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ORIGINAL RESEARCH

Pharmacovigilance Analysis of Heart Failure Associated With Anti-HER2 Monotherapies and Combination Regimens for Cancer

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ABSTRACT

BACKGROUND Trastuzumab improves outcomes in patients with HER2-overexpressing malignancies but is associated with decreases in left ventricular ejection fraction. Heart failure (HF) risks from other anti-HER2 therapies are less clear.

OBJECTIVES Using World Health Organization pharmacovigilance data, the authors compared HF odds across anti-HER2 regimens.

METHODS In VigiBase, 41,976 patients had adverse drug reactions (ADRs) with anti-HER2 monoclonal antibodies (trastuzumab, n = 16,900; pertuzumab, n = 1,856), antibody-drug conjugates (trastuzumab emtansine [T-DM1], n = 3,983; trastuzumab deruxtecan, n = 947), and tyrosine kinase inhibitors (afatinib, n = 10,424; lapatinib, *n* = 5,704; neratinib, n = 1,507; tucatinib, n = 655); additionally, 36,052 patients had ADRs with anti-HER2-based combination regimens. Most patients had breast cancer (monotherapies, n = 17,281; combinations, n = 24,095). Outcomes included comparison of HF odds with each monotherapy relative to trastuzumab, within each therapeutic class, and among combination regimens.

RESULTS Of 16,900 patients with trastuzumab-associated ADRs, 2,034 (12.04%) had HF reports (median time to onset 5.67 months; IQR: 2.85-9.32 months) compared with 1% to 2% with antibody-drug conjugates. Trastuzumab had higher odds of HF reporting relative to other anti-HER2 therapies collectively in the overall cohort (reporting OR [ROR]: 17.37; 99% CI: 14.30-21.10) and breast cancer subgroup (ROR: 17.10; 99% CI: 13.12-22.27). Pertuzumab/T-DM1 had 3.4 times higher odds of HF reporting than T-DM1 monotherapy; tucatinib/trastuzumab/capecitabine had similar odds as tucatinib. Among metastatic breast cancer regimens, HF odds were highest with trastuzumab/pertuzumab/docetaxel (ROR: 1.42; 99% CI: 1.17-1.72) and lowest with lapatinib/capecitabine (ROR: 0.09; 99% CI: 0.04-0.23).

CONCLUSIONS Trastuzumab and pertuzumab/T-DM1 had higher odds of HF reporting than other anti-HER2 therapies. These data provide large-scale, real-world insight into which HER2-targeted regimens would benefit from left ventricular ejection fraction monitoring. (J Am Coll Cardiol CardioOnc 2023;5:85-98) © 2023 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/).

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ABBREVIATIONS AND ACRONYMS

ACTH = doxorubicin/cyclophosphamide followed by trastuzumab/paclitaxel

AC-THP = doxorubicin/cyclophosphamide followed by paclitaxel/trastuzumab/pertuzumab

ADC = antibody-drug conjugate

ADR = adverse drug reaction

AI = aromatase inhibitor

FDA = U.S. Food and Drug Administration

HF = heart failure

IC = information component

LVEF = left ventricular ejection fraction

ROR = reporting odds ratio

T-DM1 = trastuzumab emtansine

T-DXd = trastuzumab deruxtecan

HER2 is a major therapeutic target for patients with HER2-overexpressing malignancies, including 15% to 20% of breast cancers,[1-3] 10% to 30% of gastroesophageal cancers,[4,5] and others. Anti-HER2 therapies include the monoclonal antibodies trastuzumab and pertuzumab, tyrosine kinase inhibitors (tucatinib, neratinib, lapatinib, afatinib, and others), and the antibody-drug conjugates (ADCs) trastuzumab deruxtecan (T-DXd) and trastuzumab emtansine (T-DM1). HER2 receptors are an effective oncologic target because of the role of HER2 signaling in cell proliferation, tumor angiogenesis, and prevention of apoptosis.[6,7] However, inhibiting HER2 with trastuzumab has known risk for cardiotoxicity, potentially due to the role of neuregulin-1/HER2 signaling in cardiomyocyte survival and maintenance of normal myofibrillar structure.[8,9]

Previous studies of trastuzumab showed an 8% to 13% incidence of left ventricular ejection fraction (LVEF) decrease.[10-12] Despite the use of anti-HER2 therapies across multiple malignancy types and the emergence of multiple anti-HER2-based combination regimens, to our knowledge, no previous studies have systematically compared the risk for heart failure (HF) among different monotherapies or combination regimens. We used a pharmacovigilance database to evaluate the association between different anti-HER2 monotherapies and combination regimens with HF.

METHODS

STUDY DESIGN. This retrospective pharmacovigilance study used VigiBase, the World Health Organization database of reports of deidentified adverse drug reactions (ADRs) from >130 countries that is managed by Uppsala Monitoring Centre in Sweden.[13] VigiBase contains >28 million ADRs from cancer and noncancer therapies reported by health care professionals, pharmaceutical companies, and patients during the postmarketing period. The Stanford Institutional Review Board determined that this study was exempt from review because of the deidentified nature of the VigiBase data.

We extracted all HF cases (symptomatic and asymptomatic) reported between database inception on November 14, 1967, and November 30, 2021. ADRs in VigiBase are coded using the World Health Organization Adverse Reactions Terminology and the Medical Dictionary for Regulatory Activities (Supplemental Table 1).

We included distinct patients with ADRs suspected to be caused by drugs from the following anti-HER2 therapies: 1) monoclonal antibodies (trastuzumab and pertuzumab); 2) ADCs (T-DM1 and T-DXd); 3) the selective HER2 tyrosine kinase inhibitor tucatinib; and 4) nonselective HER2 tyrosine kinase inhibitors (neratinib, lapatinib, and afatinib). We also included patients who received regimens combining anti-HER2 drugs with other anti-HER2 therapy (eg, pertuzumab/T-DM1) or with chemotherapy (eg, lapatinib/capecitabine). Drugs with <250 ADRs were excluded: dacomitinib (n = 208), mobocertinib (n = 84), poziotinib (n = 31), margetuximab (n = 7), and pyrotinib (n = 0).

For each patient, we retrieved demographic characteristics (sex and age), clinical characteristics (malignancy type), administrative information (country of origin, report date, and reporter qualification), drug characteristics, and reaction details (time to onset, seriousness, and recovery status). Serious adverse events were life threatening or resulted in death, significant disability, or hospitalization.

STATISTICAL ANALYSIS. Disproportionality analyses evaluated if cardiotoxicities were differentially reported with anti-HER2 therapies relative to the full VigiBase database. Case-noncase disproportionality analyses compared the proportion of patients with ADRs associated with specific drugs or drug classes with the proportion of those same ADRs for a comparison group.[14] Reporting odds ratios (RORs) were calculated to compare rates of cardiovascular ADRs from each anti-HER2 monotherapy relative to: 1) other agents in same class (eg, T-DM1 vs T-DXd); 2) trastuzumab (eg, T-DM1 vs trastuzumab); 3) the other 7 anti-HER2 drugs collectively (eg, lapatinib vs the other 7 therapies); and 4) all drugs in VigiBase (not exclusive to antineoplastic drugs). To reduce the risk for type I error, a 2-sided alpha level of 0.01 was used to determine statistical significance. We performed analyses both in the full cohort and breast cancer subgroup. Non-normally distributed data are

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.

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TABLE 1 Characteristics of Patients With ADRs Associated With Anti-HER2 Monotherapies or Combination/Sequential Therapies

	Monotherapies		Combination/Sequential Therapies	
	All ADRs (n = 41,976)[a]	Heart Failure (n = 2,230)	All ADRs (n = 36,052)[a]	Heart Failure (n = 2,057)
Reporting region				
Africa	251 (0.60)	20 (0.90)	357 (0.99)	8 (0.39)
Americas	17,477 (41.64)	820 (36.77)	14,731 (40.86)	833 (40.50)
Asia	12,388 (29.51)	321 (14.39)	8,508 (23.60)	323 (15.70)
Europe	11,312 (26.95)	981 (43.99)	12,079 (33.50)	876 (42.59)
Oceania	548 (1.31)	88 (3.95)	377 (1.05)	34 (1.65)
Reporters				
Health care professional	28,679 (68.32)	1,842 (82.60)	28,513 (79.09)	1,794 (87.21)
Non-health care professional	12,266 (29.22)	301 (13.50)	6,590 (18.28)	195 (9.48)
Unknown	1,031 (2.46)	87 (3.90)	949 (2.63)	68 (3.31)
Reporting year				
Before 2008	462 (1.10)	75 (3.36)	1,024 (2.84)	47 (2.28)
2008-2012	4,864 (11.59)	507 (22.74)	5,846 (16.22)	285 (13.86)
2013-2017	14,955 (35.63)	894 (40.09)	14,358 (39.83)	893 (43.41)
2018-2021	21,695 (51.68)	754 (33.81)	14,824 (41.12)	832 (40.45)
Sex				
Female	32,346 (77.06)	1,991 (89.28)	32,589 (90.39)	1,834 (89.16)
Male	5,044 (12.02)	61 (2.74)	1,304 (3.62)	77 (3.74)
Unknown	4,586 (10.93)	178 (7.98)	2,159 (5.99)	146 (7.10)
Age				
18-44 y	3,452 (8.22)	178 (7.98)	5,394 (14.96)	247 (12.01)
45-64 y	13,935 (33.20)	706 (31.66)	15,570 (43.19)	811 (39.43)
65-74 y	5,910 (14.08)	272 (12.20)	4,399 (12.20)	278 (13.51)
≥75 y	3,302 (7.87)	110 (4.93)	1,302 (3.61)	104 (5.06)
Unknown	15,377 (36.63)	964 (43.23)	9,684 (26.86)	617 (30.00)
Indication				
Breast	17,281 (41.17)	1,574 (70.58)	24,095 (66.83)	1,689 (82.11)
Lung	7,477 (17.81)	41 (1.84)	56 (0.16)	0 (0)
Gastroesophageal	350 (0.83)	18 (0.81)	825 (2.29)	32 (1.56)
Head and neck	112 (0.27)	2 (0.09)	47 (0.13)	4 (0.19)
Colon	79 (0.19)	0 (0)	101 (0.28)	2 (0.10)
Cervical/vulvar/vaginal	43 (0.10)	0 (0)	37 (0.10)	0 (0)
Endometrial	35 (0.08)	0 (0)	35 (0.10)	1 (0.05)
Bladder	27 (0.06)	0 (0)	40 (0.11)	5 (0.24)
Pancreatic	24 (0.06)	0 (0)	24 (0.07)	0 (0)
Prostate	22 (0.05)	1 (0.04)	5 (0.01)	0 (0)
Biliary	19 (0.05)	0 (0)	26 (0.07)	1 (0.05)
Hematological cancer and lymphoma	17 (0.04)	1 (0.04)	29 (0.08)	0 (0)
Hepatic	10 (0.02)	0 (0)	9 (0.02)	2 (0.10)
Central nervous system	6 (0.01)	0 (0)	0 (0)	0 (0)
Renal	4 (0.01)	1 (0.04)	3 (0.01)	0 (0)
Cutaneous	3 (0.01)	0 (0)	173 (0.48)	4 (0.19)
Other/unspecified	16,467 (39.23)	592 (26.55)	10,547 (29.25)	317 (15.41)

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presented as median (IQR) and were compared using Kruskal-Wallis tests followed by Dunn's post hoc multiple comparison tests.

The information component (IC) was calculated to compare each drug relative to the full VigiBase database, assessing the strength of each drug-ADR association. Calculated using a Bayesian confidence propagation neural network, the IC is a logarithm of the ratio of observed rate of ADRs to the expected rate assuming the null hypothesis (Supplemental Figure 1). A positive (>0) value of IC_{025} (the lower end of the IC 95% credibility interval) indicates a statistically significant drug-ADR association. As IC has been validated only for comparing drugs against the full VigiBase database,[14-16] we used both ROR and IC when comparing each anti-HER2 therapy against

TABLE 1 Continued

	Monotherapies		Combination/Sequential Therapies	
	All ADRs (n = 41,976)[a]	Heart Failure (n = 2,230)	All ADRs (n = 36,052)[a]	Heart Failure (n = 2,057)
Serious adverse event	–	358 (16.05)	–	626 (30.43)
Fatal adverse event	–	67 (3.00)	–	143 (6.95)
Drug/regimen received				
Trastuzumab	16,900 (40.26)	2,034 (91.21)	–	–
Afatinib	10,424 (24.83)	42 (1.88)	–	–
Lapatinib	5,704 (13.59)	36 (1.61)	–	–
Trastuzumab emtansine	3,983 (9.49)	66 (2.96)	–	–
Pertuzumab	1,856 (4.42)	36 (1.61)	–	–
Neratinib	1,507 (3.59)	3 (0.13)	–	–
Trastuzumab deruxtecan	947 (2.26)	11 (0.49)	–	–
Tucatinib	655 (1.56)	2 (0.09)	–	–
Lapatinib + capecitabine	–	–	6,275 (17.41)	39 (1.90)
Docetaxel + trastuzumab	–	–	5,462 (15.15)	435 (21.15)
Trastuzumab + platinum-based chemotherapy	–	–	4,875 (13.52)	195 (9.48)
Trastuzumab + pertuzumab	–	–	3,613 (10.02)	286 (13.90)
Trastuzumab + pertuzumab + docetaxel	–	–	3,401 (9.43)	268 (13.03)
Docetaxel + carboplatin + trastuzumab	–	–	2,161 (5.99)	93 (4.52)
Trastuzumab + HER2 tyrosine kinase inhibitor	–	–	1,800 (4.99)	149 (7.24)
Trastuzumab + pertuzumab + paclitaxel	–	–	1,580 (4.38)	150 (7.29)
Lapatinib + trastuzumab	–	–	1,138 (3.16)	75 (3.65)
Lapatinib + taxane-based chemotherapy			1,052 (2.92)	67 (3.26)
Pertuzumab + trastuzumab emtansine	–	–	898 (2.49)	48 (2.33)
Docetaxel + carboplatin + trastuzumab + pertuzumab	–	–	844 (2.34)	26 (1.26)
Lapatinib + trastuzumab + capecitabine	–	–	575 (1.59)	29 (1.41)
Trastuzumab + pertuzumab + capecitabine	–	–	444 (1.23)	36 (1.75)
Doxorubicin + cyclophosphamide + trastuzumab + paclitaxel	–	–	402 (1.12)	89 (4.33)
Lapatinib + vinorelbine	–	–	287 (0.80)	14 (0.68)
Tucatinib + trastuzumab + capecitabine	–	–	270 (0.75)	5 (0.24)
Lapatinib + platinum-based chemotherapy			264 (0.73)	8 (0.39)
Pertuzumab + lapatinib	–	–	216 (0.60)	10 (0.49)
Lapatinib + carboplatin + paclitaxel	–	–	152 (0.42)	5 (0.24)
Trastuzumab + immune checkpoint inhibitor	–	–	152 (0.42)	8 (0.39)
Trastuzumab + AI (or fulvestrant) + CDK4/6 inhibitor	–	–	116 (0.32)	5 (0.24)
Doxorubicin + cyclophosphamide + trastuzumab + pertuzumab + paclitaxel	–	–	75 (0.21)	17 (0.83)

Values are n (%). [a]Reflects the number of distinct patients with any adverse drug reaction reported from anti-HER2 monotherapies or combination/sequential regimens.
ADR = adverse drug reactions; AI = aromatase inhibitor; CDK4/6 = cyclin-dependent kinase 4 and 6.

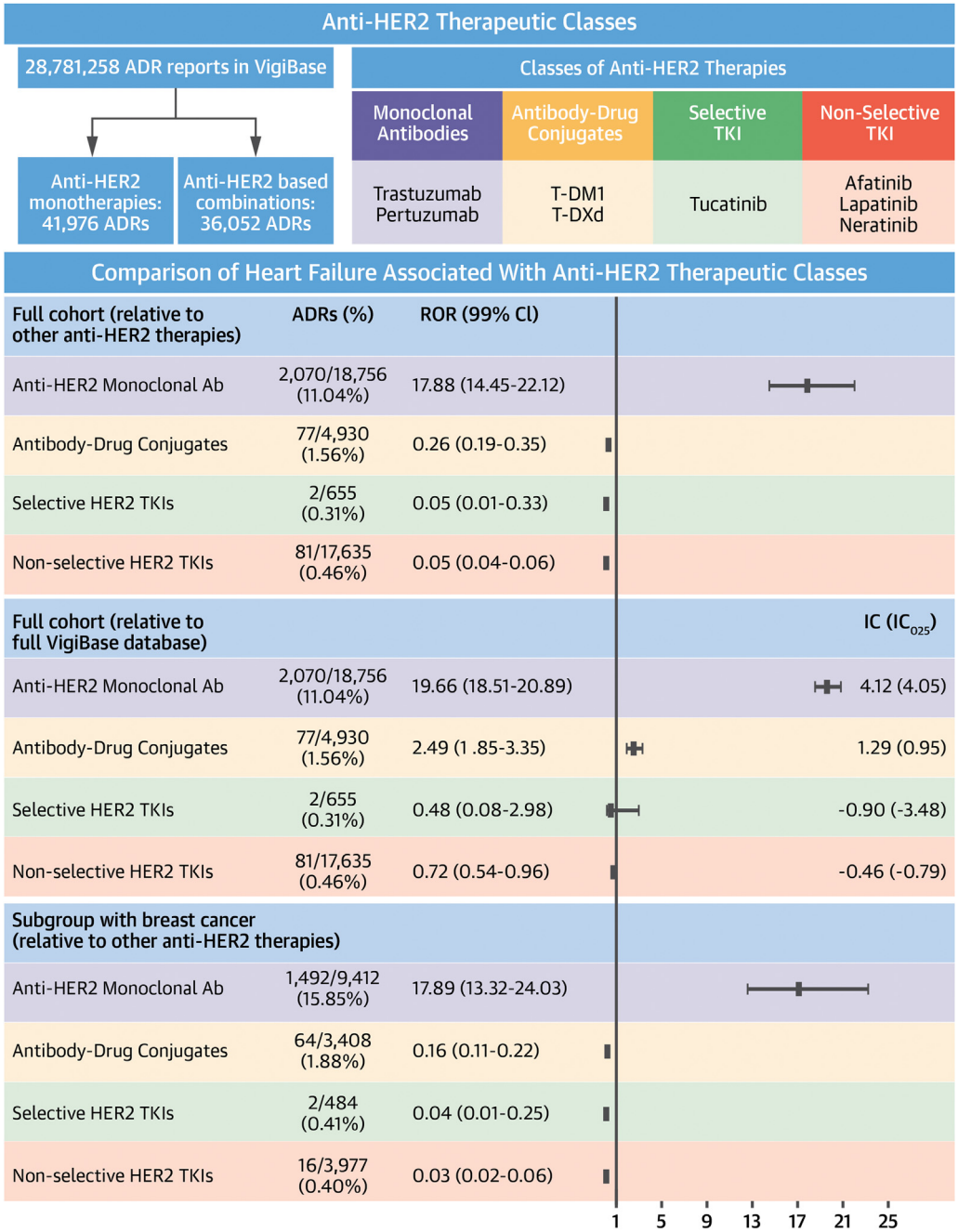
the full database and only ROR when comparing anti-HER2 drugs and classes with each other. Statistical analyses were performed using SAS version 9.4 (SAS Institute).

RESULTS

HF ASSOCIATED WITH ANTI-HER2 MONOTHERAPIES. Of 41,976 patients with ADR reports with any anti-HER2 monotherapy in VigiBase, 2,230 (5.31%) were reported to have HF (Table 1). Of 18,756 patients with ADRs with anti-HER2 monoclonal antibodies, 2,070 (11.04%) had HF reports, compared with 1.56% (77 of 4,930) with ADCs, 0.31% (2 of 655) with selective HER2 tyrosine kinase inhibitors, and 0.46% (81 of 17,635) with nonselective HER2 tyrosine kinase inhibitors (Central Illustration). Collectively, anti-HER2 monoclonal antibodies had higher odds of HF reports relative to other anti-HER2 therapeutic classes, both in the full cohort (ROR: 17.88; 99% CI: 14.45-22.12) and in the breast cancer subgroup (ROR: 17.89; 99% CI: 13.32-24.03).

Trastuzumab had higher odds of HF reports relative to the full VigiBase database (ROR: 21.69; 99% CI: 20.40-23.05; IC_{025} = 4.18 [indicating a significant drug-ADR association]) and relative to other anti-HER2 therapies collectively (ROR: 17.37; 99% CI: 14.30-21.10) (Figure 1A), with similar findings in the

CENTRAL ILLUSTRATION **Heart Failure Associated With Anti-HER2 Monotherapies**



Waliany S, et al. J Am Coll Cardiol CardioOnc. 2023;5(1):85-98.

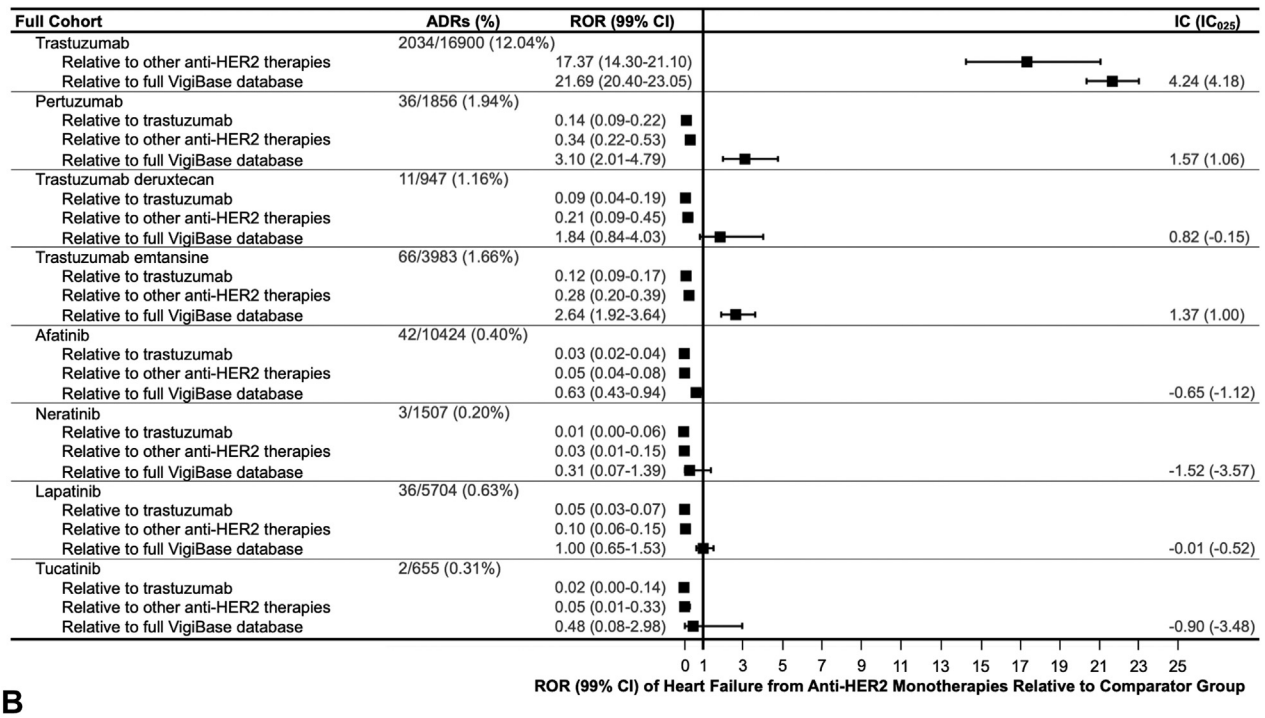
Anti-HER2 monoclonal antibodies (Abs) had ~17 times higher odds of heart failure relative to other anti-HER2 therapeutic classes in the full cohort and breast cancer subgroup. Monoclonal antibodies and antibody-drug conjugates had ~19 and ~2.5 times higher odds of heart failure relative to the full VigiBase database. In this illustration, the collective drug classes are compared with the full VigiBase database. ADR = adverse drug reaction; IC = information component; ROR = reporting odds ratio; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan; TKI = tyrosine kinase inhibitor.

JACC: CARDIOONCOLOGY, VOL. 5, NO. 1, 2023
FEBRUARY 2023:85–98

FIGURE 1 Heart Failure With Individual Anti-HER2 Monotherapies in Full Cohort and Breast Cancer Subgroup

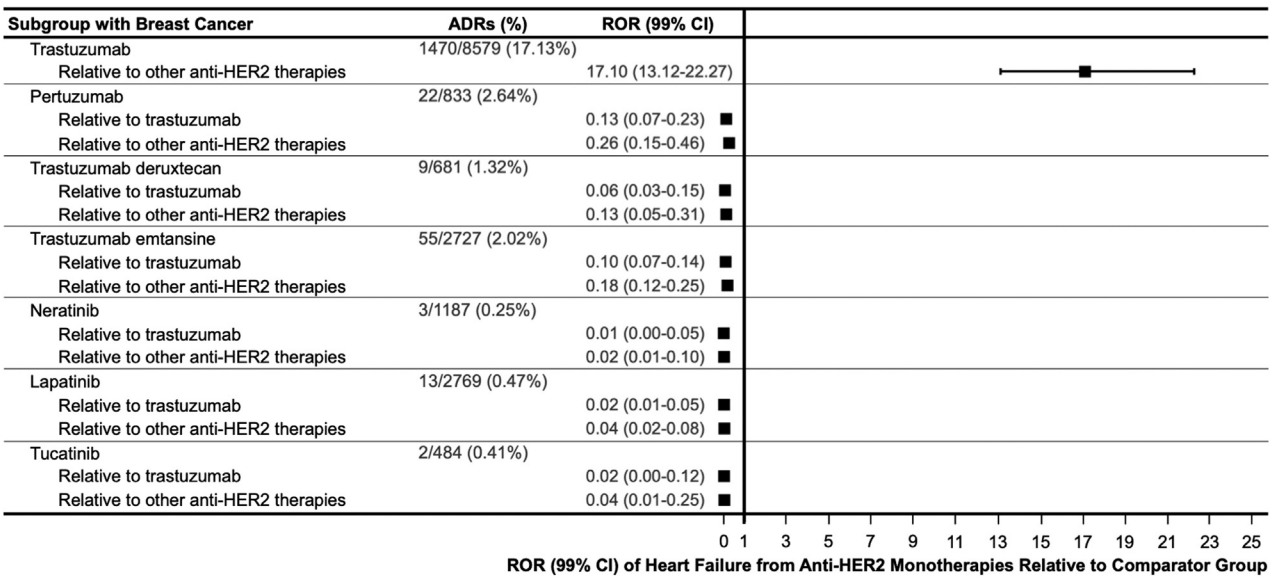
A

Full Cohort	ADRs (%)	ROR (99% CI)	IC (IC_{025})
Trastuzumab	2034/16900 (12.04%)		
Relative to other anti-HER2 therapies		17.37 (14.30-21.10)	
Relative to full VigiBase database		21.69 (20.40-23.05)	4.24 (4.18)
Pertuzumab	36/1856 (1.94%)		
Relative to trastuzumab		0.14 (0.09-0.22)	
Relative to other anti-HER2 therapies		0.34 (0.22-0.53)	
Relative to full VigiBase database		3.10 (2.01-4.79)	1.57 (1.06)
Trastuzumab deruxtecan	11/947 (1.16%)		
Relative to trastuzumab		0.09 (0.04-0.19)	
Relative to other anti-HER2 therapies		0.21 (0.09-0.45)	
Relative to full VigiBase database		1.84 (0.84-4.03)	0.82 (-0.15)
Trastuzumab emtansine	66/3983 (1.66%)		
Relative to trastuzumab		0.12 (0.09-0.17)	
Relative to other anti-HER2 therapies		0.28 (0.20-0.39)	
Relative to full VigiBase database		2.64 (1.92-3.64)	1.37 (1.00)
Afatinib	42/10424 (0.40%)		
Relative to trastuzumab		0.03 (0.02-0.04)	
Relative to other anti-HER2 therapies		0.05 (0.04-0.08)	
Relative to full VigiBase database		0.63 (0.43-0.94)	-0.65 (-1.12)
Neratinib	3/1507 (0.20%)		
Relative to trastuzumab		0.01 (0.00-0.06)	
Relative to other anti-HER2 therapies		0.03 (0.01-0.15)	
Relative to full VigiBase database		0.31 (0.07-1.39)	-1.52 (-3.57)
Lapatinib	36/5704 (0.63%)		
Relative to trastuzumab		0.05 (0.03-0.07)	
Relative to other anti-HER2 therapies		0.10 (0.06-0.15)	
Relative to full VigiBase database		1.00 (0.65-1.53)	-0.01 (-0.52)
Tucatinib	2/655 (0.31%)		
Relative to trastuzumab		0.02 (0.00-0.14)	
Relative to other anti-HER2 therapies		0.05 (0.01-0.33)	
Relative to full VigiBase database		0.48 (0.08-2.98)	-0.90 (-3.48)



B

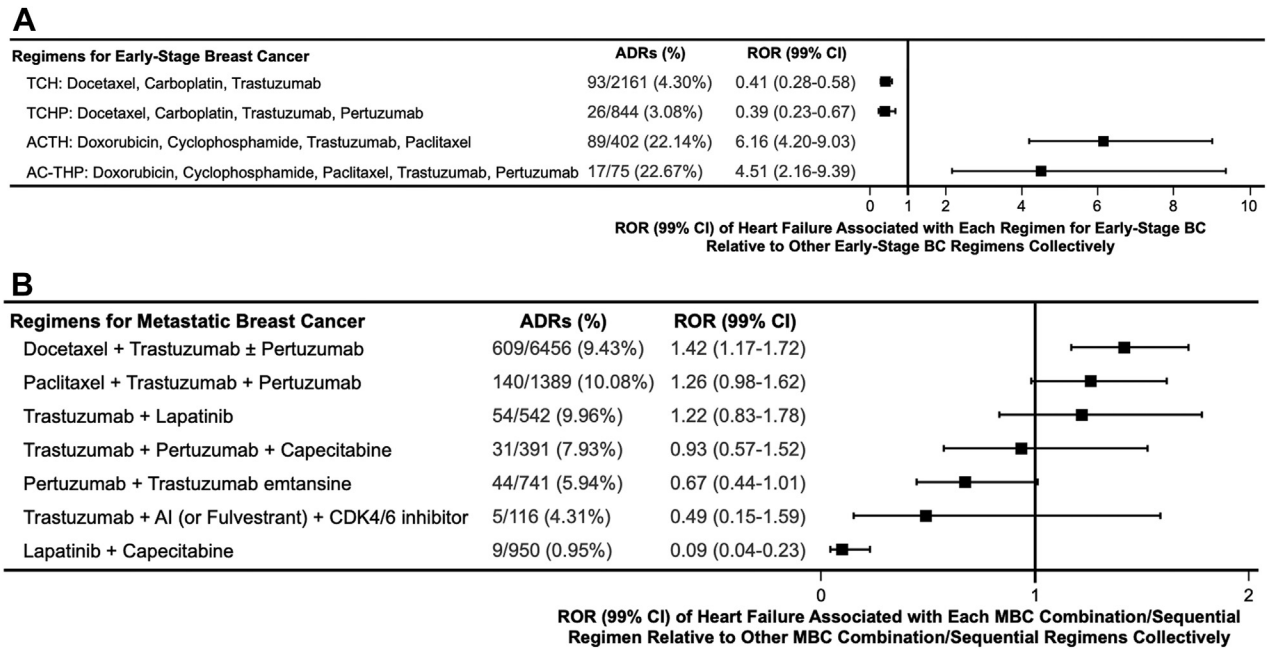
Subgroup with Breast Cancer	ADRs (%)	ROR (99% CI)
Trastuzumab	1470/8579 (17.13%)	
Relative to other anti-HER2 therapies		17.10 (13.12-22.27)
Pertuzumab	22/833 (2.64%)	
Relative to trastuzumab		0.13 (0.07-0.23)
Relative to other anti-HER2 therapies		0.26 (0.15-0.46)
Trastuzumab deruxtecan	9/681 (1.32%)	
Relative to trastuzumab		0.06 (0.03-0.15)
Relative to other anti-HER2 therapies		0.13 (0.05-0.31)
Trastuzumab emtansine	55/2727 (2.02%)	
Relative to trastuzumab		0.10 (0.07-0.14)
Relative to other anti-HER2 therapies		0.18 (0.12-0.25)
Neratinib	3/1187 (0.25%)	
Relative to trastuzumab		0.01 (0.00-0.05)
Relative to other anti-HER2 therapies		0.02 (0.01-0.10)
Lapatinib	13/2769 (0.47%)	
Relative to trastuzumab		0.02 (0.01-0.05)
Relative to other anti-HER2 therapies		0.04 (0.02-0.08)
Tucatinib	2/484 (0.41%)	
Relative to trastuzumab		0.02 (0.00-0.12)
Relative to other anti-HER2 therapies		0.04 (0.01-0.25)



(A) Full cohort. **(B)** Breast cancer subgroup. Trastuzumab had 17 times higher odds of heart failure relative to other anti-HER2 therapies. Trastuzumab, pertuzumab, and trastuzumab emtansine had 21, 3, and 2.6 times higher odds of heart failure relative to the full VigiBase database. ADR = adverse drug reaction; IC = information component; ROR = reporting odds ratio.

breast cancer subgroup (Figure 1B). Of 16,900 patients with ADR reports with trastuzumab, 2,034 (12.04%) had HF reports (median time to onset 5.67 months; IQR: 2.85-9.32 months), compared with 1.94% with pertuzumab (36 of 1,856), 1.66% with T-DM1 (66 of 3,983), and 1.16% with T-DXd (11 of 947). Trastuzumab, pertuzumab, and T-DM1 had higher odds of HF reports relative to the full VigiBase database

FIGURE 2 Heart Failure With Regimens for Early-Stage Breast Cancer and MBC



(A) AC-THP and ACTH had 4.5 and 6.2 times higher odds of heart failure, respectively, relative to non-anthracycline-based regimens for early-stage breast cancer. **(B)** Among regimens for metastatic breast cancer (MBC), docetaxel/trastuzumab with or without pertuzumab had the highest odds and lapatinib/capecitabine had the lowest odds of heart failure. AI = aromatase inhibitor; BC = breast cancer; other abbreviations as in Figure 1.

(Figure 1A). Of patients with available data on recovery status, about 66.58% (534 of 802) of trastuzumab-associated HF cases had recovery; 14.75% of trastuzumab-associated HF cases were determined to be serious.

On within-class analyses, nonselective HER2 tyrosine kinase inhibitors (lapatinib, neratinib, and afatinib) had similar odds of HF reports; T-DXd had similar odds relative to T-DM1, with similar results in the breast cancer subgroup (Supplemental Table 2). Characteristics of patients with HF associated with anti-HER2 monotherapies are shown in Supplemental Tables 3 to 10.

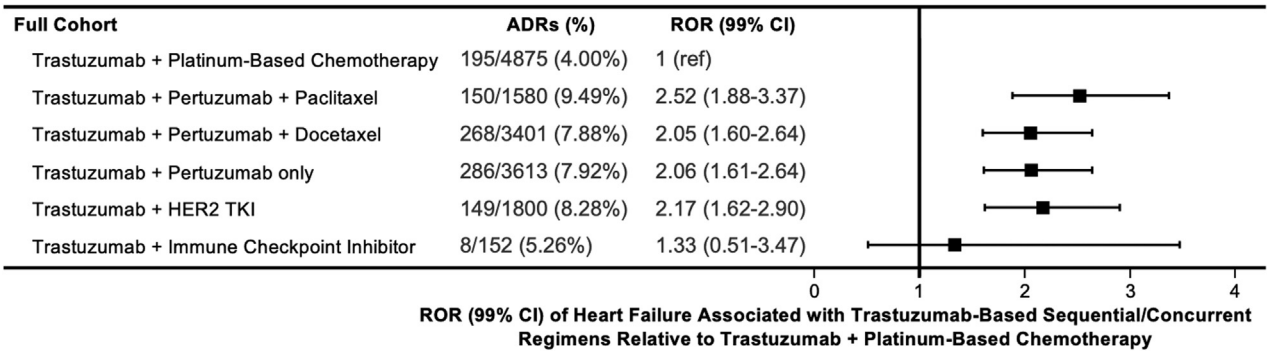
As most ADR reports with T-DXd were from 2020 and 2021, subgroup analyses limited to patients with ADRs reported in 2020 and 2021 produced similar results (Supplemental Table 11), with higher odds of HF reports with trastuzumab relative to other anti-HER2 agents in the full cohort (ROR: 12.17; 99% CI: 7.91-18.72) and breast cancer subgroup (ROR: 11.80; 99% CI: 6.93-20.09).

REGIMENS FOR EARLY-STAGE AND METASTATIC BREAST CANCER. About 22% of patients treated with ACTH (doxorubicin/cyclophosphamide followed by trastuzumab/paclitaxel) or AC-THP (doxorubicin/cyclophosphamide followed by paclitaxel/trastuzumab/pertuzumab) were reported to have HF. Both ACTH and AC-THP were associated with 4 to 6 times higher odds of HF reporting among early-stage breast cancer regimens compared with docetaxel/carboplatin/trastuzumab and docetaxel/carboplatin/trastuzumab/pertuzumab (Figure 2A).

In analyses comparing the odds of HF reports associated with 7 regimens for metastatic breast cancer collectively (Figure 2B), docetaxel/trastuzumab with or without pertuzumab had higher odds of HF relative to other regimens (ROR: 1.42; 99% CI: 1.17-1.72), and lapatinib/capecitabine had lower odds of HF relative to other regimens (ROR: 0.09; 99% CI: 0.04-0.23). Characteristics of patients with HF associated with early-stage and metastatic regimens are shown in Supplemental Tables 12 to 23.

Using Kruskal-Wallis analysis, treatment duration had a statistically significant difference among the 7 metastatic breast cancer regimens collectively; using Dunn's post hoc test for multiple comparisons, docetaxel/trastuzumab with or without pertuzumab had similar treatment duration (median 4.02 months;

FIGURE 3 Heart Failure Associated With Trastuzumab-Based Combination/Sequential Regimens in the Full Cohort



Relative to trastuzumab/platinum-based chemotherapy, most trastuzumab-based combination and sequential regimens had higher odds of heart failure, with the exception of trastuzumab/immune checkpoint inhibitor. TKI = tyrosine kinase inhibitor; other abbreviations as in Figure 1.

IQR: 1.9-8.0 months) as lapatinib/capecitabine (median 4.00 months; IQR: 1.92-8.25 months; $P = 0.99$), paclitaxel/trastuzumab/pertuzumab (median 4.17; IQR: 2.04-7.56 months; $P = 0.98$), and trastuzumab/aromatase inhibitor (AI)/CDK4/6 inhibitor (median 3.83; IQR: 1.93-11.92 months; $P = 0.76$); longer treatment duration than lapatinib/trastuzumab (median 2.98; IQR: 1.17-6.50 months; $P < 0.001$); and shorter treatment duration than pertuzumab/T-DM1 (median 4.98; IQR: 2.89-8.18 months; $P < 0.001$) and trastuzumab/pertuzumab/capecitabine (median 5.00; IQR: 2.92-8.57 months; $P = 0.002$). Lapatinib/capecitabine had a similar treatment duration as paclitaxel/trastuzumab/pertuzumab and trastuzumab/AI/CDK4/6 inhibitor but shorter treatment duration than lapatinib/trastuzumab ($P < 0.001$), pertuzumab/T-DM1 ($P = 0.003$), and trastuzumab/pertuzumab/capecitabine ($P = 0.004$).

OTHER COMBINATION REGIMENS. In the full cohort, relative to trastuzumab/platinum-based chemotherapy, 2 to 3 times higher odds of HF reporting were observed with trastuzumab/pertuzumab/paclitaxel, trastuzumab/pertuzumab/docetaxel, trastuzumab/pertuzumab, and trastuzumab/HER2 tyrosine kinase inhibitor; trastuzumab/immune checkpoint inhibitor combinations were not associated with higher odds of HF reporting relative to trastuzumab/platinum-based chemotherapy (Figure 3). Characteristics of patients with HF associated with trastuzumab-containing combinations are shown in Supplemental Tables 24 to 27.

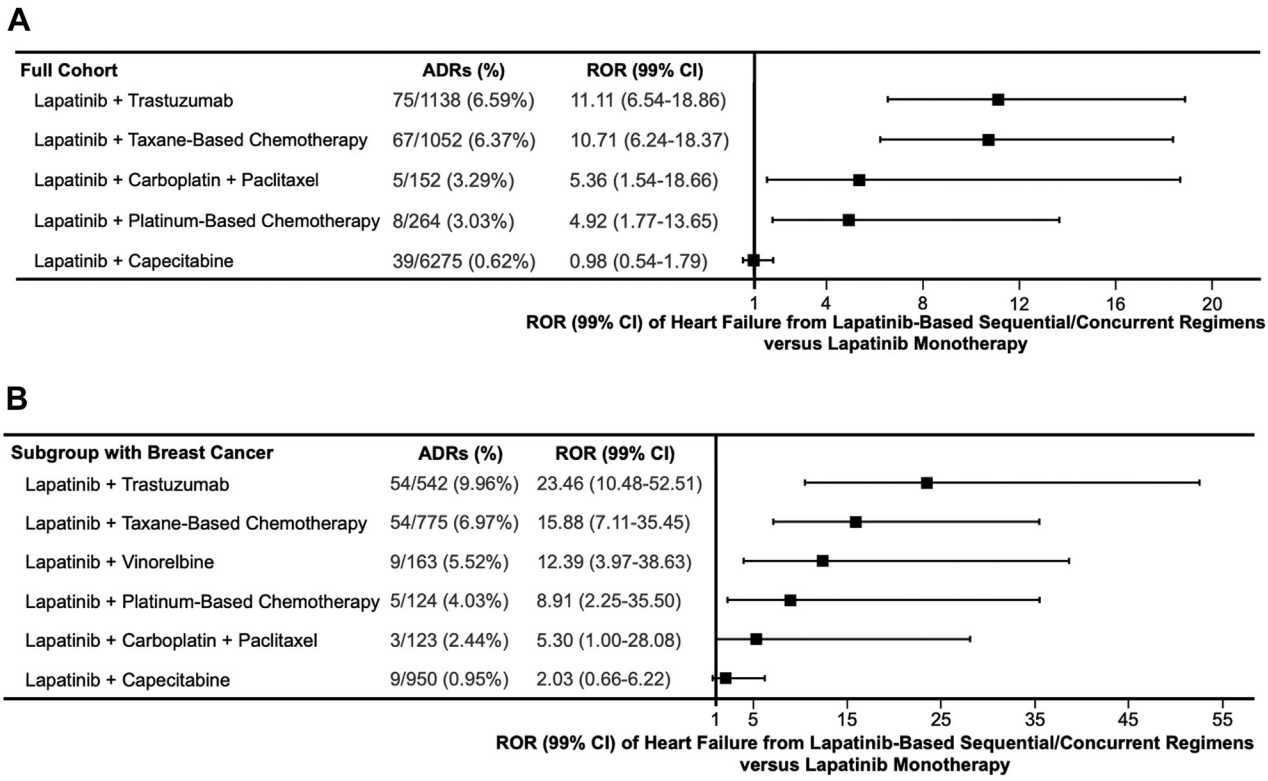
Among 5,704 patients with ADRs with lapatinib monotherapy, only 36 (0.63%) were reported to have HF. Relative to lapatinib monotherapy, lapatinib/trastuzumab and lapatinib/taxane-based chemotherapy had 10 to 11 times higher odds of HF reports, and lapatinib/platinum-based chemotherapy, and lapatinib/carboplatin/paclitaxel had 4 to 5 times higher odds of HF reports (Figure 4A). Similar findings were observed in the subgroup with breast cancer (Figure 4B). Lapatinib/capecitabine had similar odds of HF reports relative to lapatinib monotherapy. Characteristics of patients with reports of HF associated with lapatinib-based combinations are shown in Supplemental Tables 28 to 32.

Pertuzumab/T-DM1 also had higher odds of HF reporting relative to T-DM1 monotherapy (ROR: 3.35; 99% CI: 2.04-5.52), with similar treatment duration between the 2 regimens (median 4.98 months [IQR: 2.89-8.18 months] vs 3.48 months [IQR: 0.84-8.26 months], respectively; $P = 0.35$). Tucatinib/trastuzumab/capecitabine had similar odds of HF reporting relative to tucatinib monotherapy (ROR: 6.26; 99% CI: 0.76-51.66), with similar treatment duration between the 2 regimens (median 1.47 months [IQR: 0.73-4.08 months] vs 1.54 months [IQR: 0.46-2.75 months], respectively; $P = 0.59$). Patient characteristics are shown in Supplemental Table 33.

DISCUSSION

To our knowledge, this is the first comprehensive analysis systematically comparing cardiovascular toxicities across different classes of anti-HER2 monotherapies and combination regimens. Our pharmacovigilance analyses indicate that trastuzumab has higher odds of HF reporting relative to other anti-HER2 therapies. We describe for the first time

FIGURE 4 Heart Failure With Lapatinib-Based Combination/Sequential Regimens in Full Cohort and Breast Cancer Subgroup



(A) Full cohort. **(B)** Breast cancer subgroup. Most lapatinib-based combinations were associated with increased odds of heart failure relative to lapatinib monotherapy, except for lapatinib/capecitabine. Abbreviations as in Figure 1.

that lapatinib/chemotherapy combinations had higher odds of HF reporting relative to lapatinib monotherapy, although this effect was not observed with lapatinib/capecitabine, the only U.S. Food and Drug Administration (FDA)-approved lapatinib-based combination. Moreover, we found that pertuzumab/T-DM1 had higher odds of HF reporting relative to T-DM1 monotherapy, whereas tucatinib/trastuzumab/capecitabine did not have higher odds of HF reporting relative to tucatinib monotherapy.

Among 16,900 patients with ADRs attributed to trastuzumab monotherapy, about 12% were reported to have HF. Previous studies have shown an 8% to 13% incidence of LVEF decrease with trastuzumab monotherapy.[10-12] Median time to HF onset was 5.7 months, similar to findings from prior studies.[17] About 14.8% of trastuzumab-associated HF cases (representing 1.8% of 16,900 patients with trastuzumab-associated ADRs) were serious, consistent with prior findings that trastuzumab-associated HF is predominantly a lower grade adverse event.[11,12] About 67% of patients with HF associated with trastuzumab monotherapy were reported as having cardiac function recovery. Prior studies have shown rates of recovery of about 80%, especially with HF guideline-directed medical therapy.[18,19]

Although the pathophysiology underlying trastuzumab-induced cardiotoxicity is not fully understood, various mechanisms have been implicated. Trastuzumab inhibits neuregulin-1 signaling pathways involved in cardiomyocyte survival and proliferation, thereby leading to cardiomyocyte apoptosis.[9] By activating the mammalian target of rapamycin signaling pathway, trastuzumab also down-regulates autophagy in cardiomyocytes, enhancing reactive oxygen species production and contributing to cardiotoxicity.[20] Trastuzumab also decreases the expression of genes with vital roles in DNA repair and mitochondrial function, leading to cardiomyocyte ultrastructural changes.[21]

T-DM1 and T-DXd had lower odds of HF reports relative to trastuzumab monotherapy; among 3,983

and 947 patients with ADRs with T-DM1 and T-DXd, respectively, about 1.7% and 1.2% had HF reports. Clinical trials demonstrated a similarly low incidence of LVEF decrease, including 1.7% to 5.9% with T-DM1[22-24] and 1.6% with T-DXd.[25] It is unclear why T-DM1 and T-DXd have lower cardiotoxicity risk than trastuzumab. T-DM1 and T-DXd contain trastuzumab coupled with linkers to cytotoxic microtubule inhibitor emtansine or topoisomerase I inhibitor deruxtecan, respectively. These ADCs target HER2-expressing tumor cells, are internalized via endocytosis, and release the cytotoxic payload (emtansine or deruxtecan) into those cells.[26,27] Although preclinical models found that T-DM1 retains anti-HER2 signaling of trastuzumab,[28] it is possible that trastuzumab concentrations achieved with T-DM1 and T-DXd may be lower than with trastuzumab.[29] Future research is needed to uncover mechanisms underlying disparate rates of cardiotoxicity between ADCs and trastuzumab. Notably, T-DM1 was associated with 2.6 times higher odds of HF relative to the full VigiBase database. Although this finding may be secondary to surveillance bias if patients underwent regular echocardiography, follow-up data are needed to determine whether anti-HER2 ADCs have long-term risk for cardiotoxicity.

Low proportions (<1%) of patients with ADRs with tyrosine kinase inhibitors had HF reports, similar to trial findings of low HF incidence, including 1.5% with lapatinib monotherapy,[30] 1% with neratinib,[31] and 4.6% with afatinib,[32] with most trials excluding patients with histories of congestive HF. Our findings confirm lower HF odds with anti-HER2 tyrosine kinase inhibitors.

Mechanisms underlying disparate risks for cardiotoxicity between trastuzumab and anti-HER2 tyrosine kinase inhibitors are not fully understood. One possibility is that trastuzumab is frequently given sequentially after anthracycline-based chemotherapy in adjuvant settings, whereas anti-HER2 tyrosine kinase inhibitors such as lapatinib are usually given with non-anthracycline-based regimens.[33] Additionally, whereas trastuzumab inhibits the adenosine monophosphate–activated protein kinase pathway, leading to cardiomyocyte death, lapatinib activates the adenosine monophosphate-activated protein kinase pathway, which increases adenosine triphosphate production, potentially maintaining contractile function.[34] Further studies are needed to understand the mechanisms underlying higher odds of cardiotoxicity from trastuzumab relative to other anti-HER2 therapies.

Combination regimens with anti-HER2 agents are a promising oncologic therapeutic strategy because of risk for drug resistance with monotherapy.[29,35] We demonstrate for the first time, to our knowledge, several combination regimens associated with higher odds of HF reporting relative to anti-HER2 monotherapy. Pertuzumab/T-DM1 had 3.4 times higher odds of HF reporting relative to T-DM1 monotherapy. Several lapatinib-based combinations had higher odds of HF reports relative to lapatinib monotherapy, including 5 times higher odds with lapatinib/platinum-based chemotherapy, 11 times higher odds with lapatinib/trastuzumab, and 11 times higher odds with lapatinib/taxane-based chemotherapy. However, lapatinib/capecitabine, the only FDA-approved lapatinib-containing combination, was not associated with higher odds of HF reporting relative to lapatinib monotherapy. Further studies are needed to confirm these findings and identify potential mechanisms for increased cardiotoxicity from certain combination regimens.

Among regimens for early-stage breast cancer, doxorubicin-containing regimens (ACTH and AC-THP) were associated with higher odds of HF reporting relative to docetaxel/carboplatin/trastuzumab and docetaxel/carboplatin/trastuzumab/pertuzumab, with HF observed in 22% of patients treated with ACTH and AC-THP. Previous studies similarly revealed high risk for cardiotoxicity with sequential anthracycline and trastuzumab regimens, with any grade severity in 12% to 27% of patients,[36-41] but the mechanism for increased cardiotoxicity is poorly understood. Anthracyclines cause intracellular oxidative stress, mitochondrial dysfunction, and cardiomyocyte necrosis. Compensatory mechanisms include neuregulin/HER2 signaling, as neurregulin-1 released from microvascular endothelial cells is an important prosurvival signal for cardiomyocytes during oxidative stress[42,43]; it is possible that increased cardiotoxicity with sequential anthracycline/trastuzumab results from inhibition of that compensatory signaling by trastuzumab.[44-47]

Among regimens for metastatic breast cancer, the odds of HF reporting were highest with docetaxel/trastuzumab/pertuzumab and lowest with lapatinib/capecitabine; other regimens for metastatic breast cancer had comparable odds of HF reporting, including trastuzumab/pertuzumab/paclitaxel, lapatinib/trastuzumab, trastuzumab/pertuzumab/capecitabine, pertuzumab/T-DM1, and trastuzumab/AI/CDK4/6 inhibitor. Although some of these findings may be attributable partially to differences in treatment duration, notably docetaxel/trastuzumab/pertuzumab only had longer treatment duration than lapatinib/trastuzumab but otherwise had either similar or shorter treatment duration than the other

analyzed regimens. Lapatinib/capecitabine had similar treatment duration as docetaxel/trastuzumab/pertuzumab, paclitaxel/trastuzumab/pertuzumab, and trastuzumab/AI/CDK4/6 inhibitor but shorter treatment duration than lapatinib/trastuzumab, pertuzumab/T-DM1, and trastuzumab/pertuzumab/capecitabine. Future studies with matching by treatment duration are needed to evaluate these findings.

The demonstrated associations between specific monotherapies or combination regimens with HF highlight which patients may benefit from LVEF surveillance. For trastuzumab, the National Comprehensive Cancer Network recommends LVEF assessment at baseline and during adjuvant treatment for breast cancer but without specifying monitoring frequency.[48] The FDA recommends LVEF evaluation at baseline and every 3 months during treatment with trastuzumab, pertuzumab, or T-DM1.[49-51] With lapatinib or T-DXd, the FDA recommends LVEF evaluation at baseline and during treatment without specifying monitoring frequency.[52,53]

The FDA recommendations for LVEF monitoring frequency for trastuzumab stemmed from the pivotal phase III trial in patients with metastatic breast cancer that detected a 27% incidence of cardiac dysfunction and 16% incidence of New York Heart Association functional class III or IV HF with concurrent use of trastuzumab, doxorubicin, and cyclophosphamide (vs 8% and 4%, respectively, from doxorubicin/cyclophosphamide alone).[54] Given the greater cardiotoxicity with concurrent anthracycline/trastuzumab, concomitant use of these agents has been avoided in subsequent trials and clinical practice. Notably, trials of trastuzumab in adjuvant settings such as HERA (Herceptin Adjuvant)[19] and NSABP (National Surgical Adjuvant Breast and Bowel Project) B-31 have detected lower rates of LVEF decrease (HERA, 3.6% at 3.6 years) and New York Heart Association functional class III or IV HF or cardiac death (HERA, 0.8% at 3.6 years; NSABP B-31, 4.1% at 3 years).

Our analysis provides a real-world assessment of differences in odds of reporting of decreases in LVEF between anti-HER2 therapies, but we did not compare outcomes among various surveillance strategies. However, our findings suggest that certain agents, such as tyrosine kinase inhibitor monotherapies, may warrant less frequent surveillance, whereas specific combination regimens (such as lapatinib- or pertuzumab-based combinations) may warrant closer monitoring. Future studies are needed to determine optimal LVEF surveillance strategies for patients treated with anti-HER2 therapies.

STUDY LIMITATIONS. VigiBase allows signal detection to recognize drug-ADR associations. ADRs reported to national pharmacovigilance centers are reviewed and sent to VigiBase by >130 member countries of the World Health Organization Programme for International Drug Monitoring. VigiBase data are limited to patients with reported ADRs, precluding calculation of incidence of cardiac ADRs with each drug. Consequently, RORs were calculated using the total number of patients who experienced any ADR with each drug or regimen as a surrogate for the total number of patients who received that therapy; although this limitation has potential to affect the magnitude of RORs if one drug has a significantly higher incidence of all ADRs compared with other drugs, trials have shown similar incidence of any adverse event across different anti-HER2 monotherapies and combination regimens, including 90% with trastuzumab monotherapy,[10] 98% with sequential anthracycline/trastuzumab,[37] 93% with pertuzumab,[55] 96% with T-DM1,[24] 99% with T-DXd,[25] 99% with afatinib,[56] 98% with neratinib,[31] and 92% with lapatinib.[57] However, patients who received trastuzumab may have had more frequent LVEF monitoring than patients treated with other anti-HER2 therapies, leading to risk for surveillance bias. The FDA also recommends LVEF monitoring for pertuzumab, T-DXd, T-DM1, and lapatinib, but other anti-HER2 therapies in this study may have involved less frequent LVEF surveillance, increasing the risk for surveillance bias.

VigiBase ADRs are submitted by health care and non-health care professionals, reviewed by the Uppsala Monitoring Centre, and coded according to Medical Dictionary for Regulatory Activities classifications (Supplemental Table 1); this system has risk for misclassification bias because of potential for inaccurate classification of certain ADRs as HF by those who submitted reports to VigiBase or during the Medical Dictionary for Regulatory Activities coding process. Although HF cases are categorized as serious or nonserious, VigiBase lacks data on whether HF was symptomatic and on degree of LVEF decline. Additionally, there is risk for reporting bias, as individuals may be more likely to report severe ADRs.

As VigiBase does not have data on prior therapies received, it is unknown whether patients had prior anthracycline exposure or radiation to the thorax. Patient characteristics such as comorbidities, baseline LVEF, and concurrent cardiotoxic or cardioprotective medications are unavailable or incomplete in VigiBase, precluding adjustment for those potential confounders.

CONCLUSIONS

Trastuzumab had 17 times higher odds of HF reporting relative to other anti-HER2 therapies. Although only 1% to 2% of patients with ADRs with T-DM1 or T-DXd had HF reports, T-DM1 had higher HF odds relative to the full database, suggesting that longer term follow-up data are needed. Among regimens for metastatic breast cancer, docetaxel/trastuzumab/pertuzumab had the highest odds of HF with similar treatment duration as other regimens. Pertuzumab/T-DM1 had 3.4 times higher odds of HF reporting relative to T-DM1, while tucatinib/trastuzumab/capecitabine had similar odds of HF relative to tucatinib with similar treatment duration. Most lapatinib-based sequential and concurrent regimens had higher odds of HF relative to lapatinib monotherapy, except for lapatinib/capecitabine. Future studies are needed to confirm these findings. Providers should be aware of potential variability in cardiotoxicity among different anti-HER2 therapies.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Trastuzumab has higher odds of HF relative to other anti-HER2 therapies, including the newer ADCs T-DM1 and T-DXd and anti-HER2 tyrosine kinase inhibitors afatinib, lapatinib, neratinib, and tucatinib. Certain anti-HER2-based combination regimens have higher odds of HF than monotherapies, including pertuzumab/T-DM1 relative to T-DM1 monotherapy and most lapatinib-based combinations except the FDA-approved combination lapatinib/capecitabine. On the basis of these findings, LVEF monitoring should be considered with certain anti-HER2 regimens.

TRANSLATIONAL OUTLOOK: Further research is needed to uncover mechanisms underlying disparate rates of HF among trastuzumab, other HER2-targeted monotherapies, and certain combination regimens.

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