JACC: CARDIOONCOLOGY VOL. 6, NO. 6, 2024

MINI-FOCUS ISSUE: HEART DISEASE IN WOMEN

ORIGINAL RESEARCH

Cardiovascular Disease With Hormone Therapy and Ovarian Suppression in Premenopausal Breast Cancer Survivors

Elizabeth J. Polter, PhD,[a] Anna E. Prizment, PhD,[b] Rob F. Walker, MPH,[a] Zoe Ryan, BS,[c] Wendy Wang, PhD,[a] Anne H. Blaes, MD,[d] Pamela L. Lutsey, PhD[a]

ABSTRACT

BACKGROUND Hormone therapies, including aromatase inhibitors and tamoxifen, are used with ovarian suppression to improve outcomes in premenopausal patients with breast cancer. Cardiovascular impacts of these treatments among premenopausal women are unknown.

OBJECTIVES The aim of this study was to test the hypothesis that the use of aromatase inhibitors in combination with ovarian suppression, relative to tamoxifen, is associated with greater incident cardiovascular disease (CVD) risk in premenopausal breast cancer survivors.

METHODS The MarketScan administrative claims databases (2013-2020) were used to identify enrollees younger than 55 years who had incident breast cancer and were treated with either an aromatase inhibitor and ovarian suppression or tamoxifen. Propensity score matching was used to balance treatment groups across confounding variables including age, breast cancer treatments, and comorbidities. The HR for CVD (including atrial fibrillation, myocardial infarction, stroke, heart failure hospitalization, angina, or coronary revascularization) was calculated by treatment group.

RESULTS In the matched cohort, over a median follow-up time of 1.55 years, the incidence rate was 2.3 per 100 person-years among users of aromatase inhibitors plus ovarian suppression (51 CVD events in 2,205 person-years) and 1.0 per 100 person-years for tamoxifen users (102 CVD events in 9,913 person-years). Users of aromatase inhibitors plus ovarian suppression had a 2.20-fold higher hazard of CVD than tamoxifen users (HR: 2.20; 95% CI: 1.57-3.09). In absolute terms, the incidence rate difference was 0.012 (95% CI: 0.006-0.019). Findings were robust to several sensitivity analyses.

CONCLUSIONS Premenopausal patients with breast cancer treated with aromatase inhibitors and ovarian suppression may be at elevated risk for CVD and should be monitored for cardiovascular risk. (JACC CardioOncol. 2024;6:907–918)

From the [a]Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, Minneapolis, Minnesota, USA; [b]Department of Laboratory Medicine and Pathology, University of Minnesota, Minneapolis, Minnesota, USA; [c]University of Minnesota Medical School, University of Minnesota, Minneapolis, Minnesota, USA; and the [d]Division of Hematology/Oncology/Transplantation, University of Minnesota, Minneapolis, Minnesota, USA.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received February 3, 2024; revised manuscript received July 31, 2024, accepted August 20, 2024.

ISSN 2666-0873 https://doi.org/10.1016/j.jaccao.2024.08.006

ABBREVIATIONS AND ACRONYMS

CVD = cardiovascular disease

GnRH = gonadotropin-releasing hormone

IRD = incidence rate difference

Two hormone therapies, aromatase inhibitors and tamoxifen, improve outcomes for patients with hormone receptor–positive breast cancer.[1,2] Aromatase inhibitors are preferred over tamoxifen for most postmenopausal patients because they are more protective against cancer recurrence and mortality.[3] However, in premenopausal patients with breast cancer, ovarian estrogen production bypasses aromatase inhibitors' function, rendering them ineffective unless ovarian function is suppressed.[4]

Over the past decade, the use of aromatase inhibitors with ovarian suppression in premenopausal patients with breast cancer has become increasingly common.[5] Ovarian function is typically suppressed through surgical removal (bilateral oophorectomy) or temporary medical suppression using gonadotropin-releasing hormone (GnRH) agonists. A combined analysis of 2 clinical trials (SOFT [Suppression of Ovarian Function Trial] and TEXT trials) of 3,066 premenopausal patients with breast cancer showed that cancer recurrence risk was 35% lower among enrollees receiving the aromatase inhibitor exemestane and ovarian suppression compared with tamoxifen alone (HR: 0.65; 95% CI: 0.49-0.87).[6] Since 2016, the National Comprehensive Cancer Network has included ovarian suppression with aromatase inhibitors or tamoxifen in its hormone therapy recommendations for premenopausal patients.[7]

Although hormone therapies combined with ovarian suppression improve breast cancer survival among younger people, they may also increase the risk for cardiovascular disease (CVD). In postmenopausal patients, the use of aromatase inhibitors yields a near total reduction of endogenous estrogen, which may have adverse effects on blood cholesterol, potentially leading to atherosclerotic CVD.[8] A meta-analysis of clinical trials in postmenopausal women revealed that aromatase inhibitor users had a 30% higher CVD hazard than tamoxifen users.[9] Among premenopausal women, ovarian suppression may also affect CVD risk.[10,11]

No study has formally compared the combined cardiovascular effects of ovarian suppression with aromatase inhibitors vs tamoxifen in premenopausal people with breast cancer. The incidence of breast cancer in young women has increased by approximately 10% over the past 20 years, affecting 0.5% of women younger than 40 years.[12] It is crucial to understand the long-term impacts of breast cancer treatments among these younger patients. Using real-world data, we tested the hypothesis that premenopausal patients with breast cancer treated with aromatase inhibitors plus ovarian suppression would have greater risk for incident CVD and hyperlipidemia than those treated with tamoxifen.

METHODS

REGULATORY AND ETHICS APPROVAL. The University of Minnesota Institutional Review Board deemed analysis of these deidentified data exempt.

STUDY POPULATION. We used data from the Merative MarketScan Commercial Claims and Encounters Database for the time period from January 1, 2013, to December 31, 2020. MarketScan claims databases include enrollment information, health plan type, and claims for inpatient care, outpatient care, and pharmacy services for health insurance enrollees each year.[13] U.S. residents and their dependents with employer-based health insurance are the source cohort for these deidentified data sets.

STUDY DESIGN. This analysis used a target trial[14] framework: study population, timing, and covariate adjustment were chosen to match a hypothetical clinical trial as closely as possible to estimate a more accurate causal effect from observational data. Our study design aimed to emulate an extension of the SOFT trial, which evaluated the impact of aromatase inhibitors and ovarian suppression on breast cancer recurrence in premenopausal patients with breast cancer.[15,16] A comparison of our real-world analysis with this target trial is shown in **Table 1**. A graphical depiction of the study design is shown in **Figure 1**, according to the framework of Schneeweiss et al.[17] Enrollees were included if they were female, were 18 to 55 years of age at the date of their first breast cancer–related claim, and had incident breast cancer. Incident breast cancer was defined as at least 1 inpatient claim or 2 outpatient claims (7-365 days apart) with invasive breast cancer as the primary diagnosis code, in addition to mastectomy, lumpectomy, or axillary lymph node dissection. This definition is modified from a previously validated algorithm designed for use in analyses of Medicare claims (positive predictive value 89%-93%, sensitivity 80%).[18] To this algorithm, we incorporated definitions used in recent MarketScan analyses of hormone therapy in premenopausal patients.[5] Additionally, patients were required to have at least 6 months (183 days) of continuous enrollment before their first breast cancer claim and continuous enrollment from their first breast cancer claim to their first hormone therapy or ovarian suppression claim. Enrollees were excluded if during all available lookback preceding the first breast cancer claim (minimum of 6 months required) they had: 1) any hormone therapy or

TABLE 1 Target Trial Framework Used to Estimate the Association of Treatment Group With Incident CVD

	Target Trial (eg, SOFT)	This Study
Inclusion criteria	Operable breast cancer; all enrollees had undergone mastectomy with optional radiotherapy or breast-conserving surgery with radiotherapy[15,28,35]	Incident operable breast cancer: 1) incident breast cancer, defined as at least 1 inpatient claim or 2 outpatient claims (between 7 and 365 d apart) with invasive breast cancer as the primary diagnostic code, in addition to mastectomy, lumpectomy, or axillary lymph node dissection; and 2) at least 183 d of continuous enrollment prior to the first breast cancer claim and continuous enrollment from the first breast cancer claim to the first hormone therapy or ovarian suppression claim.
	Premenopausal status, confirmed by blood estradiol levels[28]	Premenopausal status: 1) female; and 2) between 18 and 55 y of age at the date of the first breast cancer–related claim (sensitivity analysis restricted to age <50 y)
Exclusion criteria	Several including: Distant metastasis Severe illness (including CVD) that might prevent long-term follow-up Mental illness or substance use disorders that might limit follow-up or adherence[28]	Any hormone therapy or ovarian suppression claim in a washout period composed of continuous enrollment (at least 183 d) immediately preceding the first breast cancer claim Any CVD (for analyses of incident CVD) or hyperlipidemia claim (for analyses of incident hyperlipidemia) before the index date
Treatment groups	Tamoxifen only: 20 μg daily,[28] intention-to-treat for primary analysis	Tamoxifen only: any dose of tamoxifen; no ovarian suppression claims from MarketScan initiation through 60 d after the first tamoxifen claim
	Aromatase inhibitor: 25 μg exemestane daily for up to 5 y plus Ovarian suppression: choice of GnRH agonist, bilateral oophorectomy, or bilateral ovarian irradiation[28]	Aromatase inhibitor: any dose of exemestane, anastrozole, or letrozole plus Ovarian suppression: GnRH agonist or bilateral oophorectomy occurring within 30 d before or 60 d after the first aromatase inhibitor fill
	Tamoxifen: 20 μg daily plus Ovarian suppression: choice of GnRH agonist, bilateral oophorectomy, or bilateral ovarian irradiation[28]	Because only 7 participants met the definition for this treatment group, users of tamoxifen plus ovarian suppression were excluded from this analysis
Assignment procedure	Random allocation: potentially confounding variables are assumed to be balanced across treatment groups[6,28]	After propensity score matching and regression adjustment, confounding variables are assumed to be balanced across treatment groups, although unmeasured confounding may still exist
Follow-up initiation	Follow-up initiated immediately upon randomization and treatment initiation[28]	Tamoxifen only: the date of the first tamoxifen fill Aromatase inhibitors plus ovarian suppression: the last date of aromatase inhibitor or ovarian suppression initiation; the median time between the first ovarian suppression claim and the first aromatase inhibitor claim was 0 d (Q1-Q3: −11 to 1 d); sensitivity analyses were conducted to evaluate immortal time bias
Follow-up endpoint[a]	The date of the first CVD or hyperlipidemia event, loss to follow-up, or censoring	
Outcome definition[a]	CVD, defined as The first event of stroke, myocardial infarction, hospitalization for heart failure, atrial fibrillation, angina, or coronary revascularization The first event of hyperlipidemia	
Treatment effect of interest	Intention-to-treat: enrollees were evaluated by their initial randomized treatment assignment, regardless of adherence	Intention-to-treat: enrollees were evaluated according to their first hormone therapy fill, regardless of adherence

[a]The SOFT trial evaluated the impact of aromatase inhibitors with ovarian suppression compared with tamoxifen on breast cancer outcomes (disease-free survival). The investigators of this trial tabulated CVD outcomes along with other adverse events but did not evaluate the risk for CVD. The inclusion and exclusion criteria and treatment definitions for our study are based on the SOFT trial, but follow-up endpoints and outcome definitions are based on a hypothetical target trial.

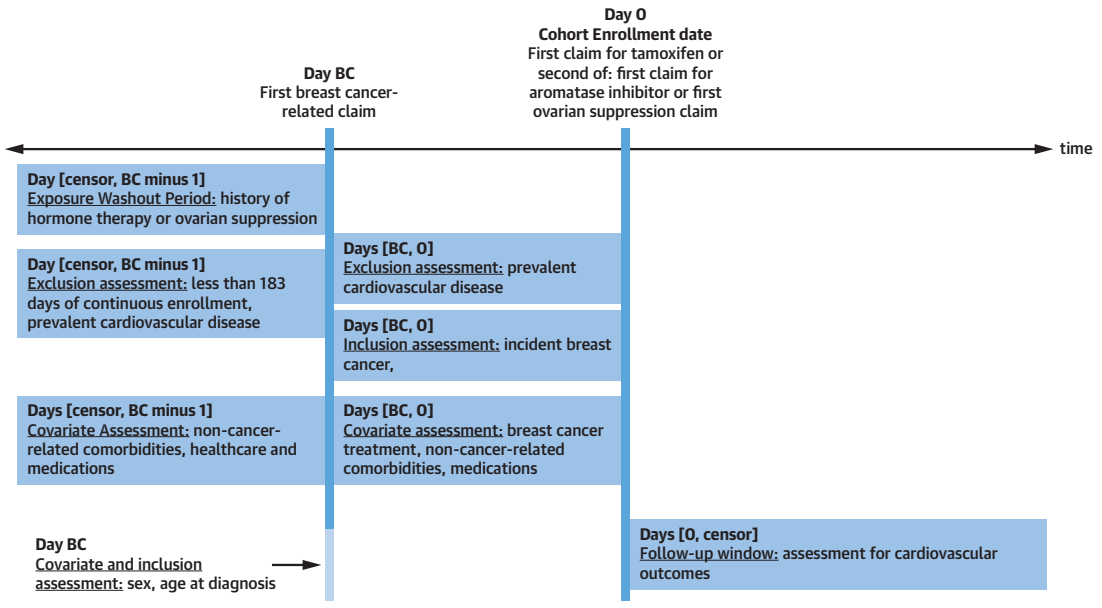
CVD = cardiovascular disease; GnRH = gonadotropin-releasing hormone; SOFT = Suppression of Ovarian Function Trial.

ovarian suppression claim; or 2) any CVD claim (including myocardial infarction, ischemic stroke, atrial fibrillation, hospitalization for heart failure, angina, or coronary revascularization, for analyses of incident CVD). For analyses of incident hyperlipidemia and hypertension, we also excluded enrollees with hyperlipidemia claims or hypertension claims, respectively, before the initiation of follow-up. Codes and algorithms variables used in the cohort construction are listed in Supplemental Table 1.

MEASURES. All codes and algorithms for cohort definition, exposure, outcome, and covariate measures are shown in Supplemental Tables 1 to 3. We used previously published, validated algorithms wherever available to identify each variable.[5,19] When algorithms were unavailable, codes and unvalidated algorithms listed in similar studies were compiled and evaluated for face validity in online code tables.

Exposure. Tamoxifen and aromatase inhibitors are taken orally daily, and ovarian suppression medications are delivered via subcutaneous injection (3.5 mg at weekly intervals) or implantation (for goserelin, typically delivered monthly). Medical ovarian suppression use was defined as any GnRH agonist implantation or injection within 30 days before or 60 days after the first hormone therapy fill. Surgical ovarian suppression was defined as bilateral oophorectomy occurring between 30 days before and 60 days after the first hormone therapy fill. Procedure and drug codes used to define hormone therapies and

FIGURE 1 Graphical Depiction of Variable and Follow-Up Assessment, MarketScan 2013 to 2020



This figure graphically depicts the study design according to the framework of Schneeweiss et al[17] for describing studies conducted in health care databases. Vertical lines represent the day of first breast cancer (BC) claim and the cohort enrollment date (day 0) for the present analysis, respectively. Boxes on the left side of the figure describe data collated prior to the first BC claim, including those related to the exposure washout period, assessment of exclusion criteria, and gathering covariate information using all available prior records. The boxes between the vertical bars describe information obtained between the first BC claim and the date when follow-up began for this analysis (ie, cohort enrollment date, day 0). Information collated in this window includes additional assessment for presence of exclusion criteria, inclusion criteria assessment, and additional assessment of covariates including those related to BC treatment. The box to the right of the cohort enrollment date vertical line represents follow-up for cardiovascular outcomes.

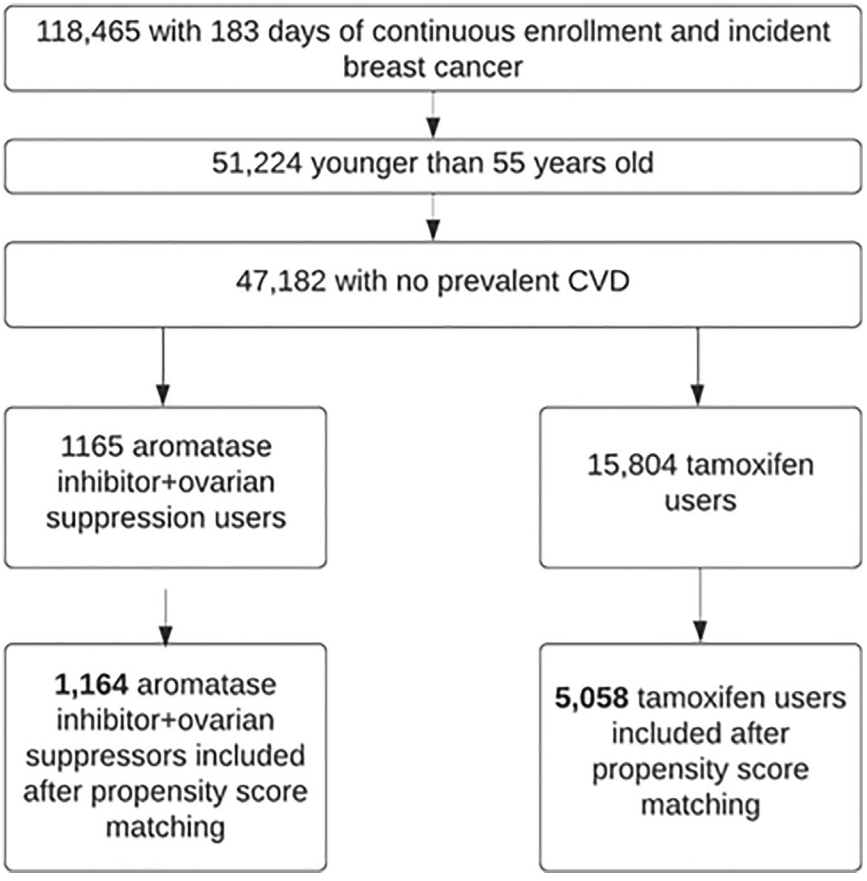
ovarian suppression are shown in Supplemental Table 2. Enrollees were categorized into treatment groups:

- Combination of aromatase inhibitors and ovarian suppression (hereafter referred to as "aromatase inhibitors"): At least 1 aromatase inhibitor fill after breast cancer diagnosis and either bilateral oophorectomy or GnRH agonist claim (occurring within 30 days before or 60 days after the first aromatase inhibitor fill). The index date (which signals the start of follow-up) for these enrollees was the day of the first aromatase inhibitor fill or first ovarian suppression claim, whichever came last (median time 0 days; sensitivity analyses using alternative windows are described later). Overall, 1,165 eligible aromatase inhibitor users were available for inclusion (Figure 2).
- Tamoxifen: At least 1 tamoxifen prescription fill after a breast cancer diagnosis, with no ovarian suppression claims any time before the first tamoxifen fill or within 60 days after. The index date for these enrollees was the day of the first tamoxifen fill. Overall, 15,804 eligible tamoxifen users were available for inclusion (Figure 2).

Because our goal was to mimic the estimation of the intention-to-treat effect in a clinical trial, treatment group was treated as a time-invariant variable. This approach is consistent with recommended practices in pharmacoepidemiology.[20] Aromatase inhibitor users who began ovarian suppression more than 60 days after aromatase inhibitor initiation (or never) were assumed to be postmenopausal or otherwise anomalous and were excluded from the analysis.

Outcomes. The primary outcome was a composite measure of incident CVD, defined as the first event of atrial fibrillation, myocardial infarction, stroke (ischemic or hemorrhagic stroke or transient ischemic

FIGURE 2 Flowchart Showing Eligible Enrollees Included in the Main Analysis



This figure reports the number of patients with breast cancer who were eligible on the basis of having the required continuous enrollment and International Classification of Diseases codes indicating evidence of breast cancer and details how the implementation of exclusion and matching criteria resulted in our final analytical sample. CVD = cardiovascular disease.

attack), hospitalization for heart failure, angina, or coronary revascularization. We also evaluated 3 secondary endpoints: first, a stricter composite measure of CVD (hereafter called "hard" CVD), including only atrial fibrillation, myocardial infarction, stroke, or hospitalization for heart failure. Next, we evaluated incident hyperlipidemia and hypertension, as both are CVD risk factor pathways that may be influenced by these hormone therapies. The algorithms, definitions, and codes used for each CVD outcome are listed in Supplemental Table 1.[21-26]

Covariates. Covariates were chosen a priori as measured variables that may confound the association between hormone therapy assignment and CVD. We included the following breast cancer-related covariates: metastasis, chemotherapy (including anthracyclines), radiation, type of surgery (mastectomy or other), and trastuzumab or pertuzumab use for $HER2^{+}$ cancer. In addition, we included the following comorbidities: hypertension, chronic kidney disease, chronic obstructive pulmonary disease, peripheral artery disease, liver disease, hematological disorders, diabetes mellitus, and obesity, as well as hysterectomy. Assessment of covariates used all claims in the MarketScan databases occurring before the index date (**Figure 1**). More recently approved breast cancer treatments, including pembrolizumab and CDK4/6 inhibitors, were not included in this analysis.

STATISTICAL ANALYSIS. We calculated the proportion of aromatase inhibitor users using medical vs surgical ovarian suppression, the median (Q1-Q3) time between aromatase inhibitor and ovarian suppression initiation, and the median (range) follow-up time for each group.

TABLE 2 Baseline Characteristics of Enrollees by Hormone Therapy and Ovarian Suppression Group, MarketScan 2013 to 2020

	Tamoxifen (n = 5,058)	Aromatase Inhibitors Plus Ovarian Suppression (n = 1,164)	Standardized Mean Difference (After Matching)
Person-years at risk	9,913	2,205	
Age, y	44.8 ± 5.7	43.7 ± 6.1	0.22
Cancer characteristics			
Chemotherapy	2,847 (56.3)	708 (60.8)	−0.08
Radiation	2,841 (56.2)	642 (55.2)	0.03
Mastectomy	2,384 (47.1)	586 (50.3)	−0.06
Trastuzumab	685 (13.5)	157 (13.5)	−0.006
Pertuzumab	492 (9.7)	115 (9.9)	−0.002
Metastasis	2,183 (43.2)	578 (49.7)	−0.13
Hysterectomy	123 (2.4)	28 (2.4)	0.003
Comorbidities			
Hypertension	1,181 (23.3)	257 (22.1)	0.02
Diabetes	407 (8)	93 (8)	0.005
Kidney disease	78 (1.5)	18 (1.5)	0.001
Liver disease	575 (11.4)	143 (12.3)	−0.03
Peripheral artery disease	186 (3.7)	43 (3.7)	0.001
COPD	920 (18.2)	214 (18.4)	<0.001
Hematological disorders	447 (8.8)	105 (9)	−0.003
Obesity	1,159 (22.9)	270 (23.2)	−0.001

Values are mean ± SD or n (%).
COPD = chronic obstructive pulmonary disease.

We conducted prospective analyses comparing each outcome across treatments. Propensity scores were created to balance covariates between groups. To create propensity scores, we fit logistic regression models to estimate the probability of aromatase inhibitor use vs tamoxifen use. We included as predictors in the models all covariates listed previously as well as diagnosis date, hormone therapy initiation date, enrollment date, and age at diagnosis. The propensity score for each enrollee was their model-predicted conditional odds of receiving the treatment. Enrollees were matched by propensity score to their nearest neighbors using a greedy matching algorithm with a caliper of 0.2 SDs of the propensity score. Each aromatase inhibitor user was matched to up to 5 tamoxifen users.

Both before matching and in the matched cohorts, we computed the mean and SD (for age) and frequencies and proportions (for all other variables) for each covariate in each treatment group. The standardized difference for each covariate across treatment groups was calculated as the absolute value of the difference in means across the treatment groups, divided by the SD. Each covariate was considered well balanced across treatment groups if the standardized difference was <0.1. We used histograms to determine the distribution of propensities in each group.

After propensity score matching, Cox proportional hazards models were fit to estimate the effect (ie, HR and 95% CI) of aromatase inhibitors vs tamoxifen on each CVD outcome, adjusting for age at breast cancer diagnosis and propensity score. Person-time accrued from the index date until the occurrence of an outcome, disenrollment (reason unknown), or December 31, 2020. Models also adjusted for metastatic cancer, which was more common in aromatase inhibitor users even after propensity score matching. We assessed the proportional hazards assumption by visual inspection of log-log survival curves; no violations were observed. To calculate an absolute measure of association, in propensity score-matched cohorts, we fit Poisson models to calculate the incidence rate ratio. Again, models were adjusted for age at breast cancer diagnosis, metastasis, and propensity score. Then, the delta method was used to calculate the adjusted incidence rate difference (IRD) with its 95% CI. To visually display the findings, we also created a Kaplan-Meier curves for the matched cohort. Kaplan-Meier curves were created using R version 4.4.0 (R Foundation for Statistical Computing). Poisson analyses were conducted using Stata version 18 (StataCorp). All other analyses were conducted using SAS version 9.4 (SAS Institute).

SENSITIVITY ANALYSES. We conducted several sensitivity analyses to help ensure the robustness of our findings.

- The main analysis was repeated using a different matching ratio: 1 aromatase inhibitor to 7 tamoxifen users.
- The main analysis was repeated with calipers of 0.1 and 0.01 SD of the propensity score.
- Analyses were repeated using stabilized inverse-probability weighting instead of matching to control for confounding. For analyses of CVD, hard CVD, and hypertension, 1 observation with a very large weight was removed (this individual was already excluded from analyses of hyperlipidemia).
- Analyses were repeated with no matching or inverse probability weighting. To control for confounding, Cox proportional hazards models were adjusted for age at cancer diagnosis, metastasis, and the propensity score.
- To avoid any impact of the COVID-19 pandemic on our estimates, we repeated the analysis excluding all claims after March 1, 2020.
- We repeated the main analysis after excluding all enrollees with metastatic cancer.
- Because some postmenopausal enrollees were likely misclassified as premenopausal by our

definition (limiting enrollees to 55 years of age), we conducted sensitivity analyses capping diagnosis age at 50 years.

- Because our analysis compared 1 combined treatment with 1 single drug, our analysis was susceptible to immortal time bias. For our main analysis, tamoxifen users started follow-up on the day of their first hormone therapy fill but aromatase inhibitor users on the day of their second claim (for aromatase inhibitors or ovarian suppression). To evaluate the impact of this choice, we repeated the analysis: 1) initiating follow-up for tamoxifen enrollees 60 days after their first tamoxifen prescription fill; and 2) initiating follow-up 60 days after the full criteria were met for both treatment cohorts.

RESULTS

Prior to matching, tamoxifen users were approximately 3 years older than aromatase inhibitor users on average. Aromatase inhibitor users were more than twice as likely to have metastatic cancer and nearly twice as likely to have claims for chemotherapy (Supplemental Table 4).

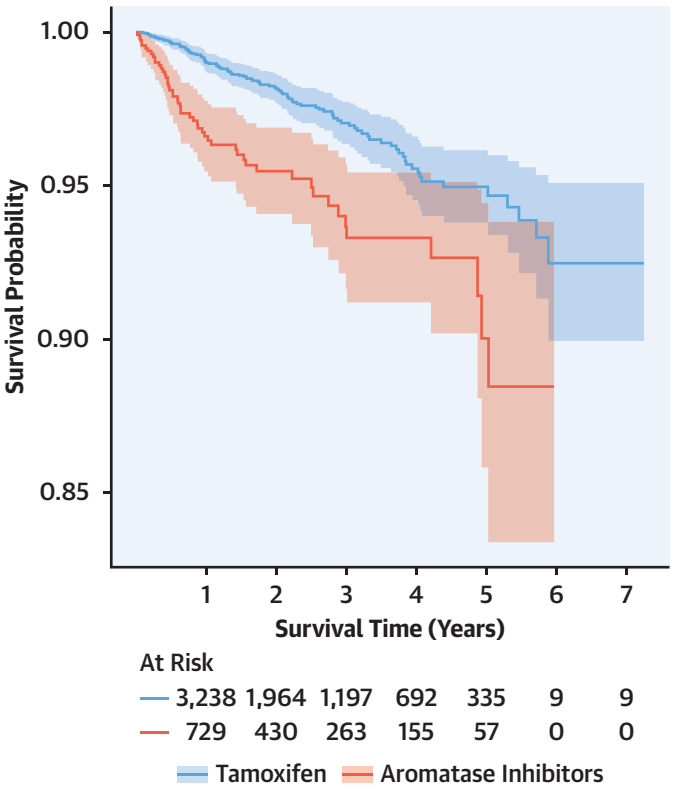
The final matched analytical sample included 5,058 patients managed with tamoxifen and 1,164 with aromatase inhibitors. In the matched cohort, the mean age was 44.8 ± 5.7 years for tamoxifen users and 43.7 ± 6.1 years for aromatase inhibitor users. Forty-three percent of tamoxifen users had metastatic cancer compared with 49.7% of aromatase inhibitor users (**Table 2**). All covariates other than age and metastasis (which were included as predictors in our final models) were well balanced in our matched cohorts (**Table 2**). Propensity scores were approximately equally distributed across groups in each cohort (Supplemental Figure 1).

Of aromatase inhibitor users, 95.6% used GnRH agonists as ovarian suppression, while 4.4% underwent bilateral oophorectomy. The median time between aromatase inhibitor and ovarian suppression initiation was 0 days (Q1-Q3: −11 to 1 days). The median follow-up time was 1.57 years for tamoxifen users (range: 0.003-7.25 years) and 1.50 years for aromatase inhibitor users (range: 0.01-5.97 years).

For the primary CVD outcome in our matched analysis, we observed 51 incident CVD events in aromatase inhibitor users (incidence rate: 0.023) and 102 in tamoxifen users (incidence rate: 0.010). The Kaplan-Meier plot is displayed in **Figure 3**. The HR was 2.20 (95% CI: 1.57-3.09) for the aromatase inhibitor group vs tamoxifen (**Table 3**). In absolute terms, the IRD was 0.012 (95% CI: 0.006-0.019). Several sensitivity analyses were conducted (**Table 4**), and most had point HR estimates close to 2. The HR for "hard" CVD overall was 1.68 (95% CI: 0.73-3.86) for aromatase inhibitors vs tamoxifen (**Table 3**). The IRD for "hard" CVD was 0.001 (95% CI −0.001 to 0.004) for aromatase inhibitors vs tamoxifen. Again, most sensitivity analyses were close to this value (Supplemental Table 5).

For incident hyperlipidemia, the HR was 1.49 (95% CI: 1.00-2.23) and the IRD was 0.007 (95% CI: −0.000 to 0.014) for aromatase inhibitors vs tamoxifen (**Table 3**), with sensitivity analysis HRs of 1.36 to 1.84 (Supplemental Table 6). For incident hypertension, the HR was 1.19 (95% CI: 0.88-1.60) and the IRD was 0.005 (95% CI: −0.004 to 0.014) for

FIGURE 3 Kaplan-Meier Curves of Composite CVD Incidence by Treatment Group



Kaplan-Meier curves of survival probability over time for users of aromatase inhibitors with ovarian suppression vs tamoxifen. Survival time in years after beginning hormone therapy (range: 0-8) is provided on the x-axis, and survival probability (scale: 1.00-0.80) is provided on the y-axis. Users of aromatase inhibitors plus ovarian suppression are represented in red and tamoxifen users in blue. The Kaplan-Meier curves for incident cardiovascular disease (CVD) diverge early, with a suggestion of worse survival for users of aromatase inhibitors plus ovarian suppression relative to tamoxifen users, and continue to show separation through follow-up. CIs, represented by bands around the Kaplan-Meier curves, are wider later in follow-up, because fewer people in the analytical sample had reached that length of follow-up.

TABLE 3 HRs and Incidence Rate Differences for Incident CVD by Treatment Group, MarketScan 2013 to 2020

	Number of Events	Person-Years	HR (95% CI)[a]	Incidence Rated (Number of CVD Events/Person-Years)	Incidence Rate Difference[b] (95% CI)
Composite CVD[c]					
Aromatase inhibitors plus ovarian suppression	51	2,205	2.20 (1.57-3.09)	0.023	0.012 (0.006 to 0.019)
Tamoxifen only (reference)	102	9,913	1.00 (reference)	0.010	1.00 (reference)
Hard CVD[d]					
Aromatase inhibitors plus ovarian suppression	8	2,242	1.68 (0.73-3.86)	0.004	0.001 (−0.001 to 0.004)
Tamoxifen only (reference)	20	9,996	1.00 (reference)	0.002	1.00 (reference)
Hyperlipidemia					
Aromatase inhibitors plus ovarian suppression	30	3,286	1.49 (1.00-2.23)	0.012	0.007 (−0.000 to 0.014)
Tamoxifen only (reference)	74	12,657	1.00 (reference)	0.019	1.00 (reference)
Hypertension					
Aromatase inhibitors plus ovarian suppression	55	1,839	1.19 (0.88-1.60)	0.026	0.005 (−0.004 to 0.014)
Tamoxifen only (reference)	209	8,061	1.00 (reference)	0.031	1.00 (reference)

[a]Analysis matched via propensity score matching by age at breast cancer diagnosis, date of breast cancer diagnosis, date of breast cancer surgery, start date of MarketScan® enrollment, hysterectomy, breast cancer surgery (mastectomy vs other), chemotherapy, radiation, trastuzumab and pertuzumab, metastasis, hypertension, diabetes, kidney disease, peripheral artery disease, liver disease, hematological disease, and obesity. Models were further adjusted for age at diagnosis, propensity score, and metastatic cancer status. [b]Incidence rate and incidence rate differences were derived from adjusted Poisson models matched via propensity score matching by age at breast cancer diagnosis, date of breast cancer diagnosis, date of breast cancer surgery, start date of MarketScan enrollment, hysterectomy, breast cancer surgery (mastectomy vs other), chemotherapy, radiation, trastuzumab and pertuzumab, metastasis, hypertension, diabetes, kidney disease, peripheral artery disease, liver disease, hematological disease, and obesity. Models were further adjusted for age at diagnosis, propensity score, and metastatic cancer status. [c]The first event of myocardial infarction, atrial fibrillation, heart failure hospitalization, ischemic stroke, coronary revascularization, or angina. [d]The first event of myocardial infarction, atrial fibrillation, heart failure, or ischemic stroke.

CVD = cardiovascular disease.

aromatase inhibitors vs tamoxifen (**Table 3**), with sensitivity analysis HRs of 0.93 to 1.36 (Supplemental Table 7).

DISCUSSION

Using real-world data, we emulated a target trial to compare the potential adverse cardiovascular impacts of hormone therapies and ovarian suppression for the treatment of breast cancer among premenopausal women. CVD incidence was low in both treatment groups, as expected given that the study population was composed of premenopausal women.[27] However, as noted in the **Central Illustration**, compared with tamoxifen users, aromatase inhibitor users who also had ovarian suppression were at 2-fold greater risk for incident CVD. Aromatase inhibitor users were also at greater risk for the secondary endpoints, being at 68% greater risk for incident hard CVD (although precision was poor) and 49% greater risk for hyperlipidemia. This analysis provides novel insights regarding the incidence of CVD and hyperlipidemia associated with these therapies in premenopausal women. Trials that have evaluated these hormone therapies were underpowered for CVD endpoints and often had logistics-driven exclusions such as metastatic cancer or other severe illness (NCT00066690). Thus, findings from our emulation of the target trial, which had broad inclusion criteria, may apply to a broader population of patients with breast cancer than that typically enrolled in clinical trials.

BREAST CANCER MANAGEMENT STRATEGIES AND RISK FOR CVD AMONG PREMENOPAUSAL WOMEN. Our analysis, designed to emulate an extension of the SOFT and TEXT trials, provides new insights into cardiotoxicity associated with aromatase inhibitors. The hazard of CVD was twice as high in aromatase inhibitor users compared with tamoxifen users. A crude tabulation of adverse events in the SOFT and TEXT trials among premenopausal women also suggested that cardiac ischemia or infarction was more common among aromatase inhibitor users.[28] However, these clinical trials were not powered to evaluate cardiovascular endpoints. Additionally, there was no information about cardiovascular risk factors, such as hyperlipidemia.

The overall absolute CVD risk was low (as expected in premenopausal women[27]): we observed only 15 CVD events per 1,000 person-years among all participants (**Table 3**). However, the 2-fold greater risk for CVD we observed among premenopausal women using aromatase inhibitors, compared with tamoxifen, is of greater magnitude than associations reported in most prior clinical trials and observational studies of postmenopausal women.[9,29] A meta-analysis of 19,818 participants in randomized clinical trials reported a relative risk for incident CVD of 1.31 (95% CI: 1.07-1.60) for aromatase

TABLE 4 Sensitivity Analyses: HRs and Incidence Rate Differences for Incident CVD[a] by Treatment Group

	Aromatase Inhibitor Plus Ovarian Suppression	Tamoxifen		
	Incidence Rate[b] (Number of CVD Events/Person-Years)		HR (95% CI)[c]	Incidence Rate Difference (95% CI)[b,c]
Main analysis[d]	0.023 (51/2,205)	0.010 (102/9,913)	2.20 (1.57-3.09)	0.012 (0.006-0.019)
Main analysis, modifying approach to matching				
Main analysis repeated with up to 7 tamoxifen users per 1 aromatase inhibitor user	0.022 (51/2,205)	0.010 (127/12,936)	2.25 (1.62-3.14)	0.013 (0.006-0.019)
Main analysis, decreasing caliper width from 0.2 to 0.1	0.023 (51/2,202)	0.011 (100/9,783)	2.21 (1.57-3.11)	0.013 (0.008-0.019)
Main analysis, decreasing caliper width from 0.2 to 0.01	0.023 (50/2,163)	0.011 (98/9,530)	2.18 (1.55-3.08)	0.013 (0.005-0.019)
Nonmatching approaches to account for confounding				
Confounding control by stabilized inverse probability of treatment weighting, regression[e]	0.020 (51/2,206)	0.009 (331/37,399)	2.15 (1.60-2.90)	0.011 (0.003-0.018)
Confounding control by regression adjustment for age and propensity score (no matching or weighting)	0.019 (51/2,206)	0.009 (331/37.399)	2.31 (1.68-3.19)	0.010 (0.004-0.017)
Censoring because of potential impact of COVID-19 pandemic on medical care				
Censoring participants on March 1, 2020	0.022 (37/1,609)	0.010 (72/7,451)	2.24 (1.51-3.34)	0.013 (0.005-0.020)
Restricting sample to populations of interest				
Removing all enrollees with metastatic cancer	0.019 (22/1,191)	0.008 (48/5,573)	2.45 (1.46-4.10)	0.011 (0.002-0.019)
Removing all enrollees older than 50 y (more conservative definition of premenopausal)	0.024 (43/1,780)	0.010 (71/7,730)	2.54 (1.73-3.73)	0.015 (0.007-0.022)
Varying person-time to consider potential impact of different options on immortal time bias				
Main analysis, starting follow-up for tamoxifen users 60 d after the first prescription fill and on the first day both treatment components have been fulfilled for aromatase inhibitor users	0.023 (51/2,206)	0.011 (97/9,439)	2.16 (1.53-3.04)	0.013 (0.006-0.019)
Main analysis, starting follow-up for all participants 60 d after the last component is complete	0.022 (46/2,046)	0.012 (106/9,339)	1.93 (1.36-2.73)	0.011 (0.004-0.018)

[a]First event of myocardial infarction, atrial fibrillation, heart failure hospitalization, ischemic stroke, coronary revascularization, or angina. [b]Incidence rate and incidence rate differences were derived from adjusted Poisson models matched via propensity score matching by age at breast cancer diagnosis, date of breast cancer diagnosis, date of breast cancer surgery, start date of MarketScan enrollment, hysterectomy, breast cancer surgery (mastectomy vs other), chemotherapy, radiation, trastuzumab and pertuzumab, metastasis, hypertension, diabetes, kidney disease, peripheral artery disease, liver disease, hematological disease, and obesity. Models were further adjusted for age at diagnosis, propensity score, and metastatic cancer status. [c]Analysis matched via propensity score matching by age at breast cancer diagnosis, date of breast cancer diagnosis, date of breast cancer surgery, start date of MarketScan enrollment, hysterectomy, breast cancer surgery (mastectomy vs other), chemotherapy, radiation, trastuzumab and pertuzumab, metastasis, hypertension, diabetes, kidney disease, peripheral artery disease, liver disease, hematological disease, and obesity. Models were further adjusted for age at diagnosis, propensity score, and metastatic cancer status. [d]Repeated from Table 3. Propensity score matching with a ratio of 1 aromatase inhibitor enrollee to 5 tamoxifen enrollees and a caliper width of 0.2 SDs of the propensity score. [e]One observation was removed because of an influentially large stabilized inverse probability weight.

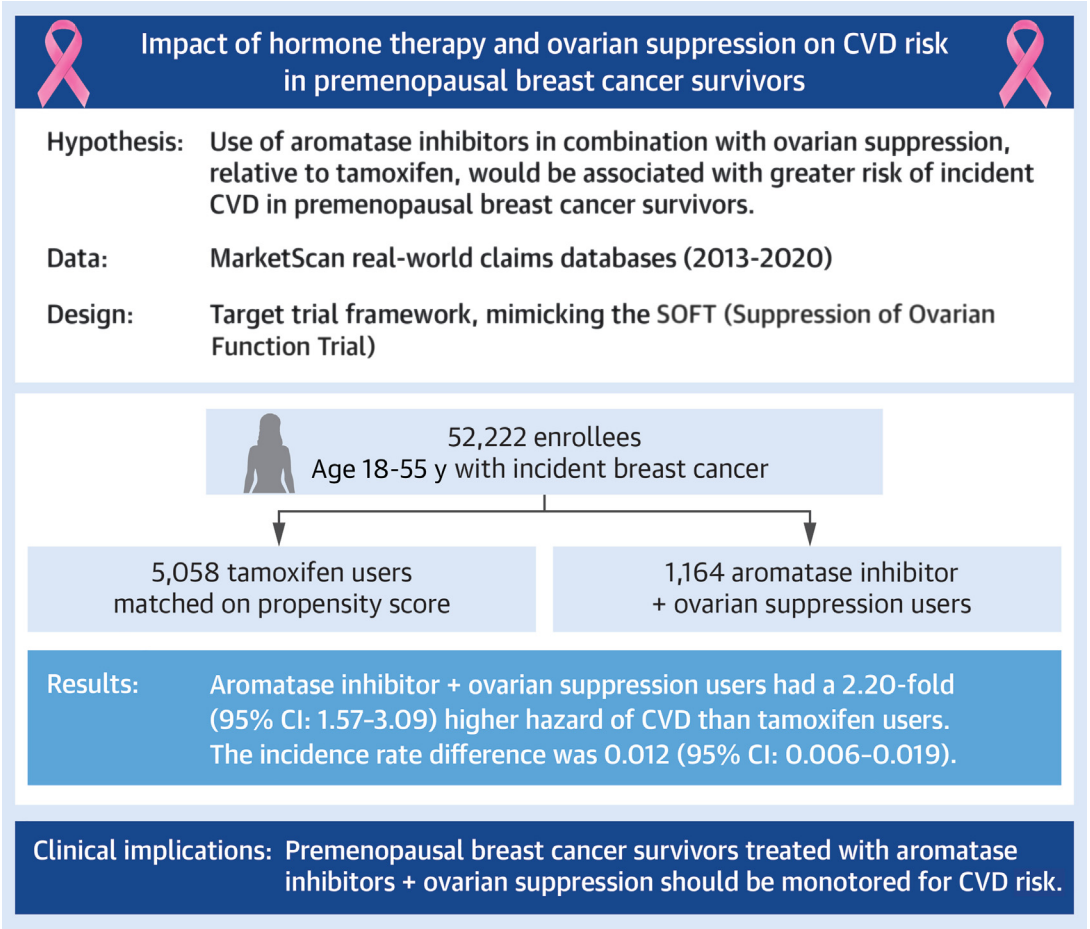
inhibitors vs tamoxifen.[9] The most apparent possible explanation for our stronger findings among premenopausal women is an additive or multiplicative effect of ovarian suppression. Among 30,117 participants of the Nurses' Health Study 30 to 50 years of age who underwent hysterectomy for benign disease and did not use estrogen therapy, those who underwent bilateral oophorectomy had 2.35 times higher risk for coronary heart disease mortality (HR: 2.35; 95% CI: 1.22-4.27) compared with those who had ovarian conservation.[10,11] However, the impact of GnRH agonists on CVD risk in female patients is still being elucidated.[11]

BREAST CANCER MANAGEMENT STRATEGIES AND THE RISK FOR HYPERLIPIDEMIA AND HYPERTENSION. The risk for hyperlipidemia was higher in aromatase inhibitor users compared with tamoxifen users. This finding was expected given the hypothesized role of blood cholesterol in aromatase inhibitor-induced cardiotoxicity.[8] However, it is also possible that confounding by indication may explain this finding. As hyperlipidemia is underdiagnosed in the U.S. population[30] and aromatase inhibitors have a known association with blood cholesterol, aromatase inhibitor users might have been monitored more closely for hyperlipidemia. Additionally, validated algorithms for incident hyperlipidemia in claims analyses were not available.

We found no association between aromatase inhibitor use (compared with tamoxifen) and incident hypertension. This finding was in keeping with studies of these hormone therapies in postmenopausal women: a meta-analysis of 10 clinical trials recently revealed no statistically significant

JACC: CARDIOONCOLOGY, VOL. 6, NO. 6, 2024
DECEMBER 2024:907–918

CENTRAL ILLUSTRATION **Effects of Hormone Therapy and Ovarian Suppression on Risk for CVD in Premenopausal Breast Cancer Survivors**



Polter EJ, et al. JACC CardioOncol. 2024;6(6):907-918.

In a real-world analysis of more than 52,000 women with newly diagnosed breast cancer that used a target trial framework, 1,164 women treated with aromatase inhibitors and ovarian suppression were matched to 5,058 tamoxifen users on the basis of propensity scores. A 2.20-fold greater risk for cardiovascular disease (CVD) was observed among aromatase inhibitor users vs tamoxifen users in the matched cohort. Clinical implications of this work are that premenopausal breast cancer survivors treated with aromatase inhibitors plus ovarian suppression should be monitored for CVD risk.

association (OR: 1.31; 95% CI: 0.47-3.65).[31] As with hyperlipidemia, validated algorithms for incident hypertension in claims analyses were not available, and misclassification may explain our findings.

STUDY LIMITATIONS. Analyses of administrative claims data are susceptible to bias introduced by misclassification, unmeasured confounding, and confounding by indication. We attempted to limit these biases by using validated algorithms to define variables whenever possible, using propensity score matching to reduce confounding, and using numerous sensitivity analyses to gauge the impact that confounding or immortal time bias may have had on our findings.

Another limitation is that median follow-up time in this analysis was 1.6 years, so we were not able to explore the long-term impact of these hormone therapies on CVD risk. However, we observed a strong association even in this relatively short time frame, suggesting that there may be acute adverse impacts of combined aromatase inhibitor and ovarian suppression use on CVD risk.

Another limitation is that the MarketScan data do not include information on out-of-hospital deaths, so instances of incident CVD that presented as out-of-hospital cardiovascular death were missed. However, only approximately 18% of incident CVD cases results in death before hospitalization.[32] This percentage would likely be lower among younger women who experience incident events.[32]

Not having cause-specific mortality information also prohibited our ability to conduct analyses accounting for competing risk for breast cancer death. Although unfortunate, this likely did not have a major impact on our findings, as our follow-up duration was relatively short (median 1.55 years), and according to the American Cancer Society, the 5-year survival rates for breast cancer were 91% overall (by Surveillance, Epidemiology, and End Results stage, rates were 99% for localized invasive cancer, 86% for regional, and 31% for distant) from 2013 to 2019.[33] This time frame is almost identical to that of our analysis (2013-2020), and given the shorter follow-up period in our analysis, we would expect breast cancer survival rates to be even higher than the 5-year rates provided by the American Cancer Society. Nonetheless, acknowledging the potential impact of breast cancer mortality on our findings, we adjusted for metastatic cancer in our primary analysis, and in a sensitivity analysis, we excluded all enrollees with metastatic cancer. Results of this analysis (HR for aromatase inhibitor plus ovarian suppression vs tamoxifen: 2.45; 95% CI: 1.46-4.10) were similar to those of the primary analysis (HR for aromatase inhibitor plus ovarian suppression vs tamoxifen: 2.20; 95% CI: 1.57-3.09), suggesting that competing risk for breast cancer mortality does not explain our findings.

Aromatase inhibitor users in our study had a higher prevalence of metastatic disease than tamoxifen users. The competing (and unmeasured) cancer death risk and short follow-up may have introduced bias to our estimates, and the aggressive treatments used in metastatic cancer may have introduced confounding. However, as noted earlier, findings were similar when women with metastatic breast cancer were excluded. Also, as the aromatase inhibitor group had both a higher metastatic cancer prevalence and a higher CVD event rate, we speculate that the competing risk for cancer death may have attenuated our HRs for incident CVD. Furthermore, ovarian suppression is recommended primarily for patients at high risk for breast cancer recurrence, and these participants were excluded from the SOFT and TEXT trials.[34] Thus, our findings provide broader generalizability to real-world premenopausal patients being managed with these therapies.

Despite these limitations, the rigor of this analysis is bolstered by using the target trial framework, the use of validated algorithms for variable definitions whenever possible, multiple sensitivity analysis, and propensity score matching to balance many potential confounders across groups.

CONCLUSIONS

Our findings suggest that among premenopausal patients with breast cancer, treatment with aromatase inhibitors with ovarian suppression may elevate CVD risk compared with tamoxifen. Patients and their providers need to understand the CVD risk profiles of different hormone therapy and ovarian suppression choices. If our conclusions are confirmed in other large prospective studies, premenopausal patients should be closely monitored for CVD when using aromatase inhibitors with ovarian suppression for adjuvant breast cancer treatment.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr Lutsey was supported by National Heart, Lung, and Blood Institute grant K24 HL159246. Dr Wang was supported by National Heart, Lung, and Blood Institute grant T32 HL007779. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr Pamela Lutsey, University of Minnesota, 1300 South 2nd Street, Suite 300, Minneapolis, Minnesota 55454, USA. E-mail: lutsey@umn.edu. X handle: @plutsey.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Premenopausal patients treated for breast cancer with aromatase inhibitor and ovarian suppression, compared with tamoxifen, were at 2-fold greater risk for incident CVD, which translates to 1.2 additional cases per year per 100 women treated. Elevated lipids may partially explain the association.

TRANSLATIONAL OUTLOOK: Patients and their providers need to understand the CVD risk profiles of different hormone therapy and ovarian suppression choices. If our conclusions are confirmed in other large prospective studies, premenopausal patients should be closely monitored for CVD when using aromatase inhibitors with ovarian suppression for adjuvant breast cancer treatment.

REFERENCES

1. DeSantis CE, Fedewa SA, Goding Sauer A, Kramer JL, Smith RA, Jemal A. Breast cancer statistics, 2015: convergence of incidence rates between Black and White women. *CA Cancer J Clin*. 2016;66(1):31–42. https://doi.org/10.3322/caac.21320

2. DeSantis CE, Ma J, Gaudet MM, et al. Breast cancer statistics, 2019. *CA Cancer J Clin*. 2019;69(6):438–451. https://doi.org/10.3322/caac.21583

3. Bradley R, Burrett J, Clarke M, et al. Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. *Lancet*. 2015;386(10001):1341–1352. https://doi.org/10.1016/S0140-6736(15)61074-1

4. Dowsett M, Howell A. Breast cancer: aromatase inhibitors take on tamoxifen. *Nat Med*. 2002;8(12):1341–1344. https://doi.org/10.1038/nm1202-1341

5. Reeder-Hayes KE, Mayer SE, Lund JL. Adherence to endocrine therapy including ovarian suppression: a large observational cohort study of US women with early breast cancer. *Cancer*. 2021;127(8):1220–1227. https://doi.org/10.1002/cncr.33367

6. Francis PA, Regan MM, Fleming GF, et al. Adjuvant ovarian suppression in premenopausal breast cancer. *N Engl J Med*. 2015;372(5):436–446. https://doi.org/10.1056/nejmoa1412379

7. Gradishar W, Salerno KE. NCCN guidelines update: breast cancer. *J Natl Compr Canc Netw*. 2016;14(5S):641–644. https://doi.org/10.6004/jnccn.2016.0181

8. Khosrow-Khavar F, Filion KB, Al-Qurashi S, et al. Cardiotoxicity of aromatase inhibitors and tamoxifen in postmenopausal women with breast cancer: a systematic review and meta-analysis of randomized controlled trials. *Ann Oncol*. 2017;28(3):487–496. https://doi.org/10.1093/annonc/mdw673

9. Cuppone F, Bria E, Verma S, et al. Do adjuvant aromatase inhibitors increase the cardiovascular risk in postmenopausal women with early breast cancer? Meta-analysis of randomized trials. *Cancer*. 2008;112(2):260–267. https://doi.org/10.1002/cncr.23171

10. Parker WH, Feskanich D, Broder MS, et al. Long-term mortality associated with oophorectomy compared with ovarian conservation in the Nurses' Health Study. *Obstet Gynecol*. 2013;121(4):709–716. https://doi.org/10.1097/AOG.0b013e3182864350

11. Bergami M, Manfrini O, Cenko E, Bugiardini R. Combined therapy with anthracyclines and GnRH analogues for breast cancer: impact on ischemic heart disease. *J Clin Med*. 2023;12(21):6791. https://doi.org/10.3390/jcm12216791

12. Cathcart-Rake EJ, Ruddy KJ, Bleyer A, Johnson RH. Breast cancer in adolescent and young adult women under the age of 40 years. *JCO Oncol Pract*. 2021;17(6):305–313. https://doi.org/10.1200/OP.20.00793

13. Merative. MarketScan research databases for life sciences researchers. Accessed September 17, 2024. https://www.merative.com/content/dam/merative/documents/brief/marketscan-research-databases-for-life-sciences-researchers.pdf

14. Hernán MA, Robins JM. Using big data to emulate a target trial when a randomized trial is not available. *Am J Epidemiol*. 2016;183(8):758–764. https://doi.org/10.1093/aje/kwv254

15. Pagani O, Regan MM, Fleming GF, et al. Randomized comparison of adjuvant aromatase inhibitor exemestane (E) plus ovarian function suppression (OFS) vs tamoxifen (T) plus OFS in premenopausal women with hormone receptor positive (HR plus) early breast cancer (BC): update of the combined TEXT and SOFT trials. *Cancer Res*. 2018;78(4):1.

16. Francis PA, Regan MMD, Fleming GF, et al. Adjuvant ovarian suppression in premenopausal breast cancer. *N Engl J Med*. 2014;372:436–482. https://doi.org/10.1056/NEJMoa1412379

17. Schneeweiss S, Rassen JA, Brown JS, et al. Graphical depiction of longitudinal study designs in health care databases. *Ann Intern Med*. 2019;170(6):398–406.

18. Nattinger AB, Laud PW, Bajorunaite R, Sparapani RA, Freeman JL. An algorithm for the use of Medicare claims data to identify women with incident breast cancer. *Health Serv Res*. 2004;39(6):1733–1749. https://doi.org/10.1111/j.1475-6773.2004.00315.x

19. Quan H, Li B, Couris CM, et al. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. *Am J Epidemiol*. 2011;173(6):676–682. https://doi.org/10.1093/aje/kwq433

20. Strom BL, Kimmel SE, Hennessy S. *Pharmacoepidemiology*. 6th ed. Hoboken, NJ: Wiley-Blackwell; 2020.

21. Kiyota Y, Schneeweiss S, Glynn RJ, Cannuscio CC, Avorn J, Solomon DH. Accuracy of Medicare claims-based diagnosis of acute myocardial infarction: estimating positive predictive value on the basis of review of hospital records. *Am Heart J*. 2004;148(1):99–104. https://doi.org/10.1016/j.ahj.2004.02.013

22. Andrade SE, Harrold LR, Tjia J, et al. A systematic review of validated methods for identifying cerebrovascular accident or transient ischemic attack using administrative data. *Pharmacoepidemiol Drug Saf*. 2012;21:100–128. https://doi.org/10.1002/pds.2312

23. Jensen PN, Johnson K, Floyd J, Heckbert SR, Carnahan R, Dublin S. A systematic review of validated methods for identifying atrial fibrillation using administrative data. *Pharmacoepidemiol Drug Saf*. 2012;21(S1):141–147. https://doi.org/10.1002/pds.2317

24. Kumar A, Lutsey PL, St Peter WL, et al. Comparative effectiveness of ticagrelor, prasugrel, and clopidogrel for secondary prophylaxis in acute coronary syndrome: a propensity score-matched cohort study. *Clin Pharmacol Ther*. 2023;113(2):401–411. https://doi.org/10.1002/cpt.2797

25. Gill K, Chia VM, Hernandez RK, Navetta M. Rates of vascular events in patients with migraine: a MarketScan® database retrospective cohort study. *Headache*. 2020;60(10):2265–2280. https://doi.org/10.1111/head.14001

26. Franklin M, Burns L, Perez S, Yerragolam D, Makenbaeva D. Incidence of type 2 diabetes mellitus and hyperlipidemia in patients prescribed dasatinib or nilotinib as first- or second-line therapy for chronic myelogenous leukemia in the US. *Curr Med Res Opin*. 2018;34(2):353–360. https://doi.org/10.1080/03007995.2017.1399870

27. Mosca L, Barrett-Connor E, Wenger NK. Sex/gender differences in cardiovascular disease prevention. *Circulation*. 2011;124(19):2145–2154. https://doi.org/10.1161/CIRCULATIONAHA.110.968792

28. Francis PA, Pagani O, Fleming GF, et al. Tailoring adjuvant endocrine therapy for premenopausal breast cancer. *N Engl J Med*. 2018;379(2):122–137. https://doi.org/10.1056/NEJMoa1803164

29. Yu Q, Xu Y, Yu E, Zheng Z. Risk of cardiovascular disease in breast cancer patients receiving aromatase inhibitors vs. tamoxifen: a systematic review and meta-analysis. *J Clin Pharm Ther*. 2022;47(5):575–587.

30. Zallman L, Himmelstein DH, Woolhandler S, et al. Undiagnosed and uncontrolled hypertension and hyperlipidemia among immigrants in the US. *J Immigr Minor Health*. 2013;15(5):858–865. https://doi.org/10.1007/s10903-012-9695-2

31. Boszkiewicz K, Piwowar A, Petryszyn P. Aromatase inhibitors and risk of metabolic and cardiovascular adverse effects in breast cancer patients—a systematic review and meta-analysis. *J Clin Med*. 2022;11(11):3133. https://doi.org/10.3390/jcm11113133

32. Marshall RJ, Milne RJ, Lynn R, Jackson R. Quantifying the effect of age on short-term and long-term case fatality in 14000 patients with incident cases of cardiovascular disease. *Eur J Cardiovasc Prev Rehabil*. 2008;15(2):179–184. https://doi.org/10.1097/HJR.0b013e3282f14a7f

33. American Cancer Society. Survival rates for breast cancer. Accessed May 12, 2024. https://www.cancer.org/cancer/types/breast-cancer/understanding-a-breast-cancer-diagnosis/breast-cancer-survival-rates.html

34. Singhal M, Sahoo TP, Aggarwal S, et al. Practical consensus recommendations on ovarian suppression in early breast cancer (adjuvant). *South Asian J Cancer*. 2018;7(2). https://doi.org/10.4103/sajc.sajc_125_18

35. Chlebowski RT, Pan K, Col NF. *Ovarian Suppression in Combination Endocrine Adjuvant Therapy in Premenopausal Women With Early Breast Cancer*. New York: Springer; 2017.

KEY WORDS aromatase inhibitors, breast cancer, cardiovascular disease, ovarian suppression, premenopausal, tamoxifen

APPENDIX For supplemental tables and figures, please see the online version of this paper.