




# openheart **Cardiotoxicity of adjuvant chemotherapy with trastuzumab: a Japanese claim-based data analysis**

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## ABSTRACT

**Objective** Adjuvant chemotherapy with trastuzumab improves the postoperative life expectancy of women with early-stage breast cancer. Although trastuzumab is reportedly cardiotoxic, quantification based on real-world evidence is lacking. Therefore, in this study, we aimed to analyse trastuzumab cardiotoxicity using a nationwide claim-based database.

**Methods** In this retrospective study, we used data from a nationwide claims database (Japan Medical Data Center, Tokyo, Japan) under the universal healthcare system. Women with breast cancer who underwent initial surgery were included. Patients with recurrent or advanced-stage breast cancer, with a history of heart failure, receiving neoadjuvant chemotherapy or a preoperative history of less than 6 months were excluded. Propensity score (PS) was calculated using logistic regression based on age, cardiovascular risk factors, radiotherapy and concomitant anthracyclines (AC).

**Results** We identified 12 060 eligible patients (mean age 50.8±8.56 years) between January 2010 and December 2019. After 1:2 PS matching (trastuzumab users, TZ, n=1005; non-users, NT, n=2010), Cox proportional hazards model analysis showed that the rate of heart failure development within 18 months postoperative was significantly higher in the TZ group than in the NT group (adjusted HR 2.28, 95% CI 1.38 to 3.77). Baseline cardiac evaluation in the combined AC/TZ cases was 27.2% preoperative, 66.0% pre-AC and 86.6% pre-TZ, respectively.

**Conclusion** Trastuzumab cardiotoxicity remained relevant in the claim-based analysis adjusted for AC effects. Further collaborative studies in cardio-oncology with real-world data are warranted to improve the rate of baseline cardiovascular risk assessment in patients with cancer scheduled for cardiotoxic cancer treatment.

## INTRODUCTION

Breast cancer (BC) is the most prevalent type of cancer in women.<sup>1</sup> Trastuzumab, a humanised monoclonal antibody, plays an essential role in treating patients with human epidermal growth factor receptor 2 (HER2)-positive BC, as it significantly reduces mortality in metastatic<sup>2</sup> and adjuvant settings.<sup>3</sup> However, trastuzumab-induced cardiotoxicity

## WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Trastuzumab, a postoperative adjuvant chemotherapy agent used to treat human epidermal growth factor receptor 2-positive early-stage breast cancer, prolongs patients' life expectancy. However, a baseline assessment of cardiac function is required because of the known complications of trastuzumab-induced cardiotoxicity, including heart failure.

## WHAT THIS STUDY ADDS

⇒ Heart failure had a higher cumulative rate with the combination of trastuzumab and anthracycline than with trastuzumab alone. However, patients on the combination therapy tended to have a lower baseline cardiovascular risk assessment rate.

## HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ In the new interdisciplinary field of cardio-oncology, there is a lack of clinical evidence as a basis for guideline development. Therefore, real-world evidence studies using various data sources and methodologies, including insurance claim databases, electronic health records and patient registries, are warranted.

is a concern that must be addressed while administering the drug.<sup>4,5</sup> Currently, adjuvant and neoadjuvant chemotherapy with trastuzumab is the standard treatment for patients with HER2-positive early-stage BC (ESBC) and is usually administered preoperatively or postoperatively for 1 year.<sup>3</sup> Early discontinuation of trastuzumab due to symptomatic heart failure can affect life expectancy,<sup>6</sup> and practice guidelines recommend baseline cardiovascular risk assessment and regular monitoring depending on the level of risk.<sup>7,8</sup> In contrast, there are concerns that cancer treatment may be unnecessarily interrupted due to overdiagnosis of cardiac dysfunction,<sup>9</sup> and low rates of preoperative echocardiography have been reported in real-world situations.<sup>10</sup> Therefore, strategies for preventing,



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diagnosing, and treating trastuzumab-induced cardiotoxicity must be optimised for improved patient outcomes.

Cardio-oncology is a new interdisciplinary field encompassing cardiology and oncology.<sup>11</sup> However, in developing evidence-based guidelines, the shared goal of improving patient outcomes has highlighted challenges related to traditional research approaches.<sup>7 9 12</sup> For instance, patients with cancer have been excluded from major cardiovascular studies, while many cancer clinical trials have not fully validated cardiovascular end points. Moreover, cancer and cardiovascular disease share common risk factors, such as smoking and obesity, presumably because of similar underlying mechanisms, including chronic inflammation.<sup>13 14</sup> One of the most promising new methodologies in regulatory science is real-world evidence (RWE), a new concept recently proposed by the US Food and Drug Administration.<sup>15</sup> By definition, real-world data (RWD) are data routinely collected from a variety of sources, including insurance claim databases, patient registries, electronic medical records and social networking services. Moreover, RWE is clinical evidence derived from RWD analysis. Therefore, obtaining RWE from relevant RWD to serve evidence-based practice guidelines is one of the most critical challenges in cardio-oncology.<sup>16</sup>

Japan Medical Data Center (JMDC) is one of the most promising RWD sources because this health insurance claim database takes advantage of anonymous data linkage, universal coverage and fee-for-service (FFS) payment systems.<sup>17–19</sup> The anonymous linkage algorithm of this claim database enables the provision of a patient-centred relational database, including monthly billing receipts collected from hospitals, clinics and pharmacies, with codes for diagnosis, drugs, surgeries and diagnostic tests.<sup>17</sup> Under the national universal health insurance system, JMDC has grown to enrol approximately 8.4 million insured subscribers registered by 2020, although there is known ‘healthy-worker bias’.<sup>18</sup> In addition, the FFS payment system allows for a low rate of missing values, especially for expensive drugs and surgical procedures.<sup>20</sup> However, to the best of our knowledge, no study in Japan has applied insurance claims databases to cardio-oncology. Therefore, in this study, we analysed trastuzumab cardiotoxicity using the nationwide claim-based database JMDC to provide reliable and relevant RWD in the field of cardio-oncology.<sup>16</sup>

## METHODS

### Data source

In this retrospective cohort study, we used deidentified individual-level data obtained from JMDC, Tokyo, Japan.<sup>17–19</sup> The data provided by the JMDC have characteristics that are less likely to have outliers and time-series inconsistencies because the consistency of the data has been confirmed through an external review process.<sup>18</sup> In addition, the data are standardised with codes provided by the JMDC, such as International Classification of

Diseases (ICD-10) and Anatomical Therapeutic Chemical Classification (ATC).<sup>17</sup> In this study, standard codes provided by the JMDC are indicated in square brackets.

### Patient selection

The subjects were women with a diagnosis code of BC who underwent a breast surgery between January 2010 and December 2019. Based on monthly insurance claims, codes for diagnoses, tests, prescriptions and surgeries were anonymously linked to each patient from multiple providers. Recurrent and advanced cases were excluded to focus on those with ESBC. Patients with a history of heart failure, receiving neoadjuvant chemotherapy or with preoperative records less than 6 months old were also excluded to minimise the influence on trastuzumab cardiotoxicity.

### Treatment strategies for BC

To delineate treatment strategies for ESBC,<sup>13</sup> we summarised the data of patients prescribed anthracyclines, taxanes or anti-tumour hormone antagonists at least once, and at least one dose of radiation therapy. In addition, subjects prescribed trastuzumab at least once were included in the exposed group. Finally, claims data for mammography, breast ultrasound, needle biopsy procedures and diagnostic testing for oestrogen receptor and HER2 were collected.

### Cardiovascular risk factors

Preoperative cardiovascular risk factors,<sup>13</sup> including diabetes mellitus, hypertension and dyslipidaemia, were defined using combinations of diagnosis and treatment in the same monthly billing receipt. Furthermore, as claim-based databases used in Japan include the category ‘tentative diagnosis’ for reimbursement, diagnosis and prescription were combined for specificity.<sup>21</sup> Additionally, age 50 years and older was included as an explanatory variable, as cardiovascular risk factors and cancer treatment strategies change dynamically during menopause.<sup>13</sup>

### Baseline cardiac assessment and patient outcomes

As an indicator for baseline cardiac assessment, at least one order for echocardiography was adopted because the specificity of the test order, as opposed to the diagnosis code, is high in the Japanese FFS health insurance.<sup>21</sup> In this claim-based analysis, we defined congestive heart failure (CHF) based on a combination of diagnosis and prescriptions on the same monthly receipt. The primary outcome of this study was the development of CHF within 18 months postsurgery. We focused on the first 1.5 years based on previous reports on trastuzumab cardiotoxicity.<sup>22–24</sup> The other outcomes were also evaluated.

We set the cut-off date as the end of September 2020 and censored at the end of follow-up, at the time of withdrawal, or at 18 months after surgery.

### Statistical analyses

Baseline characteristics are summarised using mean values (SD) for continuous data and counts (percentage; %) for categorical data. Intergroup comparisons were performed using crude analysis and propensity score

(PS) matching.<sup>25</sup> PS was generated using logistic regression, with the dependent variable being trastuzumab treatment. Independent variables were selected as potential confounding factors based on the results of a previous study,<sup>24</sup> and included age at surgery (>50 years), sequential anthracyclines, concomitant hormone antagonists and preoperative cardiovascular risk factors (diabetes, hypertension and dyslipidaemia). PS matching was performed using the greedy pair algorithm with a 1:2 ratio without replacements and 0.2 as the calliper width.<sup>25</sup> Standardised differences were used to assess residual differences in the subset of matched patients.

The rates of CHF during the first 18 months after BC surgery with and without trastuzumab exposure were compared. We used Cox hazards regression models to examine the relationship between the development of CHF and exposure to trastuzumab. In addition, we calculated the cumulative rate of development of CHF using the Kaplan-Meier method and compared with

and without trastuzumab use using the log-rank test. All analyses were performed using SAS Windows, V.9.4 (SAS Institute, Cary, North Carolina).

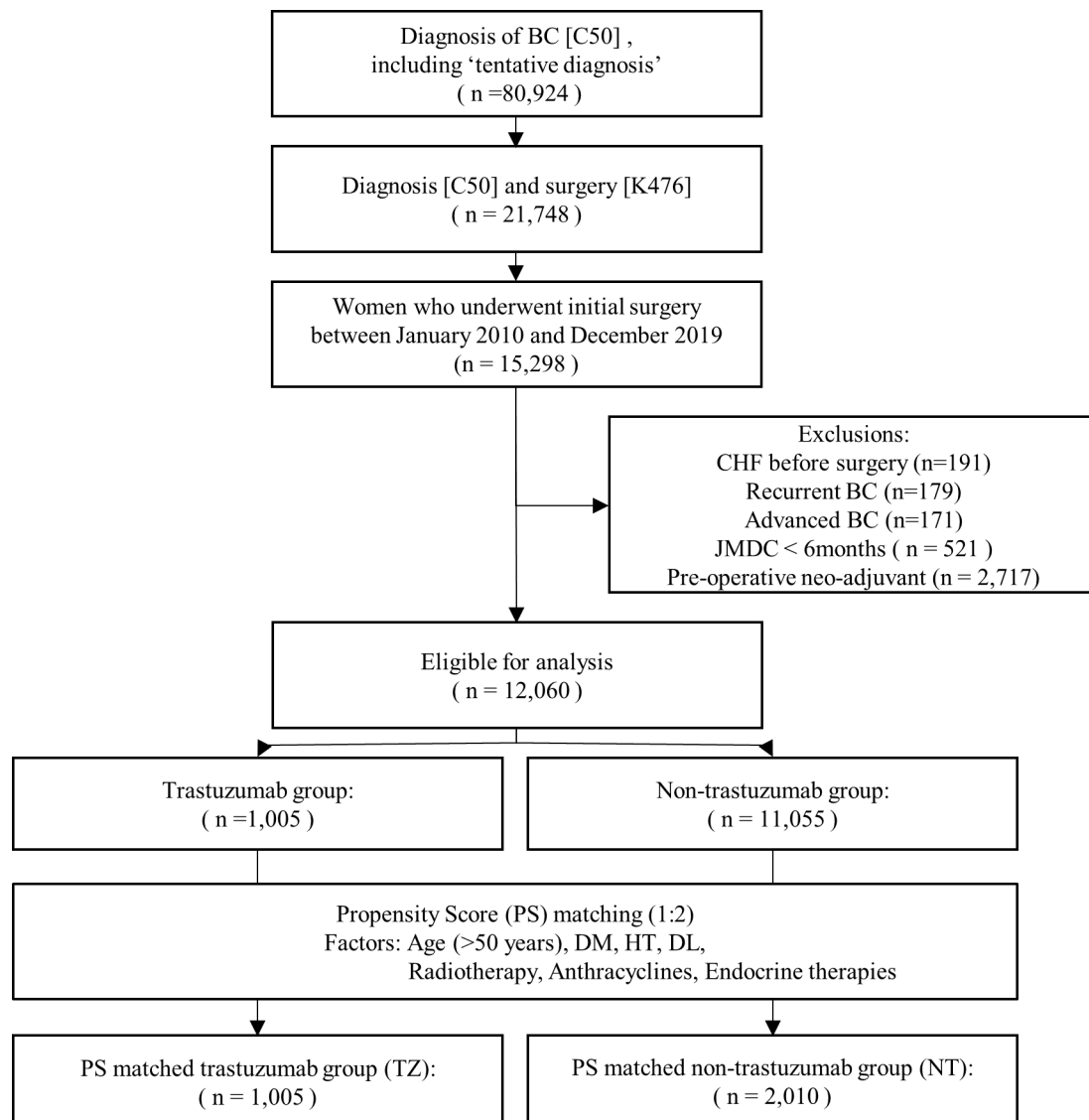
### Patient and public involvement

Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

## RESULTS

### Data source and patient selection

At the time of data collection, the JMDC database contained 80924 BC cases, including tentatively diagnosed cases. Among those, 21748 patients had undergone surgery for BC. After excluding patients with data recorded for less than 6 months in the JMDC, 15298 women with ESBC who underwent their first surgery between January 2010 and December 2019 were selected. Patients with a history of heart failure and



**Figure 1** Flowchart of patient selection. BC, breast cancer; DL, dyslipidaemia; DM, diabetes mellitus; HT, hypertension; JMDC, Japan Medical Data Center database.

metastatic or recurrent BC were excluded, yielding 12060 patients. [Figure 1](#) shows the flowchart of patient selection. As the JMDC is a claims database using the FFS insurance system in Japan, there were no missing data other than withdrawals during the study period.

### Baseline patient characteristics

[Table 1](#) summarises the baseline characteristics of the patients before and after PS matching.

Before matching, the mean age was 50.8±8.56 years. Trastuzumab was prescribed in 1005 cases (8.3%) and anthracycline in 2185 (18.1%) cases; preoperative mammography was performed in 11275 cases (93.5%) and breast ultrasound in 11932 (98.9%) cases. A needle biopsy was performed in 8474 (70.3%) cases, and echocardiography was recorded in 2461 (20.4%) cases. The number of cases with the preoperative cardiovascular risk factors such as diabetes mellitus, hypertension and dyslipidaemia were 251 (2.1%), 729 (6.0%) and 501 (4.2%), respectively.

There were 3015 patients in the 1:2 PS matching for trastuzumab administration (trastuzumab use group; TZ, n=1005 vs no trastuzumab use group; NT, n=2010), and covariates were balanced between the groups after PS matching. The mean age was 51.3±8.77 years (TZ 51.1±8.90 years vs NT 51.4±8.71 years).

Preoperative cardiovascular risk of diabetes, hypertension and dyslipidaemia was noted in 83 (2.8%) (TZ 26 (2.6%), NT 57 (2.8%)), 217 (7.2%) (TZ 68 (6.8%), NT 149 (7.4%)) and 109 (3.6%) (TZ 36 (3.6%), NT 73 (3.6%)) cases, respectively.

### Treatment strategy for BC

Preoperative diagnosis of ESBC, systemic therapies and endocrine therapy are summarised in [table 1](#). The mean duration of trastuzumab therapy was 11.7 months (SD: 2.98). The time lag between the surgery and the first dose of trastuzumab had a median of 4.0 (IQR: 2.0–5.0) months. Radiotherapy was performed in 1446 cases (48.0%) (TZ 486 (48.4%) vs NT 960 (47.8%)).

### Baseline cardiac assessment and patient outcomes

[Table 2](#) shows the cumulative incidence in the PS-matched population with age, cardiovascular risk factors and treatment strategies, including anthracyclines. Within 18 months after surgery, the number of CHF cases was 115 (1.0%), with 31 all-cause mortalities (0.3%).

After PS matching, the number of patients for whom CHF therapy was initiated after surgery and included diuretics, beta-blockers and angiotensin-converting enzyme inhibitors or receptor blockers was 504 (16.7%) (TZ 205 (20.4%) vs NT 299 (14.9%)), 60 (2.0%) (TZ 29 (2.9%) vs NT 31 (1.5%)) and 108 (3.6%) (TZ 45 (4.5%) vs NT 63 (3.1%)), respectively. The number of patients for whom CHF therapy was initiated within 18 months was 61 (2.0%) (TZ 33 (3.3%) vs NT 28 (1.4%)), with 18 all-cause deaths within 18 months (0.5%) (TZ 4 (0.4%) vs NT 10 (0.5%)).

The HR of CHF in the trastuzumab group was 2.28 (95% CI 1.38 to 3.77) in the PS-matched population. In the crude population, the HR was 4.32 (95% CI 2.88 to 6.47), exhibiting the same trend. The cumulative rate of CHF with trastuzumab is shown in the Kaplan-Meier curve in [figure 2](#). As a subgroup analysis, because the known cardiotoxicity of concomitant anthracyclines (AC) may modify the effect of trastuzumab, we calculated the HR and Kaplan-Meier curve using AC (online supplemental table 1, figure 1).

The number of patients with preoperative echocardiography was 750 (24.9%) (TZ 286 (28.5%) vs NT 464 (23.1%)) ([table 1](#)). Within the trastuzumab with anthracycline combination group (n=591), the percentage of baseline cardiac assessment with echocardiography (%echocardiography) was 27.2% (preoperatively), 66.0% (pre-AC) and 86.6% (pre-TZ) ([table 3](#)).

### DISCUSSION

To the best of our knowledge, this is the first RWD study in Japan to investigate trastuzumab cardiotoxicity using a nationwide claim-based database. A significant increase in the incidence of heart failure following adjuvant chemotherapy was observed, although there is room for improvement in baseline cardiovascular risk assessment.

One of the most important deliverables of this study is the RWD on ethnic factors of trastuzumab cardiotoxicity for the new interdisciplinary field of cardio-oncology.<sup>26</sup> Early studies in Japan, a country with a traditionally low incidence of cardiovascular disease, showed low trastuzumab cardiotoxicity.<sup>27</sup> A population-based study in Taiwan also suggested that cardiotoxicity may be lower in East Asia.<sup>28</sup> In contrast, our previous study conducted in a Japanese teaching hospital identified a mild decrease in left ventricular ejection fraction (LVEF) in 26% of the examined cases, severe decreases in LVEF in 13%, symptomatic heart failure in 6% and premature termination of cancer treatment in 2% in patients undergoing adjuvant trastuzumab therapy.<sup>24</sup> In our current RWD study, trastuzumab cardiotoxicity remained statistically significant after adjusting for the effect of AC administration. The advantages of using claims data from FFS payment systems under universal healthcare systems are low rates of missing values and high generalisability.<sup>20</sup> Thus, our combined results support that all patients require optimum care with cancer therapeutic-related cardiac dysfunction in mind, regardless of ethnicity.

To maximise the specificity of our definitions of heart failure and cardiotoxicity, we employed a combination of diagnosis (ICD-10) and prescription (ATC) rather than diagnosis codes alone. The key to increasing the specificity of JMDC derives from a report by Fujihara *et al*,<sup>21</sup> who showed that diagnosis codes alone in the Japanese insurance claims database might be insufficient to identify heart failures. In their validation study using intensive chart review as the gold standard, 'tentative diagnosis' codes for billing purposes increased false-positive rates. In addition, false-negative rates were higher with

**Table 1** Patient characteristics and treatment strategies of crude and propensity score (PS)-matched cohorts

	Crude			After PS match		
	TZ	NT	Total	TZ	NT	Total
	(N=1005)	(N=11 055)	(N=12 060)	(N=1005)	(N=2010)	(N=3015)
Age						
N	1005	11 055	12 060	1005	2010	3015
Mean (SD)	51.1 (8.90)	50.8 (8.53)	50.8 (8.56)	51.1 (8.90)	51.4 (8.71)	51.3 (8.77)
Median	51	50	50	51	51	51
(IQR)	(45.0, 57.0)	(45.0, 56.0)	(45.0, 56.0)	(45.0, 57.0)	(45.0, 57.0)	(45.0, 57.0)
Cardiovascular risk factors						
DM(E10-E14,A10)	26 (2.6%)	225 (2.0%)	251 (2.1%)	26 (2.6%)	57 (2.8%)	83 (2.8%)
HT(I10-I15,C03,C07-C09)	68 (6.8%)	661 (6.0%)	729 (6.0%)	68 (6.8%)	149 (7.4%)	217 (7.2%)
DL(E78,C10)	36 (3.6%)	465 (4.2%)	501 (4.2%)	36 (3.6%)	73 (3.6%)	109 (3.6%)
Baseline assessments						
Echocardiography(I60072-510)	286 (28.5%)	2175 (19.7%)	2461 (20.4%)	286 (28.5%)	464 (23.1%)	750 (24.9%)
MMG(I70026-910)	911 (90.6%)	10 364 (93.7%)	11 275 (93.5%)	911 (90.6%)	1899 (94.5%)	2810 (93.2%)
US_Br(I60165-010)	994 (98.9%)	10 938 (98.9%)	11 932 (98.9%)	994 (98.9%)	1987 (98.9%)	2981 (98.9%)
CNB(D410)	727 (72.3%)	7747 (70.1%)	8474 (70.3%)	727 (72.3%)	1444 (71.8%)	2171 (72.0%)
ER(I60060-350)	881 (87.7%)	9445 (85.4%)	10 326 (85.6%)	881 (87.7%)	1737 (86.4%)	2618 (86.8%)
HER2(I60173-550)	863 (85.9%)	9017 (81.6%)	9880 (81.9%)	863 (85.9%)	1689 (84.0%)	2552 (84.6%)
Treatment strategies						
Radiotherapy(M000,M001)	486 (48.4%)	6019 (54.4%)	6505 (53.9%)	486 (48.4%)	960 (47.8%)	1446 (48.0%)
Systemic therapy(L01,L02)	1005 (100.0%)	4822 (43.6%)	5827 (48.3%)	1005 (100.0%)	1449 (72.1%)	2454 (81.4%)
Alkyl(L01A)	738 (73.4%)	2385 (21.6%)	3123 (25.9%)	738 (73.4%)	1233 (61.3%)	1971 (65.4%)
Anti Metab(L01B)	230 (22.9%)	820 (7.4%)	1050 (8.7%)	230 (22.9%)	455 (22.6%)	685 (22.7%)
Vinca(L01C1)	6 (0.6%)	24 (0.2%)	30 (0.2%)	6 (0.6%)	12 (0.6%)	18 (0.6%)
Taxan(L01C2)	780 (77.6%)	2109 (19.1%)	2889 (24.0%)	780 (77.6%)	997 (49.6%)	1777 (58.9%)
Anthra(L01D)	591 (58.8%)	1594 (14.4%)	2185 (18.1%)	591 (58.8%)	1182 (58.8%)	1773 (58.8%)
Trastuzumab(L01XC03)	1005 (100.0%)	0 (0.0%)	1005 (100.0%)	1005 (100.0%)	0 (0.0%)	1005 (100.0%)
Hormone Anti(L02B)	651 (64.8%)	8032 (72.7%)	8683 (72.0%)	651 (64.8%)	1310 (65.2%)	1961 (65.0%)
SERM(L02B1)	388 (38.6%)	5486 (49.6%)	5874 (48.7%)	388 (38.6%)	841 (41.8%)	1229 (40.8%)
Aroma (L02B3)	327 (32.5%)	3370 (30.5%)	3697 (30.7%)	327 (32.5%)	646 (32.1%)	973 (32.3%)
AntiEmet(A04A)	831 (82.7%)	2681 (24.3%)	3512 (29.1%)	831 (82.7%)	1271 (63.2%)	2102 (69.7%)

Continued

**Table 1** Continued

	Crude			After PS match			
	TZ (N=1005)	NT (N=11 055)	Total (N=12 060)	TZ (N=1005)	NT (N=2010)	Total (N=3015)	P value
CSF(L03A1)	455 (45.3%)	1359 (12.3%)	1814 (15.0%)	455 (45.3%)	713 (35.5%)	1168 (38.7%)	<0.0001 †
Trastuzumab use							
Duration (months)							
Mean (SD)	11.7 (2.98)			11.7 (2.98)			
Median	13			13			
(IQR)	(12.0, 13.0)			(12.0, 13.0)			
First dose after surgery (months)							
Median	4			4			
(IQR)	(2.0, 5.0)			(2.0, 5.0)			

\*Equal variance two sample t-test.

† Chi-square p value.

Alkyl, alkylating agents (eg, cyclophosphamide [L01AA01]); Anthra, anthracyclines (eg, doxorubicin [L01DB01], epirubicin [L01DB03]); Anti Emet, antiemetics; Anti Metab, antimetabolites (eg, 5-fluorouracil [L01BC02]), capecitabine [L01BC06]); Aroma\_1, aromatase inhibitors (eg, anastrozole [L02BG03], letrozole [L02BG04]); CNB, needle biopsy; CSF, colony-stimulating factors; DL, dyslipidaemia; DM, diabetes mellitus; ER, oestrogen receptor; HER2, human epidermal growth factor receptor 2; HT, hypertension; MMG, mammography; NT, non-users; SEAM, anti-oestrogens (eg, tamoxifen [L02BA01], toremifene [L02BA02], fulvestrant [L02BA03]); Taxan(s), (eg, paclitaxel [L01CD01], docetaxel [L01CD02]); TZ, trastuzumab users; US\_Br, breast ultrasound; Vinca, vinca alkaloids.

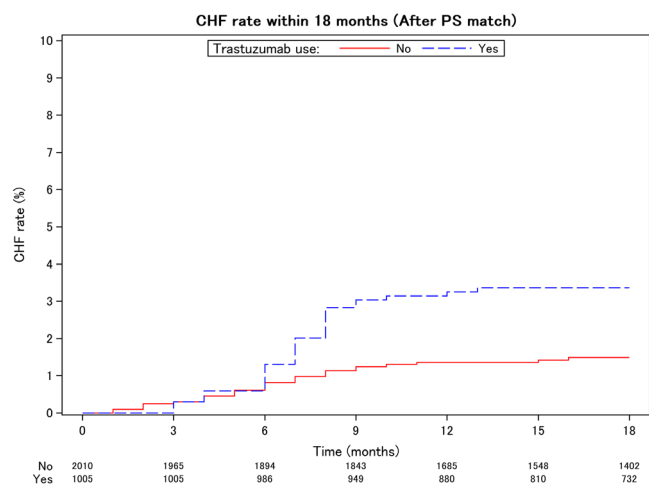
**Table 2** Patient outcomes of crude and propensity score (PS)-matched cohorts

	Crude			After PS match			P value
	TZ (N=1005)	NT (N=11 055)	Total (N=12 060)	TZ (N=1005)	NT (N=2010)	Total (N=3015)	
Months after surgery							0.0881*
N	1005	11 055	12 060	1005	2010	3015	0.2018*
Mean (SD)	36.9 (25.15)	35.5 (25.59)	35.6 (25.55)	36.9 (25.15)	35.7 (25.67)	36.1 (25.50)	
Median	30	29	29	30	29	29	
(IQR)	(18.0, 50.0)	(16.0, 49.0)	(16.0, 49.0)	(18.0, 50.0)	(16.0, 50.0)	(17.0, 50.0)	
DM(E10-E14,A10)	10 (1.0%)	89 (0.8%)	99 (0.8%)	10 (1.0%)	20 (1.0%)	30 (1.0%)	1.0000*
HT(I10-I15,C03,C07-C09)	55 (5.5%)	317 (2.9%)	372 (3.1%)	55 (5.5%)	90 (4.5%)	145 (4.8%)	0.2287*
DL(E78,C10)	50 (5.0%)	239 (2.2%)	289 (2.4%)	50 (5.0%)	62 (3.1%)	112 (3.7%)	0.0097*
Diuretics(C03)	205 (20.4%)	784 (7.1%)	989 (8.2%)	205 (20.4%)	299 (14.9%)	504 (16.7%)	0.0001*
Fosfamide(C03CA01)	178 (17.7%)	628 (5.7%)	806 (6.7%)	178 (17.7%)	266 (13.2%)	444 (14.7%)	0.0011*
Spirolactone(C03DA01)	61 (6.1%)	225 (2.0%)	286 (2.4%)	61 (6.1%)	105 (5.2%)	166 (5.5%)	0.3372*
Tolvaptan(C03XA01)	3 (0.3%)	8 (0.1%)	11 (0.1%)	3 (0.3%)	3 (0.1%)	6 (0.2%)	0.3860*
BB(C07)	29 (2.9%)	173 (1.6%)	202 (1.7%)	29 (2.9%)	31 (1.5%)	60 (2.0%)	0.0128*
Carvedilol(C07AG02)	7 (0.7%)	26 (0.2%)	33 (0.3%)	7 (0.7%)	9 (0.4%)	16 (0.5%)	0.3755*
Bisoprolol(C01AA05)	1 (0.1%)	6 (0.1%)	7 (0.1%)	1 (0.1%)	2 (0.1%)	3 (0.1%)	1.0000*
RAS(C09)	45 (4.5%)	304 (2.7%)	349 (2.9%)	45 (4.5%)	63 (3.1%)	108 (3.6%)	0.0614*
Captopril(C09AA01)	2 (0.2%)	16 (0.1%)	18 (0.1%)	2 (0.2%)	3 (0.1%)	5 (0.2%)	0.7516*
Enalapril(C09AA02)	5 (0.5%)	15 (0.1%)	20 (0.2%)	5 (0.5%)	3 (0.1%)	8 (0.3%)	0.0797*
Amiodarone(C01BD01)	1 (0.1%)	5 (0.0%)	6 (0.0%)	1 (0.1%)	1 (0.0%)	2 (0.1%)	0.6170*
Digoxin(C07AB07)	17 (1.7%)	78 (0.7%)	95 (0.8%)	17 (1.7%)	16 (0.8%)	33 (1.1%)	0.0259*
Death	19 (1.9%)	111 (1.0%)	130 (1.1%)	19 (1.9%)	53 (2.6%)	72 (2.4%)	0.2058*
Death (18mo)	4 (0.4%)	27 (0.2%)	31 (0.3%)	4 (0.4%)	10 (0.5%)	14 (0.5%)	0.7048*
CHF	44 (4.4%)	132 (1.2%)	176 (1.5%)	44 (4.4%)	48 (2.4%)	92 (3.1%)	0.0027*
CHF (18mo)	33 (3.3%)	82 (0.7%)	115 (1.0%)	33 (3.3%)	28 (1.4%)	61 (2.0%)	0.0005*
Events/n	33/1005	82/11055	115/12060	33/1005	28/2010	61/3015	0.0009†
HR (95% CI)	4.32 (2.88 to 6.47)	Reference		2.28 (1.38 to 3.77)	Reference		

\*Chi-square p value.

†Logrank p value.

BB, beta-blocking agents; CHF, congestive heart failure; Death, all-cause deaths; Death (18 months), all-cause deaths within 18 months post-surgery; DL, dyslipidaemia; DM, diabetes mellitus; RAS, angiotensin-converting enzymes or angiotensin II receptor blocking agents.



**Figure 2** Cumulative incidence of postoperative heart failure within 18 months among women with early-stage breast cancer after propensity score (PS) matching. Cumulative incidence of postoperative heart failure within 18 months between groups was significantly different (log-rank test  $p=0.0009$ , HR=2.28 (95% CI: 1.38 to 3.77). CHF, congestive heart failure.

diuretics or cardioprotective drugs without heart failure codes. In our current study, a combination of diagnosis and prescription codes allowed us to quantify the clinical course of the patients consistently with our previous chart review.<sup>24</sup> In addition, interhospital aggregation using the JMDC anonymised link system increased the sensitivity by revealing real-world risks of heart failure recorded outside cancer centres. Thus, we believe that our algorithms to identify heart failure and cardiotoxicity in this claim-based analysis are clinically relevant.

RWE requires validations from several perspectives, including temporality and biological gradient.<sup>16</sup> We focused on heart failure at 18 months postsurgery, as adjuvant trastuzumab is associated with a temporal risk of cardiotoxicity during the treatment period but not thereafter.<sup>22 23</sup> In addition, our previous study<sup>24</sup> showed that most incidences of heart failure occurred during trastuzumab therapy (mean 12 months), although it was confounded by the concomitant use of anthracyclines. We used a large insurance claim database for the present investigation to allow PS matching

**Table 3** Timing of baseline cardiac assessment with echocardiography

	Anthracyclines		Total (N=1005)
	No (N=414)	Yes (N=591)	
Pre-ope	125 (30.2%)	161 (27.2%)	286 (28.5%)
Pre-AC		390 (66.0%)	
Pre-TZ	323 (78.0%)	512 (86.6%)	835 (83.1%)

Pre-AC, period from surgery to anthracycline prescription; Pre-ope, preoperative; Pre-TZ, period from surgery to trastuzumab prescription.

using age, cardiovascular risk factors and treatment strategies, including anthracyclines and antitumour hormone therapy. Heart failure within 18 months remained associated with trastuzumab after adjustment for potential confounders (HR=2.28 (CI 1.38 to 3.77)) (table 2). Even after adjusting for confounding factors, trastuzumab and heart failure were associated during the initial 1.5 years of treatment (figure 2), after which no independent association was observed. The timing of the median first dose of trastuzumab (table 1), a median of 4 months (IQR: 2–5 months), was consistent with the steep rise in the cumulative rate of CHF from 6 to 9 months (figure 2). In this study, we could not evaluate the dose-dependency of trastuzumab because the cumulative dose could be either a cause or a result of cardiotoxicity. However, the combination group, in particular, exhibited a stronger trend and higher increase in the cumulative rate of cardiotoxicity than those in the other groups, suggesting a biological gradient in cardiotoxicity (online supplemental figure 1). Therefore, our RWD study is consistent with our previous chart review<sup>24</sup> and other studies.<sup>22 23</sup>

We also detected a suboptimal baseline cardiovascular risk assessment as a quality indicator for improvement from this RWD study. Although our Japanese claims database analysis is consistent with the previously known cardiotoxicity, there is room for improving the rates of baseline echocardiography for patients receiving trastuzumab, especially with AC. In our study, especially in the combination anticancer therapy group (n=591), 66.0% (pre-AC) and 86.6% (Pre-TZ) of the patients underwent echocardiography, which raises the concern that prophylactic decision-making may have been delayed (table 3). The low compliance in Japan may be due to the insufficient allocation of cardiologists to cancer centres.<sup>25</sup> Alternatively, it may be because of the global concern that frequent imaging and biomarker measurements for cardiac function may lead to an unnecessary interruption of cancer treatment.<sup>9</sup> As cardiac monitoring is expected to support the completion of trastuzumab-based therapy effectively, clinical validations in new biomarkers<sup>29</sup> and imaging modalities<sup>30</sup> for monitoring cardiac function during cancer treatment are underway. Therefore, the latest guidelines recommend at least baseline cardiovascular risk assessment in patients with cancer scheduled to undergo cardiotoxic cancer treatment.<sup>31</sup> We believe that future RWD studies in cardio-oncology should help narrow the gap between guidelines and practice by efficiently providing data to improve patient outcomes.<sup>16</sup>

### Study limitations

As with any observational study, ours had some limitations. First, RWE requires validations from several perspectives, including biological gradient, temporality, strength, consistency, specificity and validity.<sup>16</sup> However, there may be unknown temporality factors in trastuzumab beyond our focus of 18 months. Furthermore, the effect of unmeasured confounders remains even after the PS matching. Therefore, randomised controlled trials remain the gold standard. Second, the JMDC has a ‘healthy-worker bias’ with a high proportion of employed people and a low prevalence of hypertension.<sup>18</sup> However, robust research needs



'triangulation' with many lines of evidence.<sup>16</sup> Therefore, RWD from claims databases need to be interpreted using other data sources with different characteristics, such as randomised controlled trials and patient registries. Third, although we leveraged our previous study<sup>24</sup> to increase clinical relevance, the terms 'heart failure' and 'cardiotoxicity' used in this claim-based analysis should be interpreted with caution. Although we matched diagnosis, prescription and surgery codes on the same monthly insurance claim receipts to exclude 'tentative diagnosis' and increase specificity, the sensitivity might have been compromised. Therefore, clinical validation for heart failure diagnosis with imaging,<sup>30</sup> biomarkers<sup>29</sup> and other data sources<sup>16</sup> is needed to support RWD studies. Fourth, the JMDC does not include all factors related to intrinsic or extrinsic ethnic factors. Therefore, a fit-for-purpose design is needed to evaluate the gene, environment and gene–environment interactions. Finally, although echocardiography is the guideline-recommended modality for baseline cardiovascular risk assessment,<sup>31 32</sup> it is far from ideal as a risk stratification tool for cancer outcomes. Therefore, there is a need for cardio-oncology studies to evaluate the rate of cancer treatment completion and, ultimately, overall survival.

## CONCLUSIONS

We found an increased risk of heart failure development in women who underwent adjuvant trastuzumab therapy compared with the control group matched with risk factors and the effect of anthracyclines based on Japanese claims data. Notably, the RWD revealed a lower implementation of baseline cardiac assessment in the patients with a higher risk of trastuzumab cardiotoxicity due to AC use. Therefore, further studies applying this new methodology to improve quality indicators in the emerging field of cardio-oncology are warranted.

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data collection, analysed all cardiovascular endpoints and critically reviewed the manuscript. SK designed the claim-based analysis, analysed the data, drafted the manuscript, and is the guarantor of the study. All authors provided final approval of the manuscript.

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## REFERENCES

- Bray F, Ferlay J, Soerjomataram I, *et al*. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018;68:394–424.
- 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;344:783–92.
- Piccant-Gebhart MJ, Procter M, Leyland-Jones B, *et al*. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *N Engl J Med* 2005;353:1659–72.
- Seidman A, Hudis C, Pierri MK, *et al*. Cardiac dysfunction in the trastuzumab clinical trials experience. *J Clin Oncol* 2002;20:1215–21.
- Rosen SD. Trastuzumab induced cardiomyopathy: wider implications for cardio-oncology. *Heart* 2013;99:599–600.
- Rushton M, Lima I, Tuna M, *et al*. Impact of Stopping Trastuzumab in Early Breast Cancer: A Population-Based Study in Ontario, Canada. *J Natl Cancer Inst* 2020;112:1222–30.
- Armenian SH, Lacchetti C, Barac A, *et al*. Prevention and monitoring of cardiac dysfunction in survivors of adult cancers: American Society of clinical oncology clinical practice guideline. *J Clin Oncol* 2017;35:893–911.
- Curigliano G, Lenihan D, Fradley M, *et al*. Management of cardiac disease in cancer patients throughout oncological treatment: ESMO consensus recommendations. *Ann Oncol* 2020;31:171–90.

- 9 Dang CT, Yu AF, Jones LW, *et al.* Cardiac surveillance guidelines for trastuzumab-containing therapy in early-stage breast cancer: getting to the heart of the matter. *J Clin Oncol* 2016;34:1030–3.
- 10 Subar M, Lin W, Chen W, *et al.* Lack of uniformity in cardiac assessment during trastuzumab therapy. *Breast J* 2011;17:383–90.
- 11 Lenneman CG, Sawyer DB. Cardio-oncology: an update on cardiotoxicity of cancer-related treatment. *Circ Res* 2016;118:1008–20.
- 12 Levis BE, Binkley PF, Shapiro CL. Cardiotoxic effects of anthracycline-based therapy: what is the evidence and what are the potential harms? *Lancet Oncol* 2017;18:e445–56.
- 13 Mehta LS, Watson KE, Barac A, *et al.* Cardiovascular disease and breast cancer: where these entities intersect: a scientific statement from the American heart association. *Circulation* 2018;137:e30–66.
- 14 de Boer RA, Hulot J-S, Tocchetti CG, *et al.* Common mechanistic pathways in cancer and heart failure. A scientific roadmap on behalf of the translational research Committee of the heart failure association (HFA) of the European Society of cardiology (ESC). *Eur J Heart Fail* 2020;22:2272–89.
- 15 Sherman RE, Anderson SA, Dal Pan GJ, *et al.* Real-world evidence - what is it and what can it tell us? *N Engl J Med* 2016;375:2293–7.
- 16 Ohtsu H, Shimomura A, Sase K. Real-world evidence in cardio-oncology: what is it and what can it tell us? *JACC CardioOncol* 2022;4:95–7.
- 17 Kimura S, Sato T, Ikeda S, *et al.* Development of a database of health insurance claims: standardization of disease classifications and anonymous record linkage. *J Epidemiol* 2010;20:413–9.
- 18 Nagai K, Tanaka T, Kodaira N, *et al.* Data resource profile: JMDC claims database sourced from health insurance societies. *J Gen Fam Med* 2021;22:118–27.
- 19 Fujioka I, Ohtsu H, Yonemoto N, *et al.* Association between prenatal exposure to antidepressants and neonatal morbidity: an analysis of real-world data from a nationwide claims database in Japan. *J Affect Disord* 2022;310:60–7.
- 20 Behrendt C-A, Debus ES, Mani K, *et al.* The strengths and limitations of claims based research in countries with fee for service reimbursement. *Eur J Vasc Endovasc Surg* 2018;56:615–6.
- 21 Fujihara K, Yamada-Harada M, Matsubayashi Y, *et al.* Accuracy of Japanese claims data in identifying diabetes-related complications. *Pharmacoepidemiol Drug Saf* 2021;30:594–601.
- 22 Goldhar HA, Yan AT, Ko DT, *et al.* The temporal risk of heart failure associated with adjuvant trastuzumab in breast cancer patients: a population study. *J Natl Cancer Inst* 2016;108. doi:10.1093/jnci/djv301. [Epub ahead of print: 16 10 2015].
- 23 Cameron D, Piccart-Gebhart MJ, Gelber RD, *et al.* 11 years' follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive early breast cancer: final analysis of the HERceptin Adjuvant (HERA) trial. *Lancet* 2017;389:1195–205.
- 24 Shinano H, Miyazaki S, Miura K, *et al.* Risk profiling of cancer treatment-related cardiovascular disorders in breast cancer patients who received adjuvant chemotherapy with trastuzumab. *Circ Rep* 2020;2:235–42.
- 25 Austin PC. Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. *Pharm Stat* 2011;10:150–61.
- 26 Oka T, Akazawa H, Sase K, *et al.* Cardio-Oncology in Japan. *JACC CardioOncol* 2020;2:815–8.
- 27 Ishihara M, Mukai H, Nagai S, *et al.* Cardiac safety of trastuzumab as adjuvant treatment for Japanese patients with early breast cancer. *Int J Clin Oncol* 2009;14:431–5.
- 28 Chien H-C, Kao Yang Y-H, Bai JPF. Trastuzumab-related cardiotoxic effects in Taiwanese women: a nationwide cohort study. *JAMA Oncol* 2016;2:1317–25.
- 29 Pudil R, Mueller C, Čelutkienė J, *et al.* Role of serum biomarkers in cancer patients receiving cardiotoxic cancer therapies: a position statement from the Cardio-Oncology Study group of the heart failure association and the Cardio-Oncology Council of the European Society of Cardiology. *Eur J Heart Fail* 2020;22:1966–83.
- 30 Čelutkienė J, Pudil R, López-Fernández T, *et al.* Role of cardiovascular imaging in cancer patients receiving cardiotoxic therapies: a position statement on behalf of the Heart Failure Association (HFA), the European Association of Cardiovascular Imaging (EACVI) and the Cardio-Oncology Council of the European Society of Cardiology (ESC). *Eur J Heart Fail* 2020;22:1504–24.
- 31 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;22:1945–60.
- 32 de Baat EC, Naaktgeboren WR, Leiner T, *et al.* Update in imaging of cancer therapy-related cardiac toxicity in adults. *Open Heart* 2021;8:e001506.