

The Role of Angiotensin-Converting Enzyme Inhibitors and β -Blockers in Primary Prevention of Cardiac Dysfunction in Breast Cancer Patients

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Approximately 4 million American women are currently living with a history of invasive breast cancer, with 270 000 diagnosed within the past year.¹ Among these women, 64% are aged ≥ 65 years.¹ Among older women who are survivors of breast cancer, cardiovascular disease (CVD) is the leading cause of death.² Consequently, their overall survival depends on effective management of cardiovascular risk factors (eg, hypertension).³ Cardiovascular risk factors affect the rate of developing cardiovascular toxicities around the time of cancer therapies and for decades thereafter.^{3,4} In patients with breast cancer, the use of anthracyclines and trastuzumab is notoriously associated with decline in left ventricular ejection fraction (LVEF), termed *chemotherapy-related cardiac dysfunction*.⁵ This effect, along with other cardiovascular toxicities from cancer therapies, has led to the development of a new subspecialty: cardio-oncology. Cardio-oncology involves the prevention and management of cardiovascular risk factors and disease before, during, and after cancer treatment to mitigate cardiovascular toxicities, minimize interruptions in cancer therapy, and improve overall cardiovascular outcomes. Severity and relevance of cardiovascular risk vary widely depending on the cancer and cancer treatment regimens. In addition to traditional chemotherapy, cancer therapies frequently include targeted

therapy, immunotherapy, and radiation therapy. Contemporary treatment of nonmetastatic invasive breast cancer, for example, typically includes surgery, radiation, and conventional chemotherapy, in addition to hormonal therapy (for hormone receptor-positive cancer) and/or therapy targeted to HER2+ (human epidermal growth factor receptor 2-positive) breast cancer.

In this Viewpoint, we discuss opportunities for primary prevention in patients with breast cancer at risk for cardiac dysfunction. Although multimodality cancer therapies may also increase the risk of coronary artery disease and other cardiovascular toxicities, we focus on cardiac dysfunction as the most well-studied side effect during contemporary breast cancer treatment, in particular with the use of anthracyclines and/or trastuzumab.^{6–12} Angiotensin-converting enzyme inhibitors (ACEIs) or β -blockers have been the most frequently investigated pharmacologic options for cardioprotection.^{6–12} We reviewed several recent randomized trials that included these 2 classes of medications. We also briefly review some recommendations and risk scores that may help inform our practice in the primary prevention of cardiovascular toxicities in patients with breast cancer.

ACEIs and β -Blockers in Primary Prevention

Are ACEIs and β -blockers indicated and efficacious for everyone with breast cancer? Should we offer these medications prophylactically to all patients planned for chemotherapy, radiation, or targeted therapy? Alternatively, should we restrict these medications to patients deemed to be high risk for developing cardiovascular toxicity? How is risk defined? Will precision medicine be useful for making this determination?

The American Society for Clinical Oncology (ASCO) published a clinical practice guideline for prevention and monitoring of cardiac dysfunction in survivors of adult cancers.¹² This document recommends cardioprotective measures for patients at high risk (stage A heart failure) for developing cardiac dysfunction based on the following treatment and patient factors¹²:

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1. Treatment that includes high-dose anthracycline (eg, doxorubicin ≥ 250 mg/m² or epirubicin ≥ 600 mg/m²), high-dose radiotherapy (≥ 30 Gy) with the heart in the treatment field, or lower dose of anthracycline (eg, doxorubicin < 250 mg/m² or epirubicin < 600 mg/m²) in combination with lower dose of radiation (< 30 Gy) with the heart in the treatment field.
2. Treatment with lower dose anthracycline or trastuzumab alone and presence of older age (≥ 60 years) or at least 2 existing cardiovascular risk factors or known CVD.
3. Treatment with low-dose anthracycline with subsequent trastuzumab.

The ASCO guideline considered a variety of studies evaluating the efficacy of ACEIs and β -blockers for primary prevention, defined as cardiovascular intervention before the initiation of cancer treatment. The guideline stated that no sufficient evidence is present to recommend a single neurohormonal inhibition strategy to prevent cardiac dysfunction in breast

cancer patients. Over the past 2 decades, several prospective studies using ACEIs and β -blockers demonstrated decreased risk of cardiomyopathy from anthracyclines or trastuzumab therapy.^{6–11} These studies are reviewed in the following section and summarized in Table 1.^{7–10}

A meta-analysis published in 2019 investigated the efficacy of neurohormonal drugs in preventing cardiovascular toxicity in patients receiving chemotherapy.⁶ Neurohormonal drugs included ACEIs, angiotensin receptor blockers, and mineralocorticoid receptor antagonists. The comparison groups received placebo. Seventeen randomized controlled trials were included in the meta-analysis. Sample sizes ranged from 83 to 210 study participants for trials published before 2019. The largest sample size for trials in the meta-analysis was 468 patients for the latest and largest individual study, which was published in 2019. The final meta-analysis of studies completed in Europe, Asia, South America, and North America included 1984 individuals. Follow-up across all 17 trials ranged from 24 weeks to

Table 1. Summary of 5 Randomized Controlled Trials Evaluating the Effect of β -Blockers and Neurohormonal Medications in Preventing Cardiac Dysfunction During Treatment With Trastuzumab, Anthracyclines, or Their Combination

Year, Citation (Trial Name)	Cancer Therapy; Primary End Point	N	Medication	Follow-Up Period	Results	Conclusion
2006, Cardinale et al ⁷	Anthracycline; LVEF decreased by 10%	114	Enalapril	12 mo	0 vs 43%; $P < 0.001$	Benefit
2016, Gulati ⁸ (PRADA)	Anthracycline with or without trastuzumab; change in LVEF by cMRI	130	Candesartan	10–61 wk	Modest decline in LVEF with candesartan vs placebo ($P = 0.025$)	Mild benefit with candesartan
			Metoprolol	10–61 wk	No change in LVEF with metoprolol vs placebo ($P = NS$)	No benefit
2016, Boekhout et al ⁹	Trastuzumab; change in LVEF	206	Candesartan	2 mo	Candesartan had higher incidence of cardiac events vs placebo ($P = NS$)	No benefit, possible harm
2017, Pituskin et al ¹⁰ (MANTICORE 101-Breast)	Trastuzumab (25% with anthracyclines); reduce LV remodeling	94	Perindopril	52 wk	Attenuated LVEF decline but did not prevent LV remodeling	Possible benefit
			Bisoprolol	52 wk	Attenuated LVEF decline prevent LV remodeling	Possible benefit
2019, Guglin et al ¹¹	Trastuzumab only; LVEF decline and treatment interruptions	468	Lisinopril	1+2 y follow-up	No difference from placebo	No benefit
			Carvedilol	1+2 y follow-up	No difference from placebo	No benefit
	Trastuzumab plus anthracyclines; LVEF decline and treatment interruptions		Lisinopril	1+2 y follow-up	HR: 0.53; $P = 0.015$	Benefit
	Trastuzumab plus anthracyclines; LVEF decline and treatment interruptions		Carvedilol	1+2 y follow-up	HR: 0.49; $P = 0.009$	Benefit

cMRI indicates cardiac magnetic resonance imaging; HR, hazard ratio; LV, left ventricular; LVEF, left ventricular ejection fraction; MANTICORE-101 Breast, Multidisciplinary Approach to Novel Therapies in Cardiology Oncology Research; NS, not significant; PRADA, Prevention of Cardiac Dysfunction During Adjuvant Breast Cancer Therapy. 1+2 y; 1 year and 2 years of follow up.

2 years. All studies included some participants with diabetes mellitus, hypertension, or both. Patients were treated with anthracyclines, HER2 antagonists, or a combination. Twelve studies assessed β -blockade and 10 assessed the use of ACEIs, angiotensin receptor blockers, or mineralocorticoid receptor antagonism; 5 studies assessed both. The median baseline LVEF was 59% to 71% across the studies. Pooling the 17 trials, the overall absolute attenuation of LVEF decline between patients who received prophylactic neurohormonal therapies and those who did not was 3.96% (95% CI, 2.90–5.02%). Heterogeneity in the estimates of treatment effect was wide across the trials. The trials were generally completed in single centers or a few centers and with small sample sizes. No appropriately powered, large, multicenter clinical trials were available for analysis. Among the 17 trials pooled in the meta-analysis, 4 studies are among the most cited over time and have perhaps given the most insight into the use of ACEIs and β -blockers for primary prevention in women with breast cancer. These 4 studies are reviewed below in chronological order.

In study by Cardinale et al,⁷ patients with increased troponin I levels (>0.07 ng/mL) during anthracycline-based chemotherapies were prophylactically treated with the ACEI enalapril for prevention of anthracycline-induced cardiac dysfunction. More than 50% of patients in the study were treated for breast cancer. Relative to control patients who received no cardioprotective ACE inhibition, β -blockade, or placebo, patients who received enalapril showed decreased rates of cardiac dysfunction over 12 months of follow-up (0% versus 43%, $P<0.001$). Cardiac dysfunction was defined as a >10 -point decrease in LVEF to below normal.

In the PRADA (Prevention of Cardiac Dysfunction During Adjuvant Breast Cancer Therapy) trial, patients receiving anthracycline therapy with or without trastuzumab were randomized to also receive an angiotensin receptor blocker, candesartan; a β -blocker (metoprolol); or placebo.⁸ A modest LVEF decline was noted in study participants who received candesartan (-0.8% ; 95% CI, -1.9% to 0.4%) over 10 to 61 weeks of follow-up compared with those who received placebo (-2.6% ; 95% CI, -3.8% to -1.5%).⁸ No significant change in LVEF decline was noted in participants receiving metoprolol (-1.6% ; 95% CI, -2.8% to -0.4%) compared with those receiving placebo (-1.8% ; 95% CI, -3.0% to -0.7%). Of interest in the circulating biomarker analysis was attenuation of cardiac troponin increase among patients who received metoprolol but not those who received candesartan, suggesting that attenuation of myocardial injury may not be reflected in changes in left ventricular (LV) function.¹³

In a study by Boekhout et al,⁹ candesartan or a placebo drug was administered to patients being treated with trastuzumab for breast cancer. After 2 months of follow-up, cumulative incidence of cardiac events of 0.28 (95% CI, 0.13–0.40) was

noted in the group receiving candesartan and 0.16 (95% CI, 0.08–0.22) in those receiving placebo ($P=0.56$). Among many limitations of this investigation, it is important to mention that candesartan/placebo intervention started on the day of trastuzumab initiation, which, in these patients, meant after completion of epirubicin-based chemotherapy.¹⁴ In addition, changes in LV function were based on the community reports of either echocardiogram or radionuclide testing without independent verification by the core laboratory.¹⁴

A more recent study assessed the efficacy of ACE inhibition or β -blockade for primary prevention in the MANTICORE-101 Breast (Multidisciplinary Approach to Novel Therapies in Cardiology Oncology Research) trial.¹⁰ In the trial, women with HER2+ early breast cancer were treated with trastuzumab; 25% of patients were also receiving concurrent anthracyclines. Use of the ACEI perindopril and the β -blocker bisoprolol was associated with widely less frequent trastuzumab therapy interruption compared with the placebo group. In addition, LVEF decline was attenuated by the use of bisoprolol (-1% [$\pm 5\%$]) compared with the use of perindopril (-3% [$\pm 4\%$]) or placebo (-5% [$\pm 5\%$]; $P=0.001$). Of interest, the primary end point of this study (change in the LV end-diastolic volume index measured by cardiac magnetic resonance) was negative. After 12 months of trastuzumab treatment, LV end-diastolic volume index increased in study participants regardless of the receipt of bisoprolol ($+8$ mL ± 9 mL/m²), perindopril ($+7 \pm 14$ mL/m²), or placebo ($+4 \pm 11$ mL/m²; $P=0.36$). This suggested limited ability of ACEIs or β -blockers to reduce LV remodeling.

The most recent randomized controlled trial reported in 2019 also included women treated with trastuzumab for nonmetastatic breast cancer.¹¹ Results for patients receiving prophylactic treatment with ACEI lisinopril, beta-blocker carvedilol, and placebo were compared. Primary study end points were LV dysfunction in response to trastuzumab therapy and interruption of trastuzumab therapy. LV dysfunction was defined as $>10\%$ decrease in LVEF overall or $>5\%$ decrease in LVEF if the new LVEF was $<50\%$. Participants were stratified by anthracycline use with subsequent randomization to receive lisinopril, carvedilol, or placebo. After 12 months of treatment with trastuzumab, study participants were followed for an additional 2 years. Trastuzumab treatment interruption (due to decrease in LVEF) was found to be lower in those patients receiving either lisinopril or carvedilol, compared with placebo. Overall, cardiotoxicity (primary end point) was comparable for the 3 groups, yielding 30% for those receiving lisinopril, 29% for those receiving carvedilol, and 32% for those on placebo. However, in prespecified analysis among patients who also received anthracycline therapy, there was greater survival free of cardiotoxicity with lisinopril (hazard ratio: 0.53; 95% CI, 0.30–0.94; $P=0.015$) or carvedilol (hazard ratio: 0.49; 95% CI, 0.27–0.89; $P=0.009$)

compared with placebo. Based on this study, it may be reasonable to use the ACEI lisinopril or the β -blocker carvedilol for primary prevention in patients being treated with a combination of anthracyclines and trastuzumab for breast cancer, although many questions remain, particularly regarding women with higher risk.

Table 1 provides a summary of the primary prevention trials in breast cancer patients with specific cancer treatment regimen (anthracyclines and/or trastuzumab), definition of primary end point, choice of neurohormonal medications, and main study results and conclusions. In brief, the use of different ACEIs, angiotensin receptor blockers, and β -blockers; different end points; and durations of follow-up periods make it difficult to draw a universal conclusion about the effects of these potentially cardioprotective medications. Additional studies are ongoing, including a prospective evaluation of carvedilol for cardioprotection in women with metastatic HER2+ breast cancer, with an estimated enrollment of >800 participants.¹³

Multivariable Risk Scores for Primary Prevention in Breast Cancer

Various groups have attempted to define risk for cardiovascular toxicity, with a number of publications reporting clinical risk scores. The risk score proposed by the Mayo Clinic assigns patients to high, intermediate, or low risk based on the class of chemotherapeutics and patient-related factors.¹⁵ In the score algorithm, anthracyclines and trastuzumab confer the highest medication-related risk. Patient characteristics include existing CVD or risk factors, prior or concurrent use of anthracyclines, prior or current administration of radiation,

younger (<15 years) or older (>65 years) age, and female sex. In this algorithm, ACE inhibition or β -blockade is recommended before initiation of therapy for those at highest cardiovascular risk.

Abdel-Qadir et al¹⁶ developed and validated a clinical score for risk stratification of women who completed therapy for early breast cancer in Ontario, Canada. The score included the factors and conditions that were widely associated with major adverse cardiovascular events in the derivation cohort and incorporated age, the number of preexisting CVDs (ie, coronary heart disease, heart failure, and atrial fibrillation), cerebrovascular disease, peripheral artery disease, cardiovascular risk factors (ie, hypertension and diabetes mellitus), and chronic kidney disease and chronic obstructive pulmonary disease. Major adverse cardiovascular events was defined as hospitalizations for heart failure, stroke, transient ischemic attack, coronary heart disease, peripheral artery disease, or cardiovascular death.

Some groups have attempted anthracycline- or trastuzumab-specific scores. The predictive model by Dranitsaris et al¹⁷ successfully estimated cardiotoxicity risk for patients with metastatic breast cancer. The cumulative number of cycles of doxorubicin, age, weight, performance status, and prior anthracycline use were all found to modify risk. In contrast, Ezaz et al¹⁸ developed a model for estimation of cardiotoxicity risk among patients receiving trastuzumab for early breast cancer. The risk score consists of age, type of adjuvant chemotherapy (anthracycline versus nonanthracycline), and CVD or risk factors (ie, coronary heart disease, atrial fibrillation or flutter, diabetes mellitus, hypertension, and renal failure). Table 2 summarizes the differences in the risk score prediction models.

Table 2. Multivariable Risk Scores for Primary Prevention in Breast Cancer

Citation	Year	Follow-Up	Treatment	N	Results of Predictive Risk Model—Primary Outcome	Factors Used to Calculate Risk of Cardiac Toxicity
Dranitsaris et al ¹⁷	2008	3 mo	Anthracyclines	509	ROC AUC: 0.84 (95% CI, 0.79–0.89) —cardiac toxicity including CHF, hospitalization and need to stop therapy	Age, weight, baseline anthracycline exposure, previous mediastinal irradiation, cycle number WHO PS ≥ 1 , vs 0, baseline LVEF <63%, adjuvant therapy
Ezaz et al ¹⁸	2014	3 y	Trastuzumab	1664	Low (0–3): 16.2%; medium (4–5): 26%; high (≥ 6): 39.5%—heart failure or cardiomyopathy	Age, coronary artery disease, atrial fibrillation/flutter, diabetes mellitus, hypertension, renal failure, adjuvant therapy
Abdel-Qadir et al ¹⁶	2019	10 y (2003–2014/5)	Not specified	29 810	Wolber's C-index, 5 y: –81.9% (80.9–82.9%); 10 y: 79.8% (78.8–80.8%)—major adverse cardiovascular events	Age, heart failure, atrial fibrillation, peripheral vascular disease, hypertension, ischemic heart disease, diabetes mellitus, chronic kidney disease, COPD, cerebrovascular disease

CHF indicates congestive heart failure; COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction; ROC AUC, receiver operating characteristic area under the curve; WHO PS, World Health Organization performance status.

Although a multivariable risk score has been designed to include genomic data to improve risk prediction for development of cardiomyopathy in childhood cancer,¹⁹ no precision risk score is available yet for breast cancer. A number of biotechnology tools are being studied for risk prediction of cardiovascular toxicities. Most studies have focused on anthracycline-induced cardiac dysfunction. Genomics, transcriptomics, proteomics, and mathematical and computational modeling have all been investigated for precision prediction of patients treated with anthracyclines with breast cancer.²⁰ However, no study has implemented this approach in the clinic for primary prevention (or management) of cardiovascular toxicity in these patients.

Conclusions

Identifying and managing risk in women with breast cancer undergoing therapy with anthracyclines with or without trastuzumab is critical for primary prevention of cardiovascular toxicity. Several small studies suggest that using ACEIs and β -blockers for primary prevention may be efficacious in some women (Table 1), but the differences in the studies prevent universal conclusions. It is prudent to recommend taking careful history and performing risk assessment, taking into consideration clinical factors, treatment regimen, radiation and existing CVD, risk factors, and comorbid conditions. Multivariable risk scores may become available in the future, particularly with incorporation of precision medicine tools such as genomics. Further research is needed to strengthen recommendations for treatment and to investigate new means of cardioprotection.

Disclosures

None.

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