

## ORIGINAL RESEARCH

# Cardiotoxicity Surveillance and Risk of Heart Failure During HER2 Targeted Therapy



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**ABSTRACT**

**BACKGROUND** Guidelines recommend left ventricular ejection fraction (LVEF) assessments every 3 months for cardiotoxicity monitoring during human epidermal growth factor receptor 2 (HER2) targeted therapy. Evidence in support of this practice is lacking.

**OBJECTIVES** This study examines the association between adherence to cardiotoxicity surveillance guidelines and heart failure (HF) in HER2-positive breast cancer patients.

**METHODS** A case-control study was performed in 53 patients who developed cardiotoxicity during HER2 targeted therapy, and 159 controls matched by age, anthracycline exposure, and year of treatment. Cardiotoxicity was defined as HF (New York Heart Association functional class III or IV) or cardiac death. Adherence to cardiotoxicity surveillance guidelines was ascertained from the beginning of HER2 targeted therapy to the diagnosis date of HF for cases or the corresponding timepoint for matched controls. Conditional logistic regression was used for case-control comparisons.

**RESULTS** Eighty-one percent of cases and controls were previously treated with an anthracycline. Adherence to cardiotoxicity surveillance guidelines during the entire observation period or during the first 6 months of treatment was not associated with lower risk of HF. An LVEF <55% at any surveillance timepoint was identified in 49% of cases and 3% of controls, and an LVEF <55% during the final surveillance timepoint before developing HF was identified in 54% of cases and 4% of controls. In multivariable-adjusted analyses, LVEF <55% at any timepoint or during the final surveillance timepoint (odds ratio: 27.0; 95% confidence interval: 9.3 to 78.8 and odds ratio: 25.6; 95% confidence interval: 7.3 to 90.3, respectively) was associated with HF.

**CONCLUSIONS** Patients with LVEF <55% on routine surveillance during HER2 targeted therapy are at increased risk for HF. Additional studies to define their optimal management are warranted. (J Am Coll Cardiol CardioOnc 2020;2:166-75)

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Left ventricular ejection fraction (LVEF) is an important imaging biomarker used for the screening and diagnosis of cardiotoxicity associated with cancer therapy. In cardio-oncology, LVEF measurements are used to determine a patient's eligibility to initiate and continue widely used breast cancer treatment regimens containing anthracyclines and/or targeted human epidermal growth factor receptor 2 (HER2) therapy.

Cardiotoxicity, manifesting as heart failure (HF) or LVEF decline, is the most frequent cause of premature treatment interruption or discontinuation of sequential anthracycline chemotherapy followed by HER2 targeted therapy (1). The reported incidence of HF associated with this regimen ranges from 2% to 4%, whereas asymptomatic LVEF declines occur more frequently in up to 19% of patients (2,3). In the clinical trial setting, routine cardiac surveillance with echocardiograms or radionuclide ventriculography was required at baseline and every 3 months during trastuzumab administration (3,4). In these studies, a significant reduction in LVEF, defined using various criteria including a decrease of 10 or more absolute percentage points to below the lower limit of normal or an absolute decrease of 16 or more percentage points, prompted an interruption in treatment until the LVEF improved. However, there are no published data to show that routine LVEF surveillance during HER2 targeted therapy leads to improved cardiac safety or reduced risk of treatment-induced HF. Despite this gap in knowledge, routine LVEF surveillance during HER2 targeted therapy has been adopted into clinical practice as the standard of care and is endorsed by several clinical practice guidelines (5-8).

The primary objective of this study was to determine if there is an association between adherence to current guidelines for routine LVEF surveillance during HER2 targeted therapy and treatment-induced HF. In this case-control study, we focused exclusively on cases of severe cardiotoxicity defined by New York Heart Association (NYHA) functional class III or IV HF or cardiac death during HER2 targeted therapy because of the clear clinical significance of these events on cardiac- and cancer-related outcomes. Any data on the association between LVEF surveillance and HF would inform future efforts to improve upon the current strategy of cardiotoxicity surveillance.

## METHODS

**DESIGN AND SETTING.** This was a case-control study of female patients age 18 years or older receiving trastuzumab-based treatment for HER2-

positive breast cancer (stage I to IV) at Memorial Sloan Kettering Cancer Center between 2005 and 2015. To evaluate the association between cardiac surveillance and risk for HF, the adherence to routine LVEF assessments (every 3 months) was compared between patients who developed HF or cardiac death during trastuzumab-based treatment (cases) versus matched patients who completed trastuzumab-based treatment without severe cardiotoxicity (controls). The study was approved by the institutional review board of Memorial Sloan Kettering Cancer Center.

## CASE PATIENT DEFINITION AND CONTROL PATIENT SELECTION.

Case patients included in this study were women who developed severe cardiotoxicity during trastuzumab-based treatment, defined as an event meeting one of the following criteria: 1) HF symptoms such as dyspnea, decreased exercise tolerance, or fatigue during less than ordinary activity or at rest (NYHA functional class III or IV), with evidence of new or worsening HF on physical examination (e.g., peripheral edema, crackles, increased jugular venous pressure, or rapid weight gain related to fluid retention) or diagnostic testing (e.g., increased B-type natriuretic peptide, pulmonary congestion on chest x-ray, or abnormal left ventricular systolic function); or 2) cardiac death. Case patients were identified through one of the following mechanisms: 1) review of the institutional echocardiogram database for patients receiving trastuzumab with an LVEF <55%; 2) review of pharmacy administration data to identify patients with an interruption or discontinuation of trastuzumab; 3) review of laboratory data for elevated B-type natriuretic peptide >100 pg/ml (9); 4) review of institutional billing data for 2 outpatient or 1 inpatient International Classification of Diseases-9th revision codes for HF (402.01, 402.11, 402.91, 404.01, 404.11, 404.91, 404.93, and 428.x) or cardiomyopathy (425.x) (10); or 5) review of an institutional database containing cardiotoxicity outcomes from all breast cancer patients treated with adjuvant trastuzumab at our institution from 2005 to 2010, as previously described (11). The medical records of all 53 cardiotoxicity cases were independently reviewed by 2 cardiologists (A.F.Y., J.Y.) to confirm that each met the criteria for severe cardiotoxicity. Each case patient was individually matched to 3 control patients according to age strata at the time of cancer treatment (<35, 35 to 39, 40 to 44, 45 to 49, 50 to 54, 55 to 59, 60 to 64, 65 to 69, 70 to 74, and ≥75 years), current or prior treatment with

## ABBREVIATIONS AND ACRONYMS

<b>BMI</b>	= body mass index
<b>CI</b>	= confidence interval
<b>HER2</b>	= human epidermal growth factor receptor 2
<b>HF</b>	= heart failure
<b>IQR</b>	= interquartile range
<b>LVEF</b>	= left ventricular ejection fraction
<b>NYHA</b>	= New York Heart Association
<b>OR</b>	= odds ratio

anthracycline chemotherapy (yes vs. no), and year of breast cancer treatment ( $\pm 1$  year). The electronic medical record was reviewed to confirm that all control patients were free of HF symptoms during the trastuzumab treatment period.

**DATA COLLECTION.** Electronic medical records were reviewed for each eligible case and control patient, and a standard form was used to abstract the following data: age at treatment, sex, body mass index (BMI), race, and cancer treatment regimen. Other variables collected at the time of initiation of HER2 targeted therapy included the following: cardiovascular risk factors (hypertension, hyperlipidemia, diabetes, and tobacco use), concomitant cardiovascular medications (beta-blockers, angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), and calcium channel blockers), and history of cardiovascular disease (coronary artery disease, arrhythmia, or cardiomyopathy). Three consecutive systolic and diastolic blood pressure measurements obtained after the initiation of HER2 targeted therapy were averaged.

**EXPOSURES.** Data from all cardiac imaging studies (i.e., echocardiogram, multigated acquisition scan, or cardiac magnetic resonance imaging) performed at our institution as well as externally were collected from the medical record, and the frequency and timing of routine surveillance LVEF assessments during HER2 targeted therapy were ascertained. Any cardiac imaging study that was ordered for the diagnostic workup of a patient presenting with signs/symptoms of HF or performed after the diagnosis date of HF was not considered to be a surveillance study and was censored. For case patients, the time window of exposure to LVEF surveillance tests (hereafter referred to as the “observation period”) began 6 months before the start date of trastuzumab treatment and ended on the date of HF or death. The length of the observation period for each control patient was matched to the corresponding case patient to ensure equal time windows of exposure to LVEF surveillance for both groups. Among controls, any LVEF assessment performed after the corresponding date of HF or cardiac death in the matched case patient was excluded. The rate of cardiac surveillance was calculated as the proportion of subjects (cases or controls) at risk for cardiotoxicity who underwent a surveillance LVEF assessment at a specific timepoint.

Based on current clinical practice guidelines which recommend LVEF assessments every 3 months during targeted HER2 treatment, patients were considered adherent if the following 2 conditions were met: 1) an LVEF assessment was performed up to 6 months

before trastuzumab treatment; and 2) a follow-up LVEF assessment was performed during each 3-month interval ( $\pm 45$  days) after the initiation of trastuzumab. LVEF assessments performed before the initiation of anthracycline chemotherapy were not included in the criteria for adherence. A 45-day window was included to account for differences in scheduling and/or patient availability to undergo cardiotoxicity surveillance in the real-world setting. Adherence as a categorical variable was ascertained for the following timepoints: 1) during the entire observation period; 2) during the first 6 months of the observation period; and 3) during the last 3-month interval of the observation period, corresponding to the 3-month interval immediately preceding the HF or cardiac death event for case patients. Given the uncertain clinical significance of an asymptomatic LVEF decline during HER2 targeted therapy, we also identified patients with an abnormal LVEF ( $<55\%$ ) detected during routine surveillance at the following timepoints: 1) at any time during the observation period, or 2) during the last 3-month interval of the observation period.

**STATISTICAL ANALYSIS.** Continuous measures are summarized as mean  $\pm$  SD or median (interquartile range [IQR]) and categorical measures as frequency and percentage. Conditional logistic regression was used to estimate the unadjusted odds ratios (ORs) and 95% confidence intervals (CIs) for the association between patient characteristics and case-control status. Conditional logistic regression models were fit to estimate the association between LVEF surveillance and HF, adjusting for significant factors from the univariable analysis at a p value threshold of  $<0.10$ . Covariates in the final multivariable model included pre-trastuzumab LVEF and BMI as continuous variables and the following categorical variables: stage of disease (local versus metastatic), race (white, black, or other), hypertension, and treatment with a calcium channel blocker or statin. Firth’s penalized likelihood logistic regression was used to evaluate the association between abnormal surveillance LVEF  $<55\%$  and HF due to the low prevalence of an abnormal surveillance LVEF  $<55\%$  among the control group, adjusting for case-control matching factors, BMI, stage of disease, race, hypertension, and treatment with a calcium channel blocker or statin. Only patients who underwent a routine LVEF surveillance assessment during the last 3-month interval of the observation period were considered in the analysis of LVEF  $<55\%$  (during the last 3-month interval of the observation period) and HF. A p value of  $<0.05$  was considered significant. All statistical analysis was

performed in Stata 15.1 (StataCorp, College Station, Texas).

**RESULTS**

**PATIENT CHARACTERISTICS.** A total of 212 patients (53 cases and 159 matched controls) were included in this study. **Table 1** shows the characteristics of the study sample by case-control status. The median age at the time of breast cancer treatment among the cases was 57 years, and 81% had previously been treated with anthracycline chemotherapy. Controls were well matched to cases on these variables as shown in **Table 1**. Cases, compared to controls, had a higher BMI (median 29.7 kg/m<sup>2</sup> vs. 26.9 kg/m<sup>2</sup>, OR: 1.05; 95% CI: 1.0 to 1.1) and were more likely to be black (40% vs. 14%, OR: 4.5 (relative to white); 95% CI: 2.0 to 10.1).

Among patients who were treated with sequential anthracyclines and trastuzumab, the median (IQR) LVEF before beginning anthracycline chemotherapy was 60% (IQR: 58% to 65%) among cases versus 66% (IQR: 63% to 70%) among controls. For all patients, the median LVEF before beginning trastuzumab was 60% (IQR: 55% to 65%) among cases compared to 66% (IQR: 62% to 69%) among controls. A higher LVEF before trastuzumab treatment was associated with lower risk for cardiotoxicity, with an OR of 0.3 (95% CI: 0.1 to 0.5) for every 10-point increase in LVEF. Hypertension (49% vs. 32%, OR: 2.7; 95% CI: 1.2 to 5.7) and treatment with a calcium channel blocker (19% vs. 8%, OR: 3.2; 95% CI: 1.2 to 8.6) were more prevalent among the cases compared to controls. Presence of other cardiovascular risk factors including diabetes, hyperlipidemia, coronary artery disease, arrhythmia, and tobacco use were not significantly different between cases and controls. Similar percentages of case and control patients were treated with beta blockers, ACEIs or ARBs, aspirin, and statins before beginning HER2 targeted therapy. There was no significant difference in systolic or diastolic blood pressure between cases or controls measured at the time of trastuzumab initiation.

Among the cases, criteria for cardiotoxicity included NYHA functional class III or IV HF in 52 patients (2 with preserved LVEF ≥50%; 10 with mid-range LVEF 40% to 49%; 40 with reduced LVEF <40%) and HF-related death in 1 patient. The median (IQR) time interval between the start date of HER2 targeted therapy and the diagnosis of cardiotoxicity was 159 (IQR: 94 to 242) days. HER2 targeted therapy was discontinued in 51 of 53 cases

<b>TABLE 1 Patient Characteristics</b>				
	<b>Cases (n = 53)</b>	<b>Controls (n = 159)</b>	<b>Unadjusted OR (95% CI)</b>	<b>p Value</b>
Age at BCA treatment, yrs	57 (49-65)	59 (49-64)	—	—
Age at BCA treatment, yrs			—	—
<45	9 (17)	27 (17)		
45-54	12 (23)	36 (23)		
55-64	20 (38)	60 (38)		
≥65	12 (23)	36 (23)		
Anthracycline treatment			—	—
Yes	43 (81)	129 (81)		
No	10 (19)	30 (19)		
BMI, kg/m <sup>2</sup>	29.7 (25.8-33.4)	26.9 (23.6-31.0)	1.05 (1.0-1.1)	0.037
Radiotherapy				0.127
Yes	31 (58)	111 (70)	0.6 (0.3-1.2)	
No	22 (42)	48 (30)	1.0	
Metastatic				0.087
Yes	11 (21)	18 (11)	2.1 (0.9-5.0)	
No	42 (79)	141 (89)	1.0	
Race				<0.001
Other	1 (2)	10 (6)	0.4 (0.0-3.3)	
Black	21 (40)	22 (14)	4.5 (2.0-10.1)	
White	31 (58)	127 (80)	1.0	
Pre-trastuzumab LVEF, %	60 (55-65)	65.5 (62-69)	0.3 (0.1-0.5)*	<0.001
Pre-trastuzumab LVEF, %			—†	—
<55	10 (19)	0 (0)		
55-64	26 (49)	59 (37)		
≥65	13 (25)	75 (47)		
Not performed	4 (8)	25 (16)		
Pre-trastuzumab systolic BP, mm Hg	125 (115-135)	122.5 (112-133)	1.0 (1.0-1.0)	0.243
Pre-trastuzumab diastolic BP, mm Hg	76 (71-81)	73 (69-79)	1.0 (1.0-1.1)	0.235
Hypertension				0.010
Yes	26 (49)	51 (32)	2.7 (1.2-5.7)	
No	27 (51)	108 (68)	1.0	
Diabetes				0.102
Yes	10 (19)	16 (10)	2.1 (0.9-5.1)	
No	43 (81)	143 (90)	1.0	
Hyperlipidemia				0.409
Yes	11 (21)	41 (26)	0.7 (0.3-1.6)	
No	42 (79)	118 (74)	1.0	
CAD				0.747
Yes	1 (2)	2 (1)	1.5 (0.1-16.5)	
No	52 (98)	157 (99)	1.0	
Arrhythmia				0.283
Yes	2 (4)	2 (1)	3.0 (0.4-21.3)	
No	51 (96)	157 (99)	1.0	
Smoking				0.189
Current	4 (8)	3 (2)	3.9 (0.9-17.6)	
Former	16 (30)	54 (34)	0.9 (0.5-1.7)	
Never	33 (62)	102 (64)	1.0	
Beta-blocker				0.190
Yes	9 (17)	17 (11)	2.0 (0.7-5.4)	
No	44 (83)	142 (89)	1.0	
ACEI/ARB				0.556
Yes	13 (25)	33 (21)	1.3 (0.6-27.0)	
No	40 (75)	126 (79)	1.0	

Continued on the next page

TABLE 1 Continued				
	Cases (n = 53)	Controls (n = 159)	Unadjusted OR (95% CI)	p Value
CCB				0.021
Yes	10 (19)	12 (8)	3.2 (1.2-8.6)	
No	43 (81)	147 (92)	1.0	
Aspirin				0.798
Yes	5 (9)	17 (11)	0.9 (0.3-2.4)	
No	48 (91)	142 (89)	1.0	
Statin				0.094
Yes	7 (13)	37 (23)	0.5 (0.2-1.2)	
No	46 (87)	122 (77)	1.0	

Values are median (interquartile range) or n (%), unless otherwise indicated. Percentages in the table may not add to 100% given rounding. \*ORs are reported for the effect of a 10% absolute change in LVEF. †Testing for differences between cases and controls was not performed due to the small sample size.

ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin II receptor blocker; BCA = breast cancer; BMI = body mass index; BP = blood pressure; CAD = coronary artery disease; CCB = calcium channel blocker; CI = confidence interval; LVEF = left ventricular ejection fraction; OR = odds ratio.

(96%). Of the remaining 2 cases, 1 patient who developed HF after receiving the final planned dose of trastuzumab and 1 patient with metastatic disease who developed HF with preserved LVEF were allowed to continue trastuzumab without interruption. Only 3 case patients were re-challenged with trastuzumab after HF recovery. During the same observation period, HER2 targeted therapy was discontinued due to asymptomatic LVEF declines in 3 of 159 controls (2%), of which 1 patient was re-challenged with trastuzumab after improvement of LVEF.

**CARDIOTOXICITY SURVEILLANCE DURING HER2 TARGETED THERAPY.** Overall, the rates of cardiac surveillance during the observation period were similar between cases and controls (**Central Illustration**). Thirty-seven of 43 (86%) cases and 117 of 129 (91%) controls underwent a surveillance LVEF assessment before initiation of anthracyclines, and 49 of 53 (92%) cases and 134 of 159 (84%) controls underwent a surveillance LVEF before beginning trastuzumab. The rate of cardiac surveillance decreased to 59% (22 of 37) for cases and 67% (74 of 111) for controls at month 3 and 59% (13 of 22) for cases and 70% (46 of 66) for controls at month 6. The median LVEF decreased from 60% (IQR: 55% to 65%) before trastuzumab to 50% (IQR: 43% to 55%) at month 6 in the case patients but remained overall stable from 66% (IQR: 62% to 69%) before trastuzumab to 64% (IQR: 60% to 68%) at month 6 in the control patients.

**ASSOCIATION BETWEEN CARDIOTOXICITY SURVEILLANCE AND HF.** Overall, 62% (33 of 53) of cases and 58% (92 of 159) of controls adhered to cardiotoxicity surveillance guidelines during the entire observation period.

There was no association between adherence and HF (OR: 1.2; 95% CI: 0.4 to 3.9). Among the 53 cases, the median (IQR) time interval from the final surveillance LVEF to the HF event was 86 (IQR: 41 to 133) days, and the median time from the last normal LVEF (>55%) to the HF event was 129 (IQR: 88 to 193) days. Twelve of 53 (23%) cases did not undergo a routine LVEF assessment during the final 3-month surveillance interval of the observation period before developing HF. The proportion of control patients who did not undergo a routine LVEF assessment during the final 3-month interval of the observation period was similar to the cases (46 of 159 [29%]). There was no association between adherence to LVEF surveillance during the first 6 months or last 3 months (i.e., final surveillance timepoint) of the observation period and HF (**Table 2**); this did not change after adjusting for relevant factors identified in **Table 1**.

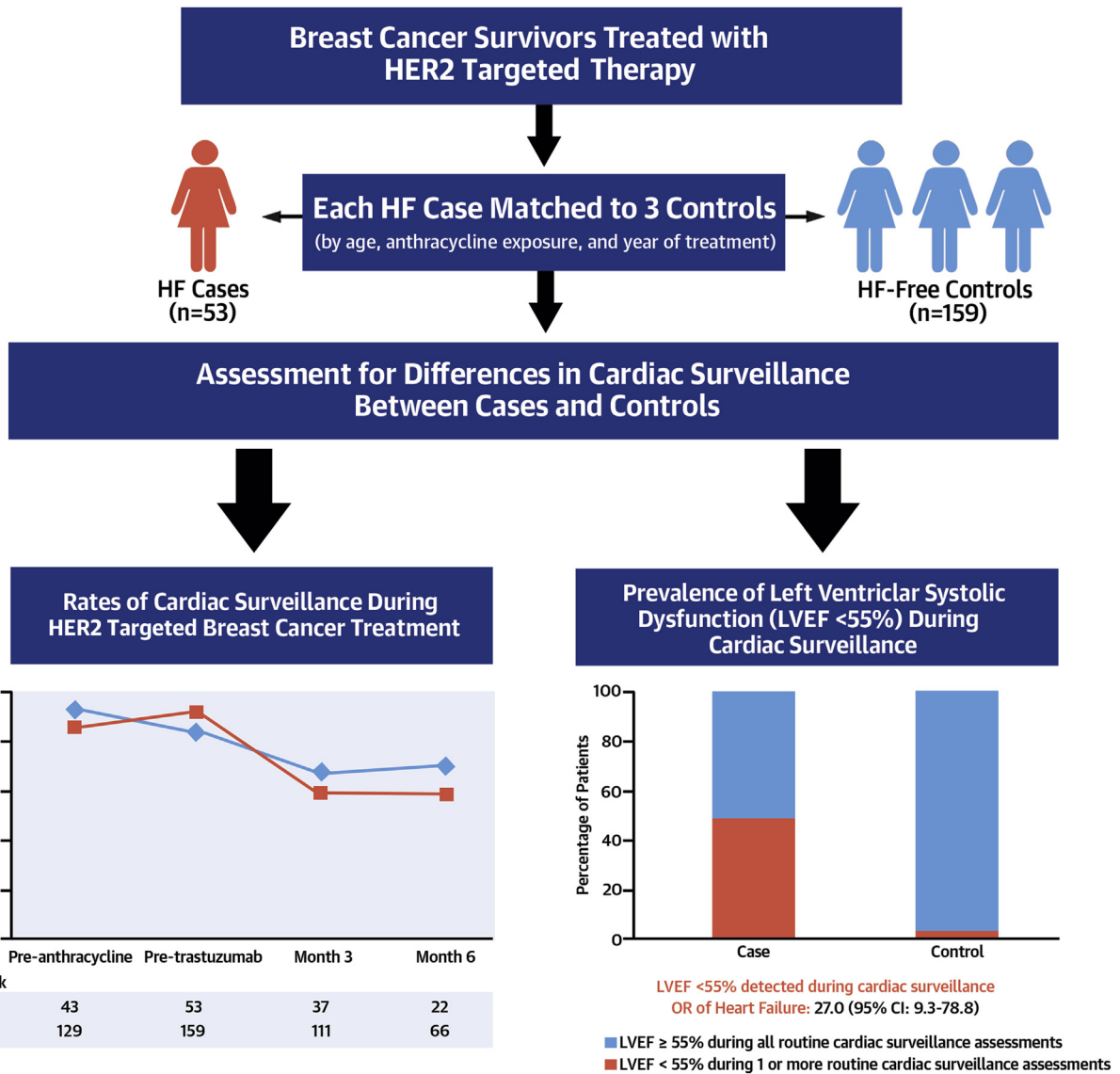
**ASSOCIATION BETWEEN ABNORMAL SURVEILLANCE LVEF AND HF.** An LVEF <55% during a surveillance LVEF assessment at any timepoint in the observation period was observed in 26 of 53 cases (49%; 95% CI: 35% to 63%) but only 5 of 157 controls (3%; 95% CI: 1% to 7%) (**Central Illustration**). The lowest LVEF detected during surveillance was between 45% and 54% in 18 cases and 2 controls, between 35% and 44% in 5 cases and 2 controls, and <35% in 3 cases and 1 control. An LVEF <55% during a surveillance LVEF assessment in the final 3-month interval of the observation period was observed in 22 of 41 cases (54%; 95% CI: 37% to 69%) but only 4 of 113 controls (4%; 95% CI: 1% to 9%). Of the 26 cases with a surveillance LVEF <55%, 12 (46%) underwent initiation or intensification of beta-blocker or ACEI/ARB therapy, 7 (27%) were already on beta blockers or ACEI/ARBs but received no intensification of therapy, and 7 (27%) received no beta blocker or ACEI/ARB therapy.

In multivariable adjusted analyses, an LVEF <55% at any timepoint during the observation period (OR: 27.0; 95% CI: 9.3 to 78.8) and during the final 3-month interval of the observation period (OR: 25.6; 95% CI: 7.3 to 90.3) were significantly associated with HF (**Table 2, Supplemental Tables 1 and 2**). The association between an abnormal surveillance LVEF (at any timepoint) and HF remained significant when the criterion for abnormal LVEF was modified to <53% (OR: 29.8; 95% CI: 8.8 to 101.1) or <50% (OR: 14.5; 95% CI: 4.1 to 51.0).

## DISCUSSION

Several important findings emerge from this case-control study of cardiotoxicity surveillance practices during HER2 targeted therapy and treatment-induced

**CENTRAL ILLUSTRATION** Effects of Cardiotoxicity Surveillance on Heart Failure Risk During HER2 Targeted Therapy for Breast Cancer



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Study design and summary of major findings in a case control study of 53 patients who developed heart failure (HF) during human epidermal growth factor receptor 2 (HER2) targeted therapy and 159 control patients. Adherence to cardiotoxicity surveillance guidelines was suboptimal for both cases and controls and was not associated with lower HF risk. However, a left ventricular ejection fraction (LVEF) <55%, as shown in red, was detected during routine surveillance in 49% of cases (before the development of HF) but only 3% of controls and was associated with increased HF risk. CI = confidence interval; OR = odds ratio.

HF among a predominantly anthracycline-treated cohort. First, risk factors associated with HF included BMI, pre-existing hypertension, and race, consistent with results of prior studies (1,12-14). Findings from this study also confirm and extend those of prior retrospective and prospective studies which report an increase in HF risk associated with a

lower LVEF at baseline (2,11,15,16). Second, adherence to routine cardiac surveillance during HER2 targeted therapy as recommended by current guidelines was suboptimal among case patients. However, a similar proportion of control patients were also non-adherent to the recommended intervals for cardiac surveillance. The lack of an association between

**TABLE 2 Associations of Cardiotoxicity Surveillance With Heart Failure During HER2 Targeted Therapy**

	Cases (n = 53)	Controls (n = 159)	Crude OR (95% CI)	Adjusted OR (95% CI)
Compliant with LVEF surveillance (at all timepoints)				
Yes	33 (62)	92 (58)	1.3 (0.6-2.6)*	1.2 (0.4-3.9)†
No	20 (38)	67 (42)	1.0	1.0
Compliant with LVEF surveillance (baseline to 6 months)				
Yes	33 (62)	96 (60)	1.1 (0.6-2.2)*	1.0 (0.3-3.1)†
No	20 (38)	63 (40)	1.0	1.0
Compliant with LVEF surveillance (at final surveillance timepoint)				
Yes	41 (77)	113 (71)	1.5 (0.7 to 3.2)*	1.1 (0.3-3.7)†
No	12 (23)	46 (29)	1.0	1.0
Abnormal surveillance LVEF <55% (at any timepoint)				
Yes	26 (49)	5 (3)	26.2 (9.6-71.5)‡	27.0 (9.3-78.8)§
No	27 (51)	152 (96)	1.0	1.0
Abnormal surveillance LVEF <55% (at final surveillance timepoint)#				
Yes	22 (54)	4 (4)	27.7 (8.8-87.8)‡	25.6 (7.3-90.3)§
No	19 (46)	109 (96)	1.0	1.0

Values are n (%), unless otherwise indicated. Percentages may not add to 100 given rounding. \*ORs computed with conditional logistic regression. Controls were matched to cases on age, year of treatment, and history of prior or current anthracycline treatment. †Odds ratios computed with conditional logistic regression, adjusted for BMI, pre-trastuzumab LVEF, stage of disease (local or metastatic), race, hypertension, calcium channel blocker treatment, and statin treatment. ‡Firth's penalized maximum likelihood logistic regression was used to estimate ORs due to the low prevalence of abnormal LVEF among the controls, adjusting for case-control matching factors (age, year of treatment, history of prior or current anthracycline treatment). §Firth's penalized maximum likelihood logistic regression was used to estimate the OR after adjustment for case-control matching factors, BMI, stage of disease, race, hypertension, calcium channel blocker treatment, and statin treatment. #This analysis was restricted to 41 case patients and 113 control patients who underwent an LVEF assessment at the final surveillance timepoint.

Abbreviations as in Table 1.

adherence to routine cardiac monitoring and HF suggests that the performance of routine LVEF assessments in isolation may be insufficient to mitigate the risk of HF. Finally, this study found that an abnormal LVEF <55% during routine surveillance is significantly associated with risk of HF. This data supports the notion that an abnormal LVEF during targeted HER2 treatment represents a clinically relevant stage within the cardiotoxicity spectrum that precedes the onset of HF. If abnormal LVEF is an early phase of cardiotoxicity, then early detection of an abnormal LVEF during routine surveillance combined with effective interventions aimed at preventing progression to HF are likely to be of clinical benefit.

There is uncertainty within the cardio-oncology community over the clinical utility and optimal frequency of routine cardiac surveillance during cardiotoxic cancer therapy, specifically anthracyclines and/or trastuzumab. In 2006, when the U.S. Food and Drug Administration approved trastuzumab for use in the adjuvant setting, LVEF assessments were recommended at baseline and every 3 months during therapy (17). These recommendations were subsequently endorsed as the standard-of-care by several clinical practice guidelines such as the National Comprehensive Cancer Network (8). However, an update to the National Comprehensive Cancer Network guidelines in 2016 acknowledges that the optimal frequency of

LVEF monitoring during trastuzumab is unknown (7). Similarly, clinical practice guidelines published by the American Society of Clinical Oncology in 2016 recommend that the frequency of surveillance during cardiotoxic cancer treatment, in general, be based on clinical judgment and patient circumstances rather than a one-size-fits-all approach of every 3 months for all patients (5).

In the current study, cardiac monitoring for both cases and controls was less rigorous than recommended in current guidelines, consistent with prior observational studies. In a Surveillance, Epidemiology, and End Results-Medicare study by Chavez-MacGregor et al. (18), only 36% of participants receiving adjuvant trastuzumab underwent adequate cardiac monitoring, defined by a baseline cardiac evaluation (echocardiogram or multiple gated acquisition scan) and a subsequent follow-up at least every 4 months during trastuzumab. Similarly, only 46% of patients were adherent to guideline-recommended cardiac monitoring in a claims-based study of 4,325 patients treated with trastuzumab (19). In these studies, several factors influenced the rate of cardiac monitoring during breast cancer therapy including treatment with anthracyclines, age, and sex or year of training of the treating physician. However, evidence is lacking on whether adherence to current cardiac monitoring

guidelines results in improved patient outcomes. Among the 12 patients in the current study who were not adherent with cardiac monitoring recommendations during the interval immediately before developing HF, it is possible but not proven that a routine LVEF assessment could have detected a LVEF decline and led to an intervention to prevent HF. This knowledge gap must be addressed before efforts to improve cardiac monitoring adherence are strongly endorsed.

This study shows that an abnormal LVEF detected through routine surveillance during HER2 targeted therapy has important clinical implications, specifically an increased risk of HF. This raises the question of whether early intervention with cardioprotective medications (e.g., beta blockers or ACEIs) in patients who develop an asymptomatic LVEF decline is an effective treatment to prevent further impairment of left ventricular systolic function and halt progression to HF. Another important consideration is whether patients who develop an asymptomatic LVEF decline can safely continue to receive HER2 targeted therapy. These 2 questions have been addressed in 2 small prospective trials which report a low cardiac event rate in patients who receive additional HER2 targeted therapy after an asymptomatic LVEF decline (20,21). Patients in both studies were followed closely by a cardiologist, underwent frequent serial LVEF assessments, and received maximal tolerated doses of cardioprotective medications. While these findings should be confirmed in larger studies, they provide evidence to further support the utility of routine LVEF surveillance as shown in this study.

To date there have been several randomized clinical trials evaluating cardioprotective medications for the primary prevention of cardiotoxicity. Most of these studies have reported a marginal improvement in measures of left ventricular systolic function (22-25). Findings from this study of a possible association between calcium channel blocker treatment and HF may be consistent with current HF guidelines stating that calcium channel blockers may be harmful in patients with low LVEF; however, this must be further investigated (26).

There is general agreement that the risk of cardiotoxicity is highest among patients treated with sequential anthracyclines and HER2 targeted therapy. Therefore, it is likely that routine LVEF surveillance would have the greatest clinical utility during treatment with these high-risk regimens in which an estimated 15% to 20% will develop asymptomatic LVEF decline. Given that the majority of participants in the current study were treated with an anthracycline, study findings may not be

generalizable to patients receiving alternative treatment regimens. For example, the need for routine LVEF surveillance during treatment with lower-risk regimens (i.e., non-anthracycline-based regimens) in which the incidence of asymptomatic LVEF decline is significantly lower remains less certain (27). To maximize the benefit of cardiac monitoring, the current one-size-fits-all approach should be replaced with a strategy in which the frequency of LVEF monitoring is tailored to a patient's individualized risk of cardiotoxicity.

In the current study, several strategies were used to minimize methodological bias associated with the case-control study design. First, cases and controls were matched for known factors associated with risk of HF (i.e., age and exposure to anthracyclines) as well as characteristics that could affect the likelihood of undergoing a surveillance LVEF assessment (i.e., year of treatment). Second, a comprehensive review of the medical record was used to ensure that only LVEF assessments performed for surveillance purposes (rather than for diagnostic purposes) were included in the analysis. Third, the same observation period was used for cases and matched controls in determining exposure to cardiac surveillance studies to avoid a time window bias. Finally, the definition of adherence to LVEF surveillance was varied based on several different time intervals including the full observation period, the first 6 months of the observation period, and the last 3 months of the observation period, and the results were similar regardless of the definition used.

**STUDY LIMITATIONS.** The relatively small sample size of 53 cases limits our power to definitively exclude an association between adherence to cardiac monitoring and HF, although our finding of the association between a LVEF <55% and subsequent HF may justify efforts to improve cardiac monitoring among high-risk patients. Most patients in this study were exposed to prior anthracycline chemotherapy; therefore, findings are not generalizable to patients treated with non-anthracycline-based therapy. Given the increase in the use of safer regimens in which anthracyclines are excluded, such as taxanes plus trastuzumab, future studies are warranted to evaluate the effectiveness of LVEF surveillance with these alternative treatments. Because of the retrospective nature of this study, the possibility of selection bias or detection bias among the cases or controls or the possibility of unmeasured confounders cannot be excluded. However, multiple strategies were used to account for potential



limitations inherent in the case-control design as noted above. The optimal LVEF monitoring interval and the relative contribution of provider versus patient-related factors on the adherence to guideline-recommended LVEF surveillance could not be assessed. Despite these limitations, this study provides new information regarding the importance of LVEF surveillance during HER2 targeted therapy, especially among those with prior anthracycline exposure.

In summary, this study suggests that an abnormal LVEF <55% detected during routine surveillance is a powerful indicator that the patient is at high risk for the subsequent development of HF during HER2 targeted therapy. Additional studies are needed to determine whether intervening with cardioprotective medications and/or interruption of HER2 targeted therapy for an asymptomatic LVEF decline detected on routine surveillance can prevent HF without adversely impacting breast cancer outcomes. This will provide important evidence needed to support current cardiotoxicity monitoring guidelines and justify future initiatives to improve adherence with routine cardiac surveillance, particularly among patients at increased cardiotoxicity risk.

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## PERSPECTIVES

**COMPETENCY IN MEDICAL KNOWLEDGE:** Patients who develop an abnormal LVEF (<55%) detected on routine cardiac surveillance during HER2 targeted therapy are at increased risk for HF. This study shows the important clinical implications of an asymptomatic LVEF decline associated with HER2 targeted therapy and may justify efforts to improve adherence to guideline-recommended cardiac monitoring.

**TRANSLATIONAL OUTLOOK:** Improved methods for risk stratification of cardiotoxicity associated with HER2 targeted therapy are needed. Among the subset of patients at high risk for cardiotoxicity, routine cardiac monitoring to detect an abnormal LVEF which often precedes the development of symptomatic HF may be of clinical benefit. Future studies are needed to further inform LVEF monitoring and the optimal management strategies for patients who develop an abnormal LVEF during HER2 targeted therapy.

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**KEY WORDS** breast cancer, cardiac monitoring, cardio-oncology, cardiotoxicity, heart failure

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**APPENDIX** For supplemental tables, please see the online version of this paper.