.[126] For patients with moderate to severe CTRCD, a multidisciplinary team may consider resuming anthracycline therapy if HF symptoms resolve, LVEF improves with HF treatment, and no other options are available.[5] Continuation of anthracycline treatment is only recommended for patients with mild asymptomatic CTRCD (LVEF ≥ 50% and new relative decline in global longitudinal strain by >15% from baseline and/or new rise in cardiac biomarkers) with ongoing cardiac surveillance.[5] Angiotensin-converting enzyme inhibitor/ARB and/or beta-blockers treatment should be considered in these patients (Class IIa-B).[5] The ICOS-ONE trial reported a low incidence of CTRCD (<1%) in patients treated with enalapril after troponin elevation.[127] The SUCCOUR trial showed no difference in the initiation of cardioprotection based on decline in global longitudinal strain compared with the group initiating cardioprotection based on LVEF decline (<55%) suggesting the overall risk with mild CTRCD is low.[128]

While HF related to BC therapy should be considered in patients with new-onset dyspnoea, other aetiologies should also be ruled out. The presence of cancer is frequent in takotsubo series, ranging between 6% and 20%.[129,130] Takotsubo syndrome is more common in patients with solid tumours, although further research is needed to define the specific incidence in patients with BC. Pathophysiological mechanisms are complex and involve both psychological stressors and cancer therapies (i.e. fluoropyrimidines, ICI, tyrosine kinase inhibitors, or combination therapies). In these patients, QT-prolonging drugs should be avoided. Furthermore, clinicians should employ coronary computed tomography or angiography to exclude CAD and use cardiac magnetic resonance imaging to confirm or exclude the diagnosis (*Figure 3*).[131]

There is currently a paucity of evidence on the management of patients with active BC and advanced HF. Consequently, a case-by-case multidisciplinary team discussion is necessary to make appropriate clinical decisions. For BC survivors with advanced HF refractory to medical and device therapy, heart transplantation may be considered after 2–5 years of cancer remission.[132] Despite the higher incidence of secondary malignancies and infection in this population, their survival is comparable with that of individuals undergoing heart transplantation for other cardiomyopathies.[133] Long-term left ventricular assist devices may be considered as a bridge to transplantation or as destination therapy for BC survivors who are ineligible for transplantation and who are expected to survive for more than 1 year.[125,134]

Immuno-related myocarditis

The existing knowledge on diagnosing and managing ICI-related myocarditis is derived from the treatment of patients with other malignancies.[23,24] As several immune-related adverse events may coexist at the same time, exclusion of myocarditis is recommended in patients who develop myositis, myasthenia, pneumonitis, or hepatitis.[5] Early recognition and aggressive treatment of ICI-related myocarditis are recommended to reduce mortality.[5,23,118]

In asymptomatic patients, a mild increase in cardiac troponin levels with normal CPK and liver function is unlikely to be associated with myocarditis. However, if CPK, AST, and ALT rise concomitantly or patients develop ECG abnormalities at any time, cardiac troponin levels should be closely monitored within 48 h, and prompt cardio-oncological evaluation is strongly recommended. The optimal management of mild isolated asymptomatic elevations of cardiac troponin remains to be established.[135]

In patients who develop new CV symptoms, consideration of the timing of ICI initiation and biomarker trends is essential for early differential diagnosis. Patients with abnormal CPK levels and stable or rising troponin levels within 60 days of ICI initiation have a high likelihood of ICI-related myocarditis.[135] Immune checkpoint inhibitor withdrawal, hospitalization, and ECG monitoring should be strongly considered. High-dose corticosteroids are recommended (500–1000 mg methylprednisolone i.v. bolus once daily for a minimum of 3 days; Class I-C) pending further confirmatory testing (*Figure 3*).[5,136] This strategy differs from non-ICI-related myocarditis, where corticosteroids are only recommended for subsets of patients with specific aetiologies such as autoimmune myocarditis.[137] Cardiac magnetic resonance is recommended to diagnose ICI-associated myocarditis (Class I-B). Endomyocardial biopsy is recommended in haemodynamically unstable patients or when the results of a cardiac magnetic resonance are inconclusive or negative in patients with a high clinical suspicion of myocarditis.[5,18] Coronary cardiac tomography or angiography should exclude coronary syndrome if findings for myocarditis are negative. This approach is further supported by the recent data showing that atherosclerosis may progress during ICI treatment.[138] A contemporary analysis revealed that severe ICI myocarditis, according to ICOS criteria,[18] was associated with a six-fold increase in CV mortality at 1-year follow-up compared with non-severe ICI myocarditis.[139] In these patients, additional immunosuppression with abatacept ± ruxolitinib[140] should be considered, as well as mechanical circulatory support in selected cases.

Hypertension

Management of hypertension should follow general guidelines.[141] During cancer treatment, blood pressure thresholds may be adjusted based on symptoms and BC prognosis. To keep blood pressure < 140/<90 mmHg, ACEI or ARBs are recommended as first-line treatments, with the addition of a dihydropyridine calcium channel blocker if further intervention is needed. Uncontrolled hypertension (≥180/≥110 mmHg) heightens the risk of CTRCD and atrial fibrillation. It is recommended to postpone or temporarily stop any cancer treatment associated with hypertension (*Figure 1*) until the blood pressure is controlled below 160/100 mmHg.[5] The SPRINT trial shows that intensive blood pressure control reduces CV risks in cancer survivors.[142]

Atrial fibrillation

Atrial fibrillation is more common early after BC diagnosis,[116,143] in patients with metastatic disease,[144] and is associated with cancer therapies such as anthracycline chemotherapy, ICI, or radiotherapy. Anticoagulation can be challenging, and clinicians should be aware of the potential for increased thromboembolic and/or bleeding risks in patients with cancer and those undergoing cancer treatment. These risks should be reassessed during follow-up. Anticoagulation treatment is recommended in patients with $CHA_2DS_2VASc \geq 2$ in men and ≥3 in women and should be considered in patients with lower CHA_2DS_2VASc scores unless there is an unacceptable risk of bleeding.[145,146] The 2024 ESC Guidelines for the management of atrial fibrillation propose that gender criteria should no longer be used to guide decisions about anticoagulant therapy. Therefore, oral anticoagulant therapy is recommended in patients with a CHA_2DS_2-VA score of 2 or more and should be considered in those with a score of 1.[147] Non-vitamin K antagonist oral anticoagulants (NOACs) are the preferred anticoagulant therapy. Low-molecular-weight heparins should be considered in patients ineligible for NOACs (gastrointestinal toxicity, severe renal impairment, major drug–drug interactions, or platelet count < 50 000/μL). Left atrial appendage occlusion may be an option when long-term anticoagulation is contraindicated (*Figure 4*).[5]

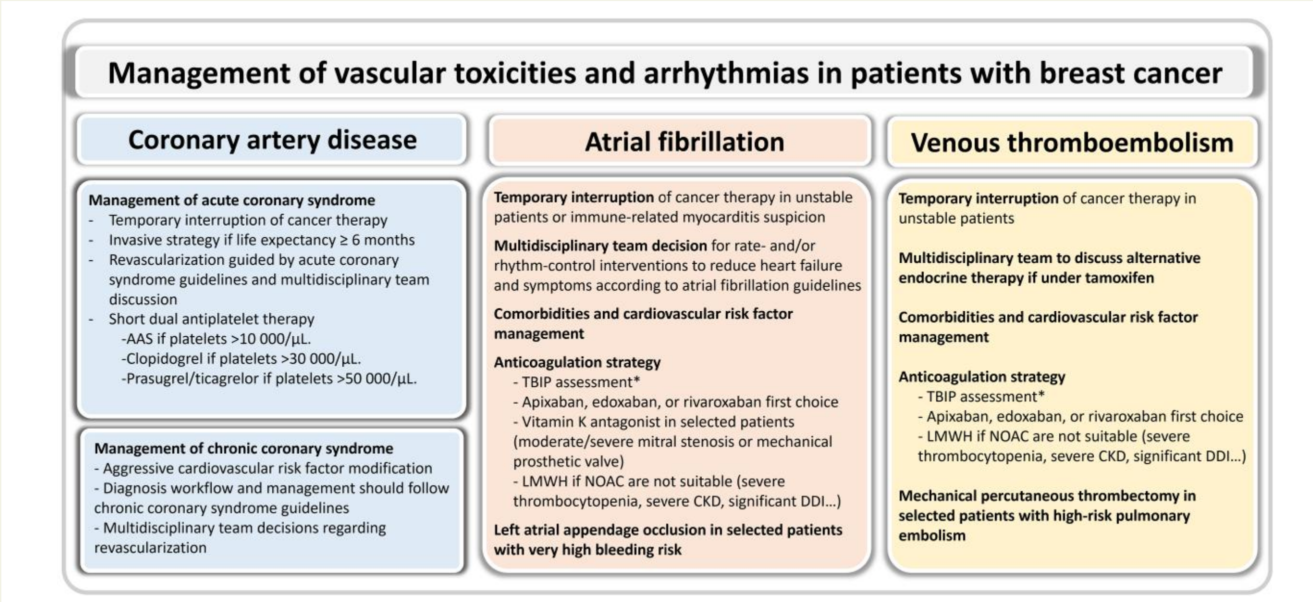


Figure 4 Management of vascular toxicities and arrhythmias in patients with breast cancer. *T: thromboembolic risk: CHA_2DS_2VA score (atrial fibrillation) and cancer-related risks (cancer stage and treatment); B: bleeding risk: thrombocytopenia, gastrointestinal comorbidities, or toxicity, active or recent major bleeding, estimated glomerular filtration rate < 30 mL/min/1.73 m^2, HAS-BLED; I: drug–drug interactions; P: patients' preferences. CKD, chronic kidney disease; DDI, drug–drug interaction; eGFR, estimated glomerular filtration rate; LMWH, low-molecular-weight heparin; NOAC, non-vitamin K antagonist oral anticoagulants

Venous thromboembolism

Patients with metastatic disease and those receiving tamoxifen are at elevated risk of venous thromboembolism.[148] Treatment should follow general guidelines and NOACs are the preferred anticoagulant treatment.[5,149] Interestingly, mechanical percutaneous thrombectomy is a promising therapy for high-risk pulmonary embolism in this population, where fibrinolysis is generally contraindicated (*Figure 4*).[150]

Coronary artery disease

Capecitabine-induced cardiotoxicity may cause chest pain, which may be due to vasospasm or acute coronary syndrome.[151] The presence of underlying CVD disease or CVRF should not prevent treatment with capecitabine; however, it is essential to optimize CV conditions before initiation of treatment and educate patients. Prophylactic treatment for coronary vasospasm is not recommended. The diagnosis and management of acute coronary syndrome or vasospasm should follow standard principles. Due to the potential for atypical presentations of chest pain, a high index of suspicion is recommended in this population.[5]

The incidence of radiotherapy-induced CAD is influenced by the patient's CVRF and the radiation dose to cardiac structures. While screening for CAD in patients with chest pain is advised, routine screening in asymptomatic patients is primarily supported by expert opinion.[5,45] Non-cardiac computed tomography scans can help identify asymptomatic atherosclerosis, thereby informing therapeutic decisions.

Antithrombotic therapy and revascularization should be individualized according to the patient's thrombotic and bleeding risk, both of which are higher in the proinflammatory context of cancer. A recent study found that percutaneous coronary intervention in patients with early-stage BC was not associated with an increased risk of mortality or major complications.[152] Particular attention should be paid to the presence of thrombocytopenia to tailor the antiplatelet regimen (*Figure 4*).[5] Recently, Ameri *et al.*[153] have published a state-of-the-art review with updated strategies for the management of acute and chronic coronary syndrome in patients with cancer.

Other cancer therapy-related cardiovascular toxicity

The management of chronic pericardial disease and valvular lesions resulting from radiotherapy should follow standard clinical practice guidelines, bearing in mind that cardiac surgery after radiotherapy is often challenging and that percutaneous non-coronary intervention (e.g. transcatheter aortic valve implantation) may reduce recovery time and delays in cancer treatment.[5]

Conclusions

Although cardio-oncology strategies play a key role in the management of patients with BC, further research is needed.[5,154] Until new evidence is available, clinical care should follow current ESC guidelines and incorporate multidisciplinary team discussions to make appropriate clinical decisions. Addressing knowledge gaps is essential to advance patient care and improve long-term health outcomes of patients undergoing treatment for BC.

Strategies to reduce disparities in cardio-oncology care are critical, given the higher risk of mortality among under-represented ethnic and racial groups, even after adjustment for socioeconomic and behavioural factors.[155,156] Implementing a comprehensive cardio-oncology programme, which encompasses not only pharmacological approaches to management of CV toxicities but also addresses modifiable CV risk factors such as diet and exercise.[157,158] The development of telemedicine platforms offers an opportunity to improve patient access to cardio-oncology subspecialists, survivorship care, and delivery of exercise therapy, thus overcoming socioeconomic and geographical barriers. Further research is needed to determine genetic predispositions to CTR-CVT and to assess the impact of personalized prevention strategies on cancer and CV clinical outcomes.

Supplementary data

Supplementary data are available at *European Heart Journal* online.

Declarations

Disclosure of Interest

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Data Availability

No data were generated or analysed for this manuscript.

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