JACC: CARDIOONCOLOGY VOL. ■, NO. ■, 2025


ORIGINAL RESEARCH

# Risk Stratification for Trastuzumab-Induced Cardiac Dysfunction and Potential Implications for Surveillance

Abdelrahman Ali, MD,[a] Efstratios Koutroumpakis, MD,[a] Juhee Song, PhD,[b] Daniel Booser, MD,[c] Carlos H. Barcenas, MD, MSc,[c] Debu Tripathy, MD,[c] Ana Barac, MD, PhD,[d] Nicolas L. Palaskas, MD, MPH,[a] Anita Deswal, MD, MPH[a]

## ABSTRACT

**BACKGROUND** Although patient factors and sequential anthracycline use contribute to risk for cancer therapy–related cardiac dysfunction (CTRCD) with HER2-directed cancer therapy, frequent (every 3 months) left ventricular ejection fraction (LVEF) surveillance is recommended irrespective of baseline risk.

**OBJECTIVES** The aim of this study was to examine the incidence of trastuzumab-associated CTRCD in a contemporary cohort with HER2-positive breast cancer and assess the performance of a risk assessment tool to identify patients at low risk for CTRCD to guide risk-based surveillance strategies.

**METHODS** A retrospective cohort of patients with HER2-positive breast cancer treated with trastuzumab at a tertiary cancer center was examined. Patients were categorized as low, medium, and high or very high risk for CTRCD by Heart Failure Association/International Cardio-Oncology Society risk assessment.

**RESULTS** Of 496 patients treated with trastuzumab, 29.8% also received anthracyclines. Over a median follow-up period of 51 months, 8.7% developed CTRCD, but only 1.6% had associated heart failure (HF). CTRCD rates were 3.6%, 12.8%, and 32.1% in low-risk, medium-risk, and high or very high risk groups, respectively. HF incidence was 0.4% in the low-risk group and 2.1% in the medium-risk group, with no HF in patients at low- or medium-risk who received trastuzumab without anthracyclines. HF was observed in 11% of high-risk patients. The risk assessment had a negative predictive value for CTRCD in low vs moderate- or high-risk patients of 96.4% (95% CI: 93.5%-98.3%).

**CONCLUSIONS** The findings support the exploration of a prospective personalized risk-based approach to cardiac LVEF surveillance during trastuzumab therapy. Less frequent LVEF monitoring in low-risk patients may optimize resource use and reduce patient burden without compromising safety. (JACC CardioOncol. 2025;■:■–■) © 2025 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

From the [a]Department of Cardiology, University of Texas MD Anderson Cancer Center, Houston, Texas, USA; [b]Department of Biostatistics, University of Texas MD Anderson Cancer Center, Houston, Texas, USA; [c]Department of Breast Medical Oncology, University of Texas MD Anderson Cancer Center, Houston, Texas, USA; and [d]Inova Schar Heart and Vascular, Inova Schar Cancer, Fairfax, Virginia, USA.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received June 12, 2024; revised manuscript received December 9, 2024, accepted December 16, 2024.

ISSN 2666-0873 https://doi.org/10.1016/j.jaccao.2024.12.007

**ABBREVIATIONS AND ACRONYMS**

**AUC** = area under the curve

**CTRCD** = cancer therapy-related cardiac dysfunction

**ESC** = European Society of Cardiology

**GLS** = global longitudinal strain

**HF** = heart failure

**HFA** = Heart Failure Association

**HFrEF** = Heart failure with reduced ejection fraction

**IC-OS** = International Cardio-Oncology Society

**LV** = left ventricular

**LVEF** = left ventricular ejection fraction

**MDACC** = MD Anderson Cancer Center

**RCT** = randomized clinical trial

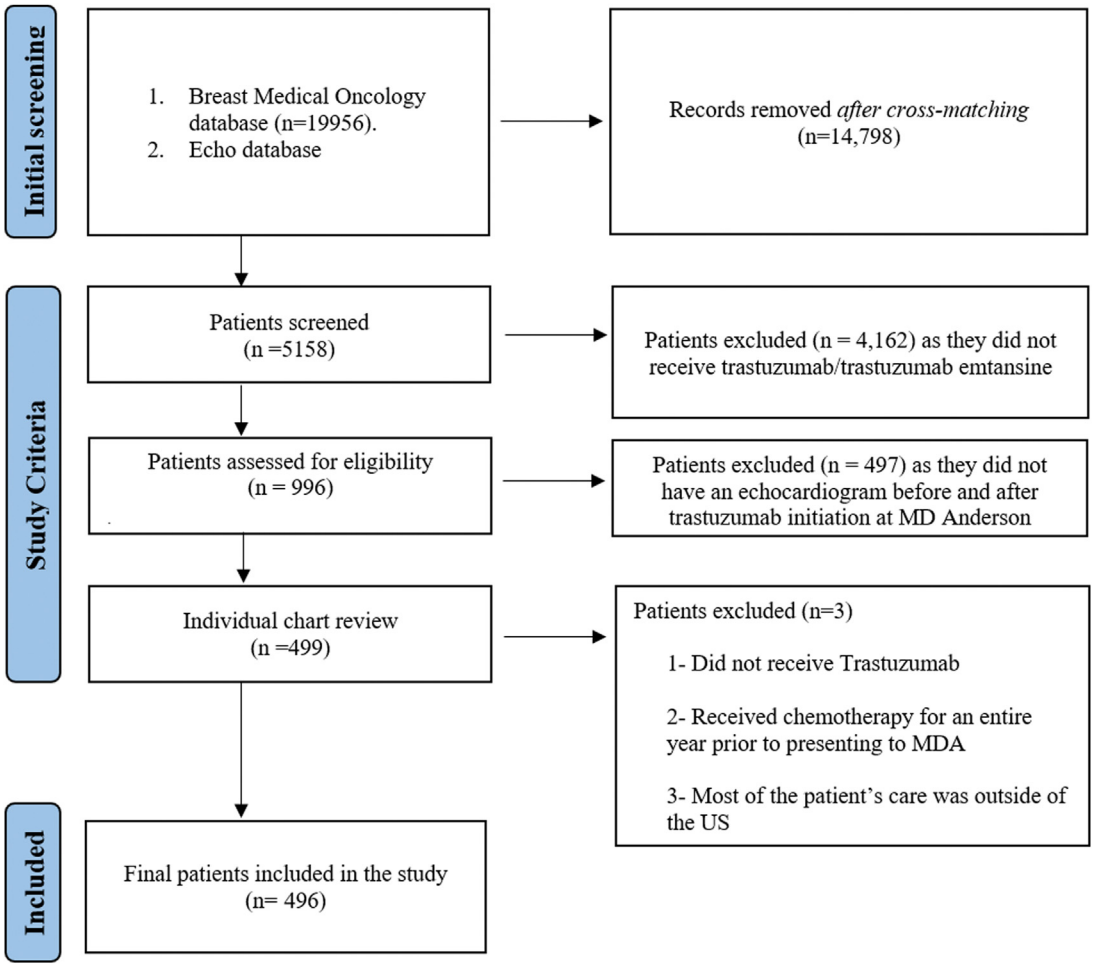
Randomized clinical trials (RCTs) have consistently demonstrated the benefit of targeted therapy with trastuzumab on disease progression and survival in patients with HER2 receptor-positive breast cancer.[1-3] However, clinical trials and observational data have also confirmed the adverse effects of trastuzumab on cardiac function, leading to asymptomatic cardiac systolic dysfunction or symptomatic heart failure (HF).[4,5] The initial trial in which trastuzumab was given concurrently with anthracyclines demonstrated a high rate of cardiac dysfunction (28%) and NYHA functional class III or IV HF (19%).[3] Although sequential administration of anthracyclines and trastuzumab demonstrated lower rates of cardiotoxicity, cancer therapy-related cardiac dysfunction (CTRCD) remains a concern when patients are treated with trastuzumab.[4,6] The U.S. Food and Drug Administration prescribing information for trastuzumab since 2002 continues to recommend frequent surveillance of left ventricular ejection fraction (LVEF) irrespective of patient risk for CTRCD, at baseline, at 3-month intervals during therapy and at completion of therapy, and every 6 months for at least 2 years after the completion of therapy as a component of adjuvant therapy.[7] The 2022 European Society of Cardiology (ESC) cardio-oncology guidelines provide a Class 1 recommendation for LVEF monitoring at baseline, every 3 months during treatment, and within 1 year after treatment for patients receiving HER2-targeted therapies.[6] As an initial step to incorporate patient risk-based monitoring, the ESC guidelines provide a weak recommendation (Class 2b) in low-risk patients who are asymptomatic and have normal assessments at 3 months, for consideration of reduction in monitoring frequency to every 4 months during therapy.[6] With contemporary management including reduction in the use of anthracyclines in patients with breast cancer treated with HER2-targeted therapy,[8] and the lower frequency of cardiotoxicity compared with original data, there is a need to re-examine the incidence of symptomatic and asymptomatic CTRCD in a contemporary cohort of patients to guide an individualized CTRCD risk-based approach for monitoring. Accordingly, the objectives of our study were to 1) examine the incidence of asymptomatic and symptomatic CTRCD in a large contemporary cohort of patients with HER2-positive breast cancer treated with trastuzumab at a tertiary referral cancer center; and 2) examine the performance of the empirically proposed risk assessment tool from the Heart Failure Association (HFA) of the ESC in conjunction with the International Cardio-Oncology Society (IC-OS) to identify risk for CTRCD in order to guide tailored monitoring strategies.[6,9]

## METHODS

**STUDY COHORT.** We conducted a retrospective cohort study of patients diagnosed with HER2-positive breast cancer and treated with neoadjuvant or adjuvant trastuzumab, planned for 1 year at MD Anderson Cancer Center (MDACC). All patients were planned to receive either paclitaxel or docetaxel for 12 weeks. Patients were included if baseline echocardiography was performed on or after January 18, 2013, and final follow-up echocardiography by December 29, 2022, with clinical follow-up until March 3, 2023 (**Figure 1**). The study cohort was constructed by cross-referencing the breast medical oncology database with the institutional echocardiography database. Patients were included in the study cohort if they underwent at least 1 echocardiographic examination before and at least 1 examination after trastuzumab initiation at MDACC. Trastuzumab initiation dates and demographic and clinical data were extracted by individual chart review of electronic medical records, including multiple clinic visits. Therefore, there were no missing data on key variables. Patients were categorized as low, medium, and high or very high risk for CTRCD, adapted from the risk evaluation framework for trastuzumab proposed by the ESC HFA and IC-OS (Supplemental Table 1).[9] We summarized risk levels as follows: 1) patients with no risk factors or 1 medium risk factor were classified as low risk; 2) patients with 2 to 4 medium risk factors were classified as medium risk; and 3) patients with 1 or more very high risk factors or high risk factors or with 5 or more medium risk factors were classified as high risk (combining the high and very high risk groups). The study complied with the Declaration of Helsinki and was approved by the MDACC Institutional Review Board with a waiver of the requirement to obtain informed consent given the retrospective study design.

**TRANSTHORACIC ECHOCARDIOGRAPHY FOR LVEF ASSESSMENT.** As standard of care, LVEF at our center is routinely calculated using biplane quantitative volumetric assessment via Simpson's disc method. In the few instances in which biplane LVEF cannot be calculated because of the technical quality of the study, single-plane LVEF or, very rarely, a visual estimation of LVEF is reported. Ultrasound enhancing agents are used, as standard of care, when endocardial definition is inadequate. For this study, LVEF

**FIGURE 1** Flowchart of the Study Cohort




Overview of the study cohort selection within the time period of the first baseline echocardiographic examination on January 18, 2013, to the last follow-up examination on December 29, 2022. MDA = MD Anderson Cancer Center.

was extracted from the echocardiography database and manually crosschecked with the electronic medical reports. The date of trastuzumab initiation was confirmed with chart review, and baseline dates of echocardiograms were then identified as those available closest to and before trastuzumab initiation.

**STUDY OUTCOMES.** The primary outcome was the incidence of any CTRCD (asymptomatic and symptomatic) after trastuzumab therapy initiation, overall and by baseline risk groups. CTRCD was defined as an absolute decrease from baseline LVEF of at least 10 percentage points to an LVEF of <53%, on the basis of the expert consensus from the American Society of Echocardiography and the European Association of Cardiovascular Imaging.[10] For patients with LVEFs <50% prior to trastuzumab initiation, CTRCD was defined by an additional reduction of LVEF of at least 10% from baseline. Symptomatic CTRCD was defined as evidence of clinical signs or symptoms of HF identified by review of follow-up notes in patients with CTRCD.

**STATISTICAL ANALYSIS.** Patient characteristics are summarized as mean ± SD or median (Q1-Q3) (non-normal distribution) for continuous variables and frequency (percentage) for categorical variables. Comparisons between treatment subgroups were made using Student's *t*-tests or Wilcoxon rank-sum tests for continuous variables as appropriate and

**TABLE 1 Baseline Characteristics of the Study Cohort: All Patients and by Development of CTRCD**

| | All (n = 496) | No CTRCD (n = 453) | CTRCD (n = 43) | *P* Value[a] |
|---|---|---|---|---|
| Age, y | 52.3 ± 13.2 | 51.9 ± 13.2 | 56.6 ± 13.0 | 0.028 |
| Race | | | | 0.007 |
| White | 340 (68.5) | 318 (70.2) | 22 (51.2) | |
| Black | 65 (13.1) | 52 (11.5) | 13 (30.2) | |
| Asian/Pacific Islander | 43 (8.7) | 41 (9.1) | 2 (4.7) | |
| Hispanic | 35 (7.1) | 31 (6.8) | 4 (9.3) | |
| Other | 13 (2.6) | 11 (2.4) | 2 (4.7) | |
| Female | 495 (99.8) | 452 (99.8) | 43 (100) | 1.00 |
| Baseline echocardiographic LVEF | 61.2 ± 4.1 | 61.4 ± 3.9 | 59.3 ± 5.1 | 0.010 |
| Baseline echocardiography LVEF < 55% | 22 (4.4) | 14 (3.1) | 8 (18.6) | 0.002 |
| Hypertension | 167 (33.7) | 148 (32.7) | 19 (44.2) | 0.16 |
| Diabetes mellitus | 58 (11.7) | 49 (10.8) | 9 (20.9) | 0.049 |
| Hyperlipidemia | 117 (23.6) | 104 (23) | 13 (30.2) | 0.28 |
| Smoking | | | | 0.007 |
| None | 424 (85.5) | 389 (85.9) | 35 (81.4) | |
| Former | 51 (10.3) | 49 (10.8) | 2 (4.7) | |
| Current | 21 (4.2) | 15 (3.3) | 6 (14) | |
| Coronary artery disease | 9 (1.8) | 9 (1.9) | 0 (0) | 1.00 |
| History of PCI | 5 (1) | 5 (1.1) | 0 (0) | 1.00 |
| History of CABG | 2 (0.4) | 2 (0.4) | 0 (0) | 1.00 |
| History of heart failure | 9 (1.8) | 2 (0.4) | 7 (16.3) | <0.001 |
| HFrEF[b] | 5 (1) | 0 (0) | 5 (11.6) | <0.001 |
| HFpEF | 4 (0.8) | 2 (0.4) | 2 (4.7) | 0.039 |
| Atrial fibrillation | 6 (1.2) | 4 (0.9) | 2 (4.7) | 0.088 |
| History of CVA/TIA | 6 (1.2) | 4 (0.9) | 2 (4.7) | 0.088 |
| BMI, kg/m$^2$ | | | | 0.82 |
| <30 | 308 (62.1) | 282 (62.3) | 26 (60.5) | |
| ≥30 | 188 (37.9) | 171 (37.7) | 17 (39.5) | |
| Baseline medications | | | | |
| Beta-blockers | 65 (13.2) | 57 (12.6) | 8 (18.6) | 0.27 |
| ACEIs/ARBs | 112 (22.7) | 98 (21.6) | 14 (32.6) | 0.11 |
| Statins | 69 (14) | 60 (13.3) | 9 (20.9) | 0.17 |
| Anthracyclines | 148 (29.8) | 127 (28) | 21 (48.8) | 0.004 |
| Pertuzumab | 378 (76.2) | 342 (75.5) | 36 (83.7) | 0.23 |
| Breast radiation therapy | 339 (68.3) | 307 (67.8) | 32 (74.4) | 0.37 |
| HFA/IC-OS risk group | | | | <0.001 |
| Low | 279 (56.3) | 269 (59.4) | 10 (23.3) | |
| Medium | 189 (38.1) | 165 (36.4) | 24 (55.8) | |
| High/very high | 28 (5.6) | 19 (4.2) | 9 (20.9) | |
| Number of echocardiography studies at follow-up | 5.6 ± 2.8 | 5.3 ± 2.4 | 8.9 ± 4.0 | <0.001 |

Values are mean ± SD or n (%). [a]Compares CTRCD and no CTRCD groups. [b]Patients with histories of HFrEF had LVEFs of 45% to 55% at the time of trastuzumab initiation.

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; BMI = body mass index; CABG = coronary artery bypass grafting; CTRCD = cancer therapy-related cardiac dysfunction; CVA = cerebrovascular accident; HFA = Heart Failure Association; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; IC-OS = International Cardio-Oncology Society; LVEF = left ventricular ejection fraction; PCI = percutaneous coronary intervention; TIA = transient ischemic attack.

chi-square or Fisher exact tests for categorical variables. The association of risk classification by HFA/IC-OS risk assessment on the cumulative incidence function for CTRCD was evaluated in a univariable Fine-Gray model, considering death without LVEF decline as a competing risk event. The proportion of patients with CTCRD and the proportion of patients with incident CTRCD with HF were calculated by the risk classification and treatment. The discriminatory accuracy of the HFA/IC-OS risk model for CTRCD[9] was assessed using receiver-operating characteristic curves with the area under the curve (AUC) for all patients and for the subgroup of patients receiving trastuzumab without anthracyclines. Model calibration was illustrated using calibration plots, comparing predicted vs observed risk and its 95% CI. The HFA/IC-OS risk score, which was based on expert opinion, suggested the predicted risk by categories for CTRCD as follows: low, <2%; medium, 2% to 9%; high, 10% to 19%; and very high, >20%. We used the midpoints for these ranges as predicted risk for the calibration plots (ie, predicted low risk at 1%, medium risk at 5%, and combined high or very high risk at 15%). The observed risk was calculated by dividing the number of patients who experienced CTRCD during follow-up by the total number of patients in each risk group, and 95% Clopper-Pearson CIs were calculated. Given our emphasis on identifying the low-risk group, we calculated the diagnostic accuracy of the risk tool (ie, sensitivity, specificity, positive predictive value, and negative predictive value), for the low-risk vs moderate-, and combined high risk groups. The associations of prognostic factors with the cumulative incidence function for CTRCD were assessed in both univariable and multivariable Fine-Gray models. The final multivariable model was developed using backward selection, and subdistribution HRs were calculated with 95% CIs. The cumulative incidence of CTRCD with its 95% CI was estimated using Aalen-Johansen estimation. Gray's test was used to compare cumulative incidence functions. Treatment and outcomes of patients with CTRCD were summarized using descriptive statistics. Pre-post comparisons were performed using Wilcoxon signed rank test. *P* values <0.05 indicated statistical significance. SAS version 9.4 (SAS Institute) was used for statistical analysis.

## RESULTS

The study cohort included 496 patients with HER2-positive breast cancer who were initiated on trastuzumab between February 2013 and November 2021 with last follow-up to March 2023. The baseline characteristics of the overall cohort as well as by the subgroups that did (n = 43 [8.7%]) and did not (n = 453 [91.3%]) develop CTRCD after the initiation of trastuzumab are summarized in Table 1. The patients had a mean age of 52 ± 13 years, were almost

exclusively women, and self-identified as 68.5% White, 13.1% Black, 8.7% Asian, and 7.1% Hispanic. At baseline, 14.5% had history of smoking, 33.7% had hypertension, 11.7% had diabetes mellitus, and 37.9% were obese. Coronary artery disease was uncommon (1.8%), only 4.4% had baseline LVEF <55%, and 1.8% had history of HF.

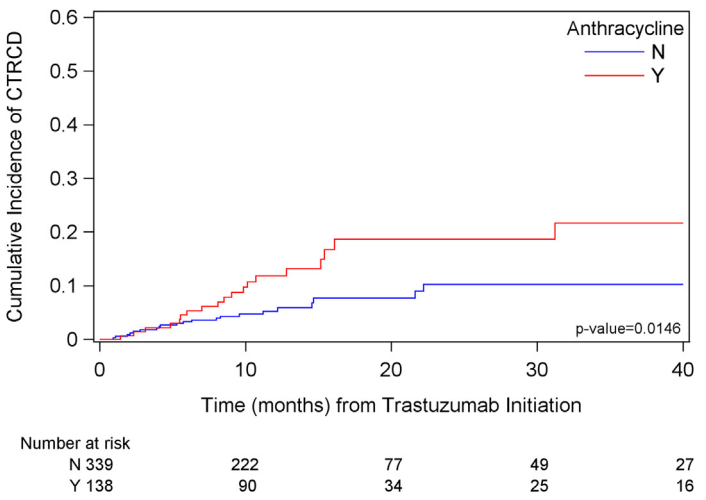
**THERAPY AND OUTCOMES.** Of the 496 patients who received trastuzumab, 148 (29.8%) had also received anthracyclines. The median dose of anthracyclines (doxorubicin equivalent) was 240 mg/m$^2$ (Q1-Q3: 240-240 mg/m$^2$). Over a median follow-up period of 51.2 months (95% CI: 48.9-54.1 months), the average number of echocardiographic examinations per patient was 5.6 ± 2.8, and the median time between examinations was 3.3 months (Q1-Q3: 2.8-4.7 months). During follow-up, 43 patients (8.7%) experienced CTRCD, as defined by a decline in LVEF of at least 10 percentage points from baseline to LVEF < 53%, on any echocardiographic study subsequent to trastuzumab initiation. The median time to CTRCD for those with CTRCD was 8 months (Q1-Q3: 4.1-12.2 months). Only 8 patients (1.6%) developed CTRCD with clinical HF, with a median time to incident HF of 7.3 months (Q1-Q3: 5.9-10.9 months) for those with clinical HF. During follow-up, 20 patients (4.0% of the cohort) died, of whom 4 patients died after incident CTRCD, including 1 who died of end-stage renal disease after the development of HF. By the end of follow-up, 11 patients (2.2%) of those alive had LVEFs <53%. **Figure 2** demonstrates the cumulative incidence of CTRCD, which increased gradually over the monitoring period of 18 months after trastuzumab initiation and at a higher rate in those who received both trastuzumab and anthracyclines compared with trastuzumab only (Supplemental Table 2A).

**BASELINE PREDICTORS OF INCIDENT CTRCD.** Patients who subsequently developed CTRCD were older, more likely to be Black, more likely to be current smokers, and more often had baseline LVEFs <55% and history of HF compared with those without CTRCD (**Table 1**). The proportion of patients experiencing CTRCD was significantly higher among patients who received sequential anthracyclines and trastuzumab compared with those who received trastuzumab only (14.2% vs 6.3%; $P = 0.004$) (**Table 2**). Similarly, although much less common, the incidence of HF was also numerically almost 4-fold higher among those who received sequential anthracyclines and trastuzumab compared with those who received trastuzumab only (3.4% vs 0.9%; $P = 0.055$) (**Table 2**). In multivariable analysis, among all patients who received trastuzumab, factors including increasing age, baseline LVEF < 55%, history of HF, current smoking status, and anthracycline use were significantly associated with a higher incidence of CTRCD (**Table 3**). In a sensitivity analysis, using an LVEF of <50% to define CTRCD, 6.0% of patients developed CTRCD: 4.6% in the trastuzumab-only arm and 9.5% in the sequential anthracycline and trastuzumab arm. The same risk factors, except for current smoking, remained significantly associated with a higher incidence of CTRCD, as shown in Supplemental Table 3.

**STRATIFICATION BY THE HFA/IC-OS RISK ASSESSMENT TOOL AND INCIDENT CTRCD.** **Figure 3** shows the percentage of patients who developed any CTRCD or CTRCD with HF on the basis of the baseline HFA/IC-OS risk group and further subdivided by treatment with trastuzumab only or trastuzumab and anthracycline. Overall, CTRCD was observed in 3.6%, 12.8%, and 32.1% of the low-risk (n = 279), medium-risk (n = 189), and high-risk (n = 28) groups. CTRCD-associated HF was infrequent in the low- and medium-risk groups (0.4% and 2.1%) but occurred in 11% of high-risk patients. Of the patients who received only trastuzumab, the proportions of those experiencing CTRCD in the low-, medium-, and high- or very high risk subgroups were 3.2%, 6.7%, and 33.3%, respectively, compared with the higher rates of 5%, 20.2%, and 25% in those also receiving anthracyclines. Notably, none of the patients in the low- and medium-risk groups who received trastuzumab only developed HF, whereas 1.7% and 4.8% of patients in the low- and medium-risk groups who received both agents developed HF. In contrast, within the high-risk group, CTRCD with HF was noted in 12.5% of patients who received trastuzumab without anthracyclines. Although no HF was recorded in the high-risk group with both agents, there were only 4 patients in that group. Among all low-risk patients, the cumulative incidence of CTRCD was 0.7%. 1.1%, 3.4%, and 5.4% at 3, 6, 12, and 15 months, respectively, with no increased incidence of CTRCD noted after that (Supplemental Table 2B).

**DISCRIMINATION, CALIBRATION AND DIAGNOSTIC ACCURACY OF THE HFA/IC-OS RISK TOOL.** The receiver-operating characteristic curves with the AUCs for the HFA/IC-OS risk tool in the overall cohort and the subgroup of patients who received trastuzumab without anthracyclines are shown in **Figures 4A and 4B**, respectively; both had an overall AUC of 0.71. The corresponding calibration plots for the same groups are shown in **Figures 4C and 4D**, with acceptable calibration between observed and predicted risk, especially in the low- and moderate-risk groups

**FIGURE 2 Cumulative Incidence of CTRCD After Trastuzumab Initiation in Patients With and Those Without Anthracyclines**




The incidence curves exclude patients who reinitiated trastuzumab at a later date.
CTRCD = cancer therapy-related cardiac dysfunction; N = no; Y = yes.

overall, and somewhat better among patients treated with trastuzumab without anthracyclines. The diagnostic accuracies of the HFA/IC-OS risk assessment tool for CTRCD development in all patients and those who received trastuzumab without anthracyclines are summarized in **Table 4**. Of note, the negative predictive values for CTRCD development for the low-risk vs moderate- and high-risk patients in both these groups were high at 96.4% (95% CI: 93.5%-98.3%) and 96.8% (95% CI: 93.5%-98.7%), respectively.

**MANAGEMENT OF PATIENTS WITH CTRCD AND LVEF RECOVERY.** The median LVEF nadir was 45% (Q1-Q3: 36%-51%; range: 10%-53%) among patients with incident CTRCD. The majority of patients with CTRCD (70%) had mild left ventricular (LV) systolic dysfunction with LVEF ≥ 40%, while 14% experienced moderate dysfunction (LVEF 30% to <40%), and 16% had severe dysfunction (LVEF < 30%). In contrast, of those who developed symptomatic HF, the majority (63%) had nadir LVEFs in the severe dysfunction range, while 25% were in moderate and 12% in the mild systolic dysfunction range. The LVEFs at the time of incident CTRCD, the nadir LVEFs, and the subsequent highest LVEFs are shown in **Figure 5** (all measured LVEFs shown in Supplemental Figure 1), subgrouped by whether anthracycline was used. **Figure 6** shows the same data grouped by baseline low or medium and high risk. Of note, CTRCD was observed after the completion of trastuzumab therapy in 19% of patients (**Table 5**). Trastuzumab was interrupted or stopped earlier than planned in 66% of patients who developed CTRCD while treatment was ongoing. Seventy-four percent of patients with CTRCD had LVEF improvements to ≥53% at follow-up.

Of the patients with CTRCD, 83.7% were referred to cardiology either within or outside the institution. A new or continued prescription of neurohormonal blockers for reduced LVEF, including renin-angiotensin system inhibitors (angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or angiotensin neprilysin inhibitors) and/or beta-blockers was recorded for 77% of patients with CTRCD.

## DISCUSSION

The salient findings in this contemporary cohort of 496 patients with HER2-positive breast cancer treated with trastuzumab (only 30% of whom also received anthracyclines) and followed for a median of 51 months are as follows: 1) the overall incidence of CTRCD was 8.7%, with a low rate of symptomatic HF of 1.6%, and the rates were lower among patients who received trastuzumab only (6.3% and 0.9%, respectively) compared with those who received anthracyclines and trastuzumab sequentially; 2) the majority of patients with CTRCD had only mild LV systolic dysfunction, with a median nadir LVEF of 45%; and 3) among patients categorized as low risk for trastuzumab-associated cardiotoxicity according to

**TABLE 2 CTCRD Outcomes After Trastuzumab and by Subgroups According to Anthracycline Use**

| | All (n = 496) | Trastuzumab (n = 348) | Anthracycline + Trastuzumab (n = 148) | *P* Value |
|---|---|---|---|---|
| Duration of trastuzumab, mo, median (Q1-Q3) | 11.8 (11.1-13.3) | 11.7 (11.1-12.8) | 12.9 (11.0-14.8) | 0.001 |
| Number of echocardiograms | 5.62 ± 2.8 | 5.4 ± 2.6 | 6.1 ± 3.1 | 0.009 |
| CTRCD, n (%) (95% CI) | n = 43 (8.7%) (95% CI: 6.4%-11.5%) | n = 22 (6.3%) (95% CI: 4.0%-9.4%) | n = 21 (14.2%) (95% CI: 9.0%-20.9%) | 0.004 |
| Incident HF, n (%) (95% CI) | n = 8 (1.6%) (95% CI: 0.7%-3.2%) | n = 3 (0.9%) (95% CI: 0.2%-2.5%) | n = 5 (3.4%) (95% CI: 1.1%-7.7%) | 0.055 |

The proportions are raw percentages.
CI = confidence interval; CTRCD = cancer therapy-related cardiac dysfunction; HF = heart failure.

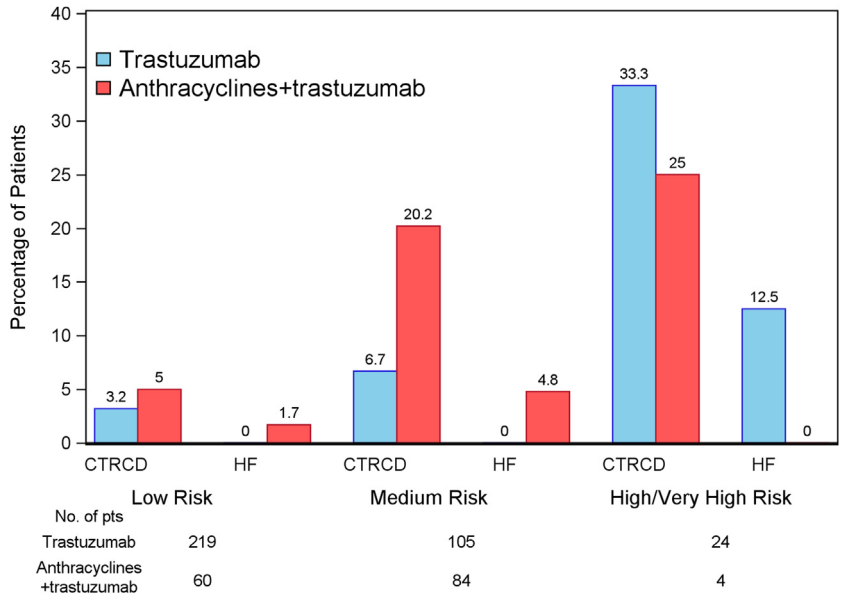
**TABLE 3** Risk Factors Associated With Incident CTRCD

| | | Univariable Fine-Gray Model | | Multivariable Fine-Gray Model | |
|---|---|---|---|---|---|
| | Level | sHR (95% CI) | *P* Value | sHR (95% CI) | *P* Value |
| Age | 1-unit change | 1.03 (1.00-1.05) | 0.031 | 1.04 (1.01-1.06) | 0.003 |
| BMI | ≥30 kg/m$^2$ vs <30 kg/m$^2$ | 0.96 (0.52-1.75) | 0.89 | | |
| Race | White | 1.00 | | | |
| | Black | 3.03 (1.54-5.96) | 0.001 | | |
| | Asian/Pacific | 0.76 (0.18-3.19) | 0.71 | | |
| | Hispanic | 2.05 (0.69-6.09) | 0.20 | | |
| | Other | 2.54 (0.67-9.67) | 0.17 | | |
| Baseline LVEF | <55% vs ≥55% | 5.65 (2.62-12.19) | <0.001 | 5.66 (2.14-14.97) | < 0.001 |
| Hypertension | | 1.53 (0.83-2.81) | 0.17 | | |
| Diabetes mellitus | | 2.12 (1.02-4.41) | 0.044 | | |
| Hyperlipidemia | | 1.34 (0.69-2.62) | 0.39 | | |
| Heart failure | | 13.37 (5.20-34.40) | <0.001 | 10.69 (3.82-29.90) | <0.001 |
| Smoking status | Current vs none or former | 4.07 (1.68-9.88) | 0.002 | 5.86 (2.37-14.44) | < 0.001 |
| Anthracycline | | 2.13 (1.17-3.89) | 0.014 | 4.35 (2.08-9.08) | < 0.001 |
| Pertuzumab | | 1.66 (0.73-3.80) | 0.23 | | |
| Beta-blockers | | 1.39 (0.64-3.05) | 0.41 | | |
| ACEIs/ARBs | | 1.61 (0.84-3.08) | 0.15 | | |
| Statins | | 1.54 (0.72-3.27) | 0.27 | | |
| HFA/IC-OS risk group[a] | Low | 1.000 | | | |
| | Medium | 3.35 (1.60-7.00) | 0.001 | | |
| | High/very high | 9.21 (3.65-23.22) | <0.001 | | |

If age was considered as a categorical variable, age > 45 years was independently associated with a significantly higher sHR for CTCRD (sHR: 2.44; 95% CI: 1.13-5.29) (multivariable Fine-Gray model 2, not shown). [a]This covariate was not considered in a multivariable model, because it is a function of the individual covariates examined in the multivariable model.

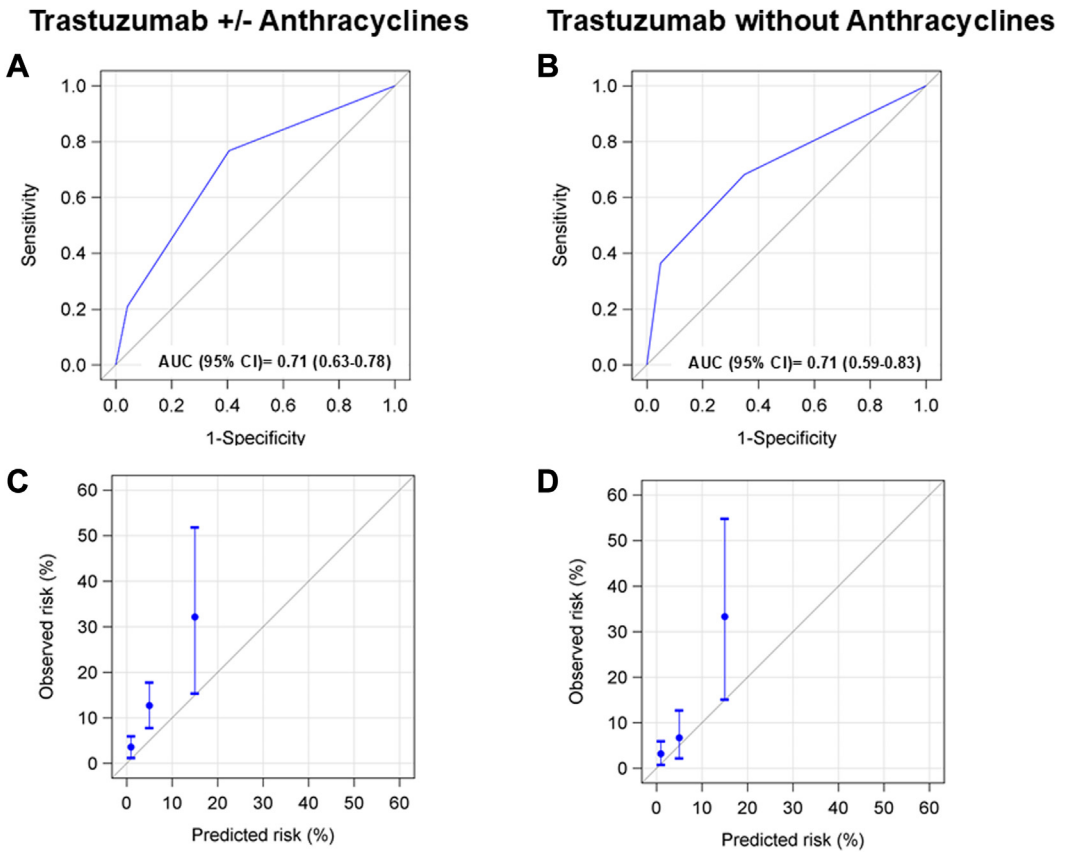
sHR = subdistribution HR; other abbreviations as in Table 1.

**FIGURE 3** Incidence of CTRCD and Symptomatic HF by Baseline Risk Groups




Patients were stratified into risk groups using the European Society of Cardiology Heart Failure Association/International Cardio-Oncology Society risk tool and further subdivided within each risk category by those who received anthracyclines and sequential trastuzumab vs trastuzumab only. CTRCD = cancer therapy-related cardiac dysfunction; HF = heart failure.

**FIGURE 4** Discrimination and Calibration of the Heart Failure Association/International Cardio-Oncology Society Risk Tool for Development of Trastuzumab-Related Cancer Therapy-Related Cardiac Dysfunction




Receiver-operating characteristic curves with their areas under the curve (AUCs) (95% CIs) and the calibration plots are shown for the overall cohort (A,C) and for patients who received trastuzumab without anthracyclines (B,D). In (C) and (D), the gray line indicates perfect calibration. The blue dots represent the observed risk for cancer therapy–related cardiac dysfunction for each risk group, while the blue bars represent the 95% CIs of the observed risks. The calibration plots indicate that the low-risk group had the lowest observed risk, while the high- and very high-risk group had the highest observed risk.

the ESC HFA/IC-OS risk score, the incidence rates of CTRCD and symptomatic HF were low at 3.6% and 0.4%, respectively. In contrast, a significant proportion of patients classified as high or very high risk by the HFA/IC-OS risk assessment developed CTRCD (32.1%), with 11% having associated HF (**Figure 3, Central Illustration**).

After the initial RCT in patients with metastatic breast cancer demonstrated a high rate of cardiac toxicity with concurrent administration of anthracyclines and trastuzumab,[3] subsequent clinical trials using these therapies sequentially have documented a lower prevalence of CTRCD, ranging from 4% to 14%, and of symptomatic HF, ranging from 0.8% to 4%,[2,4,11,12] at the lower end in recent pooled analyses of trials with extended cardiac follow-up.[4,12] Higher incidence rates in other studies may result partly from less stringent definitions of CTRCD as well as a much higher rate of anthracycline use (78%-97%) compared with our cohort, in which anthracyclines

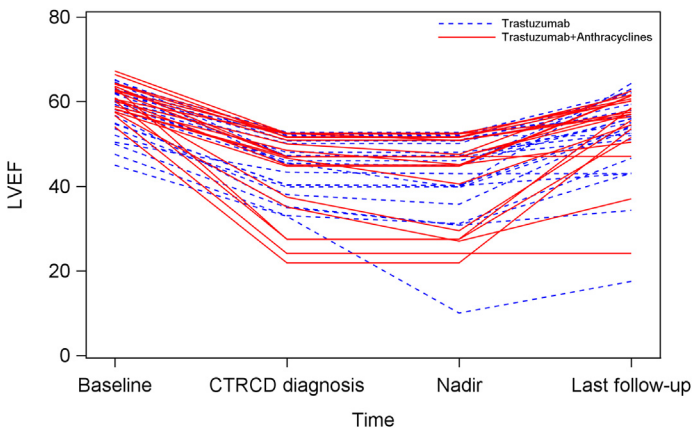
**TABLE 4** Diagnostic Accuracy of the Heart Failure Association/International Cardio-Oncology Society Risk Tool for Trastuzumab-Related Cancer Therapy-Related Cardiac Dysfunction Comparing Low-Risk vs Moderate- and High-Risk Patients

| | All Patients With Trastuzumab ± Anthracyclines | Patients With Trastuzumab Without Anthracyclines |
|---|---|---|
| Sensitivity (95% CI) | 76.7% (61.4%-88.2%) | 68.2% (45.1%-86.1%) |
| Specificity (95% CI) | 59.4% (54.7%-63.9%) | 65% (59.6%-70.2%) |
| Positive predictive value (95% CI) | 15.2% (10.7%-20.7%) | 11.6% (6.7%-18.5%) |
| Negative predictive value (95% CI) | 96.4% (93.5%-98.3%) | 96.8% (93.5%-98.7%) |

were used in only 29.8% of patients.[13,14] This is exemplified by the higher rate and early divergence of the cumulative incidence curves for CTRCD (Figure 2), along with a 4-fold higher incidence of symptomatic HF in those receiving sequential anthracyclines and trastuzumab compared with trastuzumab only, in keeping with the well-established increased risk for CTRCD and HF with the addition of anthracyclines.[5,12,15] The overall rate of clinical HF of <1% in patients treated with trastuzumab only is very reassuring. Given that CTRCD occurred in one-fifth of patients after trastuzumab was stopped, the longer follow-up time of 51 months in the present study was more likely to capture symptomatic HF events even if they occurred later during follow-up. Prior RCTs have highlighted longer term cardiac adverse events, with most cardiotoxicity events occurring during treatment or within the initial 3 to 4 years of therapy.[12,16]

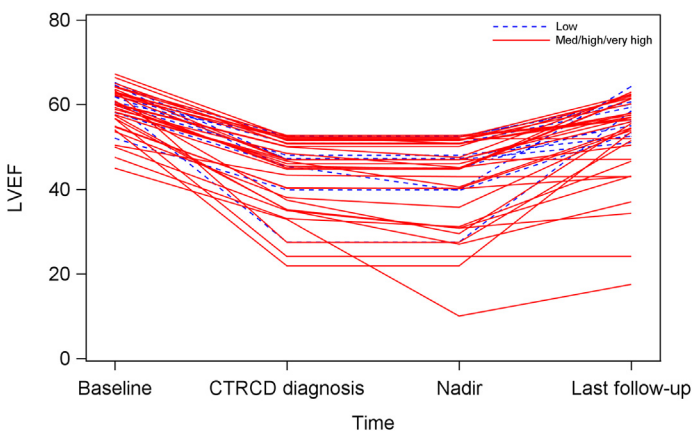
Given the trend in current clinical practice away from the routine use of anthracyclines in patients with early stages of breast cancer,[8] and with 70% of patients in our contemporary cohort not receiving anthracyclines, we were also able to examine the incidence of CTRCD and HF on the basis of baseline risk category in this larger subgroup. Of the patients who received trastuzumab only and were low risk by the HFA/IC-OS score (ie, none or 1 medium risk factor), only 3.2% of patients developed CTRCD, and none developed symptomatic HF; all except 1 of these patients had improved LVEF to 53% or greater at follow-up. In contrast, patients without any risk factors other than sequential therapy with anthracycline (and thus also designated as low risk) developed CTRCD and symptomatic HF slightly more frequently at 5.0% and 1.7%, respectively. These findings, along with the high negative predictive value of the risk assessment tool for CTRCD that we observed in the low-risk group (compared with the moderate- and high-risk group) (Table 4), support the need for prospective studies to examine the safety of more personalized and less frequent monitoring of LVEF in low-risk patients compared with the current standard of every 3 months irrespective of risk. Among low-risk patients, the frequent monitoring that is currently recommended may lead to unnecessary logistic and financial challenges for patients and health systems and potentially delay trastuzumab therapy. Interruptions for milder declines in LVEF not reaching definitions of CTRCD can also contribute to patient anxiety and cause an unnecessary interruption in therapy, which has been shown to be associated with worse disease-free and overall survival.[17,18] Furthermore, if available resources for imaging are to be efficiently used, better targeting those at a moderate to high risk for CTRCD with timely imaging follow-up may be more relevant. In our study, only 4 patients who were high or very high risk at baseline screening received both anthracyclines and trastuzumab, suggesting that clinicians may already be using this combination infrequently in these select patients.

**FIGURE 5 Changes in LVEF in Patients Treated With Trastuzumab With Incident CTRCD by Use of Anthracyclines**




Left ventricular ejection fraction (LVEF) is shown at baseline, time of cancer therapy–related cardiac dysfunction (CTRCD) diagnosis, LVEF nadir, and last follow-up visit. The median nadir LVEF for trastuzumab only was 45% (Q1-Q3: 38%-50%) and for anthracycline plus trastuzumab was 47% (Q1-Q3: 29%-51%).

**FIGURE 6 Changes in LVEF in Patients Treated With Trastuzumab With Incident CTRCD by Baseline Risk**




LVEF is shown at baseline, time of CTRCD diagnosis, LVEF nadir, and last follow-up visit. Patients in the baseline low-risk group who developed CTRCD had lesser reductions in LVEF (almost all ≥40%) compared with those in the medium- and high-risk groups. Abbreviations as in Figure 5.

**TABLE 5 Treatment and Outcomes of Patients With CTRCD (n = 43)**

| | |
|---|---|
| Incident CTRCD after completion of trastuzumab treatment | 8/43 (18.6) |
| Trastuzumab interrupted or stopped early for CTRCD | 23/35 (65.7) |
| Trastuzumab restarted among those with treatment interruption | 14/23 (60.9) |
| Patients with improved LVEF (≥53%) at any follow-up | 32/43 (74.4) |
| LVEF Improvement to ≥ 53% | |
| Patients with trastuzumab interruption or early discontinuation | 17/23 (73.9) |
| Patients without trastuzumab interruption or CTRCD after completion | 15/20 (75.0) |
| Referral to cardiology | |
| Within institution | 31/43 (72.1) |
| Outside the institution | 5/43 (11.6) |

| Medications | Baseline | After CTRCD |
|---|---|---|
| Beta-blockers | 8 (18.6) | 30 (69.8) |
| RAS inhibitors | 14 (32.6) | 26 (60.5) |
| Beta-blockers and/or RAS inhibitors | 18 (41.9) | 33 (76.7) |

Values are n/N (%) or n (%). Percentages are unweighted.
RAS = renin-angiotensin system; other abbreviations as in Table 1.

However, high-risk patients who receive only trastuzumab also clearly need continued close monitoring of LVEF given the high rate of CTRCD of 32.1% and associated HF in 11% patients in this group.

With regard to individual risk factors for CTRCD, we found that increasing age, baseline LVEF < 55%, history of HF, current smoking status, and anthracycline use were independently associated with risk for CTRCD. For each 1-year increase in age, there was an associated 4% higher risk for CTRCD, corroborating age being listed as a medium-risk (65-79 years) or high-risk (≥80 years) factor for CTRCD in the HFA/IC-OS risk score on the basis of prior studies.[5,9,12,19] Although current smoking is listed as a medium-risk factor in the HFA/IC-OS risk score,[12] we found that current smoking was a strong predictor of CTRCD. This stresses the importance of cardiovascular risk assessment and counseling regarding risk factor modification at baseline with continued efforts during therapy. Furthermore, as expected, we found that a lower baseline LVEF (<55%) and a history of HF were also significant prognostic factors for the development of CTRCD, in keeping with the medium or high risk and very high risk attributed to these 2 factors in the HFA/IC-OS score and in prior studies.[5,12] Our results show concordance to a recent clinical trial safety analysis with 4,769 patients treated with dual HER2 blockade. That study showed that similar factors were associated with a higher likelihood of adverse cardiac events, constituted mostly by asymptomatic CTRCD or clinical HF. Notably, age, anthracycline use, and an LVEF at the lower end of the enrolled spectrum were significant predictors. Conversely, similar to our study, hypertension, diabetes mellitus, use of cardioprotective medications, and left-sided radiation therapy were not significant in that study.[12] Although increased body mass index was identified in that analysis and in some other studies to be a risk factor, we did not find any signal for the same. Some studies have identified hypertension and/or diabetes mellitus to be predictors of CTRCD.[5,6] We noted diabetes mellitus to be associated with CTRCD in univariable analysis, but it was not significant in multivariable analysis. Suggested explanations include varying demographics across studies, potentially better control of risk factors in more contemporary cohorts such as ours, or a smaller number of CTRCD events in our cohort related to less anthracycline use.

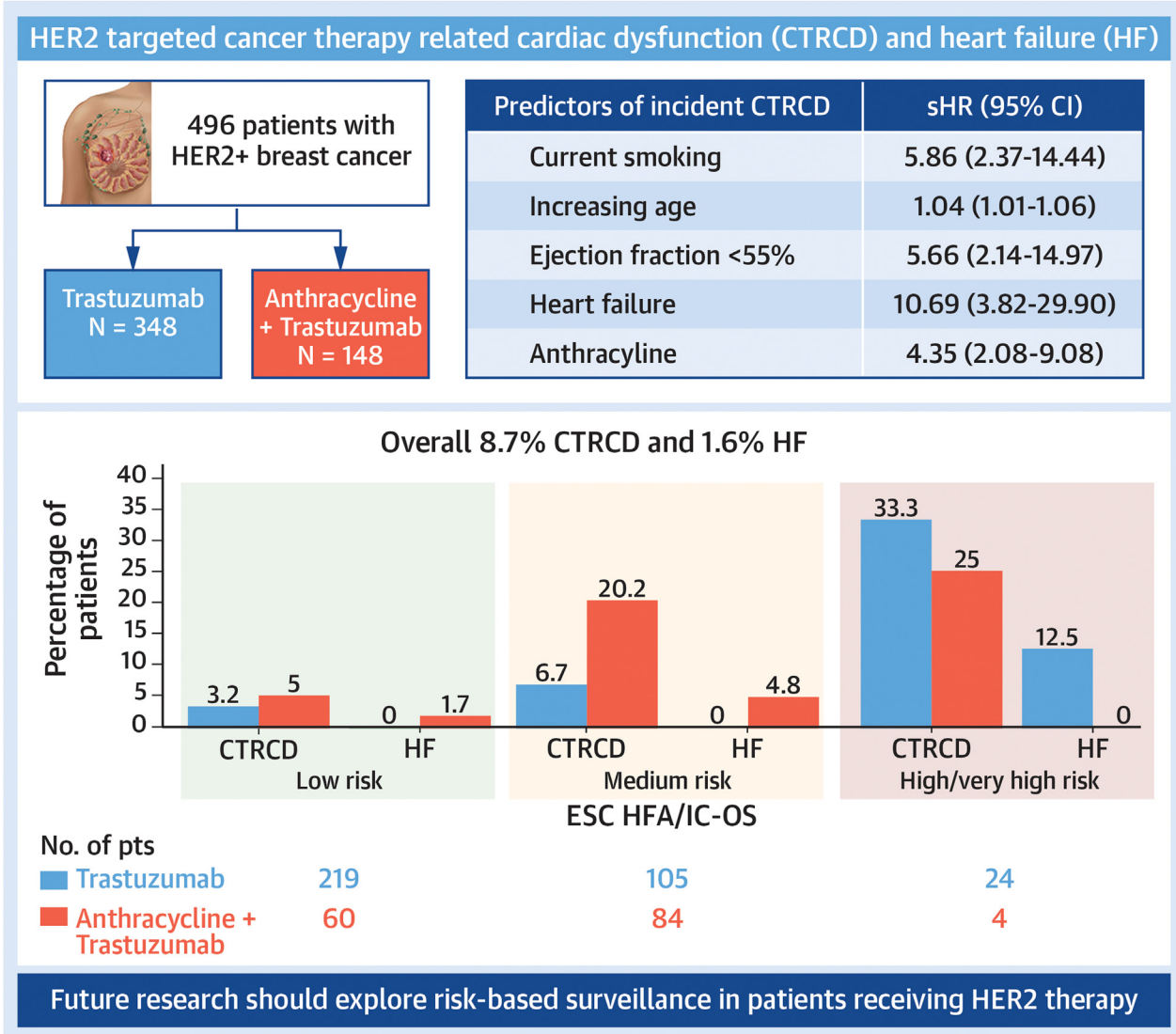
Last, given the high proportion of patients classified as high or very high risk by the HFA/IC-OS risk score who developed CTRCD and symptomatic HF in our study, such patients could be used to enrich trials of upfront cardioprotective therapy given that trials of patients enrolled irrespective of risk have not demonstrated consistent benefit of primary prevention strategies.[13,20,21]

**STUDY LIMITATIONS.** First, this was a retrospective observational study, and the characterization of CTRCD was driven by the frequency of echocardiograms obtained. However, we found that even patients without CTRCD had an average of more than 5 echocardiograms, suggesting adequate monitoring, in general.

Second, being a single-center cohort at a tertiary cancer center may limit generalizability, and the findings need to be validated in other health care settings. However, the large number of patients enrolled over 8 years provides a robust sample.

Third, definitions of CTRCD have varied across studies. Although we used a definition suggested by the American Society of Echocardiography, more recent definitions have used a similar decrease in LVEF of at least 10 points from baseline, but to a slightly lower cutoff of LVEF to <50% rather than 53%.[22] Given the implications of this study to identify a low-risk group of patients that could be monitored less frequently going forward, we did not want to underestimate the risk for CTRCD and believed that the slightly higher cutoff for LVEF may be better suited for this study, especially given the variability of LVEF quantitation by echocardiography. Furthermore, global longitudinal strain (GLS) was not reported for the majority of patients, especially in the earlier years of this cohort. Although abnormal GLS or reduction in GLS can identify a group of patients at higher risk for reduced LVEF or HF at follow-up,

**CENTRAL ILLUSTRATION** **Risk Stratification for Patients Receiving HER2-Targeted Therapy to Guide Personalized Risk-Based LVEF Surveillance**




**Ali A, et al. JACC CardioOncol. 2025;■(■):■-■.**

In a contemporary cohort of patients with HER2-positive breast cancer treated with trastuzumab, the overall incidence of cancer therapy-related cardiac dysfunction (CTRCD) was 8.7%, with a low rate of symptomatic heart failure (HF) of 1.6%. Among patients categorized as low risk for CTRCD at baseline according to the European Society of Cardiology (ESC) Heart Failure Association (HFA)/International Cardio-Oncology Society (IC-OS) risk score, the incidence rates of CTRCD and symptomatic HF were very low at 3.6% and 0.4%, respectively, while they were much higher in those classified as high or very high risk (32% and 11%, respectively). This provides support to consider personalized risk-based left ventricular ejection fraction (LVEF) surveillance during treatment decreasing the frequency of LVEF monitoring in low-risk patients. sHR = subdistribution HR.

recent data do not support the addition of cardioprotective therapy or the interruption of HER2 cardiotoxic cancer therapy on the basis of changes in GLS alone.[23]

Last, we did not recalculate all LVEFs using a single reader for this study. However, using the LVEFs quantified as standard of care makes this study more applicable to clinical practice.

## CONCLUSIONS

Our findings support a more personalized risk-based approach to cardiac LVEF surveillance during and after trastuzumab therapy. Risk stratification prior to trastuzumab initiation using clinical factors as well as baseline LVEF will be important to guide the surveillance strategy. The findings of the very low rate of CTRCD and HF in patients treated with trastuzumab without anthracyclines and categorized as low risk for CTRCD present an opportunity to prospectively explore de-escalated LVEF monitoring for such patients. Of course, further imaging on the basis of abnormalities on any of the surveillance echocardiograms or clinical symptoms should be performed as clinically appropriate. Such an approach has the potential to optimize resource use and patient experience without compromising safety. Furthermore, identifying the high-risk group will guide not only LVEF but also clinical monitoring with timely identification of CTRCD and HF, to allow optimal management of CTRCD and potential reinitiation or even continuation of HER2-targeted therapy in patients with mild asymptomatic LV systolic dysfunction, as has been suggested by smaller trials exploring permissive cardiotoxicity.[22] In addition, stratification as high risk for CTRCD provides the opportunity to optimize cardiovascular treatment before and during HER2-directed therapy to potentially prevent CTRCD, given that the use of preventive cardioprotective therapy, irrespective of baseline risk, has not demonstrated consistent benefit.[6,13,24]

**ACKNOWLEDGMENTS** We would like to dedicate this manuscript to the memory of Dr Daniel Booser. As a breast medical oncologist and master clinician, he dedicated his career to excellent patient care. He was a driving force for this study given his passion to find ways to improve and personalize the delivery of care to his patients.

## FUNDING SUPPORT AND AUTHOR DISCLOSURES

The statistical analysis work was supported in part by the Cancer Center Support Grant (National Cancer Institute grant P30 CA016672). Dr Deswal is supported in part by the Ting Tsung and Wei Fong Chao distinguished chair. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

**ADDRESS FOR CORRESPONDENCE:** Dr Anita Deswal, MD Anderson Cancer Center, Department of Cardiology, 1400 Pressler Street, Unit 1451, Houston, Texas 77030, USA. E-mail: adeswal@mdanderson.org. X handle: @anita_deswal, @Abdelcards, @PalaskasN, @EKoutroumpakis, @AnaBaracCardio, @DrDebuTripathy.

## PERSPECTIVES

**COMPETENCY IN PATIENT CARE:** This study emphasizes the importance of a risk-based approach in surveillance for CTRCD in patients with HER2-positive breast cancer treated with trastuzumab. Using the HFA/IC-OS risk stratification tool, CTRCD rates varied significantly among low-, medium-, and high-risk patients, with no HF observed in low- and medium-risk patients treated with trastuzumab without anthracyclines. By tailoring LVEF monitoring frequency to individual risk levels, clinicians can enhance patient care efficiency and better use resources without compromising patient safety.

**TRANSLATIONAL OUTLOOK:** Future research should explore the safety of personalized surveillance strategies on the basis of risk stratification in larger and more diverse patient cohorts. Prospective studies should explore de-escalated LVEF surveillance for low-risk patients receiving HER2-targeted therapy, while high-risk patients would benefit from close monitoring during therapy and could be candidates for clinical trials of cardioprotective therapies for CTRCD prevention.

## REFERENCES

1. Romond EH, Perez EA, Bryant J, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *N Engl J Med*. 2005;353:1673–1684.

2. Slamon D, Eiermann W, Robert N, et al. Adjuvant trastuzumab in HER2-positive breast cancer. *N Engl J Med*. 2011;365:1273–1283.

3. Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med*. 2001;344:783–792.

4. de Azambuja E, Ponde N, Procter M, et al. A pooled analysis of the cardiac events in the trastuzumab adjuvant trials. *Breast Cancer Res Treat*. 2020;179:161–171.

5. Yu AF, Lin IH, Jorgensen J, et al. Nomogram for predicting risk of cancer therapy-related cardiac dysfunction in patients with human epidermal growth factor receptor 2-positive breast cancer. *J Am Heart Assoc*. 2023;12:e029465.

6. Lyon AR, López-Fernández T, Couch LS, et al. 2022 ESC guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS). *Eur Heart J*. 2022;43:4229–4361.

7. Herceptin (trastuzumab) package insert. Accessed December 28, 2023. https://wwwaccessdatafdagov/drugsatfda_docs/label/2018/103792s5345lblpdf

8. Giordano SH, Lin YL, Kuo YF, Hortobagyi GN, Goodwin JS. Decline in the use of anthracyclines for breast cancer. *J Clin Oncol*. 2012;30:2232–2239.

**9.** Lyon AR, Dent S, Stanway S, et al. Baseline cardiovascular risk assessment in cancer patients scheduled to receive cardiotoxic cancer therapies: a position statement and new risk assessment tools from the Cardio-Oncology Study Group of the Heart Failure Association of the European Society of Cardiology in collaboration with the International Cardio-Oncology Society. *Eur J Heart Fail*. 2020;22:1945–1960.

**10.** Plana JC, Galderisi M, Barac A, et al. Expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy: a report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2014;27:911–939.

**11.** Piccart-Gebhart MJ, Procter M, Leyland-Jones B, et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *N Engl J Med*. 2005;353:1659–1672.

**12.** de Azambuja E, Agostinetto E, Procter M, et al. Cardiac safety of dual anti-HER2 blockade with pertuzumab plus trastuzumab in early HER2-positive breast cancer in the APHINITY trial. *ESMO Open*. 2023;8:100772.

**13.** Guglin M, Krischer J, Tamura R, et al. Randomized trial of lisinopril versus carvedilol to prevent trastuzumab cardiotoxicity in patients with breast cancer. *J Am Coll Cardiol*. 2019;73:2859–2868.

**14.** Suntheralingam S, Fan CS, Calvillo-Argüelles O, Abdel-Qadir H, Amir E, Thavendiranathan P. Evaluation of risk prediction models to identify cancer therapeutics related cardiac dysfunction in women with HER2+ breast cancer. *J Clin Med*. 2022;11(3):847.

**15.** Thavendiranathan P, Abdel-Qadir H, Fischer HD, et al. Breast cancer therapy-related cardiac dysfunction in adult women treated in routine clinical practice: a population-based cohort study. *J Clin Oncol*. 2016;34:2239–2246.

**16.** Romond EH, Jeong JH, Rastogi P, et al. Seven-year follow-up assessment of cardiac function in NSABP B-31, a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel (ACP) with ACP plus trastuzumab as adjuvant therapy for patients with node-positive, human epidermal growth factor receptor 2-positive breast cancer. *J Clin Oncol*. 2012;30:3792–3799.

**17.** Gong IY, Verma S, Yan AT, et al. Long-term cardiovascular outcomes and overall survival of early-stage breast cancer patients with early discontinuation of trastuzumab: a population-based study. *Breast Cancer Res Treat*. 2016;157:535–544.

**18.** Sardesai S, Sukumar J, Kassem M, et al. Clinical impact of interruption in adjuvant Trastuzumab therapy in patients with operable HER-2 positive breast cancer. *Cardiooncology*. 2020;6:26.

**19.** Suter TM, Procter M, van Veldhuisen DJ, et al. Trastuzumab-associated cardiac adverse effects in the herceptin adjuvant trial. *J Clin Oncol*. 2007;25:3859–3865.

**20.** Omland T. Cardio-protective therapy in cardio-oncology: quo vadis? *Circulation*. 2021;144:667–669.

**21.** Pituskin E, Mackey JR, Koshman S, et al. Multidisciplinary Approach to Novel Therapies in Cardio-Oncology Research (MANTICORE 101-Breast): a randomized trial for the prevention of trastuzumab-associated cardiotoxicity. *J Clin Oncol*. 2017;35:870–877.

**22.** Herrmann J, Lenihan D, Armenian S, et al. Defining cardiovascular toxicities of cancer therapies: an International Cardio-Oncology Society (IC-OS) consensus statement. *Eur Heart J*. 2022;43:280–299.

**23.** Negishi T, Thavendiranathan P, Penicka M, et al. Cardioprotection using strain-guided management of potentially cardiotoxic cancer therapy: 3-year results of the SUCCOUR trial. *JACC Cardiovasc Imaging*. 2023;16:269–278.

**24.** Barac A, Blaes A, Lynce F. Lessons from primary cardiac prevention trials during trastuzumab therapy: end of one size fits all. *J Am Coll Cardiol*. 2019;73:2869–2871.

**KEY WORDS** anthracycline, breast cancer, cancer therapy–related cardiac dysfunction, cardiomyopathy, echocardiography, heart failure, HER2-targeted therapy, imaging, risk prediction, screening, surveillance, trastuzumab

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