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ORIGINAL RESEARCH

Cardiovascular Risks of Aromatase Inhibitors versus Tamoxifen in Postmenopausal Breast Cancer: A Multinational Cohort Study

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Background: Aromatase inhibitors (AIs) are the preferred treatment for postmenopausal women with hormone receptor-positive (HR+) breast cancer, but their cardiovascular safety remains uncertain. This study compared cardiovascular risks associated with AIs versus tamoxifen in two distinct populations.

Patients and methods: This retrospective cohort study used data from the US SEER-Medicare database (2007–2020) and Taiwan's National Health Insurance claims database and cancer registry (2010–2021). Postmenopausal women with HR+ stage I–III breast cancer were categorized by their initial endocrine therapy. Study outcomes included major adverse cardiovascular events (MACE), venous thromboembolism (VTE), and heart failure (HF). Covariate balance was achieved through inverse probability of treatment weighting, and cause-specific hazard models were used for risk assessment in each cohort.

Results: The study included 36,950 US patients (89% AI users) and 22,676 Taiwan patients (71% AI users). In the US, AIs were associated with an HR of 1.13 (95% CI 0.83–1.52) for MACE and 1.17 (95% CI 0.93–1.48) for HF, compared to tamoxifen. In Taiwan, the HRs were 1.23 (95% CI 0.87–1.73) for MACE and 0.93 (95% CI 0.73–1.21) for HF. AI use was linked to a lower VTE risk in the US (HR: 0.35, 95% CI 0.27–0.45), while the Taiwan cohort showed a non-significant trend (HR: 0.72, 95% CI 0.42–1.25).

Conclusion: AIs were not associated with a definitive increase in MACE or HF risk compared with tamoxifen, although confidence intervals suggest some uncertainty in the estimates. The observed differences in VTE risk across cohorts highlight the need for population-specific considerations when selecting endocrine therapy.

Keywords: aromatase inhibitors, tamoxifen, cardiotoxicity, major adverse cardiovascular events, venous thromboembolism, heart failure

Introduction

Adjuvant endocrine therapy, including aromatase inhibitors (AIs) and tamoxifen, is the standard treatment for hormone receptor-positive (HR+) non-metastatic breast cancer.[1] In postmenopausal women, AIs are preferred over tamoxifen due to their association with lower recurrence rates.[2] However, tamoxifen remains an option for some postmenopausal patients, particularly those with contraindications to AIs, intolerance to AI-related adverse effects (eg, musculoskeletal symptoms or bone loss), or specific clinical considerations, such as an elevated risk of osteoporosis or fracture. Despite the efficacy of AIs, the potential cardiotoxic effects remain a concern. Unlike tamoxifen, which inhibits the growth of breast cancer cells by blocking estrogen receptors, AIs reduce estrogen production, thereby lowering systemic estrogen levels. Estrogen plays a cardioprotective role through several mechanisms, including facilitating lipid metabolism and

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promoting vasodilation, which may mitigate cardiovascular risks in women.[3,4] As a result, the estrogen depletion caused by aromatase inhibition can potentially elevate the risk of cardiovascular events in postmenopausal women.

Several studies have reported an association between the use of AIs and increased risk of cardiovascular events. Meta-analyses have revealed a higher incidence of cardiovascular events among AI users compared with tamoxifen users, although the risk of cerebrovascular events appears similar between the two treatments.[5,6] However, findings from observational studies have been inconsistent. Some studies reported a greater risk of acute myocardial infarction (AMI),[7,8] heart failure (HF),[8–10] and arrhythmia[8] among AI users, while other studies did not find a significantly increased cardiovascular risk related to AI use.[11,12] The risk of ischemic stroke has generally been comparable between AIs and tamoxifen, which aligns with findings from previous meta-analyses. Most of the existing research, however, has been conducted in Western populations, raising concerns about the generalizability of these results to Asian populations. The few studies involving Asian populations have generally not identified a significant association between AIs and cardiovascular events,[13,14] contributing to the ongoing uncertainty surrounding these risks.

Cardiovascular events are a significant cause of mortality in breast cancer patients.[15] Whether the use of AIs is associated with cardiovascular event risk has been debated across studies involving different populations and study designs. Addressing these concerns is crucial for improving prognostic outcomes of these patients. Therefore, this study aimed to compare the cardiovascular risks associated with AIs and tamoxifen in postmenopausal women across distinct populations using data from the US and Taiwan, and to provide insights into the cardiovascular safety of AIs in diverse populations. The Taiwan cohort addresses the gap in knowledge about cardiovascular risks in Asian populations, while the US cohort provides a basis for validation.

Methods

Study Design and Data Source

This retrospective multinational cohort study was conducted in the US and Taiwan using population-based databases linked with cancer registries. Data sources included the 2007–2020 Surveillance, Epidemiology, and End Results (SEER)-Medicare-linked database in the US and the 2010–2021 National Health Insurance Research Database (NHIRD) linked with the Taiwan Cancer Registry Database (TCRD) and Cause of Death Registry in Taiwan. The SEER database provides comprehensive information on cancer patients, capturing tumor characteristics at diagnosis, cancer treatments, and survival outcomes. The Medicare database documents healthcare services received by beneficiaries, primarily individuals aged 65 years and older.[16] In Taiwan, the NHIRD covers over 99% of the population, providing detailed claims data encompassing disease diagnoses, medication prescriptions, and medical expenditures.[17] The TCRD is a high-quality database that provides detailed and accurate recording of cancer patient information, as demonstrated by previous research.[18]

Ethical approval for this study was waived by the Research Ethics Committee of the University of Illinois Chicago (approval number: STUDY2023-0388) and National Taiwan University Hospital (approval number: 202408057W).

Study Population and Exposure Definition

The study included women newly diagnosed with HR+ stage I–III breast cancer from 2010 to 2019 in the US and from 2011 to 2020 in Taiwan. Patients aged 66 years or older in the US and 60 years or older in Taiwan at breast cancer diagnosis were included (Supplemental Figure S1 provides a visualization of the study design). Eligible patients were classified into tamoxifen or AI groups based on their first post-surgery endocrine therapy prescription, with this prescription date defined as the index date. Exclusions were applied to those with prior prescription of tamoxifen or an AI, no history of breast cancer surgery, or initiation of adjuvant endocrine therapy more than one year after breast cancer diagnosis. Patients who received both an AI and tamoxifen as initial therapy or had a history of other cancers were also excluded. For the US cohort, lack of continuous Medicare Parts A, B, and D enrollment or having Health Maintenance Organization coverage within one year prior to the index date were additional exclusions. Further exclusions for each outcome analysis are detailed in the Outcome Ascertainment and Follow-up section.

Outcome Ascertainment and Follow-Up

The study outcomes were major adverse cardiovascular events (MACE), VTE, and HF. Outcome occurrences were mainly identified using the International Classification of Diseases, 9th and 10th revisions, Clinical Modification (ICD-9-CM and ICD-10-CM) codes. MACE was defined as a composite of AMI, ischemic stroke, and cardiovascular mortality (CVM), with each component also analyzed individually. VTE, comprising pulmonary embolism (PE), deep vein thrombosis (DVT), and other venous thrombosis, was identified using diagnosis codes and records of anticoagulant prescription. For composite outcomes (MACE or VTE), only the first occurring event was considered in the analysis if a patient experienced multiple components (eg, AMI followed by ischemic stroke). However, each event was also analyzed separately. Validated algorithms were used to identify cardiovascular events, with details provided in Supplemental Tables S1-S3.[19–24] The positive predictive value (PPV) of these algorithms ranged from 76% to 99%.

For each outcome analysis, patients with specific cardiovascular histories that could interfere with outcome identification were excluded to accurately identify incident cardiovascular events. For the MACE outcome, patients with a history of AMI or ischemic stroke within 30 days before the index date were excluded. For the VTE outcome, exclusions were applied to patients with a history of DVT or PE within one year before the index date or those prescribed an anticoagulant within 183 days prior. For the HF outcome, patients with any previous diagnosis history of HF before the index date were excluded, using all available claims data to ensure comprehensive identification of HF history.

The main analysis used an as-treated approach. Patients were followed from the index date until occurrence of study outcome, treatment discontinuation or alteration, diagnosis of another cancer, death, or end of the study, whichever occurred first. A 30-day grace period was applied to identify treatment discontinuation. Patients with a refill gap of more than 30 days between prescription supplies were considered to have discontinued therapy. Those who switched medications were censored at the date of the new prescription.

Covariates

Baseline characteristics included demographic data, cancer-related variables, frailty status, healthcare resource utilization, Charlson Comorbidity Index, relevant individual comorbidities, and concomitant medications (Table 1). Cancer stage, grade, laterality, and human epidermal growth factor receptor 2 (HER2) status were evaluated based on data at cancer diagnosis, while cancer treatments received between the cancer diagnosis and index date were measured and adjusted for in the analysis. Comorbidities were identified based on at least one inpatient diagnosis or two outpatient diagnoses more than 30 days apart within the year preceding the index date, regardless of diagnosis position (detailed diagnostic codes provided in Supplemental Table S4). Concomitant medications prescribed within 183 days before the index date were recorded. Baseline frailty status was determined using a validated claims-based frailty index specific to the US databases[25,26] and a separate validated index for the Taiwan database.[27,28] The frequency of healthcare visits in the prior year was calculated separately for emergency department and hospital admissions.

Statistical Analysis

For each country's cohort, inverse probability of treatment weighting (IPTW) was employed to balance the baseline characteristics between treatment groups. Propensity scores for receiving an aromatase inhibitor versus tamoxifen were estimated using logistic regression models including all baseline covariates listed in Table 1. Potential confounders were adjusted using IPTW, and extreme weights were managed by applying stabilized weights in combination with weight truncation at the 1st and 99th percentiles. The baseline characteristics of the AI and tamoxifen groups were assessed for imbalances using the absolute standardized mean difference (ASMD) before and after weighting, with an ASMD exceeding 0.1 indicating covariate imbalance.

Cause-specific hazard models were utilized to estimate the risk of each outcome associated with AIs versus tamoxifen. These models account for competing risks, which is essential when studying cardiovascular outcomes. In the analysis of CVM, non-cardiovascular deaths were treated as competing events, whereas all-cause deaths were considered competing events for other outcomes. Additionally, weighted cumulative incidence functions were constructed to assess the risks of MACE, VTE, and HF over time (Supplemental Figure S2-S7).

Table 1 Baseline Characteristics of the US and Taiwan Cohorts for MACE Analysis Before Weighting[a]

	US Cohort			Taiwan Cohort		
	AI Users (n=33,106)	**TAM Users (n=3,825)**	**ASMD[b]**	**AI Users (n=16,109)**	**TAM Users (n=6,555)**	**ASMD[b]**
Demographic characteristics						
Age, mean ± SD	73.9 ± 6.0	75.3 ± 6.7	**0.22**	68.4 ± 6.8	69.0 ± 7.3	0.09
Race, n (%)			**0.17**	NA		
White	28,831 (87.1)	3,447 (90.1)				
Black	2,185 (6.6)	115 (3.0)				
Other	2,090 (6.3)	263 (6.9)				
Marital status, n (%)			0.05			
Single	15,583 (47.1)	1,887 (49.3)				
Married	15,976 (48.3)	1,787 (46.7)				
Unknown	1,547 (4.7)	151 (3.9)				
Rurality/urbanity, n (%)			**0.15**			
Urban	25,143 (75.9)	2,678 (70.0)				
Suburban/Small urban	5,772 (17.4)	776 (20.3%)				
Rural/Unknown[b]	2,191 (6.6)	371 (9.7)				
SEER region, n (%)			**0.27**			
Northeast	7,310 (22.1)	464 (12.1)				
South	7,853 (23.7)	943 (24.7)				
West	13,896 (42.0)	1,882 (49.2)				
Midwest	4,047 (12.2)	536 (14.0)				
Year of diagnosis, n (%)			0.10			**0.93**
2010-11 (US)/2011-12 (TW)	4,948 (14.9)	680 (17.8)		733 (4.6)	2,248 (34.3)	
2012-13 (US)/2013-14 (TW)	5,997 (18.1)	749 (19.6)		2,559 (15.9)	1,479 (22.6)	
2014-15 (US)/2015-16 (TW)	7,425 (22.4)	835 (21.8)		3,604 (22.4)	1,005 (15.3)	
2016-17 (US)/2017-18 (TW)	8,195 (24.8)	857 (22.4)		4,707 (29.2)	1,050 (16.0)	
2018-19 (US)/2019-20 (TW)	6,541 (19.8)	704 (18.4)		4,506 (28.0)	773 (11.8)	
Tumor characteristics, n (%)						
Cancer grade			**0.13**			**0.15**
Well differentiated	9,830 (29.7)	1,339 (35.0)		3,297 (20.5)	1,646 (25.1)	
Moderately differentiated	16,895 (51.0)	1,897 (49.6)		9,436 (58.6)	3,619 (55.2)	
Poorly/Undifferentiated	5,686 (17.2)	519 (13.6)		2,944 (18.3)	1,011 (15.4)	
Unknown	695 (2.1)	70 (1.8)		432 (2.7)	279 (4.3)	
Cancer stage			**0.15**			**0.33**
Stage I	21,607 (65.3)	2,745 (71.8)		6,517 (40.5)	3,527 (53.8)	
Stage II	9,218 (27.8)	906 (23.7)		6,881 (42.7)	2,504 (38.2)	
Stage III	2,281 (6.9)	174 (4.5)		2,711 (16.8)	524 (8.0)	
HER2-positive status	2,813 (8.5)	257 (6.7)	0.07	2,658 (16.5)	1,019 (15.5)	0.03
Laterality			0.01			0.02
Left	16,745 (50.6)	1,907 (49.9)		8,545 (53.0)	3,515 (53.6)	
Right/Unknown[b]	16,361 (49.4)	1,918 (50.1)		7,564 (46.9)	3,040 (46.4)	
Cancer therapies, n (%)						
Anthracyclines	1,534 (4.6)	79 (2.1)	**0.14**	4,673 (29.0)	1,305 (19.9)	**0.21**
Taxanes	5,165 (15.6)	289 (7.6)	**0.25**	3,711 (23.0)	587 (9.0)	**0.39**
Trastuzumab	1,780 (5.4)	113 (3.0)	**0.12**	1,361 (8.4)	261 (4.0)	**0.19**
Other chemotherapy	5,137 (15.5)	320 (8.4)	**0.22**	5,951 (36.9)	1,728 (26.4)	**0.23**
Radiotherapy	14,965 (45.2)	1,747 (45.7)	0.01	2,398 (14.9)	882 (13.5)	0.04

(*Continued*)

Table 1 (Continued).

	US Cohort			Taiwan Cohort		
	AI Users (n=33,106)	**TAM Users (n=3,825)**	**ASMD[b]**	**AI Users (n=16,109)**	**TAM Users (n=6,555)**	**ASMD[b]**
CCI in categories, n (%)			0.08			0.03
0	15,930 (48.1)	1,986 (51.9)		7,680 (47.7)	3,081 (47.0)	
1	8,509 (25.7)	959 (25.1)		4,468 (27.7)	1,882 (28.7)	
2	4,163 (12.6)	423 (11.1)		2,337 (14.5)	973 (14.8)	
≥3	4,504 (13.6)	457 (11.9)		1,624 (10.1)	619 (9.4)	
Frailty status, n (%)			0.05			**0.11**
Non-frail	13,115 (39.6)	1,594 (41.7)		11,110 (69.0)	4,193 (64.0)	
Prefrail	16,577 (50.1)	1,831 (47.9)		2,684 (16.7)	1,210 (18.5)	
Frail	3,414 (10.3)	400 (10.5)		2,315 (14.4)	1,152 (17.6)	
Healthcare resource utilization in the prior year before index date, n (%)						
Number of ED visits			0.06			0.04
0	22,978 (69.4)	2,694 (70.4)		11,338 (70.4)	4,716 (71.9)	
1	6,398 (19.3)	723 (18.9)		3,057 (19.0)	1,199 (18.3)	
2	2,142 (6.5)	266 (7.0)		992 (6.2)	387 (5.9)	
≥3	1,588 (4.8)	142 (3.7)		722 (4.5)	253 (3.9)	
Number of hospital admissions			0.04			**0.16**
0	25,382 (76.7)	2,998 (78.4)		128 (0.8)	98 (1.5)	
1	5,775 (17.4)	627 (16.4)		8,595 (53.4)	3,746 (57.1)	
2	1,329 (4.0)	141 (3.7)		2,590 (16.1)	1,187 (18.1)	
≥3	620 (1.9)	59 (1.5)		4,796 (29.8)	1,524 (23.2)	
Comorbidities, n (%)						
Atrial fibrillation/flutter	3,215 (9.7)	348 (9.1)	0.02	286 (1.8)	117 (1.8)	0
Congestive heart failure	2,452 (7.4)	291 (7.6)	0.01	555 (3.4)	256 (3.9)	0.02
Hemorrhagic stroke	40 (0.1)	–[c]	0	65 (0.4)	33 (0.5)	0.01
Ischemic stroke/TIA	962 (2.9)	88 (2.3)	0.04	516 (3.2)	248 (3.8)	0.03
Myocardial infarction	949 (2.9)	83 (2.2)	0.04	50 (0.3)	33 (0.5)	0.03
Other ischemic heart disease	4,723 (14.3)	483 (12.6)	0.05	1,692 (10.5)	833 (12.7)	0.07
Peripheral vascular disease	2,888 (8.7)	332 (8.7)	0	257 (1.6)	91 (1.4)	0.02
Valvular heart disease	3,056 (9.2)	302 (7.9)	0.05	608 (3.8)	258 (3.9)	0.01
Venous thromboembolism	927 (2.8)	50 (1.3)	**0.11**	119 (0.7)	36 (0.5)	0.02
Diabetes	8,994 (27.2)	805 (21.0)	**0.14**	4,657 (28.9)	1,902 (29.0)	0
Hyperlipidemia	21,057 (63.6)	2,184 (57.1)	**0.13**	5,471 (34.0)	2,156 (32.9)	0.02
Hypertension	24,400 (73.7)	2,601 (68.0)	**0.13**	8,890 (55.2)	3,729 (56.9)	0.03
COPD	3,154 (9.5)	394 (10.3)	0.03	363 (2.3)	201 (3.1)	0.05
Liver disease	948 (2.9)	86 (2.2)	0.04	1,909 (11.9)	727 (11.1)	0.02
Renal disease	2,841 (8.6)	288 (7.5)	0.04	804 (5.0)	310 (4.7)	0.01
Arthritis	8,690 (26.2)	1,035 (27.1)	0.02	2,663 (16.5)	1,220 (18.6)	0.05
Osteoporosis	6,111 (18.5)	1,303 (34.1)	**0.36**	625 (3.9)	318 (4.9)	0.05
Anxiety	4,063 (12.3)	456 (11.9)	0.01	1,683 (10.4)	654 (10.0)	0.02
Dementia	671 (2.0)	73 (1.9)	0.01	371 (2.3)	165 (2.5)	0.01
Depression	4,524 (13.7)	487 (12.7)	0.03	924 (5.7)	355 (5.4)	0.01
Parkinson's disease	284 (0.9)	36 (0.9)	0.01	256 (1.6)	104 (1.6)	0
Concomitant medications, n (%)						
ACEI/ARB/ARNI	16,196 (48.9)	1,693 (44.3)	0.09	5,403 (33.5)	2,264 (34.5)	0.02
Beta blockers	11,537 (34.8)	1,195 (31.2)	0.08	3,921 (24.3)	1,664 (25.4)	0.02
Calcium channel blockers	8,924 (27.0)	920 (24.1)	0.07	5,866 (36.4)	2,567 (39.2)	0.06
Class I and III antiarrhythmics	689 (2.1)	70 (1.8)	0.02	650 (4.0)	224 (3.4)	0.03

(*Continued*)

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Table 1 (Continued).

	US Cohort			Taiwan Cohort		
	AI Users (n=33,106)	**TAM Users (n=3,825)**	**ASMD[b]**	**AI Users (n=16,109)**	**TAM Users (n=6,555)**	**ASMD[b]**
Digoxin	711 (2.1)	75 (2.0)	0.01	103 (0.6)	52 (0.8)	0.02
Diuretics	13,243 (40.0)	1,329 (34.7)	**0.11**	2,741 (17.0)	1,224 (18.7)	0.04
Nitrates/Vasodilators	1,589 (4.8)	156 (4.1)	0.04	591 (3.7)	315 (4.8)	0.06
Antiplatelets	1,712 (5.2)	174 (4.5)	0.03	2,791 (17.3)	1,326 (20.2)	0.07
Oral anticoagulants	2,760 (8.3)	279 (7.3)	0.04	335 (2.1)	109 (1.7)	0.03
Insulin	1,727 (5.2)	146 (3.8)	0.07	769 (4.8)	307 (4.7)	0
Oral hypoglycemic drugs/GLP1-RA	5,710 (17.2)	474 (12.4)	**0.14**	3,949 (24.5)	1,614 (24.6)	0
Statins	16,414 (49.6)	1,615 (42.2)	**0.15**	4,624 (28.7)	1,757 (26.8)	0.04
Other lipid-lowering drugs	2,023 (6.1)	198 (5.2)	0.04	826 (5.1)	307 (4.7)	0.02
Bisphosphonates	2,759 (8.3)	558 (14.6)	**0.20**	113 (0.7)	58 (0.9)	0.02
Denosumab	698 (2.1)	132 (3.5)	0.08	–[d]	–[d]	0.02
Antidepressants	8,924 (27.0)	953 (24.9)	0.05	1,550 (9.6)	590 (9.0)	0.02
Antipsychotics	3,659 (11.1)	272 (7.1)	**0.14**	2,546 (15.8)	866 (13.2)	0.07
Anxiolytics/hypnotics	9,038 (27.3)	1,036 (27.1)	0	7,100 (44.1)	2,824 (43.1)	0.02
NSAIDs	5,383 (16.3)	594 (15.5)	0.02	8,184 (50.8)	3,684 (56.2)	**0.11**
Opioids	23,608 (71.3)	2,738 (71.6)	0.01	1,978 (12.3)	839 (12.8)	0.02
Systemic glucocorticoids	5,617 (17.0)	519 (13.6)	0.09	7,082 (44.0)	2,223 (33.9)	**0.21**

Notes: [a]This table presents baseline characteristics of the cohorts for MACE analysis prior to weighting. Detailed baseline characteristics for each outcome analysis, both before and after weighting, are provided in Supplemental Tables S5-S7. [b]Covariate imbalance was defined as ASMD >0.1 and was shown in bold. [c]Cell sizes fewer than 11 were not reported or combined with the next lowest category to comply with SEER-Medicare data use guidelines. [d]Cell numbers less than 3 were not allowed to be presented due to Taiwan's NHIRD confidentiality policies.

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AIs, aromatase inhibitors; ARB, angiotensin II receptor antagonist; ARNI, angiotensin receptor-neprilysin inhibitor; ASMD, absolute standardized mean differences; CCI, Charlson comorbidity index; COPD, chronic obstructive pulmonary disease; ED, emergency department; GLP1-RA, glucagon-like peptide-1 receptor agonists; HER2, human epidermal growth factor receptor 2; NA, not available; NCI, National Cancer Institute; NSAIDs, nonsteroidal anti-inflammatory drugs; SEER, Surveillance, Epidemiology, and End Results; SD, standard deviation; TAM, tamoxifen; TIA, transient ischemic attack.

All analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC, USA) and R 4.4.1 (R Foundation for Statistical Computing, Vienna, Austria).

Sensitivity and Subgroup Analyses

Several sensitivity analyses were conducted to evaluate the robustness of our findings. First, patients with HER2-positive status or those receiving HER2-targeted therapy were excluded due to potential cardiotoxic effects from these treatments. Second, follow-up period was capped at 400 days to address imbalances in follow-up duration within the Taiwan cohort, in which the median follow-up was approximately 400 days for the tamoxifen group and 700 days for the AI group. Third, the grace period for defining treatment discontinuation was extended from 30 days to 60 days and 90 days. Fourth, the intention-to-treat approach with a five-year follow-up cap was applied. Lastly, the index date was adjusted to 90 days after the initial prescription of adjuvant endocrine therapy following surgery. This adjustment accounted for patients who may have received concurrent or sequential radiotherapy due to administrative delays, which could lead to misclassification and complicate covariate adjustment in the main analysis.

Four subgroup analyses were conducted to examine potential effect modification. These subgroups included (i) patients aged younger than 75 years and those aged 75 years or older, (ii) patients diagnosed with stage I and stage II/III breast cancer, (iii) non-frail and pre-frail/frail patients, and (iv) patients with or without a history of cardiovascular diseases, including atrial fibrillation, HF, cerebrovascular events (hemorrhagic and ischemic stroke, transient ischemic attack), ischemic heart conditions (AMI, other ischemic heart diseases), peripheral vascular diseases, valvular heart disease, and VTE.

Results

Study Cohorts and Baseline Characteristics

In the US cohort, 36,931 patients (89.6% treated with AI) were included in the MACE analysis, 31,706 (89.4% treated with AI) in the VTE analysis, and 29,180 (89.4% treated with AI) in the HF analysis. Among AI users in the US, approximately 73% received anastrozole, 3% exemestane, and 24% letrozole. The Taiwan cohort included 22,664 patients (71.1% receiving AI) for MACE analysis, 22,045 (71.0% receiving AI) for VTE analysis, and 20,508 (71.0% receiving AI) for HF analysis. Among AI users in Taiwan, approximately 4% received anastrozole, 1% exemestane, and 95% letrozole. The flow diagram of cohort selection in the US and Taiwan studies is presented in Figure 1.

Before weighting, AI users in both countries were more likely to have advanced cancer stages and cancer grades and to receive other cancer treatments than tamoxifen users (Table 1, Supplemental Tables S5-S7). In the US cohort, AI users had a higher prevalence of VTE, diabetes, hyperlipidemia, and hypertension than tamoxifen users, while the prevalence of other cardiovascular diseases was similar between groups. Conversely, fewer AI users in the US cohort were diagnosed with osteoporosis or prescribed bisphosphonates. In the Taiwan cohort, the prevalence of most comorbidities and frequency of concomitant medications were similar between groups, except for a slightly higher frailty rate and greater use of nonsteroidal anti-inflammatory drugs and systemic glucocorticoids among tamoxifen users.

MACE Outcome

In the US cohort, 582 events were identified in the AI group and 58 in the tamoxifen group (Table 2). In the Taiwan cohort, 199 events occurred in the AI group and 65 in the tamoxifen group. After weighting, the incidence rates of MACE in the US cohort were approximately twice as high as those in the Taiwan cohort (AIs: 10.73 vs 5.64 per 1,000 person-years; tamoxifen: 9.53 vs 4.61 per 1,000 person-years). However, the cause-specific hazard ratios (HR)

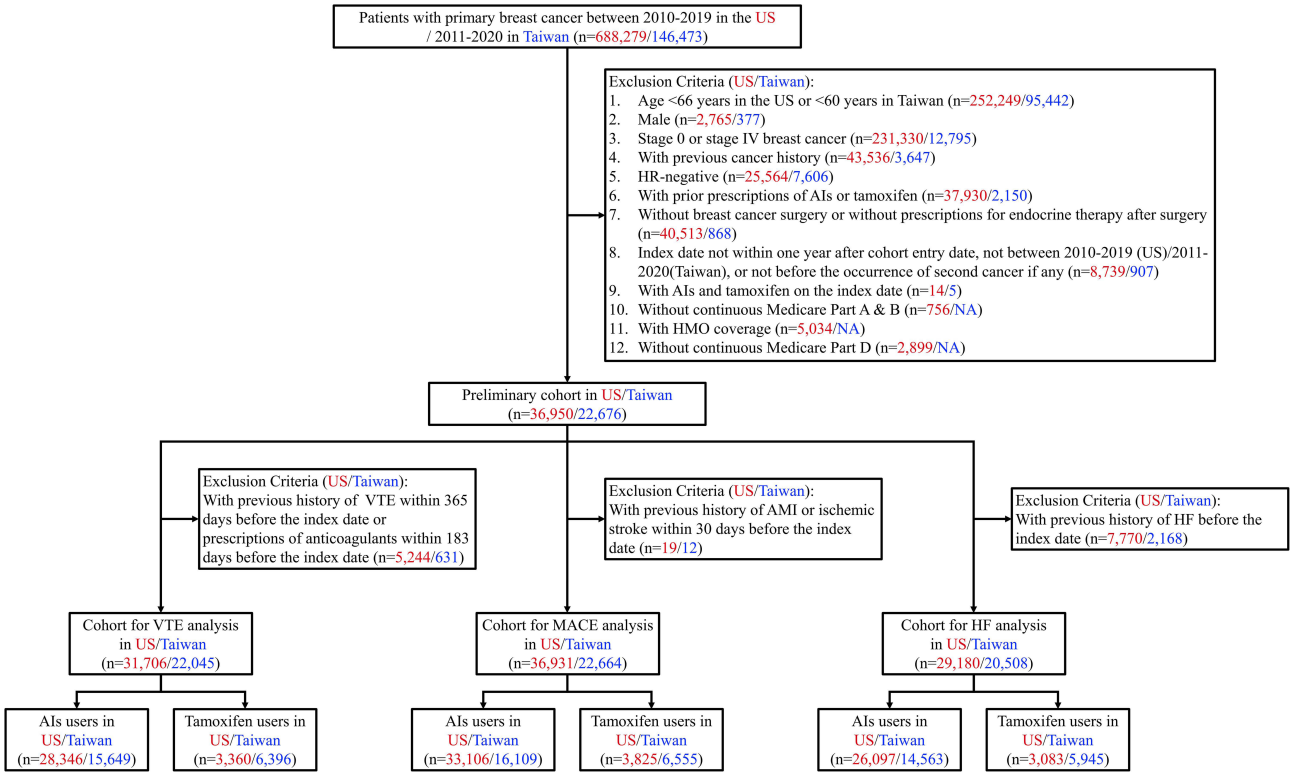

Figure 1 Flow chart of cohort selection. Patients with specific disease histories were excluded to ensure the identification of new-onset events for each study outcome. The index date was set as the date of the first endocrine therapy prescription following surgery. Numbers shown in red denote the US cohort, and those in blue denote the Taiwan cohort.

Abbreviations: AIs, aromatase inhibitors; AMI, acute myocardial infarction; HF, heart failure; HMO, health maintenance organization; HR, hormone receptor; MACE, major adverse cardiovascular events; NA, not applicable; VTE, venous thromboembolism.

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Table 2 Study Outcomes in the US and Taiwan Cohorts Before Weighting

Study Outcome	Treatment Group	US Cohort			Taiwan Cohort		
		No. Of Events/ Subjects	Median Follow-Up, Days (Q1-Q3)	Unweighted HR (95% CI)	No. Of Events/ Subjects	Median Follow-Up, Days (Q1-Q3)	Unweighted HR (95% CI)
MACE	AIs	582/33,106	394 (103–890)	1.13 (0.86–1.47)	199/16,109	699 (212–1,374)	1.01 (0.76–1.33)
	TAM	58/3,825	394 (107–864)	Reference	65/6,555	417 (78–1,081)	Reference
AMI	AIs	188/33,106	397 (104–895)	1.52 (0.88–2.61)	36/16,109	702 (215–1,385)	1.47 (0.68–3.16)
	TAM	14/3,825	394 (107–866)	Reference	8/6,555	421 (78–1,084)	Reference
Ischemic stroke	AIs	237/33,106	397 (104–895)	1.32 (0.84–2.09)	114/16,109	700 (213–1,377)	0.88 (0.62–1.25)
	TAM	20/3,825	394 (107–865)	Reference	42/6,555	418 (78–1,081)	Reference
CVM	AIs	197/33,106	400 (105–898)	0.88 (0.58–1.33)	53/16,109	706 (216–1,386)	1.00 (0.58–1.72)
	TAM	25/3,825	394 (107–869)	Reference	18/6,555	421 (78–1,085)	Reference
VTE	AIs	298/28,346	397 (104–896)	0.35 (0.28–0.44)	47/15,649	709 (216–1,389)	0.60 (0.37–0.97)
	TAM	97/3,360	390.5 (101–875)	Reference	26/6,396	423.5 (77–1,085)	Reference
PE	AIs	96/28,346	402 (105–902)	0.32 (0.21–0.47)	–[a]	711 (216–1,393)	0.89 (0.24–3.37)
	TAM	35/3,360	394 (105–881)	Reference	–[a]	424 (78–1,087.5)	Reference
DVT[b]	AIs	232/28,346	398 (104–897)	0.39 (0.29–0.50)	39/15,649	709 (216–1,389)	0.57 (0.34–0.95)
	TAM	69/3,360	391 (101.5–876)	Reference	23/6,396	423.5 (77–1,085)	Reference
New-onset HF	AIs	954/26,097	395 (103–886)	1.12 (0.91–1.38)	336/14,563	696 (209–1,380)	0.86 (0.70–1.06)
	TAM	99/3,083	398 (107–874)	Reference	129/5,945	412 (77–1,068)	Reference

Notes: [a]Cell numbers less than 3 were not allowed to be presented due to Taiwan's NHIRD confidentiality policies. [b]Include other venous thrombosis.

Abbreviations: AIs, aromatase inhibitors; AMI, acute myocardial infarction; CI, confidence interval; CVM, cardiovascular mortality; DVT, deep vein thrombosis; HF, heart failure; HR, hazard ratio; MACE, major adverse cardiovascular events; PE, pulmonary embolism; TAM, tamoxifen; VTE, venous thromboembolism.

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indicated no statistically significant difference in MACE risk between AIs and tamoxifen in either cohort (US HR: 1.13, 95% confidence interval [CI] 0.83–1.52; Taiwan HR: 1.23, 95% CI 0.87–1.73). The risks of individual MACE components, including AMI, ischemic stroke, and CVM, did not significantly differ between treatment groups in either country (Figure 2).

VTE Outcome

In the US cohort, 298 VTE diagnoses occurred in the AI group and 97 in the tamoxifen group, while in the Taiwan cohort, there were 47 VTE diagnoses in the AI group and 26 in the tamoxifen group. As shown in Figure 2, the weighted incidence rates of VTE were substantially higher in the US than in Taiwan (AIs: 6.34 vs 1.31 per 1,000 person-years; tamoxifen: 18.12 vs 1.87 per 1,000 person-years). The associations also differed between the two cohorts: in the US cohort, AIs were associated with a lower VTE risk (HR: 0.35, 95% CI 0.27–0.45), while in the Taiwan cohort, AIs showed only a non-significant trend toward decreased risk (HR: 0.72, 95% CI 0.42–1.25); the small VTE diagnosis counts in the Taiwan cohort led to low precision. The risk patterns for DVT and PE were consistent with those observed for overall VTE.

HF Outcome

In the US cohort, 954 patients in the AI group and 99 in the tamoxifen group were diagnosed with new-onset HF. In the Taiwan cohort, 336 patients in the AI group and 129 in the tamoxifen group were diagnosed with new-onset HF. The

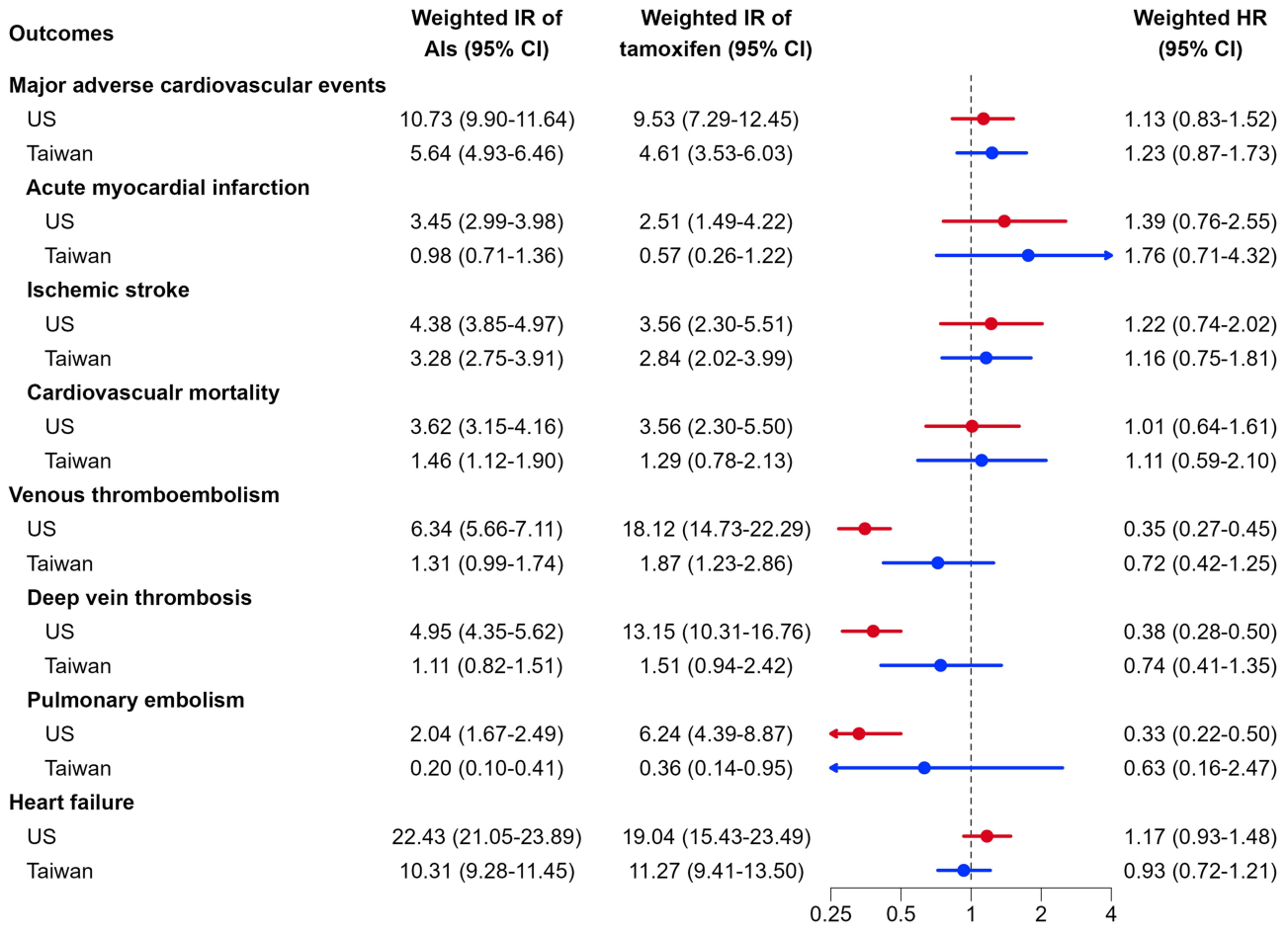

Figure 2 Weighted incidence rates and hazard ratios for study outcomes in the US and Taiwan cohorts. Incidence rates are expressed as the number of events per 1,000 person-years.

Abbreviations: AIs, aromatase inhibitors; HR, hazard ratio; IR, incidence rate.

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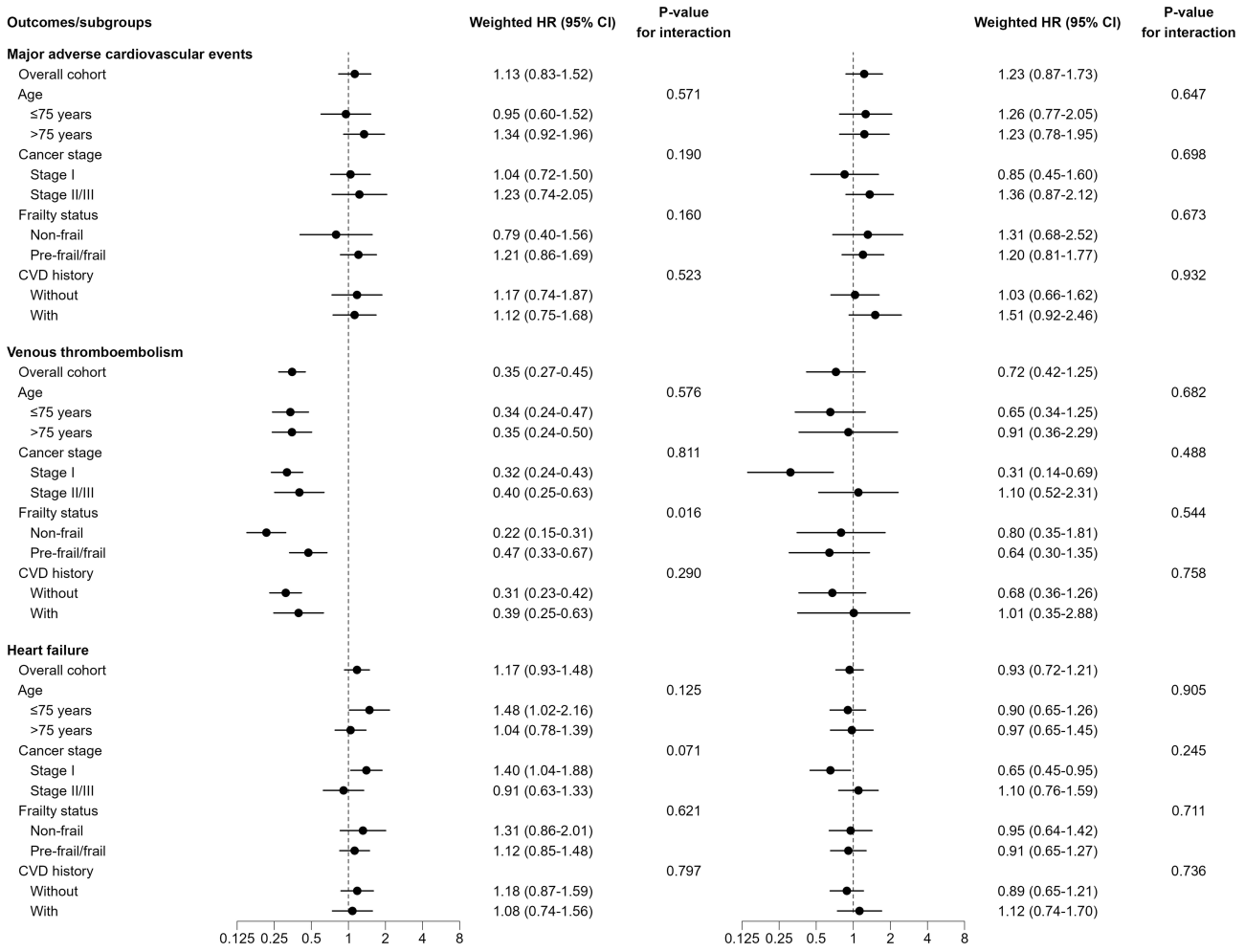

Figure 3 Subgroup analyses in the US and Taiwan cohorts. This figure presents the weighted hazard ratios for study outcomes across various subgroups in the US cohort (displayed on the left) and the Taiwan cohort (displayed on the right). Patients were re-weighted based on propensity scores estimated within each subgroup to ensure balanced covariates and accurate outcome comparisons.

Abbreviations: CVD, cardiovascular diseases; AIs, aromatase inhibitors; HR, hazard ratio; IR, incidence rate.

weighted incidence rates of HF in the US were approximately double those in Taiwan (AIs: 22.43 vs 10.31 per 1,000 person-years; tamoxifen: 19.04 vs 11.27 per 1,000 person-years) (Figure 2). Although the HR was slightly higher in the US cohort compared to the Taiwan cohort, neither country observed an increased risk of HF associated with AI use (US HR: 1.17, 95% CI 0.93–1.48; Taiwan HR: 0.93, 95% CI 0.72–1.21).

Sensitivity and Subgroup Analyses

The results of the sensitivity analyses were consistent with the main findings, as shown in Supplemental Figure S8-S13. Figure 3 presents the results of subgroup analyses. No significant effect modification was observed in most subgroups. However, in the US cohort, the reduced VTE risk among AI users was more pronounced in non-frail patients, a trend not observed in the Taiwan cohort. Additionally, the risk of HF associated with AI use among stage I patients varied between the countries: an increased risk was observed in the US cohort (HR: 1.40, 95% CI 1.04–1.88), whereas a decreased risk was found in the Taiwan cohort (HR: 0.66, 95% CI 0.47–0.93).

Discussion

This multinational cohort study evaluated cardiovascular risks among postmenopausal patients with HR+ non-metastatic breast cancer treated with AIs versus tamoxifen. While AIs were not statistically associated with an increased risk of

MACE or HF, the observed HRs and wide CIs suggest that a modest elevation in risk cannot be ruled out, particularly in the US cohort. In contrast, AI use was associated with a significantly lower risk of VTE in the US, with a consistent but non-significant trend in the Taiwan cohort. We did not pool results across cohorts as there could be significant heterogeneity between the US and Taiwan populations. US patients were older and had higher baseline cardiovascular risk, as shown by the greater prevalence of comorbidities. The differences likely reflect not only underlying population heterogeneity but also differences in clinical practice and potential channeling bias (eg, differential prescribing of AIs vs tamoxifen based on baseline history). Our findings provide a more nuanced understanding of the cardiovascular risks associated with adjuvant endocrine therapy across different populations.

For MACE, our findings are broadly in line with a previous meta-analysis,[5] which reported an elevated cardiovascular risk associated with AIs compared to tamoxifen as upfront therapy (HR: 1.19, 95% CI 1.07–1.34). This meta-analysis, however, included trials with highly selected patient populations and inconsistent definitions for composite cardiovascular events; for instance, some trials incorporated arrhythmia or angina into their definitions, potentially influencing the reported risk estimates. Observational studies have shown mixed results regarding the risk of composite cardiovascular outcomes associated with AIs, such as the study conducted in Taiwan by Chang et al (HR: 0.97, 95% CI 0.91–1.04)[13] and another in Italy by Franchi et al (HR: 1.14, 95% CI 1.00–1.29).[10] In contrast, our study employed a standardized protocol and utilized claims data from two large, racially diverse populations. By applying validated algorithms for outcome identification, we aimed to provide a more robust and representative comparison of cardiovascular risks in real-world settings. Although our estimates in the US (HR: 1.13, 95% CI 0.83–1.52) and Taiwan (HR: 1.23, 95% CI 0.87–1.73) did not reach statistical significance, they were directionally consistent with these prior findings. The lack of significance in our study likely reflects lower event counts and limited precision rather than clear evidence of no difference. Therefore, caution is warranted in interpreting these findings as conclusive.

We also examined the risks of individual MACE components. For ischemic stroke, our findings showed comparable risk between AI and tamoxifen users, aligning with most previous studies. The association between AIs and AMI, however, showed greater variability across studies. Kamaraju et al, using SEER-Medicare data, reported no significant association (HR: 1.01, 95% CI 0.72–1.42),[29] while Chang et al also found no increased risk in a Taiwanese population (HR: 1.02, 95% CI 0.79–1.31).[13] In contrast, Matthews et al observed an elevated AMI risk with AIs in their SEER-Medicare analysis (HR: 1.81, 95% CI 1.28–2.58), with a similar direction of effect in their UK cohort, though it did not reach statistical significance (HR: 1.56, 95% CI 0.96–2.52).[8] These discrepancies may stem from differences in population characteristics, study design, analytic approaches, and covariate adjustment across studies.

For HF, our study found no statistically significant difference in risk between AI and tamoxifen users. While some studies have suggested an increased HF risk with AIs,[8–10] others found comparable risks between the two treatments.[11,13] This inconsistency may have resulted from variations in study design, methodology, and study populations, which limit direct comparisons. Drawing on data from large, population-based cohorts in both the US and Taiwan, our study adds real-world evidence suggesting no clear association between AI use and increased HF risk. However, subgroup analysis revealed opposing HF risk trends among stage I breast cancer patients in the US and Taiwan, highlighting the need for further investigation to explore the underlying causes and the potential clinical significance.

Prior studies suggest that the potentially increased cardiovascular risks observed in AI users, compared with tamoxifen users, may be primarily attributed to the cardioprotective effects of tamoxifen rather than any inherent cardiotoxicity of AIs. In the BIG 1–98 trial, tamoxifen significantly reduced cholesterol levels, while AIs did not affect these values.[30] Meta-analyses have also reported a marked decrease in cholesterol and low-density lipoprotein levels with tamoxifen use, whereas these values were slightly increased in AI users.[31,32] Moreover, some studies have suggested that aromatase inhibition may contribute to endothelial dysfunction or vascular damage, which are early signs of atherosclerosis.[33,34] In these studies, AI users were observed to have decreased vascular relaxation or deteriorated reactive hyperemia index, a surrogate marker for endothelial function. However, the small sample sizes and short follow-up periods in these studies have limited their ability to draw definitive conclusions about the relationship between aromatase inhibition, endothelial dysfunction, and cardiovascular events.

Our study found a reduced risk of VTE associated with AIs in the US cohort, consistent with the findings of Xu et al (HR: 0.59, 95% CI 0.43–0.81).[35] In contrast, AI use in the Taiwan cohort was associated with a non-significant trend toward reduced

VTE risk, a pattern in line with previous studies conducted in Asian populations. For example, Kim et al observed a non-significant lower VTE risk among AI users in Korea (HR: 0.80, 95% CI 0.60–1.06),[14] and another Taiwan study found no significant difference in VTE risk between tamoxifen and non-tamoxifen users.[36] Previous epidemiologic research has shown that VTE incidence rates in Asians are only 15 to 20% of those reported in Western populations,[37] a trend also reflected in our study. The higher VTE risk associated with AI use in the US population compared with the Taiwan population may be attributable to factors such as racial differences and a higher prevalence of comorbidities in the US cohort.

Our study possesses several notable strengths. To our knowledge, this is the first to employ a consistent design and similar protocol across Western and Asian populations to examine cardiovascular risks associated with adjuvant endocrine therapy, where differences observed could offer insights into racial variations. Second, we used IPTW to address potential confounders, achieving a balanced comparison between the AI and tamoxifen groups. Unlike traditional matching, IPTW increases the effective sample size and enhances the generalizability of our results.[38] Furthermore, we applied validated algorithms to identify cardiovascular events, with several algorithms showing a PPV above 90%, thereby minimizing the likelihood of false-positive results. Lastly, we conducted various sensitivity analyses, which consistently supported our main findings, reinforcing the robustness of our results.

There are several limitations in our study. First, using claims databases may introduce covariate misclassification. For instance, self-paid trastuzumab prescriptions are not captured, potentially resulting in the misclassification of anti-HER2 therapy use. However, sensitivity analyses were conducted to address this limitation. Second, endocrine therapy was analyzed based on the initial prescription, and this approach may not fully reflect the long-term cardiovascular risks associated with changes in therapy. Third, while prescription refill records were used to track treatment persistence, claims data do not confirm whether patients took the medication as prescribed. Differences in actual drug administration could influence the observed cardiovascular risks. Fourth, despite comprehensive covariate adjustment, unmeasured confounders such as body mass index, smoking status, and menopausal age may still contribute to residual confounding. Lastly, our study did not include postmenopausal patients diagnosed with breast cancer before age 60 (or 66 in the US cohort), which may limit the applicability of our findings to this group.

Conclusions

In this large, two-country cohort study of postmenopausal women with HR+ breast cancer, AI use was not clearly associated with an increased risk of MACE or HF compared with tamoxifen, although wide confidence intervals suggest a potential for modest risk elevation, particularly in the US cohort. Additionally, a lower risk of VTE with AIs was observed in the US cohort, while the Taiwan cohort showed a non-significant trend toward reduced risk, suggesting possible differences between Western and Asian populations. These findings provide insights into balancing cardiovascular risks and the effectiveness of adjuvant endocrine therapy. Further research with greater statistical precision and exploration of high-risk subgroups is warranted to inform cardio-oncology care in diverse populations.

Abbreviations

AI, aromatase inhibitor; AMI, acute myocardial infarction; CVM, cardiovascular mortality; DVT, deep vein thrombosis; HF, heart failure; HR, hazard ratio; IPTW, inverse probability of treatment weighting; MACE, major adverse cardiovascular events; PE, pulmonary embolism; VTE, venous thromboembolism.

Data Sharing Statement

This study utilized data from the SEER-Medicare database in the United States and the National Health Insurance Research Database (NHIRD) linked with the Taiwan Cancer Registry Database (TCRD) and Cause of Death Registry in Taiwan. The SEER-Medicare is available upon approval of a research protocol from the National Cancer Institute. Instructions for accessing these data are available at https://healthcaredelivery.cancer.gov/seermedicare/obtain/. The Taiwan data are managed by the Health and Welfare Data Science Center (HWDC) under Taiwan's Ministry of Health and Welfare (MOHW). Due to legal and privacy restrictions, these data are not publicly available. Access requires formal approval from the MOHW and is restricted to researchers affiliated with approved institutions in Taiwan. For more information, please visit the MOHW website (https://dep.mohw.gov.tw/dos/) or contact the HWDC directly.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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