Gender-Related Differences In Treatment Patterns And Outcomes of Patients With Atrial Fibrillation: Insights From The MISOAC-AF Trial

Ioannis Voulouagkas (✉ jochannVL@gmail.com)

University General Hospital of Thessaloniki AHEPA First Cardiology Clinic: Panepistemiako Geniko Nosokomeio Thessalonikes ACHEPA A' Kardiologike Klinike <https://orcid.org/0000-0001-8180-4067>

Anastasios Kartas

University General Hospital of Thessaloniki AHEPA First Cardiology Clinic: Panepistemiako Geniko Nosokomeio Thessalonikes ACHEPA A' Kardiologike Klinike

Athanasios Samaras

University General Hospital of Thessaloniki AHEPA First Cardiology Clinic: Panepistemiako Geniko Nosokomeio Thessalonikes ACHEPA A' Kardiologike Klinike

Andreas S. Papazoglou

University General Hospital of Thessaloniki AHEPA First Cardiology Clinic: Panepistemiako Geniko Nosokomeio Thessalonikes ACHEPA A' Kardiologike Klinike

Dimitrios V. Moysidis

University General Hospital of Thessaloniki AHEPA First Cardiology Clinic: Panepistemiako Geniko Nosokomeio Thessalonikes ACHEPA A' Kardiologike Klinike

Eleni Vrana

University General Hospital of Thessaloniki AHEPA 1st Cardiology Department: Panepistemiako Geniko Nosokomeio Thessalonikes ACHEPA A' Kardiologike Klinike

Anastasios Papanastasiou

University General Hospital of Thessaloniki AHEPA First Cardiology Clinic: Panepistemiako Geniko Nosokomeio Thessalonikes ACHEPA A' Kardiologike Klinike

Amalia Baroutidou

University General Hospital of Thessaloniki AHEPA First Cardiology Clinic: Panepistemiako Geniko Nosokomeio Thessalonikes ACHEPA A' Kardiologike Klinike

Michail Botis

University General Hospital of Thessaloniki AHEPA First Cardiology Clinic: Panepistemiako Geniko Nosokomeio Thessalonikes ACHEPA A' Kardiologike Klinike

Georgios Kotzampasis

University General Hospital of Thessaloniki AHEPA First Cardiology Clinic: Panepistemiako Geniko Nosokomeio Thessalonikes ACHEPA A' Kardiologike Klinike

Evangelos Liampas

University General Hospital of Thessaloniki AHEPA First Cardiology Clinic: Panepistemiako Geniko Nosokomeio Thessalonikes ACHEPA A' Kardiologike Klinike

Thomas Zegkos

University General Hospital of Thessaloniki AHEPA First Cardiology Clinic: Panepistemiako Geniko Nosokomeio Thessalonikes ACHEPA A' Kardiologike Klinike

Sophia Anastasia Mouratoglou

University General Hospital of Thessaloniki AHEPA First Cardiology Clinic: Panepistemiako Geniko Nosokomeio Thessalonikes ACHEPA A' Kardiologike Klinike

Haralambos Karvounis

University General Hospital of Thessaloniki AHEPA First Cardiology Clinic: Panepistemiako Geniko Nosokomeio Thessalonikes ACHEPA A' Kardiologike Klinike

Apostolos Tzikas

Iatriko Diavalkaniko Kentro

George Giannakoulas

University General Hospital of Thessaloniki AHEPA First Cardiology Clinic: Panepistemiako Geniko Nosokomeio Thessalonikes ACHEPA A' Kardiologike Klinike

Research Article

Keywords: Atrial Fibrillation, Gender, Sex, Rate control, rhythm control, stroke, mortality

Posted Date: August 11th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-772332/v1>

License: This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Purpose

To assess the gender-related differences in the treatment patterns of patients with atrial fibrillation (AF), and their prognostic value.

Methods

In this post-hoc analysis of a randomized controlled trial, 1140 hospitalized patients with comorbid AF were followed-up for a median of 2.6 years. Kaplan-Meier and multivariable Cox-regression analyses assessed the adjusted hazard ratios (aHRs) for outcomes in males and females, according to oral anticoagulation (OAC) type (vitamin K antagonist or non-vitamin K antagonist oral anticoagulants), rhythm or rate control treatment. The primary outcome was all-cause mortality and the secondary outcomes were stroke and the composite of any hospitalization or cardiovascular death.

Results

Among 622 males and 518 females, use of OAC (61% vs 62%), rate control (56% vs 57%), and rhythm control (31% vs 28%) treatments was similar (all $p > 0.05$). In males, use of rate control, as compared with rhythm control, was independently associated with higher rates of all-cause mortality (aHR=2.06; 95% confidence interval [CI] 1.24-3.41) and the composite of hospitalization or cardiovascular death (aHR=1.34, 95% CI 1.01-1.85). In females, use of rhythm control was significantly associated with higher rates of hospitalization-or cardiovascular mortality (aHR=1.74, 95% CI 1.03-2.94). Among genders, stroke rates were similar regardless of OAC type, rate or rhythm control treatment.

Conclusions

In patients discharged from the hospital with comorbid AF, the use of OAC, rhythm or rate control treatment was similar among genders. However, males seemed to benefit more from rhythm, whereas females from rate control treatment.

Introduction

Atrial fibrillation (AF) has developed into a true 21st - century pandemic among both female and male individuals, claiming a disproportionate amount of the physicians' devotion [1, 2]. Treatment strategies in these patients mainly include oral anticoagulation (OAC) agents, in combination with a rate or rhythm control drug. Whether OAC type, rate, or rhythm control treatment translate into different outcomes in the real-world is an active research field. In theory, these treatments apply similarly to male and female patients.

Nevertheless, one can name more than a few medical conditions, such as coronary heart disease [3], hypertension [4], or heart failure [5], in which there are surprising differences between the two genders, as

far as the therapeutic paths followed and the subsequent clinical outcomes are concerned. Distinct disparities in the clinical presentation among men and women have also been reported in AF, which could influence decisions on discharge treatment [6, 7]. However, data on gender-related differences in AF treatment patterns, along with prospective outcomes, remain sparse.

In the current study, we analyzed a contemporary cohort of patients with AF. We attempted to depict gender-related disparities in the main axes of AF treatment, namely OAC, rate and rhythm control. We further aimed to investigate the association of these treatment modalities with fatal and non-fatal clinical outcomes in males and females.

Methods

STUDY DESIGN AND DATA SOURCES

This is a retrospective cohort study using data from the MISOAC-AF (Motivational Interviewing to Support Oral Anti Coagulation adherence in patients with non-valvular AF) randomized controlled trial. The protocol, as well as the baseline characteristics and main results of the MISOAC-AF registry have been previously published elsewhere. [8, 9]. Briefly, the objective of the MISOAC-AF trial was to assess the impact of a motivational intervention on the adherence of patients to OAC medication. Study protocols were approved by the appropriate Institutional Review Board at the Aristotle University of Thessaloniki and every trial procedure conformed to the Declaration of Helsinki [10].

All clinical baseline characteristics, as well as demographic, laboratory, echocardiographic and medication data of the patients were provided by the MISOAC-AF database.

DEFINITION OF COVARIATES

Atrial fibrillation was defined as an electrocardiographically confirmed irregular heart rate that lasted more than 30 seconds, with an absence of p waves [11]. Patients denoted on rhythm control treatment at discharge were those treated with amiodarone, propafenone, or sotalol, with or without concomitant rate-control treatment. Patients on rate control were those treated with any combination of b-blocker, non-dihydropyridine calcium channel blocker, or digoxin, without antiarrhythmic drug use.

STUDY POPULATION

The study involved adult individuals with primary or secondary diagnosis of non-valvular AF. All patients had been hospitalized in the cardiology ward of AHEPA University Hospital of Thessaloniki. Exclusion criteria in our study included: 1) patients whose end-stage disease made impossible the collection of follow-up data and 2) patients with unobtainable or unknown data concerning their rhythm or rate control treatment.

STUDY OUTCOMES AND FOLLOW-UP

The primary outcome was all-cause mortality, defined as death from any cause. The secondary outcomes were the composite of any hospitalization- or cardiovascular (CV) death, and stroke, during the follow-up period.

Follow-up data were collected via in-person or telephone interviews at 12 and 24 months from the enrollment in our database. Patients were considered censored at the time of an outcome event, or death. The follow-up process was completed in April 2020. All deaths were searched in the Greek web-based civil registration insurance system.

STATISTICAL ANALYSIS

Patient demographics, physical and laboratory findings, medical history, and medication were summarized using frequencies and percentages for categorical variables and mean $\pm$ standard deviation (SD) values for continuous ones. Differences between groups were tested using a chi-square or Fisher's exact test for descriptive variables and Students T-test for continuous ones. To examine the association between treatment decision (OAC, rate or rhythm control) and study outcomes, cumulative incidence was calculated based on Kaplan– Meier estimates and differences between groups were tested using a log-rank test. Cox regression analysis for the primary outcome and the secondary outcomes was performed. To account for potential confounding by characteristics influencing treatment decisions and outcome of AF patients, we adjusted our analysis with the following, clinically relevant, covariates: gender, age, body mass index (BMI), diabetes mellitus (DM), hypertension, alcohol consumption, use of OAC agents, n-terminal pro-hormone blood natriuretic peptide (NT-proBNP) and estimated glomerular filtration rate (eGFR). The adjusted hazard ratios (aHR) along with the respective confidence intervals (CI) are presented. The performed tests were two-sided, while the probability value of less than $p = 0.05$ was considered statistically significant. The SPSS Statistics for Windows, Version 26.0 (Armonk, NY: IBM Corp) and Stata statistical software 13.0 were used for our analysis.

Results

Baseline clinical characteristics

Of 1140 patients included in this post-hoc analysis, 622 (57%) were male and 518 (43%) were female.

The baseline clinical characteristics of male and female individuals are presented in Table 1. Women were significantly older, with a higher left ventricular ejection fraction, and were less often bearing a pacemaker or an implantable cardioverter defibrillator. A higher percentage of men had a history of smoking, alcohol use, and a lower percentage had a history of thyroid disease.

Table 1
Baseline characteristics and comorbidities in AF patients by gender

Demographics	Males	Females	p value
Age (years)	72.09	75.42	< 0.001
BMI (Kg/m ²)	28.102	29.011	< 0.001
LVEF	46.0204	52.9755	< 0.001
D-dimers (ng/ml)	400.32	394.55	.911
Estimated GFR on admission	63.61	60.02	< 0.001
Smoking	45.6%	20.5%	< 0.001
Alcohol consumption > = 7 portions/week	252 (42.4%) 91 (mean portions 12.6)	140 (28%) 10 (mean portions 7.7)	= 0.001
Pacemaker	34 (5.7%)	28 (5.6%)	< 0.001
ICD	32 (5.4%)	2 (0.4%)	< 0.001
Hypertension	474 (79.7%)	414 (82.8%)	.187
Dyslipidemia	295 (49.6%)	232 (46.4%)	.294
Diabetes Mellitus	190 (31.9%)	173 (34.6%)	.350
Vascular Disease	309 (52%)	200 (40%)	< 0.001
Thyroid Disease	82 (13.8%)	152 (30.4%)	< 0.001
CKD	104 (17.5%)	58 (11.6%)	.006
Treatment and risk stratification scores			
Intervention to restore rhythm control			.865

AF, atrial fibrillation; LVEF, Left Ventricular Ejection Fraction; TTE, Transthoracic Echocardiography; TEE, Transesophageal Echoardiography; GFR, Glomerular Filtration Ratio; ICD, Implantable Cardioverter Defibrillator; CKD, Chronic Kidney Disease; HAS-BLED, Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile International Normalized Ratio, Elderly, Drugs/alcohol concomitantly;

Demographics	Males	Females	p value
Pharmaceutical	159 (26.7%)	136 (27.2%)	
Electrical	32 (5.4%)	31 (6.2%)	
Both	26 (4.4%)	25 (5%)	
HAS-BLED score	1.76	1.72	0.530
AF Ablation	15 (2.5%)	6 (1.2%)	0.112
CHADS2-VASc	3.89	4.97	< 0.001
AF, atrial fibrillation; LVEF, Left Ventricular Ejection Fraction; TTE, Transthoracic Echocardiography; TEE, Transesophageal Echoardiography; GFR, Glomerular Filtration Ratio; ICD, Implantable Cardioverter Defibrillator; CKD, Chronic Kidney Disease; HAS-BLED, Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile International Normalized Ratio, Elderly, Drugs/alcohol concomitantly;			

Atrial fibrillation medication differences

No significant discrepancies between the two genders were noted regarding the use of OAC, rate or rhythm control medication (all p-value > 0.05, using the Pearson chi-square test), as depicted in Fig. 4.

Out of 622 male patients, 352 (61%) were under OAC treatment. Of those, 122 (35%) were under VKA, and 230 (65%) received NOAC agents. In females, 324 (62%) were under OAC treatment and out of these 119 (37%) were under VKA, and 295 (63%) received NOAC agents.

Rate control treatment was administered to 347 (56%) males and 295 (57%) female patients. The majority of patients under rate control received only a b-blocker in both genders (90% in males, 89% in females).

Rhythm control treatment was administered to 194 (31%) male patients and 147 (28%) females. In both genders, the majority of individuals under rhythm control received solely amiodarone (89% in males, 85% in females). It is of note that OAC, rate or rhythm control treatment did not differ significantly between males and females.

Outcomes

Males

In the course of a median follow-up of 2.6 years, 229 (36.9%) male patients died. Use of VKA, or NOAC treatment at discharge was not associated with a significant difference in mortality rates in males (p > 0.001 by the log-rank test). In males, rate control medication was significantly associated with worse survival rates than rhythm control, whereas males receiving neither rate nor rhythm control at discharge were shown to have better survival rates than both of the previous categories (p < 0.001 by the log-rank

test). Unadjusted outcomes per treatment modality in males are shown in the Kaplan Meier curves of Fig. 1.

After multivariate adjustment, use of rate control treatment at discharge, as compared with rhythm control, was associated with a higher risk of all-cause mortality (aHR 2.06, 95% CI 1.24–3.41), and of the composite outcome of any hospitalization-or CV death (aHR 1.34, 95% CI 1.01–1.85), but not with an altered risk of stroke (aHR 0.77, 95% CI 0.20–3.07).

Females

During the median follow-up of 2.6 years, 198 (38.3%) females died. Use of VKA agents, or NOAC treatment in females was not independently correlated with altered survival rates. Likewise, neither a rate, nor a rhythm control treatment strategy was associated with different all-cause mortality rates of female patients in our study (all $p > 0.001$ by the log-rank test). Unadjusted outcomes per treatment modality in females are depicted in the Kaplan-Meier curves of Fig. 1.

After multivariate analysis, rhythm control treatment, as compared with rate control, did not have any significant prognostic value for all-cause mortality (aHR 1.27, 95% CI 0.67–2.41), was associated with an increased risk of any hospitalization-or CV death (aHR 1.74, 95% CI 1.03–2.94), but was not associated with altered rates of stroke (aHR 0.38, 95% CI 0.03–4.34).

Table 2

Follow-up outcomes by rhythm or rate control in male and female AF patients with corresponding HR, in comparison with the subgroup of patients receiving no rhythm or rate control

	aHR*, males rhythm	aHR*, males rate	aHR*, females rhythm	aHR*, females rate
All-cause death	1.42 (0.73–2.79)	2.06 (1.24–3.41)	1.27 (0.67–2.41)	1.37 (0.82–2.30)
CV-Death	1.42 (0.66–3.03)	2.14 (1.2–3.83)	1.02 (0.45–2.28)	1.49 (0.81–2.30)
Hospitalization-or CV Death	1.24 (0.79–1.91)	1.34 (1.01–1.85)	1.74 (1.03–2.94)	1.43 (0.90–2.14)
Stroke	1.2 (0.25–5.82)	0.77 (0.2–3.07)	0.38 (0.03–4.34)	1.62 (0.37–6.75)

*Adjusted for: gender, age, BMI, DM, hypertension, alcohol consumption, use of OAC agents, NT-proBNP, eGFR, rhythm and rate control medication after discharge.

BMI, body mass index; DM, diabetes mellitus; OAC, oral anticoagulant; NT-proBNP, n-terminal pro-hormone blood natriuretic peptide; eGFR, estimated glomerular filtration rate; HR, hazard ratio; AF, atrial fibrillation; CV, cardiovascular; HF, heart failure.

Discussion

In this study of AF patients who were discharged following an acute hospitalization, the rates of essential medication use at discharge concerning OAC agents, rhythm or rate control, were similar between the two genders. Significant gender-related differences in outcomes according to treatment modality emerged by multivariate Cox regression analysis. In specific, use of rhythm control, as compared with rate control, was associated with lower rates of all-cause mortality in males. On the contrary, rhythm control treatment showed a correlation with higher rates of all-cause hospitalization or cardiovascular death in females.

No significant gender-related disparity was noted regarding the use of OAC medication. Nonetheless, use of OAC agents has been reported to be underused in female patients with AF, when compared to their male counterparts, a worrying prospect considering the fact that female gender has been linked to an increased risk of stroke in the setting of other coexisting stroke-related factors [12–15]. However, Lip et al have suggested that thromboprophylaxis is underused in AF patients of both genders and more so in those with higher CHADS₂-VASc scores [16, 17]. It has been suggested that acutely hospitalized patients could be at the center of this paradox, as their severe main illness may divert physicians from prescribing OAC treatment [18].

In addition, we found no significant difference between men and women, concerning use of rate or rhythm control medication at discharge. Nevertheless, some international studies concur on the fact that women with AF tend to receive significantly more rate, than rhythm control therapy, when compared to their male counterparts [12, 13, 19]. Euro Heart Survey researchers proposed that physicians may have considered a rate control strategy more advantageous for women, especially asymptomatic ones, as potential antiarrhythmic drug adverse effects occur more often in them [13]. No such treatment trend emerged among patients in our study.

Rate control medication in our study was associated with worse survival prospects in males. This finding comes in contrast to the results of previous trials, such as the ROCKET-AF [20], AFFIRM [21] and PIAF [22] ones, who showcased that there is no significant difference between use of rate and rhythm control medication in AF patients, regarding all-cause mortality. A possible explanation is that the increased comorbidity burden of males in our study may have influenced survival rates. Males in our study were found to have a lower LVEF when compared to female counterparts, were bearing more often a pacemaker or ICD, and a higher percentage of men had a history of smoking or alcohol use (see Table 1). Interestingly, it has been suggested that b-blockers are associated with a reduced effect on AF males who have a lower systolic LVEF, when compared to sinus rhythm ones [23], a finding that possibly reinforces our comorbidity hypothesis.

In our cohort, rhythm control was associated with an increased rate of hospitalization or CV death in females. Our findings concur with those of the RACE trial, which indicated that rhythm control in females with AF leads to three times higher cardiovascular morbidity and mortality [24]. It has been suggested that a higher rate of antiarrhythmic drug adverse effects in female patients could constitute the underlying cause [24–26], as well as their increased risk for torsades de pointes when treated with sotalol

and bradyarrhythmias under antiarrhythmic medication [27]. However, Roy et al. demonstrated that rhythm-control did not result in a reduction in all-cause mortality [28]. Interestingly, Ionescu et al. have suggested that rhythm control is associated with higher long-term survival rates when handling the arrhythmia regardless of gender, in a population-based sample of hospitalized patients with AF [29].

Neither a rate, nor a rhythm control strategy was significantly associated with reduced stroke rates in males or females with AF. No international consensus has been reached on which treatment choice is correlated with better outcomes, concerning stroke. Tsadok et al proposed a superiority of rhythm control in minimizing stroke incidence in both genders [30], a finding not reinforced by a large meta-analysis [31]. Moreover, the ATHENA trial showcased a notable stroke risk reduction in high-risk patients using the antiarrhythmic drug dronedarone [32]. Nonetheless, the above are in contrast with data from the RACE study, as well as the EuroHeart Survey, who claimed that female AF patients under rhythm control had a higher risk of developing thromboembolic complications such as stroke [13, 24].

Limitations

Our study is an observational retrospective one, with all the inherent limitations this entails, however we minimized definition errors or missing data everywhere possible, and we conducted adequate follow-up. Furthermore, one cannot claim to adjust for all possible confounders, especially when keeping in mind the different baseline characteristics of each gender. As far as the drugs administered are concerned, data such as drug compliance or therapeutic range are missing, when it comes to rate or rhythm control medication. The patients' preferences and their effect upon the choice of treatment could not be assessed either. Finally, our study represents the treatment strategies followed in daily clinical practice in a single-center in Greece; however, deductions about other countries always entail the risk that the healthcare system there is fundamentally different than ours.

Conclusion

Among patients being discharged from the hospital with comorbid AF, the use of OAC, rate, and rhythm control treatment did not differ significantly between the two genders. Use of OAC treatment at discharge was not associated with a significant difference in mortality rates in either gender. A rhythm control strategy was associated with lower all-cause mortality and any hospitalization- or CV mortality in males, whereas it was associated with higher hospitalization- or CV death rates in females.

Abbreviations

AF = atrial fibrillation

(a)HR = (adjusted) hazard ratio

BMI = body mass index

CI = confidence interval

CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration

eGFR = estimated glomerular filtration rate

HF = heart failure NOAC = non-vitamin K antagonist oral anticoagulants

NT-proBNP = N-terminal pro b-type natriuretic peptide

OAC = oral anticoagulant VKA = vitamin K antagonists

Declarations

Funding

No funding.

Conflicts of interest

No such conflict to be declared.

Availability of data and material

Data are available from George Giannakoulas (e-mail: ggiannakoulas@auth.gr) upon reasonable request and with permission of AHEPA University Hospital.

Code availability

Not applicable

Ethics approval

The Institutional Review Board of Aristotle University of Thessaloniki approved the protocol of our study. and

Consent to participate

Every individual bestowed written and informed consent before taking part in the study.

Consent for publication

The patients participating in the study gave their written informed consent for publication.

Acknowledgements

Not applicable

References

1. Ikemura N, Kohsaka S, Kimura T, et al. Assessment of Sex Differences in the Initial Symptom Burden, Applied Treatment Strategy, and Quality of Life in Japanese Patients With Atrial Fibrillation. *JAMA network open*. 2019;2(3):e191145. doi:10.1001/jamanetworkopen.2019.1145
2. Samaras A, Kartas A, Akrivos E, et al. A novel prognostic tool to predict mortality in patients with atrial fibrillation: The BASIC-AF risk score. *Hellenic journal of cardiology: HJC = Hellenike kardiologike epitheorese*. Published online January 29, 2021. doi:10.1016/j.hjc.2021.01.007
3. Khamis RY, Ammari T, Mikhail GW. Gender differences in coronary heart disease. *Heart*. 2016;102(14):1142-1149. doi:10.1136/heartjnl-2014-306463
4. Song J-J, Ma Z, Wang J, Chen L-X, Zhong J-C. Gender Differences in Hypertension. *Journal of Cardiovascular Translational Research*. 2019;13(1):47-54. doi:10.1007/s12265-019-09888-z
5. Bozkurt B, Khalaf S. Heart Failure in Women. *Methodist DeBakey cardiovascular journal*. 2017;13(4):216-223. doi:10.14797/mdcj-13-4-216
6. Mohanty S, Trivedi C, Gianni C, Natale A. Gender specific considerations in atrial fibrillation treatment: a review. *Expert Opinion on Pharmacotherapy*. 2018;19(4):365–374. doi:10.1080/14656566.2018.1434144
7. Ko D, Rahman F, Schnabel RB, Yin X, Benjamin EJ, Christophersen IE. Atrial fibrillation in women: epidemiology, pathophysiology, presentation, and prognosis. *Nature Reviews Cardiology*. 2016;13(6):321-332. doi:10.1038/nrcardio.2016.45
8. Tzikas A, Samaras A, Kartas A, et al. Motivational Interviewing to Support Oral AntiCoagulation adherence in patients with non-valvular Atrial Fibrillation (MISOAC-AF): a randomized clinical trial. *European Heart Journal Cardiovascular Pharmacotherapy*. 2020;(32339234). doi:10.1093/ehjcvp/pvaa039
9. Samaras A, Kartas A, Vasdeki D, et al. Rationale and design of a randomized study comparing Motivational Interviewing to Support Oral Anticoagulation adherence versus usual care in patients with nonvalvular atrial fibrillation: The MISOAC-AF trial. *Hellenic journal of cardiology: HJC = Hellenike kardiologike epitheorese*. Published online April 4, 2020. doi:10.1016/j.hjc.2020.02.007
10. World Medical Association. World Medical Association Declaration of Helsinki. *JAMA*. 2013;310(20):2191. doi:10.1001/jama.2013.281053
11. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *European Heart Journal*. 2016;37(38):2893-2962. doi:10.1093/eurheartj/ehw210

12. Anselmino M, Battaglia A, Gallo C, et al. Atrial fibrillation and female sex. *Journal of Cardiovascular Medicine (Hagerstown, Md)*. 2015;16(12):795–801. doi:10.2459/JCM.0000000000000239
13. Dagres N, Nieuwlaat R, Vardas PE, 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. *Journal of the American College of Cardiology*. 2007;49(5):572–577. doi:10.1016/j.jacc.2006.10.047
14. Piccini JP, Simon DN, Steinberg BA, et al. Differences in Clinical and Functional Outcomes of Atrial Fibrillation in Women and Men: Two-Year Results From the ORBIT-AF Registry. *JAMA cardiology*. 2016;1(3):282–291. doi:10.1001/jamacardio.2016.0529
15. Kavousi M. Differences in Epidemiology and Risk Factors for Atrial Fibrillation Between Women and Men. *Frontiers in Cardiovascular Medicine*. 2020;7(32118043):3. doi:10.3389/fcvm.2020.00003
16. Lip GYH, Rushton-Smith SK, Goldhaber SZ, et al. Does sex affect anticoagulant use for stroke prevention in nonvalvular atrial fibrillation? The prospective global anticoagulant registry in the FIELD-Atrial Fibrillation. *Circulation Cardiovascular Quality and Outcomes*. 2015;8(2 Suppl 1):S12–20. doi:10.1161/CIRCOUTCOMES.114.001556
17. Lip GYH, Laroche C, Boriani G, et 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: European Pacing, Arrhythmias, and Cardiac Electrophysiology: Journal of the Working Groups on Cardiac Pacing, Arrhythmias, and Cardiac Cellular Electrophysiology of the European Society of Cardiology*. 2015;17(1):24–31. doi:10.1093/europace/euu155
18. Kartas A, Samaras A, Vasdeki D, et al. Flaws in Anticoagulation Strategies in Patients With Atrial Fibrillation at Hospital Discharge. *Journal of Cardiovascular Pharmacology and Therapeutics*. 2019;24(3):225-232. doi:10.1177/1074248418821712
19. Andrade JG, Deyell MW, Lee AYK, Macle L. Sex Differences in Atrial Fibrillation. *Canadian Journal of Cardiology*. 2018;34(4):429-436. doi:10.1016/j.cjca.2017.11.022
20. ElMaghawry M. ROCKET AF adds more concerns about Digoxin safety in patients with atrial fibrillation. *Global Cardiology Science and Practice*. 2015;2015(3):35. doi:10.5339/gcsp.2015.35
21. Whitbeck MG, Charnigo RJ, Khairy P, et al. Increased mortality among patients taking digoxin—analysis from the AFFIRM study. *European Heart Journal*. 2013;34(20):1481–1488. doi:10.1093/eurheartj/ehs348
22. Hohnloser SH, Kuck K-H, Lilienthal J. Rhythm or rate control in atrial fibrillation—Pharmacological Intervention in Atrial Fibrillation (PIAF): a randomised trial. *The Lancet*. 2000;356(9244):1789-1794.

doi:10.1016/s0140-6736(00)03230-x

23. Rienstra, Michiel, et al. "Beta-Blockers and Outcome in Heart Failure and Atrial Fibrillation." *JACC: Heart Failure*, vol. 1, no. 1, Feb. 2013, pp. 21–28, 10.1016/j.jchf.2012.09.002. Accessed 27 Apr. 2021.

24. Rienstra M, Van Veldhuisen DJ, Hagens VE, et al. Gender-related differences in rhythm control treatment in persistent atrial fibrillation: data of the Rate Control Versus Electrical Cardioversion (RACE) study. *Journal of the American College of Cardiology*. 2005;46(7):1298–1306.
doi:10.1016/j.jacc.2005.05.078

25. Wyse DG, Waldo AL, DiMarco JP, et al. A comparison of rate control and rhythm control in patients with atrial fibrillation. *The New England journal of medicine*. 2002;347(23):1825-1833.
doi:10.1056/NEJMoa021328

26. 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(21):2590-2597.
doi:10.1001/jama.270.21.2590

27. Michelena HI, Powell BD, Brady PA, Friedman PA, Ezekowitz MD. Gender in atrial fibrillation: Ten years later. *Gender Medicine Official Journal of the Partnership for Gender-Specific Medicine at Columbia University*. 2010;7(3):206-217. doi:10.1016/j.genm.2010.06.001

28. Roy D, Talajic M, Nattel S, et al. Rhythm Control versus Rate Control for Atrial Fibrillation and Heart Failure. *New England Journal of Medicine*. 2008;358(25):2667-2677. doi:10.1056/nejmoa0708789

29. Ionescu-Iltu R, Abrahamowicz M, Jackevicius CA, et al. Comparative effectiveness of rhythm control vs rate control drug treatment effect on mortality in patients with atrial fibrillation. *Archives of Internal Medicine*. 2012;172(13):997–1004. doi:10.1001/archinternmed.2012.2266

30. Tsadok MA, Jackevicius CA, Essebag V, et al. Rhythm Versus Rate Control Therapy and Subsequent Stroke or Transient Ischemic Attack in Patients With Atrial Fibrillation. *Circulation*. 2012;126(23):2680-2687. doi:10.1161/circulationaha.112.092494

31. de Denus S. Rate vs Rhythm Control in Patients With Atrial Fibrillation. *Archives of Internal Medicine*. 2005;165(3):258. doi:10.1001/archinte.165.3.258

32. Page RL, Connolly SJ, Crijns HJGM, et al. Rhythm- and rate-controlling effects of dronedarone in patients with atrial fibrillation (from the ATHENA trial). *The American Journal of Cardiology*. 2011;107(7):1019–1022. doi:10.1016/j.amjcard.2010.11.02

Figures

Figure 1

Secondary Kaplan- Meier analysis, all- cause mortality assessed in terms of rhythm or rate control medication at discharge, or absence thereof, 1a) in males 1b) in females.

Figure 2

Secondary Kaplan- Meier analysis, hospitalization- or CV Death assessed in terms of use of rhythm, or rate control medication at discharge, or absence thereof, 2a) in males, 2b) in females.

Figure 3

Secondary Kaplan-Meier analysis, stroke during follow up assessed in terms of rhythm, or rate control medication at discharge, or absence thereof, 3a) in males 3b) in females.

Figure 4

The bar charts illustrate the percentage (%) of individuals using each treatment modality (use of OAC, rhythm control and rate control) in the group of males and females in our study.