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EPIDEMIOLOGY

Aromatase inhibitor and tamoxifen use and the risk of venous thromboembolism in breast cancer survivors

Xiaoqing Xu[1] · Rowan T. Chlebowski[2,3] · Jiaxiao Shi[1] · Ana Barac[4,5] · Reina Haque[1]

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Abstract

Purpose Venous thromboembolism (VTE) is the second most common cause of death in hospitalized patients with cancer, and cancer treatments may exacerbate VTE risk. Patients with hormone-receptor-positive breast cancer usually receive adjuvant endocrine therapy for 5 years or longer. The aim of this study is to examine VTE risk following long-term use of aromatase inhibitor (AI) compared with tamoxifen use among breast cancer survivors.

Methods A prospective cohort of 12,904 postmenopausal women who were diagnosed with a first primary hormone-receptor-positive breast cancer and free from previous cardiovascular disease or VTE from 1991 to 2010 were followed through December 2011. Data elements were captured from the comprehensive electronic health records of a large California health plan, Kaiser Permanente. Women who developed deep vein thrombosis (DVT) or pulmonary embolism (PE) were identified as having VTE. We calculated person-year rates of VTE by endocrine therapy groups. Multivariable Cox proportional hazards models were applied to assess the association between time-dependent endocrine therapy and VTE risk.

Results We identified 623 VTE events during a median follow-up of 5.4 years. The crude rates were 4.6 and 2.8 per 1000 person-years for DVT and PE, respectively. Compared with tamoxifen use, AI use was associated with at least 41% lower VTE risk (adjusted HR 0.59, 95% CI 0.43, 0.81). Greater risk reductions in AI users were seen in women who also underwent adjuvant chemotherapy.

Conclusions These findings supplement existing evidence to inform treatment decisions that balance cancer control and cardiovascular toxic outcomes.

Keywords Aromatase inhibitors · Tamoxifen · Breast cancer · DVT · PE

Introduction

Venous thromboembolism (VTE), typically manifests as deep vein thrombosis (DVT) and pulmonary embolism (PE), is the second most common cause of death in hospitalized patients with cancer [1–3]. In patients with breast cancer, the VTE prevalence ranges from 3 to 15% [4–6], and adjuvant endocrine therapy can enhance the prothrombotic tendency independent of other anticancer treatments [7].

Endocrine therapy has substantially improved breast cancer survival [8–12]. Aromatase inhibitor (AI) particularly has become incorporated into the adjuvant endocrine therapy for postmenopausal women with hormone receptor-positive invasive breast cancer as up-front monotherapy or as extended sequential therapy following completion of tamoxifen treatment [8] based on its superior efficacy [9–12]. While deciding different treatment strategies, the long-term adverse event profile of the drug should also be considered.

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✉ Reina Haque
Reina.Haque@kp.org

[1] Department of Research & Evaluation, Kaiser Permanente Southern California, 100 South Los Robles, 2nd Floor, Pasadena, CA 91101, USA

[2] City of Hope, 1500 E. Duarte Rd., Duarte, CA 91010, USA

[3] Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, 1124 West Carson Street, Torrance, CA 90502, USA

[4] Medstar Heart and Vascular Institute, 110 Irving Street, Washington, DC 20010, USA

[5] Georgetown University, Washington, DC, USA

Controversy exists about how AIs affect the cardiovascular systems, and if long-term use may inadvertently increase women's VTE risk [7, 13].

Randomized controlled trials suggest that AIs are associated with a lower VTE risk versus tamoxifen [11, 12, 14, 15]. However, all of these RCTs were primarily designed to compare efficacy of AI compared to tamoxifen in reducing breast cancer recurrence not safety. Therefore, the ascertainment and classification of VTE risk were not accurate or complete, particularly due to the self-reported adverse events, and importantly, patients were not followed for any adverse effects after the efficacy (recurrence) outcomes occurred [15]. Only one observational cohort analysis evaluated the absolute incidence rates of VTE in both AI users and tamoxifen users using the England health care database where much higher VTE rates were reported among women who received AI therapy compared to tamoxifen therapy [16]; however, no adjusted relative incidence rate was modeled and important covariates were not considered. Moreover, one study found an increase in circulating fibrinogen after first-line AI therapy, which may augment the tendency of developing blood clots [17]. Therefore, VTE adverse events associated with AI use remains a concern. Given the growing numbers of postmenopausal breast cancer survivors being prescribed AIs, characterizing the safety or risk of VTE is necessary in community populations with long follow-up. Our objective was to examine the association between AIs and the risk of VTE (DVT or PE) in breast cancer survivors compared with tamoxifen use, accounting for key confounding factors such as ongoing treatment for cancer, diabetes, hypertension, statins, and use of prophylaxis anticoagulants [13].

Methods

Data sources and setting

This study was conducted at Kaiser Permanente Southern California (KPSC), a large managed care system that comprises nearly 14 hospitals with 4.2 million members and over 100 medical clinics. Patients receive all their medical care within this integrated healthcare delivery system, and information on outside procedures are available through claims databases. The health plan's U.S. National Cancer Institute-Surveillance, Epidemiology, and End Results (SEER)-affiliated tumor registry was used to identify subjects with breast cancer. The KPSC Institutional Review Board reviewed and approved this study.

Subjects and design

A prospective cohort of women diagnosed with first primary breast cancer in 1991–2010 was assembled and followed through December 2011 (maximum of 21 years). Eligibility was restricted to women who were postmenopausal, with continuous enrollment, had hormone receptor-positive tumors, and with known stage of cancer. Of 17,447 breast cancer survivors meeting eligibility criteria, those with prior CVD or VTE, and patients who initiated long-term anticoagulant therapy were excluded, leaving a final cohort of 12,904 women (eFigure 1).

Venous thromboembolism (VTE) ascertainment

To identify incident VTE that occurred after breast cancer diagnosis, we used two specifications: (1) at least two outpatient diagnoses within 3 months, or (2) any inpatient diagnosis, both based on ICD9/ICD10 code (International Classification of Diseases) of DVT or PE on the date of their first diagnosis (eTable 2). Those with DVT and PE diagnosed on the same day were assigned to PE. These diagnosis codes were extracted from the Electronic Health Record (EHR) using a validated computerized algorithm [18], and inpatient codes were prioritized over outpatient codes.

Endocrine treatment

All members of this health plan had pharmacy coverage. Tamoxifen and AI (letrozole, anastrozole, exemestane) prescriptions were extracted from pharmacy database including the dispensing dates and days supplied. Women were classified into one of four endocrine therapy categories: (1) tamoxifen only, (2) aromatase inhibitor only, (3) both, and (4) non-users according to at least one actual filled prescriptions before the study endpoint event occurred. Women were categorized as "switchers" if they switched endocrine therapy before the occurrence of the study endpoint regardless of the sequence (the majority 83% used tamoxifen followed by AIs).

Confounding factors

Considering VTE development is multifactorial, a comprehensive set of covariates were captured from multiple data sources to balance potential confounding factors in different endocrine therapy groups. Information on first-course cancer therapy, diagnosis year, age and stage, and other tumor characteristics were obtained from the health plan's SEER-affiliated tumor registry. Race/ethnicity, median household income (at census block level in year 2000), comorbidities,

previous musculoskeletal disorders, body mass index (kg/m^2), and smoking history were extracted from EHR and KPSC's geocoded databases. Medications to treat or prevent VTE and CVD were also extracted from the pharmacy dispensing records and treated as time-varying covariates in the analyses.

Statistical analyses

Follow-up commenced on the breast cancer diagnosis date and ended on the date of the earliest study endpoint: first VTE diagnosis date, death, termination of health plan membership, or study's end. Comparison of demographics, healthcare utilization, and tumor characteristics by endocrine therapy group were presented. We also calculated median time to VTE, crude person-year rates of VTE, and separately for DVT and PE. Crude and adjusted hazard ratios (HR) and 95% confidence intervals (CI) were estimated by time-dependent Cox proportional hazards models using tamoxifen only users as the reference group; time since breast cancer diagnosis was used as the time scale. In the incident rate calculation and time-dependent modeling, each patient contributed person-time to the endocrine therapy exposure category based on the treatment received during that time. The time between breast cancer diagnosis and the initiation of the first endocrine therapy contributed to "non-user time." Women who switched treatment contributed person-time to the "switched" category on the date when they started the second endocrine agent. All covariates selected for adjustment in the model were based on clinical importance and descriptive statistics. The proportional hazards assumption was tested via graphic plots and Schoenfeld residuals; no violations were found. All analyses were performed using SAS Version 9.3 (SAS Institute, Cary NC).

Sensitivity analyses

We conducted multiple sensitivity analyses to assess the robustness of the results taking into account potential confounding bias, the presence of competing event, non-adherence issue, and potential interactive effect. First, we performed stratified analyses in women who received adjuvant chemotherapy to assess the safety of AIs given the potential interaction effect of endocrine therapy and chemotherapy. Second, we censored women ($n=98$) who initiated long-term anticoagulant therapy for VTE prophylaxis on the date of the preventive intervention. Third, additional sensitivity analyses were based on medication adherence to endocrine therapies incorporating the subset of women with an $>80\%$ medication possession ratio (MPR), a standard adherence [19]. The MPR was estimated as the number of days supplied (excluding the last refill) divided by the number of days between first and last dispense date. Fourth, to disentangle the effect of metastatic state of cancer and endocrine therapy on VTE [3], we restricted analyses to women diagnosed with stage I–III disease.

Results

In the cohort of 12,904 breast cancer survivors, we observed 623 incident VTE events (382 DVT, 239 PE and 2 deaths from VTE) during the 83,753 person-years of follow-up (median of 5.4 years [IQR 2.7, 9.4]). Eighty-four percent of the women stayed within the health plan through the study's end. Among the breast cancer survivors, 31.5% ($N=4062$) received tamoxifen alone for a median of 6.8 years (IQR 2.9, 12.1), and 29.7% ($N=3837$) used AIs alone for a median of 3.2 years (IQR 1.6, 5.3); 22.6% ($N=2922$) of women used both tamoxifen and AIs during their therapeutic course, and the remaining 16.1% ($N=2083$) did not initiate any endocrine therapy. Baseline demographic conditions and VTE risk factors are displayed in Table 1. More than 7.3% of the cohort were women greater than 80 years old and 24.1% had Charlson comorbidity index with a greater than zero. Compared to tamoxifen only users, AI users were more likely to be younger, from minority backgrounds, and live in neighborhoods with higher geocoded median household income. Hypertension (72.6%) and diabetes (26.3%) prevalence was balanced between tamoxifen only users and AI only users. Of note, height and weight were not captured in the electronic health record until 2009, and thus more women who used AIs (the newer drug) had height/weight data. Among a sub-cohort of patients with BMI, women who used AIs exclusively were more likely to be overweight or obese (70.7%). Except for the evenly distributed breast cancer laterality (data not shown), tumor characteristics as well as primary therapy varied by endocrine therapy group (Table 2). Table 3 presents the distribution of cardiovascular medications women used at any time after their breast cancer diagnosis. Nearly half (48.9%) of the cohort were exposed to statins. Anticoagulants/antiplatelets were less likely to be taken by AI only users (6.2%) and women who did not initiate endocrine therapy (5.3%) compared to tamoxifen users and switchers (8.2% and 8.0%).

Venous thromboembolism risk

In the full cohort, the crude VTE incidence rate (Table 3) was 7.4 per 1000 person-years (4.6/1000 person-years for DVT, and 2.8/1000 person-years for PE). Further, the individual rates of DVT and PE were lower in AI only users (3.3/1000 person-years for DVT and 2.2/1000 person-years for PE) as compared to tamoxifen only users (4.5/1000 person-years for DVT and 3.0/1000 person-years for PE). Median time to VTE was 2.9 years (IQR 0.8, 6.1). Table 4

Table 1 Demographic characteristics of postmenopausal breast cancer survivors diagnosed between 1991 and 2010

	Tamoxifen only *N* (%)	AI only *N* (%)	Switchers *N* (%)	No hormones *N* (%)	Total *N* (%)
Total	4062 (31.5)	3837 (29.7)	2922 (22.6)	2083 (16.1)	12,904 (100)
Age					
55–59	837 (20.6)	976 (25.4)	768 (26.3)	460 (22.1)	3041 (23.6)
60–69	1705 (42.0)	1791 (46.7)	1405 (48.1)	880 (42.2)	5781 (44.8)
70–79	1163 (28.6)	814 (21.2)	621 (21.2)	539 (25.9)	3137 (24.3)
80+	357 (8.8)	256 (6.7)	128 (4.4)	204 (9.8)	945 (7.3)
Race/ethnicity					
Non-Hispanic White	3021 (74.4)	2522 (65.7)	2092 (71.6)	1504 (72.2)	9139 (70.8)
Hispanic	319 (7.8)	416 (10.8)	286 (9.8)	171 (8.2)	1192 (9.2)
Black	376 (9.7)	448 (11.7)	271 (9.3)	211 (16.2)	1306 (10.1)
Asian/Pacific Islander	307 (7.6)	395 (10.3)	257 (8.8)	176 (8.4)	1135 (8.8)
Other/unknown*	39 (1.0)	56 (1.5)	16 (0.5)	21 (1.0)	132 (1.0)
Geocoded median household income					
Lower 25% (≤$49,529)	1085 (27.6)	920 (24.2)	676 (23.4)	503 (24.7)	3184 (25.0)
> 25–50% ($49,530–$67,296)	1005 (25.5)	905 (23.8)	719 (24.9)	530 (26.1)	3159 (24.9)
> 50–75% ($67,297–$89,103)	968 (24.6)	997 (26.2)	717 (24.8)	478 (23.5)	3160 (24.9)
Top 25% (≥$89,104)	879 (22.3)	983 (25.8)	779 (26.9)	521 (25.6)	3162 (25.0)
Unknown/missing	125	32	31	51	239
Charlson comorbidities					
0	3400 (83.7)	2594 (67.6)	2259 (77.3)	1544 (74.1)	9797 (75.9)
1–2	568 (14.0)	978 (25.5)	586 (20.0)	421 (20.2)	2553 (19.8)
3+	94 (2.3)	265 (6.9)	77 (2.6)	118 (5.7)	554 (4.3)
Hypertension (anytime up to end of follow-up)					
Yes	2976 (73.3)	2773 (72.3)	2241 (76.7)	1382 (66.3)	9372 (72.6)
No	1086 (26.7)	1064 (27.7)	681 (23.3)	701 (33.6)	3532 (27.4)
Diabetes (anytime up to end of follow-up)					
Yes	1088 (26.8)	1029 (26.8)	809 (27.7)	468 (22.5)	3394 (26.3)
No	2974 (73.2)	2808 (73.2)	2113 (72.3)	1615 (77.5)	9510 (73.7)
Smoking					
Current smoker	204 (8.2)	326 (9.2)	217 (9.4)	133 (9.2)	880 (9.0)
Former smoker	652 (26.2)	1011 (28.6)	666 (29.0)	389 (26.9)	2718 (27.8)
Never smoker	1632 (65.6)	2199 (62.2)	1415 (61.6)	924 (63.9)	6170 (63.2)
Unknown/missing	1574	301	624	637	3136
BMI (closest to breast cancer diagnose)					
Underweight	7 (1.1)	12 (0.4)	5 (1.0)	8 (0.9)	32 (0.7)
Normal	226 (35.4)	767 (28.8)	152 (31.5)	279 (32.4)	1424 (30.7)
Overweight	195 (30.5)	911 (34.3)	180 (37.3)	272 (31.5)	1558 (33.6)
Obese	211 (33.0)	969 (36.4)	145 (30.1)	303 (35.1)	1628 (35.1)
Missing	3423	1178	2440	1221	8262

AI Aromatase inhibitors

presents the adjusted HRs of VTE following endocrine treatments after accounting for key confounding factors. Compared with tamoxifen use, AI use was associated with a markedly lower risk of developing VTE (adjusted HR 0.59, 95% CI 0.43, 0.81), as well as reduced risks of DVT and PE as individual outcomes. We found an even lower risk of VTE in women who received chemotherapy and in women with stage I–III disease. The inverse association persisted in the analysis censoring patients on the date they initiated long-term anticoagulant therapy (eTable 1). In the analyses limited to women with good adherence to the endocrine therapy, the protective effect of AI use was stronger (eTable 1). In stratified models by duration of the endocrine therapy, we observed lower risks for VTE with greater duration of AI use, but with wide confidence intervals (Table 5). For tamoxifen use, the VTE risk was higher in the first 3 years of use

Table 2 Tumor characteristics of postmenopausal breast cancer survivors diagnosed between 1991 and 2010

	Tamoxifen only *N* (%)	AI only *N* (%)	Switchers *N* (%)	No hormones *N* (%)	Total *N* (%)
Total	4062 (31.5)	3837 (29.7)	2922 (22.6)	2083 (16.1)	12,904 (100)
Year of diagnosis					
1991–1995	1193 (29.4)	14 (0.4)	262 (9.0)	322 (15.5)	1791 (13.9)
1996–2000	1518 (37.4)	30 (1.1)	871 (29.8)	377 (18.1)	2796 (21.7)
2001–2005	735 (18.1)	1187 (30.9)	1335 (45.7)	524 (25.2)	3781 (29.3)
2006–2010	616 (15.2)	2606 (67.9)	454 (15.5)	860 (41.3)	4536 (35.1)
Stage at diagnosis					
Stage 0	424 (10.4)	54 (1.4)	37 (1.3)	583 (28.0)	1098 (8.5)
Stage I	2179 (53.6)	2061 (53.7)	1248 (42.7)	1028 (49.3)	6516 (50.5)
Stage II	1269 (31.2)	1261 (32.9)	1295 (44.3)	339 (16.3)	4164 (32.3)
Stage III	132 (3.2)	345 (9.0)	235 (8.0)	74 (3.5)	786 (6.1)
Stage IV	58 (1.4)	116 (3.0)	107 (3.7)	59 (2.8)	340 (2.6)
Primary therapy					
Breast conserving surgery + RT	1540 (38.5)	1621 (42.5)	1113 (39.3)	671 (32.4)	4945 (38.9)
BCS (no radiation)	639 (16.0)	636 (16.7)	448 (15.8)	505 (24.4)	2228 (17.5)
Mastectomy (with or w/o RT)	1774 (44.3)	1415 (37.1)	1218 (43.0)	761 (36.8)	5168 (40.7)
Treatment outside health plan	47 (1.2)	137 (3.6)	53 (1.9)	132 (6.4)	369 (2.9)
Other/unknown	62	28	90	14	194
Adjuvant radiation					
Yes	1653 (40.8)	1845 (48.1)	1296 (44.6)	710 (34.1)	5504 (42.7)
No	2400 (59.2)	1991 (51.9)	1612 (55.4)	1372 (65.9)	7375 (57.3)
Unknown/missing	9	1	14	1	25
Adjuvant chemotherapy					
Yes	650 (16.3)	1395 (36.5)	1173 (41.5)	279 (13.5)	3497 (27.5)
No	3347 (83.7)	2424 (63.5)	1653 (58.5)	1787 (86.5)	9211 (72.5)
Unknown/missing	65	18	96	17	196
Histology					
DCIS (ductal carcinoma in situ)	175 (4.3)	26 (0.7)	19 (0.6)	228 (10.9)	448 (3.5)
LCIS (lobular ca in situ)	2 (0.05)	2 (0.05)	1 (0.03)	12 (0.6)	17 (0.1)
IDC (invasive ductal carcinoma)	2293 (56.4)	2342 (61.0)	1664 (57.0)	925 (44.4)	7224 (56.0)
ILC (invasive lobular carcinoma)	409 (10.1)	351 (9.1)	319 (10.9)	134 (6.4)	1213 (9.4)
Other/mixed category	1183 (29.1)	1116 (29.7)	919 (31.4)	784 (39.6)	4002 (31.0)
Grade					
1	1059 (29.6)	1086 (29.1)	768 (28.4)	524 (28.2)	3437 (29.0)
2	1836 (51.3)	1853 (49.7)	1350 (50.0)	890 (48.0)	5929 (50.0)
3	683 (19.1)	788 (21.4)	581 (21.5)	441 (23.8)	2493 (21.0)
Unknown/missing	484	110	223	228	1045

AI Aromatase inhibitors

versus non-user time. However, the VTE risk decreased after > 5 years of tamoxifen use versus non-use time (Table 6).

Discussion

Among 12,904 postmenopausal breast cancer patients free from pre-existing CVD or VTE, AI use was associated with at least 41% decreased risk of developing venous thromboembolic events compared to tamoxifen during a median of 5.4 years follow-up. Further, when considering both AI monotherapy and sequential AI treatment after tamoxifen by using time-dependent analysis, we did not observe increased risk of VTE in women used AI for more than three years. To our knowledge, our study is the first to integrate comprehensive confounding factors in the analysis of the long-term effects of AIs on separate VTE outcomes in the real-world clinical practices. In parallel to clinical trial

Table 3 Covariate drugs used by breast cancer survivors

	Tamoxifen only *N* (%)	AI only *N* (%)	Switchers *N* (%)	No hormones *N* (%)	Total *N* (%)
Total	4062 (31.5)	3837 (29.7)	2922 (22.6)	2083 (16.1)	12,904 (100)
Antiarrhythmics					
Yes	26 (0.6)	2 (0.05)	5 (0.2)	10 (0.5)	43 (0.3)
No	4036 (99.4)	3835 (99.9)	2917 (99.8)	2073 (99.5)	12,861 (99.7)
Anticoagulant/antiplatelet					
Yes	333 (8.2)	237 (6.2)	235 (8.0)	111 (5.3)	916 (7.1)
No	3729 (91.8)	3600 (93.8)	2687 (92.0)	1972 (94.7)	11,988 (92.9)
Antihypertensives					
Yes	348 (8.6)	576 (15.0)	307 (10.5)	175 (8.4)	1406 (10.9)
No	3714 (91.4)	3261 (85.0)	2615 (88.5)	1908 (91.6)	11,498 (89.1)
Antilipemics					
Yes	1758 (43.3)	2123 (55.3)	1598 (54.7)	830 (39.8)	6309 (48.9)
No	2304 (56.7)	1714 (44.7)	1324 (45.3)	1253 (60.1)	6595 (51.1)
Calcium channel blocker					
Yes	807 (19.9)	649 (16.9)	596 (20.4)	293 (14.1)	2345 (18.2)
No	3255 (80.1)	3188 (83.1)	2326 (79.6)	1790 (85.9)	10,559 (81.8)
Digoxin/lanoxin					
Yes	148 (3.6)	18 (0.5)	78 (2.7)	37 (1.8)	281 (2.2)
No	3914 (96.4)	3819 (99.5)	2844 (97.3)	2046 (98.2)	12,623 (97.8)
Antidiabetic					
Yes	503 (12.4)	574 (15.0)	448 (15.3)	194 (9.3)	1719 (13.3)
No	3559 (87.6)	3263 (85.0)	2474 (84.7)	1889 (90.7)	11,185 (86.7)

AI Aromatase inhibitors

Table 4 Crude incidence rates of venous thromboembolism by endocrine therapy use

	Tamoxifen only	AI only	Switchers	No hormones	Total
Total	4062 (31.5%)	3837 (29.7%)	2922 (22.6%)	2083 (16.1%)	12,904 (100%)
VTE (including death due to VTE)					
Number of event	309	80	102	132	623
Person-time rate (per 1000 Pys)	7.61 (6.79, 8.51)	5.57 (4.42, 6.93)	7.84 (6.39, 9.52)	8.35 (6.99, 9.90)	7.44 (6.86, 8.05)
Median years to VTE (Q1, Q3)	3.41 (1.43, 6.59)	2.16 (1.05, 4.02)	5.57 (2.91, 8.61)	0.48 (0.24, 2.76)	2.87 (0.85, 6.07)
DVT					
Number of event	184	48	71	79	382
Person-time rate (per 1000 Pys)	4.53 (3.90, 5.24)	3.34 (2.46, 4.43)	5.46 (4.26, 6.89)	5.00 (3.96, 6.23)	4.56 (4.11, 5.04)
Median years to DVT (Q1, Q3)	3.42 (1.53, 6.95)	2.11 (0.69, 3.69)	4.75 (2.70, 9.08)	0.48 (0.25, 2.77)	2.87 (0.81, 6.38)
PE					
Number of event	123	32	31	53	239
Person-time rate (per 1000 Pys)	3.03 (2.52, 3.62)	2.23 (1.52, 3.15)	2.38 (1.62, 3.38)	3.35 (2.51, 4.38)	2.85 (2.50, 3.24)
Median years to PE (Q1, Q3)	3.27 (1.35, 6.25)	2.43 (1.30, 4.82)	6.07 (4.57, 7.82)	0.43 (0.23, 2.64)	2.91 (0.91, 5.96)
Death due to breast cancer	183	152	466	107	908
Death due to reasons other than VTE	738	133	191	249	1311
Health plan disenrollment	983	343	293	493	2112

VTE Venous thromboembolism (The composite outcome, deep vein thrombosis (DVT) and/or pulmonary embolism (PE)); *AI* Aromatase inhibitors, *Pys* Person-years

Table 5 Adjusted hazard ratios for DVT/PE events by endocrine treatment use

	Tamoxifen only		AI only		Switchers		No hormones	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
VTE (including death)								
Crude HR	1.00	Ref	0.66	(0.52, 0.85)	1.29	(1.02, 1.63)	0.82	(0.65, 1.02)
Adjusted[a] HR	1.00	Ref	0.59	(0.43, 0.81)	1.07	(0.81, 1.41)	0.97	(0.75, 1.25)
Subset, received adjuvant chemotherapy ($N=3497$)	1.00	Ref	0.47	(0.28, 0.81)	1.20	(0.75, 1.93)	0.92	(0.55, 1.55)
DVT								
Crude HR	1.00	Ref	0.67	(0.48, 0.93)	1.57	(1.18, 2.10)	0.81	(0.61, 1.09)
Adjusted[a] HR	1.00	Ref	0.68	(0.46, 1.03)	1.41	(0.99, 2.00)	1.08	(0.77, 1.49)
Subset, received adjuvant chemotherapy ($N=3497$)	1.00	Ref	0.53	(0.26, 1.10)	1.68	(0.90, 3.16)	1.02	(0.53, 1.95)
PE								
Crude HR	1.00	Ref	0.66	(0.44, 0.97)	0.92	(0.61, 1.38)	0.83	(0.58, 1.19)
Adjusted[a] HR	1.00	Ref	0.48	(0.29, 0.78)	0.68	(0.42, 1.10)	0.83	(0.55, 1.30)
Subset, received adjuvant chemotherapy ($N=3497$)	1.00	Ref	0.38	(0.17, 0.82)	0.78	(0.38, 1.60)	0.79	(0.34, 1.83)

DVT Deep vein thrombosis, *PE* pulmonary embolism, *AI* aromatase inhibitors

[a]To balance the confounding factors in different endocrine treatment groups, the model accounted for the following covariates: CVD medications, race/ethnicity, age at breast cancer diagnosis, diabetes, primary therapy of cancer, adjuvant chemotherapy, adjuvant radiation therapy, year of cancer diagnosis, tumor stage, grade, and histology

Table 6 Adjusted Hazard Ratios for venous thromboembolic events by cumulative duration of endocrine treatment

All women ($N=12,904$)	No. of subjects	N with DVT/PE	Crude		Adjusted[a]	
			HR	95% CI	HR	95% CI
Tamoxifen duration (years)[b]						
Non-user time	5920	212	1.00	Ref	1.00	Ref
< 1 year of use	1505	120	1.27	(1.00, 1.61)	1.17	(0.90, 1.53)
≥ 1–3 years of use	2047	149	1.80	(1.40, 2.30)	1.38	(1.04, 1.83)
≥ 3–5 years of use	2462	115	1.34	(1.00, 1.79)	1.12	(0.80, 1.56)
≥ 5 years of use	970	27	0.87	(0.55, 1.37)	0.71	(0.42, 1.19)
AI duration (years)[b]						
Non-user time	6145	441	1.00	Ref	1.00	Ref
< 1 year of use	1732	83	1.16	(0.90, 1.48)	0.95	(0.72, 1.26)
≥ 1–3 years of use	2433	65	1.02	(0.77, 1.35)	0.75	(0.54, 1.04)
≥ 3 years of use	2594	34	0.87	(0.59, 1.27)	0.63	(0.41, 0.97)

DVT Deep vein thrombosis, *PE* pulmonary embolism, *AI*: aromatase inhibitors

[a]To balance the confounding factors in different endocrine treatment groups, the model accounted for the following covariates: CVD medications, race/ethnicity, age at breast cancer diagnosis, diabetes, primary therapy of cancer, adjuvant chemotherapy, adjuvant radiation therapy, year of cancer diagnosis, tumor stage, grade, and histology

[b]Duration of tamoxifen or AI use was assessed regardless of the use of the other endocrine agent. Person time does not accumulate in a certain category until reaching the corresponding years of exposure

data that demonstrate extended AI use to 10 years reduces breast cancer recurrence, our results further indicate safety of AI use with regard to risk of VTE [9, 20].

A favorable adverse event profile with regard to thromboembolic events has been consistently reported in double-blinded, randomized clinical trials (RCT) in women with advanced breast cancer when comparing AIs to tamoxifen [13, 21–23]. However, because all these RCTs were designed to assess efficacy rather than safety, there was a lack of adequate ascertainment of the VTE events, especially those adverse events occurred after the efficacy outcome of interest [16]. Given the several intrinsic limitations of the trial design such as the restricted study participants, small sample size, and insufficient follow-up time, our carefully designed prospective analysis better addresses the chronic toxicity of AI in real-world practices [24]. Our population-based study results support previous clinical trial findings and extend generalizability because

we included diverse patients with a broad range of tumor characteristics who were followed longer.

The higher VTE risk in women who received tamoxifen can be explained by the altered circulating coagulation inhibitors induced by tamoxifen, including reduced antithrombin III, protein C levels, and protein S levels [6, 7]. Same alterations in hemostatic parameters were not found in studies of AIs, but increased plasma fibrinogen levels following AI treatment were reported and interpreted as a result of tamoxifen withdrawal rather than the direct effect from AI [14]. Chemotherapy also reduces protein C and protein S levels, and exerts detrimental effect on endothelial cells, all of which contribute to the pathogenesis of VTE [6, 7]. In women who received adjuvant chemotherapy, our finding of the over 50% reduced risk among AI users compared to tamoxifen users confirmed the synergetic effects of chemotherapy and tamoxifen on VTE risk that has been consistently reported.

Because platelet-aggregation, a hallmark of tumor metastasis, also contributes to the hypercoagulable state and makes it hard to disentangle the effect of the advanced tumor stage and endocrine drugs [6], we conducted a sensitivity analysis restricted to patients with Stages I–III invasive disease (eTable 1), and we again observed the 40% lower VTE risk by AI use. Due to the adverse effects associated with endocrine treatments (hot flashes and musculoskeletal complaints for AIs), patients might have discontinued the treatment. To evaluate the possible diluted effect by drug non-compliance, we conducted another sensitivity analysis among patients with high medication adherence and again found a strengthened protective effect of AI use.

A 41% increased risk of DVT, but not PE, was observed in women who used switched endocrine therapy. It is possible that the procoagulant effect caused by both drugs was stronger than tamoxifen alone. In the ATAC trial (Arimidex and Tamoxifen, Alone or in Combination), women who were randomized to receiving a combination of anastrozole and tamoxifen had increased VTE risk compared to women received tamoxifen only or anastrozole only [12]. Similarly, the Tamoxifen Exemestane Adjuvant Multinational (TEAM) phase III trial observed a lower DVT risk in women who received AI monotherapy versus those who switched to AIs after using tamoxifen for 2–3 years [4]. An alternative explanation could be the presence of unmeasured confounding factors as a result of cancer recurrence, which is more likely in women who experienced a drug switch. We cannot rule out the possibility that some VTE events that were categorized for the "switcher" group were simply the cross-over effect from the first drug due to the study's design feature. Additionally, longer duration of AI did not increase the VTE risk. Similar to an observational study in Denmark, we found a declining pattern of risk by duration of tamoxifen, possibly due to the adaptation to the procoagulant effects of tamoxifen [25].

Our study has several strengths. Firstly, our outcome ascertainment as well as the identification of other key variables were based on high validity data. We performed medical chart review for 10% of patients with VTE and found 80.9% of them were confirmed with objective imaging test (i.e., Duplex Doppler ultrasound for DVT and computed tomographic pulmonary angiography for PE). In contrast, only less than 50% of DVT or PE diagnosed in general was confirmed by objective imaging [7]. Importantly, our analysis was based on filled prescriptions which ensured accuracy for both exposure and covariate drug ascertainment. Secondly, given the managed care setting, our study has sufficient long follow-up time and bias through variable medical insurance coverage was minimized. Over 25% of participants had greater than 9 years of follow-up, and nearly 84% of breast cancer survivors stayed within the health plan through the study's end. Thirdly, we applied different analytic strategies to address various sources of bias in observational studies and conducted multiple sensitivity analyses to assure the robustness of the conclusion. The HR estimates in our study accounted for tumor characteristics, cancer treatments, indications of drug selection, and VTE risk factors. Because the adverse effect of tamoxifen on VTE risk has been established in previous research, tamoxifen may be selectively prescribed to women taking preventive anticoagulants. We further adjusted for concurrent cardiovascular medications use to address potential confounding by indication [25, 26]. Moreover, our two additional sensitivity analyses restricted to women with stage I-III disease, and women with good medication adherence, confirmed and strengthened the finding of the inverse association between AI use and VTE risk. Lastly, our results are generalizable to the larger California population given that the cohort's racial/ethnicity distribution is similar to that of the overall community.

Certain limitations must be considered. Because imaging tests for peripheral vascular disease is not routine in breast cancer survivorship care plans, we were not able to capture any asymptomatic VTE, although the crude rate estimates for symptomatic VTE have strong validity. We did not have complete data on BMI. However, in a sensitivity analysis with known BMI ($N = 4642$), the adjusted HR estimates did not change substantially. Based on existing RCTs that favored AI over Tamoxifen regarding the adverse effect on VTE, physicians may preferentially prescribe AI to patients older than 60, or to those with concerns for thromboembolism [27]. Although we included a comprehensive set of covariates, including time-varying anticoagulant and other CVD medication use, residual confounding by indication cannot be precluded in our study. In the dose–response analysis, the decreasing HR in prolonged tamoxifen users might be an artifact of the data

because patients might have discontinued tamoxifen due to incident DVT/PE. But this artefactual effect is less likely to happen among AI users, because the typical reason to discontinue AI use is joint and muscle pain, and is not related to VTE risk. Nearly 16% of the women disenrolled from the health plan. They were less likely to use endocrine therapy, younger, with less comorbidities, have less health care utilization, and more likely to have early stage breast cancer. Since the VTE outcome was not identifiable in this population, we cannot rule out the possibility of selection bias. Lastly, we did not account for the second round of therapeutic methods for breast cancer recurrence (we did not censor women at time of cancer recurrence in efforts to avoid underestimation of VTE).

In summary, in our large prospective cohort of postmenopausal women with breast cancer, we observed an inverse association between AI use and VTE compared to tamoxifen. This study bridged the gap between clinical trials and real-world clinical practice data and substantially adds to the literature on the other favorable effects of AIs (e.g., suppression of endometrial cancer, no increased risk of cardiovascular events versus tamoxifen) [28, 29]. Although AIs display a favorable safety profile in venous thromboembolic disease compared with tamoxifen, its harmful effects on bone health must still be considered when selecting the optimal endocrine therapy for individual patients.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval Only secondary data analyses were performed. The KPSC Institutional Review Board reviewed and approved this study.

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