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Potential Benefits of Spironolactone in the Pharmacological Management of Patients with Atrial Fibrillation Who Have Achieved Sinus Rhythm

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ABSTRACT

Atrial fibrillation (AF) is a progressive condition with significant health implications, where fibrosis plays a central role. This study aimed to evaluate the impact of adding mineralocorticoid receptor blockade to standard therapy in patients with AF after restoration of sinus rhythm, focusing on arrhythmia recurrence, hospitalizations, and changes in Galectin-3 levels as a fibrosis marker. We prospectively enrolled 101 consecutive patients (56 females; mean age 68.2 ± 7 years) with AF who had achieved sinus rhythm. Participants were randomized to receive spironolactone in addition to standard therapy or standard therapy alone ("usual care") and were followed for arrhythmia recurrence, hospitalizations, and mortality. The Safety of spironolactone was also assessed. AF recurrence occurred in 64% of patients in the non-spironolactone group versus 57% in the spironolactone group ($p = 0.44$). Spironolactone was associated with fewer AF-related hospitalizations, though this reduction was not statistically significant ($p = 0.14$). Cox regression analysis indicated a protective trend of spironolactone against AF hospitalizations (HR = 0.48; 95% CI = 0.2–1.15; $p = 0.098$). For all-cause hospitalizations, spironolactone significantly reduced events (HR = 0.44; 95% CI = 0.2–0.94; $p = 0.035$). There was no significant difference in the composite endpoint of recurrence, all-cause hospitalizations, and death. Treatment with spironolactone did not alter Galectin-3 levels or significantly affect serum potassium or creatinine. Spironolactone appears to reduce all-cause hospitalizations and shows a protective trend against AF-related hospitalizations, but it does not affect fibrosis marker Galectin-3 over one year. Spironolactone is safe in patients with AF, though regular monitoring is recommended, and further research is needed to clarify its potential to improve AF outcomes.

Keywords: Hospitalization, Atrial fibrillation, Recurrences, Fibrosis

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Introduction

Atrial fibrillation (AF) represents the most prevalent cardiac arrhythmia in clinical practice, affecting nearly 2% of the general population, and is linked to increased mortality, stroke, heart failure, and impaired quality of life [1, 2]. The development and persistence of AF involve a combination of structural, electrical, and contractile changes that together establish the arrhythmic substrate [3, 4]. Cardiac fibrosis is a defining feature of atrial remodeling in AF and plays a crucial role in the onset of atrial cardiomyopathy [5-7]. Aldosterone, a mineralocorticoid hormone, has been implicated in promoting myocardial fibrotic processes [8]. While mineralocorticoid receptor antagonists (MRAs) are well established in the management of heart failure [9], their therapeutic potential in AF is not well defined.

The present study investigates whether adding mineralocorticoid receptor blockade to standard therapy in patients with AF who have achieved sinus rhythm affects arrhythmia recurrence, hospitalization rates, and levels of Galectin-3 (Gal-3), a biomarker of fibrosis.

Materials and Methods

Study design

This single-center, randomized clinical trial evaluated the effect of spironolactone combined with standard therapy on patients with AF following sinus rhythm restoration, with follow-up for arrhythmia recurrence, hospitalizations, and Gal-3 levels over 12 months. Eligible patients were randomly assigned to either the treatment group, receiving 25 mg of spironolactone in addition to their regular antiarrhythmic regimen, or the control group, managed according to standard rhythm control practices ("usual care"). Patients attended five follow-up visits during the study at 14 days, 1 month, 3 months, 6 months, 9 months, and 12 months.

Patient selection

AF diagnosis was confirmed by ECG during hospitalization or at the emergency department. AF subtypes were classified based on the 2010 and 2016 ESC Guidelines [2, 10, 11]. Patients were eligible if they were older than 55 years, had restored sinus rhythm following paroxysmal or persistent AF, and provided informed consent. Exclusion criteria included severe chronic heart failure (NYHA class III–IV), recent open-heart surgery or myocardial infarction within 3 months, pregnancy, substance abuse, life-limiting comorbidities, advanced kidney disease (serum creatinine >200 μmol/L or eGFR <40 mL/min/1.73 m²), Child-Pugh C liver cirrhosis, use of strong CYP3A4 modulators, serum potassium >5 mmol/L, hypersensitivity to MRAs, metabolic acidosis, or significant thyroid dysfunction.

Outcome measures

During follow-up visits, patients were interviewed about arrhythmia recurrences, confirmed by an ECG performed by their physician or during emergency visits. Data regarding hospitalizations and vital status were collected from patients or relatives. Investigators (AK, YY, EG) classified hospitalizations as cardiovascular-related or due to other causes. Event dates were recorded when available; otherwise, the 15th of the month was used as an estimated date.

Galectin-3 assessment

Blood samples for Gal-3 analysis were obtained at baseline and at 12 months. Ten milliliters of blood were collected via antecubital venipuncture into BD Vacutainer SST II Advance Tubes, allowed to clot for 30 minutes at room temperature, and centrifuged at 1,500×g for 15 minutes at 4 °C. Serum was aliquoted into 1.5 mL polypropylene tubes and stored at –80 °C until assay, with hemolyzed samples excluded.

Quantification of Gal-3 was performed using a commercial ELISA kit (Galectin-3 AssayTM, REF# 12642-04, 12684, BG Medicine, Waltham, MA, USA) per manufacturer instructions, measured on a StatFax 3200 microplate reader (Awareness Technology, Inc., USA). Concentrations were calculated using a 4-parameter logistic fit of the calibration curve via MikroWin 2000 software (ver. 4.31, Mikrotek Laborsysteme GmbH, Germany) and expressed in ng/mL. The assay's detection limit was 1.13 ng/mL, with a range of 1.4–94.8 ng/mL, an intra-assay CV of ~3.4%, and an inter-assay CV of ~8.5%.

Electrocardiography (ECG)

A standard 12-lead ECG was performed at each follow-up visit.

Statistical analysis

Continuous variables with approximately normal distribution are reported as mean ± standard deviation, while variables deviating from normality are presented as median and interquartile range. For normally distributed variables, comparisons between independent groups were performed using Student's t-test or repeated-measures ANOVA for within-patient comparisons. Galectin-3 (Gal-3) values, which were right-skewed, were log-transformed to approximate normality. Paired t-tests or one-sample t-tests were used to assess changes between baseline and follow-up visits. When normality assumptions were not met, nonparametric tests such as the Mann–Whitney U test were applied. Categorical variables are reported as counts and percentages, with differences tested using the chi-square test or Fisher's exact test when expected cell counts were below five. A p-value <0.05 was considered statistically significant.

Time to first AF recurrence during follow-up was analyzed using Kaplan–Meier survival curves. Cox proportional hazards models were employed to evaluate the association between independent variables and AF occurrence. Univariate analyses were conducted first, followed by multivariate adjustment for key covariates including age

(<64 [reference], 64–67, 67–72, >72 years), sex (male vs female), diabetes status (none vs diabetes vs impaired glucose tolerance), hypertension (yes/no), and AF duration, using backward selection criteria ($p < 0.05$ to retain, $p > 0.1$ to remove). Wald's test assessed statistical significance, and results are expressed as hazard ratios (HR) with 95% confidence intervals (CI). All analyses were performed using SPSS version 19 (SPSS, Texas, USA).

Ethics

The study protocol was approved by the local Committee of Medical Ethics of the University Hospital "St. Marina," Varna, and conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent.

Results and Discussion

Out of 124 patients with AF and restored sinus rhythm who were screened, 101 met the inclusion criteria and were enrolled in the study. The mean age was 68.2 ± 7.0 years (range 55–83), with 56 participants (56%) being female. Baseline characteristics of the study groups are presented in **Table 1**.

Table 1. Baseline demographic, clinical, laboratory and echocardiographic parameters of study population; BMI – body mass index, sBP – systolic blood pressure, dBP – diastolic blood pressure, HR – heart rate, eGFR – estimated glomerular filtration rate, LA – left atrium.

Parameter	Not on spironolactone treatment group			On spironolactone treatment group			p value
	N	Mean	St dev	N	Mean	St dev	
Age (years)	51	67.58	6.62	50	68.46	7.4	0.53
Female sex	23			33			0.069
BMI (kg/m^2)	51	30.03	5.46	50	29.3	5.67	0.52
sBP (mmHg)	51	126.91	12.69	50	126.12	12.68	0.76
dBP (mmHg)	51	77.28	6.55	50	74.28	6.737	0.03
HR/min	51	61.56	8.26	50	66.06	10.51	0.02
Creatinin (mmol/l)	50	87.21	16.78	50	86.06	18.17	0.74
eGFR (ml/min/1.73 m2)	51	71.78	13.12	50	68.44	16.97	0.27
Serum potassium (mmol/l)	51	4.1	0.37	50	4.08	0.47	0.85
LA area (cm^2)	46	20.54	4.22	42	21.14	4.46	0.14
LA volume (ml/m^2)	42	33.05	10.36	41	35.13	12.78	0.42
EF LV (%)	51	59.36	6.89	50	60.52	6.27	0.38
E/A ratio mitral valve	51	1.31	1.17	50	1.22	0.64	0.62

By chance, the randomization resulted in a higher number of female participants in the spironolactone group; however, this difference was not statistically significant ($p = 0.069$). Other risk factors were similarly balanced between the two groups **(Table 2)**.

Table 2. Risk factors distribution.

Risk factor	Not on spironolactone treatment group	On spironolactone treatment group	P value
Smoking	78.3%	76.1%	0.96
Hypertension	86%	86%	1
Diabetes	22%	32.7%	0.47
Ischaemic heart disease	12%	20%	0.32
Gout	6.8%	6.8%	1

No significant differences were observed between the groups regarding therapies used for sinus rhythm restoration ($p = 0.61$) or subsequent antiarrhythmic treatment ($p = 0.43$). AF recurrences occurred in 64% of patients in the

non-spironolactone group compared to 57% in the spironolactone group (p = 0.44). By the end of the study, three patients (5.9%) in the placebo group remained in permanent AF, whereas none in the spironolactone group did (p = 0.93, Fisher's exact test; p = 0.081, chi-square test). Spironolactone was associated with a 46% reduction in AF-related hospitalizations in both the intention-to-treat and per-protocol analyses, though these reductions were not statistically significant (p = 0.14 and p = 0.2, respectively), as illustrated in **Figure 1**.

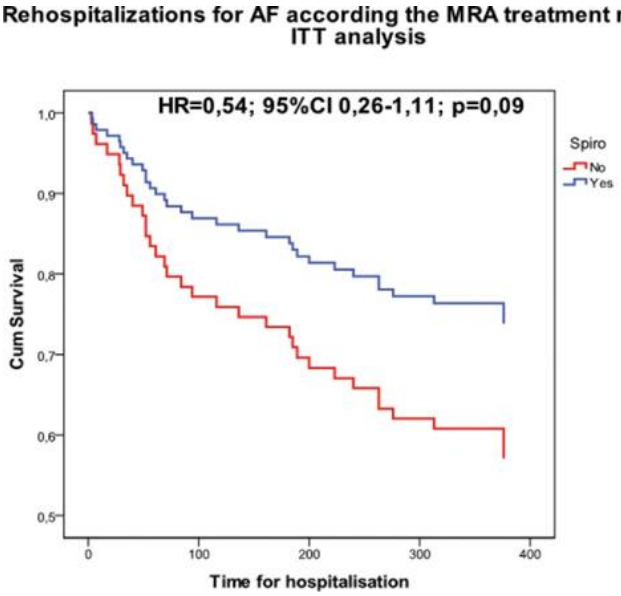

Figure 1. Rehospitalizations for AF according to MRA therapy; HR = hazard ratio, CI= confidence interval.

A Cox regression analysis adjusting for age categories, sex, hypertension, diabetes, and spironolactone use demonstrated a protective trend of spironolactone against AF-related hospitalizations (HR = 0.48; 95 percent CI, 0.2–1.15; p = 0.098). Using the same model for all-cause hospitalizations, spironolactone was associated with a significant reduction in events (HR = 0.44; 95 percent CI, 0.2–0.94; p = 0.035), as summarized in **Table 3**.

Table 3. Cox regression model for all cause hospitalization.

Variables	Hazard ratio	95% Ci	Significance
Diabetes	3.69	0.76–18	p = 0.11
Female sex	1.13	0.49–2.6	p = 0.77
Hypertension	2.37	0.55–10.2	p = 0.25
Age category 64–66.9	2.24	0.64–7.8	p = 0.2
Age category 67–71.9	1.7	0.47–6.3	p = 0.41
Age category ≥72	3.25	0.94–11.3	p = 0.06
Spironolactone use	0.44	0.2–0.94	p = 0.03

No significant difference was observed between the two groups for the composite endpoint, which included AF recurrences, all-cause hospitalizations, and death. Spironolactone treatment did not significantly affect Gal-3 levels; interestingly, Gal-3 increased by 0.84 ng/mL in the spironolactone group, while it decreased by 0.56 ng/mL in the non-spironolactone group (p = 0.127).

Safety

Spironolactone was discontinued in one patient due to gynecomastia. Serum creatinine and potassium levels were measured at visits 3, 5, and 7. As expected, potassium was higher in the spironolactone group, with mean differences ranging from 0.2 to 0.36 mmol/L. In patients receiving spironolactone for ≥9 months, all values remained within reference limits, and standard deviations did not exceed the upper normal range **(Figure 2)**. Additionally, patients on spironolactone tended to exhibit lower systolic blood pressure.

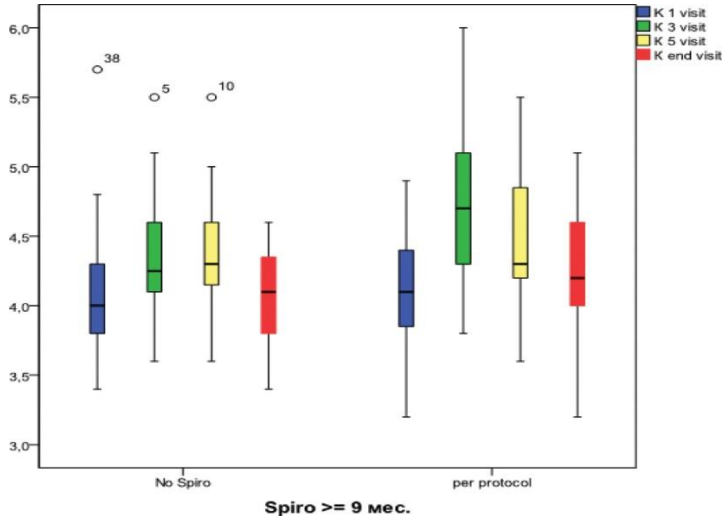

Figure 2. Serum potassium levels; K – potassium.

AF recurrences

Evidence regarding the effect of spironolactone on AF burden is inconsistent, particularly in patients without heart failure. In the TOPCAT trial (Treatment of Cardiac Function with an Aldosterone Antagonist), over a median follow-up of 3.3 years, no difference in AF recurrence rates was observed between spironolactone and placebo in patients with HFpEF [12]. Conversely, Dabrowski *et al*. reported that spironolactone combined with beta-blockers reduced AF recurrences [13]. Experimental studies in animals have shown that spironolactone may positively affect the fibrotic substrate, although data on recurrence rates are lacking [14, 15]. Tase *et al*. retrospectively analyzed 1,008 patients with characteristics similar to our population, comparing those receiving spironolactone in addition to amiodarone, propafenone, or sotalol versus those on potassium supplementation with the same antiarrhythmics [16]. They found a significant reduction in AF episodes in the spironolactone group over 24 months. The absence of a significant effect in our study may be partly due to the widespread use of ACE inhibitors or angiotensin receptor blockers, which already provide RAAS blockade, reducing differences between groups. Additionally, the one-year follow-up may have been too short for spironolactone to meaningfully affect atrial fibrosis.

Composite endpoint

In the TOPCAT study, spironolactone did not reduce the primary composite outcome of cardiovascular death, aborted cardiac arrest, or hospitalization for heart failure, regardless of AF history at baseline [17].

Spironolactone and galectin-3

Preclinical studies suggest that spironolactone and modified citrus pectin can inhibit aldosterone-induced fibrosis [18]. In our study, Gal-3 levels increased in the spironolactone group, consistent with the Aldo-DHF trial in HFpEF patients, where Gal-3 rose more rapidly over six months in the spironolactone arm [19]. By contrast, Deveci *et al*. observed a decrease in Gal-3 from 39 ± 21 to 33 ± 22 ng/mL after six months of spironolactone treatment in patients with reduced ejection fraction (<35%, $p < 0.001$) [20]. This difference may relate to higher aldosterone levels in HFrEF patients, where spironolactone can lower Gal-3, whereas in patients without heart failure, baseline aldosterone levels are lower, potentially leading to increased Gal-3.

Conclusion

Spironolactone appears to be a promising strategy to target fibrosis, a key pathogenic mechanism in AF. It demonstrates a protective effect against AF-related hospitalizations and significantly reduces all-cause hospitalizations. However, it does not alter the fibrosis biomarker Gal-3 over one year. Spironolactone is safe in patients with AF, though regular monitoring is advised. It may also aid in better blood pressure control, potentially lowering cardiovascular risks, including AF. Further studies are needed to determine its full potential to improve AF outcomes.

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Conflict of Interest: None

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Ethics Statement: None

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