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Atrial fibrillation in a couple: a case report

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Summary. We present a case report confirming previous findings of epidemiological studies: not only does atrial fibrillation (AF) show different features between genders, related to biological differences, in terms of prevalence, clinic characteristics and complications, but there is also possibility for people of different gender to receive different treatments.

Key words: atrial fibrillation, gender, anticoagulant oral therapy.

Un caso clinico di fibrillazione atriale (di coppia)

Riassunto. Presentiamo un caso che conferma quanto già segnalato dagli studi epidemiologici: non solo la fibrillazione atriale può avere caratteristiche diverse nei due generi, legate a differenze biologiche, in termini di prevalenza, caratteristiche cliniche e complicanze, ma esiste anche la possibilità che persone di diverso genere ricevano un differente trattamento farmacologico.

Parole chiave: fibrillazione atriale, genere, terapia anticoagulante orale.

Atrial fibrillation (AF), a common cardiac arrhythmia in Western countries and Japan, not only has a different prevalence between men and women[1], but, as reported in different studies, shows also sex-related difference in clinical and pharmacological treatment[1,2]. There is often a tendency to believe that women are protected against cardio-vascular diseases, but this wrong cultural assumption comes from a possible difficult and/or delayed diagnosis because women may show more nuanced symptomatic features that differ from those of males. We have to consider that until a few years ago women were left out from trials and studies and that the conclusions were drawn from observations on men that are not necessarily applicable to women. Moreover, women tend to underestimate their symptoms, to be more hesistant to accept medical check-ups and drug prescriptions and in general to put the care of others before themselves.

Like other cardiac pathologies, some studies have found gender differences in AF treatment, showing that at times a most conservative approach is preferred for women, while other studies have highlighted a less frequent use of oral anticoagulant therapy (OAT).

Case report

We report two cases of patients with AF who received different diagnostic and therapeutic approach.

- Male, 83 years old, F.B., former smoker, with arterial hypertension, chronic kidney disease stage III-IV, dilated cardiomyopathy (EF 35-40%), AF with good response to cardioversion in 2003. After AF relapse, OAT was started with warfarin (in 2003 CHADS2 = 3 and in 2009 CHA_2Ds_2-VASc = 4, with a thromboembolic risk of 5.9%/year; HAS-BLED = 2), as recommended by guidelines, and heart rate control with betablockers. Two echocardiograms were performed in 2003 and in 2009, confirming damage to the anatomic structure of the heart damage and impaired cardiac function: he presented progressive left ventricular and atrial dilatation and mitral valve and tricuspid regurgitation. He died of cardiogenic shock in 2010, few months after his first admission to our Internal Medicine Unit.
- Female, 80 years old, L.R., clinical history of arterial hypertension, hyperthyroidism, previous NSAID-related gastric bleeding, obesity, persistent AF (CHA_2DS_2-VASc = 4, HAS-BLED = 3), diagnosed in the cardiology unit and treated with digoxin and ASA. At the time of the first medical examination at our unit, the echocardiogram was never performed.

We calculated stroke risk with $CHADS_2$ and CHA_2Ds_2-VASc at the time of the first diagnosis of AF and at the time of hospitalization at our unit respectively, and HAS-BLED was also calculated (Table 1)[3,5,7,8].

Our patients had a similar risk of stroke and bleeding, but they were treated differently. Differences in HAS-BLED risk did not warrant the choice of antiplatelet therapy (with almost similar gastric bleeding rate) in the female patient, L.R..

It is amazing to note that our patients were married, had a similar age at time of diagnosis, lived in the same home, with the same primary care physician and were not conscious of having a similar yet differently treated disease, despite guidelines (Tables 2A, 2B)[4,6-8].

The woman accepted to start OAT only after her spouse's death, because before then she thought she did not have time to take care of her own health, but only that of her sick husband.

She started a novel oral anticoagulant a year ago, because she was in therapeutic range for insufficient time.

Conclusions

AF is the most common cardiac arrhythmia and independent risk factor for thromboembolism. Periodic guidelines are drawn up concerning rhythm/rate control and OAT in order to avoid thromboembolic stroke[9].

Some studies have highlighted differences between genders in AF treatment and underutilization of OAT, despite the higher risk of stroke in women[9], who also receive frequently more conservative treatment[10]. However, reports are not consistent.

Indeed, while the Canadian AF Registry quoted underutilization of OAT in 2001 (as many other reports), in 2013 the ATA-AF Study did not find differences and, in the same year, according to the FALP observational study, the male gender was negatively correlated to OAT[11,12].

According to the Euro Heart Survey on AF, women frequently were asymptomatic or had AF with atypical symptoms (dyspnea, chest pain, dizziness and fatigue), while men displayed mainly typical symptoms (palpitations and syncope). In overall symptomatic cases, the authors did not find differences between genders, but the treatment was more conservative in asymptomatic women or women with atypical symptoms: they received electrical cardioversion less frequently (rate control was preferred), but no differences were found in OAT, in contrast with other studies[10,13]. Women showed higher stroke risk, according to the Framingham and ATRIA studies that reported a high risk of thromboembolism if they did not receive OAT[14].

Compared to the men, several potential mechanisms could contribute to prothrombotic milieu and thromboembolic risk in women, above all in menopause: estrogen decline-related upregulation in the production of inflammatory cytokines, alterations in the vascular and myocardial structure, impaired endothelial function, increased platelet aggregation and increase in arterial pressure, pulse pressure and pressure variability[9].

Female gender should be an independent risk factor for thromboembolic stroke in AF and has been added to CHA_2DS_2VASC by the Birmingham 2009 Schema and employed in the ESC 2010 guidelines[8,15]. The NEMESIS Study has demonstrated that women have more severe

Table 1. Stroke risk assessment scores.

Stroke risk in patients with nonvalvular AF not treated with anticoagulation according to the $CHADS_2$ Index

$CHADS_2$ risk criteria	Score
Prior stroke or TIA	2
Age >75 y	1
Hypertension	1
Diabetes mellitus	1
Heart failure	1

Patients (N = 1733)	Adjusted stroke Rate (%/y) (95% CI)	$CHADS_2$ Score
120	1.9 (1.2 to 3.0)	0
463	2.8 (2.0 to 3.8)	1
523	4.0 (3.1 to 5.1)	2
337	5.9 (4.6 to 7.3)	3
220	8.5 (6.3 to 11.1)	4
65	12.5 (8.2 to 17.5)	5
5	18.2 (10.5 to 27.4)	6

Modified from Gage BF, et al., JAMA 2001[3].

CHA_2DS_2VASc score

(a) Risk factors for stroke and thrombo-embolism in non-valvular AF

'Major' risk factors	*'Clinically relevant non-major' risk factors*
Previous stroke, TIA, or systemic embolism Age ≥75 years	Heart failure or moderate to severe LV systolic dysfunction (e.g. LV EF ≤ 40%) Hypertension - Diabetes mellitus Female sex - Age 65–74 years Vascular disease

(b) Risk factor-based approach expressed as a point based scoring system, with the acronym CHA_2DS_2-VASc ***(Note: maximum score is 9 since age may contribute 0, 1, or 2 points)***

Risk factor	*Score*
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age ≥ 75	2
Diabetes mellitus	1
Stroke/TIA/thrombo-embolism	2
Vascular disease	1
Age 65–74	1
Sex category (i.e. female sex)	1
Maximum score	***9***

Modified from Camm JA, et al., Eur Heart J 2010[8].

HAS-BLED bleeding risk score

Letter	Clinical characteristic	Points awarded
H	Hypertension	1
A	Abnormal renal and liver function (1 point each)	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INRs	1
E	Elderly	1
D	Drugs or alcohol (1 point each)	1 or 2
		Maximum 9 points

Modified from Pisters R, Lane DA, Chest 2010[5].

Table 2A. Antithrombotic therapy for patients with atrial fibrillation.

Recommendations for antithrombotic therapy in patients with AF

Class I

1. Administer antithrombotic therapy (oral anticoagulation or aspirin) to all patients with AF, except those with lone AF, to prevent thromboembolism. (*Level of Evidence: A*)
2. Individualize the selection of the antithrombotic agent based on assessment of the absolute risks of stroke and bleeding and the relative risk and benefit for a particular patient. (*Level of Evidence: A*)
3. Chronic oral anticoagulant therapy in a dose adjusted to achieve a target intensity of INR 2 to 3 in patients at high risk of stroke, unless contraindicated. (*Level of Evidence: A*)
   - ***a.*** The need for anticoagulation should be reevaluated at regular intervals. (*Level of Evidence: A*)
   - ***b.*** INR should be determined at least weekly during the initiation of oral anticoagulation therapy and monthly when the patient is stable. (*Level of Evidence: A*)
4. Aspirin in a dose of 325 mg daily as an alternative in low-risk patients or in those with certain contraindications to oral anticoagulation. (*Level of Evidence: A*)
5. Oral anticoagulation for patients with AF who have rheumatic mitral valve disease or prosthetic heart valves (mechanical or tissue valves). (*Level of Evidence: B*)
6. Base the target intensity of anticoagulation on the particular type of prosthesis, but it should not be less than INR 2 to 3. (*Level of Evidence: B*)

Modified from Fuster V, Rydén LE, Circulation, 2001[6].

Antithrombotic therapy for patients with atrial fibrillation

Risk category	*Recommended therapy*
No risk factors	Aspirin, 81 to 325 mg daily
One moderate-risk factor	Aspirin, 81 to 325 mg daily, or warfarin (INR 2.0 to 3.0, target 2.5)
Any high-risk factor or more than 1 moderate-risk factor	Warfarin (INR 2.0 to 3.0, target 2.5)*

Less validated or weaker risk factors	*Moderate-risk factors*	*High-risk factors*
Female gender	Age greater than or equal to 75 y	Previous stroke, TIA or embolism
Age 65 to 74 y	Hypertension	Mitral stenosis
Coronary artery disease	Heart failure	Prosthetic heart valve*
Thyrotoxicosis	LV ejection fraction 35% or less	
	Diabetes mellitus	

*If mechanical valve, target international normalized ratio (INR) greater than 2.5. INR indicates international normalized ratio; LV, left ventricular; and TIA, transient ischemic attack.

Modified from Fuster V, Rydén LE, Circulation, 2006[7].

stroke symptoms and worse post-stroke impairment as opposed to men[9].

In the ATRIA study, OAT was more protective for women with AF than among men with the same disease and they had a similar rate of major bleeding[14], but several studies have shown suboptimal time in the therapeutic range compared to men[9].

These results, as well as our case report, confirm gender differences, despite guidelines for the management of patients with AF and similar stroke risk.

This demonstrates an underutilization of OAT among women, which should be considered instead with greater attention in this gender, although inequality of treatment or therapeutic choices should not always be considered evidence of discrimination: at times, it may prove to be beneficial to women. For instance, rate control versus rhythm control could improve outcomes in female gender[10].

Gender medicine, which applies the idea of the "difference between genders", aims at providing the best treatment to everybody, whether men or women, and at achieving better gender-related therapy.

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Table 2B. Approach to thromboembolism guidelines.

Approach to thromboprophylaxis in patients with AF

Risk category	CHA_2DS_2-VASc score	Recommended antithrombotic therapy
One 'major' risk factor or ≥2 'clinically relevant non-major' risk factors	≥ 2	OAC
One 'clinically relevant non-major' risk factor	1	Either OAC or aspirin 75-325 mg daily. Preferred: OAC rather than aspirin.
No risk factors	0	Either aspirin 75–325 mg daily or no antithrombotic therapy. Preferred: no antithrombotic therapy rather than aspirin.

AF = atrial fibrillation; CHA_2DS_2-VASc = cardiac failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled)-vascular disease, age 65–74 and sex category (female); INR = international normalized ratio; OAC = oral anticoagulation, such as a vitamin K antagonist (VKA) adjusted to an intensity range of INR 2.0–3.0 (target 2.5).

Modified from Camm JA, Kirchhoff P, Eur Heart J, 2010[8].

Recommendations for prevention of thromboembolism in non-valvular AF—general

Recommendations	Class	Level	Ref
Antithrombotic therapy to prevent thromboembolism is recommended for all patients with AF, except in those patients (both male and female) who are at low risk (aged <65 years and lone AF), or with contraindications.	I	A	21, 63, 104, 105, 106
The choice of antithrombotic therapy should be based upon the absolute risks of stroke/thromboembolism and bleeding and the net clinical benefit for a given patient.	I	A	21, 63, 105
The CHA_2DS_2-VASc score is recommended as a means of assessing stroke risk in non-valvular AF.	I	A	25, 36, 39
In patients with a CHA_2DS_2-VASc score of 0 (i.e., aged <65 years with lone AF) who are at low risk, with none of the risk factors, no antithrombotic therapy is recommended.	I	B	21, 36, 82
In patients with a CHA_2DS_2-VASc score ≥2, OAC therapy with: • adjusted-dose VKA (INR 2–3); or • a direct thrombin inhibitor (dabigatran); or • an oral factor Xa inhibitor (e.g. rivaroxaban, apixaban)[d] ... is recommended, unless contraindicated.	I	A	3, 4, 70, 82
In patients with a CHA_2DS_2-VASc score of 1, OAC therapy with • adjusted-dose VKA (INR 2–3); or • a direct thrombin inhibitor (dabigatran); or • an oral factor Xa inhibitor (e.g. rivaroxaban, apixaban)[d] .... should be considered, based upon an assessment of the risk of bleeding complications and patient preferences.	IIa	A	33, 44
Female patients who are aged <65 and have lone AF (but still have a CHA_2DS_2-VASc score of 1 by virtue of their gender) are low risk and no antithrombotic therapy should be considered.	IIa	B	33, 44
When patients refuse the use of any OAC (whether VKAs or NOACs), antiplatelet therapy should be considered, using combination therapy with aspirin 75–100 mg plus clopidogrel 75 mg daily (where there is a low risk of bleeding) or—less effectively—aspirin 75–325 mg daily.	IIa	B	21, 26, 51, 109

Modified from Camm JA, Lip GYH, Eur Heart J, 2012[4].

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