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Original article

## Gender differences in management and clinical outcomes of atrial fibrillation patients

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### ABSTRACT

**Background:** Prior research has identified gender differences in the epidemiology and clinical management of atrial fibrillation (AF). The primary aim of this study is to systematically analyze a cohort of AF men and women and evaluate their baseline demographics, treatment, and clinical outcomes by gender.

**Methods:** We examined the records of 5976 (42% women) consecutive AF patients who were prescribed at least one anti-arrhythmic drug between 2006 and 2013. From this cohort, 4311 (72%) patients had anticoagulation data available and were included in the final analysis. Time to clinical events was assessed using survival analysis and adjusted for covariates using Cox regression.

**Results:** Compared to men, women were older (73 years vs. 67 years,  $p < 0.001$ ), had higher CHADS<sub>2</sub> scores (1.9 vs. 1.5,  $p < 0.001$ ), and fewer cardiac comorbidities. Compared to men, women were more often prescribed sotalol and less often dofetilide ( $p < 0.001$ ). Women were also less likely to be anticoagulated (76.8% vs. 82.5%,  $p < 0.001$ ). Over a mean follow-up of 40 months, women were more likely to die (HR 1.21,  $p = 0.037$ ) or to have an ischemic stroke (HR 1.35,  $p = 0.058$ ). Women also had higher rates of atrioventricular-nodal ablation (adjusted HR 2.11,  $p < 0.001$ ) and pacemaker implantation (adjusted HR 1.69,  $p < 0.001$ ) procedures, but lower rates of electrical cardioversions, AF ablations, and maze surgeries.

**Conclusions:** There are significant gender differences in baseline demographics and clinical outcomes of AF patients. Women have higher mortality and ischemic strokes and are less often prescribed anticoagulation therapy despite higher CHADS<sub>2</sub> scores. These data have important clinical implications.

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### Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia in the USA and developed nations, with a predicted 2.5-fold increase in prevalence in the USA by 2050 [1,2]. There is a greater incidence of AF in men at all ages; however, the prevalence of AF in women 75 years and older is nearly twice that of men secondary to an average longer lifespan in women [3]. Although gender differences in the epidemiology, clinical management, and outcomes of AF have been described [4–8], leading to the development of the CHA<sub>2</sub>DS<sub>2</sub>-VASc scoring system which accounts for female gender as an independent risk predictor for stroke [9–11], no

studies have comprehensively evaluated the gender differences in baseline demographics, treatment strategies, and clinical outcomes of AF patients in the USA. This study was therefore designed to systematically analyze a cohort of patients with AF and examine by gender their baseline demographics, their treatment strategy focusing primarily on anticoagulation, and their clinical outcomes including mortality and stroke.

### Methods

The original dataset consisted of 5976 consecutive patients diagnosed with paroxysmal (58%) or persistent (42%) AF, who were prescribed one or more anti-arrhythmic drug with the goal of achieving rhythm control, at the University of Pittsburgh Medical Center hospitals and clinics from January 2006 to November 2013. The cohort was created via examination of the electronic medical record for encounters classified under the diagnosis of AF (427.31) by the International Classification of Diseases, Ninth

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Revision, Clinical Modification (ICD-9-CM) [12]. Associated pharmacologic databases were searched for a prescription of Vaughan Williams Class IA, IC, or Class III anti-arrhythmic drug [13]. The cohort was prospectively followed starting from the date of first anti-arrhythmic drug prescription (after January 1st, 2006) through May 30th, 2014 with review of outpatient and inpatient medical records. Patients who died or were lost to follow-up during this period were censored at their date of death or last encounter. Demographic data were obtained from the clinical records and information on comorbidities was generated from ICD-9-CM codes in the clinical database [14]. For risk stratification, the CHADS<sub>2</sub> score, CHA<sub>2</sub>DS<sub>2</sub>-VASc score, and Charlson comorbidity index were also calculated for each patient [15–17]. Information on anticoagulation therapy was obtained from the pharmacologic database search, which generated results for 4311 (72.1%) patients, which constituted the final cohort included for analysis in this study. Clinical outcomes included mortality, ischemic stroke, AF recurrence, admission for AF, admission for congestive heart failure, and need for AF-related procedures, including direct-current electrical cardioversion, AF ablation, permanent pacemaker implantation, atrioventricular nodal ablation, and surgical maze procedures. AF recurrence was defined by recurrence of AF on surface electrocardiogram, electrocardiographic monitoring, or recurrence of AF symptoms. Causes for admission to the hospital were adjudicated by review of admission notes and were subclassified into AF, congestive heart failure, and other cardiovascular reasons. Patient death and occurrence of ischemic stroke were identified by review of the institutional electronic medical record. The University of Pittsburgh Institutional Review Board approved this study.

Baseline characteristics are presented as means ± standard deviation for continuous variables and as occurrence rates for dichotomous variables and were compared using the Student's *t* and chi-square tests, respectively. Clinical outcomes were reported as incidence rate (number of events per 100 person-years) and compared by gender using the log-rank test. Univariate and multivariate Cox proportional-hazard models were constructed to estimate the hazard ratio (HR) of females (vs. males) for each clinical outcome. In the multivariate models, the HR of females was adjusted for cofactors that were significantly different by gender. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

## Results

The study cohort comprised 4311 patients with AF, of whom 1774 patients (41.3%) were women. Mean follow-up time was 38.6 months for women and 42.0 months for men ( $p = 0.01$ ). Baseline demographic information, clinical data, and medications are summarized in Table 1. Compared to men, women were older (72.5 years vs. 66.8 years,  $p < 0.001$ ), had higher CHADS<sub>2</sub> (1.9 vs. 1.5,  $p < 0.001$ ) and CHA<sub>2</sub>DS<sub>2</sub>-VASc (3.7 vs. 2.2,  $p < 0.001$ ) scores, and higher rates of hypertension and prior strokes, but lower rates of coronary artery disease, heart failure, prior percutaneous coronary interventions, and prior coronary artery bypass grafting.

The most common anti-arrhythmic medication prescribed for both men and women was amiodarone (42.8% and 41.1%, respectively). Women had lower rates of dofetilide use (11.6% compared to 20.5%,  $p < 0.001$ ) and higher rates of sotalol use (36.1% compared to 30.9%,  $p < 0.001$ ). Rates of anticoagulation were significantly lower in women compared to men (76.8% compared to 82.5%,  $p < 0.001$ ). Rates of warfarin use were similar between men and women (71.7% and 69.1%, respectively,  $p = 0.066$ ) but the use of the direct oral anticoagulants (DOACs) was significantly lower in women (19.9% compared to 24.6%,  $p < 0.001$ ). Rates of anticoagulation by age and gender are shown in Fig. 1. As demonstrated in that figure, there was no difference in

**Table 1**

Demographic and clinical characteristics of patient population by gender (Full Study Cohort).

	Female	Male	<i>p</i> -Value
Number of patients	1774	2537	
Age	72.5 ± 11.7	66.8 ± 12.4	<0.001
Race			0.131
White	1677 (94.6%)	2394 (94.3%)	
Black	72 (4.1%)	90 (3.5%)	
Asian	4 (0.2%)	10 (0.4%)	
Other/not specified	21 (1.1%)	43 (1.8%)	
Atrial flutter	106 (6.0%)	199 (7.8%)	0.019
CHADS <sub>2</sub> score	1.9 ± 1.3	1.5 ± 1.3	<0.001
CHA <sub>2</sub> DS <sub>2</sub> -VASc score	3.7 ± 1.6	2.2 ± 1.6	<0.001
Charlson index	1.5 ± 1.8	1.4 ± 1.6	0.006
Coronary artery disease	468 (26.4%)	921 (36.3%)	<0.001
Hypertension	1195 (67.4%)	1525 (60.1%)	<0.001
Diabetes mellitus	346 (19.5%)	497 (19.6%)	0.944
Heart failure	351 (19.8%)	587 (23.1%)	0.009
Chronic kidney disease	122 (6.9%)	177 (7.0%)	0.899
Chronic pulmonary disease	176 (9.9%)	241 (9.5%)	0.645
Depression	279 (15.7%)	191 (7.5%)	<0.001
Follow-up time (months)	38.6 (0.4–101.1)	42.0 (0.3–101.4)	0.012
Prior medical events			
Prior stroke	19 (1.1%)	9 (0.4%)	0.004
Prior cardioversion	2 (0.1%)	3 (0.1%)	0.958
Prior atrioventricular nodal ablation	14 (0.8%)	31 (1.2%)	0.169
Prior AF ablation	53 (3.0%)	129 (5.1%)	<0.001
Prior pacemaker implantation	171 (9.6%)	189 (7.4%)	0.011
Prior maze surgery	27 (1.5%)	45 (1.8%)	0.526
Prior defibrillator implantation	66 (3.7%)	260 (10.2%)	<0.001
Prior coronary intervention	113 (6.4%)	232 (9.1%)	<0.001
Prior coronary bypass surgery	140 (7.9%)	386 (15.2%)	<0.001
Anti-arrhythmic drugs			
Amiodarone	730 (41.1%)	1087 (42.8%)	0.267
Dronedarone	253 (14.3%)	314 (12.4%)	0.072
Dofetilide	206 (11.6%)	520 (20.5%)	<0.001
Flecainide or propafenone	405 (22.8%)	538 (21.2%)	0.204
Sotalol	641 (36.1%)	785 (30.9%)	<0.001
Anticoagulation			
Anticoagulation (any)	1362 (76.8%)	2092 (82.5%)	<0.001
Warfarin	1226 (69.1%)	1819 (71.7%)	0.066
Enoxaparin	83 (4.7%)	119 (4.7%)	0.985
Direct anticoagulation agents	353 (19.9%)	625 (24.6%)	<0.001

AF, atrial fibrillation.

the rate of anticoagulation by gender in patients aged <75 years, whereas in patients aged ≥75 years, women were significantly less likely than men to be on anticoagulation.

Table 2 summarizes the clinical outcomes of patients by gender. During follow-up, women had higher all-cause mortality rates (3.18 in women vs. 2.64 in men per 100 person-years,  $p = 0.037$ , Fig. 2A) and a strong trend toward a higher incidence of stroke (1.17 in women vs. 0.87 in men per 100 person-years,  $p = 0.057$ , Fig. 2B). There were no significant differences in AF recurrence or AF hospitalization rates between the two genders. Women had higher rates of atrioventricular nodal ablation and permanent pacemaker implantation than men, but had lower rates of electrical cardioversion, AF ablation, and maze surgery.

The HRs by gender for various clinical outcomes by unadjusted and adjusted Cox proportional-hazard models are displayed in Table 3. In the multivariate models, the differences in the risk of death and stroke seen in univariate analyses were no longer significant (HR = 0.94,  $p = 0.50$  for death; HR = 1.16,  $p = 0.37$  for stroke). However, the increased rates of atrioventricular nodal ablation and permanent pacemaker implantation in women were still present in the multivariate models (HR of 2.11 and 1.69,

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