Sex-specific differences in adverse outcome events among patients with atrial fibrillation

Simone Evers-Dörpfeld MD*[1,2], Stefanie Aeschbacher PhD*[1,2], Elisa Hennings MD[1,2], Ceylan Eken PhD[1,2], Michael Coslovsky PhD[1,2,3], Nicolas Rodondi MD MAS[4,5], Jürg H. Beer MD[6], Giorgio Moschovitis MD[7], Peter Ammann MD[8], Richard Kobza MD[9], Selinda Ceylan MD[1,2], Melina Krempke BMed[1,2], Christine Meyer-Zürn MD[1,2], Elisavet Moutzouri MD PhD[4,5], Anne Springer PhD[1,2], Christian Sticherling MD[1,2], Leo H. Bonati MD[10], Stefan Osswald MD[1,2], Michael Kühne MD[1,2], David Conen MD MPH[11], **for the Swiss-AF Investigators**[§]

[1] Cardiology Division, Department of Medicine, University Hospital Basel, University of Basel, Basel, Switzerland

[2] Cardiovascular Research Institute Basel, University Hospital Basel, University of Basel, Basel, Switzerland

[3]Clinical Trial Unit Basel, Department of Clinical Research, University Hospital Basel, Switzerland

[4] Institute of Primary Health Care (BIHAM), University of Bern, Bern, Switzerland

[5] Department of General Internal Medicine, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland

[6] Department of Medicine, Cantonal Hospital of Baden and Molecular Cardiology, University Hospital of Zurich, Zurich, Switzerland

[7] Division of Cardiology, Regional Hospital of Lugano, Ente Ospedaliero Cantonale (EOC), Lugano, Ticino, Switzerland

[8] Department of Cardiology, Kantonsspital St. Gallen, St. Gallen, Switzerland

[9] Department of Cardiology, Luzerner Kantonsspital, Lucerne, Switzerland

[10] Department of Neurology and Stroke Center, University Hospital Basel, University of Basel, Switzerland

[11] Population Health Research Institute, McMaster University, Hamilton, Canada

*contributed equally, shared first authors

[§] all Swiss-AF and Beat-AF investigators are listed in the supplement

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Address for correspondence:

David Conen MD MPH

Population Health Research Institute

237 Barton Street East

Hamilton Ontario, Canada

Phone: +1 905 522-1155

Fax: +1 905 521 6068

Email: David.Conen@phri.ca

Abstract

Objective: To assess, whether women with atrial fibrillation (AF) have a higher risk of adverse events than men during long-term follow-up since controversial data have been published.

Methods: In context of the observational multicenter cohort study Swiss-AF, we prospectively followed 3894 patients (28% women) with previously documented AF for a median of 4.02 (3.00; 5.83) years. The primary outcome was a composite of ischemic stroke, myocardial infarction, and cardiovascular death. Secondary outcomes included the individual components of the composite outcome, hospitalization for heart failure, major and clinically relevant non-major bleedings, stroke or systemic embolism and non-cardiovascular death.

Results: Mean age was 73.1 years in women versus 70.8 years in men. The incidence of the primary endpoint in women versus men was 2.46 versus 3.24 per 100 patient-years, respectively (adjusted Hazard Ratio (aHR) 0.74, 95% CI 0.58-0.94; p=0.01). Women died less frequently from cardiovascular (aHR 0.57, 95% CI 0.41-0.78; p<0.001) and non-cardiovascular causes (aHR 0.68, 95% CI 0.47-0.98; p=0.04). There were no significant sex-specific differences in stroke (incidence 1.05 versus 1.00; aHR 1.02, 95% CI 0.70-1.49, p=0.93), myocardial infarction (incidence 0.67 versus 0.72; aHR 0.98, 95% CI 0.61-1.57, p=0.94), major and clinically relevant non-major bleeding (incidence 4.51 versus 4.34; aHR 0.95, 95% CI 0.79-1.15, p=0.63), or heart failure hospitalization (incidence 3.28 versus 3.07; aHR 1.06, 95% CI 0.85-1.32, p=0.60).

Conclusion: In this large study of patients with established AF, women had a lower risk of death than men, but there were no sex-specific differences in other adverse outcomes.

Keywords: Atrial fibrillation, women, sex differences, cardiovascular events, death, risk factors

Key Messages:

What is already known about this subject? Controversial data have been published about whether women with atrial fibrillation (AF) have a higher risk of adverse events than men during long-term follow-up.

What does this study add? Our study provides long-term follow-up data up to ten years in a large contemporary sample of AF patients. Our results show that in well anticoagulated patients with established AF, women had a lower risk of death than men, but no sex-specific differences in risk of stroke other adverse outcome events were observed.

How might this impact on clinical practice? Our data emphasize the importance of anticoagulation in both women and men given the observed low risk of stroke in our data.

Introduction

Patients with atrial fibrillation (AF) face an increased risk of death and other adverse events, including stroke, heart failure and cognitive dysfunction [1-4]. Whether or not women with AF have a higher risk of adverse outcomes than men is controversial [5-10]. In the RACE II study, which included 403 men and 211 women with permanent AF, women had a higher incidence of a cardiovascular composite outcome, but also presented with more risk factors than men.[6] The risk of adverse events between men and women was not statistically significant after adjusting for these risk factors, indicating that sex-related differences in event rates may be in part driven by differences in risk factors.[6] In contrast, findings from a much larger registry suggested that women had a higher risk of stroke and systemic embolism than men even after multivariable adjustment.[8] However, follow-up duration was only one year.

Therefore, more data from large studies with long-term follow-up are needed to better understand whether there are sex-specific differences in adverse events among AF patients, and whether these associations are independent of differences in comorbidities and risk factors. For this purpose, we investigated sex-specific differences in adverse clinical outcomes among 3894 contemporary AF patients followed for up to 10 years.

Methods

Study Design and Participants

For this analysis we combined data from two ongoing observational prospective multicenter studies with very similar methodology: Swiss Atrial Fibrillation Study (Swiss-AF) and Basel Atrial Fibrillation Study (Beat-AF). We previously published details about study methodology.[11, 12] In brief, Swiss-AF enrolled 2415 patients with documented AF between 2014 and 2017 across 14 centers throughout Switzerland. Recruitment of the Beat-AF study took place between 2010 and 2014 and 1553 patients were included across seven centers in Switzerland.

In both cohorts, patients were required to have an age ≥65 years with previously documented AF. A convenience sample of patients <65 years was enrolled in both cohorts, to assess the effects of AF on individuals in the active workforce. Main exclusion criteria were the inability to sign informed consent, any acute illness within the past 4 weeks and any secondary forms of AF (e.g. post-operative or sepsis). Patients participating in Beat-AF were not allowed to take part in Swiss-AF. All participants signed a written informed consent. Both studies were conducted in accordance with the Declaration of Helsinki and approved by the lead Ethics committee EKNZ (Ethikkommission Nordwest- und Zentralschweiz). Of 3968 study patients enrolled in both studies, seven were removed from Beat-AF due to accidental enrollment in both cohorts, and 67 participants were excluded because they had no follow-up information, resulting in 3894 (98%) patients included in this analysis (Figure 1).

Study variables

The same standardized questionnaires were used in both cohorts to assess personal and medical information during yearly follow-up visits. Health perception was determined using a visual analogue scale ranging from 0-100, with 0 being the worst and 100 being the best imaginable health status. Patients provided information about AF-related symptoms, such as palpitations, weakness, dyspnea, chest pain, dizziness, fatigue, exercise intolerance, or syncope. Smoking status was categorized into current smokers and current non-smokers (past or never smokers). Body weight and height were measured using calibrated devices and body mass index (BMI) was calculated as weight in kilograms

divided by height in meters squared. The mean of three consecutive blood pressure measurements obtained in a supine position was used in this analysis. AF type was classified by the local investigators into paroxysmal, persistent and permanent AF according to the 2010 AF guidelines of the European Society of Cardiology[13]. We classified rhythm control medications according to the Vaughan-Williams classification[14].

Follow- up and clinical outcome events

All Beat-AF patients had a face-to-face study visit at baseline. Subsequent follow-up information was collected by mailed questionnaires and phone interviews. In Swiss-AF, yearly follow-up study visits were done in person.

The primary endpoint for this study consisted of a composite of ischemic stroke, myocardial infarction and cardiovascular death. Secondary outcomes included cardiovascular and non-cardiovascular death, stroke or systemic embolism, myocardial infarction, hospitalization for heart failure, and major and clinically relevant non-major bleeding. Event definitions are provided in Table S1. We collected detailed information for every clinical outcome detected. All events were confirmed by two independent reviewers.

Statistical analysis

Baseline characteristics were stratified by sex. Continuous data are presented as numbers (percentages) and means ± standard deviation or medians (interquartile range) and compared using t-tests or Mann-Whitney U tests, as appropriate. Categorical variables were compared using Chi-square tests.

Person-years of follow-up were calculated as the time from study enrollment until the first occurrence of an outcome event, last follow-up visit, death, drop-out or loss to follow-up. Cox proportional-hazards models were constructed to investigate the associations of sex with clinical outcome events, and to adjust for differences in comorbidities and risk factors. Results were presented as hazard ratios (HR) and 95% confidence intervals (CI). In a first step, all models were adjusted for age. In a subsequent step, these models were further adjusted for education, BMI, smoking status, alcohol intake, oral

anticoagulation, AF type (paroxysmal vs non-paroxysmal), rhythm control medication, and a history of AF intervention therapy, hypertension, diabetes mellitus, history of heart failure, history of coronary heart disease, history of stroke/TIA, sleep apnea syndrome, or renal failure. A third model additionally adjusted for health perception and AF-related symptoms. The proportional hazards assumption was checked for each model using Schönfeld residuals, and no violations were detected.

We conducted pre-specified subgroup analyses for the primary endpoint according to age (≥75 versus <75 years), oral anticoagulation, AF type (paroxysmal vs. non-paroxysmal), history of stroke, history of diabetes, and history of coronary artery disease. We included multiplicative interaction terms in separate non-stratified models to test for a subgroup effect. All interaction tests used the same p-value threshold as indicate below, and they were considered to be hypothesis-generating. All statistical analyses were performed using R (version 1.3.1073). A p-value <0.05 was considered to indicate statistical significance.

Patient and Public Involvement

Patients and the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Results

Baseline characteristics of the 3894 patients stratified by sex are presented in Table 1. Of all patients, 1095 (28%) participants were women and the mean age of the overall population was 71.4 years. Compared to men, women were older (73 ± 9 vs. 71 ± 10 years, p < 0.001), had a lower health perception (69 ± 19 vs. 73 ± 18, p <0.001), reported more often AF-related symptoms (78% vs. 62%, p<0.001) and had higher systolic blood pressure levels (137 ± 20 mmHg vs. 133 ± 18 mmHg, p<0.001). In contrast, men more often had diabetes mellitus (18% vs. 11%, p<0.001) and coronary artery disease (CAD) (32% vs. 15%, <0.001).

During a median follow-up time of 4.02 (interquartile range, 3.00-5.83) years, we confirmed 502 primary outcome events. Incidence rates per 100 patient-years were 2.46 in women and 3.24 in men (Table 2, Figure 2). After multivariable adjustment, the HR for female sex was 0.74; 95% CI, 0.58-0.94, p=0.01. The absolute and relative risks of all secondary outcomes are presented in Table 2. The incidence rate of stroke/systemic embolism in women and men was 1.05 and 1.00 per 100 person-years, respectively. In multivariable models, we found no evidence that sex was associated with stroke/systemic embolism (adjusted HR 1.02; 95% CI, 0.70-1.49, p=0.93). As shown in Table 2, we found no evidence that sex was associated with myocardial infarction, major and clinically relevant non-major bleedings, or heart failure hospitalizations.

Overall, 505 all-cause deaths occurred, of which 313 (62%) were of cardiovascular origin. In women versus men, the incidence rate per 100 person-years was 2.28 versus 3.22 for all-cause death, 1.27 versus 2.05 for cardiovascular death, and 0.99 versus 1.17 for non-cardiovascular death. The multivariable adjusted HRs for female sex were 0.62; 95% CI, 0.49-0.79, p<0.001 for all cause death, 0.57; 95% CI, 0.41-0.78, p<0.001 for cardiovascular death, and 0.68; 95% CI, 0.47-0.98, p=0.04 for non-cardiovascular death (Table 2).

There were no statistically significant interactions across all subgroups analyzed, as shown in Table 3, with one potential exception. We observed a potentially stronger sex-specific effect in patients taking

oral anticoagulation compared to those not taking oral anticoagulation at baseline (p for interaction 0.05).

Discussion

Several important findings emerged from this prospective analysis of sex-specific differences in AF patients. First, there were many differences in baseline characteristics between men and women. While women suffered more often from AF- related symptoms and lower health perception, men had more cardiovascular comorbidities and risk factors. Second, women had a significantly lower risk of having a primary outcome event than men. Third, this reduced risk was due to an increased risk of cardiovascular and non-cardiovascular mortality in men. In contrast, men and women had a similar risk of stroke/systemic embolism, myocardial infarction, heart failure hospitalization or bleeding.

Women and men in our study had different baseline characteristics. Women were on average two years older, had more often paroxysmal AF and higher blood pressure levels. Those findings are comparable with other studies[6, 8]. As reported previously, rhythm control therapies such as PVI, ECV or radiofrequency ablations were less likely in women despite a higher prevalence of AF-related symptoms[6, 10, 15] and a lower health perception [10, 15, 16]. These important differences need to be taken into account in the interpretation of sex-specific analyses. Despite multivariable adjustment, some residual confounding likely persists.

Women had a lower risk of the primary composite outcome than men. This association was driven by a lower risk of death in women. After multivariable adjustment, both cardiovascular and non-cardiovascular death were significantly lower in women. Our findings are similar to those from the ORBIT-AF registry[10], but differ from findings of the RACE II and GARFIELD-AF studies, where no significant sex-specific differences in mortality were observed [6, 8]. A meta-analysis found that women with AF had higher risks for all-cause and cardiovascular mortality than men[5], whereas another meta-analysis published more recently found no sex-specific differences for CV death, all-cause death and major bleedings[17]. The differential associations of men and women with mortality across different studies are likely multifactorial and reflect differences in baseline characteristics, different setting as well as somewhat different eligibility criteria. It is possible that improved treatment of women in more recent studies has reduced some of the sex-specific differences in earlier studies. A possible

explanation why men experienced more fatal events in our cohort could be that they had a higher burden of coronary artery disease, heart failure and other comorbidities than women, leading to more severe events in men with a higher case fatality rate. Alternatively, it is also possible that the higher rate of sudden death in men compared with women may reduce the number of make potentially lifesaving hospital admissions in men. [18] While we have taken into account differences in risk factors and co-morbidities, the observed differences in mortality may reflect the survival advantage in women seen in population based statistics in Switzerland [19] and elsewhere [20, 21].

On the other hand, women did not have a higher risk of stroke or systemic embolism. These results are in contrast to various previous studies [8, 10], but in line with data from the RACE II study that described similar stroke rates in men and women after multivariable adjustments[6]. Women in our study were well anticoagulated (85% versus 84% men) and the age difference was only two years. These differences were more extreme in the ORBIT-AF registry (women 4 years older, anticoagulation rate 10% lower in women), and in the GARFIELD-AF registry (women 4 years older, women were more likely to have subtherapeutic anticoagulation). Our results are therefore consistent with the fact that widespread oral anticoagulation translates into lower stroke rates in both men and women. [22-24]

We found no significant associations of female sex with the occurrence of heart failure hospitalization, myocardial infarction and major and clinically relevant non-major bleeding. Recent observational studies regarding sex-specific differences in patients with AF showed similar results[6, 8-10], but meta-analyses presented conflicting results.[5, 17] Data from the ORBIT-AF registry after two years of follow up were in line with our data and did not find significant differences between men and women.[10] Most previous studies reported similar events rates for bleeding in women and men[6, 8], while some studies reported higher rates of heart failure hospitalization and myocardial infarction in men compared to women during their one year of follow up.[9] Again, residual confounding and intrinsic differences between men and women could explain some of these study specific differences.

Strengths of our study include the large sample size of 3894 well-characterized AF patients with up to 10 years of prospective follow-up and high anticoagulation rates. Some potential limitations also need to be considered. The present data cannot reveal causal mechanisms given the observational nature of our study. Participants in our cohort were mostly white and enrolled in the Swiss health insurance system. It is unclear to what extent our data are generalizable to other population settings. Women constituted 28% of all participants and are therefore underrepresented, similar to previous studies. [6, 25, 26] The relatively wide confidence intervals for the outcomes stroke/systemic embolism and myocardial infarction suggest that our study may have been underpowered to detect small sex-specific differences for these events.

In conclusion, in a contemporary population of AF patients with high anticoagulation rates, men died more often from both cardiovascular and non-cardiovascular causes than women. However, we observed no differences in the occurrence of cardiovascular events, including stroke or systemic embolism, myocardial infarction, hospitalization for heart failure or bleeding.

Contributorship Statement:

Conception and design: **DC, SED, SA, MK, SO**

Analysis and interpretation of the data: **SED, SA, EH, DC, MC;** all authors provided input in the interpretation of the data.

Drafting of the manuscript: **SED, SA, DC**

Critical revision for important intellectual content: all authors.

Final approval of the manuscript: all authors

Guarantor: **DC**

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Figure legend

Figure 1: Flow chart

Figure 2: Cumulative incidence of the primary composite outcome stratified by sex

The composite outcome was defined as time to first occurrence of ischemic stroke, myocardial infarction, or cardiovascular death. HR=Hazard ratio; CI=Confidence interval. HR adjusted for age

Table 1: Baseline characteristics stratified by sex

	Overall **N=3894**	**Men** **N=2799 (72%)**	**Women** **N=1095 (28%)**	P – value
Age, y	71.4 ± 10	70.8 ± 10	73.1 ± 9	<0.001
BMI, kg/m^2	27.5 ± 4.8	27.6 ± 4.3	27.1 ± 5.7	0.003
Education level				<0.001
Basic	463 (12.0)	195 (7.0)	268 (24.7)	
Middle	1909 (49.3)	1325 (47.5)	584 (53.9)	
Advanced	1501 (38.8)	1269 (45.5)	232 (21.4)	
Currently smoking	304 (7.8)	218 (7.8)	86 (7.9)	0.98
Alcohol intake (drinks per day) (median, IQR)	0.56 (0.07; 1.28)	0.79 (0.20; 1.64)	0.13 (0.00; 0.56)	<0.001
Systolic blood pressure, mmHg	134 ± 19	133 ± 18	137 ± 20	<0.001
Diastolic blood pressure, mmHg	78 ± 12	78 ± 12	77 ± 12	0.14
History of diabetes mellitus (n, %)	621 (16.0)	498 (17.8)	123 (11.2)	<0.001
History of hypertension (n, %)	2682 (68.9)	1914 (68.4)	768 (70.1)	0.31
History of coronary artery disease (n, %)	1045 (26.8)	883 (31.6)	162 (14.8)	<0.001
History of heart failure (n, %)	925 (23.8)	696 (24.9)	229 (20.9)	0.01
History of Stroke or TIA (n, %)	666 (17.1)	478 (17.1)	188 (17.2)	0.98
History of renal failure (n, %)	723 (18.6)	523 (18.7)	200 (18.3)	0.81
History of Sleep apnea (n, %)	512 (13.2)	437 (15.6)	75 (6.9)	<0.001

CHA_2DS_2-VASc score	3.2 ± 1.7	2.95 ± 1.8	3.87 ± 1.5	-
Paroxysmal AF	1914 (49.2)	1300 (46.5)	614 (56.1)	<0.001
AF-related symptoms (n, %)	2583 (66.3)	1724 (61.6)	859 (78.4)	<0.001
Health perception, 0-100*	72 ± 18	73 ± 18	69 ± 19	<0.001
Oral anticoagulation (n,%)	3278 (84.2)	2344 (83.8)	934 (85.3)	0.27
Rhythm Medication (n,%)	3161 (81.2)	2252 (80.5)	909 (83.0)	0.07
Statin therapy (n, %)	1709 (43.9)	1340 (47.9)	369 (33.7)	<0.001
Lipid lowering treatment, other (n,%)	106 (2.7)	85 (3.0)	21 (1.9)	0.07
Rhythm Intervention	1881 (48.3)	1408 (50.4)	473 (43.2)	<0.001
History of PVI (n, %)	825 (21.2)	605 (21.6)	220 (20.1)	0.31
History of ECV (n, %)	1346 (34.6)	1032 (36.9)	314 (28.7)	<0.001
History of RFA (n, %)	467 (12.0)	363 (13.0)	104 (9.5)	0.003
Pacemaker (n, %)	445 (11.4)	299 (10.7)	146 (13.3)	0.02

Data are presented as mean ± standard deviation, median (interquartile range) or numbers (percentage). CHA_2DS_2-VASc score was defined as follows: female sex = 1 point; age ≥65 and <75 years = 1 point; age ≥75 years = 2 points, history of stroke or TIA = 2 points; history of heart failure = 1 point; hypertension = 1 point; diabetes = 1 point; vascular disease, consisting of history of myocardial infarction, history of PTCA, history of coronary artery bypass graft surgery or periphery artery disease = 1 point. Missings: systolic blood pressure n=35; education n=21; alcohol consumption n=13; smoking n=10; RFA intervention n=6; BMI and CHADS-Vasc n=5; sleep apnea and electroconversion and heart failure n=4; stroke or TIA and renal failure and AF type n=3; oral anticoagulation and PVI 2; coronary heart disease and hypertension and diabetes n=1

AF = atrial fibrillation; BMI = body mass index; ECV = electro cardioversion; IQR = Interquartile range; PTCA = Percutaneous transluminal coronary angioplasty; PVI = pulmonary vein isolation; RFA = radiofrequency ablation; TIA = transient ischemic attack

Table 2: Associations of sex with primary and secondary outcome events

		Number of Events	Incidence rate per 100 py	Age-adjusted HR (95% CI)	Multivariable adjusted Model 1 HR (95% CI)	Multivariable adjusted Model 2 HR (95% CI)
Primary composite*	Women	116	2.46	0.65 (0.53; 0.80)	0.77 (0.61; 0.97)	0.74 (0.58; 0.94)
	Men*	386	3.24	1.0	1.0	1.0
	P value			p<0.001	p=0.03	p=0.01
Stroke or systemic embolism	Women	50	1.05	0.94 (0.67; 1.30)	1.05 (0.72; 1.52)	1.02 (0.70; 1.49)
	Men*	120	1.00	1.0	1.0	1.0
	P value			p=0.70	p=0.81	p=0.93
All-cause death	Women	111	2.28	0.59 (0.48; 0.73)	0.67 (0.52; 0.84)	0.62 (0.49; 0.79)
	Men*	394	3.22	1.0	1.0	1.0
	P value			p<0.001	p<0.001	p<0.001
Cardiovascular death	Women	62	1.27	0.51 (0.39; 0.68)	0.60 (0.44; 0.83)	0.57 (0.41; 0.78)
	Men*	251	2.05	1.0	1.0	1.0
	P value			p<0.001	p=0.002	p<0.001
Non-cardiovascular death	Women	48	0.99	0.71 (0.51; 0.99)	0.74 (0.51; 1.07)	0.68 (0.47; 0.98)
	Men*	143	1.17	1.0	1.0	1.0
	P value			p=0.04	p=0.11	p=0.04
Myocardial Infarction	Women	32	0.67	0.80 (0.53; 1.21)	1.00 (0.63; 1.59)	0.98 (0.61; 1.57)
	Men*	87	0.72	1.0	1.0	1.0
	P value			p=0.29	p=0.99	p=0.94

Major and clinically relevant non-major bleeding	Women	193	4.51	0.84 (0.71;1.00)	0.97 (0.80; 1.17)	0.95 (0.79; 1.15)
	Men*	503	4.34	1.0	1.0	1.0
	P value			p=0.05	p=0.73	p=0.63
Heart failure hospitalization	Women	151	3.28	0.90 (0.75; 1.09)	1.10 (0.89; 1.38)	1.06 (0.85; 1.32)
	Men*	358	3.07	1.0	1.0	1.0
	P value			p=0.30	p=0.37	p=0.60

*Primary composite consists of ischemic stroke, myocardial infarction and cardiovascular death

Model 1 was adjusted for age, educational status, body mass index, current smoking, alcohol consumption, history of hypertension, history of diabetes, history of heart failure, history of coronary heart disease, history of stroke or TIA, history of sleep apnea, history of renal failure, atrial fibrillation type, oral anticoagulation, rhythm control medication, rhythm intervention. Model 2 was additionally adjusted for health perception and atrial fibrillation related symptoms. Model 1: n=3851; model 2: 3845. CI = Confidence Interval; HR = Hazard Ratio; py = person-years

* Refererence group.

Table 3 Associations of female sex with the composite outcome across various subgroups

		Number of events	Person -years	Incidence (per 100 py)	HR (95% CI)	p-value for interaction with sex
				Primary Event		
Age	≥75	292	5474	5.33	0.73 (0.54; 0.99), p=0.05	0.39
	<75	210	11141	1.88	0.84 (0.57; 1.23), p=0.38	
Oral Anticoagulation	Yes	435	13594	3.20	0.68 (0.53; 0.88), p=0.003	0.05
	No	65	3019	2.15	1.20 (0.66; 2.17), p=0.55	
AF type	Paroxysmal	197	8695	2.27	0.91 (0.64; 1.30), p=0.62	0.48
	Non-paroxysmal	304	7907	3.84	0.69 (0.50; 0.96), p=0.03	
History of stroke	Yes	114	2587	4.41	0.82 (0.50; 1.34), p=0.42	0.75
	No	386	14020	2.75	0.75 (0.58; 0.98), p=0.04	
History of diabetes	Yes	141	2288	6.16	0.57 (0.33; 0.97), p=0.04	0.27
	No	360	14324	2.51	0.81 (0.62; 1.05), p=0.11	
History of coronary heart disease	Yes	205	3985	5.14	0.70 (0.44; 1.12), p=0.14	0.79
	No	296	12627	2.34	0.78 (0.59; 1.02), p=0.07	

The model was adjusted for age, educational status, body mass index, current smoking, alcohol consumption, history of hypertension, history of diabetes, history of heart failure, history of coronary heart disease, history of stroke or TIA, history of sleep apnea, history of renal failure, atrial fibrillation type, oral anticoagulation, rhythm control medication, rhythm intervention. AF = atrial fibrillation; CI = Confidence Interval; HR = Hazard Ratio; py = person-years