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Abstract

Objectives

To examine the long-term risk of thromboembolism and bleeding in patients with atrial fibrillation comparing patients with and without recent breast cancer in subgroups with or without anticoagulation therapy, respectively.

Design

Using nationwide registries, patients with breast cancer from 1998-2015 and subsequent atrial fibrillation within 3 years were stratified on anticoagulation and matched 1:3 on age, sex and comorbidities with atrial fibrillation patients without breast cancer. Risks of thromboembolism and bleeding were estimated by Aalen-Johansen and multivariable cox regression models.

Results

Atrial fibrillation patients with and without anticoagulation were matched, respectively (201 and 525 with breast cancer matched with 603 and 1,575 without breast cancer). In patients with CHA_2DS_2-VASc-score >1 and anticoagulation the three years risks of thromboembolism were 4.2% (95% confidence interval (CI) 1.1-7.3) and 3.2 % (CI 1.5-4.9) in patients with and without breast cancer. The risks of bleeding were 5.3% (CI 1.7-8.9) and 5.1% (CI 3.0-7.1), respectively. Breast cancer was associated with a similar risk of thromboembolism in patients with and without anticoagulation, respectively (Hazard ratio (HR) 1.10, CI 0.63-1.92 and HR 1.11, CI 0.82-1.50) and a similar risk of bleeding in patients with and without anticoagulation, respectively (HR 1.01, CI 0.56-1.84 and HR 0.85, CI 0.57-1.27) compared with the matched controls.

Conclusions

Breast cancer was not associated with altered risk of thromboembolism or bleeding in patients with atrial fibrillation irrespective of treatment with anticoagulation. Our analyses suggest that atrial fibrillation diagnosed in patients with breast cancer should be considered as primary atrial fibrillation.

Keywords: Atrial fibrillation, Breast cancer, Anticoagulation, Thromboembolism, Stroke, Bleeding, Mortality

Introduction

Breast cancer (BC) is the most common cancer among women worldwide, but it is not the leading cause of cancer related death.[1] The good prognosis is probably due to the effective diagnostics and treatments used, and today most patients with BC will become long term survivors.[2] However, survivorship may be hampered by side effects, cardiovascular side effects in particular.[3–5] Patients with BC may have greater risk of developing atrial fibrillation (AF) than the background population.[6] [7]Additionally, the risks of thromboembolism and bleeding associated with AF in patients with recent BC are unknown. Information on risk of thromboembolism in patients with BC is scarce, and both increased[8], similar[9–13], and decreased risks[14] have been reported in studies comparing patients with BC with the background population with no information of presence of AF. A single study has found similar risks of thromboembolism and bleeding associated with anticoagulation in patients with AF and prior BC.[13] Furthermore, the current anticoagulation guidelines provides no recommendations regarding these patients.[15,16] In order to address this knowledge gap[17,18], we examined the long-term risks of thromboembolism and bleeding in AF patients with BC compared with AF patients without BC in analyses stratified on anticoagulation.

Materials and methods

Nationwide databases

The Danish health care system is tax financed and accessible to all citizens without charge. All Danish citizens have a unique permanent identification number that is registered every time the citizen uses a healthcare service. This system enables linkage of information from highnationwide cohort study was based on information from four of these administrative

databases. The Danish Civil Registration System holds information on identification number and date of birth.[19] The Danish Register of Causes of Death has information on vital status and date and cause of death.[20] The Danish National Patient Registry holds information on admissions, discharges and outpatient contacts from Danish hospitals since 1978 including international classification of diseases (ICD-10) codes.[21] Definitions based on ICD-10 codes from the Danish National Patient Register have an overall high validity, e.g. stroke (I60-64) has a high positive predictive value of 97%.[21,22] Finally, the Danish National Prescription Registry holds all prescriptions dispensed from Danish pharmacies complete with data on expedition date, drug type, dose, quantity and anatomical therapeutic chemical (ATC) classification code.[23]

Study population

All female patients diagnosed with BC from 1st of January 2000 to 31st of November 2015 were identified and included after a quarantine period of 30 days. The quarantine period ensured that BC and AF were not diagnosed during the same hospitalization, and that BC preceded AF in the individuals of the study population. Patients who developed incident AF within 3 years after this date were included in the study, and the index date was 14 days after the discharge date following hospitalization for AF. AF was defined as being discharged after hospitalization with AF as the primary diagnosis (ICD-10 code I-48 AF or atrial flutter). The definition has been shown to have a positive predictive value of 93% and a 6% proportion of patients with atrial flutter. Exclusion criteria were age < 18 or > 100 years at index, AF prior to BC, anticoagulation or antiarrhythmic therapy within 6 months preceding AF hospitalization, prior valvular heart disease, missing data or emigration before the index date. The patients were grouped according to anticoagulation at baseline. Receiving anticoagulation treatment was defined as having a prescription for anticoagulation filled during the first 14

days following hospitalization for AF. Later prescription fillings were not assessed. The patients were then followed for 3 years and observed for the outcomes thromboembolism and bleeding and the competing risk of death. Censoring was performed at the end of follow up (maximum 3 years) or if a patient emigrated during the study period.

Outcomes, comorbidities and pharmacotherapy

We analyzed the two primary outcomes thromboembolism and bleeding in separate analyses with all cause death as the secondary outcome. In all analyses a primary event censored any secondary events. The outcomes thromboembolism and bleeding were based on ICD-10 discharge diagnoses after hospitalization and death causes. Admissions with thromboembolism and bleeding, respectively, as the primary diagnosis were defined as events. Additionally, death caused by stroke was defined as an event.

Baseline comorbidities were defined as registration with discharge diagnoses or outpatient contacts within 5 years preceding index date as listed in Table 1. Baseline treatment with a specific drug was defined as redeemed prescriptions during the 6 months preceding inclusion to the study. The definitions based on ICD-10 codes and ATC codes are described in Supplementary Table A.1.

Statistical methods

The study population was stratified according to anticoagulation at baseline yielding two subpopulations; a subpopulation with and a subpopulation without anticoagulation. Risk-set matching using the R package ‘heaven’ was used to match women with BC and incident AF 1:3 with women with incident AF without BC on the match criteria age, diabetes mellitus, hypertension, heart failure, stroke, and history of thrombosis in the two subpopulations, respectively.[24] The risk-set matching function sorted controls and cases according to the

matching criteria and subsequently consecutively selected unique controls without outcomes prior to the study start of the cases they were matched to. Incidence rates per 100 person years were estimated. The Aalen-Johansen non-parametric method was used for generating cumulative incidence estimates and curves with competing risk of death. Cox proportional hazards regression models were applied to analyze the associations between BC and thromboembolism and bleeding, respectively. The models used to analyze the associations in the subpopulation with anticoagulation were adjusted for chronic kidney disease and the models used to analyze the associations in the subpopulation without anticoagulation were additionally adjusted for chronic liver disease. All models were stratified according to the matching and tested for proportional hazards of the covariates. As a sensitivity analysis we conducted the same cox models additionally adjusted for statins and aspirin therapy. The Mann-Whitney test was used to test for differences in the time interval from BC to AF diagnosis between patients with and without anticoagulation. Statistical significance was defined as two-sided p-value <0.05. Parameter estimates were reported with 95% confidence intervals (CI), means with standard deviations, and medians with interquartile range (IQR). Statistical analyses were performed using SAS Software version 9.4 (SAS Institute Inc.) and R: A language and environment for statistical computing.[25]

Results

A total of 726 patients with BC developed AF within 3 years after discharge. Among patients with BC and AF 201 were treated with anticoagulation; 136 (67.6%) with vitamin K antagonists, 59 (29.4%) with non-vitamin K oral anticoagulation (NOAC) and 8 (4%) with heparins. Among the controls with AF without BC 603 were treated with anticoagulation; 312 (51.7%) with vitamin K antagonists, 288 (47.8 %) with NOACs and 13 (2.2%) with heparins.

The median time interval from BC to AF diagnoses was 1.52 years (IQR 0.73-2.32) for patients with anticoagulation and 1.36 years (IQR 0.57-2.19) for patients without anticoagulation. We found no difference in time intervals comparing AF patients with and without BC (Mann-Whitney test, p=0.1). In the subpopulation with anticoagulation 201 AF patients with BC matched with 603 AF patients without BC, while in the subpopulation without anticoagulation 525 AF patients with BC matched with 1,575 AF patients without BC. The inclusion is depicted in Figure 1 and baseline characteristics are described in Table 1.

Cumulative incidence of thromboembolism, bleeding and mortality

The three year cumulative incidence analyses were stratified according to CHA_2DS_2VASc score >1 or =0. In AF patients with CHA_2DS_2VASc scores >1 and anticoagulation the three year risk of thromboembolism was 4.2% (95% CI 1.1-7.3) in patients with BC and 3.2% (95% CI 1.5-4.9) in patients without BC. The risks of bleeding were 5.3% (95% CI 1.7-8.9) and 5.1% (95% CI 3.0-7.1), and the mortality risks were 21.9% (95% CI 15.3-28.4) and 17.6% (95% CI 13.9-21.3) in patients with and without BC, respectively. We found no differences in the three year risks comparing patients with and without BC (Fine-Gray's test, p=0.5 for thromboembolism, p=0.9 for bleeding and p=0.2 for mortality). In AF patients with CHA_2DS_2VASc scores >1 without anticoagulation the three year risk of thromboembolism was 4.3% (95% CI 2.4-6.3) in patients with BC and 5.2% (95% CI 3.9-6.4) in patients without BC. The risks of bleeding were 3.5% (95% CI 1.7-5.2) and 5.8 (95% CI 4.5-7.1) and the mortality risks were 47.1% (95% CI 42.4-51.8) and 28.3% (95% CI 25.8-30.9) in patients with and without BC, respectively. We found an increased mortality risk (Fine-Gray's test, p<0.0001) and a similar risk of thromboembolism and bleeding (Fine-Gray's test, p=0.7and p=0.06) comparing patients with and without BC. The curves on 3 year cumulative incidences of thromboembolism, bleeding and death are displayed in Figure 2 A and B.

Multivariable cox regression analyses

In multivariable cox regression models stratified according to the matching and adjusted for relevant baseline comorbidities, we found that BC was associated with a similar risk of thromboembolism and bleeding in patients treated with anticoagulation (thromboembolism: Hazard ratio (HR) 1.10, 95% CI 0.63-1.92, p=0.73 and bleeding: HR 1.01, 95% CI 0.56-1.84, p=0.97) and in patients not treated with anticoagulation (thromboembolism: HR 1.11, 95% CI 0.82-1.50, p=0.49 and bleeding: HR 0.85, 95% CI 0.57-1.27, p=0.43). The HRs and incidence rates are displayed in Figure 3. Additional adjustment for statins and aspirin use at baseline yielded results similar to the main analyses.

Discussion

In the current study we investigated the long term risks of thromboembolism and bleeding in a contemporary nationwide cohort of patients with AF and recent BC. The study had two major findings; 1) the three year risks of thromboembolism were similar, and 2) the three years risks of bleeding were similar in patients with AF comparing patients with and without recent BC. The findings were consistent in both patients with and without anticoagulation therapy.

The risks of thromboembolism

The similar risks of thromboembolism in patients with AF with and without recent BC who were not treated with anticoagulation, is a novel finding. The current study adds important knowledge to the field, as most previous research has investigated the risk of stroke in BC patients regardless of AF[9–11] or has focused on the in-hospital risk of cerebrovascular outcomes.[14] A study of 10 year survivors of BC from 1970-1986[9] and cohort studies on BC patients from 2000-2007[10] and 2001-2007[11] did not find any increased risk of stroke

in patients with BC compared with the female background population. Conversely, a Scandinavian cohort study found a higher risk of stroke in BC patients diagnosed from 1970-2000 compared with the background population (relative risk 1.12 (95% CI 1.07–1.17)).[8] Regarding patients treated with anticoagulation a recent study supports the finding, that thromboembolic and bleeding risks were similar in patients with AF with and without recent cancer, including BC.[13]

The risks of bleeding

Another main finding of this study was the similar risks of bleeding in patients with AF comparing patients with and without BC in the subpopulations with and without anticoagulation, respectively. A recent study has reported an increased risk of bleeding in AF patients with a history of unspecified cancer.[12] However, the body of previous research has focused on associations between active cancer (different cancer types) and the related treatments and increased risk of bleeding.[26,27] These studies examined cancer patients in general, not patients with BC separately, and did not control for presence of AF, anticoagulation therapy or CHA_2DS_2-VASc score. Our results suggest that AF patients with recent BC suffer from bleeding complications to the same extent as regular AF patients, as it has been shown for unspecified cancer patients[28] and for patients with AF and BC who were treated with anticoagulation.[13]

Atrial fibrillation in patients with recent breast cancer

The findings from this study indicate that AF in patients with recent BC may be considered as primary AF. Our results underline that patients with BC should be included in future randomized controlled trials on thrombo-prophylaxis in AF patients to assess the cost/benefit balance.[17,18] Notably, the current guidelines have no recommendations for anticoagulation in patients with previous or current cancer, including BC[15,16], as there are no existing data

in the field. In this study the frequencies of patients treated with vitamin K antagonists, NOACs and heparins, respectively, were different comparing patients with AF with and without recent BC. Future studies investigating different anticoagulation strategies and outcomes in patients with recent breast cancer would be highly relevant.

Mortality risks

The 3 year mortality risks in this study were higher than estimates from the major randomized controlled trials on anticoagulation in AF patients.[29–33] However, this was expected, as our study comprised real world patients who were older and had more comorbidities than the study populations from the mentioned randomized trials. A Scandinavian cohort study of patients with AF with and without warfarin found 3 year mortality estimates similar to the risks in this study.[34] In line with existing knowledge we found increased mortality risk in AF patients without anticoagulation comparing patients with and without BC.[35] However, in patients with AF and anticoagulation the three year mortality risk was similar comparing patients with and without BC. The latter finding was potentially explained by confounding by indication. Confounding by indication could occur, if patients with BC and a good or moderate prognosis were treated with anticoagulation more often than patients with a poor prognosis.

Strengths and limitations

The study was a nationwide real life cohort study including all patients with BC and subsequent AF in a 15 year inclusion period. We aimed to investigate whether AF in conjunction with breast cancer was associated with increased risks of thromboembolism and bleeding. For this reason the inclusion criterion of development of AF within the first 3 years after breast cancer diagnosis was chosen. Additionally, we chose to conduct a strict exclusion of all AF-diagnoses and AF-treatments at baseline to ensure that the patients and controls

were truly patients with incident AF. However, the numbers of patients and events were relatively small, influencing the power of the statistical analyses, but at the same time reflecting real life conditions. The results provide unique estimates for patients with recent BC developing AF, which we hope will be of use to the clinicians treating this patient group. The study population was comprised of unselected patients grouped by anticoagulation and matched on age, sex and CHA_2DS_2-VASc score components to raise more comparable groups. Furthermore, all patients had a full follow up with valid information on endpoints. The outcomes thromboembolism and bleeding, respectively, included only patients admitted with the diagnosis as their primary diagnosis. This definition was chosen to ensure that the diagnoses were of clinical importance. Alternatively, if outpatient contacts with thromboembolism and bleeding had been included the events would have been more heterogenic and the analyses would have been based on complications that would probably not restrain OAC in the clinic.

A number of clinical conditions and baseline characteristics could be suspected of confounding the analyses. To control for the known and registered confounders such as age, sex, baseline comorbidity and CHA_2DS_2-VASc score, we used conventional methods. We matched on age and CHA_2DS_2-VASc score components and adjusted for baseline comorbidities in the regression analyses. We did not have information on stage of BC or related adjuvant treatment, what may have caused residual confounding to some extent. Especially tamoxifen and aromatase inhibitors, used in adjuvant treatment of estrogen sensitive BC, have been suspected of increasing the risk of cardiovascular disease.[36]
The study was designed as an intention to treat analysis. We defined anticoagulation treatment as having a prescription for anticoagulation filled within the first 14 days of discharge after hospitalization for AF. As some patients potentially change or terminate their anticoagulation

treatment, future studies of the exposure duration of anticoagulation and associated risks of thromboembolism and bleeding are of interest.

In this study we focused on the risk of thromboembolism developed in patients with both recent BC and subsequent AF. We did not investigate the risk of other stroke etiologies in patient with recent BC, but the issue constitutes a relevant future research question, as this risk may be increased.

As this study was an observational cohort study and not a randomized controlled trial, we cannot make inferences on causality or effect of anticoagulation treatment, but merely refer the observed associations.

Conclusion

In conclusion the three year risks of thromboembolism and bleeding were similar in patients with AF and recent BC compared with patients with AF without BC among both patients with and without anticoagulation treatment. Our results suggest that AF in conjunction with BC should be considered as primary AF.

Disclosure statement

Torp-Pedersen has received grants and personal fees from Bayer and grants from Biotronic. Gislason has received research grants fra Bayer, Bristol Myers Squibb, Boehringer Ingelheim og Pfizer and holds shares in Novo Nordisk, Lundbeck, ALK and Coloplast. Fosbøl has previously received independent research grants from Janssen and Janssen Pharmaceutical and the Lundbeck Foundation. Smedegaard has received grants from Helsefonden. No other authors reported disclosures.

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Approval from the local ethics committee

As the study was based on anonymous registers, individual informed consent and approval from the local ethics committee was not required.

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Figure captions

Figure 1: Study population. AF: atrial fibrillation. CPR: Central person registration number.

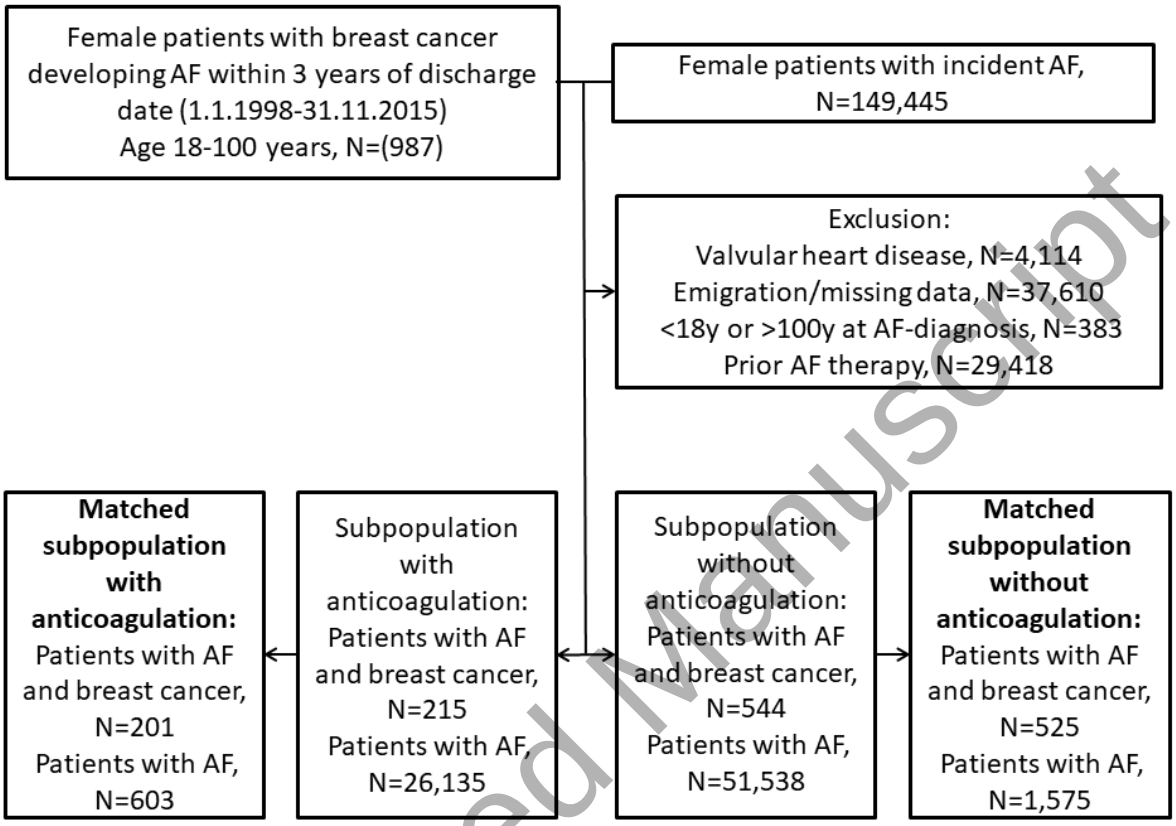
Figure 2: Three years cumulative incidence of outcomes in patients with CHA_2DS_2-VASc score >1 stratified on baseline anticoagulation treatment. **Figure 2A: Thromboembolism and bleeding. Figure 2B: Mortality.** Patients with atrial fibrillation and recent breast cancer are compared with patients with atrial fibrillation without breast cancer. AC: anticoagulation. AF: atrial fibrillation. BC: breast cancer.

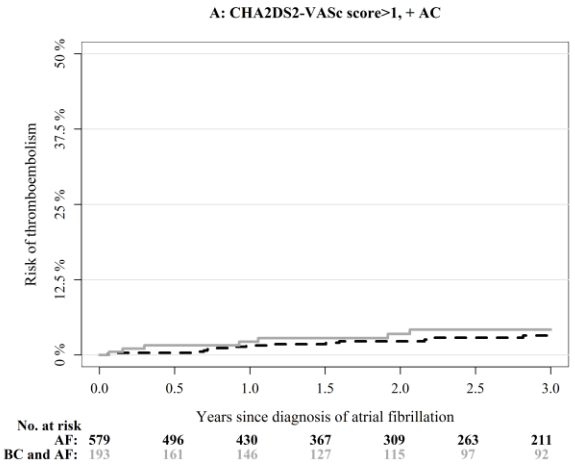
Figure 3: Number of events, incidence rates pr.100 person years and hazard ratios from multivariable cox regression models. Patients with atrial fibrillation and recent breast cancer are compared with patients with atrial fibrillation without breast cancer. AF: atrial fibrillation. BC: Breast cancer. IR: incidence rates per 100 person years. HR: Hazard ratio. CI: Confidence interval.

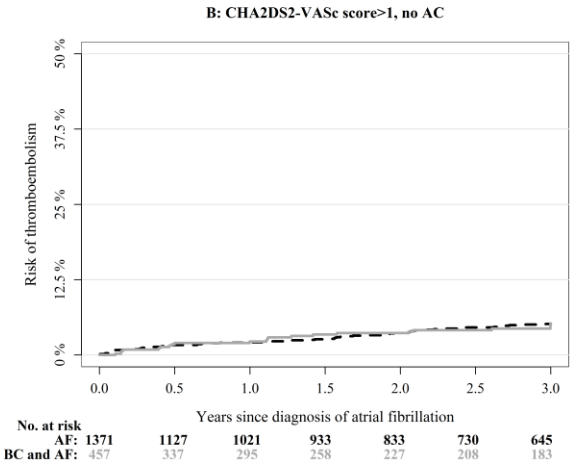
Table 1: Baseline characteristics in patients with atrial fibrillation (AF) according to treatment with anticoagulation and history of breast cancer (BC).

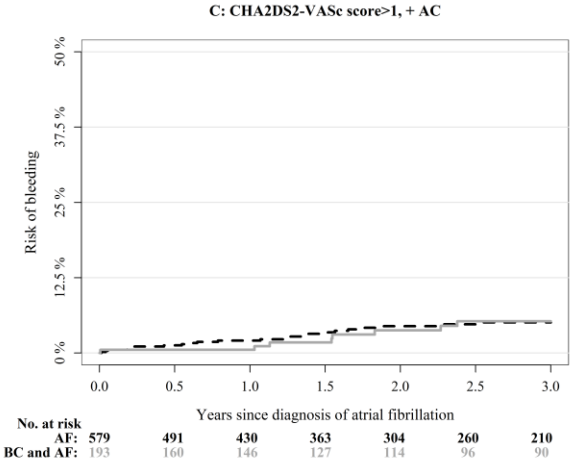
	Anticoagulation			No Anticoagulation		
	AF	**BC and AF**	**p**	**AF**	**BC and AF**	**p**
	603	201		1,575	525	
Age, median [IQR]	76 [69, 82]	76 [69, 82]	1.000	77 [66, 85]	77 [66, 85]	1.000
Medical history						
Hypertension, n (%)	405 (67.2)	135 (67.2)	1.000	819 (52.0)	273 (52.0)	1.000
Heart failure, n (%)	108 (17.9)	36 (17.9)	1.000	201 (12.8)	67 (12.8)	1.000
Diabetes mellitus, n (%)	54 (9.0)	18 (9.0)	1.000	93 (5.9)	31 (5.9)	1.000
Stroke, n (%)	66 (10.9)	22 (10.9)	1.000	81 (5.1)	27 (5.1)	1.000
Vascular disease, n (%)	117 (19.4)	39 (19.4)	1.000	237 (15.0)	79 (15.0)	1.000
Ischemic heart disease, n (%)	102 (16.9)	35 (17.4)	0.957	209 (13.3)	72 (13.7)	0.853
Thyroid disease, n (%)	85 (14.1)	24 (11.9)	0.513	185 (11.7)	57 (10.9)	0.636
Chronic kidney disease, n (%)	12 (2.0)	4 (2.0)	1.000	65 (4.1)	19 (3.6)	0.700
Peripheral arterial disease, n (%)	22 (3.6)	5 (2.5)	0.572	42 (2.7)	12 (2.3)	0.750
Chronic obstructive pulmonary disease, n (%)	70 (11.6)	35 (17.4)	0.046	218 (13.8)	60 (11.4)	0.181
Chronic liver disease, n (%)	<3	<3	1.000	27 (1.7)	11 (2.1)	0.705
Diagnoses related to increased alcohol assumption, n (%)	5 (0.8)	<3	1.000	31 (2.0)	9 (1.7)	0.854
CHA2DS2-VASc score >1, n (%)	579 (96.0)	193 (96.0)	1.000	1371 (87.0)	457 (87.0)	1.000
CHA2DS2-VASc score, median[IQR]	4 (3-5)	4 (3-5)	1.000	4 (3-4)	4 (3-4)	1.000
Baseline pharmacotherapy						
Anticoagulation therapy, n (%)	603 (100.0)	201 (100.0)	NA	NA	NA	NA
Vitamin K antagonists, n (%)	312 (51.7)	136 (67.7)	<0.001	NA	NA	NA
NOACs, n (%)	288 (47.8)	59 (29.4)	<0.001	NA	NA	NA
Heparin, n (%)	13 (2.2)	8 (4.0)	0.251	NA	NA	NA
Calcium channel blockers, n (%)	183 (30.3)	68 (33.8)	0.404	407 (25.8)	127 (24.2)	0.487
Beta blockers, n (%)	441 (73.1)	136 (67.7)	0.161	783 (49.7)	265 (50.5)	0.801
Non loop diuretics, n (%)	231 (38.3)	91 (45.3)	0.096	563 (35.7)	206 (39.2)	0.166
Renin angiotensin inhibitors, n (%)	295 (48.9)	87 (43.3)	0.192	540 (34.3)	164 (31.2)	0.220
Adrenerg blockers, n (%)	4 (0.7)	<3	0.563	18 (1.1)	6 (1.1)	1.000
Statins, n (%)	214 (35.5)	56 (27.9)	0.058	362 (23.0)	85 (16.2)	0.001
Aspirin, n (%)	212 (35.2)	68 (33.8)	0.798	664 (42.2)	221 (42.1)	1.000

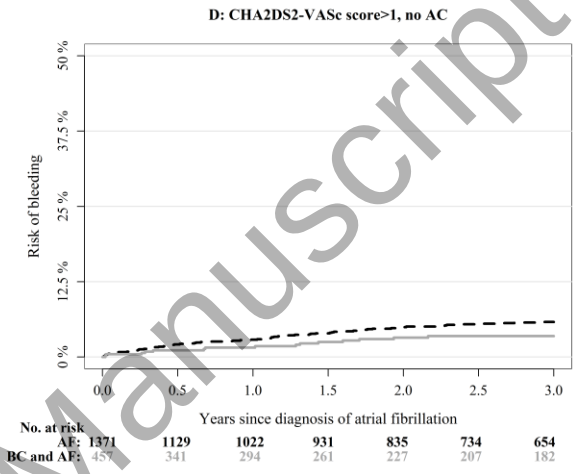
BC: Breast cancer. AF: atrial fibrillation. CHA_2DS_2-VASc score: (congestive heart failure, hypertension, age ≥75 years, diabetes, stroke/transient ischemic attack/thromboembolism, vascular disease, age 65-74 years, sex category). NOAC: Novel oral anticoagulation.

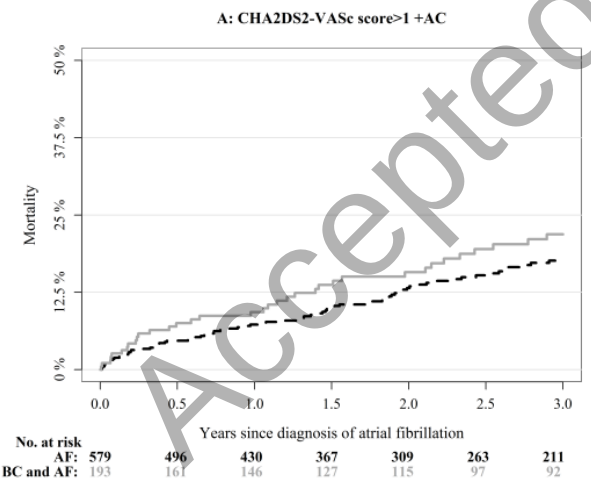


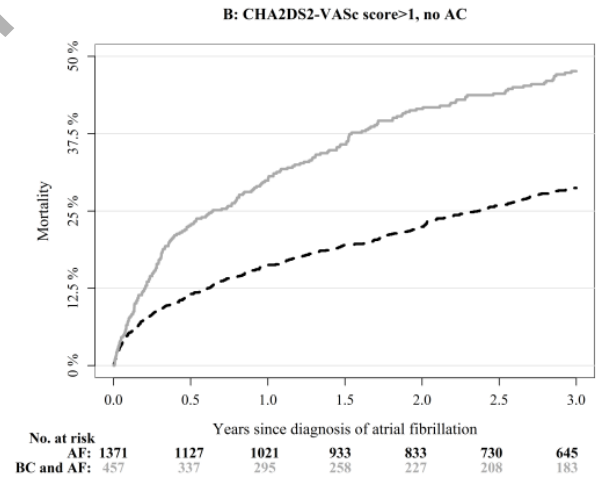












	Outcome	Events	IR[95%CI]	HR[95%CI]
Anticoagulation				
AF	Thromboembolism	24	2.0[1.4- 3.1]	1.00[1.00-1.00]
BC and AF	Thromboembolism	10	2.5[1.3- 4.6]	1.10[0.63-1.92]
AF	Bleeding	23	2.0[1.3- 3.0]	1.00[1.00-1.00]
BC and AF	Bleeding	8	2.0[1.0- 4.0]	1.01[0.56-1.84]
AF	Mortality	79	6.7[5.4- 8.4]	1.00[1.00-1.00]
BC and AF	Mortality	39	9.7[7.1-13.2]	1.30[0.97-1.74]
No Anticoagulation				
AF	Thromboembolism	99	3.0[2.5- 3.7]	1.00[1.00-1.00]
BC and AF	Thromboembolism	36	3.8[2.7- 5.3]	1.11[0.82-1.50]
AF	Bleeding	75	2.3[1.8- 2.9]	1.00[1.00-1.00]
BC and AF	Bleeding	17	1.8[1.1- 2.9]	0.85[0.57-1.27]
AF	Mortality	363	11.1[10.0-12.3]	1.00[1.00-1.00]
BC and AF	Mortality	226	23.8[20.9-27.1]	1.78[1.56-2.03]