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# Cardiotoxicity of HER2-targeted therapies

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## Abstract

**Purpose of review—**Cardiotoxicity is a well recognized adverse effect of human epidermal growth factor receptor 2 (HER2)-targeted therapies. The goal of this review is to highlight recent studies that have advanced our knowledge of the diagnosis, prevention, and management of cardiotoxicity associated with HER2-targeted agents.

**Recent findings—**Several clinical risk factors for cardiotoxicity associated with HER2-targeted therapies have been identified including age, low-baseline left ventricular ejection fraction, and treatment with anthracyclines; however, these remain insufficient to identify all patients at risk for cardiotoxicity. Routine cardiac monitoring remains the standard for cardiotoxicity surveillance, although the optimal frequency and modality of monitoring remains uncertain. Global longitudinal strain, T1/T2 weighted CMR imaging protocols, and circulating biomarkers can detect early signs of cardiotoxicity, but studies are needed to investigate whether use of these markers in clinical practice improves patient outcomes. Cardioprotective medications (e.g. beta-blockers or ACE-inhibitors) may be of benefit to patients at increased risk for cardiotoxicity from HER2-taregeted therapies, particularly those who are treated with an anthracycline-containing regimen.

**Summary—**Improved risk stratification of patients during HER2-targeted therapy and effective prevention and management strategies for cardiotoxicity are needed to enhance the value of longitudinal cardiac monitoring and increase cardiac safety so that optimal breast cancer treatment can be delivered.

### Keywords

breast cancer; cardiooncology; cardiotoxicity; trastuzumab

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Conflicts of interest

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## INTRODUCTION

Breast cancer is the most commonly diagnosed cancer in women [1]. Up to 25% of breast cancers overexpress the human epidermal growth factor 2 (HER2) cell surface tyrosine kinase receptor [2]. Patients with HER2-positive breast cancers have an aggressive form of the disease associated with higher risk for recurrence and reduced survival [3]. Trastuzumab (Herceptin; Genetech Inc, San Francisco, California, USA), a humanized monoclonal antibody targeting the extracellular domain of the HER2 receptor, was approved for the treatment of metastatic and early stage HER2-positive breast cancer in 1998 and 2005, respectively [2,4,5]. Several additional HER2-targeted therapies were since developed, including pertuzumab, lapatinib, ado-trastuzumab emtansine, and neratinib. Collectively, these targeted agents have improved progression-free and overall survival in patients with HER2-positive breast cancer [6–12].

Cardiotoxicity is a well recognized adverse effect associated with HER2-targeted therapies and is characterized by left ventricular systolic dysfunction, manifesting clinically as decreased left ventricular ejection fraction (LVEF) and/or symptomatic heart failure. The goal of this review is to highlight recent studies that have advanced our knowledge on the diagnosis and management of cardiotoxicity associated with HER2-targeted agents.

## INCIDENCE

The incidence of cardiotoxicity associated with an anthracycline-based trastuzumab regimen ranges from 4.0 to 18.6% for decreased LVEF and 0.4–4.1% for severe heart failure. The risk of cardiotoxicity appears lower among patients treated with trastuzumab in the absence of anthracyclines, with LVEF decline and symptomatic heart failure occurring in 3.2 and 0.5%, respectively [13,14]. Potential factors associated with increased risk for trastuzumab cardiotoxicity include age, preexisting cardiovascular comorbid conditions (e.g. hypertension), lower baseline LVEF, obesity, and prior treatment with anthracycline chemotherapy [15–18]. In a retrospective analysis by Litvak *et al.* [17], the rate of cardiotoxicity was higher among black patients compared with white patients, although black patients had more cardiovascular comorbidities. Long-term follow-up studies from clinical trials of trastuzumab in the adjuvant setting provide reassuring evidence that late occurrence of cardiotoxicity is uncommon [19–22].

In the early-stage setting, the recommended duration of trastuzumab treatment is 1 year, although investigation of shorter courses of trastuzumab have been investigated, particularly given the known risk of cardiotoxicity with extended durations of trastuzumab [21]. Two studies failed to show that 6 months of trastuzumab treatment was noninferior to 1 year of trastuzumab [23,24]. More recently, the Short-HER and Synergism or Long Duration (SOLD) studies failed to show the noninferiority of 9 weeks of trastuzumab compared with 1 year with 5-year disease free survival (DFS) in the 1-year and 9-week arms of 88 versus 85% and 90.5 versus 88%, respectively, though fewer adverse cardiac events were noted with the shorter duration of trastuzumab [25,26]. Although 1 year of trastuzumab remains the standard treatment for HER2-positive breast cancer, these studies suggest that patients

who receive a shorter duration of trastuzumab are still anticipated to have a favorable cancer outcome.

## MECHANISMS

In contrast to anthracycline-related cardiotoxicity, which is mediated by lipid peroxidation and DNA damage causing myocardial necrosis/fibrosis, trastuzumab is not associated with apparent ultra-structural changes. Instead, cardiomyopathy is hypothesized to occur via disruption of the protective functions of HER2 in the cardiomyocyte and is often reversible upon interruption of treatment [27–29]. Preclinical studies demonstrate that interference with HER2 signaling can increase sensitivity to anthracycline-induced injury and pressure overload [30,31]. The HER receptor is a network of multiple molecularly kindred transmembrane proteins which comprise four main subtypes (HER1, HER2, HER3, HER4) [8]. Receptor activation leads to dimerization of these proteins, triggering tyrosine kinase signaling and downstream effects. Disruption of these interactions by multiple HER-targeted agents both attenuates breast cancer-proliferative effects and augments cell protective actions. Pertuzumab inhibits HER2 signaling via activity at a different site than trastuzumab, preventing heterodimerization of HER2 and HER3 and disrupting downstream activity. Dual anti-HER2 therapy improves tumor response and is currently recommended in the treatment of early stage and metastatic HER2-positive breast cancer [8–10,32]. On the basis of the recent findings from the ExteNET trial of neratinib, a small molecular tyrosine kinase inhibitor of HER1, HER2, and HER4, neratinib is now approved for extended adjuvant treatment following trastuzumab for early HER2-positive breast cancer [12]. Cardiotoxicity was not observed with neratinib, although this could be attributed to the inclusion of lower risk patients with no significant cardiac comorbidities who had completed trastuzumab with a normal LVEF. Therefore, the safety of neratinib among patients with preexisting LV systolic dysfunction or a prior history of trastuzumab cardiotoxicity remains uncertain.

## NONINVASIVE CARDIAC IMAGING

LVEF assessments are recommended every 3 months during trastuzumab treatment, based on the cardiac surveillance strategies used in clinical trials [33]. Potential advantages of routine cardiac surveillance include early detection of cardiotoxicity prior to the development of clinical symptoms, which allows for early initiation of cardioprotective medications. However, current practice guidelines from the National Comprehensive Cancer Network (NCCN) and the American Society of Clinical Oncology (ASCO) acknowledge that the optimal frequency of cardiac monitoring remains unclear, and no specific schedule for LVEF assessments is provided in these recommendations [34■■,35]. Over screening for cardiotoxicity also poses potential harms to patients, such as unnecessary interruption of cancer treatment and increased healthcare spending. One potential strategy is to tailor the cardiac monitoring regimen based on an individual’s risk of cardiotoxicity, as determined by baseline cardiovascular risk factors and the cardiotoxicity risk associated with the cancer treatment regimen. This would ensure that patients with known cardiovascular risk factors who are treated with high-risk cancer treatment regimens undergo more intensive monitoring to reduce risk for cardiotoxicity, whereas patients with no cardiovascular risk factors who are treated with low-risk treatment regimens undergo less monitoring.

Echocardiography-based strain imaging identifies early subclinical changes in LV systolic function during cancer treatment. Several studies demonstrate that global longitudinal strain (GLS) can be a predictive marker of cardiotoxicity and detects early declines in ventricular mechanics prior to an overt reduction in LVEF [36–38]. In a study by Ali *et al.* [39], GLS measured prior to chemotherapy was effective in identifying patients at high risk for cardiac events after anthracycline chemotherapy. Other studies have similarly shown that GLS is an early predictor of cardiotoxicity during trastuzumab therapy [36,40,41]. In clinical practice, GLS can also help to reconcile the significance of asymptomatic fluctuations in LVEF, which occur during serial imaging. Further investigation is needed to determine whether incorporation of GLS measurements into current clinical practice will improve cardiac outcomes among patients undergoing cardiotoxic cancer therapy. The Surveillance of Chemotherapy for Improving Cardiovascular Outcomes (SUCCOUR) Trial is an international prospective randomized controlled trial that seeks to evaluate whether a strategy of cardioprotective therapy guided by GLS results in improved cardiac function [42■■].

Cardiovascular magnetic resonance (CMR) imaging is an important tool used for the noninvasive cardiac assessment of a cancer patient. CMR is considered the reference standard for measurement of ventricular volumes, function, and mass, and provides tissue characterization of the myocardium, which can be helpful in identifying the cause of a myocardial disease process. Two CMR-based studies highlighted that a decline in LVEF during cancer treatment for some patients can be attributed to an isolated decline in left ventricular end diastolic volume (LVEDV) rather than an increase in left ventricular end systolic volume (LVESV) [43,44]. Given that volume depletion is common during cancer treatment and can be easily corrected, assessment for changes in LVEDV and LVESV at the time of cardiac surveillance may help to inform the proper management. This is of importance given decisions to cease or interrupt cancer therapy are frequently based on changes in LVEF [44].

T1 and T2-weighted imaging series as well as newer T1 and T2 mapping sequences are promising techniques for the early identification of cardiotoxicity. T1-weighted CMR protocols can detect focal and/or diffuse cardiomyopathic processes, such as myocardial inflammation related to myocarditis [45,46]. Postcontrast T1-mapping protocols quantify extracellular volume, an additional marker of myocardial fibrosis, and were shown to be elevated among cancer survivors previously treated with anthracyclines [47,48]. T2-weighted imaging detects myocardial edema. T2-mapping protocols enhance predictive value and are gaining interest as early imaging biomarker of cardiotoxicity. A recent study by Galan *et al.* [49] suggests that changes in T2 relaxation time using T2 mapping techniques may be an early marker of reversible anthracycline cardiotoxicity; however, further investigation is needed to determine whether this can be translated into clinical practice. Despite the additional information that can be obtained with CMR, cost and lack of widespread availability are limitations to the integration of CMR into routine cardio-oncology practice.

## BIOMARKERS

Blood-based biomarkers have been investigated for the early detection and/or prediction of trastuzumab cardiotoxicity (Table 1). Conventional and high-sensitivity troponin assays have been the most widely studied among patients treated with trastuzumab. Several studies show that troponin elevations are predictive of subsequent LVEF decline during trastuzumab [40,51,53,54■]. In a cardiac biomarker sub-study of the Herceptin Adjuvant (HERA) study, elevated levels of troponin I and T before trastuzumab were associated with increased risk of LVEF decline [54■]. Of note, nearly all patients in HERA received anthracyclines and thus the elevated troponin may be a manifestation of anthracycline-induced myocardial injury. In contrast, troponin T was not predictive of cardiotoxicity in the NeoALTTO trial in which patients were treated with neoadjuvant HER2-targeted therapy (lapatinib, trastuzumab, or lapatinib and trastuzumab), although patients in this trial did not receive anthracycline chemotherapy until after the last biomarker time-point [55]. These findings suggest troponin testing is of greatest utility after exposure to anthracyclines [52].

Brain natriuretic peptide (BNP) is widely used in the diagnosis and follow-up of heart failure but has limited value for the prediction of trastuzumab cardiotoxicity [36,40,51,53]. Myeloperoxidase, amarker of oxidative stress, was associated with cardiotoxicity in a small study of 78 breast cancer patients treated with doxorubicin and trastuzumab and may identify patients at increased risk for cardiotoxicity, but requires further validation [51].

## PREVENTION

Several trials evaluated the efficacy of prophylactic treatment with neurohormonal antagonist medications [beta adrenergic blockers, angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs)] for the prevention of cardiotoxicity during treatment with trastuzumab (Table 2). In the PRADA trial, breast cancer patients were randomized to receive candesartan and metoprolol succinate, both alone and in combination, versus placebo [56■]. All patients received an anthracycline-based regimen, although the prevalence of cardiovascular risk factors was low and only 22% were treated with trastuzumab. Candesartan, but not metoprolol, protected against a modest decline in LVEF associated with breast cancer treatment. In contrast, a study by Boekhout *et al.* [57] failed to show a benefit of candesartan for the prevention of trastuzumab cardiotoxicity. In this trial of 210 patients with HER2-positive breast cancer receiving treatment with anthracyclines followed by trastuzumab, candesartan (32 mg/day) failed to protect against LVEF decline, although candesartan was initiated nearly 3 months after anthracyclines were given. The MANTICORE trial evaluated the benefit of perindopril or bisoprolol in patients receiving trastuzumab, the majority (77%) of whom received a nonanthracycline-based regimen [58■]. Treatment with both perindopril and bisoprolol led to attenuation of LVEF decline during trastuzumab treatment and fewer patients in the perindopril or bisoprolol arms required trastuzumab interruption because of LVEF decline, underscoring another potential benefit of a preventive strategy. However, these treatments had no effect on the primary endpoint of LV remodeling as measured by left ventricular end diastolic volume index.

In a prospective study by Guglin *et al.* [59] of lisinopril or carvedilol in patients with HER2-positive breast cancer treated with trastuzumab, preliminary findings point to an important interaction between anthracycline exposure and beneficial effects of pharmacologic prophylaxis to prevent trastuzumab cardiotoxicity. In this randomized trial of 468 patients, treatment with carvedilol or lisinopril was effective in reducing the occurrence of LVEF decline among the subset of patients who received anthracycline chemotherapy followed by trastuzumab (hazard ratio 0.49 for extended release carvedilol and 0.53 for lisinopril). These preliminary data suggest that neurohormonal antagonists may be of greatest benefit to patients at high risk for trastuzumab cardiotoxicity who are treated with an anthracycline-containing regimen.

A recent meta-analysis of eight trials examined the effect of neurohormonal antagonists for primary prevention of cardiotoxicity in 1048 patients receiving anthracyclines [60]. Of these, 333 patients received trastuzumab containing regimens. Beta-blockers, but not ACE inhibitors, were associated with a lesser reduction in LVEF compared with control, although this effect was less certain for patients treated with anthracyclines alone. A study using the Surveillance, Epidemiology, and End Results (SEER)-Medicare-linked database showed favorable effects of both beta-blockers and ACE-inhibitors on preventing cardiotoxicity and improving survival, with adjusted hazard ratio of 0.77 (95% CI 0.62–0.95) and 0.79 (95% CI 0.70–0.90), respectively [61]. Overall, these data suggest that in patients at sufficiently increased risk for cardiotoxicity, cardioprotective medications may be beneficial for primary prevention of cardiotoxicity.

## MANAGEMENT

Optimal management of patients at risk for cardiotoxicity includes control of cardiovascular risk factors, such as hypertension and diabetes, and routine cardiac monitoring during cardiotoxic cancer treatment. Although some clinical risk factors for cardiotoxicity have previously been identified, there is a need to translate these findings into a validated risk assessment tool. On the basis of long-term follow-up of the NSABP-B31 study, Romond *et al.* [19] proposed a risk score that was based on age and baseline LVEF to predict the risk of cardiotoxicity. Acknowledging the selection bias of patients in clinical trials, another group analyzed Medicare claims data to develop a risk score (constituted of age, cancer treatment type, and cardiovascular conditions including coronary artery disease, atrial fibrillation/flutter, diabetes, hypertension, and renal failure) to stratify risk of trastuzumab cardiotoxicity in an older breast cancer population [62]. Despite these efforts, clinical factors alone are unable to identify all patients who are at risk. This unexplained variability suggests that genetics factors may play a role in an individual’s susceptibility to adverse cardiovascular effects of HER2-targeted therapies. Once developed, an accurate risk prediction tool can be used to inform decisions about the optimal frequency of cardiac monitoring, the potential benefit of prophylactic cardioprotective medications, or identify patients who should receive alternative cancer treatment regimens associated with lower cardiotoxicity risk. Further validation of any current or future candidate risk scores in a large patient population is required for incorporation into routine practice.

Cardiotoxicity associated with HER2-targeted therapy most often results in interruption or discontinuation of treatment. However, the safety of continuing treatment in patients with an asymptomatic LVEF decline has recently been shown in several small retrospective studies [63–65]. The SAFE-HEaRt trial is prospectively evaluating the cardiac safety of HER2-targeted therapy in combination with frequent cardiac monitoring and maximally tolerated beta-blocker and ACE-inhibitor therapy among patients with a LVEF of 40–49% [66■]. Until more safety data are available, collaboration of cardiologists and oncologists is critical to educate patients on the cardiac risks of continuing treatment with an abnormal LVEF, monitor for signs or symptoms of heart failure, and prescribe medications recommended by the current ACC/AHA heart failure treatment guidelines [67].

## CONCLUSION

HER2-targeted therapies are fundamental to current breast cancer treatment and have improved the prognosis for patients with HER2-positive disease. Strategies to identify patients at greatest risk for cardiotoxicity during therapy are vital to maximizing the safety and efficacy of HER2-targeted therapy. Exploration on the utility of genetic markers will likely yield greater insight into an individual patient's risk for cardiotoxicity. Primary prevention trials to date suggest the potential benefit of prophylactic administration of cardioprotective medications, although the magnitude of benefit remains modest. Future primary prevention studies are warranted in patients at high-risk for cardiotoxicity. Advances in noninvasive imaging techniques, such as speckle tracking strain echocardiography or T1/T2-based CMR sequences have improved our ability to detect subclinical signs of cardiotoxicity associated with anti-HER2 therapy. Patients at high risk for cardiotoxicity and/or those who have subclinical signs of cardiotoxicity may represent a key demographic with potential to benefit from more intensive cardiac monitoring or treatment with cardioprotective medications, whereas less cardiac monitoring may be appropriate for patients without cardiovascular comorbidities treated with low-risk cancer treatment regimens. Key unanswered questions include how interruption of trastuzumab because of cardiac toxicity affects cancer and cardiovascular-related outcomes, and whether continuation of targeted-HER2 therapy is well tolerated in patients who develop cardiotoxicity without heart failure. Continued collaboration between the cardiology and oncology communities will enable the clinical studies necessary to answer these important questions and further optimize the long-term outcomes of breast cancer patients.

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## KEY POINTS

- Cardiotoxicity is a well recognized adverse effect associated with HER2-targeted therapies and is characterized by left ventricular systolic dysfunction, manifesting clinically as decreased left ventricular ejection fraction (LVEF) and/or symptomatic heart failure.
- Global longitudinal strain (GLS) and troponin assays may detect early cardiotoxicity prior to an overt reduction in LVEF and can be an early predictive marker.
- Emerging data suggest that neurohormonal antagonists may be of greatest benefit to patients at increased risk for trastuzumab cardiotoxicity, such as those who are treated with an anthracycline-containing regimen.
- Key unanswered questions needing further investigation include how to modify cardiac-monitoring strategies to eliminate unnecessary testing while ensuring cardiac safety, how interruption of trastuzumab because of cardiotoxicity toxicity affects cancer and cardiovascular-related outcomes, and whether continuation of treatment may be well tolerated among patients who develop cardiotoxicity.

**Table 1.**

Studies of biomarkers of cardiotoxicity in patients with HER2-positive breast cancer

| Study | Patients | Markers | Primary outcome | Findings |
|---|---|---|---|---|
| Cardinale *et al.* [50] | 251 patients treated with trastuzumab<br>78% received prior anthracyclines<br>51% with metastatic disease | Tn-I | ↓ LVEF > 10% from baseline to < 50% | Cardiotoxicity occurred in 42 (17%) patients. Cardiotoxicity was more frequent in patients with an elevated TnI >0.08 ng/ml (62 versus 5%, p < 0.001). |
| El Sherbeny *et al.* [36] | 61 patients treated with AC followed by paclitaxel + trastuzumab | GLS NT-proBNP | ↓ LVEF >10% to < 55% with or without signs and symptoms of heart failure. | GLS (absolute) <18% measured at month 3 of trastuzumab predicts development of cardiotoxicity<br>NT-proBNP was not predictive of cardiotoxicity |
| Ky *et al.* [52] | 78 patients treated with an anthracycline-based regimen followed by a taxane and trastuzumab | hsTn-I<br>MPO<br>CRP<br>GDF-15<br>PlGF<br>sFlt-1<br>gal-3 | ↓ LVEF ≥5% to <55% with CHF symptoms<br>Asymptomatic ↓ LVEF ≥10% to <55% | Increases in hsTn-I and MPO from baseline to month 3 (postanthracyclines) are associated with cardiotoxicity (hazard ratio 1.38 per SD increase in TnI, $P = 0.02$; hazard ratio 1.34 per SD increase in MPO, $P = 0.048$) |
| Morris *et al.* [53] | 95 patients treated with ddAC followed by weekly paclitaxel with trastuzumab + lapatinib | Tn-I<br>CRP | Change in LVEF | Tn-I elevations preceded maximal LVEF decline but did not correlate with development of CHF<br>No correlation between CRP levels and LVEF decline or CHF |
| Negishi et al. [41] | 81 patients treated with trastuzumab<br>46% received an anthracycline-based regimen | GLS | ↓ LVEF ≥ 10% from baseline | A decrease in GLS of 11% measured at 6 months is predictive of subsequent reductions in LVEF at 12 months. |
| Sawaya *et al.* [40] | 81 patients treated with anthracyclines, taxanes, and trastuzumab | GLS<br>hsTn-I<br>NT-proBNP<br>ST-2 | ↓ LVEF ≥5% to < 55% with CHF symptoms<br>Asymptomatic ↓ LVEF ≥10% to < 55% | GLS (absolute) < 19% measured after completing anthracycline chemotherapy is predictive of cardiotoxicity during trastuzumab.<br>Elevated usTn-I ≥ 30 pg/ml measured after completing anthracycline chemotherapy is predictive of cardiotoxicity during trastuzumab. |
| Zardavas *et al.* [54■] | 452 patients treated with adjuvant chemotherapy followed by trastuzumab in the HERA trial<br>94% received an anthracycline-based regimen | Tn-I<br>Tn-T<br>NT-proBNP | NYHA class III-IV CHF<br>↓ LVEF >10% from baseline to <50%<br>Death from cardiac cause | Elevated baseline troponin I (>40 ng/l) and T (> 14 ng/l) are associated with risk of significant LVEF decline (hazard ratio = 4.52; $P<0.001$ and hazard ratio 3.57; $P<0.001$, respectively) |

AC, doxorubicin + cyclophosphamide; CRP, C-reactive protein; ddAC, dose dense doxorubicin + cyclophosphamide; FEC, 5-fluorouracil, epirubicin, and cyclophosphamide; gal-3, galectin 3; GDF-15, growth differentiation factor-15; GLS, global longitudinal strain; hsTnI, high-sensitivity troponin I; MPO, myeloperoxidase; NT-proBNP, n-terminal pro-B type natriuretic peptide; NYHA, New York Heart Association; Pl-GF, placental growth factor; sFlt-1, soluble fms-like tyrosine kinase receptor-1; ST2, interleukin family member; Tn-I, cardiac troponin-I.

**Table 2.**

Trials of primary prevention strategies for cardiotoxicity in patients with breast cancer

| Study | Population | Interventions | Cardiotoxicity Outcome | Findings |
|---|---|---|---|---|
| PRADA [55] | 130 patients treated with FEC 22% received trastuzumab | Candesartan<br>Metoprolol XL<br>Candesartan + metoprolol XL<br>Placebo | Change in LVEF by cardiac MRI | Decline in LVEF from baseline to end of study was lower in the candesartan group (−0.8%) compared with the placebo group (−2.6%). LVEF decline in the metoprolol group (−1.6%) was not significantly different compared with placebo. |
| MANTICORE [58■] | 94 patients treated with adjuvant chemotherapy (FEC 22%, TC 77%, ACT 1%) plus trastuzumab | Perindopril<br>Bisoprolol<br>Placebo | Change in LVEDVi by cardiac MRI | No difference in change in LVEDVi from baseline to end of study in the perindopril or bisoprolol groups compared with placebo (+7 ml/m$^2$ versus + 8 ml/m$^2$ versus +4 ml/m$^2$, $P$ = 0.36).<br>Small reduction in LVEF decline with bisoprolol but not perindopril compared with placebo (−1 versus −3 versus −5%, $P$ = 0.001) |
| Boekhout *et al.* [56■] | 206 patients treated with anthracyclines plus trastuzumab | Candesartan<br>Placebo | ↓ LVEF ≥ 15% from baseline or to <45% | No difference in rate of cardiotoxicity between candesartan group versus placebo (19 versus 16%, $P$ = 0.58)<br>NT-proBNP and hs-TnT were not associated with changes in LVEF. Candesartan did not affect changes in biomarkers. |
| Guglin *et al.* [59] | 468 patients treated with adjuvant chemotherapy plus trastuzumab<br>39% with prior exposureto anthracycline-based chemotherapy | Lisinopril<br>Carvedilol ER<br>Placebo | ↓ LVEF ≥10% or ≥5 to <50% | No difference in rate of cardiotoxicity between lisinopril group or carvedilol group versus placebo (30 versus 29 versus 32%, $P$ = ns).<br>In the subset of patients treated with anthracyclines, the rate of cardiotoxicity was lower in the lisinopril and carvedilol groups versus placebo (37 versus 31 versus 47%, $P$ = 0.009) |

ACT, doxorubicin, cyclophosphamide, docetaxel; FEC, 5-fluorouracil, epirubicin, and cyclophosphamide; LVEDVi, left ventricular end diastolic volume index; TC, docetaxel, carboplatin.