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REVIEW

Cardiovascular toxicity of breast cancer treatments: from understanding to enhancing survivorship care

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The significant decline in breast cancer (BC) mortality, largely driven by advancements in drug development, makes survivorship an absolute priority. Adverse events induced by anticancer treatments, particularly long-term and irreversible complications, have emerged as a major concern for BC survivors. Many anticancer therapies used in BC are associated with an increased risk of cardiovascular (CV) toxicity which may lead to treatment discontinuation and negatively affect clinical outcomes including long-term survival. Moreover, the occurrence of late CV adverse events can significantly impact the quality of life of BC survivors. Timely recognition and management of CV toxicity is therefore crucial. Before the initiation of potentially cardiotoxic therapies, a careful risk—benefit evaluation should be carried out in all patients with BC. Over the past decades, the field of cardio-oncology has emerged to deal with these challenges. Importantly, a better understanding of the mechanisms underlying CV toxicity is crucial in order to improve strategies to diagnose, monitor, and treat and ideally prevent the CV events related to different cancer treatments.

In this review, we aim to provide an overview of the main CV toxicities associated with contemporary BC treatments. Moreover, we highlight the need to balance the expected benefits of anticancer therapies while preserving CV health in both the early and advanced settings.

Key words: breast cancer, cardiotoxicity, cardio-oncology

INTRODUCTION

Breast cancer (BC) is the most common malignancy in women. It represents the second leading cause of cancer-related death among women worldwide and the leading cause in developed countries.[1] Early diagnosis and advancements in treatment strategies have led to a decrease in BC mortality over the past decades.[1] The trend towards improved survival outcomes makes survivorship an absolute priority, and in this matter, anticancer treatment-related adverse events (AEs), particularly long-term and irreversible ones, represent a major concern. Cardiovascular disease (CVD) is the leading cause of mortality in developed countries and has overtaken cancer-related death in long-term cancer survivors.[2,3] Both CVD and BC share some risk factors, and addressing the modifiable ones has the potential to reduce the risk of both conditions.[4] Many anticancer agents administered to patients with BC, in both early and advanced settings, are associated with an increased risk of cardiovascular (CV) toxicity.[5] Recently, emerging targeted therapies and immunotherapies with innovative mechanisms of action, while improving BC outcomes, pose additional challenges in managing CV toxicity and introduce a wide spectrum of cardiac complications.[6,7] The field of cardio-oncology has emerged as a new subspeciality of medicine for patients with cancer exposed to potentially cardiotoxic cancer therapies with prevention, monitoring of CVD, and optimization of treatment strategies as its main goals.[8] A collaborative approach involving different health care professionals such as oncologists, cardiologists, nurses, pharmacists, and allied health

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care professionals is essential to ensure high quality and multidisciplinary patient care.[9] This review aims to provide an overview of the main types of CV toxicities associated with BC treatments and to summarize recommendations regarding prevention, diagnosis, and long-term monitoring.

EVOLUTION OF CARDIOVASCULAR TOXICITY DEFINITIONS

The concept of CV toxicity has significantly evolved over the years. Historically, CV toxicity in the context of cancer treatment was associated with overt myocardial damage resulting in a reduction in left ventricular ejection fraction (LVEF) or heart failure (HF).[10] There has been a lack of universal agreement on the definition of CV toxicity with oncology trials relying on reported drops in LVEF with different thresholds to define toxicity.[11,12] The ongoing development and introduction of new anticancer drugs into clinical practice have expanded the modern understanding of CV toxicity.[9] The recent 2022 European Society of Cardiology (ESC) guidelines define the broad spectrum of cardiotoxicity as cancer therapy-related CV toxicity (CTR-CVT) to include all treatment-related cardiac AEs, with different pathogenesis, diagnosis, and management strategies.[13] Among these, a new definition of cancer therapy-related cardiac dysfunction (CTRCD) emerged, which encompasses additional parameters beyond LVEF.[8] The commonly used criteria in clinical practice to define asymptomatic CTRCD include a decline in LVEF to $<$50% or a decrease of $>$10% from baseline.[13] Early detection and prompt initiation of treatment are key, as they may significantly improve the likelihood of LVEF normalization in cases of reversible cardiotoxicity.[13,14] It is important to consider that CTRCD and HF can occur without a drop in LVEF, however, underscoring the importance to evaluate other parameters, such as global longitudinal strain (GLS) and biomarker concentrations, to ensure a comprehensive evaluation (Table 1).

CARDIOVASCULAR TOXICITY IN ONCOLOGY: BEYOND HEART FAILURE

Traditionally, asymptomatic CTRCD and HF have been the only recognized cardiotoxicities in the context of cancer treatment. Contemporary cancer treatments are associated with a broad spectrum of CTR-CVT. Vascular toxicities include a heterogeneous group of clinical entities characterized by the injury of arterial and/or venous vessels (e.g. vasospasm, acute thrombosis), the incidence of which varies according to the type of anticancer drug and patient-related risk factors.[15] Cancer treatments may also alter the cardiac electrophysiology, leading to alterations in normal rhythm.[16] Arrhythmias ($\sim$1%-4%) can range from benign ectopic beats to life-threatening conditions such as ventricular tachycardia and can occur as a direct consequence of myocarditis or HF but also independently.[17] In the context of BC treatment, there is particular interest in the therapy-induced prolongation of the corrected QT (QTc) interval ($\sim$5%-10%) that may predispose to potential life-threatening arrhythmias.[18] Managing arrhythmias may be challenging due to potential drug interactions between anticancer treatment and antiarrhythmics.[13] Immune checkpoint inhibitors (ICIs) are associated with a number of CV toxicities; however, myocarditis is one of the most serious forms considered rare (0.04%-1.14%) but associated with high mortality rates (25%-50%).[19]

PRETREATMENT RISK ASSESSMENT

Baseline risk stratification is crucial before starting patients with cancer on potentially cardiotoxic therapies. A baseline assessment should include a physical examination and a detailed assessment of medical history, focusing on individual patient risk factors that may increase the risk of cardiotoxicity (Figure 1). Obesity, hypertension, high blood cholesterol, smoking, sedentarism, and diabetes mellitus are the main modifiable risk factors for atherosclerotic CV disease.[20] Non-modifiable risk factors such as age, sex, and genetic predisposition should also be considered in the evaluation.[21] Cancer is an independent risk factor for CVD, especially for its prothrombotic effect, which may trigger the onset and worsen the clinical course of ischemic heart disease and HF. Balancing the risks and benefits of giving a potentially cardiotoxic treatment for each patient is crucial at this stage. The frequency of cardiac function assessment during cancer therapy should be adapted based on the

Table 1. Classification of cancer therapy-related cardiovascular dysfunction according to ESC guidelines 2022[13]

Cancer therapy-related cardiovascular dysfunction		
Heart failure (symptomatic CTRCD)	Very severe	HF requiring inotropic support, mechanical circulatory support, or consideration of transplantation
	Severe	HF hospitalization
	Moderate	Need for outpatient intensification of diuretic and HF therapy
	Mild	HF symptoms, no intensification of therapy required
Asymptomatic CTRCD	Severe	New LVEF reduction to 40%
	Moderate	New LVEF reduction by $\geq$10 percentage points to an LVEF of 40%-49% OR New LVEF reduction by 10 percentage points to an LVEF of 40%-49% AND either new relative decline in GLS by $-$15% from baseline OR new rise in cardiac biomarkers
	Mild	LVEF $\geq$50% AND new relative decline in GLS by $-$15% from baseline AND/OR new rise in cardiac biomarkers

CTRCD, cancer treatment-related cardiac dysfunction; ESC, European Society of Cardiology; GLS, global longitudinal strain; HF, heart failure; LVEF, left ventricular ejection fraction.

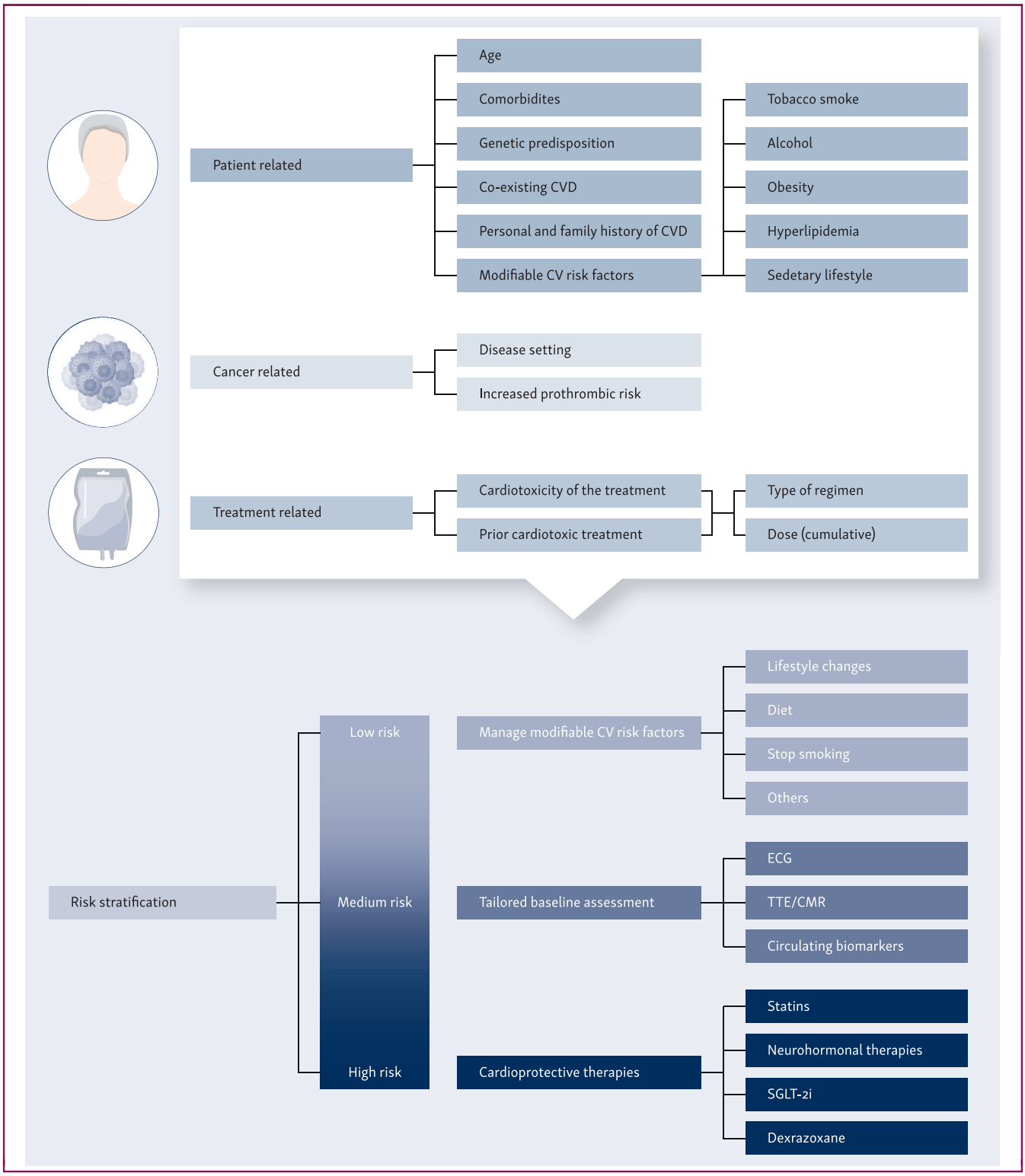

Figure 1. Baseline assessment before starting potentially cardiotoxic treatment.
CMR, cardiovascular magnetic resonance; CVD, cardiovascular disease; ECG, electrocardiogram; SGLT2i, sodium-glucose cotransporter-2 inhibitors; TTE, transthoracic echocardiogram.

baseline CV risk, the underlying cancer type, and the cancer therapy regimen. To detect early signs and symptoms of cardiotoxicity, clinical evaluation and physical examination should be carried out regularly.[22] A baseline 12-lead electrocardiogram (ECG) can help to identify at-risk patients.[13] Serial monitoring of serum cardiac biomarkers may also be useful in high-risk patients. Ideally, the use of the same imaging modality is preferred to reduce

inter-technique variability. Finally, for drugs known to potentially cause QTc prolongation (e.g. ribociclib, tamoxifen), regular ECG monitoring is recommended depending on clinical risk as per the ESC guidelines and the license.[13]

Circulating biomarkers

Cardiac serum biomarkers could be useful, combined with other clinical information, to detect subclinical cardiac disease before changes in LVEF occur,[23] yet several confounders may affect their concentrations. Therefore, baseline biomarkers assessment, particularly in high- and very high-risk patients, should be done in association with complementary diagnostic modalities.[13]

Increased concentrations of B-type natriuretic peptide (BNP) and its associated peptide, N-terminal proBNP (NT-proBNP), are associated with volume overload and/or impaired cardiac contractility.[24] In patients with no history of HF but with risk factors, assessing baseline concentrations of natriuretic peptides (NPs) can guide further investigations. Significant elevation of baseline NP concentrations (BNP >100 pg/ml or NT-proBNP >400 pg/ml), can help identify patients at risk of CTRCD.[24] Monitoring trends over time can help detect subclinical cardiac complications. In symptomatic patients, low NP concentrations (BNP <35 pg/ml and NT-proBNP <125 pg/ml) have a strong negative predictive value, making an HF diagnosis unlikely.[25] NP concentrations, however, are influenced by many factors (e.g. high body mass index, renal dysfunction) that should be considered when interpreting them.

Cardiac troponin I (cTnI) and cardiac troponin T (cTnT) are sensitive and specific biomarkers of myocardial injuries, released in the blood when cardiac myocytes are damaged and routinely used to diagnose acute myocardial infarction and myocarditis. High-sensitive cardiac troponins (hs-cTn) accurately quantify very low concentrations of plasma troponin and enable early detection of cardiomyocyte injury before the development of myocardial dysfunction.[26] In cardio-oncology, increased baseline plasma concentrations of cTn may be predictive of LV dysfunction in cancer patients undergoing potential cardiotoxic treatment.[27]

A meta-analysis highlighted the predictive value of baseline troponins for LV dysfunction in patients with cancer treated with cardiotoxic therapies [odds ratio 11.9, 95% confidence interval (CI) 4.4-32.1].[27] In patients with BC treated with cardiotoxic agents, a large prospective cohort trial assessed the association between cardiac serum biomarker concentrations and CTRCD occurrence. While hs-cTnT elevation was common following anthracycline treatment, early increase in its values was not associated with an increased risk of CTRCD. In contrast, NT-proBNP elevations were associated with LVEF decline and higher risk of CTRCD, especially in patients who received subsequent therapy with anthracycline and trastuzumab.[28] In the HERA trial, increased baseline concentrations of cTnI and cTnT were associated with higher risk of CTRCD in patients with early human epidermal growth factor receptor 2 (HER2)-positive BC treated with adjuvant trastuzumab.[29] Of note, ∼94% of patients were previously treated with an anthracycline-based chemotherapy.[29]

Among emerging cardiac circulating biomarkers, myeloperoxidase has been proposed for detecting cardiotoxicity in patients treated with anthracyclines.[30] While further validation is needed, studies showed a relationship between the elevation of myeloperoxidase and an increased risk of CTRCD in BC patients.[28,31] Additionally, circulating microRNAs recently emerged as a promising biomarker to detect early cardiac damage during therapy with anthracyclines and/or trastuzumab.[32] In the NeoALTTO trial, concentrations of eight microRNAs have been found to be increased in patients with BC treated with anti-HER2 therapy who subsequently developed a cardiac event.[33]

While it is important to include circulating biomarkers in the decision-making algorithm, there is no evidence that the isolated alteration of these values in absence of other clinical/radiological signs, should guide treatment decision. Furthermore, the optimal timing of reassessment during treatment is still controversial and largely dependent on the type of treatment administered.[34]

Cardiac imaging

Transthoracic echocardiography (TTE) has a pivotal role as first-line investigation in patients undergoing potentially cardiotoxic treatments. It is an accessible and radiation-free modality that provides important information for risk stratification, helping to identify pre-existing cardiac conditions. Importantly, it also serves as a baseline reference for subsequent monitoring. A complete baseline echocardiography protocol to assess LV and right ventricular (RV) functions, including evaluations of two-dimensional (2D) LV GLS and three-dimensional (3D) LVEF, should be carried out before starting potentially cardiotoxic drugs initiation.[13] When available, 3D echocardiography is preferred as it is more accurate and associated with lower intra- and inter-observer variability.[35]

Despite some limitations, 2D LVEF remains an important indicator of LV function. Cut-off for abnormal LV function is <50%.[36] 2D-LVEF assessment, however, lacks sensitivity to detect subclinical cardiac damage. Additionally, many modern cancer treatments can induce cardiotoxicity without variations in LVEF. Therefore, for early detection of cardiac dysfunction, the imaging evaluation should not be limited to a single-parametric cardiac function assessment.

There is growing evidence supporting the use of GLS, measured by 2D speckle-tracking echocardiography, as a new promising, sensitive, and reproducible marker of myocardial damage, detecting changes in cardiac function before modifications in 2D LVEF occur.[37] GLS reflects the longitudinal shortening of myocardial fibers during contractions which is strongly related with myocardial function.[38] As it indicates the shortening of cardiomyocytes during contraction divided by baseline length, GLS is generally expressed as a negative number or percentage (normal GLS is ≤18%). Most studies of serial GLS measurements have then identified a reduction in GLS ≥15% as

evidence of subclinical LV dysfunction.[39] In BC patients treated with trastuzumab, peak systolic longitudinal myocardial strain measured after anthracycline treatment was predictive of CV toxicity.[40] Recent evidence suggests that GLS may effectively guide cardioprotective therapy in patients treated with anthracyclines.[41]

Poor acoustic windows in BC patients who have undergone thoracic surgery, radiotherapy or in BC patients with prostheses could result in suboptimal image quality and inconclusive diagnostic assessment at TTE. Cardiac magnetic resonance (CMR) allows to overcome these limitations. CMR is a noninvasive technique that provides a highly reproducible and accurate assessment of heart morphology and function. Moreover, CMR enables tissue characterization providing more granular information on the specific type of cardiotoxicity.[42] New CMR technology allows to assess longitudinal and circumferential strain to complement LVEF evaluation.[43] Fast strain-encoded CMR (fast-SENC) is a new, short CMR assessment acquired in 10-15 min which provides a detailed assessment of myocardial function and provides a global cardiac health score known as MyoHealth. Fast-SENC has been studied in BC patients and been shown to be more sensitive than echocardiography for detecting new CTRCD.[44] Given its limited accessibility and high cost, CMR is recommended as first-line assessment only for patients with poor acoustic windows at TTE and should be considered in those with pre-existing complex CVD.[13] Recently, CMR also emerged as the first-line diagnostic test when ICI-related myocarditis is suspected.[13]

Multi-uptake gated acquisition (MUGA) is a nuclear medicine technique, originally employed in earlier clinical trials for serial monitoring of LVEF.[10] Compared with other modern modalities, MUGA has several limitations such as the inability to provide comprehensive information (e.g. GLS, RV function) and the required exposure to ionizing radiation.[22] For this reason, MUGA should be considered as an option only if both TTE and CMR are inconclusive, unavailable or cannot be carried out, as in the presence of CMR incompatible devices.[13]

Risk prediction tools

Numerous tools have been developed to facilitate cardiotoxicity risk assessment in clinical practice and guide personalized decision making.[45,46] The 2022 ESC guidelines recommend the use of the Heart Failure Association-International Cardio-Oncology Society (HFA-ICOS) baseline risk classification score, a comprehensive expert consensus-based tool, which includes seven proformas for each class of potentially cardiotoxic therapies.[13] Each proforma includes a list of CV risk factors depending on the specific drug class as well as clinical and demographic information. The tool assigns one or more points for each variable, and based on the cumulative score, patients are classified as at low (<2%), medium (2%-9%), high (10%-19%) or very high (≥20%) risk of CV toxicity.[47] Retrospective studies evaluated the use of HFA-ICOS proformas in patients with HER2-positive BC, showing an increasing risk of cardiotoxicity with higher score values.[48,49] While further prospective studies are needed to validate this approach, it represents a reasonable available strategy to identify patients at higher risk of CV toxicity.

TREATMENT-SPECIFIC CARDIOTOXICITY

Figure 2 illustrates the main CV toxicities that may be associated with BC therapies.

Chemotherapy

Despite the development of new therapeutic agents, chemotherapy still remains a cornerstone of BC treatment. Anthracyclines are among the most widely used cytotoxic agents for BC. Anthracycline-induced cardiotoxicity is multifactorial, and several molecular mechanisms have been proposed over the years to explain its underlying pathogenesis. Oxidative stress, due to the imbalance between the production and the elimination of reactive oxygen species (ROS), seems to play a crucial role in damaging myocyte cell membranes.[50] Anthracyclines can also alter mitochondria membrane function by binding cardiolipin, a phospholipid that is present in the inner mitochondrial membrane. Moreover, anthracyclines interact with iron metabolism leading to mitochondrial iron accumulation and dysfunction.[51] Additionally, the anthracycline—DNA—topoisomerase II beta complex can cause enzyme dysfunction, impair ATP production and increase ROS generation.[52] Anthracycline-induced cardiac damage is generally dose dependent and might still be reversible in the early phase, hence timely detection and management are crucial. The risk of CTRCD with anthracycline regimens is directly related to the cumulative dose administered and the damage may manifest across different phases, including acute toxicity (within days), early-onset chronic toxicity (within the first year), and late-onset chronic toxicity (developing years to decades after treatment). Monitoring patients during and after treatment termination, especially within the first year, is recommended.[13] Efforts have been made in recent decades to find new strategies to avoid anthracycline-induced cardiotoxicity. Anthracycline-free regimens have been evaluated in several clinical trials but are reserved to selected patients with low-risk BC.[53] Liposomal doxorubicin, with or without pegylation, altering anthracyclines pharmacokinetics, is associated with lower incidence of CV events.[54] Prolonged infusion of anthracyclines (>6 h) is associated with lower incidence of HF compared with bolus infusion [risk ratio (RR) 0.27, 95% CI 0.09-0.81].[55] Concurrent administration of cardioprotective drugs, such as dexrazoxane, has demonstrated the potential to reduce the incidence of cardiotoxicity in patients treated with high cumulative doses of anthracyclines.[56] Concerns in the oncology community regarding the increased secondary malignancies risk, however, limited the use of this cardioprotective drug, a concern largely disproven by later clinical trials and long-term follow-up studies.[57]

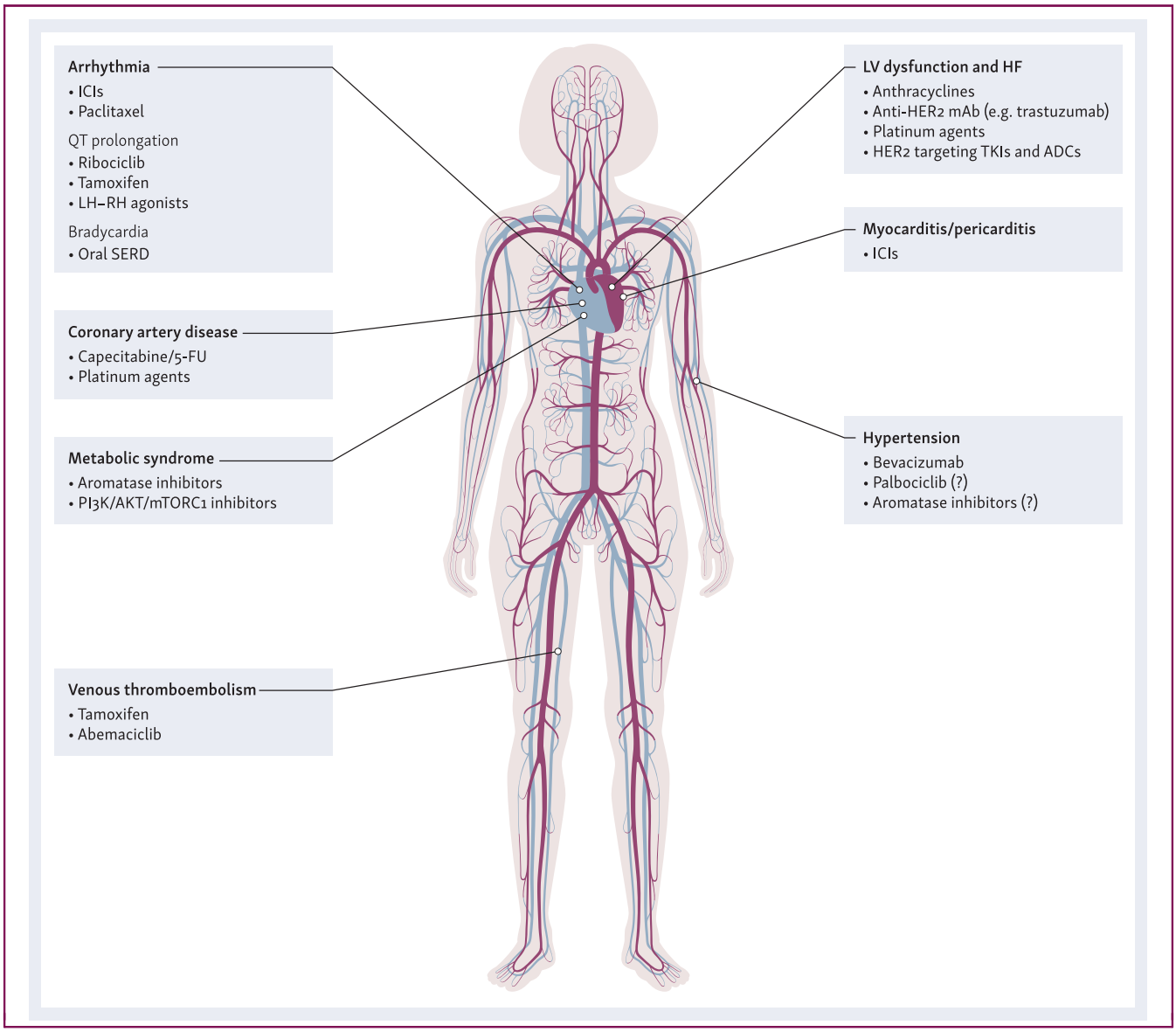

Figure 2. Main cardiovascular adverse events related to breast cancer treatments.
5-FU, 5-fluorouracil; ADCs, antibody—drug conjugates; AKT, protein kinase B; HER2, human epidermal growth factor receptor 2; HF, heart failure; ICIs, immune checkpoint inhibitors; LH-RH, luteinizing hormone-releasing hormone; LV, left ventricular; mAB, monoclonal antibody; mTORC1, mammalian target of rapamycin complex 1; PI3K, phosphatidylinositol 3-kinase; SERD, selective estrogen receptor degraders; TKIs, tyrosine kinase inhibitors.

Paclitaxel, another widely used agent in the treatment of BC, can induce arrhythmias, mainly asymptomatic sinus bradycardia.[58]

Platinum compounds can directly harm cardiomyocytes, by interacting with their cellular elements and leading to apoptosis and necrosis.[59] Additionally, platinum-based agents increase ROS production and mitochondrial dysfunction.[59] The severity of cardiac complications associated with platinum-based agents can vary, ranging from isolated arterial hypertension to myocardial infarction and arrhythmias.[13] Cisplatin-induced CV toxicity includes a broad spectrum of manifestations, such as ECG abnormalities, arrhythmias, myocarditis, pericarditis, myocardial infarction, and vascular dysfunction.[60] Carboplatin, which is the most commonly used platinum compound in BC, is less cardiotoxic than cisplatin and more frequently associated with isolated hypertension.[59]

Within the antimetabolite class, capecitabine and 5-fluorouracil can induce coronary vasospasm and endothelial injury which may result in angina pectoris and myocardial ischemia.[61] The risk of these CV events is higher in patients with preexisting coronary artery disease.[62]

HER2-targeted therapies

Trastuzumab, a key HER2-targeted agent in the treatment of patients with HER2-positive BC, is characterized by a potential well-known cardiotoxicity risk. Several mechanisms have been proposed to explain its cardiotoxicity,

including the impairment of ErbB/neuregulin-1 signaling pathway involved in cardiac homeostasis.[63]

Trastuzumab-associated cardiotoxicity may manifest as asymptomatic LV dysfunction or, less frequently, overt HF.[64] These effects are generally reversible after drug discontinuation, and are non-dose dependent. A baseline LVEF <55%, previous use of anthracyclines, and obesity are among the main factors associated with higher risk of CV events.[65] Administering trastuzumab with standard of care chemotherapies revealed an additive cardiotoxic effect with anthracyclines in early clinical trials.[66] For this reason, sequencing instead of concurrent administration of trastuzumab and anthracyclines is now regarded as the standard of care. Several trials have investigated the possibility of de-escalating treatment either with single or dual HER2 blockade while sparing anthracyclines, allowing for the possibility of anthracycline-free regimens in selected patients.[67,68] Better patient selection, baseline LVEF assessment, and the sequential administration of anthracyclines and trastuzumab have led to lower rates of cardiotoxicity compared with those observed in the earlier trials. The concerns about trastuzumab-induced cardiotoxicity, however, also increased awareness about the cardiac safety of subsequently developed anti-HER2 therapies. It is important to consider that newer agents are usually assessed in low CV risk populations in clinical trials, and the rates in real-world BC populations including high and moderate CV risk patients are higher than the rates reported in the trials.

By inhibiting HER2/HER3 dimerization, pertuzumab is currently administered in combination with trastuzumab to improve its efficacy in both metastatic and early BC.[69,70] A recent meta-analysis of eight randomized, controlled trials (RCTs) showed that the addition of pertuzumab in the early and metastatic settings was related with an increased risk of HF (RR 1.97, 95% CI 1.05-3.70), but not associated with an increased risk of asymptomatic LV dysfunction (RR 1.19, 95% CI 0.89-1.61).[71] Notably, most of the included trials reported the concomitant or previous use of anthracyclines and excluded high CV risk patients including those with prior trastuzumab-related cardiac dysfunction.

Lapatinib, neratinib and tucatinib are currently available oral tyrosine kinase inhibitors for HER2-positive BC. Lapatinib activates the AMP-kinase pathway, potentially protecting cardiomyocytes from tumor necrosis factor alpha-induced cell death.[72] In a phase III study in HER2-positive metastatic BC patients, lapatinib showed a favorable cardiac safety profile, with 12 cases of LVEF drop in patients previously exposed to cardiotoxic agents and/or with CV risk factors.[73] The safe cardiac profile of lapatinib was also confirmed in both the neoadjuvant and adjuvant setting.[74,75] The NEfERT-T trial compared neratinib versus trastuzumab in combination with paclitaxel in HER2-positive metastatic BC, reporting grade ≥3 cardiac events in 1.3% and 3.0%, respectively.[76] Adjuvant neratinib therapy after 1 year of trastuzumab did not affect cardiac safety.[77] In the HER2CLIMB trial, evaluating tucatinib or placebo in combination with trastuzumab and capecitabine in HER2-positive metastatic BC no cardiac safety signals emerged.[78]

Antibody—drug conjugates

Trastuzumab emtansine (T-DM1) is associated with a low rate of CV events. Consistent with trastuzumab-based trials, older age and baseline LVEF <55% are considered risk factors for the occurrence of CV events in patients with metastatic BC.[79] The low incidence of CV events was confirmed also with 1-year post-neoadjuvant T-DM1 in a low CV risk trial population.[80] A pooled analysis showed a low incidence of LVEF drop (1.95%) and QTc prolongation (7.7%) in patients with metastatic BC treated with trastuzumab deruxtecan.[81] While most of them were asymptomatic, HF was reported in four patients.[81]

Despite the reassuring cardiac safety profile of HER2-directed antibody—drug conjugates, cardiac monitoring is always recommended. Patients should be eligible to receive these treatments if presenting with preserved baseline LV function and the discontinuation of these agents should be considered if any CV events occur.

Endocrine therapies and combinations

Endocrine therapies have a crucial role in patients with hormone receptor-positive BC. Circulating estrogens play a key role in maintaining CV health and their depletion due to endocrine therapies may predispose to CV events. Moreover, the duration of these therapies can span from 5 to 10 years and the long-term impact of these drugs should be considered.

Tamoxifen, due to its estrogen-agonistic effect, can increase the risk of venous thromboembolism. The 5-year risk of thromboembolic events associated with tamoxifen is estimated to be around 1%, with a higher incidence in the first 2 years of treatment.[82] A meta-analysis involving 28 406 subjects found 118 cases of venous thromboembolism in the tamoxifen group compared with 62 cases in the placebo group (RR 1.9, 95% CI 1.4-2.6).[83] Additionally, tamoxifen use doubled the risk of superficial thrombophlebitis.[84] An evaluation of the baseline predisposition to developing venous thromboembolism is crucial in assessing the risk—benefit balance of tamoxifen, especially in early BC. Thromboembolic events during tamoxifen therapy are more common in patients who have undergone recent surgery, prolonged immobilization or fractures. A potential link between atherosclerosis and thromboembolic risk has been suggested, as these conditions may share common risk factors like hyperlipidemia and hypertension.[85] Furthermore, tamoxifen may increase the risk of QT prolongation, particularly when used with other medications that carry the same risk.[86] Therefore, concomitant medications should be carefully evaluated.

Compared with placebo, the use of aromatase inhibitors (AIs) has not been shown to increase the rate of CV events.[87] When compared with tamoxifen, however, AIs are associated with a higher incidence of dyslipidemia and a 19% increased

relative risk of CV events.[58,88,89] These findings may be partly explained by the cardioprotective properties of tamoxifen, possibly related to its favorable effects on serum lipid profiles.[87,89] The higher rate of CV events with prolonged therapy with AIs beyond 5 years should be taken into consideration when extended treatment is indicated.[90] While the underlying mechanisms have not been fully elucidated, a population-based study showed a 50% increase in the risk of cardiac mortality in patients treated with AIs.[91]

Fulvestrant is an injectable selective estrogen receptor degrader (SERD) and it is associated with low rates of thromboembolic events (0.8%) and ischemic CV events (1.4%).[92] Recently, new oral SERDs have been introduced for clinical use. In the EMERALD III trial, there was no evidence of significant CV toxicity in patients treated with elacestrant, the first oral SERD approved for ESR1-mutant hormone receptor-positive metastatic BC.[93] Dose-dependent bradycardia, however, has been observed with other novel oral SERDs. In the phase I SERENA-1 trial, camizestrant was associated with 44% occurrence of grade 1-2 bradycardia during dose escalation from 25 to 450 mg.[94] Giredestrant was tested in a phase I trial and bradycardia, mostly grade 1, was observed in 7% of patients.[95] In the EMBER-3 trial, bradycardia of any grade was reported in 2.1% of patients treated with imlunestrant.[96]

Metabolic AEs such as hyperglycemia, hypercholesterolemia, and hypertriglyceridemia are common in patients treated with phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin inhibitors and are considered class effects of these drugs. Specifically, hyperglycemia occurs in up to 17% of patients with hormone receptor-positive, HER2-negative BC treated with everolimus, resulting from an impaired activity of the PI3K/AKT pathway that controls insulin sensitivity and glucose metabolism.[97] Hyperglycemia is also a significant AE with PI3K and AKT inhibitors[98,99] and can be managed with antidiabetic medications, treatment interruption, and/or dose modification, depending on the severity.

A real-world study explored the cardiac safety of cyclin-dependent kinase 4/6 (CDK4/6) inhibitors in patients with metastatic BC showing CV events in 24% of the included patients, in particular hypertension, HF, and atrial fibrillation, regardless of the type of CDK4/6 inhibitor.[100] Ribociclib should only be prescribed to patients with QTc$<$450 ms and is contraindicated in those at high risk of QTc prolongation, such as patients with long QT syndrome or underlying cardiac disease (e.g. recent myocardial infarction, unstable angina, bradyarrhythmia). A pooled analysis of MONALEESA-2, MONALEESA-3, and MONALEESA-7 revealed a 6.5% incidence of all grade QT prolongation when administering ribociclib in a metastatic setting.[101] In the adjuvant setting, at a 400 mg dose, QT prolongation was observed in 5.2% of patients treated with ribociclib in the NATALEE trial.[102] The concomitant use of ribociclib with medications known to prolong the QTc interval is strongly discouraged. Baseline ECG and electrolyte monitoring are required before starting ribociclib and should be repeated on day 14 and subsequently as clinically indicated. In case of electrolyte imbalances and/or QT prolongation, interruption, dose reduction, and/or discontinuation might be needed, depending on the severity of the disturbance and should follow international guidelines.[103] The 2022 ESC guidelines on cardio-oncology provide an algorithm for the management of QTc prolongation. If the QTc reaches $\geq$500 ms, the cancer treatment must be immediately discontinued, as arrhythmia risk increases significantly above this threshold.[13]

Venous thromboembolism events (VTEs) occurred in 4.8% and 6.1% of patients in the MONARCH-2 and MONARCH-3 trials, respectively, which evaluated abemaciclib in mBC.[104] Most of the patients with VTEs had risk factors for VTEs and were treated with anticoagulants.[104] In the MonarchE trial, VTEs were observed in 2.5% of patients treated with abemaciclib in the adjuvant setting, and patients treated with abemaciclib in combination with tamoxifen had a numerically higher risk of VTEs.[105] A pooled analysis including RCTs of palbociclib in metastatic BC showed a relatively low risk of QT prolongation (0.8%) and VTE (3.2%) in the palbociclib arm.[106] In the PALLAS trial, 5.6% of patients experienced grade 1-2 hypertension and only 1.6% experienced grade 3 hypertension.[107]

Immunotherapy

Immunotherapy has revolutionized the treatment of several solid tumors, including BC.[108-110] Acting through the activation of the immune system, ICIs demonstrated peculiar CV toxicities that require special attention and prompt treatment.[111] The underlying mechanisms of these cardiac toxicities are not fully understood. It is believed, however, that activation of the immune system could cause non-specific inflammation that may primarily damage cardiac tissue.[19] ICIs may lead to an excessive immune response against antigens which are present in the heart, causing inflammation and subsequent cellular damages.[112] Among ICI-related cardiac AEs, myocarditis is the most common and it is characterized by massive inflammatory cell infiltration and loss of cardiomyocytes.[23] It may manifest with non-specific symptoms such as fatigue, dyspnea, and chest pain, which often make early diagnosis difficult.[111] Moreover, overlap syndrome with other immune-related AEs, such as myositis and myasthenia gravis, is associated with worse prognosis and should always be ruled out.[113] Studies suggest that ICI-related myocarditis may occur at any time during treatment, but often arises within the first few weeks of therapy.[111] Despite its low incidence, ICI-related myocarditis has a substantial prognostic impact and is associated with the highest mortality rate compared with other immune-related AEs.[114] Myocarditis is more common in patients treated with ICIs in combination than with a single agent, which is the only approved indication in BC.[19] The suspicion of myocarditis warrants rapid hospital admission and consultation with a cardiologist. Prompt discontinuation of immunotherapy and early initiation of immunosuppressive treatment are necessary.[115] Myocarditis is not the only possible immune-related cardiac AE; arrhythmias, pericardial disease, vasculitis, non-

Table 2. Selection of RCTs evaluating cardioprotective therapies in patients with breast cancer

RCTs evaluating cardioprotective therapies in patients with breast cancer

Trial	Intervention	BC subtype	Cancer therapy	*N*	Primary endpoint	Results
Heck SL, et al. *Circulation.* 2021 (PRADA)[121]	Metoprolol/candesartan/ metoprolol plus candesartan	Early HER2-positive and HER2-negative BC	Anthracycline regimen with or without trastuzumab	130	Change in LVEF from baseline to the completion of adjuvant therapy, as determined by cardiac MRI	At extended follow-up (median 23 months) no difference in change in LVEF from baseline to extended follow-up in either treatment arm
Avila MS, et al. *J Am Coll Cardiol.* 2018 (CECCY)[122]	Carvedilol	Early HER2-negative BC	Anthracycline regimen	192	Early onset drop in LVEF of at least 10% from baseline until the end of chemotherapy at 6 months	At 2-year follow-up no difference in change of LVEF
Livi L, et al. *JAMA Oncol.* 2021 (SAFE)[123]	Bisoprolol/ramipril/ bisoprolol plus ramipril	Early HER2-negative and HER2-positive BC	Anthracycline regimen with or without trastuzumab	174	Detection of any subclinical impairment (worsening $\geq$10%) in myocardial function and deformation measured with standard and 3D-echocardiography, LVEF, GLS	Bisoprolol, enalapril, and bisoprolol plus enalapril attenuated the reduction in LVEF Bisoprolol and enalapril prevented worsening in peak GLS
Pituskin E, et al. *J Clin Oncol.* 2017 (MANTICORE 101 —Breast)[124]	Perindopril/bisoprolol	Early HER2-positive BC	Trastuzumab with or without anthracyclines	99	Cardiac remodeling expressed as the change in indexed left ventricular end diastolic volume (LVEDVi) on cardiac MRI from baseline to completion of trastuzumab therapy	No effect on LV remodeling Both treatments reduced trastuzumab-mediated LVEF decline
Boekhout AH, et al. *JAMA Oncol. 2016*[125]	Candesartan	Early HER2-positive BC	Trastuzumab and anthracycline regimen	206	Occurrence of a cardiac event (defined as decline in LVEF of $>$15% or an absolute value $<$45%) during trastuzumab treatment and 40 weeks after discontinuation of trastuzumab.	No impact on occurrence of cardiac events
Guglin M, et al. *J Am Coll Cardiol.* 2019 (SCUSF 0806)[126]	Lisinopril/carvedilol	Early HER2-positive BC	Trastuzumab with or without anthracycline regimen	468	Decrease in rate of cardiotoxicity	No difference in cardiotoxicity rate
Hundley WG, et al. *NEJM Evid.* 2022 (PREVENT)[127]	Atorvastatin	BC and lymphoma	Anthracycline regimen	279	Difference in 24-month LVEF	No difference in LVEF
Thavendiranathan P, et al. *Eur Heart J Cardiovasc Pharmacother.* 2023 (SPARE-HF)[128]	Atorvastatin	BC, lymphoma, leukemia, sarcoma, or thymoma	Anthracycline regimen	112	CMR-measured LVEF at end of anthracycline-based treatment	No difference in change between pre- and post-anthracycline LVEF
Nabati M, et al. *J Cardiovasc Pharmacol Ther.* 2019[129]	Rosuvastatin	Early HER2-negative BC	Anthracycline regimen without trastuzumab	89	Changes in the LVEF and GLS after completion of chemotherapy compared with the baseline values	No difference in in the mean LVEF and GLS

3D, three-dimensional; BC, breast cancer; CMR, cardiovascular magnetic resonance; GLS, global longitudinal strain; HER2, human epidermal growth factor receptor 2; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging.

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inflammatory HF, and acute coronary syndrome due to plaque destabilization have also been described as potential toxicities induced by ICIs.[23]

CARDIOPROTECTIVE STRATEGIES

Since the presence of CV risk factors may increase the risk of CTR-CVT, their management should be recommended in all patients receiving cardiotoxic treatments. This includes treating hypertension, diabetes, and hyperlipidemia as well as promoting smoking cessation and regular physical exercise.[116] Of note, the achievement of target goals for CV risk factors has been shown to be protective against cancer development in a trial of >10 000 patients.[117] A cardio-oncological evaluation should be carried out before the initiation of a potentially cardiotoxic therapy in patients considered at risk. Among non-pharmacological strategies, the role of physical activity in preventing CTR-CVT is still not clear. The ONCORE trial evaluated the effectiveness of a physical exercise program in preventing CTRCD in patients with early BC undergoing anthracycline and/or anti-HER2 therapy.[118] While no patient experienced CTRCD during the trial, the decline in LVEF was attenuated in the interventional group.[118] Whenever possible, pharmacological primary prevention strategies should be initiated before starting potentially cardiotoxic treatments in high- and very high-risk patients.[13]

Dexrazoxane

Dexrazoxane is an intravenous iron-chelating drug with demonstrated cardioprotective activity in high-risk patients treated with anthracyclines.[119] In BC patients treated with anthracycline with or without trastuzumab, a meta-analysis showed a reduced risk of HF (RR 0.19, 95% CI 0.09-0.40) and cardiac events (RR 0.36, 95% CI 0.27-0.49) with dexrazoxane, irrespective of prior exposure to anthracycline.[56] Dexrazoxane is currently indicated in metastatic BC patients who received a cumulative dose of anthracycline of 300 mg/m^2 of doxorubicin or equivalent. Data on dexrazoxane in early BC is controversial and, therefore, it is not recommended. Alternatively, in high- or very-high risk patients requiring (neo)adjuvant chemotherapy, an anthracycline-free regimen is suggested.

Neurohormonal therapy

Neurohormonal antagonists, including beta blockers, mineralocorticoid receptor antagonists, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, are the pillars of HF treatment.[120] While many trials tested the preventive use of neurohormonal therapies in BC patients, the benefit was modest and variable depending on the type of drug (Table 2). A recent meta-analysis showed a protective effect of neurohormonal therapies on LVEF among patients with BC treated with anthracyclines and/or trastuzumab.[130] Notably, most of the evidence supporting the use of neurohormonal therapies derives from studies in patients treated with anthracyclines with or without HER2-targeted therapy. The PRADA trial evaluated the use of candesartan and metoprolol in early BC patients receiving adjuvant chemotherapy with anthracycline with or without trastuzumab. At 2 years after randomization, it failed to show the protective role of both agents in terms of LVEF decline.[121] The PRADA II trial is now ongoing, evaluating the use of sacubitril/valsartan versus placebo to prevent LVEF changes in early BC patients.[131]

Statins

The effectiveness of statins as cardioprotective agents is controversial (Table 2). The PREVENT trial evaluated atorvastatin in patients with early BC or lymphoma undergoing treatment with anthracyclines showing no difference in LVEF decline.[127] Conversely, in the STOP-CA trial the use of atorvastatin in patients affected by lymphoma treated with anthracyclines was associated with lower CTRCD and less LVEF reduction.[132] A retrospective study investigated the impact of statin exposure in high-risk patients with early BC treated with anthracycline and/or trastuzumab. Among patients treated with anthracyclines, the use of statins was associated with a reduced risk of HF.[133] Currently, the 2022 ESC guidelines suggest the use of statin only in high- and very high-risk patients.[13]

Sodium-glucose cotransporter-2 inhibitors

Originally introduced as antidiabetic medications, sodium-glucose cotransporter-2 inhibitors (SGLT2i) are now at the cornerstone of HF treatment.[134] The cardioprotective effects of SGLT2i, which are still not fully elucidated, extend beyond blood glucose lowering.[135] Encouraging data from preclinical models have demonstrated that SGLT2i attenuate myocardial fibrosis and LV dysfunction in mice with doxorubicin-induced cardiomyopathy.[136] Despite the absence of RCTs, several retrospective studies support a cardioprotective effect of SGLT2i therapy in cancer patients treated with anthracyclines.[137] Ongoing RCTs, such as EMPACT, are currently testing the use of SGLT2 inhibitors in patients treated with potentially cardiotoxic agents and might lead to the addition of empagliflozin and dapagliflozin to the armamentarium of cardioprotective agents.

CARDIOVASCULAR MONITORING IN SURVIVORSHIP CARE

It is important to note that from 1989 to 2021, BC mortality has decreased by 42%.[1] Cardiotoxicity can lead to late side-effects that may manifest only years later.[138] With the significant improvement in survival outcomes, late CV toxicities are an increasing issue in the curative setting. A population-based study demonstrated that BC is associated with the highest incidence of CV death.[139] Moreover, BC survivors, particularly those who previously received cardiotoxic chemotherapy or left-sided radiotherapy, have an increased risk of HF compared with women without a history of BC, regardless of baseline LVEF values.[140] As part of the survivorship plan, oncologists and cardiologists should encourage healthy behavior, including lifestyle modifications such as dietary changes, regular physical exercise, and

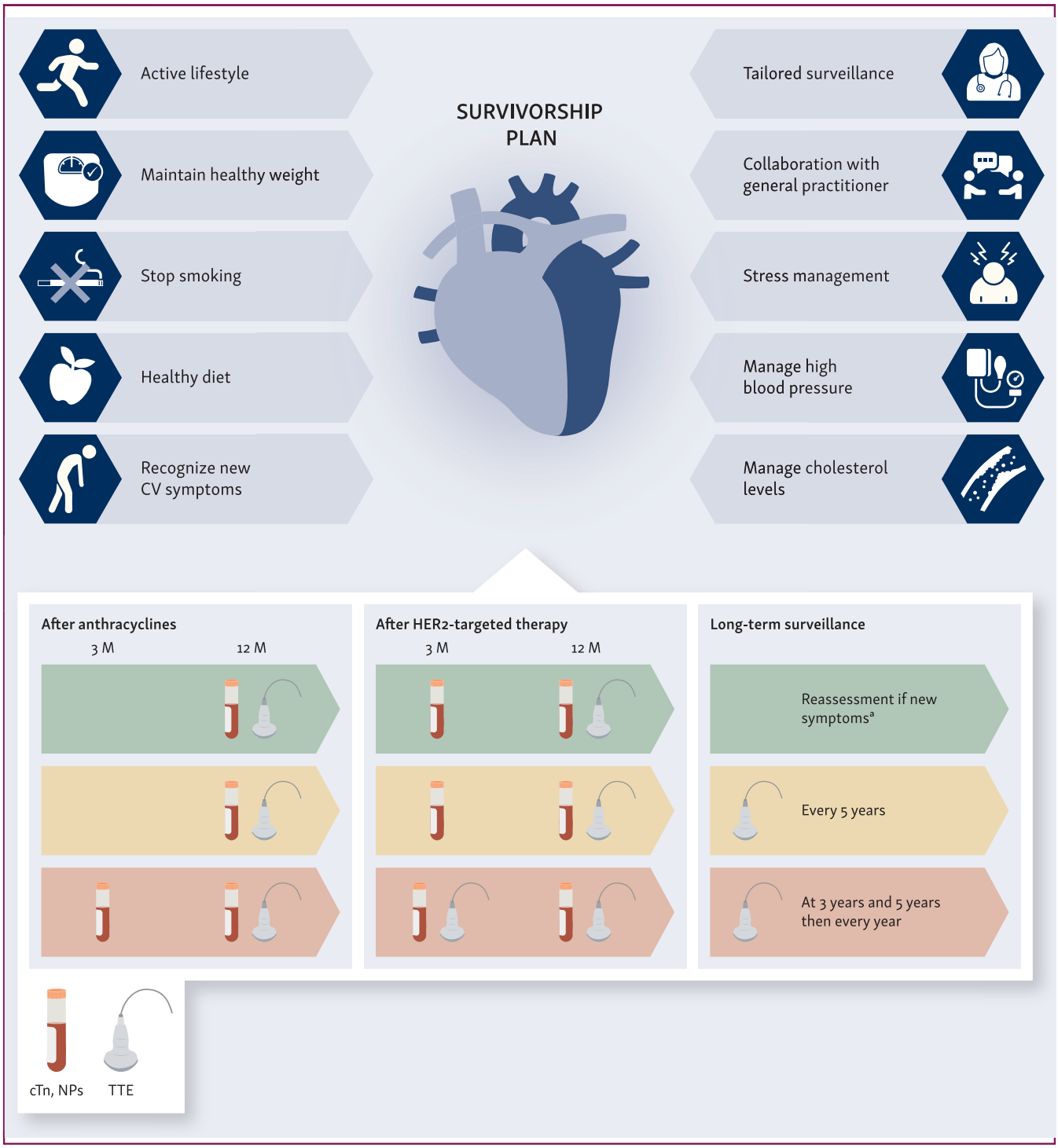

Figure 3. Survivorship plan and tailored surveillance after anthracyclines and HER2-targeted therapies. Patients are categorized as low (in green), medium (in orange) and high risk (in red) based on baseline risk assessment.
cTn, cardiac troponins; CV, cardiovascular; HER2, human epidermal growth factor receptor 2; NPs, natriuretic peptides; TTE, transthoracic echocardiogram.
[a]Annual risk assessment should be carried out.

smoking cessation.[141] In Europe, the Systematic Coronary Risk Evaluation model (SCORE2) has been developed and validated to estimate the 10-year risk of fatal and non-fatal CV events in a healthy population.[142] There are, however, no validated tools to predict CV risk in cancer survivors. Thus, long-term cardiac follow-up should be tailored according to the initial risk stratification, the type of cardiotoxic treatment administered, and the eventual occurrence of CTR-CVT during the treatment.[13] Late cardiac complications can occur particularly in patients who underwent therapy with anthracyclines or radiotherapy. Periodic monitoring of LVEF during the first year after the completion of therapy is strongly recommended for the early detection of CV toxicity (Figure 3).

CONCLUSIONS

CV toxicity in patients with BC can severely affect patient outcomes and quality of life. Despite the critical importance of risk stratification, prevention, and management of CV toxicity, the engagement of oncologist and primary care providers remains limited. Initiatives focused on education, improved accessibility to cardio-oncology services, and formal training programs are essential measures to address current gaps. Management of the common modifiable CV risk factors is paramount to lower the risk of cardiac events. Identifying patients at higher risk of CV toxicity and ensuring close monitoring during treatment are essential to improve both cancer-related and CV prognosis.

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