ORIGINAL RESEARCH

Cardiology Involvement in Patients With Breast Cancer Treated With Trastuzumab

Biniyam G. Demissei, MD, MSc, PhD,[a],* Srinath Adusumalli, MD, MSc,[a],* Rebecca A. Hubbard, PhD,[b]
Srinivas Denduluri, PhD,[a] Vivek Narayan, MD, MSCE,[c,d] Amy S. Clark, MD, MSCE,[c,d] Payal Shah, MD,[c,d]
Hayley Knollman, MD,[c,d] Kelly D. Getz, MPH, PhD,[e] Richard Aplenc, MD, PhD, MSCE,[e] Joseph R. Carver, MD,[a,d]
Bonnie Ky, MD, MSCE[a,b,d]

ABSTRACT

BACKGROUND There is limited evidence regarding the impact of cardiology involvement in the care of cancer patients.

OBJECTIVES This study evaluated the impact of cardiology involvement on guideline-adherent cardiovascular monitoring and risk factor management in patients with breast cancer treated with trastuzumab.

METHODS In a single-center retrospective cohort study, electronic health records from 1,047 patients with breast cancer receiving trastuzumab between January 2009 and July 2018 were evaluated. A visit to a cardiology provider beginning from the 3 months before cancer therapy initiation until the last contact date defined cardiology involvement. Guideline-adherent monitoring, defined by echocardiography assessment within the 4 months before trastuzumab initiation and follow-up echocardiography at least every 4 months during therapy, was compared in patients with and without cardiology involvement before treatment initiation. Multivariable associations between cardiology involvement and the time-varying risk factors blood pressure and body mass index (BMI) were assessed by using generalized estimating equations.

RESULTS Cardiology involvement occurred in 293 (28%) patients. A higher proportion of patients with cardiology involvement before trastuzumab initiation had guideline-adherent monitoring (76.4% vs. 60.1%; p = 0.007). Cardiology involvement was associated with an average 1.5 mm Hg (95% CI: –2.9 to –0.1; p = 0.035) lower systolic blood pressure, which was more pronounced in those with hypertension (–2.7 mm Hg; 95% CI: –4.6 to –0.7; p = 0.007). Cardiology involvement was associated with a lower BMI in patients with baseline BMI $\geq$25 kg/m^2 (mean difference: –0.5 kg/m^2; 95% CI: –1.0 to –0.1; p = 0.027).

CONCLUSIONS Cardiology involvement in patients with breast cancer treated with trastuzumab is associated with greater adherence to cardiovascular monitoring and modest improvements in risk factor control. (J Am Coll Cardiol CardioOnc 2020;2:179–89) © 2020 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/).

ABBREVIATIONS AND ACRONYMS

BMI = body mass index

CVD = cardiovascular disease

CVRF = cardiovascular risk factor

BP = blood pressure

EHR = electronic health record

GEE = generalized estimating equation

HF = heart failure

HR = hazard ratio

ICD-9-CM = International Classification of Diseases-9th Revision-Clinical Modification

ICD-10-CM = International Classification of Diseases-10th Revision-Clinical Modification

LVEF = left ventricular ejection fraction

NT-proBNP = N-terminal pro-B-type natriuretic peptide

OR = odds ratio

PPV = positive predictive value

As the population of cancer patients and survivors increases, morbidity and mortality from cardiovascular disease (CVD) are increasingly important concerns (1). These concerns are secondary to, in part, the risk of cardiotoxicity associated with commonly used cancer therapies. In breast cancer, for example, the humanized monoclonal antibody trastuzumab, a highly effective treatment for human epidermal growth factor receptor 2-positive breast cancer, is associated with a well-established risk of left ventricular ejection fraction (LVEF) declines, cardiomyopathy, and heart failure (HF) (2).

Cardiologists are playing a growing role in the care of oncology patients treated with cardiotoxic cancer therapy. Indeed, recent years have witnessed the emergence of multidisciplinary, dedicated cardio-oncology programs (3). Cardiology involvement in the care of oncology patients can occur in multiple contexts, including risk assessment before cancer therapy initiation, cardiovascular monitoring during or after therapy, administration of primary and secondary cardioprotective therapy, and cardiovascular risk factor (CVRF) and CVD management.

Data suggest that the involvement of cardiologists in the management of oncology patients may lead to improved care, particularly with optimized care delivery processes (4,5). Early involvement of cardiologists in patients with atrial fibrillation and cancer has been associated with increased anticoagulant prescription fills and improved atrial fibrillation–related outcomes (4). Cancer centers with cardio-oncology clinics have been shown to perform more intensive cardiovascular monitoring of patients treated with systemic cardiotoxic or radiation therapy than cancer centers without dedicated cardio-oncology clinics (5). However, to the best of our knowledge, there are no studies to date evaluating the impact of cardiology involvement on adherence to guideline-directed cardiovascular monitoring, CVRF management, and clinical outcomes in patients treated with cardiotoxic cancer therapies.

The overall objective of the current study was to determine the impact of cardiology involvement in the care of patients with breast cancer treated with a trastuzumab-based cancer therapy regimen. We specifically aimed to: 1) define the burden of CVRFs and CVDs; 2) characterize the involvement of cardiologists; and 3) determine the impact of cardiology involvement on cardiovascular monitoring, risk factor management, and clinical outcomes in patients with breast cancer treated with a trastuzumab-based cancer therapy regimen.

METHODS

STUDY DESIGN, DATA SOURCE, AND DATA EXTRACTION.

We performed a retrospective cohort study of patients with breast cancer >18 years of age who received trastuzumab therapy between January 2009 and July 2018 at an outpatient infusion center affiliated with Penn Medicine, a 6-hospital quaternary care academic medical center. The study used Penn Data Store, the enterprise data warehouse for Penn Medicine that contains aggregated longitudinal clinical data from the electronic health record (EHR) and multiple other clinical source systems. Information was extracted on patient demographic characteristics, hospital and office encounters, comorbidities, inpatient and outpatient medications, cancer therapies, and procedures. The study was approved by the Institutional Review Board at the University of Pennsylvania.

Available data related to trastuzumab or other intravenous infusions (e.g., anthracycline chemotherapy) including dosages and infusion dates were extracted from the Penn Data Store. Each ambulatory office visit to a cardiology or cardio-oncology provider in any location affiliated with Penn Medicine and additional data encompassing provider identification, department, encounter date, and encounter type were also obtained. In addition, demographic information and available longitudinal data on vital signs (systolic blood pressure [BP], diastolic BP, and weight), laboratory values (low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, total cholesterol, troponin, and natriuretic peptides),

cardiovascular medications (statins, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, mineralocorticoid receptor antagonists, and diuretics) and cardiac procedures were extracted. International Classification of Diseases-9th Revision-Clinical Modification (ICD-9-CM) and International Classification of Diseases-10th Revision-Clinical Modification (ICD-10-CM) diagnosis codes were used to ascertain CVRFs and CVDs documented in the EHR medical history, problem list, and encounter diagnosis tables. Vital status was obtained from the Social Security Administration Death Master File and imported into the Penn Data Store.

The first trastuzumab administration date determined the baseline visit date in patients who did not receive an anthracycline within the prior 6 months. In patients who received an anthracycline within the 6 months before trastuzumab initiation, the start of anthracycline chemotherapy defined the baseline visit date. Patients were followed until the date of last contact with the health care system. At least 1 visit to a Penn Medicine-affiliated cardiology or cardio-oncology provider at any time starting from the 3 months before the baseline visit until the date of last contact defined cardiology involvement.

DEFINITIONS. CVRFs and CVDs. Hypertension was defined by the presence of either: 1) ICD-9-CM or ICD-10-CM diagnosis codes recorded on at least 1 encounter; or 2) systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg during at least 2 encounters within a 6-month time period (6,7). Previous validation studies reported that ICD-9-CM- or ICD-10-CM-based case definitions for hypertension have a sensitivity ranging from 63% to 79% and specificity ranging from 88% to 98% with a positive predictive value (PPV) of 90% to 98% (7–9). The presence of ICD-9-CM or ICD-10-CM diagnosis codes or a statin prescription during at least 1 encounter was used to define dyslipidemia. Diabetes mellitus and CVDs, including coronary artery disease, cerebrovascular disease, peripheral arterial disease, atrial fibrillation, and HF, were defined by the presence of ICD-9-CM or ICD-10-CM diagnosis codes during at least 1 encounter. Sensitivity and specificity estimates ranging from 63% to 96% and 92% to 99%, respectively, and PPV of 71% to 96% were reported for ICD-9-CM- or ICD-10-CM-based case definitions for diabetes mellitus; estimates of sensitivity, specificity, and PPV >90% were reported for CVDs, including coronary artery disease, cerebrovascular disease, atrial fibrillation, and HF (9–11). CVRFs and CVDs were considered to be present at baseline if the event occurred before or at the time of the

baseline visit. Prescriptions recorded within the 6 months of the baseline visit were considered to define cardiovascular medication use at baseline. All CVRFs and CVDs that occurred after the baseline visit were considered incident cases. All ICD-9-CM or ICD-10-CM diagnosis codes used in these analyses are presented in Supplemental Table 1.

Cardiovascular monitoring. The U.S. Food and Drug Administration recommends monitoring of LVEF before trastuzumab initiation and every 3 months during therapy. In the current study, only echocardiography procedures performed at our health system were considered. To account for variability in scheduling, we used previously described criteria to define guideline-adherent monitoring, defined by echocardiography assessment within the 4 months before the first dose of trastuzumab and follow-up echocardiography performed at least every 4 months during trastuzumab treatment (12). On-therapy monitoring was determined in the time interval from the first to the last recorded trastuzumab administration date. We also evaluated the frequency of cardiovascular biomarker testing with troponin or N-terminal pro–B-type natriuretic peptide (NT-proBNP) as an additional metric of monitoring, given previous studies have also suggested that biomarkers are a quality of care metric in cardio-oncology (5).

STATISTICAL ANALYSIS. Baseline characteristics were summarized by using proportions for categorical variables; median [quartile 1 [Q1], quartile 3 [Q3]) are presented for continuous variables. Differences between groups were tested by using the chi-squared test for categorical variables and the Wilcoxon rank sum test for continuous variables. The incidence rates of CVRFs and CVDs were calculated by dividing the number of incident cases by the total person-years of follow-up among those who did not have the outcome of interest at baseline.

To fully understand the effects of the timing of cardiology involvement, we considered cardiology involvement at baseline, during follow-up, and as a time-varying variable. Baseline cardiology involvement was defined by a visit to a cardiology or cardio-oncology provider within the 3 months prior to the baseline visit date. Follow-up cardiology involvement was defined in those without a baseline cardiology visit. Those without any cardiology involvement were censored at the last contact date. Cardiology involvement was also treated as a time-varying variable specifically for the longitudinal analyses of the associations with CVRFs and overall survival, and coded as 0 at all prior times, including the first

TABLE 1 Baseline Characteristics and Differences According to Cardiology Involvement Either at Baseline or at Any Time During Follow-Up

	Overall Population (N = 1,047)	Cardiology Involvement Either at Baseline or at Any Time During Follow-Up		p Value
		No (n = 754)	Yes (n = 293)	
Age, yrs	54.0 [45.0, 63.0]	54.0 [45.0, 63.0]	54.0 [46.0, 63.0]	0.259
Race				0.650
White	757 (72.3)	553 (73.3)	204 (69.6)	
Black or African American	175 (16.7)	118 (15.6)	57 (19.5)	
Asian	36 (3.4)	25 (3.3)	11 (3.8)	
Other	47 (4.5)	34 (4.5)	13 (4.4)	
Unknown	32 (3.1)	24 (3.2)	8 (2.7)	
Smoking	339 (32.4)	241 (32.0)	98 (33.4)	0.700
Body mass index, kg/m^2	26.4 [22.9, 31.1]	26.4 [22.8, 30.7]	26.9 [23.4, 32.1]	0.170
Anthracycline treatment within 6 months of trastuzumab initiation	144 (13.8)	89 (11.8)	55 (18.8)	0.004
Anthracycline treatment >6 months before trastuzumab initiation	11 (1.1)	9 (1.2)	2 (0.7)	0.700
Hypertension	425 (40.6)	279 (37.0)	146 (49.8)	<0.001
Dyslipidemia	242 (23.1)	158 (21.0)	84 (28.7)	0.010
Diabetes mellitus	62 (5.9)	35 (4.6)	27 (9.2)	0.008
Heart failure	33 (3.2)	9 (1.2)	24 (8.2)	<0.001
Atrial fibrillation	18 (1.7)	4 (0.5)	14 (4.8)	<0.001
Coronary artery disease	26 (2.5)	13 (1.7)	13 (4.4)	0.021
Peripheral arterial disease	14 (1.3)	6 (0.8)	8 (2.7)	0.032
Cerebrovascular disease	21 (2.0)	11 (1.5)	10 (3.4)	0.075
Angiotensin-converting enzyme inhibitors	62 (5.9)	32 (4.2)	30 (10.2)	<0.001
Angiotensin receptor blockers	63 (6.0)	33 (4.4)	17 (5.8)	0.420
Beta-blockers	42 (4.0)	18 (2.4)	24 (8.2)	<0.001
Diuretics	88 (8.4)	83 (11.0)	37 (12.6)	0.530
Mineralocorticoid receptor antagonists	5 (0.5)	3 (0.4)	2 (0.7)	0.920
Statins	127 (12.1)	87 (11.5)	40 (13.7)	0.400

Values are n (%) or median [quartile 1, quartile 3]. Cardiovascular risk factors and cardiovascular diseases documented at any time before baseline were included; cardiovascular medication use at baseline was considered present if there was a documentation of prescription within the prior 6 months of the baseline visit.

adherent cardiac monitoring, proportions in those with and without an encounter with a cardiology or cardio-oncology provider prior to the initiation of trastuzumab therapy were compared. Moreover, the utilization of cardiac biomarkers (including troponin and NT-proBNP) was evaluated by comparing the proportion of patients with at least 1 biomarker assessment during trastuzumab therapy in those with and without cardiology involvement prior to trastuzumab initiation. These analyses of cardiovascular monitoring were limited to the subset of patients treated with a maximum interval of 18 months between the first and last date of trastuzumab administration; this approach was chosen because it is more congruent with the standard duration of trastuzumab therapy in the adjuvant setting (13).

We then evaluated the associations between any prior cardiology involvement and measures reflective of the CVRFs hypertension (BP) and obesity (BMI). The impact of cardiology involvement on BP control was assessed by evaluating longitudinal associations with time-varying measures of systolic, diastolic, and mean BPs. Associations were modeled by using repeated measures linear regression estimated via generalized estimating equations (GEE). Each of the models was adjusted for the baseline values of the corresponding BP variable under consideration, antihypertensive medication use at baseline, and the time of BP measurement relative to baseline. These associations were also specifically explored in the subgroup of patients with hypertension at baseline. The association between cardiology involvement and the attainment of target systolic BP (i.e., <140 mm Hg) and diastolic BP (i.e., <90 mm Hg) values was further evaluated in this subgroup by using repeated measures logistic regression models estimated via GEE. The association with time-varying measures of BMI was similarly evaluated by using repeated measures linear regression estimated via GEE, with adjustment for baseline BMI and the time of assessment relative to baseline. This association was additionally explored in the subgroup of overweight or obese (i.e., BMI ≥25 kg/m^2) patients at baseline. In all GEE models, time was included as a covariate using a cubic spline with 3 degrees of freedom to account for nonlinearity.

The impact of cardiology involvement at any time on overall survival was evaluated by using a marginal structural model with inverse probability weighting. This approach provides a less biased estimation of treatment effect in observational studies in which confounding by indication is a concern (14,15). Inverse-probability-of-treatment weighted marginal structural models also allow for the adjustment of

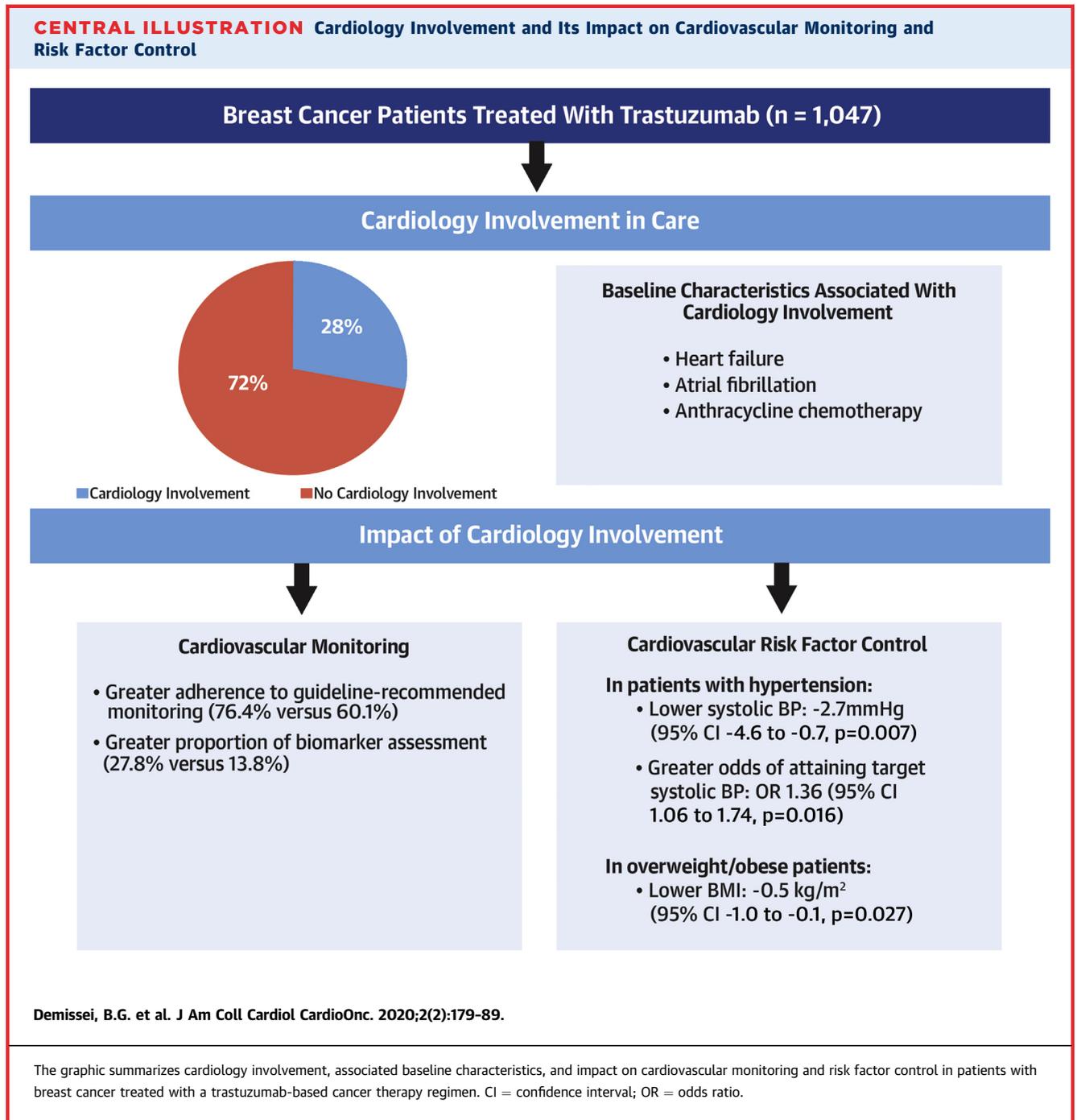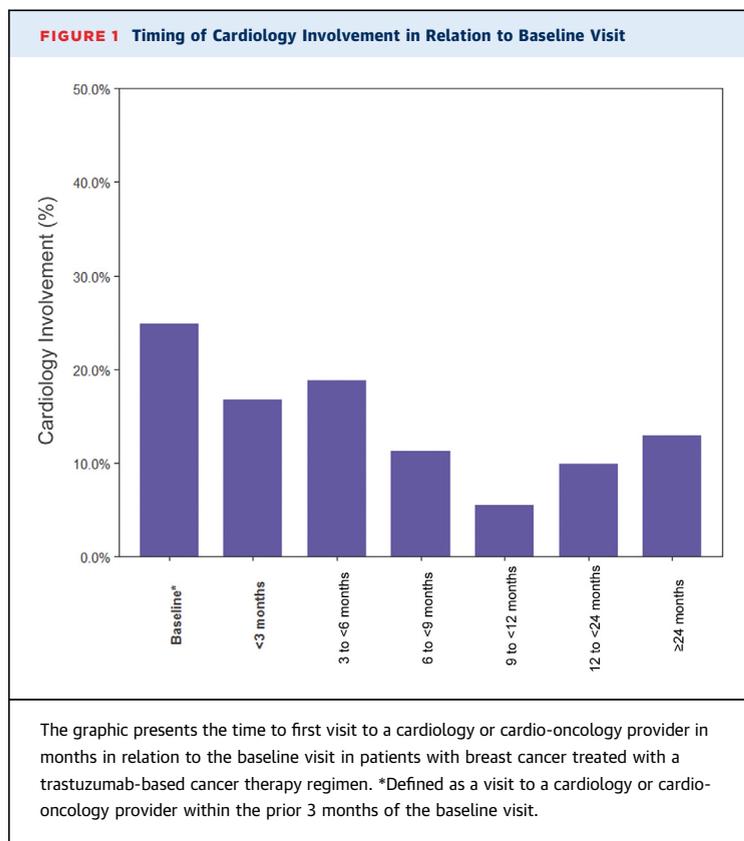encounter date with a cardiology provider and 1 at all times thereafter.

The associations between baseline clinical variables, including age, race, smoking, body mass index (BMI), anthracycline treatment, hypertension, diabetes mellitus, HF, coronary artery disease, cerebrovascular disease and peripheral arterial disease, and cardiology involvement at baseline, were evaluated by using a multivariable logistic regression model. The associations between these baseline variables and time to cardiology involvement during follow-up were evaluated by using a multivariable Cox proportional hazards model. Patients with cardiology involvement at baseline were excluded from this latter analysis.

To determine whether baseline cardiology involvement could lead to a higher rate of guideline-

CENTRAL ILLUSTRATION Cardiology Involvement and Its Impact on Cardiovascular Monitoring and Risk Factor Control

Breast Cancer Patients Treated With Trastuzumab (n = 1,047)

Cardiology Involvement in Care

28%

72%

■ Cardiology Involvement   ■ No Cardiology Involvement

Baseline Characteristics Associated With Cardiology Involvement

- Heart failure
- Atrial fibrillation
- Anthracycline chemotherapy

Impact of Cardiology Involvement

Cardiovascular Monitoring

- Greater adherence to guideline-recommended monitoring (76.4% versus 60.1%)
- Greater proportion of biomarker assessment (27.8% versus 13.8%)

Cardiovascular Risk Factor Control

In patients with hypertension:
- Lower systolic BP: -2.7mmHg (95% CI -4.6 to -0.7, p=0.007)
- Greater odds of attaining target systolic BP: OR 1.36 (95% CI 1.06 to 1.74, p=0.016)

In overweight/obese patients:
- Lower BMI: -0.5 kg/m² (95% CI -1.0 to -0.1, p=0.027)

Demissei, B.G. et al. J Am Coll Cardiol CardioOnc. 2020;2(2):179–89.

The graphic summarizes cardiology involvement, associated baseline characteristics, and impact on cardiovascular monitoring and risk factor control in patients with breast cancer treated with a trastuzumab-based cancer therapy regimen. CI = confidence interval; OR = odds ratio.

time-varying covariates that are simultaneously confounders and mediators (e.g., BP). Covariates were selected based on clinical judgment; those included in the current analysis were baseline measures of age, race, anthracycline treatment, smoking, and BMI, and time-varying measures of systolic BP, diastolic BP, hypertension, dyslipidemia, HF, and atherosclerotic cardiovascular events (coronary artery disease, cerebrovascular disease, or peripheral arterial disease). These covariates were used to construct the inverse probability weights. Due to the small number of patients with longer follow-up times, this analysis was limited to a follow-up period of 48 months after the baseline visit.

FIGURE 1 Timing of Cardiology Involvement in Relation to Baseline Visit

The graphic presents the time to first visit to a cardiology or cardio-oncology provider in months in relation to the baseline visit in patients with breast cancer treated with a trastuzumab-based cancer therapy regimen. *Defined as a visit to a cardiology or cardio-oncology provider within the prior 3 months of the baseline visit.

Regression coefficients with 95% confidence intervals (CIs) are presented for linear regression models, and odds ratios (ORs) and hazard ratios (HRs) with 95% CIs are presented for logistic regression and Cox proportional hazards models, respectively. A 2-sided alpha level of 0.05 was used to assess statistical significance. All analyses were performed by using R 3.4.0 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

PATIENT POPULATION. A total of 1,047 eligible patients with breast cancer were included in the study. The median [Q1, Q3] baseline age was 54 [45, 63] years, 72.3% were white, 16.7% were Black or African American, and 3.4% were Asian. The median [Q1, Q3] duration of trastuzumab therapy was 11 [6, 12] months. Anthracycline treatment was documented in 14.9% of the patients before trastuzumab initiation (Table 1).

BASELINE AND INCIDENT CVRFs AND CVDs. Table 1 summarizes the prevalence of CVRFs, CVDs, and medication use at baseline in the overall population. The prevalence estimates were 40.6%, 23.1%, and 5.9% for hypertension, dyslipidemia, and diabetes mellitus, respectively. Baseline prevalence estimates for coronary artery disease, peripheral arterial disease, and cerebrovascular disease were 2.5%, 1.3%, and 2.0%; HF and atrial fibrillation were documented in 3.2% and 1.7% of the patients. At least 1 class of cardiovascular medications, including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta blockers, mineralocorticoid receptor antagonists, or diuretics, was prescribed in 17.8% of the patients within the prior 6 months of the baseline visit. Statin prescriptions were documented in 12.1%.

The incidence rates of hypertension, dyslipidemia, and diabetes mellitus were 182.0, 53.1, and 10.9 per 1,000 person-years of follow-up, respectively. The incidence rate of HF was 40.5 per 1,000 person-years of follow-up, whereas coronary artery disease, peripheral arterial disease, cerebrovascular disease, and atrial fibrillation rates ranged from 4.3 to 12.4 per 1,000 person-years of follow-up. The distribution of CVRFs in relation to the time of incident CVD occurrence is provided in Supplemental Table 2.

CARDIOLOGY INVOLVEMENT. A visit to a cardiology or cardio-oncology provider at any time from the 3 months before the baseline visit to the last contact date occurred in 293 (28%) patients (**Central Illustration**). The timing of cardiology involvement in relation to the baseline visit is summarized in **Figure 1**. Cardiology involvement occurred within the prior 3 months of the baseline visit in 73 (24.9%) of the cases and during follow-up in the remainder. Among the patients who had cardiology involvement during follow-up, 153 (70.0%) of the visits occurred within 12 months of the baseline visit. Overall, patients with cardiology involvement either at baseline or during follow-up had a significantly higher frequency of CVRFs (hypertension, dyslipidemia, and diabetes mellitus) and CVDs (HF, atrial fibrillation, coronary artery disease, and peripheral arterial disease) at baseline compared with those without cardiology involvement (**Table 1**). In addition, treatment with anthracyclines was more frequent in this subgroup (18.8% vs. 11.8%; p = 0.004).

ASSOCIATIONS BETWEEN BASELINE CLINICAL VARIABLES AND BASELINE CARDIOLOGY INVOLVEMENT. In a multivariable logistic regression analysis, preexisting HF (OR: 11.83; 95% CI: 4.84 to 29.10; p < 0.001) and atrial fibrillation (OR: 6.17; 95% CI: 1.70 to 22.18; p = 0.005) were significantly associated with higher odds of cardiology involvement at baseline. Moreover, although not statistically significant, hypertension (OR: 1.76; 95% CI: 0.95 to 3.28; p = 0.073) and dyslipidemia (OR: 1.89; 95% CI: 0.99 to

3.56; p = 0.051) tended to have a higher odds of cardiology involvement at baseline (**Table 2**).

ASSOCIATIONS BETWEEN BASELINE CLINICAL VARIABLES AND CARDIOLOGY INVOLVEMENT DURING FOLLOW-UP. We then sought to define the associations between baseline clinical variables and cardiology involvement during follow-up, over a median [Q1, Q3] time of 16 [7, 35] months. The subgroup of 974 patients without cardiology involvement at baseline was included in this analysis. In a multivariable Cox proportional hazards model, pre-existing HF (HR: 3.32; 95% CI: 1.36 to 8.13; p = 0.009) and anthracycline chemotherapy (HR: 1.66; 95% CI: 1.20 to 2.30; p = 0.002) were independently associated with cardiology involvement during follow-up (**Table 2**).

IMPACT OF CARDIOLOGY INVOLVEMENT. **Cardiovascular monitoring during trastuzumab therapy.** Overall, at least 1 echocardiographic assessment before trastuzumab initiation (i.e., within 4 months of the first date of administration) or during trastuzumab therapy was recorded in 931 (89%) patients. A total of 7,623 echocardiography procedures were ordered during this period. Among the 5,815 cases wherein data on provider specialty were documented in the EHR, the majority of the echocardiography orders (i.e., ~84% in those with no cardiology involvement before trastuzumab initiation and ~79% in those with cardiology involvement before trastuzumab initiation) were authorized by oncology providers (Supplemental Table 3).

To determine the potential impact of cardiology involvement on the adherence to guideline-recommended cardiac monitoring during trastuzumab therapy, we specifically compared proportions in the subgroups with and without cardiology involvement before trastuzumab initiation. The proportion of patients with guideline-adherent cardiac monitoring was significantly higher in those with cardiology involvement before trastuzumab initiation compared with those without (76.4% vs. 60.1%; p = 0.007) (**Table 3**). Moreover, the proportion of patients with at least 1 assessment of troponin or NT-proBNP during trastuzumab therapy was greater in those with cardiology involvement before trastuzumab initiation (27.8% vs. 13.8%; p = 0.001).

CVRF management. *Blood pressure.* We analyzed a total of 42,352 BP measurements in 1,039 patients with available values at baseline and during at least 1 follow-up visit (median [Q1, Q3] of 34 [22, 51] BP measurements per patient). In the overall population, cardiology involvement at any prior visit was associated with an average 1.5 mm Hg

	Cardiology Involvement at Baseline*		Cardiology Involvement During Follow-Up†	
	OR (95% CI)	p Value	HR (95% CI)	p Value
Age, per 10 years	0.91 (0.72–1.16)	0.449	1.04 (0.92–1.17)	0.557
Race		0.088		0.980
White	Ref		Ref	
Black or African American	1.22 (0.60–2.40)		1.03 (0.71–1.49)	
Other	2.26 (1.05–4.55)		1.03 (0.64–1.65)	
BMI, per 5 kg/m²	0.98 (0.78–1.21)	0.857	0.99 (0.88–1.12)	0.901
Smoking	1.01 (0.57–1.76)	0.967	1.03 (0.77–1.37)	0.862
Anthracycline treatment‡	0.55 (0.19–1.31)	0.222	1.66 (1.20–2.30)	0.002
Hypertension	1.76 (0.95–3.28)	0.073	1.31 (0.96–1.79)	0.091
Dyslipidemia	1.89 (0.99–3.56)	0.051	0.94 (0.65–1.36)	0.744
Diabetes mellitus	0.68 (0.21–1.91)	0.495	1.16 (0.65–2.08)	0.608
Heart failure	11.83 (4.84–29.10)	<0.001	3.32 (1.36–8.13)	0.009
Coronary artery disease	0.91 (0.20–3.34)	0.891	0.99 (0.38–2.6)	0.986
Peripheral arterial disease	0.72 (0.11–3.55)	0.708	1.74 (0.64–4.72)	0.277
Atrial fibrillation	6.17 (1.70–22.18)	0.005	2.60 (0.81–8.32)	0.107
Cerebrovascular disease	0.81 (0.14–3.35)	0.788	0.69 (0.22–2.16)	0.525

TABLE 2 Associations Between Baseline Clinical Variables and Cardiology Involvement at Baseline or During Follow-Up

*Defined based on the presence of at least 1 visit to a cardiology or cardio-oncology provider within 3 months before (and including) the baseline visit. †Defined based on the presence of at least 1 visit to a cardiology or cardio-oncology provider after the baseline visit in those without cardiology involvement at baseline. ‡Anthracycline treatment within 6 months of trastuzumab initiation was considered; the associations between baseline clinical variables and cardiology involvement at baseline were modeled by using a logistic regression model; the associations between baseline clinical variables and cardiology involvement during follow-up were modeled by using a Cox proportional hazards model.

BMI = body mass index; CI = confidence interval; HR = hazard ratio; OR = odds ratio.

(95% CI: -2.9 to -0.1) lower systolic BP after adjustment for baseline systolic BP and antihypertensive medication use (p = 0.035) (**Table 4**). This association was more pronounced in the subgroup of patients with hypertension at baseline. Here, cardiology involvement was associated with an average 2.7 mm Hg (95% CI: -4.6 to -0.7) lower systolic BP (p = 0.007). Cardiology involvement was also associated with favorable odds (OR: 1.36; 95% CI: 1.06 to 1.74; p = 0.016) of attaining systolic BP <140 mm Hg in patients with hypertension at baseline (Supplemental Table 4). There were no statistically significant associations with diastolic BP and mean BP in the overall group or in the subgroup of patients with hypertension at baseline (**Table 4**).

Body mass index. A total of 40,313 (median [Q1, Q3]: 34 [23, 50] per patient) weight measurements were analyzed in 1,000 patients with available values at baseline or during at least 1 follow-up visit. In a multivariable model adjusted for baseline BMI, no statistically significant association was observed between cardiology involvement at any prior visit and BMI in the overall patient population (mean difference: -0.3 kg/m²; 95% CI: -0.7 to 0.0; p = 0.075). However, cardiology involvement was

TABLE 3 Cardiac Function Monitoring According to Cardiology Involvement Before Trastuzumab Initiation

| | Overall | Cardiology Involvement Before Trastuzumab Initiation | | p Value |
		No (n = 868)	Yes (n = 72)	
Guideline-adherent cardiac function monitoring*	577 (61.4%)	522 (60.1%)	55 (76.4%)	0.007
Cardiac biomarker assessment during trastuzumab therapy†	140 (14.9%)	120 (13.8%)	20 (27.8%)	0.001

*Defined as a baseline echocardiographic evaluation performed within 4 months before the first dose of trastuzumab was administered and a follow-up evaluation performed at least every 4 months during trastuzumab therapy. †The availability of at least 1 assessment of either cardiac troponin I or T or N-terminal pro-B-type natriuretic peptide during the course of trastuzumab therapy was considered. This analysis was performed in the subset of patients with a maximum interval of 18 months between the first and last date of trastuzumab administration (n = 940). Few patients (n = 29) had only 1 record of trastuzumab administration, and in these patients, the availability of echocardiography evaluation within 4 months of the date of trastuzumab administration was used to define guideline-adherent cardiac function monitoring.

associated with a modestly lower BMI in the subgroup of overweight or obese patients at baseline (mean difference: –0.5 kg/m^2; 95% CI: –1.0 to –0.1; p = 0.027).

OVERALL SURVIVAL. All-cause death was documented in 87 (8.3%) patients over a median [Q1, Q3] follow-up period of 26 [12, 47] months. In an inverse-probability-of-treatment weighted marginal structural model, cardiology involvement was not associated with all-cause mortality (HR: 0.87; 95% CI: 0.45 to 1.68; p = 0.680).

DISCUSSION

In this retrospective EHR-based cohort study of 1,047 patients with breast cancer treated with a trastuzumab-based regimen, cardiology involvement and its impact on cardiovascular monitoring, CVRF management, and overall survival were characterized. We found that cardiology involvement occurred in 28% of the patients beginning 3 months before the baseline visit or thereafter until the last contact date, and that preexisting HF and atrial fibrillation and

TABLE 4 Longitudinal Associations Between Cardiology Involvement and BP

| | Overall (N = 1,039) | | Hypertension at Baseline (n = 425) | |
	Beta (95% CI)	p Value	Beta (95% CI)	p Value
Systolic BP	–1.5 (–2.9 to –0.1)	0.035	–2.7 (–4.6 to –0.7)	0.007
Diastolic BP	–0.2 (–1.0 to 0.7)	0.729	0.1 (–1.2 to 1.4)	0.881
Mean BP	–0.6 (–1.6 to 0.3)	0.197	–0.9 (–2.2 to 0.5)	0.199

Beta should be interpreted as the mean difference in the outcome under consideration between those with and without cardiology involvement. Cardiology involvement was treated as a time-varying variable coded as 0 at all times before and including the first encounter with a cardiology or cardio-oncology provider and 1 at all times thereafter; models were adjusted for the baseline values of the blood pressure (BP) variable under consideration, antihypertensive medication use at baseline, and time of BP measurement from baseline (time was included using a cubic spline with 3 degrees of freedom).

CI = confidence interval.

anthracycline treatment were independently associated with cardiology involvement either at baseline or at any time during follow-up. Cardiology involvement was associated with a higher rate of guideline-adherent cardiac monitoring and improved systolic BP control. There was no significant association between cardiology involvement and overall survival.

CVD is one of the leading causes of morbidity and mortality in patients with breast cancer (16). As such, there is increasing recognition of the need for the involvement of cardiologists in the care of these patients. Currently, the role of cardiologists is largely focused on the management of cardiovascular complications associated with commonly used cancer therapies such as anthracyclines and trastuzumab (17). However, these specialists can also play a broader role, including CVRF and CVD assessment and management and long-term cardiac surveillance. This is particularly important given the burden of pre-existing CVRFs and CVDs in this patient population. For instance, in our study, the baseline prevalence of hypertension, dyslipidemia, obesity, and smoking was in the range of 23% to 40%, and nearly 6% had diabetes mellitus at baseline. CVDs including HF, atrial fibrillation, coronary artery disease, peripheral arterial disease, and cerebrovascular disease were present in 1.7% to 3.2% at baseline.

At our center, cardiology involvement occurred in approximately one-third of patients with breast cancer treated with trastuzumab. Pre-existing CVDs, particularly HF and atrial fibrillation, showed strong associations, with higher odds of cardiology involvement at baseline. Anthracycline treatment did not exhibit significant association with cardiology involvement at baseline. However, it was significantly associated with cardiology involvement during follow-up. It can be postulated that the association between anthracycline treatment and cardiology involvement during follow-up is at least partly mediated by the development of cardiac dysfunction (e.g., asymptomatic declines in LVEF and symptoms of HF) given the increased cardiotoxicity risk associated with sequential anthracycline and trastuzumab therapy (2). Furthermore, hypertension and dyslipidemia tended to be associated with higher odds of cardiology involvement at baseline, although these associations were not statistically significant (likely due to limited statistical power). The possibility of CVRFs as potential contributors to cardiology involvement at baseline cannot be excluded. These data provide some guidance that can potentially inform referral patterns to cardiology or cardio-oncology clinical practice. Consistent with general cardiology practice patterns, patients with baseline

HF or atrial fibrillation should be under cardiology care. Moreover, those with an increased burden of CVRFs such as hypertension or dyslipidemia, as well as anthracycline use, could be referred for cardiovascular care before trastuzumab therapy, with careful consideration for oncology and cardiology providers' and patient preference.

Nearly 90% of the patients had at least 1 echocardiography assessment recorded within our health care system before trastuzumab initiation or during therapy. Moreover, guideline-adherent cardiac monitoring during trastuzumab therapy was performed in 61% of the patients. This rate is higher compared with those reported in previous studies; others have shown that 36% to 46% of patients with breast cancer treated with adjuvant trastuzumab-based cancer therapy had guideline-adherent monitoring (12,18). Importantly, we observed that the rate of guideline-adherent monitoring was significantly higher in those with cardiology involvement before the initiation of trastuzumab; 76% of the patients in this subgroup had guideline-adherent monitoring. Moreover, the utilization of biomarkers was higher in the subgroup of patients with cardiology involvement, in line with previously reported findings (5).

Hypertension has been identified in multiple studies as an important modifiable risk factor for the development and progression of cardiac complications after cardiotoxic cancer therapy, including anthracyclines and trastuzumab (19,20). Our findings show that cardiology involvement is associated with a modestly lower systolic BP during follow-up, independent of systolic BP and antihypertensive medication use at baseline. The impact of cardiology involvement on systolic BP was more pronounced in the subgroup of patients with hypertension at baseline. On average, systolic BP was ~3 mm Hg lower during follow-up in patients with cardiology involvement in this subgroup. Whether these modest improvements in systolic BP control could help mitigate both the short- and long-term risk of CVD in this patient population is unclear at this time but warrants further investigation. However, there are indications that even modest reductions in BP in the general population can reduce cardiovascular morbidity and mortality. For instance, a 2 mm Hg reduction in systolic BP has been associated with a 10% reduction in stroke mortality and a 7% reduction in mortality from ischemic heart disease in middle-aged individuals (21). A recent Mendelian randomization study examining the association between genetically determined systolic BP and the lifetime risk of CVD also suggested

that small declines of ~3 mm Hg were associated with a reduced lifetime CVD risk (OR: 0.82; 95% CI: 0.79 to 0.85; p < 0.001) (22).

Our study provides important insights into the burden of CVRFs and CVDs, the current state of cardiology involvement in the management of patients with breast cancer treated with trastuzumab, and its impact on patient care. Our findings indicate a high burden of CVRFs, particularly hypertension, in this patient population. Interestingly, cardiology involvement was associated with potentially beneficial effects on BP control. Altogether, these findings suggest a need for additional comparative effectiveness studies evaluating the impact of routine involvement of cardiologists on cardiovascular and cancer-related clinical outcomes, including patient-reported outcomes, particularly in patients with elevated baseline cardiovascular risk such as hypertension.

STUDY LIMITATIONS. The current study was observational, and the limitations inherent to such studies (e.g., unmeasured confounding) should be considered in the interpretation of the findings. In addition, we analyzed data extracted from a single health system EHR. Diagnoses of CVRFs and CVDs, cardiac medication prescriptions, or procedures such as echocardiograms occurring outside our health care system were not captured, potentially leading to misclassification. Although we do not anticipate the number to be high based on our clinical practice patterns, it is also possible that patients might have been seen by providers outside our health care system. The possibility of differential misclassification related to the availability of echocardiography procedures between those with and without cardiology involvement needs consideration. Specifically, patients with cardiology involvement within our health care system before treatment initiation may be more likely to be followed up within the system, compared with those without, and this could potentially bias the comparison of guideline-adherent cardiac monitoring in favor of the subgroup with cardiology involvement. Data on cholesterol levels were also available only in a very small subset. We also limited the assessment of cardiac function to echocardiography alone, given limitations to access to nuclear imaging data. This approach may underestimate the actual proportion of patients with guideline-adherent cardiac monitoring. We used previously published and validated ICD codes to ascertain CVRFs and CVDs. Although this remains the standard method for EHR research, prior validation studies suggest that

ICD code-based case definitions might have limitations (7-10). In addition, detailed characterization of the factors that prompted cardiology involvement could not be performed due to the lack of availability of discrete documentation of specific indications for consultations in our EHR system. Detailed information on a cardiac monitoring plan and the input from cardiology providers was not available in the EHR, and we therefore could not perform further analysis to better understand the mechanisms through which cardiology involvement could lead to improved adherence to monitoring. Moreover, our study was conducted in a large academic hospital system, and our findings may not be generalizable to other settings.

CONCLUSIONS

This study found that cardiology involvement occurs in 28% of patients with breast cancer treated with a trastuzumab-based cancer therapy regimen. The presence of pre-existing HF and atrial fibrillation and anthracycline treatment was independently associated with cardiology involvement. Cardiology involvement was associated with a higher rate of guideline-adherent cardiac monitoring and improved systolic BP control. Our study motivates future studies evaluating the effectiveness of cardiology involvement in patients with breast cancer treated with a trastuzumab-based cancer therapy regimen, particularly in those with elevated cardiovascular risk before treatment initiation.

ADDRESS FOR CORRESPONDENCE: Dr. Bonnie Ky, University of Pennsylvania School of Medicine, Smilow Center for Translational Research, 3400 Civic Center Boulevard, 11-105, Philadelphia, Pennsylvania 19104. E-mail: bonnie.ky@pennmedicine.upenn.edu. Twitter: @BiniyamD, @pennmedicine, @sri_adu.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In patients with breast cancer treated with a trastuzumab-based cancer therapy regimen, cardiology involvement was associated with a higher rate of guideline-adherent cardiac monitoring and modest improvements in cardiovascular risk factor control.

TRANSLATIONAL OUTLOOK: Our findings suggest a need for additional comparative effectiveness studies evaluating the impact of routine involvement of cardiologists on cardiovascular and cancer-related clinical outcomes, including patient-reported outcomes, particularly in patients with elevated baseline cardiovascular risk.

REFERENCES

1. Lenihan DJ, Fradley MG, Dent S, et al. Proceedings from the Global Cardio-Oncology summit: the top 10 priorities to actualize for cardio-oncology. J Am Coll Cardiol CardioOnc 2019;1:256–72.

2. Seidman A, Hudis C, Pierri MK, et al. Cardiac dysfunction in the trastuzumab clinical trials experience. J Clin Oncol 2002;20:1215–21.

3. Bhatt DL. Birth and maturation of cardio-oncology. J Am Coll Cardiol CardioOnc 2019;1:114–6.

4. O'Neal WT, Claxton JS, Sandesara PB, et al. Provider specialty, anticoagulation, and stroke risk in patients with atrial fibrillation and cancer. J Am Coll Cardiol 2018;72:1913–22.

5. Gujral DM, Lloyd G, Bhattacharyya S. Provision and clinical utility of cardio-oncology services for detection of cardiac toxicity in cancer patients. J Am Coll Cardiol 2016;67:1499–500.

6. Armah KA, Chang CC, Baker JV, et al. Pre-hypertension, hypertension, and the risk of acute myocardial infarction in HIV-infected and -uninfected veterans. Clin Infect Dis 2014;58:121–9.

7. Quan H, Khan N, Hemmelgarn BR, et al. Validation of a case definition to define hypertension using administrative data. Hypertension 2009;54:1423–8.

8. Tu K, Campbell NR, Chen ZL, Cauch-Dudek KJ, McAlister FA. Accuracy of administrative databases in identifying patients with hypertension. Open Med 2007;1:e18–26.

9. Quan H, Li B, Saunders LD, et al. Assessing validity of ICD-9-CM and ICD-10 administrative data in recording clinical conditions in a unique dually coded database. Health Serv Res 2008;43:1424–41.

10. Khokhar B, Jette N, Metcalfe A, et al. Systematic review of validated case definitions for diabetes in ICD-9-coded and ICD-10-coded data in adult populations. BMJ Open 2016;6:e009952.

11. Cozzolino F, Montedori A, Abraha I, et al. A diagnostic accuracy study validating cardiovascular ICD-9-CM codes in healthcare administrative databases. The Umbria data-value project. PLoS One 2019;14:e0218919.

12. Chavez-MacGregor M, Niu J, Zhang N, et al. Cardiac monitoring during adjuvant trastuzumab-based chemotherapy among older patients with breast cancer. J Clin Oncol 2015;33:2176–83.

13. Curigliano G, Cardinale D, Suter T, et al. Cardiovascular toxicity induced by chemotherapy, targeted agents and radiotherapy: ESMO clinical practice guidelines. Ann Oncol 2012;23 Suppl 7:vii155-66.

14. Robins JM, Hernan MA, Brumback B. Marginal structural models and causal inference in epidemiology. Epidemiology 2000;11:550–60.

15. Hernan MA, Brumback B, Robins JM. Marginal structural models to estimate the causal effect of zidovudine on the survival of HIV-positive men. Epidemiology 2000;11:561–70.

16. Abdel-Qadir H, Austin PC, Lee DS, et al. A population-based study of cardiovascular mortality following early-stage breast cancer. JAMA Cardiol 2017;2:88–93.

17. Pareek N, Cevallos J, Moliner P, et al. Activity and outcomes of a cardio-oncology service in the United Kingdom—a five-year experience. Eur J Heart Fail 2018;20:1721–31.

18. Henry ML, Niu J, Zhang N, Giordano SH, Chavez-MacGregor M. Cardiotoxicity and cardiac

monitoring among chemotherapy-treated breast cancer patients. J Am Coll Cardiol Img 2018;11: 1084–93.

19. Armstrong GT, Oeffinger KC, Chen Y, et al. Modifiable risk factors and major cardiac events among adult survivors of childhood cancer. J Clin Oncol 2013;31:3673–80.

20. Russo G, Cioffi G, Gori S, et al. Role of hypertension on new onset congestive heart failure in patients receiving trastuzumab therapy for breast cancer. J Cardiovasc Med (Hagerstown) 2014;15:141–6.

21. Lewington S, Clarke R, Qizilbash N, et al. Prospective studies collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet 2002;360:1903–13.

22. Ference BA, Bhatt DL, Catapano AL, et al. Association of genetic variants related to combined exposure to lower low-density lipoproteins and lower systolic blood pressure with lifetime risk of cardiovascular disease. JAMA 2019;322:1381–91.

KEY WORDS breast cancer, electronic health record, HER2 therapy

---

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