



## Use of C-Reactive Protein for Prediction of Sinus Rhythm Maintenance after Pharmacologic Cardioversion in Patients with Metabolic Syndrome

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### Abstract

**Background:** Approximately 50% of patients undergoing cardioversion usually present with recurrence of AF within 3 to 6 months of cardioversion despite ongoing Antiarrhythmic Treatment (AAD). Inflammation have been involved in the pathogenesis of both Metabolic Syndrome (MS) and Atrial Fibrillation (AF). Many evidences indicated that inflammatory changes are essential for recurrence of AF. Therefore, identifying patients at high risk of AF recurrence remains challenging.

**Objective:** We tested hypothesis: Increased CRP levels are associated with greater risk of AF recurrence after PCV.

**Methods:** We conducted a multicenter observational cross-sectional study. Recruited were 215 consecutive adult participants ( $\geq 18$  and  $<65$  years of age), with MS and symptomatic AF (paroxysmal and persistent), attempted at 6 general cardiology Health Care Clinics, who underwent Pharmacologic Cardioversion (PCV), during 1 calendar year follow-up period, stratified in two group according to CRP levels, (105 participants (50 females and 55 males) with level of CRP  $\geq 3$  mg/l, and 110 (58 females and 52 males) with level of CRP  $<3$  mg/l). Recurrence of AF, during follow-up period was defined as the study end-point.

**Results:** After the follow-up of 1.0 years, 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 patient with MS and CRP levels below the cut-off of 3 mg/l ( $p=0.002$ ).

**Conclusion:** 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.

**Keywords:** CRP levels; Inflammation; Metabolic Syndrome; Atrial Fibrillation

### Introduction

Atrial Fibrillation (AF), in recent years has increasingly become a focus of attention because it represents the most encountered arrhythmia I clinical practice a major cause of morbidity, mortality and has adverse effects on overall quality of life. Several studies reported that Metabolic Syndrome (MS) a cluster of atherogenic risk factors, could influence the development of atrial fibrillation. An association between atrial fibrillation and the 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 to 6 months of cardioversion despite ongoing antiarrhythmic treatment [4]. The precise mechanisms of AF recurrence have not been fully elucidated. Many evidences indicated that inflammatory changes are essential for recurrence of AF [5,6] and increased level of markers

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of inflammation such as C-Reactive Protein (CRP), are associated with greater risk of AF recurrence, although 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 of C-reactive protein levels for prediction of sinus rhythm maintenance after Pharmacologic Cardioversion (PCV) in patients with Metabolic Syndrome. We tested hypothesis: Increased CRP levels are associated with greater risk of AF recurrence after pharmacologic cardioversion, in patients with MS.

## Methods

### Study design

We conducted a multicenter observational cross-sectional study. Recruited were 215 consecutive adult participants ( $\geq 18$  and  $<65$  years of age), with MS and symptomatic AF (paroxysmal and persistent). Defined on the basis of the classification guidelines of ESC [11], admitted at 6 general cardiology Health Care Clinics, who underwent Pharmacologic Cardioversion (PCV) during 1 calendar year (from November 2021, through November 2022.), stratified in two group: 105 participants (50 females and 55 males) with level of CRP  $\geq 3$  mg/l, and 110 (58 females and 52 males) with level of CRP  $<3$  mg/l.

Exclusion criteria were as follows: Hemodynamically unstable patients, a previous Cardioversion (CV) within 1-year, previous AF ablation, moderate-to-severe valvular heart disease, hypertrophic cardiomyopathy, cardiac implantable electrical devices, congenital heart disease, poor left ventricular function ( $n(EF < 35\%)$ ). Previous cardiac surgery and thyroid disease.

Health screening included a physical examination, standard 12-lead ECG anthropometrics and echocardiographic examination. Blood Pressure (BP) obtained after 10 min of rest in the sitting position, expressed as the average of 3 consecutive measurements. Hypertension was defined as a systolic blood pressure  $\geq 140$  mmHg, diastolic blood pressure  $\geq 90$  mmHg and/or current anti-hypertensive therapy [12]. Diabetes mellitus was defined as a fasting serum glucose level  $\geq 126$  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), serum Triglycerides (TG). The sample analysis was performed using standard biochemical analytical methods.

### Metabolic syndrome

Was defined according to the harmonized definition of the International Diabetes Federation and other organizations [14]. On the basis of the baseline examination, the metabolic syndrome was diagnosed when at least 3 of the following criteria were met. (1) Central adiposity {Waist Circumference (WC)}  $>102$  cm in men and  $>88$  cm 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  $\geq 140$  mmHg or DBP  $\geq 90$  mmHg or use of antihypertensive drugs; (5) The presence of Diabetes Mellitus (DM) or use of anti-diabetic drugs.

### Plasma CRP levels

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.

### Conventional echocardiography

Prior to the procedure, all patients underwent a comprehensive transthoracic echocardiographic examination to assess 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 PHCV. 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.

**Pharmacological cardioversion:** 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) Propafenone (at a rate of 2 mg/kg over 15 min), Flecainide (at rate of 2 mg/kg over 10 min), Amiodarone (at rate of 5 mg/kg over 1 h) and metoprolol 5 mg. q5 min, or oral medications (pill-in-the-pocket" single doses of propafenone 450 mg to 600 mg, Flecainide 200 mg to 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 h to 48 h or until the QT interval normalizes. Patients with persistent AF, of more than 48 h or unknown duration was treated with anticoagulation for at least 3 weeks before pharmacological cardioversion. Also, anticoagulation was continued for 4 weeks after the procedure, INR was maintained between 2 IU to 3 IU [17].

The follow-up period was 1 year. Heart rate, PQ, QRS and QT intervals were measured in the 12-lead ECG 1 day and 1 month after successful cardioversion and at 3 monthly intervals thereafter. Recurrence of AF, was defined as the study end-point. In cases 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  $\pm$  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,  $\chi^2$  test. The association between variables were 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, stratified in two groups: 105 participants (51 females and 54 males) with level of CRP<3 mg/l, and 110 participants (59 females and 51 males) with level of CRP>3 mg/l, completed the survey.

After the follow-up of 1.0 years, only 35 (31.8%) of patients with MetS and CRP levels above 3.0 mg/L, remain in sinus rhythm, compared to 68 (64.7%) of patient with MetS and CRP levels below 3.0 mg/L. (Fisher exact p=0.002) (Table 1, Figure 1). The recurrence rate of AF in participants with MetS and CRP levels above 3.0 mg/L was higher when compared with participants with MetS and CRP levels below 3.0 mg/L {75 (68.1%) vs. 37 (35.2%), Fisher exact p=0.002}.

Of all recurrences of atrial fibrillation, 45% occurred within the first 3-month, with significant difference between the two groups (55% in patients with MetS and CRP levels above 3.0 mg/L, vs. 24% patients with MetS and CRP levels below 3.0 mg/L, Fisher exact p=0.003) and last 3-mounth (12% in patients with MetS and CRP levels above 3.0 mg/L, vs. 35% patients with MetS and CRP levels below 3.0 mg/L, Fisher exact p=0.04).

There was not significant difference between groups in used ADDs after PCV during follow up period. Amiodarone was used in (49% of patients with MetS and CRP levels above 3.0 mg/L, vs. 44% patients with MetS and CRP levels below 3.0 mg/L, p=0.48), Flecainide (13% vs. 16%, p=0.47), Propiophenone (21% vs. 22%, p=0.34), Metoprolol (2% vs. 3%, p=0.52). Also, there was not significant difference between participants those which use did not use any of AADs during follow up period, regarding maintenance in SR (17% vs. 11.7%, Fisher exact

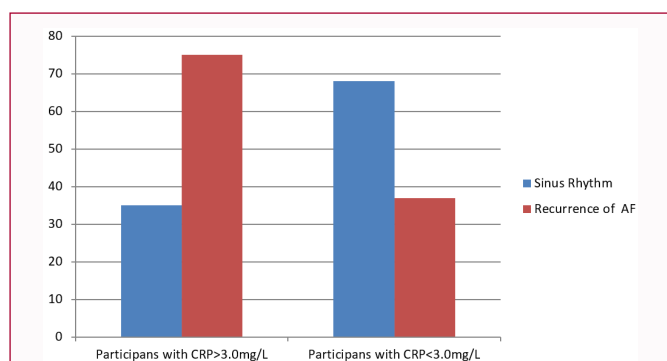
p=0.38).

The baseline demographic, clinical, electrocardiographic, echocardiographic and laboratory characteristics of each study group are summarized in (Table 2). There were no statistically significant differences between the participants with level of CRP>3 mg/l and participants with level of CRP<3 mg/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 ± 7.8; p=0.31), WC (94 ± 3.4 vs. 92.4 ± 5.2; p=0.18), Trig (2.1 ± 0.5 vs. 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; persistent 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, Propiophenone p=0.49; Metoprolol p=0.24, oral medications (pill-in-the-pocket”) Propiophenone p=0.54, Flecainide p=0.36), AADs used after pharmacological cardioversion (Amiodarone p=0.55, Flecainide p=0.32, Propiophenone 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<3 mg/l and 82 (74.5%) participants in group with level of CRP>3 mg/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<3 mg/l and 7 in group with level of CRP>3 mg/l, p=0.42), Heart failure in 15 (6.9%) participants (6 in group with level of CRP<3 mg/l and 9 in group with level of CRP>3 mg/l, p=0.34), Kidney disease in 9 (4.1%) participants (4 in group with level of CRP<3 mg/l, and 5 in group with level of CRP>3 mg/l, p=0.53), Strok in 19 (8.8%) participants (9 in group with level of CRP<3 mg/l and 10 in group with level of CRP>3 mg/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, was significantly higher in participants with level of CRP>3 mg/l than participants with level of CRP<3 mg/l (2.7 ± 0.13 vs. 9.8 ± 9.1 p=0.00), glycemia level, was significantly higher in participants with level of CRP>3 mg/l than participants with level of CRP<3 mg/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 not 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 3 mg/l, had higher LVMI than patients with levels below 3 mg/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 3 mg/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=0.009)}.



**Figure 1:** Frequency of maintenance sinus rhythm and AF-recurrence in participants with MS (n.215) according to CRP levels.

**Table 1:** Results for maintenance of sinus rhythm and AF-recurrence in participants with MS (n.215) according to CRP levels.

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

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

Variables	MS (N.215)						P - value
	Gr. with CRP levels ≥ 3 mg/l (n-110)			Gr. with CRP levels <3 mg/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 <sup>2</sup> )		27.4	± 6.5		25	± 4.0	<b>0.001</b>
AF (paroxysmal)	62(56.3)			58 (55.2)			<b>0.51</b>
AF (persistent)	48 (44.7)			47 (44.8)			<b>0.5</b>
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 <sup>2</sup> )		4.1	± 0.3		3.8	± 0.2	<b>0.001</b>
LAVI (mL/m <sup>2</sup> )		30.6	± 4.6		28.5	± 4.3	<b>0.001</b>
LVMI (g/m <sup>2</sup> )		96.8	± 1.1		66.8	± 5.2	<b>0</b>
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 Fibrillation; CRP-c-Reactive 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: Ejection Fraction

**Table 3:** Logistic regression model: Association of CRP levels (>3.0 mg/L) with AF-recurrence, LAd, LAVI, LVMI and BMI.

	OR*	Significance	95% CI for Exp (B)	
			Lower	Upper
AF recurrence	3.938	0.000	2.234	6.942
LAd	3.817	0.000	0.989	1.544
LAVI	1.74	0.000	1.549	1.975
LVMI	1.041	0.000	1.022	1.061
BMI	2.072	0.000	1.203	3.571

AF: Atrial Fibrillation; LAD: Left Atrial dimension; LAVI: Left Atrial Vollum Index; LVMI: Left Ventricular mass Index; BMI: Body Mass Index

In a logistic regression (Table 3), there was observed significant association of CRP levels above the cut-off of 3 mg/l with: 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 1.0 years of pharmacologic cardioversion, in participants with MS and CRP levels above the cut-off of 3 mg/l, was significantly lower than among participants with MS and CRP levels below 3 mg/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 possibilities 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 not in all reports, some of reports failed to demonstrate such a relationship [21,22].

Is well-established that inflammation is independently associated with the development of AF [23,24]. Experimental and clinical data indicate that inflammation have been involved in the pathogenesis of both, metabolic syndrome and atrial fibrillation [6], 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 [25]. In both, cross sectional and longitudinal studies, CRP has been consistently and significantly predictive of early AF relapse after successful cardioversion, even after adjustment for risk factors for AF, such as hypertension and CAD [26]. Even in the present study we found that of all recurrences of atrial fibrillation, greatest incidence of AF recurrence occurred within the first 3-month, with significant different occurrence between the two groups, with higher AF recurrence occurred in participants with CRP levels above a cut-off at 3 mg/l. It also has been suggested that atrial electrical remodeling resolves during the first days after cardioversion of persistent AF and may be related to early recurrence rates [27].

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 [3]. 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 [28].

Several placebo-controlled studies have demonstrated the absolute efficacy of AADs as superior to placebo in maintenance of SR after rhythm cardioversion [29]. In present study maintenance rate of SR after rhythm cardioversion in participants which are not received any AADs in a 1-year follow-up, were observed in 13.5%. A 13% to 25% maintenance rate of sinus rhythm after cardioversion of atrial fibrillation in a 1-year follow-up without antiarrhythmic drug therapy has been reported [30]. It is well known that inflammatory processes have been associated with AF, but is uncertain whether this represents the course or the effect of inflammation [31]. Although mechanisms by which AF cause inflammation are unknown [32]. Regardless of the presence or not of a causal relationship, the study of baseline CRP levels, may provide significant prognostic information regarding sinus rhythm maintenance [33].

Pharmacologic cardioversion is a widely conducted procedure that restores the AF to SR in a patient 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 and when a causal link between inflammation and AF is proved, novel approaches to targeting inflammation, might lead to better therapeutic options.

**Several limitations deserve mention.** 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 h 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.

## Conclusion

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. An AF patient 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 may be a next logical step in AF care, one not burdened by proarrhythmic risk.

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