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Impact of Stopping Trastuzumab in Early Breast Cancer: A Population-Based Study in Ontario, Canada

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Abstract

Background: Adjuvant trastuzumab for early-stage (I-III) HER2-positive breast cancer (BC) has led to statistically significant improvement in cancer outcomes but carries a risk of cardiotoxicity. Trastuzumab is discontinued early in many patients for asymptomatic changes in left ventricular ejection fraction. We evaluated the impact of early discontinuation of trastuzumab on cancer outcomes. **Methods:** We conducted a retrospective population-based cohort study of early BC patients treated with adjuvant trastuzumab in Ontario, Canada, 2007-2016. Four groups were analyzed: group A was full treatment, 17-18 cycles trastuzumab; group B was cardiac event (CE) within treatment period; group C was ≤16 cycles, no CEs, stopped within 30 days from last cardiac imaging; and group D was ≤16 cycles, no CEs, stopped more than 30 days from cardiac imaging. Primary outcome was disease-free survival (DFS); secondary outcomes were: overall survival, cancer-specific mortality, and cardiovascular mortality. Sensitivity analyses were performed 14 months after cycle 1 trastuzumab to control for early relapse. **Results:** A total of 5547 patients met the inclusion criteria: group A = 3921, group B = 309, group C = 362, and group D = 955. The 5-year DFS was 94.1% in group A, 80.1% in group B, 81.4% in group C, and 82.4% in group D. Using a Cox model, the hazard ratio for 5-year DFS was 3.15 (95% confidence interval [CI] = 2.13 to 4.65) for group B, 1.94 (95% CI = 1.30 to 2.89) for group C, and 1.92 (95% CI = 1.46 to 2.53) for group D. Overall, 26 patients (0.5%) died of cardiac causes. **Conclusions:** BC patients in Ontario who did not complete adjuvant trastuzumab had a statistically significantly higher risk of BC relapse and death and low incidence of cardiac death. These findings support 1 year of adjuvant trastuzumab in early-stage BC.

Since the early 2000s, 1 year of adjuvant trastuzumab has been standard of care for patients with HER2-positive early breast cancer (BC) (1,2). Clinically significant rates of heart failure (HF) were observed when trastuzumab was administered concurrently with anthracyclines in advanced BC, leading to adoption of intensive cardiac monitoring in the adjuvant setting. International guidelines recommend cardiac monitoring every 3-4 months for early-stage (I-III) BC patients receiving adjuvant trastuzumab (3–6). Despite almost 15 years of clinical experience with trastuzumab, there is little high-quality evidence to support the clinical utility of routine cardiac monitoring in preventing long-term cardiac dysfunction or optimizing cancer care in this patient population (7,8).

The risk of clinically significant HF with adjuvant trastuzumab is low. A meta-analysis of adjuvant trastuzumab trials demonstrated the risk of symptomatic HF was 2.5% (range = 0%-4%); 11.2% of patients experienced an asymptomatic drop in left ventricular ejection fraction (LVEF) (1). A recent population-based study found that the cumulative incidence of HF in BC patients who received chemotherapy and trastuzumab was 3.08% compared with 0.96% in an age-matched sample of women without breast cancer (9). Trastuzumab-associated cardiotoxicity, particularly when administered without anthracyclines, is often considered reversible. Long-term follow-up of the pivotal adjuvant trastuzumab trials has failed to demonstrate an increased risk of cardiotoxicity (10–15) after trastuzumab completion. Outside of clinical trials, the evidence on long-term risk is mixed, with some evidence showing that the HF risk did not extend beyond 1.5 years after initiation of therapy (16), whereas elsewhere the risk was shown to persist up to 5 years after completing trastuzumab (17).

Concerns about cardiotoxicity can lead to disruptions in the curative treatment plan for HER2+ BC patients. In our own experience with patients in a dedicated cardio-oncology clinic, 33% of patients experienced delays in trastuzumab therapy because of asymptomatic declines in LVEF detected during routine cardiac monitoring [18] and 15% had trastuzumab terminated for cardiotoxicity.

In Ontario, Canada, the majority (75%) of early BC patients undergo cardiac screening every 3-4 months during treatment with adjuvant trastuzumab [19]. We hypothesized that there is a population of patients who have trastuzumab discontinued early because of asymptomatic changes in cardiac function, potentially compromising cancer outcomes. We conducted a retrospective population-based cohort study in BC patients who received adjuvant trastuzumab in Ontario, Canada, to assess the impact of stopping trastuzumab early on disease-free survival (DFS) and overall survival (OS) as well as cancer and cardiac specific mortality.

Methods

Study Design

This was a retrospective population-based cohort study of early-stage (I-III) BC patients, aged 18 years or older, who received their first cycle of adjuvant trastuzumab in Ontario, Canada, between January 1, 2007, and March 31, 2016. The main exposure was trastuzumab-based therapy, calculated as the number of (every 3 weeks) cycles each patient received. The secondary exposure was development of a cardiac event (CE) between first treatment and 90 days after completion of trastuzumab. A clinically significant CE was defined as a new diagnosis of HF, pulmonary edema, or cardiomyopathy. We categorized patients into 4 groups based on the number of completed cycles of trastuzumab and incidence of CEs.

The comparator arm—group A—completed a full course of adjuvant trastuzumab (17-18 cycles) without any CEs. Group B had a CE between first dose and 90 days after completion of trastuzumab. Group C had no CEs but received 16 or fewer cycles of trastuzumab and stopped within 30 days of their last cardiac imaging. Group D had no CEs, they received 16 or fewer cycles of trastuzumab, and treatment was discontinued more than 30 days since last cardiac imaging. We initially planned the study with only arms A, B, and C in an effort to isolate patients with asymptomatic changes in LVEF (group C). However, the protocol was revised after finding a large population that did not fit our prespecified cohort definitions.

Data Sources

Patients were identified using health administrative databases in Ontario, Canada, that contain patient-level information on cancer diagnosis and cancer drug administration as well as inpatient and outpatient data, cancer registry data, and demographics. Deidentified databases were accessed through the Institute for Clinical Evaluative Sciences (ICES), and all data sources were linked through a unique encrypted identifier and analyzed at ICES. ICES is an independent, nonprofit research institute funded by an annual grant from the Ontario Ministry of Health and Long-Term Care. As a prescribed entity under Ontario's privacy legislation, ICES is authorized to collect and use health-care data for the purposes of health system analysis, evaluation, and decision support. Secure access to these data is

governed by policies and procedures approved by the Information and Privacy Commissioner of Ontario. Details on the databases used in this study are presented in the Supplementary Methods (available online). Ethics approval was obtained from the Ottawa Health Sciences Research Ethics Board, Ottawa, Canada.

Patients

All patients in Ontario, Canada, with early-stage (I-III) HER2-positive BC, aged 18 years or older, who initiated adjuvant trastuzumab-based therapy between January 1, 2007, and March 31, 2016 were included. Patients were excluded if they had a diagnosis of HF or cardiomyopathy within 12 months before trastuzumab treatment or were treated with neoadjuvant trastuzumab. Only 1 patient was lost to follow-up.

Endpoints

The primary endpoint in this study was DFS, defined as time between initial BC diagnosis and new diagnosis of BC, disease recurrence (defined as starting new systemic therapy ≥ 6 months after completion of trastuzumab), or death from any cause [20]. Secondary endpoints were OS, BC-specific mortality, cardiovascular morality, and noncancer mortality.

Statistical Methods

Descriptive statistics were performed to report baseline characteristics of patients in each group. Categorical variables were compared using χ^2 test or Fisher exact test; continuous variables were compared using an analysis of variance. Statistical significance was tested at an alpha of .05. All tests were 2-sided.

For survival outcomes, Kaplan-Meier analysis was performed. Cumulative incidence functions were performed for disease-specific mortality (BC and cardiovascular). The 5-year survival estimates were calculated with 95% confidence intervals (CI). Survival outcomes were reported as an overall result for each group and also stratified by stage to compare results for stages I, II, and III.

Cox-proportional hazards (PH) model was used to adjust for all the covariates (age at treatment, disease stage, estrogen receptor or progesterone receptor status, Charlson comorbidity index, anthracycline treatment history [yes or no], cardiologist visit history, teaching vs community hospital, and neighborhood income quintile) to estimate the hazard risk of DFS and OS in arms B, C, and D compared with arm A. The PH model assumptions were tested by calculating Martingale and Schoenfeld residuals. Subdistribution hazard models were performed to estimate hazard risk of disease-specific mortality to adjust for all covariates in arms B, C, and D compared with arm A. Results are presented as hazard ratios (HRs) with 95% confidence intervals. The analyses were performed with SAS Software (version 9.4.3.0).

Sensitivity analysis was performed on the results by repeating survival analyses 14 months after initiation of trastuzumab. In Ontario, Canada, where the study population was based, treatment costs are covered by Cancer Care Ontario, which mandates that providers have a maximum of 14 months to provide 18 cycles of trastuzumab. This was done as an internal control for early relapse.

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Results

Patient Characteristics

There were 7588 patients, aged 18 years or older, with early-stage HER2-positive BC started on adjuvant trastuzumab in Ontario, Canada, between January 1, 2007, and March 31, 2016. A total of 34 patients were excluded for history of HF and 2007 were excluded because they were treated with neoadjuvant trastuzumab, leaving 5547 for analysis. There were 3921 patients who met the criteria for group A (70.7%), 309 for group B (5.6%), 362 for group C (6.5%), and 955 for group D (17.2%). Baseline characteristics are listed in Table 1. The median age at diagnosis for the entire group was 56 (±11) years. Median cycles of trastuzumab in each arm were 18, 13, 12, and 13, respectively (see Figure 1). All 4 arms had a median of 4 cardiac imaging tests performed. The median follow-up was 6.4 years for the entire cohort, 6.8 years for group A, 5.7 years for group B, and 5.2 years each for groups C and D.

DFS and OS

For the primary endpoint, all groups had statistically significantly lower estimated 5-year DFS compared with group A. The 5-year DFS was estimated to be 94.1% (95% CI = 93.3% to 94.9%) in group A compared with 80.1% (95% CI = 74.8% to 84.6%) in group B, 81.4% (95% CI = 76.7% to 85.2%) in group C, and 82.4% (95% CI = 79.7% to 84.8%) in group D. Figure 2 shows Kaplan-Meier survival estimates for DFS and OS. Five-year survival estimates are listed in Table 2 along with estimates from the sensitivity analysis for survival 14 months after initiation of trastuzumab. OS was statistically significantly lower in all groups (B, C, D) compared with arm A. The 5-year OS was estimated to be 95.0% (95% CI = 94.3% to 95.7%) in group A vs 84.4% (95% CI = 79.6% to 88.2%) in group B, 82.8% (95% CI = 78.4% to 86.4%) in group C, and 83.7% (95% CI = 81.2% to 86.0%) in group D. A similar difference in DFS and OS estimates was seen during the sensitivity analysis done with time zero starting 14 months after initiation of trastuzumab (see Table 2 for DFS and OS estimates). Kaplan-Meier curves illustrating DFS and OS are presented in Figure 2. Kaplan-Meier curves for DFS and OS stratified by stage are presented in Figure 3.

The PH model was used to calculate hazard ratios for groups B, C, and D compared with group A accounting for baseline patient covariates (see Table 3 for primary and sensitivity analysis). When the PH assumptions were tested, the calculated Martingale residuals deviated from what was observed for groups C and D and the Schoenfeld residuals were not independent of time in groups C and D. To account for the nonproportionality, instead of 1 hazard ratio estimate, we have reported 4 time-point hazard ratio estimates at 6 months, 1 year, 5 years, and 10 years, which are each statistically valid, although change with time as can be seen in Table 3. Groups B-D had a statistically significantly increased risk of DFS or OS events at time points of 6 months, 1 year, and 5 years (except group C for OS), but by 10 years the effect was lost. The hazard ratio for 5-year DFS was 3.15 (95% CI = 2.13 to 4.65, P < .001) in group B, 1.94 (95% CI = 1.30 to 2.89, P = .001) in group C, and 1.92 (95% CI = 1.46 to 2.53, P < .001) in group D. The hazard ratio for 5-year OS was 2.12 for group B (95% CI = 1.25 to 3.58, P = .005), 1.24 (95% CI = 0.72 to 2.13, P = .44) for group C, and 1.56 (95% CI = 1.11 to 2.18, P = .01) for group D. In the adjusted survival analysis, older age

(>70 years), higher disease stage, Charlson comorbidity score greater than 3, and not completing adjuvant chemotherapy had statistically significantly increased hazard ratios for DFS. A full list of hazard ratios for all variables can be found in the Supplementary Tables 1-4 (available online).

In total, 9.4% (523 of 5547) of patients died during the study follow-up period. Group A had 234 (6.0%) deaths compared with 50 (16.2%) deaths in group B, 68 (18.8%) deaths in group C, and 171 (17.9%) deaths in group D. The majority of the 523 deaths were related to cancer (267 of 523), with 5.0% of deaths due to cardiac causes (26 of 523).

BC-Specific Mortality

A statistically significant difference between groups B, C, and D compared with group A was found in the incidence of BC-specific mortality. Estimating 5-year BC-specific mortality was done using a cumulative incidence function: group A had 2.7% (95% CI = 2.2% to 3.3%) compared with 6.5% in group B (95% CI = 4.0% to 9.7%), 9.2% in group C (95% CI = 6.5% to 12.5%), and 10.2% (95% CI = 8.3% to 12.2%) in group D. Using a subdistribution model for risk analysis to control for covariates, the hazard ratio for group B was 3.30 (95% CI = 1.89 to 5.75, P < .001), group C was 3.47 (95% CI = 2.31 to 5.20, P < .001), and group D was 4.11 (95% CI = 3.12 to 5.41, P < .001).

Cardiovascular Mortality

Although we planned an analysis to examine cardiovascular mortality, there was a very small number (n = 26, 0.5%) of cardiovascular deaths in the entire population. Using the subdistribution model, there was an increased risk of cardiovascular mortality in group B compared with group A (HR = 3.64, 95% CI = 1.04 to 12.70, P = .04), which just met statistical significance although the absolute difference was very low.

Discussion

We examined real-world outcomes of patients treated with adjuvant trastuzumab therapy in Ontario, Canada. We were able to identify 3 groups of patients who did not complete a standard course of adjuvant trastuzumab (17-18 cycles) treatment. In the absence of patient-level data on cardiac monitoring (ie, LVEF results), we attempted to infer causality as to why patients stopped trastuzumab prematurely. In group B, patients developed a clinically significant CE, so we assumed trastuzumab was stopped for that reason. In group C, there was no evidence of a CE, but there was a temporal association between timing of cardiac imaging and stopping trastuzumab, suggesting discontinuation could be related to an asymptomatic decline in LVEF. Group D included patients who stopped trastuzumab early with no apparent CE and no temporal association with cardiac imaging. This may have been due to patient preference, comorbidities, or oncologist recommendation, but without patient-level data we were unable to ascertain the cause so treated them separately for analysis. All BC patients (groups B, C, D) who received fewer than 17-18 cycles of adjuvant trastuzumab had statistically significantly inferior BC outcomes.

The optimal duration of trastuzumab therapy is an ongoing area of investigation with a number of studies exploring shorter durations of therapy. Several phase III trials have examined

Table 1. Baseline characteristics of study population

Variable and value	Group A[a]	Group B[b]	Group C[c]	Group D[d]	Total	P[e]
Patients, No. (%)[f]	3,921 (70.7)	309 (5.6)	362 (6.5)	955 (17.2)	5547	
Follow-up time, median (IQR), y	6.83 (4.80-8.82)	5.67 (3.35-8.33)	5.15 (3.98-8.00)	5.18 (3.93-7.59)	6.41 (4.40-8.66)	<.001
Age, y						
Median (IQR)	55.00 (48.00-64.00)	58.00 (50.00-67.00)	57.00 (49.00-66.00)	56.00 (48.00-66.00)	56.00 (48.00-64.00)	<.001
<40, No. (%)	342 (8.7)	10 (3.2)	18 (5.0)	80 (8.4)	450 (8.1)	<.001
40-49, No.(%)	955 (24.4)	68 (22.0)	91 (25.1)	243 (25.4)	1357 (24.5)	
50-59, No. (%)	1268 (32.3)	98 (31.7)	105 (29.0)	267 (28.0)	1738 (31.3)	
60-69, No. (%)	977 (24.9)	87 (28.2)	94 (26.0)	218 (22.8)	1376 (24.8)	
70-79, No. (%)	347 (8.8)	40 (12.9)	49 (13.5)	125 (13.1)	561 (10.1)	
≥80, No. (%)	32 (0.8)	—[g]	—	22 (2.3)	65 (1.2)	
Charlson comorbidity index, No. (%)						
0	1793 (45.7)	127 (41.1)	167 (46.1)	460 (48.2)	2547 (45.9)	.30
1-2	609 (15.5)	55 (17.8)	50 (13.8)	154 (16.1)	868 (15.6)	
≥3	1519 (38.7)	127 (41.1)	145 (40.1)	341 (35.7)	2132 (38.4)	
Nearest census-based neighborhood income quintile						
Lowest income	610 (15.6)	68 (22.0)	62 (17.1)	166 (17.4)	906 (16.3)	<.001
Q2	739 (18.8)	51 (16.5)	66 (18.2)	166 (17.4)	1022 (18.4)	
Q3	826 (21.1)	51 (16.5)	86 (23.8)	194 (20.3)	1157 (20.9)	
Q4	873 (22.3)	50 (16.2)	72 (19.9)	211 (22.1)	1206 (21.7)	
Highest income	858 (21.9)	78 (25.2)	63 (17.4)	193 (20.2)	1192 (21.5)	
Missing	15 (0.4)	11 (3.6)	13 (3.6)	25 (2.6)	64 (1.2)	
Hospital setting, No. (%)						
Community	2,99 (56.1)	175 (56.6	222 (61.3)	582 (60.9	3178 (57.3)	.02
Teaching	1722 (43.9)	134 (43.4)	140 (38.7)	373 (39.1)	2369 (42.7)	
Estrogen receptor status, No. (%)						
Negative	801 (20.4)	69 (22.3)	77 (21.3)	211 (22.1)	1158 (20.9)	.58
Positive	1423 (36.3)	116 (37.5)	138 (38.1)	361 (37.8)	2038 (36.7)	
Missing	1697 (43.3)	124 (40.1)	147 (40.6)	383 (40.1)	2351 (42.4)	
Progesterone receptor status, No. (%)						
Negative	1120 (28.6)	93 (30.1)	112 (30.9)	299 (31.3)	1624 (29.3)	.51
Positive	1104 (28.2)	92 (29.8)	103 (28.5)	273 (28.6)	1572 (28.3)	
Missing	1697 (43.3)	124 (40.1)	147 (40.6)	383 (40.1)	2,351 (42.4)	
Breast cancer stage, No. (%)						
Stage I	1054 (26.9)	67 (21.7)	75 (20.7)	206 (21.6)	1402 (25.3)	<.001
Stage II	1645 (42.0)	133 (43.0)	135 (37.3)	372 (39.0)	2285 (41.2)	
Stage III	679 (17.3)	62 (20.1)	77 (21.3)	183 (19.2)	1001 (18.0)	
Missing	543 (13.8)	47 (15.2)	75 (20.7)	194 (20.3)	859 (15.5)	
No. of trastuzumab cycles						
Mean ± SD	17.73 ± 0.44	11.98 ± 5.71	10.17 ± 5.40	10.98 ± 4.96	15.76 ± 4.19	<.001
Median (IQR)	18.00 (17.00-18.00)	13.00 (7.00-18.00)	12.00 (5.00-15.00)	13.00 (7.00-15.00)	18.00 (16.00-18.00)	<.001
Prior anthracycline treatment, No. (%)						
No	1846 (47.1	159 (51.5)	191 (52.8)	544 (57.0)	2740 (49.4)	<.001
Yes	2075 (52.9)	150 (48.5)	171 (47.2)	411 (43.0)	2807 (50.6)	
Cardiac test within 30 d of last trastuzumab cycle, No. (%)						
Missing or no imaging	284 (7.2)	26 (8.4)	0 (0.0)	216 (22.6)	526 (9.5)	<.001
No	2463 (62.8)	180 (58.3)	0 (0.0)	739 (77.4)	3382 (61.0)	
Yes	1174 (29.9)	103 (33.3)	362 (100.0)	0 (0.0)	1639 (29.5)	
Cardiologist visit during study period, No. (%)						
No	3540 (90.3)	79 (25.6)	290 (80.1)	850 (89.0)	4759 (85.8)	<.001
Yes	381 (9.7)	230 (74.4)	72 (19.9)	105 (11.0)	788 (14.2)	
No. of cardiac imaging tests						
Median (IQR)	4.00 (4.00-5.00)	4.00 (2.00-6.00)	4.00 (2.00-5.00)	2.00 (1.00-4.00)	4.00 (3.00-5.00)	<.001
Cause of death, No. (%)						
All-cause mortality	234 (6.0)	50 (16.2)	68 (18.8)	171 (17.9)	523 (9.4)	<.001
Cancer mortality	110 (2.8)	21 (6.8)	34 (9.4)	102 (10.7)	267 (4.8)	
Cardiac mortality	11 (0.3)	—	—	7 (0.7)	26 (0.5)	

[a]Group A received a full course of trastuzumab (17-18 cycles) without any cardiac events between day 1, cycle 1, and 90 days after the final cycle. CI = confidence interval; IQR = interquartile range.
[b]Group B had a cardiac event within the study period.
[c]Group C had 16 or fewer cycles of trastuzumab, had no cardiac events, and stopped treatment within 30 days of the last cardiac imaging test.
[d]Group D had 16 or fewer cycles of trastuzumab, had no cardiac events, and stopped treatment more than 30 days after the last cardiac imaging test.
[e]P values were calculated using χ^2 test or Fisher exact test for categorical variables; continuous variables were compared using an analysis of variance.
[f]Number of patients per group are row percentages; all other percentages listed are column percentages.
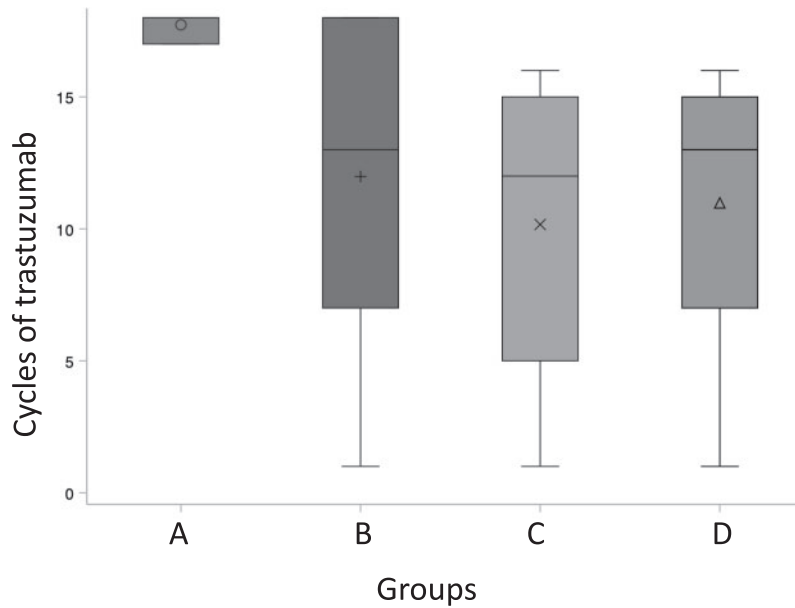[g]In instances where n is ≤5, values are suppressed per ICES policy.

Figure 1. Box plot displaying distribution of cycles of trastuzumab in groups A-D. Group A received a full course of trastuzumab (17-18 cycles) without any (CEs) between day 1, cycle 1, and 90 days after the final cycle. Group B had a CE within the study period. Group C had 16 or fewer cycles of trastuzumab, had no CEs, and stopped treatment within 30 days of the last cardiac imaging test. Group D had 16 or fewer cycles of trastuzumab, had no CEs, and stopped treatment more than 30 days after the last cardiac imaging test. Symbolson each boxplot indicate the mean value, horizantal line the median and the boxes represent the interquartile range of values for each group. Whiskers above and below the boxes represent the minimum and maximum values for each group.
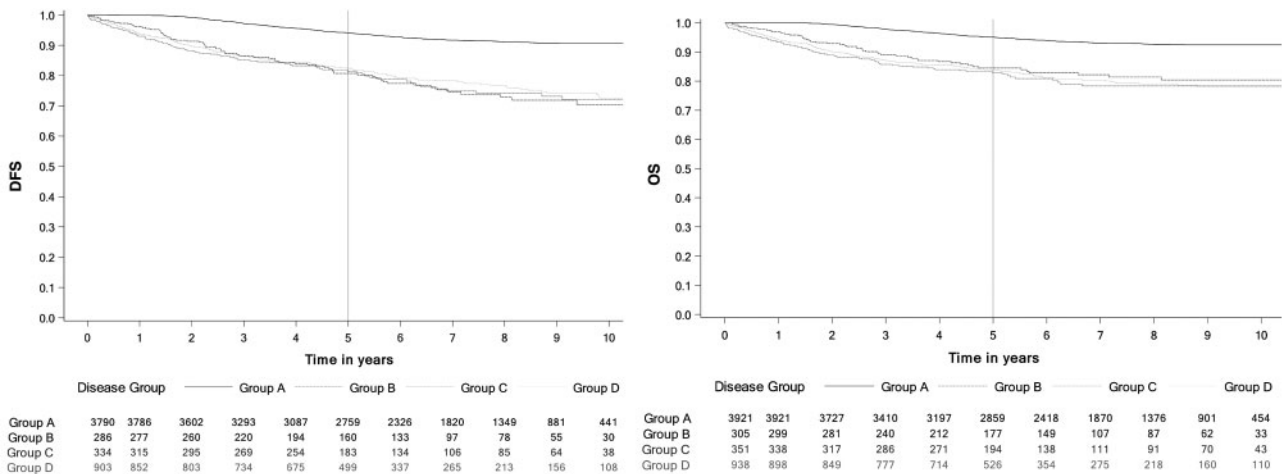

Figure 2. Kaplan-Meier curves disease-free survival (DFS) and overall survival (OS) to estimate survival for arms A-D. **A)** DFS. **B)** OS. Group A received a full course of trastuzumab (17-18 cycles) without any cardiac events (CEs) between day 1, cycle 1, and 90 days after the final cycle. Group B had a CE within the study period. Group C had 16 or fewer cycles of trastuzumab, had no CEs, and stopped treatment within 30 days of the last cardiac imaging test. Group D had 16 or fewer cycles of trastuzumab, had no CEs, and stopped treatment more than 30 days after the last cardiac imaging test.

shorter durations of trastuzumab (9 weeks to 6 months vs 1 year), but only 1 was able to demonstrate noninferiority (21–25). A meta-analysis of these trials demonstrated that shorter durations of trastuzumab therapy are associated with inferior DFS and OS (26). Our findings are consistent with a previous real-world study that reported inferior OS in patients who did not complete 1 year of adjuvant trastuzumab (27). We observed that the impact of discontinuing trastuzumab early was greatest in higher stage (II/III) patients; future research on deescalation of anti-HER2 therapy should focus on stage I patients or, in the

setting of neoadjuvant therapy, patients who achieve a pathologic complete response (pCR).

An initial criticism of our study was that survival differences could be explained by early relapse. To address this, we performed a sensitivity analysis 14 months after initiation of trastuzumab. In Ontario, Canada, the government funding agency Cancer Care Ontario requires all adjuvant trastuzumab be given within a 14-month window regardless of reasons for treatment delays. The sensitivity analysis did not change the main findings of the study, adding strength to our findings. The risk of

Table 2. Five-year survival estimates and cumulative incidence estimates from time of initiation of trastuzumab and sensitivity analysis 14 months after initiation of trastuzumab

Study outcome	Primary analysis, % (95% CI)	Sensitivity analysis, % (95% CI)
5-year survival estimates		
DFS		
Group A[a]	94.1 (93.3 to 94.9)	92.6 (91.6 to 93.5)
Group B[b]	80.2 (74.8 to 84.6)	80.6 (74.7 to 85.3)
Group C[c]	81.4 (76.7 to 85.2)	84.9 (79.7 to 88.8)
Group D[d]	82.4 (79.7 to 84.8)	84.7 (81.7 to 87.2)
OS		
Group A	95.0 (94.3 to 95.7)	93.7 (92.9 to 94.5)
Group B	84.4 (79.6 to 88.2)	86.2 (81.2 to 89.9)
Group C	82.8 (78.4 to 86.4)	86.7 (82.0 to 90.3)
Group D	83.7 (81.2 to 86.0)	86.3 (83.5 to 88.7)
5-year cumulative incidence estimates		
Cancer-specific death		
Group A	2.7 (2.2 to 3.3)	3.1 (2.5 to 3.7)
Group B	6.5 (4.0 to 9.7)	6.0 (3.5 to 9.3)
Group C	9.2 (6.5 to 12.5)	6.5 (4.0 to 9.8)
Group D	10.2 (8.3 to 12.2)	7.7 (5.8 to 9.8)
Cardiovascular-specific death		
Group A	0.3 (0.1 to 0.5)	0.3 (0.1 to 0.5)
Group B	2.0 (0.7 to 4.4)	2.1 (0.8 to 4.6)
Group C	0.6 (0.1 to 1.9)	0.3 (0.0 to 1.7)
Group D	0.4 (0.2 to 1.1)	0.7 (0.2 to 1.8)

[a]Group A received a full course of trastuzumab (17-18 cycles) without any cardiac events between day 1, cycle 1, and 90 days after the final cycle. CI = confidence interval; DFS = disease-free survival; OS = overall survival.
[b]Group B had a cardiac event within the study period.
[c]Group C had 16 or fewer cycles of trastuzumab, had no cardiac events, and stopped treatment within 30 days of the last cardiac imaging test.
[d]Group D had 16 or fewer cycles of trastuzumab, had no cardiac events, and stopped treatment more than 30 days after the last cardiac imaging test.

cancer death exceeded cardiac death in all groups, even in group B, where patients experienced a CE. We used a Cox model for analysis of our survival outcomes. The assumptions of the model were violated, meaning that the hazard ratio changed over time. This observation is consistent with recent results from NCCTGN9837/NRG.NSABP B-31 examining the incidence of late recurrence. The authors found that the risk of recurrence in HER2-positive BC after adjuvant trastuzumab is greatest in the first 5 years and levels out in years 6-10 (28). To account for nonproportionality, we have reported hazard ratio estimates at 4 different time points, and those hazard ratio estimates are valid for those time points.

This study is not without its weaknesses. It is a retrospective cohort study derived from population-based administrative databases. This is a rich source of information; however, it does not provide patient-level data on some variables, including cardiac imaging results, cardiovascular risk factors, or clinical rationale for deviations from standard adjuvant treatment plans. Access to cardiac test results and/or clinical notes would have allowed a more granular analysis of the relationship between discontinuing trastuzumab for asymptomatic changes in LVEF and cancer outcomes. Knowledge of cardiovascular risk factors would also have added to the study results by allowing us to add further patient characteristics to our statistical model and strengthen our conclusion. Our results are limited to those treated with adjuvant trastuzumab alone; adjuvant pertuzumab

was not available or funded during the study period, so we cannot comment on the optimal duration of therapy for patients treated with multiple anti-HER2 agents. We excluded patients treated with neoadjuvant therapy in an effort to keep the population as homogenous as possible; potential postsurgical complications could disrupt trastuzumab therapy in ways we could not account for. We acknowledge that neoadjuvant therapy for stage II-III HER2+ BC is now considered standard of care, based on the Katherine study that demonstrated in patients who did not achieve a pCR, switching adjuvant anti-HER2 therapy to trastuzumab emtansine led to improved OS (29). For those patients who do achieve a pCR, the optimal duration of trastuzumab remains unknown.

Clinical utility has been described as the ability of a test's results to make a treatment decision that positively changes the outcome for a patient (30,31). Frequent cardiac monitoring in BC patients receiving trastuzumab was intended to enhance cardiac safety; however, in the real-world setting this practice may have a negative impact on patient care if it results in early discontinuation of treatment for asymptomatic changes in left ventricular function. Despite nearly 2 decades of experience treating patients with trastuzumab, there is still no direct evidence to support the clinical utility of cardiac imaging in all early-stage BC patients receiving HER2-based targeted therapy. Current guidelines (3–6) continue to support routine cardiac monitoring (every 3 to 4 months) regardless of risk and in the absence of demonstrable improvement in cardiac safety for the majority of patients. Changes in LVEF should lead to discussion between oncologists and cardiologists to discuss the risks vs benefits of disrupting anti-HER2 therapy. Recent studies have demonstrated that trastuzumab can be administered safely even in the face of mild cardiac dysfunction with concurrent cardiology management (32–34).

Rather than continue routine cardiac imaging for all patients, resources could be redirected toward optimizing cardiovascular risk factors and risk-stratifying patients before initiation of cancer treatment. In patients at high risk of cardiotoxicity, including those older than 60 years with baseline abnormal LVEF, personal history, or more than 1 risk factor for cardiovascular disease (smoking, diabetes, obesity, dyslipidemia, etc) (5,13,35,36), we suggest continuing the current approach of regular LVEF assessments every 3-4 months during anti-HER2 therapy as per current guidelines (3–6). In contrast, low- or average-risk patients could be monitored clinically to avoid unnecessary testing and mitigate the risk of treatment interruptions; this would also reduce health-care use costs. Although there has been some reluctance on the part of clinicians to consider less frequent cardiac monitoring in this patient population, in a 2015 study of Medicare patients in the United States, only 36% had cardiac monitoring as per current guidelines (37). Prospective evaluation of a risk-stratified approach to cardiac monitoring should be done to fully understand the impact this would have on cardiac safety and cancer outcomes.

In this large retrospective population-based cohort study, less than 1 year of adjuvant trastuzumab in patients with HER2+ early BC resulted in inferior clinical outcomes regardless of reason for treatment discontinuation. We hypothesized, based on our clinical experience of patients referred to a cardiooncology clinic, that some patients had interruption or permanent discontinuation of trastuzumab therapy based on asymptomatic drops in LVEF. The overall CE rate in this study was low, suggesting that intensive cardiac monitoring of all patients
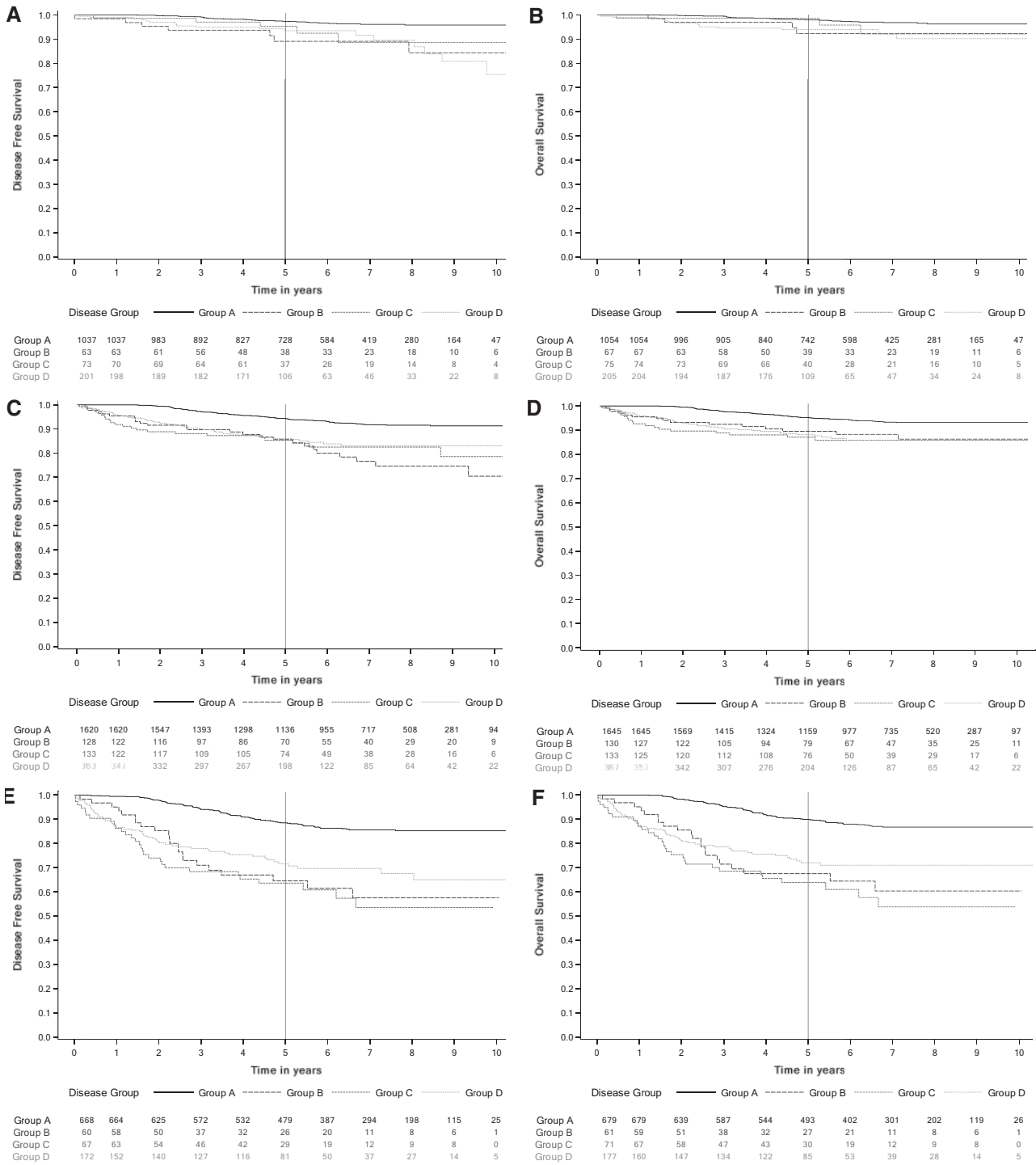
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A

Disease Group	Group A										
Group A	1037	1037	983	892	827	728	584	419	280	164	47
Group B	63	63	61	56	48	38	33	23	18	10	6
Group C	73	70	69	64	61	37	26	19	14	8	4
Group D	201	198	189	182	171	106	63	46	33	22	8

B

Disease Group	Group A										
Group A	1054	1054	996	905	840	742	598	425	281	165	47
Group B	67	67	63	58	50	39	33	23	19	11	6
Group C	75	74	73	69	66	40	28	21	16	10	5
Group D	205	204	194	187	176	109	65	47	34	24	8

C

Disease Group	Group A										
Group A	1620	1620	1547	1393	1298	1136	955	717	508	281	94
Group B	128	122	116	97	86	70	55	40	29	20	9
Group C	133	122	117	109	105	74	49	38	28	16	6
Group D	353	347	332	297	267	198	122	85	64	42	22

D

Disease Group	Group A										
Group A	1645	1645	1569	1415	1324	1159	977	735	520	287	97
Group B	130	127	122	105	94	79	67	47	35	25	11
Group C	133	125	120	112	108	76	50	39	29	17	6
Group D	367	357	342	307	276	204	126	87	65	42	22

E

Disease Group	Group A										
Group A	668	664	625	572	532	479	387	294	198	115	25
Group B	60	58	50	37	32	26	20	11	8	6	1
Group C	67	63	54	46	42	29	19	12	9	8	0
Group D	172	152	140	127	116	81	50	37	27	14	5

F

Disease Group	Group A										
Group A	679	679	639	587	544	493	402	301	202	119	26
Group B	61	59	51	38	32	27	21	11	8	6	1
Group C	71	67	58	47	43	30	19	12	9	8	0
Group D	177	160	147	134	122	85	53	39	28	14	5

Figure 3. Kaplan-Meier curves for disease-free survival (DFS) and overall survival (OS) stratified by stage. **A)** Stage I DFS. **B)** Stage I OS. **C)** Stage II DFS. **D)** Stage II OS. **E)** Stage III DFS. **F)** Stage III OS. Group A received a full course of trastuzumab (17-18 cycles) without any cardiac events (CEs) between day 1, cycle 1, and 90 days after the final cycle. Group B had a CE within the study period. Group C had 16 or fewer cycles of trastuzumab, had no CEs, and stopped treatment within 30 days of the last cardiac imaging test. Group D had 16 or fewer cycles of trastuzumab, had no CEs, and stopped treatment more than 30 days after the last cardiac imaging test.

Table 3. Hazard ratios for DFS and OS calculated for both standard analysis and sensitivity analysis at 14 months after cycle 1 trastuzumab using Cox model

Study outcome		Group B[a]		Group C[b]		Group D[c]	
		HR[d] (95% CI)	P[e]	HR[d] (95% CI)	P[e]	HR[d] (95% CI)	P[e]
Standard analysis							
Time since 1st cycle trastuzumab							
DFS	6 mo	5.3 (3.32 to 8.58)	<.001	6.13 (4.04 to 9.30)	<.001	5.30 (3.83 to 7.32)	<.001
	1 y	5.03 (3.27 to 7.73)	<.001	5.39 (3.73 to 7.79)	<.001	4.73 (3.55 to 6.31)	<.001
	5 y	3.15 (2.13 to 4.65)	<.001	1.94 (1.30 to 2.89)	.001	1.92 (1.46 to 2.52)	<.001
	10 y	1.75 (0.69 to 4.40)	.24	0.54 (0.20 to 1.48)	.23	0.62 (0.31 to 1.24)	.18
OS	6 mo	8.11 (4.71 to 13.98)	<.001	11.76 (7.45 to 18.56)	<.001	9.32 (6.44 to 13.49)	<.001
	1 y	6.99 (4.31 to 11.33)	<.001	9.16 (6.18 to 13.57)	<.001	7.64 (5.54 to 10.54)	<.001
	5 y	2.12 (1.25 to 3.58)	.01	1.24 (0.72 to 2.13)	.44	1.56 (1.11 to 2.18)	.01
	10 y	0.48 (0.13 to 1.75)	.26	0.10 (0.03 to 0.40)	.001	0.21 (0.09 to 0.52)	<.001
Sensitivity analysis							
Time since 1st cycle trastuzumab + 14 mo							
DFS	6 mo	2.96 (1.81 to 4.82)	<.001	2.11 (1.31 to 3.38)	.002	2.03 (1.45 to 2.82)	<.001
	1 y	2.94 (1.90 to 4.55)	<.001	2.09 (1.38 to 3.17)	<.001	2.01 (1.50 to 2.69)	<.001
	5 y	2.78 (1.68 to 4.62)	<.001	1.94 (1.18 to 3.20)	.01	1.89 (1.34 to 2.66)	.001
	10 y	2.60 (0.78 to 8.63)	.12	1.78 (0.51 to 6.21)	.37	1.74 (0.74 to 4.12)	.20
OS	6 mo	3.61 (2.09 to 6.21)	<.001	3.31 (2.02 to 5.43)	<.001	2.92 (2.05 to 4.16)	<.001
	1 y	3.31 (2.05 to 5.35)	<.001	2.96 (1.94 to 4.51)	<.001	2.74 (2.02 to 3.71)	<.001
	5 y	1.68 (0.82 to 3.47)	.16	1.21 (0.59 to 2.48)	.61	1.61 (1.04 to 2.51)	.03
	10 y	0.72 (0.13 to 4.04)	.71	0.39 (0.07 to 2.31)	.30	0.83 (0.28 to 2.53)	.75

[a]Group B had a cardiac event within the study period. CI = confidence interval; DFS = disease-free survival; HR = hazard ratio; OS = overall survival.
[b]Group C had 16 or fewer cycles of trastuzumab, had no cardiac events, and stopped treatment within 30 days of the last cardiac imaging test.
[c]Group D had 16 or fewer cycles of trastuzumab, had no cardiac events, and stopped treatment more than 30 days after the last cardiac imaging test.
[d]Hazard ratios are adjusted for age at treatment, Charlson comorbidity index, hospital type (teaching or community), breast cancer stage, estrogen receptor status, progesterone receptor status, neighborhood income quintile, rurality, anthracycline treatment history, and cardiologist visit history.
[e]P values were calculated using 2-sided Wald χ^2 test.

treated with HER2-targeted therapy does not improve cardiac safety and may be detrimental if life-saving HER2-targeted therapy is prematurely discontinued. As the evidence evolves, we anticipate that a risk-based approach to cardiac monitoring will emerge; the results presented here will add to the evidence supporting 1 year of trastuzumab for optimal cancer outcomes.

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