

# Cardio-oncology: protecting the heart from curative breast cancer treatment

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**Abstract:** Patients with breast cancer have higher rates of cardiovascular disease than age-matched controls. Anthracyclines and trastuzumab increase the risk of heart failure (HF) and radiation increases the risk of ischemic heart disease, valvular disease and HF. Older age, low normal ejection fraction, history of coronary artery disease (CAD), cardiac risk factors, higher cumulative anthracycline exposure, combination anthracycline and trastuzumab and/or radiation all increase the risk of cardiac events post treatment. Clinical prediction models (CPMs) and/or genetic testing may be useful in guiding treatment decisions but further external validation is necessary. Screening for asymptomatic cardiotoxicity using echocardiography after completion of therapy is reasonable in patients receiving anthracyclines and/or radiation, especially in those with traditional cardiac risk factors such as hypertension, diabetes, hyperlipidemia, and obesity or with low normal baseline left ventricular ejection fraction (LVEF). Elevated cardiac troponins during anthracycline therapy and early reductions in myocardial deformation may predict subsequent reductions in LVEF but further research is needed to demonstrate clinical benefit to routine screening and early treatment. Neurohormonal antagonist therapy with ACEi/ARBs and beta-blockers are indicated in patients with reduced ejection fraction and ongoing research will clarify the role for neurohormonal antagonists and statins for the prevention of breast cancer therapy cardiotoxicity. Patients treated for breast cancer should be educated on the evidence for optimal lifestyle behaviors such as not smoking, regular exercise, healthy diet and maintaining a healthy weight in reducing the risk of cardiovascular disease. Traditional cardiac risk factors such as hypertension, diabetes and hyperlipidemia should be optimally managed to reduce the risk of cardiovascular events in patients treated for breast cancer.

**Keywords:** Breast cancer; heart failure (HF); coronary artery disease (CAD); prevention; screening

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## Introduction

As advances in screening and treatment have improved survival for patients with breast cancer (1), cardiovascular disease has emerged as a major cause of long-term non-cancer related morbidity and mortality (2,3). In the general population, cardiovascular disease is the leading cause of death in both women and men (4). However, patients with breast cancer have even higher rates of cardiovascular disease compared to age matched controls without cancer

(2,5). This increased risk of cardiovascular disease likely reflects the role of shared risk factors for breast cancer and cardiovascular disease (6) as well as cancer therapy related cardiac effects (7-9). This review will describe (I) rates of cardiac disease with different breast cancer therapies; (II) risk factors and risk models for cardiac outcomes; (III) strategies for cardiotoxicity monitoring during and after cancer therapy and (IV) strategies to reduce the risk of cardiac disease with breast cancer therapy.

## Section 1: what is the risk of cardiac disease with different breast cancer therapies?

### *Anthracycline-containing chemotherapeutic regimens*

Anthracycline chemotherapeutic agents are effective cytotoxic antineoplastic agents and regimens containing doxorubicin or epirubicin are commonly used in the treatment of patients with breast cancer (10,11). Anthracycline agents cause oxidative and nitrosative stress, mitochondrial dysfunction and double stranded DNA breaks leading to cardiomyocyte apoptosis and fibrosis that manifests most commonly as asymptomatic reductions in left ventricular ejection fraction (LVEF) early after treatment that can progress to clinical heart failure (HF) with reduced ejection fraction (HFrEF) (12-14). The risk of cardiomyopathy and HF increases exponentially with increasing cumulative anthracycline dose (13,15). In a metastatic breast cancer population with rigorous assessment of LVEF using multigated acquisition (MUGA) scans, reductions in LVEF to less than normal or clinical HF occurred in 6%, 14%, 33%, 59% and 76% of patients at a cumulative doxorubicin dose of 250, 300, 400, 500 and 600 mg/m<sup>2</sup> (13). In most early breast cancer trials using anthracyclines, the risk of clinical congestive HF over several years of follow up reported using the National Cancer Institute common terminology criteria for adverse events (CTCAE) has ranged from 0.5–1% (16-18), which is likely an underestimate of the true risk as most randomized trials of anthracycline regimens for early stage breast cancer have not included longitudinal LVEF assessment or detailed ascertainment of clinical HF events. In the 10 year follow-up of the BCIRG 001 trial (TAC, doxorubicin 300 mg/m<sup>2</sup>), the largest anthracycline trial to report longitudinal LVEF and clinical assessment in participants with early breast cancer, clinical HF rates continue to increase over time occurring in 3% of the population at 10 years. In the same cohort, 12% of the population had a reduction in LVEF to less than the lower limit of normal (19) (Table 1). In a substudy of the FASG 05 trial (FEC, epirubicin cumulative dose either 300 or 600 mg/m<sup>2</sup>) participants who were cancer free and agreed to cardiac assessment a median of 8.5 years after treatment, clinical HF rates were 2.3% and reductions in LVEF to less than the lower limit of normal occurred in 5% of study participants (20). Even these well-done studies potentially underestimate the true risk given the younger age of participants in clinical trials and only a minority of the cohort participated in the long-term follow up imaging studies. Prospective cohort studies with more

rigorous collection of longitudinal echocardiographic data but smaller numbers of clinical events suggest that about 10–15% of women treated with an anthracycline without trastuzumab will have a reduction in LVEF to <50% (22,28); however, the long-term implications on risk of HF or other cardiac events requires further study. In an analysis of the Surveillance, Epidemiology, and End Results (SEER)-Medicare database of women 66 to 80 with early stage breast cancer and no history of HF, treatment with an anthracycline-containing chemotherapeutic regimen was associated with a 30% higher hazard of HF compared to women treated without anthracyclines (HR 1.3, 95% CI: 1.1–1.4) (7). Much of the research on cardiac effects of anthracyclines has focused on asymptomatic reductions in LVEF or HFrEF; however, smaller studies have shown changes in diastolic function with anthracycline therapy (29-31), suggesting that patients treated with anthracyclines may also be at increased risk for HFpEF. Further research into the association between anthracycline use and HFpEF is needed.

### *HER2 targeted therapies*

The addition of monoclonal antibodies that block HER2/ ErbB2 signaling improves survival outcomes in both the metastatic and adjuvant setting in patients with breast cancer that overexpresses HER2 (23,32-35). HER2/ErbB2 is also expressed in the myocardium and anti HER2 therapy disrupts cardiac homeostasis and myocardial repair and can result in LVEF reductions and clinical HF. The HER2/ErbB2 pathway is important for cardiomyocyte repair in response to anthracyclines and thus it is not surprisingly that concomitant anthracycline and trastuzumab therapy was associated with New York Heart Association Class III or IV (severe) HF in 16% of patients with metastatic breast cancer treated with the combination (32). Subsequent trials in early breast cancer showed lower rates of HF when anthracyclines and trastuzumab were given sequentially instead of concomitantly and with strict cardiac exclusion criteria mandating a normal LVEF after chemotherapy prior to starting trastuzumab therapy as well as frequent monitoring of LVEF every 3 months with standardized protocols for holding trastuzumab with LVEF reductions (23,34,35). In the BCIRG 006 trial, among women with HER2 positive early breast cancer randomized to treatment with doxorubicin and cyclophosphamide followed by docetaxel and 1 year of trastuzumab in those with a normal LVEF after anthracycline treatment, a total of 2%

**Table 1** Cardiotoxicity events estimated from select clinical trials and population cohort studies in which anthracyclines and/or trastuzumab were used in the treatment of early stage breast cancer

Author (citation)	Study population	Baseline cardiac risk factors reported	Cancer; therapy	Cardiotoxicity definitions and event rates
Mackey <i>et al.</i> (19)	LN+ early breast cancer (n=1,491); BCIRG 001 RCT	Median age 49 years	TAC vs. FAC; 300 mg/m <sup>2</sup> doxorubicin in both arms	(I) Clinical HF—NCI common terminology criteria for adverse events assessed for entire cohort over 10 years—3% (II) LVEF reduction to < LLN—12% (III) LVEF reduction >20%—17% Above results for TAC arm; LVEF assessed annually from years 5–10 in a subset (n=617)
Bonneterre <i>et al.</i> (20)	LN+ early breast cancer long-term outcome substudy (n=150); FASG 05	Median age 50 years	FEC 50 vs. FEC 100; total epirubicin 300 mg/m <sup>2</sup> (FEC 50) or 600 mg/m <sup>2</sup> (FEC 100)	(I) Clinical HF—NCI common terminology criteria for adverse events—2% (II) LVEF to < LLN—5% (III) LVEF reduction >20% of baseline value—13% Above results for FEC 100 arm; single time point LVEF assessment median 8.5 years after treatment
Sparano <i>et al.</i> (16)	LN+ or high risk LN- early breast cancer (n=4,950); ECOG 1199	Median age 51 years; no other cardiac risk factor data reported	AC with various taxane strategies; 240 mg/m <sup>2</sup> doxorubicin in all arms	NCI common terminology criteria for adverse events “Cardiac left ventricular function”—1–2%
Budd <i>et al.</i> (17)	LN+ or high risk LN- early breast cancer (n=2,716); SWOG S0221	Median age 51 years; no cardiac risk factor data reported	Different AC and paclitaxel dosing strategies; 240 mg/m <sup>2</sup> doxorubicin in all arms	NCI common terminology criteria for adverse events “General cardiac Grade 3–5”—1%
Levine <i>et al.</i> (18)	LN+ early breast cancer (n=710); MA5		CEF vs. CMF	NCI common terminology criteria for adverse events “Congestive heart failure” CEF—1.1%
Finkelman <i>et al.</i> (21)	Cohort of breast cancer patients treated with either doxorubicin alone or doxorubicin + trastuzumab	Median age 48 years; HTN—28%; DM—8%; HL—24%; tobacco use ever 41%	Doxorubicin dose 240 mg/m <sup>2</sup> +/- trastuzumab	Cancer therapeutics related cardiac dysfunction (CTRCD) defined as ≥10% decrease in LVEF from baseline to LVEF <50%  Doxorubicin, no trastuzumab—18% Doxorubicin + trastuzumab—42%

Table 1 (continued)

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Author (citation)	Study population	Baseline cardiac risk factors reported	Cancer; therapy	Cardiotoxicity definitions and event rates
Cardinale <i>et al.</i> (22)	Cohort of patients treated with anthracyclines; 51% of cohort with breast cancer; patients treated with trastuzumab excluded from this analysis	Mean age 50 years; HTN—21%; DM—3%; HL—6%; Tobacco use ever—20%	Variable regimens, containing doxorubicin or epirubicin	Cardiotoxicity defined as a reduction in LVEF $\geq 10\%$ from baseline to LVEF $< 50\%$ . Breast cancer cohort—9.7%
Slamon <i>et al.</i> (23)	LN+ or high risk LN- HER2+ early breast cancer; BCIRG 006 RCT	Age >50 (48%); HTN—17%; DM—3%; HL—5%; Obesity—21%	AC-T vs. AC-TH vs. TCH	LVEF reduction of >10% at the last follow-up evaluation: AC-T—11%; AC-TH—19%; TCH—9% Clinical HF: AC-T—0.7%; AC-TH—2%; TCH—0.4% Reduction in LVEF with AC precluding trastuzumab initiation—2%
Procter <i>et al.</i> (24)	HER2 positive early breast cancer; HERA RCT	Median age 49; no cardiac risk factor data reported	Trastuzumab 1 year, 2 years or observation after completion of adjuvant chemotherapy (prior treatment with anthracyclines in 94%)	LVEF reduction of $\geq 10\%$ from baseline to LVEF $< 50\%$ Trastuzumab—9.8% Observation—2.9% Symptomatic HF: trastuzumab—1.9%; observation—0.1%
Romond <i>et al.</i> (25)	HER2 positive early breast cancer; NSABP B-31	Age >50 (49%)	AC-PH vs. ACP doxorubicin 240 mg/m <sup>2</sup> ; trastuzumab for 1 year	Cardiac event—symptomatic HFrEF or cardiac death (7 years follow up) ACPH—4% ACP—1.3% Reduction in LVEF with AC precluding trastuzumab initiation—7%
Perez <i>et al.</i> (26)	HER2 positive early breast cancer; N9831	Age >50 (50%)	AC-P vs. AC-P-H vs. AC-PH; doxorubicin 240 mg/m <sup>2</sup> ; trastuzumab for 1 year	Cardiac event—symptomatic HFrEF or cardiac death (3-year cumulative incidence) AC-P—0.3% AC-P-H—2.8% AC-PH—3.3% Reduction in LVEF with AC precluding trastuzumab initiation—5%

Table 1 (continued)

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Author (citation)	Study population	Baseline cardiac risk factors reported	Cancer; therapy	Cardiotoxicity definitions and event rates
Finkelman <i>et al.</i> (21)	Cohort of Breast cancer patients treated with either doxorubicin alone or doxorubicin + trastuzumab	Median age 48 years; HTN—28%; DM—8%; HL—24%; tobacco use ever 41%	Doxorubicin dose 240 mg/m <sup>2</sup> + trastuzumab for 1 year	Cancer therapeutics related cardiac dysfunction (CTRCD) defined as ≥10% decrease in LVEF from baseline to LVEF <50%  Doxorubicin + trastuzumab—42%
Chen <i>et al.</i> (27)	Women 67 and older with a diagnosis of invasive breast cancer; SEER-Medicare data from 2000 to 2007	Age >70 (83%); age >80 (29%); HTN—58%; DM—17%; HL—51%; CAD—4%; stroke—5%	Treatment regimens classified into four groups: trastuzumab (T); anthracycline + trastuzumab (A + T); anthracycline without trastuzumab (A); no adjuvant chemotherapy or trastuzumab	Adjusted 3-year incidence rates using ICD-9-CM codes for HF or cardiomyopathy (inpatient or outpatient)  T: 32 per 100 patients A + T: 42 per 100 patients A: 20 per 100 patients None: 18 per 100 patients  Of note, 81% of women received no adjuvant chemotherapy or trastuzumab

LN, lymph node; TAC, taxotere, adriamycin and cyclophosphamide; FAC, 5-fluorouracil, adriamycin and cyclophosphamide; HF, heart failure; NCI, National Cancer Institute; LVEF, left ventricular ejection fraction; LLN, lower limit of normal; FEC, 5-fluorouracil, epirubicin, cyclophosphamide; AC, adriamycin cyclophosphamide; HTN, hypertension; DM, diabetes; HL, hyperlipidemia; AC-T, adriamycin, cyclophosphamide and docetaxel; AC-TH, adriamycin, cyclophosphamide, docetaxel and trastuzumab; TCH, docetaxel, carboplatin and trastuzumab; AC-P, adriamycin, cyclophosphamide, paclitaxel; SEER, Surveillance, Epidemiology and End Results; CAD, coronary artery disease; CEF, cyclophosphamide, epirubicin and fluorouracil; CMF, cyclophosphamide, methotrexate and fluorouracil; HERA, Herceptin Adjuvant Trial; RCT, randomized controlled trial; AC-P-H, adriamycin, cyclophosphamide, paclitaxel and trastuzumab.

developed HF over a median follow up of 5 years. Although rates of clinical HF were relatively low, 18% of participants had a greater than 10% reduction in LVEF with incomplete recovery at 4 years. Mean LVEF was lower in the sequential anthracycline- trastuzumab arm than other arms of the study (Table 1). Longitudinal LVEF and clinical assessments from other large trials of sequential anthracyclines, taxanes and trastuzumab with strict criteria for withholding trastuzumab in participants with prior cardiac disease or with LVEF reductions after adjuvant chemotherapy and protocols for holding or discontinuing trastuzumab according to LVEF monitoring, confirm HFREF in 1–4% and asymptomatic reductions in LVEF in 10–15% of participants (Table 1) (24,26,36). Recovery of LVEF to >50% is seen in more than half of those with a symptomatic or asymptomatic reduction in LVEF with sequential anthracycline and trastuzumab therapy; however, a significant number of women have persistent cardiomyopathy (25,26). Prospective cohort studies of unselected women with HER2 positive

breast cancer undergoing treatment with doxorubicin and trastuzumab show rates of LVEF reductions to less than normal in upwards of 40% of women with only partial recovery of LVEF after treatment (21,28). Data from the SEER-Medicare registry suggest higher rates of clinical HF with trastuzumab therapy in women over the age of 65 years with rates of CHF of 29% among trastuzumab users and 19% among trastuzumab nonusers with breast cancer (37). In another SEER-Medicare analysis, among women 67 to 94 years of age, 3-year HF or cardiomyopathy incidence rates were 32.1 per 100 patients for those receiving trastuzumab without anthracyclines, 41.9 per 100 patients for those receiving both anthracyclines and trastuzumab and 18.1 per 100 patients in those receiving no adjuvant therapy; although only 2% of the cohort received trastuzumab (27). As the incidence of HF increases with older age it is not surprising that rates of HF are higher in observational studies that include a higher number of older patients than in clinical trial populations.

### **Radiation**

Radiation therapy (RT) that includes the heart in the treatment field can cause a myriad of cardiac late effects. RT causes microvascular endothelial damage, capillary loss, inflammation and fibrosis and can affect all the layers of the heart (38). Late effects of RT include coronary artery disease (CAD), constrictive pericarditis, valvular stenosis or regurgitation, restriction, HFpEF and HFrEF (8,39-41). Multiple large cohort studies have demonstrated an increased risk of clinically meaningful cardiac events such as myocardial infarction (MI), HF or cardiac mortality with higher estimated mean heart dose, although mean heart dose has been estimated using various methods ranging from breast cancer laterality alone to sophisticated three dimensional dose distributions using computed tomography RT planning scans (39-43). Given that RT is associated with involvement of multiple cardiac substructures, it is not surprising that short and long-term cardiac mortality is higher in patients with prior RT undergoing percutaneous coronary intervention or cardiac surgery than in matched controls undergoing the same procedures without a history of RT. These data underscore the importance of efforts to prevent radiation-related heart disease (44-47). RT techniques continue to evolve with the goal of reducing the RT dose to normal structures with strategies such as computed tomography-based RT planning, intensity-modulated RT, lower total RT doses, reductions in RT field and deep-inspiration breath holding (38). As most of the data about long-term cardiac risks of RT are from studies of patients treated with older radiation techniques and the cardiac effects of radiation continue to increase decades after exposure, it is impossible to know to what extent modern RT has reduced the cardiac late effects of breast cancer RT.

### **Section 2: mitigating risk step 1—predicting risk prior to initiating therapy**

Multiple studies have explored risk factors for the development of cardiotoxicity with breast cancer therapy and are categorized in this review as clinical risk factors, therapy related risk factors and genetic risk factors.

#### **Clinical risk factors**

Patients with reduced or low normal LVEF, known CAD, or atrial fibrillation prior to the initiation of anthracycline

or trastuzumab treatment have been shown to be at increased risk of developing HF (7,25,26,37,48,49). In addition, traditional cardiac risk factors for CAD or HF such as hypertension, diabetes, tobacco use, hyperlipidemia, obesity and increasing age have been associated with an increased risk of cardiotoxicity with breast cancer therapy that includes anthracyclines, trastuzumab or radiation (5,7,22,25,26,37,41,48,49). Given these findings, screening and treatment of potentially modifiable risk factors to reduce the risk of cardiac events in patients with breast cancer is indicated (50).

#### **Therapy risk factors**

As described in Section 1, the risk of cardiomyopathy and HF increases exponentially with increasing cumulative anthracycline dose (13,15) and thus patients receiving higher doses of anthracyclines should be closely monitored for the development of asymptomatic reductions in LVEF or clinical HF. Both observational and clinical trial data shows that treatment with anthracyclines followed by trastuzumab is associated with higher risks of reduced LVEF and HF compared to either agent alone and these patients should also be considered high risk for the development of cardiotoxicity (14,23,27,51). Any combination of anthracyclines and radiation with the heart in the treatment field likely increases the risk of cardiotoxicity, although data for this is extrapolated from cohort studies of patients with Hodgkin lymphoma (52). Finally, multiple studies have shown that the risk of radiation induced cardiotoxicity increases with higher estimated dose to the heart and thus patients with the heart in the treatment field should be considered at risk for CAD, valvular disease, constrictive pericarditis and HFpEF and HFrEF (39-43).

#### **Genetic risk factors**

There has been interest in discovering germline genetic markers of increased risk for cancer therapy related cardiotoxicity. Most of the studies to date have focused on anthracycline cardiotoxicity with the majority of studies performed in childhood cancer survivors and most using a candidate gene or candidate single nucleotide polymorphism (SNP) approach (53-57). A recent genome-wide association study (GWAS) using three separate cohorts from randomized trials in breast cancer patients with validation and external validation suggested the rs28714259 SNP, which is located in an intergenic region in chromosome 15, was associated with



an increased risk of HF (OR 1.9–4.2) (58). GWAS analysis of a pediatric population treated with anthracyclines suggested a SNP in RARG was associated with increased risk of HF (59); however, this SNP was associated with decreased rather than increased HF risk in an adult breast cancer population (58).

Several small studies have evaluated the association between candidate SNPs in the germline *ERBB2* (Her2/Neu) gene and risk of trastuzumab cardiotoxicity with two studies showing an association with the proline allele of Pro1170 Ala (Rs1058808) and subsequent risk of trastuzumab cardiotoxicity (60,61). In the future, genetic information may be integrated with clinical and treatment related risk factors to personalize the treatment of patients with breast cancer; however, further studies evaluating the incremental value of genetic information above known clinical prognostic factors and additional validation studies in multiracial cohorts are necessary before genetic testing becomes a routine component of cardiotoxicity risk assessment.

### ***Clinical prediction models (CPMs)***

There are two reported CPMs for trastuzumab associated cardiotoxicity (*Table 2*) (25,48). The first trastuzumab CPM was developed using the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-31 study cohort that included 947 patients with Node positive HER2 positive early breast cancer who were treated with doxorubicin (240 mg/m<sup>2</sup>) and cyclophosphamide followed by paclitaxel and trastuzumab for 1 year. In order to receive trastuzumab, participants had to be free from clinical HF events and meet LVEF criteria—LVEF could not have dropped more than 15% from baseline after doxorubicin and also had to be greater than the lower limit of normal (25). The NSABP B-31 prediction model includes two variables—baseline LVEF and age—and predicts the composite of cardiac death, NYHA Class III/IV HF or LVEF decrease >10% from baseline to <55% or >5% to less than the lower limit of institutional normal value after initiation of trastuzumab over 7 years of follow-up with fair discrimination (c-statistic 0.72, optimism corrected c-statistic 0.70) but has not been externally validated. Of note, this model excludes the 6% of patients that had reductions in LVEF or cardiac symptoms during or immediately after anthracycline treatment and thus did not receive trastuzumab and the number of trastuzumab related cardiac events was 37 (4% of the population). Another CPM for trastuzumab cardiotoxicity was derived using the SEER-Medicare database and includes 1,664 women over 66 years of age without a pre-existing

diagnosis of HF or cardiomyopathy who had operable HER2 positive breast cancer and received trastuzumab (*Table 2*) (48). The SEER-Medicare model includes seven predictors—age, adjuvant chemotherapy (anthracycline based, non-anthracycline chemotherapy *vs.* none), history of CAD, atrial fibrillation/atrial flutter, diabetes, hypertension and renal failure and predicts the development of HF or cardiomyopathy over 3 years, which occurred in 19% of the cohort. All comorbidities and outcome variables were derived from International Classification of Disease, 9<sup>th</sup> edition (ICD-9) billing codes. The model was converted into a risk score (range 0–9) with risk of HF being 16% with risk score of <4 and 40% with risk score of ≥6; however, no discrimination or calibration were performed and the risk score has not been externally validated. The BETTER-CARE study included 165 patients with early breast cancer (both HER2 negative and positive disease), but excluded patients with known cardiac risk factors such as hypertension, diabetes, or kidney disease and used an outcome of questionable clinical significance—subclinical cardiotoxicity defined as LVEF change of 5% (*Table 2*) (62). There are no CPMs for anthracycline cardiotoxicity and external validation of the existing trastuzumab cardiotoxicity models is needed.

### **Section 3: mitigating risk step 2—monitoring during and after cancer therapy**

Strategies to identify patients potentially at high risk for cardiotoxicity with breast cancer therapy may affect cancer treatment decisions and in some cases less cardiotoxic regimens may be selected. However, due to tumor biology, clinical stage or other factors affecting oncologic risk, many patients with risk factors for cardiotoxicity will need to be treated with anthracyclines, trastuzumab and/or radiation with the heart in the treatment field. In addition, patients without any known risk factors for the development of cardiotoxicity may develop cardiac effects after treatment. This section reviews the current evidence regarding screening for asymptomatic cardiotoxicity in patients with breast cancer receiving potentially cardiotoxic treatment.

#### ***Rationale for screening for asymptomatic cardiotoxicity***

In the general population, individuals with a reduced LVEF but no previous or current signs or symptoms of HF have been shown to have a 5-fold increased risk of subsequent symptomatic HF and death as compared

**Table 2** Existing clinical prediction models (CPMs) for cardiotoxicity in patients with breast cancer

CPM	Ezaz <i>et al.</i> (48)	Romond <i>et al.</i> (25)	Kotwinski <i>et al.</i> (62)
Population	SEER-Medicare database; women 67–94 stage III, HER2+ breast cancer all treated with trastuzumab; 36% anthracycline CMY; 30% left sided radiation	NSABP B-31 multicenter RCT; node positive, HER2+, nonmetastatic disease all treated with anthracyclines and trastuzumab; LVEF had to be normal after AC to receive trastuzumab and be included in this model	BETTER-CARE; prospective cohort study from UK; 12 centers of early breast cancer patients planned to receive anthracycline-based chemotherapy (HER2+ or HER2-); excluded patients with known cardiac disease or cardiac risk factors (HTN, DM, CKD, BMI >35 all excluded) thus very low risk population to develop cardiotoxicity
Sample size	N=1,664	N=960 (trastuzumab arm with normal LVEF after AC)	N=165
Outcome definition	Heart failure or cardiomyopathy defined using ICD-9 codes from inpatient claim or 2 outpatient claims at least 30 days apart	“Cardiac event” = definite or probable cardiac death or NYHA Class III/IV congestive heart failure symptoms + LVEF decrease >10% from baseline to <55% or >5% to less than the LLN; LVEF assessed by MUGA scans in everyone after AC, 6, 9, 18 months	“Subclinical cardiotoxicity”—a decrease in LVEF of 5% from baseline to >12 months post chemotherapy by CMR; no patients developed clinical heart failure and no patients had reduction in LVEF >10% to less than LLN
Outcome prevalence	19% (318 events)	4% (37 events)	21% (34 events)
Follow up duration	3 years	7 years	Median 19 months (IQR 15–23 months)
Predictors included in final model	Age, adjuvant chemotherapy, CAD, Afib/AFL, DM, HTN, renal failure	Baseline LVEF and age	Number anthracycline cycles, higher BSA, BP >140/90 and trastuzumab therapy
Tool	Point score	Regression equation risk score with plot correlating risk score to predicted probability	None
Discrimination	Not reported	0.72, optimism corrected c-statistic 0.70	0.78
External validation	None	None	None

SEER, Surveillance, Epidemiology and End Results; CMY, cardiomyopathy; LVEF, left ventricular ejection fraction; AC, adriamycin cyclophosphamide; HTN, hypertension; DM, diabetes; HL, hyperlipidemia; BMI, body mass index; NYHA, New York Heart Association; CMR, cardiac MRI; CAD, coronary artery disease; Afib, atrial fibrillation; AFL, atrial flutter; NSABP, National Surgical Adjuvant Breast and Bowel Project; LLN, lower limit of normal; MUGA, multigated acquisition; RCT, randomized controlled trial; IQR, interquartile range; BSA, body surface area; BP, blood pressure.

with those with normal LVEF (63). In addition, several randomized controlled trials have shown that treatment with an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker in patients with reduced LVEF but without HF symptoms reduces mortality, the development of HF symptoms, and prevents left ventricular remodeling (64–66). There is also randomized controlled

trial data that beta-blocker therapy in addition to an ACE inhibitor can prevent HF events and reduce mortality in post MI patients with a reduced LVEF but no HF symptoms (67). Based on the compelling evidence for early intervention in patients with structural heart disease in order to prevent the development of HF, the American College of Cardiology/American Heart Association (ACC/AHA) categorize these



individuals as having stage B HF (at considerable risk of HF events) and recommends consideration of ACE inhibitor and beta-blocker therapy to prevent progressive HF in select individuals with reduced LVEF (68,69). While much of the data in the general population comes for patients with ischemic cardiomyopathy or hypertensive nonischemic cardiomyopathy, studies of anthracycline-induced cardiotoxicity (22,70) and trastuzumab cardiotoxicity (71) also suggest that early treatment with neurohormonal antagonist therapy may prevent progressive HF, at least over the duration of these studies (median follow up 1.5–5 years). However, longer term follow-up of survivors of childhood cancer suggests that early improvements in LVEF with enalapril are followed by subsequent worsening of LV function and cardiac events in patients with early signs of “recovery”. Given this data in childhood survivors treated with anthracyclines, more studies of the long-term outcomes of neurohormonal therapy in breast cancer therapeutic cardiotoxicity is warranted (72).

### *Echocardiographic screening*

The diagnosis of ACC/AHA stage B HF is often made by echocardiographic assessment. As described in Section 1, rates of asymptomatic LVEF reduction after anthracycline and/or trastuzumab therapy can be seen in 10–20% of the population and early initiation of neurohormonal therapy may prevent the development of HF and progressive LV dysfunction (73). For these reasons, the recent American Society of Clinical Oncology (ASCO) Practice Guidelines for the Prevention and Monitoring of Cardiac Dysfunction in Survivors of Adult Cancers suggest that an echocardiogram may be performed between 6 to 12 months after completion of cancer-directed therapy in asymptomatic patients considered to be at increased risk based on cardiac risk factors or therapy related risk factors (50). In patients with poor sonographic windows and poor echocardiographic quality, a cardiac magnetic resonance imaging (MRI) or MUGA scan can be considered with preference given to cardiac MRI. The ASCO guidelines also suggest that patients at increased risk for cardiac dysfunction can be monitored with periodic echocardiographic assessment during cancer therapy and patients with cardiac symptoms should be evaluated with careful history and physical exam as well as consideration of cardiac biomarkers such as troponin or natriuretic peptides as well as cardiac imaging, with preference for echocardiogram. Compared to MUGA scans, echocardiograms are not associated with

radiation exposure and provide important information about valvular function, diastolic function, hemodynamic clues and pericardial disease in addition to LVEF assessment.

### *Serum biomarkers*

The utility of serum biomarkers as a screening test for early signs of cardiotoxicity before there is a reduction in LVEF has been evaluated in several cohorts. In a large single-center cohort of 703 inpatients with various malignancies including patients with breast cancer who were treated with high dose chemotherapy with autologous stem cell rescue, troponin I (TnI) concentrations 12, 24, 36, 72 hours and 1 month after the chemotherapy infusion predicted subsequent reductions in LVEF and cardiac events including HF and sudden death with the highest risk patients being those with TnI >0.08 ng/mL in the first 72 hours after chemotherapy and at 1 month after chemotherapy (74). The same group further showed that treatment with ACE inhibitor in patients with elevated TnI after high dose chemotherapy can prevent reductions in LVEF and HF events (70). In a multicenter study of 81 patients with HER2 positive breast cancer treated with doxorubicin followed by trastuzumab, elevated high sensitivity TnI 2–3 months after doxorubicin initiation was associated with increased risk of cardiotoxicity, defined as a reduction in LVEF; however, the sensitivity of early elevations in TnI for subsequent cardiotoxicity was only 48% (75,76). Thus more research is needed to assess the sensitivity and predictive power of TnI or other serum biomarkers in screening for clinically relevant subclinical cardiotoxicity in patients treated with current breast cancer therapy regimens.

### *Strain*

Similar to serum biomarkers, echocardiographic measures of myocardial deformation have been studied as potential early indicators of myocardial injury with the hypothesis that early detection of subclinical cardiotoxicity will allow for earlier treatment and thus a greater likelihood of preventing long-term HF events. Commonly evaluated measures of myocardial deformation include strain (the total deformation of the ventricular myocardium during a cardiac cycle expressed as a percentage) and strain rate (the rate of deformation) with measurements of each possible in the longitudinal, radial and circumferential directions in two-dimensional echocardiography. Of the available techniques, change in global longitudinal strain (GLS)

using two-dimensional speckle-tracking echocardiography has been shown to have the most consistent association with subsequent reductions in LVEF (14,28,30,76-79). Multiple studies have shown that changes in strain or strain rate occur earlier than reductions in LVEF and thus may be sensitive early markers of cardiotoxicity (77). The ongoing Strain Surveillance during Chemotherapy for Improving Cardiovascular Outcomes (SUCCOUR) study is testing the hypothesis that a strain-based screening approach with recommended initiation of ACE inhibitor and beta blocker therapy in patients with reductions in strain of more than 11% will be associated with improved cardiovascular (reduced HF events, higher LVEF) and oncologic (fewer treatment interruptions) outcomes as compared with a screening algorithm employing LVEF changes alone as the threshold to initiate cardioprotective medical therapy.

#### **Section 4: mitigating risk step 3—therapeutic strategies to reduce risk of cardiac events**

##### *Dexrazoxane*

Dexrazoxane has been shown to substantially reduce the risk of cardiotoxicity of anthracycline chemotherapy in several randomized trials of patients with metastatic breast cancer (80-86). The mechanism of cardioprotection appears to involve the inhibition of DNA topoisomerase II $\beta$ -anthracycline mediated ds DNA breaks as well as the reduction of oxygen free radical formation in cardiomyocytes (87). Most of the patients in these studies received high cumulative anthracycline doses and most had metastatic disease. Dexrazoxane has not been studied in patients with early breast cancer.

Continuous infusion and liposomal formulations of anthracyclines have been compared in several small RCTs, usually in the setting of metastatic disease and generally in patients treated with high cumulative anthracycline doses (81). In these settings there appeared to be reduced cardiotoxicity with both of these strategies.

As with dexrazoxane, continuous infusion and liposomal formulations of anthracyclines have not been studied in the setting of early breast cancer.

##### *Neurohormonal therapy*

Given that ACE inhibitor and beta-blocker therapy is the cornerstone of treatment of stage B and stage C HF (68)

and that animal models suggest these therapies can mitigate or reverse anthracycline cardiotoxicity (88), there have been multiple single center studies evaluating the role of neurohormonal therapy for prevention of chemotherapy related cardiotoxicity. In a seminal single center study out of Italy, patients receiving high dose chemotherapy with autologous stem cell rescue (25% with breast cancer), most of who had prior anthracycline exposure with mean doses of 300 mg/m<sup>2</sup>, were assessed with serum troponin values 12, 24, 36 and 72 hours after chemotherapy. Patients with elevated troponin values (TnI >0.07 ng/mL) were then randomized to enalapril starting 1 month after chemotherapy and continued for 1 year with the primary endpoint being a change in LVEF of >10% to less than the normal limit value. While no patients in the enalapril met the primary endpoint, 48% of those in the control group had a significant reduction in LVEF. In other observational analyses by the same group there was significant LVEF recovery after anthracycline-related reduction in LVEF with combined ACE inhibitor (enalapril) and beta-blocker (carvedilol) (22,89).

These and other observational and small single center data suggesting that early treatment with neurohormonal antagonist therapy can be beneficial in patients with early signs of cardiotoxicity, have led to the design of trials seeking to test the hypothesis that neurohormonal antagonist therapy given PRIOR to the initiation of cancer therapy may prevent cardiotoxicity. The prevention of cardiac dysfunction during adjuvant breast cancer therapy (PRADA) study randomized 130 patients with early breast cancer with planned treatment with adjuvant anthracycline therapy with epirubicin (FEC-5-fluorouracil, epirubicin and cyclophosphamide; 22% received subsequent trastuzumab) in a 2 $\times$ 2 factorial design to receive candesartan, metoprolol succinate or matching placebo prior to receiving anthracycline (90). The study was single center and the primary outcome measure was change in LVEF as measured by cardiac MRI at the completion of chemotherapy with a modest but statistically significant difference in LVEF decline with candesartan (P=0.026) but not metoprolol succinate (P=0.772). Absolute reductions in LVEF from baseline were low in all arms (-2.6% placebo, -1.6% metoprolol and -0.8% candesartan) and longer follow up of this cohort is ongoing. The Multidisciplinary approach to Novel Therapies in Cardio-Oncology Research (MANTICORE 101-Breast) trial randomized

94 patients with HER2-positive early breast cancer from two centers with planned treatment with trastuzumab and LVEF  $\geq 50\%$  to perindopril, bisoprolol or placebo prior to initiation of trastuzumab (77% of patients received a non-anthracycline-based chemotherapy regimen) (91). The study was stopped early due to DSMB assessment of futility in reaching the primary endpoint, which was change in left ventricular end diastolic volume index by cardiac MRI at the completion of trastuzumab therapy, which was similar among the three groups. A secondary endpoint, change in LVEF from baseline to completion of therapy was different between the three groups with LVEF reduced by 5% in the placebo group, 3% perindopril group and 1% bisoprolol group ( $P=0.001$ ). There were also fewer interruptions of trastuzumab therapy in both of the treatment groups compared with the placebo group ( $P=0.02$ ).

An ongoing multicenter randomized trial of carvedilol CR, lisinopril or placebo in 468 patients with HER2 positive breast cancer prior to trastuzumab initiation has completed enrollment and will be the largest trial to date to test the utility of these agents in preventing trastuzumab cardiotoxicity, trastuzumab treatment interruptions and cardiac events.

### Statins

3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins) reduce oxidative/nitrosative stress in addition to lowering cholesterol. Animal model data (92), a small RCT (93) and observational data (94) suggests that statin therapy may reduce the risk of cardiotoxicity with anthracycline chemotherapy. The ongoing Preventing Anthracycline Cardiovascular Toxicity with Statins (PREVENT) trial is randomizing patients with breast cancer or lymphoma with planned anthracycline treatment to atorvastatin or placebo to be initiated prior to initiating chemotherapy with a primary outcomes of change in LVEF as assessed by cardiac MRI.

### Healthy lifestyle behaviors

In the general population without cancer, healthy lifestyle behaviors such as regular exercise, healthy diet, not smoking and maintaining a healthy weight are associated with lower risk of cardiovascular events and cardiovascular mortality (95). In patients with breast cancer, self-reported exercise is associated with reduced risk of breast cancer mortality (96,97), total mortality (96,97) and reduced cardiovascular

events (98). Given the increased risk of cardiovascular disease in patients with breast cancer, focusing on optimizing healthy lifestyle behaviors and cardiac risk factors is important to reducing cardiovascular risk and is endorsed by the ASCO guidelines (50).

### Section 5: unanswered questions

While we know a lot about the cardiac effects of breast cancer therapy, there are many unanswered questions remaining. Some of these questions include:

- (I) To what extent have modern RT techniques reduced the cardiac late effects of breast cancer RT?
- (II) Are anthracycline and trastuzumab agents associated with an increased risk HFpEF?
- (III) What is the prognosis and long-term implications of transient reductions in LVEF with subsequent recovery or partial recovery of LV function?
- (IV) Should patients be screened for subclinical cardiotoxicity with TnI and/or strain measurements during anthracycline or trastuzumab therapy? What are the appropriate cut-points and how should management change in response to these measures?
- (V) Is there a role for primary prevention strategies for some or all patients treated with anthracyclines, trastuzumab or radiation? Which patients should be treated and with which agents?

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### Footnote

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