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Influence of sex on long-term prognosis in patients with atrial fibrillation treated with oral anticoagulants. Results from the prospective, nationwide FANTASIIA study

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Abstract

Background

While many risk factors for Atrial Fibrillation (AF) have been identified, there are important differences in their relative impact between sexes. The aim of our study was to investigate the influence of sex as a long-term predictor of adverse events in “real world” AF patients treated with direct oral anticoagulants.

Methods

The FANTASIIA registry is a prospective, national and multicentric study including outpatients with anticoagulated AF patients. Baseline characteristics and adverse events at 3 years of follow-up were collected and classified by sex. Cox multivariate analysis was performed to investigate the role of sex in major events and composite outcomes.

Results

A total of 1956 patients were included in the study. 43.9% of them were women, with a mean age of 73.8 ± 9.4 years (women were older 76.5 ± 7.9 vs 71.7 ± 10.1, $p<0.001$). Women had higher rate of cardiovascular risk factors and higher mean of CHA_2DS_2-VASc (4.4 ± 1.4 vs 3.7 ± 1.6, $p<0.001$) and HAS-BLED (2.1 ± 1.0 vs 1.9 ± 1.1, $p<0.001$) than men. After 3 years of follow-up, rates of major events were similar in both groups with limit difference for all-cause mortality (4.4%/year in women vs 5.6%/year in men; $p = 0.056$). However, all the composite events were more frequent in women. We observed in the non-adjusted adverse events lower rate of all-cause mortality (HR 0.62, 95%CI 0.47–0.81; $p<0.001$), composite 1 outcomes (HR 0.80, 95%CI 0.65–0.98; $p = 0.029$) and composite 2 (HR 0.77, 95%CI 0.64–0.94; $p = 0.010$) in women compared with men. In multivariate Cox regression analysis observed that female sex was an independently protector factor for all-cause mortality and for the composite outcomes 1 and 2.

Conclusions

In this "real world" study of anticoagulated AF patients, women could have a protective role against development of adverse events, mainly on all-cause mortality and combined events.

Keywords

Atrial fibrillation; Role of sex; Direct oral anticoagulants; Vitamin K antagonists; FANTASIIA registry

AF	Atrial fibrillation
INR	International normalized ratio
LVEF	Left ventricular ejection fraction
DOAC	Direct oral anticoagulants
TTR	Time in therapeutic range
VKA	Vitamin K antagonists

Introduction

Atrial fibrillation (AF) is the most frequently cardiac arrhythmia in developed countries [1] and several studies have been described that in both developed and developing countries, the age-adjusted incidence and prevalence of AF are lower in women [1]. The detection of AF is associated with an important morbidity and mortality rate, with an increase in admissions and health costs [1], [2], [3], [4], [5], [6]. AF is a leading risk factor for stroke and related with one-third of all ischemic cerebrovascular events [3], [7]. Different clinical factors included in thromboembolic and bleeding scores are markers of prognosis in AF patients [1], [8]. Female sex has been considered a prognostic factor of AF embolic complications and therefore confers 1 point on CHA_2DS_2-VASc score [1], [2], [3]. However, the presence of female sex as risk factor has not been strongly confirmed in the literature and nowadays there are important doubts about the role of women *per se* as an independent factor of poor prognosis in AF [10], [11]. For that reason, the European Society of Cardiology (ESC) AF guidelines [1] do not recommend oral anticoagulant treatment in patients with AF and a CHA_2DS_2-VASc score of 1 when the only factor present is female sex itself.

It is well known that women presented AF at least a decade later than men and paroxysmal AF form the most common presentation in addition to the presence of dyspnea, fatigue or palpitations [12], [13]. Although women received similar anticoagulant therapies than men, electrical cardioversion or ablation procedures are less frequent in women [14], [15], [16], [17]. However, the analysis of direct effect of sex as long-term predictor of adverse events in "real world" AF patients under oral anticoagulation therapy in the literature is scarce and not homogeneous in the conclusions [18].

The objective of this study was to investigate the role of sex as a long-term predictor of adverse events in "real world" patients with AF treated with DOAC or VKA in a nationwide observational study.

Methods

Study design

The data from this study come from the FANTASIIA Registry (Spanish acronym of "Fibrilación Auricular: influencia del Nivel y Tipo de Anticoagulación Sobre la incidencia de Ictus y Accidentes hemorrágicos"), a national, multicentric, observational and prospective study that collects general information about the baseline characteristics and situation of AF population (paroxysmal, permanent or persistent AF) in Spain. The main objective of The FANTASIIA registry was to evaluate the incidence of thromboembolic and hemorrhagic events in a prospective sample of patients with AF over 3 years of follow-up, in relation to the type of antithrombotic agents used, VKA or DOAC, and the quality of anticoagulation (in those who receive VKA). The design of FANTASIIA registry was previously published [14], [19]. In brief, this registry includes an initial visit and three follow-up visits, after one, two and three years. Clinical and analytical data of patients were collected in an electronic data notebook. In this substudy, we focused on the role of sex as a long-term predictor of adverse events in this population.

Study population

A total of 1956 consecutive outpatients treated with VKA or DOAC were included in the analysis of the present study. All patients were followed in an outpatient clinics by 81 researchers, 81% of them were cardiologists, 11% were primary care physicians and 8% were internists, from June 2013 to December 2014. Above 50 centers throughout Spain were involved, stratified by levels of assistance and randomly selected. According to the FANTASIIA registry design, all patients

received anticoagulant treatment, per protocol 25% with DOAC and 75% with VKA, at least during six months prior to inclusion. AF patients were older than 18 years old and clinical management was carried out according current clinical practice. Demographic, clinical and analytical variables were collected from all patients in medical records. Symptoms related with AF presence were evaluated following the European Heart Rhythm Association (EHRA). Patients were classified as follows: EHRA I: 'No symptoms'; EHRA II: 'Mild symptoms', normal daily activity not affected; EHRA III: 'Severe symptoms', normal daily activity affected; EHRA IV: 'Disabling symptoms', normal daily activity discontinued. Patients with rheumatic mitral valvular disease or prosthetic valve patients were excluded [20].

The FANTASIIA Registry complies with all the requirements of the Helsinki Declaration and the study protocol was approved by the Clinical and Ethical Testing Committee of the Hospital Universitario San Juan de Alicante (approval number 12/220) by all Ethics Committees of the participating centers, as well as the Spanish Agency for Medicine and Health Products (SEC-ACO-2012-01 post-authorization approval code). All the participating patients signed the informed consent.

For the present analysis, we included all patients that have been completed three years of follow up.

Role of sex as predictor of prognosis

We compared two groups of patients divided by sex, women versus men. Baseline characteristics, risk factors, comorbidities such as history of heart disease, previous stroke or renal dysfunction were collected. Time in therapeutic range (TTR) was assessed by Rosendaal method. We also collected all adverse events (stroke, embolic events, major bleeding, major adverse cardiovascular events (MACE), all-cause and cardiovascular mortality rates) after 3 years of follow-up. Thromboembolic events were defined as ischaemic stroke or transient ischaemic attack and peripheral artery embolism. Strokes were defined as ischaemic stroke, transitory ischaemic attack and haemorrhagic stroke. All strokes were evaluated by computed tomographic (CT) scan or magnetic resonance imaging (MRI) according to the neurologist criteria. Major bleeding events were assessed according to the 2005 International Society of Thrombosis and Haemostasis criteria [21] fatal bleeding or symptomatic bleeding in a critical anatomical site (intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, pericardial or intramuscular with compartment syndrome) and/or bleeding causing a fall in Hb≥2 g/dL, or transfusion of ≥2 units of packed red blood cells. We also recorded all-cause mortality and cardiovascular mortality, with the latter defined if it was secondary to a cardiovascular event (acute coronary syndrome, heart failure, lethal arrhythmia or sudden death, artery aneurysm rupture or stroke). Major adverse cardiovascular event (MACE) was defined as the composite of ischaemic stroke, myocardial infarction and cardiovascular mortality. We also performed composite events to assess the differences between sexes. Composite outcomes 1 included stroke, embolism, major bleeding or all-cause mortality. Composite outcomes 2 included stroke, embolism, major bleeding, all-cause mortality or myocardial infarction. Composite outcomes 3 included stroke, embolism, major bleeding or cardiovascular mortality.

To guarantee the quality of the FANTASIIA registry, an external event assignment committee was formed to evaluate all adverse events. Cox multivariate analysis after adjusting for baseline confounding factors was performed to investigate the role of sex in predicting major adverse events.

Statistical analysis

Quantitative variables are described by mean and standard deviation or median and interquartile range based on whether they followed a normal distribution. To test the normal distribution, the Kolmogorov–Smirnov test was used. For comparisons among groups, *T*-student test was used in the case of continuous variables and Chi-square in the case of qualitative variables, considering the value of $p < 0.05$ as statistically significant. Cox regression analyses were used to determine the associations between women sex and adverse outcomes. The independent effect of clinical variables on adverse clinical outcomes was calculated using a Cox proportional hazards regression, considering the clinical variables age, female sex, hypertension, diabetes mellitus, COPD, previous bleeding, previous stroke, CKD, heart disease, Charlson Index and antiarrhythmic drugs. After that, we included in the multivariate model only those values with $p < 0.15$ on univariate analysis. The results are presented as hazard ratio (HR) with a 95% confidence interval. STATA statistical version 12.0 was employed for the statistical analysis.

Results

Comparison of baseline characteristics of both groups

Of 1956 patients analyzed, 860 (43.9%) were women. The mean age was 73.8 ± 9.4 years, women older than men (76.5 ± 7.9 vs 71.7 ± 10.1, $p<0.001$). Table 1 shows the baseline characteristics of the population. Regarding to oral anticoagulation therapy in women, 219 (25.5%) received DOAC and 641 (74.5%) VKA (without differences by sex; $p = 0.240$). Regarding the quality of oral anticoagulation under VKA therapy, 52.4% of the whole sample had poor quality assessed by Rosendaal method (TTR<65%), without differences by sex (53.3% in women vs 51.8%; $p = 0.548$). We also assessed cardiovascular risk factors and we only observed significant differences for hypertension (more frequent in women than men [84.3% vs 77.3%, $p<0.001$]), COPD apnea (less frequent in women than men [10% vs 23.4%, $p<0.001$]), mean CHA_2DS_2-VASc and HAS-BLED (both higher in women than men [4.35±1.37 vs 3.67±1.64, $p<0.001$] and [2.13±0.95 vs 1.91±1.11, $p<0.001$], respectively). Paroxysmal AF was more frequent in women than men (33.0% vs 26.1%, $p = 0.004$) but, regarding the management of AF, previous electrical cardioversion (14.1% vs 21.3%, $p<0.001$) and radiofrequency ablation (3.3% vs 5.1%, $p = 0.045$) were less frequent in women than men. The left ventricular ejection fraction was higher in women (60.9 ± 9.1% vs 56.7 ± 12.5%, $p < 0.001$) than in men. Related with that finding, women showed less previous heart disease such as heart failure (25.2% vs 31.8%, $p<0.001$) and coronary heart disease (10.8% vs 24.0%, $p<0.001$) (Table 1).

Table 1. Baseline characteristics

	Total *1956*	Women *n = 860 (43.9%)*	Men *n = 1096 (56.1%)*	*p*-value
Age (years)	73.8 ± 9.4	76.4 ± 7.8	71.7 ± 10.11	<0.001
Hypertension	1574 (80.5)	725 (84.3)	847 (77.3)	<0.001
Dyslipidaemia	1021 (52.2)	446 (51.9)	573 (52.3)	0.860
Diabetes	571 (29.2)	245 (28.6)	331 (30.2)	0.340
COPD/sleep apnea	338 (17.3)	88 (10.0)	256 (23.4)	<0.001
Renal failure	378 (19.3)	168 (19.5)	209 (19.1)	0.790
Previous stroke	334 (17.1)	136 (15.9)	195 (17.8)	0.276
Thyroid dysfunction	219 (11.2)	150 (17.5)	67 (6.1)	<0.001
Drugs/alcohol abuse	74 (3.8)	6 (0.7)	67 (6.1)	<0.001
Major bleeding	80 (4.1)	33 (3.8)	47 (4.3)	0.617
Charlson index	1.14±1.15	0.95±1.05	1.29±1.21	<0.001
EHRA functional class	767 (39.2)	284 (33.0)	483 (44.1)	
(1-functional class I)				
2-functional class II	1025 (52.4)	475 (55.2)	554 (50.1)	<0.001
3- functional class III	156 (8.0)	95 (11.1)	63 (5.7)	
4-functional class IV	8 (0.4)	6 (0.7)	2 (0.2)	
Previous heart disease	941 (48.1)	359 (41.8)	578 (52.7)	<0.001
CHD	354 (18.1)	93 (10.8)	263 (24.0)	<0.001
Heart failure	569 (29.1)	217 (25.2)	349 (31.8)	0.001
Coronary stents	180 (9.2)	44 (5.2)	139 (12.7)	<0.001
LVEF<40%	229 (11.7)	42 (4.9)	185 (16.9)	<0.001
Paroxysmal AF	569 (29.1)	284 (33.0)	286 (26.1)	0.004
Permanent AF	966 (49.4)	405 (47.1)	560 (51.1)	0.004
Rhythm control	773 (39.5)	332 (38.7)	413 (37.7)	0.660
Ablation for AF	84 (4.3)	30 (3.3)	56 (5.1)	0.045
LVEF	58.6 ± 11.4	60.9 ± 9.09	56.7 ± 12.5	<0.001
CHA2DS2-Vasc	3.72±1.59	4.35±1.37	3.67±1.64	<0.001
HAS-BLED	2.01±1.05	2.13±0.95	1.91±1.11	<0.001
VKA	1483 (75.8)	641 (74.5)	842 (76.8)	0.240
DOAC	473 (24.2)	219 (25.5)	254 (23.2)	
Diuretics	1123 (57.4)	549 (63.9)	572 (52.2)	<0.001
ACE inhibitors	602 (30.8)	208 (24.2)	392 (35.8)	<0.001
ARA	796 (40.7)	385 (44.8)	410 (37.4)	0.001
MRA	272 (13.9)	99 (11.6)	172 (15.7)	0.008
Statins	1078 (55.1)	448 (52.1)	628 (57.3)	0.022
Antiplatelets	205 (10.5)	53 (6.2)	152 (13.9)	<0.001
Digoxin	354 (18.1)	173 (20.1)	183 (16.7)	0.060
Antiarrhythmic	481 (24.6)	229 (26.6)	256 (23.4)	0.160
CCB	472 (24.1)	224 (26.1)	246 (22.4)	0.160
Beta-blockers	1179 (60.3)	523 (60.8)	657 (59.9)	0.690
TTR (Rosendaal)	61.3 ± 25.1	60.8 ± 24.8	61.8 ± 25.2	0.357
TTR < 65%	1025 (52.4)	458 (53.3)	568 (51.8)	0.548
TTR<70%	1156 (59.1)	517 (60.1)	639 (58.3)	0.497

AF: Atrial Fibrillation. COPD: Chronic obstructive pulmonary disease. EHRA: European Heart Rhythm Association. CHD: Coronary Heart Disease, LVEF: Left ventricular ejection fraction. ACE inhibitors: Angiotensin-converting-enzyme inhibitors, ARA: Aldosterone-receptor antagonists, MRA: Mineralocorticoid receptor antagonists. CCB Calcium channel blockers. VKA: Vitamin K Antagonists. DOAC: Direct oral anticoagulants. TTR: Time in Therapeutic Range.

Adverse events during the follow-up

After 3 years of follow-up, 5005.45 patients/year of observations were accumulated. Annual incidence of major events (women versus men, patients/year) for stroke, total embolisms, major bleedings, MACE, cardiovascular death and myocardial infarction were similar in both groups of patients, and with limit difference for all-cause mortality (4.4%/year in women vs 5.6%/year in men; $p = 0.056$). However, the composite events were more frequent in women. Table 2 reflected the distribution of adverse events according to sex and we observed significantly lower rate of the composite 1 outcomes (stroke, embolism, major bleeding or all-cause mortality) in women than men (6.8%/year vs 8.4%/year; $p = 0.027$) as well as lower rate of the composite 2 outcomes (stroke, embolism, major bleeding, all-cause mortality or myocardial infarction) in women than men (7.3%/year vs 9.3%/year; $p = 0.009$). We observed in the non-adjusted adverse events lower rate of all-cause mortality (HR 0.62, 95%CI 0.47–0.81; $p<0.001$), composite 1 outcomes (HR 0.80, 95%CI 0.65–0.98; $p = 0.029$) and composite 2 (HR 0.77, 95%CI 0.64–0.94; $p = 0.010$) in women compared with men.

We also performed a univariate (Supplementary Tables 1 and 2) and multivariate Cox regression analysis (Table 3) and observed that female sex was an independently protector factor for all-cause mortality and for the composite outcomes 1 and 2.

Table 2. Distribution of adverse events according to sex after 3 years of follow-up.

	Overall *(n = 1956)*	**Women** *(n = 860)*	**Men** *(n = 1096)*	***p*-value**
Stroke	45	17	28	
Annual rate *(%/year)*	0.9%/year	0.8%/year	1.0%/year	0.397
Major bleeding	146	63	83	
Annual *rate (%/year)*	2.9%/year	2.8%/year	3.0%/year	0.836
Total embolisms	48	17	31	
Annual *rate (%/year)*	0.9%/year	0.8%/year	1.1%/year	0.227
All-cause mortality	255	98	157	
Annual *rate (%/year)*	5.1%/year	4.4%/year	5.6%/year	0.056
Cardiovascular mortality	107	51	56	
Annual *rate (%/year)*	2.1%/year	2.3%/year	2.0%/year	0.428
MACE	168	70	98	
Annual *rate (%/year)*	3.4%/year	3.2%/year	3.5%/year	0.530
Acute myocardial infarction	53	19	34	
*Annual rate (%/*year*)*	1.2%/year	0.9%/year	1.3%/year	0.227
Composite outcomes 1	385	150	235	
Annual *rate (%/year)*	7.7%/year	6.8%/year	8.4%/year	0.227
Composite outcomes 2	420	161	259	
Annual *rate (%/year)*	8.4%/year	7.3%/year	9.3%/year	0.009
Composite outcomes 3	266	114	152	
Annual *rate (%/year)*	5.3%/year	5.1%/year	5.5%/year	0.695

Stroke included ischaemic stroke, haemorrhagic stroke and transitory ischaemic attack. Thromboembolic events were defined as ischaemic stroke or transient ischaemic attack and peripheral artery embolism. MACE included the composite of ischaemic stroke, myocardial infarction and cardiovascular mortality. Composite outcomes 1: included stroke, embolism, major bleeding or allcause mortality. Composite outcomes 2: included stroke, embolism, major bleeding, all-cause mortality or myocardial infarction. Composite outcomes 3: included stroke, embolism, major bleeding or cardiovascular mortality.

Table 3. Independent predictors of adverse clinical events by multivariate Cox regression analysis.

	HR 95%	*CI*	*p-value*
Thromboembolic events			
Previous stroke	2.13	1.16–3.91	0.014
Major bleeding			
CKD	1.76	1.23–2.53	0.002
Previous bleeding	2.76	1.58–4.82	<0.001
Mortality			
Sex (female)	0.62	0.47–0.81	<0.001
Age	1.08	1.06–1.10	<0.001
COPD/sleep apnea	1.44	1.07–1.94	0.016
CKD	1.47	1.13–1.93	0.005
Previous bleeding	2.15	1.37–3.39	0.001
Cardiovascular mortality			
Age	1.08	1.05–1.11	<0.001
Heart failure	1.68	1.06–2.65	0.028
Composite outcomes 1			
Sex (female)	0.64	0.52–0.80	<0.001
Age	1.05	1.04–1.06	<0.001
CKD	1.38	1.10–1.73	0.006
Charlson index	1.19	1.09–1.30	<0.001
Previous bleeding	2.02	1.35–2.95	<0.001
Composite outcomes 2			
Sex (female)	0.65	0.52–0.80	<0.001
Age	1.05	1.04–1.06	<0.001
CKD	1.30	1.05–1.62	0.019
Charlson index	1.18	1.08–1.28	<0.001
Previous bleeding	1.94	1.33–2.83	0.001
Composite outcomes 3			
Sex (female)	0.76	0.59–0.99	0.039
Age	1.03	1.02–1.05	<0.001
CKD	1.40	1.06–1.84	0.016
Charlson Index	1.21	1.10–1.34	<0.001
Previous major bleeding	1.75	1.07–2.88	0.027

CKD: Chronic Kidney disease. COPD: Chronic obstructive pulmonary disease. HR: Hazard ratio.
CI: Confidence interval. (For detailed multivariate analysis adjusted by different variables see supplementary tables.)

Discussion

The principal results of this ancillary study from the FANTASIIA Registry showed that female sex was associated with a less development of major cardiovascular events at long-term follow up, mainly in total death and combined events including embolisms and bleedings.

The main result of our study indicates that women showed better long term prognosis with lower rates of all-cause mortality, and composite events besides they were older and with higher incidence of hypertension and higher CHA_2DS_2-VASc and HAS-BLED scores than men, like previous studies [22], [23], [24]. Probably, one of the main causes is related with less rate of previous heart disease in women and other is related with better oral anticoagulation therapy than men [12], [18]. In the same line, Pastori et al. [25] observed higher rate of adverse events in men with AF than in women and male sex was independent predictor of cardiovascular events.

In previous studies female sex has been described as a risk factor for cardiovascular disease and death. Emdin et al. [9] in a systematic review and meta-analysis of cohort studies showed that AF was associated with a higher relative risk of all-cause mortality, stroke, cardiovascular mortality, cardiac events, and heart failure in women compared with men. On the other side, Nielsen et al. [11] performed a big study with 239,671 patients with AF with similar baseline characteristics as our registry (such as women with higher CHA_2DS_2-VASc score and older and they observed higher rates of stroke in women. Or that reason, the authors concluded that female sex is a risk modifier of stroke but with excess of risk in those with more than 2 non-sex related risk factors.

Several reasons can explain the discrepancies between our results and those of Emdin et al. [9] First, the *meta-analysis effect* where previous studies have presented conflicting evidence of the effect of AF on the risk of death and cardiovascular disease in women: the ratio of relative risk was greater than one but not significant for 11 of the 19 studies (for death) and for 6 six of the 13 studies (for stroke). Besides, in meta-analysis of observational studies, sex differences in the association of AF with risk of death and cardiovascular disease might be caused by unobserved confounding between sexes [17], [26]. Second, *publication bias*, because studies that detect an interaction between AF and risk of death and cardiovascular disease by sex might be more likely to be published. Third, *differences in treatment*, mainly anticoagulation, between the different observational studies with underuse of anticoagulants in women reported in many of the studies included [28]. Sex-specific differences in anticoagulant use have been observed in relation to OAC prescription (women were more likely to be prescribed antiplatelet agents rather than OAC), the chosen OAC agent (women were more likely to receive a DOAC when compared to warfarin), and OAC dosing (women require a lower mean warfarin dose [approximately 4.5 mg less per week when compared to men; $p < 0.001$], and women are more likely to be prescribed the lower approved DOAC dose) [1], [2], [3], [4], [5]. In this sense, our study population was fully anticoagulated without any difference by sex in quality and type of oral anticoagulation therapy [29].

Moreover, in the current analysis, we observed differences in presentation and clinical symptoms of AF between sexes; women presented more frequently symptomatic paroxysmal AF and were more symptomatic compared with men with a functional ERHA class II, III and IV significantly more frequent in women ($p<0.001$) than men. These facts were in accordance to previous studies such as ORBIT-AF registry [30], EORP-AF pilot survey [15], and PREFER AF registry [22]. In our study, as in those others before [15], [22], rhythm control strategy was less frequent in women despite a higher rate of symptomatic AF. Indeed, electrical cardioversion and radiofrequency ablation were less frequent in women. In this way, a meta-analysis of all AF ablation clinical trials reported that women constitute only one-fifth of the study population [31]. However, in this analysis, all explorations, diagnosis and initial treatments data were similar in both groups. Thus, the use of anticoagulants was also similar in both, women and men.

Finally, after multivariate adjustment, we observed lower rates of adverse events in women, specially in the rate of stroke although female sex is a risk factor in CHA_2DS_2-VASc score. The results of this study due to their limited statistical power should be analyzed with caution; however, our results were in accordance to the current literature. In accordance, the study of Renoux et al. [32] from the Quebec cohort did not support female sex as an independent risk factor for stroke and they found that mortality rates were lower in women compared with men at any age, whereas the risk of bleeding was also slightly lower in women. However, Andrade et al. [27] observed that risk was elevated for both sexes, but the relative increase in mortality has been suggested to be higher for women. Although the results of individual studies can be contradictory, a large meta-analysis demonstrated that the pooled ratio of relative risks for of all-cause mortality was 12% greater in women versus men (RR 1.12, 95%CI 1.07–1.17). This meta-analysis also showed the poor oral anticoagulation management in women unlike our results.

Study limitations

The principal limitation of this "real world" analysis, come from its design as an observational study. Indeed, the les rate of structural heart disease in women could be unobserved confounding factor. Although the prospective design of the study, acceptable duration of the follow up and correct statistical analysis made improbable the presence of confounding factors, any bias due the sample size could have influenced the principal results

Conclusions

In this substudy from the real world FANTASIIA prospective registry, female sex seems to play a protective role against the development of major cardiovascular events, mainly on total death and combined events including embolisms and bleedings in AF patients. These data suggest that, after control the influence of poor oral anticoagulation therapy, female sex is not a risk factor of worse prognosis in AF patients.

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Declaration of Competing Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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