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From the pathophysiology to the treatment of atrial fibrillation in women

De la fisiopatología al tratamiento de la fibrilación auricular en la mujer

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EPIDEMIOLOGY AND PARTICULARITIES

Atrial fibrillation (AF) is the most common sustained arrhythmia, with a growing impact on global public health.[1] It is associated with developing dilated cardiomyopathy (with heart failure), stroke, and high mortality.[2]

Although it affects men and women, however, several studies show differences between the two genders related to biological characteristics (concerning sex) and gender (concerning the social role of individuals observed in epidemiology, risk factors (RF), clinical presentation, interventions, and prognosis.[1,2]

The cumulative risk of developing AF in life is similar for men and women. In women, AF appears later (men from 40 and women from 50 years of age).[1] The incidence and prevalence are higher in men in all age groups. In both genders, the prevalence increases with age.[1] Epidemiological studies show that mortality from AF is more elevated in women.[1,2]

In addition, women are underrepresented in clinical trials evaluating therapeutic interventions (drugs, electrical cardioversion, and catheter ablation) for AF.[2] In *Figure 1*, the particularities of AF in women are listed.

PATHOPHYSIOLOGY AND RISK FACTORS

Several mechanisms, including stretch fibrosis, hypocontractility, fatty infiltration, inflammation, vascular remodeling, ischemia, ion channel dysfunction, and calcium instability, contribute to complex atrial changes that increase the propensity to develop/maintain AF and facilitate a hypercoagulable state in both genders.[2,3]

Aging is a prominent RF for the development of AF; however, other comorbidities play an essential role in its mechanisms: high blood pressure (HBP), diabetes mellitus (DM), heart failure (HF), coronary artery disease (CHD), kidney disease (CKD), obesity and obstructive sleep apnea (OSA).[3] In addition, other modifiable factors (excessive alcohol consumption, smoking, physical inactivity, extreme exercise) have also been proposed as potential contributors to the development and progression of AF.[3] Thus, women with AF are older, have a higher prevalence of hypertension, valve disease, HF with preserved ejection fraction, and have a lower prevalence of CAD than men.[3]

RHYTHM CONTROL AND RATE CONTROL

Treatment of AF includes anticoagulation (AC), control of symptoms through strategies to control heart rate and rhythm, and therapy of RF and comorbidities.[2]

Meta-analyses on rhythm vs. rate control therapies have not shown a significant difference in reducing the risk of stroke and all-cause mortality. Thus, rate control remains an option to improve symptoms in patients with AF.[2]

Recent evidence from the EAST-AFNET4 study supports the use of early rhythm control

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(antiarrhythmics and or catheter ablation) to decrease cardiovascular events.[4] There are gender differences in the clinical presentation of AF: women have atypical, more severe symptoms and more significant deterioration in the quality of life. Despite this, they tend to receive fewer rhythm control therapies. In the ORBIT-AF registry (42% of women), the use of antiarrhythmic drugs (AD) was similar in men and women; however, electrical cardioversion and catheter ablation (ABL) were less frequent in women; the use of digoxin was more significant, and in symptomatic cases, they only received drugs to control heart rate.[5]

A subanalysis of outcomes by sex from the CABANA study (included 37% women; (ABL vs AD) showed that the benefits of ABL are similar in men and women; Adverse drug events were rare in both.[6] Rhythm control therapy is effective in patients with AF, regardless of gender.

ANTICOAGULATION

In patients with AF and a high risk of thrombus formation, identified using specific scores (the most used is the CHA2DS2-VASc), AC reduces the risk of stroke by 60%. Direct oral anticoagulants (DOAs) are currently recommended over warfarin in patients with AF.[7,8]

The representation of women in the different clinical studies with DOAs was 37%, and in subgroup analysis, no significant differences were found in the clinical outcomes between men and women.[9]

Data on gender differences in CA in patients with AF are not consistent. In the Euro Heart Survey, a cohort of 5,000 patients (42% women) showed no difference in CA rates. Another cohort study (6,000 patients) showed a significant difference in the AC of women and men, 76.8% and 82.5%, respectively; one of the possible explanations for this difference in AC between women and men over 75 years of age was perhaps the perception of more significant bleeding in older women. The CODE-AF registry showed no significant difference in the prescription of AC between women and men, although women were more likely to receive subtherapeutic doses of AODs. The

Risk factors
- Hypertension
- Obesity
- Valve disease
- Depression

Rate & rhythm
- More treatment for heart rate control
- Minus probability or electrical cardioversion
- Minus probability of ablation
- More extopic foci no pulmonary veins

Structural differences
- Small left atrium
- More atrial fibrosis
- More inflammation

Prognosis
- More serious cerebrovascular events (CVE)
- Greater limitation after CVE
- Higher mortality
- Less therapeutic anticoagulation

Epidemiology
- Lower prevalence, but similar absolute number with AF
- Later age of onset (to 10 years)

Clinical presentation
- More symptomatic
- More atypical symptoms
- Worse quality of life

Representation in studios
- Less presentation in anticoagulant and ablations

Figure 1: Peculiarities of atrial fibrillation in women. CVE = cerebrovascular event. CVE = electrical cardioversion. AF = atrial fibrillation. HR = heart rate. HBP = high blood pressure. BMI = body mass index. PV = pulmonary veins. Modified from: Linde C et al.[7]

PINNACLE Registry (2008-2014) showed that women were less likely to receive oral AC across all CHA_2DS^2-VASc scores.[9]

CATHETER ABLATION

Catheter ABL offers an effective option to maintain sinus rhythm and improve symptoms, exercise capacity, and quality of life when ADs have been ineffective, contraindicated, or not tolerated.[2,7]

Compared to men, women receive more AD treatment for rhythm control and are referred less for ABL. They are also older, have a longer duration of AF, a lower proportion of paroxysmal AF, more comorbidities, more dilated left atria and more extrapulmonary venous triggers.[9]

The ablation success rate is comparable to that of men; however, the FIRE AND ICE[10] study, which evaluated cryoablation vs. radiofrequency ablation for paroxysmal AF, showed that women had a 36% higher rate of recurrence and a 37% higher rate of cardiovascular re-hospitalization after ablation.

Recognition of differences based on sex/gender offers a good opportunity to improve treatment outcomes (including ablation) in women with AF.

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