Cardio-Oncology

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CARDIAC-STAR: prevalence of cardiovascular comorbidities in patients with HR + / HER2 – metastatic breast cancer

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Abstract

Background Cardiovascular (CV) comorbidities and concurrent medications with risk of heart rate-corrected QT interval (QTc) prolongation can impact treatment decisions and safety discussions for patients with breast cancer. However, limited data are available regarding their prevalence in patients with HR + /HER2– metastatic breast cancer (mBC). We evaluated the prevalence of CV comorbidities, the use of concurrent medications with risk of QTc prolongation, and treatment patterns in patients with newly diagnosed HR + /HER2 – mBC.

Methods This retrospective analysis utilized claims data from Merative™ Marketscan® Commercial and Medicare databases. Claims-based algorithms identified patients with newly diagnosed HR + /HER2– mBC between January 2016 and December 2022. The index date was defined as the first date of an mBC claim during this period. For each patient, data on pre-existing CV comorbidities and first-line treatments were captured for 12 months before and 6 months after the index date, respectively.

Results A total of 6525 patients with newly diagnosed HR + /HER2 – mBC were identified. At mBC diagnosis, 61.7% of patients had ≥ 1 CV comorbidity. Of patients with CV comorbidities, 22.5% and 30.6% took 1 or ≥ 2 medications, respectively, with risk of QTc prolongation. First-line use of cyclin-dependent kinase 4/6 (CDK4/6) inhibitors increased from 22.1% of patients with CV comorbidities diagnosed in 2016–2017 to 31.5% of those diagnosed in 2018–2022.

Conclusions We found that CV comorbidities and use of medications with risk of QTc prolongation were common in patients with newly diagnosed HR + /HER2 – mBC. These factors should inform treatment decision-making (including CDK4/6 inhibitor selection), safety discussions with patients, and CV monitoring.

Keywords Cardiovascular comorbidities, Cyclin-dependent kinase 4/6 inhibitor, HR + /HER2–, Medical claims, Metastatic breast cancer, QTc prolongation, Retrospective, Torsades de Pointes

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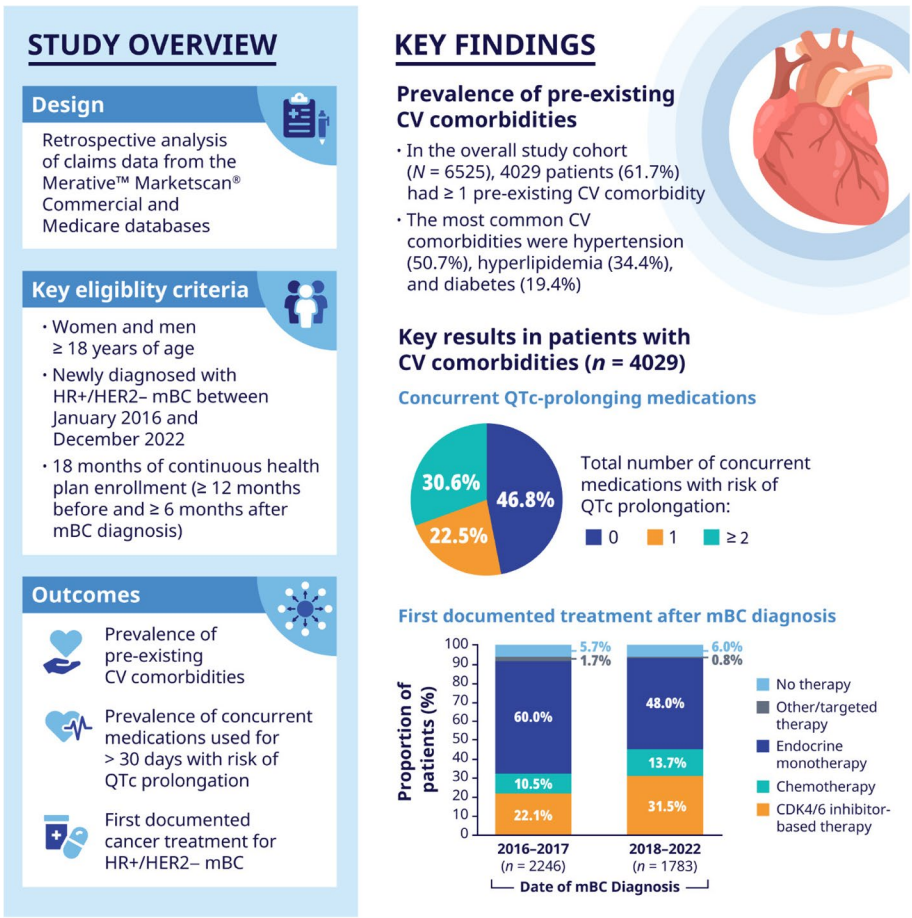
Graphical Abstract



Background

Despite improved treatment approaches for early breast cancer, nearly 30% of patients will develop distant metastatic disease [1]. Metastatic breast cancer (mBC) can be described by hormone receptor (HR) status and human epidermal growth factor receptor 2 (HER2) status. Approximately 70% of patients with mBC in the United States have HR + /HER2 − disease [2].

The presence of pre-existing cardiovascular (CV) comorbidities can markedly impact treatment decisions and outcomes in patients with breast cancer [3]. Since the prevalence of CV diseases tends to increase with age [3, 4], pre-existing CV comorbidities are a particularly relevant consideration for patients with mBC, the majority of whom are aged ≥ 45 years [5]. Moreover, CV comorbidities and the concurrent use of systemic cancer therapies and supportive care medications place patients with breast cancer at increased risk of developing QT prolongation [6]. Heart rate-corrected QT interval (QTc) prolongation is a potentially life-threatening toxicity that increases the risk of CV arrhythmias (eg, Torsades de Pointes [TdP]) and sudden CV death [7–10]. Limited literature exists regarding the proportion of patients with breast cancer who are at risk for QTc prolongation secondary to cancer therapies and concurrent medications.

CV comorbidities are associated with reduced overall survival and a higher risk of mortality in patients with breast cancer [11, 12]. Long-term breast cancer survivors also have a higher risk of death due to CV disease compared to women without a history of breast cancer [13, 14]. However, limited data are currently available regarding the prevalence of CV comorbidities in patients with HR + /HER2− mBC. Furthermore, established comorbidity indices, such as the National Cancer Institute (NCI) Comorbidity Index [15], are not

completely inclusive of the broad range of CV comorbidities that may contribute to risk of mortality.

CV comorbidities and QTc prolongation risk are especially important factors to consider in the context of treatment decision-making for patients with newly diagnosed HR + /HER2 − mBC, for whom the combination of a cyclin-dependent kinase 4/6 (CDK4/6) inhibitor and endocrine therapy (ET) is the current standard-of-care [16, 17]. Ribociclib has been associated with QTc prolongation and is the only CDK4/6 inhibitor with a warning against concomitant use with other QTc-prolonging medications and recommendations for cardiac monitoring in its United States Prescribing Information [8, 18, 19]. A prior retrospective analysis of health care claims data in the US reported that 17.1% of patients with HR + /HER2 − mBC received a concomitant medication that could increase the risk of developing QTc prolongation [20]. However, this study only evaluated medication claims data during the 7-day period before the index date (ie, date of first secondary neoplasm diagnosis) [20]. More comprehensive and long-term data are needed to better characterize the use of chronic medications with risk of QTc prolongation in this population, particularly as these patients may be receiving chronic medications for their CV comorbidity.

Given the potential impact of CV comorbidities and concurrent medications with risk of QTc prolongation on treatment decisions and outcomes, it is important to understand their prevalence in patients with newly diagnosed HR + /HER2 − mBC. The objectives of this retrospective study were to describe the prevalence of pre-existing CV comorbidities, the use of concurrent medications with a potential risk of QTc prolongation, and the first documented cancer treatment in patients with newly diagnosed HR + /HER2 − mBC.

Methods

Study design

This retrospective, observational study utilized closed claims data from the Merative™ Marketscan® Commercial and Medicare databases [21]. These databases contain patient-level claims and specialty data for employees, dependents, and retirees in the United States with primary or Medicare coverage through privately insured fee-for-service, point-of-service, or capitated health plans. All enrollment records and outpatient, inpatient, ancillary, and drug claims data were collected and used for identifying the study population and measuring outcomes. This study used Health Insurance Portability and Accountability Act–compliant and deidentified data, which did not meet the criteria for human subject research as specified in the United States Department of Health and Human Services 45 Code of Federal Regulations Part 46. Therefore, neither institutional review board approval nor informed consent was required. This study was conducted in accordance with legal and regulatory requirements and followed research practices as described in guidelines issued by the International Society for Pharmacoepidemiology, the International Epidemiological Association, the International Society for Pharmacoeconomics and Outcomes Research, and the United States Food and Drug Administration.

The study focused on patients with newly diagnosed HR + /HER2 − mBC between January 1, 2016, and December 31, 2022 (Fig. 1). The index date for each patient was defined as the first date of an mBC claim during this time frame, when an mBC claim was made. Diagnosis of mBC was defined as having at least 2 claims containing at least 1 diagnosis code for breast cancer at least 30 days apart and at least 2 secondary malignancy diagnosis codes on separate days (with the first claim occurring no more than 30 days before or any time after the first diagnosis of primary breast cancer) [22, 23]. Patients who solely had secondary malignancy diagnosis codes of the breast, local regional lymph nodes, or non-melanoma of the skin were not considered to have mBC. Pre-existing CV comorbidity data were captured for the 1-year period before the index date (ie, the look-back period), and data for the first documented breast cancer treatments were captured for the 6-month period after the index date (ie, the look-forward period).

Patients

The study cohort consisted of women and men aged 18 years or older with HR + /HER2 − mBC. HR + patients were defined as those who received at least 1 prescription fill or administration of an ET on or before the index date and up to 1 month after the index date. HER2 − patients were defined as those who did not receive claims for treatments indicated for HER2 + breast cancer on or before the index date and up to one month after the index date. One month after diagnosis was selected to reflect HR and HER2 status at baseline. Patients were required to have 18 months of continuous health plan enrollment in the look-back and look-forward periods, which means that their medical and pharmacy claims were available for analysis for 1 year before and 6 months after the index date; those without continuous 18-month enrollment (including those who died < 6 months after the index date) were excluded. Patients without 6 months continuous health plan enrollment after diagnosis were excluded because those who did not receive treatment within 6 months may have had meaningful unobserved characteristics that influenced their treatment decisions. Patients with HER2 + disease on or before the index date and up to 1 month after the index date, cancers other

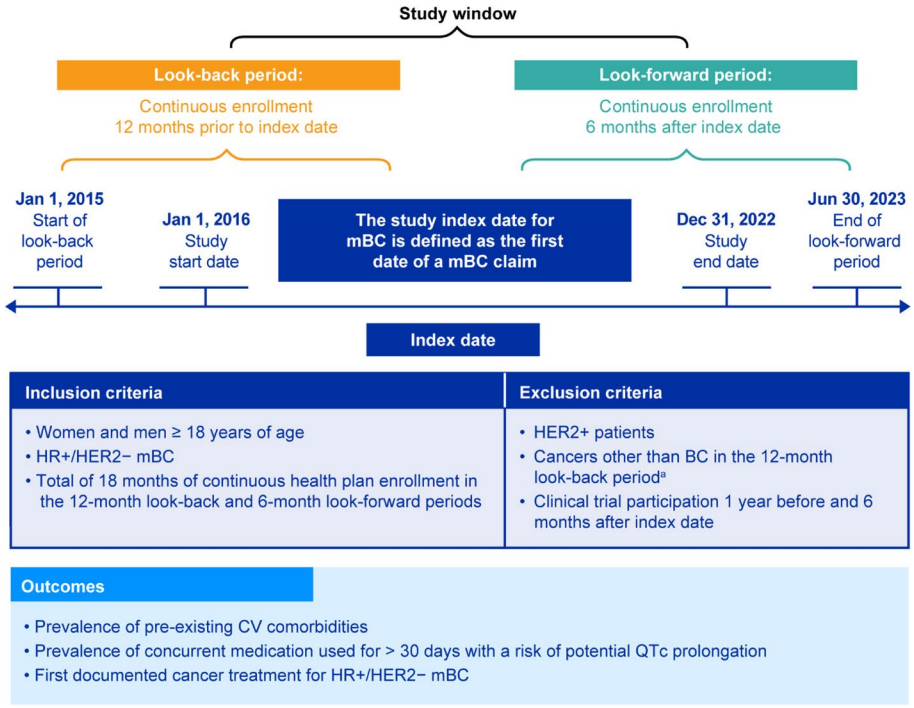


Fig. 1 Study design. A high-level overview of the study design and methodology is presented. Additional information, including detailed definitions of eligibility criteria and outcomes, is provided in the Methods section. [a]Except for non-melanoma of the skin. BC, breast cancer; CV, cardiovascular; HER2+, human epidermal growth factor receptor 2-positive; HER2−, human epidermal growth factor receptor 2-negative; HR+, hormone receptor-positive; mBC, metastatic breast cancer; QTc, heart rate-corrected QT interval

than breast cancer (except for non-melanoma of the skin) in the 12-month look-back period, and those who participated in clinical trials 1 year before and 6 months after the index date were excluded from the study. International Classification of Diseases (ICD)−9/10-Clinical Modification codes were used to identify patients with mBC and secondary malignancies (Supplementary Table 1).

Outcomes

Outcomes evaluated in this analysis included the prevalence of pre-existing CV comorbidities, the prevalence of concurrent medication used for more than 30 days with a risk of potential QTc prolongation or TdP, and the first documented cancer treatment after HR+/HER2− mBC diagnosis.

To determine the prevalence of pre-existing CV comorbidities, the study utilized ICD-9/10-Clinical Modification codes in the look-back period from the index date (Supplementary Table 1). Pre-existing CV comorbidities and the ICD-9/10 codes were selected based on published literature and expert opinions from key opinion leaders. Given the complex interplay between diabetes and CV disease, including CV complications often associated with diabetes [24], ICD-9/10-Clinical Modification codes for diabetes were captured as part of the analysis (Supplementary Table 1). In addition, specific medications for commonly undercoded CV comorbidities (diabetes, hyperlipidemia, and hypertension) were utilized to describe the prevalence (Supplementary Table 2) [25].

The prevalence of concurrent medication used for more than 30 days (ie, chronically utilized medications) with a risk of potential QTc prolongation or TdP was determined using pharmacy claims. All medications with a risk of QTc prolongation or TdP (known, possible, or conditional), as listed on www.crediblemeds.org, were captured if prescribed within 45 days before and 45 days after the index date for those medications that have at least 30 days of supply [7]. Prevalence was described overall and stratified by type of risk.

The first documented cancer treatment for HR+/HER2− mBC was captured using pharmacy claims. The medications included in this analysis were those recommended as preferred for treatment of HR+/HER2− mBC in the first-line setting according to the National Comprehensive Cancer Network® guidelines version 4.2023 [16]. CDK4/6 inhibitor–based therapy, endocrine monotherapy, chemotherapy, and other targeted treatments were defined based on the presence or absence of specific medication claims within certain time frames.

Specifically, CDK4/6 inhibitor–based therapy was defined as any CDK4/6 inhibitor claim within ± 60 days (to account for potential delays in approval of treatment) of first fill date of the non-CDK4/6 treatment. Endocrine monotherapy was defined as no CDK4/6 inhibitor claim within ± 60 days of first fill date of the ET, or no other targeted treatment claim or chemotherapy claim within ± 28 days of first fill date of the ET. Chemotherapy was defined as no CDK4/6 inhibitor claim within ± 60 days or no other targeted treatment claim within ± 28 days of first fill date of the chemotherapy. An ET treatment claim or other targeted treatment claim with chemotherapy claim within ± 28 days was defined as chemotherapy. Other targeted treatment (olaparib, talazoparib, everolimus, alpelisib, or pembrolizumab) was defined as no CDK4/6 inhibitor claim within ± 60 days or chemotherapy claim within ± 28 days of first fill date of the other targeted treatment regardless of claim for ET treatment. Treatment patterns were captured in mutually exclusive subgroups and were stratified by the year of mBC diagnosis (2016–2017 vs 2018–2022) to reflect the change in availability of CDK4/6 inhibitors in the United States.

Statistical analysis

All study analyses were descriptive in nature and conducted using SAS version 9.4. Summary statistics were calculated to describe baseline demographics, clinical characteristics, and treatment patterns. For continuous data, the mean (standard deviation [SD]) or median (interquartile range [IQR]) were assessed. For categorical data, the frequencies and percentages were reported.

Results

Patients

Of 66,608,054 patients who were included in the database during the index period (January 2016 to December 2022), 6525 patients with HR + /HER2 − mBC met the study eligibility criteria and were included in this analysis (Fig. 2). Patient characteristics at the time of HR + / HER2 − mBC diagnosis are shown in Table 1. Among the overall study cohort ($n = 6525$), most patients (98.8%) were female, the median age was 59.0 (IQR, 15.0) years, and most patients (73.2%) were below the age of 65 years. In addition, 39.6% resided in the South, and 83.7% of patients had a health plan provided by their employer. In terms of clinical characteristics, 37.3% of patients had bone-only metastasis, 13.5% had visceral metastasis, and 2.2% had brain or central nervous system metastasis. Patients had a median NCI Comorbidity Index score of 0 (IQR, 1.6); the prevalence of various comorbidities, as captured by the NCI Comorbidity Index, is presented in Supplementary Table 3.

Prevalence of pre-existing CV comorbidities

At the time of mBC diagnosis, 4029 of 6525 (61.7%) patients in the overall study cohort had at least 1 pre-existing CV comorbidity. The median number of pre-existing CV comorbidities in the overall study cohort was 2.0 (IQR, 2.0). The most commonly reported CV comorbidities were hypertension (50.7%), hyperlipidemia (34.4%), and diabetes (19.4%; Table 2). When comparing patients with and without CV comorbidities, it was observed that the median age of patients with CV comorbidities was 62 years, while the median age of patients without CV comorbidities was 53 years. Among patients aged 65 years or older, 86.9% had at least 1 CV comorbidity at the time of mBC diagnosis, compared to 52.5% of patients under the age of 65.

Prevalence of concurrent medication with risk of potential QTc prolongation or TdP

The use of concurrent medications with a risk of potential QTc prolongation or TdP was assessed among patients with and without CV comorbidities. The median number of medications with a risk of QTc prolongation was 2, both for patients with CV comorbidities (IQR, 2) and patients without CV comorbidities (IQR, 3). Among patients with CV comorbidities, over half (53.2%) were prescribed at least 1 medication with a risk of QTc prolongation, with 22.5% taking 1 medication and 30.6% taking 2 or more medications (Fig. 3). Among patients without CV comorbidities, 15.5% took 1 medication with a risk of QTc prolongation, and 29.4% took 2 or more medications (Fig. 3). The most frequently prescribed chronic medications with risk of QTc prolongation were hydrochlorothiazide (28.0%), venlafaxine (10.8%), and omeprazole (10.3%) in patients with CV comorbidities (Table 3); and venlafaxine (10.0%), escitalopram (7.1%), and hydrocodone (5.8%) in patients without CV comorbidities (Table 4).

The concurrent use of chronic medications with a known, possible, or conditional risk of TdP was observed in 25.2%, 16.4%, and 34.6% of patients with CV comorbidities, respectively, and in 26.5%, 22.4%, and 16.3% of patients without CV comorbidities, respectively (Fig. 4). Two or more medications with a known risk of TdP were prescribed to 14.3% of patients with CV comorbidities and 15.6% of patients without CV comorbidities. In both patients with and without CV comorbidities, the most frequently prescribed medications with a known risk of TdP were escitalopram (5.5% vs 7.1%), citalopram (4.6% vs 3.9%), and ondansetron (4.3% vs 3.0%; Tables 3 and 4).

First documented cancer treatment for HR + /HER2 − mBC

First-line treatments for HR + /HER2 − mBC were analyzed by year of mBC diagnosis among patients with

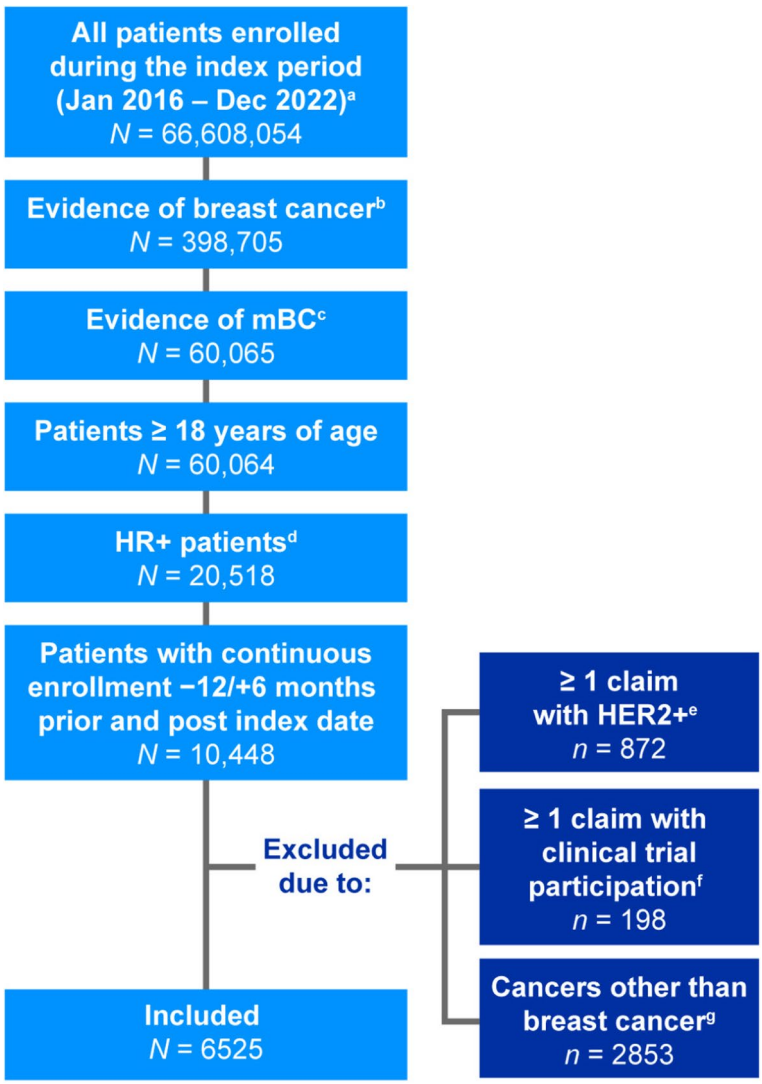


Fig. 2 Flowchart of patients included in the study. The flowchart shows the selection of patients included in the analysis. [a]In Marketscan Commercial Claims and Encounters (CCAE) database & Medicare Supplemental and Coordination of Benefits (MDCR) database. [b]Defined as ≥ 2 claims containing ≥ 1 diagnosis code for breast cancer ≥ 30 days apart. [c]Defined as ≥ 2 claims for a secondary neoplasm on separate days (with the first claim occurring ≤ 30 days before or any time after the first diagnosis of primary breast cancer); patients who solely had secondary malignancy diagnosis codes of the breast, local regional lymph nodes, or non-melanoma of the skin were not considered to have mBC. [d]Defined as patients who received ≥ 1 prescription fill of endocrine therapy on or before index date or within 30 days after index date. [e]During – 12/ + 6 months prior and post index date. [f]Use before index date or within 30 days after index date. [g]During the look-back period, except for non-melanoma of the skin. HER2 + , human epidermal growth factor receptor 2-positive; HR + , hormone receptor-positive; mBC, metastatic breast cancer

and without CV comorbidities. For patients diagnosed with mBC between 2016 and 2017, the most common first-line treatments were endocrine monotherapy (60.0% of patients with CV comorbidities vs 55.6% of patients without CV comorbidities), CDK4/6 inhibitor–based therapy (22.1% vs 22.9%, respectively), and chemotherapy (10.5% vs 14.2%, respectively; Fig. 5). Among patients diagnosed with mBC between 2018 and 2022, the most common first-line treatments were endocrine monotherapy (48.0% of patients with CV comorbidities vs 44.3% of patients without CV comorbidities), CDK4/6 inhibitor–based therapy (31.5% vs 29.9%, respectively), and chemotherapy (13.7% vs 19.4%, respectively; Fig. 5). Notably, palbociclib was the most frequently used CDK4/6 inhibitor as a first-line treatment, accounting for 86.0% and 84.3% of CDK4/6 inhibitor use among patients with and without CV comorbidities, respectively (Fig. 6).

Table 1 Patient demographics

Patient characteristics at HR + /HER2 − mBC diagnosis	Total (*N* = 6525)	CV comorbidities at HR + /HER2 − mBC diagnosis	
		Yes (*n* = 4029)	No (*n* = 2496)
Sex, *n* (%)			
Female	6448 (98.8)	3966 (98.4)	2482 (99.4)
Age, years			
Median (IQR)	59.0 (15.0)	62.0 (16.0)	53.0 (15.0)
Age group, *n* (%)			
< 55 years	2325 (35.6)	895 (22.2)	1430 (57.3)
55–64 years	2450 (37.5)	1614 (40.1)	836 (33.5)
65–74 years	833 (12.8)	675 (16.8)	158 (6.3)
≥ 75 years	917 (14.1)	845 (21.0)	72 (2.9)
Geographic region[a], *n* (%)			
Northeast	1426 (21.9)	892 (22.1)	534 (21.4)
North Central	1539 (23.6)	1003 (24.9)	536 (21.5)
South	2585 (39.6)	1638 (40.7)	947 (37.9)
West	966 (14.8)	490 (12.2)	476 (19.1)
Health data type, *n* (%)			
Fee for service	4236 (64.9)	2231 (55.4)	2005 (80.3)
Encounter	590 (9.0)	317 (7.9)	273 (10.9)
Medicare	1510 (23.1)	1325 (32.9)	185 (7.4)
Medicare encounter	189 (2.9)	156 (3.9)	33 (1.3)
Health plan, *n* (%)			
Employer	5464 (83.7)	3400 (84.4)	2064 (82.7)
Health plan	1061 (16.3)	629 (15.6)	432 (17.3)
Metastasis, *n* (%)			
Bone-only	2434 (37.3)	1604 (39.8)	830 (33.3)
Visceral	884 (13.5)	583 (14.5)	301 (12.1)
Brain/CNS	143 (2.2)	96 (2.4)	47 (1.9)
NCI Comorbidity Index Score			
Median (IQR)	0 (1.6)	1.3 (2.1)	0 (0)
Mean (SD)	1.0 (1.4)	1.4 (1.6)	0.3 (0.8)

CNS Central nervous system, *CV* Cardiovascular; HER2 −, human epidermal growth factor receptor 2-negative, *HR* + Hormone receptor-positive, *IQR* Interquartile range, *mBC* Metastatic breast cancer, *NCI* National Cancer Institute, *SD* Standard deviation

[a] Region of residence: Northeast (Connecticut, Maine, Massachusetts, New Hampshire, Vermont, Rhode Island, New Jersey, New York, and Pennsylvania); North Central (Illinois, Indiana, Michigan, Ohio, Wisconsin, Iowa, Kansas, Minnesota, Missouri, Nebraska, North Dakota, and South Dakota); South (Delaware, District of Columbia, Florida, Georgia, Maryland, North Carolina, South Carolina, Virginia, Alabama, Kentucky, Mississippi, Tennessee, West Virginia, Arkansas, Louisiana, Oklahoma, and Texas); West (Arizona, Colorado, Idaho, Montana, Nevada, New Mexico, Utah, Wyoming, Alaska, California, Hawaii, Oregon, and Washington). The geographic region was unknown for 9 patients (0.1%)

Table 2 CV comorbidities at HR + /HER2 − mBC diagnosis (grouped by similar ICD-9/10 codes[a])

CV comorbidity, *n* (%)	All patients (*N* = 6525)
Hypertension	3306 (50.7)
Hyperlipidemia	2247 (34.4)
Diabetes	1269 (19.4)
Congestive heart failure[b]	500 (7.7)
Ischemic heart disease[c]	401 (6.1)
Stroke[d]	276 (4.2)
Atrial fibrillation[e]	232 (3.6)
Bradyarrhythmia (and other CV arrhythmias)	181 (2.8)
Peripheral artery disease	130 (2.0)
Supraventricular tachycardia	67 (1.0)
Severe valvular heart disease	10 (0.2)

CV Cardiovascular, *HER2* − Human epidermal growth factor receptor 2-negative, *HR* + Hormone receptor-positive, *ICD* International Classification of Diseases, *mBC* Metastatic breast cancer

[a] ICD-9/10 codes captured for each CV comorbidity listed are reported in Supplementary Table 1

[b] Congestive heart failure includes heart failure and cardiomyopathy

[c] Ischemic heart disease includes coronary artery bypass graft, acute coronary syndrome, myocardial infarction, and STEMI/nSTEMI

[d] Stroke includes cerebrovascular disease, ischemic stroke, and hemorrhagic stroke.

[e] Atrial fibrillation includes heart flutter

Discussion

In this retrospective, observational analysis of closed claims data from the Merative Marketscan database, we evaluated the prevalence of pre-existing CV comorbidities and first-line treatment patterns among patients with newly diagnosed HR + /HER2 − mBC in the United States. By expanding our analysis beyond severe CV comorbidities and utilizing both ICD-9/10 codes and pharmacy claims, our study provides a comprehensive assessment of CV comorbidities. Overall, we found that pre-existing CV comorbidities were common among patients with HR + /HER2 − mBC, with more than half of patients (62%) having at least 1 pre-existing CV comorbidity at the time of mBC diagnosis. Among patients aged 65 years and older, the prevalence of CV comorbidities was even higher, with 87% of these patients having at least 1 CV comorbidity.

Of patients with a pre-existing CV comorbidity, over half (53%) were prescribed at least 1 medication with a risk of potential QTc prolongation at the time of mBC diagnosis, and 25% were prescribed at least 1 medication with a known risk of TdP. These findings are of particular importance in this population because female sex and age over 65 years are also considered non-modifiable patient risk factors that increase the risk of TdP with QTc-prolonging drugs [26]. Importantly, we evaluated QTc-prolonging medication use over an extended period compared with a similar prior study (90 vs 7 days, respectively) [20], thereby capturing a more complete representation of chronic medication use in this population. Antidepressants (eg, escitalopram and citalopram) and

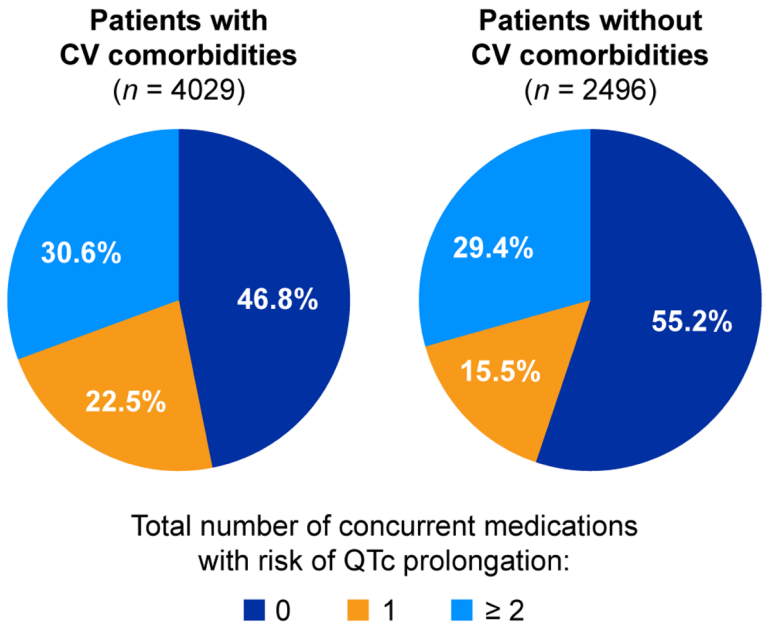


Fig. 3 Medications with risk of QTc prolongation used for > 30 days. The proportions of patients with or without CV comorbidities who received 0, 1, or ≥ 2 medications with a risk of QTc prolongation are presented. CV, cardiovascular; QTc, heart rate-corrected QT interval

antiemetics (eg, ondansetron) were some of the most frequently prescribed medications with a known risk of TdP in our study, mirroring the results of recent reports evaluating risk factors for QTc prolongation in patients with HR + /HER2 − mBC [20, 27]. Although beyond the scope of our current analysis, further research evaluating the pharmacological management of psychiatric comorbidities in patients with HR + /HER2 − mBC is warranted, considering the risk of TdP associated with certain antidepressants [6]. Notably, certain antidepressants such as venlafaxine or escitalopram may have been used in our study cohort for the management of ET-related side effects, reflecting prior evidence showing their utility in the control of hot flashes in breast cancer survivors [28].

Our study also observed an increase in the use of CDK4/6 inhibitors as first-line treatment for patients with HR + /HER2 − mBC and CV comorbidities over time. Specifically, the use of CDK4/6 inhibitors as first-line treatment increased from 22.1% of patients treated in 2016–2017 to 31.5% of patients treated in 2018–2022. This rise in CDK4/6 inhibitor use corresponds with the timing of their regulatory approvals in the United States [29]. Similar trends in the use of CDK4/6 inhibitors have been observed in other studies, including an analysis of data from patients aged 65 years and older with HR + / HER2 − mBC in the Surveillance, Epidemiology and End Results–Medicare Database [30]. These findings likely reflect clinical practice guidelines, such as those from the National Comprehensive Cancer Network or American Society of Clinical Oncology, which recommend first-line treatment with a CDK4/6 inhibitor plus ET for patients with HR + /HER2− mBC based on the significant progression-free survival benefit observed across a number of phase 3 trials [16, 31].

Although not a class effect of CDK4/6 inhibitors, ribociclib has been associated with QT interval prolongation and its concomitant use with agents that prolong the QT interval is discouraged [3, 8]. Ribociclib is the only CDK4/6 inhibitor with labeling recommendations for cardiac monitoring (including electrocardiogram and electrolyte monitoring) [8, 32]. Across pivotal phase 3 trials that evaluated ribociclib + ET in patients with HR + / HER2 − advanced or mBC (MONALEESA-2, −3, and −7), the incidence of grade 3/4 QTc prolongation ranged from 0.6% to 1.7% of patients [32]. This context, and the frequent use of concurrent medications with a risk of QTc prolongation as observed in our study, underscores the importance of considering concomitant use of QTc prolongation agents when selecting a CDK4/6 inhibitor for patients with HR + /HER2 − mBC.

The European Society of Cardiology (ESC) Cardio-Oncology Guidelines recommend QTc monitoring at baseline (day 1) and days 14 and 28, (published prior to package insert monitoring update) and with any dose increase for all patients receiving ribociclib (Class I recommendation); QTc monitoring is also suggested for patients receiving palbociclib or abemaciclib who have baseline QTc above the normal range or other conditions

Table 3 Most frequently prescribed medications associated with QTc prolongation in patients with CV comorbidities

Medications with risk of QTc prolongation used for > 30 days	Patients with CV comorbidities (*n* = 4029)
The 5 most frequently prescribed medications with risk of QTc prolongation, *n* (%)	
Hydrochlorothiazide	1130 (28.0)
Venlafaxine	434 (10.8)
Omeprazole	417 (10.3)
Hydrocodone	402 (10.0)
Furosemide	323 (8.0)
The 5 most frequently prescribed medications with known risk of TdP[a], *n* (%)	
Escitalopram	221 (5.5)
Citalopram	184 (4.6)
Ondansetron	173 (4.3)
Injection, ondansetron HCl, per 1 mg	160 (4.0)
Hydroxychloroquine	106 (2.6)
The 5 most frequently prescribed medications with possible risk of TdP[b], *n* (%)	
Venlafaxine	434 (10.8)
Hydrocodone	402 (10.0)
Tramadol	141 (3.5)
Injection, palonosetron HCl, 25 mcg	92 (2.3)
Tizanidine	72 (1.8)
The 5 most frequently prescribed medications with conditional risk of TdP[c], n (%)	
Hydrochlorothiazide	1130 (28.0)
Omeprazole	417 (10.3)
Furosemide	323 (8.0)
Pantoprazole	322 (8.0)
Sertraline	245 (6.1)

CV Cardiovascular, *QTc* Heart rate-corrected QT interval, *TdP* Torsades de Pointes

[a] Drugs that prolong QTc and are clearly associated with a known risk of TdP, even when taken as recommended

[b] Drugs that can cause QTc prolongation, but currently lack evidence for a risk of TdP when taken as recommended

[c] Drugs that are associated with TdP, but only under certain conditions of their use or by creating conditions that facilitate or induce TdP

that may prolong the QTc interval (Class IIa recommendation) [17]. The ribociclib product monograph has recently been updated with QTc monitoring recommended at baseline, day 14 and as clinically indicated as the majority of QT prolongation in clinical studies occurred within the first 4 weeks of treatment (kisqalihcp.com). Although the ESC guidelines suggest baseline CV risk stratification for all patients with cancer prior to starting treatment, they do not provide comprehensive guidance for baseline assessment of CV comorbidities or risk when specifically considering CDK4/6 inhibitor treatment. Considering the prevalence of CV comorbidities and the frequent use of medications with a risk of QTc prolongation observed in our study of patients with newly diagnosed HR + /HER2 − mBC, future research is needed to better inform CV risk assessment and monitoring in those patients receiving CDK4/6 inhibitor treatment.

Study limitations

The limitations of this study should also be acknowledged. The specific CV disease could not be determined if the ICD-9/10 code included multiple diseases, and for this reason, pre-existing CV comorbidities with similar ICD-9/10 codes were grouped together in the analyses (Table 2 and Supplementary Table 1). HR + / HER2 − status and diagnosis of mBC were based on claims data algorithms and not medical records; therefore, misclassification was possible and likely impacted both groups of patients (those with or without CV comorbidities) consistently. Furthermore, claims data may have missing data and incomplete capture of CV conditions and prescription claims [33–35]. The COVID-19 pandemic may have impacted diagnoses and treatments in the years 2020 and 2021. As a retrospective claims analysis, our study was not designed to evaluate clinical outcomes and did not collect data on

Table 4 Most frequently prescribed medications associated with QTc prolongation in patients without CV comorbidities

Medications with risk of QTc prolongation used for > 30 days	Patients without CV comorbidities (*n* = 2496)
The 5 most frequently prescribed medications with risk of QTc prolongation, *n* (%)	
Venlafaxine	250 (10.0)
Escitalopram	178 (7.1)
Hydrocodone	146 (5.8)
Injection, diphenhydramine HCl, up to 50 mg	137 (5.5)
Pantoprazole	116 (4.6)
The 5 most frequently prescribed medications with known risk of TdP[a], *n* (%)	
Escitalopram	178 (7.1)
Citalopram	98 (3.9)
Ondansetron	74 (3.0)
Injection, ondansetron HCl, per 1 mg	43 (1.7)
Hydroxychloroquine	38 (1.5)
The 5 most frequently prescribed medications with possible risk of TdP[b], *n* (%)	
Venlafaxine	250 (10.0)
Hydrocodone	146 (5.8)
Injection, granisetron HCl, 100 mcg	89 (3.6)
Injection, palonosetron HCl, 25 mcg	89 (3.6)
Levetiracetam	40 (1.6)
The 5 most frequently prescribed medications with conditional risk of TdP[c], *n* (%)	
Injection, diphenhydramine HCl, up to 50 mg	137 (5.5)
Pantoprazole	116 (4.6)
Sertraline	113 (4.5)
Omeprazole	90 (3.6)
Trazodone	46 (1.8)

CV Cardiovascular, *QTc* Heart rate-corrected QT interval, *TdP* Torsades de Pointes

[a] Drugs that prolong QTc and are clearly associated with a known risk of TdP, even when taken as recommended

[b] Drugs that can cause QTc prolongation, but currently lack evidence for a risk of TdP when taken as recommended

[c] Drugs that are associated with TdP, but only under certain conditions of their use or by creating conditions that facilitate or induce TdP

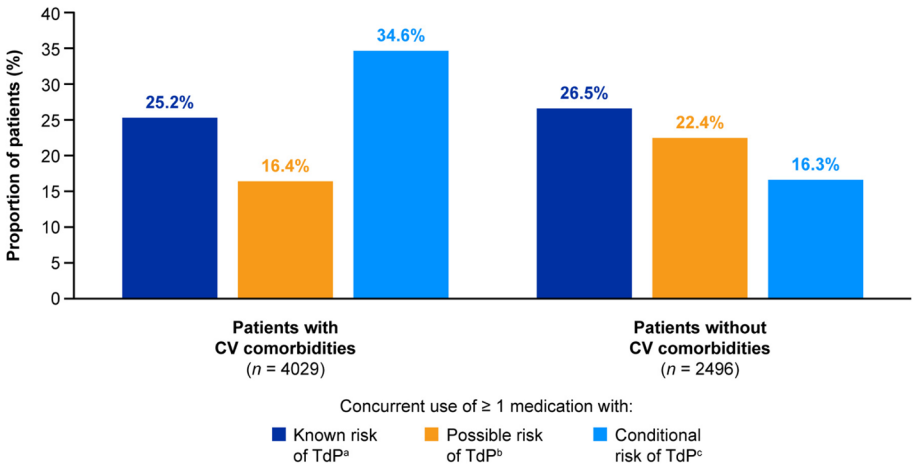


Fig. 4 Medications with risk of TdP used for > 30 days. The proportions of patients with or without CV comorbidities who received ≥ 1 medication with a known, possible, or conditional risk of TdP are presented. [a]Drugs that prolong QTc and are clearly associated with a known risk of TdP, even when taken as recommended. [b]Drugs that can cause QTc prolongation but currently lack evidence for a risk of TdP when taken as recommended. [c]Drugs that are associated with TdP, but only under certain conditions of their use or by creating conditions that facilitate or induce TdP. CV, cardiovascular; QTc, heart rate-corrected QT interval; TdP, Torsades de Pointes

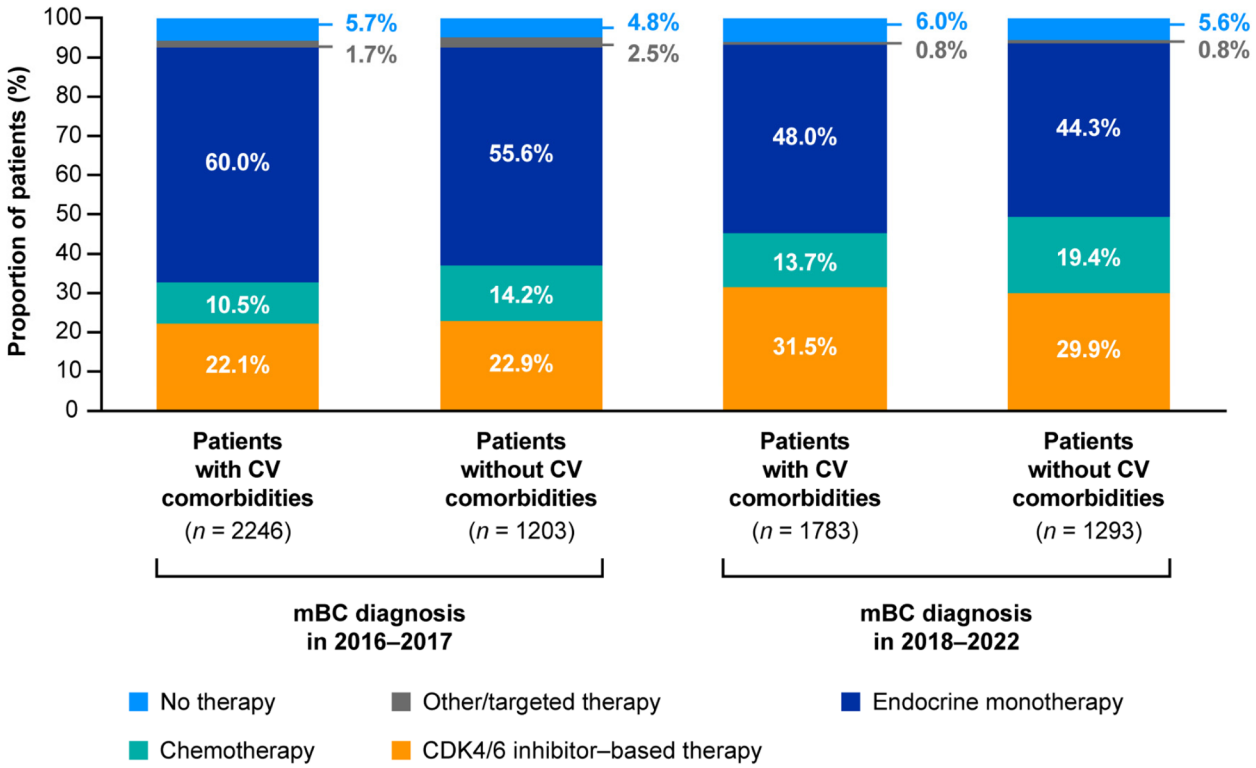


Fig. 5 First documented treatment after mBC diagnosis. First documented treatments after mBC diagnosis are presented for patients with or without CV comorbidities, stratified by year of mBC diagnosis (2016–2017 or 2018–2022). CDK4/6, cyclin-dependent kinase 4/6; CV, cardiovascular; ET, endocrine therapy; mBC, metastatic breast cancer

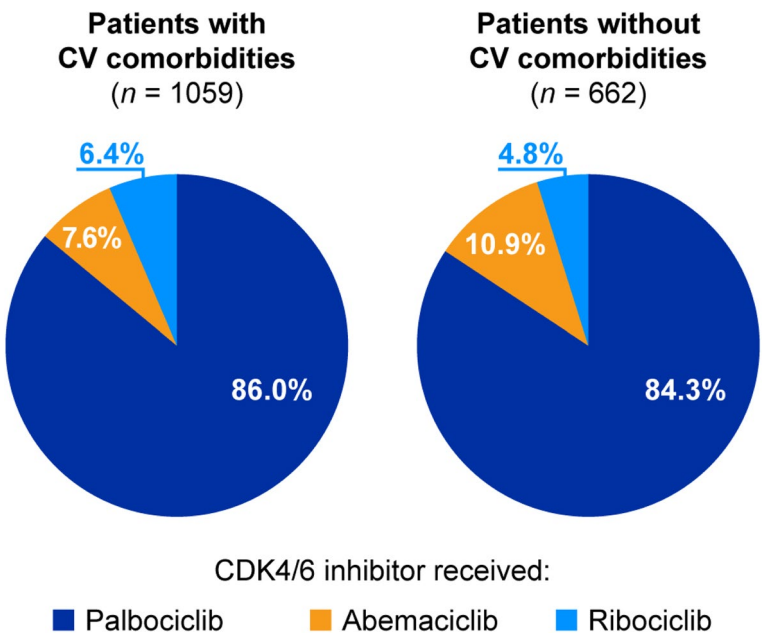


Fig. 6 First documented treatment after mBC diagnosis: CDK4/6 inhibitors. Among patients with or without CV comorbidities who received a CDK4/6 inhibitor as the first documented treatment for mBC ($n = 1721$), the proportions of those who received palbociclib, ribociclib, or abemaciclib are presented. CDK4/6, cyclin-dependent kinase 4/6; CV, cardiovascular; mBC, metastatic breast cancer

CV events, QTc prolongation, or survival. Lastly, the findings presented in this study may not be generalizable to patient populations not represented in the Merative Marketscan database, such as those aged > 65 years who are receiving patient assistance.

Conclusion

This observational study provides valuable insights into the prevalence of pre-existing CV comorbidities and first-line treatment patterns among patients with newly diagnosed HR + /HER2 − mBC in the United States. The findings highlight the common occurrence of CV comorbidities in this patient population and the importance of considering concomitant use of QT-prolonging agents, especially when selecting a CDK4/6 inhibitor. The study also demonstrates the increasing use of CDK4/6 inhibitors as first-line treatment over time. Evaluation of CV events and survival outcomes weighted for CV comorbidities in patients receiving CDK4/6 inhibitors is an area of future study that will help inform clinical guidelines for CV risk assessment and monitoring.

Abbreviations

CDK4/6	Cyclin-dependent kinase 4/6
CV	Cardiovascular
ET	Endocrine therapy
HER2 −	Human epidermal growth factor receptor 2–negative
HR +	Hormone receptor–positive
ICD	International Classification of Diseases
mBC	Metastatic breast cancer
NCI	National Cancer Institute
QTc	Heart rate-corrected QT interval
TdP	Torsades de Pointes

Supplementary Information

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Supplementary Material 1

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Authors' contributions

SD, AG, HM, DM, RM, IA, SS, and MF contributed to study conception or design. All authors contributed to analysis or interpretation of data and drafting or critical review/revision of the manuscript. All authors provided final approval of the submitted manuscript.

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Data availability

Upon request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions and exceptions, Pfizer may also provide access to the related individual de-identified participant data. See https://www.pfizer.com/science/clinical-trials/data-and-results for more information.

Declarations

Ethics approval and consent to participate

This study used Health Insurance Portability and Accountability Act–compliant and deidentified data, which did not meet the criteria for human subject research as specified in the United States Department of Health and Human Services 45 Code of Federal Regulations Part 46. Therefore, neither institutional review board approval nor informed consent was required.

Consent for publication

Not applicable.

Competing interests

- SD reports consulting for Pfizer Inc., AstraZeneca, Gilead Sciences, Myocardial Solutions, Novartis, and Lilly.
- AG reports being a ZERO Cancer Health Equity Task Force member; American Heart Association Council on Clinical Cardiology and Genomics and Precision Medicine Cardio-Oncology Committee member and site principal investigator; and an advisory board member for Myovant, Pfizer Inc., and Novartis.
- HM reports consulting for Novartis, Lilly, AstraZeneca, Gilead, Genetech, and Pfizer Inc.
- DM, RM, IA, and BL are employees of, and stockholders in, Pfizer Inc.
- SS is an employee of and stockholder in Pfizer Inc., and a stockholder in Roche.
- MF reports grant support from Medtronic and AstraZeneca; and has consulted for AstraZeneca, AbbVie, Johnson & Johnson, Janssen, Pfizer Inc., and Zoll.

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References

1. Redig AJ, McAllister SS. Breast cancer as a systemic disease: a view of metastasis. J Intern Med. 2013;274(2):113–26.
2. Howlader N, Altekruse SF, Li CI, Chen VW, Clarke CA, Ries LA, et al. US incidence of breast cancer subtypes defined by joint hormone receptor and HER2 status. J Natl Cancer Inst. 2014;106(5):dju055.
3. Mehta LS, Watson KE, Barac A, Beckie TM, Bittner V, Cruz-Flores S, et al. Cardiovascular disease and breast cancer: Where these entities intersect: A scientific statement from the American Heart Association. Circulation. 2018;137(8):e30–66.
4. Liu D, Ma Z, Yang J, Zhao M, Ao H, Zheng X, et al. Prevalence and prognosis significance of cardiovascular disease in cancer patients: a population-based study. Aging (Albany NY). 2019;11(18):7948–60.
5. Gogate A, Wheeler SB, Reeder-Hayes KE, Ekwueme DU, Fairley TL, Drier S, et al. Projecting the prevalence and costs of metastatic breast cancer from 2015 through 2030. JNCI Cancer Spectr. 2021;5(4):pkab063.
6. Fogli S, Del Re M, Curigliano G, van Schaik RH, Lancellotti P, Danesi R. Drug-drug interactions in breast cancer patients treated with CDK4/6 inhibitors. Cancer Treat Rev. 2019;74:21–8.
7. Woosley RL, et al. https://www.CredibleMeds.org. QTdrugs List [Accessed: April 23, 2023]. AZCERT, Inc. 1457 E. Desert Garden Dr., Tucson, AZ 85718.
8. U.S. Food and Drug Administration. Kisqali (ribociclib) - prescribing information. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/209092Orig1s018lbl.pdf. Accessed 8 Nov 2024.

9. Porta-Sánchez A, Gilbert C, Spears D, Amir E, Chan J, Nanthakumar K, et al. Incidence, diagnosis, and management of QT prolongation induced by cancer therapies: A systematic review. J Am Heart Assoc. 2017;6(12):e007724.
10. Duan J, Tao J, Zhai M, Li C, Zhou N, Lv J, et al. Anticancer drugs-related QTc prolongation, torsade de pointes and sudden death: Current evidence and future research perspectives. Oncotarget. 2018;9(39):25738–49.
11. Möhl A, Behrens S, Flaßkamp F, Obi N, Kreienbrinck A, Holleczek B, et al. The impact of cardiovascular disease on all-cause and cancer mortality: Results from a 16-year follow-up of a German breast cancer case-control study. Breast Cancer Res. 2023;25(1):89.
12. Patnaik JL, Byers T, Diguiseppi C, Denberg TD, Dabelea D. The influence of comorbidities on overall survival among older women diagnosed with breast cancer. J Natl Cancer Inst. 2011;103(14):1101–11.
13. Bradshaw PT, Stevens J, Khankari N, Teitelbaum SL, Neugut AI, Gammon MD. Cardiovascular disease mortality among breast cancer survivors. Epidemiology. 2016;27(1):6–13.
14. 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.
15. National Cancer Institute. NCI Comorbidity Index Overview. Available at: https://healthcaredelivery.cancer.gov/seermedicare/considerations/comorbidity.html Accessed 30 Aug 2023.
16. Gradishar WJ, Moran MS, Abraham J, Abramson V, Aft R, Agnese D, et al. NCCN Guidelines® Insights: Breast Cancer, Version 4.2023: Featured Updates to the NCCN Guidelines. J Natl Compr Canc Netw. 2023;21(6):594–608.
17. Lyon AR, López-Fernández T, Couch LS, Asteggiano R, Aznar MC, Bergler-Klein J, et al. 2022 ESC Guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS). Eur Heart J Cardiovasc Imaging. 2022;23(10):e333–465.
18. U.S. Food and Drug Administration. Ibrance (palbociclib) - prescribing information. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/212436s005s006lbl.pdf. Accessed 19 Aug 2024.
19. U.S. Food and Drug Administration. Verzenio (abemaciclib) - prescribing information. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/208716s010s011lbl.pdf. Accessed 19 Aug 2024.
20. Ward M, Harnett J, Bell TJ, Mardekian J. Risk factors of QTc prolongation in women with hormone receptor-positive/human epidermal growth factor receptor 2-negative metastatic breast cancer: A retrospective analysis of health care claims data. Clin Ther. 2019;41(3):494–504.
21. Merative. Merative MarketScan Research Databases. Available at: https://www.merative.com/documents/brief/marketscan-explainer-general. Accessed 23 Apr 2024.
22. Whyte JL, Engel-Nitz NM, Teitelbaum A, Gomez Rey G, Kallich JD. An evaluation of algorithms for identifying metastatic breast, lung, or colorectal cancer in administrative claims data. Med Care. 2015;53(7):e49-57.
23. Blumen H, Fitch K, Polkus V. Comparison of treatment costs for breast cancer, by tumor stage and type of service. Am Health Drug Benefits. 2016;9(1):23–32.
24. Jyotsna F, Ahmed A, Kumar K, Kaur P, Chaudhary MH, Kumar S, et al. Exploring the complex connection between diabetes and cardiovascular disease: Analyzing approaches to mitigate cardiovascular risk in patients with diabetes. Cureus. 2023;15(8):e43882.
25. Peng M, Southern DA, Williamson T, Quan H. Under-coding of secondary conditions in coded hospital health data: Impact of co-existing conditions, death status and number of codes in a record. Health Informatics J. 2017;23(4):260–7.
26. Khatib R, Sabir FRN, Omari C, Pepper C, Tayebjee MH. Managing drug-induced QT prolongation in clinical practice. Postgrad Med J. 2021;97(1149):452–8.
27. Guha A, Moore H, Fradley M, Rose CG, Stergiopoulos S, Chen C, et al. QT STAR: Concurrent QTc-prolonging medication use among patients with HR+/HER2– mBC receiving a CDK4/6 inhibitor in the first line. Poster presented at: Global Cardio-Oncology Summit; September 22–24, 2024; Minneapolis, MN, USA
28. Franzoi MA, Agostinetto E, Perachino M, Del Mastro L, de Azambuja E, Vaz-Luis I, et al. Evidence-based approaches for the management of side-effects of adjuvant endocrine therapy in patients with breast cancer. Lancet Oncol. 2021;22(7):e303–13.
29. Shah M, Nunes MR, Stearns V. CDK4/6 inhibitors: Game changers in the management of hormone receptor–positive advanced breast cancer? Oncology (Williston Park). 2018;32(5):216–22.
30. Goyal RK, Holmes HM, Chen H, Abughosh S, Candrilli SD, Johnson ML. Impact of CDK4/6 inhibitors on chemotherapy utilization in earlier therapy lines for HR+/HER2- metastatic breast cancer in the United States. Breast Cancer Res Treat. 2023;198(1):159–66.
31. Burstein HJ, Somerfield MR, Barton DL, Dorris A, Fallowfield LJ, Jain D, et al. Endocrine treatment and targeted therapy for hormone receptor-positive, human epidermal growth factor receptor 2-negative metastatic breast cancer: ASCO Guideline Update. J Clin Oncol. 2021;39(35):3959–77.
32. Fiste O, Mavrothalassitis E, Apostolidou K, Trika C, Liontos M, Koutsoukos K, et al. Cardiovascular complications of ribociclib in breast cancer patients. Crit Rev Oncol Hematol. 2024;196:104296.
33. Psaty BM, Delaney JA, Arnold AM, Curtis LH, Fitzpatrick AL, Heckbert SR, et al. Study of cardiovascular health outcomes in the era of claims data: The Cardiovascular Health Study. Circulation. 2016;133(2):156–64.
34. Guimarães PO, Krishnamoorthy A, Kaltenbach LA, Anstrom KJ, Effron MB, Mark DB, et al. Accuracy of medical claims for identifying cardiovascular and bleeding events after myocardial infarction: A secondary analysis of the TRANSLATE-ACS study. JAMA Cardiol. 2017;2(7):750–7.
35. Cepeda MS, Fife D, Denarié M, Bradford D, Roy S, Yuan Y. Quantification of missing prescriptions in commercial claims databases: results of a cohort study. Pharmacoepidemiol Drug Saf. 2017;26(4):386–92.

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