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Trastuzumab-Associated Cardiac Adverse Effects in the Herceptin Adjuvant Trial

Thomas M. Suter, Marion Procter, Dirk J. van Veldhuisen, Michael Muscholl, Jonas Bergh, Chiara Carlomagno, Timothy Perren, Rodolfo Passalacqua, Claudia Bighin, Jan G.M. Klijn, Fail T. Ageev, Erika Hitre, Juergen Groetz, Hiroji Iwata, Malgorzata Knap, Michael Gnant, Susanne Muehlbauer, Alison Spence, Richard D. Gelber, and Martine J. Piccart-Gebhart

From the Swiss Cardiovascular Center, University Hospital Bern; F. Hoffmann-La Roche, Basel, Switzerland; Frontier Science, Kincraig, Kingussie, Scotland; Department of Cardiology, University of Groningen, Groningen; Department of Medical Oncology, Daniel den Hoed Cancer Center/Erasmus MC, Rotterdam, the Netherlands; Kardiologische Praxis, Munich; Cardiology Wilhelm-Marx-Haus and Krankenhaus Gerresheim, Duesseldorf; Department of Cardiology, University Hospital Hamburg-Eppendorf, Germany; Department of Oncology, Karolinska Institute and University Hospital, Stockholm, Sweden; Department of Molecular and Clinic Endocrinology and Oncology, Università Federico II, Napoli; Division of Medical Oncology, Istituti Ospitalieri, Cremona; Medical Oncology, National Cancer Institute, Genoa, Italy; Cancer Research UK Clinical Centre Leeds; St James's University Hospital, Leeds, United Kingdom; Cardiology Research Complex, Moscow, Russia; National Institute of Oncology, Budapest, Hungary; Aichi Cancer Center Hospital, Nagoya, Japan; Medical University of Vienna, Austria; Department of Biostatistics and Computational Biology, Dana-Farber Cancer Institute, Boston, MA; and the Department of Medicine and Breast International Group, Jules Bordet Institute, Université Libre de Bruxelles, Brussels, Belgium.

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Address reprint requests to Thomas M. Suter, MD, Swiss Cardiovascular Center, University Hospital Bern, Inselspital, CH-3010 Bern, Switzerland; e-mail: thomas.suter@insel.ch.

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ABSTRACT

Purpose
The purpose of this analysis was to investigate trastuzumab-associated cardiac adverse effects in breast cancer patients after completion of (neo)adjuvant chemotherapy with or without radiotherapy.

Patients and Methods
The Herceptin Adjuvant (HERA) trial is a three-group, multicenter, open-label randomized trial that compared 1 or 2 years of trastuzumab given once every 3 weeks with observation in patients with HER-2–positive breast cancer. Only patients who after completion of (neo)adjuvant chemotherapy with or without radiotherapy had normal left ventricular ejection fraction (LVEF $\geq$ 55%) were eligible. A repeat LVEF assessment was performed in case of cardiac dysfunction.

Results
Data were available for 1,693 patients randomly assigned to 1 year trastuzumab and 1,693 patients randomly assigned to observation. The incidence of trastuzumab discontinuation due to cardiac disorders was low (4.3%). The incidence of cardiac end points was higher in the trastuzumab group compared with observation (severe congestive heart failure [CHF], 0.60% *v* 0.00%; symptomatic CHF, 2.15% *v* 0.12%; confirmed significant LVEF drops, 3.04% *v* 0.53%). Most patients with cardiac dysfunction recovered in fewer than 6 months. Patients with trastuzumab-associated cardiac dysfunction were treated with higher cumulative doses of doxorubicin (287 mg/m^2 *v* 257 mg/m^2) or epirubicin (480 mg/m^2 *v* 422 mg/m^2) and had a lower screening LVEF and a higher body mass index.

Conclusion
Given the clear benefit in disease-free survival, the low incidence of cardiac adverse events, and the suggestion that cardiac dysfunction might be reversible, adjuvant trastuzumab should be considered for treatment of breast cancer patients who fulfill the HERA trial eligibility criteria.

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INTRODUCTION

The human epidermal growth factor receptor 2 (HER-2/erbB2) is expressed in the adult myocardium and plays an important role in the modulation of anthracycline-associated cardiotoxicity.[1-3] Trastuzumab benefits patients with metastatic breast cancer and improves disease-free and overall survival after adjuvant chemotherapy.[4-6] However, trastuzumab treatment is also associated with congestive heart failure and cardiac dysfunction.[7-9] In the Herceptin Adjuvant (HERA) trial, we therefore prospectively monitored cardiac function in all patients and report herein the cardiac safety data from this trial.

PATIENTS AND METHODS

Study Design

The HERA trial was a three-group, multicenter, open-label, phase III randomized trial involving women with HER-2–positive early-stage invasive breast cancer who completed locoregional therapy and a minimum of four cycles of a standard (neo)adjuvant chemotherapeutic regimen plus radiotherapy if indicated. The patients were randomly assigned to the following three groups: women who had observation only; those adjuvantly treated with trastuzumab (first dose 8 mg per kilogram of body weight, then 6 mg per kilogram every 3 weeks) for 1 year; and those treated with trastuzumab at the same dose and on the same schedule for 2 years.

The primary end point was disease-free survival and secondary end points included cardiac safety, overall survival, time to recurrence, and time to distant recurrence.

An interim efficacy analysis after 475 disease-free survival events showed a highly significant improvement of disease-free survival for patients who were randomly assigned to both 1 and 2 years of trastuzumab compared with the observation group. The independent data monitoring committee recommended release of the 1-year trastuzumab versus observation results. The detailed efficacy results for 1-year trastuzumab versus observation with a median follow-up period of 1 year were published.[4] All patients adhered to the same schedule of follow-up visits.

To ensure comparability in both groups, patients in whom trastuzumab treatment was stopped prematurely were asked to attend all planned remaining study visits, if possible.

Eligibility Criteria

Patients with completely excised HER-2–positive early invasive breast cancer were eligible for the study if they had completed at least four cycles of a standard (neo) adjuvant chemotherapy regimen and radiotherapy (if applicable). Chemotherapy could have included regimens with anthracyclines with or without taxanes or nonanthracycline regimens. Anthracycline-containing chemotherapy was not allowed to exceed a cumulative dose of 360 mg/m^2 doxorubicin or 720 mg/m^2 epirubicin. Irradiation of the mediastinal internal mammary node had to be planned using three-dimensional computerized axial tomography scanning or a similar technique to minimize cardiac irradiation.

Cardiac Eligibility Criteria

Only patients who had a screening LVEF after completion of chemo- and radiation therapy with a normal left ventricular ejection fraction (LVEF $\geq$ 55% measured by echocardiography or multiple-gated acquisition [MUGA] scan) were enrolled. Patients with a history of documented congestive heart failure (CHF), coronary artery disease (angina pectoris requiring antianginal medication or transmural infarction on ECG), uncontrolled hypertension (blood pressure systolic $>$ 180 mmHg or diastolic $>$ 100 mmHg), high-risk arrhythmias or clinically significant valvular disease were excluded.

Cardiac Monitoring

A cardiac questionnaire, physical examination, ECG, and an assessment of LVEF by echocardiography or MUGA scanning were performed in all three study groups at baseline, 3, 6, 12, 18, 24, 30, 36, and 60 months after random assignment. Among the first 900 patients enrolled, echocardiograms up to 6 months (the first three LVEF assessments) were reviewed by a core laboratory blinded to the treatment group as a quality control measure and feedback to the study site was given when necessary. The results of the review of echocardiograms by the core laboratory were presented to the independent data monitoring committee. Three prespecified interim cardiac safety analyses were performed after 300, 600, and 900 patients were treated or observed for 6 months.

Definitions

Cardiac safety and tolerability of trastuzumab were assessed on the basis of prespecified cardiac end points. Cardiac death was defined as death definitely due to heart failure, myocardial infarction or documented arrhythmia, or probable cardiac death within 24 hours of a cardiac event. A significant LVEF drop was defined as an absolute decline of at least 10 percentage points from baseline LVEF and to below 50% identified by MUGA scan or echocardiogram. Severe CHF was defined as New York Heart Association (NYHA) class III or IV, confirmed by a cardiologist, and a significant LVEF drop. Symptomatic CHF was defined as symptomatic CHF confirmed by a cardiologist and a significant LVEF drop. Confirmed significant LVEF drop was defined as an asymptomatic (NYHA class I) or mildly symptomatic (NYHA class II) significant LVEF drop, unless the next subsequent assessment of LVEF indicated a return to levels that did not meet the definition of a significant LVEF drop; or as identified by the treatment unblinded cardiac advisory board. A repeat LVEF assessment was to be performed approximately 3 weeks after the first documented significant LVEF drop and NYHA class II was to be confirmed by a cardiologist. If such a repeat assessment or confirmation of NYHA class was not available, the cardiac advisory board reviewed the patient and adjudicated the cardiac end point. The primary cardiac end point of this study was cardiac death or severe CHF. The secondary cardiac end point of the study was a confirmed significant LVEF drop.

Discontinuation of Trastuzumab and Dose Modification

Trastuzumab had to be permanently discontinued in patients who experienced severe CHF (a primary cardiac end point) and heart failure treatment was recommended. For patients with a significant LVEF drop, continuation or discontinuation with trastuzumab was guided by the algorithm depicted in Appendix Figure A1 (online only). If the patient reached a confirmed significant LVEF drop (a secondary cardiac end point) trastuzumab had to be permanently discontinued. Reasons for premature discontinuation of trastuzumab during the scheduled treatment period are presented in Table 1. A total of 153 patients (9.1%) discontinued for reasons other than recurrence of disease. Seventy-two patients (4.3%) discontinued trastuzumab treatment due to cardiac disorders. The cardiac disorders leading to discontinuation were CHF (n = 30), left ventricular dysfunction (n = 32), manifestation of coronary artery disease (n = 1), tachyarrthymias (n = 2), pericardial effusion (n = 1), new ECG abnormalities (n = 2), and unspecific cardiotoxicity (n = 4). Forty patients (2.4%) refused trastuzumab treatment and 29 patients (1.7%) discontinued due to other non-cardiac adverse events.

Statistical Analysis

The clinical cutoff date for this analysis was March 29, 2005. Data were available for 3,386 patients randomly assigned between December 2001 and March 2005: 1,693 were randomly assigned to observation and 1,693 patients were randomly assigned to 1 year of trastuzumab.

The safety population groups were defined by whether a patient received trastuzumab before disease recurrence. There were 19 patients randomly assigned to the 1-year trastuzumab group who did not receive any trastuzumab before disease recurrence and four patients randomly assigned to observation who received at least one dose of trastuzumab. Therefore, there were 1,678 patients in the trastuzumab safety analysis population group and 1,708 patients in the observation safety analysis population group.

The difference in incidence of cardiac adverse events between safety analysis population groups was compared with an approximate 95% CI for the difference of two incidences using the Hauck-Anderson correction.[10] The mean cumulative dose of chemotherapy agents was compared among patients with and without any cardiac end points in the trastuzumab safety analysis population group using a *t*-test assuming equal variances. The incidence of any cardiac end point was estimated for the trastuzumab safety analysis population group according to potential cardiac risk factors.

RESULTS

Patient Characteristics

The demographic characteristics of patients in the two safety analysis population groups with respect to age, race (white, 84% *v* 83%), menopausal status (postmenopausal, 45% in both groups), smoking habits (smoker, 14% *v* 13%), previous or active cardiovascular diseases (22% *v* 23%), hypertension (17% in both groups), diabetes (3% in both groups), and previous radiotherapy (received radiotherapy, 77% *v* 76%) were balanced in both groups. The mean age

Table 1. Reason for Discontinuation of Trastuzumab

Reason for Discontinuation	Patients (N = 1,678) No.	%
Cardiac disorders	72	4.3
Other non-cardiac adverse events	29	1.7
Death	3	0.2
Recurrence of disease	69	4.1
Refused treatment	40	2.4
Other reason	9	0.5
Total	222	

(± standard deviation) of patients in the two groups was 49 ± 10 years. Patients received a minimum of four cycles of adjuvant (89%), neoadjuvant (5%), or both (6%) types of chemotherapy. The (neo)adjuvant chemotherapy was anthracycline based in 94% of patients, and in addition, 26% received taxanes. The median time between finishing any type of chemotherapy and start of trastuzumab treatment was 89 days.

Cardiac End Points

The incidence of CHF is shown in Table 2. One patient in the observation group suffered cardiac death. As expected, the incidence of severe CHF (0.60 *v* 0.00; 95% CI for difference in incidence, 0.20% to 0.99%), symptomatic CHF (2.15 *v* 0.12; 95% CI for difference in incidence, 1.29% to 2.77%) and confirmed significant LVEF drop (3.04% *v* 0.53%; 95% CI for difference in incidence, 1.59% to 3.43%) was significantly higher in the trastuzumab group compared with observation. The incidence of an occurrence at any time of at least one significant LVEF drop was also significantly higher in the trastuzumab group (7.03% *v* 2.05%; 95% CI for the difference in incidence, 3.56% to 6.41%).

Recovery After a Cardiac End Point

Of the 10 patients in the trastuzumab group with severe CHF, eight were asymptomatic at the last scheduled assessment on December 15, 2005 (Table 3). A patient's LVEF was considered recovered from a cardiac end point if the patient had an LVEF of ≥ 55% at any time after the cardiac end point until December 15, 2005. As presented in Table 3, six of 10 patients with severe CHF recovered their LVEF in a median of 124 days (range, 36 to 409 days). Among the 36 patients with symptomatic CHF, 24 patients recovered their LVEF in a median of 151 days (range, 26 to 831 days) and among the 51 patients with a confirmed significant LVEF drop, 35 patients recovered in a median of 191 days (range, 13 to 831 days).

Table 3. Recovery After a Cardiac Event (trastuzumab safety analysis population)

Event	No.	%	Time to Recovery (days) Median	Range
Severe CHF*† (n = 10)				
Recovery to asymptomatic	8	80		
Recovery of LVEF ≥ 55%	6	60	124	36-409
Symptomatic CHF‡ (n = 36)				
Recovery of LVEF ≥ 55%	24	67	151	26-831
Confirmed significant LVEF drop§ (n = 51)				
Recovery of LVEF ≥ 55%	35	69	191	13-831
Any type of cardiac end point (n = 61)				
Recovery of LVEF ≥ 55%	41	67	189	13-831

Abbreviations: CHF, congestive heart failure; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.
*Treatment included angiotensin converting enzyme inhibitors (67%), digoxin (44%), and beta blocker (33%).
†Severe CHF, which does not include death from cardiac causes, was defined as NYHA III or IV functional class confirmed by a cardiologist and a decrease in LVEF of ≥ 10 percentage points below baseline and to less than 50%.
‡Symptomatic CHF, which includes severe CHF, was defined as CHF that was considered symptomatic by a cardiologist and a decrease in LVEF of ≥ 10 percentage points below baseline and to less than 50%.
§Confirmed asymptomatic (NYHA class I) or mildly symptomatic (NYHA class II) LVEF drop to ≥ 10 percentage points below baseline and to less than 50%, which was confirmed after approximately 3 weeks. If such a repeat assessment was not available, the cardiac advisory board reviewed the patient and determined if the patient experienced a confirmed significant LVEF drop. This does not include patients with severe CHF.

Cumulative Dose of Chemotherapy Agents

The mean cumulative dose of chemotherapy agents cyclophosphamide, doxorubicin, epirubicin, docetaxel, and paclitaxel was calculated for patients who had reached a cardiac end point and patients who did not reach a cardiac end point (Table 4). The mean cumulative dose among patients with a cardiac end point was significantly higher for doxorubicin (287 mg/m^2 *v* 257 mg/m^2) and epirubicin (480 mg/m^2 *v* 422 mg/m^2). There were four patients treated with paclitaxel who developed a cardiac end point. The mean cumulative dose of

Table 2. Cardiac Adverse Events (safety analysis population)

Variable	Trastuzumab (n = 1,678) No.	%	Observation (n = 1,708) No.	%	Difference in Incidence	95% CI for Difference in Incidence
Cardiac death	0	0.00	1	0.06	−0.06	−0.20 to 0.09
Severe CHF* (not including cardiac death)	10	0.60	0	0.00	0.60	0.20 to 0.99
Symptomatic CHF (including severe CHF, not including cardiac death)†	36	2.15	2	0.12	2.03	1.29 to 2.77
Confirmed significant LVEF drop (asymptomatic or mildly symptomatic)‡	51	3.04	9	0.53	2.51	1.59 to 3.43
Any type of cardiac end point (at least one occurrence of cardiac adverse events above)§	61	3.64	10	0.59	3.05	2.05 to 4.05
At least one significant LVEF drop¶	118	7.03	35	2.05	4.98	3.56 to 6.41

Abbreviations: CHF, congestive heart failure; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.
*Severe CHF, which does not include death from cardiac causes, was defined as NYHA III or IV functional class confirmed by a cardiologist and a decrease in LVEF of ≥ 10 percentage points below baseline and to less than 50%.
†Symptomatic CHF, which includes severe CHF, was defined as CHF that was considered symptomatic by a cardiologist and a decrease in LVEF of ≥ 10 percentage points below baseline and to less than 50%.
‡Confirmed asymptomatic (NYHA class I) or mildly symptomatic (NYHA class II) LVEF drop to ≥ 10 percentage points below baseline and to less than 50%, which was confirmed after approximately 3 weeks. If such a repeat assessment was not available, the Cardiac Advisory Board reviewed the patient and determined if the patient experienced a confirmed significant LVEF drop. This does not include patients with severe CHF.
§Any type of cardiac endpoint was defined as at least one occurrence of cardiac death, severe CHF, symptomatic CHF or confirmed significant LVEF drop.
¶Significant LVEF drop was defined as a decrease in LVEF of ≥ 10 percentage points below baseline and to less than 50% at any time during the study.

Table 4. Mean Cumulative Dose of Chemotherapy Agents by Cardiac End Point Status (trastuzumab safety analysis population)

Agent	Cardiac End Point (n = 61)		No Cardiac End Point (n = 1,617)		95% CI for Difference in Means	*P*
	Mean Cumulative Dose (mg/m^2)	SD	Mean Cumulative Dose (mg/m^2)	SD		
Cyclophosphamide (n = 1,606)	3,442	1,146	3,253	1,293	−161 to 538	.29
Doxorubicin (n = 577)	287	58	257	54	5 to 55	.02
Epirubicin (n = 1,018)	480	119	422	105	25 to 92	< .01
Docetaxel (n = 187)	386	76	375	105	−69 to 89	.80
Paclitaxel (n = 267)	838	170	642	223	−25 to 415	.08

Abbreviation: SD, standard deviation.

paclitaxel showed a trend to a higher dose among patients with a cardiac end point that was not significant and was based on small numbers.

Potential Cardiac Risk Factors

Several potential cardiac risk factors were analyzed, as presented in Table 5. The potential risk factors that were considered at baseline were screening LVEF, history of cardiac disease, CHF, coronary artery disease, previous radiotherapy, hypertension, high body mass index, low body mass index, current smoker, hyperlipidemia, diabetes mellitus, hyperthyroidism, hypothyroidism, and age. The incidence of any type of cardiac end point among patients with the risk factor was compared with the incidence of any type of cardiac end point among patients without the risk factor for the trastuzumab group. Patients with a screening LVEF of 55% $\leq$ LVEF $<$ 60% had a significantly higher incidence of cardiac end points than patients with a higher screening LVEF $\geq$ 60% (6.90% *v* 2.72%; 95% CI for the difference in incidence, 1.33% to 7.02%). Patients with a screening LVEF of 60% $\leq$ LVEF $<$ 65% had significantly higher incidence of cardiac end points than patients with a higher screening LVEF $\geq$ 65% (3.89% *v* 1.88%; 95% CI for the difference in incidence, 0.02% to 4.01%). It is to be expected that patients with a lower screening LVEF have a higher incidence of cardiac end points. Patients with a high body mass index ($>$ 25) had a significantly higher incidence of cardiac end points than patients with a body mass index in the normal range (20 $\leq$ BMI $\leq$ 25). Patients with a risk factor of hypertension, current smoker, diabetes, hypothyroidism, or age $\geq$ 60 showed a trend to a higher incidence of cardiac end points that was not significant. There are small numbers of patients ($<$ 60) with the following risk factors: CHF, coronary artery disease, and diabetes mellitus, leading to wide CIs. It was not possible to consider metabolic syndrome as a potential risk factor as only one patient had been diagnosed with this condition.

Cumulative Incidence

The cumulative incidence for cardiac death or severe CHF (Fig 1A), cardiac death, severe CHF or symptomatic CHF (Fig 1B), and any cardiac end point (Fig 1C) were calculated and are displayed along with the competing risk of a disease-free survival event.[11] The median follow-up for patients was 12 months.

DISCUSSION

HER signaling plays an important role in modulating myocardial response to chemotherapy-induced injury and inhibition of the HER-2/erbB2 receptor worsens anthracycline-associated cardiotoxicity.[1,12] Early clinical experience with trastuzumab in the pivotal trials indicated a high potential for cardiotoxicity.[6] To ensure safety for patients in the HERA trial, we therefore applied an algorithm for discontinuation of trastuzumab in individual patients based on periodic LVEF assessment and we carefully monitored cardiac symptoms and function in all patients.

Cardiac events were infrequent in the HERA trial. No cardiac deaths occurred in the trastuzumab group and the rate of severe heart failure was $<$ 1%. Trastuzumab treatment was discontinued because of cardiac dysfunction for 4.3% of patients.

The comparison with other trials is complicated by the fact that different definitions of cardiac end points, eligibility criteria, and treatment regimens were used. For example, the investigators of the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-31 trial defined a cardiac event as a probable/definite cardiac death or NYHA III/IV CHF, confirmed by the cardiac review panel, which was blinded to treatment.[9] In the HERA trial, to meet the definition of severe CHF, NYHA III/IV CHF was confirmed by a local, unblinded cardiologist and a significant LVEF drop was required. The eligibility criteria of the NSABP B-31 trial stated that a patient must not begin treatment with trastuzumab if the patient's LVEF was below the institution's lower limit of normal (which is most often an LVEF $>$ 49%) or the patient's LVEF after anthracyclines or cyclophosphamide was at least 15% below baseline. Furthermore, the treatment regimen in the NSABP B-31 trial combined paclitaxel with weekly trastuzumab in the first 4 weeks after four cycles of anthracyclines or cyclophosphamide whereas in the HERA trial once every 3weeks trastuzumab was given after a median time of 89 days after completion of chemotherapy. However, despite these complications, comparing the incidence of severe CHF in the treatment groups, the incidence in the HERA trial (0.6%) appears noticeably lower than in the NSABP B-31 (3.6%). The percent of patients who prematurely discontinued trastuzumab because of cardiac dysfunction was 4.3% in HERA compared with 15.6% (133 of 850) in NSABP B-31.

It may also be possible to compare the incidence of left ventricular (LV) dysfunction in the two trials. The NSABP B-31 reports the cumulative incidence of asymptomatic cardiac dysfunction, defined as at least once a drop in LVEF $\geq$ 10 percentage points and to less than

Table 5. Summary of Incidence of Cardiac End Point by Risk Factors (trastuzumab safety analysis population)

Variable	No. of Patients	Incidence		95% CI for Incidence*	Difference in Incidence (%)	95% CI for the Difference†
		No	%			
Screening LVEF						
55% ≤ LVEF < 60% *v*	377	26	6.90	4.55 to 9.94	4.17	1.33 to 7.02
≥ 60%	1,286	35	2.72	1.90 to 3.76		
60% ≤ LVEF < 65% *v*	540	21	3.89	2.42 to 5.88	2.01	0.02 to 4.01
≥ 65%	746	14	1.88	1.03 to 3.13		
Cardiac history						
Yes	374	16	4.28	2.46 to 6.85	0.83	−1.59 to 3.24
No	1,304	45	3.45	2.53 to 4.59		
Congestive heart failure						
Yes	4	0	0.00	0.00 to 60.24	−3.64	−17.04 to 9.75
No	1,674	61	3.64	2.80 to 4.66		
Coronary artery disease						
Yes	16	0	0.00	0.00 to 20.59	−3.67	−7.70 to 0.36
No	1,662	61	3.67	2.82 to 4.69		
Previous radiotherapy						
Left sided	654	24	3.67	2.37 to 5.41	−0.60	−3.24 to 2.04
None	375	16	4.27	2.46 to 6.84		
Hypertension						
Yes	290	13	4.48	2.41 to 7.54	1.02	−1.72 to 3.77
No	1,388	48	3.46	2.56 to 4.56		
High BMI						
> 25 *v*	841	40	4.76	3.42 to 6.42	2.64	0.78 to 4.50
20 ≤ BMI ≤ 25	708	15	2.12	1.19 to 3.47		
Low BMI						
< 20	118	6	5.08	1.89 to 10.74	2.97	−1.58 to 7.51
20 ≤ BMI ≤ 25	708	15	2.12	1.19 to 3.47		
Smoker						
Yes	239	12	5.02	2.62 to 8.61	1.62	−1.52 to 4.75
No	1,439	49	3.41	2.53 to 4.48		
Hyperlipidaemia						
Yes	74	1	1.35	0.03 to 7.30	−2.39	−5.87 to 1.09
No	1,604	60	3.74	2.87 to 4.79		
Diabetes						
Yes	56	5	8.93	2.96 to 19.62	5.48	−3.01 to 13.96
No	1,622	56	3.45	2.62 to 4.46		
Hyperthyroidism						
Yes	17	0	0.00	0.00 to 19.51	−3.67	−7.52 to 0.17
No	1,661	61	3.67	2.82 to 4.69		
Hypothyroidism						
Yes	74	5	6.76	2.23 to 15.07	3.27	−3.24 to 9.77
No	1,604	56	3.49	2.65 to 4.51		
Age, years						
≥ 50 to ≤ 59 *v*	539	18	3.34	1.99 to 5.23	−0.44	−2.52 to 1.63
< 50	872	33	3.78	2.62 to 5.27		
≥ 60 *v*	267	10	3.75	1.81 to 6.78	0.13	−2.54 to 2.80
< 60	1,411	51	3.61	2.70 to 4.73		

Abbreviations: LVEF, left ventricular ejection fraction; BMI, body mass index.
*Exact 95% CI for one sample binomial using Pearson-Clopper method.
†Approximate 95% CI for difference of two rates using Hauck-Anderson correction.

55%, of 34% in the treatment group, and of 17% in the observation group. We report the incidence of at least one significant LVEF drop (≥ 10 percentage points below baseline and < 50%), which may include symptomatic patients, of 7.0% in the treatment group, and of 2.1% in the observation group. Although not a formal comparison, this suggests that trastuzumab-treatment regimen in the HERA trial leads to a smaller increase in LV dysfunction. Administering trastuzumab after completing chemotherapy and radiotherapy, and restricting enrollment to patients with LVEF ≥ 55% after chemotherapy, might contribute to the lower incidence of LV dysfunction.

An important feature of trastuzumab-associated cardiotoxicity might be reversibility of symptoms and LV dysfunction.[13,14] As of the last scheduled visit in December 15, 2005, 80% of patients with severe CHF were asymptomatic. Sixty percent had a recovery of their LV dysfunction to at least 55% as of December 15, 2005. For patients with

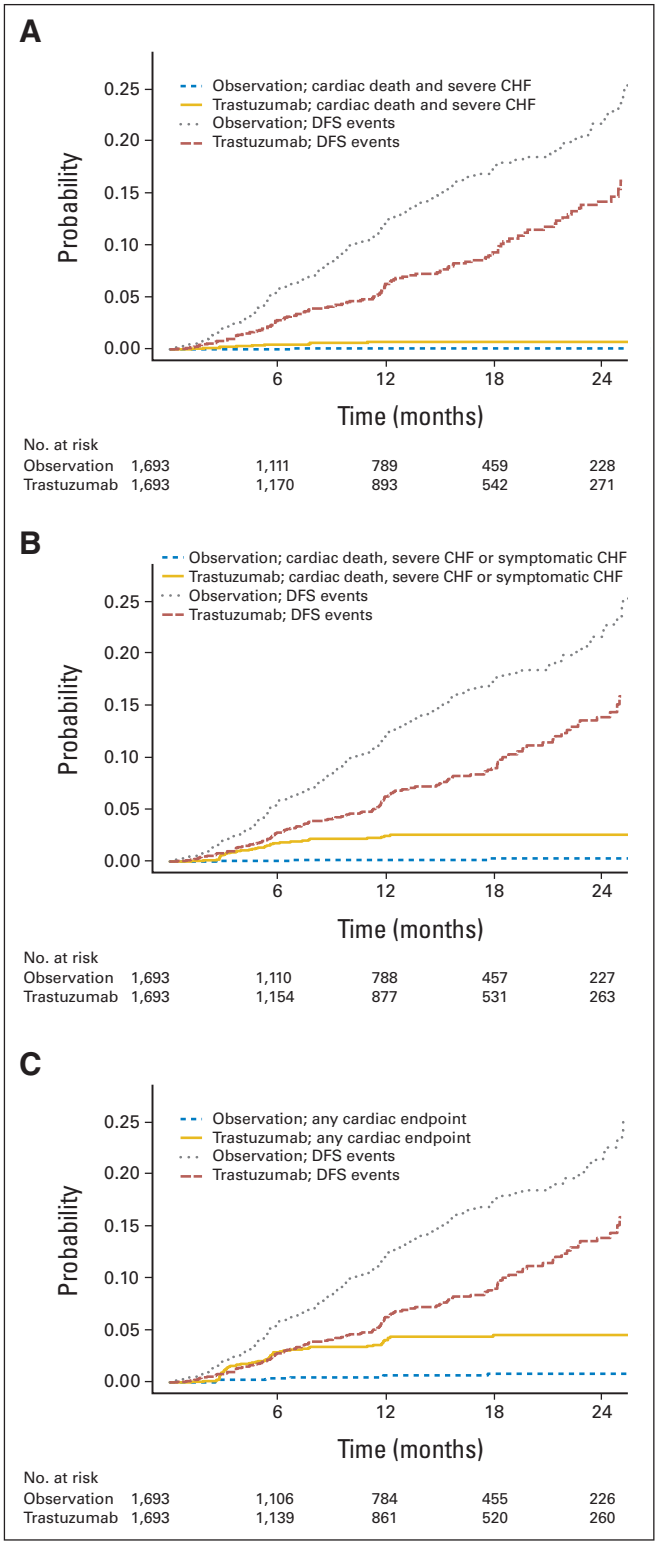

Fig 1. The cumulative incidence of competing risks showing the risk of a disease-free survival (DFS) event alongside (A) the risk of cardiac death or severe congestive heart failure (CHF), (B) the risk of cardiac death, severe CHF or symptomatic CHF, or (C) the risk of any cardiac event.

severe CHF whose LV dysfunction recovered, the median time to recovery was fewer than 6 months. A similar percentage of patients with symptomatic CHF or confirmed significant LVEF drops had a recovery of the LV function. It remains possible that with longer follow-up time a higher incidence of LV dysfunction recovery would be observed. Continued follow-up is required to determine long-time cardiac prognosis in these patients.

In the HERA trial, the patients who had a cardiac end point received a significantly higher dose of epirubicin and doxorubicin than the patients without. As in other trials, we found that patients with a lower screening LVEF had a significantly higher incidence of a cardiac end point. However, unlike the investigators in the NSABP B-31, we found no evidence of older patients being at greater risk for trastuzumab-associated cardiac dysfunction.[8] In contrast to the retrospective analysis of the pivotal trials in metastatic breast cancer, we found no evidence that previous cardiac disease, hyperlipidemia, or hypertension was a risk factor for a cardiac end point. Of interest is that patients with a high body mass index have a significantly higher incidence of a cardiac end point. However, it is important to remember that analysis of potential risk factors are exploratory based on a small number of cardiac end points.

The cumulative incidence functions shown in Figure 1 illustrate that the benefit of trastuzumab in terms of reducing the risk of a disease-free survival event is greater than the increased risk of cardiac adverse effects even within the first year of follow-up. In addition, the benefit appears to increase into the second year of follow-up while the cumulative incidence of any type of cardiac end point appears stable after completion of trastuzumab at 12 months.

Limitations

Median follow-up was 12 months, and therefore, at the time of analysis many patients were still receiving trastuzumab. We acknowledge that we have a limited picture of the risks associated with trastuzumab treatment. However, the incidence of cardiac end points is low and as the cumulative incidence of cardiac end points appears to be stable after 12 months, we expect the incidence of cardiac end points to remain low with further follow-up. The low incidence of cardiac end points made the exploratory analysis of risk factors more difficult.

In conclusion, given the clear benefit in disease-free survival of 1-year trastuzumab, the low incidence of cardiac end points, and the suggestion that cardiac dysfunction may be reversible, adjuvant trastuzumab should be considered a standard treatment option for patients who fulfill the HERA trial eligibility criteria.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Employment: Susanne Muehlbauer, F. Hoffmann-La Roche Ltd **Leadership:** N/A **Consultant:** Thomas M. Suter, F. Hoffmann-La Roche, Basel, Switzerland; Jonas Bergh, Roche; Timothy Perren, F. Hoffmann-La Roche; Martine J. Piccart, GlaxoSmithKline **Stock:** N/A **Honoraria:** Thomas M. Suter, F. Hoffmann-La Roche, Basel, Switzerland; Jonas Bergh, Roche; Timothy Perren, F. Hoffmann-La

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AUTHOR CONTRIBUTIONS

Conception and design: Thomas M. Suter, Jonas Bergh, Rodolfo Passalacqua, Jan GM Klijn, Richard D. Gelber, Martine J. Piccart
Provision of study materials or patients: Jonas Bergh, Chiara Carlomagno, Timothy Perren, Claudia Bighin, Jan GM Klijn, Fail T. Ageev, Erika Hitre, Hiroji Iwata, Michael Gnant, Martine J. Piccart
Collection and assembly of data: Claudia Bighin, Jan GM Klijn, Fail T. Ageev, Erika Hitre, Juergen Groetz, Hiroji Iwata, Malgorzata Knap, Susanne Muehlbauer, Alison Spence
Data analysis and interpretation: Thomas M. Suter, Marion Procter, Dirk J. van Veldhuisen, Michael Muscholl, Susanne Muehlbauer, Richard D. Gelber, Martine J. Piccart
Manuscript writing: Thomas M. Suter, Marion Procter, Richard D. Gelber
Final approval of manuscript: Thomas M. Suter, Dirk J. van Veldhuisen, Michael Muscholl, Jonas Bergh, Chiara Carlomagno, Timothy Perren, Rodolfo Passalacqua, Claudia Bighin, Jan GM Klijn, Fail T. Ageev, Erika Hitre, Juergen Groetz, Hiroji Iwata, Malgorzata Knap, Michael Gnant, Alison Spence, Richard D. Gelber, Martine J. Piccart
Other: Thomas M. Suter [Chair of the Cardiac Advisory Board], Timothy Perren [Coordination of United Kingdom Yorkshire Breast Cancer Group contribution to the HERA trial]

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Appendix

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).