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Original Article

A randomized placebo-controlled trial with amiodarone for persistent atrial fibrillation in rheumatic mitral stenosis after successful balloon mitral valvuloplasty

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ABSTRACT

Objective: Atrial fibrillation is the most common sustained arrhythmia in patients with rheumatic heart disease (RHD). This study was conducted to determine the maintenance of sinus rhythm with amiodarone therapy following DC cardioversion (DCCV), early after successful balloon mitral valvuloplasty (BMV).

Methods: Patients were randomized to amiodarone group and placebo group and their baseline characteristics were recorded. DCCV was done 48 h after BMV. After cardioversion, oral amiodarone was started initially 200 mg three times a day for 2 weeks, then 200 mg twice daily for two weeks followed by 200 mg once daily for 12 months. Patients in placebo group received DCCV alone without preloading amiodarone. After DCCV, they were given placebo for 12 months.

Results: The 3 months follow-up period was completed by 77 patients (95%). Of them, 31 (77.5%) patients in amiodarone group and 14 (34.1%) in placebo group remained in sinus rhythm (SR). The 12 months follow-up period was completed by 73 patients (90.1%). Of them, 22 (55%) patients in amiodarone group and 7 (17.1%) in placebo group remained in SR.

Conclusion: We conclude that amiodarone is more effective than placebo in maintenance of SR at the end of 3 months following successful cardioversion and more patients continued to remain in SR even at the end of 12 months without major serious adverse effects.

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1. Introduction

Atrial fibrillation (AF) is common in patients with rheumatic valvular heart disease.[1] Strategies to maintain sinus rhythm (SR) in nonvalvular AF have been shown to improve functional capacity and quality of life (QoL).[2–4] The failure to reduce the mortality associated with rhythm-control strategies is in part due to the toxicity of the therapies used to maintain SR[5] Attempts to restore SR in rheumatic mitral stenosis (MS) have been rare because the long duration of AF and left atrial (LA) enlargement does not bode well for maintenance of normal SR.[6–9] Successful balloon mitral valvuloplasty (BMV) in MS by reducing LA pressure and chronic atrial stretch has been reported to result in a favorable reversal of electrical remodeling and reduced AF vulnerability.[10] Electrical DC cardioversion (DCCV) following successful BMV may lead to a better chance of successful cardioversion and a better chance of maintaining SR.[11] Large et al. demonstrated that surgical correction of mitral valve disease in patients who have AF resulted in spontaneous conversion to SR in 46%.[12,13] However, the rate of spontaneous conversion was much lower in other reports.[8]

In rheumatic MS after BMV, DCCV combined with amiodarone therapy successfully restored SR and maintained it in 49–81% patients at a mean follow-up of 18–31 months,[7,8] a success rate apparently surpassing that achieved by catheter-based radiofrequency ablation in this particular group of patients.[14,15] Amiodarone is preferred as the antiarrhythmic drug because it has been reported to be more effective than sotalol or class I agents for maintenance of SR in AF[11] and is particularly effective in rheumatic AF patients after mitral valve surgery[6] or BMV.[7,8]

The primary objectives of this study were to determine the maintenance rate of SR at 3 months and 12 months following amiodarone therapy and to assess the improvement in QoL by maintaining SR and also to determine the success rate of DCCV early after successful BMV in patients with symptomatic rheumatic MS with persistent AF.

2. Material and methods

2.1. Study population

From August 2010 to May 2012, we studied 89 patients with rheumatic MS with persistent AF without significant other valvular heart disease who underwent successful BMV. The duration of AF varied from 3 months to more than 2 years. In all patients, transthoracic echocardiographic examinations were performed to measure mitral valve area, mitral pressure gradient; LA diameter and LA pressure gradient were recorded immediately before and 24 h after BMV. LA diameter was measured during the diastolic phase using M-Mode study in the parasternal long axis view. LA pressure and mitral gradient were recorded in catheterization lab before and after BMV.

2.1.1. Inclusion criteria

Patients over 18 years of age who underwent successful BMV and Electrocardiogram (ECG) evidence of AF for more than 3 months.

2.1.2. Exclusion criteria

Prior history of cardioversion, significant mitral, tricuspid or aortic regurgitation, significant tricuspid and aortic stenosis, LA thrombus (detected by transesophageal echocardiography), LA diameter ≥6 cm, inability to comply with 12 months follow-up period or contraindications to anticoagulation and amiodarone. BMV was performed using accura balloon and the transseptal approach.

2.2. Study protocol

All eligible patients provided informed written consent before participation and all procedures followed institutional ethical standards and guidelines. The study complies with Declaration of Helsinki.

Patients were anticoagulated with warfarin and International normalized ratio was required to be between 2 and 3 for at least one month prior to DCCV. Patients were randomized to amiodarone group and placebo group and their baseline characteristics were recorded. DCCV was done 48 h after BMV. All of them were kept fasting through the night before they underwent cardioversion.

Patients in the amiodarone group were given amiodarone IV bolus 150 mg followed by 1 g IV infusion for 12 h prior to DCCV. After cardioversion, oral amiodarone was started initially 200 mg three times a day for 2 weeks, then 200 mg twice daily for two weeks followed by 200 mg once daily for 12 months.

Patients in placebo group received DCCV alone without preloading amiodarone. After DCCV, they were given placebo for 12 months.

Before DCCV, patients were administered IV midazolam or diazepam for sedation and meperidine for analgesia. Synchronized DCCV was given using biphasic defibrillators using the following protocol: 100 J, 200 J, 300 J, and 360 J. Unsuccessful DCCV was considered to include those who did not revert with 360 J.

2.3. Follow-up and assessment

Patients were followed up at 1, 3, 6, 9, and 12 months. During the visits, cardiac rhythm was determined by ECG. QoL was assessed using SF8 questionnaire. The physical component scores (PCS8) as well as the mental component scores (MCS8) were assessed separately. Patients under amiodarone group were assessed for drug side effects and drug interaction. All patients continued to take oral anticoagulants throughout the study period irrespective of their rhythm.

2.4. Endpoints of the study

The primary endpoint was the comparison of amiodarone versus placebo in maintaining SR at 3 and 12 months following successful cardioversion in patients with rheumatic MS with persistent AF undergoing BMV. The secondary endpoints were to identify the success rate of cardioversion following successful BMV, to identify the success rate of IV amiodarone in converting AF to SR, to identify the factors affecting maintenance of SR, changes in the QoL scores at follow-up and frequency of adverse events.

2.5. Statistical analysis

All statistical analyses were performed using SPSS version 17.0. Continuous variables are presented as mean ± SDs and categorical variables were described with frequencies and percentages. 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 3 and 12 months and predictors of successful cardioversion were assessed by univariate analysis. Kaplan–Meier analysis was performed for analysis of probability of freedom from AF between patients in amiodarone and placebo group. The difference between these two groups was compared by the log-rank test.

3. Results

Forty-eight hours following successful BMV, 89 patients with rheumatic MS with persistent AF were included for the study. They were randomized to amiodarone ($n = 44$) and placebo group ($n = 45$). The baseline characteristics (Table 1) were equally distributed between amiodarone and placebo group.

3.1. Outcomes of cardioversion

Cardioversion was successful in 81 patients (91%) and failed in 8 (9%) patients. 100 J energy was used in 53 (65.4%), 200 J in 22 (27.2%) and 300 J in 6 (7.4%). 6 (7.4%) patients developed marked bradycardia after conversion to SR and they recovered spontaneously after 6 h. There was no significant difference in the success rate of DCCV between amiodarone and placebo group ($p = 0.974$). Of the 44 patients who received pretreatment with IV amiodarone, SR was not restored in any patient with IV amiodarone alone. 4 patients (9.1%) in this group developed significant bradycardia. No other complications were encountered (Table 2).

3.2. Cardiac rhythms during 3 months follow-up

The 3 months follow-up period was completed by 77 patients (95%). Four patients were lost to follow-up after the first month visit. Of the 40 patients in amiodarone group and 41 patients in placebo group, 38 and 39 patients completed 3 months follow-up respectively. Of them, 31 (77.5%) patients in amiodarone group and 14 (34.1%) in placebo group remained in SR. Table 3 shows amiodarone to be superior in maintaining SR at the end of 3 months ($p < 0.001$) than placebo. The PCS8 and MCS8 scores at the end of 3 months were found to be significantly better in amiodarone group ($p = 0.039$ and 0.023, respectively) (Table 4).

The Kaplan–Meier analysis (Fig. 1) revealed significant difference in the probability of freedom from AF between patients in amiodarone and placebo groups ($p < 0.001$ in log-rank test); of the 45 patients who remained in SR in both the groups, univariate analysis of the possible factors that might influence the probability of AF recurrence (Table 5). The LA diameter was the only factor that significantly determined the cardiac rhythm at 3 months ($p = 0.047$) on logistic regression analysis. Of those who remained in SR, the PCS8 and MCS8 scores were significantly better ($p < 0.001$ and $p < 0.001$, respectively) than those who were in AF (Table 6).

Table 1 – Baseline clinical and ECG parameters in amiodarone and placebo group.

Parameters	Amiodarone group ($n = 44$)	Placebo group ($n = 45$)	p value
Demographic parameters			
Age (mean ± SD, years)	38.80 ± 8.426	37.62 ± 9.260	0.534
Male, %	20.5%	34.1%	0.151
Female, %	79.5%	65.9%	0.853
Duration of AF (mean ± SD, months)	10.05 ± 5.718	10.27 ± 5.495	
PCS 8 (mean ± SD)	48.03 ± 5.005	46.46 ± 4.628	0.126
MCS 8 (mean ± SD)	45.08 ± 4.928	43.94 ± 5.276	0.297
Pre-BMV echocardiographic parameters			
MVA (mean ± SD, cm^2)	0.873 ± 0.178	0.876 ± 0.188	0.942
MVG (mean ± SD, mmHg)	21.25 ± 4.457	22.49 ± 3.758	0.159
LA size (mean ± SD, cm)	4.918 ± 0.436	4.920 ± 0.430	0.984
LA pressure (mean ± SD, mmHg)	27.11 ± 4.909	28.29 ± 4.966	0.265
PASP (mean ± SD, mmHg)	60.80 ± 12.08	64.96 ± 14.44	0.144
Other valve disease			
Mild AR, %	13.6%	13.3%	0.684
Moderate AR, %	11.4%	15.6%	
Mild AS, %	18.2%	15.6%	
Moderate AS, %	2.3%	8.9%	
Mild AR and AS, %	0.0%	2.2%	
None, %	54.5%	44.4%	
Other medical illness			
None, %	86.4%	86.7%	0.999
Hypertension, %	4.5%	6.7%	
Diabetes, %	4.5%	2.2%	
Hypertension and diabetes, %	2.3%	4.4%	
Diabetes and coronary heart disease, %	2.3%	0.0%	
NYHA class I, %	20.5%	4.4%	0.999
NYHA class II, %	63.6%	75.6%	
NYHA class III, %	11.4%	13.3%	
NYHA class IV, %	4.5%	6.7%	
Concomitant drugs			
Beta blockers, %	48.9%	43.2%	0.672
Calcium channel blockers, %	24.4%	22.7%	1.000
Digoxin, %	64.4%	68.2%	0.823

AF – atrial fibrillation; PCS8 – physical component scores; MCS8 – mental component scores; MVA – mitral valve area; MVG – mitral valve gradient; LA – left atrium; PASP – pulmonary artery systolic pressure; AR – aortic regurgitation; AS – aortic stenosis; NYHA – New York Heart Association.

3.3. Cardiac rhythms during 12 months follow-up

The 12 months follow-up period was completed by 73 (90.1%) patients. Four patients were lost to follow-up after 3 months. Thirty-six patients in amiodarone group and 37 patients in

Table 2 – Rhythm pattern at 3rd and 12th months in amiodarone vs placebo group.

Rhythm		Group		p value
		Amiodarone, n (%)	Placebo, n (%)	
3rd month	Sinus rhythm	31 (77.5%)	14 (34.1%)	<0.001
	Atrial fibrillation	7 (17.5%)	25 (61.0%)	
12th month	Sinus rhythm	22 (55.0%)	7 (17.1%)	0.001
	Atrial fibrillation	14 (35.0%)	30 (73.2%)	

Table 3 – QoL scores and NYHA functional class between both groups during follow-up at 3 months.

Factors	Amiodarone group (mean ±SD)	Placebo group (mean ±SD)	p value
PCS8 at 3 months	49.72 ± 6.522	46.82 ± 5.594	0.039
MCS8 at 3 months	53.43 ± 6.529	50.32 ± 5.152	0.023
PCS8 at 12 months	49.79 ± 6.794	46.62 ± 5.917	0.037
MCS8 at 12 months	53.89 ± 6.244	50.15 ± 5.216	0.007

PCS8 – physical component scores; MCS8 – mental component scores.

Table 4 – Univariate analysis of parameters for remaining in SR at 3 months.

Factors	Rhythm at 3 months		p value
	Sinus rhythm	Atrial fibrillation	
Age (mean ± SD, years)	38.09 ± 8.279	39.81 ± 9.683	0.404
Duration of AF (mean ± SD, months)	8.40 ± 4.520	10.03 ± 5.313	0.151
Pre-MVA (mean ± SD, cm^2)	0.89 ± 0.182	0.88 ± 0.170	0.695
Pre-MVG (mean ± SD, mmHg)	21.49 ± 4.531	22.38 ± 3.508	0.357
Pre-LA size (mean ± SD, cm)	4.78 ± 0.416	4.96 ± 0.354	0.047
Pre-LA pressure (mean ± SD, mmHg)	27.38 ± 4.692	28.69 ± 5.127	0.249
Pre-PASP (mean ± SD, mmHg)	60.73 ± 12.86	64.44 ± 14.91	0.247

AF – atrial fibrillation; MVA – mitral valve area; MVG – mitral valve gradient; LA – left atrium; PASP – pulmonary artery systolic pressure.

placebo group completed 12 months follow-up. Of them, 22 (55%) patients in amiodarone group and 7(17.1%) in placebo group remained in SR. Amiodarone was found to be superior in maintaining SR at the end of 12 months ($p = 0.001$), as shown in Table 3 and Fig. 1. The PCS8 and MCS8 scores at the end of 12 months were found to be significantly better in amiodarone group ($p = 0.037$ and 0.007, respectively) (Table 6).

Of the 29 patients who remained in SR in both the groups, univariate analysis of the possible factors that might influence

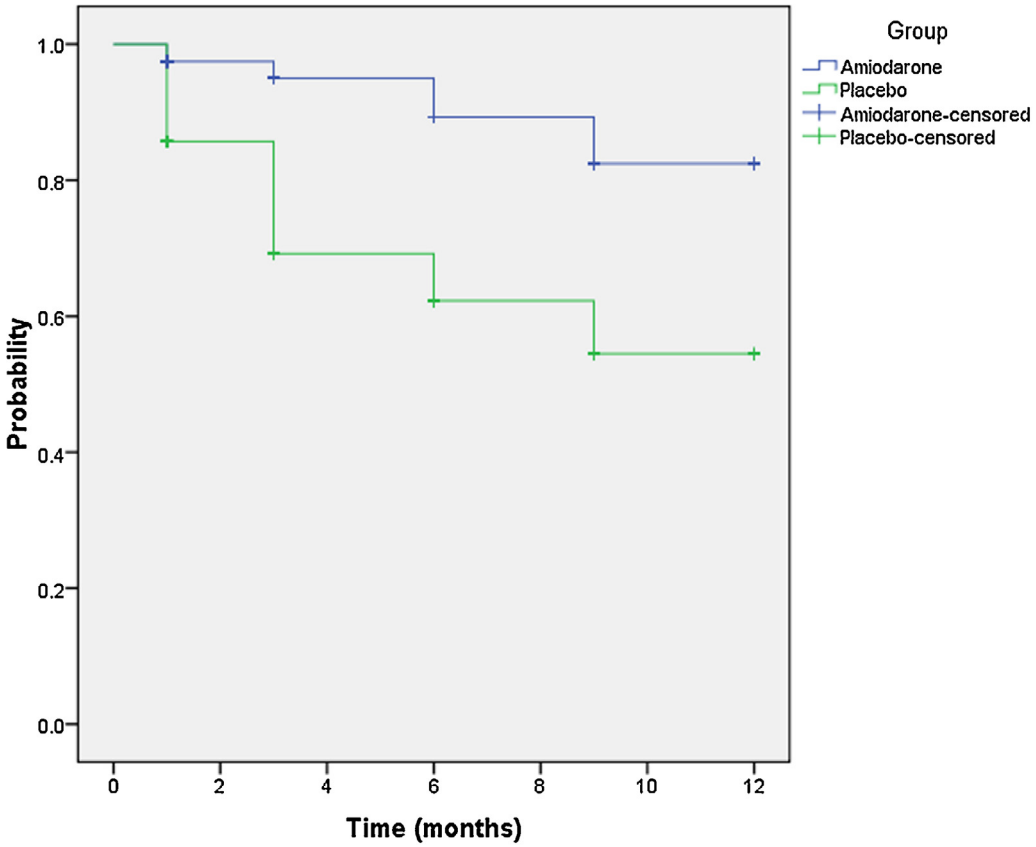

Fig. 1 – Kaplan–Meier analysis showing the probability of freedom from atrial fibrillation between amiodarone and placebo group patients.

Table 5 – QoL scores and functional NYHA class in patients with SR at 3 months.

Factors at 3 months	Rhythm at 3 months		p value
	Sinus rhythm	Atrial fibrillation	
PCS8 (mean ± SD)	50.92 ± 5.594	44.50 ± 5.006	<0.001
MCS8 (mean ± SD)	54.92 ± 5.273	47.55 ± 4.141	<0.001
NYHA I, %	48.9%	21.9%	0.022
NYHA II, %	50.1%	75%	
NYHA III, %	0%	3.1%	

PCS8 – physical component scores; MCS8 – mental component scores; NYHA – New York Heart Association.

the probability of AF recurrence (Table 7). The duration of AF was the only factor that significantly determined the cardiac rhythm at 12 months ($p = 0.023$) on logistic regression analysis. Of those who remained in SR the PCS8 and MCS8 scores were significantly better ($p < 0.001$ and $p < 0.001$, respectively) than those who were in AF (Table 8).

3.4. *Other findings*

The improvement in New York Heart Association functional class at 3 months was more pronounced in patients with SR than in those with AF ($p = 0.022$). This was not significantly different at the end of 12 months. Of the 36 patients who received amiodarone and followed up for a period of 12 months, 9 patients required dose reduction because of sinus bradycardia in 3 (8.3%), abnormal liver function test in 2 (5.6%), clinical and subclinical hypothyroidism respectively in 2 (5.6%) and 1 (2.8%) and QT prolongation in 1 (2.8%) patient.

BMV results (Table 8) showed a significant improvement in mitral valve area, and reduction in LA size, pressure, mitral gradient and pulmonary artery systolic pressure.

Table 6 – Univariate analysis of parameters for remaining in SR at 12 months.

Factors	Rhythm at 12 months		p value
	Sinus rhythm	Atrial fibrillation	
Age (mean ± SD, years)	39.45 ± 7.899	39.14 ± 9.469	0.884
Duration of AF (mean ± SD, months)	7.24 ± 3.612	9.77 ± 5.076	0.023
Pre MVA (mean ± SD, cm^2)	0.91 ± 0.152	0.87 ± 0.195	0.355
Pre MVG (mean ± SD, mmHg)	21.45 ± 4.239	22.34 ± 4.057	0.369
Pre LA size (mean ± SD, cm)	4.75 ± 0.359	4.90 ± 0.397	0.121
Pre LA pressure (mean ± SD, mmHg)	26.76 ± 4.257	28.59 ± 5.087	0.113
Pre PASP (mean ± SD, mmHg)	58.66 ± 12.30	64.20 ± 14.32	0.091

AF – atrial fibrillation; MVA – mitral valve area; MVG – mitral valve gradient; LA – left atrium; PASP – pulmonary artery systolic pressure.

Table 7 – QoL scores and functional NYHA class in patients with SR at 12 months.

Factors at 12 months	Rhythm at 12 months		p value
	Sinus rhythm	Atrial fibrillation	
PCS8 (mean ± SD)	53.59 ± 4.345	44.98 ± 4.942	<0.001
MCS8 (mean ± SD)	57.12 ± 3.824	48.82 ± 4.818	<0.001
NYHA I, %	51.7%	31.8%	0.174
NYHA II, %	48.3%	65.9%	
NYHA III, %	0%	2.3%	

PCS8 – physical component scores; MCS8 – mental component scores; NYHA – New York Heart Association.

Table 8 – Pre- vs post-BMV results.

Factors	Pre-BMV	Post-BMV	p value
MVA (mean ± SD, cm^2)	0.87 ± 0.183	1.81 ± 0.231	<0.001
MVG (mean ± SD, mmHg)	21.88 ± 4.142	11.82 ± 4.122	<0.001
LA size (mean ± SD, cm)	4.92 ± 0.431	4.63 ± 0.453	<0.001
LA pressure (mean ± SD, mmHg)	27.71 ± 4.946	14.46 ± 4.734	<0.001
PASP (mean ± SD, mmHg)	62.90 ± 13.415	39.16 ± 11.590	<0.001
EF (mean ± SD, %)	58.06 ± 3.472	59.39 ± 2.859	<0.001

MVA – mitral valve area; MVG – mitral valve gradient; LA – left atrium; PASP – pulmonary artery systolic pressure; EF – ejection fraction.

4. Discussion

Our study explored the maintenance of sinus rhythm with amiodarone therapy following DCCV, early after successful BMV. Hofmann et al.[16] showed that IV amiodarone is effective in restoring SR in 28% of patients with AF but in our study AF did not convert to SR with IV amiodarone alone. In our study, pretreatment with amiodarone did not alter the efficacy of DCCV or the energy required for restoration of SR in those patients with persistent AF. These results were similar to those of Channer et al. study.[17]

Most recurrences of AF occur within the first 3 months of DCCV.[17] Oral prophylactic drugs are given to reduce this recurrence rate although until recently, clear efficacy data based on controlled trials has been limited. Amiodarone may be the most effective oral prophylaxis, although all randomized trials of amiodarone for long-term maintenance of SR in patients with recurrent persistent AF have used active-control groups. Amiodarone is more effective than class-I antiarrhythmic agents, without the purported risk of increased mortality associated with quinidine and others in this class.[18,19] Amiodarone is more effective than other class III agents, with maintenance of SR in 75% on amiodarone compared to only 37% on sotalol after a mean follow-up of 16 months in one

large randomized comparison trial.[20] A further randomized, open-label study has demonstrated greater efficacy of amiodarone compared to the class IV agent diltiazem at 2 months (68% SR on amiodarone compared to 48% SR on diltiazem 180 mg daily).[21] Our study demonstrated a clear benefit with amiodarone compared to placebo in the maintenance of SR at 3 months following DCCV, persisting to 12 months when amiodarone was continued. Patients in the amiodarone group were also found to have better quality of both physical and mental health during the 3rd and 12th month follow-up as assessed by SF8 QoL survey.

Randomized trials have not demonstrated any outcome advantage to rhythm control strategies, but many patients are symptomatic in AF despite adequate rate control, with complaints such as palpitations, dyspnea, or poor exercise tolerance. Such patients often feel better if SR can be maintained. Studies that compared rhythm control and rate control strategies have found no differences in the QoL.[22–24] In contrast, among patients in whom SR is successfully maintained, exercise capacity and QoL are improved.[25] Our study also clearly demonstrated that QoL was significantly improved in patients who were restored and maintained in SR.

The mean age in AFFIRM and a RACE trial was 70 and 68 years, respectively. In our study, the mean age in the amiodarone group was 38.8 years and in the placebo group 37.6 years. So in our study, the average age was much lower than the AFFIRM and RACE trials. So younger group of patients might benefit from more aggressive rhythm control strategy. In the AFFIRM study, the antiarrhythmic drug used to maintain SR was left to the discretion of the treating physician but in our study amiodarone was the only drug used. The incidence of adverse effects was not significant enough warranting discontinuation of drug in patients taking amiodarone even at 12 months in our study.

4.1. *Limitations*

The time course of changes in mitral valve area and LA size was not systematically followed, as recurrence of AF may be caused by restenosis of the mitral valve. Follow-up period was only 1 year and serious long-term adverse side effects of amiodarone may not have been evident.

4.2. *Conclusion*

Amiodarone is more effective than placebo in maintenance of SR at the end of 3 months following successful cardioversion and more patients continued to remain in SR even at the end of 12 months without major serious adverse effects. Weighing the risks and benefits long-term amiodarone therapy following successful DCCV may be a preferred rhythm control strategy. The study also concludes that by restoring and maintaining SR; QoL scores are improved when compared with patients in whom AF is allowed to persist.

Conflicts of interest

The authors have none to declare.

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