

Risk factors of trastuzumab-induced cardiotoxicity in breast cancer

A meta-analysis

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Abstract

Background: Trastuzumab targets the human epidermal growth factor receptor 2 oncogene and in combination with first-line therapy results in significantly improved survival outcomes and has thus become standard of care in both adjuvant and metastatic settings. While it is estimated that 1% to 4% of patients treated with trastuzumab will develop heart failure and ~10% will experience a reduction in left ventricular ejection fraction (LVEF), the patient risk factors associated with trastuzumab-induced cardiotoxicity (TIC) are unclear. This meta-analysis aims to consolidate previously published data to identify the risk factors most likely leading to TIC.

Methods: A search of the MEDLINE literature database using the keywords trastuzumab/Herceptin, risk factors, outcomes, cardiac, cardiotoxicity, cardiomyopathy, LVEF, and chemotherapy was performed. Only prospective/retrospective human studies were included, with additional studies excluded if they reported baseline LVEF > 68%, a cohort of <50 patients, or results that were not stratified based on cardiotoxic events. Pooled odds ratio (OR) and 95% confidence interval (CI) for each potential risk factor were calculated, with heterogeneity of data and samples explored using random-effects modeling.

Results: Data were collected from 17 articles, capturing 6527 patients. Hypertension (OR 1.61, 95% CI 1.14–2.26; $P < 0.01$), diabetes (OR 1.62; 95% CI 1.10–2.38; $P < 0.02$), previous anthracycline use (OR 2.14; 95% CI 1.17–3.92; $P < 0.02$), and older age ($P = 0.013$) were all shown to be associated with TIC.

Conclusion: Cardiac performance should be closely monitored in women treated with trastuzumab. Recognizing potential risk factors along with careful attention to symptoms/LVEF measurements could minimize the occurrence of TIC in this population.

Abbreviations: CI = confidence interval, HER2+ = human epidermal growth factor receptor 2, I^2 = Cochran Q test, LVEF = left ventricular ejection fraction, MUGA = multigated acquisition scan, OR = odds ratio, SEER = surveillance epidemiology and end results, TIC = trastuzumab-induced cardiotoxicity.

Keywords: breast cancer, cardiotoxicity/cardiomyopathy, chemotherapy, left ventricular ejection fraction, meta-analysis, risk factors, targeted therapy, trastuzumab/herceptin

1. Introduction

Breast cancer affects 1 in 8 (12%) women in the United States and is one of the most common cancers among American women.^[1] Advances in chemo- and targeted gene therapy have made treatment of breast cancer more effective than ever before as evidenced by increased survival rates; however, this success was

achieved with a price, namely, additional treatment-related stress to patients' cardiovascular system. About 2.3 million American women with a history of breast cancer are now living with a greater lifetime risk of congestive heart failure because of the received cancer treatment.^[2] The risk for cardiovascular events is further magnified by an overlap of therapy-specific subclinical damages with comorbidities and unfavorable lifestyle choices like reduced physical activity and obesity.^[3]

Trastuzumab, a monoclonal antibody developed by Genentech Inc. (South San Francisco, CA) targets the human epidermal growth factor receptor 2 (HER2+/*neu*) oncogene, which is overexpressed in ~25% to 30% of breast cancer patients. The drug gained US Food and Drug Administration approval in September 1998. In combination with first-line chemotherapy for HER2-positive metastatic breast cancer (HER2+), trastuzumab resulted in significant improvement in survival outcomes.^[4–7] Trastuzumab is also used as adjuvant drug therapy in HER2+ early-stage breast cancer and was shown to reduce recurrence and improve survival.^[8–10] Previously, the recognition of cancer therapy-related cardiac dysfunction in cancer patients was predominantly focused on anthracycline-induced cardiotoxicity. However, this field became further complicated when newer drugs like trastuzumab were applied clinically, as the dose-dependent effect, short- and long-term effects, and cellular mechanisms of anthracycline-induced cardiotoxicity are relatively known compared to trastuzumab-induced cardiotoxicity (TIC).

Editor: Weimin Guo.

The authors have no funding and conflicts of interest to disclose.

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Medicine (2016) 95:44(e5195)

Received: 24 August 2015 / Received in final form: 13 September 2016 /

Accepted: 29 September 2016

<http://dx.doi.org/10.1097/MD.0000000000005195>

An estimated 1% to 4% of patients treated with trastuzumab will develop overt heart failure,^[11–13] and ~10% will experience asymptomatic left ventricular ejection fraction (LVEF) reduction.^[6,12,14] When combined with anthracycline, the incidence of TIC was reported to be as high as 34%.^[6,15] TIC is not dose-dependent and is often reversible with discontinuation of treatment and/or standard medical therapy for congestive heart failure.^[16,17] Risk factors for TIC have been studied by different groups, but results have been inconsistent. A study by Seidman et al^[18] indicated that of all the factors studied (age, hypertension, previous radiation therapy to the chest wall, baseline LVEF, etc.), only age was significantly associated with increased risk of developing TIC and only in the trastuzumab plus anthracycline subgroup. In contrast, another study^[19] of mostly the same factors reported that baseline LVEF might be the only significant risk factor for developing TIC. Other studies have indicated that age, hypertension, preexisting cardiac dysfunction, baseline LVEF < 50%, and previous anthracycline treatment or radiotherapy to left chest wall and concomitant chemotherapy are associated with higher incidence of cardiotoxicity.^[20–22] The discrepancies among different studies may arise from overall low cardiotoxicity rates limiting size of study populations as well as use of different inclusion/exclusion criteria.

The objective of this meta-analysis is to consolidate the published data and identify potential risk factors for developing strategies to minimize TIC occurrence in clinical practice.

2. Methods

A literature search using the MEDLINE database was executed using the following keywords trastuzumab/herceptin, risk factors, outcomes, cardiac, cardiotoxicity, cardiomyopathy, LVEF, and chemotherapy. Articles were limited to those in the English language and published within the past 15 years (1999–2014). We included prospective and retrospective studies of patients with breast cancer who were treated with anthracycline and trastuzumab. Systematic reviews or meta-analyses, along with basic science, animal, and modeling studies, were excluded. Also excluded were study populations < 50 patients, cohorts that included subjects aged < 18 years, or cohorts with a mean baseline LVEF > 68%. As the goal of our analysis was to determine the risk factors for TIC, included studies were required to stratify by those who had or had not experienced cardiotoxic events. This review incorporated interventional randomized clinical trial and observational studies that provided the necessary and pertinent data for analysis. The primary outcome of interest was the development of TIC, manifested as heart failure or deterioration in LVEF based on the criteria presented within each study.

This meta-analysis met the criteria for waiving Institutional Review Board review and approval.

2.1. Data extraction

The following data were independently collected by 3 reviewers (RMP, LG, and ZJ): age; smoking history; LVEF; evidence of hypertension, diabetes, coronary artery disease, and dyslipidemia/hyperlipidemia; body mass index; use of radiotherapy or anthracycline; and location of tumor (right/left breast). Discrepancies were reviewed and resolved by consensus.

2.2. Statistical analysis

Pooled odds ratio (OR) and 95% confidence interval (CI) for each variable were calculated. To explore heterogeneity, a random-effect

model was used. Heterogeneity among studies was assessed using Cochran Q test and also by measuring consistency (I^2). For variables showing high heterogeneity, funnel plots were used to assess visual asymmetry. In addition, Egger test was used for analysis. No judgments were made comparing sample sizes between studies. As such, random-effect modeling was used to capture any true difference as well as the effect size while considering a heterogeneous sample. Statistical analysis was performed using Comprehensive Meta-Analysis Version 2.0 software (Biostat, Englewood, NJ), and $P < 0.05$ was considered significant.

3. Results

Initial MEDLINE search resulted in 635 citations. After excluding based on study criteria (Fig. 1), a total of 17 studies^[15,19,23–37] were included for analysis, characteristics for which can be found in Table 1 along with details on treatment regimens and tumor types. Included articles were a mix of retrospective and prospective studies. The total number of breast cancer patients treated with trastuzumab in all 17 studies combined was 6527 patients. Patients were treated both in adjuvant and metastatic settings. All studies had patients with HER2+ breast cancer, and all were treated with trastuzumab. Treatment for adjuvant/neoadjuvant therapy varied, as did dosing and regimen. The primary endpoints given for these studies were manifestation of a cardiac event, decline in LVEF greater than 10%, or occurrence of cardiotoxicity. Studies included 1 or more of the following risk factors for cardiotoxicity (Table 2): race, age, familial history of cardiac disease, smoking history, hypertension, diabetes, history of coronary artery disease, LVEF, body mass index, dyslipidemia, history of radiotherapy, anthracycline use, and originating site of breast cancer (left/right breast).

3.1. Incidence of TIC

The majority of studies included in this meta-analysis defined cardiotoxicity as a 10% to 20% decline in LVEF, a decline in LVEF to a level < 50%, or patients exhibiting signs and symptoms of heart failure. All studies used either echocardiography or a multigated acquisition scan (MUGA) as a tool to serially assess LVEF. The overall incidence of cardiotoxicity was 12.0% with 95% CI 11.3% to 12.9%. A total of 786 patients (out of 6527 patients) experienced TIC; however, only a small portion of patients had overt trastuzumab-induced heart failure, with the rest being asymptomatic (i.e., had a decline in LVEF without experiencing any signs or symptoms of heart failure). Only 6 patients (about 0.09%) died due to cardiac complications of trastuzumab.

3.2. Risk factors associated with TIC

Our analysis of the 17 included studies revealed that diagnoses of hypertension (OR: 1.61; 95% CI: 1.14–2.26; $P < 0.01$; Fig. 2A), diabetes (OR: 1.62; 95% CI: 1.10–2.38; $P < 0.02$; Fig. 2B), and previous anthracycline use (OR: 2.14; 95% CI: 1.17–3.92; $P < 0.02$; Fig. 2C) were all associated with risk of TIC (Fig. 3). Increased age ($P = 0.013$; Fig. 2D) also was found to be significantly associated with TIC. Familial history of cardiac disease showed significance ($P < 0.001$), but this finding was not reliable as too few studies reported these results ($n = 3$). Diabetes and age showed the least amount of heterogeneity ($I^2 = 1\%$ and 22%, respectively), whereas hypertension and previous

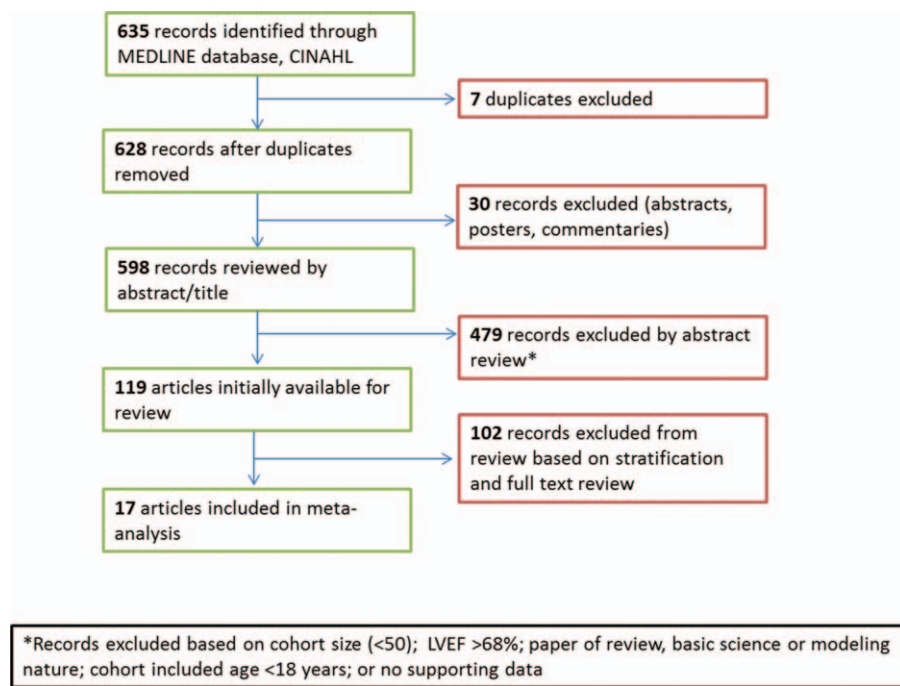


Figure 1. Flowchart of review design. LVEF = left ventricular ejection fraction.

anthracycline use showed the most evidence ($I^2=60\%$ and 76% , respectively). Due to the evidence of heterogeneity, funnel plots were used for a visual representation of asymmetry. However, when we formally tested for asymmetry using Egger test, asymmetry did not appear to be significant ($P=0.706$ and 0.340 , respectively; Fig. 4A and B) for hypertension and anthracycline use. Our results failed to show any significant association between TIC and a patient's race, body mass index, dyslipidemia, or history of coronary artery disease. There was not a sufficient number of articles describing cumulative anthracycline dosage, metastatic disease, familial history of cardiac disease, or left/right breast tumor site to allow for statistical analysis.

3.3. Study bias

After reviewing our results and subsequent funnel plots, we determined that reporting bias may be evident when interpreting the data on family history of cardiac disease as only 3 studies^[23,34,35] reported this variable in a manner usable to our analysis. Of the 3 studies, the one reporting significant result was weighted at approximately the cumulative of the other 2. Publication bias was assessed and determined acceptable for all collected variables. Results obtained from all other factors indicate that increased age, a diagnosis of hypertension or diabetes, and anthracycline use are the most substantial risk factors for cardiotoxicity in women treated with trastuzumab. Familial history of cardiac disease may contribute additional risk; however, the evidence supporting this conclusion is quite heterogeneous, primarily due to small sample size.

4. Discussion

Research has shown that trastuzumab significantly improves outcomes in women with HER2+ breast cancers, but its use is

associated with the potential risk of cardiotoxicity. Historically, the question to balance the success of cancer therapy at the expense of the "heart" has laid a lot of emphasis on early diagnosis. Some studies have tested the role of cardiac biomarkers (troponin, pro-BNP) and various imaging modalities (echocardiography, MUGA, cardiac magnetic resonance imaging, etc.) to aid in preclinical diagnosis. Indeed, it is imperative to identify the at-risk population from the pool of all exposed patients and monitor them more vigorously. Knowledge of various clinical risk factors associated with development of TIC can help clinicians immensely in this regard. Published reports have identified various risk factors for developing cardiotoxicity, including age, comorbidities, and use of radiotherapy. Our meta-analysis (which included strictly studies that stratified those who had experienced cardiotoxic events to those that had not) found that age, hypertension, diabetes, and previous anthracycline use are risk factors for a cardiac event.

Several studies have identified increased age as an important cardiotoxic risk factor for patients treated with trastuzumab. According to surveillance epidemiology and end results (SEER) Cancer Statistics Review, a report published by National Cancer Institute's Surveillance, Epidemiology, and End Results Program,^[38] the risk of breast cancer increases with age; at age 30 years, a woman has a 0.4% chance of developing breast cancer, when she reaches age 60, this jumps to 3.6%, and at age 70, the chance is about 3.8%. The cumulative age range in our meta-analysis was 25 to 100 years, and most of the studies reported a range cluster of 28 to 80 years. The mean age of patients in the studies that included age as a risk factor was 54 years, which may represent a slightly younger than average population of breast cancer, a disease most commonly diagnosed in women aged 55 to 64 years.^[38] Interestingly, cardiovascular disease and breast cancer incidence are likely to overlap, as major cardiovascular disease also increases with age. Since older age is likely associated with increased presence of cardiovascular comorbidities and

Table 1

Characteristics of the studies and patients included in the meta-analysis.

Reference	Patient population	Therapy	Primary endpoint	Number of patients
Cardinale et al ^[23]	HER2+ BC	Trastuzumab for metastatic disease or trastuzumab as adjuvant treatment	Occurrence of cardiotoxicity (absolute decrease in LVEF of >10)	251
Cochet et al ^[24]	HER2+ early stage invasive BC	6 cycles docetaxel and concurrent trastuzumab or AC w/cum dose 300 mg/m ² + trastuzumab or epirubicin w cum dose of 600 mg/m ² + trastuzumab	Cardiotoxic event	118
Guarneri et al ^[19]	HER2+ MBC	>1-year trastuzumab	Time to cardiac event	173
Guglin et al ^[15]	HER2+ BC	>1-year trastuzumab	Time to development of cardiomyopathy (decline of EF by ≥10%, decline of EF to <50%, symptoms and physical signs of heart failure)	156
Morris et al ^[25]	EBC HER2+/neu	ddAC + PTL + TL	Onset of CHF?	95
Naumann et al ^[26]	Primary and MBC	Trastuzumab for any indication (neoadjuvant, adjuvant, or metastatic)	Onset of cardiotoxicity (defined as decrease in LVEF ≥ 10% and reduction to <50% or clinical reduction in cardiac function as defined by NYHA)	388
Negishi et al ^[27]	HER2+ BC	Receiving trastuzumab for therapy (either with or without AC use)	Time to cardiotoxicity (10% decline in baseline EF)	81
Onitilo et al ^[28]	HER2+ BC stages 1–3	Trastuzumab adjuvant therapy	Time to cardiotoxicity (decrease of LVEF by ≥15% or to a value below 50%)	54
Romond et al ^[29]	HER2+ BC, no metastasis	AC + trastuzumab with at least 1 dose of post-AC therapy	Time to cardiac toxicity	944
Russo et al ^[30]	HER2+ EBC	Trastuzumab as adjuvant therapy	Development of cardiotoxicity	499
Russo et al ^[31]	EBC	AC + trastuzumab (18 doses)	Onset of CHF	499
Sawaya et al ^[36]	Newly diagnosed HER2+ BC	ACT followed by trastuzumab	Development of cardiotoxicity	81
Serrano et al ^[32]	Early or advanced BC	>1 dose trastuzumab based regimen	Onset of symptomatic cardiotoxicity (absolute drop ≥10% resulting in a final LVEF <50% or absolute drop >20%)	45
Suter et al ^[33]	HER2+ early stage invasive BC	1 or 2 years of trastuzumab every 3 weeks	Disease-free survival and cardiac adverse event	1678
Tan-Chiu et al ^[34]	HER2+ BC	ACT followed by 52 weeks trastuzumab	Time to cardiac event	814
Tarantini et al ^[37]	EBC treated with trastuzumab	Adjuvant trastuzumab	Time to cardiac dysfunction/heart failure	499
Wadhwa et al ^[35]	HER2+ BC	Adjuvant trastuzumab	Onset of cardiac dysfunction (decline of 10% in LVEF)	152 6527

AC = anthracycline, ACT = AC + taxanes, BC = breast cancer, EBC = early breast cancer, HER2+ = overexpression of HER 2, LVEF = left ventricular ejection fraction, MBC = metastatic breast cancer.

Table 2

Cardiotoxicity risk factors evaluated in the included literatures. The plus sign signifies that information was included for that variable and that it was found to be significant. The minus sign signifies that information was included for that variable and it was not found to be significant. The blanks are variables not included within that particular study.

Reference	Race	Age	Fam hx of cardiac dx	Smoking hx	HTN	DM	Hx of CAD	LVEF	Obese	Dyslipidemia	Radiotherapy	AC use	Left breast	Right breast
Guarneri et al ^[19]					–	–	–				–	–		
Russo et al ^[31]		+		–	+	–	–	–	–	–	–	–		
Cochet et al ^[24]		–		–	–	–	–	–			–	–	–	–
Cardinale et al ^[23]		–	–	–	–	–	–	+		–	–	+	–	–
Wadhwa et al ^[35]	–	–			+	–			–					
Guglin et al ^[15]		–			–	–	+	–		–	–			
Suter et al ^[33]		–			–	–	–		+					
Tan-Chiu et al ^[34]	–	+	–	–	–	–	–	+		–				
Sawaya et al ^[36]		–			–	–	–	–	–	–	–	–	–	–
Tarantini et al ^[37]	–	+			–	–	–	+			+	–	–	–
Serrano et al ^[32]		–			–	–	+	–	+	–	–	–	–	–
Onitilo et al ^[28]		–			–	–	–	–	–	–	–	–	–	–
Negishi et al ^[27]		–			–	–	–	–	–	–	–	–	–	–
Romond et al ^[29]		+	–	–	+	–	–	+		–	–	–	–	–
Russo et al ^[30]		+			–	–	–	+		–	+	–	–	–
Morris et al ^[25]		–			–	–	–	–		–	–	–	–	–
Naumann et al ^[26]		–										–	–	–

+ Denotes variable was analyzed and found to be significant; – denotes variable was analyzed and found not to be significant; blank denotes variable was not present in study; DM = diabetes, Fam hx of cardiac dx = family history of cardiac disease, HTN = hypertension, Hx of CAD = history of coronary artery disease, LVEF = left ventricular ejection fraction, Smoking hx = smoking history.

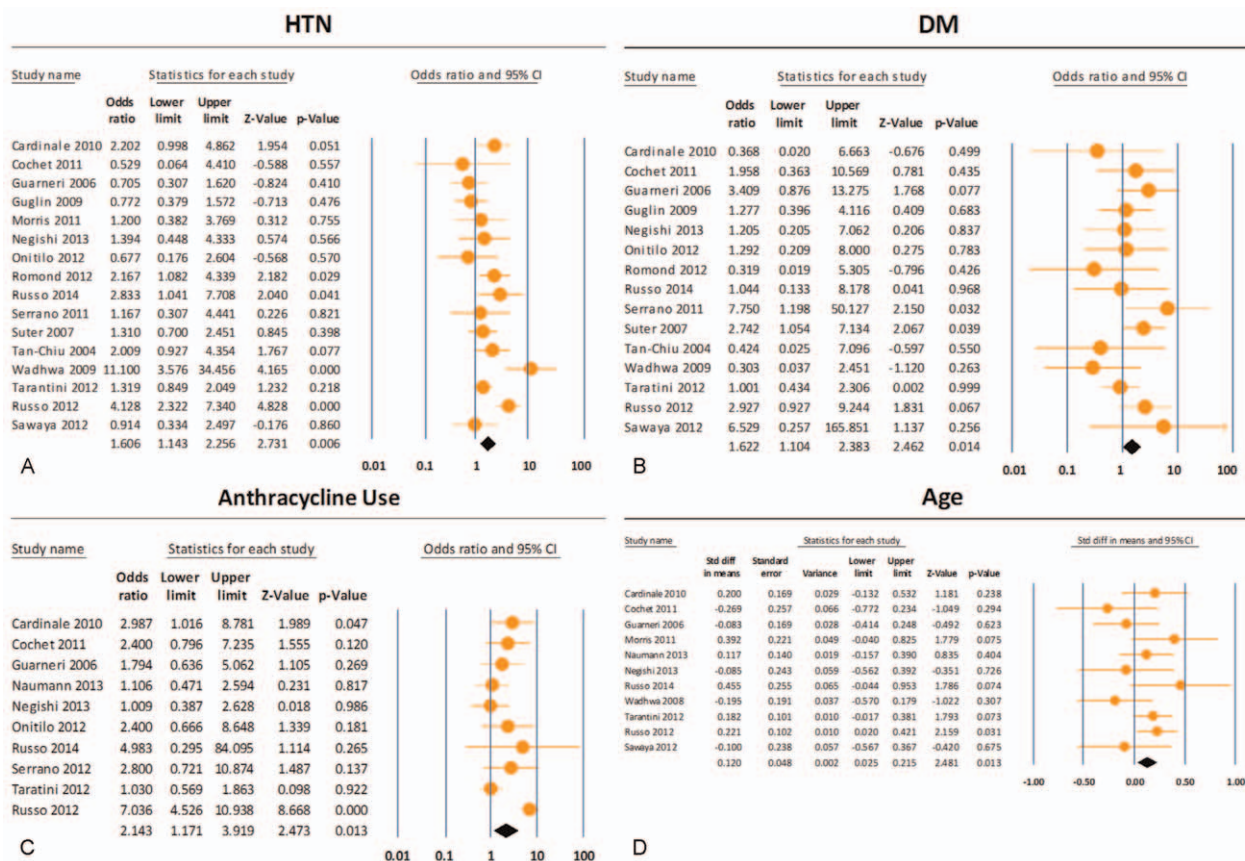


Figure 2. (A)–(D) Data analysis of risk factors associated with trastuzumab-induced cardiotoxicity (TIC). Hypertension (odds ratio [OR]: 1.61; 95% confidence interval [CI]: 1.14–2.26; $P < 0.01$), diabetes mellitus (OR: 1.62; 95% CI: 1.10–2.38; $P < 0.02$), and previous anthracycline use (OR: 2.14; 95% CI: 1.17–3.92; $P < 0.02$) were all shown to be associated with TIC. DM = diabetes mellitus, HTN = hypertension.

unfavorable lifestyle choices that decrease overall physical fitness, such as reduced physical activity and obesity, it is unclear whether age, which was identified as a risk factor in our study, is an independent risk factor or inherently associated with other cardiovascular comorbidities for developing TIC.

Large clinical trials testing trastuzumab included relatively younger and healthier patients with limited comorbidities and therefore may not reflect the true breast cancer population. Our study identified the comorbidities hypertension and diabetes as significant risk factors for a cardiac event in patients who were treated with trastuzumab. A recent study^[39] using the SEER-Medicare and Texas Cancer Registry Medicare-linked databases reported a retrospective cohort with older breast cancer patients (median age of 71 years). This study found that among patients

treated with trastuzumab, those with cardiac comorbidities and older age may be at a higher risk. Prospective studies with more patients are needed to confirm the roles specific cardiac comorbidities play in the development of TIC. Strategies for monitoring, intervention, and management of cardiac comorbidities for those who are receiving trastuzumab need to be developed. Another recent study^[40] showed that older women receiving trastuzumab tend to have suboptimal cardiac monitoring, with only a third of the patients getting recommended screening per current guidelines. Patients undergoing trastuzumab therapy should at least have cardiac monitoring at baseline and then at 3, 6, and 9 months, respectively. Routine monitoring is really imperative as TIC, unlike anthracycline-induced cardiotoxicity, is not dose-dependent, mostly occurs earlier in the course of treatment, and is reversible in the vast majority of cases via drug withdrawal and conventional heart failure therapy.

As treatment plans for breast cancer patients are generally complex, with more than 1 modality, it is often hard to dissect the cardiotoxic effect of each individual regimen. These treatments may interact with each other and have added effect to the cardiovascular system. Indeed, our study found that previous anthracycline use is a significant risk factor for developing TIC. When we further tried to determine if accumulated dosage of previous anthracycline contributed to increased cardiotoxicity, we were unable to draw any solid conclusion, as the study data were limited (only 4 studies collected data for accumulated dosage of anthracycline) and produced large standard deviation.

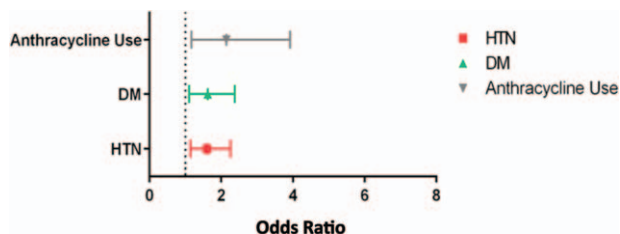


Figure 3. Data analysis of significant variables reporting effect measures for each included study.

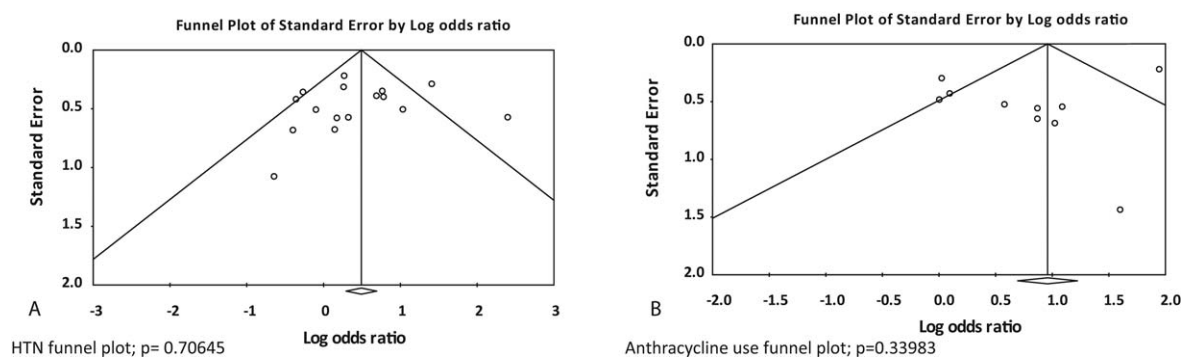


Figure 4. Testing for bias and asymmetry for hypertension and anthracycline use by funnel plot and Egger test.

Our institution's own experience with retrospective studies of chemotherapy-related cardiotoxicity has found that obtaining accurate records of accumulated anthracycline dosage is difficult since treatment history may not be well documented or easily obtained. However, accumulated dosage of previous anthracycline use is an important factor that should not be overlooked and has the potential to serve a crucial role in the monitoring of TIC. Therefore, it is highly recommended that records of accumulated anthracycline dosage be better monitored by providers.

4.1. Limitations

There are inherent limitations to systematic reviews and meta-analysis. The main limitation in our analysis is the definition of cardiotoxic event. Our analysis was based on the stratification of those having experienced a cardiotoxic event versus those who had not. Within the 17 articles analyzed, a cardiotoxic event was defined as any one of the following: a decline in cardiac function as measured by a decrease in LVEF of 10%, 15%, or 20% or the onset of heart failure. To date, there is no 1 clear definition of cardiotoxicity. Sengupta et al^[11] reviewed and evaluated clinical trials and defined chemotherapy-induced cardiotoxicity as one of the following: reduction of LVEF; symptoms or signs associated with heart failure; reduction in LVEF from baseline by $\geq 5\%$ to $< 55\%$ in the presence of signs or symptoms of heart failure, or a reduction in LVEF $\geq 10\%$ to $< 55\%$ without signs or symptoms of heart failure. Plana et al^[41] documented a new definition of cardiac toxicity in 2014, which both the American Society of Echocardiography and European Association of Cardiovascular Imaging have endorsed. This definition states that cardiac toxicity is a decrease in LVEF of $> 10\%$ to a value $< 53\%$ and if the value is confirmed by repeated cardiac imaging at 2 to 3 weeks after initial decline. Moving forward, these organizations have encouraged researchers to use this definition when qualifying a patient as having TIC or not. The second limitation in our study is the small sample size of subgroup analyses in testing for significance of variables, such as the case for familial history of cardiac disease. In addition, publication bias could account for the overall effects measured.

As with any treatment, it is imperative for patients and providers to have an open conversation on the risks/benefits of any therapy before commencing. For patients with multiple comorbidities, such as hypertension and diabetes, or those with previous anthracycline use, it is important for both cardiologists and oncologists to partner in the care of patients being treated

with trastuzumab. The intention of this study was not to prescribe or deter providers from using trastuzumab but to highlight the importance of closely monitoring a patient's cardiac function when on trastuzumab and assess when the potential risks of this treatment outweigh the benefits. The recent study posed by Gavila et al^[42] outlines a plan in which both cardiologists and oncologists work together in managing the potential of cardiotoxicity, an approach we believe should become common practice for taking care of cancer patients who undergo treatment with potential for cardiotoxicity^[43] and will ultimately maximize both quality of life and survival.

5. Conclusion

Our study identified hypertension, diabetes, age, and previous anthracycline use as risk factors for a cardiac event, but this should not be taken as exhaustive. Also, the weight of each risk factor is unknown. Even though our study included 17 independent studies and more than 6500 patients, numbers were still limited when trying to dissect the role of each risk factor in TIC. Still, we feel this review of the risks that can accompany trastuzumab therapy provides valuable support to the comprehensive teams of caregivers responsible for treating breast cancer patients.

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