Pharmacotherapy of patients with atrial fibrillation and restored sinus rhythm – is the medication with spironolactone beneficial in this case?

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Abstract

Objective: Atrial fibrillation is progressive disease with important health consequences, in which fibrosis is a key player. The aim of our study is to assess the effect of mineralcorticoid blockade on top of standard treatment in patients with atrial fibrillation after sinus rhythm restoration on the recurrence of the arrhythmia, hospitalizations and on the changes in levels of Galectin-3 as a marker of fibrosis.

Methods: We prospectively studied 101 consecutive patients (56 females) at mean age 68.2 ± 7 with atrial fibrillation and sinus rhythm restoration, who were randomized on treatment with spironolactone on top of standard treatment or "usual care". They were followed up for recurrences, hospitalization and death. The effect of spironolactone on safety was evaluated.

Results: Recurrences of AF were detected in 64% of non-spironolactone group vs 57% in spironolactone group (p = 0.44). Spironolactone reduced the hospitalizations for AF, but it was not significant (p = 0.14). A Cox regression model showed only protective effect of spironolactone on AF hospitalizations, HR = 0.48, 95%CI = 0.2–1.15, p = 0.098. The same survival model for all-cause hospitalizations reached significance, with reduction of the events in the spironolactone group, HR= 0.44, 95% CI 0.2–0.94, p = 0.035. There was no difference regarding the composite endpoint (recurrences, all cause hospitalizations and death). Treatment with spironolactone did not influence the Gal-3 levels. Treatment with spironolactone has not influenced significantly the levels of serum potassium and creatinine.

Conclusion: Treatment with spironolactone has protective effect regarding hospitalization for atrial fibrillation and significantly reduces all cause hospitalizations. It does not influence the biomarker of fibrosis Gal-3 after one-year treatment. The use of spironolactone in patients with AF is safe, but regular follow up is needed and recommended. Further studies are necessary, to clarify the potential of spironolactone to improve the AF prognosis.

Keywords

atrial fibrillation, fibrosis, recurrences, hospitalization
Introduction

Atrial fibrillation (AF) is the most common arrhythmia in clinical practice, which affects about 2% of the general population. It is a progressive disease, associated with an increased risk of mortality, stroke, heart failure and worsened quality of life (Nattel et al. 2008; Kirchof et al. 2016). The structural, electrical, and contractile remodeling are important synergic factors for the formation of the arrhythmia substrate (Burstein and Nattel 2008; January et al. 2014). Cardiac fibrosis is the hallmark of atrial remodeling in AF and is closely associated with development of atrial cardiomyopathy (Zhang et al. 2015; Goette et al. 2016; Guichard and Nattel 2017). There is evidence that the mineralocorticoid hormone aldosterone promotes the fibrotic process in the heart (Catena et al. 2012). The use of mineralocorticoid receptor antagonists (MRA) has proven benefit in patients with heart failure (Pinokowski et al. 2016), but the data about its role in AF is sparse.

The aim of our study is to assess the effect of mineralocorticoid blockade on top of standard treatment in patients with atrial fibrillation after sinus rhythm restoration on the recurrence of the arrhythmia, hospitalizations and on the changes in levels of Galectin-3 (Gal-3) as a marker of fibrosis.

Patients and methods

Study design

This is a randomized single-center clinical trial of the effect of spironolactone on top of standard treatment in patients with atrial fibrillation after sinus rhythm restoration on the recurrence of the arrhythmia, hospitalizations and on the changes in Gal-3 levels after 12 months.

After initial screening about the inclusion criteria, the patients were randomized in two groups. The active group received 25 mg Spironolactone on top of their usual therapy including antiarrhythmic medications, and the control group was treated according to the ‘usual (standard) care’ rhythm control.

The patients were followed up for 1 year and had 5 follow-up visits – at 14 days, 1 month, 3 months, 6 months, 9 months, and, finally, at 12 months.

Patient selection

The diagnosis of AF was accepted by ECG criteria during hospitalization or visit to the Emergency Department of the hospital. The type of AF was classified according to the ESC Guidelines on AF 2010 and 2016 (Camm et al. 2010; Camm et al. 2012; Kirchof et al. 2016). Inclusion criteria were as follows: age more than 55 years, restored sinus rhythm after an episode of paroxysmal/persistent AF, signed inform consent. Exclusion criteria included the following: history of, clinical and echocardiographic evidence of chronic heart failure NYHA class III–IV; open heart surgery during the last 3 months for any indication; survivors of acute myocardial infarction and left ventricular dysfunction within 3 months of randomization; pregnancy; drug and alcohol abuse; presence of severe progressive concomitant disease with life expectancy less than 1 year; chronic kidney disease defined as serum creatinine more than 200 mcmol/l or eGFR less than 40 ml/min/1.73 m2; liver cirrhosis Child C; treatment with powerful CYP3A4 inhibitors or inducers; serum potassium levels >5 mmol/l at screening; hypersensitivity towards MRA; metabolic acidosis; known thyroid pathology with lab results consistent with hyper- or hypothyroidism.

Outcome measures

At each visit, the patients were interviewed for episodes of recurrent arrhythmia, ECG proven by their physicians or at the follow-up visits or incidental visits to the EDs. Information about their vital status or other hospitalizations was also collected personally or by their relatives. The etiology was considered to be due to CVD or other reasons by the investigators (AK, YY, EG). The date of each episode was recorded, if known, or imputations of day 15th for each month were done in case of unknown exact date of occurrence.

Galectin-3 measurements

Blood for Gal-3 determination was collected at baseline and one year after. Ten mL of blood was drawn from the antecubital vein into BD Vacutainer SST II Advance Tubes. The blood was allowed to clot for 30 min at room temperature and then centrifuged at 1,500g for 15 min at 4°C. The separated serum was aliquoted into 1.5 mL polypropylene tubes, and stored at –80 °C until analysis. Samples with visible hemolysis were discarded from analysis.

Serum Gal-3 levels were determined using enzyme-linked immunosorbent assay kit for quantitative measurement (Galectin-3 AssayTM, REF# 12642-04, 12684 BG Medicine, Waltham, MA, USA) according to manufacturer’s instructions and were measured on StatFax 3200 microplate reader (Awareness Technology, Inc., USA). Calculation of results was based on 4 parameter logistic curve fit of the calibration curve and was performed with MikroWin 2000 ver. 4.31 software (Mikrotek Laborsysteme GmbH, Germany) and expressed in ng/mL units. The lower limit of detection (LoD) is 1.13 ng/mL, measurement range 1.4 to 94.8 ng/mL, average intra-assay CV: approximately 3.4% and average inter-assay CV: approximately 8.5%.

ECG

Standard 12-lead ECG was performed at each visit.

Statistical analyses

All continuous variables are presented as means ± standard deviation for relatively normally distributed and as median/interquartile range/ for these with deviation from normality. When approximately normal distribution is present,
the independent variables are compared by Student's t-test or ANOVA test in repeated measures in one patient. Because of skewed to the right distribution of Gal-3 values, we made a log transformation to improve the non-normal distribution. The paired t-test or one-sample t-test are applied for the differences in variables between the end and first visits. In case of lack of normality, nonparametric tests are also used like Mann-Whitney's test. For categorical variables, absolute values and percentages are presented and the chi-square test or the exact Fisher's test, when the expected cell numbers are smaller than 5 are used to test the null hypothesis. P-value <0.05 is used for significance testing.

For the occurrence of AF episodes during follow-up, the Kaplan-Meier curves were constructed with time to first event as dependent variable. Cox proportional hazard analyses were performed for the occurrence of AF events with different independent variables. First, univariate analysis was done and then, adjustment for major factors, like age (in categories <64 as reference, 64–67, 67–72, >72 years), sex (males vs females), diabetes (no vs DM vs impaired glucose tolerance), hypertension (yes/no), and duration of AF, was applied with backward selection selection modelling. The significance level 0.05 for keeping in the model and 0.1 for removing a variable from the model is used. Wald's test for significance was done. The results are presented as hazard ratios (HR) with 95% confidence intervals (CI).

All analyses are performed on SPSS version 19 (SPSS, Texas, USA).

**Ethics**

The project was approved by the local Committee of Medical Ethics of the University Hospital ‘St. Marina’ Varna and complied with the Declaration of Helsinki. Informed consent was obtained in all patients.

**Results**

Overall, 124 patients with AF and restored sinus rhythm were screened and 101 were included in the study. Mean age was 68.2 ± 7.00, (range 55–83 years), and 56 (56%) of the participants were female. Baseline group characteristics are shown in Table 1.

The randomization process designated more females, by chance, in the spironolactone group, but the difference was not significant (p = 0.069). Risk factors were equally distributed in both groups (Table 2).

There was no significant difference in the therapy for sinus rhythm restoration (p = 0.61) and the following antiarrhythmic therapy (p = 0.43).

Recurrences of AF were detected in 64% of non-spi- ronolactone group vs 57% in the spironolactone group (p = 0.44). At the end of study 3 pts (5.9%) from the placebo group were in permanent AF versus 0 from the group on spironolactone (p = 0.93 Fisher test, p = 0.081 chi-square test).

Spironolactone reduced the hospitalizations for AF with 46% in the intention to treat group and per protocol, but it was not significant (p = 0.14 and p = 0.2 respectively), graphically shown on Fig. 1.

A Cox regression model, including age categories, sex, hypertension, diabetes and spironolactone showed only protective effect of spironolactone on AF hospitaliza-

![Figure 1.](image)

### 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 |
|-----------|--------------------------------------|----------------------------------|---------|
| Age (years) | 51 67.58 6.62 50 68.46 7.4 | 0.53 |
| Female sex | 23 0.069 | 33 |
| BMI (kg/m²) | 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 (cm²) | 46 20.54 4.22 44 21.14 4.46 | 0.14 |
| LA volume (ml/m³) | 42 33.05 10.36 41 35.13 12.78 | 0.42 |
| EF % | 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 |

**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 |

**Rehospitalizations for AF according to MRA treatment regimen ITT analysis**

![Figure 1.](image)
Regarding the composite endpoint (recurrences, all cause hospitalizations and death) there was no difference between the two groups.

Treatment with spironolactone did not influence the Gal-3 levels. It is interesting that in patients on spironolactone Gal-3 increases with 0.84 ng/mL and in these without Gal-3 decreases with 0.56 ng/mL, $p = 0.127$.

### Safety

In one patient spironolactone was stopped because of gynecomastia. In all patients creatinine and serum potassium were measured at visit 3.5 and 7. As expected, potassium levels were higher in spironolactone group. The mean difference between the groups is 0.2–0.36 mmol/l. All the measurements in patients, who has taken spironolactone ≥ 9 months are in the reference limit and the standard deviation does not exceed the upper normal limit, Fig. 2. Patients on spironolactone tend to have lower systolic blood pressure.

### Composite endpoint

In TOPCAT spironolactone did not reduce the risk of the primary composite outcome of death from cardiovascular causes, aborted cardiac arrest or hospitalization for the management of HF in patients either with or without a history of AF at baseline (Cikes et al. 2018).

### Spironolactone’s influence on Gal-3

There are some preclinical data that spironolactone and modified citrus pectin inhibit the aldosterone-induced fibrosis (Calvier et al. 2013). In our study levels of Gal-3 increased in spironolactone group. This is in agreement with Aldo-DHF study in patients with HFP EF, in which Gal-3 increased in 6 months more rapidly in the spironolactone group (Edelmann et al. 2015). In contrast Deveci et al. (2015) found regression of Gal-3 after 6-months treatment with spironolactone on top of standard therapy from $39 \pm 21$ to $33 \pm 22$, $p < 0.001$, but in patients with reduced ejection fraction <35%. Patients with HFrEF usually have higher levels of aldosterone and may be this is why levels of Gal-3 decrease in such group an increases in non-HF patients, in which the levels of aldosterone are not elevated (Deveci et al. 2015).

### Conclusions

Treatment with spironolactone seems an intriguing possibility to influence the fibrosis, as a main pathogenic mechanism in AF. It has protective effect regarding hospitalization for AF and significantly reduces all cause hospitalization.

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| 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 | 0.7  | 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 | $p = 0.03$  |

Figure 2. Levels of serum potassium; K – potassium.
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