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Conversion of recent onset paroxysmal atrial fibrillation to normal sinus rhythm: the effect of no treatment and high-dose amiodarone

A randomized, placebo-controlled study

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Background Spontaneous conversion of recent onset paroxysmal atrial fibrillation to normal sinus rhythm occurs commonly and is not affected by low-dose amiodarone treatment.

Methods In a randomized, placebo-controlled trial of 100 patients with paroxysmal atrial fibrillation of recent onset (<48 h) we compared the effects of treatment with continuous intravenous amiodarone 125 mg per hour (total 3 g) and intravenous placebo. Patients in the placebo group who did not convert to normal sinus rhythm within 24 h were started on amiodarone therapy.

Results Conversion to normal sinus rhythm occurred within 24 h in 32 of 50 patients (64%) in the placebo group, most of whom converted within 8 h. Lower conversion rates were observed in patients with hypertension, ischaemic heart disease or congestive heart failure and in patients with echocardiographic findings of left atrial diameter above 45 mm, ejection fraction below 45% or significant mitral regurgitation. However, in most patients these clinical or echocardiographic risk factors of decreases in conversion rate were not present. In such patients the spontaneous conversion rate was approximately 90%. The conversion rate during 24 h of treatment in the amiodarone group was 92% ($P = 0{\cdot}0017$, compared to the placebo group). In this group, the conversion rate was largely unaffected by baseline characteristics. Of the 18 patients who did not convert with placebo, 15 (85%) converted after being crossed over to amiodarone. All patients not responding to high-dose amiodarone were in chronic atrial fibrillation within 1 month. In patients still in atrial fibrillation after 8 h of treatment, the pulse rate decreased significantly more in the amiodarone as compared to the placebo group (83 ± 15 vs 114 ± 20 beats . min^{-1}, $P = 0{\cdot}0014$).

Conclusion The spontaneous conversion of recent onset paroxysmal atrial fibrillation is high and approaches 90% in specific clinical and echocardiographically defined subgroups. Intravenous high-dose amiodarone safely facilitates conversion of paroxysmal atrial fibrillation. However, such treatment should be reserved for patients with unfavourable risk factor profiles, not converting during 8 h of observation or requiring rate control.
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Key Words: Paroxysmal atrial fibrillation, conversion to normal sinus rhythm, amiodarone.

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Introduction

Paroxysmal atrial fibrillation is among the most common diseases encountered by physicians. Its prevalence and incidence is high and increasing with age and associated disease[1]. Restoration and maintenance of

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normal sinus rhythm is important since it may relieve symptoms and decrease the rate of complications such as congestive heart failure and thromboembolic events[2]. However, despite extensive research and numerous therapeutic approaches, the proper management of recent onset paroxysmal atrial fibrillation has not been determined.

Many factors contribute to the failure to establish an accepted and efficacious therapeutic approach. In approximately 50% of patients with paroxysmal atrial fibrillation of recent onset, spontaneous conversion to normal sinus rhythm occurs within 24 h of admission[3–7]. The conversion rate of paroxysmal atrial fibrillation to normal sinus rhythm achieved by antiarrhythmic drugs of classes Ia, Ic and III in different studies varies between 50 to 70%[4–13]. Thus, the absolute benefit of antiarrhythmic treatment with these drugs does not exceed 20%. Moreover, this benefit occurs only during the first few hours of drug administration. If patients are followed for 24 h, the benefit of antiarrhythmic therapy is further reduced due to an increased rate of spontaneous conversion[6] and increased reversion to atrial fibrillation. Furthermore, the acute loading of each of the above-mentioned drugs for the rapid conversion of paroxysmal atrial fibrillation has been related to adverse events[14]. These drawbacks may offset almost completely the beneficial effect of current antiarrhythmic treatment.

Amiodarone has been used extensively in the treatment of atrial fibrillation and flutter both in the short and long-term. Its efficacy in maintaining normal sinus rhythm after conversion of paroxysmal atrial fibrillation is well established[9,15]. However, in patients with recent onset paroxysmal atrial fibrillation, Galve *et al.*[3] have demonstrated that amiodarone administered intravenously at a rate of 1·2 g . 24 h^{-1} is only marginally better than placebo in converting paroxysmal atrial fibrillation to normal sinus rhythm. On the other hand, the administration of higher doses of amiodarone has been shown in previous studies to increase the rate of conversion when compared to placebo[16,17].

Therefore, in the present study we compared the effect of placebo to intravenous high-dose amiodarone (3 g . 24 h^{-1}) in patients with recent onset paroxysmal atrial fibrillation.

Methods

Study population

All patients with recent onset paroxysmal atrial fibrillation who were admitted to the Department of Medicine 'A' at Assaf-Harofeh Medical Center were screened to enter the study. Patients were included if the paroxysmal atrial fibrillation lasted less than 48 h and if they had had at least one previous episode of paroxysmal atrial fibrillation. Patients were excluded if they had one or more of the following: severe bradyarrythmia including significant sinoatrial and atrioventricular node disease, need for emergency cardioversion due to symptomatic hypotension, ischaemia or congestive symptoms, significant chronic lung disease, hepatic failure or active hepatitis, previous recent treatment with amiodarone or known hypersensitivity or significant side effects related to amiodarone, treatment with any class I or III antiarrhythmia drugs, recent treatment with digoxin or acute myocardial infarction in the previous 7 days.

Each patient underwent a medical interview (including the exact time of paroxysmal atrial fibrillation onset), a complete physical examination, 12-lead electrocardiography (ECG), chest X-ray, a full laboratory evaluation including cardiac enzymes, FT4 and TSH, and an echocardiographic evaluation. Patients were on continuous monitoring for heart rhythm and blood pressure. An interview, physical examination, laboratory evaluation and ECG were repeated every 24 h and immediately upon conversion to normal sinus rhythm.

The study was approved by the national ethics review board and each patient gave informed consent.

Study protocol

All patients received oxygen via nasal prongs. On admission, all patients with a peripheral pulse rate higher than 100 beats . min^{-1} received intravenous digoxin 0·5 mg. If a patient's pulse rate remained above 100 beats . min^{-1} 8 h from admission, a second bolus of intravenous digoxin 0·5 mg was administered. All patients who were still in paroxysmal atrial fibrillation after 24 h were started on heparin treatment.

Patients were randomly assigned to one of two treatment groups:

(1) Group A (n = 50, placebo group): patients received intravenous saline infusion at a rate of 20 ml . h^{-1} for 24 h.

(2) Group B (n = 50, amiodarone group): patients received intravenous amiodarone through a peripheral vein at a rate of 125 mg . h^{-1} for 24 h (total dose 3 g).

In both groups pulse and blood pressure were recorded every 8 h. After 24 h of treatment patients were re-evaluated. Group A (placebo) patients who had not converted to normal sinus rhythm were started on amiodarone treatment, which was continued for 24 h. Patients who had not converted to normal sinus rhythm after 24 h of high-dose amiodarone treatment (i.e. group A patients after 48 h of treatment and group B patients after 24 h of treatment) were treated by electrical cardioversion.

After establishment of normal sinus rhythm, patients in the placebo group (including those that were crossed-over to amiodarone after not converting at 24 h), were given propafenon 150 mg three times a day. Unless contraindicated, patients in the amiodarone group were given amiodarone 400 mg three times a day for 2 weeks and then 200 mg daily.

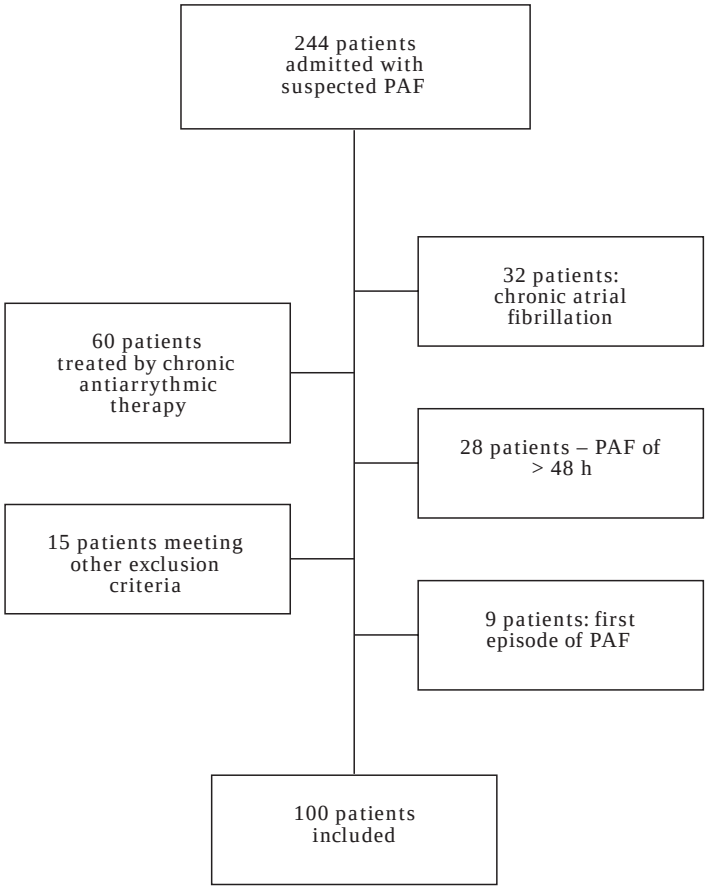

Figure 1 **A flow chart of the study.**

End-points

The primary end-points of the study were the rate of conversion to normal sinus rhythm during the first 24 h after randomization and the time to conversion, in both groups, and the safety of high-dose amiodarone administration. In the placebo group, conversion to normal sinus rhythm after starting on amiodarone treatment was also a primary end-point.

Secondary end-points were the predictive effect of predetermined baseline characteristics on the conversion rate of paroxysmal atrial fibrillation to normal sinus rhythm in both groups, heart rate control in both groups, and the efficacy of electrical cardioversion after high-dose intravenous amiodarone administration.

Statistical methods

Patients were assigned by lot to group A or group B. On the assumption of a 30% difference in conversion to normal sinus rhythm, 50 patients were admitted to each treatment group. The two-tailed Student's t-test was used to compare continuous variables and the chi-square or Fisher-exact test to compare the distribution of categorical variables. Results are expressed as means ± standard deviation (SD). *P* values lower than 0·05 were considered significant. Correlations between variables and treatment were obtained by univariate analysis and chi-square calculation. Thereafter, a logistic regression was performed to establish the independent effect of each variable on the probability to convert. The difference in time to conversion between the groups was examined using the actuarial method of Kaplan–Meyer using the log-rank test.

Results

Between 1 March 1997 and 31 December 1997, 244 patients were screened for enrolment in this study. Of these, 69 failed to meet the inclusion criteria and 75 met one or more of the exclusion criteria. A total of 100 patients with acute repeated episodes of paroxysmal atrial fibrillation of less than 48 h duration were enrolled (Fig. 1). Their baseline characteristics are presented in Table 1. No statistically significant differences in baseline characteristics were detected.

Safety

No severe arrhythmic or other adverse events were recorded in the amiodarone group. Five patients (10%)

Table 1 Baseline characteristics

	Group A (Placebo)	Group B (Amiodarone)
Clinical characteristics		
Age (years)	68 ± 13	64·5 ± 14
Gender		
Male	19	24
Female	31	26
Hypertension	62%	72%
Ischemic heart disease	38%	48%
Congestive heart failure	8%	4%
Paroxysmal atrial fibrillation		
No. of prior episodes	3·8 ± 1·9	3·4 ± 2·0
Hours in paroxysmal atrial fibrillation	9·9 ± 6·0	10·1 ± 6·3
ECG characteristics		
Q waves	12%	8%
ST depression	24%	44%
T wave inversion	24%	24%
Echocardiographic characteristics		
Aortic stenosis (significant)	2%	4%
Aortic regurgitation (significant)	6%	0%
Mitral stenosis (significant)	2%	0%
Mitral regurgitation (significant)	8%	14%
Left atrium diameter >45 mm	30%	28%
Ejection fraction <45%	18%	12%

in this group developed significant sinus bradycardia (<50 beats . min^{-1}). All bradyarrythmic episodes occurred after conversion to normal sinus rhythm. None was symptomatic and all patients recovered after discontinuation of amiodarone therapy. Episodes of bradycardia occurred in two patients in the placebo group (4%), again only after conversion to normal sinus rhythm ($P = 0{\cdot}24$). None of the patients in either group developed second or third degree atrioventricular blocks or tachyarrhythmia. Eight patients (16%) in the amiodarone group and three in the placebo group (6%) developed phlebitis at the intravenous access ($P = 0{\cdot}11$). In both groups, patients who developed significant phlebitis were treated with oral cloxacillin for 3 days. No significant further complications of phlebitis were recorded. No significant episodes of hypotension were recorded in either group. In the placebo group one patient developed a transient ischaemic attack 10 h after admission while in paroxysmal atrial fibrillation. The episode resolved without any long-term consequences. Another patient, in the placebo group, sustained a small non-Q wave myocardial infarction 24 h after admission while in paroxysmal atrial fibrillation. No complications were recorded.

Conversion to normal sinus rhythm

By 24 h after admission, 32 patients in the placebo group (64%) had converted to normal sinus rhythm as compared to 46 patients (92%) in the amiodarone group ($P = 0{\cdot}0017$). In the placebo group, 29 out of the 32 patients who had converted to normal sinus rhythm (91%) did so within 8 h of admission. The corresponding number in the amiodarone group was 31 patients (67%), but the remaining 15 patients converted between 8 and 24 h (Fig. 2).

Of the 18 patients in the placebo group who did not convert to normal sinus rhythm, 15 (83%) converted after commencing amiodarone therapy (Fig. 3). Seven patients (four from the amiodarone group and three from the placebo group) who failed to convert while on amiodarone underwent electrical cardioversion. This was successful in four of them (57%). The overall results are summarized in Fig. 4.

Rate control

Although the mean pulse rate and mean arterial pressure were equal in both groups at baseline (Table 1), the mean pulse rate in patients who had not converted to normal sinus rhythm by 8 h after admission was significantly higher in the placebo group (115 ± 22 beats . min^{-1}) than in the amiodarone group (86 ± 15 beats . min^{-1}, $P = 0{\cdot}0001$). The mean arterial blood pressure among these patients was slightly higher in the amiodarone group (101 ± 8 mmHg as compared to 97 ± 13 mmHg in the placebo group).

Follow-up

Of the 32 patients who converted to normal sinus rhythm while on placebo, three relapsed during the first 24 h of follow-up in spite of treatment with propafenon. One case of early relapse was recorded in the amiodarone group. Thus, after 24 h of follow-up 45 patients in the amiodarone group (90%) were in normal sinus rhythm as compared to 29 patients (58%) in the placebo group ($P = 0{\cdot}00063$) (Fig. 5).

After 1 month of follow-up, 82 of the 93 patients who had converted to normal sinus rhythm spontaneously or after receiving amiodarone (88%) remained in normal sinus rhythm. However, all seven of those who had not converted to normal sinus rhythm after amiodarone treatment were in chronic atrial fibrillation. Of these, three could not be converted by electrical cardioversion and the four who had been converted by electrical cardioversion had relapsed into chronic atrial fibrillation.

Long-term follow-up of the patients in this cohort is not available at this time.

Predictors of conversion

In the placebo group, the predictors of decreased conversion to normal sinus rhythm were found to be: age above 70 years; female gender; concomitant ischaemic heart disease, hypertension or congestive heart failure; echocardiographic findings of left atrial size above

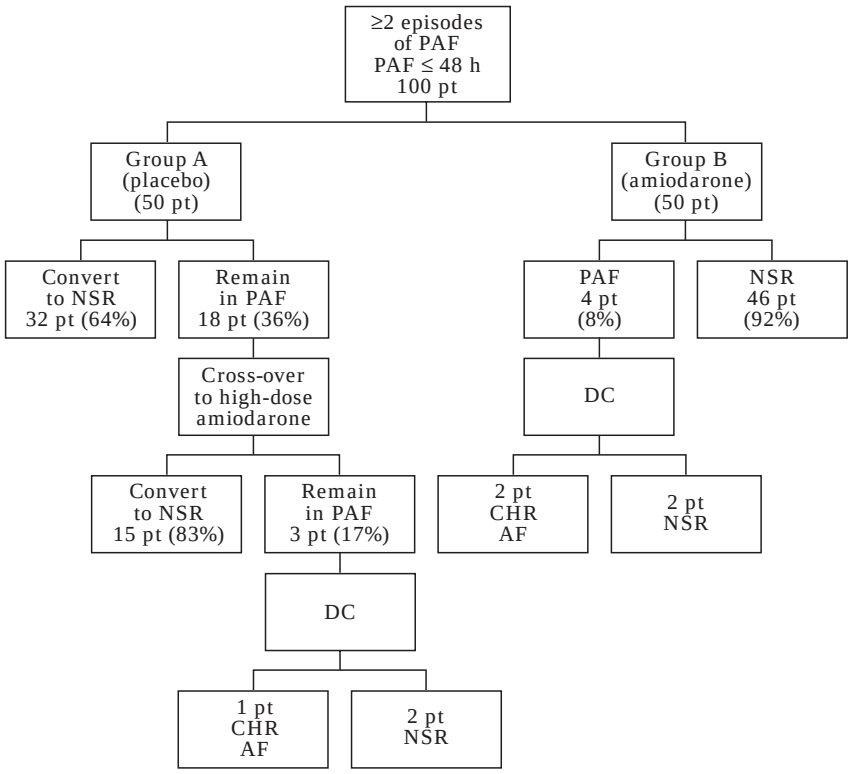

Figure 2 **A flow chart of conversion rate and fate of patients in groups A and B.**

45 mm; ejection fraction below 45%; significant mitral regurgitation (Table 2). However, such factors were not detected in most patients in the placebo arm. Thirty percent of patients had none of the clinical predictors of decreased conversion rate. In this subgroup the spontaneous conversion rate was 93·3%. Equally, 56% of patients had no significant echocardiographic abnormality. In this group the spontaneous conversion rate was 85·7%.

On multivariate analysis female gender was not found to be an independent predictor since it was associated with older age, high risk of hypertension, ischaemic heart disease and congestive heart failure and a worse echocardiographic profile (Table 3).

Most of the factors predicting a decrease in the rate of conversion in the placebo group did not influence the conversion rate in the amiodarone group, where the only such predictors were the presence of ischaemic heart disease and ST depressions on the baseline ECG. However, even in the presence of these factors, patients in the amiodarone group had higher conversion rates than those in the placebo group (83·3% compared with 52·6% for patients with a history of ischaemic heart disease, ($P = 0{\cdot}046$), and 81·8% compared with 58·3% for patients with ST segment depressions ($P = 0{\cdot}282$)).

Discussion

The results of this study indicate that patients with recent onset paroxysmal atrial fibrillation have a high rate of spontaneous conversion to normal sinus rhythm. The rate of conversion can be increased by continuous administration of intravenous amiodarone at a rate of 125 mg . h^{-1}, without causing significant side effects.

The effect of no treatment

One of the main difficulties when attempting to determine the appropriate treatment for recent onset paroxysmal atrial fibrillation is that a high proportion of patients convert to normal sinus rhythm without any specific treatment. Reported rates of spontaneous conversion range from 40 to 90%[3–7]. This finding is in agreement with the results of Galve *et al.*[3], who used inclusion and exclusion criteria identical to those in our study.

In the only reported study of factors influencing spontaneous conversion rate of paroxysmal atrial fibrillation to normal sinus rhythm, Boriani *et al.*[18] demonstrated that the spontaneous conversion rate within 8 h of admission was 27% in hypertensive patients and 17% in patients with structural heart disease was. Patients without these risk factors had a spontaneous conversion rate of 56%.

Echocardiographic indices of atrial size and ejection fraction were found to be significant predictors of maintaining normal sinus rhythm after conversion from paroxysmal atrial fibrillation while patients were treated

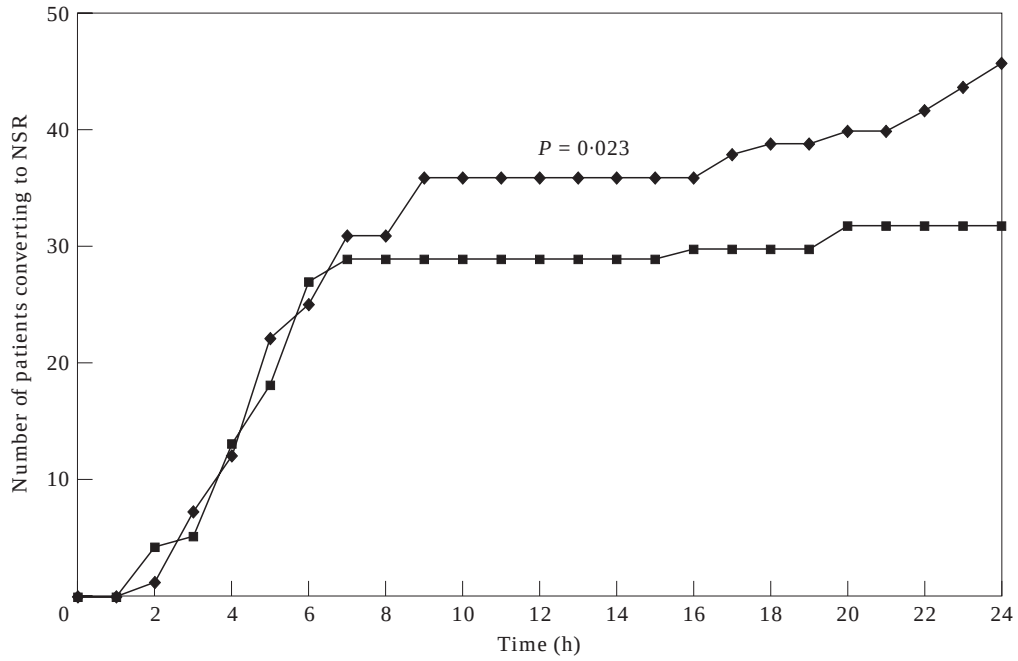

Figure 3 **Conversion from paroxysmal atrial fibrillation with 24 h (amiodarone (◆) vs placebo (■) groups).**

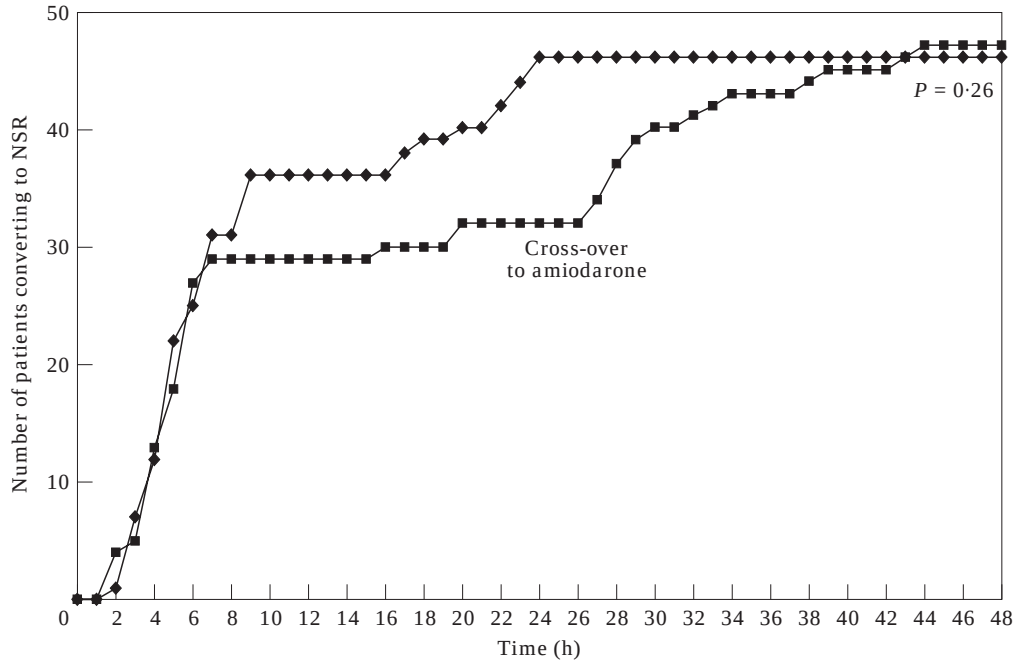

Figure 4 **Conversion from paroxysmal atrial fibrillation within 48 h (amiodarone (◆) vs placebo (■) groups), including the cross-over to amiodarone in the placebo group at 24 h.**

with amiodarone[19] or other modalities[20,21]. However, their influence on spontaneous conversion of recent onset paroxysmal atrial fibrillation has not been previously determined.

In the present study many factors were found to predict a reduced rate of spontaneous conversion from paroxysmal atrial fibrillation to normal sinus rhythm (Table 2). Most importantly, it seems that in patients with favourable echocardiographic findings (left atrial size below 45 mm, ejection fraction above 45% and no significant mitral regurgitation) the rate of spontaneous conversion is approximately 90%.

Table 2 Predictors of conversion from paroxysmal atrial fibrillation to normal sinus rhythm

		Group A (Placebo)			Group B (Amiodarone)		
		No.	% Convert	*P*	No.	% Convert	*P*
Sex	Male	19	75·0	0·27	24	96·3	0·26
	Female	31	58·8		26	97·0	
Age (years)	<70	25	76·0	**0·077**	28	96·4	0·19
	>70	25	52·0		22	86·4	
Clinical predictors							
Hypertension	Yes	31	54·8	**0·085**	36	91·7	0·90
	No	19	79·0		14	92·9	
Ischaemic heart disease	Yes	19	52·6	0·19	24	83·3	0·03
	No	31	71·0		26	100	
Congestive heart failure	Yes	4	50·0	0·543	12	83·3	0·20
	No	46	65·0		38	94·7	
Any clinical risk factors?	Yes	35	51·4	**0·005**	40	90·0	0·30
	No	15	93·3		10	100·0	
ECG predictors							
Q waves	Yes	6	33·3	0·095	4	100·0	0·54
	No	44	68·2		46	91·3	
ST depression	Yes	12	58·3	0·64	22	81·8	0·019
	No	38	65·8		28	100·0	
T wave inversion	Yes	12	50·0	0·25	12	91·7	0·96
	No	38	68·4		38	92·1	
Echocardiographic predictors							
Left atrial diameter (mm)	>45	15	33·3	**0·003**	14	85·7	0·84
	<45	35	77·1		36	94·4	
Ejection fraction	>45%	41	76·7	**0·034**	44	90·9	0·44
	<45%	9	33·3		6	100·0	
Mitral regurgitation (> +12)	Yes	4	0·0	**0·013**	7	85·7	0·51
	No	46	69·6		43	93·0	
Any echo abnormality?	Yes	22	36·4	**0·001**	22	90·0	0·80
	No	28	85·7		28	92·9	

P values in bold are significant or nearly significant.

However, in the present study most patients had none of the above mentioned risk factors for decreased conversion rate. Additional treatment may not be required in such patients. On the other hand, patients with an unfavourable risk-factor profile have a relatively low rate of spontaneous conversion. Such patients should be identified early and subjected to antiarrhythmic therapy that would facilitate conversion to normal sinus rhythm.

Table 3 Baseline characteristics in men and women in the placebo group

	Females (n=31)	Males	*P*
Clinical characteristics			
Age >70 years	16 (52%)	9 (47%)	0·98
Ischaemic heart disease	13 (42%)	6 (32%)	0·56
Hypertension	20 (65%)	11 (58%)	0·77
Congestive heart failure	14 (45%)	5 (26%)	0·24
Any clinical risk factor	23 (74%)	12 (63%)	0·53
Echocardiographic characteristics			
Left atrial diameter>45 mm	11 (35%)	4 (21%)	0·35
Ejection fraction <45%	6 (19%)	3 (16%)	0·98
Mitral regurgitation (significant)	2 (6%)	2 (11%)	0·63
Any echo abnormality	16 (52%)	6 (32%)	0·24

The effect of antiarrhythmic drugs

Many antiarrhythmic drugs have been examined with regard to their activity in the conversion of recent onset paroxysmal atrial fibrillation to normal sinus rhythm. A number of studies have demonstrated that such a conversion could be facilitated by the administration of antiarrhythmic drugs from classes Ia, Ic and III. For example, the use of the currently popular drugs propafenon and ibutalide has increased the short-term (up to 8 h) conversion rate to about 50–70%[5–13]. However, this small apparent benefit decreases sharply if such patients are followed beyond 8 h. In a recent study Azpitarte *et al.*[6] administered propafenon to patients with recent onset paroxysmal atrial fibrillation and followed them for 24 h. Although at 8 h a significant difference in conversion rate was evident when comparing the propafenon and placebo groups, such a difference was no longer detected at 24 h of follow-up due to the increasing rate of conversion in the placebo arm.

Furthermore, some patients treated with these drugs experienced early relapse. In our study 10% of patients who underwent spontaneous conversion subsequently relapsed, despite prompt administration of propafenon after conversion. In the amiodarone group, only one patient (2%) relapsed early. Reported rates of relapse during the first 24 h in patients treated by antiarrhythmic drugs other than amiodarone range from 10 to 20% compared to an early relapse rate of 5–10% in patients converted while on placebo[13].

Lastly, it was demonstrated that the administration of any of the currently used antiarrhythmic drugs, aimed at the rapid conversion of paroxysmal atrial fibrillation, has significant side effects. In a recent analysis, Maisel *et al.*[14] showed that even during short-term administration of antiarrhythmic drugs for conversion of recent onset paroxysmal atrial fibrillation, approximately 20% of patients sustain significant adverse events, mostly bradyarrythmia.

The use of antiarrhythmic treatment might be warranted in patients with significant risk factors militating against converting to normal sinus rhythm. Thus, Boriani *et al.*[18] demonstrated increased relative conversion efficacy of propafenon in patients with hypertension or structural heart disease. In their study the absolute advantage of propafenon treatment in conversion of paroxysmal atrial fibrillation to normal sinus rhythm in such patients was 43 to 64%. This advantage surpasses the disadvantage of therapy and seems to offer a real benefit over no treatment. It should be pointed out, however, that these patients were followed-up for only 8 h; a longer period of follow-up might have been associated with higher rates of spontaneous conversion diminishing the apparent benefit of this treatment[6]. Moreover, there is doubt about the safety of most antiarrhythmic drugs, including propafenon, in patients with structural heart disease, offsetting its increased efficacy in this group.

The effect of amiodarone

Although shown to be superior over most antiarrhythmic treatments in maintaining sinus rhythm[4,15], amiodarone has not been consistently more efficacious than placebo in converting paroxysmal atrial fibrillation to normal sinus rhythm. Galve *et al.*[3], showed that amiodarone, administrated at a rate of approximately 60 mg . h^{-1}, was not significantly superior to placebo (the conversion rates were 68% and 60%, respectively). Earlier, however, using higher doses of amiodarone Vietti-Ramus *et al.*[16] demonstrated an improved conversion rate of paroxysmal atrial fibrillation. Hou *et al.*[17] also administered high-dose amiodarone (1890 mg . 24 h^{-1}), with a resulting increase in the conversion rate of paroxysmal atrial fibrillation from 72% (in the placebo arm) to 92%. We therefore selected a dosage of 125 mg . h^{-1} for amiodarone administration in our study. The conversion rate of paroxysmal atrial fibrillation that we obtained in the amiodarone group was 92%, similar to that reported by Vietti-Ramus *et al.*[16] and Hou *et al.*[17].

The conversion of paroxysmal atrial fibrillation in our study was time-dependent. During the first 8 h of treatment, the conversion rate in the amiodarone group was similar to that with placebo. After 10 h of treatment, however, when patients had received approximately 1250 mg of amiodarone, the curves began to diverge (graph 3) and continued to do so for 24 h. Galve *et al.*[3] administered a total of 1200 mg of amiodarone to patients with recent onset paroxysmal atrial fibrillation, achieving a conversion rate of 68%. In our study this dose was administered within 10 h, at which time the conversion rate in the amiodarone group was 72%, which is remarkably similar finding to that of Galve *et al.*[3].

An important finding of the present study is that the high conversion rate achieved by high-dose amiodarone was less subject to the influence of baseline conditions that decreased the rate of spontaneous conversion in the placebo group (Table 2). The only parameter that affected the conversion rate achieved with high-dose amiodarone was ischaemic heart disease. Patients with a history of ischaemic heart disease or ST depression on baseline ECG had lower conversion rates (83·3 and 81·8% respectively) as compared to 100% conversion rate in patients without these baseline risk-factors treated with high-dose amiodarone. However, even in such patients the conversion rate with high-dose amiodarone treatment was higher than in patients in the placebo group.

What is the best strategy for patients with recent onset paroxysmal atrial fibrillation?

Although many different antiarrhythmic drugs and strategies of drug administration have been utilized to examine the best antiarrhythmic strategy for the treatment of recent onset paroxysmal atrial fibrillation, no single treatment strategy has yet been generally accepted. In our opinion, this can be explained by the simple fact that in most cases the short-term advantage of antiarrhythmic treatment is small and is usually offset by the significant proportion of patients experiencing significant side effects or later relapses.

We therefore believe that, in most cases, the best approach in patients with recent onset paroxysmal atrial fibrillation is no specific treatment at all. With this strategy most patients will convert spontaneously to normal sinus rhythm, and any decision regarding the desirability and nature of long-term antiarrhythmic therapy can be made at that stage. Patients not converting to normal sinus rhythm after 8 h of observation have a low rate of spontaneous conversion. This is especially true for patients older than 70 years or with concomitant diseases such as hypertension, ischaemic heart disease or congestive heart failure. Such patients should probably

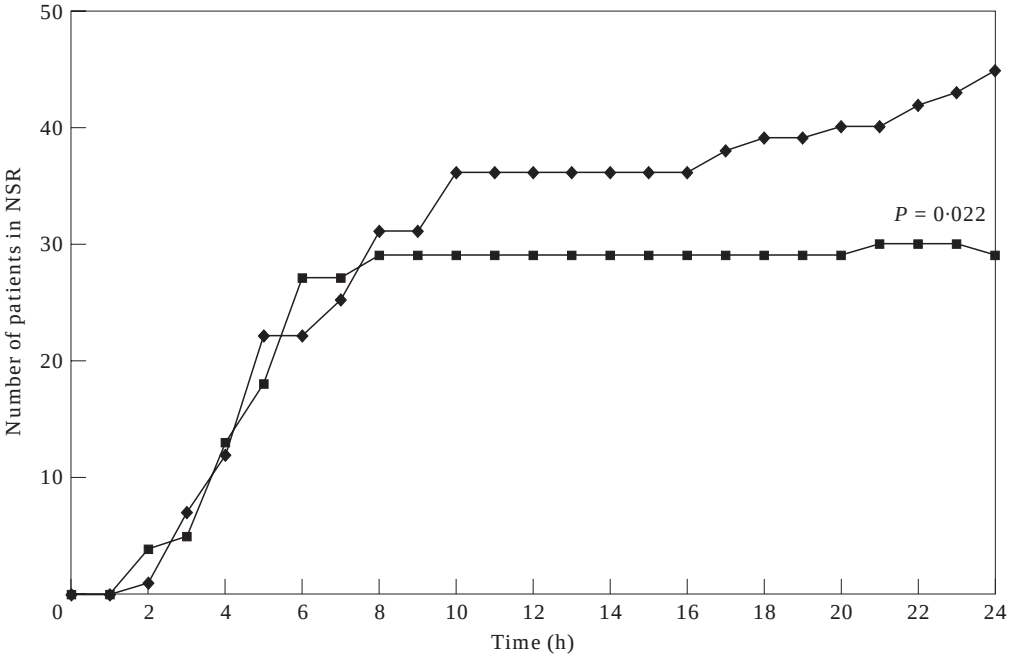

Figure 5 **Number of patients in normal sinus rhythm during the 24 h from admission (amiodarone (◆) vs placebo (■) groups).**

be admitted to hospital and undergo echocardiographic evaluation. If the left atrial diameter is over 45 mm or the ejection fraction is under 45%, or if significant mitral regurgitation is detected, the rate of spontaneous conversion to normal sinus rhythm will be low and another method of cardioversion should be attempted. In some cases electrical cardioversion can be attempted.

However, patients with recurrent paroxysmal atrial fibrillation, especially those who experience repeated episodes, should be started on antiarrhythmic therapy that will facilitate conversion to long-term maintenance of normal sinus rhythm. The antiarrhythmic drug of choice for most of these patients is amiodarone. This drug was shown to be superior in maintaining normal sinus rhythm, and is currently the only safe treatment for patients with ischaemic heart disease or with impaired left ventricular function. Such patients comprise approximately 50% of our cohort. We suggest that they should be treated with high-dose intravenous amiodarone at a rate of 125 mg . h^{-1} . 24 h^{-1}, continued by oral amiodarone. Patients without ischaemic heart disease or impaired left ventricular function can be treated with other antiarrhythmic drugs. However, because such treatment modalities have a high rate of adverse effects and early relapses to paroxysmal atrial fibrillation, these patients should receive the antiarrhythmic drug loading in hospital and be monitored for 24 h prior to discharge.

Patients failing to convert to normal sinus rhythm despite treatment with high-dose amiodarone can be converted in most cases by electrical cardioversion. However, all such patients in our study converted to chronic atrial fibrillation within a month of discharge. We would therefore recommend that such patients should be followed carefully in order to detect and treat such conversion to chronic atrial fibrillation.

Conclusions

The spontaneous conversion of recent onset paroxysmal atrial fibrillation is approximately 60% and approaches 90% in patients without hypertension, ischaemic heart disease or congestive heart failure or echocardiographical findings of enlarged left atrium, decreased ejection fraction or significant mitral regurgitation. Intravenous high-dose amiodarone (3 g . 24 h^{-1}) safely facilitates conversion of recent onset paroxysmal atrial fibrillation to normal sinus rhythm. However, due to the high spontaneous conversion rate we observed, such treatment should be reserved for patients with unfavourable risk factor profiles, not converting during 8 h of observation or requiring rate control.

References

[1] Myerburg RJ, Kessler KM, Castellanos A. Recognition, clinical assessment and management of arrhythmias and conduction disturbances. In: The Heart, 8th ed. Hurst 725–8.

[2] Pritchett E. Management of atrial fibrillation. N Engl J Med 1992; 326: 1264–9.

[3] Galve E, Rivs T, Ballester R *et al*. Intravenous amiodarone in treatment of recent onset atrial fibrillation: results of a randomized, controlled study. J Am Coll Cardiol 1996; 27: 1079–82.

[4] Nattel S. Newer developments in the management of atrial fibrillation. Am Heart J 1995; 130: 1094–106.

[5] Botto GL, Capucci A, Boriani G *et al*. Conversion of recent onset atrial fibrillation to sinus rhythm using a single oral loading dose of propafenon: comparison of two regiments. Int Cardiol 1997; 58: 55–61.
[6] Azpitarte J, Alvarez M, Baun O *et al*. Value of single oral loading dose of propafenon in converting recent-onset atrial fibrillation. Results of a randomized, double blind, controlled study. Eur Heart J 1997; 18: 1649–54.
[7] Buscarini L, Imberti D. Increased incidence of spontaneous conversion to sinus rhythm in patients with paroxysmal atrial fibrillation. G Ital Cardiol 1992; 22: 949–52.
[8] Botto GL, Bonini T, Broffonui S *et al*. Conversion of recent onset atrial fibrillation with single oral dose of propafenon: is in hospital admission absolutely necessary? PACE 1996; 19: 1939–43.
[9] Fresco C, Proclemer A, Pavan A *et al*. Intravenous propafenon in paroxysmal atrial fibrillation: a randomized placebo controlled, double blind, multicenter clinical trial. Paroxysmal atrial fibrillation Italian trial (PAFIT) -2 investigators. Clin Cardiol 1996; 19: 409–12.
[10] Boriani G, Capucci A, Lenzi T, Sanguinetti M, Magnani B. Propafenon for conversion of recent-onset atrial fibrillation. Chest 1995; 108: 355–8.
[11] Bellandi F, Dabizzi RB, Cantini F, DiNatale M, Nicoli L. Intravenous propafenon: efficacy and safety in the conversion to sinus rhythm of recent onset atrial fibrillation- a single blind placebo controlled study. Card Drug Ther 1996; 10: 153–7.
[12] Ellenbogen KA, Clemo HF, Stambler BS, Wood MA, VerderLugt JT. Efficacy of ibutalide for termination of atrial fibrillation and flutter. Am J Cardiol 1996; 78 (Suppl 8A): 42–5.
[13] Stambler BS, Wood MA, Ellenbogen KA *et al*. Efficacy and safety of repeated intravenous doses of ibutalide for rapid conversion of atrial flutter or fibrillation. Circulation 1996; 94: 1613–21.
[14] Maisel WH, Kuntz KM, Reimond SL *et al*. Risk of initiating antiarrhythmic drug therapy for atrial fibrillation in patients admitted to a university hospital. Ann Intern Med 1997; 127: 281–4.
[15] Podrid PJ. Amiodarone: reevaluation of an old drug. Ann Intern Med 1995; 122: 689–700.
[16] Vietti-Ramus G, Veglio F, Marchisio U, Burzio P, Latini R. Efficacy and safety of short intravenous amiodarone in supraventricular tachyarrhythmias. Int J Cardiol 1992; 35: 77–85.
[17] Hou ZY, Chang MS, Chen CY *et al*. Acute treatment of recent-onset atrial fibrillation and flutter with a tailored dosing regiment of intravenous amiodarone. A randomized, digoxin-controlled study. Eur Heart J 1995; 16: 521–8.
[18] Boriani G, Biffi M, Capucci A *et al*. Oral propafenon to convert resent onset atrial fibrillation in patients with and without underlying heart disease: a randomized, controlled trial. Ann Intern Med 1997; 126: 621–5.
[19] Horowitz LN, Spielman SR, Greenspan AM *et al*. Use of amiodarone in the treatment of persistent and paroxysmal atrial fibrillation resistant to quinidine therapy. J Am Coll Cardiol 1985; 6: 1402–7
[20] Hoglund C, Rosenhamer G. Echocardiographic left atrial dimension as a predictor of maintaining sinus rhythm after conversion of atrial fibrillation. Acta Med Scand 1985; 217: 411–5.
[21] Flaker GC, Fletcher KA, Rothbart RM, Halperin JL, Hart RG. Clinical and echocardiographic features of intermittent atrial fibrillation that predict recurrent atrial fibrillation. Stroke prevention in atrial fibrillation (SPAF) investigators. Am J Cardiol 1995; 76: 355–8.