

Epidemiology, diagnosis, and management of atrial fibrillation in women

Daniela Poli¹
Emilia Antonucci²

¹Thrombosis Centre, Department of Heart and Vessels, Azienda Ospedaliero-Universitaria Careggi, Florence, Italy; ²Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy

Abstract: Atrial fibrillation (AF) is the most common arrhythmia and has become a serious public health problem. Moreover, epidemiological data demonstrate that incidence and prevalence of AF are increasing. Several differences in epidemiological patterns, clinical manifestations, and incidence of stroke have been reported between AF in women and in men, particularly in elderly women. Elderly women have higher blood pressure than men and a higher prevalence of heart failure with preserved ejection fraction, both independent risk factors for stroke. On the basis of the evidence on the higher stroke risk among AF in women, recently, female sex has been accepted as a risk factor for stroke and adopted to stratify patients, especially if they are not at high risk for stroke. This review focuses on available evidence on sex differences in AF patients, and examines factors contributing to different stroke risk, diagnosis, and prognosis of arrhythmia in women, with the aim to provide an analysis of the available evidence.

Keywords: anticoagulants, bleeding, hypertension, stroke

Introduction

Atrial fibrillation (AF) is the most common arrhythmia and has become a serious public health problem and an important cause of health care expenditure in developed countries. Moreover, epidemiological data demonstrate that incidence and prevalence of AF are increasing.^{1,2} This arrhythmia significantly influences quality of life and leads to high risk of hospitalization, absence from work, and increased mortality. In particular, AF confers a fivefold risk of stroke, with serious disability and higher rate of recurrence than other causes of stroke.¹

Several differences in epidemiological patterns, clinical manifestations, and incidence of stroke have been reported between AF in women and in men. This review focuses on available evidence on sex differences in AF patients, and examines factors contributing to different stroke risk, diagnosis, and prognosis of the arrhythmia in women, with the aim to provide an analysis of the available evidence.

Epidemiology and prognosis

The incidence of AF is increasing worldwide, with an estimated number of new cases per year of 2.7 million (95% confidence interval [CI] 2.3 million to 3.3 million) for men and 2.0 million (95% CI 1.7 million to 2.6 million) for women.³ In Europe, more than six million patients suffer from AF¹ and it has been estimated that in the United States in the next 30 years the number of AF patients will reach 16 million.² Sex differences in epidemiology and prognosis of AF have been outlined by several studies.³⁻⁵ The Global Burden of Disease Study³ estimated in 2010 a prevalence of AF of 373.1/100,000 for women and 596.2/100,000 for men. The highest incidences and prevalences of the disease are registered in developed countries, as opposed to

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Correspondence: Daniela Poli
Centro Trombosi, Viale Morgagni,
85-50134 Firenze, Italy
Tel +39 055 794 5453
Fax +39 055 794 6218
Email polida@aou-careggi.toscana.it



in developing countries where incidence and prevalence are lower.³ In particular, in the sub-Saharan region and Asia-Pacific region, the incidence rates are the lowest, with similar rates between sexes. Recently, Marcus et al⁶ reported that persons of European ancestry have an increased predisposition to AF. The higher prevalence of AF in developed countries is probably due to older mean age of the population and to better surveillance. The prevalence of AF increases with age, and it is present in 0.12%–0.16% of subjects younger than 49 years, 3.7%–4.2% of those aged 60–70 years, and 10%–17% of those aged >80 years.⁷ Despite the higher incidence of AF in men, the prevalence of the disease among women increases among elderly. As a matter of fact, the number of women is higher in aged populations as a consequence of their longer lifespan, and the absolute number of AF in women and men is estimated to be similar.^{1,8}

Women suffering from AF show a different prognosis, with a higher incidence of stroke and a higher mortality rate with respect to men.^{3,4,9} The Framingham Heart Study found that patients with AF showed a risk-factor-adjusted odds ratio (OR) for death of 1.5 in men and 1.9 in women.⁴ These data have been confirmed by the Global Burden of Disease Study.³ Higher mortality is mainly due to heart failure and stroke. Heart failure, and in particular new-onset AF in heart failure, is associated with poor prognosis,^{10,11} and patients with heart failure with preserved ejection fraction (EF) are mainly women.¹² Conversely, “lone” AF that is not associated with other comorbidities and is present in younger subjects with otherwise normal cardiac function and no structural cardiac disease, seems not to be related to increased mortality.¹³

Clinical presentation and diagnosis

AF is a supraventricular arrhythmia that is usually associated with an irregular pulse, and this sign at physical examination of patients should always raise the suspicion of AF. To definitely diagnose AF, it is necessary to perform a surface electrocardiogram (ECG) recording, where the characteristic findings are irregular R-R intervals without distinct P waves for at least 30 seconds on a rhythm strip.¹ ECG recording is needed to differentiate AF from other rare supraventricular rhythms with irregular RR intervals, or the common occurrence of ventricular extrasystoles. The risk of AF-related complications is not different between short AF episodes and sustained forms of the arrhythmia.¹⁴ It is not rare that AF is first detected after an ischemic stroke or transient ischemic attack, because of the high frequency of asymptomatic or paucisymptomatic episodes, which are often self-terminating.

The diagnostic work-up of a patient suffering from cerebral ischemia always requires ECG for AF detection. The measurement of peripheral pulse is recommended by international guidelines as the first approach to symptomatic patients.¹ Moreover, the systematic pulse screening should be performed at each medical visit, in particular for patients of both sexes aged >65 years. The use of ECG Holter (24 hours to 7 days) monitoring or of external loop recorder will further increase AF detection rate, but should be limited to patients with sinus rhythm at baseline ECG.¹⁵ Recent data outlined the higher efficacy of ECG monitoring by means of insertable cardiac monitors in the detection of AF in highly selected patients with cryptogenetic stroke.¹⁶

The time of onset of the arrhythmia episode should be established to define the type of AF (Table 1). Epidemiological studies have shown that AF usually begins with the paroxysmal form and evolves into the permanent form in 18%–25% of cases after 5 years.⁷ The variables independently related to progression to permanent AF are age, an enlarged left atrium, lack of antiarrhythmic drugs, VVI pacing, and the presence of valvular heart disease, heart failure, hypertension, or chronic obstructive pulmonary disease.⁷ Conversely, no difference between sexes have been found for the progression of AF from paroxysmal to permanent chronic form. Heart failure symptoms such as dyspnoea, chest pain, and fatigue are similarly reported in women and men. However, women report palpitations and fear or anxiety more frequently than men.¹⁷ Women had longer and more symptomatic episodes of AF, with more frequent recurrence of paroxysmal episodes.¹⁸ These features are associated with a lower quality of life with AF in women compared to men.¹⁹

Table 1 Types of AF

Type of AF	Description
First diagnosed	Every patient who presents with AF for the first time
Paroxysmal	Self-terminating events, usually within 48 h
Persistent	AF episode either lasts longer than 7 days or requires termination by cardioversion
Long-standing persistent	AF episode has lasted for ≥ 1 year
Permanent	When the presence of AF is accepted by the patient and physician
Silent	Asymptomatic, detected after an AF-related complication (ischemic stroke or tachycardiomyopathy) or by an opportunistic ECG Any of the temporal forms of AF can be silent

Note: Data from Camm et al.¹

Abbreviations: AF, atrial fibrillation; ECG, electrocardiogram.

Patients with AF and signs of heart failure require echocardiogram to evaluate valvular function, left ventricle EF, and right ventricular pressure, and to detect atrial disease or rare congenital heart disease. Patients with persistent signs of left ventricular dysfunction and/or signs of myocardial ischemia must undergo diagnostic work-up aimed to identify underlining coronary artery disease.

Heart failure patients are affected by AF in 30%–40% of cases and about one-third of AF patients show moderate to severe heart failure (New York Heart Association [NYHA] classes II–IV).²⁰ AF can cause a fast ventricular rate inducing left ventricular dysfunction and, on the other hand, heart failure can precipitate AF determining increased atrial pressure and volume overload.²⁰

Risk of stroke among AF in women

A higher incidence of stroke in AF women has been reported by several authors.^{21–37} However, conflicting evidences are available and if some studies found an increased risk in females, others were unable to confirm this finding at multivariate analysis.^{21,22,28,30} Therefore, the Stroke Risk in AF Working Group in 2007 did not include female sex as one of the independent risk factors for stroke.³⁶ A higher stroke risk among women was reported in a meta-analysis conducted by Madias and Trohman³⁸ and, more recently, in a meta-analysis carried out by Wagstaff et al.⁹ The meta-analysis of Wagstaff et al⁹ included 17 studies, five randomized-controlled trials, and 12 observational studies on anticoagulated and

non-anticoagulated AF patients. Ten studies reported female sex as an independent risk factor for stroke, three studies reported only univariate analysis, and four studies showed equivocal results (Table 2). Three large population studies^{27,35,36} that enrolled about 200,000 persons overall reported age-stratified risk for stroke. These studies found that female sex is significantly associated with stroke only among women aged ≥ 75 years. Stroke rates in patients aged < 65 years and without other associated risk factors are low both in males and females. The meta-analysis found that women carry a risk ratio of 1.31 (95% CI 1.18–1.46) for stroke and the risk appears greater for women ≥ 75 years. Even if a considerable heterogeneity was found between included studies, these data clearly confirm the higher incidence of stroke among women with AF. More recently, a nationwide, retrospective cohort study confirmed the higher incidence of stroke in elderly women with AF;³⁹ however, data from the Japanese RHYTHM Registry did not confirm the higher stroke risk in Japanese females.⁴⁰

Stroke risk stratification models and female sex

The recognition of various stroke risk factors in AF has enabled the formulation of several stroke risk stratification models to identify patients who benefit from anticoagulation and those for whom the bleeding risk is higher than the benefit.⁴¹ Due to inconsistency of previous data on the higher risk of stroke among women, female sex was included only in the

Table 2 Studies in AF patients and reported risk ratio for stroke

Study (year)	Treatment during follow-up	N (% of women)	Risk ratio (95% CI)
Randomized-controlled studies			
AFI ²¹ (1994)	None	3,432 (34)	1.2 (0.8–1.8)
EAF ²² (1995)	None	345 (47)	1.6 (1.0–2.5)
SPAF ²⁴ (1999)	Aspirin/low-dose VKA	2,012 (28)	1.6 (NA)
BAFTA ²⁸ (2007)	No anticoagulation	665 (45)	0.99 (0.6–1.7)
SPORTIF ³¹ (2010)	None	7,329 (31)	1.4 (1.1–1.9)
Prospective observational studies			
Stöllerberger et al ²³ (1998)	VKA/aspirin	409 (36)	1.3 (0.7–2.2)
Framingham ²⁵ (2003)	No anticoagulation	705 (48)	1.9 (1.2–3.1)
Copenhagen City ²⁶ (2004)	None (few VKA)	276 (40)	1.6 (2.3–5.4)
ATRIA ²⁷ (2005)	No anticoagulation	13,559 (43)	1.9 (1.6–2.4)
Euro Heart Study ²⁹ (2007)	None/VKA/aspirin	5,333 (42)	1.83 (1.1–3.0)
Poli et al ³⁰ (2009)	VKA	780 (35.3)	2.1 (1.2–4.0)
Van Staa et al ³² (2011)	None	79,844 (50)	0.95 (0.84–1.06)
Olesen et al ³³ (2011)	No anticoagulation	73,558 (51.2)	1.6 (1.02–2.49)
Mikkelsen et al ³⁴ (2012)	None	87,202 (51.3)	1.2 (1.12–1.28)*
Avgil Tsadok et al ³⁵ (2012)	None	83,513 (52.8)	1.14 (1.1–1.2)
Friberg et al ³⁶ (2012)	None	100,802 (50.3)	1.18 (1.13–1.25)
Poli et al ³⁷ (2013)	VKA	3,015 (54.9)	1.2 (0.8–1.9)

Note: *Only for age ≥ 75 years.

Abbreviations: AF, atrial fibrillation; CI, confidence interval; NA, not applicable; VKA, vitamin K antagonist; N, total number of patients.

Framingham model²⁵ and in those proposed by Stroke Prevention in Atrial Fibrillation (SPAF) investigators.² Other models, including Atrial Fibrillation Investigators,⁴² The American College of Chest Physicians⁴³ and CHADS₂⁴⁴ did not include female sex in the calculation of stroke risk. However, these models have shown a limited ability to identify patients at truly low risk for stroke.^{45–47} In 2010, the CHADS₂ score was revised and a refined version known by the acronym CHA₂DS₂-VASc was proposed.⁴⁸ This model is based on a points system and attributes 1 point also to female sex (Table 3).

The American College of Chest Physicians⁴⁹ in the last version of the antithrombotic treatment guidelines in 2012 still indicate the use of CHADS₂ score for risk-based treatment recommendations, because it is extensively validated and is easy to remember and to use. Similarly, the Canadian Cardiovascular Society and the Japanese Cardiovascular Society more recently recommend the use of the same model.^{40,50} However, the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society guidelines⁵¹ recommend the use of CHA₂DS₂-VASc score without any specific indication for female sex. Instead, the European Society of Cardiology suggests the use of CHADS₂ score for the initial assessment of stroke risk, and a further evaluation of patients with CHADS₂ score of 0–1, considering also weaker risk factors for stroke through the application of the CHA₂DS₂-VASc score.¹ Actually, Olesen et al give evidence that stroke risk in females <65 years is as low as in males.³³ On this basis, the more recent edition of the European Society of Cardiology guidelines suggest to apply one point only to females aged ≥65 years.⁵² Therefore, in females aged <65 years with sex alone as a single risk factor (with CHA₂DS₂-VASc score =1), antithrombotic therapy for the prevention of stroke is not recommended. It should be noted that data on stroke risk of females aged 65–74 years are conflicting. Olesen et al³³ found that this age group of females carries a higher risk of hospital admission and death

due to thromboembolism with respect to males. Friberg et al³⁶ found a higher risk of stroke in females of all ages; however, only among women aged ≥75 years was the risk significantly higher when compared with men (hazard ratio 1.23; $P<0.001$). Further studies are needed to better clarify this aspect.

Why women with AF carry a higher stroke risk?

Hypertension

Hypertension is the most common modifiable risk factor for stroke both in men and women.⁵³ However, there are a number of important sex differences in the prevalence and pathophysiology of hypertension that should be highlighted. Men suffer hypertension more frequently than women; however, this pattern changes among the elderly, and women aged >70 years typically have higher blood pressures than men.⁵⁴ Arterial stiffness with collagen deposition and wall thickening are associated with hypertension, often with arterial dilation due to elastin degradation.⁵⁵ A greater left ventricular wall thickness with impaired relaxation among postmenopausal women in comparison to premenopausal women has been found and confirms this association.⁵⁶

Heart failure

Heart failure has been classified in two different forms according to echocardiographic examination of ventricular function: failure with preserved or reduced EF. The first form is increasingly prevalent and accounts for more than 50% of all heart failure, and is also more prevalent among elderly women.^{57,58} It is associated with increased stiffness of the ventricle with reduced diastolic relaxation and increased atrial pressure and dysfunction. In the Framingham Heart Study, heart failure with preserved EF was more frequent in women compared to men with an age-adjusted OR of 2.55 (95% CI 1.77–3.68, $P<0.001$).⁵⁹ This finding has been confirmed by other authors.¹² Heart failure with preserved EF has also recently been found to be an independent risk factor for stroke in AF.⁶⁰

Hypercoagulability

Left atrial enlargement is associated with blood stasis in the left atrium and especially in the left atrial appendage, both sites of intracavitary thrombus formation in patients with and without AF.⁶¹ Left atrium enlargement at echocardiography is associated with an increased prevalence of surrogate markers of stroke in patients with non-valvular AF. The presence of thrombus in the left atrial appendage, spontaneous echocardiographic contrast, and low left atrium appendage flow velocities are strongly associated

Table 3 CHA₂DS₂-VASc score model

Risk factor	Score
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age >75 years	2
Diabetes mellitus	1
Stroke/TIA/thromboembolism	2
Vascular diseases	1
Age 65–74 years	1
Sex category (ie, female sex)	1
Maximum score	9

Abbreviations: LV, left ventricular; TIA, transient ischemic attack.

with thromboembolism and adverse outcomes in patients with AF.⁶² The SPAF investigators found that left atrium enlargement is independently associated with stroke in non-rheumatic AF.^{63,64} Reduced blood flow and dilation, favored by the anatomic characteristics of these cardiac structures, are associated with changes in endothelial and muscular wall. A higher deposition of collagens with increased fibrosis has been detected in the left atrium of AF patients.⁶⁵ Moreover, the reduced blood flow favors an enhanced prothrombotic state. In particular, several prothrombotic markers have been demonstrated to be present in higher concentration in AF patients compared with controls. Prothrombin fragment 1+2, thrombin–antithrombin complexes, D-dimer, von Willebrand factor, and β -thromboglobulin levels have been investigated by several authors, confirming their association with the presence of AF.^{66–68} Von Willebrand factor and soluble E-selectin are known markers of endothelial dysfunction or damage, and elevated plasma levels of both parameters have been associated with stroke and vascular events, and have been found to be associated with stroke occurrence in AF patients.⁶⁹ Sex differences have been found in von Willebrand factor levels, which are higher in women with respect to males.⁷⁰ Conversely, studies failed to demonstrate difference in the other prothrombotic markers between sexes. These aspects have been recently revised and discussed by Cove et al.⁷¹

Moreover, congestive heart failure may contribute to hypercoagulability and thrombotic risk in AF through an increase of von Willebrand factor levels as a consequence of endothelial damage and dysfunction.⁷² Another plausible mechanism behind the prothrombotic state in AF is inflammation. A study by Thambidorai et al⁷³ reported an association between high risk for stroke and circulating levels of the inflammatory marker C-reactive protein. The inflammatory state of the atrium may lead to an increased synthesis of tissue factor, with a direct role in the production of the thrombogenic milieu in the atria. Moreover, there was a strong correlation between interleukin-6, another inflammatory cytokine, and tissue factor levels in blood obtained from within the atria of AF patients during cardiac catheterization.

Finally, the presence of homocysteine plasma levels over the 90th percentile both in male and female AF patients with multiple risk factors for stroke was associated with an increased risk of stroke during oral anticoagulant treatment.⁷⁴

Hormonal replacement therapy

The risk for ischemic stroke in women doubles between the ages of 55 and 65 years, coinciding with the menopausal

period. Menopause is associated with severe estradiol levels and estrogen receptor reduction, and these modifications contribute to an increased production of inflammatory cytokines that could favor a hypercoagulable state.⁷¹ Moreover, an increased risk of stroke has been found in women on hormonal replacement treatment (HRT) after menopause.⁷⁵ The risk of stroke doubles if HRT is administered to women who had had a previous stroke.⁷⁶ Available data on AF patients on HRT are scarce, probably due to the low rate of HRT prescription in elderly women. Women enrolled in the SPAF trial²⁴ showed a higher risk for stroke when exposed to HRT, but this association was not confirmed by the ATRIA study;²⁷ however, both studies enrolled small groups of women on HRT. The larger group of AF women on HRT was followed in the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM).⁷⁷ A recently published analysis of this data set shows that 376 women were on HRT and this treatment was not independently associated with stroke.⁷⁸ Moreover, HRT does not independently predict mortality, thromboembolism, or bleeding.⁷

Known cardiovascular risk factors

Obesity is an independent risk factor for stroke; however, there is no clear evidence that its impact on stroke is different between sexes.^{79,80} Instead, the presence of metabolic syndrome seems to be associated with a higher stroke risk in women compared to men (30% versus 4%, respectively).^{81,82} Mechanisms for this difference are not completely understood. The correction of established risk factors for stroke by adequate lifestyle is associated with lower stroke incidence and better outcomes after stroke. Healthy lifestyle favors the control of obesity by eating a diet rich in fruits and vegetables⁸³ and regular exercise.^{84,85} Moderate alcohol use is also related to lower risks; in particular, the sensitivity of women to alcohol damage is higher compared to men.⁸⁶ Moreover, abstaining from smoking is associated with the reduction of stroke and cardiovascular disease.⁸⁷ However, no differences between sexes in the effect on stroke incidence and outcomes have been described in relation to smoking.⁸⁸

Characteristic of stroke in women

The NEMESIS Study⁸⁸ reported sex differences in the presentation of stroke, post-stroke management, future risk reduction, and post-stroke morbidity independent of baseline antithrombotic treatment. Women with stroke are usually older than men and may have more severe neurological symptoms and higher mortality. Moreover, a lower frequency of statin use was found with less frequent performance of

cardiologic investigation. However, all these differences were not confirmed at a multivariate analysis adjusted for age, suggesting that differences should be mainly due to older age of women at stroke presentation. The Risk Stroke Collaboration⁸⁹ confirms the older age of stroke occurrence in females who are more physically and mentally impaired 3 months after the stroke. There are also sex differences in the medical management of stroke, and women with AF were less frequently treated with oral anticoagulants at discharge (OR 0.79; 95% CI 0.68–0.93), probably as a consequence of the older age.

Management

Blood pressure lowering by sex

Women have been adequately represented in the trials studying the effects of antihypertensive drugs on stroke-risk reduction,⁹⁰ but none of these trials have specifically examined a differential effect of pharmacological treatment on stroke between sexes. A recent meta-analysis⁹¹ of 31 large, randomized trials on treatment of hypertension showed that both men and women benefit significantly from these interventions, particularly in younger and black women. Moreover, no evidence indicates differences in the response to treatment between the sexes.⁹² However, sex differences exist in the treatment in AF patients: the prescription of beta-blockers and statins are lower in AF patients in primary prevention of stroke.⁸⁹ Hypertension control is also less adequate in females as reported by the Women's Health Initiative,⁹³ and elderly women show a poor control of hypertension. Data from the Framingham Heart Study showed that only 23% of women aged >80 years (versus 38% of men) had normal blood pressure levels.⁹⁴ A higher prevalence of other concomitant cardiovascular risk factors, such as central obesity, elevated total cholesterol, and low high-density lipoprotein cholesterol levels,⁹⁵ are frequently found among elderly women and are likely to contribute to poorer blood pressure control. Moreover, side effects of antihypertensive therapy are more frequent among women compared to men. Diuretic-induced disturbances of electrolyte concentration have been reported more frequently in women.⁹⁶

Rhythm control

AF causes symptoms such as palpitations, dyspnea, and fatigue that are associated with reduced quality of life,⁹⁷ particularly among women, both with persistent^{19,97,98} and paroxysmal AF.^{19,29,99} It is still unknown why women with AF have lower quality of life. However, restoration and maintenance of sinus rhythm have not been associated with

reduction in cardiovascular morbidity and mortality^{77,97,98} nor in quality of life in both sexes. No differences between sexes are reported in the response to antiarrhythmic drugs.^{100,101}

Cardioversion to normal sinus rhythm is equally successful in women and men; however, women were less likely to undergo electric cardioversion than men.²⁹ In addition, women were less likely to undergo catheter ablation and, when this procedure is performed, they are older and with larger left atrial dimension.^{102,103}

Thromboprophylaxis and quality of anticoagulation by sex

A reduced rate of oral anticoagulants prescription has been reported in women.^{18,104} However, the Euro Observational Research Program on AF did not confirm this finding.¹³ Among AF patients on oral vitamin K antagonists, a worse quality of treatment (measured as time in the therapeutic range) for women compared to men has been reported by some studies.¹⁰⁵ However, this observation has not been confirmed by others.^{27,30,37} In particular, similar quality of anticoagulation between sexes has been reported among younger^{27,30} and elderly cohorts of AF patients.³⁷ The amount of warfarin needed to maintain adequate anticoagulation is higher in men than in women (30 versus 25 mg per week, respectively; $P < 0.0001$).¹⁰⁴ Moreover, both males and females undergo a reduction of dosage with increasing age, with women aged ≥ 80 years of age requiring only 3.1 mg/day and young men requiring 6.4 mg/day.¹⁰⁴

In the last few years, four non-vitamin K antagonist oral anticoagulant drugs have been studied in randomized clinical trials in comparison to warfarin, showing noninferiority, and in some cases superiority, to warfarin in stroke-risk reduction and lower risk of intracranial bleeding in patients with AF.^{106–109} The higher stroke risk among AF females has been confirmed by these trials (Table 4); however, the benefit of anticoagulation was similar between sexes, even if none of the studies has been powered to determine a sex difference in the efficacy of new oral anticoagulants over warfarin. More recently, data on plasma concentration of dabigatran¹¹⁰ have been published and showed that dabigatran levels were dependent on renal function, age, weight, and female sex. The study¹¹⁰ reported that both ischemic stroke and bleeding outcomes were correlated to dabigatran concentrations. The higher concentration in females with respect to males is probably related to the lower body weight and to lower creatinine clearance usually present in females. Therefore, the drug should be used carefully in elderly women, especially if they are thin and have a reduced renal function.¹¹¹

Table 4 Efficacy and safety of non-vitamin K antagonist oral anticoagulant among participants in the ARISTOTLE, RELY, ROCKET AF, and ENGAGE Trials, stratified by sex

Study	Women %	Stroke in males (% per year)	Stroke in women (% per year)	Bleeds in males (% per year)	Bleeds in women (% per year)
RELY ¹⁰⁶	36.4				
Dabigatran 110 mg bid		1.35	1.86	2.92	2.79
Dabigatran 150 mg bid		1.10	1.14	3.37	3.23
Warfarin (INR 2.0–3.0)		1.49	2.03	3.63	3.46
ROCKET AF ¹⁰⁷	39.7				
Rivaroxaban 20 mg od		1.52	1.97	3.92	3.11
Warfarin (INR 2.0–3.0)		1.95	2.47	3.68	3.10
ARISTOTLE ¹⁰⁸	35.3				
Apixaban 5 mg bid		1.3	1.40	2.3	1.9
Warfarin (INR 2.0–3.0)		1.5	1.80	3.0	3.3
ENGAGE ¹⁰⁹	38.1				
Edoxaban 60 mg od		1.45	1.76	2.90	2.48
Edoxaban 30 mg od		1.86	2.32	1.66	1.54
Warfarin (INR 2.0–3.0)		1.68	2.00	3.47	3.35

Abbreviations: bid, twice daily; od, once daily; INR, international normalized ratio.

Bleeding risk on anticoagulation by sex

In a nationwide study conducted between 2000 and 2005 in the Netherlands on all drug-adverse-events-related hospitalization, the risk of hospitalizations for bleeding related to anticoagulants use was higher in men than in women.⁹⁶ In particular, intracranial bleeding was lower among females (adjusted relative risk 0.51; 95% CI 0.45–0.58). However, available evidences on this topic are still inconsistent. The ATRIA study²⁷ reported a similar rate of major bleeding between sexes, even if women showed a lower risk of intracranial hemorrhage (0.36% versus 0.55%; adjusted relative risk 0.5; 95% CI 0.3–0.9). We found similar results in an observational study conducted in our center.³⁰ In addition, in a large prospective multicenter study conducted on very old patients (median age 83 years), elderly males showed a higher rate of bleeding complications as compared to females, with an OR of 1.5, even if not statistically significant at multivariate analysis.³⁷ Further studies are needed to better clarify this aspect.

Conclusion

Incidence of AF is lower in women in comparison to men; however, the longer life span of females exposes them to a similar rate of prevalence of AF. Women with AF carry a higher stroke risk that is persistently higher compared to men when adequate anticoagulation is prescribed. The bleeding risk on anticoagulation treatment is similar or probably lower with respect to males, and when appropriate stroke risk stratification indicates the need for anticoagulation, women should receive treatment. Women are frequently affected by several

other modifiable risk factors for stroke, such as hypertension, obesity, and metabolic syndrome, and the control of these risk factors will help to optimize stroke prevention.

Disclosure

The authors report no conflicts of interest in this work.

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