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ORIGINAL RESEARCH

Aromatase Inhibitor Therapy Increases the Risk of New-Onset Atrial Fibrillation in Patients With Breast Cancer

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ABSTRACT

BACKGROUND Previous studies suggest that aromatase inhibitors (AIs) increase the risk of adverse cardiovascular events and cardiac arrhythmias in patients with breast cancer, but it is unclear whether AIs also increase the risk of new-onset atrial fibrillation (AF).

OBJECTIVES The purpose of this study was to investigate whether the use of AIs was associated with an increased risk of new-onset AF in patients with breast cancer.

METHODS We performed a retrospective analysis involving 5,707 patients with breast cancer (mean age 63.9 ± 11.2 years and 99.9% women) who received adjunctive hormone therapy with an AI (AI group, n = 4,878) or tamoxifen (tamoxifen group, n = 829) in Hong Kong between January 1, 1999, and December 31, 2020. After propensity score matching, there were 1,658 and 829 patients with balanced characteristics in the AI group and tamoxifen group, respectively.

RESULTS After 8,863 patient-years of follow-up, patients who were prescribed AI had a trend toward more new-onset arrhythmias compared with those prescribed tamoxifen (0.62 vs 0.30 per 100 patient-years; crude HR: 2.05; $P = 0.053$). The difference in arrhythmic risk was mainly driven by a higher incidence rate of new-onset AF in the AI group (0.59 vs 0.27 per 100 patient-years; crude HR: 2.18; $P = 0.046$). The use of AIs was confirmed to be an independent risk factor for new-onset AF on multivariate analysis (adjusted HR: 2.75; $P = 0.01$).

CONCLUSIONS Among breast cancer patients prescribed adjunctive hormonal therapy, AI was associated with an increased risk of new-onset AF. Regular surveillance for new-onset AF should be considered in breast cancer patients treated with an AI. (JACC: Asia 2024;4:150-160) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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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.

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Endocrine agents, including selective estrogen receptor modulators (SERMs) and aromatase inhibitors (AIs), had gained wide application in the field of oncology. AIs unselectively inhibit estrogen synthesis catalyzed by aromatase enzymes in peripheral tissue. On the contrary, SERMs, such as tamoxifen, exert tissue-specific effects. Tamoxifen and AIs have been prescribed as adjunctive or palliative therapy to premenopausal and postmenopausal women with breast cancer, respectively.[1,2] In postmenopausal women, AIs are the preferred agent because they have been shown to decrease 10-year breast cancer mortality in an adjuvant setting[3] and improve overall survival in a palliative setting.[4] Nevertheless, whether AIs increase the risk of various cardiovascular events compared with tamoxifen is controversial.[5,6] The effect of AIs on arrhythmic risk has not been extensively studied. Prior cohort studies suggested that breast cancer patients prescribed an AI were at higher risk of developing arrhythmia than a matched control group.[7] Moreover, the risk of arrhythmias associated with AIs in such patients also increased with duration of exposure.[8] Nevertheless, the types of cardiac arrhythmia have not been determined.

Depletion of estrogen is known to be associated with an increased risk of atrial fibrillation (AF) in patients with premature menopause.[9,10] Because AIs reduce tissue estrogen level, we hypothesized that their use in patients with breast cancer might increase the risk of AF. We sought to determine whether the use of an AI as an adjunctive hormone therapy in breast cancer patients is associated with an increased risk of new-onset AF compared with tamoxifen.

METHODS

The study was approved by the Institutional Review Board of the University of Hong Kong and Hospital Authority Hong Kong West Cluster. Informed consent was waived because the study involved retrospective analysis of anonymized data from the hospital registry. The study was performed in accordance with the Declaration of Helsinki.

STUDY PARTICIPANTS. Adult patients aged 18 years or older who were prescribed an AI or tamoxifen for breast cancer at a public hospital managed by the Hospital Authority in Hong Kong from January 1, 1999, to December 31, 2020, were included in the study. Patients who received both an AI and tamoxifen were excluded from analysis.

STUDY PROCEDURE. Patients were identified using the Clinical Data Analysis and Reporting System of the Hospital Authority in Hong Kong. The Hospital Authority manages all public hospitals and clinics, providing 90% of hospital services in Hong Kong.[11] Demographic data, including age and date of birth; cardiovascular comorbidities; and outcomes including hypertension, diabetes mellitus, AF, myocardial infarction, heart failure, ischemic stroke, ventricular tachycardia, ventricular fibrillation, deep vein thrombosis, pulmonary embolism, and all-cause mortality, were extracted from the Clinical Data Analysis and Reporting System. Details regarding International Classification of Diseases-9th Revision-Clinical Modification and International Classification

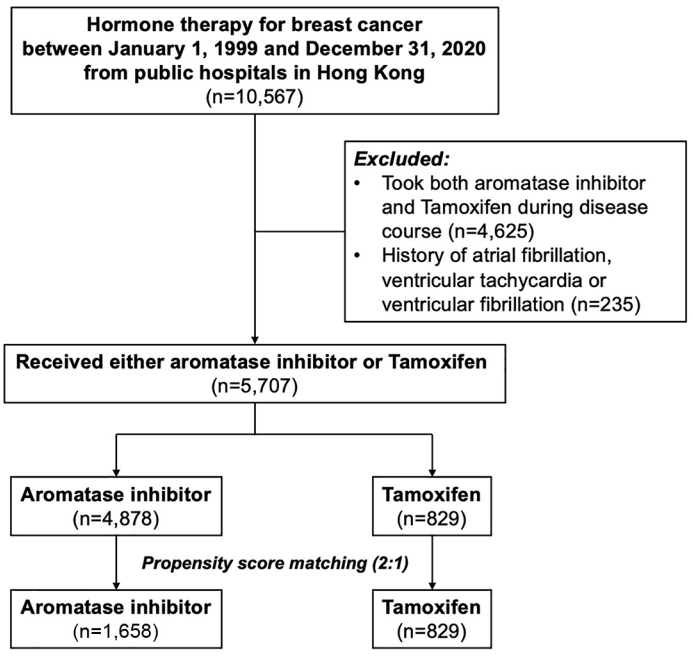
ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

AI = aromatase inhibitor

SERM = selective estrogen receptor modulator

FIGURE 1 Cohort Selection



A total of 10,567 patients with breast cancer treated in Public Hospitals in Hong Kong between January 1, 1999, and December 31, 2020, were selected. 4,625 who received both an aromatase inhibitor and tamoxifen during their disease course were excluded from analysis. 235 cases with history of atrial fibrillation, ventricular tachycardia, or ventricular fibrillation were also excluded from analysis. Among the 5,707 patients analyzed, 4,878 were prescribed an aromatase inhibitor and 829 were treated with tamoxifen. After propensity score matching in a 2:1 ratio, 3,316 patients were included in the final analysis.

TABLE 1 Baseline Characteristics

	Before PSM					After PSM[a]			
	Combined (n = 5,707)	Tamoxifen (n = 829)	AI (n = 4,878)	*P* Value	SMD[b]	Combined (n = 2,487)	Tamoxifen (n = 829)	AI (n = 1,658)	SMD[b]
Age, y	63.9 ± 11.2	59.3 ± 13.9	64.7 ± 10.5	<0.001[c]	−0.024	60 ± 12.1	59.3 ± 13.9	60.4 ± 11.1	−0.024
Male/female	5,699/5,707 (99.9)	827/829 (99.8)	4,872/4,878 (99.9)	0.615	−0.386	2,483/2,487 (99.8)	827/829 (99.8)	1,656/1,658 (99.9)	−0.081
Hypertension	2,052/5,707 (36)	197/829 (23.8)	1,855/4,878 (38)	<0.001[c]	−0.335	645/2,487 (25.9)	197/829 (23.8)	448/1,658 (27)	−0.076
DM	762/5,707 (13.4)	64/829 (7.72)	698/4,878 (14.3)	<0.001[c]	−0.247	228/2,487 (9.17)	64/829 (7.72)	164/1,658 (9.89)	−0.081
AMI	40/5,707 (0.701)	4/829 (0.483)	36/4,878 (0.738)	0.501	−0.036	14/2,487 (0.563)	4/829 (0.483)	10/1,658 (0.603)	−0.017
Stroke	274/5,707 (4.8)	12/829 (1.45)	262/4,878 (5.37)	<0.001[c]	−0.328	60/2,487 (2.41)	12/829 (1.45)	48/1,658 (2.9)	−0.121
DVT	52/5,707 (0.911)	1/829 (0.121)	51/4,878 (1.05)	0.0088[c]	−0.266	3/2,487 (0.121)	1/829 (0.121)	2/1,658 (0.121)	0
PE	17/5,707 (0.298)	0/829 (0)	17/4,878 (0.349)	0.157	−0.064	0/2,487 (0)	0/829 (0)	0/1,658 (0)	0
CHF	97/5,707 (1.7)	11/829 (1.33)	86/4,878 (1.76)	0.394	−0.038	40/2,487 (1.61)	11/829 (1.33)	29/1,658 (1.75)	−0.037

Values are mean ± SD or n/N (%). [a]Propensity score matching (PSM) was performed by matching age, sex, hypertension, diabetes mellitus (DM), history of acute myocardial infarction (AMI), stroke, deep vein thrombosis (DVT), pulmonary embolism (PE), and congestive heart failure (CHF) in 1:2 ratio. [b]Standardized mean difference (SMD) of <0.2 after propensity score matching was considered satisfactory. [c]$P < 0.05$.

AI = aromatase inhibitor.

of Primary Care codes used are listed in Supplemental Table 1. Outcomes up to 4 years from the date of endocrine therapy commencement or death were analyzed.

OUTCOMES. Primary outcome was composite arrhythmia occurrence and included new-onset AF, ventricular tachycardia, and ventricular fibrillation. Key secondary outcomes included occurrence of newly-onset AF, ventricular tachycardia and ventricular fibrillation, and ischemic stroke. Other outcomes analyzed included occurrence of myocardial infarction, deep vein thrombosis and pulmonary embolism.

STATISTICAL ANALYSIS. Continuous variables were tested for normal distribution using skewness statistics. Baseline data are reported as mean ± SD for continuous data and as number (percentage) for categorical data. The crude incidence rate of cardiovascular outcomes per 100 patient-years was calculated by dividing the number of events by the total patient-years at risk. Cardiovascular outcome-free survival was illustrated using Kaplan-Meier curves. Crude HR between AI and tamoxifen groups was calculated using Cox proportional hazard regression model. Adjusted HR of cardiovascular outcome was adjusted for age, sex, and presence of hypertension, diabetes mellitus, or pre-existing cardiovascular comorbidities. Propensity score matching was performed using R package "MatchIt" version 4.5.4 using Generalized Linear Models and "nearest" match algorithm. Standardized mean

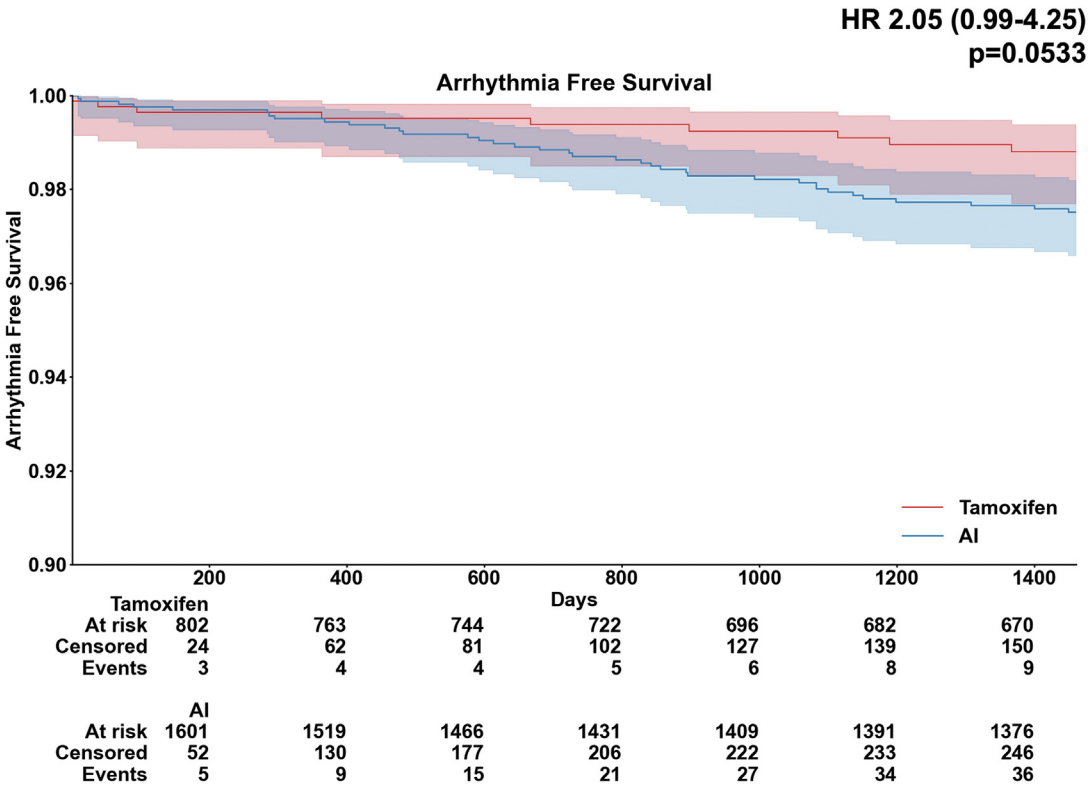
TABLE 2 Cardiovascular Outcomes

	Crude Incidence (Per 100 Patient-Years)			Cox Proportional Hazard Model			
	Combined (n = 2,487)	Tamoxifen (n = 829)	AI (n = 1,658)	Crude HR (95% CI)	*P* Value (Crude)	Adjusted HR (95% CI)[a]	*P* Value (Adjusted)
Arrhythmia[b]	0.519	0.306	0.625	2.05 (0.99-4.25)	0.0533	–	–
AF	0.485	0.272	0.591	2.18 (1.01-4.70)	0.0465[c]	2.75 (1.27-5.97)	0.0103[c]
VT and VF	0.034	0.034	0.034	0.995 (0.0902-11)	0.997		
AMI	0.203	0.136	0.236	1.75 (0.575-5.30)	0.326	–	–
Stroke	0.474	0.272	0.574	2.13 (0.984-4.59)	0.055	–	–
VTE[d]	0.293	0.34	0.27	0.798 (0.362-1.76)	0.575	–	–
DVT	0.169	0.204	0.152	0.748 (0.266-2.10)	0.581	–	–
PE	0.124	0.136	0.118	0.872 (0.255-2.98)	0.827	–	–

[a]Adjusted HR was calculated using Cox proportional hazard model with sex, age, hypertension, DM, history of AMI, and CHF as covariates. [b]Arrhythmia includes new-onset atrial fibrillation (AF), ventricular tachycardia (VT), and/or ventricular fibrillation (VF). [c]$P < 0.05$. [d]Venous thromboembolism (VTE) includes DVT and/or PE.

Abbreviations as in Table 1.

FIGURE 2 Arrhythmia-Free Survival of Patients on Aromatase Inhibitors and Tamoxifen



This Kaplan-Meier curve shows that the aromatase inhibitor group had a trend toward higher risk of arrhythmia than the tamoxifen group, with an incidence of 0.625 and 0.306 per 100 patient-years, respectively (crude HR: 2.05; 95% CI: 0.99-4.25; $P = 0.053$).

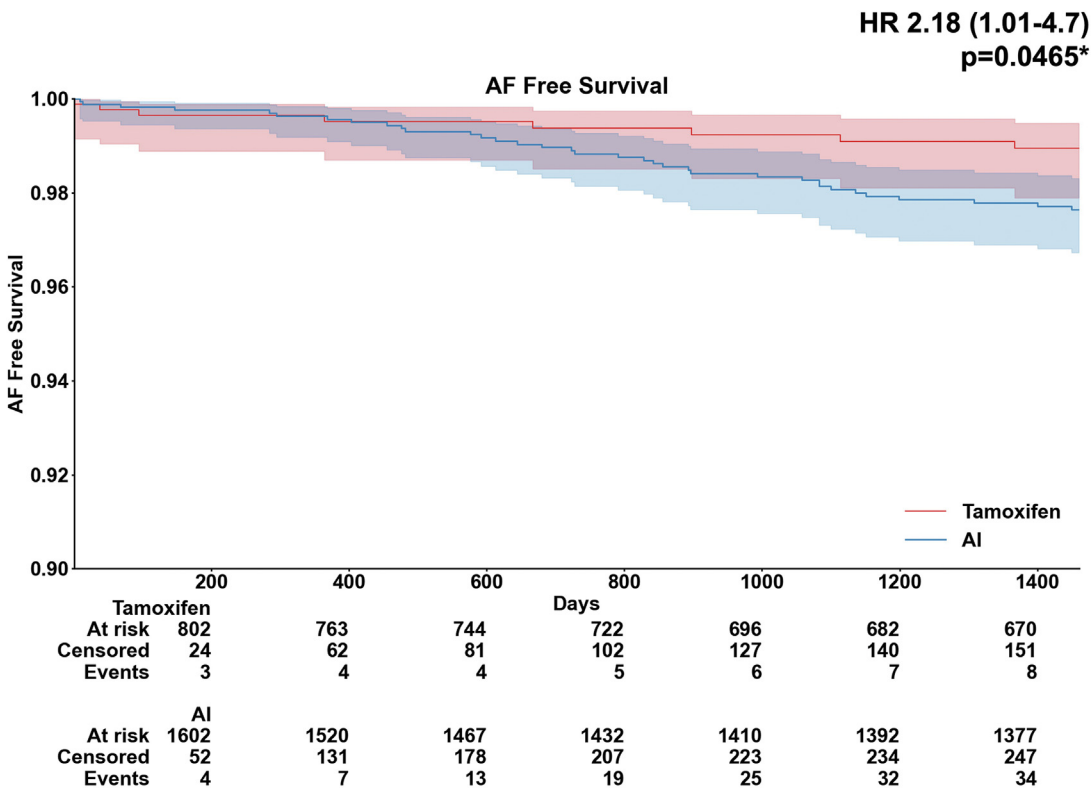
difference of <0.2 after propensity score matching was considered significantly balanced. A P value <0.05 was considered statistically significant. Calculations were performed using SPSS Statistics version 27 (IBM Corporation).

RESULTS

COHORT SELECTION. From January 1, 1999, to December 31, 2020, 10,567 patients who attended public hospitals in Hong Kong were prescribed hormone therapy for breast cancer. Of these, 4,625 who received both an AI and tamoxifen during their disease course and 235 who had history of AF or ventricular tachyarrhythmias were excluded from analysis. Among the 5,707 patients analyzed, 4,878 were prescribed an AI and 829 tamoxifen (Figure 1).

PROPENSITY SCORE MATCHING. Because AIs were prescribed to postmenopausal women and tamoxifen to premenopausal women, patients in the AI group were generally older (64.7 ± 10.5 years vs 59.3± 13.9 years; $P < 0.001$) and more likely to suffer from pre-existing cardiovascular, including a higher prevalence of hypertension (38.0% vs 23.8%; $P < 0.001$), diabetes mellitus (14.3% vs 7.72%; $P < 0.001$), ischemic stroke (5.37% vs 1.45%; $P < 0.001$), and deep vein thrombosis (1.05% vs 0.121%; $P = 0.0088$). To reduce the potential confounding effect, propensity score matching was performed by matching age, sex, hypertension, diabetes mellitus, history of acute myocardial infarction, stroke, deep vein thrombosis, pulmonary embolism, and congestive heart failure in 1:2 ratio. After matching, there were 1,658 patients in the AI group and 829 patients in the tamoxifen group. The baseline characteristics

FIGURE 3 New-Onset Atrial Fibrillation-Free Survival of Patients on Aromatase Inhibitors and Tamoxifen



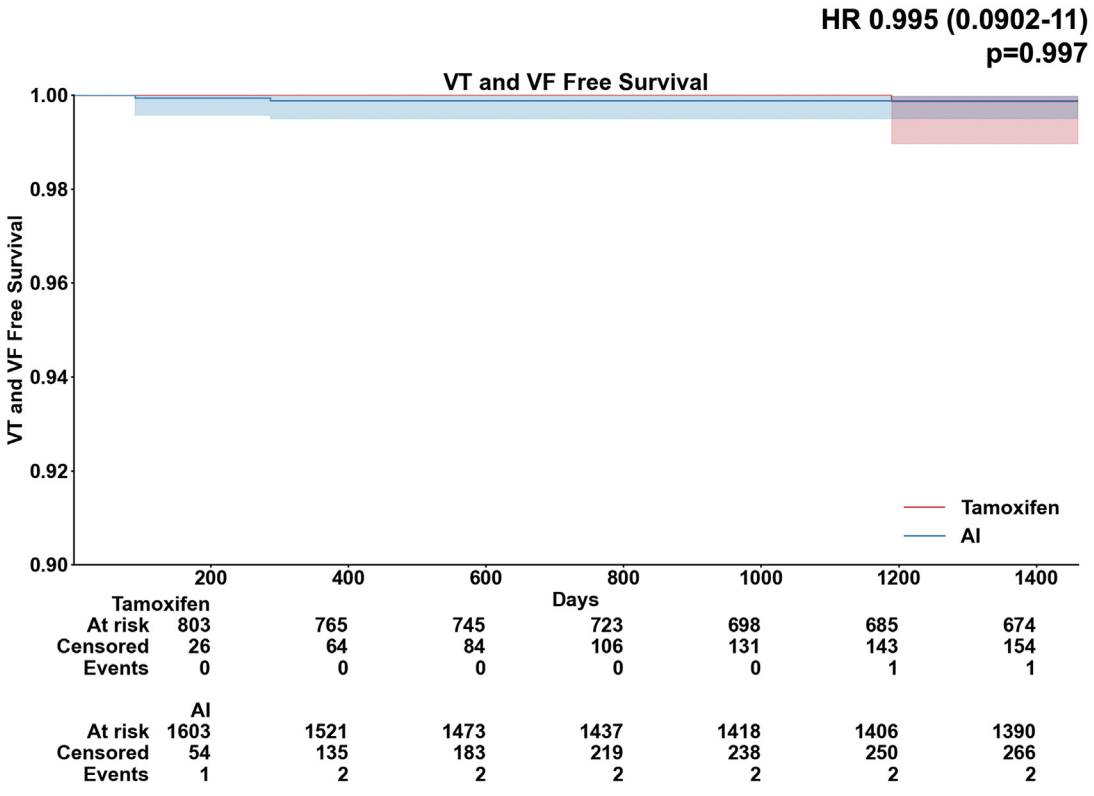
This Kaplan-Meier curve shows that the aromatase inhibitor group has a higher incidence of new-onset atrial fibrillation, with an incidence of 0.591 and 0.272 per 100 patient-years, respectively, in the aromatase inhibitor and tamoxifen groups. (crude HR: 2.18, 95% CI: 1.01-4.70; $P = 0.046$). *$P < 0.05$.

between 2 groups were balanced with standardized mean difference <0.2 after propensity score matching (Table 1).

ARRHYTHMIA AND NEW-ONSET AF. A total of 8,863 patient-years, including 5,920 and 2,493 patient-years for the AI and tamoxifen groups, respectively, were analyzed with a mean follow-up of 3.56 ± 1.03 years. Table 2 summarizes their cardiovascular outcomes including crude incidence per 100 patient-years and HR in the AI group compared with the tamoxifen group.

The AI group had a trend toward a higher risk of arrhythmia than the tamoxifen group with an incidence of 0.625 vs 0.306 per 100 patient-years, respectively (crude HR: 2.05; 95% CI: 0.99-4.25; $P = 0.053$) (Figure 2, Table 2). Further analysis of our cohort revealed that the arrhythmic risk was driven by the occurrence of new-onset AF with an incidence of 0.591 and 0.272 per 100 patient-years in AI and tamoxifen groups, respectively (crude HR: 2.18; 95% CI: 1.01-4.7; $P = 0.04$) (Figure 3, Table 2). Cox proportional hazard regression was performed with adjustment for sex, age, hypertension, diabetes mellitus, history of myocardial infarction, and heart failure. Exposure to AIs was found to be an independent risk factor for development of new-onset AF (adjusted HR: 2.75; 95% CI: 1.27-5.97; $P = 0.01$) (Table 2). Cox proportional hazards model was utilized to calculate the P value for interaction between age group (≥65 years) and choice of hormonal

FIGURE 4 Ventricular Tachycardia or Fibrillation-Free of Patients on Aromatase Inhibitors and Tamoxifen



This Kaplan-Meier curve shows that there was no significant difference between the aromatase inhibitor and tamoxifen groups in the incidence of ventricular tachyarrhythmias ($P = 0.997$).

therapy, and no interaction between the 2 covariates were found ($P = 0.288$).

There was no significant difference in the occurrence of ventricular tachycardia or ventricular fibrillation ($P = 0.99$), with an incidence of 0.034 and 0.034 per 100 patient-years in the AI and tamoxifen groups, respectively (Figure 4, Table 2).

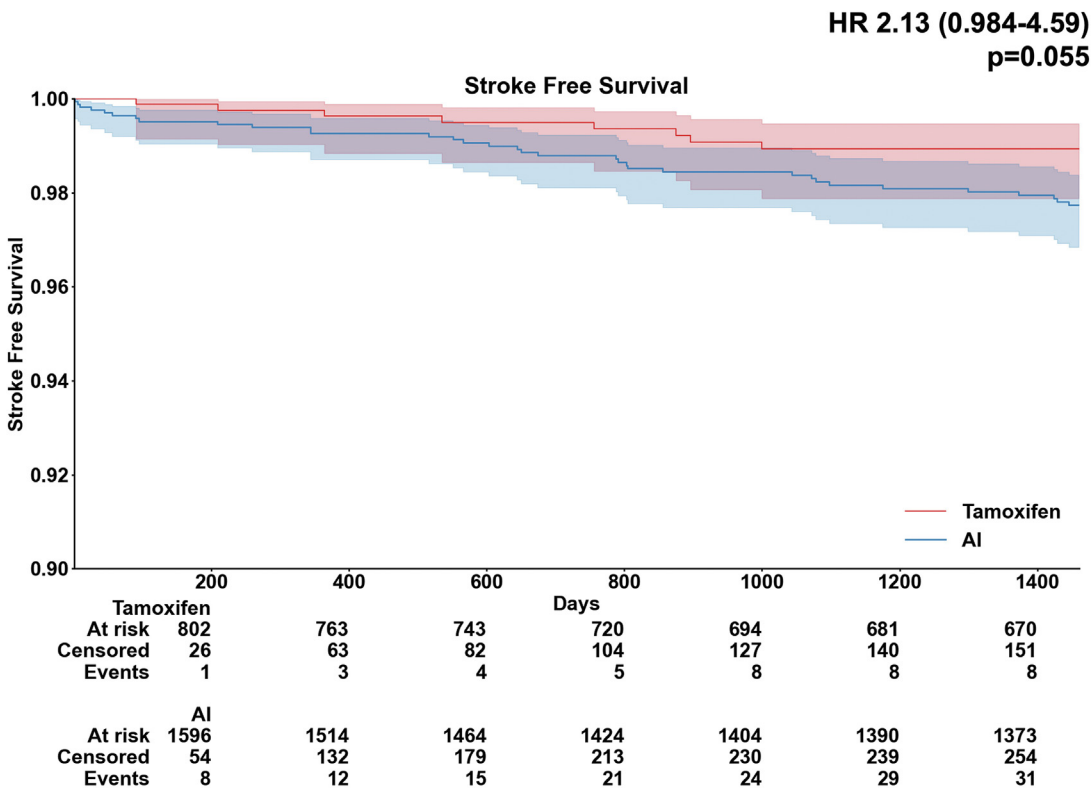
ISCHEMIC STROKE. Patients prescribed an AI had a trend toward more ischemic stroke with an incidence of 0.574 and 0.272 per 100 patient-years, respectively, in the AI and tamoxifen groups (crude HR: 2.13; 95% CI: 0.984-4.59; $P = 0.055$) (Figure 5, Table 2), but statistical significance was not reached. Among 42 patients who developed ischemic stroke during the study period, 26.5% and 12.5% had stroke with new-onset AF in the AI and tamoxifen groups, respectively. There was no statistically significant difference in proportion of stroke patients with new-onset AF between the 2 groups ($P = 0.697$).

OTHER CARDIOVASCULAR OUTCOMES. There were no significant differences in the incidence of myocardial infarction ($P = 0.326$) (Figure 6, Table 2) or venous thromboembolism, which comprises deep vein thrombosis or pulmonary embolism ($P = 0.575$) (Figure 7, Table 2).

DISCUSSION

This study revealed that patients with breast cancer who were prescribed endocrine therapy using AIs had trend toward higher incidence of arrhythmia. More

FIGURE 5 Ischemic Stroke-Free Survival of Patients on Aromatase Inhibitors and Tamoxifen



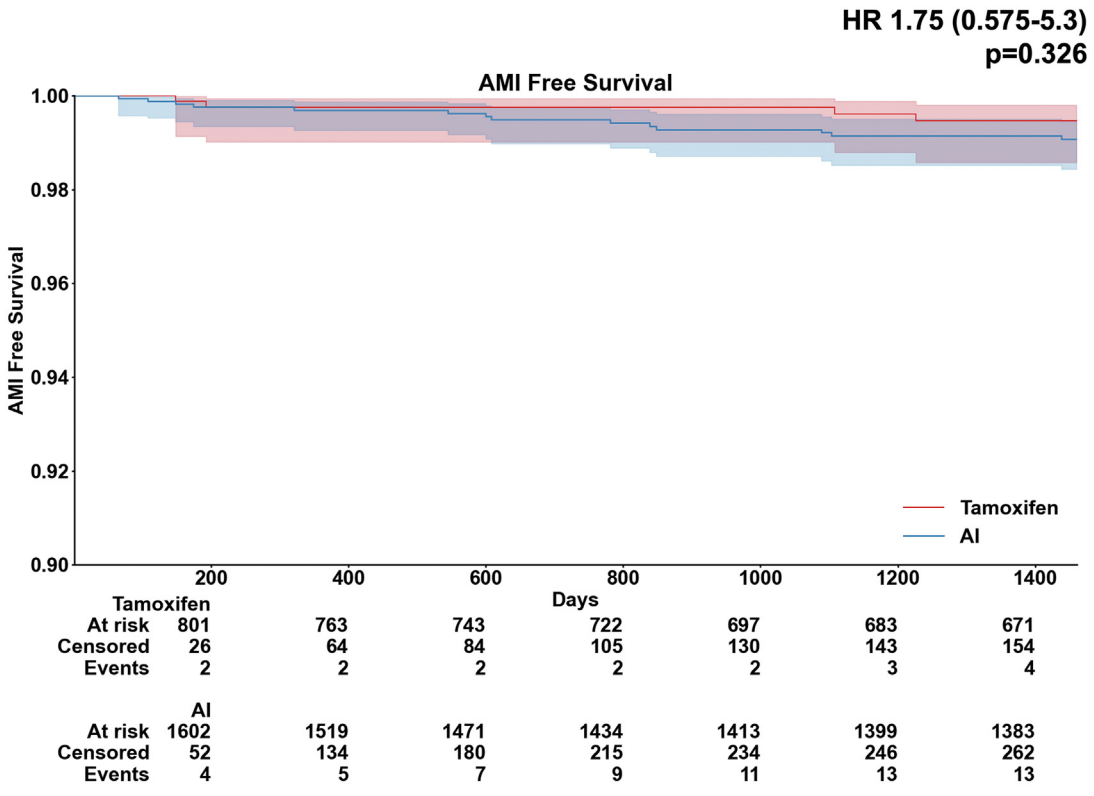
This Kaplan-Meier curve shows that patients prescribed an aromatase inhibitor had a trend toward higher incidence of ischemic stroke than those prescribed tamoxifen, with an incidence of 0.574 and 0.272 per 100 patient-years, respectively, in the aromatase inhibitor and tamoxifen groups (crude HR: 2.13; 95% CI: 0.984-4.59; $P = 0.055$).

specifically, when compared with tamoxifen, the increased occurrence of arrhythmias with use of an AI was mainly caused by the occurrence of new-onset AF (**Central Illustration**).

EFFECT OF HORMONAL THERAPIES ON AF. Estrogen level is known to affect electrophysiological properties of the heart.[12] In animal models of ischemia-reperfusion injury, estrogen reduced the risk of arrhythmia by opening calcium-activated potassium channels and inhibiting sodium–hydrogen exchanger isoform 1.[13,14] Estrogen depletion also leads to adipocyte hyperplasia, insulin resistance, and dyslipidemia,[15-17] known predisposing factors for both atherosclerotic disease and AF.

Among the hormonal therapies for breast cancer, AIs unselectively inhibit estrogen synthesis catalyzed by aromatase enzymes in peripheral tissue. On the contrary, SERMs, such as tamoxifen, exert tissue specific effects.[18,19] Moreover, SERMs are antagonistic in breast tissue but agonistic in the cardiovascular system.[20,21] Because AIs unselectively deplete estrogen synthesis in the cardiovascular system, it has been hypothesized that their use is associated with an increased risk of developing cardiovascular complications, including arrhythmia. Previous cohort studies from the United States and Sweden found that women with breast cancer who were taking AIs had a higher risk of arrhythmia than control subjects.[7,8] Nevertheless, neither study delineated the type of

FIGURE 6 Myocardial Infarction-Free Survival of Patients on Aromatase Inhibitors and Tamoxifen



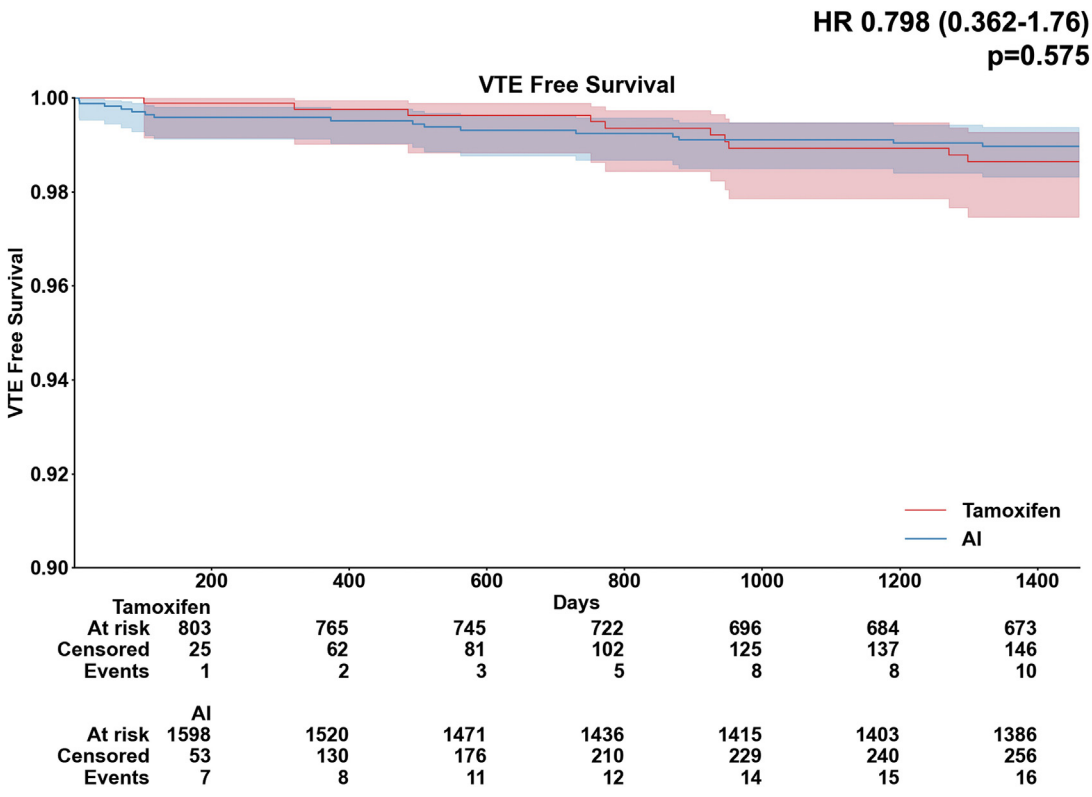
This Kaplan-Meier curve shows that there was no significant difference between the aromatase inhibitor and tamoxifen groups in the incidence of myocardial infarction ($P = 0.326$).

arrhythmia. In this study, we demonstrated that the increased incidence of arrhythmia was mainly driven by new-onset AF. After adjusting for age and underlying cardiovascular risk factors using multivariate analysis and propensity score matching, the use of AIs remained an independent predictor for development of new-onset AF in patients with breast cancer. Previous studies indicated that tamoxifen leads to action potential duration at 90% repolarization prolongation.[22] However, the effects of both tamoxifen and AI on atrial cardiomyocytes remain unknown. Further studies utilizing in vitro cell line studies or animal models are required to further investigate the effect of AI and tamoxifen on atrial cardiomyocytes and to unravel the pathogenic mechanisms.

CLINICAL IMPLICATIONS. Given the increasing use of adjunctive AIs caused by the improved survival of breast cancer patients, it is expected that the disease burden of AF in these patients will likewise increase. Because AF can be asymptomatic, many patients may not be diagnosed until stroke occurs.[23,24] Furthermore, the CHA_2DS_2-VASc score of breast cancer patients is generally high because they are women, are of relatively advanced age, and have cardiovascular comorbidities. It is therefore imperative to remain vigilant for subclinical AF among AI recipients and initiate appropriate anticoagulation therapies for stroke prevention. The potential role of screening for AF in this high-risk population of breast cancer patients treated with AIs remains unclear.

STUDY LIMITATIONS. First, the study is retrospective and observational in nature, and may result in more residual confounding and bias than a prospective randomized study. Nonetheless, key confounding

FIGURE 7 Venous Thromboembolism-Free Survival of Patients on Aromatase Inhibitors and Tamoxifen



This Kaplan-Meier curve shows that there was no significant difference between the aromatase inhibitor and tamoxifen groups in the incidence of venous thromboembolism ($P = 0.575$).

factors including age and cardiovascular comorbidities were already adjusted. However, we also acknowledge the fact that AI was selectively prescribed to postmenopausal patients compared with tamoxifen for premenopausal patients. Meanwhile, menopausal state was not available on our registry data, which makes statistical matching impossible. These could have contributed to a selection bias. Second, as our study mainly comprised patients of Chinese ethnicity, generalization of our conclusions to other populations and ethnicities may not be possible. Third, detection of arrhythmias in our cohort was achieved by screening electrocardiogram as per physician decision or symptom-driven ambulatory electrocardiogram monitoring. The true incidence of AF may have been underestimated because of the lack of systematic protocolized screening for AF. It is known that systematic AF screening results in a significantly higher detection rate of AF than conventional care.[25]

CONCLUSIONS

Among patients with breast cancer who were prescribed adjunctive hormone therapy, treatment with an AI was associated with an increased risk of new-onset AF on long-term follow-up. Regular surveillance for new-onset AF should be considered in patients prescribed an AI.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

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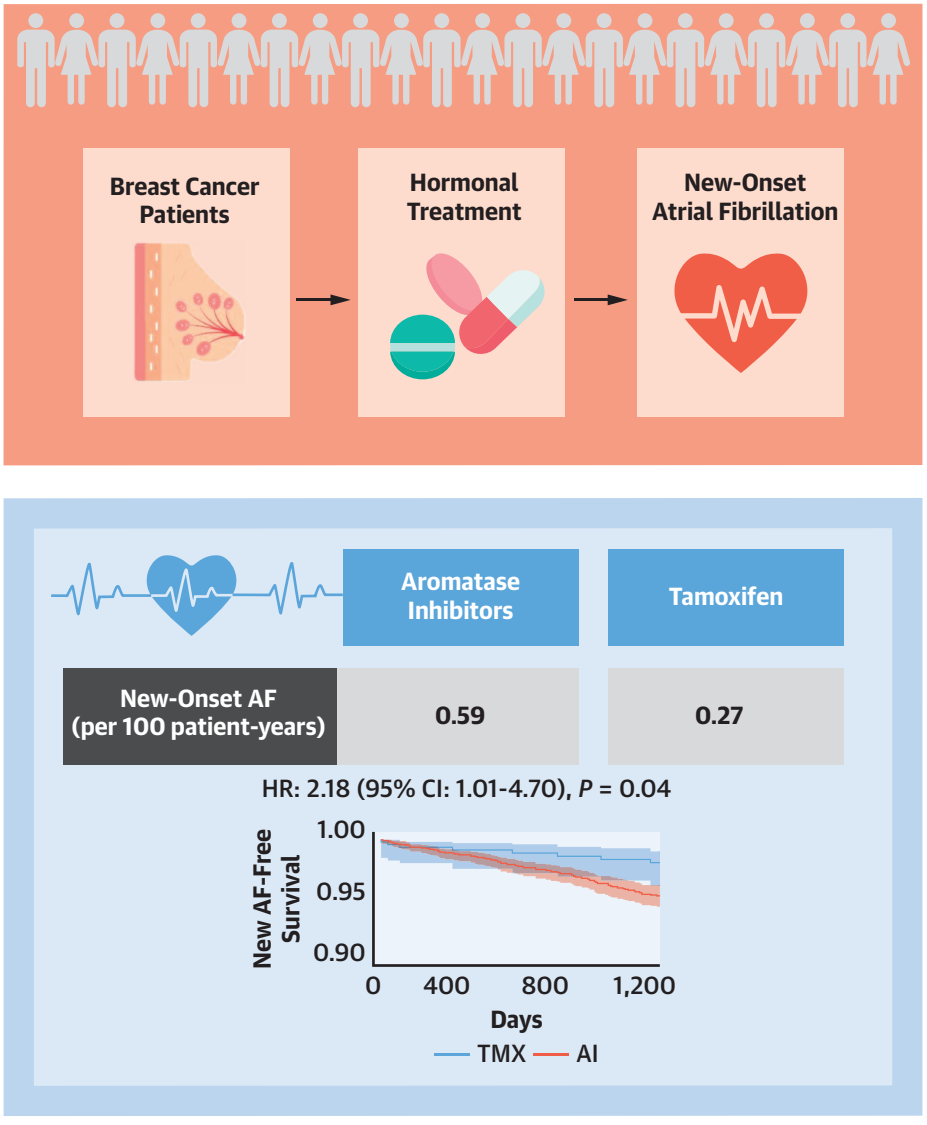
CENTRAL ILLUSTRATION **Increased New-Onset Atrial Fibrillation in Patients on Aromatase Inhibitors**



Treatment with AI is associated with an increased risk of new-onset AF compared with tamoxifen in breast cancer patients

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In our retrospective cohort study utilizing propensity score matching, it was found that the use of aromatase inhibitors (AIs) was associated with an increased risk of new-onset atrial fibrillation (AF) compared with tamoxifen (TMX) in breast cancer patients (crude HR: 2.18; 95% CI: 1.01-4.70; $P = 0.04$).

University of Hong Kong; and by the Li Shu Fan Medical Fellowship for Internal Medicine, Li Shu Fan Medical Foundation, and the University of Hong Kong, Hong Kong SAR. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The overall survival of breast cancer patients has been improving because of improved systemic therapies including the use of hormone therapies. It was previously observed that breast cancer patients who received AIs had increased risk of arrhythmia. Further studies are required to evaluate the effect of AIs on each subtype of arrhythmia.

COMPETENCY IN PATIENT CARE: In this retrospective cohort study with propensity score matching, it was shown that usage of AIs is an independent risk factor for developing new-onset atrial fibrillation, after adjusting for risk factors of atrial fibrillation including hypertension, diabetes mellitus, and other cardiovascular diseases.

TRANSLATIONAL OUTLOOK: The CHA_2DS_2-VASc score of breast cancer patients is generally high, because they are women, are of relatively advanced age, and have cardiovascular comorbidities. It is therefore imperative for oncologists and cardiologists to remain vigilant to identify new-onset atrial fibrillation among breast cancer survivors and initiate appropriate anticoagulation therapies for stroke prevention.

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APPENDIX For a supplemental table, please see the online version of this paper.