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Research Article

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 worsen 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 mineralcorticoid hormone aldosterone promotes the fibrotic process in the heart (Catena et al. 2012). The use of mineralcorticoid 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 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 (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 (standart) 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; Kirchhof 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 inductors; 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 1,500×g 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 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-spironolactone 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,

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/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	42	21.14	4.46	0.14
LA volume (ml/m²)	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

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

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

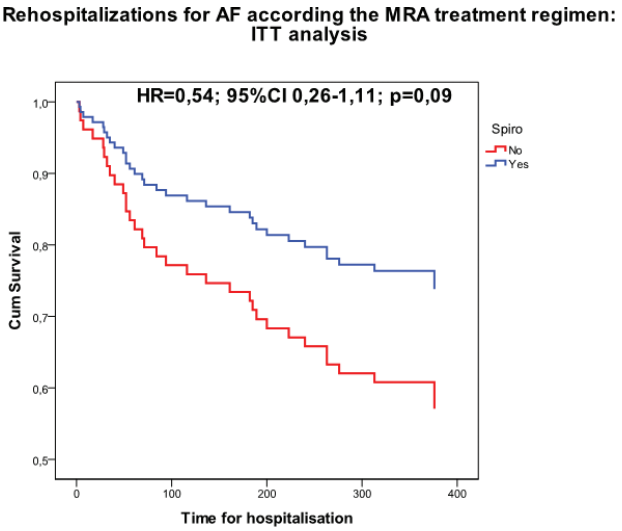

Figure 1. Rehospitalizations for AF according to MRA treatment; HR – hazard ratio, CI –confidence interval.

only protective effect of spironolactone on AF hospitalizations, HR = 0.48, 95% CI = 0.2–1.15, p = 0.098. The same model, but for all-cause hospitalizations reveals significant reduction of the events in the spironolactone group, p = 0.035, HR- 0.44, 95% CI 0.2–0.94, which is shown on 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

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.

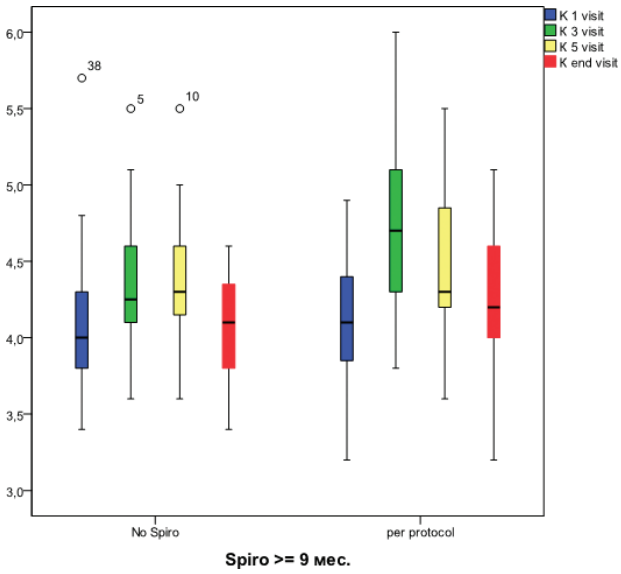

Figure 2. Levels of serum potassium; K – potassium.

Discussion

AF recurrences

The data about the influence of spironolactone on AF burden are inconsistent, especially in patients without heart failure. In TOPCAT (Treatment of Cardiac Function with an Aldosterone Antagonist) during a median follow-up of 3.3 years there was no differences in the rate of recurrences according to the treatment of spironolactone in patients with HFpEF (Neefs et al. 2020). Dabrowski et al showed that spironolactone in combination with beta-blocker has preventive effect on AF recurrences (Dabrowski et al. 2010). Other authors reported favourable effect of spironolactone on the fibrotic substrate in animal models, but there were no data about the number of recurrences (Lendeckel et al. 2010; Zhao et al. 2010). Tase et al. (2014) made a retrospective analysis of 1008 patients with similar characteristics as our population, divided in two groups – patients, who received spironolactone on top of amiodarone, propafenone or sotalol and patients on potassium supplementation on top of amiodarone, propafenone or sotalol (Tase et al. 2014). The AF recurrences 24 months before and so long after spironolactone initiation were detected. They found significant reduction of AF episodes in the spironolactone group. One possible reason for the lack of effect of spironolactone on AF recurrences is the great number of patients, who received ACE-inhibitors or angiotensin receptor blockers as antihypertensive agents, which contribute for RAAS blockade and diminish the difference between both groups. Another explanation is the relatively short duration of the study (one year), which period is not enough for spironolactone to influence the fibrotic process.

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 HFpEF, 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 ± 21 to 33 ± 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 hospi-

talizations. 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. It helps achieving better antihypertensive control, which can potentially reduce the cardiovascular adverse event, including AF. Further studies are needed to clarify the potential of spironolactone to improve the AF prognosis.

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