



Original Article

A pilot study on the acute conversion and maintenance of sinus rhythm in rheumatic atrial fibrillation using oral flecainide

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ABSTRACT

Background: Achievement of sinus rhythm (SR) is an important goal in rheumatic atrial fibrillation (AF). Studies in rheumatic AF have often used amiodarone for rhythm control. Flecainide has not been studied in these patients due to concerns of underlying structural heart disease.

Methods: Pharmacological cardioversion by oral single loading dose (SLD) of Flecainide (4 mg/kg, ≤ 300 mg) was tested in 50 patients with rheumatic AF (MVA 1.51 ± 0.19 mm², age 46.2 ± 10.28 yrs, AF duration 3.10 ± 1.7 yrs, LA size: 44.42 ± 7.48 mm). Non-converters underwent DC cardioversion (DCC) at 24 h. All patients received oral flecainide and $\beta\beta$ /diltiazem at discharge.

Results: At 24 h, 38/50 (76%) achieved SR (2 with SLD; 36 after DCC). At 30 days (mean Flecainide dose 116.5 ± 10.5 mg) successful maintenance of SR was noted in 31/38 (89%). At 1 year, 30/38 (79%) of the initial converters and 60% of the overall population maintained SR. Those in SR had significantly better NYHA Class (1.1 ± 0.12 vs 1.3 ± 0.10 , $p = 0.03$) and mean PCS8 score (50.11 ± 5.337 vs 46.84 ± 5.379 , $p = 0.02$). AF duration (OR 0.594 CI 0.375–0.940, $p = 0.02$) and LA size (OR 0.840, CI 0.757–0.933, $p = 0.001$) were found to be the only significant predictors of successful outcomes. Patients with AF duration < 3.5 years and LA size < 51 mm had 85% and 75% chance of maintaining SR at 1 year, respectively.

Conclusion: Flecainide is safe and effective for achieving and maintaining SR in patients of rheumatic AF who are unlikely to have underlying coronary artery disease or ventricular dysfunction.

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1. Introduction

Most of the previous randomized control trials studying rate vs rhythm control in atrial fibrillation (AF) did not demonstrate a superiority of either strategy.^{1–5} Therefore, management of AF in many of these patients is initially by rate control drugs, while rhythm control by Class III (Amiodarone, Sotalol) or Class IC (Flecainide, Propafenone) anti-arrhythmic drugs (AAD) is attempted either in more symptomatic patients or those who fail initial rate control. Since majority of patients in these trials had non-valvular AF, these data cannot be extrapolated to patients with rheumatic AF. Rheumatic mitral valve disease is the most frequent underlying condition in patients with AF, especially in the developing world.^{6–8} Patients with rheumatic AF have adverse outcomes including poorer NYHA class, lower quality of life scores, heart

failure and significantly higher thrombo-embolic complications as compared to those with non-valvular AF.^{9–12} Although it is not currently established as to which approach, rate control or maintenance of sinus rhythm (SR), might be most appropriate in patients with chronic rheumatic AF, intuitively rhythm control seems to be a more clinically relevant target. As the major substrate for AF is an increased left atrial (LA) size and pressure overload of LA, to rationally assess any therapeutic modality to achieve SR, it is important that the underlying hemodynamic abnormality has been adequately addressed either by balloon mitral valvotomy (BMV) or mitral valve replacement (MVR). While these procedures can effectively reduce transvalvular gradients and correct the hemodynamic alterations, SR may not be necessarily restored in all cases. Data for long term rhythm control of rheumatic AF is scanty and amiodarone has been the usual rhythm control strategy in previous studies.^{13–18} However, long-term drug related adverse effects can be an important concern, especially so as many of these patients are relatively young.

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Flecainide which is one of the first line drugs for pharmacological conversion as well as maintenance of sinus rhythm in non-valvular AF¹⁹ could theoretically represent an attractive rhythm control option in these patients. It is a class IC AAD which is a selective blocker of the cardiac fast inward sodium (Na⁺) current, with slow unbinding kinetics. It also inhibits opening of potassium channels and the rapid component of delayed rectifier K⁺ current (IKr), prolonging the action potential duration (APD) in ventricular and atrial myocardium.^{20,21} The therapeutic inertia for using flecainide in patients with structural heart disease stems from the Cardiac Arrhythmia Suppression Trial (CAST) which actually enrolled patients with previous myocardial infarction and impaired left ventricular (LV) function.²² As patients with rheumatic AF are young and have normal ventricular function, they can be potential candidates for oral flecainide. In this study, we have for the first time, assessed the safety and efficacy of oral flecainide for pharmacological conversion and maintenance of SR in rheumatic AF.

2. Materials and methods

This is a prospective, single centre study performed in patients with chronic persistent/long standing persistent/permanent rheumatic AF (n = 50) who had undergone a successful BMV ≥ 3 months ago {Mitral valve area (MVA) ≥ 1.5 cm²}. All eligible patients provided informed written consent before participation and all procedures followed institutional ethical standards and guidelines. Those with clinical heart failure, LV/RV dysfunction (EF < 50%), Left

atrium (LA) dimension ≥ 60 mm, AF duration ≥ 5 years, known coronary artery disease (CAD) or risk factors for CAD, evidence of left atrial or appendage clot, severe pulmonary artery hypertension, baseline HR < 60 bpm, second- or third-degree AV block and bundle branch block were excluded.

The study protocol is depicted in Fig. 1. All patients received oral flecainide (loading dose LD: 4 mg/kg, maximum 300 mg). A 12 lead ECG was recorded at 2 h, 6 h, 12 h and 24 h to assess acute pharmacological conversion with single dose (Group A). Those who remained in AF (Group B) underwent DC cardioversion (DCCV) at 24 h (synchronized, biphasic shocks of increasing energy of 100 J, 200 J, 300 J and 360 J, respectively) to assess efficacy of conversion to SR with a combined approach (pharmacological + DCCV; Group B). Those who did not revert to SR with 360 J were considered as failures. Irrespective of the rhythm at discharge, all patients received oral flecainide (50 mg bd) to assess efficacy of maintenance of SR at follow up. Dose escalation was done by 50 mg bd every 4–5 days, if needed till a maximum dose of 300 mg was reached. This was based on ECGs examined either in-person or transmitted telephonically by the patient. A second DCCV was performed at 4 weeks in those who had failed conversion at first attempt. Oral flecainide was continued in all patients for the duration of follow up.

Transesophageal echocardiography was performed immediately before each cardioversion to exclude left atrial/appendage thrombus. All patients were continued on oral anticoagulants throughout, with the target international normalized ratio (INR)

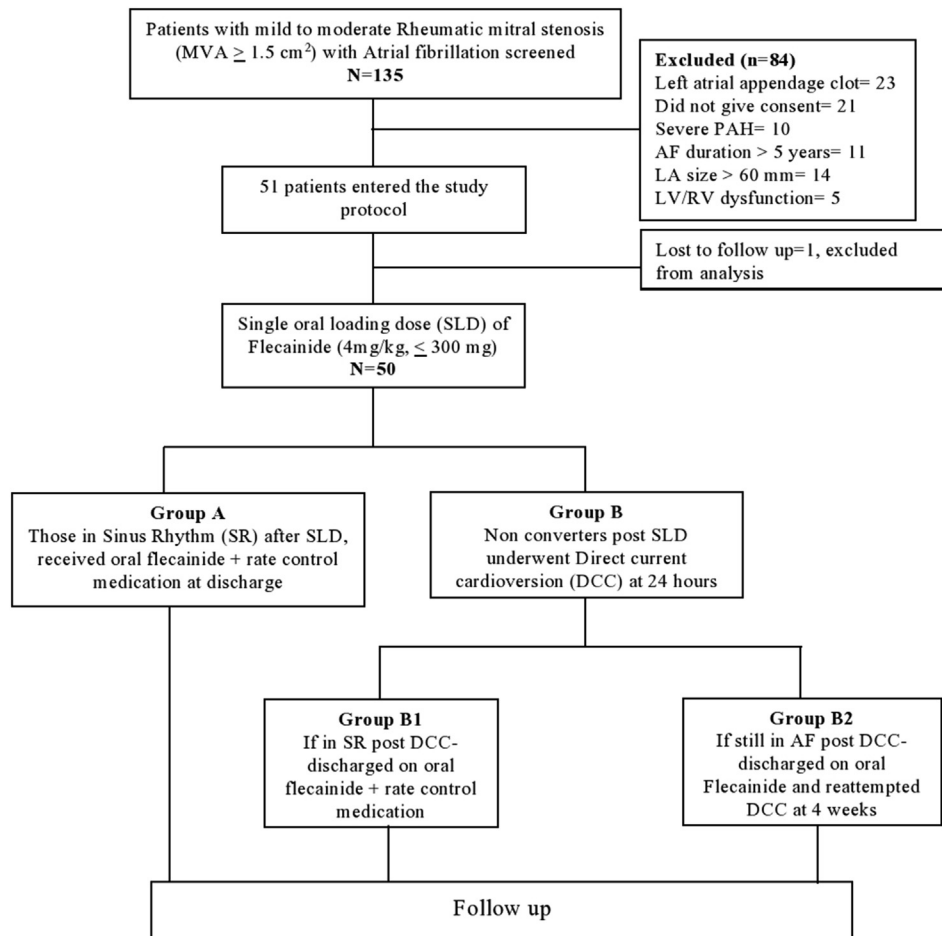


Fig. 1. Study protocol.

between 2 and 3 along with rate control drugs (beta-blockers or calcium-channel blockers) in addition to flecainide. Patients were followed at 1, 3, 6, 9 and 12 months after cardioversion and at each visit, a 12 lead ECG, NYHA Class and quality of life (QoL) using the SF 8 Quality of life scores was recorded. The physical (PCS 8) and mental component scores (MCS8) were assessed separately. A Holter study was also performed at 6 and 12 months to detect AF recurrence. Flecainide pill count was also used to assess patient compliance to medications at each visit.

Primary outcome measures included the rate of achievement of SR at 30 days and 12 months. **Secondary outcomes** were improvement in functional class (NYHA), QoL scores, occurrence of stroke, death and complications, if any, related to flecainide.

Statistical Analysis was done using IBM SPSS Ver 23.0 software (SPSS Inc, Chicago, Illinois, USA). Categorical variables were represented as frequencies and continuous variables were expressed as mean \pm standard deviation. The comparison of continuous variables was performed by independent sample *t* test. The categorical variables were compared using chi-square test or fisher's exact test. Significance was assumed if $p < 0.05$. The predictors of maintenance of SR at 30 days and 12 months and predictors of successful cardioversion were assessed by regression analysis. Binary logistic regression analysis was applied for multivariate analysis after applying Hosmer - Lemeshow goodness of fit test. Receiver operator characteristic curves were formulated for LA size and duration of AF and Youden index was used to define cut off points. Significance was assumed with a two sided $p < 0.05$.

3. Results

After screening 135 consecutive patients, 51 patients were enrolled in the study ($n = 84$ excluded, Fig. 1). Final data analysis was performed for 50 patients (1 lost to follow up) with a median follow up of 380.92 days. The mean age of the patient population was 46.2 ± 10.28 yrs, 46% females with mean MVA 1.51 ± 0.19 mm² and mean AF duration 3.10 ± 1.7 years. Other baseline demographics are summarized in Table 1. Previous thromboembolism (stroke: 3, peripheral embolism: 3) was present in 6/50 patients.

Baseline AF was documented in all patients (mean ventricular rate 90.66 ± 24.54). **Acute conversion to SR with flecainide SLD** was noted in 2/50 (4%). All other patients ($n = 48$) underwent DCCV as per protocol at 24 h. Of these, 75% (36/48) were successfully cardioverted and had SR at discharge. Successful cardioversion was noted in majority of patients with 100 J (34/36), while 2 patients achieved SR with 200 J. Therefore at discharge, **38/50 (76%) achieved SR with a combined approach of pharmacological + DCCV** while 12/50 (24%) continued to be in AF.

Of the 12/50 who did not convert to SR at 24 h (with SLD flecainide + DCCV), a second attempt at DCCV at 4 weeks was successful in only 1 patient. This patient too reverted to AF within 24 h. All these 12 patients remained in AF at 1 year, despite being on oral flecainide.

Follow up: At 30 days (mean Flecainide dose 116.5 ± 10.5 mg), successful maintenance of SR was noted in 31/38 (81%), while 7/38 (19%), who had SR at discharge, had reverted back to AF. These 7 patients underwent DCCV but SR was achieved only transiently in 4 and all reverted back to AF at discharge. At 6 months and 1 year, SR was successfully maintained in 30/38 patients, with 1 patient redeveloping AF at 6 months. Hence, of the 38 patients who initially achieved SR, **30 (79%) maintained SR at 1 year**. Holter was performed at 6 months and at 1 year confirming absence of AF or any other arrhythmias in all these 30 patients.

A line diagram showing the proportion of patients in SR in the entire population of 50 patients, through the study period is shown in Fig. 2.

Table 1
Baseline demographic and echocardiographic characteristics.

	Mean \pm SD (range)
N = 50	
Age	46.2 \pm 10.28 (29–67)
Sex	F-23 M-27
NYHA	
I	35 (70%)
II	14 (28%)
III	1 (2%)
IV	0
Duration of AF (years)	3.10 \pm 1.7 (0.8–5)
Time since BMV (months)	36.6 \pm 23.06 (4–54)
Body surface area (kg/m ²)	1.57 \pm 0.16 (1.27–1.91)
Prior stroke	3
Prior peripheral embolism	3
Diabetes mellitus	0
Hypertension	1
LA size (mm)	44.42 \pm 7.48
LA volume index (mL/m ²)	30.8 \pm 14.4
LVEDD (mm)	28.4 \pm 3.23
LVEDD (mm)	45.3 \pm 3.56
Ejection fraction (%)	61.1 \pm 6.4
Mitral valve area (cm ²)	1.51 \pm 0.19 (1.2–2.0)
Peak gradient (mm Hg)	13.2 \pm 5.02 (7–28)
Mean gradient (mm Hg)	6.5 \pm 2.6 (3–14)
RVSP (mm Hg)	35.4 \pm 9.6 (24–59)
Mitral regurgitation	
None	26
Mild	18
Moderate	6
Aortic regurgitation	
None	32
Mild	17
Moderate	1

No major complications following cardioversion were noted and no patient developed systemic embolism. Following DCCV at 24 h, 2 patients had junctional rhythm and 1 patient had a transient 2:1 AV block; spontaneous return to SR was noted in all three within 6 h. Patient compliance for flecainide was good and all patients tolerated it well without any need for dose reduction or any complications. Mean PR interval, QRS duration and QTc at follow up are listed in Table 2. There was no significant difference in mean PR (193.4 ± 30.05 vs 178.6 ± 26.53 msec), mean QRS (90.54 ± 10.57 vs 100.33 ± 9.8 msec) and mean QTc (433.7 ± 30.06 vs $466 + 74.96$ msec) at baseline vs those at 1 year, respectively. Mean changes in PR interval, QRS duration and QTc from baseline to 1 year were -15.3 ± 3.02 msec, 10.96 msec and 4.86 msec respectively. The mean heart rate of patients in sinus rhythm at 1 year was significantly lower than those with persistent AF (65.63 ± 14.09 /min vs 93.09 ± 14.14 /min, $p=0.009$). No patient died or had any

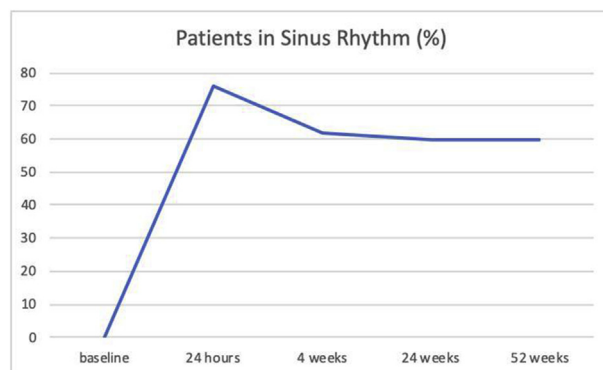


Fig. 2. Percentage of patients in Sinus Rhythm during follow up, at 24 h, 4 weeks, 6 months and 1 year respectively.

Table 2
Acute conversion and maintenance of SR at follow up.

	Mean ± SD				
Follow up (Days)	380.92 ± 157.7 (170–457)				
SR after SLD Flecainide	2/50 (4%)				
	Baseline	24 h	30 days	6 months	1 year
SR after DCCV at 24 h		38/50 (76%)	31/50 (62%)	30/50 (60%)	30/50 (60%)
QTc interval (msec)	433.7 ± 30.06	462 ± 24.3	463 ± 22.2	463.3 ± 20.9	466 ± 74.96
PR int msec (those in SR)		193.4 ± 30.05	180.6 ± 28.34	178.2 ± 25.3	178.6 ± 26.53
QRS Duration (msec)	90.54 ± 10.57	95.50 ± 9.20	98.96 ± 8.93	98.56 ± 9.02	100.33 ± 9.8
Change in QRS (msec)	10.96 ± 1.07				
Change in QTc (msec)	4.86 ± 0.99				

SR: Sinus rhythm.

SLD: Single loading dose.

DCCV: DC cardioversion.

episodes of systemic thrombo-embolism at follow up. Only 1 patient (case#1) had menorrhagia attributed to uterine fibroid, for which she underwent hysterectomy. There were no hospitalizations or major bleeding episodes during this period.

Diltiazem hydrochloride was used as the rate control agent in 33/50 (66%) patients in the extended release formulation (mean dose 95.45 ± 14.22 mg) and metoprolol in 17/50 (34%) patients, also as an extended release formulation (mean dose 92.8 ± 11.8 mg). We did not have any incidence of atrial flutter with or without rapid ventricular response.

3.1. NYHA class, QOL scores

Patients who had SR at 1 year had significantly better functional status (NYHA class 1.1 ± 0.12 vs 1.3 ± 0.10, $p = 0.03$), mean PCS8 score (50.11 ± 5.337 vs 46.84 ± 5.379, $p = 0.02$) and mean MCS8 score (53.94 ± 6.421 vs 50.08 ± 5.22, $p = 0.01$) as compared to those who persisted in AF.

3.2. Predictors of attaining SR

Patients who achieved SR had significantly shorter AF duration and LA size as compared to non-responders (Table 3). All predictors were subject to multivariate analysis and after stepwise elimination, age, AF duration and LA size came out significant. On binary logistic regression analysis duration of AF (odds ratio, 0.594 CI 0.375–0.940, $p=0.026$) and LA size (odds ratio 0.840, CI 0.757–0.933, $p=0.001$) were found to be the only significant predictors of successful outcomes at 1 year.

The receiver-operating characteristics curve (ROC) for LA diameter demonstrated an area under curve (AUC) of 0.793 (95% CI 0.665–0.922) with a threshold of LA diameter <51 mm (calculated using Youden index) predicting SR at 12 months with a sensitivity

and specificity of 93.3% and 55%, respectively. Of all the patients with LA diameter ≤51 mm ($n = 37$), 28 (75%) patients were in SR at the end of 1 year while only 2 (18%) of the 11 patients with LA diameter >51 mm were in SR.

The ROC curve for AF duration demonstrated an AUC of 0.783 (95% CI 0.641–0.926) with a threshold of AF duration <3.5 years predicting SR at 12 months with a sensitivity and specificity of 76.66% and 50%, respectively. Of the 27 patients who had AF ≤3.5 years, 23 (85%) patients were in SR at the end of 1 year. In contrast, only 7 (30%) of 23 patients with AF duration >3.5 years were in SR.

4. Discussion

No previous data exists regarding the use of flecainide in rheumatic AF. In this study, which for the first time assessed the use of flecainide in 50 patients of rheumatic AF, acute conversion with single loading dose of flecainide was achieved in 4%. A combined approach of DCCV (at 24 h) and oral flecainide achieved successful conversion to SR in 76% (38/50). Most patients achieved SR with the first attempt at 100 J. Amongst those who achieved SR at discharge; successful maintenance of SR on oral flecainide was possible in 81% at 30 days. At 6 months and 1 year, SR was successfully maintained in 79% of the initial converters and 60% of the overall patient population. Holter was performed at 6 months and at 1 year confirming absence of AF in all these patients.

Initial non-responders who remained in AF (following oral loading with flecainide and DCCV, $n = 12$) or those who reverted to AF at 30 days after initially achieving SR ($n = 7$), did not achieve SR despite repeat DCCV at 4 weeks. There were no complications related to DCCV and all patients tolerated flecainide well. No significant changes in mean PR interval, QRS duration and QT interval were noted in patients on flecainide. Our study adds to the existent literature regarding effectiveness of a combined strategy of pharmacological + electrical cardioversion in restoring and maintaining SR in rheumatic AF.

Strategies of rate vs rhythm control previously tested in various randomized trials mostly included patients of non-valvular AF from a Western population cohort. Rheumatic AF is the commonest etiology of AF in the developing world, with mitral stenosis being the most frequent underlying cause.^{6,7,23} The incidence of systemic thromboembolism in rheumatic AF is significantly more (annual incidence 17–18%/year) as compared to the risk of stroke in non-valvular AF (4%/year).^{9–12,24} Therefore, restoration of SR should be preferred for these patients. The Indian Heart Rhythm Society– AF (IHRS-AF) registry which is the largest evaluation of clinical presentation, management, and outcomes in patients with AF in India, however reported that rate control was the predominant therapeutic strategy used in 75.2% patients.⁶

Table 3
Differences in parameters in those who achieved SR vs non-responders.

Variables	SR (N-30)	Non responders (N- 20)	p value
Gender distribution (M/F)	16/14	11/9	0.56
Mean Age	43.20 ± 9.279	50.70 ± 10.037	0.20
Mean Duration of AF (yrs)	2.43 ± 1.547	4.11 ± 1.519	0.010
LA size (mm)	41.3 ± 6.04	49.1 ± 7.09	0.001
Mean LA volume index (mL/m ²)	22.7 ± 10.1	37.4 ± 11.2	<0.001
MR	12/30 (40%)	12/20 (60%)	0.11
AR	11/30 (36.6%)	7/20 (35%)	0.98
MV peak gradient	11.90 ± 4.27	14.60 ± 5.06	0.44
Mean gradient	6.13 ± 2.37	7.00 ± 2.406	0.85
MVA	1.57 ± 0.504	1.65 ± 0.489	0.81
RVSP	34.70 ± 9.248	36.10 ± 10.71	0.86

It is often difficult to convert and maintain SR in rheumatic AF, especially if the underlying hemodynamic abnormality has not been relieved. According to our study protocol, a minimum time interval of ~3 months post BMV was mandatory for patients to be included, as has been described earlier.^{17,18} Although adverse atrial remodelling which perpetuates sustained AF can be potentially reversed by relieving the stenosis, alleviating transvalvular gradients and favourably affecting hemodynamics by BMV or MVR may not always restore SR on its own. Allowing some period to elapse after the procedure gives a time window for any procedure related potential reverse atrial remodelling to occur.

4.1. In contrast to our study, current data in rheumatic AF for rhythm control is limited only to use of amiodarone

In patients undergoing mitral valve replacement, intravenous (IV) amiodarone given before institution of cardiopulmonary bypass significantly reduced the incidence of AF after release of aortic cross clamp as well as at 24 h.^{25,26} However these studies only used a single dose infusion and did not assess maintenance of SR over long term.

Long term rhythm control in rheumatic MS has been assessed using different protocols with pharmacological conversion alone ± DCCV in patients either immediately following BMV or after 3–6 months of MV intervention. Reported success rates vary from 38% using only pharmacological conversion with oral amiodarone¹³; performing DCCV in patients pre-administered oral or IV amiodarone is known to further improve success rates to 55–96% (maintenance of SR at 1 year follow up).^{14,15,27,28}

We have previously reported that in patients of rheumatic AF 3–6 months post BMV, pharmacological cardioversion with amiodarone alone was achieved at 6 weeks in 39% and addition of DCCV in those with persistent AF, achieved SR in an additional 48%.¹⁷ At a mean FU of 30.6 ± 7.1 months, successful maintenance of SR was possible in 82%. The CRRRAFT study randomized patients of rheumatic AF (n = 144, 72.9% of whom had undergone a previous valvular intervention) to rhythm control (DCCV followed by either amiodarone or placebo) vs ventricular rate control (using diltiazem). Maintenance of SR was significantly more frequent with amiodarone (69% vs 36%, p = 0.008).¹⁸

As outlined above, previous studies in rheumatic AF have exclusively used Class III AAD. Since many of these patients are young, giving drugs like amiodarone or sotalol for long term rhythm control may not be the best option. Conversion rate in the current study using flecainide ± DCCV (~76%) compare well with what has been reported with amiodarone. Successful maintenance of SR was achieved in 79% of the initial converters and 60% of the overall patient population.

Benefits of restoring SR include symptomatic relief, improved exercise capacity and quality of life, possible reduction in embolic strokes and improved survival.^{14,15,18,28} We also observed significant improvement in NYHA class and QOL scores in patients who were in SR as compared to those with persistent AF. Predictors of successful outcomes at 1 year were shorter duration of AF (<3.5 years) and smaller left atrial size (<51 mm). Patients with AFD <3.5 years and LA size <51 mm had 85% and 75% chance of maintaining SR at 1 year respectively. Hence the duration of AF and left atrial size which are known predictors of successful conversion and maintenance of SR in rheumatic AF can be used to identify patients likely to have successful outcomes.

Flecainide was well tolerated in the current study and no drug related pro-arrhythmia was observed. There was no significant change in mean QRS duration, QTc, or PR intervals and LV ejection fraction. Physicians are often reluctant to use flecainide in patients with structural heart disease, based on the CAST study which

actually enrolled patients with CAD and/or depressed ventricular function. Based on our data, Flecainide is a safe and efficacious choice in young patients with rheumatic AF, who often have no CAD and normal LV function.

4.2. Limitations

The obvious limitations include a single centre study with limited patient numbers and absence of a placebo arm. We initially just wanted to primarily assess the safety of flecainide in such patients and are now planning to perform a study comparing flecainide + DCCV vs placebo + DCCV in rheumatic AF with rate control in both arms. We need more randomized multi-centric studies, with larger patient numbers and longer follow up to further document the safety and efficacy of flecainide in this patient population. Another facet that needs to be studied is regarding how long to continue the drug after achieving and maintaining SR. Whether discontinuing it after 6 months- 1 year of successful maintenance of SR, leads to increased recurrences needs to be studied. A clinical follow up and holter monitoring for assessing AF recurrence has its limitations and perhaps using an implantable loop recorder would provide more comprehensive data. However, the latter was not feasible due to logistic and financial constraints.

5. Conclusion

We have demonstrated, for the first time, that oral flecainide is safe and effective in achieving and maintaining SR in patients with rheumatic AF. The immediate conversion rate at 24 h with a combined approach of pharmacological + DCCV was 76%. Successful maintenance of SR at 1 year was achieved in 60% of the overall population using oral flecainide. Flecainide was well tolerated with no proarrhythmic effects. Since patients of rheumatic AF are often young and unlikely to have underlying coronary artery disease or severe LV dysfunction, flecainide is a potentially attractive modality for achieving and maintaining SR in these patients. More studies are needed to validate these results.

Declaration of Competing Interest

The authors declare that there is no conflict of interest.

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