REUE | Special Article

Atrial fibrillation in women

Fibrilación auricular y mujer

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Introduction

Sex and gender are 2 of the most important characteristics of individuals. We are born with a biological sex that determines our internal and external phenotype, and we identify with a gender that influences our behavior and interaction with the environment.

Health and disease, as inherent conditions of each person, are also influenced by sex and gender. Biological sex determines anatomical and structural differences—not only related to genital organs and breast development, but also to weight, height, body fat distribution, skin thickness, the size and shape of some organs, and the caliber of arteries and veins. It also implies histological differences, variations in receptor presence and expression, and hormonal differences that, in turn, influence metabolism.[1-3] All these differences affect the prevalence and expression of diseases, their progression, prognosis, therapeutic response, and side effects.[1-9]

Similarly, gender-related aspects—such as specific risk behaviors, occupational factors, health perception, self-care, and interaction with the healthcare system—affect disease risk, early diagnosis, adherence, therapeutic response, and prognosis.[1-4,8-11]

Atrial fibrillation (AF) is no exception to the influence of sex and gender. An increasing number of studies support the importance of this influence. However, most studies do not distinguish between sex and gender or consider nonbinary categories. Therefore, in this article we will primarily use the terms woman/man, assuming that women represent the female sex and men the male sex, while acknowledging that a precise analysis of sex influence and gender bias in AF (and in medicine in general) requires addressing the diversity of genders in society and their interactions with other characteristics, such as age, ethnicity, or socioeconomic factors.[12]

Despite growing awareness of the importance of considering sex and gender in AF, the sex–gender perspective in AF research remains insufficient. Globally, only about one-third of patients enrolled in clinical trials are women, representing an underrepresentation of more than 12% vs their prevalence in the general population. Moreover, only one-fourth of studies report results disaggregated by sex, and not all include statistical testing for sex interaction.[13] Moreover, information regarding the interaction of sex and gender with other factors (age, socioeconomic level, ethnicity) is practically nonexistent.[14]

This lack of scientific evidence results in a lack of sex-specific recommendations. While clinical practice guidelines have become increasingly sensitive to sex and gender perspectives—with specific sections addressing AF in women[15,16]—evidence remains insufficient to make distinct recommendations for each sex. Except for anticoagulation, all recommendations remain general. This lack of sex-specific guidance, compounded by limited professional training in this area, translates into insufficient consideration of sex and gender in AF management and treatment, leading to less personalized medicine and suboptimal clinical practice.

This review summarizes current knowledge on the importance of considering sex and gender in AF to provide an initial overview of their relevance and to optimize health outcomes.

Electrophysiologic and anatomic differences

Men and women differ in cardiac electrophysiologic properties due to variations in substrate related to the effects of sex hormones on cellular development, differences in autonomic function, and the impact of circulating sex hormones after puberty. Estrogens, progesterone, and testosterone affect the synthesis and function of ion channel proteins. These variations influence the refractory period, conduction velocity, action potential, and arrhythmia vulnerability. Generally, women exhibit a higher heart rate than men, a narrower QRS interval, and a longer QT interval—especially after puberty. In AF specifically, men tend to have larger atria and greater atrial contractility, predisposing them to ar-

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rhythmia, while women often have more non–pulmonary vein triggers, which may have therapeutic implications.[17]

Epidemiology

AF incidence rate differs between men and women. Men have a higher incidence rate until the 6th decade of life, after which it equalizes; consequently, due to women's longer life expectancy, overall prevalence is similar.[14,18-21] Additionally, AF onset occurs at an older age in women. The precise causes of sex-based differences in AF incidence rate are unclear and likely multifactorial. One explanation is the protective effect of estrogens, which could account for the lower incidence rate in premenopausal women. Other explanations include men's larger atrial size and the differing influence of other AF-related risk factors by sex.[14,19-21]

AF-related risk factors and comorbidities also differ. Overall, women are older, more often have valvular heart disease, hyperthyroidism, hypertension, and heart failure with preserved ejection fraction, and generally exhibit more comorbidities. In contrast, men more frequently present ischemic heart disease, heart failure with reduced ejection fraction, chronic obstructive pulmonary disease, higher body mass index, and postoperative AF.[18-26]

Regarding AF-related factors, numerous studies in the past 2 decades have shown that high-intensity exercise increases the risk of developing AF; however, most of these studies included only or mostly men.[27,28] In women, high-intensity exercise generally confers a protective effect vs AF development.[29-31] Recently, some studies have suggested that elite athletic activity may also increase AF risk in women, though the relative risk is lower than in men.[32] These sex differences likely reflect distinct patterns of atrial remodeling induced by intense physical activity.[33,34] Understanding these differences is crucial, as they may justify distinct exercise recommendations by sex.

Presentation, symptoms, and diagnosis

Women tend to be more symptomatic than men. They more frequently report palpitations and usually present with higher heart rates. They also report nonspecific symptoms such as dizziness, dyspnea, or fatigue more often.[35-37] This greater symptom burden is associated with poorer quality of life in women,[23,37-39] although men exhibit greater exercise intolerance.[26]

Women also tend to delay seeking emergency care and present with longer symptom duration. Combined with nonspecific or anxiety-related initial symptoms, this delay often results in later diagnosis.[39,40]

Prognosis

In the prognosis of AF, there are also notable sex-related differences. Women with AF have a higher risk of ischemic stroke than men.[36,41-48] Although some studies indicate that female sex alone is not an independent risk factor, its association with other factors markedly increases the risk.[45] Moreover, in women, AF-associated strokes are characterized by greater severity, morbidity, and mortality vs men[46-48] with a higher proportion of large-vessel strokes.[46] Following cardioversion, stroke risk also remains higher in women, regardless of whether cardioversion is electrical, pharmacologic, or spontaneous.[49,50] Similarly, vascular dementia is more frequent and carries a higher risk of progression in women than in men with AF.[51]

Conversely, women have a lower risk of bleeding—both major and intracranial—than men do.[48]

Overall, all-cause and cardiovascular mortality are higher in women with AF,[42,52,53] particularly in developing countries,[53] though some studies report higher early mortality in men.[36,54] Evidence regarding heart failure is mixed: most studies show that female sex is associated with higher risk, particularly for heart failure with preserved ejection fraction,[43,53] though some report higher incidence in men.[40]

These prognostic differences are not fully explained. While women's older age and greater comorbidity may play a role, these factors do not fully account for the higher adjusted morbidity and mortality. Other proposed explanations include lower atrial contractility and greater atrial fibrosis in women—associated with higher stroke and mortality risk[17,55-57]—as well as suboptimal treatment, which may explain both the higher thromboembolic and lower hemorrhagic risks.

Response to treatment

Anticoagulant therapy

Some studies suggest that women may derive greater benefit from anticoagulant therapy than men do. In several, anticoagulation was associated with increased efficacy and lower mortality,[52,58] particularly among older women,[58] whereas in others, the benefit stemmed primarily from enhanced safety, with a lower risk of bleeding.[59] However, most of these studies were not specifically designed to evaluate sex-based differences, and their results should therefore be interpreted with caution. The mechanisms behind this potentially greater safety and efficacy profile in women remain unclear.

On the other hand, women appear to benefit more from direct oral anticoagulants (DOACs) vs vitamin K antagonists (VKAs), particularly due to improved safety—lower rates of major and intracranial bleeding—except in the case of rivaroxaban.[45,60-65] A plausible explanation, though not the only one, is that women treated with VKAs spend less time within the therapeutic range,[59,65] which may lead to poorer outcomes compared with DOACs.

Rate vs rhythm control

Few studies report outcomes stratified by sex or gender, and the available data are inconsistent. In one of the first pivotal trials, AFFIRM, which showed no difference between rate and rhythm control strategies, no sex-related differences in outcomes were observed.[66] In the more recent EAST-AFNET 4 trial, which demonstrated the benefit of early rhythm control, no interaction by sex was identified either.[67] However, in the RACE trial—whose overall results were similar to AFFIRM—sex-based differences emerged: while men showed no differences between the 2

strategies, women randomized to rhythm control had significantly higher mortality, heart failure, thromboembolic complications, and adverse drug reactions vs those under rate control.[68] Similarly, an observational study of 139,767 women and 135,850 men aged ≥ 75 years found a higher incidence rate of heart failure among women treated with rhythm control, though no sex-related differences in stroke or bleeding risk were observed.[69]

Antiarrhythmic drugs

Overall, women generally experience greater drug-related toxicity due to higher systemic drug concentrations, as they have a lower volume of distribution (less body water), higher fat mass, greater accumulation of lipophilic drugs, slower hepatic metabolism, and reduced glomerular filtration rate.[3,4]

Antiarrhythmic agents are no exception.[70] Because the QT interval is physiologically longer in women, any QT-prolonging drug carries a higher risk of proarrhythmia.[16,71]

Specifically, the risk of torsades de pointes due to sotalol use is higher in women.[72] This risk is also increased in women treated with amiodarone, although overall it is lower than that associated with sotalol.[70] Regarding amiodarone, a higher rate of pacemaker implantation has also been reported in women.[73] Conversely, digoxin use has been linked to an increased risk of mortality in women with heart failure.[74] Beta-blockers are generally well tolerated; however, there are exceptions—plasma metoprolol levels can be up to 40% higher in women than in men at equivalent doses, resulting in a greater incidence of adverse effects.[4]

Nonpharmacologic interventions

Women generally have worse outcomes than men after AF ablation, though data across studies are inconsistent. They experience higher complication rates, both procedural and cardiovascular.[75-77] The reasons for this are not fully understood. Women's atria are smaller, with thinner walls and narrower vessels, potentially increasing the risk of complications when using instruments primarily designed for men.

Several studies also report higher recurrence rates after ablation in women,[76-78] and similar findings have been observed after electrical cardioversion.[79]

Pregnancy

Pregnancy, inherently linked to female sex, is associated with AF in approximately 60 per 100,000 pregnancies. Although the prevalence is low, incidence is rising due to increasing maternal age and improved survival of women with congenital heart disease. However, pregnant women are typically excluded from clinical trials, resulting in limited evidence to guide management.[15,16]

In general, rhythm control is preferred over rate control. Electrical cardioversion is considered safe for both mother and fetus[80] and is the recommended therapy. In hemodynamically stable patients without structural heart disease, pharmacologic cardioversion with procainamide or flecainide may also be used.[15,16,80] Nevertheless, due to potential teratogenicity, pharmacologic therapy should be reserved as a second-line option, particularly within the first trimester. Some studies report favorable outcomes with catheter ablation from the second trimester onward, suggesting it may be a reasonable alternative to long-term potentially teratogenic drug therapy.[15,80]

Anticoagulation is recommended for pregnant women at high thrombotic risk.[81] Pregnancy per se increases thromboembolic risk. VKAs may be used after the first trimester, while low-molecular-weight heparin (LMWH) should be monitored via anti–factor Xa levels. DOACs are contraindicated during pregnancy due to insufficient evidence on safety and efficacy.[16,80]

Interaction with the health care system

Treatment in women tends to be more conservative than in men, even after adjusting for confounders. Despite being more symptomatic, women are less likely to undergo rhythm control interventions. When rhythm control is attempted, it is more frequently achieved pharmacologically, with fewer electrical cardioversions and pulmonary vein ablations performed.[36,52,70,82,83] Conversely, women more frequently undergo AV node ablation with pacemaker implantation and receive rate-control drugs more often.[36,75] Women are prescribed fewer beta-blockers and more digoxin, despite its higher adverse event risk in this population.[14,24,36]

They are also less likely to receive anticoagulation—even when risk is equivalent—and are prescribed DOACs less often.[52,68,84] These disparities lack a scientific basis.

Clinical differences in outcomes across the various therapeutic options are insufficient to explain the sex and gender biasobserved in the treatment of AF, as the studies demonstrating this bias are adjusted for confounding factors. Furthermore, regarding anticoagulant therapy, women appear to derive even greater benefit—particularly from DOACs. Possible explanations for this bias may include racial disparities, differences in access to care, patient preferences, or unmeasured clinical characteristics; however, unjustified biases likely play a significant role.

Implications and future directions

The differences described above are not merely descriptive—they have clinical implications that influence diagnosis, treatment, and prognosis. Key questions arise: Are we providing the most appropriate treatment for each patient? Are dosing regimens optimal? Are we practicing equitable medicine? Are we truly individualizing care?

In the emergency department, these questions are especially relevant, as critical decisions—such as rhythm vs rate control and anticoagulation—are often made solely by emergency physicians, given the high proportion of AF patients discharged directly from the ED.

We cannot ignore such consistent and logical evidence. Optimal management of patients with AF requires individualized consideration of sex and gender across research, education, and clinical practice—and this responsibility lies in our hands.

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REFERENCES

1. Mauvais-Jarvis F, Bairey Merz N, Barnes PJ, Brinton RD, Carrero JJ, DeMeo DL, et al. Sex and gender: modifiers of health, disease, and medicine. Lancet. 2020;396:565-82.
2. Gendered Innovations in Science, Health & Medicine, Engineering and Environment. Gendered Innovations | Stanford University. Última visita en junio 2024.
3. Rodríguez-Reyes M. Perspectiva de género y problemas de salud relacionados con los medicamentos. En: Monografías de Farmacia Hospitalaria: Salud con perspectiva de género (nº 21). Barcelona: Bayer Hispania SL, 2024.
4. Farkouh A, Riedl T, Gottardi R, Czejka M, Kautzky-Willer A. Sex-Related Differences in Pharmacokinetics and Pharmacodynamics of Frequently Prescribed Drugs: A Review of the Literature. Adv Ther. 2020;37:644-55.
5. Marrugat J, Sala J, Masiá R, Pavesi M, Sanz G, Valle V, et al. Mortality differences between men and women following first myocardial infarction. RESCATE Investigators. Recursos Empleados en el Síndrome Coronario Agudo y Tiempo de Espera. JAMA. 1998;280:1405-9.
6. Lakbar I, Einav S, Lalevée N, Martin-Loeches I, Pastene B, Leone M. Interactions between Gender and Sepsis-Implications for the Future. Microorganisms. 2023;11:746.
7. Chowdhury NU, Guntur VP, Newcomb DC, Wechsler ME. Sex and gender in asthma. Eur Respir Rev. 2021;30:210067.
8. Morrison LJ, Schmicker RH, Weisfeldt ML, Bigham BL, Berg RA, Topjian AA, et al; Resuscitation Outcomes Consortium Investigators. Effect of gender on outcome of out of hospital cardiac arrest in the Resuscitation Outcomes Consortium. Resuscitation. 2016;100:76-81.
9. Ruiz Azpiazu JI, Fernández del Valle P, Escriche MC, Royo Embid S, Fernández Barreras C, Azeli Y, et al. Incidencia, tratamiento y factores asociados con la supervivencia de la parada cardiaca extrahospitalaria atendida por los servicios de emergencias en España: informe 2022 del registro OHSCAR. Emergencias. 2024;36:131-9.
10. Flores-Umanzor E, Cepas-Guillén P, Freixa X, Regueiro A, Tizón-Marcos H, Brugaletta S, et al. Perfil clínico y pronóstico de pacientes jóvenes con infarto agudo de miocardio con elevación del segmento ST tratados en la red Codi IAM. Rev Esp Cardiol. 2023;76:881-90.
11. Lichtman JH, Leifheit EC, Safdar B, Bao H, Krumholz HM, Lorenze NP, et al. Sex Differences in the Presentation and Perception of Symptoms Among Young Patients With Myocardial Infarction: Evidence from the VIRGO Study (Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients). Circulation. 2018;137:781-90.
12. Martín-Sánchez FJ, Valls Carbó A, Miró Ò, Llorens P, Jiménez S, Piñera P, et al. Socio-Demographic Health Determinants Are Associated with Poor Prognosis in Spanish Patients Hospitalized with COVID-19. J Gen Intern Med. 2021 ; 36: 3737-3742.
13. Noubiap JJ, Thomas G, Nyaga UF, Fitzgerald JL, Gallagher C, Middeldorp ME, Sanders P. Sex disparities in enrollment and reporting of outcomes by sex in contemporary clinical trials of atrial fibrillation. J Cardiovasc Electrophysiol. 2022;33:845-54.
14. Gomez SE, Fazal M, Nunes JC, Shah S, Perino AC, Narayan SM, et al. Racial, ethnic, and sex disparities in atrial fibrillation management: rate and rhythm control. J Interv Card Electrophysiol. 2023;66:1279-90.
15. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, et al; ESC Scientific Document Group. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. Eur Heart J. 2021;42:373-498.
16. Joglar JA, Chung MK, Armbruster AL, Benjamin EJ, Chyou JY, Cronin EM, et al; Peer Review Committee Members. 2023 ACC/AHA/ACCP/HRS Guideline for the Diagnosis and Management of Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2024;149:e1-e156.
17. Zeitler EP, Birgersdotter-Green U, Poole JE, Albert CM, Al-Khatib SM, Ali-Ahmed F, et al. Arrhythmias in Female Patients: Incidence, Presentation and Management. Circulation Research. 2022;130:474-95.
18. Magnussen C, Niiranen TJ, Ojeda FM, Gianfagna F, Blankenberg S, Njølstad I, et al; BiomarCaRE Consortium. Sex Differences and Similarities in Atrial Fibrillation Epidemiology, Risk Factors, and Mortality in Community Cohorts: Results From the BiomarCaRE Consortium (Biomarker for Cardiovascular Risk Assessment in Europe). Circulation. 2017;136:1588-97.
19. Shiyovich A, Chodick G, Azani L, Tirosh M, Shuvy M, Pereg D, et al. Sex-specific contemporary trends in incidence, prevalence and survival of patients with non-valvular atrial fibrillation: A long-term real-world data analysis. PLoS One. 2021;16:e0247097.
20. Volgman AS, Benjamin EJ, Curtis AB, Fang MC, Lindley KJ, Naccarelli GV, et al; American College of Cardiology Committee on Cardiovascular Disease in Women. Women and atrial fibrillation. J Cardiovasc Electrophysiol. 2021;32:2793-807.
21. Westerman S, Wenger N. Gender Differences in Atrial Fibrillation: A Review of Epidemiology, Management, and Outcomes. Curr Cardiol Rev. 2019;15:136-44.
22. McManus DD, Xanthakis V, Sullivan LM, Zachariah J, Aragam J, Larson MG, et al. Longitudinal tracking of left atrial diameter over the adult life course: clinical correlates in the community. Circulation. 2010;121:667-74.
23. Durán-Bobín O, Elices-Teja J, González-Melchor L, Vázquez-Caamaño M, Fernández-Obanza E, González-Babarro E, et al. Differences in the Clinical Profile and Management of Atrial Fibrillation According to Gender. Results of the REgistro GallEgo Intercéntrico de Fibrilación Auricular (REGUEIFA) Trial. J Clin Med. 2021;10:3846.
24. Dagres N, Nieuwlaat R, Vardas PE, Andresen D, Lévy S, Cobbe S, et al. Gender-related 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;48:572-7.
25. Ball J, Løchen ML, Wilsgaard T, Schirmer H, Hopstock LA, Morseth B, et al. Sex Differences in the Impact of Body Mass Index on the Risk of Future Atrial Fibrillation: Insights From the Longitudinal Population-Based Tromsø Study. J Am Heart Assoc. 2018:e008414.
26. Lip GY, Laroche C, Boriani G, Cimaglia P, Dan GA, Santini Met 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.
27. Newman W, Parry-Williams G, Wiles J, Edwards J, Hulbert S, Kipourou K, et al. Risk of atrial fibrillation in athletes: a systematic review and meta-analysis. Br J Sports Med. 2021;55:1233-8.
28. Li X, Cui S, Xuan D, Xuan C, Xu D. Atrial fibrillation in athletes and general population: A systematic review and meta-analysis. Medicine (Baltimore). 2018;97:e13405.
29. Mozaffarian D, Furberg CD, Psaty BM, Siscovick D. Physical activity and incidence of atrial fibrillation in older adults: the cardiovascular health study. Circulation 2008;118:800-7.
30. Sun GZ, Guo L, Wang XZ, Song HJ, Li Z, Wang J, et al. Prevalence of atrial fibrillation and its risk factors in rural China: a cross-sectional study. Int J Cardiol 2015;182:13-7.
31. Azarbal F, Stefanick ML, Salmoirago-Blotcher E, Manson JE, Albert CM, LaMonte MJ, et al. Obesity, physical activity, and their interaction in incident atrial fibrillation in postmenopausal women. J Am Heart Assoc. 2014;3:e001127.
32. Drca N, Larsson SC, Grannas D, Jensen-Urstad M. Elite female endurance athletes are at increased risk of atrial fibrillation compared to the general population: a matched cohort study. Br J Sports Med. 2023;57:1175-9.
33. Aaroee M, Tischer SG, Christensen R, Dall CH, Thune JJ, Rasmusen H. Atrial remodelling associated with sporting discipline, sex and duration in elite sports: a cross-sectional echocardiographic study among Danish elite athletes. BMJ Open Sport Exerc Med. 2024;10:e001880.
34. Mont L, Elosua R, Brugada J. Endurance sport practice as a risk factor for atrial fibrillation and atrial flutter. Europace. 2009;11:11-7.
35. Schnabel RB, Pecen L, Ojeda FM, Lucerna M, Rzayeva N, Blankenberg S et al. Gender differences in clinical presentation and 1-year outcomes in atrial fibrillation. Heart. 2017;103:1024-30.
36. Piccini JP, Simon DN, Steinberg BA, Thomas L, Allen LA, Fonarow GC, et al. Outcomes registry for better informed treatment of atrial fibrillation I and patients. Differences in clinical and functional outcomes of atrial fibrillation in women and men: two-year results from the ORBIT-AF Registry. JAMA Cardiol. 2016;1:282-91.
37. Blum S, Muff C, Aeschbacher S, Ammann P,

Erne P, Moschovitis G, et al. Prospective assessment of sex-related differences in symptom status and health perception among patients with atrial fibrillation. J Am Heart Assoc. 2017;6:6.
38. Gleason KT, Dennison Himmelfarb CR, Ford DE, Lehmann H, Samuel L, Han HR, et al. Association of sex, age and education level with patient reported outcomes in atrial fibrillation. BMC Cardiovasc Disord. 2019;19:85.
39. 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.
40. Scheuermeyer FX, Mackay M, Christenson J, Grafstein E, Pourvali R, Heslop C, et al. There are sex differences in the demographics and risk profiles of emergency department (ED) patients with atrial fibrillation and flutter, but no apparent differences in ED management or outcomes. Acad Emerg Med. 2015;22:1067-75.
41. Emdin CA, Wong CX, Hsiao AJ, Altman DG, Peters SA, Woodward M, Odutayo AAt 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.
42. Islam S, Dover DC, Daniele P, Hawkins NM, Humphries KH, Kaul P, Sandhu RK. Sex Differences in the Management of Oral Anticoagulation and Outcomes for Emergency Department Presentation of Incident Atrial Fibrillation. Ann Emerg Med. 2022;80:97-107.
43. 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 nonvalvular atrial fibrillation treated with oral anticoagulants. Am J Cardiol. 2014;113:485-90.
44. 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.
45. Nielsen PB, Skjøth F, Overvad TF, Larsen TB, Lip GYH. Female sex is a risk modifier rather than a risk factor for stroke in atrial fibrillation: should we use a CHA2DS2-VA score rather than CHA2DS2-VASc? Circulation. 2018;137:832-40.
46. Fang MC, Singer DE, Chang Y, Hylek EM, Henault LE, Jensvold NG et al. Gender differences in the risk of ischemic stroke and peripheral embolism in atrial fibrillation: the AnTicoagulation and Risk factors In Atrial fibrillation (ATRIA) study. Circulation. 2005;112:1687-91.
47. Friberg L, Benson L, Rosenqvist M, Lip GY. Assessment of female sex as a risk factor in atrial fibrillation in Sweden: nationwide retrospective cohort study. BMJ 2012;344:e3522.
48. Khunte M, Chen H, Colasurdo M, Chaturvedi S, Malhotra A, Gandhi D. Sex discrepancies in the population incidence of stroke and hemorrhage related to atrial fibrillation or flutter. Cerebrovasc Dis. 2024. doi: 10.1159/000538108. Epub ahead of print.
49. Airaksinen KE, Gronberg T, Nuotio I, Nikkinen M, Ylitalo A, Biancari F et al. Thromboembolic complications after cardioversion of acute atrial fibrillation: the FinCV (Finnish CardioVersion) study. J Am Coll Cardiol 2013;62:1187-92.
50. Bah A, Nuotio I, Grönberg T, Ylitalo A, Airaksinen KEJ, Hartikainen JEK. Sex, age, and time to cardioversion. Risk factors for cardioversion of acute atrial fibrillation from the FinCV study. Ann Med. 2017;49:254-9.
51. Wood KA, Han F, Ko YA, Wharton WW. Is the association between cognitive disease progression and atrial fibrillation modified by sex? Alzheimers Dement. 2023;19:4163-73.
52. Kassim NA, Althouse AD, Qin D, Leef G, Saba S. Gender differences in management and clinical outcomes of atrial fibrillation patients. J Cardiol. 2017;69:195-200.
53. 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.
54. Renoux C, Patenaude V, Suissa S. Incidence, mortality, and sex differences of non-valvular atrial fibrillation: a population-based study. J Am Heart Assoc. 2014;3:e001402.
55. Guo Y, Lip GY, Apostolakis S. Inflammatory biomarkers and atrial fibrillation: potential role of inflammatory pathways in the pathogenesis of atrial fibril lation-induced thromboembolism. Curr Vasc Pharmacol. 2015;13:192-201.
56. Li Z, Wang Z, Yin Z, Zhang Y, Xue X, Han J, et al. Gender differences in fibrosis remodeling in patients with long-standing persistent atrial fibrillation. Oncotarget 2017;8:53714-29.
57. Akoum N, Mahnkopf C, Kholmovski EG, Brachmann J, Marrouche NF. Age and sex differences in atrial fibrosis among patients with atrial fibrillation. Europace. 2018;20:1086-92.
58. Varona M, Martín A, Sánchez J, Tamargo J, Cancio M, Sánchez S, et al. Diferencias de sexo en los beneficios de la anticoagulación en pacientes ancianos con fibrilación auricular: un subanálisis del estudio EMERG-AF. Emergencias. 2023;35:252-60.
59. Senoo K, Lip GHY. Female Sex, Time in Therapeutic Range, and Clinical Outcomes in Atrial Fibrillation Patients Taking Warfarin. Stroke. 2016;47:1665-8.
60. Zelniker TA, Ardissino M, Andreotti F, O'Donoghue ML, Yin O, Park JG, et al. Comparison of the Efficacy and Safety Outcomes of Edoxaban in 8040 Women Versus 13 065 Men With Atrial Fibrillation in the ENGAGE AF-TIMI 48 Trial. Circulation. 2021 16;143:673-84.
61. Proietti M, Cheli P, Basili S, Mazirek M, Lip GYH. Balancing thromboembolic and bleeding risk with non-vitamin K antagonist oral anticoagulants (NOACs): a systematic review and meta-analysis on gender differences. Pharmacol Res. 2017;117:274-82.
62. Law SWY, Lau WCY, Wong ICK, Lip GYH, Mok MT, Siu CW, et al. Sex-Based Differences in Outcomes of Oral Anticoagulation in Patients With Atrial Fibrillation. J Am Coll Cardiol. 2018;72:271-82.
63. Carnicelli AP, Hong H, Connolly SJ, Eikelboom J, Giugliano RP, Morrow DA, et al; COMBINE AF (A Collaboration Between Multiple Institutions to Better Investigate Non-Vitamin K Antagonist Oral Anticoagulant Use in Atrial Fibrillation) Investigators. Direct Oral Anticoagulants Versus Warfarin in Patients With Atrial Fibrillation: Patient-Level Network Meta-Analyses of Randomized Clinical Trials With Interaction Testing by Age and Sex. Circulation. 2022;145:242-55.
64. Palamaner Subash Shantha G, Bhave PD, Girotra S, Hodgson-Zingman D, Mazur A, Giudici M, et al. Sex-Specific Comparative Effectiveness of Oral Anticoagulants in Elderly Patients With Newly Diagnosed Atrial Fibrillation. Circ Cardiovasc Qual Outcomes. 2017;10:e003418.
65. Rago A, Pirozzi C, D'Andrea A, Di Micco P, Papa AA, D'Onofrio A, et al. Gender Differences in Atrial Fibrillation: From the Thromboembolic Risk to the Anticoagulant Treatment Response. Medicina (Kaunas). 2023;59:254.
66. Curtis AB, Gersh BJ, Corley SD, DiMarco JP, Domanski MJ, Geller N, et al; AFFIRM Investigators. Clinical factors that influence response to treatment strategies in atrial fibrillation: the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study. Am Heart J. 2005;149:645-9.
67. Van Gelder IC, Ekrami NK, Borof K, Fetsch T, Magnussen C, Mulder BA, et al; EAST-AFNET 4 Trial Investigators. Sex Differences in Early Rhythm Control of Atrial Fibrillation in the EAST-AFNET 4 Trial. J Am Coll Cardiol. 2023;81:845-7.
68. Rienstra M, Van Veldhuisen DJ, Hagens VE, Ranchor AV, Veeger NJ, Crijns HJ et al. Gender-related differences in rhythm control treatment in persistent atrial fibrillation: data of the Rate Control Versus Electrical Cardioversion (RACE) study. J Am Coll Cardiol. 2005;46:1298-306.
69. Subramanya V, Claxton JS, Lutsey PL, MacLehose RF, Chen LY, Chamberlain AM, et al. Sex differences in treatment strategy and adverse outcomes among patients 75 and older with atrial fibrillation in the MarketScan database. BMC Cardiovasc Disord. 2021;21:598.
70. Weberndörfer V, Beinart R, Ricciardi D, Ector J, Mahfoud M, Szeplaki G, et al; DAS-CAM participants 2017/2018. Sex differences in rate and rhythm control for atrial fibrillation. Europace. 2019;21:690-7.
71. Makkar RR, Fromm BS, Steinman RT, Meissner MD, Lehmann MH. Female gender as a risk factor for torsades de pointes associated with cardiovascular drugs. JAMA. 1993;270:2590-7.
72. Lehmann MH, Hardy S, Archibald D, Quart B, MacNeil DJ. Sex difference in risk of torsade de pointes with d,l-sotalol. Circulation. 1996;94:2535-41.
73. Essebag V, Reynolds MR, Hadjis T, Lemery R, Olshansky B, Buxton AE, et al. Sex differences in the relationship between amiodarone use and the need for permanent pacing in patients with atrial fibrillation. Arch Intern Med. 2007;167:1648-53.
74. Rathore SS, Wang Y, Krumholz HM. Sex-based differences in the effect of digoxin for the treatment of heart failure. N Engl J Med. 2002;347:1403-11.
75. Grecu M, Blomström-Lundqvist C, Kautzner J, Laroche C, Van Gelder IC, Jordaens L, at al; ESC-EORP EHRA Atrial Fibrillation Ablation Long-Term Registry investigators. In-hospital and 12-month follow-up outcome from the ESC-EORP EHRA Atrial Fibrillation Ablation Long-Term registry: sex differences. Europace. 2020;22:66-73.
76. Russo AM, Zeitler EP, Giczewska A, Silverstein AP, Al-Khalidi HR, Cha YM, et al; CABANA Investigators. Association Between Sex and Treatment Outcomes of Atrial Fibrillation Ablation Versus Drug Therapy: Results From the CABANA Trial. Circulation. 2021;143:661-72.
77. Kuck KH, Brugada J, Fürnkranz A, Chun KRJ, Metzner A, Ouyang F, et al; FIRE AND ICE Investigators. Impact of Female Sex on Clinical Outcomes in the FIRE AND ICE Trial of Catheter Ablation for Atrial Fibrillation. Circ Arrhythm Electrophysiol. 2018;11:e006204.
78. Veen D, Verbeek EC, Kavousi M, Huigen J, Mijnen-Schra A, Cocchieri R, et al. Sex differences in characteristics of atrial fibrillation recurrence post surgical pulmonary vein isolation. Int J Cardiol Heart Vasc. 2023;48:101262.
79. Gurevitz OT, Varadachari CJ, Ammash NM, Malouf JF, Rosales AG, Herges RM et al. The effect of patient sex on recurrence of atrial fibrillation following suc cessful direct current cardioversion. Am Heart J 2006;152:155.e9-13.
80. Georgiopoulos G, Tsiachris D, Kordalis A, Kontogiannis C, Spartalis M, Pietri P et al. Pharmacotherapeutic strategies for atrial fibrillation in pregnancy. Expert Opin Pharmacother. 2019;20:1625-36.
81. Jiménez S. Tromboembolia de pulmón y ges-

tación: una aproximación actualizada para urgencias. Rev Esp Urg Emerg. 2023;2:48-51.
82. Bhave PD, Lu X, Girotra S, Kamel H, Vaughan Sarrazin MS. Race- and sex-related differences in care for patients newly diagnosed with atrial fibrillation. Heart Rhythm. 2015;12:1406-12.
83. Björkenheim A, Fengsrud E, Blomström-Lundqvist C. Catheter ablation of symptomatic atrial fibrillation: Sex, ethnicity, and socioeconomic disparities. Heart Rhythm O2. 2022;3:766-70.
84. Coll-Vinent B, Martín A, Malagón F, Suero C, Sánchez J, Varona M, et al; HERMES-AF Investigators; HERMES-AF Investigators. Stroke prophylaxis in atrial fibrillation: searching for management improvement opportunities in the emergency department: the HERMES-AF study. Ann Emerg Med. 2015;65:1-12.