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Major cardiovascular adverse events in older adults with early-stage triple-negative breast cancer treated with adjuvant taxane + anthracycline versus taxane-based chemotherapy regimens: A SEER-medicare study

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Abstract

Background: Triple-negative breast cancer (TNBC) is more aggressive as compared to other subtypes of breast cancer with characteristic metastatic patterns and a poor prognosis. The standard of care for early-stage TNBC is historically anthracycline and taxane-based chemotherapy (ATAX). Despite the effectiveness of this regimen, anthracyclines carry a small but important risk of cardiotoxicity, which is specifically a concern in the older population. This study evaluates major adverse cardiovascular events (MACE) in older women with TNBC treated with ATAX compared to taxane-based chemotherapy (TAX).

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Ethics Approval and Consent to Participate

This study was conducted following local institutional review board approval and a limited data set was obtained via the National Cancer Institute's Surveillance, Epidemiology and End Results program's policies.

CRediT authorship contribution statement

Savannah Roy, Stephanie Lakritz, Anna R. Schreiber, Cathy J. Bradley, Lavanya Kondapalli, Jennifer R. Diamond contributed to study design and concept. Savannah Roy, Stephanie Lakritz, Anna R. Schreiber, Elizabeth Molina Kuna, Cathy J. Bradley, Lavanya Kondapalli, Jennifer R. Diamond contributed to analysis and interpretation of data. Savannah Roy, Jennifer R. Diamond wrote and edited the original draft. All authors contributed to the critical revision of the manuscript.
All authors read and approved the final manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2023.113426.

Methods: Using the Surveillance, Epidemiology, and End Results (SEER)-Medicare database, we identified women aged 66 and older with TNBC diagnosed between 2010 and 2015 (N = 2215). We compared patient and clinical characteristics according to adjuvant chemotherapy regimen (chemotherapy versus no chemotherapy and ATAX versus TAX). Logistic regression was performed to estimate the odds ratios (OR) and 95% confidence intervals (CIs), Kaplan-Meier survival curves were generated to estimate three-year overall survival (OS) and cancer specific survival (CSS). Cox proportional hazards models were used to analyze OS and CSS while controlling for patient and tumor characteristics. MACE was defined as acute myocardial infarction, heart failure, potentially fatal arrhythmia, and cerebral vascular incidence. Few patients experienced a cardiac death and therefore this was excluded in the analysis.

Results: Of the 2215 patients in our cohort, most patients (n = 1334; 60.26%) received TAX compared to ATAX (n = 881; 39.78%). Patients who received ATAX were not statistically significantly more likely than those who received TAX to experience acute myocardial infarction, cerebral vascular accident (CVA), or potentially fatal arrhythmia when controlling for traditional risk factors. Among patients who experienced MACE, there was no difference in OS or CSS in patients who received TAX vs ATAX. Patients who received ATAX were less likely to develop heart failure than those who received TAX (OR 0.63, 95% CI [0.45–0.88], $p < 0.01$). Patients who developed MACE and who were ≥ 76 years old had worse OS compared to those who experienced MACE and were age 66–75 years old (HR 1.67, 95% CI [1.07–2.62], $p = 0.02$).

Conclusion: Among older women with TNBC, receipt of adjuvant chemotherapy with ATAX was not associated with increased risk of major adverse cardiac events. For those who experienced a cardiac event, there was no difference in survival amongst those who received TAX vs ATAX. Other factors including additional chemotherapy toxicities should be investigated as a potential etiology for the inferior OS previously observed with ATAX vs TAX in older women with node negative or 1–3 positive lymph nodes.

Keywords

Breast cancer; Older adults; Chemotherapy; Triple-negative breast cancer; Anthracyclines; Cardiotoxicity

1. Introduction

Triple-negative breast cancer (TNBC) is an aggressive breast cancer (BC) subtype characterized by a lack of estrogen and progesterone receptor expression and negative or low human epidermal growth factor 2 (HER2) expression [1]. TNBC is associated with a higher risk of metastatic recurrence, visceral and brain metastasis, and overall a poor prognosis compared to other BC subtypes [2]. TNBC accounts for 15–20% of BCs and chemotherapy is the mainstay of adjuvant treatment to prevent recurrence.

Age is one of the most important risk factors for BC, and although TNBC is associated with a younger median age of diagnosis compared with other subtypes, approximately 35% of patients diagnosed with TNBC are older than age 65 [3–5]. With an aging population, the number of older women with BC is projected to increase over the coming decades, affecting 21.5% of women age 65 and older by 2050. [6] Understanding the optimal treatment for

older patients with early-stage TNBC is an area of unmet clinical need, especially in light of small numbers of patients older than age 65 years enrolled in clinical trials.

Chemotherapy is the mainstay in the neoadjuvant, adjuvant, and metastatic treatment of TNBC. The standard of care for early-stage TNBC is anthracycline and taxane-based chemotherapy (ATAX). As demonstrated in the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis, the addition of a taxane to an anthracycline improved the 8-year BC mortality rate compared to the anthracyclines only control group [7]. When compared head-to-head, TC (docetaxel, cyclophosphamide) was superior to AC (doxorubicin, cyclophosphamide) with a benefit in disease-free and overall survival (OS) [8]. The anthracyclines in early breast cancer (ABC) trials and a recent EBCTCG meta-analysis demonstrated improved invasive disease-free survival for ATAX compared to TAX chemotherapy, with more benefit in patients with TNBC and those with node positive disease in the ABC trials [9,10]. In the phase III KEYNOTE-522 trial, a carboplatin and anthracycline-containing neoadjuvant regimen with concurrent pembrolizumab demonstrated an improvement in pathological complete response (pCR) and event free survival in patients with untreated stage II or III TNBC, establishing it as the current standard of care [11]. This is important considering that pembrolizumab also possesses the potential for immune-related cardiotoxicity.

In the context of metastatic TNBC, treatment decisions are influenced by treatment history, the expression of programmed cell death ligand 1 (PD-L1), and presence of germline BRCA mutation but chemotherapy continues to be a vital component of therapy. Sacituzumab govitecan, an antibody-drug conjugate, is effective in patients with metastatic TNBC who have undergone a minimum of two prior therapies, at least one of which was for metastatic disease [12]. Another antibody drug conjugate, trastuzumab deruxtecan, has been shown to significantly extend progression-free survival and OS when compared to physician's choice of chemotherapy in patients with previously treated HER2-low metastatic breast cancer [13].

Despite their effectiveness, anthracyclines carry a small but important risk of cardiotoxicity through multiple mechanisms such as myocardial cellular disruption and free radical formation. Cardiotoxicity may present clinically with symptoms related to arrhythmia or reduced systolic function, or be detected in asymptomatic patients during surveillance cardiac testing. Cardiotoxicity is classified into Type I, characterized by direct, dose-related, and irreversible damage, and Type II, seen as reversible and dose dependent. However, these categories have some overlap, as patients treated solely with Type II-associated agents may have persistent LV dysfunction [14]. The risk factors for development of cardiotoxicity as outlined by the cardio-oncology guidelines from the American Society of Clinical Oncology (ASCO) in 2017 and the European Society of Cardiology (ESC) in 2022 include individuals treated with high-dose anthracycline or high-dose radiotherapy involving the heart in the treatment field. This also includes patients receiving treatment with anthracyclines or trastuzumab with multiple CV risk factors including older age, compromised cardiac function, a history of myocardial infarction, or a sequence of anthracycline followed by trastuzumab [15,16]. Baseline cardiovascular toxicity risk stratification can be calculated using the Heart Failure Association-International Cardio-Oncology Society baseline (HFA-ICOS) risk assessment tool [16]. Regular monitoring of cardiac function is advised,

especially in patients who receive high-dose anthracyclines (eg, doxorubicin ≥ 250 mg/m^2, epirubicin ≥ 600 mg/m^2). Consideration should be given to cardioprotective measures, such as dexrazoxane, in high-risk patients or those receiving high cumulative doses. Treatment includes discontinuation of anthracycline chemotherapy and guideline-based heart failure therapy in patients who develop symptoms or asymptomatic patients with moderate/severe cardiac dysfunction.

If cardiotoxicity occurs, it can compromise the survival and quality of life of survivors [17–19]. A recent study among adult BC patients undergoing treatment with an anthracycline determined a high incidence rate of cardiotoxicity at 9.68% [20]. Cardiotoxicity is specifically a concern in the older population as age 65 and older is considered an independent risk factor along with having pre-existing cardiovascular (CV) conditions like hypertension and diabetes [21,22]. Therefore, older BC patients are at a higher risk of treatment-related cardiotoxicity [23, 24].

In a prior published study, our team completed retrospective analyses of adjuvant chemotherapy in older women (≥ 65 years old) with both node-negative and node-positive TNBC. We found that ATAX was associated with inferior 3-year overall survival (OS) and cancer-specific survival (CSS) compared to TAX in the node-negative and 1–3 positive lymph node groups and that there was a trend toward superior 3-year OS and CSS compared to TAX in the node-positive group with 4 or more lymph nodes involved [25,26]. We expand upon this work to evaluate the incidence of major adverse cardiovascular events (MACE) in both cohorts of older women with node-negative and node-positive TNBC. We hypothesized that cardiac event rates in the ATAX group would be higher thus providing a potential explanation for inferior survival in older women treated with ATAX.

2. Methods

Using the Surveillance, Epidemiology, and End Results (SEER)-Medicare database, we identified 178,228 patients diagnosed with primary BC from 2010 to 2015. We then identified women with TNBC who were treated with ATAX or TAX diagnosed at ages 66 and older meeting eligibility criteria for inclusion in this study (N = 2215). Individuals with missing data of interest were excluded from the analysis. Fig. 1 shows how the sample was derived. Data regarding year of diagnosis, age, race, marital/partnered status, reporting registry region, urban/rural residency, tumor stage, number of positive nodes, census poverty level, facilities visited in the first six months, tumor laterality, treatment, and presence of cardiovascular risk factors including hyperlipidemia, hypertension, diabetes, obesity, tobacco use, family history of heart disease, polysubstance/alcohol use, receipt of trastuzumab, personal history of myocardial infarction, personal history of heart failure, heart failure after diagnosis, cerebral vascular accident (CVA) after diagnosis, potentially fatal arrhythmias after diagnosis, and cardiac death were extracted. An important risk factor, radiotherapy where the heart is in the treatment field, was unavailable for analysis. To address this missing information, data on tumor laterality, left-sided tumors being a known risk factor for heart radiotherapy, was extracted. Potentially fatal arrhythmia was defined as ventricular fibrillation/flutter, ventricular tachycardia, and cardiac arrest. Cardiac death was defined as death from acute coronary syndrome, heart failure, cerebrovascular accident, or fatal

arrhythmias including cardiac arrest, ventricular tachycardia, and ventricular fibrillation. We controlled for the covariates of traditional cardiovascular risk factors. A small number of patients had a personal history of acute myocardial infarction, personal history of heart failure, hypertension, polysubstance use, and cardiac death. Therefore, these factors were excluded from the analysis as they were not good predictors to include in the model. Cardiovascular risk factors were identified based on their corresponding ICD codes, while cardiac events were defined using the criteria outlined above and were also identified by their respective ICD codes (Appendix).

Patients with T1a and T1b disease and T3 and T4a-d disease were grouped together in T1a/b and T3/4 groups to maximize sample size. To control for lymph node status, patients were grouped into 1–3 positive lymph nodes (N1), ≥ 4 positive lymph nodes (N2), negative nodes (N0), or unknown lymph node status (NX).

Treatment categories are based on the initial treatment administered after BC diagnosis which was patients' first primary tumor. There were no patients with recorded anthracycline use prior to their cancer diagnosis. The administration of neoadjuvant or adjuvant chemotherapy was determined using CPT and HCPCS procedure codes for commonly used chemotherapy drugs. Co-morbid conditions were defined by ICD9 and ICD10 codes (Appendix). Patients were identified as receiving ATAX if they received doxorubicin or epirubicin plus paclitaxel, docetaxel or nab-paclitaxel and as receiving TAX if they received docetaxel, paclitaxel or nab-paclitaxel without doxorubicin or epirubicin. Receipt of other drugs in combination with these agents was not included in this analysis.

We summarized demographic characteristics across the treatment groups. Chi-square analysis was used to determine statistical significance of differences in descriptive characteristics between treatment groups. OS was defined as death due to any cause from the month of cancer diagnosis to death. CSS was defined as death from cancer determined by the time from the month of diagnosis to death. Kaplan-Meier 3-year all-cause and CSS curves were generated for treatment groups and those patients with or without a cardiac outcome. OS and CSS between chemotherapy regimens was estimated using adjusted Cox proportional hazards models. Violations of the proportional hazard assumption were addressed using time-dependent variables. Logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (CIs) for the association between covariates and cardiac outcomes of interest. All analyses were performed in SAS version 9.4 (SAS Institute Inc., Cary, NC) and were evaluated with a p value < 0.05.

3. Results

3.1. Patient characteristics

Of the 4700 patients identified with TNBC aged 66 and older, 2615 (55.64%) patients received adjuvant chemotherapy. Among those who received adjuvant chemotherapy, 2215 patients received either ATAX or TAX. Baseline patient characteristics are summarized in Table 1. More patients were aged 66–75 years old (77.8%). Most patients were non-Hispanic white (76.1%), followed by Black (13.5%), or other (10.4%). Patients were nearly even distributed by marital status with 46.5% non-married and 53.5% married or partnered.

Many patients were diagnosed in the West region (41.7%) followed by the South (25.9%), Northeast (19.5%) and Midwest (13.0%). Most patients were diagnosed in an urban commuting area (88.3%), had T2 tumors (42.6%) and were node negative (61.8%). Of those with nodal involvement, there were more patients with N1 v. N2 disease (18.9% vs 11.0%). Most patients were free of comorbidities with a Charlston Comorbidity Index (CCI) score of 0 (60.6%), followed by a CCI score of 1 (22.3%) and CCI score of 2 or more (17.1%). Patients more commonly visited teaching hospitals (55.5%) than National Cancer Institute (NCI) centers (15.6%) or other facilities (28.9%). The most prevalent cardiovascular risk factors were hyperlipidemia (82.8%) and hypertension (84.5%).

3.2. Patterns of chemotherapy administration

Younger patients aged 66–75 received ATAX at a significantly higher rate (781/1724, 45.3%) compared to patients ages 76 and older (100/491, 20.37%), $p < 0.01$). Married or partnered patients received ATAX at a higher frequency (510/1185, 43.04%) compared to non-married or partnered patients (371/1030, 36.02%, $p < 0.01$). Patients free of comorbidities with a CCI of 0 received ATAX at the highest frequency (587/1343, 43.71%), followed by a CCI score 1(183/493, 37.12%), and a CCI score of 2 or more (111/379, 29.30%, $p < 0.01$). Patients with hypertension had a significantly lower frequency of receiving ATAX (723/1871, 38.64%) than those patients without hypertension (158/344, 45.93%, $p = 0.01$). The same was true for patients with diabetes (310/858, 36.13%) than those without diabetes (571/1357, 42.08%, $p < 0.01$). Among patients who received trastuzumab, fewer received ATAX (17/64, 26.57%) compared to those who did not receive trastuzumab (864/2151, 40.17%, $p = 0.03$). Patients who had a personal history of heart failure (22/94, 23.40%) received ATAX at a lower frequency compared to patients who did not have a personal history of heart failure (859/2121, 40.50%, $p < 0.01$). Finally, those with patients who subsequently developed heart failure after diagnosis received ATAX at a lower frequency (71/228, 24.65%) than those patients who did not develop heart failure (810/1987, 40.76%, $p < 0.01$).

3.3. Factors associated with Major Adverse Cardiovascular Event (MACE) outcomes

3.3.1. Acute myocardial infarction—Of those patients who received adjuvant chemotherapy with either ATAX or TAX (N = 2215), 85 (3.84%) developed an acute myocardial infarction after diagnosis (Table 2). Patients with diabetes were more likely to experience an acute myocardial infarction than those without diabetes (OR 2.10, 95% CI [1.29–3.43], $p < 0.01$). This was also true for those patients with an unknown number of nodes compared to patients with 1–3 positive lymph nodes (OR 2.71, 95% CI [1.15–6.39], $p = 0.02$). Those patients who received ATAX were not more likely to have an acute myocardial infarction than those who received TAX (OR 1.03, 95% CI [0.62–1.70], $p = 0.91$).

3.3.2. Heart failure—Of those patients who received adjuvant chemotherapy with either ATAX or TAX, there were 228 patients (10.29%) who developed heart failure after diagnosis (Table 3). Patients ages 76 and older were more likely to develop heart failure than those patients aged 66–75 (OR 1.60, 95% CI [1.14–2.24], $p < 0.01$). Non-married patients were more likely to develop heart failure than married or partnered patients (OR 1.39, 95% CI

[1.03–1.88], p = 0.03). Patients with an unknown number of positive nodes were more likely to develop heart failure than those with 1–3 positive lymph nodes (OR 1.80, 95% CI [1.04–3.14], p = 0.04). Patients in a non-urban or rural commuting area were more likely to develop heart failure compared to those patients in an urban commuting area (OR 1.73, 95% CI [1.15–2.61], p < 0.01). Patients who resided in an area with 20% or higher poverty level were more likely to develop heart failure than those who resided in an area with < 20% poverty (OR 1.59, 95% CI [1.13–2.26], p < 0.01). Patients with cardiovascular risk factors such as hyperlipidemia (OR 1.71, 95% CI [1.05–2.79], p = 0.03), diabetes (OR 2.39, 95% CI [1.75–3.26], p < 0.01), and obesity (OR 1.59, 95% CI [1.17–2.18], p < 0.01) were more likely to develop heart failure. Interestingly, those who received ATAX had a lower risk at subsequently developing of heart failure than those who received TAX (OR 0.63, 95% CI [0.45–0.88], p < 0.01).

3.3.3. Potentially fatal arrhythmia—Of those patients who received adjuvant chemotherapy with either ATAX or TAX, 34 (1.53%) developed potentially fatal arrhythmia (e.g. VT/VF, cardiac arrest) after diagnosis (Table 4). Patients with a family history of heart disease were more likely to develop potentially fatal arrhythmia (OR 2.47, 95% CI [1.08–5.67], p = 0.03). Those patients who received ATAX were not more likely to develop potentially fatal arrhythmia than those who received TAX (OR 0.52, 95% CI [0.23–1.17], p = 0.12).

3.3.4. Cerebral vascular accident—Of those patients who received adjuvant chemotherapy with either ATAX or TAX, there were 77 patients (3.48%) who developed CVA after diagnosis (Table 5). Patients with no positive nodes were more likely to develop CVA than those patients with 1–3 positive nodes (OR 0.50, 95% CI [0.27–0.92], p = 0.03). Patients with left-sided tumors, or those at higher risk of receiving heart RT, were found to be more susceptible to developing CVA than those patients with right-sided tumors (OR 1.69, 95% CI [1.04–2.74], p = 0.03). Patients with diabetes were also statistically more likely to develop a CVA (OR 1.71, 95% CI [1.03–2.83], p = 0.04). Patients who received adjuvant chemotherapy with ATAX were not more statistically significantly more likely to develop a CVA than those who received TAX (OR 0.71, 95% CI [0.42–1.20], p = 0.20).

3.3.5. Analysis of chemotherapy type and survival—Overall, patients who received ATAX had worse CSS and OS than those who received TAX (see Fig. 2A and B). Those who experienced a cardiac outcome had worse CSS and OS than those who did not (see Fig. 2B and C). Patients who received TAX and had no cardiac event had the best survival, followed by those who received ATAX and had no cardiac event, those who received TAX and developed a cardiac event, and finally those who received ATAX and developed a cardiac event (see Fig. 2E and F).

3.3.6. Analysis of CSS and OS controlling for covariates—We evaluated factors that might influence the occurrence of MACE (Figs. 3 and 4). Patients who were 76 and older had worse OS compared to those ages 66–75 (HR 1.67, 95% CI [1.07–2.62], p = 0.02), and a trend toward worse CSS (HR 1.98, 95% CI [0.99–3.96], p = 0.05), Patients diagnosed in the Midwest had a worse CSS than those in the West (HR 3.29, 95% CI [1.09–9.95], p

= 0.03), although there was no difference in OS by geography. Patients who experienced a cardiac event in a non-urban or rural commuting area had worse CSS and OS than those who experienced a cardiac outcome in an urban commuting area (HR 2.99, 95% CI [1.32 – 6.78] p < 0.01 and HR 1.84, 95% CI [1.10–3.05], p = 0.02). Patients with no positive nodes had improved CSS and OS compared to those patients with 1–3 positive nodes (HR 0.29, 95% CI [0.12–0.75], p = 0.01 and HR 0.50, 95% CI [0.29 – 0.89] p = 0.02). Among patients with a cardiac outcome, patients who visited an NCI center had improved CSS and a trend toward improved OS compared to those who visited other facilities (HR 0.20, 95% CI [0.04 – 0.91] p = 0.04 and HR 0.40, 95% CI [0.16–0.99, p = 0.05).

Patients with a potentially fatal arrhythmia after diagnosis had worse CSS (HR 2.88, 95% CI [1.20–6.92], p = 0.02), although no difference in OS. Patients with diabetes had a trend toward improved CSS (HR 0.53, 95% CI [0.27–1.06], p = 0.07), although no difference in OS.

Among patients who experienced a cardiac outcome, there was no statistically significant difference in OS or CSS in patients who received TAX vs ATAX.

4. Discussion

Using the SEER-Medicare database, we conducted a retrospective evaluation of major adverse cardiovascular events and survival for older women diagnosed with TNBC treated with ATAX or TAX chemotherapy. Our study builds upon a previous investigation by Doyle et al. that examined the cardiac effects of chemotherapy using the SEER-Medicare database in BC patients diagnosed between 1992 and 1999 and found that chemotherapy with anthracyclines was associated with a substantially increased risk of cardiomyopathy [23]. The novelty of our current study lies in examining this specific population of older patients with TNBC diagnosed between 2010 and 2015 and comparing the adjuvant chemotherapy of ATAX vs TAX.

Several landmark studies including Lefrak et al. (1973), Von Hoff et al. (1979), Swain et al. (2003) have demonstrated the cardiotoxic effects of anthracyclines, revealing a dose-dependent increase in cardiac dysfunction, heart failure, and other cardiac abnormalities in patients treated with these drugs [18,27,28]. In contrast, we found that patients who received ATAX were not more susceptible to major adverse cardiovascular events such as acute myocardial infarction, heart failure, CVA, or potentially fatal arrhythmia when controlling for traditional cardiovascular risk factors. These findings underscore the significance of pre-existing cardiovascular risk factors as the dominant driver of MACE following adjuvant chemotherapy. However, few patients experienced cardiac outcomes in our study, which could affect the precision of our estimates. Among patients who underwent adjuvant chemotherapy with either ATAX or TAX, few experienced an acute myocardial infarction (3.84%), developed heart failure (10.29%), experienced potentially fatal arrhythmia (1.53%), or had a CVA (3.48%). Improved identification of patients at increased cardiac risk, preventative strategies with cardiologists and cardio-oncologists, and enhanced surveillance and monitoring during treatment may all have contributed to these low cardiac event rates.

Treatment with trastuzumab, a monoclonal antibody targeting HER2, is associated with an increased risk of anthracycline-induced cardiotoxicity. Numerous studies assessed the cardiac safety of combining anthracyclines with trastuzumab and consistently reported a higher incidence of cardiac dysfunction compared to those treated with anthracyclines alone [29,30]. Our study specifically focused on patients with TNBC, which lacks estrogen, progesterone, and HER2 receptors. Therefore, the use of trastuzumab was not indicated in our treatment approach. Only a small number of patients in our cohort (N = 64, 0.03%), received trastuzumab, and the reasons for this utilization in this cohort remain unclear. It is possible this factor may have contributed to the lower occurrence of cardiac events in our study compared to studies that encompass various BC types including a high proportion of patients receiving anthracyclines and trastuzumab.

Previous research suggests that anthracycline-induced cardiotoxicity may be more pronounced in older patients. Timóteo et al. (2019) found a significant worsening in diastolic dysfunction during the first year of BC treatment, with age as the only independent predictor. [31] Numerous other studies have also independently reported an increased risk of developing cardiac toxicity among older individuals, often defined as those above 65 years of age [23,32,33].

Although our study did not find a significant association between older age and cardiac toxicity, we observed a difference in survival rates between age groups. Among patients who experienced a cardiac outcome, those aged 76 and older exhibited worse OS and a trend toward worse CSS than those aged 66–75. No difference in OS or CSS was observed among patients who experienced a cardiac outcome who received TAX vs ATAX. Therefore, our results suggest that age may serve as a predictor for worse survival once a cardiac event occurs. This finding is logical, considering that CV events are inherent to human aging and continue to be a leading cause of death among women in the United States.

Our prior findings indicate that in older patients with no or limited nodal involvement, the addition of an anthracycline to a taxane-containing regimen does not confer any discernible benefit in OS or CSS [25]. Conversely, for older patients with 4 or more positive lymph nodes, there appears to be an advantage in using an anthracycline and taxane-containing regimen [26]. When we analyzed data by age groups, we observed that patients aged 76 and older with 4 or more positive lymph nodes exhibited a statistically significant improvement in CSS when treated with ATAX compared to TAX.

Our current study suggests that the risk of cardiotoxicity is low when treating with ATAX in older women aged 76 and above with significant nodal involvement with the current preventative measures in place. In fact, our study found that patients who received ATAX were less likely to develop heart failure even after adjusting for all other covariates. This result is likely impacted by the standard practice of assessing cardiac function prior to anthracycline administration and only treating patients without significant cardiac comorbidities. Although the incidence of heart failure was low in women aged 76 and above treated with ATAX, patients in this age group in our study who experienced a cardiac outcome had worse survival outcomes. That is, in older women who have received ATAX, if they develop a cardiac outcome, their prognosis tends to be worse.

Overall, ATAX would typically be administered to older individuals who are in better physical condition and have higher clinical risk of breast cancer recurrence. Conversely, patients who are older, more frail or have a lower risk BC would typically receive TAX. When considering the interplay of competing risks, those who received ATAX likely have a lower baseline CV risk and are routinely monitored and offered prompt cardioprotective measures. In contrast, patients receiving TAX may start with a higher baseline risk for CV events but are not monitored closely for cardiotoxicity following therapy.

Our study found that patients in a non-urban or rural commuting area or in an area with 20% or higher poverty level were more likely to develop heart failure. Additionally, patients experiencing cardiac events in non-urban areas had worse CSS and OS outcomes than their urban counterparts. It is known that low socioeconomic status impacts both quality and access to healthcare and is associated with adverse cancer and CV outcomes [34,35]. Patients from non-urban or rural commuting areas and poorer neighborhoods were likely influenced by social and structural determinants of health, such as health insurance status, geographical distance from specialized care, and transportation barriers. These factors likely resulted in reduced screening and surveillance, providing a plausible explanation for the observed poorer outcomes.

Non-married patients were more likely to develop heart failure than married or partnered patients. Past research has demonstrated that marriage serves as a protective factor against mortality and increased healthcare utilization. Moreover, transitions from a married to unmarried status have been linked to an escalation in adverse health behaviors [36–38]. Hence, non-married patients in our cohort may have had reduced screening and surveillance for cardiotoxicity due to lower healthcare system utilization. They may have exhibited more adverse health behaviors typically associated with heart failure than married patients, leading to this observed result.

Recent studies offer alternative treatment options for women with TNBC and significant cardiovascular risk factors. The KEYNOTE-522 trial demonstrated an improvement in pCR rate and event-free survival with the addition of pembrolizumab to an anthracycline, taxane, and platinum-based neoadjuvant chemotherapy regimen in patients with T2 + or node positive TNBC [11]. However, it is important to note that more than > 88% of patients were younger than 65 years old. The NeoCART trial showed that compared with ATAX, docetaxel carboplatin resulted in a higher pCR rate in patients with T2 + or node-positive TNBC [39]. However, it is worth mentioning that previous geriatric clinical trials, such as the ADVANCE trial, did not achieve targeted feasibility thresholds with the platinum and taxane-based regimen. [40] Furthermore, the CREATE-X trial examined the use of capecitabine in TNBC patients who had residual disease after neoadjuvant chemotherapy containing anthracyclines, taxanes, or both. The capecitabine group demonstrated effective prolongation of disease-free survival [41]. Again, the median age of enrollment in the CREATE-X trial was 48 years old, highlighting the need for more studies focused on an older population. In summary, while these alternative options show promise for women with TNBC and significant cardiovascular risk factors, further research is necessary to better define the efficacy and safety of these regimens in older patient populations.

Our study has a number of limitations which should be acknowledged. The use of a retrospective dataset may increase bias in our results. We relied on claims that may not have captured all relevant variables or potential confounders. Our study did not consider specific chemotherapy toxicities or changes in quality of life, which could have impacted treatment decisions and outcomes. Additionally, the follow up time in our study was 3 years which limits our ability to identify late-onset cardiovascular events. Unobservable differences in health status could have influenced treatment decisions, potentially resulting in selection bias where women in poorer health were not given ATAX. We accounted for cardiovascular risk factors; however, the SEER registries do not collect information about risk factors. Medicare data include diagnoses codes related to some risk factors, but their sensitivity is limited which may have affected our results. Our dataset also did not include administration of radiotherapy involving the heart within the treatment filed which could represent a significant risk factor for cardiotoxicity that was not accounted for in our analysis. It is important to note that our sample size of patients with cardiac outcomes was small, which hinders our ability to draw definitive conclusions. Further studies with larger sample sizes are warranted to validate and expand upon our findings. Lastly, our population may not accurately represent current patients receiving the standard of care, as they did not receive adjuvant capecitabine or immunotherapy, both of which are known to have potential cardiotoxic effects.

5. Conclusion

This study represents the largest cohort study to date evaluating major adverse cardiovascular events in older patients with TNBC. Among older women with TNBC, adjuvant chemotherapy with ATAX did not increase the risk of cardiac outcomes, including acute myocardial infarction, potentially fatal arrhythmia, heart failure, or CVA. Survival did not differ between those who received ATAX vs TAX among patients experiencing a cardiac outcome. However, stratifying patients with cardiac events by age revealed that those aged 76 and older may have worse survival compared to those ages 66–76. Thus, age may serve as a predictor for poorer survival once a cardiac event occurs. Clinical trials evaluating non-anthracycline containing regimens, like docetaxel carboplatin in combination with pembrolizumab, should be designed to include older patients as an alternative for women with cardiovascular risk factors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Availability of Data and Materials

The datasets used to conduct this study are available upon approval of a research protocol from the National Cancer Institute. Instructions for obtaining these data are available at https://healthcaredelivery.cancer.gov/seermedicare/obtain/.

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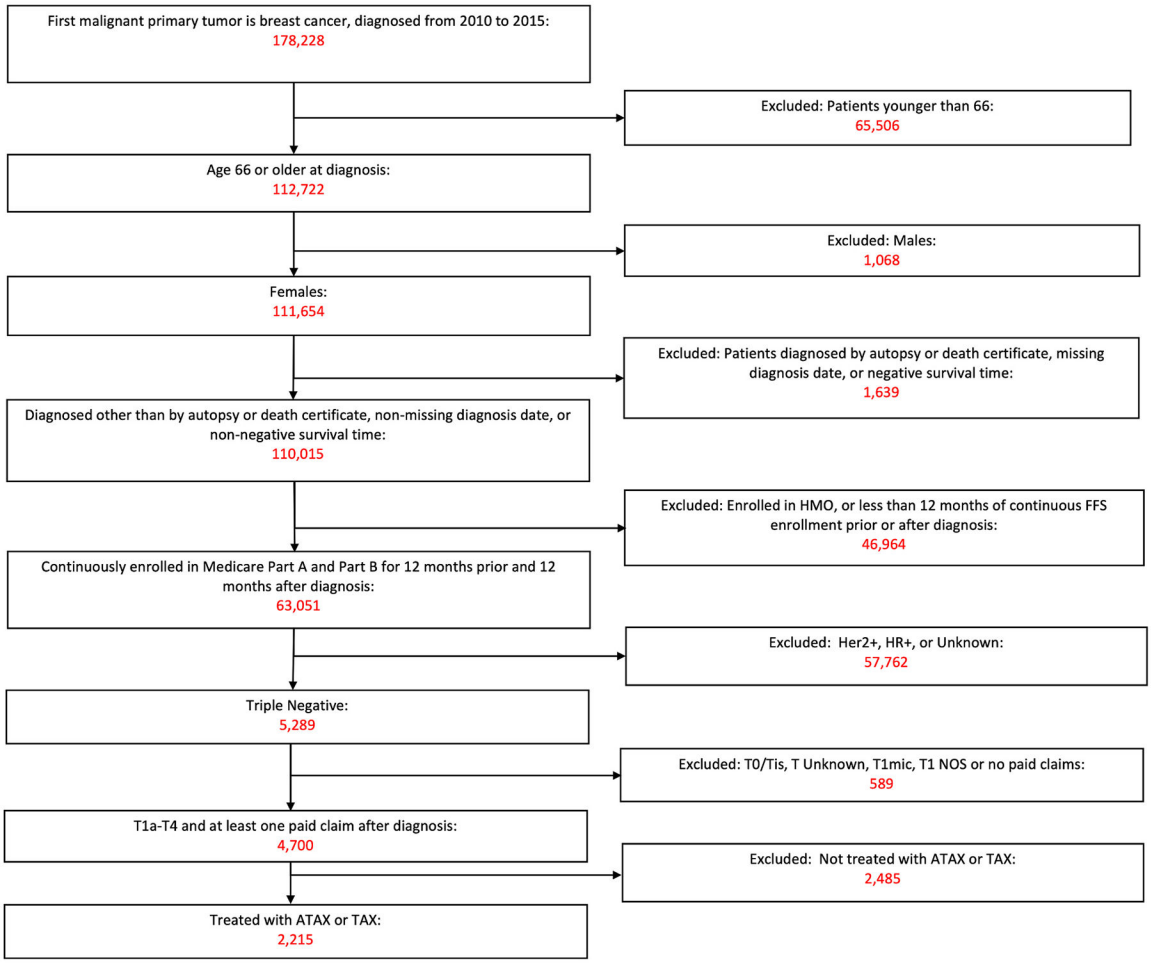

Fig. 1.

Sample selection. Newly diagnosed TNBC in women aged 66 or older between 2010 and 2015 in SEER-Medicare.

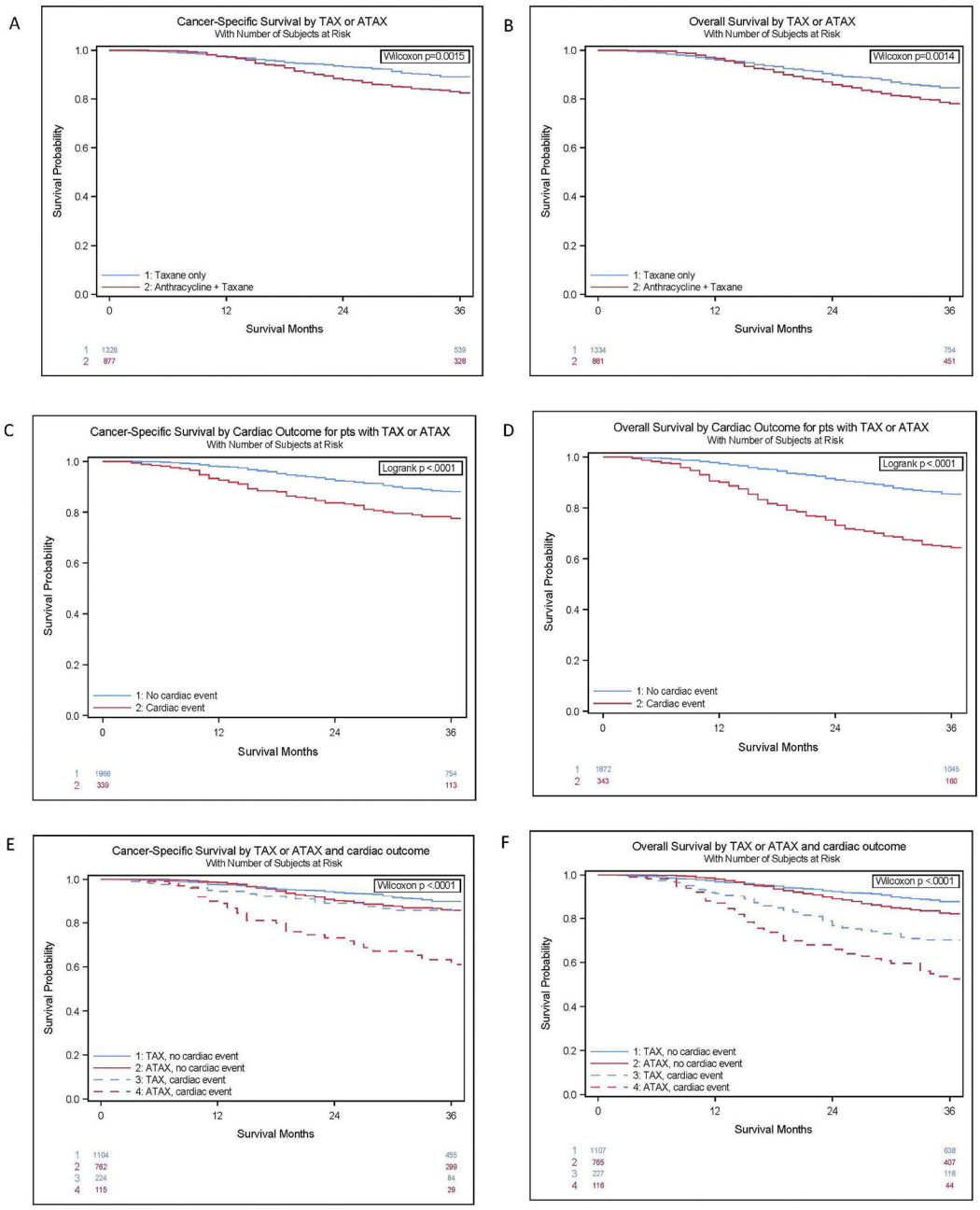

Fig. 2.
Kaplan Meier Survival Curves.

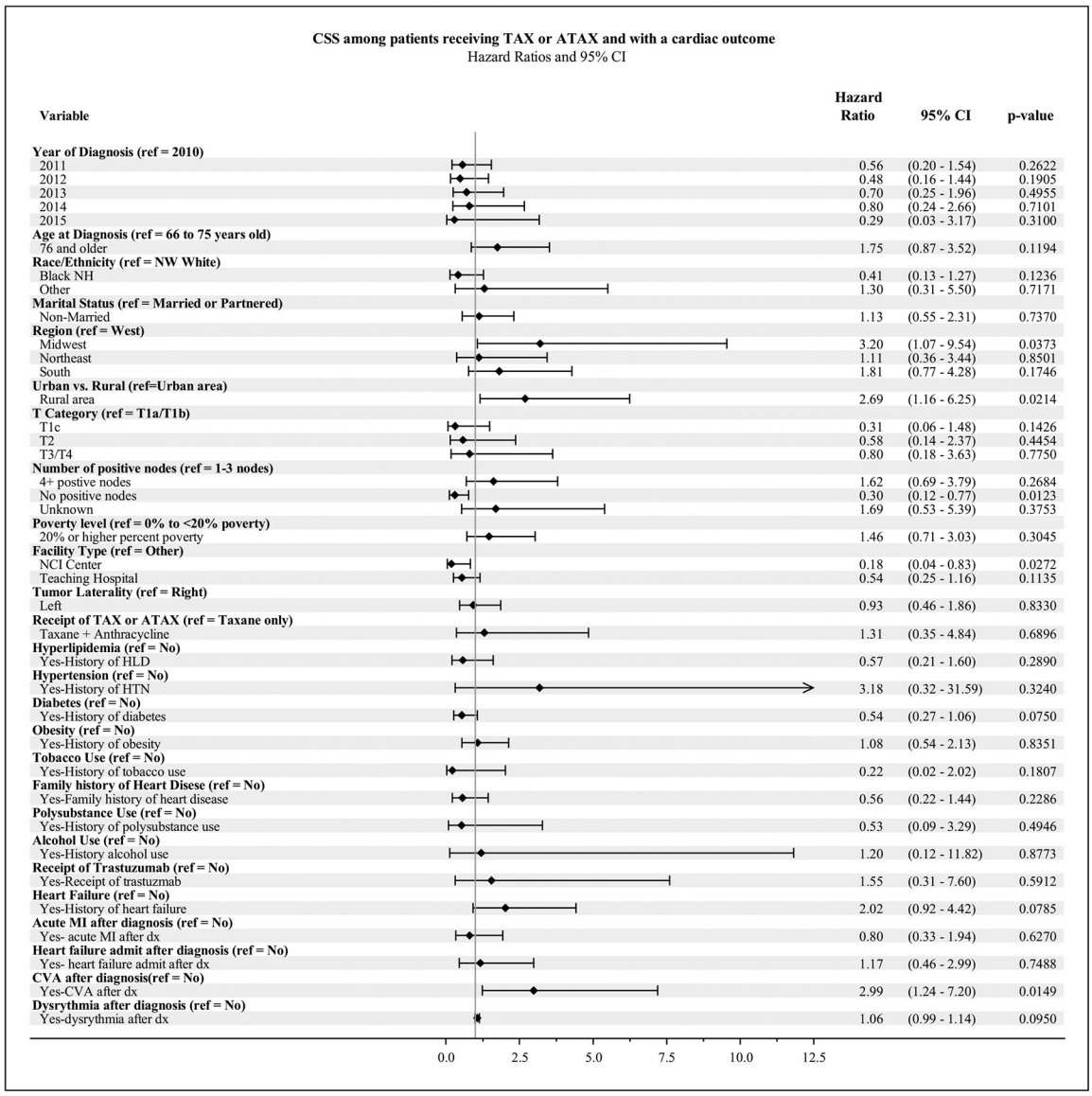

Fig. 3.

Forest Plot for multivariate analysis of Cancer-Specific Survival (CSS) among patients receiving TAX or ATAX who experienced a cardiac outcome.

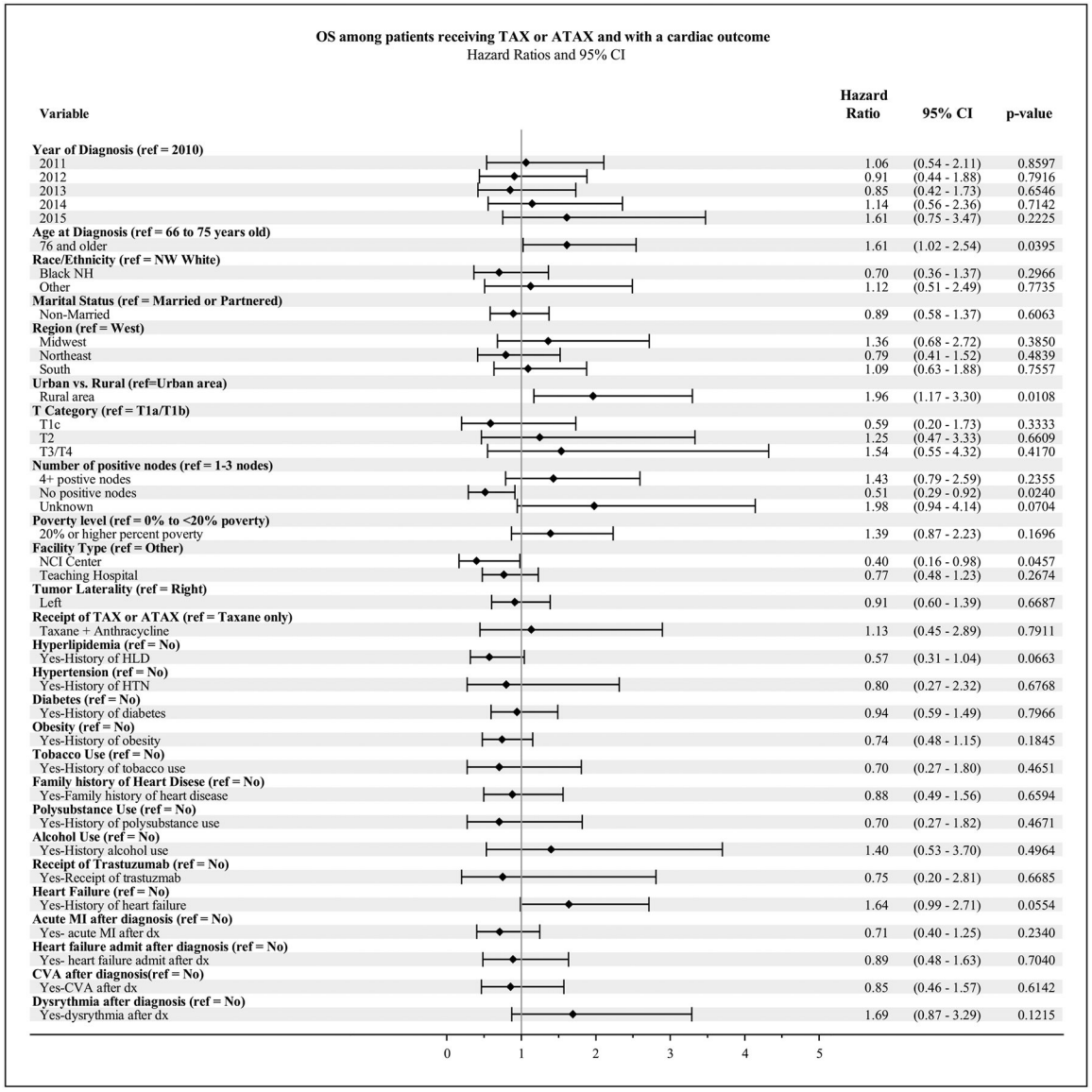

Fig. 4.

Forest Plot for multivariate analysis of Overall Survival (OS) among patients receiving TAX or ATAX who experienced a cardiac outcome.

Table 1

Descriptive characteristics and statistics, women diagnosed with TNBC by chemotherapy administration, SEER-Medicare 2010–2015.

Characteristic	Overall n (%)		TAX only n (%)		ATAX n (%)		p-value
All Patients	2215		1334		881		.
Year of Diagnosis							
2010	354	(16.0)	217	(16.3)	137	(15.6)	0.948
2011	367	(16.6)	222	(16.6)	145	(16.5)	.
2012	344	(15.5)	209	(15.7)	135	(15.3)	.
2013	347	(15.7)	206	(15.4)	141	(16.0)	.
2014	388	(17.5)	238	(17.8)	150	(17.0)	.
2015	415	(18.7)	242	(18.1)	173	(19.6)	.
Age Category							
66–75	1724	(77.8)	943	(70.7)	781	(88.6)	< **.001**
76 and older	491	(22.2)	391	(29.3)	100	(11.4)	.
Race/Ethnicity Category							
White NH	1685	(76.1)	1016	(76.2)	669	(75.9)	0.665
Black NH	300	(13.5)	175	(13.1)	125	(14.2)	.
Other	230	(10.4)	143	(10.7)	87	(9.9)	.
Marital Status Category							
Non-Married	1030	(46.5)	659	(49.4)	371	(42.1)	< **.001**
Married or Partnered	1185	(53.5)	675	(50.6)	510	(57.9)	.
Registry Region at Diagnosis							
Northeast	431	(19.5)	238	(17.8)	193	(21.9)	< **.001**
Midwest	287	(13.0)	152	(11.4)	135	(15.3)	.
South	574	(25.9)	340	(25.5)	234	(26.6)	.
West	923	(41.7)	604	(45.3)	319	(36.2)	.
Patient Urban/Rural Recode Category							
Urban Commuting Area	1955	(88.3)	1178	(88.3)	777	(88.2)	0.937
Non-Urban Commuting Area	260	(11.7)	156	(11.7)	104	(11.8)	.
DAJCC 7th Ed T Category							
T1a/T1b	247	(11.2)	189	(14.2)	58	(6.6)	< **.001**

Characteristic	Overall n (%)		TAX only n (%)		ATAX n (%)		p-value
T1c	723	(32.6)	497	(37.3)	226	(25.7)	.
T2	943	(42.6)	513	(38.5)	430	(48.8)	.
T3/T4	302	(13.6)	135	(10.1)	167	(19.0)	.
Number of positive nodes							
No nodes positive	1369	(61.8)	959	(71.9)	410	(46.5)	< **.001**
1–3 nodes positive	419	(18.9)	201	(15.1)	218	(24.7)	.
4 + nodes positive	243	(11.0)	97	(7.3)	146	(16.6)	.
Unknown	184	(11.1)	77	(5.8)	107	(12.1)	.
Charlson Comorbidity Index Category							
0	1343	(60.6)	756	(56.7)	587	(66.6)	< **.001**
1	493	(22.3)	310	(23.2)	183	(20.8)	.
2 or more	379	(17.1)	268	(20.1)	111	(12.6)	.
Census Poverty Level							
0% to <20% poverty	1758	(79.4)	1063	(79.7)	695	(78.9)	0.650
20% or higher poverty	457	(20.6)	271	(20.3)	186	(21.1)	.
Facilities Visited in First 6 months							
NCI Center	345	(15.6)	200	(15.0)	145	(16.5)	0.546
Teaching Hospital	1230	(55.5)	740	(55.5)	490	(55.6)	.
Other	640	(28.9)	394	(29.5)	246	(27.9)	.
Tumor Laterality							
Right	1098	(49.6)	671	(50.3)	427	(48.4)	0.399
Left	1117	(50.4)	663	(49.7)	454	(51.5)	
HLD							
No	382	(17.2)	218	(16.3)	164	(18.6)	0.166
Yes	1833	(82.8)	1116	(83.7)	717	(81.4)	.
HTN							
No	344	(15.5)	186	(13.9)	158	(17.9)	**0.011**
Yes	1871	(84.5)	1148	(86.1)	723	(82.1)	.
Diabetes							
No	1357	(61.3)	786	(58.9)	571	(64.8)	**0.005**
Yes	858	(38.7)	548	(41.1)	310	(35.2)	.

Characteristic	Overall n (%)		TAX only n (%)		ATAX n (%)		p-value
Obesity							
No	1637	(73.9)	981	(73.5)	656	(74.5)	0.628
Yes	578	(26.1)	353	(26.5)	225	(25.5)	.
Tobacco use							
No	1954	(88.2)	1179	(88.4)	775	(88.0)	0.768
Yes	261	(11.8)	155	(11.6)	106	(12.0)	.
Family History of Heart Disease							
No	1956	(88.3)	1185	(88.8)	771	(87.5)	0.345
Yes	259	(11.7)	149	(11.2)	110	(12.5)	.
Polysubstance use							
No	2171	(98.0)	1305	(97.8)	866	(98.3)	0.437
Yes	44	(2.0)	29	(2.2)	15	(1.7)	.
Alcohol use							
No	1954	(88.2)	1177	(88.2)	777	(88.2)	0.980
Yes	261	(11.8)	157	(11.8)	104	(11.8)	.
Receipt of Trastuzumab							
No	2151	(97.1)	1287	(96.5)	864	(98.1)	**0.028**
Yes	64	(2.9)	47	(3.5)	17	(1.9)	.
Personal history of HF							
No	2121	(95.8)	1262	(94.6)	859	(97.5)	< **.001**
Yes	94	(4.2)	72	(5.4)	22	(2.5)	.
Acute MI after dx							
No	2130	(96.2)	1284	(96.3)	846	(96.0)	0.788
Yes	85	(3.8)	50	(3.7)	35	(4.0)	.
HF admit after dx							
No	1987	(89.7)	1177	(88.2)	810	(91.9)	**0.005**
Yes	228	(10.3)	157	(11.8)	71	(8.1)	.
CVA after dx							
No	2138	(96.5)	1285	(96.3)	853	(96.8)	0.534
Yes	77	(3.5)	49	(3.7)	28	(3.2)	.
Dysrhythmia after dx							

Characteristic	Overall n (%)		TAX only n (%)		ATAX n (%)		p-value
No	2181	(98.5)	1311	(98.3)	870	(98.8)	0.373
Yes	34	(1.5)	23	(1.7)	11	(1.2)	.

Table 2

Logistic regression analysis estimating OR across variables to predict myocardial infarction, SEER-Medicare 2010–2015.

Predictors of acute MI			
Variable	**Odds Ratio**	**95% CI**	**p-value**
Year of Diagnosis			
2010 (ref)	.	.	.
2011	1.50	(0.76–2.98)	0.244
2012	0.82	(0.37–1.81)	0.627
2013	1.02	(0.48–2.14)	0.965
2014	0.58	(0.25–1.31)	0.188
2015	0.65	(0.28–1.48)	0.300
Age at Diagnosis			
66–75 (ref)	.	.	.
76 and older	1.36	(0.79–2.34)	0.263
Race/Ethnicity			
White NH (ref)	.	.	.
Black NH	1.32	(0.71–2.45)	0.387
Other	0.80	(0.34–1.89)	0.617
Marital Status			
Married or Partnered (ref)	.	.	.
Non-Married	1.28	(0.80–2.04)	0.309
Region			
West (ref)	.	.	.
Midwest	1.16	(0.57–2.37)	0.689
Northeast	1.17	(0.63–2.16)	0.620
South vs West	0.62	(0.32–1.21)	0.160
Urban/Rural Category			
Urban Area (ref)	.	.	.
Rural Area	0.68	(0.30–1.56)	0.362
DAJCC7 T Category			
T1a/T1b (ref)	.	.	.
T1c	0.60	(0.26–1.38)	0.228
T2	0.95	(0.44–2.08)	0.901
T3/T4	1.43	(0.59–3.48)	0.428
Number of positive nodes			
1–3 nodes positive (ref)	.	.	.
4 + nodes positive	1.87	(0.80–4.35)	0.150
No nodes positive	1.53	(0.77–3.06)	0.229
Unknown	2.71	(1.15–6.39)	0.023
Census-Level Poverty			
0–20% poverty (ref)	.	.	.

Predictors of acute MI			
Variable	**Odds Ratio**	**95% CI**	**p-value**
20% or higher poverty	1.22	(0.69–2.16)	0.487
Facility Type			
Other (ref)	.	.	.
NCI Center	0.88	(0.42–1.84)	0.741
Teaching Hospital	0.90	(0.52–1.54)	0.692
Tumor Laterality			
Right (ref)			
Left	0.91	(0.58–1.42)	0.685
Chemo			
Taxane only (ref)	.	.	.
Taxane + Anthracycline	1.03	(0.62–1.70)	0.909
HLD			
No (ref)	.	.	.
Yes	1.80	(0.82–3.95)	0.143
Diabetes			
No (ref)	.	.	.
Yes	2.10	(1.29–3.43)	0.003
Obesity			
No (ref)	.	.	.
Yes	1.34	(0.83–2.19)	0.236
Tobacco Use			
No (ref)	.	.	.
Yes	1.56	(0.45–5.37)	0.480
Family history of heart disease			
No (ref)	.	.	.
Yes	1.22	(0.65–2.28)	0.537
Alcohol Use			
No (ref)	.	.	.
Yes	1.60	(0.46–5.55)	0.456
Receipt of Trastuzumab			
No (ref)	.	.	.
Yes	0.67	(0.15–2.93)	0.597

Table 3

Logistic regression analysis estimating OR across variables to predict heart failure, SEER-Medicare 2010–2015.

Predictors of heart failure			
Variable	**Odds Ratio**	**95% CI**	**p-value**
Year of Diagnosis			
2010 (ref)	.	.	.
2011	1.14	(0.68–1.90)	0.630
2012	1.33	(0.80–2.21)	0.272
2013	1.34	(0.80–2.23)	0.264
2014	0.94	(0.56–1.59)	0.824
2015	1.27	(0.77–2.10)	0.355
Age at Diagnosis			
66–75 (ref)	.	.	.
76 and older	1.60	(1.14–2.24)	0.007
Race/Ethnicity			
White NH (ref)	.	.	.
Black NH	0.73	(0.47–1.14)	0.162
Other	1.15	(0.70–1.88)	0.581
Marital Status			
Married or Partnered (ref)	.	.	.
Non-Married	1.39	(1.03–1.88)	0.032
Region			
West (ref)	.	.	.
Midwest	1.26	(0.79–2.01)	0.339
Northeast	1.12	(0.73–1.71)	0.611
South vs West	0.90	(0.60–1.36)	0.615
Urban/Rural Category			
Urban Area (ref)	.	.	.
Rural Area	1.73	(1.15–2.61)	0.008
DAJCC7 T Category			
T1a/T1b (ref)	.	.	.
T1c	1.22	(0.66–2.23)	0.530
T2	1.69	(0.94–3.05)	0.082
T3/T4	2.14	(1.10–4.14)	0.025
Number of positive nodes			
1–3 nodes positive (ref)	.	.	.
4 + nodes positive	1.37	(0.82–2.30)	0.226
No nodes positive	0.97	(0.65–1.45)	0.883
Unknown	1.80	(1.04–3.14)	0.037
Census-Level Poverty			
0–20% poverty (ref)	.	.	.

Predictors of heart failure			
Variable	**Odds Ratio**	**95% CI**	**p-value**
20% or higher poverty	1.59	(1.13–2.26)	0.009
Facility Type			
Other (ref)	.	.	.
NCI Center	0.95	(0.58–1.57)	0.841
Teaching Hospital	1.29	(0.91–1.84)	0.153
Tumor Laterality			
Right (ref)			
Left	1.02	(0.76–1.36)	0.922
Chemo			
Taxane only (ref)	.	.	.
Taxane + Anthracycline	0.63	(0.45–0.88)	0.006
HLD			
No (ref)	.	.	.
Yes	1.71	(1.05–2.79)	0.032
Diabetes			
No (ref)	.	.	.
Yes	2.39	(1.75–3.26)	< 0.001
Obesity			
No (ref)	.	.	.
Yes	1.59	(1.17–2.18)	0.004
Tobacco Use			
No (ref)	.	.	.
Yes	1.54	(0.69–3.43)	0.288
Family history of heart disease			
No (ref)	.	.	.
Yes	1.36	(0.91–2.05)	0.134
Alcohol Use			
No (ref)	.	.	.
Yes	1.17	(0.52–2.65)	0.702
Receipt of Trastuzumab			
No (ref)	.	.	.
Yes	0.70	(0.28–1.71)	0.431

Table 4

Logistic regression analysis estimating OR across variables to predict potentially fatal arrhythmia, SEER-Medicare 2010–2015.

Predictors of potentially fatal arrhythmia			
Variable	**Odds Ratio**	**95% CI**	**p-value**
Year of Diagnosis			
2010 (ref)	.	.	.
2011	0.72	(0.23–2.23)	0.570
2012	0.96	(0.32–2.88)	0.943
2013	0.69	(0.21–2.25)	0.540
2014	0.47	(0.13–1.66)	0.241
2015	0.59	(0.18–1.93)	0.380
Age at Diagnosis			
66–75 (ref)	.	.	.
76 and older	0.83	(0.34–2.00)	0.671
Race/Ethnicity			
White NH (ref)	.	.	.
Black NH	0.75	(0.26–2.16)	0.591
Other	0.62	(0.14–2.84)	0.542
Marital Status			
Married or Partnered (ref)	.	.	.
Non-Married	1.05	(0.51–2.16)	0.903
Region			
West (ref)	.	.	.
Midwest	0.83	(0.24–2.87)	0.769
Northeast	1.80	(0.69–4.66)	0.228
South vs West	0.95	(0.35–2.54)	0.915
Urban/Rural Category			
Urban Area (ref)	.	.	.
Rural Area	1.02	(0.33–3.15)	0.973
DAJCC7 T Category			
T1a/T1b (ref)	.	.	.
T1c	0.86	(0.22–3.45)	0.833
T2	1.54	(0.41–5.75)	0.519
T3/T4	3.19	(0.76–13.38)	0.114
Number of positive nodes			
1–3 nodes positive (ref)	.	.	.
4 + nodes positive	2.36	(0.64–8.77)	0.198
No nodes positive	1.65	(0.54–5.05)	0.383
Unknown	2.83	(0.70–11.44)	0.144
Census-Level Poverty			
0–20% poverty (ref)	.	.	.

Predictors of potentially fatal arrhythmia			
Variable	**Odds Ratio**	**95% CI**	**p-value**
20% or higher poverty	1.98	(0.85–4.62)	0.113
Facility Type			
Other (ref)	.	.	.
NCI Center	1.42	(0.42–4.78)	0.569
Teaching Hospital	1.52	(0.61–3.80)	0.371
Tumor Laterality			
Right (ref)			
Left	1.52	(0.75–3.09)	0.248
Chemo			
Taxane only (ref)	.	.	.
Taxane + Anthracycline	0.52	(0.23–1.17)	0.116
HLD			
No (ref)	.	.	.
Yes	1.24	(0.45–3.45)	0.679
Diabetes			
No (ref)	.	.	.
Yes	0.70	(0.32–1.50)	0.355
Obesity			
No (ref)	.	.	.
Yes	1.82	(0.86–3.86)	0.117
Tobacco Use			
No (ref)	.	.	.
Yes	2.40	(0.39–14.67)	0.345
Family history of heart disease			
No (ref)	.	.	.
Yes	2.47	(1.08–5.67)	0.032
Alcohol Use			
No (ref)	.	.	.
Yes	0.42	(0.06–3.03)	0.392
Receipt of Trastuzumab			
No (ref)	.	.	.
Yes	0.77	(0.10–6.03)	0.392

Table 5

Logistic regression analysis estimating OR across variables to predict CVA, SEER-Medicare 2010–2015.

Predictors of CVA			
Variable	**Odds Ratio**	**95% CI**	**p-value**
Year of Diagnosis			
2010 (ref)	.	.	.
2011	1.07	(0.47–2.44)	0.866
2012	1.01	(0.43–2.37)	0.986
2013	1.58	(0.72–3.46)	0.257
2014	1.00	(0.43–2.30)	0.996
2015	1.19	(0.52–2.71)	0.680
Age at Diagnosis			
66–75 (ref)	.	.	.
76 and older	1.14	(0.65–1.99)	0.641
Race/Ethnicity			
White NH (ref)	.	.	.
Black NH	1.36	(0.70–2.62)	0.365
Other	< 0.001	(<0.001–>999.999)	0.968
Marital Status			
Married or Partnered (ref)	.	.	.
Non-Married	1.07	(0.66–1.75)	0.783
Region			
West (ref)	.	.	.
Midwest	1.23	(0.56–2.69)	0.614
Northeast	1.76	(0.93–3.32)	0.083
South vs West	0.91	(0.48–1.75)	0.779
Urban/Rural Category			
Urban Area (ref)	.	.	.
Rural Area	1.17	(0.56–-.43)	0.675
DAJCC7 T Category			
T1a/T1b (ref)	.	.	.
T1c	0.73	(0.29–1.81)	0.498
T2	1.16	(0.50–2.73)	0.726
T3/T4	1.08	(0.40–2.93)	0.881
Number of positive nodes			
1–3 nodes positive (ref)	.	.	.
4 + nodes positive	1.52	(0.75–3.09)	0.246
No nodes positive	0.50	(0.27–0.92)	0.026
Unknown	0.74	(0.29–1.87)	0.521
Census-Level Poverty			
0–20% poverty (ref)	.	.	.
20% or higher poverty	0.82	(0.43–1.57)	0.551

Predictors of CVA			
Variable	**Odds Ratio**	**95% CI**	**p-value**
Facility Type			
Other (ref)	.	.	.
NCI Center	0.64	(0.28–1.44)	0.277
Teaching Hospital	0.79	(0.46–1.38)	0.413
Tumor Laterality			
Right (ref)			
Left	1.69	(1.04–2.74)	0.033
Chemo			
Taxane only (ref)	.	.	.
Taxane + Anthracycline	0.71	(0.42–1.20)	0.201
HLD			
No (ref)	.	.	.
Yes	1.63	(0.75–3.55)	0.219
Diabetes			
No (ref)	.	.	.
Yes	1.71	(1.03–2.83)	0.038
Obesity			
No (ref)	.	.	.
Yes	0.98	(0.57–1.66)	0.925
Tobacco Use			
No (ref)	.	.	.
Yes	0.87	(0.25–3.08)	0.833
Family history of heart disease			
No (ref)	.	.	.
Yes	1.30	(0.69–2.48)	0.417
Alcohol Use			
No (ref)	.	.	.
Yes	2.27	(0.66–7.85)	0.194
Receipt of Trastuzumab			
No (ref)	.	.	.
Yes	1.64	(0.48–5.60)	0.430