Comparing the effects of various β-blockers on cardiovascular mortality in breast cancer patients

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Abstract

Background Cardiovascular (CV) disease is a leading cause of death in breast cancer (BC) patients due to the increased age and treatments. While individual β-blockers have been investigated to manage CV complications, various β-blockers have not been compared for their effects on CV death in this population. We aimed to compare CV mortality in older BC patients taking one of the commonly used β-blockers.

Methods This retrospective cohort study was conducted using the Surveillance, Epidemiology and End Results (SEER) - Medicare data (2010–2015). Patients of age 66 years or older at BC diagnosis receiving metoprolol, atenolol, or carvedilol monotherapy were included. The competing risk regression model was used to determine the risk of CV mortality in the three β-blocker groups. The multivariable model was adjusted for demographic and clinical covariates. The adjusted hazard ratio (HR) and 95% confidence intervals (CI) were reported for the risk of CV mortality.

Results The study cohort included 6,540 patients of which 55% were metoprolol users, 30% were atenolol users, and 15% were carvedilol users. Metoprolol was associated with a 37% reduced risk of CV mortality ($P=0.03$) compared to carvedilol after adjusting for the covariates (HR = 0.63; 95% CI 0.41–0.96). No significant difference in the risk of CV mortality between atenolol and carvedilol users was observed (HR = 0.74; 95% CI 0.44–1.22).

Conclusions Our findings suggest that metoprolol is associated with a reduced risk of CV mortality in BC patients. Future studies are needed to confirm these findings and understand the mechanism of action.

Keywords Cardiovascular mortality, Breast cancer, β-blockers, Metoprolol, Atenolol, Carvedilol, Heart failure

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Background

Cardiovascular (CV) mortality poses a major threat in survival of patients with breast cancer (BC) even though cancer-specific survival has improved since 1990 due to enhanced screening and effective therapies [1–4]. CV diseases account for up to 1.9 times higher risk of death in BC patients than the general population [1]. The risk for CV mortality in BC is higher with increasing age at diagnosis, with women who are 65 years of age or older being the most vulnerable [3–7]. The increased risk of CV mortality in long-term BC survivors stems from cardiotoxic chemotherapies, radiotherapy, and immunotherapies [1, 5, 8–11]. Cytotoxic and targeted chemotherapies including anthracyclines, cyclophosphamide, and trastuzumab targeting human epidermal growth factor receptor 2 (HER2) account for 27% of cardiac dysfunctions, 19% of which is New York Heart Association (NYHA) class III/IV in BC patients [12–15]. In general, anti-HER2 drugs have a higher incidence of cardiotoxicity, accounting for 0.5 to 3.9% [16, 17]. Radiotherapy has been a known factor for inducing dose-dependent cardiotoxicity which accounts for 1.76-fold higher risk of cardiac mortality than patients not exposed to radiation [8, 11, 18]. Immune checkpoint inhibitors, which are being used in BC patients only recently, have a rare (<1%) but significant risk of severe myocarditis with a mortality rate of up to 50% [18, 19]. The major CV adverse effects of these therapies are ischemic heart disease, heart failure, as well as cardiac dysrhythmias [3, 6, 12, 20, 21].

Several pharmacologic strategies are used to reduce the disease progression and CV mortality in non-cancer patients with heart failure with a reduced ejection fraction (HFrEF). These strategies include the usage of β-blockers, angiotensin-converting enzyme inhibitors (ACEi), and angiotensin receptor blockers (ARBs) [22]). These agents have also been investigated prospectively for their effects on left ventricular ejection fraction (LVEF) as a surrogate of CV incidences with the objective of mitigating or reducing CV toxicities associated with anti-HER2 agents and anthracyclines in BC patients [23–33]. Among β-blockers, nebivolol [24] and bisoprolol (with or without lisinopril) [25, 26] significantly attenuated anthracycline-containing chemotherapy- or trastuzumab-induced LVEF decline compared to control/placebo group. While carvedilol [23, 27–30] had mixed data, metoprolol [31–33] did not have a significant effect on LVEF decline associated with anthracycline-containing chemotherapy. Despite the promising results of some studies, a major limitation has been smaller sample size, with most enrolling less than 100 patients per study arm. Additionally, previous studies have evaluated a surrogate endpoint with LVEF but there is a lack of data evaluating outcomes with β-blockers and CV mortality in this patient population. The objective of this study was to compare three commonly used β-blockers (metoprolol, atenolol, and carvedilol) for their effects on CV-related mortality in BC patients using the Surveillance, Epidemiology, and End Results (SEER) - Medicare dataset.

Methods

Data sources

This was an administrative claims and registry-based retrospective cohort study conducted using the SEER - Medicare data from 2010 to 2015. This data links the SEER registry information from seventeen states to Medicare utilization claims data for patients diagnosed with cancer [34].

Study population

Patients who were diagnosed with breast cancer as their first cancer if they had more than one cancer diagnoses or only cancer between 01/01/2010 and 12/31/2014 were identified using International Classification of Diseases for Oncology, third edition (ICD-O-3 codes) (C500-C509). Those 66 years of age or older at BC diagnosis were included in this study because the SEER - Medicare data primarily includes patients older than 65 [35]. The earliest date of BC diagnosis was termed as the index date, and patients had to be continuously enrolled in Medicare parts A, B and D and not enrolled in Part C or Health Maintenance Oranizations (HMOs) during the 1-year baseline period before the index date. Patients receiving the three most commonly used β-blockers: metoprolol or atenolol or carvedilol monotherapy, for at least 6-months before the index date were included and β-blocker monotherapy was the exposure of interest, with these groups being mutually exclusive. The outcome was CV mortality and was defined using the vital status recode variable (value=dead) and the cause of death to site recode variable (value= '50060' indicating death due to diseases of the heart), from the Patient Entitlement and Diagnosis Summary File. Sociodemographic and clinical characteristics were based on the Andersen Behavioral model and measured during the baseline period. The study design is described in Fig. 1.

Statistical analysis

Descriptive characteristics were calculated to show the difference in sociodemographic and clinical characteristics across the cohorts. Means and standard deviation was reported for continuous variables, and frequency and percentages were reported for binary or categorical variables. The Fine and Grey subdistribution hazard model was used to assess the risk of CV mortality associated with the three β-blocker groups, accounting for the competing risk of death due to other reasons. We also tested to ensure the hazard of the CV mortality was proportional over time. Patients were followed
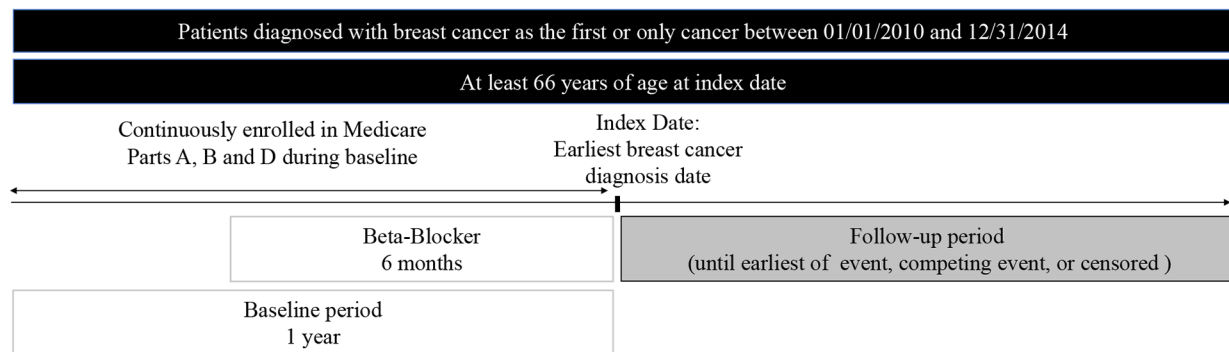
Fig. 1 Study design

until the occurrence of CV mortality (event of interest), or until they were censored. Patients were censored if they were lost to follow-up, switched β-blockers for any reason, discontinued the β-blocker for any reason, or at end of follow-up (12/31/2015). Patients were considered lost to follow-up at the point when they were no longer enrolled in Medicare Parts A, B, and D during the follow-up period. The multivariable model was adjusted for age at BC diagnosis, sex, race-ethnicity, stage and subtype of BC, Charlson comorbidity index (CCI, calculated at baseline), statin use, and indicator for multiple cancers. The adjusted hazard ratio (HR) and 95% confidence intervals (CI) were reported for the risk of CV-related mortality for metoprolol and atenolol compared to carvedilol.

Results
Patient demographics and clinical characteristics
The study cohort included 6,540 BC patients diagnosed between 2010 and 2014, of which 3,622 (55.38%) were metoprolol users, 1,929 (29.49%) were atenolol users, and 989 (15.12%) were carvedilol users. Table 1 summarizes demographic and clinical characteristics of patients in the three cohorts. Most patients in each cohort were older than 75 years of age (56.25%), White (86.82%), and female (99.19%). A majority of the patients had BC as the only cancer (87.81%) and were diagnosed at stage 0 or 1 (55.64%). Stage 0 refers to in situ tumors where cancer cells have not spread out of the ductal or lobular structure.

CV mortality among β-blockers
In the three β-blocker groups, 1.9% (*n*=70) of patients using metoprolol, 1.9% (*n*=36) of patients using atenolol, and 4.0% (*n*=40) of patients using carvedilol died due to CV-related events. Median time to CV-related mortality was 528 days in the metoprolol group, 411 days in the atenolol group, and 356 days in the carvedilol group.

Adjusted CV mortality among β-blockers
Table 2 displays the multivariable competing risk model assessing the CV-related mortality risk in the 3 groups after adjusting for patient demographics like age at BC diagnosis, sex, race-ethnicity, stage and subtype of BC, CCI, statin use, and indicator for multiple cancers. Metoprolol was associated with a 37% reduced risk of CV-related mortality [adjusted HR (95% CI): 0.63 (0.41 to 0.96), *P*=0.03] compared to carvedilol. There was no significant difference in the risk of CV-related mortality found between atenolol compared to carvedilol users [adjusted HR (95% CI): 0.74 (0.44 to 1.22)].

Discussion
In this study, we compared the incidence of CV mortality in BC patients taking the 3 most prescribed β-blockers (metoprolol, atenolol, and carvedilol) using the SEER - Medicare database from 2010 to 2015. We found that metoprolol users were less likely to experience CV death compared to carvedilol users in the adjusted model. Atenolol use did not have a significant effect on CV mortality compared to carvedilol. The novelty of our study comes from the comparison of three commonly used β-blockers for their effect on CV mortality in patients with BC. While other studies have tested and reported effects of β-blockers on LVEF decline [23–33] and on BC mortality [36–41], none of the studies have evaluated CV mortality in patients with BC. Furthermore, none of the studies in BC patients have compared different β-blockers.

In the general population without cancer, β-blockers are utilized to reduce CV mortality in a variety of disease states, including heart failure, acute myocardial infarction, and hypertension [42, 43]. Of the β-blockers evaluated in various studies, metoprolol succinate [44] and carvedilol [45–47] have shown a statistically significant decrease in mortality compared to other β-blockers or placebo in patients with HFrEF and are two of the three β-blockers recommended for management of this disease state (bisoprolol being the third) [48]. In comparison

Table 1 Baseline demographics and clinical characteristics of patients by different β-Blocker usage

Variable	Metoprolol N=3622	Atenolol N=1929	Carvedilol N=989	Total N=6540	P-value
	N (%)	N (%)	N (%)	N (%)	
DEMOGRAPHIC VARIABLES					
Age at index, in years					<0.0001
65–70	689 (19.02)	465 (24.10)	165 (16.68)	1319 (20.17)	
71–75	870 (24.02)	456 (23.64)	216 (21.84)	1542 (23.58)	
>75	2063 (56.96)	1008 (52.26)	608 (61.48)	3679 (56.25)	
Race					<0.0001
White	3177 (87.71)	1685 (87.35)	816 (82.51)	5678 (86.82)	
Black	252 (6.96)	108 (5.60)	110 (11.12)	470 (7.19)	
Other	171 (4.72)	122 (6.32)	*	352 (5.38)	
Unknown	*	*	*	40 (0.61)	
Hispanic or Latino	158 (4.36)	87 (4.51)	75 (7.58)	320 (4.89)	0.0001
Gender					0.7066
Female	3595 (99.25)	*	*	6487 (99.19)	
Male	27 (0.75)	*	*	53 (0.81)	
CLINICAL VARIABLES:					
Charlson comorbidity Index					<0.0001
0	1429 (39.45)	959 (49.72)	209 (21.13)	2597 (39.71)	
1–3	1869 (51.60)	870 (45.10)	573 (57.94)	3312 (50.64)	
4 or greater	324 (8.95)	100 (5.18)	207 (20.93)	631 (9.65)	
Statin use					<0.0001
Yes	2163 (59.72)	1104 (57.23)	671 (67.85)	3938 (60.21)	
No	1459 (40.28)	825 (42.77)	318 (32.15)	2602 (39.79)	
Breast Cancer stage					<0.0001
0	493 (13.61)	291 (15.09)	119 (12.03)	903 (13.81)	
I	1532 (42.30)	853 (44.22)	351 (35.49)	2736 (41.83)	
II	928 (25.62)	484 (25.09)	312 (31.55)	1724 (26.36)	
III	274 (7.56)	151 (7.83)	98 (9.91)	523 (8.00)	
IV	180 (4.97)	75 (3.89)	51 (5.16)	306 (4.68)	
Unknown	215 (5.94)	75 (3.89)	58 (5.86)	348 (5.32)	
Diagnosed at breast cancer stage 0 or 1					<0.0001
Yes	2025 (55.91)	1144 (59.31)	470 (47.52)	3639 (55.64)	
No	1597 (44.09)	785 (40.69)	519 (52.48)	2901 (44.36)	
Breast Cancer subtypes					0.7382
HR-/HER2+	193 (5.33)	101 (5.24)	44 (4.45)	338 (5.17)	
HR+/HER2-	2256 (62.29)	1217 (63.09)	635 (64.21)	4108 (62.81)	
HR-/HER2-	269 (7.43)	125 (6.48)	69 (6.98)	463 (7.08)	
HR+/HER2+	219 (6.05)	114 (5.91)	67 (6.77)	400 (6.12)	
Unknown	685 (18.91)	372 (19.28)	174 (17.59)	1231(18.82)	
Breast Cancer as the only cancer					0.7100
Yes	3191 (88.10)	1685 (87.35)	867 (87.66)	5743 (87.81)	
No	431 (11.9)	244 (12.65)	122 (12.34)	797 (12.19)	

Table 2 Adjusted Risk of CV Mortality among β-blocker users in breast cancer

Adjusted Model	Reference	HR (95% CI)	P-value
Metoprolol	Carvedilol	0.63 (0.41–0.96)	0.03
Atenolol		0.74 (0.44–1.22)	0.24

to metoprolol tartrate, carvedilol treatment results in a greater reduction in mortality when used in the treatment of HFrEF [49–52]. However, this difference seems more pronounced in men than in women [50]. No significant survival differences are reported between metoprolol and carvedilol in the treatment of acute myocardial infarction [53, 54].

The landmark trial (COMET) comparing carvedilol and metoprolol tartrate in the HFrEF population found

carvedilol to be superior for reducing all deaths and CV deaths [49]. A critique of this study is that the median daily dose of metoprolol tartrate was only 85 mg daily where in the trial that found mortality benefit with metoprolol succinate, the median dose was 159 mg daily [55]. This lower daily median dose may have impacted results of COMET, but ultimately metoprolol tartrate was not found to have mortality benefit. Therefore, future studies should evaluate different salts and doses of metoprolol for the CV survival benefit in BC patients.

Both metoprolol and atenolol are second generation selective β1-blockers. Metoprolol and carvedilol are also inverse agonists and capable of inhibiting basal β receptors activity [56]. Carvedilol is a third-generation non-selective β-blocker with selective alpha 1-adrenoceptor antagonist and vasodilatory effects [57]. Both metoprolol and carvedilol are lipophilic compounds in contrast with atenolol, which is hydrophilic. Additionally, carvedilol has antioxidant properties that may contribute to the benefit it has shown in patients with HFrEF [58]. However, these differences do not explain the superiority of metoprolol in our studies. It is possible that carvedilol doses were not sufficient in our cohort as the daily doses of 12.5 mg seem to be necessary to improve LVEF in patients receiving anthracycline-containing regimen [23, 27].

There are several limitations to our study. First, we did not assess the type of metoprolol salts patients were on, as metoprolol succinate had been found to have mortality benefit in HFrEF patients and metoprolol tartrate has not in robust, randomized controlled trials. Additionally, β-blocker dosing and information of other baseline medications patients were on (i.e., ACEi/ARBs) were not extracted but could have impacted the outcome we observed. The use of CCI only to assess baseline CV disease and risk factors is another limitation. For example, the CCI does not include hypertension, which is prevalent in postmenopausal BC patients [59]. Certain BC treatments such as anthracyclines, radiation therapy, anti-HER2 agents, and other targeted therapies are associated with cardiac complications, such as cardiomyopathy [14]. These patient-, cancer-, and treatment-specific risks are also not explicitly considered in the CCI. However, with the signals identified in the current study, subsequent studies can aim at addressing these limitations in future analysis. Finally, patient baseline LVEF as well as % of patients with HFrEF in different arms were not available and could have impacted results. Future studies incorporating these parameters can further validate our findings and answer the key question on the selection of β-blocker for improving CV survival in BC patients.

Conclusions

In summary, our study is the first one comparing the effects of various β-blockers on CV mortality in BC patients and suggests superiority of metoprolol in these patients. Our findings prompt additional investigation with larger sample size to investigate the effects of doses and type of individual β-blockers in reducing CV mortality in BC patients. In addition, similar investigation on individual ACEi and ARBs on CV mortality are also needed to select appropriate agents to improve CV-specific survival in patients with BC.

List of Abbreviations

ACEi	Angiotensin-converting enzyme inhibitors
ARBs	Angiotensin receptor blockers
BC	Breast cancer
CCI	Charlson comorbidity index
CI	Confidence interval
CV	Cardiovascular
HFrEF	Heart failure with a reduced ejection fraction
HMO	Health Maintenance Oranization
HR	Hazard ratio
ICD-O-3	International Classification of Diseases for Oncology, third edition
LVEF	Left ventricular ejection fraction
NYHA	New York Heart Association
SEER	Surveillance, Epidemiology and End Results

Declarations

Ethics approval
The study was approved by the University of Houston institutional review board with a waiver of informed consent.

Consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

References
1. Bradshaw PT, Stevens J, Khankari N, Teitelbaum SL, Neugut AI, Gammon MD. Cardiovasc Disease Mortal among Breast Cancer Survivors Epidemiol. 2016;27(1):6–13.
2. Patnaik JL, Byers T, DiGuiseppi C, Dabelea D, Denberg TD. Cardiovascular disease competes with breast cancer as the leading cause of death for older females diagnosed with breast cancer: a retrospective cohort study. Breast Cancer Res. 2011;13(3):R64.
3. Ramin C, Schaeffer ML, Zheng Z, Connor AE, Hoffman-Bolton J, Lau B, et al. All-cause and Cardiovascular Disease Mortality among breast Cancer survivors in CLUE II, a long-Standing Community-based cohort. J Natl Cancer Inst. 2021;113(2):137–45.
4. Schairer C, Mink PJ, Carroll L, Devesa SS. Probabilities of death from breast cancer and other causes among female breast cancer patients. J Natl Cancer Inst. 2004;96(17):1311–21.
5. Abdel-Qadir H, Austin PC, Lee DS, Amir E, Tu JV, Thavendiranathan P, et al. A Population-based study of Cardiovascular Mortality following early-stage breast Cancer. JAMA Cardiol. 2017;2(1):88–93.
6. Colzani E, Liljegren A, Johansson AL, Adolfsson J, Hellborg H, Hall PF, et al. Prognosis of patients with breast cancer: causes of death and effects of time since diagnosis, age, and tumor characteristics. J Clin Oncol. 2011;29(30):4014–21.
7. Weberpals J, Jansen L, Muller OJ, Brenner H. Long-term heart-specific mortality among 347 476 breast cancer patients treated with radiotherapy or chemotherapy: a registry-based cohort study. Eur Heart J. 2018;39(43):3896–903.
8. Bouillon K, Haddy N, Delaloge S, Garbay JR, Garsi JP, Brindel P, et al. Long-term cardiovascular mortality after radiotherapy for breast cancer. J Am Coll Cardiol. 2011;57(4):445–52.
9. Hooning MJ, Aleman BM, van Rosmalen AJ, Kuenen MA, Klijn JG, van Leeuwen FE. Cause-specific mortality in long-term survivors of breast cancer: a 25-year follow-up study. Int J Radiat Oncol Biol Phys. 2006;64(4):1081–91.
10. Montisci A, Vietri MT, Palmieri V, Sala S, Donatelli F, Napoli C. Cardiac Toxicity Associated with Cancer Immunotherapy and Biological drugs. Cancers (Basel). 2021;13:19.
11. Valachis A, Nilsson C. Cardiac risk in the treatment of breast cancer: assessment and management. Breast Cancer (Dove Med Press). 2015;7:21–35.
12. Slamon DJ, Leyland-Jones B, Shak S, Fuchs H, Paton V, Bajamonde A, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med. 2001;344(11):783–92.
13. Dempsey N, Rosenthal A, Dabas N, Kropotova Y, Lippman M, Bishopric NH. Trastuzumab-induced cardiotoxicity: a review of clinical risk factors, pharmacologic prevention, and cardiotoxicity of other HER2-directed therapies. Breast Cancer Res Treat. 2021;188(1):21–36.
14. Liu C, Chen H, Guo S, Liu Q, Chen Z, Huang H, et al. Anti-breast cancer-induced cardiomyopathy: mechanisms and future directions. Biomed Pharmacother. 2023;166:115373.
15. Ginzac A, Passildas J, Gadea E, Abrial C, Molnar I, Tresorier R, et al. Treatment-Induced cardiotoxicity in breast Cancer: a review of the interest of practicing a physical activity. Oncology. 2019;96(5):223–34.
16. Copeland-Halperin RS, Liu JE, Yu AF. Cardiotoxicity of HER2-targeted therapies. Curr Opin Cardiol. 2019;34(4):451–8.
17. Dent SF, Morse A, Burnette S, Guha A, Moore H. Cardiovascular toxicity of Novel HER2-Targeted therapies in the treatment of breast Cancer. Curr Oncol Rep. 2021;23(11):128.
18. Broberg AM, Geisler J, Tuohinen S, Skytta T, Hrafnkelsdottir Thorn J, Nielsen KM, et al. Prevention, Detection, and management of Heart failure in patients treated for breast Cancer. Curr Heart Fail Rep. 2020;17(6):397–408.
19. Agunbiade TA, Zaghlol RY, Barac A. Heart failure in relation to Tumor-targeted therapies and immunotherapies. Methodist Debakey Cardiovasc J. 2019;15(4):250–7.
20. Riihimaki M, Thomsen H, Brandt A, Sundquist J, Hemminki K. Death causes in breast cancer patients. Ann Oncol. 2012;23(3):604–10.
21. Hooning MJ, Botma A, Aleman BM, Baaijens MH, Bartelink H, Klijn JG, et al. Long-term risk of cardiovascular disease in 10-year survivors of breast cancer. J Natl Cancer Inst. 2007;99(5):365–75.
22. Barish R, Lynce F, Unger K, Barac A. Management of Cardiovascular Disease in Women with breast Cancer. Circulation. 2019;139(8):1110–20.
23. Kalay N, Basar E, Ozdogru I, Er O, Cetinkaya Y, Dogan A, et al. Protective effects of carvedilol against anthracycline-induced cardiomyopathy. J Am Coll Cardiol. 2006;48(11):2258–62.
24. Kaya MG, Ozkan M, Gunebakmaz O, Akkaya H, Kaya EG, Akpek M, et al. Protective effects of nebivolol against anthracycline-induced cardiomyopathy: a randomized control study. Int J Cardiol. 2013;167(5):2306–10.
25. Pituskin E, Mackey JR, Koshman S, Jassal D, Pitz M, Haykowsky MJ, et al. Multidisciplinary Approach to Novel therapies in Cardio-Oncology Research (MANTICORE 101-Breast): a Randomized Trial for the Prevention of Trastuzumab-Associated Cardiotoxicity. J Clin Oncol. 2017;35(8):870–7.
26. Wihandono A, Azhar Y, Abdurahman M, Hidayat S. The role of Lisinopril and Bisoprolol to prevent Anthracycline Induced Cardiotoxicity in locally advanced breast Cancer patients. Asian Pac J Cancer Prev. 2021;22(9):2847–53.
27. Nabati M, Janbabai G, Baghyari S, Esmaili K, Yazdani J. Cardioprotective effects of Carvedilol in Inhibiting Doxorubicin-induced cardiotoxicity. J Cardiovasc Pharmacol. 2017;69(5):279–85.
28. Guglin M, Krischer J, Tamura R, Fink A, Bello-Matricaria L, McCaskill-Stevens W, et al. Randomized Trial of Lisinopril Versus Carvedilol to Prevent Trastuzumab Cardiotoxicity in patients with breast Cancer. J Am Coll Cardiol. 2019;73(22):2859–68.
29. Avila MS, Ayub-Ferreira SM, de Barros Wanderley MR Jr., das, Dores Cruz F, Goncalves Brandao SM, Rigaud VOC et al. Carvedilol for Prevention of Chemotherapy-Related Cardiotoxicity: The CECCY Trial. J Am Coll Cardiol. 2018;71(20):2281-90.
30. Lee M, Chung WB, Lee JE, Park CS, Park WC, Song BJ, et al. Candesartan and carvedilol for primary prevention of subclinical cardiotoxicity in breast cancer patients without a cardiovascular risk treated with doxorubicin. Cancer Med. 2021;10(12):3964–73.
31. Heck SL, Gulati G, Hoffmann P, von Knobelsdorff-Brenkenhoff F, Storas TH, Ree AH, et al. Effect of candesartan and metoprolol on myocardial tissue composition during anthracycline treatment: the PRADA trial. Eur Heart J Cardiovasc Imaging. 2018;19(5):544–52.
32. Heck SL, Mecinaj A, Ree AH, Hoffmann P, Schulz-Menger J, Fagerland MW, et al. Prevention of Cardiac Dysfunction During Adjuvant Breast Cancer Therapy (PRADA): Extended Follow-Up of a 2x2 Factorial, Randomized, Placebo-Controlled, Double-Blind Clinical Trial of Candesartan and Metoprolol. Circulation. 2021;143(25):2431–40.
33. Gulati G, Heck SL, Ree AH, Hoffmann P, Schulz-Menger J, Fagerland MW, et al. Prevention of cardiac dysfunction during adjuvant breast cancer therapy (PRADA): a 2 x 2 factorial, randomized, placebo-controlled, double-blind clinical trial of candesartan and metoprolol. Eur Heart J. 2016;37(21):1671–80.
34. Surveillance Epidemiology and End Results, Program NCI. National Institutes of Health. List of SEER Registries. https://seer.cancer.gov/registries/list.html. Accessed April 19, 2020.
35. Enewold L, Parsons H, Zhao L, Bott D, Rivera DR, Barrett MJ, et al. Updated overview of the SEER-Medicare Data: enhanced content and applications. J Natl Cancer Inst Monogr. 2020;2020(55):3–13.
36. Powe DG, Voss MJ, Zanker KS, Habashy HO, Green AR, Ellis IO, et al. Beta-blocker drug therapy reduces secondary cancer formation in breast cancer and improves cancer specific survival. Oncotarget. 2010;1(7):628–38.
37. Ganz PA, Habel LA, Weltzien EK, Caan BJ, Cole SW. Examining the influence of beta blockers and ACE inhibitors on the risk for breast cancer recurrence: results from the LACE cohort. Breast Cancer Res Treat. 2011;129(2):549–56.
38. Melhem-Bertrandt A, Chavez-Macgregor M, Lei X, Brown EN, Lee RT, Meric-Bernstam F, et al. Beta-blocker use is associated with improved relapse-free

survival in patients with triple-negative breast cancer. J Clin Oncol. 2011;29(19):2645–52.

39. Barron TI, Connolly RM, Sharp L, Bennett K, Visvanathan K. Beta blockers and breast cancer mortality: a population- based study. J Clin Oncol. 2011;29(19):2635–44.

40. Scott OW, Tin Tin S, Elwood JM, Cavadino A, Habel LA, Kuper-Hommel M, et al. Post-diagnostic beta blocker use and breast cancer-specific mortality: a population-based cohort study. Breast Cancer Res Treat. 2022;193(1):225–35.

41. Lofling LL, Stoer NC, Sloan EK, Chang A, Gandini S, Ursin G, et al. beta-blockers and breast cancer survival by molecular subtypes: a population-based cohort study and meta-analysis. Br J Cancer. 2022;127(6):1086–96.

42. Gottlieb SS, McCarter RJ, Vogel RA. Effect of beta-blockade on mortality among high-risk and low-risk patients after myocardial infarction. N Engl J Med. 1998;339(8):489–97.

43. Whelton PK, Carey RM, Aronow WS, Jr. Casey DE, Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice guidelines. Circulation. 2018;138(17):e426–83.

44. Goldstein S, Hjalmarson A. The mortality effect of metoprolol CR/XL in patients with heart failure: results of the MERIT-HF trial. Clin Cardiol. 1999;22(Suppl 5):V30–5.

45. Packer M, Bristow MR, Cohn JN, Colucci WS, Fowler MB, Gilbert EM, et al. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. U.S. Carvedilol Heart failure Study Group. N Engl J Med. 1996;334(21):1349–55.

46. Packer M, Coats AJ, Fowler MB, Katus HA, Krum H, Mohacsi P, et al. Effect of carvedilol on survival in severe chronic heart failure. N Engl J Med. 2001;344(22):1651–8.

47. Bristow MR, Gilbert EM, Abraham WT, Adams KF, Fowler MB, Hershberger RE, et al. Carvedilol produces dose-related improvements in left ventricular function and survival in subjects with chronic heart failure. MOCHA Investigators Circulation. 1996;94(11):2807–16.

48. Writing Committee M, Members AAJC. 2022 AHA/ACC/HFSA Guideline for the management of heart failure. J Card Fail. 2022;28(5):e1–167.

49. Poole-Wilson PA, Swedberg K, Cleland JG, Di Lenarda A, Hanrath P, Komajda M, et al. Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol or Metoprolol European Trial (COMET): randomised controlled trial. Lancet. 2003;362(9377):7–13.

50. Delea TE, Stanford R, Hagiwara M, Edelsberg JS, Oster G. Death and hospitalization in heart failure patients receiving carvedilol vs. metoprolol tartrate. Int J Cardiol. 2005;99(1):117–24.

51. DiNicolantonio JJ, Lavie CJ, Fares H, Menezes AR, O'Keefe JH. Meta-analysis of carvedilol versus beta 1 selective beta-blockers (atenolol, bisoprolol, metoprolol, and nebivolol). Am J Cardiol. 2013;111(5):765–9.

52. Ajam T, Ajam S, Devaraj S, Mohammed K, Sawada S, Kamalesh M. Effect of carvedilol vs metoprolol succinate on mortality in heart failure with reduced ejection fraction. Am Heart J. 2018;199:1–6.

53. Mrdovic IB, Savic LZ, Perunicic JP, Asanin MR, Lasica RM, Jelena MM, et al. Randomized active-controlled study comparing effects of treatment with carvedilol versus metoprolol in patients with left ventricular dysfunction after acute myocardial infarction. Am Heart J. 2007;154(1):116–22.

54. Zaatari G, Fintel DJ, Subacius H, Germano JJ, Shani J, Goldberger JJ, et al. Comparison of Metoprolol Versus Carvedilol after Acute myocardial infarction. Am J Cardiol. 2021;147:1–7.

55. Effect of metoprolol CR/XL in chronic heart failure. Metoprolol CR/XL Randomised intervention trial in congestive heart failure (MERIT-HF). Lancet. 1999;353(9169):2001–7.

56. Fumagalli C, Maurizi N, Marchionni N, Fornasari D. beta-blockers: their new life from hypertension to cancer and migraine. Pharmacol Res. 2020;151:104587.

57. Fisker FY, Grimm D, Wehland M. Third-generation beta-adrenoceptor antagonists in the treatment of hypertension and heart failure. Basic Clin Pharmacol Toxicol. 2015;117(1):5–14.

58. Flesch M, Maack C, Cremers B, Baumer AT, Sudkamp M, Bohm M. Effect of beta-blockers on free radical-induced cardiac contractile dysfunction. Circulation. 1999;100(4):346–53.

59. Drosdowsky A, Gough K. The Charlson Comorbidity Index: problems with use in epidemiological research. J Clin Epidemiol. 2022;148:174–7.

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