# Factors Predicting Trastuzumab-related Cardiotoxicity in a Real-world Population of Women with HER2+ Breast Cancer

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**Abstract.** *Background: Trastuzumab may improve disease-free survival after chemotherapy for HER2-positive breast cancer. However, it carries a risk of cardiotoxicity and counseling patients about such risks is part of informed consent. The National Institute for Health and Clinical Excellence has published guidelines for cardiac assessment before and during treatment with trastuzumab in order to minimize the risk of cardiotoxicity. The aim of the present study was to identify risk factors for cardiotoxicity attributed to trastuzumab in a cohort population treated for primary and metastatic breast cancer. Patients and Methods: This study included all women who started a course of trastuzumab from February 2006 – February 2011 at three NHS Trusts in the UK. Their cardiac function during treatment was recorded and cardiotoxicity was defined as a decrease in left ventricular ejection fraction (LVEF) ≥10% and a reduction to <50%, or a clinical reduction in cardiac function as defined by the New York Heart Association. An independent samples t-test was used to assess whether patient age predicted cardiotoxicity. Pearson's chi-squared tests of independence were used to investigate the association between cardiotoxicity, the indication for trastuzumab, exposure to anthracycline chemotherapy, and Adult Comorbidity Evaluation-27 index (ACE-27) scores. Results: There were 388 female patients included in this study, with a mean age of 54 (range= 25–100 years). Cardiotoxicity was recorded during 61 (15.72%) courses of trastuzumab treatment. There were no associations between cardiotoxicity and the three factors (indication, exposure to anthracyclines, or ACE-27 score), and no significant difference in age between patients with and those without cardiotoxicity. However, subgroup analysis of patients who experienced cardiotoxicity (n= 61) showed that there was a negative correlation (–0.455; p=0.001) between time-to-first cardiotoxicity event and age in the group who had received concurrent anthracycline therapy (n=49). Conclusion: In a real-world 5-year population of patients who received trastuzumab, the incidence of drug-related cardiotoxicity was higher than expected, and the age of the patients appeared to predict the first cardiotoxic event amongst those who experienced cardiotoxicity and had received prior anthracyclines. However, incidence of cardiotoxicity in the whole cohort did not appear to be predicted by age, comorbidity, indication, or exposure to anthracylines. Vigilance, therefore, seems justified when conducting cardiac surveillance for all patients during treatment with trastuzumab, but especially for those who are elderly and receiving concurrent anthracycline therapy.*

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The role of adjuvant trastuzumab in improving disease-free survival after chemotherapy in women with Human Epidermal Growth Factor Receptor-2 (HER2)-positive breast cancer, advanced, non-operative or metastatic cancer is well-established (1, 2). However, trastuzumab carries a risk of cardiotoxicity attributable to cardiomyocyte dysfunction, resulting in reduced heart contractile efficiency (3, 4). This spectrum of cardiotoxicity ranges from asymptomatic drop in left ventricular ejection fraction (LVEF) to clinical heart failure (5-8). Therefore, counselling patients about such risks plays a part in the process of informed consent, before the drug is delivered. The National Institute for Health and Clinical Excellence (NICE) has published specific guidelines for cardiac assessment before and during treatment with trastuzumab in order to minimize the risk of cardiotoxicity to patients (9).

Data from clinical trials suggests that trastuzumab has a relatively low risk of inducing cardiotoxicity when used as monotherapy (3-7%), which is slightly higher when used in combination with other anthracycline chemotherapy agents

(27%) (10). However, the limited data available regarding cardiotoxicity outside clinical trial settings reports a higher percentage of cardiotoxicity than reported in these trials (11).

The aim of the present study was to identify risk factors for cardiotoxicity attributed to trastuzumab in a cohort population treated for primary and metastatic breast cancer.

## Patients and Methods

The pharmacy records at three NHS Trusts in the West Midlands, UK were reviewed in order to establish a list of all patients who started a course of trastuzumab for any indication (neo-adjuvant, adjuvant and metastatic) from February 2006 – February 2011. This represented a 5-year period after the publication of the NICE Guidelines for cardiac surveillance (9). The electronic records for these patients were examined to gather data concerning cardiac function during treatment with trastuzumab. LVEF as measured by echocardiography or multi-gated acquisition (MUGA) was used as an objective marker of cardiac function. Cardiotoxicity during treatment was defined as a decrease in LVEF ≥10% and reduction to LVEF <50%, or a clinical reduction in cardiac function as defined by the New York Heart Association (NYHA) Functional Classification (12).

Adult Comorbidity Evaluation-27 index (ACE-27) scores (13) were calculated for each patient based on their electronic records. The indication for trastuzumab was recorded (metastatic or adjuvant), as well as prior exposure to anthracycline chemotherapy agents (0=no anthracyclines, 1=previous treatment, 2=concurrent treatment). Patients were excluded if there was inadequate or insufficient data in their records about the dates and clinical history for their entire course of trastuzumab treatment.

An independent samples *t*-test was used to assess whether patient age at time of receiving trastuzumab predicted cardiotoxicity. Pearson's chi-squared tests of independence were used to investigate the association between cardiotoxicity, the initial indication for trastuzumab, exposure to anthracycline chemotherapy, and ACE-27 score. Further multiple binary-logistic regression was used to predict cardiotoxicity, allowing all four factors to be entered simultaneously. Further subgroup analysis was conducted for the patient group who experienced cardiotoxicity; we recorded the time period between starting trastuzumab and the first clinical episode of cardiotoxicity and its relation to the initial indication for trastuzumab, exposure to anthracycline chemotherapy, and ACE-27 score.

## Results

According to pharmacy records, 476 patients were registered as starting trastuzumab at these three NHS Trusts in the time period February 2006 – February 2011. Using these patient details, a clinical records search found 388 patients with recorded details of their entire course of trastuzumab. All patients were female, with a mean age of 54 (range= 25-100 years). Cardiotoxicity was recorded during 61 (15.72%) courses of trastuzumab treatment. A Pearson's chi-squared tests of independence identified no associations between cardiotoxicity and the three factors: i) the initial indication for trastuzumab (Chi-square=0.371, DF=1, *p*-value=0.542); ii) exposure to anthracycline chemotherapy (Chi-square=0.531, DF=2, *p*-value=0.767); iii) ACE-27 score (Chi-square=2.007, DF= 2, *p*-value=0.367) (see Tables I-III). A two-sample t-test revealed no significant difference in age between patients with and those without cardiotoxicity (Table IV). When all of the above factors (trastuzumab, exposure to anthracycline chemotherapy, ACE-27 score and age) were entered into a binary logistic regression analysis to predict cardiotoxicity (Yes vs. No), none were found to be significantly associated with cardiotoxicity, whether entered simultaneously, or using backward elimination (*i.e.* at each step, the least important variable was dropped from the current model).

Table I. *The number of patients with or without cardiotoxicity during adjuvant or metastatic administration of trastuzumab.*

| | Cardiotoxicity, n (%) | | |
|---|---|---|---|
| | No | Yes | All, n (%) |
| Trastuzumab | | | |
| Adjuvant | 274 (83.79) | 53 (16.21) | 327 (100) |
| Metastatic | 53 (86.89) | 8 (13.11) | 61 (100) |
| All | 327 (84.28) | 61 (15.72) | 388 (100) |

Chi-square=0.371, DF=1, *p*-value=0.542.

Table II. *The number of patients with or without cardiotoxicity according to exposure to anthracycline chemotherapy.*

| | Cardiotoxicity, n (%) | | |
|---|---|---|---|
| | No | Yes | All, n (%) |
| Anthracycline | | | |
| None | 41 (85.42) | 7 (14.58) | 48 (100) |
| Previous | 19 (79.17) | 5 (20.83) | 24 (100) |
| Concurrent | 267 (84.49) | 49 (15.51) | 316 (100) |
| All | 327 (84.28) | 61 (15.72) | 388 (100) |

Chi-square=0.531, DF=2, *p*-value=0.767.

Table III. *The number of patients with or without cardiotoxicity according to calculated Adult Comorbidity Evaluation-27 index (ACE-27) scores.*

| | Cardiotoxicity, n (%) | | |
|---|---|---|---|
| | No | Yes | All, n (%) |
| ACE-27 score | | | |
| 0 | 234 (84.48) | 43 (15.52) | 277 (100) |
| 1 | 67 (87.01) | 10 (12.99) | 77 (100) |
| 2 or 3 | 26 (76.47) | 8 (23.53) | 34 (100) |
| All | 327 (84.28) | 61 (15.72) | 388 (100) |

Chi-square=2.007, DF=2, *p*-value=0.367.

Table IV. *The number of patients (N), their mean age, standard deviation (StDev), standard error (SE) and t-test for cardiotoxicity on trastuzumab therapy.*

| Cardiotoxicity | N | Mean (years) | StDev | SE |
|---|---|---|---|---|
| No | 327 | 54 | 11.9 | 0.66 |
| Yes | 61 | 55.4 | 12.6 | 1.6 |

$t_{386}$=–0.82 ($p$=0.411).

Subgroup analysis of patients who experience cardiotoxicity (n=61) showed that there was a significant negative correlation (–0.455; $p$=0.001) between time-to-first cardiotoxicity event and age, but only in the group which had received concurrent anthracycline therapy (n=49). However, there was no statistically significant correlation between age and time to first event for patients recorded as having received anthracyclines in the past (n=5), or for those never exposed to anthracyclines (n=7) ($p$=0.311 and $p$=0.898, respectively) (Figure 1).

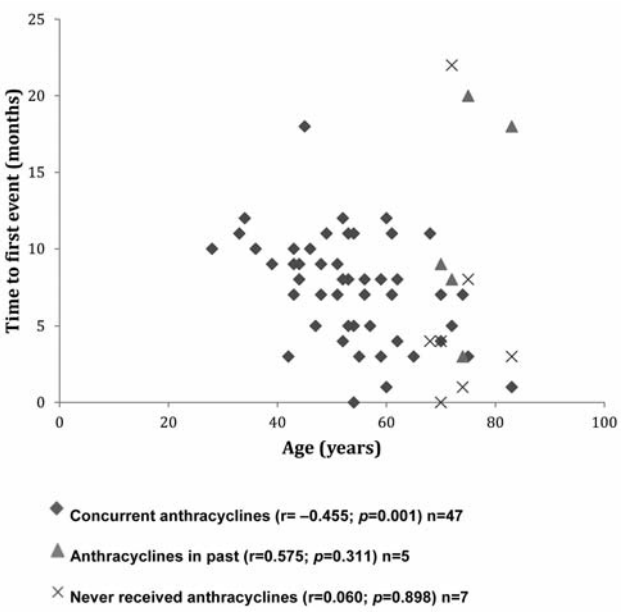


Figure 1. *Cardiotoxicity subgroup: Time to first event and age of patient.*

## Discussion

Trastuzumab has made a major impact in the treatment of both early and advanced breast cancer, but carries a risk of cardiotoxicity that must be taken into account when considering its use. The present study of a representative cohort of patients with breast cancer from the UK found a higher percentage of cardiotoxicity than recorded in randomized clinical trials such as the Fin her (14), BCIRG 006 (15), NSABP-31 (16), N9831 (15, 16) and HERA (17) trials. Such differences may be accounted for by the wider exclusion criteria used in the methodology of these trials. For example, all of these trials excluded metastatic disease, and the HERA trial excluded T4 disease and patients with previous breast cancer (17). The BCIRG 006 trial excluded those with any serious medical or psychiatric conditions (15), and the Fin her trial excluded patients with cardiac failure of any degree (14). In the real-world scenario, where each patient's comorbidities and personal circumstances are taken on their own merit with a well balanced risk/benefit analysis, some patients may receive trastuzumab despite not meeting the inclusion criteria for these trials.

Cardiotoxicity in this real-world population did not seem to be predicted by age, other comorbidities, indication, or prior anthracycline therapy. This may be because patients who had been prescribed trastuzumab had already been assessed for cardiac suitability by the prescribing clinician – adding a selection bias to the sample population. This might indicate that the involved clinicians had accounted for clinical risk with relative consistency so that comorbidity and age were balanced with the benefits of trastuzumab. Our findings may suggest that rather than being reluctant to prescribe trastuzumab to an elderly population, an appropriate clinical risk assessment may be adequate without being biased against age.

In the subgroup that did experience cardiotoxicity, increasing age appears to predict an earlier onset of the first episode of cardiotoxicity for those who received concurrent anthracycline therapy. This may be accounted for by the increased risk of cardiotoxicity from the interaction of anthracyclines and trastuzumab (18). It may, therefore, seem prudent to adopt a more cautious approach to cardiac surveillance and early detection of cardiac compromise for elderly patients, especially those receiving concurrent anthracyclines.

Trastuzumab-related cardiotoxicity is usually reversible by both removing the agent and delivering conventional heart failure therapy (19, 20). Treatment with beta blockers and angiotensin-converting enzyme inhibitors may have a role in cardiac prophylaxis during trastuzumab treatment, but whether such prophylaxis becomes routine will depend on the results and recommendations from randomized prospective trials such as MANTICORE (21).

## Conclusion

In a real-world 5-year population of patients with HER2-positive breast cancer who received trastuzumab, the incidence of drug-related cardiotoxicity was higher than expected, but was not predicted by age, comorbidities,

indication, or exposure to anthracylines. In the subgroup who experienced cardiotoxicity, age was a predicting factor for the time-to-first clinical cardiotoxic event, but only for those who had received concurrent anthracycline therapy. Appropriate vigilance seems justified when conducting cardiac surveillance for all patients during treatment with trastuzumab, but especially for those who are elderly and receiving concurrent anthracycline therapy.

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