Use of C-reactive protein for prediction of sinus rhythm maintenance after pharmacologic cardioversion in patients with Metabolic Syndrome

Ylber Jani[1], Entela Neziri[2], Sokol Paparisto[1], Petrit Bara[1], Kastriot Haxhirexha[3], Bekim Pocesta[4], Atila Rexhepi[3], Sotiraq Xhunga[8], Artur Serani[9], Fatmir Ferati[3], Agim Zeqiri[6], Ahmet Kamberi[7]

Abstract

BACKGROUND: Approximately 50% of patients undergoing cardioversion present with a recurrence of Atrial Fibrillation (AF) within 3–6 months of cardioversion despite ongoing antiarrhythmic treatment (AAD). Inflammation has been involved in the pathogenesis of both metabolic syndrome (MS) and atrial fibrillation. Evidence has indicated that inflammatory changes is essential for recurrence of AF. Therefore, identifying patients at high risk of AF recurrence remains challenging.

OBJECTIVE: We tested the hypothesis: increased C-reactive protein (CRP) levels are associated with a greater risk of AF recurrence after pharmacologic cardioversion (PCV)

METHODS: We conducted a multicenter observational cross-sectional study. 215 consecutive adult participants (≥18 and <65years of age) were recruited with MS and symptomatic AF (paroxysmal and persistent). They were admitted at six general cardiology Health Care Clinics, underwent PCV, and during a one calendar year follow-up period, were stratified into two groups according to CRP levels (105 participants (50 females and 55 males) with level of CRP ≥3mg/L and 110 (58 females and 52 males) with level of CRP <3mg/L). Recurrence of AF during follow-up period was defined as the study end-point.

RESULTS: After the follow-up of one year, only (31.8%) of patients with MS and CRP levels above the cut-off of 3 mg/L remain in sinus rhythm, compared to (64. 7%) of patients with MS and CRP levels below the cut-off of 3 mg/L (p=0. 002).

CONCLUSIONS: CRP, an easily determined marker in everyday clinical practice, may provide significant prognostic information regarding sinus rhythm maintenance and could be useful for predicting the recurrence of AF after successful pharmacologic cardioversion in clinical practice.

Keywords

CRP levels, Inflammation, Metabolic Syndrome, and Atrial Fibrillation.

Introduction

Atrial Fibrillation (AF) has increasingly become a focus of attention in recent years because it is the most encountered arrhythmia in clinical practice, a major cause of morbidity and mortality, and has adverse effects on overall quality of life. Several studies reported that Metabolic Sydrome (MS), a cluster of atherogenic risk factors, could influence the development of atrial fibrillation. An association between atrial fibrillation and metabolic syndrome has been suggested[1], but the mechanisms that relate metabolic syndrome to the increased risk of atrial fibrillation occurrence are not completely understood.[2, 3]

Approximately 50% of patients undergoing cardioversion usually present with recurrence of AF within 3–6 months of cardioversion despite ongoing antiarrhythmic treatment.[4] The precise mechanisms of AF recurrence have not been fully elucidated. Many studies have indicated that inflammatory changes are essential for the recurrence of AF[5,6], and an increased level of markers of inflammation, such as CRP, is associated with a greater risk of AF recurrence. However, there was significant heterogeneity across the studies.[7-10] Therefore, identifying patients at high risk of AF recurrence remains challenging.

We set out to use CRP levels to predict sinus rhythm maintenance after Pharmacologic Cardioversion (PCV) in patients with Metabolic Syndrome (MS). We tested the hypothesis that increased CRP levels are associated with a greater risk of AF recurrence after PCV in MS patients.

Methods

1. Study design

We conducted a multicenter observational cross-sectional study and recruited 215 consecutive adult participants (between 18 and 64 years of age) with MS and symptomatic AF (paroxysmal and persistent) defined on the basis of the classification guidelines of ESC.[11] They were admitted at six general cardiology Health Care Clinics, underwent pharmacologic cardioversion during 1 calendar year (November 2022–November 2023), and were stratified in

*Corresponding author: Ylber Jani MD, PhD, Faculty of Medical Sciences "Luarasi" Tirana Republic of Albania; E-mail address: ylber_jani@hotmail

[1]Faculty of Medical Sciences "Luarasi" Tirana Republic of Albania
[2]Sport University Tirana Republic of Albania
[3]Faculty of Medicine Tetovo Republic of North Macedonia
[4]Department of Cardiology Faculty of Medicine "Ss Kiril and Metodij" University Skopje Republic of North Macedonia
[5]Department of Cardiology Medical Center Durres Republic of Albania
[6]Department of Internal Medicine-General Hospital "DR Ferit Murat" Gostivar Republic of North Macedonia
[7]Department of Cardiology Faculty of Medicine M. Teresa Tirana Republic of Albania

https://doi.org/10.2478/rjc-2024-0003
sciendo

two groups: 105 participants (50 females and 55 males) with level of CRP ≥3mg/L and 110 (58 females and 52 males) with level of CRP <3mg/L. Exclusion criteria were as follows: hemodynamically unstable patients, a previous cardioversion (CV) within one year, previous AF ablation, moderate-to-severe valvular heart disease, hypertrophic cardiomyopathy, cardiac implantable electrical devices, congenital heart disease, poor left ventricular function (EF<35%), previous cardiac surgery, and thyroid disease.

The health screening included a physical examination, standard 12-lead ECG anthropometrics, and echocardiographic examination. Blood pressure (BP) was obtained after 10 min of rest in the sitting position and expressed as the average of three consecutive measurements. Hypertension, was defined as a systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, and/or current antihypertensive therapy.[12] Diabetes mellitus (DM) was defined as a fasting serum glucose level ≥126 mg/dL and/or current medical therapy with an oral hypoglycemic agent and/or insulin.[13] An overnight fasting blood sample, was drawn from each patient to determine: blood glucose, lipid profile tests, total serum cholesterol (TC), serum high density lipoproteins cholesterol (HDL-C), and serum triglycerides (TG). The sample analysis was performed using standard biochemical analytical methods.

2. Metabolic Syndrome

MS was defined according to the harmonized definition of the International Diabetes Federation and other organizations.[14] On the basis of the baseline examination, metabolic syndrome was diagnosed when at least three of the following criteria were met. (1) central adiposity [Waist circumference (WC)] >102 cm in men and >88cm in women; (2) serum HDL-C < 50 mg/dL in women or < 40 mg/dL in men; (3) serum triglyceride levels > 150 mg/dL; (4) SBP ≥ 140mm Hg or DBP ≥ 90mm Hg or use of antihypertensive drugs; (5) the presence of diabetes mellitus (DM) or use of anti-diabetic drugs.

3. Plasma CRP levels

Measurement of the values of CRP were obtained before cardioversion. It was measured using latex particle-enhanced Immuno-assay with the nephelometry (Roche Swiss). Consistent with recommendations from Centers for Disease Control and Prevention[15], a CRP cut point of 3.0 mg/L was used to differentiate high-risk and low-risk group. Measurement of the values of CRP were obtained before cardioversion.

4. Conventional Echocardiography

Prior to the procedure, all patients underwent a comprehensive transthoracic echocardiographic examination to assess left atrial (LA) size and function, left ventricular (LV) function and to exclude structural heart disease. M-mode, two-dimensional, and Doppler echocardiography were performed and/or reviewed by experienced staff cardiologists, compliant with the recommendation of the American Society of Echocardiography and the European Association of Cardiovascular Imaging[16], stored in DICOM format, and later reviewed by two experienced echocardiographers. The transthoracic echocardiography was always performed together with transesophageal echocardiography before PCV. The LA diameter was measured in the M mode parasternal long-axis view with the probe located in the third or fourth intercostal space. The LA volume index (LAVI) was measured by the biplane area length method using the apical four-chamber and apical two-chamber view at the ventricular end-systole and indexed to the calculated body surface area using the Du Bois formula. The LV ejection fraction (LVEF) was accessed by the biplane Simpson method at ventricular end-diastole.

5. Pharmacological cardioversion

PCV was performed in electrophysiology laboratory equipped with cardiopulmonary resuscitation devices and under supervision by a cardiologist while the patient had continuous ECG, blood pressure, and oxygen saturation monitoring. According to our hospital protocol: intravenous (IV) Propafenon (at a rate of 2 mg/kg over 15 minutes), Flekainide (at rate of 2mg/kg over 10minutes), Amiodarone (at rate of 5mg/kg over 1h), and metoprolol 5 mg, q5min, or oral medications (pill-in-the-pocket single doses of propafenone 450-600mg, Flecainide 200-300 mg**)** have been administered.

Amiodarone was chosen for pharmacological cardioversion in 49% of cases, followed by Propafenone, Flecainide, and Metoprolol (28%, 18%, and 5% respectively). After successful cardioversion, the patient was observed 24 to 48 hours or until the QT interval normalizes. Patients with persistent AF of more than 48 hours or unknown duration was treated with anticoagulation for at least three weeks before pharmacological cardioversion. Also, anticoagulation was continued for 4 weeks after the procedure, and INR was maintained between 2 to 3 IU.[17]

The follow-up period was one year. Heart rate, PQ, QRS, and QT intervals were measured in the 12-lead ECG, one day and one month after successful cardioversion and at three monthly intervals thereafter. Recurrence of AF was defined as the study endpoint. When experiencing palpitations, patients were asked to visit our outpatient department or nearby hospital as soon as symptoms occur, for ECG documentation of heart rhythm, and in cases of sinus rhythm, a Holter ECG was conducted to preclude atrial fibrillation. Diagnosis of AF recurrence was made when AF was confirmed on 12-lead ECG, or AF lasting at least 30 s was documented on Holter monitoring. Time to AF recurrence was calculated from successful PCV to the first AF rhythm documentation on ECG or Holter monitoring.

Statistical Analysis

For evaluation of the data obtained from the study, descriptive statistical methods of mean ± standard deviation, frequency, and ratio values were used**.** The distribution of variables was tested for normality using the Kolmogorov-Smirnov test, and the heterogeneity of variances was evaluated by Levene's test. Analysis of quantitative variables with normal distribution was performed using the Student-*t* test and analysis of variance (ANOVA). Continuous variables with abnormal distribution and qualitative variables were analyzed using the Fisher test and χ^2 test. The association between variables was analyzed using logistic regression, odds ratio (OR),

and 95% confidence interval (CI) were estimated. A p value <0.05 was considered statistically significant for a confidence interval of 95%. Statistical analyses were performed with the SPSS software package (SPSS 19.0).

Results

A total of 215 patients with MS, after pharmacologic cardioversion, were stratified in two groups: 105 participants (51 females and 54 males) with CRP<3mg/L and 110 participants (59 females and 51 males) with level of CRP>3mg/L, completed the survey. (Table 2)

After the follow-up at one year, only 35 (31.8%) of patients with MS and CRP levels above 3.0mg/L remain in sinus rhythm, compared to 68 (64.7%) of patient with MS and CRP levels below 3.0mg/L (Fisher exact p=0. 002) (Table 1 and Fig. 1). The recurrence rate of AF in participants with MS and CRP levels above 3.0mg/L was higher when compared with participants with MS and CRP levels below 3.0mg/L [75 (68. 1%) vs. 37 (35. 2%)] (Fisher exact p=0. 002).

Of all recurrences of atrial fibrillation, 45% occurred within the first three months with significant difference between the two groups (55% in patients with MS and CRP levels above 3.0mg/L vs. 24% patients with MS and CRP levels below 3.0mg/L, Fisher exact p=0. 003) and the last three months (12% in patients with MS and CRP levels above 3.0mg/L vs. 35% in patients with MS and CRP levels below 3.0mg/L, Fisher exact p=0.04).

There was no significant difference between groups using antiarrhythmic drugs (AADs) after PCV during follow-up period. Amiodarone was used in (49% of patients with MS and CRP levels above 3.0mg/L vs. 44% patients with MS and CRP levels below 3.0mg/L, p=0.48), Flekainide (13%vs. 16%, p=0. 47), Propaphenon (21% vs. 22%, p=0. 34), and Metoprolol (2% vs. 3%, p=0.52). Also, there was no significant difference between participants those that did not use any AADs during the follow-up period, regarding maintenance in sinus rhythm (SR) (17% vs. 11.7%, Fisher exact p=0.38).

The baseline demographic, clinical, electrocardiographic, echocardiographic, and laboratoric characteristics of each study group are summarized in Table 2. There were no statistically significant differences between the participants with level of CRP >3mg/L and participants with level of CRP <3mg/L in: gender (p=0.96), ages (58. 8±5.2 vs. 56. 9±5.4; p=0.5), systolic and diastolic blood pressure (142±26 vs. 132±15 p=0.47; 89±10 vs. 83±7) (p=0. 31), WC (94±3. 4 vs. 92. 4±5. 2 p=0. 18), Trig (2. 1±0. 5vs 1. 9±0. 4 p=0. 29); HDL (0.89 vs. 0.86, p=0.46), three risk factors of MS (p=0.19), four risk factors of MS (p=0.09) and five risk factors of MS (p=0.06), type of AF (paroxysmal p=0.51; persistence p=0.50), presence of disease (coronary disease p=0.42, heart failure p=0.34; kidney disease p=0.61, stroke p=0.54), AADs used for pharmacological cardioversion (Amiodarone p=0.46, Flecainide p=0.44, Propaphenone p=0.49; Metoprolol p=0.24, oral medications (pill-in-the-pocket), Propaphenone p=0.54, Flecainide p=0.36), AADs used after pharmacological cardioversion (Amiodarone p=0, 55, Flecainide p=0.32, Propaphenone p=0.35, Metoprolol p=0.24).

Of all participants included in the study, 167 (77. 6%) participants had no evidence of organic heart disease (85 (81%) in group with level of CRP <3mg/L and 82 (74. 5%) participants in group with level of CRP >3mg/L, p=0.38). In the remaining 48 (22.3%) participants, the underlying heart disease was: coronary artery disease in 12 (5.5%) participants (5 in group with level of CRP <3mg/L and seven in group with level of CRP >3mg/L, p=0. 42), Heart failure in 15 (6.9%) participants (6 in group with level of CRP <3mg/L and nine in group with level of CRP >3mg/L, p=0. 34), Kidney disease in 9 (4.1%) participants (4 in group with level of CRP <3mg/L and five in group with level of CRP >3mg/L, p=0. 53), stroke in 19 (8.8%) participants (9 in group with level of CRP <3mg/L and 10 in group with level of CRP >3mg/L, p=0. 54). There was no significant difference in patient characteristics between either study group.

Significant differences between groups were observed in relation to: BMI – significantly higher in participants with level of CRP >3mg/L

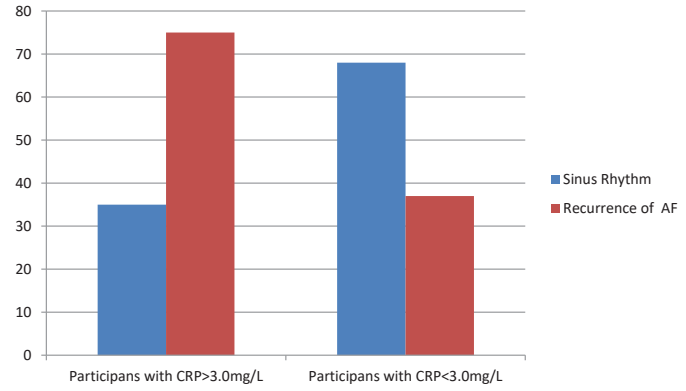


Figure 1 - Frequece of maintenance sinus rhythm and AF-recurrence in participans with MS (n.215) according to CRP levels

Table 1 – Results for maintenance of sinus rhythm and AF-Recurence in participans with MS (n.215) according to CRP levels

Results for maintenance of sinus rhythm and AF-Recurrence Study Group(n-215).					
	Participants with CRP >3.0mg/L (n.110)		Participants with CRP < 3.0mg/L(n.105)		Total(n.215)
	Sinus Rhythm	AF-Recurrence	Sinus Rhythm	AF-Recurrence	P
(No)	35	75	68	37	
(%)	**31.8**	68.1	**64.7**	35.2	**0.002**

CRP-reactiv protein;AF:Atrial Fibrilation.No-number of participans;%-perecnt of participans.p-significance

Table 2 – Baseline characteristics of patients with MS (n.215),according to CRP levels

Variables	MS (N.215)						P - value
	Gr. with CRP levels ≥ 3mg/l (n-110)			Gr.with CRP levels < 3mg/l (n.105)			
	N. (%)	Mean	±SD	N. (%)	Mean	±SD	
Gender. Females	59(52)			51(48,8)			0.4
Age (year)		58.8	±5.2		56.9	±5.4	0.5
BMI(kg/m^2)		27.4	±6.5		25.0	±4.0	**0.001**
AF(paroxysmal)	62(56.3)			58 (55.2)			0.51
AF(persistens)	48 (44.7)			47 (44.8)			0.50
CRP(mg/dL)		8.4	±2.3		2.7	±0.1	**0.04**
CAD-presence n(%)	7(5.4)			5(4.7)			0.42
HF - presence n(%)	9(8.1)			6(5.7)			0.34
RD - presence n(%)	4(3.8)			4(3.6)			0.61
STROK-pres. n(%)	10(9.5)			9(8.5)			0.54
LAd(cm/m^2)		4.1	±0.3		3.8	±0.2	**0.001**
LAVI(mL/m^2)		30.6	±4.6		28.5	±4.3	**0.001**
LVMI(g/m^2)		96.8	±1.1		66.8	±5.2	**0.000**
ESD(cm)		2.9	±0.4		2.73	±0.7	0.06
EDD(cm)		4.8	±0.5		4.8	±0.4	0.07
THS(cm)		1.2	±2.1		1.2	±1.5	0.06
THPW(cm		1.1	±0.5		1.1	±0.7	0.07
EF(%)		0.67	±0.7		0.66	±0.5	0.5

BMI:body mass index;AF:Atrial Fibrilation;CRP-c-reactiv protein;CAD:coronary disease;HF:heart failure;RD:renal disease;LAD:left atrial dimension;LAVI:left atrial vollum index;ESD:end systolic dimension;EDD:end diastolic dimension;LVMI:left ventricular mass index;THS:thickening of septum;THPW:thickening of posterior wall; EF:ejecton fraction.

than participants with level of CRP <3mg/L (2, 7±0, 13 vs. 9, 8±9. 1 p=0. 00); glycemia level – significantly higher in participants with level of CRP >3mg/L than participants with level of CRP <3mg/L (6, 8±0.9 vs. 6, 5±0.8 p=0. 006).

Echocardiographic data of cardiac structure and function according to CRP levels are presented in Table 2. There were no significant changes between groups in relation to left ventricular dimensions and ejection fraction, but in relation to LVMI, there was significant difference. Patients who had CRP levels above the cut-off of 3mg/L had higher LVMI than patients with levels below 3mg/L respectively (96.8±1.1 vs. 66.8±5.2, p=0.001). There were significant changes between groups in relation to dimension and function of LA. Patients who had CRP levels above the cut-off of 3mg/L had increased dimension of LA (4.1±0.3 vs. 3.9±0.2, p=0.001), higher prevalence of enlargement of LA [LAVI (30.6±4.6 vs. 28.5±4.3, p=0.0009)].

In a logistic regression (Table 3), there was observed significant association of CRP levels above the cut-off of 3mg/L with a rate of AF recurrence (OR=3.938, 95%CI 2.234-6.942), LAd (OR=3.817, 95%CI 0.989-1.544), LAVI (OR=1.74;95% CI 1.549-1.975), LVMI (OR=1.041, 95% CI 1.022-1.061), and BMI (OR=2.072, 95%CI 1.203-3.571).

Discussion

In the present study, we observed that frequency of maintaining sinus rhythm after the follow-up of one year of pharmacologic cardioversion in participants with MS and CRP levels above the cut-off of 3mg/L was significantly lower than among participants with MS and CRP levels below 3mg/L, indicating that increased CRP levels are associated with greater risk of AF recurrence after pharmacologic cardioversion in patients with MS. Results that confirmed our hypothesis and suggests the possibility that degree of systemic inflammation may be more proarrhythmic. A positive association between CRP levels and AF recurrence has been demonstrated in several studies[18-20], but some of reports failed to demonstrate such a relationship.[21, 22]

It is well-established that inflammation is independently associated with the development of AF.[23,24] Experimental and clinical data indicate that inflammation may have been involved in the pathogenesis of both metabolic syndrome and atrial fibrillation[25]; this makes inflammation one of many possible cofactors of AF. Markers of inflammation (CRP, leukocyte infiltrates)have been found in atrial tissue samples of subjects with AF.[26] In both cross-sectional and longitudinal studies, CRP has been consistently and significantly predictive of early AF relapse after successful cardioversion, even

Table 3 – Logistic Rgression Model:Association of CRP levels (>3.0mg/L) with: AF-recurence, LAd, LAVI, LVMI and BMI

	OR*	Significance	95% CI for Exp (B)	
			Lower	Upper
AF recurrence	3.938	.000	2.234	6.942
LAd	3.817	.000	0.989	1.544
LAVI	1.74	.000	1.549	1.975
LVMI	1.041	.000	1.022	1.061
BMI	2.072	.000	1.203	3.571

AF:Atrial Fibrilation;LAD:Left Atrial dimension;LAVI:Left Atrial Vollum Index;LVMI:Left Ventricuar mass Index;BMI:Body mas Index.

after adjustment for risk factors for AF, such as hypertension and CAD.[27] Even in the present study, we found that of all recurrences of atrial fibrillation, the greatest incidence of AF recurrence occurred within the first three months with significant different occurrence between the two groups, and higher AF recurrence occurred in participants with CRP levels above a cut-off at 3 mg/L. It has also been suggested that atrial electrical remodeling resolves during the first days after cardioversion of persistent AF and may be related to early recurrence rates.[28]

LA remodeling is a key process in AF generation and is a consequence of structural and functional maladaptation against external stress. LA remodeling, in turn, promotes electrical disturbance that can increase incident AF.[29] In the present study, we found significant association of increased rate of AF recurrence in participants with CRP levels above a cut-off at 3 mg/L and LA remodeling (LA dimensions and LAVI). Similar results have been found in others studies.[30]

Several placebo-controlled studies have demonstrated the absolute efficacy of AADs as superior to placebo in maintenance of SR after rhythm cardioversion.[31] In the present study, maintenance rate of SR after rhythm cardioversion in participants who are not received any AADs in a 1-year follow-up, were observed in 13.5%. A 13-25% maintenance rate of sinus rhythm after cardioversion of atrial fibrillation in a 1-year follow-up without antiarrhythmic drug therapy has been reported.[32] It is well known that inflammatory processes have been associated with AF but uncertain whether this represents the course or the effect of inflammation.[33] Although mechanisms by which AF cause inflammation are unknown.[34] Regardless of the presence of a causal relationship, the study of baseline CRP levels may provide significant prognostic information regarding sinus rhythm maintenance.[35]

Pharmacologic cardioversion is a widely conducted procedure that restores the AF to SR in a patients with AF, despite AADs in clinical practice. The clinical significance of this study is that CRP is an easily determined marker in everyday clinical practice worldwide that may be helpful for predicting early AF recurrence after successful pharmacologic cardioversion, even with various AADs. Therefore, this approach could guide clinicians to determine treatment plans from a simple rate control strategy to a more effective rhythm control therapy, such as catheter ablation for patients with AF refractory to AADs and pharmacologic cardioversion.

Future Directions

Understanding the pathogenesis of AF and the relationships between inflammation and AF is of both academic and clinical interest because insights might lead to better prevention and treatment of this common but dangerous dysrhythmia. The detailed imaging of inflammation by positron emission tomographic or molecular means might help to clarify the role of inflammation in AF, and microRNA could prove to be of substantial value in the study of tissue and circulating biomarkers. If a causal link between inflammation and AF is proved, novel approaches to targeting inflammation might lead to better therapeutic options.

Several limitations

Firstly, the cross-sectional design precludes the assessment of causal relationships between inflammation (CRP levels) and maintenance of SR. Secondly, detection of AF recurrence was based on ECG recordings acquired on a systematic basis and/or 24 hour Holter registration. Importantly, patients were encouraged to obtain an ECG registration when experiencing palpitations in order to confirm AF as the cause of these complaints. Nevertheless, asymptomatic episodes may have been missed. Thirdly, the present study comprised a relatively small group of patients. Therefore, the present findings need to be validated in a larger group of patients.

Conclusions

CRP, an easily determined marker in everyday clinical practice, may provide significant prognostic information regarding sinus rhythm maintenance and could be useful for predicting recurrence of AF after successful pharmacologic cardioversion in clinical practice. Atrial Fibrillation patients with CRP levels above a cut-off at 3 mg/L should be observed closely after successful pharmacologic cardioversion, even with various AADs and anti-inflammatory therapeutic strategies, and may be a next logical step in AF care, one not burdened by proarrhythmic risk.

Author Contributions

Ylber Jani, involved in conceptualization; Bekim Pocesta, Atila Rexhepi, Fatmir Ferati, Sotiraq Xhunga, Artur Serani, Agim Zeqiri, Ylber Jani, investigated the study; Kastriot Haxhirexha, formally analyzed the study; Ahmet Kamberi involved in original draft preparation; Ylber Jani, Kastriot Haxhirexha, Ahmet Kamberi reviewed and edited the study; Bekim Pocesta visualized the study; Ylber Jani, Petrit Bara, Ahmet Kamberi, involved in supervision.

Consent to participate

All patient were written informed, consent was obtained from all participating patients before they were enrolled into the study.

A local ethics committee ruled that no formal ethics approval was required in this particular case.

Ethics approval

'Not applicable' for that section.

Consent for publication

'Not applicable' for that section.

Availability of data and materials

'Not applicable' for that section.

Competing interests

'Not applicable' for that section.

Acknowledgments

We thank: Bekim Pocesta, Fatmir Ferati, Sotiraq Xhunga PhD, Artur Serani MD, and Agim Zeqiri MD for their contribution on data collection/processing.

Conflict of interest

Authors declare no conflict of interests for this article.

Funding

No funding was obtained for this study.

Highlights

Much evidence indicated that inflammatory changes are essential for recurrence of AF and the increased level of markers of inflammation, such as CRP, are associated with greater risk of AF recurrence. In the present study, we observed that the frequency of maintaining sinus rhythm after the one-year follow-up of pharmacologic cardioversion in participants with CRP levels above the cut-off of 3 mg/L was significantly lower than among participants with CRP levels below 3 mg/L. Anti-inflammatory therapeutic strategies may be a next logical step in AF care, one not burdened by proarrhythmic risk.

REFERENCES

1. Tanner RM, Baber U, Carson AP, et al. Association of the metabolic syndrome with atrial fibrillation among United States adults (from the Reasons for Geographic and Racial Differences in Stroke [REGARDS] Study). Am J Cardiol 2011;108:227–232.

2. Staerk L, Sherer JA, Ko D, Benjamin EJ, Helm RH. Atrial Fibrilation: Epidemiology, pathoph- ysiology and clinical outcomes. Circ Res 2017;120:1501-17.

3. Nattel S, Harada M. Atrial remodeling and atrial fibrillation:recent advances and translational perspectives. J Am Coll Cardiol 2014;63:2335-45.

4. Disertori M, Lombardi F, Barlera S, et al. Clinical characteristics of patients with asymptomatic recurrences of atrial fibrillation in the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico-Atrial Fibrillation (GISSI-AF) trial. Am Heart J 2011;162:382–9.

5. Wu N, Xu B, Xiang Y, et al. Association of inflammatory factors with occurrence and recurrence with atrial fibrillation:a meTanalysis. Int J Cardiol 2013;169:62-72.

6. Guo Y, Lip GY. Apostolakis S. Inflammation in atrial fibrillation. J Am Coll Cardiol 2012;60 (22):2263–70.

7. Barassi A, Pezzilli R, Morselli-Labate AM, et al. Serum amyloid a and C-reactive protein independently predict the recurrences of atrial fibrillation after cardioversion in patients with preserved left ventricular function. Can J Cardiol 2012;28(5):537-41.

8. Tong Liu, Guangping Li, Lijian Li, Korantzopoulos P. Association between C-reactive protein and recurrence of atrial fibrillation after successful electrical cardioversion: a meta-analysis. J Am Coll Cardiol 2006;12:042.

9. Yo CH, Lee SH, Chang SS, Lee MC, Lee CC. Value of high-sensitivity C-reactive protein assays in predicting atrial fibrillation recurrence: a systematic review and meta-analysis. BMJ Open 2014;20;4.

10. Yu L, Jian Z, Tao L, Zongtao Y, Yan JJ, Han Z, et al. The systemic-immune-inflammation index predicts the recurrence of atrial fibrillation after cryomaze concomitant with mitral valve surgery. BMC Cardiovascular Disorder 2022;22(45).

11. Hidrics G, Potparo T, Nikolaos D, Arbelo EJ, Bax J, Blomstron-Ludgvist C, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. EHJ 2021;42(5):373-498.

12. The seventh report of Joint National Committee on Prevention, Detection, Evaluation and treatment of Hight Blood Pressure. JAMA 2003;289:2550-72.

13. America Diabetes Association. Standards for medical care for patient with diabetes mellitus. Diabetes Care 2002;25(Suppl 1):S33-S49.

14. Alberti KG, Eckel RH, Grundy SM, et al. International Diabetes Federation Task Force on Epidemiology and Prevention, and National Heart, Lung, and Blood Institute. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation 2009;120:1640–45.

15. Center for disease control/American Heart association Workshop on inflammatory Markers, and Cardiovascular Disease: Application to clinical and public health practice: Atalanta, March 14-15, 2002. Atlanta, Ga. Centers for Disease Control and Prevention: 2002.

16. Lang RM, Badano LP, Mor-Avi, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Amer Soc Echocardio 2015;28(1):1–39.

17. Gibson CM, Basto AN, Howard ML. Direct Oral Anticoagulants in Cardioversion: A Review of Current Evidence. Annals Pharmacotherapy 2018.

18. Zarauza J, Rodriguez Lera MJ, Farinas Alvarez C, *et al.* Relationship between C-reactive protein level and early recurrence of atrial fibrillation after electrical cardioversion. Rev Esp Cardiol 2006;59:125-129.

19. Watanabe E, Arakawa T, Uchiyama T, Kodama I, Hishida H. High-sensitivity C-reactive protein is predictive of successful cardioversion for atrial fibrillation and maintenance of sinus rhythm after conversion. Int J Cardiol 2006;108:346-353.

20. Wazni O, Martin DO, Marrouche NF, *et al.* C reactive protein concentration and recurrence of atrial fibrillation after electrical cardioversion. Heart 2005;91:1303-1305.

21. Korantzopoulos P, Kolettis TM, Kountouris E, Siogas K, Goudevenos JA. Variation of inflammatory indexes after electrical cardioversion of persistent atrial fibrillation: Is there an association with early recurrence rates? Int J Clin Pract 2005;59:881-885.

22. Cosgrave J, Foley JB, Bahadur K, Bennett K, Crean P, Walsh MJ. Inflammatory markers are not associated with outcomes following elective external cardioversion. Int J Cardiol 2006;110:373-377.

23. Schnabel RB, Larson MG, Yamamoto JF, et al. Relations of biomarkers of distinct pathophysiological pathways and atrial fibrillation incidence in the community. Circulation 2010;121 (2):200–7.

24. Jani Y, Haxhirexha K, Pocesta B, et al. Impact of Inflammation on Atrial Fibrillation in patients with Metabolic Syndrome. J Cardiology Interventions 2021;2(01):1-8.

25. Guo Y, Lip GY, Apostolakis S. Inflammation in atrial fibrillation. J Am Coll Cardiol 2012;60:2263–2270.

26. Frustaci A, Chimenti C, Bellocci F, Morgante E, Russo MA, Maseri A. Histological substrate of atrial biopsies in patients with lone atrial fibrillation. Circulation 1997;96(4):1180–4.

27. Hadi AR, Alawi A, Wael AL & Jassim M. Inflammatory cytokines and atrial fibrillation: current and prospective views. Journal of Inflammation Research. 2010:75-97.

28. Tieleman RG, Van Gelder IC, Crijns HGJM, et al. Early recurrences of atrial fibrillation after electrical cardioversion: a result of fibrillation-induced electrical remodeling of the atria? J Am Coll Cardiol 1998;31:167-173.

29. Nattel S, Harada M. Atrial remodeling and atrial fibrillation: recent advances and translational perspectives. J Amer Coll Cardio 2014;63(22):2335– 2345.

30. Motoc A, Abugattas JP, Roosens B, Scheirlynck E, Heyndrickx B, de Asmundis C, et al. Left atrium remodeling predicts late recurrence of paroxysmal atrial fibrillation after second generation cryoballoon ablation. Cardiovascular Ultrasound 2018;25(19):16-19.

31. Benditt DG, Williams JH, Jim J. Maintenance of sinus rhythm with oral d, l-sotalol therapy in patients with symptomatic atrial fibrillation and/or flutter. D, l-Sotalol Atrial Fibrillation/Flutter Group. Am J Cardiol 1999;84:270–277.

32. Coplen SE, Antman EM, Berkis JA. Efficacy and safety of quinidine therapy for maintenance of sinus rhythm after cardioversion. A meta-analysis of randomized trials. Circulation 1990;82:1106–1116.

33. Letsas KP, Weber R, Burkle G, Mihas CC, Minners J, Kalusche D, Arentz T. Pre-ablative predictors of atrial fibrillation recurrence following pulmonary vein isolation: the potential role of inflammation. Europace. 2009;11(2):158–63.

34. Panagiotis K, Konstantinos P, Letsas F, Gary T, Nikolaos F, et al. Inflammation and atrial fibrillation:Acomprehesive review. J Arrhyth 2018.

35. Korantzopoulos P, Kolettis TM, Kountouris E, Siogas K, Goudevenos JA. Variation of inflammatory indexes after electrical cardioversion of persistent atrial fibrillation. Is there an association with early recurrence rates? Int J Clin Pract 2005 Aug;59(8):881-5.