ESC HEART FAILURE
ESC Heart Failure 2021; **8**: 5149–5158
Published online 4 September 2021 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.13591

ORIGINAL ARTICLE

Risks of trastuzumab-related cardiotoxicity in breast cancer patients in Taiwan

Wei-Ting Chang[1,2,3], Po-Wei Chen[1,4], Hui-Wen Lin[4,5], Sheng-Hsiang Lin[1,5,6] and Yi-Heng Li[4]*

[1]*Institute of Clinical Medicine, College of Medicine, National Cheng Kung University, Tainan, Taiwan;* [2]*Division of Cardiology, Department of Internal Medicine, Chi-Mei Medical Center, Tainan, Taiwan;* [3]*Department of Biotechnology, Southern Taiwan University of Science and Technology, Tainan, Taiwan;* [4]*Department of Internal Medicine, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan;* [5]*Biostatistics Consulting Center, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan; and* [6]*Department of Public Health, College of Medicine, National Cheng Kung University, Tainan, Taiwan*

Abstract

Aims In contrast to Western patients with breast cancer, Asian patients are relatively younger at diagnosis, and most are free from traditional cardiovascular risk factors. Despite trastuzumab-related major adverse cardiac and cerebrovascular event (MACCE) being reported, its incidence and predictors remain unknown in Taiwan.

Methods and results Through a three-hospital retrospective cohort study, we analysed the incidence of MACCE in 386 breast cancer patients' exposure to trastuzumab from 2010 to 2018. To further reconfirm our findings, in a nationwide study using the Taiwanese National Health Insurance Research Database and National Cancer Registry, we identified 13 502 women diagnosed with breast cancer who received chemotherapy from 2010 to 2015 and found 6751 women who received initial treatment with trastuzumab. After 1:1 propensity score matching with trastuzumab non-users, the incidence of MACCE was measured with a median follow-up of 36 months. In the hospital-based study, among 386 patients receiving trastuzumab, the 5-year incidences of MACCE and heart failure (HF) were 5.4 and 2.8%, respectively. In the national cohort, the crude incidences of MACCEs and HF were 4.67 and 3.21%, respectively. After adjustment for age and comorbidities, the hazard ratio of MACCE was 1.485 (95% CI 1.246–1.769). Notably, among the endpoints, only the hazard ratio of HF was significantly higher in patients receiving trastuzumab than in nonusers. In the subgroup analysis, except for patients also using taxanes, those receiving trastuzumab had a higher risk of MACCE than non-users.

Conclusions From clinical observations in a nationwide cohort, we found an increased risk of MACCE, especially HF, in patients receiving trastuzumab. Given that its cardiotoxicity is independent of traditional cardiovascular risks, our findings highlight critical concerns regarding the cardiac safety of trastuzumab use.

Keywords Breast cancer; Trastuzumab; Cardiotoxicity; MACCE

Received: 29 April 2021; Revised: 15 July 2021; Accepted: 19 August 2021
**Correspondence to: Dr. Yi-Heng Li, Department of Internal Medicine, National Cheng Kung University Hospital, 138 Sheng Li Road, Tainan, Taiwan. Telephone: 886-6-2353535 ext. 2389; Fax: 886-6-2753834. Email: weiting9901@stust.edu.tw*
Wei-Ting Chang and Po-Wei Chen contribute equally to this article.

Introduction

With the advances in anticancer therapies, the mortality of patients with breast cancer has decreased, but survivors may face risks of cardiovascular complications, including heart failure (HF), arrhythmia and thrombosis.[1,2] Trastuzumab, a humanized monoclonal antibody, is currently the standard of care for patients with HER2-positive (HER2+) breast cancer.[1–3] Although trastuzumab significantly improves the survival of these patients, some of them have been forced to discontinue therapy because they subsequently developed HF.[2] According to the previous literature, patients receiving trastuzumab have a 9.54-fold higher risk of HF within the first 2 years after treatment than those not taking trastuzumab, although the 10-year risk of HF is increased up to 4.8 times.[4] Notably, one-third of patients who developed HF after trastuzumab had long-term impaired cardiac function.[5–7] However, given the various definitions of myocardial dysfunction, the diagnostic criteria of HF and durations of follow-up, the reported incidence of

trastuzumab-induced cardiotoxicity ranges from 4 to 20%.[5–8] Additionally, our knowledge regarding trastuzumab-related cardiotoxic effects comes mainly from studies conducted in western countries, although the incidences of HF in patients with breast cancer in Asia are lacking.

Notably, the incidence of breast cancer in Asia has continuously increased by 3–6% per year in recent years.[9] Asian women currently account for 40% of newly diagnosed breast cancer cases worldwide, and the number of patients in Asia has increased to 2.29 million. In contrast to Western patients with breast cancer, Asian patients are relatively younger at diagnosis, with peak ages of 60 and 40 years, respectively.[9–11] This implies that most patients with breast cancer in Asia are diagnosed before menopause and have few cardiovascular risk factors. Additionally, despite trastuzumab inducing cardiovascular complications from several different perspectives, previous studies focused only on myocardial dysfunction, such as HF, whereas other vascular morbidities, including acute myocardial infarction (AMI) and stroke, were underestimated.[8,12] Most importantly, most nationwide cohort studies lack reliable multicentre validation to evaluate the accuracy of diagnosis, social habits and cancer stages.[8,12] Therefore, it is mandatory to evaluate the incidences and clinical characteristics of trastuzumab-induced cardiotoxicity in Asian women with breast cancer. In this study, using the Taiwan national database and a three-hospital cohort, we aimed to estimate the risk of trastuzumab-related major adverse cardiac and cerebrovascular event (MACCE) in an Asian population.

Methods

Study design

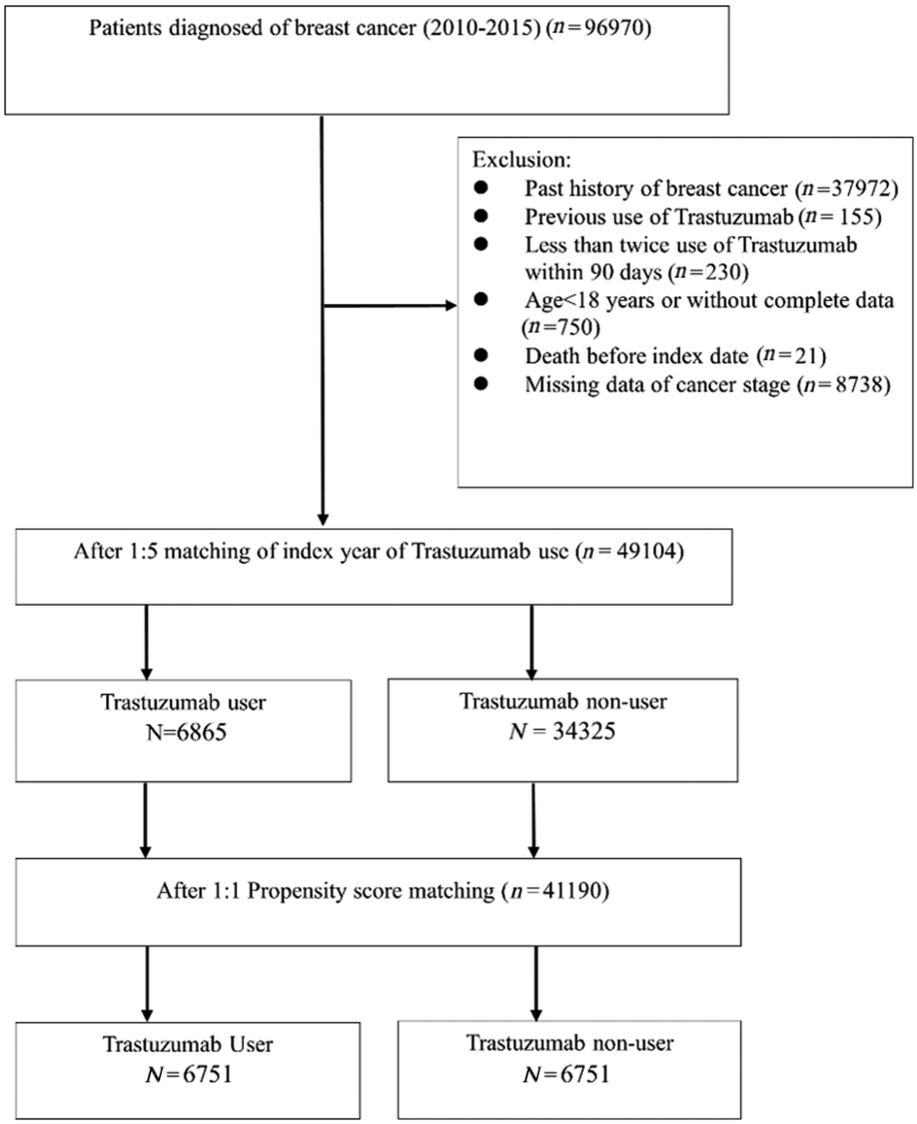
This study applied two methods on data derived from different sources. First, a three-hospital-based, retrospective, observational study was conducted. From January 2010 to December 2018, the clinical and follow-up data of patients with breast cancer who received trastuzumab were collected. Information regarding electrocardiography and echocardiography was collected prior to and 6 months after trastuzumab treatment. Second, to further extend our findings for validation, we used the National Health Insurance Research Database (NHIRD) released by the Health and Welfare Data Science Center. The data used in this study were the original claims database for reimbursement of all Taiwanese residents from the NHIRD.[13,14] The cohort dataset included age, sex, medications, procedures and all medical diagnoses. The patients were not involved in any way in this study because the patients' original identification numbers were encrypted in the dataset to protect their privacy. There is a high reliability of the diagnosis of common medical diseases and the identification of procedures or medications in the NHIRD by using International Classification of Diseases (ICD) codes. It is also feasible to link and continuously follow up all of the claims data belonging to the same patient within the NHIRD. This study was approved by our institutional review committee (IRB A-EX-109-021; CV code: 10406-E01), and they granted a waiver of informed consent due to its retrospective nature.

The patients newly diagnosed with breast cancer from 2010 to 2015 were enrolled and identified from the registry for catastrophic illness patients in Taiwan, and their detailed information is listed in *Figure 1*. We defined women who received trastuzumab within 90 days after the index date of first diagnosis as the exposed group. The control group was defined as matched case–control subjects without trastuzumab exposure during the same period, and they were matched 5:1 with trastuzumab users for the variables of the index year. The exclusion criteria for this study were a history of breast cancer (registry for catastrophic illness patients diagnosed before 2010), previous exposure to trastuzumab, not fulfilling our criteria (exposure to trastuzumab two times within 90 days), incomplete medical records, age less than 18 years and non-female sex. In addition, we identified patients with breast cancer of all stages using the nationwide cancer registration system in Taiwan. All comorbid conditions and corresponding treatments starting a year prior to diagnosis were extracted from the NHIRD, as well as medication records of breast cancer diagnosis and treatments. The ICD diagnosis and treatment codes were used to identify concomitant medical diseases, medications and procedures (*Table S1*). Information on age, sex, medical history, concomitant medications within the previous 6 months and medications or procedures used during the index admission were captured from the database.

Study endpoint

The primary outcome was a composite endpoint of MACCE, which included new-onset AMI, HF hospitalization and ischaemic stroke within 3 years after the index date. All patients were followed up from the index date to death, lost to follow-up or 3 years. The clinical diagnoses of myocardial infarction, HF hospitalization and ischaemic stroke were identified by primary care physicians and confirmed by cardiologists, neurologists and oncologists. Also, the diagnoses of HF and ischaemic stroke were based on the definition of clinical guidelines.[15–18] On the basis of echocardiographic findings of left ventricular ejection fraction (LVEF) as the diagnosis of HF, the aetiologies of HF were divided to heart failure with reduced ejection fraction (HFrEF; LVEF $<$ 40%), heart failure with mid-range ejection fraction (HFmrEF; 50% $>$ LVEF ≥ 40%) and heart failure with preserved ejection fraction (HFpEF; LVEF ≥ 50%).[17,18] Because ICD-9-CM was

Figure 1 The illustration of study design.



replaced by ICD-10-CM by the Taiwan National Health Insurance in 2016, both ICD-9 and ICD-10 codes (*Table S1*) were used to identify endpoints in the primary outcome during the follow-up.

Statistical analysis

Continuous variables are presented as the means ± standard deviations, and categorical variables are presented as numbers and percentages. The differences in continuous variables were evaluated with unpaired Student's *t*-tests, and differences in proportions were evaluated with the chi-square tests or Fisher's exact tests. Because of the non-randomized nature of the study, propensity score analysis was performed to minimize any selection bias caused by differences in the clinical characteristics between groups. The propensity score is defined as the probability of exposure to the treatment conditional on a study subject's baseline characteristics. In this study, the propensity score for receiving trastuzumab was computed using multivariate logistic regression analysis, conditional on the covariates including index year, age, sex, procedure during index admission, medications and comorbidities before enrolment. We used a greedy matching algorithm to generate matches with a caliper of 0.25 of the standard deviation of the logit of the propensity score. Distributions of the clinical characteristics in the two groups were evaluated with the absolute standardized mean difference (ASMD) rather than statistical testing. ASMD was calculated as the mean or proportion of a variable divided by the pooled

DOI: 10.1002/ehf2.13591

estimate of the standard deviation of that variable, and an ASMD < 0.1 indicates a negligible difference between the two groups. A multivariate Cox proportional hazards model was then used to examine the relationship between the endpoints and different treatments. The same variables used for multivariate logistic regression analysis after propensity score matching were also used in the multivariate Cox model. The hazard ratios (HRs) and their 95% confidence intervals (CIs) were calculated from the Cox models after adjusting for all of these potential confounders. A Kaplan–Meier curve was constructed for the primary outcome of MACCE and new-onset HF, and the log-rank test was used to compare the difference between groups. We used the same Cox proportional hazards model to estimate *P*-values for interactions in the subgroup analysis. SAS 9.4 for Windows (SAS Institute Inc., Cary, NC) was used for all data analyses.

Results

Characteristics of the three-hospital based cohort (trastuzumab use)

In terms of the three-hospital based study, a total of 386 patients received trastuzumab (*Table 1*). The mean age of the patients was 54 ± 11.4 years, and most of them were at breast cancer Stage 2 or 3. Around half of the studied patients also received radiotherapies and anthracycline or taxane treatment, whereas approximately one-third of them had hormone therapies. Notably, only a small number of the studied patients had chronic diseases such as hypertension, diabetes, hyperlipidaemia or coronary artery disease (CAD), whereas only 2.8% of them were current or ex-smokers. Likewise, less than 5% were prescribed cardiovascular drugs at baseline. In terms of electrocardiographic examinations, although most of patients (93.2%) had electrocardiography at baseline, only very few (less than 5%) had the follow-up electrocardiography. Despite clinical guideline recommended a serial echocardiography during trastuzumab treatment, only 57.7% of patients had echocardiography at baseline and surprisingly, and only 32.9% had follow-up echocardiography. The averaged LVEF was 74.4 ± 7.7% at baseline and 69.6 ± 10.5% 6 months post-trastuzumab use. The detailed characteristics are provided in *Table 1*. During the 5-year follow-up, 65 (16.8%) patients reached the endpoint of mortality, whereas among them, 12 (3.1%) died of cardiovascular aetiologies. Notably, 21 (5.4%) patients were hospitalized for MACCE, including AMI, HF or ischaemic stroke, although the incidence of HF was relatively higher (2.8%) than that of the others. Among 11 patients who were hospitalized for HF, five were diagnosed of HFrEF (45.5%), two of HFmrEF (18.2%), and four of HFpEF (36.3%) at diagnosis. Among six patients who

Table 1 The baseline characteristics and outcomes of patients of receiving *trastuzumab in the three-hospital cohort*

	Trastuzumab user *N* = 386
Age (y/o)	
Mean (SD)	54 ± 11.4
Median (IQR)	54.00
Body height (cm)	156 ± 5.8
Body weight (kg)	60 ± 11.9
Site of cancer	
Right, *n* (%)	193 (50)
Left, *n* (%)	189 (48.9)
Bilateral, *n* (%)	4 (1)
Cancer stage, *n* (%)	
0	4 (1)
1	20 (5.2)
2	145 (37.5)
3	162 (41.9)
4	55 (14.2)
Coronary artery disease, *n* (%)	8 (2)
PAD, *n* (%)	3 (0.8)
HTN, *n* (%)	101 (26.1)
DM, *n* (%)	57 (14.7)
AF, *n* (%)	3 (0.7)
Chronic kidney disease/ESRD, *n* (%)	19 (4.9)
Smoking, *n* (%)	11 (2.8)
Anticancer therapy, *n* (%)	
Operation	
Lumpectomy	31 (8)
Mastectomy	273 (70.7)
No surgery	82 (21.2)
Hormone Tx, *n* (%)	
Tamoxifen	108 (27.9)
Aromatase inhibitors	82 (21.2)
Radiotherapy, *n* (%)	226 (58.5)
Right, *n* (%)	119 (52.6)
Left, *n* (%)	107 (47.3)
Adjuvant therapy, *n* (%)	128 (33.2)
Neoadjuvant therapy, *n* (%)	65 (16.8)
Anthracyclines, *n* (%)	187 (48.4)
Taxanes, *n* (%)	199 (51.5)
5-Fluorouracil, *n* (%)	68 (17.6)
Cyclophosphamide, *n* (%)	104 (26.9)
CV medications, *n* (%)	
ACEI/ARB, *n* (%)	15 (3.8)
Beta blocker, *n* (%)	14 (3.6)
Statins, *n* (%)	19 (4.9)
Antiplatelet agents, *n* (%)	8 (2.1)
Anticoagulants, *n* (%)	2 (0.5)
Digoxin, *n* (%)	1 (0.3)
MRA, *n* (%)	4 (1)
EKG at baseline, *n* (%)	360 (93.2)
Sinus rhythm, *n* (%)	358 (99.4)
AF, *n* (%)	2 (0.6)
Echocardiography at baseline, *n* (%)	223 (57.7)
LVEF (%)	74.4 ± 7.7
Echocardiography post-*trastuzumab*, *n* (%)	127 (32.9)
LVEF (%)	69.6 ± 10.5
Outcomes	
Mortality, *n* (%)	65(16.8)
Time to events (months, IQR)	38 (12,67)
CV death, *n* (%)	12(3.1)
Time to events (months, IQR)	31 (20,51)
MACCE (AMI + HF + ischaemic stroke), *n* (%)	21(5.4)
Time to events (months, IQR)	
AMI, *n* (%)	6(1.6)
Time to events (months, IQR)	29 (12, 52)

(*Continues*)

Table 1 (continued)

	Trastuzumab user *N* = 386
HF hospitalization, n (%)	11(2.8)
Time to events (months, IQR)	31 (21,52)
HFpEF, *n* (%)	4 (36.3)
HFmrEF, *n* (%)	2 (18.2)
HFrEF, *n* (%)	5 (45.5)
Ischaemic stroke, *n* (%)	4(1)
Time to events (months, IQR)	29 (5,28)

Data are presented as relative and absolute frequencies.
ACEI/ARB, angiotensin-converting enzyme inhibitor/*angiotensin* receptor blocker; AF, atrial fibrillation; AMI, acute myocardial infarction; CV, cardiovascular; DM, diabetes mellitus; EKG, electrocardiography; ESRD, end-stage renal disease; HF, heart failure; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HTN, hypertension; LVEF, left ventricular ejection fraction; MACCE, major adverse cardio-cerebral events; MRA, mineralocorticoid-receptor antagonists; PAD, peripheral arterial disease.

developed AMI post-trastuzumab use, only three of them received percutaneous coronary intervention, whereas the other three received only medical therapies for AMI. Upon three-hospital observation, we found that although only a very small portion of patients receiving trastuzumab had traditional cardiovascular risk factors, close to 5% of them still developed cardiovascular events.

Characteristics in the nationwide cohort

To determine whether our findings reflect the nationwide phenomenon, using the NHIRD from 2010 to 2015, we identified 13 502 women diagnosed with breast cancer who received chemotherapy. Among them, 6751 women were initially treated with trastuzumab (*Table 2*). After 1:1 propensity score matching with trastuzumab non-users, their

Table 2 The clinical parameters of *Trastuzumab users and non-users in NHIRD cohort*

	ALL *N = 13 502*	*Trastuzumab* user *N* = 6751	*Trastuzumab* non-user *N* = 6751	Standardized difference
Age				
Mean (SD)	54.04 (10.90)	54.27 (11.00)	53.81 (10.79)	0.043
Median (IQR)	54.00 (14.00)	54.00 (14.00)	53.00 (15.00)	
Stage				0.114
0	264 (1.96)	149 (2.21)	115 (1.70)	
1	1670 (12.37)	814 (12.06)	856 (12.68)	
2	7029 (52.06)	3391 (50.23)	3638 (53.89)	
3	2847 (21.09)	1479 (21.91)	1368 (20.26)	
4	1692 (12.53)	918 (13.60)	774 (11.46)	
Anticancer therapy				
Operation				0.022
Lumpectomy	755 (5.59)	377 (5.58)	378 (5.60)	
Mastectomy	8796 (65.15)	4441 (65.78)	4355 (64.51)	
No surgery	3951 (29.26)	1933 (28.63)	2018 (29.89)	
Hormone Tx				
Tamoxifen	4256 (31.52)	2022 (29.95)	2234 (33.09)	0.068
Aromatase inhibitors	3572 (26.46)	1681 (24.90)	1891 (28.01)	0.071
Anthracyclines	9648 (71.46)	4818 (71.37)	4830 (71.54)	0.004
Taxanes	12 130 (89.84)	6060 (89.76)	6070 (89.91)	0.005
5-Fluorouracil	5569 (41.25)	2769 (41.02)	2800 (41.48)	0.009
Cyclophosphamide	10 345 (76.62)	5133 (76.03)	5212 (77.20)	0.028
CV medications				
ACEI/ARB	2329 (17.25)	1192 (17.66)	1137 (16.84)	0.022
Beta blocker	3019 (22.36)	1547 (22.92)	1472 (21.80)	0.027
Statins	1365 (10.11)	706 (10.46)	659 (9.76)	0.023
Antiplatelet agents	1015 (7.52)	535 (7.92)	480 (7.11)	0.031
Anticoagulants	160 (1.19)	84 (1.24)	76 (1.13)	0.011
Digoxin	88 (0.65)	45 (0.67)	43 (0.64)	0.004
MRA	647 (4.79)	342 (5.07)	305 (4.52)	0.026
Coronary artery disease	547 (4.05)	280 (4.15)	267 (3.95)	0.010
PAD	86 (0.64)	43 (0.64)	43 (0.64)	0.000
HTN	3709 (27.47)	1879 (27.72)	1830 (27.11)	0.016
DM	1902 (14.09)	972 (14.40)	930 (13.78)	0.018
Hyperlipidaemia	1746 (12.93)	888 (13.15)	858 (12.71)	0.013
Valve disease	431 (3.19)	228 (3.38)	203 (3.01)	0.021
COPD	243 (1.80)	127 (1.88)	116 (1.72)	0.012
Asthma	277 (2.05)	142 (2.10)	135 (2.00)	0.007
AF	85 (0.63)	42 (0.62)	43 (0.64)	0.002
Chronic kidney disease	379 (2.81)	183 (2.71)	196 (2.90)	0.012
ESRD	9 (0.07)	5 (0.07)	4 (0.06)	0.006

Abbreviation as listed in *Table 1*.

DOI: 10.1002/ehf2.13591

average age was approximately 54 years old, whereas most were at cancer Stage 2. Similarly, more than 70% of them also received anthracycline, taxane or cyclophosphamide treatment, and approximately 30% had hormone therapies. Noticeably, the ratios of HTN (27%), DM (14%) and hyperlipidaemia (13%) in the national cohort were relatively higher than those we observed in the three-hospital based study. A higher portion of patients received ACEIs/ARBs (17.66%), beta blockers (22.92%) and statins (10.64%) compared with our three-hospital observational study.

Incidences and risks of MACCE and/or HF in the nationwide cohort

In the national cohort, the crude incidences of MACCE and HF were 4.67 and 3.21% among trastuzumab users, respectively (*Table 3*). The ratios were significantly higher than the crude incidences of MACCEs and HF among trastuzumab non-users (3.17 and 1.97%). After adjusting for age, comorbidities and cardiovascular drugs, the HR of MACCEs was 1.485 (95% CI 1.246–1.769, $P < 0.001$). Notably, among the different cardiovascular endpoints, only the HR of HF (1.623, 95% CI 1.305–2.018, $P < 0.001$) was significantly higher in patients receiving trastuzumab than in those free from trastuzumab. These findings echo our results from the three hospital-based cohort, where the risks of MACCE and HF were significantly increased in trastuzumab users compared with non-users. Notably, in the nationwide cohort, among 29 patients diagnosed of AMI, only nine (31%) of them received percutaneous coronary interventions. Likewise, among the 350 patients who developed HF after cancer therapies, only 145 (41.4%), 148 (42.3%) and 82 (23.4%) of them received ACEIs/ARBs, beta blocker and MRAs, respectively. Our findings highlight an unmet need for patients who had concomitant breast cancer and cardiovascular diseases to receive guideline-directed medical therapies.

Long-term risks of MACCE and/or HF in the nationwide cohort

In the 36-month follow-up period, the patients receiving trastuzumab had worse outcomes than the non-users. The estimated probabilities of patients being free from MACCE and/or HF among trastuzumab users declined significantly with time (*Figure 2*). After 12, 24 and 36 months from the index date, the rates free from MACCE were 97.4, 96.2 and 95.3%, respectively, among trastuzumab users, compared with 98.8, 97.8 and 96.8% in the matched nonusers (*Figure 2A*). Likewise, the rates free from HF were 98, 97.2 and 96.8%, respectively, among the trastuzumab users, compared with 99.2, 98.6 and 98.1% in the matched non-users (*Figure 2B*). Collectively, the results of both the three-hospital and national cohorts showed that the risk of MACCE, especially HF, was significantly higher in breast cancer patients receiving trastuzumab than in non-users.

The subgroup analysis of MACCE in the nationwide cohort

In the subgroup analysis, except for patients with a cumulative course of taxanes, patients receiving trastuzumab had a higher risk of MACCE than non-users independent of concomitant hormone, anthracycline, 5-FU or cyclophosphamide therapies (*Figure 3*). Among the studied patients, the higher the cancer stage, the higher the risk of MACCE. For instance, patients at Stage 4 had a higher HR of MACCE than those at Stages 2–3 (HR: 1.776; CI: 1.067–2.956 vs. 1.532; CI: 1.249–1.880). Patients who underwent operations for breast cancers had a higher risk of MACCE than non-operated patients. Of note, the increasing risk of MACCE among trastuzumab users was not associated with conventional cardiovascular risk factors, including HTN, DM, CAD and CKD. Additionally, the use of cardiovascular drugs such as ACEi, ARBs, beta blockers or statins failed to reduce the risk of MACCE among trastuzumab users.

Discussion

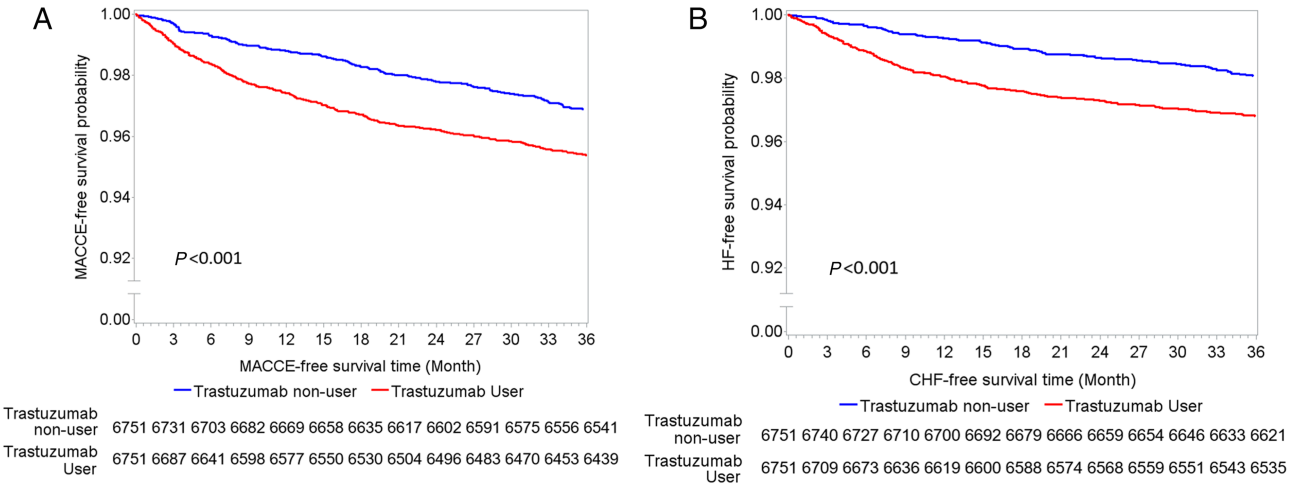
In contrast to previous studies, this project included two cohorts—a nationwide cohort and a three-hospital-based cohort—to investigate trastuzumab-related cardiovascular toxicities in Taiwan. Although myocardial dysfunction, such as HF, is believed to be the major pathology that contributes to trastuzumab-related cardiac complications, trastuzumab

Table 3 The crude and adjusted hazard ratio (HR) of MACCE, AMI, HF and ischaemic stroke in *trastuzumab users and non-users in NHIRD cohort*

	ALL $N = 13\,502$	*Trastuzumab* user N = 6751	*Trastuzumab* non-user (ref) $N = 6751$	Crude HR	*P*-value	Adjusted HR	*P*-value
MACCE (AMI + HF+ ischaemic stroke)	529 (3.92)	315 (4.67)	214 (3.17)	1.490 (1.253–1.773)	<0.001	1.485 (1.246–1.769)	<0.001
AMI	29 (0.21)	19 (0.28)	10 (0.15)	1.901 (0.884–4.089)	0.100	1.681 (0.770–3.670)	0.192
HF	350 (2.59)	217 (3.21)	133 (1.97)	1.648 (1.328–2.045)	<0.001	1.623 (1.305–2.018)	<0.001
Ischaemic stroke	191 (1.41)	99 (1.47)	92 (1.36)	1.078 (0.811–1.431)	0.605	1.038 (0.779–1.381)	0.801

Abbreviation as listed in *Table 1*.

Figure 2 The estimated probabilities of patients being free from (A) major adverse cardio-cerebral events (MACCE) and/or (B) congestive heart failure (CHF) among trastuzumab users declined significantly with time in the nationwide cohort.

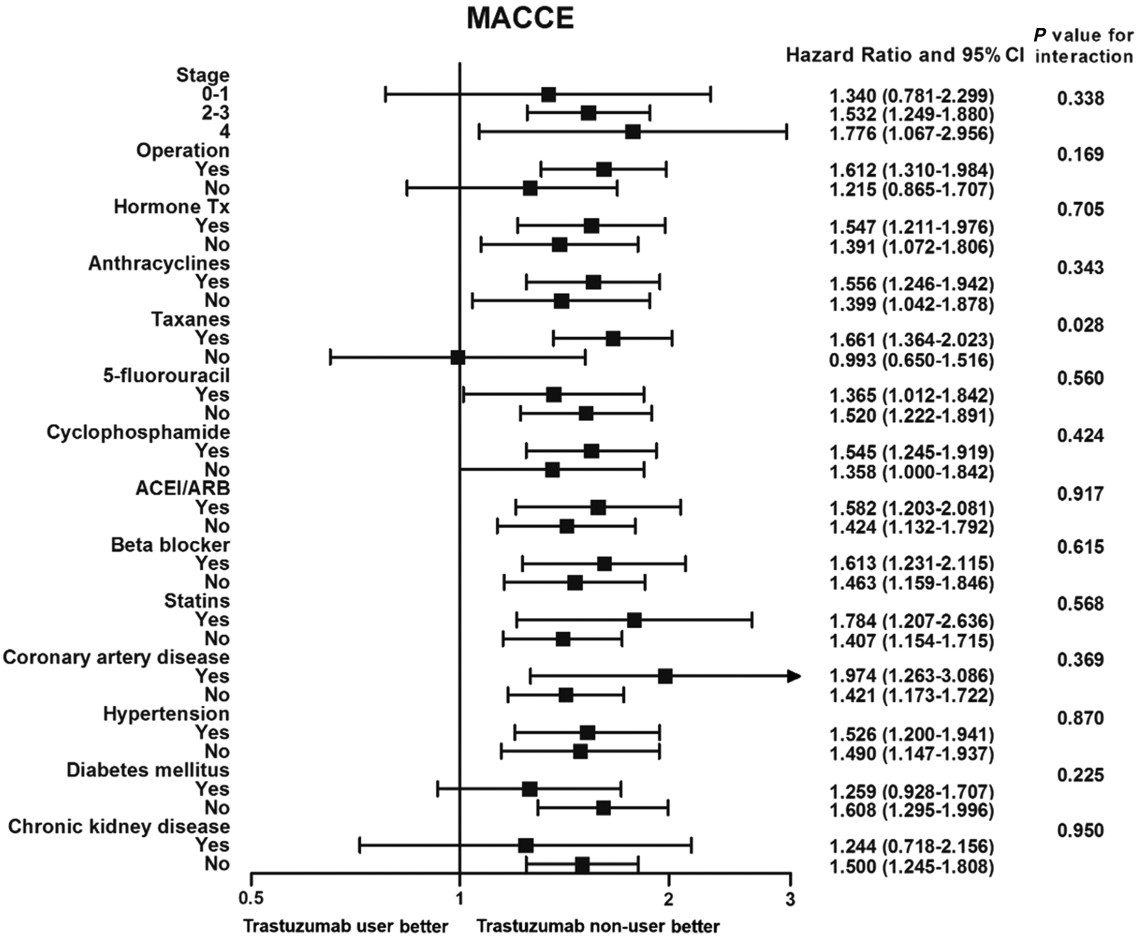


has also been observed to increase the risks of thromboembolic events, including AMI and ischaemic stroke, in cancer patients. Here, we found that in both cohorts, only a small portion of patients receiving trastuzumab had traditional cardiovascular risk factors. However, up to 5% of them developed cardiovascular events, and the accumulating incidences between trastuzumab users and non-users were 4.67 and 3.17, respectively, whereas the HR was up to 1.49 (CI: 1.253–1.773). Notably, compared with thromboembolic complications, most patients developing MACCE had HF. To our knowledge, this is the first observational study leveraging both nationwide and three-hospital-based databases focusing on trastuzumab-related cardiovascular toxicities in patients with breast cancer in Asia. Although all clinical diagnoses of myocardial infarction, HF hospitalization and ischaemic stroke were made by cardiologists, neurologists and oncologists based on the current practice consensus,[15–18] given that ICD codes fail to delineate different phenotypes of HF, the comparison of the hospital-based and nationwide cohorts may face inherent challenges. However, the accuracy of ICD codes in NHIRD has been validated in several diseases.[8,13,14] Also, unlike nationwide database-driven studies that lack information regarding the cancer stage and social habits, our three-hospital analysis provides more comprehensively reported cardiovascular risk factors such as smoking and impaired LVEFs.

It has been reported that the incidence of trastuzumab-induced HF widely ranges from 15 to 30%.[4–8,19] The major reason for this may be attributed to the various definitions of myocardial dysfunction, which frequently manifest as decreased LVEF, although these patients may be free from HF symptoms.[4,5,7] In a US-conducted, population-based study, the adjusted HF rates of trastuzumab users and nonusers were 18.5 and 4.5%, which were higher than the rates in our study (4.67 and 3.21%, respectively).[20] Using the Taiwanese NHIRD, Chien et al. reported a similar incidence of 4.48% in patients with trastuzumab-related cardiotoxicity.[8] It is worth noting that Chien et al. included patients receiving chemotherapy from 2006 to 2009, and in the past 10 years, the medical environment was different.[8] Conversely, our study focusing on patients under treatment of trastuzumab from 2010 to 2015 provides updated information as the treatment strategies for breast cancer and HF have changed. The Herceptin Adjuvant (HERA) trial, which focused on the long-term cardiac safety of trastuzumab, reported that the highest incidence of cardiotoxicity occurred within 24 months. Correspondingly, our study also showed the most significant drop in the rate free from MACCE within the first 2-year post-trastuzumab treatment.

Nonetheless, given only around 10% of the patients were Asian in the HERA trial, the cardiovascular safety of trastuzumab among Asian users remains largely uncertain.[21,22] It is worth noting that compared with Western patients with breast cancer, those in Asia are relatively younger at diagnosis and most of them receiving trastuzumab are premenopausal and have fewer traditional cardiovascular risk factors.[9–11] Although the Japan Breast Cancer Research Group (JBCRG) reported that the 3-year cumulative incidence of trastuzumab-related cardiotoxicity was only 0.54% among 2024 patients, in other single-centre studies in Saudi Arabia, Singapore and China, 17 showed that the overall percentages of LVEF reduction ranged from 11.2 to 39.1%.[4,23,24] However, most of these studies had small sample sizes and lacked comparison groups. Notably, although a relative large portion of patents included in this study were premenopause and free from traditional cardiovascular risk factors, the incidence of trastuzumab-related cardiotoxicity was not significantly different from that in the Western countries. Notably, although

Figure 3 The subgroup analysis of risks of major adverse cardio-cerebral events (MACCEs) in patients receiving trastuzumab in the nationwide cohort.



current consensus suggests a serial follow-up of echocardiography during trastuzumab treatment,[1,25] in our three-hospital-based cohort, only 57.7 and 32.9% of patients had echocardiography at baseline and post-treatment, respectively. In addition to echocardiography, biomarkers including BNP, NT-proBNP and troponin were also reported to timely reflect trastuzumab-related myocardial injury.[1,26] Nevertheless, only limited numbers of the studied patients had above-mentioned biomarkers at baseline or after treatment. Also, among patients who developed AMI post-trastuzumab use, only less than half of them received percutaneous coronary intervention, whereas the others received only medical therapies instead. These finding highlighted the phenomenon that trastuzumab-related cardiotoxicity is underestimated and under-treated. More attention should be paid to both prompt diagnoses, and aggressive therapies regarding cancer therapies induced cardiovascular complications.

Interestingly, in the subgroup analysis, we found that patients receiving trastuzumab had a higher risk of MACCE than non-users independent of the concomitant therapies except for those treated with taxanes. Compared with anthracycline and trastuzumab, patients treated with concomitant taxanes, including docetaxel and paclitaxel, presented with lower rates of cardiotoxicity (2.3–8%). As previously noted, there is no abundance of evidence implicating taxanes in HF, and for that reason, routine heart monitoring during their usage is not recommended.[1,27] It is therefore reasonable to speculate that patients with a history or high risk of HF may receive taxanes instead of anthracycline or trastuzumab. Additionally, we found that patients at an advanced stage of breast cancer had a higher risk of MACCE than those at an earlier stage. Recent epidemiological analyses found an increased risk of co-occurrence of HF and cancer, not only a high rate of tumours in patients with HF but also vice versa.[28,29] Beyond the reason of intensified medical observations, biological data also support that systemic inflammasomes, including cytokine release and neurohormonal activation, are related to HF initiation and progression.[28,30] As reported by the National Cancer Institute, within 5 years of a cancer diagnosis, the risk of HF is three times higher in patients treated for breast cancer or lymphoma than in those without cancer.[31] Within 20 years, 10% of the cancer survivors had developed

HF, compared with 6% of the control population.[29] Different from previous studies reporting that age, cardiovascular comorbidities and concomitant chemo- or radiotherapy are risk factors for chemotherapy-related HF,[1,32] our findings are the first to identify an association between cancer stage and the risk of HF. Notably, the risk of MACCE in trastuzumab users is not associated with conventional cardiovascular risk factors and the use of traditional therapies for HF did not suppress the development of HF in trastuzumab users.

Conclusions

Collectively, using both clinical observations and a nationwide cohort, we observed an increased risk of MACCE, especially HF, in patients receiving trastuzumab. Independent of traditional cardiovascular risk factors, our findings shed light on concerns about trastuzumab use.

Conflict of interest

None declared.

Funding

This study is supported by National Cheng Kung University Hospital and Chi-Mei Medical Center. Wei-Ting Chang is granted by Ministry of Science and Technology (MOST 109-2326-B-384-001-MY3).

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Supporting Information.

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