

# Cardiotoxicity From Human Epidermal Growth Factor Receptor-2 (HER2) Targeted Therapies

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**B**reast cancer is the most commonly diagnosed cancer in women and the second-leading cause of death among women with cancer.<sup>1</sup> Whereas outcomes for many breast cancers are favorable, human epidermal growth factor receptor-2 (HER2)-positive breast cancers may have an aggressive clinical course and are associated with higher rates of disease recurrence and mortality.<sup>2,3</sup> Such tumors are characterized by overexpression of HER2 and/or amplification of the ERBB2 gene.<sup>2,4</sup> Development of the monoclonal antibody that targets the extracellular domain of HER2, trastuzumab, revolutionized the care of these patients, leading to large improvements in disease-free and overall survival.<sup>5</sup> In addition, development of newer anti-HER2 therapies has led to further improvements in cancer outcomes for this population.<sup>6–9</sup>

HER2 targeted therapies, such as trastuzumab, are generally well tolerated. They do not have significant myelosuppressive side effects nor do they cause typical symptoms associated with chemotherapy, such as emesis and alopecia. However, the safety of therapies directed at HER2, in particular trastuzumab, has been questioned by concerns regarding cardiotoxic effects.<sup>10</sup>

## Clinical Presentation

Cardiac adverse effects from trastuzumab therapy involve decreases in the left ventricular systolic function with or

without clinical signs and symptoms of heart failure (HF). Decreases in left ventricular ejection fraction (LVEF) typically manifest during the course of treatment and long-term follow-up data up to 10 years do not show evidence of late-onset cardiac dysfunction associated with HER2 targeted therapy.<sup>11–13</sup> Additional key features that differentiate cardiotoxicity associated with trastuzumab use from that associated with anthracycline therapy, which may occur late and be irreversible, are lack of ultrastructural changes in endomyocardial biopsy specimens, and possible reversibility of cardiac dysfunction.<sup>14,15</sup>

Although various groups have proposed a set of criteria to define cardiotoxicity from cancer therapies (Table 1), none have been uniformly accepted.<sup>16–19</sup> The use of various definitions for cardiac adverse events in the trastuzumab trials makes direct comparison of these studies difficult and limits our understanding of the true clinical burden of cardiotoxicity associated with HER2 targeted therapies.

## The Benefits of HER2 Targeted Therapies

The evidence indicating increased rates of cardiotoxicity with the use of HER2 targeted therapies needs to be taken in the context of the significant cancer-related benefits.

Trastuzumab was the first approved HER2 monoclonal antibody (approved by the US Food and Drug Administration in 1998). Initial trials showed it was well tolerated and produced durable response in patients who had failed first- and second-line chemotherapy.<sup>21–23</sup> Subsequent large, phase III trials showed significant improvements in time to treatment failure and overall mortality in patients with progressive metastatic breast cancer.<sup>5</sup> A systematic review published in 2014 concluded that trastuzumab led to 18% and 39% improvements in overall and progression-free survival in this population (hazard ratio, 0.82; 95% confidence interval [CI], 0.71–0.94;  $P=0.004$ ; and hazard ratio, 0.61; 95% CI, 0.54–0.70;  $P<0.00001$ , respectively).<sup>24</sup>

In 2005, results of 3 large phase III clinical trials were published showing high efficacy of adjuvant trastuzumab in combination with poly-chemotherapy for patients with early

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*J Am Heart Assoc.* 2017;6:e006915. DOI: 10.1161/JAHA.117.006915.

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**Table 1.** Definitions of Cardiotoxicity Used by Different Organizations

National Cancer Institute Common Terminology Criteria for Adverse Events (HF) version 4 <sup>18</sup>				
Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Asymptomatic elevation in biomarkers or imaging abnormalities	Symptoms with mild-to-moderate exertion	Symptoms with minimal exertion or at rest	Life-threatening consequences	Death
Cardiac Review and Evaluation Committee (CREC) <sup>19</sup>				
LVEF decrease >5%, to less than 55%, that is either global or more severe in the septum, with or without symptoms or HF				
American Society of Echocardiography (ASE) and European Association of Cardiovascular Imaging (EACVI) <sup>17</sup>				
LVEF decrease >10%, to less than 53%, confirmed on repeat imaging, with or without symptoms of HF				
European Society of Cardiology (ESC) <sup>20</sup>				
LVEF decrease >10%, to less than 50%, with or without symptoms or HF				
Trastuzumab labeling				
LVEF decreased $\geq$ 16% from baseline or LVEF decrease $\geq$ 10% to institutionally defined normal				

HF indicates heart failure; LVEF, left ventricular ejection fraction.

breast cancer (node positive or high-risk node negative). In a joint analysis from the NSABP (National Surgical Adjuvant Breast and Bowel Project) trial B-31 and NCCTG (North Central Cancer Treatment Group) trial N9831, the addition of trastuzumab to standard chemotherapy was associated with 33% and 50% improvements in overall and disease-free survival,<sup>25</sup> which persisted at 10 years of follow-up.<sup>26</sup> Similar results were reported from the HERA (Herceptin Adjuvant) trial.<sup>27</sup> The BCIRG (Breast Cancer International Research Group) 006 trial extended these findings by showing benefit from trastuzumab regimens both with and without anthracyclines.<sup>28</sup> Most recently, extremely low risk of recurrence was demonstrated with the use of trastuzumab and a single chemotherapy agent (paclitaxel) in patients with small, node-negative, early-stage breast cancer.<sup>29</sup>

Three additional HER2-directed therapies have been approved for use in patients with breast cancer: lapatinib, pertuzumab, and ado-trastuzumab emtansine. In the recent CLEOPATRA (A Phase III, Randomized, Double-blind, Placebo-controlled Clinical Trial to Evaluate the Efficacy and Safety of Pertuzumab + Trastuzumab + Docetaxel vs. Placebo + Trastuzumab + Docetaxel in Previously Untreated HER2-positive Metastatic Breast Cancer) trial, the addition of pertuzumab to trastuzumab and chemotherapy led to dramatic improvements in overall and progression-free survival of patients with metastatic HER2-positive breast cancer.<sup>8</sup> Additionally, pertuzumab is approved for use in the neoadjuvant setting in patients with early breast cancer, and a large trial evaluating its use in the adjuvant setting in combination with trastuzumab has recently reported favorable outcomes.<sup>30–32</sup> The use of lapatinib and ado-trastuzumab emtansine is restricted to patients with disease progression on trastuzumab in the metastatic setting.<sup>33</sup> The addition of lapatinib led to a 51% decrease in the risk of progression in women with

advanced breast cancer that had previously progressed after treatment with trastuzumab.<sup>8</sup> In the EMILIA (A Study of Trastuzumab Emtansine Versus Capecitabine + Lapatinib in Participants With HER2-positive Locally Advanced or Metastatic Breast Cancer) trial, ado-trastuzumab prolonged overall and progression-free survival of patients with advanced breast cancer who had been previously treated with trastuzumab.<sup>9</sup>

## The Cardiac Risks of HER2 Targeted Therapies

The first signal for cardiotoxicity associated with trastuzumab did not appear until the first phase III trial of the monoclonal antibody in patients with metastatic breast cancer published in 2001. In this study, risk of symptomatic or asymptomatic cardiac dysfunction was highest among individuals who received trastuzumab in combination with anthracycline and cyclophosphamide, followed by those who received the monoclonal antibody in combination with paclitaxel, as compared with either chemotherapeutic regimen alone (incidence, 27% versus 13% versus 8% versus 1%, respectively).<sup>5</sup> Additionally, a significant proportion of these patients developed New York Heart Association class III or IV HF (incidence; 16%, 2%, 3%, and 1%, respectively).<sup>5</sup> Such differences in the rates of cardiac dysfunction with the use of different chemotherapeutic regimens raised suspicion for a synergism between trastuzumab and anthracycline. Given these unexpectedly high rates of HF, subsequent trials of trastuzumab adopted stringent criteria for patient enrollment excluding those at increased risk for cardiac adverse events. Exclusion criteria have included: history of uncontrolled hypertension, arrhythmias, valvular disease, coronary artery disease, HF, or asymptomatic left ventricular systolic dysfunction. Enrollment of a lower-risk population, implementation of strict protocols

for monitoring of cardiac function, and changes in chemotherapeutic regimens so that anthracyclines were not given concurrently with trastuzumab or were omitted, likely explain the lower rates of cardiotoxicity observed in the subsequent trials of the monoclonal antibody.

Rates of severe HF, defined as New York Heart Association class III or IV symptoms, were 0.8% and 4.1% in the placebo and trastuzumab groups of the NSABP trial B-31.<sup>34,35</sup> Similar rates were reported in the NCCTG trial N9831, whether trastuzumab was administered concomitantly or sequentially with adjuvant chemotherapy.<sup>13,36</sup> Although lower rates were reported in the HERA (Herceptin Adjuvant) trial with administration of the monoclonal antibody after completion of chemotherapy,<sup>37</sup> these likely reflect differences in timing of randomization of the trials, with the latter only reporting events that occurred following completion of adjuvant chemotherapy. In the HERA and PHARE (Protocol for Herceptin as Adjuvant therapy with Reduced Exposure) trials, longer duration of therapy was associated with higher rates of cardiotoxicity.<sup>12,38,39</sup> Rates of cardiotoxicity appear to be similar when trastuzumab is added to chemotherapy containing epirubicin as opposed to doxorubicin.<sup>40–43</sup> In a meta-analysis of adjuvant trastuzumab trials published by the Cochrane group in 2012, there were 135 cases (2.5%) of HF of 5471 patients in the trastuzumab groups compared with 20 cases (0.4%) of 4810 in the control groups, yielding a statistically significant relative risk of 5.1 for development of HF in patients treated with the monoclonal antibody. Additionally, 11.2% of patients in the trastuzumab group had a decline in the LVEF as compared with 5.6% in the control group (relative risk, 1.83; 95% CI, 3.0–8.72).<sup>44</sup>

Rates of cardiotoxicity appear to be significantly lower when trastuzumab is used with regimens that do not include anthracyclines. In the BCIRG006 trial, docetaxel administered with carboplatin and trastuzumab showed similar efficacy to an anthracycline-based regimen, while having significantly less cardiac adverse events (0.4% symptomatic HF).<sup>45</sup> Similar rates of cardiac adverse events were reported in a recent single-arm study of paclitaxel plus trastuzumab for small, node-negative, HER2-positive breast cancer (0.5% symptomatic HF).<sup>46</sup>

The combination of pertuzumab and trastuzumab does not appear to increase the risk of cardiotoxicity beyond that expected with trastuzumab alone.<sup>8</sup> Similarly, data suggest that lapatinib has a more-favorable cardiac risk profile than trastuzumab,<sup>7,47</sup> and the combination of both does not appear to be more cardiotoxic than the use of trastuzumab alone.<sup>6</sup> Trials of ado-trastuzumab suggest low rates of cardiotoxicity during follow-up to date.<sup>9</sup>

A summary of key trastuzumab trials, cardiac monitoring schema used in each trial, and reported rates of cardiotoxicity are provided in Table 2.

## Risk of Cardiotoxicity Outside of Clinical Trials

Experience outside of clinical trials suggests higher risks of cardiac toxicity associated with trastuzumab compared with that reported in clinical trials.<sup>50</sup> In a retrospective analysis of older women with early-stage breast cancer, compared with patients who did not receive either adjuvant chemotherapy or trastuzumab, use of trastuzumab alone or the combination of trastuzumab and anthracycline were associated with absolute increases in the adjusted incidence rate of HF or cardiomyopathy of 14% and 23.8%.<sup>51</sup> Similarly, in a retrospective analysis of women treated for metastatic breast cancer at the MD Anderson where 5% had a history of cardiovascular disease (CVD), 26.5% of those who received HER2 targeted therapies had symptomatic HF, which was reversible in the majority of cases.<sup>52</sup> Data from the health maintenance organization Cancer Research Network reported the cumulative incidence of HF at 1 and 5 years was 6.2% and 20.1% for women who received a combination of anthracycline and trastuzumab and 3.6% and 12.1% for women who received trastuzumab alone.<sup>50</sup> Such cumulative incidence increased significantly, with increasing age at cancer diagnosis being as high as 40.7% among women who were aged  $\geq 75$  years and received a combination of anthracycline and trastuzumab.<sup>49</sup> Importantly, there were significant differences in the number of comorbidities of each treatment group, which may reflect treatment selection biases by providers. The increased rates of cardiotoxicity in such observational studies likely reflect the use of trastuzumab in older populations with more-adverse cardiac risk profiles and reduced cardiac reserve.

## Risk Factors for Cardiotoxicity Associated With HER2 Targeted Therapy

Characteristics associated with increased risk of cardiotoxicity from trastuzumab use are summarized in Table 3. Past use of anthracyclines, especially at high cumulative doses ( $>250$  mg/m<sup>2</sup> of doxorubicin or  $>600$  mg/m<sup>2</sup> of epirubicin),<sup>53</sup> appears to be the most important risk factor for subsequent cardiac dysfunction.<sup>49</sup> In 1 retrospective analysis, past anthracycline use was the only significant predictor of trastuzumab-induced cardiotoxicity.<sup>54</sup> Additionally, concomitant use of anthracycline or short period (3 weeks versus 3 months) between anthracycline use and administration of trastuzumab appear to increase the risk of cardiac adverse events in some studies.<sup>14,55</sup> Given these observations, many cancer centers are now favoring chemotherapeutic regimens that do not contain anthracyclines when HER2 targeted therapies are used.<sup>56</sup>

In the N9831 trial, older age ( $\geq 60$  years), lower baseline LVEF, and use of antihypertensive medications were associated with increased risk of cardiotoxicity.<sup>48</sup> In a late follow-up of the

**Table 2.** Summary of Key Trastuzumab Trials Including Treatment Protocols, Strategies for Monitoring for Cardiac Dysfunction, and Reported Rates of Cardiac Adverse Events

Study	Study Arms	Monitoring Protocol		Rates of Cardiac Adverse Events
		Modality	Frequency	
Slamon et al, NEMJ, 2001 <sup>5</sup>	1. AC±Tras 2. Pac±Tras	Not specified	Not specified	NYHA class III or IV, or death from HF: 1. 3% vs 16% (with Tras) 2. 2% vs 1% (with Tras) Any cardiac dysfunction: 1. 8% vs 27% 2. 1% vs 13%
NSABP trial B-31 <sup>25,26,34-36</sup>	AC+Pac±Tras (concurrent with paclitaxel) for 1 y	MUGA	Study entry, after completion of doxorubicin and cyclophosphamide, and at 6, 9, and 12 mo after randomization	19% discontinued the medication for cardiac adverse events NYHA class III or IV, or death from HF: 0.8% vs 4.1% (with Tras)
NCCTG trial N9831 <sup>13,25,34,36,48</sup>	AC+Pac±Tras: 1. Sequential, for 1 y 2. Concurrent with Pac, for 1 y	MUGA or echocardiography	Study entry, after completion of doxorubicin and cyclophosphamide and at 6, 9, and 12 mo after randomization	NYHA class III or IV, or death from HF: 0.3% vs 2.8% (sequential Tras) vs 3.3% (concurrent Tras)
HERA trial <sup>12,27,37,49</sup>	Surgery+adjuvant and/or neoadjuvant chemotherapy (94% anthracycline; 26% taxane)±radiation±sequential Tras for: 1. 2 y 2. 1 y	MUGA or echocardiography	At baseline, 3, 6, 12, 18, 24, 30, 36, and 60 mo after randomization	Asymptomatic decrease in LVEF ≥10%, or to <50%: 2.2% vs 7.2 (Tras for 2 y) vs 4.1% (Tras for 1 y) Severe HF (NYHA class III or IV, or cardiac death): 0.1% vs 1.0% vs 0.8%
Neoadjuvant trastuzumab <sup>41,42</sup>	Pac+FEC±concurrent Tras for 24 wk before surgery	Echocardiography		0 symptomatic HF Asymptomatic decreases in LVEF ≥10%: 26% vs 16% (with Tras)
FinHER <sup>28</sup>	1. Docetaxel+FEC±concurrent Tras for 9 wk 2. Vinorelbine+FEC±concurrent Tras for 9 wk	Echocardiography or isotope cardiography	At baseline, after last FEC cycle, at 12 and 36 mo after chemotherapy	0% symptomatic HF in trastuzumab group >15% decrease in LVEF at any point: 6% vs 3.5%
PACS-04 <sup>40</sup>	1. FEC±sequential Tras for 1 y 2. ET±sequential Tras for 1 y	MUGA or echocardiography	At mo 1, 2, 5, 8, and 12 during trastuzumab administration, and at 6 mo and 5 y after completion of trastuzumab	Asymptomatic declined in LVEF >15% to <50%: 1. 14.1% vs 3.5% (with Tras) 2. 8% vs 1.6% (with Tras) Symptomatic HF: 1.5% vs 0.37% (with Tras)

Continued

**Table 2.** Continued

Study	Study Arms	Monitoring Protocol		Rates of Cardiac Adverse Events
		Modality	Frequency	
NOAH <sup>43</sup>	Neoadjuvant AC+Pac followed by methotrexate+fluorouracil±concurrent Tras followed by adjuvant Tras for 1 y	MUGA or echocardiography	At baseline, completion of doxorubicin+paclitaxel, completion of paclitaxel, before surgery, and end of trastuzumab treatment or 1 y from first dose of chemotherapy	Asymptomatic decrease in LVEF >10%: 17% vs 24.5% (with Tras) Symptomatic HF: 0% vs 1.7% (with Tras)
BCIRG006 <sup>45</sup>	1. ACT±concurrent Tras for 1 y 2. TCH	MUGA or echocardiography	LVEF assessment after doxorubicin+cyclophosphamide, after the second dose of docetaxel, at the end of chemotherapy, and 3, 12 and 36 mo after randomization	Asymptomatic decrease in LVEF >10%: 1. 11.2% vs 18.6% (with Tras) 2. 9.4% Grade 3 or 4 HF (According to NCI criteria): 1. 0.7% vs 2% (with Tras) 2. 0.4%
PHARE <sup>38,39</sup>	Standard chemotherapy (89% received anthracycline and 84% taxane)+6 mo of Tras±6 additional mo of Tras	MUGA or echocardiography	Every 3 mo during the first 2 y and then every 6 mo afterwards	Symptomatic or asymptomatic decrease in LVEF: 1.9% vs 5.7%
Tolaney et al, NEJM, 2015 <sup>29,46</sup>	Pac+Tras for 1 y	MUGA or echocardiography	At baseline, 12 wk, 6 mo, and 1 y	Symptomatic, grade 3 or 4 HF: 0.5% Asymptomatic decline in LVEF that lead to discontinuation of therapy: 3.2%

AC indicates doxorubicin+cyclophosphamide; ACT, doxorubicin+cyclophosphamide+docetaxel; HF, heart failure; FEC, fluorouracil, epirubicin, cyclophosphamide; LVEF, left ventricular ejection fraction; MUGA, Multigated Acquisition Scan; NCI, National Cancer Institute; NYHA, New York Heart Association; Pac, paclitaxel; TCH, docetaxel+carboplatin+trastuzumab; Tras, trastuzumab.



**Table 3.** Risk Factors for Cardiotoxicity From HER2 Targeted Therapies

High-Risk Characteristics
Anthracycline use
Heart failure
Asymptomatic systolic dysfunction at baseline (LVEF $\leq$ 50%)
Coronary artery disease
Atrial fibrillation/flutter
Hypertension
Diabetes mellitus
Obesity (BMI $\geq$ 30 kg/m <sup>2</sup> )
Dyslipidemia
Renal failure
Age $\geq$ 60 y

BMI indicates body mass index; HER2, human epidermal growth factor receptor-2; LVEF, left ventricular ejection fraction.

NSABP B-31 trial, older age and lower baseline LVEF (50–54%) were associated with trastuzumab-induced cardiotoxicity.<sup>11</sup> Risk of cardiotoxicity appears to increase progressively with increasing age in several studies.<sup>11,48,50,57</sup> Higher body mass index has also been shown to significantly increase the odds of cardiac dysfunction associated with anthracycline or sequential treatment with anthracycline and trastuzumab. In a meta-analysis of 15 studies, a body mass index  $>25$  or  $>30$  kg/m<sup>2</sup> was associated with 1.32 (95% CI, 1.06–1.80) and 1.47 (95% CI, 0.95–2.28) times the odds of cardiotoxicity compared with a normal body mass index.<sup>58</sup> Cardiac risk scores have been developed to predict the risk of cardiotoxicity associated with trastuzumab, including several risk factors such as age, hypertension, diabetes mellitus, coronary artery disease, atrial fibrillation or flutter, renal dysfunction, and use of adjuvant chemotherapy.<sup>11,57</sup> However, lack of prospective independent validation limits the use of such tools. Importantly, the risk associated with trastuzumab use in patients with pre-existing HF and systolic dysfunction is largely unknown.

Reports on the use of trastuzumab outside of clinical trials, in the “real-world” setting, have suggested similar risk factors for cardiotoxicity. Among older women exposed to trastuzumab, factors associated with a higher risk of HF included black race, history of CVD, diabetes mellitus, hypertension, and renal failure.<sup>51</sup> In the MD Anderson study, lower baseline LVEF and older age ( $\geq$ 60 years) were associated with increased risk of cardiotoxicity.<sup>52</sup>

## Pathophysiology

HER2 belongs to a family of tyrosine kinase transmembrane receptors (ErbB1-4) that regulate growth, differentiation, and

survival of cells. After ligand binding, ErbB receptors form homodimers or heterodimers, which activate tyrosine kinase function and recruit downstream effectors. Amplification or overexpression of the ErbB2 gene occurs in  $\approx$ 20% of breast cancer cases and is oncogenic.<sup>59</sup> In tumor cells, trastuzumab binds to the subdomain IV of the extracellular domain of HER2, which blocks HER2 cleavage, stimulating antibody-dependent cellular cytotoxicity and inhibiting HER2-mediated mitogenic signaling.<sup>60</sup>

The mechanisms underlying cardiotoxicity from use of trastuzumab are incompletely understood. It has been long known that ErbB2 is expressed in embryonic hearts and has a critical role in cardiac development<sup>61</sup> with relatively low expression in adult cardiomyocytes. Subsequent to the clinical trials showing cardiotoxicity from trastuzumab use, emerging research found that HER2 receptors expressed in the membranes of adult cardiomyocytes have an important role in transmitting growth and survival signals.<sup>62</sup> In response to the ligand, neuregulin-1, ErbB2 forms heterodimers that activate cell hypertrophy and survival pathways through activation of the phosphoinositide 3-kinase and protein kinase A pathways as well as the mitogen-activated protein kinase cascade.<sup>60,63</sup> In murine models, deletion of ErbB2 leads to development of spontaneous dilated cardiomyopathy and makes these mice more sensitive to triggers of cardiomyopathy such as pressure overload and anthracyclines.<sup>64,65</sup> Taken together, this evidence suggests an important role of ErbB2 in the maintenance of normal cardiac structure and function, especially under stress conditions.

A major risk factor for cardiotoxicity associated with trastuzumab is use of anthracycline-containing chemotherapy. Given the important protective role of ErbB2 in stress conditions, a “2-hit” model has been postulated as being responsible for the synergism between anthracycline and trastuzumab in causing cardiac dysfunction. In this model, anthracyclines activate cardiac stress pathways through several mechanisms that include generation of reactive oxygen species and oxidative damage of cardiomyocytes,<sup>66</sup> and inhibition of topoisomerase 2 $\beta$  leading to double-stranded breaks in DNA.<sup>67</sup> Concomitant ErbB2 inhibition disrupts cardioprotective and prosurvival signaling, diminishing the heart’s ability to tolerate noxious stimuli and recover.<sup>68–71</sup> Indeed, preclinical studies showed that activation of ErbB2 by recombinant neuregulin-1 protected cardiomyocytes from the myofibrillar disarray caused by anthracyclines,<sup>72</sup> whereas administration of an ErbB2 antibody increased susceptibility of myofilaments to doxorubicin.<sup>73</sup>

HER2 targeted therapies currently available have different mechanisms of action that might underlie the variable risks of cardiotoxicity. Ado-trastuzumab emtansine is a combination of trastuzumab with a cytotoxic agent that allows intracellular drug delivery that is specific to HER2-overexpressing cells and

**Table 4.** Recommendations for Surveillance for Cardiac Dysfunction According to Major Societies

Society	Modality of Choice	Frequency of Monitoring
American Society of Clinical Oncology (ASCO) <sup>53</sup>	<ol style="list-style-type: none"> <li>1. Echocardiography; MUGA or MRI if echocardiography is not available, with MRI preferred over MUGA</li> <li>2. Strain imaging and biomarkers (BNP, troponin) could be considered in conjunction with routine echocardiography.</li> </ol>	Frequency of surveillance should be determined by the provider based on patient’s clinical characteristics.
American Society of Echocardiography (ASE) and European Association of Cardiovascular Imaging (EACVI) <sup>17</sup>	<ol style="list-style-type: none"> <li>1. Echocardiography, ideally incorporating 3-dimensional imaging and global longitudinal strain</li> <li>2. Consider measuring high-sensitivity troponin in conjunction with imaging</li> </ol>	Every 3 mo during therapy.
European Society for Medical Oncology (ESMO) <sup>77</sup>	<ol style="list-style-type: none"> <li>1. Echocardiography or MUGA</li> <li>2. May consider MRI as an alternative</li> </ol>	Baseline, 3, 6, 9, 12, and 18 months after initiation of treatment. For patients with metastatic disease, obtain baseline measurement and only repeat if patient develops symptoms of HF.
European Society of Cardiology (ESC) <sup>20</sup>	<ol style="list-style-type: none"> <li>1. Echocardiography including 3-dimensional assessment of LVEF and global longitudinal strain</li> <li>2. MUGA and MRI may be considered as alternatives.</li> </ol>	Baseline, every 3 mo during therapy, and once after completion.
Canadian cardiovascular Society (CCS) <sup>76</sup>	<ol style="list-style-type: none"> <li>1. Echocardiography including 3-dimensional imaging and strain; MUGA and MRI as alternatives</li> <li>2. Consider concomitant measurement of biomarkers (BNP, troponin)</li> </ol>	No specific recommendation.
Trastuzumab Labeling	<ol style="list-style-type: none"> <li>1. Echocardiography or MUGA</li> </ol>	Baseline (immediately preceding initiation of trastuzumab), every 3 mo during and upon completion of therapy, and at every 6 mo for at least 2 y following completion of therapy.

BNP indicates brain natriuretic peptide; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; MUGA, multigated acquisition.

is therefore associated with low rates of cardiotoxicity.<sup>9</sup> Pertuzumab is a similar antibody to trastuzumab, but binds to a different HER2 epitope, subdomain II. After binding, it prevents its dimerization with HER3, which causes similar activation of antibody-dependent cellular cytotoxicity and prevention of HER2 downstream signaling.<sup>74</sup> Because trastuzumab and pertuzumab bind to different receptor subdomains, they have complementary mechanisms of action and clinical synergism without increased cardiotoxicity.<sup>8,75</sup> Lapatinib is an oral small molecule that inhibits the tyrosine kinases of HER2 and epidermal growth factor receptor type 1 (HER1). Clinical studies have not demonstrated significant cardiotoxicity associated with use of lapatinib.<sup>7,47</sup>

### Monitoring for Cardiac Dysfunction During HER2-Targeted Therapy

The ideal modality, frequency, and duration of monitoring for cardiac dysfunction during HER2 targeted therapy are unknown. Table 4 summarizes the published recommendations by major societies.<sup>17,20,53,76,77</sup> Clinical trials have used

various monitoring protocols, including echocardiography or multigated acquisition (MUGA) scan, none of which has been prospectively validated. Despite that, routine cardiac monitoring with either echocardiogram or MUGA is recommended in the labeling of trastuzumab.

Echocardiography is currently recommended as the modality of choice for routine monitoring and detection of cardiac dysfunction.<sup>17,53</sup> Volumetric assessment of LVEF using 3-dimensional echocardiography provides a more-accurate and reproducible measurement of LVEF than 2-dimensional echocardiography; however, this method is not available at all centers. The biplane method of disks (modified Simpson’s rule) is recommended for calculation of LVEF when 2-dimensional echocardiography is the modality of choice.<sup>17</sup> Assessment of LVEF by MUGA has higher accuracy and reproducibility than 2-dimensional echocardiography.<sup>78</sup> Limitations to the routine use of MUGA include patient exposure to radiation, lack of detailed information on right ventricular function, atrial size, valvular, or pericardial disease. Cardiac magnetic resonance is the references standard in the evaluation of cardiac volumes, mass, and function, with high

inter- and intraobserver reproducibility.<sup>79,80</sup> However, its use is limited because of lesser availability and elevated operational costs. This method can be particularly helpful when echocardiographic images are suboptimal, or when LVEF assessed by other methods is borderline and discontinuation of cancer therapy is being entertained.<sup>17,81</sup>

A growing body of research is investigating methods for early detection of subclinical cardiotoxicity that would allow for early implementation of therapies to prevent overt cardiac dysfunction and HF. Assessment of LVEF alone by either method appears insensitive to detect subclinical changes and predict subsequent cardiotoxicity. Decreases in myocardial deformation (strain) precede changes in LVEF and have been consistently predictive of cardiac dysfunction from trastuzumab.<sup>82,83</sup> The American Society of Echocardiography recommends global longitudinal strain measured by speckle tracking echocardiography as the modality of choice for detection of subclinical myocardial changes and risk prediction.<sup>17</sup> A decrease of <8% from baseline is likely insignificant, whereas a relative drop of more than 15% is likely pathological.<sup>82</sup> Importantly, there have been no studies assessing whether interventions based on changes in strain alter outcomes.

The prognostic value of several cardiac biomarkers has also been evaluated, yielding conflicting results. Cardiac troponins are well-established markers of myocardial injury and appear to correlate best with incident cardiac dysfunction following chemotherapy. Three studies have reported that elevated and increasing troponin I following chemotherapy, particularly if such increase persists at 1 month after treatment,<sup>84</sup> is associated with subsequent cardiac dysfunction as well as with lower likelihood of cardiac recovery in patients receiving trastuzumab.<sup>85–87</sup> During treatment, negative cardiac troponin has a high negative predictive value; however, minute elevations can be commonly detected in patients following chemotherapy and have low positive predictive value.<sup>88</sup> Additionally, optimal timing and frequency of measurement as well as the ideal cutoff have not yet been determined. An integrated approach using strain imaging and high-sensitivity troponin may provide incremental value in predicting subsequent cardiac dysfunction, but needs further investigation.<sup>83</sup> The recently published guidelines from the American Society of Clinical Oncology gives a moderate strength of recommendation for routine use of biomarkers and echocardiographic-derived strain imaging for surveillance of cardiotoxicity, citing intermediate quality of evidence.<sup>53</sup> Baseline N-terminal pro-B-type natriuretic peptide, a marker of hemodynamic stress, high-sensitivity C-reactive protein and growth differentiation factor-15, markers of inflammation and oxidative stress, placental growth factor, a marker of angiogenesis, galectin-3, a marker of fibrosis, soluble fms-like tyrosine kinase receptor-1, and others, have not shown significant association with future cardiac dysfunction.<sup>83,85</sup> Increases in N-terminal pro-B-type natriuretic

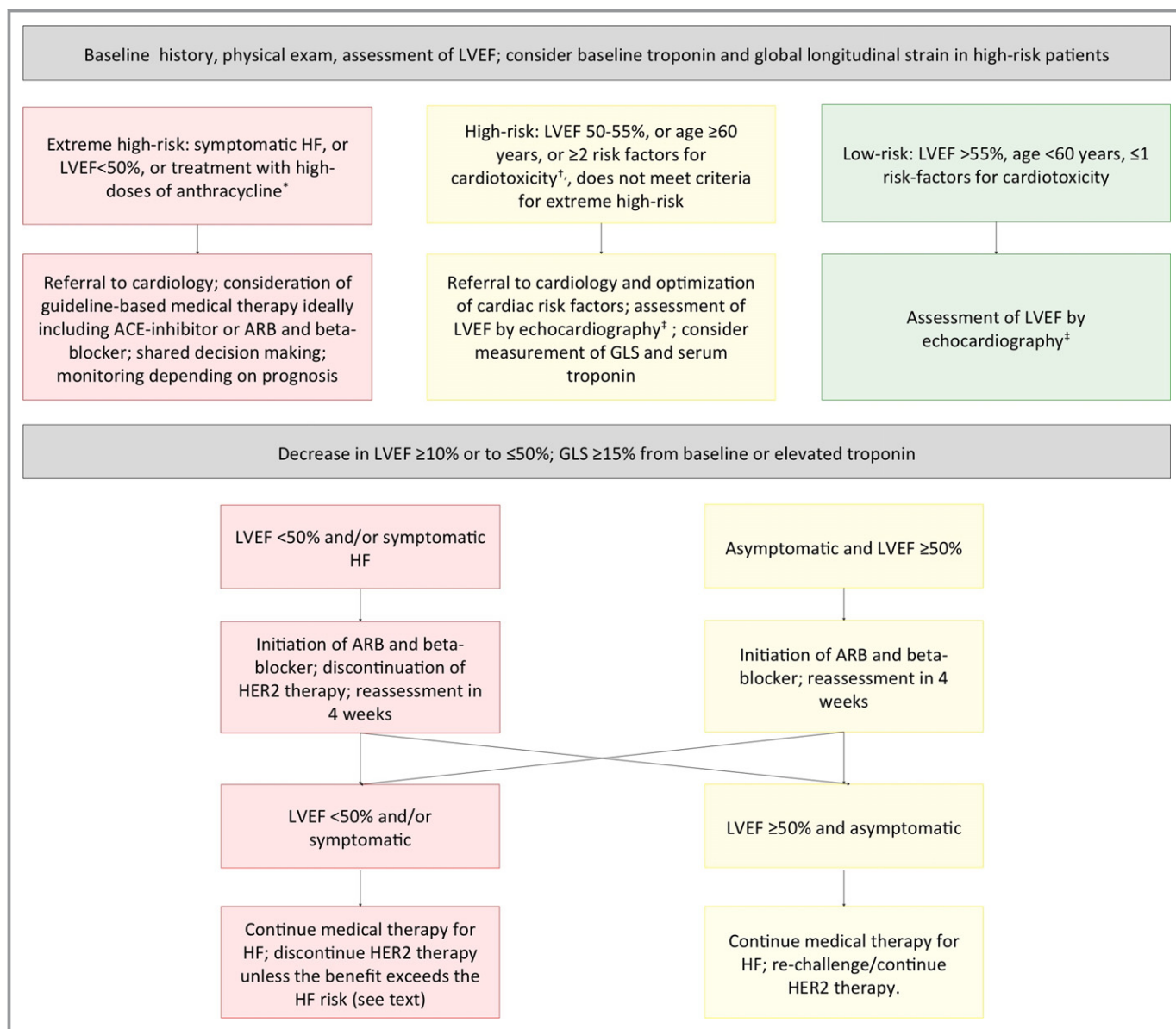
peptide over time appear to correlate with changes in cardiac function; however, no thresholds have been established.<sup>87</sup>

## Prevention and Treatment of Cardiotoxicity Associated With HER2 Targeted Therapy

Observational studies and small randomized clinical trials suggest a benefit in early initiation of angiotensin-converting enzyme inhibitors and beta-blockers for the prevention of cardiotoxicity.<sup>15,89–93</sup> The PRADA (Prevention of Cardiac Dysfunction During Adjuvant Breast Cancer Therapy) trial tested whether angiotensin receptor blockers and/or beta-blockers would be effective in preventing cardiotoxicity in patients diagnosed with breast cancer receiving anthracycline-based chemotherapy with and without trastuzumab. The study showed modest benefit of candesartan, but not metoprolol, in preventing LVEF reduction assessed by magnetic resonance imaging<sup>94</sup>; however, neither medication was effective in preventing increases in high-sensitivity troponin, a marker of subclinical myocardial injury. A more-recent randomized controlled trial failed to reproduce such beneficial effects of candesartan in patients treated with trastuzumab.<sup>95</sup> Another small trial reported modest benefit of bisoprolol and perindopril in preventing cardiac dysfunction, but not remodeling, associated with trastuzumab use.<sup>96</sup> The ongoing SAFEHEART (Spanish Familial Hypercholesterolaemia Cohort Study) study is testing whether administration of various HER2 targeted therapies is safe among patients with mild systolic dysfunction (LVEF 40–50%) who are on appropriate HF medical therapy.<sup>97</sup> At this time, there are insufficient data to recommend routine preventive use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or beta-blockers for patients receiving HER2 targeted therapies. Screening for and optimizing management of CVD risk factors (eg, smoking, hypertension, obesity, etc) is currently recommended as part of efforts to prevent cardiotoxicity; however, the impact of such measures on cardiotoxicity has not been evaluated.<sup>53</sup>

Management of cardiac adverse events associated with HER2 targeted treatment varied across clinical trials and different strategies have not been compared to one another. In most studies, following development of cardiac dysfunction, HER2 targeted therapy was temporarily discontinued for 4 weeks and initiation of guideline-directed medical therapy was left at the discretion of managing providers. Partial or complete recovery was observed in the majority of cases and following recovery of systolic function most patients tolerated restarting the HER2 targeted medication. Whether discontinuation of the HER2 targeted therapy is at all necessary is not known, but could have important implications on cancer related outcomes. In one study, interruption of trastuzumab treatment was common after diagnosis of asymptomatic cardiac dysfunction and resulted in lower cumulative doses of





**Figure.** Proposed algorithm for risk stratification, monitoring, and management of cardiotoxicity during therapy with trastuzumab. \* $>250$  mg/ $m^2$  of doxorubicin or  $>600$  mg/ $m^2$  of epirubicin. †Refer to Table 3. ‡Assessment of LVEF at baseline, every 3 months during the first year of therapy, every 6 months during the second year of therapy, and once after completion. ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; GLS, global longitudinal strain; HER2, human epidermal growth factor receptor-2; HF, heart failure; LVEF, left ventricular ejection fraction.

the medication.<sup>98</sup> Tripathy et al reported that in the trastuzumab pivotal trial published in 2001,<sup>5</sup> 33 patients continued to receive trastuzumab therapy for a median of 26 weeks after development of cardiac dysfunction, and the cardiac status of 28 (85%) either improved or remained stable.<sup>99</sup> However, not all cases of cardiotoxicity associated with the use of the trastuzumab are reversible. In the BCIRG006, of 194 patients randomized to doxorubicin+cyclophosphamide+docetaxel+trastuzumab who had a decline of at least 10% in LVEF, the decrease persisted for at least 4 years in 33%.<sup>45</sup> Even in the absence of anthracycline use,

persistent declines in LVEF following trastuzumab administration have been reported.<sup>46</sup> Further research is needed to help identify patients at high risk for persistence of left ventricular dysfunction for whom discontinuation of the antibody and more-aggressive therapeutic interventions may be advised.

### Recommendations

Although several guideline groups, including the American Society of Echocardiography, the American Society of Clinical

Oncology, the Heart Failure Association of the European Society of Cardiology (ESC), the European Society of Cardiology, and the European Society of Medical Oncology, have published recommendations and consensus statements for the diagnosis and management of cardiotoxicity from cancer therapies,<sup>17,20,53,68,77</sup> no widely accepted international guidelines are available. In the United States, neither the American Heart Association nor the American College of Cardiology have published specific recommendations.

The authors of this review suggest that all patients diagnosed with HER2-positive breast cancer who will be receiving HER2 targeted therapies have a baseline assessment of the risk of cardiotoxicity (Figure). Such evaluation should include a thorough history and physical exam focused on identification of existing CVD risk factors and established CVD, as well as predictors of trastuzumab cardiotoxicity such as age and anthracycline use. Use of risk scores has not been prospectively validated, but could facilitate risk/benefit assessment and discussions between patients and providers.

We recommend that all patients have their LVEF assessed by echocardiography at baseline. Assessment of LVEF should be done with 3-dimensional echocardiography, or using the 2-dimensional biplane Simpson's method when the first is not available. MUGA is an acceptable alternative when echocardiography is not available, but providers should be mindful of the potential harms of repeated exposure to radiation. At this time there are insufficient data to suggest additional benefit from routine use of magnetic resonance imaging for assessment of cardiac function; however, this method should be considered when echocardiographic images are suboptimal, or if the LVEF as assessed by echocardiography is borderline and discontinuation of therapy is being considered. Repeat assessment of LVEF should be carried every 3 months during the first year of therapy, every 6 months during the second year of therapy, once after completion of therapy, and when clinically indicated thereafter. Measurement of global longitudinal strain by speckle tracking echocardiography and serum troponin may be considered for high-risk patients in combination with imaging at baseline and during follow-up.<sup>17</sup>

We recommend lifestyle modification to all patients as well as optimization of medical management of CVD risk factors. Weight gain is common following the diagnosis of breast cancer and associated with poor outcomes.<sup>100</sup> Counseling on weight loss, avoidance of weight gain, and routine physical activity may have a particularly important role in this population. If patients with pre-existing CVD or baseline low LVEF (<50%) are not already on an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, and a beta-blocker, initiation should be considered.

We suggest initiation of an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker followed by a beta-blocker for any evidence of significant cardiac injury,

including: asymptomatic decrease in LVEF  $\geq 10\%$  or to  $\leq 50\%$ , or a relative change in global longitudinal strain  $\geq 15\%$ . The treating oncologist and cardiologist should collaborate to determine the course of care, but in most cases it is appropriate to temporarily discontinue HER2 targeted therapy if LVEF decreases to  $< 50\%$  or if the patient develops symptoms of HF. Rechallenge may be considered if there is partial or complete recovery on repeat assessment of cardiac function at 4 weeks.

There are no data on the ideal strategy for management of patients with pre-existing cardiac conditions or with persistent left ventricular dysfunction despite discontinuation of therapy. Patients and providers should engage in a careful review of the possible risks and benefits of starting/continuing trastuzumab versus progressive cardiac dysfunction in a shared decision-making process. The balance might favor continued therapy with the monoclonal antibody among those with advanced breast cancer, whereas the decision might be more difficult for patients with early stages of the disease. There are several factors to consider in this decision, for example: (1) the degree of cardiac dysfunction; (2) whether there is further reduction in ejection fraction with continued therapy after the initiation of HF medical therapy; (3) the degree of HF symptoms; and (4) the risk of cancer progression. The results of the ongoing SAFEHEART trial are expected to help inform this decision.

Close collaboration between oncologists and cardiologists is key for successful prevention and management of cardiotoxicity from cancer therapies. We suggest that high-risk patients, especially those with pre-existing CVD, and patients who develop cardiac dysfunction be referred for consultation with a cardiologist, ideally someone with cardio-oncology expertise. Clinical decisions about discontinuation of therapy ought to be informed by both providers and shared with patients, in a collaborative process.

## Conclusions

Trastuzumab has contributed to significant improvements in outcomes of patients with HER2-positive breast cancer over the past 15 years. The addition of the monoclonal antibody, trastuzumab, is associated with 20% and 34% improvements in overall survival of patients with metastatic and locally advanced disease, and recent evidence suggests improved outcomes in patients with early, node-negative malignancies. Trastuzumab is associated with increased rates of symptomatic and asymptomatic cardiac dysfunction, particularly if administered in older patients, those with pre-existing CVD risk factors or CVD, and those receiving anthracycline-based chemotherapy. Such risk can be significantly mitigated by the use of less-cardiotoxic chemotherapeutic regimens, preferentially without concomitant anthracyclines. Novel HER2

targeted therapies appear to have a more-favorable cardiac risk profile. Overall, the large benefits of HER2 targeted therapies in patients with HER2-positive breast cancer justify its use in most patients with cautious monitoring for cardiotoxicity. Research is needed to guide management of patients with pre-existing CVD or other risk factors.

## Disclosures

None.

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**Key Words:** breast cancer • cardiotoxicity • heart failure  
• human epidermal growth factor-2 • trastuzumab