Curr Treat Options Cardio Med (2019) 21: 30
DOI 10.1007/s11936-019-0736-1

Cardio-oncology (M Fradley, Section Editor)

Risk of Cardiomyopathy in Breast Cancer: How Can We Attenuate the Risk of Heart Failure from Anthracyclines and Anti-HER2 Therapies?

Gretchen Kimmick, MD, MS[1,*]
Susan Dent, MD[1]
Igor Klem, MD[2]

Address
[*,1]Medical Oncology, Duke Cancer Institute / Duke University Medical Center, Box 3204 DUMC, Durham, NC, 27710, USA
Email: Gretchen.kimmick@duke.edu
[2]Cardiology, Duke University Medical Center, Durham, NC, USA

Published online: 31 May 2019

This article is part of the Topical Collection on *Cardio-oncology*

Keywords Cardiotoxicity, cardiomyopathy · Anthracyclines · Anti-HER2 therapies · Trastuzumab · Breast cancer

Abstract

Purpose of review To review cardiotoxicity of and strategies to prevent cardiotoxicity from anthracyclines and anti-HER2 agents used to treat breast cancer.
Recent findings Although not common, cardiotoxicity from anthracyclines and anti-HER2 therapies is a major consideration in the use of these agents, especially in the adjuvant setting. Modifications in anthracycline agent, dosing, or schedule or use of Dexrazoxane have been shown to ameliorate the mostly irreversible cardiotoxicity from anthracyclines. Dose delays have been the primary means of addressing the possibly reversible cardiotoxicity from the anti-HER2 agent, trastuzumab, whereas the other anti-HER2 therapies, pertuzumab, lapatinib, and neratinib, are relatively nontoxic to the myocardium. Data from recent randomized clinical trials suggest that the use of angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs), and beta blockers may prevent subclinical cardiotoxicity, as measured by decline in the left ventricular ejection fraction, associated with these agents. Longer-term follow-up will be needed to confirm their role in prevention of symptomatic cardiomyopathy and subsequent cardiovascular disease in women with breast cancer.

Summary Preliminary evidence suggests that the use of ACEi, ARB, and beta blockers during treatment with anthracyclines and trastuzumab may prevent subsequent cardiomyopathy. Larger trials with meaningful clinical endpoints are needed.

Introduction

Breast cancer alone accounts for 30% of all new cancer diagnoses in women. In 2019, in the USA, it is expected that there will be 268,600 new breast cancer diagnoses and 41,760 deaths due to breast cancer [1]. The vast majority (94%) of individuals present with early stage disease, where advances in treatment, including use of anthracyclines and anti-HER2 therapies, have led to improved survival rates [2]. Between 1989 and 2016, the death rate from breast cancer dropped 40%. Although cancer is the second leading cause of death, after heart disease, in the USA, the leading causes of death vary by age: for those age 39 and younger, accidents are followed by cancer and then suicide; for ages 40–79, cancer is followed by heart disease; and for age 80 and older, heart disease is followed by cancer [1]. It is important, therefore, to not only treat breast cancer effectively, but also to minimize risk of death from heart disease.

Cardiovascular disease (CVD) is an important cause of mortality in women after treatment for early breast cancer. In an analysis of SEER data of women age 66 and older with breast cancer between 1992 and 2000, with a median follow-up of 9 years (through 2005), the distribution of causes of death varied by age and tumor stage [3]. Cardiovascular death in this study was defined as either death from myocardial infarction (MI), congestive heart failure (CHF), and peripheral vascular or cerebrovascular disease. Women who were diagnosed with higher stage cancers were much more likely to die from breast cancer than from other causes. Other causes of death are more likely among women with earlier stage (I/II) cancers. At all ages, women diagnosed with stage I breast cancer were more likely to die from CVD than from breast cancer. CVD was also the leading cause of death for women diagnosed with stage II breast cancer who were age 85 and older (42%) and 75–80 years (32%). As women age, regardless of stage, there was a decrease in proportion of all deaths due to breast cancer. Over time, proportional distribution of cumulative causes of death varies. Within the first 5–10 years following breast cancer diagnosis, breast cancer was the cumulative primary cause of death. With longer follow-up, however, CVD became the cumulative primary cause of death. Proportion of death due to other causes, such as chronic obstructive pulmonary disease (COPD), pneumonia, Alzheimer's disease, and diabetes, also increased as follow-up increased.

Some authors describe this as a snowball effect [4]. Patient who have cancer may or may not have baseline risk factors for cardiovascular disease, including diabetes, hypertension, smoking, family history of CVD, and hyperlipidemia. These risk factors include age-related changes in cardiovascular physiology and pharmacokinetics that affect chemotherapy metabolism. There may also be preexisting CVD. Breast cancer treatment, which may include chemotherapy, may amplify the risk for development of CVD. Chemotherapy, surgery, and other treatments for breast cancer may change physical activity levels and lifestyle, thereby worsening the cardiovascular risk profile. Chemotherapy itself, and other treatments for cancer, may be directly cardiotoxic and increase risk even further. This leads to augmentation of the risk of cardiovascular morbidity and mortality among cancer patients.

Anthracycline chemotherapeutic agents, including doxorubicin, daunorubicin, idarubicin, epirubicin, liposomal doxorubicin, and the anthraquinone, mitomycin, are well known to be cardiotoxic, leading to increased risk of heart failure morbidity and mortality [5–7].

Cardiotoxicity of anthracycline chemotherapy agents

The exact mechanism by which anthracyclines cause cardiotoxicity is unknown and the clinical timing ranges from acute to late onset. Proposed mechanisms of

anthracycline-mediated cardiotoxicity include the following [8–10]: (1) increased myocardial oxidative stress via redox–cycling of the quinone moiety of anthracyclines and through the formation of anthracycline–iron complexes; (2) disruption of cellular and mitochondrial calcium homeostasis; (3) disruption of mitochondrial energetics; (4) deep radiation of ultrastructural proteins including titin and dystrophin; (5) direct DNA damage via inhibition of topoisomerase 2-beta; (6) inhibition of pro survival pathways, such as neuregulin 1 and Erb B2; and (7) direct cytotoxic effects on cardiac progenitor cells diminishing repair potential after myocardial injury. How exactly these mechanisms interact and lead to cardiac toxicity is unknown. Anthracycline cardiotoxicity, however, has been described to occur primarily in three separate scenarios, with rates depending on baseline risk factors and anthracycline dose and schedule: acutely with electrocardiogram and transient changes in cardiac function typically occurring immediately after infusion in up to 3.2% [11], early onset with a chronic and progressive course typically during active therapy within first year in up to 20% [12], and late onset with a chronic progressive course, which occurs at least 1 year after completion of therapy. A recent study in 2625 patients receiving anthracycline followed for 5 years found an overall incidence of cardiotoxicity (EF decrease > 10 absolute points and < 50%) in 9%, the majority of which (98%) occurred within the first year [13].

Although the mechanism for early and late onset anthracycline cardiotoxicity remains unclear and may be multifactorial, risk factors are well described [14–16]. These include increased cumulative anthracycline dose, concurrent mediastinal radiation, extremes of age, female gender, and cardiac risk factors or pre-existing heart disease.

Prevention of anthracycline-induced cardiac toxicity

Prevention of anthracycline-induced cardiomyopathy is an area of active research. There are certain general principles, approaches, or preventive measures that can be taken. It is known that adjusting the dose and schedule of anthracyclines, to smaller more frequent doses, or continuous infusion regimens is less cardiotoxic [14, 17]. Liposomal preparations are also less cardiotoxic than non-liposomal preparations [18]. Certain anthracyclines, specifically epirubicin and mitoxantrone, are less cardiotoxic than doxorubicin. Dexrazoxane has been shown to ameliorate and/or prevent anthracycline-induced cardiotoxicity. Dexrazoxane is an iron chelator, binds free iron and prevents the formation of anthracycline–iron complexes that contribute to oxygen free radical formation and thereby decreases cardiotoxicity of anthracyclines [9, 19]. When a cumulative dose of greater than 300 mg/m^2 of doxorubicin is reached and there is ongoing need for therapy, such as in the setting of metastatic breast cancer responding to doxorubicin, use of dexrazoxane is recommended. Of note, this cumulative dose is rarely, if ever, utilized in the adjuvant/preventive setting. Historically, though, the possible association of dexrazoxane and increased risk of MDS and AML [20] and the lower objective response rate when the agent is used in treating advanced breast cancer [21], led to an understandable hesitancy to use it in the adjuvant setting. Subsequent trials have suggested no effect on response rate, time to progression, or survival for breast cancer and no higher rate of second malignancies in other

cancer types [22, 23]. Use of dexrazoxane should be considered to decrease risk of cardiac toxicity in patients who have receive > 300 mg/m^2 of doxorubicin, or the equivalent dose of an alternative anthracycline, to treat metastatic breast cancer, if ongoing treatment is controlling the cancer. Further study of its use in preventing long-term cardiotoxicity in women who receive adjuvant anthracyclines is needed prior to recommending its use with adjuvant chemotherapy regimens containing an anthracycline.

In treating early-stage breast cancer with anthracycline-based chemotherapy, studies have suggested that 3-hydroxy-3-methylglutaryl coenzyme (HMG-CoA-reductase) inhibitors, also known as statins, and neurohormonal agents, such as those proven beneficial in treatment of heart failure, may prevent long-term cardiotoxicity. Statins not only have cholesterol-lowering effects, but also have anti-inflammatory and antioxidative pleiotropic effects, both of which have shown important in anthracycline-induced cardiotoxicity [24–27]. In animal models, statins are cardioprotective against doxorubicin [28]. Data from an observational study in breast cancer patients [29] and a meta-analysis in cancer patients [30] also suggests that statins protect against cardiotoxicity from anthracyclines. A recent meta-analysis and information from studies in other cancers where anthracyclines are used suggests that prophylactic treatment with medications used in the treatment of heart failure, including renin-angiotensin-aldosterone system inhibitors or beta adrenergic blocking agents, may also prevent post-treatment left ventricular dysfunction, in particular with higher anthracycline cumulative doses [31–34].

Several studies have evaluated beta blockers, angiotensin-converting enzyme inhibitors (ACEi), and angiotensin receptor blocker (ARB) alone or in combination to prevent myocardial dysfunction in patients receiving potentially cardiotoxic therapies [35]. Kalay et al. in a single blind, placebo-controlled, randomized trial evaluated a fixed dose of carvedilol 12.5 mg once daily started prior to chemotherapy and maintained for 6 months in 34 women with breast cancer and 16 patients with other types of cancers [32]. A decline in heart function, defined as left ventricular ejection fraction (LVEF) less than 50% by echocardiogram, was seen in one patient in the carvedilol group, and in five in the control group. Another double-blind, placebo-controlled, and randomized study by Kaya et al. randomly assigned 45 breast cancer patients receiving potentially cardiotoxic anthracycline chemotherapy to nebivolol 5 mg ($n = 27$) or placebo ($n = 18$) [33]. Treatment was started before chemotherapy and continued for 6 months. There was no strict definition for decline in heart function; however, the control group had a lower LVEF than the nebivolol group (58 ± 6% vs 64 ± 4%, $p = 0.01$). In addition, NT-pro-BNP levels remained unchanged in the nebivolol group (147 ± 57 to 152 ± 69 pmol/l, $p = 0.77$), but increased slightly in the control group (144 ± 66 to 204 ± 73 pmol/l, p = 0.01). A third study by Cardinale et al. randomized 114 patients (29 with breast cancer and 85 with other cancer) who had myocardial injury as measured by troponin I release after starting high-dose chemotherapy to receive 20 mg/d or not to receive the ACEi enalapril [36]. Treatment was started 1 month after chemotherapy and maintained for 1 year. The definition of decline in heart function was an absolute decrease in LVEF of greater than 10%, with a decline below normal limit measured by echocardiogram, which was seen only in the control group (43% vs 0%, $p < 0.001$). The study was open label and randomized. Dessi et al. in a single-blind, placebo-controlled, randomized trial investigated the use

of the ARB telmisartan in 18 breast cancer patients and 31 patients with other types of cancer [37]. Treatment was started before chemotherapy and maintained up to 6 months after epirubicin was discontinued. Heart function was assessed serially with strain rate analysis by echocardiogram.

Each of these single-arm studies suggested a role of cardioprotection in the adult patient receiving anthracycline chemotherapy. These results, suggesting cardioprotective effect of either a beta blocker or an ACEi/ARB or a combination of these, led to the conduct of two more recent randomized trials, the PRevention of cArdiac Dysfunction during Adjuvant breast cancer therapy (PRADA) trial and the Carvedilol for prevEntion of Chemotherapy-related CardiotoxicitY (CECCY) study.

The PRADA study

The PRADA study was a 2 × 2 factorial, randomized, placebo-controlled, double-blind, single center trial designed to compare the use of (i) the ARB candesartan, (ii) the beta blocker metoprolol succinate, (iii) both candesartan and metoprolol, or (iv) matching placebos in preventing decline in left ventricular ejection fraction (LVEF) [38•]. PRADA included women with early stage breast cancer scheduled to start adjuvant chemotherapy with 5-fluorouracil, Epirubicin, and cyclophosphamide (FEC) who were age 18–70 years, Eastern Cooperative Oncology Group (ECOG) performance status 0–1, serum creatinine less than 1.6 mg/dL, or GFR greater than equal to 60 mL/min per 1.73 m square, systolic blood pressure greater than or equal to 110 mmHg and less than 170 mmHg, LVEF greater than or equal to 50%. Exclusion criteria included a prior history of malignancy requiring chemotherapy or chest radiation, symptomatic CHF, clinically significant coronary artery disease (CAD), valvular heart disease, arrhythmias, or conduction delays, treatment with an ACEi, ARB, or beta-blocker within the last 4 weeks prior to study start. Participants were stratified for anthracycline dose and for use of trastuzumab or not. After surgery, baseline evaluation took place and intervention was started. Candesartan starting dose was 8 mg with a target dose of 32 mg. Metoprolol starting dose was 50 mg with a target dose of 100 mg. Patients then received anthracycline-containing chemotherapy and were reevaluated at 10–19 weeks (after anthracycline therapy and before taxane therapy). Patient whose cancer was HER-2 positive received trastuzumab with a taxanes and radiation, if indicated. Patients whose cancers were HER-2 negative received taxanes and radiation, if indicated. End of study evaluation took place between 10 and 64 weeks after enrollment. The primary endpoint was change in LVEF using cardiac MRI and comparing change from baseline to end of study (Fig. 1).

Participant characteristics were evenly distributed among the treatment groups in PRADA. Mean baseline LVEF was 62–63%. Use of adjuvant trastuzumab among the treatment groups ranged from 21.9 to 23.3%.

In the placebo-placebo group of the PRADA study, anticancer treatment for breast cancer was associated with a modest decline in LVEF of – 2.8 percentage points (95% CI – .3, – 1.3) and no patient developed symptomatic heart failure during the study period. The candesartan-placebo group had a modest but statistically significant smaller decline in LVEF of – 0.9 (95% CI – 2.3, 0.4; p = 0.025 vs placebo-placebo), and the candesartan-metoprolol group had a

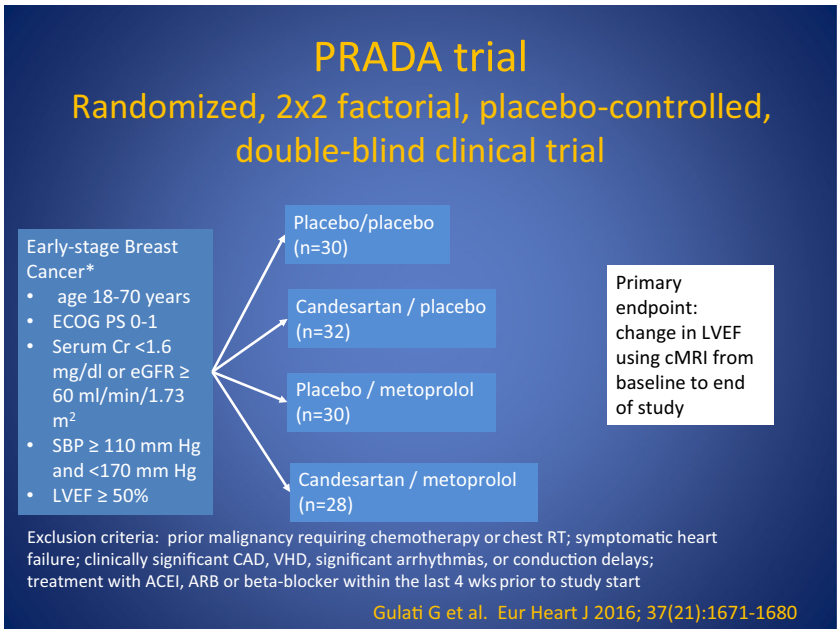

Fig. 1. PRADA trial randomized, 2 × 2 factorial, placebo-controlled, double-blind clinical trial (used with permission from Oxford University Press).

similarly small decline in LVEF of – 0.6 (– 2.1, 0.8; $p = 0.075$ vs placebo-placebo). The metoprolol-placebo group also had a modest decline in LVEF which was similar to the placebo-placebo group of – 2.5 (– 3.9, – 1.1; $p = 0.71$ vs placebo-placebo).

In subset analyses, the benefit of candesartan was particularly notable in those with lower body mass index (BMI) and in those who have had left-sided radiation. Interestingly, metoprolol succinate, a drug with proven efficacy in CHF treatment, had no apparent effect over placebo for the prevention of LVEF decline in this study. The question of whether these modest effects of preserving LVEF translate into lower risk for CHF remains unanswered, since there was no patient that developed CHF during the study period. Long-term assessment is needed to assess whether the modest benefit of candesartan is sustained, before we can consider preventive therapy as standard of care for this patient population.

CECCY study

The CECCY study compared carvedilol to placebo in women with early stage breast cancer where adjuvant anthracycline therapy was planned [39•]. Eligibility criteria included stage I–IIIA breast cancer, age 18 or older, HER-2 negative, planned adjuvant anthracycline (240 mg/m^2), informed consent, and normal baseline LVEF. The anthracycline-containing adjuvant chemotherapy regimen in this trial was Adriamycin (60 mg/m2) and cyclophosphamide (600 mg/m^2) given every 3 weeks for four cycles, followed by paclitaxel weekly for 8 weeks. Of note, compared to the PRADA study, none of the patients in this trial received adjuvant trastuzumab. Women were excluded if LVEF could not be

assessed, or there was a history of chemotherapy or radiation, previous symptoms of CHF, presence of cardiomyopathy or CAD, moderate to severe mitral or aortic valve disease, contraindication to use of beta-blocker, or use of ACEi, ARB, or beta blockers. Participants were randomized to receive either placebo or carvedilol (starting dose 3.125 mg twice a day titrated as tolerated to target dose of 25 mg twice a day). There were 96 participants in each group. The primary endpoint was prevention of $a \geq 10\%$ reduction in LVEF at 6 months measured by echocardiography. Secondary endpoints included troponin I elevation, beta-type natriuretic peptide (BNP) level, diastolic dysfunction. Follow-up for this study was 24 weeks (Fig. 2).

The mean baseline LVEF was 65.2 ± 3.6% in the placebo group, and 64.8 ± 4.7% in the carvedilol group. After 6 months of chemotherapy, there was a nonsignificant absolute LVEF reduction of 1.3% in the placebo group, and 0.9% in the carvedilol group. There was no difference in the primary endpoint between treatment and placebo groups: LVEF change ≥ 10% occurred in 14.5% of the carvedilol group and 13.5% of the placebo group ($p = 1.0$). The percentage of patients with troponin $I > 0.04$ ng/ml was, however, lower in the carvedilol group than placebo (26% versus 41%, $p = 0.03$). There was also a lower incidence of diastolic dysfunction in the carvedilol compared to placebo group (28.5% vs 37.2%, $p = 0.039$). There was a nonsignificant trend towards less pronounced increase in LV end diastolic (LVED) diameter during follow-up in the carvedilol group (41.1 ± 3.64 mm to 45.2 ± 3.2 mm versus 44.9 ± 3.6 mm to 46.4 ± 4.0 mm, $p = 0.057$). There were no differences across groups in BNP levels. There were also no differences found with respect to clinical events and side effects were similar across groups.

In summary, the CECCY study showed no difference in changes in LVEF or BNP levels between carvedilol and placebo-treated groups, but there was a

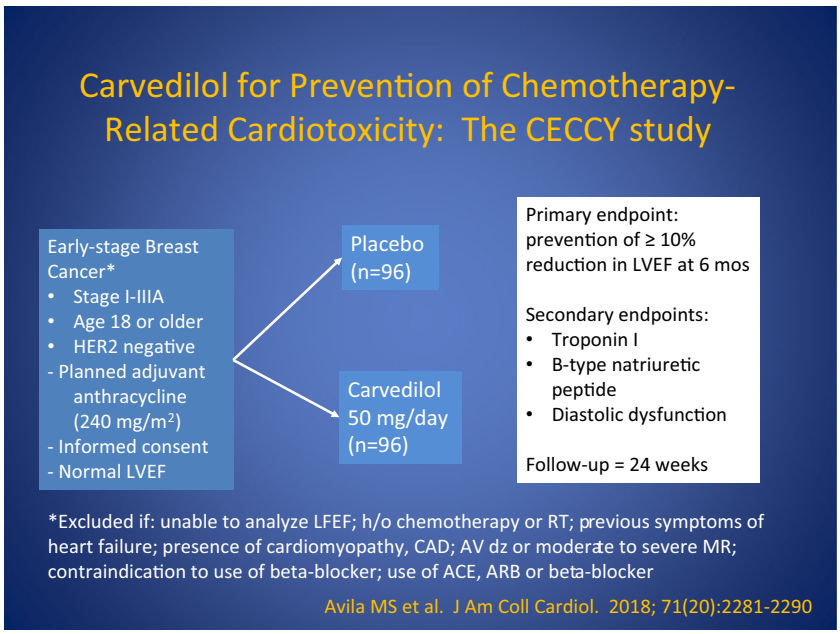

Fig. 2. Carvedilol for prevention of chemotherapy-related cardiotoxicity: the CECCY study (used with permission from Elsevier).

lower incidence of diastolic dysfunction and less troponin I elevations were seen in the carvedilol group.

These studies suggest that use of ACE-inhibitors/ARBs and beta blockers may be helpful in prevention of cardiac dysfunction in anthracycline-treated breast cancer patients, although the results are heterogeneous with different cancer treatments, different endpoints, and short duration of follow-up. The results of these trials raise several questions: does the attenuation in decline of LVEF translate into lower heart failure morbidity and mortality?; what is the optimal, combination of pharmacological interventions? and how long should patients remain on these drugs?. We know from heart failure trials, that positive treatment effects are not necessarily a drug class effect. Whereas the use of carvedilol, metoprolol succinate, and bisoprolol reduced mortality in heart failure patients with reduced LVEF [40–42], the nonselective beta-adrenergic antagonist bucindolol had a nonsignificant mortality reduction [43]. Thus only tested drugs and combinations of drugs are recommended for management of patients with CHF, and the same principle should be considered for cardioprotection in cancer patients. While more randomized controlled trials are needed to support the routine use of ACEi/ARB and beta blockers concomitant to anthracycline therapy, in selected patients requiring treatment for hypertension, for example, preferred agents are those tested in breast cancer patients. Limitations to the routine use of these medications in patients without hypertension include low baseline blood pressure, which may be exacerbated by chemotherapy.

Cardiotoxicity of anti-HER2 therapies

The human epidermal growth factor receptor 2 (HER-2) is a member of the erbB protein family [44]. It is overexpressed in 20–25% of breast cancers. Its overexpression is associated with early disease progression, in the absence of anti-HER-2 therapy [45].

Since the discovery of the HER2 receptor, therapies directed at the HER2 receptor have been designed and proven successful in treating HER2-positive breast cancer [46–48]. The cornerstone of anti-HER-2 therapies, and still the most commonly used anti-HER-2 therapy, is trastuzumab. It is a recombinant, humanized, monoclonal antibody directed against the extracellular domain IV of HER-2. Lapatinib is a small molecule dual tyrosine kinase inhibitor (TKI) of EGFR and HER-2. Pertuzumab is a monoclonal antibody that binds the subdomain II of HER-2 extracellular domain and prevents heterodimerization with other HER-2 family receptors. Ado–trastuzumab emtansine is an antibody drug conjugate of trastuzumab and maytansine. Neratinib is another TKI which irreversibly binds intracellular domain of HER-1, HER-2, and HER-3, and EGFR and inhibits phosphorylation and several HER-2 downstream signaling pathways. Interestingly, even though each of these therapies target the HER2 receptor, found on myocardial cells, clinically significant cardiotoxicity has only been shown with trastuzumab [49].

Cardiotoxicity of trastuzumab was noted in clinical trials, especially in trials with the inclusion of anthracyclines [46, 50–53]. In trials for metastatic breast cancer, cardiotoxicity with doxorubicin alone is only 8%; compared to doxorubicin when administered concurrently with trastuzumab with a cardiotoxicity

rate up to 27% [46]. Meta-analyses of randomized adjuvant trastuzumab versus placebo demonstrated an increased risk of severe CHF of 2% versus 0.4% (relative risk 5.11) [54] and a reduction in LVEF (relative risk 1.83). There were, however, no differences in cardiac death.

Randomized adjuvant trials confirm the cardiotoxicity of trastuzumab (see Table 1); although severe CHF and cardiac events remain rare, an asymptomatic drop in LVEF of 10% points or greater was seen in approximately twice the number of patients who received trastuzumab vs placebo [55–59]. Discontinuation of trastuzumab for cardiac reasons was also noted in some trials.

Risk factors for trastuzumab-related cardiomyopathy include the following: age greater than 50, previous or concurrent anthracycline use, particularly in patients who are obese or overweight, and known cardiovascular risk factors including hypertension, obesity, prior diagnosis of heart disease, and diabetes [58, 60–64].

When delivered in the palliative setting, for metastatic breast cancer, trastuzumab cardiotoxicity is largely reversible and most patients are asymptomatic. Treatment continuation and or resumption of trastuzumab after resolution of cardiac abnormalities may be safe in some women. Studies show that about 75% of patients who experience a decline in EF improved with standard heart failure treatment [46, 63, 65, 66]. In a retrospective study of 49 patients with metastatic breast cancer who developed trastuzumab-related cardiotoxicity, 79% stopped trastuzumab and recovered with CHF treatment [67]. Three of those patients did not recover and one died. Treatment was restarted in 26 patients; 16 remained on treatment without cardiac decline, 10 had recurrent decline in EF, and 5 were able to stay on treatment with slight decrease in EF. In the adjuvant setting, trastuzumab use may be associated with long-term cardiotoxicity. An observational study of trastuzumab use in the adjuvant setting showed that the long-term risk of heart failure was higher in

Table 1. Cardiotoxicity induced by trastuzumab

Trial	Design	Asymptomatic drop in LVEF (10 percentage points to < 55%)	Severe CHF/cardiac events (NYHA class III/IV CHF or death)	Discontinued for cardiac reasons
NSABP B31, *n* = 2043	AC + TH + H vs AC + T	34% vs 17%	4.1% vs 0.8%	**19%**
NCCTG N9831, *n* = 2766	AC + TH + H vs AC + T + H vs AC + T	5.8–10.4% vs 4.0–7.8% vs 4.0–5.1%	3.3% vs 2.8% vs 0.3%	**n/a**
BCIRG 006, *n* = 3222	AC + T vs AC + TH + H vs TCaH(2)	11% vs 19% vs 9%	0.7% vs 2.0% vs 0.4%	**n/a**
HERA, *n* = 5102	Adj chemo (3) → H vs Adj chemo alone	7.1% vs 2.2%	0.6% vs 0.06%	**4.3%**
FinHer, *n* = 232	V or T + H vs V or T (4)→FEC × 3	3.5% vs 8.6%	0% vs 3.4%	**n/a**

Note that 6.7% did not receive H after A due to unacceptable drops in LVEF; included a non-anthracycline arm. In addition, 96% of chemotherapy was A-containing. No prior anthracycline before H exposure; H exposure limited to 9 weeks.
Abbreviation: *A*, anthracycline; *C*, cyclophosphamide; *T*, taxane; *H*, trastuzumab; *Ca*, carboplatin; *V*, vinorelbine; *F*, 5-flourouracil; *E*, epirubicin; *n/a*, information not available

women who received trastuzumab compared to those who did not receive trastuzumab, especially when used with an anthracycline-based chemotherapy regimen and in women who are older [68]. Among women with nonmetastatic breast cancer, the cumulative incidence of heart failure and/or cardiomyopathy (HF/CM) diagnosis among those who received anthracyclines and trastuzumab was 6.2% (95% CI 4.1–8.2%) after 1-year follow-up and increased to 20.1% (95% CI 14.0–25.6%) by 5 years. Compared to no chemotherapy, the risk of incident HF/CM was increased for those receiving anthracyclines alone (HR 1.40, 95% CI 1.11–1.76), trastuzumab without anthracyclines (HR 4.12, 95% CI 2.30–7.42), anthracycline plus trastuzumab (HR 7.19, 95% CI 7.19, 95% CI 5.00–10.35), and other chemotherapy (HR 1.49, 95% CI 1.25–1.77).

The recommended monitoring for trastuzumab-related cardiotoxicity/cardiomyopathy is based on protocols required in adjuvant chemotherapy trials [55, 64, 69, 70]. It is recommended that LVEF be checked prior to the initiation of trastuzumab therapy. If trastuzumab therapy follows anthracycline treatment, LVEF should be assessed after the completion of the anthracycline treatment and then prior to initiation of trastuzumab: if normal baseline LVEF, then begin trastuzumab therapy; if mildly reduced LVEF (45–55%) consider risk versus benefit before initiating trastuzumab; if more than mild LV dysfunction, trastuzumab is not recommended. If the LVEF is mildly or more than mildly reduced (< 55%) by nuclear study or echocardiogram, it is also recommended that cardiac magnetic resonance imaging (cMRI) be done to confirmation the result and further evaluate the myocardium [71] and referral be made to a cardio-oncology specialty clinic. In some cases, the benefits of anti-HER2 therapy may outweigh the risk of cardiomyopathy, especially in cases where the cancer is a more advanced stage, so weighing the benefits and risks of treatment is important. After the start of trastuzumab and baseline LVEF assessment, in the adjuvant setting, LVEF should be checked every 3 months during therapy. If LVEF declines more than 15% from baseline or 10% from baseline to below 50%, trastuzumab should be held for a month before the LVEF is reassessed. If LVEF remains low or there is evidence of symptomatic heart failure, trastuzumab should be discontinued. In the metastatic setting, LVEF should be checked at baseline and then as clinically indicated thereafter. If LVEF declines significantly to an absolute value of < 40% then consideration of the benefits and risk of further trastuzumab therapy should be discussed.

As with anthracycline therapy, the use of beta blockers, ACEi, and ARBs have been considered to prevent trastuzumab-induced cardiomyopathy. The Multidisciplinary Approach to Novel Therapies in Cardio Oncology Research (MANTICORE) trial compared placebo versus the ACEi perindopril versus the selective beta-blocker bisoprolol in women receiving adjuvant trastuzumab [72•]. In this trial, eligible participants were women with early stage breast cancer (stage I–IIIA), HER-2 positive disease, age greater than 18, planned adjuvant trastuzumab, informed consent. Women were excluded from the study if they had a history of CHF, cardiomyopathy, or MI, contraindication to, or current treatment with ACEi, beta-blocker, or ARB, uncontrolled hypertension, prior chest radiation or chemotherapy, estimated glomerular filtration rate of less than 30 mL/min per 1.73 m^2, or contraindication to MRI. Women were randomized to one of three arms: placebo ($n = 30$), perindopril 2 mg daily titrated to target of 8 mg daily ($n = 33$), and bisoprolol 2.5 mg daily titrated up to target 10 mg daily ($n = 31$). During 17 cycles of adjuvant trastuzumab, study

medication started 7 days prior to start of trastuzumab and titrated over 3 weeks to the target dose. Study drug was continued for the entire duration of adjuvant trastuzumab. The primary outcome for the MANITCORE trial was cardiac remodeling expressed as change in indexed LV end diastolic volume (LVEDVi) on cardiac MRI from baseline to completion of trastuzumab. The rationale for this endpoint was the observation that increases in LVEDVi, indicating cardiac remodeling, is an early feature of CHF and has been reported with adjuvant trastuzumab. The secondary measure was change in LVEF from pre-trastuzumab to post-trastuzumab therapy (Fig. 3).

For the MANTOCORE trial, clinical safety was evaluated as the number of study drug-related serious adverse effects and/or premature study drug withdrawal in each group. Blood pressure, heart rate, serum potassium, and creatinine were recorded with each clinical assessment along with symptom-related adverse events. During post-hoc analysis, cancer-treatment-related cardiac dysfunction (CTRCD) was defined as a drop in LVEF of ≥ 10 percentage points to a value of < 53% on cardiac MRI. Clinical cardiotoxicity was defined as any interruption and trastuzumab therapy of greater than or equal to 7 days as a result of decline in cardiac function. Open label treatment with ACEi and beta-blocker was recommended for an absolute decline in LVEF of ≥ 5% and LVEF of < 55% with symptoms of heart failure or for an asymptomatic absolute decline in LVEF of ≥ 10% and LVEF of < 50%. Interruptions in trastuzumab therapy and/or treatment with open label ACEi and beta-blocker therapy were left to the discretion of the treating oncologist.

Maximum dose level of perindopril or bisoprolol was reached in 90% of those treated with placebo, 75% of those on perindopril (mean dose 6.8 ± 2 mg), and 65% of bisoprolol-treated patients (mean dose 7.7 ± 3 mg). There were no significant study drug-related adverse events or serious adverse events.

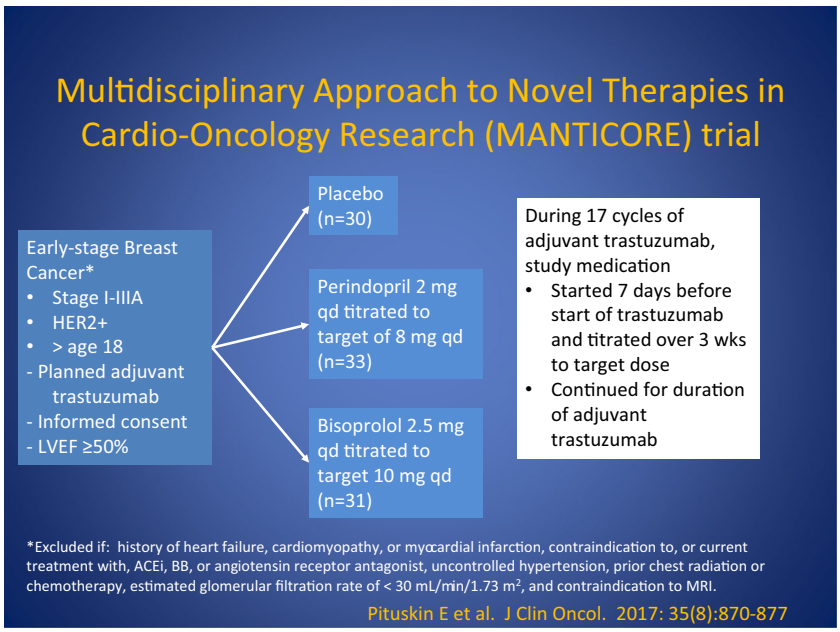

Fig. 3. Multidisciplinary Approach to Novel Therapies in Cardio-Oncology Research (MANTICORE) trial.

Blood pressure decreased in the perindopril-treated group. Heart rate was lower in the bisoprolol-treated group.

After 17 cycles of trastuzumab, there was a modest increase LVEDVi observed in all arms ranging between 4 and 8 ml/m^2 ($p = 0.36$). There was lesser decline in LVEF with bisoprolol (− 1 ± 5% vs placebo) and the perindopril-treated groups (− 3 ± 4% and − 5 ± 5%, respectively; $p = 0.001$). At mid-treatment, CTRCD was less common in the perindopril-treated and bisoprolol-treated groups, compared to placebo (1 of 33, 1 of 31, 6 of 30, respectively; $p = 0.02$). Post-treatment CTRCD was similar between groups. Interruptions in trastuzumab therapy as a result of LV dysfunction were fewer in treatment than placebo groups (3 of 33, 3 of 31, 9 of 30, respectively; $p = 0.03$).

In multivariate analysis, baseline LVEDVi was predictive of change in LVEDVi, decline in LVEF was predicted by baseline LVEF, and perindopril and bisoprolol were independent predictors of maintained LVEF. Both perindopril and bisoprolol, therefore, were well tolerated in patients with HER-2 positive early stage breast cancer treated with adjuvant trastuzumab. Both agents protected against trastuzumab related declines in EF. Neither prevented LV remodeling.

Another study, presented initially in 2018 at European Society of Medical Oncology [73] and San Antonio Breast Cancer Symposium [74] meetings, studied the ACEi lisinopril and the beta blocker carvedilol to reduce cardiotoxicity among patients with early-stage, HER2-positive breast cancer treated with trastuzumab. In this randomized, double-blind, placebo-controlled, multicenter study, 468 patients from 127 centers were randomly assigned to receive placebo, lisinopril, or carvedilol during the 1-year of adjuvant trastuzumab. Patients were stratified according to anthracycline use. The primary endpoint of the study was cardiotoxicity, defined as an absolute decrease in LVEF of 10% or greater (5% or greater if baseline LVEF was less than 50%), during treatment and the year after treatment was completed. There were baseline differences in anthracycline vs non-anthracycline cohorts, including younger age (48 vs 53 years) and lower systolic blood pressure (120 vs 130 mmHg) in those receiving anthracyclines. Overall, cardiotoxicity was similar across treatment groups: 32% placebo, 29% carvedilol, and 30% lisinopril. In the group receiving anthracyclines, however, cardiotoxicity was less in the lisinopril (37%) and carvedilol (31%) groups than in the placebo (47%), and interruptions in therapy were less, at 23%, 20%, and 40%, respectively ($p = 0.007$). In the anthracycline-treated cohort, cardiotoxicity-free survival was longer with use of carvedilol (HR = 0.49, 95% CI, 0.27–0.89, $p = .009$), and lisinopril (HR 0.53, 95% CI, 0.30–0.94, $p = 0.015$) compared with placebo (Fig. 4).

Conclusions

There is rare but definite risk of symptomatic cardiomyopathy in breast cancer patients who are treated with anthracyclines and anti-HER-2 therapies. In the adjuvant setting, especially in women with favorable-risk breast cancer, where long-term cardiovascular mortality is more common than cancer mortality, monitoring for and preventing cardiomyopathy is especially important. Randomized trials suggest that preventive therapies with neuroendocrine blockade, including treatment with ACE inhibitors, ARBs, and beta blockers, may decrease risk of cardiomyopathy. There is early evidence to suggest that drugs that we use

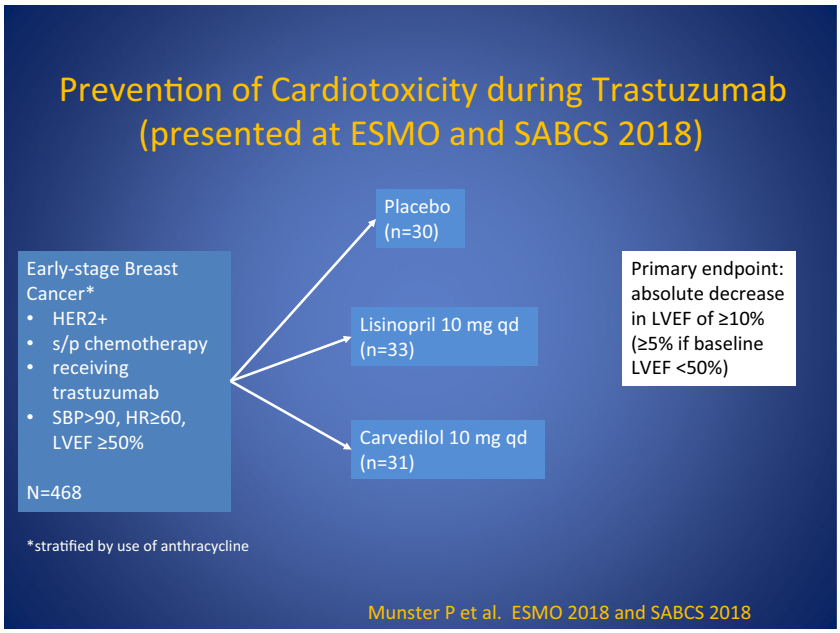

Fig. 4. Prevention of cardiotoxicity during trastuzumab (presented at ESMO and SABCS 2018) (used with permission from Pamela Munster)

to treat heart failure, such as ACEi, ARBs, and beta blockers, have the potential to preserve LV function in patients receiving anthracyclines and/or trastuzumab. The data is, however, heterogeneous and not yet strong enough to prompt universal adaptation. Larger trials with longer follow-up and clinically important endpoints will be needed before we make changes to standard practice. At this point, it is certainly reasonable to consider use of ACEi/ARB or beta blockers in patients where we find a drop in LVEF or in those with hypertension who are receiving anthracycline-containing chemotherapy or trastuzumab.

Compliance with Ethical Standards

Conflict of Interest

Gretchen Kimmick is on the Scientific Advisory Boards of Boehringer Ingelheim; Eisai [Epirubicin]; Genomic Health [OncotypeDX]; and Agendia [MammaPrint]; consulting/advising relationship with Genomic Health, AstraZeneca, Novartis, Pfizer; received Honoraria (speakers bureau) from Eisai; and Research Funding: Bionovo, PUMA, and Roche. Dr. Kimmick and group have participated, current and in past, in research funded by the following: Abbott Laboratories, AbbVie, Abraxis BioScience, Alphavax, AstraZeneca, Bionovo, BiPar Sciences, Bristol-Meyers Squibb, Celldex Therapeutics, Celsion, EMD Serono, Exelixis, Genentech, GlaxoSmithKline (CARG Trial), Incyte Corporation, Janssen, Johnson & Johnson Pharmaceuticals, Medimmune, Merck, Merrimack Pharmaceuticals, Mylan Pharmaceuticals, Myriad Genetics, Nektar Therapeutics, NRG Oncology, Novartis, Pfizer, Pharmacyclics, Roche Pharmaceuticals, Roxane Laboratories, Sanofi, Veridex LLC, and Wyeth.
Susan Dent is on the advisory board for Hoffman La-Roche.
Igor Klem declares no potential conflicts of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:
- Of importance

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin. 2019;69(1):7–34.
2. Waks AG, Winer EP. Breast cancer treatment: a review. JAMA. 2019;321(3):288–300.
3. Patnaik JL, Byers T, DiGuiseppi C, Dabelea D, Denberg TD. Cardiovascular disease competes with breast cancer as the leading cause of death for older females diagnosed with breast cancer: a retrospective cohort study. Breast Cancer Res. 2011;13(3):R64.
4. Shenoy C, Klem I, Crowley AL, Patel MR, Winchester MA, Owusu C, et al. Cardiovascular complications of breast cancer therapy in older adults. Oncologist. 2011;16(8):1138–43.
5. McGowan JV, Chung R, Maulik A, Piotrowska I, Walker JM, Yellon DM. Anthracycline chemotherapy and cardiotoxicity. Cardiovasc Drugs Ther. 2017;31(1):63–75.
6. Groarke JD, Nohria A. Anthracycline cardiotoxicity: a new paradigm for an old classic. Circulation. 2015;131(22):1946–9.
7. Smith LA, Cornelius VR, Plummer CJ, Levitt G, Verrill M, Canney P, et al. Cardiotoxicity of anthracycline agents for the treatment of cancer: systematic review and meta-analysis of randomised controlled trials. BMC Cancer. 2010;10.
8. Hahn VS, Lenihan DJ, Ky B. Cancer therapy-induced cardiotoxicity: basic mechanisms and potential cardioprotective therapies. J Am Heart Assoc. 2014;3(2):e000665.
9. Lyu YL, Kerrigan JE, Lin CP, Azarova AM, Tsai YC, Ban Y, et al. Topoisomerase IIbeta mediated DNA double-strand breaks: implications in doxorubicin cardiotoxicity and prevention by dexrazoxane. Cancer Res. 2007;67(18):8839–46.
10. Yeh ET, Bickford CL. Cardiovascular complications of cancer therapy: incidence, pathogenesis, diagnosis, and management. J Am Coll Cardiol. 2009;53(24):2231–47.
11. Wojnowski L, Kulle B, Schirmer M, Schluter G, Schmidt A, Rosenberger A, et al. NAD(P)H oxidase and multidrug resistance protein genetic polymorphisms are associated with doxorubicin-induced cardiotoxicity. Circulation. 2005;112(24):3754–62.
12. Wang L, Tan TC, Halpern EF, Neilan TG, Francis SA, Picard MH, et al. Major cardiac events and the value of echocardiographic evaluation in patients receiving anthracycline-based chemotherapy. Am J Cardiol. 2015;116(3):442–6.
13. Cardinale D, Colombo A, Bacchiani G, Tedeschi I, Meroni CA, Veglia F, et al. Early detection of anthracycline cardiotoxicity and improvement with heart failure therapy. Circulation. 2015;131(22):1981–8.
14. Von Hoff DD, Layard MW, Basa P, Davis HL Jr, Von Hoff AL, Rozencweig M, et al. Risk factors for doxorubicin-induced congestive heart failure. Ann Intern Med. 1979;91(5):710–7.
15. Swain SM, Whaley FS, Ewer MS. Congestive heart failure in patients treated with doxorubicin: a retrospective analysis of three trials. Cancer. 2003;97(11):2869–79.
16. Qin A, Thompson CL, Silverman P. Predictors of late-onset heart failure in breast cancer patients treated with doxorubicin. J Cancer Surviv. 2015;9(2):252–9.
17. Legha SS, Benjamin RS, Mackay B, Ewer M, Wallace S, Valdivieso M, et al. Reduction of doxorubicin cardiotoxicity by prolonged continuous intravenous infusion. Ann Intern Med. 1982;96(2):133–9.
18. Batist G. Cardiac safety of liposomal anthracyclines. Cardiovasc Toxicol. 2007;7(2):72–4.
19. Hasinoff BB, Herman EH. Dexrazoxane: how it works in cardiac and tumor cells. Is it a prodrug or is it a drug? Cardiovasc Toxicol. 2007;7(2):140–4.
20. Tebbi CK, London WB, Friedman D, Villaluna D, De Alarcon PA, Constine LS, et al. Dexrazoxane-associated risk for acute myeloid leukemia/myelodysplastic syndrome and other secondary malignancies in pediatric Hodgkin's disease. J Clin Oncol. 2007;25(5):493–500.
21. Swain SM, Whaley FS, Gerber MC, Weisberg S, York M, Spicer D, et al. Cardioprotection with dexrazoxane for doxorubicin-containing therapy in advanced breast cancer. J Clin Oncol. 1997;15(4):1318–32.
22. Salzer WL, Devidas M, Carroll WL, Winick N, Pullen J, Hunger SP, et al. Long-term results of the pediatric oncology group studies for childhood acute lymphoblastic leukemia 1984-2001: a report from the children's oncology group. Leukemia. 2010;24(2):355–70.
23. Vrooman LM, Neuberg DS, Stevenson KE, Asselin BL, Athale UH, Clavell L, et al. The low incidence of secondary acute myelogenous leukaemia in children and adolescents treated with dexrazoxane for acute lymphoblastic leukaemia: a report from the Dana-Farber Cancer Institute ALL consortium. Eur J Cancer. 2011;47(9):1373–9.
24. Minotti G, Menna P, Salvatorelli E, Cairo G, Gianni L. Anthracyclines: molecular advances and pharmacologic developments in antitumor activity and cardiotoxicity. Pharmacol Rev. 2004;56(2):185–229.
25. Landmesser U, Bahlmann F, Mueller M, Spiekermann S, Kirchhoff N, Schulz S, et al. Simvastatin versus ezetimibe: pleiotropic and lipid-lowering effects on

endothelial function in humans. Circulation. 2005;111(18):2356–63.
26. Riad A, Du J, Stiehl S, Westermann D, Mohr Z, Sobirey M, et al. Low-dose treatment with atorvastatin leads to anti-oxidative and anti-inflammatory effects in diabetes mellitus. Eur J Pharmacol. 2007;569(3):204–11.
27. Henninger C, Fritz G. Statins in anthracycline-induced cardiotoxicity: Rac and rho, and the heartbreakers. Cell Death Dis. 2017;8(1):e2564.
28. Riad A, Bien S, Westermann D, Becher PM, Loya K, Landmesser U, et al. Pretreatment with statin attenuates the cardiotoxicity of Doxorubicin in mice. Cancer Res. 2009;69(2):695–9.
29. Seicean S, Seicean A, Plana JC, Budd GT, Marwick TH. Effect of statin therapy on the risk for incident heart failure in patients with breast cancer receiving anthracycline chemotherapy: an observational clinical cohort study. J Am Coll Cardiol. 2012;60(23):2384–90.
30. Kalam K, Marwick TH. Role of cardioprotective therapy for prevention of cardiotoxicity with chemotherapy: a systematic review and meta-analysis. Eur J Cancer. 2013;49(13):2900–9.
31. Georgakopoulos P, Roussou P, Matsakas E, Karavidas A, Anagnostopoulos N, Marinakis T, et al. Cardioprotective effect of metoprolol and enalapril in doxorubicin-treated lymphoma patients: a prospective, parallel-group, randomized, controlled study with 36-month follow-up. Am J Hematol. 2010;85(11):894–6.
32. Kalay N, Basar E, Ozdogru I, Er O, Cetinkaya Y, Dogan A, et al. Protective effects of carvedilol against anthracycline-induced cardiomyopathy. J Am Coll Cardiol. 2006;48(11):2258–62.
33. Kaya MG, Ozkan M, Gunebakmaz O, Akkaya H, Kaya EG, Akpek M, et al. Protective effects of nebivolol against anthracycline-induced cardiomyopathy: a randomized control study. Int J Cardiol. 2013;167(5):2306–10.
34. Bosch X, Rovira M, Sitges M, Domenech A, Ortiz-Perez JT, de Caralt TM, et al. Enalapril and carvedilol for preventing chemotherapy-induced left ventricular systolic dysfunction in patients with malignant hemopathies: the OVERCOME trial (preventiOn of left ventricular dysfunction with Enalapril and caRvedilol in patients submitted to intensive ChemOtherapy for the treatment of malignant hEmopathies). J Am Coll Cardiol. 2013;61(23):2355–62.
35. Yun S, Vincelette ND, Abraham I. Cardioprotective role of beta-blockers and angiotensin antagonists in early-onset anthracyclines-induced cardiotoxicity in adult patients: a systematic review and meta-analysis. Postgrad Med J. 2015;91(1081):627–33.
36. Cardinale D, Colombo A, Sandri MT, Lamantia G, Colombo N, Civelli M, et al. Prevention of high-dose chemotherapy-induced cardiotoxicity in high-risk patients by angiotensin-converting enzyme inhibition. Circulation. 2006;114(23):2474–81.
37. Dessi M, Madeddu C, Piras A, Cadeddu C, Antoni G, Mercuro G, et al. Long-term, up to 18 months, protective effects of the angiotensin II receptor blocker telmisartan on Epirubin-induced inflammation and oxidative stress assessed by serial strain rate. SpringerPlus. 2013;2(1):198.
38.• Gulati G, Heck SL, Ree AH, Hoffmann P, Schulz-Menger J, Fagerland MW, et al. Prevention of cardiac dysfunction during adjuvant breast cancer therapy (PRADA): a 2 × 2 factorial, randomized, placebo-controlled, double-blind clinical trial of candesartan and metoprolol. Eur Heart J. 2016;37(21):1671–80
The PRADA study was a 2 x 2 factorial, randomized, placebo-controlled, double-blind, single center trial designed to compare the use of (i) the ARB candesartan, (ii) the betablocker metoprolol succinate, (iii) both candesartan and metoprolol, or (iv) matching placebos in preventing decline in left ventricular ejection fraction (LVEF) among women receiving adjuvant anthracycline (and trastuzumab if the cancer was HER2 positive). No patient developed heart failure. Patients receiving candesartan had modest, but statistically significant, smaller decline in LVEF.
39.• Avila MS, Ayub-Ferreira SM, de Barros Wanderley MR Jr, das Dores Cruz F, Goncalves Brandao SM, Rigaud VOC, et al. Carvedilol for prevention of chemotherapy-related cardiotoxicity: the CECCY Trial. J Am Coll Cardiol. 2018;71(20):2281–90
The CECCY study was a randomized study of carvedilol versus placebo in women with early stage, HER2 negative, breast cancer where adjuvant anthracycline therapy was used. The study showed no difference in changes in LVEF or BNP levels between carvedilol and placebo-treated groups, but there was a lower incidence of diastolic dysfunction and less troponin I elevations were seen in the carvedilol group.
40. Packer M, Coats AJ, Fowler MB, Katus HA, Krum H, Mohacsi P, et al. Effect of carvedilol on survival in severe chronic heart failure. N Engl J Med. 2001;344(22):1651–8.
41. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL randomised intervention trial in congestive heart failure (MERIT-HF). Lancet. 1999;353(9169):2001–7.
42. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. Lancet. 1999;353(9146):9–13.
43. Beta-Blocker Evaluation of Survival Trial I, Eichhorn EJ, Domanski MJ, Krause-Steinrauf H, Bristow MR, Lavori PW. A trial of the beta-blocker bucindolol in patients with advanced chronic heart failure. N Engl J Med. 2001;344(22):1659–67.
44. Slamon DJ, Clark GM, Wong SG, Levin WJ, Ullrich A, McGuire WL. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. Science. 1987;235:177–82.
45. Dawood S, Broglio K, Buzdar AU, Hortobagyi GN, Giordano SH. Prognosis of women with metastatic breast cancer by HER2 status and trastuzumab treatment: an institutional-based review. J Clin Oncol. 2010;28(1):92–8.
46. Slamon DJ, Leyland-Jones B, Shak S, Fuchs H, Paton V, Bajamonde A, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic

breast cancer that overexpresses HER2. N Engl J Med. 2001;344(11):783–92.
47. Meisel JL, Venur VA, Gnant M, Carey L. Evolution of targeted therapy in breast cancer: where precision medicine began. American Society of Clinical Oncology educational book/ASCO American Society of Clinical Oncology Meeting. 2018;(38):78–86.
48. Arteaga CL, Sliwkowski MX, Osborne CK, Perez EA, Puglisi F, Gianni L. Treatment of HER2-positive breast cancer: current status and future perspectives. Nat Rev Clin Oncol. 2011;9(1):16–32.
49. Ponde NF, Lambertini M, de Azambuja E. Twenty years of anti-HER2 therapy-associated cardiotoxicity. ESMO Open. 2016;1(4):e000073.
50. Seidman A, Hudis C, Pierri MK, Shak S, Paton V, Ashby M, et al. Cardiac dysfunction in the trastuzumab clinical trials experience. J Clin Oncol. 2002;20(5):1215–21.
51. Gianni L, Eiermann W, Semiglazov V, Manikhas A, Lluch A, Tjulandin S, et al. Neoadjuvant chemotherapy with trastuzumab followed by adjuvant trastuzumab versus neoadjuvant chemotherapy alone, in patients with HER2-positive locally advanced breast cancer (the NOAH trial): a randomised controlled superiority trial with a parallel HER2-negative cohort. Lancet. 2010;375(9712):377–84.
52. Buzdar AU, Ibrahim NK, Francis D, Booser DJ, Thomas ES, Theriault RL, et al. Significantly higher pathologic complete remission rate after neoadjuvant therapy with trastuzumab, paclitaxel, and epirubicin chemotherapy: results of a randomized trial in human epidermal growth factor receptor 2-positive operable breast cancer. J Clin Oncol. 2005;23(16):3676–85.
53. Spielmann M, Roche H, Delozier T, Canon JL, Romieu G, Bourgeois H, et al. Trastuzumab for patients with axillary-node-positive breast cancer: results of the FNCLCC-PACS 04 trial. J Clin Oncol. 2009;27(36):6129–34.
54. Viani GA, Afonso SL, Stefano EJ, De Fendi LI, Soares FV. Adjuvant trastuzumab in the treatment of her-2-positive early breast cancer: a meta-analysis of published randomized trials. BMC Cancer. 2007;7:153.
55. Romond EH, Perez EA, Bryant J, Suman VJ, Geyer CE Jr, Davidson NE, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. N Engl J Med. 2005;353(16):1673–84.
56. Tan-Chiu E, Yothers G, Romond E, Geyer CE Jr, Ewer M, Keefe D, et al. Assessment of cardiac dysfunction in a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel, with or without trastuzumab as adjuvant therapy in node-positive, human epidermal growth factor receptor 2-overexpressing breast cancer: NSABP B-31. J Clin Oncol. 2005;23(31):7811–9.
57. Slamon D, Eiermann W, Robert N, Pienkowski T, Martin M, Press M, et al. Adjuvant trastuzumab in HER2-positive breast cancer. N Engl J Med. 2011;365(14):1273–83.
58. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, Goldhirsch A, Untch M, Smith I, et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. N Engl J Med. 2005;353(16):1659–72.
59. Joensuu H, Kellokumpu-Lehtinen PL, Bono P, Alanko T, Kataja V, Asola R, et al. Adjuvant docetaxel or vinorelbine with or without trastuzumab for breast cancer. N Engl J Med. 2006;354(8):809–20.
60. Ewer SM, Ewer MS. Cardiotoxicity profile of trastuzumab. Drug Saf. 2008;31(6):459–67.
61. Smith I, Procter M, Gelber DR, Guillaume S, Feyereislova A, Dowsett M, et al. 2-year follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer: a randomised controlled trial. Lancet. 2007;369(9555):29–36.
62. Procter M, Suter TM, de Azambuja E, Dafni U, van Dooren V, Muehlbauer S, et al. Longer-term assessment of trastuzumab-related cardiac adverse events in the Herceptin adjuvant (HERA) trial. J Clin Oncol. 2010;28(21):3422–8.
63. Romond EH, Jeong JH, Rastogi P, Swain SM, Geyer CE Jr, Ewer MS, et al. Seven-year follow-up assessment of cardiac function in NSABP B-31, a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel (ACP) with ACP plus trastuzumab as adjuvant therapy for patients with node-positive, human epidermal growth factor receptor 2-positive breast cancer. J Clin Oncol. 2012;30(31):3792–9.
64. Serrano C, Cortes J, De Mattos-Arruda L, Bellet M, Gomez P, Saura C, et al. Trastuzumab-related cardiotoxicity in the elderly: a role for cardiovascular risk factors. Ann Oncol. 2012;23(4):897–902.
65. Perez EA, Suman VJ, Davidson NE, Kaufman PA, Martino S, Dakhil SR, et al. Effect of doxorubicin plus cyclophosphamide on left ventricular ejection fraction in patients with breast cancer in the North Central Cancer Treatment Group N9831 Intergroup Adjuvant Trial. J Clin Oncol. 2004;22(18):3700–4.
66. Guarneri V, Lenihan DJ, Valero V, Durand JB, Broglio K, Hess KR, et al. Long-term cardiac tolerability of trastuzumab in metastatic breast cancer: the M.D. Anderson Cancer Center experience. J Clin Oncol. 2006;24(25):4107–15.
67. Tripathy D, Seidman A, Keefe D, Hudis C, Paton V, Lieberman G. Effect of cardiac dysfunction on treatment outcomes in women receiving trastuzumab for HER2-overexpressing metastatic breast cancer. Clin Breast Cancer. 2004;5(4):293–8.
68. Bowles EJ, Wellman R, Feigelson HS, Onitilo AA, Freedman AN, Delate T, et al. Risk of heart failure in breast cancer patients after anthracycline and trastuzumab treatment: a retrospective cohort study. J Natl Cancer Inst. 2012;104(17):1293–305.
69. Plana JC, Galderisi M, Barac A, Ewer MS, Ky B, Scherrer-Crosbie M, et al. Expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy: a report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2014;15(10):1063–93.

70. Fox KF. The evaluation of left ventricular function for patients being considered for, or receiving Trastuzumab (Herceptin) therapy. Br J Cancer. 2006;95(10):1454.
71. Khouri MG, Klem I, Shenoy C, Sulpher J, Dent SF. Screening and monitoring for cardiotoxicity during Cancer treatment. In: Kimmick GG, Lenihan DJ, Sawyer DB, Mayer EL, Hershman DL, editors. Cardio-Oncology: The Clinical Overlap of Cancer and Heart Disease. Switzerland: Springer; 2017. p. 43–80.
72.• Pituskin E, Mackey JR, Koshman S, Jassal D, Pitz M, Haykowsky MJ, et al. Multidisciplinary Approach to Novel Therapies in Cardio-Oncology Research (MANTICORE 101-Breast): a randomized trial for the prevention of trastuzumab-associated cardiotoxicity. J Clin Oncol. 2017;35(8):870–7
The Multidisciplinary Approach to Novel Therapies in Cardio Oncology Research (MANTICORE) trial was a randomized prospective trial to compare placebo versus the ACEi perindopril versus the selective beta1-blocker bisoprolol in women receiving adjuvant trastuzumab. In multivariate analysis, baseline idex LV end-diastolic volume (LVEDVi) was predictive of change in LVEDVi, decline in LVEF was predicted by baseline LVEF, and perindopril and bisoprolol were independent predictors of maintained LVEF. Both perindopril and bisoprolol, therefore, protected against LVEF decline, but neither significantly affected LV remodeling.
73. Munster P, Krischer J, Tamura K, Bello-Matricaria L, Fink A, McCaskill-Stevens W, et al. Randomized trial of lisinopril or carvedilol for the prevention of cardiotoxicity in patients with early stage HER2-positive breast cancer receiving adjuvant trastuzumab. Ann Oncol. 2018;29(suppl_8):viii58–86.
74. Munster P, Krischer J, Tamura R, Fink A, Bello-Matricaria L, Guilin M. A randomized community-based trial of an angiotensin-converting enzyme inhibitor, lisinopril or a beta blocker, carvedilol for the prevention of cardiotoxicity in patients with early stage HER2-positive breast cancer receiving adjuvant trastuzumab. Cancer Research. 2018 (Oral presentation at: 2018 San Antonio Breast Cancer Symposium; December 4–8, 2018; San Antonio, TX.): Abstract GS5-01.

Publisher's Note