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Bisphosphonate use and incident cardiovascular events among older breast cancer survivors

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ABSTRACT

Background: Cardiovascular disease (CVD) is a leading cause of mortality in early-stage breast cancer survivors. Recent studies suggest that bisphosphonates may decrease CVD risk in older patients.
Objective: This study sought to assess whether bisphosphonate use is associated with lower rates of incident CVD events among early-stage breast cancer survivors.
Methods: Longitudinal, population-based cohort study was conducted by using data from the Surveillance, Epidemiology and End Results registry linked to Medicare claims. We identified women >65 years with no history of CVD who were diagnosed with stage 0-III primary breast cancer between 2007 and 2010. Our primary outcome was a composite of incident angina pectoris, myocardial infarction, atrial fibrillation/flutter, heart failure, or stroke within 36 months of cancer diagnosis. Bisphosphonate use was defined as the presence of ≥1 pharmacy claim from 6 months prior to cancer diagnosis to the incident CVD event. We used propensity scores to create a matched group of breast cancer survivors without bisphosphonate exposure to compare rates of incident CVD events.
Results: A total of 2178 breast cancer survivors had ≥1 bisphosphonate prescription; the average length of bisphosphonate use was 15 months. Analyses of the matched data showed that 13.0% of bisphosphonate users and 23.4% of non-bisphosphonate users experienced an incident CVD event ($p < 0.0001$) after breast cancer diagnosis. Bisphosphonate use was significantly associated with fewer incident CVD events (hazard ratio: 0.51, 95% confidence interval: 0.44 to 0.59).
Conclusions: Bisphosphonate use is associated with lower incidence of CVD events among older early-stage breast cancer survivors. Future studies should prospectively evaluate whether bisphosphonate use can decrease CVD incidence.

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1. Introduction

More than half of breast cancer patients in the United States are diagnosed at >60 years of age, and older cancer survivors have an increased risk of developing cardiovascular disease (CVD) [1]. Moreover, CVD is one of the major causes of competing mortality in women with early-stage breast cancer [2]. Hooning et al. found breast cancer patients had a 30% increased incidence of CVD events compared to women from the general population. Moreover, some of this increased risk is a consequence of cardiotoxicity due to some anticancer treatments [3].

Bisphosphonates inhibit bone resorption and are broadly used in clinical practice for the treatment and prevention of skeletal conditions characterized by increasing osteoclast-mediated bone remodeling [4,5]. Adjuvant use of bisphosphonates has been shown to reduce rates of cancer recurrence and death in patients with early-stage breast cancer [6]. Recent studies also suggest that bisphosphonates may modulate CVD risk in older patients; however results have been mixed [7,8]. Wolfe at al. reported a substantial risk reduction in myocardial infarction (MI) among patients with rheumatoid arthritis who were treated with bisphosphonates [9]. An analysis of participants in a retrospective cohort study

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investigating the safety profile of risedronate found a tendency toward a lower cardiovascular mortality, driven mainly by a reduction in stroke mortality [10]. Conversely, concerns have been raised regarding associations between bisphosphonate use and increased rates of atrial fibrillation [11,12]. However, it is not known whether bisphosphonate use impacts CVD risk among breast cancer survivors.

In this study, we used population-based cancer data to evaluate the association between bisphosphonate use and incident CVD events after cancer diagnosis in older women diagnosed with primary breast cancer.

2. Methods

2.1. Data sources

We used the Surveillance, Epidemiology and End Results (SEER) registry linked to Medicare data. This database combines two large population-based data sources that provide detailed information about Medicare beneficiaries with cancer. We excluded individuals in health care maintenance organizations or those without Part B Medicare insurance due to lack of complete claims data and those without Part D coverage for whom we could not ascertain outpatient medication use.

2.2. Study participants

We identified women >65 years who were diagnosed primary early-stage (0-III) breast cancer between January 1, 2007, and December 31, 2010. We excluded women who had CVD prior to breast cancer diagnosis, including those who had undergone heart transplant surgery, cardiac valve surgery, coronary artery bypass grafting (CABG), patients with uncorrected atrial or ventricular septal defects (congenital heart disease), or anyone with a history of angina, atrial fibrillation/flutter, heart failure, myocarditis, myocardial infarction or stroke. We also excluded patients with end-stage renal disease as these patients have a significantly higher risk for CVD or those who were diagnosed with breast cancer on autopsy or at death.

We extracted variables about sociodemographic characteristics (including age, race/ethnicity, marital status, income quartile), comorbidities, medication prescriptions, chemotherapy, radiotherapy and surgical treatment for breast cancer, and survival. We used the Deyo adaptation of Charlson's index to assess the burden of comorbidities [13,14]. Bisphosphonates included were alendronate, pamidronate, ibandronate, zoledronic acid, risedronate, and etidronate. Bisphosphonate use was defined as having at least one Medicare part D claim in the period from 6 month prior to breast cancer diagnosis to the first CVD event. CVD and other comorbidities were identified by searching the hospital discharge summary and outpatient claims for diagnostic (International Classification of Diseases, Ninth Revision [ICD-9]) codes. Specific comorbidities that were abstracted included arterial hypertension (ICD-9 codes: 401.0–402.0), type 2 diabetes mellitus (ICD-9 codes: 250.0–250.9), hyperlipidemia (ICD-9 codes: 272.4, 272.2, 272.0), hyperthyroidism (ICD-9 codes: 242.0–242.40, 242.80–242.90), and osteoporosis (ICD-9 codes: 733.0, 733.03, 733.09) Hypertension, diabetes, hyperlipidemia and hyperthyroidism were included in the adjusted analyses as these are known risk factors for CVD. The Health Care Procedure Coding System (HCPCS) was used to identify receipt of chemotherapy, radiation therapy, and surgical treatment any time from cancer diagnosis to 36 months after diagnosis.

2.3. Study outcome

We used a composite of incident CVD events as the study outcome. Incident CVD events included angina pectoris (ICD-9 codes: 411.1, 411.89, 413.0, 413.1, 413.9, 414.0, 414.01, 429.2), myocardial infarction (ICD-9 codes: 410.2–410.9), atrial fibrillation/flutter (ICD-9 codes: 427.0, 427.2, 427.3, 427.31, 427.32), heart failure (ICD-9 codes: 428.0–428.4), and stroke (ICD-9 codes: V1254, 434.91, 430, 433, 434.0, 434.1, 434.9, 435, 435.0, 435.8, 434.9, 437, 437.1, 438). We assessed for incident CVD events for three years following date of breast cancer diagnosis.

2.4. Statistical analysis

Student's t-test, Wilcoxon signed-rank test, and chi-square were used as appropriate to compare baseline characteristics between those who were users vs. nonusers of bisphosphonates. We used propensity score methods to control for potential allocation bias since differences in patient characteristics and comorbidities may have influenced bisphosphonate prescribing. The propensity score represents the probability that a patient will receive a bisphosphonate based on their known baseline characteristics. We calculated propensity scores using a logistic model that included patients' sociodemographics characteristics, income quartiles, diagnosis of osteoporosis, Charlson comorbidity score, concurrent use of cardiovascular medications (e.g., angiotensin converting enzyme inhibitor (ACE-i), aldosterone antagonist, angiotensin receptor blocker (ARB), beta-blocker and statins), cancer stage, and anticancer treatment (chemotherapy, surgery and radiotherapy). We used a greedy 1:1 matching algorithm to match bisphosphonate users and non-users by their propensity score. Nonusers were selected from patients with primary breast cancer who had not received any bisphosphonate therapy between January 1, 2007 and December 31, 2013. We used McNemar and matched-paired *t*-test to evaluate whether covariates were balanced across bisphosphonate users vs. non-users after propensity matching. Unadjusted Kaplan-Meier curves for incident CVD events were plotted for matched patients treated with or without bisphosphonates and compared using the log-rank test.

The association between bisphosphonate use and incident CVD events was evaluated using a competing risks Cox proportional hazard regression model that censored for death from any cause. The results are presented as hazard ratios (HR) with corresponding two-sided 95% confidence intervals (CI). All data analyses were conducted using SAS software 9.4 (Cary, NC). Our study was deemed exempt by the Institutional Review Board at Icahn School of Medicine at Mount Sinai.

3. Results

3.1. Participants

A total of 48,182 women with stage 0-III primary breast cancer diagnosed between 2007 and 2010 were identified from the SEER-Medicare database. Of these, 10,115 women did not have a history of CVD prior to breast cancer diagnosis, 2314 (22.8%) patients were bisphosphonate users and 7801 (77.1%) had never used bisphosphonate. After propensity score matching, 2178 bisphosphonate non-users were matched with 2178 bisphosphonate users. The flowchart for our cohort selection is presented in Fig. 1. Bisphosphonate-exposed women had an average use of 15 months. The median age (interquartile range [IQR]) of the patients was 72 (68–78) years, in both groups of patients. After propensity score matching, there were no significant differences between the two groups by race, breast cancer stage at diagnosis, comorbidities,

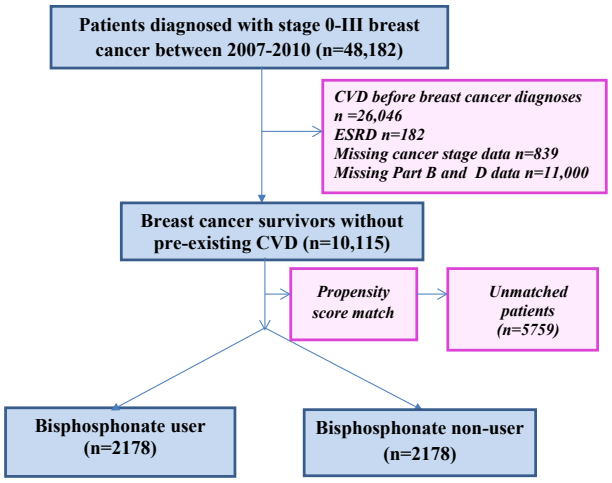

Fig. 1. Cohort selection.

anti-cancer treatment or concurrent medications (Table 1).

3.2. Relationship of bisphosphonate use with cardiovascular disease incidence

Event-free survival analyses found that overall, 87.0% of bisphosphonate users were free from any CVD events in the 36 months after cancer diagnosis, compared with 76.6% of those who did not use bisphosphonates (Fig. 2). The incidence of angina, atrial fibrillation, heart failure, myocardial infarction and stroke 36 months after breast cancer diagnosis among bisphosphonate users was 6.3%, 4.1%, 4.5%, 1.1% and 3.4%, respectively, compared to an incidence of 11.8%, 6.2%, 6.9%, 3.1% and 6.5%, respectively, among

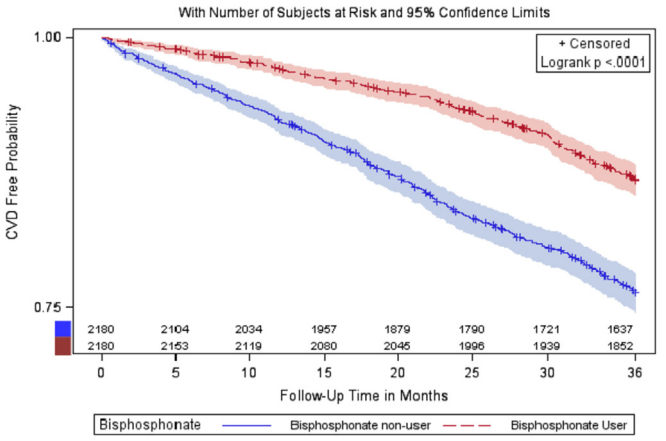

Fig. 2. Kaplan-Meier plot for incident cardiovascular disease for bisphosphonate users and matched non-users.

Table 1
Baseline characteristics of stage 0–3 breast cancer patients in the SEER-Medicare database (2007–2010) according to bisphosphonate use.

	No Bisphosphonate (n = 2178)	Bisphosphonate (n = 2178)	P-value
Age, median (IQR)	72 (68–78)	72 (68–78)	0.06
Race/Ethnicity, N (%)			
White	1995 (91.6)	1988 (91.2)	
Black	65 (2.9)	71 (3.3)	0.75
Asian	99 (4.6)	101 (4.6)	
Others	19 (0.8)	18 (0.8)	
Income Quartiles N (%)			
First quartile	561 (25.8)	547 (25.1)	
Second quartile	551 (25.3)	557 (25.6)	0.71
Third quartile	492 (22.6)	495 (22.7)	
Fourth quartile	574 (26.4)	579 (26.6)	
Marital Status N (%)			
Single	171 (7.9)	208 (9.6)	
Married	1103 (50.6)	1047 (48.1)	0.51
Separated or widowed	815 (37.4)	834 (38.3)	
Unknown	89 (4.1)	89 (4.1)	
Comorbidities, N (%)			
Diabetes Mellitus	633 (29.0)	562 (25.8)	0.01
Hyperlipidemia	1797 (82.5)	1754 (80.5)	0.08
Hypertension	1766 (80.1)	1742 (79.9)	0.48
Hyperthyroidism	109 (5.0)	103 (4.7)	0.67
Osteoporosis	1754 (80.5)	1754 (80.5)	0.99
Concurrent Medications, N (%)			
ACE-i	452 (20.75)	475 (21.8)	0.35
Aldosterone Antagonist	43 (1.9)	36 (1.6)	0.36
ARB	233 (10.7)	236 (10.8)	0.88
Beta-blocker	323 (14.8)	309 (14.2)	0.54
Statins	1025 (47.1)	1015 (46.6)	0.66
Breast Cancer Stage, N (%)			
0	378 (17.4)	383 (17.6)	
1	1123 (51.6)	1114 (51.2)	
2	540 (24.8)	544 (25.0)	0.98
3	137 (6.3)	137 (6.3)	
0	378 (17.4)	383 (17.6)	
Anticancer Treatment, N (%)			
Chemotherapy	448 (20.6)	437 (20.1)	0.67
Radiotherapy	1371 (62.9)	1390 (63.8)	0.55
Surgery	2135 (98.0)	2133 (97.9)	0.72

IQR: interquartile range, SD: standard deviation, ACE-i: angiotensin converting enzyme inhibitor, ARB: angiotensin receptor blocker.

bisphosphonate non-users.

Unadjusted analyses showed that bisphosphonate use was associated with a significant reduction in the risk of incident CVD events (hazard ratio [HR]: 0.51, 95% confidence interval [CI]: 0.44–0.59; Table 2). The HR for each individual CVD event also showed a significant decrease in incidence among bisphosphonates users (angina - HR: 0.50, 95% CI: 0.41–0.62; atrial fibrillation - HR: 0.61, 95% CI: 0.47–0.78; heart failure - HR: 0.61, 95% CI: 0.47–0.78; myocardial infarction - HR: 0.35, 95% CI: 0.22–0.57; and stroke - HR: 0.53, 95% CI: 0.40–0.71). The association remained unchanged in multivariable COX model with DM.

4. Discussion

Previous studies have suggested that bisphosphonates may be cardioprotective in older adults and decrease risk for myocardial infarction [15]; however, data have been inconclusive [16,17]. Using population-based data, we found that bisphosphonate use was associated with significantly lower incident CVD events within 36 months of cancer diagnosis among older women with stage 0-III primary breast cancer.

The overall reduction in risk of incident CVD events with bisphosphonate use in our study is comparable to other observational studies. Among patients with rheumatoid arthritis, the adjusted risk of myocardial infarction was reduced by 28% (HR: 0.72, 95% CI: 0.54–0.96) with bisphosphonate use [9]. Similarly, in a retrospective cohort study of 7981 participants in a risedronate clinical trial, investigators reported a trend toward lower CVD mortality in those taking 2.5 mg of risedronate compared to the placebo group (Relative risk: 0.69, 95% CI: 0.49–0.99). The decrease in CVD mortality observed in the study was mostly due to the effect on the risk of stroke [10]. In another study, those using bisphosphonates after vertebral or hip fracture had a lower likelihood of suffering from stroke during a 2-year follow-up period (HR: 0.79, 95% CI: 0.66–0.99) [18]. Sing et al. evaluated associations between alendronate use and CV events among patients with hip fracture. The alendronate group was linked with significantly lower risk of 1-year cardiovascular mortality (HR 0.33; 95% CI, 0.17 to 0.65) and incident myocardial infarction (HR 0.55; 95% CI, 0.34 to 0.89). At 5 years and 10 years, alendronate use was associated with marginally significant reduction in risk of stroke (HR at 5 years: 0.82; 95% CI, 0.67 to 1.00; $p = 0.049$; HR at 10 years: 0.83; 95% CI, 0.69 to 1.01; $p = 0.065$) [19]. Our data is consistent with the results of these studies and shows a homogenous effect across CVD events included in the composite outcome.

The mechanism by which bisphosphonates may reduce incident CVD may by through their effect on cholesterol. Bisphosphonates affect cholesterol synthesis through the mevalonate pathway, a well-known pathway that is the target of cholesterol lowering drugs. Statins interfere the same pathway by inhibiting methylglutaryl-CoA reductase [20,21]. Nitrogen-containing bisphosphonates (NCBPs) inhibit farnesyl-pyrophosphate synthesis and thereby disrupt the mevalonate pathway. Consequently, NCBPs and statins may share similar pharmacological effects. Similar to statins, bisphosphonates have been shown to decrease low-density lipoprotein (LDL) cholesterol levels by up to 5% and can raise high-density lipoprotein (HDL) cholesterol by 10–18% [22,23].

Experimental data have also shown that bisphosphonates might limit vascular and valvular calcifications [24,25]. Several animal studies have found that etidronate, pamidronate and ibadronate prevent aortic calcification in uremic rats [26,27]. The Multi-Ethnic Study of Atherosclerosis (MESA) study found that NCBPs reduce cardiovascular calcification in older women, but more prevalent vascular calcification was observed in younger participants [28]. A similar effect was found among patients on long-term hemodialysis [29].

Furthermore, bisphosphonates may play a pivotal role in cardioprotection by modulating vascular smooth muscle cell (VSMC) proliferation and migration. A physiologic mechanism that may link osteoporosis and CVD involves monocyte-macrophage differentiation and function, so that modification of vascular calcification and modulation of serum cytokine levels may have a beneficial effect on both diseases [30–33]. Wu at al. showed that high doses of zoledronate suppress VSMC proliferation after 48 h in rat models [34]. It is well known that proliferation and migration of VSMCs from the media to the intima determine the development of intimal hyperplasia and atherosclerosis. Therefore, an inhibitory effect of bisphosphonates on this pathway could contribute to lowering CVD risk and might be considered as a potential target for future research.

Previous studies have also shown an immunomodulatory effect of amino-bisphosphonates (N-BP) on circulating gamma-delta ($\gamma\delta$) T cells. Increase in circulating $\gamma\delta$ T cells is linked to the acute-phase response (APR) and the release of proinflammatory cytokines such as interferon gamma (IFN-γ) and tumor necrosis factor alpha (TNF-α) [35]. The lower incidence of APR in patients previously exposed to N-BPs could be potentially explained by N-BP association with a decrease in circulating $\gamma\delta$ T cells [36,37], and this decrease in inflammation may contribute to lower CVD risk.

Several strengths and limitations of this study should be noted. As this was an observational study and patients were not randomly assigned to bisphosphonates, there may be unmeasured confounding for which matching was not able to control. Use of bisphosphonates may reflect more comprehensive health care or increased health awareness, factors that may also be associated with lower risk of CVD. To address this limitation, we adjusted our analyses for potential confounders such as sociodemographics, comorbidities, anti-cancer treatment and other concurrent medications to create a comparison group that would have had similar likelihoods of receiving bisphosphonates. There are some differences in bisphosphonate dosing (even among the same bisphosphonates) when they are used for cancer indications compared with osteoporosis indications, and we were not able accurately adjust for bisphosphonates dose. Furthermore, some supplements such as vitamin D and calcium could have had a potential influence on the association of bisphosphonate use with incident CVD events but we were unable to adjust for them since they are mostly sold over-the-counter and thus, not identifiable by pharmacy claims. Medication use was also ascertained by pharmacy claims, and therefore we have no information on adherence to therapy. Despite this, pharmacy claims data have been shown to have high concordance with medication adherence [38]. Furthermore, lack of adherence would have biased our results towards the null. Our study was also limited to patients >65 years of age and consequently we were unable to assess the effect of bisphosphonates in younger breast cancer survivors, although most users of bisphosphonates are older women. Strengths of our study are the

Table 2
Comparison of incident CVD events among breast cancer survivors treated with and without bisphosphonates.

Outcome	HR	95% CI
Any CVD	0.51	0.43 0.59
Angina Pectoris	0.50	0.41 0.62
Atrial Fibrillation	0.64	0.50 0.83
Heart Failure	0.60	0.47 0.78
Myocardial Infarction	0.32	0.20 0.52
Stroke	0.49	0.37 0.64

CVD: cardiovascular disease, CI: confidence interval HR: hazard ratio.

large sample size and use of the SEER-Medicare dataset which is representative of the breast cancer population in the United States.

5. Conclusions

In summary, our study provides evidence that bisphosphonate use is associated with lower incident CVD in older, early-stage breast cancer survivors. Given that CVD is the primary cause of death among older early-stage breast cancer survivors, understanding factors that are associated with a reduction in incident CVD may have a substantial impact on decreasing overall morbidity and mortality in this group of patients. Further prospective studies evaluating the use of bisphosphonates can help determine if bisphosphonates can reduce CVD incidence and overall mortality in older breast cancer survivors and may better elucidate CVD-specific mechanisms of action for bisphosphonates.

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