

Gender differences and management of stroke risk of nonvalvular atrial fibrillation in an upper middle-income country: Insights from the CARMEN-AF registry☆

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Abbreviations: AF, Atrial fibrillation; APD, Antiplatelet drugs; ATT, Antithrombotic therapy; DOAC, Direct oral anticoagulants; VKA, Vitamin K antagonists.

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ABSTRACT

Background: Atrial Fibrillation (AF) is associated with an increased risk of stroke and systemic embolism. Several studies have suggested that female AF patients could have a greater risk for stroke. There is scarce information about clinical characteristics and use of antithrombotic therapies in Latin American patients with nonvalvular AF. **Objective:** To describe the gender differences in clinical characteristics, thromboembolic risk, and antithrombotic therapy of patients with nonvalvular AF recruited in Mexico, an upper middle-income country, into the prospective national CARMEN-AF Registry.

Methods: A total of 1423 consecutive patients, with at least one thromboembolic risk factor were enrolled in CARMEN-AF Registry during a three-year period (2014–2017). They were categorized according to Gender.

Results: Overall, 48.6% were women, mean age 70 ± 12 years. Diabetes, smoking, alcoholism, non-ischemic cardiomyopathy, coronary artery disease, and obstructive sleep apnea were higher in men. Most women were found with paroxysmal AF (40.6%), and most men with permanent AF (44.0%). No gender differences were found in the use of vitamin K antagonists (VKA) (30.5% in women vs. 28.0% in men). No gender differences were found in the use of direct oral anticoagulants (DOAC) (33.8% women vs 35.4% men).

Conclusions: CARMEN-AF Registry demonstrates that in Mexico, regardless of gender, a large proportion of patients remain undertreated. No gender differences were found in the use of VKA or DOAC.

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1. Introduction

Despite a higher prevalence of atrial fibrillation (AF) in male subjects [1], an increased risk for stroke has been described in women [2,3]. Outcomes from recent registries have proven that female gender is an independent stroke risk factor in AF, and the inclusion of female gender in stroke risk stratification models, such as the CHA2DS2-VASc score, have improved risk assessment [4].

Guidelines for atrial fibrillation recommend that oral anticoagulation should be considered in patients with ≥ 1 non-gender related risk factors for stroke [5].

Thus, oral anticoagulation seems to depend predominantly upon guideline-related differences in stroke risk stratification rather than on gender hence the decision to prescribe anticoagulants is not gender-dependent but may rely predominately upon clinical stroke risk factors.

Nevertheless, published data indicate variability in anticoagulation use by gender, ranging from a 50% lower uptake in women versus men to more frequent anticoagulation in women [5].

The objective of the present survey was to establish the sex differences in AF characteristics, thromboembolic risk factors, concomitant diseases, and thromboprophylaxis. Our aim is to highlight potential treatment discrepancies according to gender that could impact the prognosis of patients with AF.

2. Material and methods

CARMEN-AF is an ongoing, observational, longitudinal, cross-sectional, multicenter, nationwide registry of antithrombotic therapy for nonvalvular AF in Mexico. The complete protocol has already been published [6]. Mexico's economic status as an upper-middle income country is based on the 2013 World Bank Classification according to gross national income per capita [7].

Institutional ethics committees in all participant centers approved the protocol. The registry was conducted in accordance with the Declaration of Helsinki. All patients signed an informed consent.

Table 1
Baseline characteristics by Gender.

	All (n = 1423)	Male (n = 731)	Female (n = 692)	P*
Demographic characteristics				
Gender (%)		51.4	48.6	ns
Age, years $\pm$ SD	69 $\pm$ 13	68 $\pm$ 13	70 $\pm$ 12	=0.002
Weight, kg $\pm$ SD	75 $\pm$ 16	80 $\pm$ 15	69 $\pm$ 14	<0.0001
Body mass index, kg/m ² $\pm$ SD	28.5 $\pm$ 5.0	28.4 $\pm$ 4.6	28.7 $\pm$ 5.4	ns
Comorbidities				
Hypertension	72.5	71.3	73.8	ns
Diabetes	28.4	31.3	25.3	=0.007
Heart failure	23.6	25.3	21.8	ns
Smoking	16.4	23.9	8.5	<0.0001
Alcoholism	9.2	17.1	0.9	<0.0001
Nonischemic cardiomyopathy ^a	8.9	10.3	7.5	=0.042
Coronary artery disease	7.1	9.7	4.3	<0.0001
Obstructive sleep apnea	3.9	5.2	2.6	=0.008
Peripheral artery disease	1.8	1.0	2.7	=0.010

* P value was obtained comparing Gender groups using Chi-square test and Student's *t*-test.

^a Hypertensive, Idiopathic, and restrictive.

2.1. Study population

Patients ≥ 18 years old with one or more risk factors for thromboembolism evaluated by CHA2DS2-VASc score and diagnosed with nonvalvular AF with at least 6 months duration prior to their inclusion were eligible for inclusion in this Registry. Patients were recruited regardless of anti-thrombotic therapy (ATT): antiplatelet drugs (APD), vitamin K antagonists (VKA), or direct oral anticoagulants (DOAC). Demographic data, clinical variables, comorbidities, and treatment were collected by the responsible physician using a paper-based case report form, with subsequent capture in an electronic form for data storage.

Thromboembolic and bleeding risks were assessed based on CHA2DS2-VASc and HAS-BLED scores, respectively. Thromboembolic risk was defined as moderate with CHA2DS2-VASc score = 1 and high-risk with CHA2DS2-VASc score ≥ 2 , irrespectively of gender. Bleeding risk was defined as low (HAS-BLED score = 0), moderate (HAS-BLED score = 1–2) or high (score ≥ 3).

2.2. Statistical analysis

Data were analyzed using SPSS v. 22.0. Variables are presented as number (percentage) or mean ($\pm$ SD), as appropriate. Demographic differences among continuous variables with normal distribution were

examined using Student's *t*-test. Wilcoxon signed-rank test was used when variables failed normality test. Categorical variables were analyzed using Chi-square test, either Fisher's exact test or Yates's correction for continuity. A 2-tail test with a *P* value <0.05 was considered statistically significant.

3. Results

3.1. Clinical characteristics

A total of 1423 consecutive patients were enrolled in a three-year period (September 2014–December 2017), 48.6% were women. They were older than men (70 $\pm$ 12 vs 68 $\pm$ 13 years, *P* = 0.002). Complete demographic characteristics are shown in Table 1. Body mass index was not significantly different between males and females.

The history of comorbidities was significantly different between genders; men were more likely to be smokers, have higher alcohol intake, and have higher prevalence of diabetes, non-ischemic cardiomyopathy, coronary artery disease, and obstructive sleep apnea. Prevalence of hypertension was similar, and peripheral artery disease was more common in women (Table 1).

Regarding the AF type, paroxysmal AF was more prevalent in women (40.6%) and permanent AF in men (44.0%; *P* = 0.015).

AF was asymptomatic in 59.4% of patients. No differences were found between both genders.

3.2. Thromboembolic risk

Overall, the mean CHA2DS2-VASc score was 3.1 $\pm$ 1.5. Women had a significant higher risk score than men (3.7 $\pm$ 1.4 vs 2.6 $\pm$ 1.3; *P* < 0.0001).

Significant statistical differences were found comparing gender groups in stroke risk (Fig. 1). A higher stroke risk (score ≥ 2) was more frequent in women (93.5% vs 78.1%; *P* < 0.0001).

3.3. Bleeding risk

There was a significant difference in HAS-BLED score between men and women; it was higher in men (1.82 $\pm$ 1.0 vs 1.71 $\pm$ 0.9; *P* = 0.032). According to bleeding risk, more women had a low risk of bleeding than men (9.7% vs 6.3%, *P* = 0.012), while more men had a high risk (20.8% vs 16.8%, *P* = 0.030) (Fig. 2).

3.4. Antithrombotic therapy in relation to stroke and bleeding risks

Antithrombotic therapies in relation to thromboembolic risk are presented in Fig. 3.

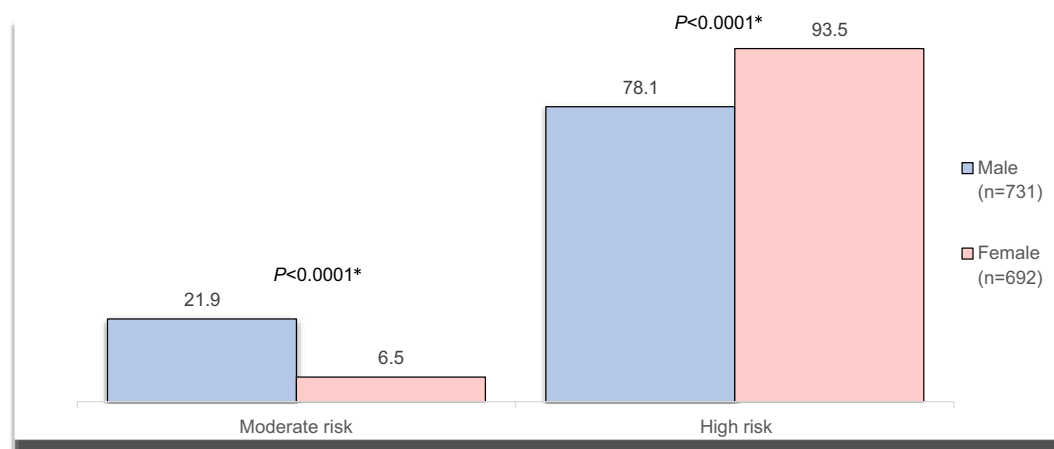


Fig. 1. Gender and stroke risk based on CHA2DS2-VASc. **P* value was obtained comparing Gender groups using Chi-square test.

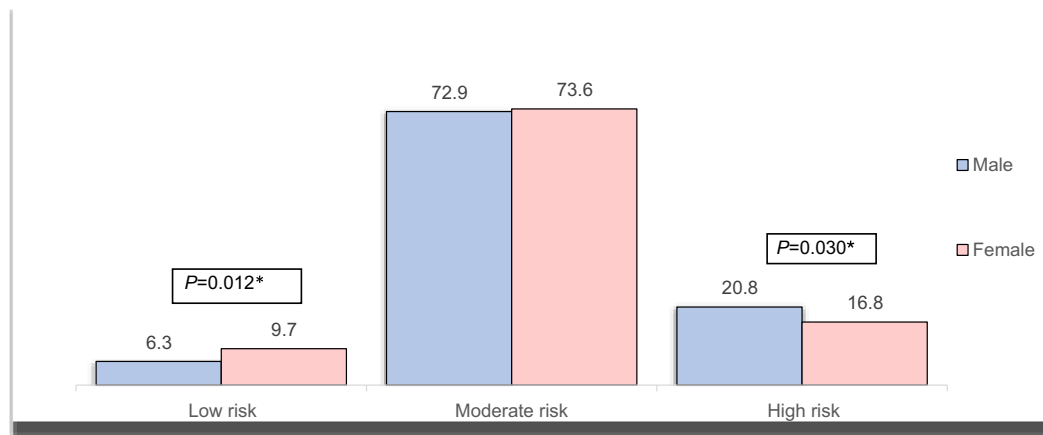


Fig. 2. Gender and bleeding risk based on HAS-BLED. *P value was obtained comparing Gender groups using Chi-square test.

For CHA2DS2-VASc = 1, 55.5% of women and 68.8% of men were prescribed anticoagulants. The rate of APD use alone was higher in women (26.7% vs. 13.1%, $P = 0.029$) in patients with moderate risk.

In the group of high risk of stroke (CHA2DS2-VASc ≥ 2), men received fewer oral anticoagulants (62.0% vs 64.9%; $P < 0.0001$), and a higher percentage did not receive antithrombotic therapy (18.6% vs 14.4%; $P = 0.029$). APD choice was similar between genders in patients with high risk.

Overall, in our analysis, the use of DOAC was similar in men and women (35.4% vs 33.8%). The use of dabigatran was not significantly different between female and male patients. Rivaroxaban was used more frequently in males (16.0% vs 11.4%, $P = 0.007$), while apixaban was preferred in women (11.4% vs 6.8%, $P = 0.002$).

Of the studied population, 9.5% of women and 19.2% men at high risk of bleeding (HAS-BLED score ≥ 3) did not receive any antithrombotic therapy ($P = 0.021$).

4. Discussion

In this nationwide survey of sex differences in patients with nonvalvular atrial fibrillation there were some differences and similarities to international data [5,8]. We found that women with AF with a high risk of stroke (CHA2DS2-VASc ≥ 2) were more likely than men to receive anticoagulants. In Asian populations, the CODE-AF registry [9] also reports that a slightly higher proportion of women with a

CHA2DS2-VASc ≥ 2 were taking oral anticoagulants than men (85.7% vs 81.9%). Data collected by other large-scale registries observed a similar anticoagulation by women and men [5,8]. Nevertheless, our findings show that among high-risk patients, anticoagulant use in Mexico, an upper middle-income country, remains suboptimal in both sexes. One-third did not receive an anticoagulant. These findings of sub-optimal thromboprophylaxis are of concern and indicate the need for improved stroke prevention in AF. However, for patients with a CHA2DS2-VASc equal to 1, there was an opposite between-gender difference in anticoagulant use (55.5% and 68.8% for women and men, respectively), an important difference already identified in GLORIA-AF and CODE-AF [5,9], which could reflect a different clinical approach to a score of 1 in both genders, rather than an underuse of anticoagulation in women compared with men. On the contrary, women with this score seem over-treated with anticoagulants. Current guidelines state that women with CHA2DS2-VASc equal to 1, (1 point for female gender) are at low risk for stroke and should not be anticoagulated [10]. Anticoagulation should be considered in patients with one non-gender related risk factor for stroke, that is CHA2DS2-VASc = 1 for men and CHA2DS2-VASc ≥ 2 for women [11].

In CARMEN-AF, the high rate of use of antiplatelet therapy in women with a CHA2DS2-VASc = 1, (26.7% and 13.1% for women and men, respectively) does not correlate with the rates of cardiovascular diseases observed in this registry among women, indicating that antiplatelets are still being given to low-risk women for stroke prevention, thus

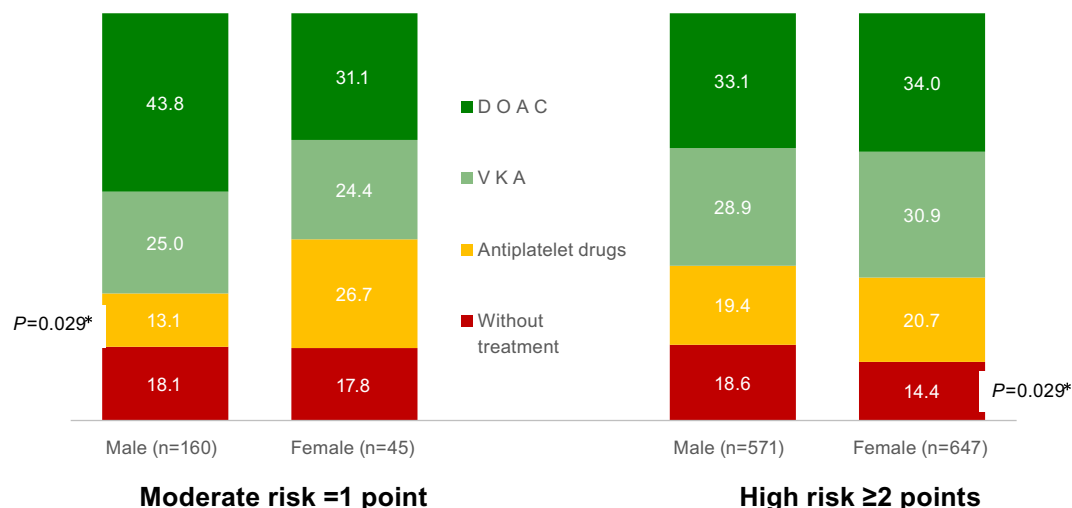


Fig. 3. Gender and antithrombotic therapy according to CHA2DS2-VASc risk. *P value was obtained comparing Gender groups using Chi-square test.

increasing bleeding risk. No gender differences were found for the use of direct oral anticoagulants, a new kind of therapy well accepted in Mexico.

Although AF is less prevalent in women than in men, women with AF have a higher risk of stroke and death than men. The risk of developing AF is higher in men than women. However, because women live longer than men and the prevalence of AF increases with age, there are more women than men with AF, basically they have the same risk as men but shifted a few years along. [12] In our registry the history of previous stroke was 13.3%, without gender differences.

Consistent with previous reports, female subjects were older, but they did not have a more prevalence of AF, or more symptoms than males as was previously found [5,8,9]. However, in comparison to men when women have AF, their risk of stroke is greater than that of men, thus they should receive more aggressive anticoagulation, what is happening in Mexico.

4.1. Limitations

CARMEN-AF was based on the prescription of antithrombotic therapy by different specialists, therefore, our data may not apply to other health care givers.

According to protocol, this survey recruited only patients with CHA₂DS₂-VASc ≥ 1 . Thus, no data on patients with score zero (low risk of stroke) were available.

Both patients and physicians knew they were participants of a registry; this might have led to higher overall anticoagulation rates compared with general population.

We did not analyze the associations between anticoagulant use and concomitant antiplatelet therapy use by gender.

5. Conclusions

In Mexico, female patients with AF are treated more aggressively than male patients with AF. They received anticoagulants more frequently than male patients. Since suboptimal use of anticoagulants was common in both sexes, it is necessary to improve current evidence-based guidelines implementation for the management of nonvalvular AF and stroke prevention. No gender differences were found in the use of VKA or DOAC.

Disclosures

The authors declare no conflict of interest in this article.

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Conflicts of interest

The authors report no relationships that could be construed as a conflict of interest.

Clinical trial registration

<http://www.clinicaltrials.gov>. Unique identifier: NCT02334852.

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