Gender-related differences in presentation and treatment of patients with non-valvular atrial fibrillation: results from RAMSES study

Kapak hastalığı dışı atriyum fibrilasyonu olan hastaların başvuru anındaki durumları ve verilen tedavilerin cinsiyete göre farklılıkları: RAMSES çalışması bulguları

Volkan Doğan, M.D., Özcan Başaran, M.D., Osman Beton, M.D.,[#] Mehmet Tekinalp, M.D.,[*] Ahmet Çağrı Aykan, M.D.,[†] Ezgi Kalaycıoğlu, M.D.,[†] İsmail Bolat, M.D.,[‡] Onur Taşar, M.D.,[§] Özgen Şafak, M.D.,[||] Macit Kalçık, M.D.,[¶] Cevat Kırma, M.D.,[**] Murat Biteker, M.D.

Department of Cardiology, Muğla Sıtkı Koçman University Faculty of Medicine, Muğla, Turkey
[#]Department of Cardiology, Sivas Cumhuriyet University Faculty of Medicine, Sivas, Turkey
[*]Department of Cardiology, Kahramanmaraş Necip Fazıl State Hospital, Kahramanmaraş, Turkey
[†]Department of Cardiology, Trabzon Ahi Evren Chest Cardiovascular Surgery Training and Research Hospital, Trabzon, Turkey
[‡]Department of Cardiology, Fethiye State Hospital, Muğla, Turkey
[§]Department of Cardiology, Elazığ Training and Research Hospital, Elazığ, Turkey
[||]Department of Cardiology, Burdur State Hospital, Burdur, Turkey
[¶]Department of Cardiology, İskilip Atıf Hoca State Hospital, Çorum, Turkey
[**]Department of Cardiology, Kartal Koşuyolu Heart Training and Research Hospital, İstanbul, Turkey

ABSTRACT

Objective: Gender is an important feature in the management of atrial fibrillation (AF). This study investigated gender-related differences in patients with AF in Turkey.

Methods: As a part of RAMSES (ReAl-life Multicenter Survey Evaluating Stroke prevention strategies in Turkey, NCT02344901) study, information of the patients with AF who successively applied to the hospital was analyzed. This cross-sectional, multicenter, nationwide observational study enrolled 6264 non-valvular AF (NVAF) outpatients (55.9% women) from Turkey.

Results: Compared with men, women with NVAF were older (71 years [range: 65–78 years] *vs.* 70 years [range: 62–77 years]; p<0.001), had lower frequency of coronary artery disease (22.0% *vs.* 38.3%; p<0.001) and congestive heart failure (18.2% *vs.* 27.2%; p<0.001). Women had higher median CHA_2DS_2-VASc score (4 [range: 3–5] *vs.* 3 [range: 2–4]; p<0.001), but similar HAS-BLED score (2 [range: 1–2] *vs.* 2 [range: 1–2]; p=0.141) when compared with men. Anticoagulant therapy use was higher in women (74.5% *vs.* 69.9%; p<0.001). Analysis of anticoagulation therapy use revealed that 68.5% of men and 61.6% of women (p=0.204) who had low risk for stroke (CHA_2DS_2-VASc score: 0 [male], 1 [female]) received anticoagulation therapy, and 30.5% of the men. Meanwhile, 25.3% of the women (p<0.001) with high risk for stroke (CHA_2DS_2-VASc score: ≥1 [male], ≥2 [female]) had not received any anticogulant therapy.

Conclusion: Although women with NVAF receive better treatment than men, anticoagulation therapy is suboptimal in large proportion of men and women, with underuse in high-risk patients and overuse in low-risk patients. There is an urgent need to improve optimization of anticoagulation in patients with NVAF.

ÖZET

Amaç: Cinsiyet atriyum fibrilasyonu (AF) yönetimini etkileyen önemli bir özelliktir. Bu çalışmada, Türkiye'de AF'si olan hastalarda cinsiyet ile ilişkili farklar araştırıldı.

Yöntemler: RAMSES (ReAl-life Multicenter Survey Evaluating Stroke prevention strategies in Turkey, NCT02344901) çalışmasının bir parçası olarak, ardışık olarak hastaneye başvuran AF'li hastaların bilgileri incelendi. Bu kesitsel, çok merkezli, ülke çapında, gözlemsel çalışmaya Türkiye'den 6264 kapak dışı AF (KDAF) poliklinik hastası (%55.9'u kadın) alındı.

Bulgular: Kapak dışı AF'si olan kadınlar erkeklerle karşılaştırıldığında daha yaşlıydı (71 [dağılım: 65–78] ve 70 [dağılım: 62–77]; p<0.001); koroner arter hastalığı (%22.0 ve %38.3; p<0.001) ve kalp yetersizliği daha azdı (%18.2 ve %27.2; p<0.001). Kadınlarda ortanca CHA_2DS_2-VASc skorları daha fazlaydı (4 [dağılım: 3–5] ve 3 [dağılım: 2–4]; p<0.001), ancak HAS-BLED skorları erkeklerle kıyaslandığında benzerdi (2 [dağılım: 1–2] ve 2 [dağılım: 1–2]; p=0.141). Kadınlarda antikoagülan tedavi kullanımı daha fazlaydı (%74.5 ve %69.9; p<0.001). Antikoagülan kullanımı incelendiğinde, inme açısından düşük riskli olan (erkeklerde CHA_2DS_2-VASc 0 ve kadınlarda CHA_2DS_2-VASc skoru 1 olanlar) erkeklerin %68.5'i ve kadınların %61.6'si (p=0.204) antikoagülan tedavi alıyordu ve inme açısından yüksek riskli olan (CHA_2DS_2-VASc ≥1 [erkek], ≥2 [kadın]) erkeklerin %30.5'i kadınların %25.3'ü (p<0.001) herhangi bir antikoagülan tedavi almıyordu.

Sonuç: KDAF'si olan kadınlar erkeklerle karşılaştırıldığında iyi tedavi edilmesine rağmen, gerek yüksek riskli hastalarda az kullanımı gerekse düşük riskli hastalarda fazla kullanımı nedeniyle, antikoagülan tedavi erkeklerde de kadınlarda da büyük oranlarda uygun olan oranların altındadır. KDAF'si olan hastalarda antikoagülan tedavisi ivedilikle daha uygun hale getirilmelidir.

Received: July 02, 2016 *Accepted:* October 25, 2016

Correspondence: Dr. Volkan Doğan. Muğla Sıtkı Koçman Üniversitesi Tıp Fakültesi, Kardiyoloji Anabilim Dalı, Muğla, Turkey.
Tel: +90 252 - 212 75 28 e-mail: drvolkandogan@hotmail.com

Atrial fibrillation (AF) is the most common sustained cardiac rhythm disorder[1] and is associated with high risk of stroke, heart failure, impaired cognitive function, and poor quality of life.[2,3] Recent European and American guidelines recommend the CHA_2DS_2-VASc score (congestive heart failure, hypertension, age [>75 years], diabetes, stroke/transient ischemic attack, vascular disease, age [65–74 years], sex category [female]) for thromboembolic risk stratification of patients with non-valvular AF (NVAF), which includes female sex as a risk factor.[4,5] Women have a longer life expectancy than men; therefore, they constitute a larger proportion of the elderly population who are at risk of complications caused by AF.[6] Previous studies have revealed that among patients with AF, women tend to be at higher risk for stroke than men,[6,7] even after adjustment for baseline comorbid conditions and vitamin K antagonist (VKA) treatment.[8–10] However, they are under-represented in mixed-sex cardiovascular trials, resulting in a deficit of information on differences in treatment effect and in side-effect profiles.[11] In the Euro Heart survey report from 2007, Dagres et al. reported that compared with males, female patients were older, had a lower quality of life, and had more comorbidities, but prescription of oral anticoagulants (OAC) was identical in both genders.[12] In an analysis from the dataset of the Euro Observational Research Programme on Atrial Fibrillation (EORP-AF) pilot survey, Lip et al. examined sex-related differences in presentation, treatment, and outcome of contemporary patients with AF in Europe.[13]

Abbreviations:

AF	*Atrial fibrillation*
INR	*International normalized ratio*
ECG	*Electrocardiogram*
NOAC	*Non-VKA oral anticoagulants*
	Novel oral anticoagulant
OAC	*Oral anticoagulant*
NVAF	*Non-valvular atrial fibrillation*
TTR	*Time in therapeutic range*
VKA	*Vitamin K antagonist*

They found that female subjects were older and more symptomatic, had more heart failure with preserved ejection fraction, were offered less rhythm control, and OACs were used in a higher proportion (95.3% of females vs 76.2% of males).[13]

However, most data on epidemiology and management of AF come from Europe and the United States. In Turkey, there are no data available about gender-related differences in presentation, management, or outcomes among AF patients. In this analysis of the baseline dataset of the Real-life Multicenter Survey Evaluating Stroke Prevention Strategies in Turkey (RAMSES) study, sex-related differences in presentation and treatment of contemporary patients with NVAF in Turkey were examined.

METHODS

The RAMSES study was a cross-sectional, multicenter, nationwide observational study conducted with NVAF patients in Turkey (ClinicalTrials.gov identifier NCT02344901). Presently described is study of clinical data of the RAMSES study patients. Design and rationale of RAMSES trial have been described in detail elsewhere.[14] In brief, the RAMSES registry population comprised consecutive outpatients with NVAF presenting to cardiologists in participating Turkish cities, and all data were collected in a single visit. To ensure inclusion of adequate geographic diversity, number of patients proportionate to the total population of every region were enrolled. State, university, education and research, and private hospitals were included in order to represent all patients treated within different health care settings. The study was initiated in February 2015 and the last patient was enrolled in May 2015. Patients were officially enrolled in the RAMSES study only if an electrocardiogram (ECG) diagnosis (12-lead ECG, or other electrocardiographic documentation) confirming AF was made.

Although definition of NVAF is controversial, valvular AF is defined as AF related to rheumatic valvular disease (predominantly mitral stenosis), or prosthetic heart valve in the RAMSES study. The RAMSES trial excluded patients with mitral stenosis, or mechanical prosthetic heart valve. Patient characteristics and demographics, including geographical diversity, and OAC use (including non-VKA oral anticoagulants [NOACs] and VKAs) were recorded. Guideline-based use of anticoagulation in eligible patients and reasons for not using OAC therapy were analyzed. Primary aim of the RAMSES study was to evaluate appropriateness of stroke prevention strategies applied for patients with NVAF. Secondary goals were to find time in therapeutic range (TTR) for patients taking warfarin, CHA_2DS_2-VASc and HAS-BLED (hypertension, renal or liver failure, stroke history, bleeding history, labile international normalized ratio, age >65 years, drugs, or alcohol) scores, and evaluate relationship to OAC use. Demographic data, including age, sex, body weight, smoking status, comorbid diseases, lev-

el of education, place of residence (rural or urban), and type of AF were noted. Ongoing pharmacological treatment for stroke prevention (antiplatelet, anticoagulant, or none) and antiarrhythmic drug therapy use were also recorded. Patients with indication for OAC therapy of CHA_2DS_2-VASc score ≥1 for male patients and score of ≥2 for female patients were accepted. Hemorrhagic events related to current therapy, international normalized ratio (INR), and creatinine levels were noted. For patients taking VKA, TTR was calculated by traditional method: The ratio of in-range (2–3) INRs to all INRs of a patient. Renal function was estimated using creatinine clearance calculated using Cockroft-Gault formula. Inappropriate use of OACs were assessed according to current guidelines.

Major bleeding was defined according to International Society on Thrombosis and Haemostasis criteria:[15] Fatal bleeding and/or symptomatic bleeding in critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome, and/or bleeding causing a drop in hemoglobin level of 2 g/dL or more, or leading to transfusion of 2 or more units of whole blood or red cells. Minor bleeding is defined as non-major bleeding. The present study was approved by the local ethics committee.

Statistical analysis

Continuous variables were summarized as median with interquartile ranges, and categorical variables were expressed as frequencies and percentages. Mann-Whitney U test was used to compare continuous variables and chi-square test was applied for categorical variables. Normality of continuous variables was tested by Kolmogorov-Smirnov test. All analyses were performed using SPSS software, version 21.0 (IBM Corp., Armonk, NY, USA). P value of <0.05 was considered significant.

RESULTS

Study population A total of 6273 patients with NVAF were enrolled from 29 provinces and 57 hospitals of Turkey. After excluding 9 patients whose medical history could not be determined, data of 6264 patients were evaluated in the present study. Median age of the patients was 70 years (range: 63–77 years) and 3503 (55.9%) were women. Nearly half of the patients (45.1%) were recruited in tertiary hospitals, 43.6% were recruited in state hospitals, and 11.3% were recruited in private hospitals. Most common comorbid condition was hypertension (68.7%), and one-fifth of the patients had at least 1 comorbid disease. Median CHA_2DS_2-VASc score was 3 (range: 2–4) and HAS-BLED score was 2 [range: 1–2]. Overall OAC use was 58.3% (30.9% NOAC, 27.4% VKA), while 18.7% of the patients were prescribed only antiplatelet drugs without any OAC therapy.

Comparison of baseline characteristics in men and women

Baseline characteristics of the cohort according to sex are shown in Table 1. Compared with men, women with NVAF were older (71 years [range: 65–78 years] vs 70 years [range: 62–77 years]; p<0.001), with 39% of all women with NVAF being older than 75 years of age vs 32.5% of all men. There were significant differences between sexes in clinical characteristics; compared with men, women had worse renal function (median estimated glomerular filtration rate: 66.6 mL/dk/1.73 m^2 [range: 51.0–85.1 mL/dk/1.73 m^2] vs 75.5 mL/dk/1.73 m^2 [range: 59.1–95.8 mL/dk/1.73 m^2]; p<0.001) but had lower frequency of coronary artery disease (22.0% vs 38.3%; p<0.001) and congestive heart failure (18.2% vs 27.2%; p<0.001). Women had higher median CHA_2DS_2-VASc score (4 [range: 3–5] vs 3 [range: 2–4], respectively; p<0.001), but similar HAS-BLED score (2 [range: 1–2] vs 2 [range: 1–2], respectively; p=0.141) compared with men.

Distribution of AF type was different between women and men; women had significantly higher prevalence of persistent/permanent AF (83.4% vs 79.2%; p<0.001) and lower prevalence of paroxysmal or first diagnosis of AF. History of prior stroke or history of any bleeding was not significantly different between males and females (p=0.683, p= 0.258, respectively). No significant difference was found between men and women in TTR value (median 50 [range: 34–71] vs 52 [range: 36–71], respectively; p=0.44).

Antithrombotic and antiarrhythmic therapy use in men and women

Medications prescribed according to gender are presented in Table 2. Women were less likely to be taking a beta-blocker (61.2% vs 66.2%; p<0.001), amiodarone (4.2% vs 5.6%; p=0.014), or digoxin (19.2% vs 21.%; p=0.019) compared to men, whereas men were

Table 1. Baseline characteristics of men and women with non-valvular atrial fibrillation

Variable	Men (n=2761)	Women (n=3503)	*p*
Age, years	70 [62–77]	71 [65–78]	<0.001
<65	884 (31.9)	873 (24.9)	
65–75	986 (35.6)	1279 (36.5)	<0.001
>75	899 (32.5)	1351 (38.6)	
Type of atrial fibrillation			
First diagnosis	167 (6.1)	123 (3.5)	
Paroxysmal atrial fibrillation	402 (14.7)	456 (13.1)	<0.001
Persistent or permanent atrial fibrillation	2165 (79.2)	2901 (83.4)	
Current/previous smoker	796 (28.8)	227 (6.5)	<0.001
Alcohol consumption	116 (4.2)	31 (0.9)	<0.001
Glomerular filtration rate (mL/dk/1.73 m^2)	75.5 [59.1–95.8]	66.6 [51.0–85.1]	<0.001
History of any bleeding	596 (21.5)	796 (22.7)	0.258
History of major bleeding	198 (7.2)	207 (5.9)	0.049
History of minor bleeding	432 (15.9)	620 (17.9)	0.035
Chronic renal disease	656 (25.3)	1270 (38.4)	<0.001
Congestive heart failure	751 (27.2)	635 (18.2)	<0.001
Coronary artery disease	1060 (38.3)	768 (22.0)	<0.001
Vascular disease	871 (31.6)	635 (18.2)	<0.001
Diabetes mellitus	583 (21.1)	805 (23.0)	0.071
History of hypertension	1790 (64.7)	2514 (71.9)	<0.001
Stroke or transient ischemic attack	371 (13.4)	482 (13.8)	0.683
CHA_2DS_2-VASc	3 [2–4]	4 [3–5]	<0.001
HAS-BLED	2 [1–2]	2 [1–2]	0.141
Time in therapeutic range (%)	50 [34–71]	52 [36–71]	0.448

CHA_2DS_2VASc: Congestive heart failure or left ventricular dysfunction, hypertension, age ≥75 years, diabetes, thromboembolism or stroke history, vascular disease, age 65–74 years, and sex; GFR: Glomerular filtration rate; HAS-BLED: Hypertension, renal or liver failure, stroke history, bleeding history, labile international normalized ratio, age >65 years, drugs, or alcohol; IQR: Interquartile range; TTR: Time in therapeutic range. Values are given as median [IQR] or number (percentage) unless otherwise indicated.

prescribed calcium channel blocker drugs less often than women (20% vs 26.6%; p<0.001). Antithrombotic therapy use was also different in men and women:

- Anticoagulant therapy was prescribed for 74.5% of female patients. Of these, 34.7% were prescribed VKA. Remaining 39.8% were prescribed NOAC; 19.1% received dabigatran, 20.7% received Factor Xa inhibitor.
- Anticoagulant therapy was prescribed for 69.9% of male patients. Of these, 35.2% were prescribed VKA. Remaining 34.7% were prescribed NOAC; 17.6% received dabigatran, 17.1% received Factor Xa inhibitor.
- Warfarin (34.7% vs 35.2%; p=0.668) and dabigatran (19.1% vs 17.6%; p=0.13) use was similar between women and men. Rivaroxaban use was higher in women compared to men (16.8% vs 12.9%; p<0.001).
- Antiplatelet drugs, including aspirin, adenosine diphosphate receptor inhibitors, and P2Y12 inhibitors were less frequently prescribed for women (27.9% vs 37.8%; p<0.001).
- Twenty-one percent of men and 17.5% of women received an antiplatelet alone, and 9.3% of men and 8.2% of women received no antithrombotic therapy.

Table 2. Use of antithrombotic drugs at diagnosis in men and women with non-valvular atrial fibrillation

Variable	Men (n=2761)		Women (n=3503)		*p*
	n	%	n	%	
Antiplatelet	1040	37.8	970	27.9	<0.001
Aspirin	809	29.4	815	23.4	<0.001
Adenosine diphosphate receptor or P2Y12 inhibitor	231	8.4	155	4.5	<0.001
Anticoagulant	1930	69.9	2610	74.5	<0.001
Vitamin K antagonist	968	35.2	1205	34.7	0.662
Factor Xa inhibitor	470	17.1	721	20.7	<0.001
Direct thrombin inhibitor	484	17.6	664	19.1	0.129
Antiarrhythmic drugs					
Beta-blocker	1809	66.2	2121	61.2	<0.001
Calcium channel blocker	546	20.0	920	26.6	<0.001
Sotalol	24	0.9	32	0.9	0.856
Amiodarone	152	5.6	146	4.2	0.014
Digoxin	525	19.2	749	21.6	0.019
Propafenone	79	2.9	99	2.9	0.939

Antithrombotic therapy use in men and women according to stroke risk scores

Overtreatment.

When analyzed according to level of stroke risk, 161 of women (4.6%) and 203 of men (7.3%) had a low risk for stroke (CHA_2DS_2-VASc score: 0 [male], 1 [female]). Of these patients who had a low risk for stroke, 68.5% of the men and 61.6% of the women received some form of anticoagulant therapy (p=0.204) (Figure 1).

Undertreatment.

3296 women (95.4%) and 1797 men (92.7%) had high risk for stroke (CHA_2DS_2-VASc score: ≥1 [male], ≥2 [female]). Of patients with high risk for stroke, 30.5% of men, and 25.3% of women did not receive any anticogulant therapy (p<0.001).

Antithrombotic therapy use in men and women according to bleeding risk score

Use of antithrombotic drugs according to bleeding risk stratum is shown in Figure 2. Patterns of anti-

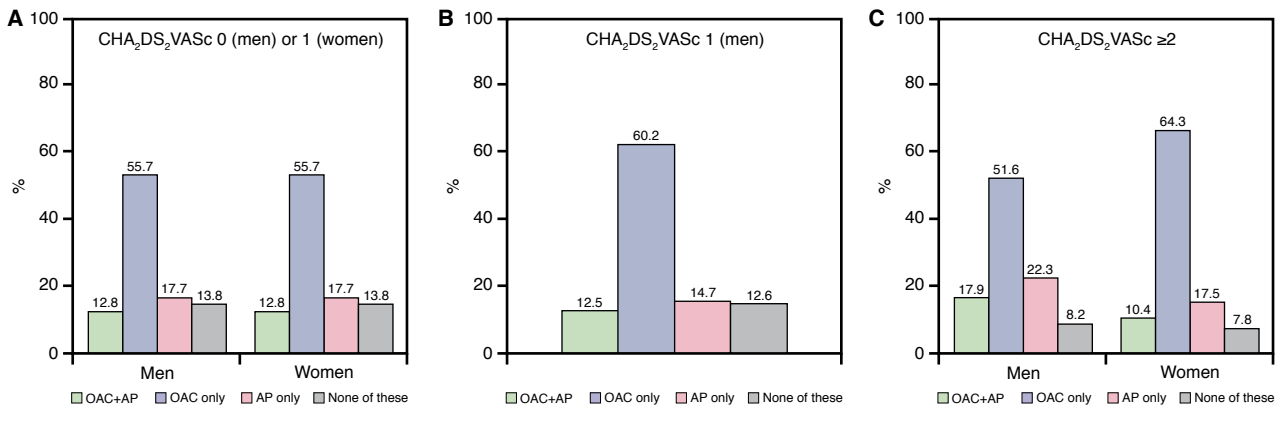

Figure 1. (A-C) Antithrombotic use for stroke prevention according to CHA_2DS_2-VASc score. AP: Antiplatelet; NOAC: Non-vitamin K antagonist oral anticoagulant; OAC: Oral anticoagulant; VKA: Vitamin K antagonist.

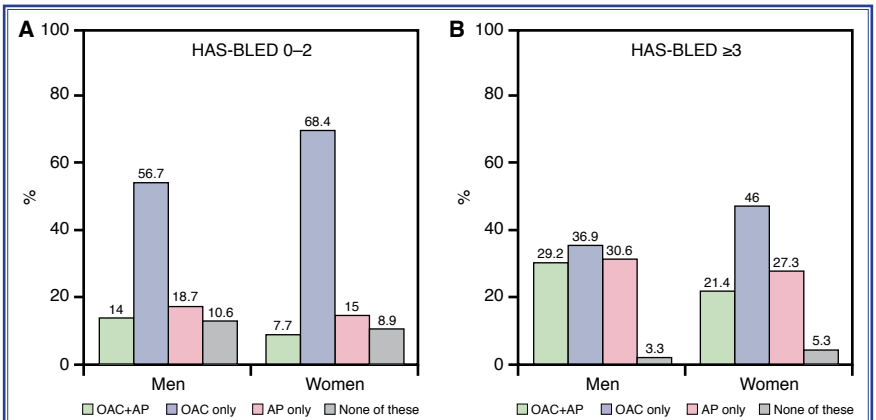

Figure 2. (A, B) Antithrombotic use according to HAS-BLED score. AP: Antiplatelet; NOAC: Non-vitamin K antagonist oral anticoagulant; OAC: Oral anticoagulant; VKA: Vitamin K antagonist.

thrombotic use were analyzed for men and women, in both low-risk (HAS-BLED score: 0–2) and high-risk (HAS-BLED score: ≥3) groups.

Overall rate of use of anticoagulants was higher in patients at low risk of bleeding (70.7% of men and 76.1% of women; p<0.001) when compared with those at high risk (66.1% of men and 67.4% of women; p=0.612).

Both men and women at high risk of bleeding were more likely than those at low risk to receive combination antithrombotic therapy or antiplatelet therapy alone.

Main reasons for undertreatment in patients for whom anticoagulation is indicated

Primary reason for not giving anticoagulant to patients at moderate to high risk of stroke (CHA_2DS_2-VASc score: ≥1 [male], ≥2 [female]) was concern over patient compliance (31.4% in men, 40.2% in women) (Table 3). Other reasons given by cardiologists for not prescribing anticoagulant drugs to these patients were first AF episode in 6 female patients (0.7%) and 5 male (1.0%); patient preference in 83 females (10.0%) and 61 males (11.2%), history of bleeding in 10 female (1.2%) and 9 male (1.6%), high risk of fall in 38 female (4.6%) and 41males (7.4%), and physician neglect in 3 female (0.4%) and 1 male (0.2%) patients (Table 3).

DISCUSSION

In this nationwide analysis, sex differences in clinical features and management of NVAF patients as managed by Turkish cardiologists participating in the RAMSES registry are reported.

Table 3. Principal reasons for not treating patients for whom anticoagulation is indicated

Reason	Men (n=548)		Women (n=834)	
	n	%	n	%
Concern about patient compliance	172	31.4	335	40.2
Other unknown	135	24.6	178	21.3
Neuropsychological reasons	112	20.4	158	18.9
Patient choice	61	11.2	83	10.0
Fall risk	41	7.4	38	4.6
Bleeding risk	9	1.6	10	1.2
Newly diagnosed atrial fibrillation	5	1.0	6	0.7
Physician neglect	1	0.2	3	0.4

Our results indicate that women with NVAF were older, had more comorbid diseases, and were at higher stroke risk overall (although prior stroke history was similar to that of men). Compared with men, OAC therapy use was higher in women. Quality of anticoagulation, as measured by TTR for patients receiving warfarin therapy, was similar for men and women. Although overtreatment rates were similar, undertreatment rates were lower in women compared with men.

AF is the most common arrhythmia, worldwide. Although estimated prevalence is lower in women (373 per 100,000) than in men (596 per 100,000),[16] true prevalence is likely to be substantially higher, especially in women, given that many individuals remain undiagnosed. In North American and European populations, age-adjusted incidence of AF has been estimated to be 2-fold higher in men than in women. A Minnesota study reported AF incidence (per 1,000 person-years) in women to be 2.7, compared with 4.7 in men.[17] Similar to incidence, age-adjusted prevalence of AF has been reported to be lower in women. A large, retrospective study of older adult (aged ≥65 years) US Medicare recipients reported prevalence of AF to be 7.4% in women and 10.3% in men.[18] However, prevalence studies of Asian populations have been less consistent than those of North American and European poulations. Li et al. reported that age-adjusted prevalence of AF was similar in women and men in Chinese population.[19] Moreover, in North American populations, despite higher incidence of AF in men, lifetime risks of AF in women and men were similar, due to longer life expectancy for women.[20] Our study demonstrated that 55.9% of NVAF patients were female. In Turkey, we do not have sufficiently broad studies to ascertain prevalence rates of AF in the population. Only a small number of studies have been performed and published within the past few years, and most of them have retrospective or observational design.[21–25] The Atrial Fibrillation in Turkey: Epidemiologic Registry (AFTER) study was the largest of these studies, which enrolled 2242 consecutive patients with AF.[25]

Similar to our findings, the AFTER study showed that female patients made up 60% of study population. The RAMSES and AFTER studies enrolled more female patients than male patients, unlike most other studies, which primarily enrolled male patients. This may be due to higher incidence of AF in Turkish female patients.[24] Our study also indicated that female patients were older and more frequently had hypertension, chronic renal disease, and diabetes. However, male patients more frequently had coronary artery disease and congestive heart failure. These findings are consistent with previous reports.[26,27] As expected, women in our study had higher CHA_2DS_2-VASc score, given the nature of this score and older age of the women. Although women with AF have more symptoms than men, and female gender is a well-recognized, independent risk factor for AF-related stroke and systemic thromboembolism,[28] previous studies have demonstrated that treatment is more conservative in women, with significantly less utilization of rhythm-control strategies, electrocardioversion, beta-blockers and OACs.[29] The Canadian Registry of Atrial Fibrillation (CARAF) study found that women were half as likely to receive warfarin and twice as likely to receive aspirin, compared with men.[30] However, contemporary global data indicate that anticoagulant use for stroke prevention is no different in men and women with NVAF, but remains suboptimal in both sexes.[31] There are no specially designed studies regarding appropriateness and guideline adherence of anticoagulant therapy in Turkey, either in general or for individual sex. The RAMSES study has documented greater use of anticoagulant in women with NVAF in Turkey (74.5% of female patients, 69.9% of male patients were prescribed OACs). However, present study has also shown that anticoagulant drugs were underprescribed in high-risk patients and overprescribed in low-risk patients in both sexes. In contrast to literature data, our study results indicated that women with NVAF tend to have lower rates of undertreatment compared with men. Although not statistically significant, overtreatment rates were also lower for female patients with NVAF than for men.

These results indicate that suboptimal thromboprophylaxis with underuse in moderate-to high-risk patients, and overuse in low-risk patients despite recent introduction of NOACs, are of concern and indicate need for improved stroke prevention in cases of AF.

When women are prescribed systemic anticoagulation, differences may also exist in terms of quality of anticoagulation. According to the Atrial Fibrillation Follow-up Investigation of Rhythm Management

(AFFIRM) study, women with AF on warfarin spent less time in TTR than men.[32] However, TTR values of females were not different from those of males, which indicates similar quality of anticoagulation in warfarin prescribed to women.

In our cohort, women were more likely to be prescribed a NOAC. Recent studies demonstrate that women may have improved outcomes with NOAC compared to warfarin therapy.[33] A recent meta-analysis that included 5 randomized control trials with gender data on warfarin and on NOACs, found improved reduction in rate of ischemic stroke and reduced major bleeding with NOACs compared with warfarin therapy in women.[33] However, prospective real-world studies evaluating impact of NOACs in reducing stroke risk in women are needed.

Although pharmacotherapy of AF has improved over time, guidelines are different regarding management of AF in women and men. The 2012 European Society of Cardiology guidelines recommend OAC therapy for male patients with CHA_2DS_2-VASc score of ≥1 and for female patients with a score of ≥2,[4] whereas the 2014 American Heart Association/American College of Cardiology/Heart Rhythm Society guidelines recommend use of OAC at CHA_2DS_2-VASc score ≥2 for patients of both sexes.[5] Further sudies are needed to determine significance of gender differences in the management of AF in our country.

Limitations

The present study is a post-hoc analysis, and therefore is not designed to determine gender differences in outcome. However, it provides useful, real-life data regarding NVAF patients seen in daily clinical practice. Study was conducted in outpatient cardiology clinics, and this may have limited coverage of all NVAF patients; however, participating institutions were geographically widely distributed across Turkey, both smaller and major cities of Turkey were represented, according to population.

Conclusion

To the best of our knowledge, our study cohort represents by far the largest number of patients with AF in Turkey. The present study provides contemporary data on sex differences in clinical features and management of AF patients who participated in the RAMSES study. Female subjects were older and had higher risk for stroke compared with males. Compared with men, women with NVAF had higher prescription of OACs, had similar quality of anticoagulation, and had lower over- and undertreatment rates. However, analysis of anticoagulation therapy showed that 61.6% of women with CHA_2DS_2-VASc score of 1 and 68.5% of men with CHA_2DS_2-VASc score of 0 received anticoagulation therapy, which is not indicated in such patients, according to the guidelines. Moreover, although clearly indicated, 30.5% of men, and 25.3% of women with high risk for stroke (CHA_2DS_2-VASc score: ≥1 [male], ≥2 [female]) had not received any anticogulant therapy. Our data suggest that women with NVAF are receiving better treatment than men, but adherence to anticoagulation guidelines is poor in practice and may be modestly improved with NOACs. Therefore, it seems essential to design and conduct longitudinal studies evaluating prevalance, management, and prognosis of AF in both sexes throughout the country.

Conflict-of-interest issues regarding the authorship or article: None declared

REFERENCES

1. Inoue H, Fujiki A, Origasa H, Ogawa S, Okumura K, Kubota I, et al. Prevalence of atrial fibrillation in the general population of Japan: an analysis based on periodic health examination. Int J Cardiol 2009;137:102–7. Crossref
2. Flegel KM, Shipley MJ, Rose G. Risk of stroke in non-rheumatic atrial fibrillation. Lancet 1987;1:526–9. Crossref
3. Dries DL, Exner DV, Gersh BJ, Domanski MJ, Waclawiw MA, Stevenson LW. Atrial fibrillation is associated with an increased risk for mortality and heart failure progression in patients with asymptomatic and symptomatic left ventricular systolic dysfunction: a retrospective analysis of the SOLVD trials. Studies of Left Ventricular Dysfunction. J Am Coll Cardiol 1998;32:695–703. Crossref
4. Camm AJ, Lip GY, De Caterina R, Savelieva I, Atar D, Hohnloser SH, et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. Eur Heart J 2012;33:2719–47. Crossref
5. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC Jr, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. Circulation 2014;130:199–267. Crossref

6. Volgman AS, Manankil MF, Mookherjee D, Trohman RG. Women with atrial fibrillation: Greater risk, less attention. Gend Med 2009;6:419–32. Crossref
7. Cove CL, Albert CM, Andreotti F, Badimon L, Van Gelder IC, Hylek EM. Female sex as an independent risk factor for stroke in atrial fibrillation: possible mechanisms. Thromb Haemost 2014;111:385–91. Crossref
8. Avgil Tsadok M, Jackevicius CA, Rahme E, Humphries KH, Behlouli H, Pilote L. Sex differences in stroke risk among older patients with recently diagnosed atrial fibrillation. JAMA 2012;307:1952–8. Crossref
9. Gomberg-Maitland M, Wenger NK, Feyzi J, Lengyel M, Volgman AS, Petersen P, et al. Anticoagulation in women with non-valvular atrial fibrillation in the stroke prevention using an oral thrombin inhibitor (SPORTIF) trials. Eur Heart J 2006;27:1947–53. Crossref
10. Mosca L, Barrett-Connor E, Wenger NK. Sex/gender differences in cardiovascular disease prevention: what a difference a decade makes. Circulation 2011;124:2145–54. Crossref
11. Kim ES, Menon V. Status of women in cardiovascular clinical trials. Arterioscler Thromb Vasc Biol 2009;29:279–83. Crossref
12. Dagres N, Nieuwlaat R, Vardas PE, Andresen D, Levy S, Cobbe S, et al. Genderrelated differences in presentation, treatment, and outcome of patients with atrial fibrillation in Europe: a report from the Euro Heart Survey on Atrial Fibrillation. J Am Coll Cardiol 2007;49:572–7. Crossref
13. Lip GY, Laroche C, Boriani G, Cimaglia P, Dan GA, Santini M, et al. Sex-related differences in presentation, treatment, and outcome of patients with atrial fibrillation in Europe: a report from the Euro Observational Research Programme Pilot survey on Atrial Fibrillation. Europace 2015;17:24–31. Crossref
14. Başaran Ö, Doğan V, Memic Sancar K, Altun İ, Mert KU, Mert GÖ, et al. Rationale, design and methodology of the RAMSES Study: ReAl-life Multicenter Survey Evaluating Stroke Prevention Strategies. Turk Kardiyol Dern Ars 2016;44:215–20. Crossref
15. Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost 2005;3:692–4.
16. Chugh SS, Havmoeller R, Narayanan K, Singh D, Rienstra M, Benjamin EJ, et al. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. Circulation 2014;129:837–47. Crossref
17. Miyasaka Y, Barnes ME, Gersh BJ, Cha SS, Bailey KR, Abhayaratna WP, et al. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. Circulation 2006;114:119–25. Crossref
18. Piccini JP, Hammill BG, Sinner MF, Jensen PN, Hernandez AF, Heckbert SR, et al. Incidence and prevalence of atrial fibrillation and associated mortality among Medicare beneficiaries, 1993-2007. Circ Cardiovasc Qual Outcomes 2012;5:85–93. Crossref
19. Li Y, Wu YF, Chen KP, Li X, Zhang X, Xie GQ, Wang FZ, et al. Prevalence of atrial fibrillation in China and its risk factors. Biomed Environ Sci 2013;26:709–16.
20. Lloyd-Jones DM, Wang TJ, Leip EP, Larson MG, Levy D, Vasan RS, et al. Lifetime risk for development of atrial fibrillation: the Framingham Heart Study. Circulation 2004;110:1042–6. Crossref
21. Biteker M, Başaran Ö, Doğan V. Prediction of atrial fibrillation risk in the community. Int J Cardiol 2016. Crossref
22. Basaran O, Filiz Basaran N, Cekic EG, Altun I, Dogan V, Mert GO, et al. PRescriptiOn PattERns of Oral Anticoagulants in Nonvalvular Atrial Fibrillation (PROPER study). Clin Appl Thromb Hemost 2015. Crossref
23. Başaran Ö, Beton O, Doğan V, Tekinalp M, Aykan AÇ, Kalaycıoğlu E, et al. ReAl-life Multicenter Survey Evaluating Stroke prevention strategies in non-valvular atrial fibrillation (RAMSES study). Anatol J Cardiol 2016;16:734–41. Crossref
24. Uyarel H, Onat A, Yüksel H, Can G, Ordu S, Dursunoğlu D. Incidence, prevalence, and mortality estimates for chronic atrial fibrillation in Turkish adults. Turk Kardiyol Dern Ars 2008;36:214–22.
25. Ertaş F, Kaya H, Kaya Z, Bulur S, Köse N, Gül M, et al. Epidemiology of atrial fibrillation in Turkey: preliminary results of the multicenter AFTER study. Turk Kardiyol Dern Ars 2013;41:99–104. Crossref
26. Ko D, Rahman F, Schnabel RB, Yin X, Benjamin EJ, Christophersen IE. Atrial fibrillation in women: epidemiology, pathophysiology, presentation, and prognosis. Nat Rev Cardiol 2016;13:321–32. Crossref
27. Volgman AS, Manankil MF, Mookherjee D, Trohman RG. Women with atrial fibrillation: Greater risk, less attention. Gend Med 2009;6:419–32. Crossref
28. Emdin CA, Wong CX, Hsiao AJ, Altman DG, Peters SA, Woodward M, et al. Atrial fibrillation as risk factor for cardiovascular disease and death in women compared with men: systematic review and meta-analysis of cohort studies. BMJ 2016;532:h7013. Crossref
29. Karatza AA, Tzavara M, Filias A, Krokidas G, Dimitriou G. Response to the article: Late onset of coronary vasospasm after administration of methyl-ergometrine for gynecologic bleeding [Santoro F, Spennati G, Ieva R, De Gennaro L, Correale M, Lopizzo A, Di Biase M, Brunetti ND. Int J Cardiol 2012;161:e29–e30]. Int J Cardiol 2013;168:5467–8. Crossref
30. Humphries KH, Kerr CR, Connolly SJ, Klein G, Boone JA, Green M, et al. New-onset atrial fibrillation: sex differences in presentation, treatment, and outcome. Circulation 2001;103:2365–70. Crossref
31. Lip GY, Rushton-Smith SK, Goldhaber SZ, Fitzmaurice DA, Mantovani LG, Goto S, et al. Does sex affect anticoagulant use for stroke prevention in nonvalvular atrial fibrillation? The prospective global anticoagulant registry in the FIELD-Atrial Fibrillation. Circ Cardiovasc Qual Outcomes 2015;8(2 Suppl 1):12–20. Crossref

32. Sullivan RM, Zhang J, Zamba G, Lip GY, Olshansky B. Relation of gender-specific risk of ischemic stroke in patients with atrial fibrillation to differences in warfarin anticoagulation control (from AFFIRM). Am J Cardiol 2012;110:1799–802.
33. Pancholy SB, Sharma PS, Pancholy DS, Patel TM, Callans DJ, Marchlinski FE. Meta-analysis of gender differences in residual stroke risk and major bleeding in patients with non-valvular atrial fibrillation treated with oral anticoagulants. Am J Cardiol 2014;113:485–90. Crossref

Keywords: Gender; non-valvular atrial fibrillation; oral anticoagulan therapy.

Anahtar sözcükler: Cinsiyet; non-valvular atriyal fibrilasyon; oral antikoagülan tedavi.