Risk factors for recurrence of atrial fibrillation

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Abstract

Objective: Atrial fibrillation (AF) is a progressive disease, associated with increased risk of mortality, stroke, heart failure, and worsens quality of life. There is a high incidence of AF recurrence despite the treatment. The aim of the study was to assess the time to recurrence of AF after sinus rhythm restoration with electrical or pharmacological cardioversion and to identify the risk factors.

Methods: This study included 101 patients with AF (56% females) at a mean age of 68.02±7 years, after sinus rhythm restoration in a clinical observation of 1-year placebo-controlled treatment with spironolactone (1:1). The patients were analyzed on the basis of AF recurrence, hospitalization, demographic parameters, comorbidities, embolic risk, and value of biomarker galectin-3 (Gal-3).

Results: The average number of AF recurrences was1.62 per patient per year. The median time of occurrence of at least one new episode was 48 days, 95% confidence interval (CI) 14.24–81.76. Female patients experienced significantly more recurrences than male—53.3% vs. 28.6% hazard ration (HR) =1.76, 95% CI 1.02–3.03, p=0.036. The recurrences were more common with increased age, although not significantly. Patients with arterial hypertension had a threefold risk of recurrences than those without hypertension (p=0.025), independently of the treatment. CHA_2DS_2-VASc score was significantly associated with AF recurrent episodes. Patients with gout had a twofold increased risk, without statistical significance (p=0.15). There was no difference in the AF episodes according to treatment with spironolactone. The levels of Gal-3 did not affect the number of AF recurrences (p=0.9).

Conclusion: AF is associated with frequent recurrences after restoration of sinus rhythm in the majority of the patients. Most of them occurred within the first 3 months. Female sex, arterial hypertension, and CHA_2DS_2-VASc score were significant predictors of AF recurrence. Spironolactone did not reduce AF recurrences.

Key words: atrial fibrillation, recurrence, risk factors, CHA_2DS_2-VASc score, galectin-3, spironolactone

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Introduction

Atrial fibrillation (AF) is the most prevalent arrhythmia in clinical practice. It affects 3% of adults aged 20 years or older, and the incidence increases with age. AF is a progressive disease, associated with an increased risk of mortality, stroke, heart failure, and it worsens quality of life (1–3). The antiarrhythmic strategy relies on drug or ablation therapy. The risk factors for AF recurrence have not been fully investigated. A number of risk scores, combining several predictors, are developed to improve the stratification of AF patients, regarding the risk of recurrences. These include the APPLE score (4), the ATLAS score (5), the HAVOC score (6), the HATCH score (7), and MB-LATER score (8). Most of them are designed for patients after ablation, but the data about recurrences in conventional treatment are sparse. Several novel biomarkers have been proposed to detect increased risk. Galectin-3 (Gal-3), α soluble β-galactoside binding lectin, is one of them. It modulates cardiac fibrosis, inflammation, and immune response (9). Cardiac fibrosis is the hallmark of structural remodeling in AF. There are studies that show how increased Gal-3 levels correlate with atrial fibrosis (10) and are related to incident AF (11, 12). Aldosterone is associated with volume retention, cardiac hypertrophy, fibrosis, and systemic inflammation seen in AF. Antifibrotic medication like mineralocorticoid receptor antagonists may reduce the fibrosis in the myocardium and may prevent AF occurrence (13).

The aim of our study was to assess the time to recurrence of AF after sinus rhythm restoration with electrical or pharmacological cardioversion and to identify the risk factors. We also

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HIGHLIGHTS

- AF is a progressive disease with important health consequences and high incidence of recurrent episodes.
- Most of the recurrences occured within the first three months after the index event.
- Significant predictors of AF recurrences were female sex, arterial hypertension and elevated CHA_2DS_2-VASc score.
- Spironolacton as an antifibrotic medication did not reduce AF recurrences.

explored the efficacy of mineralocorticoid receptor antagonist spironolactone on reducing recurrence of arrhythmia, hospitalizations, and Gal-3 levels after 12-month treatment.

Methods

Study design

This is a randomized single-center clinical observation of the effect of mineralocorticoid receptor antagonist (MRA) spironolactone on top of standard treatment in patients with AF 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 which on week 2 or later may be up-titrated to 50 mg daily, and the control group was treated according to the 'usual care' rhythm control.

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

Patient selection

Patients who had an episode of paroxysmal/persistent AF and restored normal sinus rhythm spontaneously or after medical or electrical cardioversion during the study period in our institution were screened. Those patients aged more than 55 years and signed inform consent were included. Exclusion criteria included the following: history of clinical and echocardiographic evidence of chronic heart failure New York Heart Association 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 μmol/L or estimated glomerular filtration rate (eGFR) less than 40 mL/min/1.73 m^2; liver cirrhosis Child C; treatment with powerful CYP3A4 inhibitors or inductors; serum potassium levels >5 mmol/L at screening; hypersensitivity toward MRA; metabolic acidosis; known thyroid pathology with laboratory results consistent with hyper- or hypothyroidism.

The diagnosis of AF was done by 12-lead electrocardiography (ECG). The type of AF was classified according to the ESC Guidelines on AF 2010 and 2016 (2, 14, 15). In all patients the thromboembolic risk was calculated according to CHA_2DS_2VASc-score (15). The participants were divided in three thromboembolic risk categories as per this scoring system: low risk (0–1 points), moderate risk (2–3 points), and high risk (>3 points).

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 emergency departments (EDs). Information about their vital status or other hospitalizations was also collected personally or by their relatives. The cause for hospitalization was considered to be due to cardiovascular disease (CVD) or other reasons by the investigators (A.K., Y.Y.). The date of each episode was recorded, if known, or imputations of day 15 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 1 year after.

Serum Gal-3 levels were determined using enzyme-linked immunosorbent assay kit for quantitative measurement (Galectin-3 Assay, 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 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 interassay CV: approximately 8.5%.

Electrocardiography

Standard 12-lead ECG was done at each visit.

Echocardiography

All examinations were performed by one physician (A.K.) using a commercially available equipment (Agilent Sonos 5500, Philips Ltd., The Netherlands). All measurements and analyses were performed in accordance with the recommendations of the European Association of Cardiovascular Imaging (EACVI) (16, 17).

Statistical analyses

All continuous variables were presented as means ± standard deviation for relatively normally distributed and as median/interquartile range for those with deviation from normality. The independent variables were compared by Student's t-test or ANOVA test in repeated measures in one patient when approximately normal distribution was present. Because of skewed to

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Table 1. Baseline demographic, clinical, laboratory, and echocardiographic parameters of study population

	Not on spironolactone treatment group			On spironolactone treatment group			
Parameter	**n**	**Mean**	**SD**	**n**	**Mean**	**SD**	***P*-value**
Age (years)	51	67.58	6.62	50	68.46	7.4	0.532
Female sex	23			33			0.069
BMI (kg/m^2)	51	30.03	5.46	50	29.3	5.67	0.517
sBP (mm Hg)	51	126.91	12.69	50	126.12	12.68	0.756
dBP (mm Hg)	51	77.28	6.55	50	74.28	6.737	0.026
HR/min	51	61.56	8.26	50	66.06	10.51	0.019
Creatinin (mmol/L)	50	87.21	16.78	50	86.06	18.17	0.743
eGFR (mL/min/1.73 m^2)	51	71.78	13.12	50	68.44	16.97	0.274
Serum potassium (mmol/L)	51	4.1	0.37	50	4.08	0.47	0.853
LA area (cm^2)	46	20.54	4.22	42	21.14	4.46	0.138
LA volume (mL/m^2)	42	33.05	10.36	41	35.13	12.78	0.417
LVEF (%)	51	59.36	6.89	50	60.52	6.27	0.380
E/A ratio mitral valve	51	1.31	1.17	50	1.22	0.64	0.620

BMI - body mass index; sBP - systolic blood pressure; dBP - diastolic blood pressure; HR - heart rate; LA - left atrium; LVEF - left ventricular ejection fraction; SD - standart deviation

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 was applied for the differences in variables between the end and first visits. Nonparametric test like Mann–Whitney's test was also used in case of lack of normality. Absolute values and percentages were presented for categorical variables, and the chi-square test or Kendall's τ-analysis was used to test the null hypothesis. When the expected cell numbers were smaller than 5, then the exact Fisher's test was applied. The paired Wilcoxon or signed rank tests were used in some cases. *p*-value <0.05 was used for significance testing. Correlation analyses were performed by using Pearson's or Spearman's method to test the relation between different continuous or categorical variables.

The Kaplan–Meier curves were constructed with time for the occurrence of AF episodes during follow-up 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. Multiple hazard ratio model was constructed with adjustment for important factors, like age, sex, body mass index (BMI), presence of hypertension, diabetes mellitus or dyslipidemia, smoking status, treatment with renin-angiotensin system (RAS) inhibitor, spironolactone, statins, ejection fraction (EF), left atrial (LA) volume, eGFR, logarithmically transformed galectin-3, and CHA_2DS_2-VASc score. Backward selection modelling was used with significance level 0.05 for keeping in the model and 0.1 for removing a variable from the model. Wald's test for significance was done. The results were presented as hazard ratios (HR) with 95% confidence intervals (CI).

All analyses were 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 from all patients.

Results

Overall, 124 patients with AF and restored sinus rhythm were screened, and 101 patients were included in the study. Mean age was 68.2±7 years (range 55–83 years), and 56 (56%) of the participants were female. Baseline group characteristics are presented in Table 1.

The average number of AF recurrences was 1.62 per patient per year. Thirty-nine percent patients had no AF recurrence, 35% had one to three episodes of recurrence, and 12% experienced five or more recurrences. The patients were hospitalized in 24% of the cases. The median time to occurrence of at least one new episode was 48 days, 95% CI 14.24–81.76. Recurrences happened within 1 month in 40% of patients, in 21% between 31 and 90 days, in 18% between the third and sixth month, and in 21% after 6 months (Fig. 1).

The time to first event was evaluated, where the 50% recurrence rate was at day 48 after initial enrollment (Fig. 2).

Patients with the largest number of recurrences were with the longest history of AF, but it was not significant (p=0.235 with the Bonferroni test). We divided our patients in age quartiles. Patients, aged 64–66 (second quartile, 69.6%) had significantly more recurrences than those, aged <64 (second quartile, 44%), HR=2.57, 95% CI 1.16–5.68, p=0.019. Patients from third and fourth quartile had nearly twice more recurrences, but it was not significant, may be because of the small number of patients

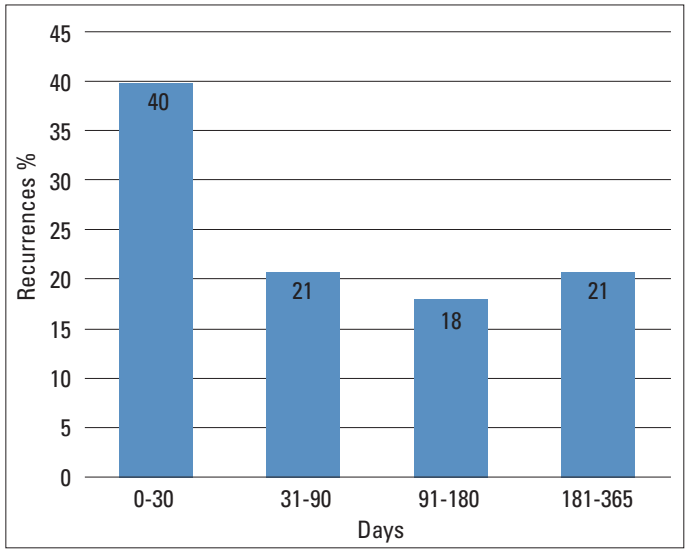

Figure 1. Occurrence rate of atrial fibrillation episodes with time

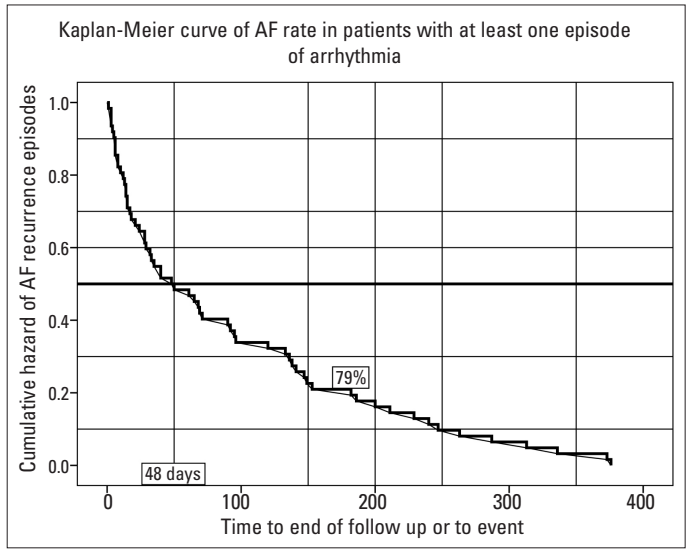

Figure 2. Time to first episode of atrial fibrillation recurrence or end of follow-up

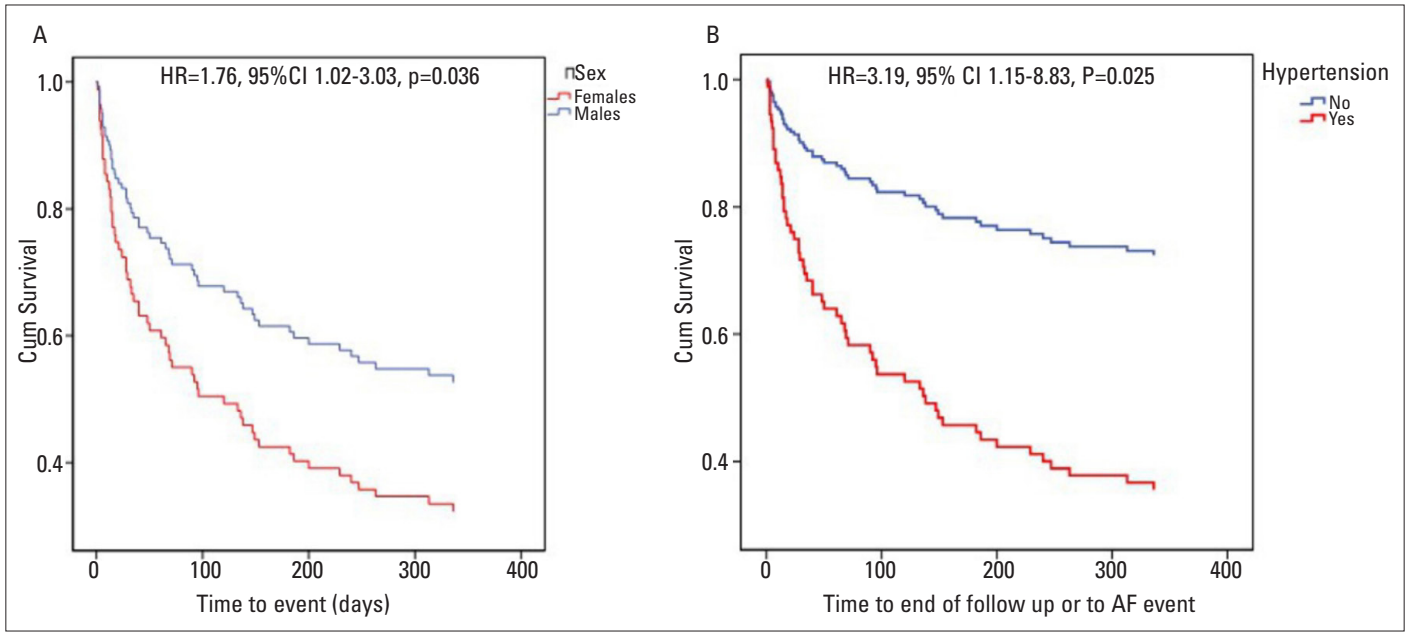

Figure 3. Recurrence of atrial fibrillation by (a) sex and (b) hypertension

in these groups. Female patients experienced significantly more recurrences than male: 53.3% vs. 28.6%, HR=1.76, 95% CI 1.02–3.03, p=0.036 (Fig. 3a, Table 2).

Patients with arterial hypertension were 86% in both groups. They had a threefold higher risk of recurrences than those without hypertension (p=0.025), independently of the treatment. Cox regression model showed that hypertension was a predictor for AF recurrence, HR=2.86 (95% CI 1.01–8.07; p=0.047) (Fig. 3b, Table 2).

The CHA_2DS_2-VASc score predicted the AF recurrence. The number of episodes was higher in those with higher score points, Figure 4a.

We explored the efficacy of antiarrhythmic treatment on AF recurrence. Twenty nine percent of the patients (28.7%) were on amiodarone. There was no significant difference in the rate of AF events between those receiving and not receiving amiodarone.

Patients with moderate- and high embolic risk have almost 2.5 times higher hazard of AF recurrence than those in the low-risk category, without significant difference between the two higher risk groups, Figure 4b. The adjustment for important factors does not practically change the result—HR=2.43 (95% CI 1.15–5.09, p=0.019) moderate vs. low risk and HR=2.45 (95% CI 1.12–5.36, p=0.025) for high- vs. low-risk group (Table 2).

Patients with gout had a twofold increased risk, without statistical significance (p=0.151). There was no association between galectin-3 levels and number of recurrences (p=0.902). Treatment with spironolactone did not influence the AF episodes (p=0.443). At the end of study, three patients

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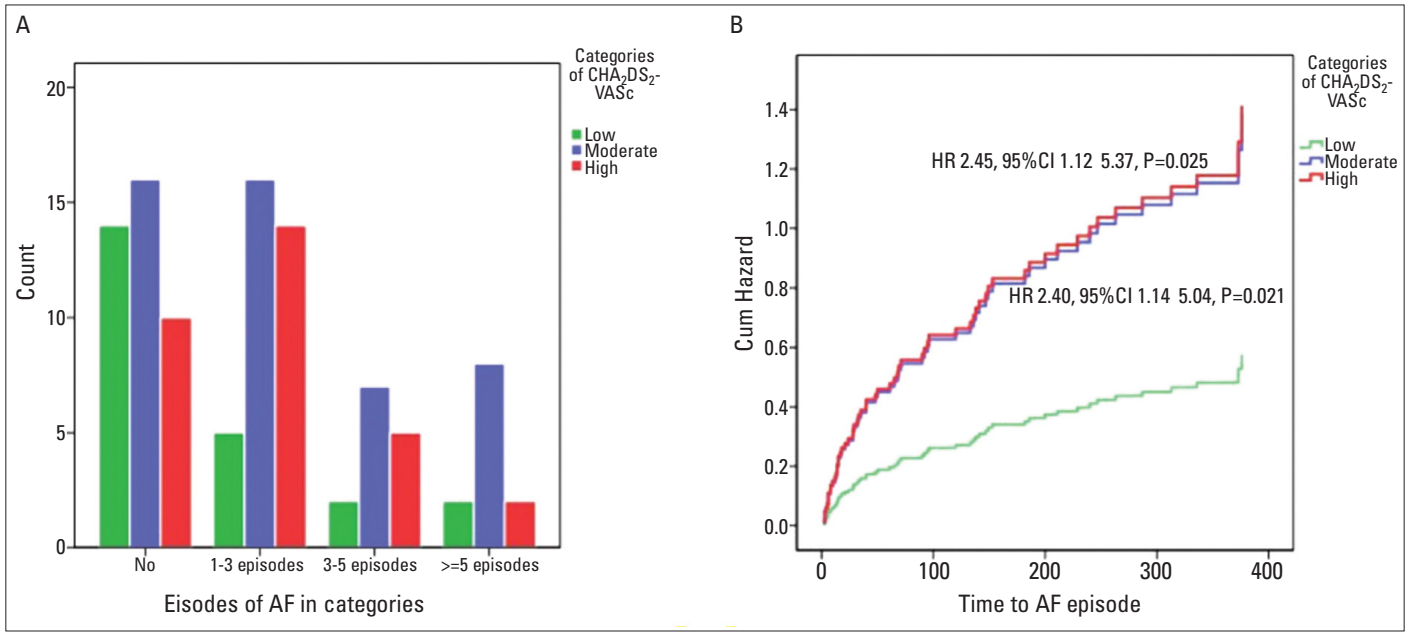

Figure 4. (a) Episodes of AF in categories by CHA_2DS_2-VASc categories. (b) Cox proportional hazard of AF recurrence according to CHA_2DS_2-VASc score categories

Table 2. Multiple Cox proportional hazard model for the occurrence of atrial fibrillation. Backward selection of the independent variables with the Wald test for significance

Variable	HR	95% CI	*P*-value
Sex	1.76	1.02–3.03	0.036
Hypertension yes/no	2.86	1.01–8.07	0.047
CHA_2DS_2-VASc score			
High versus low risk	2.43	1.15–5.09	0.019
Moderate versus low risk	2.45	1.12–5.36	0.025
Age per year	1.06	-	0.342
BMI per kg/m^2	0.99	-	0.851
Smoking yes/no	0.65	-	0.653
Diabetes mellitus yes/no	2.08	-	0.301
Dyslipidemia yes/no	0.98	-	0.164
eGFR per mL/min/1.72 m^2	1.03	-	0.222
logGal-3 per unit	0.38	-	0.213
LA volume per mL	1.00	-	0.863
EF per %	1.05	-	0.192
RAS inhibitor yes/no	1.88	-	0.442
Spironolactone yes/no	1.03	-	0.941
Statin yes/no	0.70	-	0.433

HR - hazard ratio; CI - confidence interval; CHA_2DS_2-VASc - congestive heart failure, hypertension, age, diabetes, stroke, vascular diseases, sex score; BMI - body mass index; eGFR - estimated glomerular filtration rate; logGal-3 - logarithmically transformed galectin-3 values; LA - left atrium; EF - ejection fraction; RAS - renin-angiotensin system

(5.9%) from the placebo group were in permanent AF versus 0 from the group on spironolactone (p=0.934, Fisher's exact test).

Discussion

Risk of recurrence

AF is a heterogeneous condition. It has multiple mechanisms and different clinical phenotypes (18–20). The rate of recurrences without antiarrhythmic treatment is 71%–84%, and it can be reduced to 44%–67% with antiarrhythmic drug therapy (21). Our study confirmed these data. The time to recurrence depends of the antiarrhythmic drug used. It is longer in patients treated with amiodarone: 487 days median time of recurrence in SAFE-T vs. 74 days in sotalol group (22) and 468 days in CTAF vs. 98 days in sotalol/propafenone group (23). In the real clinical practice, treatment strategies are often overlapping. Data, derived from our population, treated with different antiarrhythmics, showed that most of the recurrences happened in the first 3 months. This means that the antiarrhythmic therapy was beneficial especially in these first 3 months and the treatment could be reassessed after this period.

Risk factors for recurrences

A large number of potential risk factors for recurrences are found in different studies. Although AF occurs more frequently in males, with a male-to-female ratio of 1.2:1 (3, 24–26), females experience more recurrences as is in our study. Gurevitz et al. (27) and Suttorp et al. (28) found that females experienced more recurrences in the first year after electrical cardioversion. Female sex was the independent predictor of recurrence also after catheter ablation, despite the fact that women less likely receive catheter ablation for AF (29). Aging is related to structure and electrophysiological changes and increases the risk of onset of AF (30, 31). A trend to more recurrences with increased age was found in our study, although it was not significant for all

age categories. Hypertension and AF often coexist and share common risk factors. Hypertension is associated with structural and electrical remodeling. Some studies show that up to 90% of patients with AF are hypertensive (32–34). Data from Framingham ranked hypertension after heart failure, aging, and valvular heart disease, but because of its higher prevalence in the population, hypertension was responsible for more cases of AF than other risk factors (35, 36). In the study of Ma et al. (37), patients with hypertension were at higher risk for AF recurrences than normotensive. Our results were in agreement with these studies. Gout is a new emerging cardiovascular risk factor. A meta-analysis of seven cohort studies with 146,792 patients found that hyperuricemia was an independent predictor for AF onset [relative risk (RR)=1.92; 95% CI, 1.54, 2.40], and the risk for recurrences was also significantly associated with the levels of uric acid (RR=2.07; 95% CI, 1.61, 2.67) (38). The number of patients with history of gout in our population was too small and insufficient for significance.

CHA_2DS_2-VASc score and AF recurrences

We demonstrated that a higher CHA_2DS_2-VASc score was significantly associated with recurrent AF episodes. Few studies explored CHA_2DS_2-VASc score as a risk factor for AF onset. Hu and Lin (39) found the ability of the CHA_2DS_2-VASc score to predict AF in 69,530 patients with type 2 diabetes. Another study by Kashani et al. (40) with 2385 patients showed the significant role of this scoring system to predict postoperative atrial fibrillation. The risk factors in CHA_2DS_2-VASc score are also the risk factors for development of atrial cardiomyopathy, which can explain these results.

Role of spironolactone and Gal-3

We expected that spironolactone as an antifibrotic agent would reduce the AF recurrences, but we did not find any significant effect of MRA on the outcomes. The role of spironolactone in AF is not well studied. Dabrowski et al. (41) found that spironolactone in combination with beta-blocker was treated as a preventive for AF recurrences. Tase et al. (42) performed a retrospective analysis of 1008 AF patients with clinical characteristics similar to our population. The patients were divided in two groups: on treatment with spironolactone added to amiodarone, propafenone, or sotalol versus potassium supplements added to amiodarone, propafenone, or sotalol. AF episodes 24 months before and after initiation of spironolactone were examined. The pretreatment with beta-blocker, angiotensin-converting enzyme (ACE) inhibitor, or angiotensin receptor blocker (ARB) was exclusion criteria. Significant reduction of recurrences in spironolactone group was reported (42). We didn't find differences in recurrences with spironolactone treatment, probably because the duration of observation was too short for influencing the fibrotic process or because the number of patients enrolled was too small to have the power to detect the difference in the AF episodes. Another explanation is that the majority of our patients were with hypertension and were treated predominantly with ACE inhibitors or ARB, both in spironolactone and nonspironolactone groups.

The fibrotic biomarker Gal-3 was not predictive for AF recurrences in our study, although there are studies supporting this relation. Recently, a meta-analysis released supporting predictive power of galectin-3 for AF recurrence (43). The several possible explanations for our negative result are as follows. First, the small number of patients with Gal-3 measurements—only 67 at baseline and 62 at the end of the study. This insufficient number underpowers the study to detect the predictive role of Gal-3. Second, the duration of follow-up was too short. One year is not enough to develop significant fibrotic changes in the myocardium and, thus, to result in induction of AF episodes. Third, fibrosis is not the only reason for AF occurrence, and may be Gal-3 is not specific enough to detect the fibrosis in the atrial myocardium.

Another serious limitation of our study is that the diagnosis of AF recurrence was based on patients' symptoms and ECG only. There were no ambulatory ECG recordings or long-term rhythm monitoring as proof of arrhythmic episodes. It is well known that the silent episodes can be detected only when long-term ECG recordings are done.

Conclusion

AF is a progressive disease, characterized by frequent recurrences. Almost two-thirds of patients will have new arrhythmic episodes in the first year, and the majority of them will occur within the first 3 months. Female sex and arterial hypertension were the significant predictors of AF recurrence. CHA_2DS_2-VASc score was significantly associated with AF recurrent episodes. Spironolactone did not reduce recurrences of AF during one year, as well as the type of antiarrhythmic drugs.

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