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Intravenous Amiodarone for Cardioversion of Recent-Onset Atrial Fibrillation

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Summary

Background: Atrial fibrillation (AF) is one of the most common causes of hospital admission, with a prevalence of up to 5% of the population, increasing with advancing age. Emergency direct current cardioversion is the therapy of choice when arrhythmia leads to hemodynamic compromise, but in patients who are hemodynamically stable, antiarrhythmic drugs are usually given to restore sinus rhythm.

Hypothesis: The study was undertaken to assess the efficacy of intravenous amiodarone in cardioversion of recent-onset paroxysmal atrial fibrillation (AF). No standard antiarrhythmic therapy has been accepted for pharmacologic cardioversion of AF. Amiodarone seems to be a promising candidate, but only few randomized trials are available and the results are inconsistent.

Methods: In all, 160 patients with AF lasting < 24 h were randomly assigned (2:1 fashion) to the amiodarone group (n = 106) receiving 5 mg/kg as a 30 min intravenous (IV) infusion, followed by IV infusion of 10 mg/kg during 20 h diluted in 1000 ml of 10% glucose with 20 IU of rapid-action insulin, 80 mEq of potassium chloride, and 8 g of magnesium sulphate (GIKM), or to the control group (n = 54) receiving 1000 ml of GIKM alone. Treatment was continued up to 20 h independent of sinus rhythm restoration.

Results: Sinus rhythm was restored 20 h after initiation of therapy in 88 (83%) patients in the amiodarone group and in 24 (44%) patients in the control group ($p < 0.0001$). The difference between efficacy of the two treatment modalities became significant already after 8 h of therapy (53 vs. 14 patients with sinus rhythm, respectively, $p < 0.05$). The mean dose of amiodarone administered until sinus rhythm restoration was 740 ± 296 mg. The presence and the type of underlying heart disease did not influence the conversion rate in either group. In two patients (1.8%) treated with amiodarone, the return of sinus rhythm was preceded by asystole.

Conclusion: Amiodarone is effective in the termination of AF lasting < 24 h. It may be particularly useful in patients with organic heart disease in whom class I antiarrhythmic agents may be contraindicated. During treatment, the heart rhythm should be monitored continuously.

Key words: amiodarone, recent-onset atrial fibrillation, pharmacologic cardioversion

Introduction

Atrial fibrillation (AF) is one of the most common causes of hospital admission, with a prevalence of up to 5% of the population, increasing with advancing age.[1, 2] Emergency direct current cardioversion is the therapy of choice when arrhythmia leads to hemodynamic compromise,[3] but in patients who are hemodynamically stable, antiarrhythmic drugs are usually given to restore sinus rhythm. Randomized studies have shown that numerous drugs may be effective in the restoration of sinus rhythm; however, the results of these studies are inconsistent.[4, 5] The efficacy reported for a certain drug varied widely, and no one agent has been shown to be superior to others. Therefore, no standard antiarrhythmic therapy can be considered as a routine treatment.

Amiodarone is an antiarrhythmic class III agent with unique electrophysiologic properties. Until the present, there have been four reports on the efficacy of amiodarone in the set-

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ting of new-onset AF, but the numbers of patients were relatively small and the reported amiodarone efficacy varied from 59 to 92% of patients.[6–9]

The purpose of the present study was to assess the efficacy of intravenous amiodarone in conversion of AF in a randomized, single-blind, multicenter trial.

Materials and Methods

Study Group

Patients were recruited in 10 participating centers (see Appendix 1) between January 1998 and December 1999. In all, 225 consecutive patients with recent-onset AF were considered to be eligible on admission and screened according to exclusion criteria. Finally, 160 consecutive patients (89 men, 71 women; mean age 61.5 ± 12.5 years) with new-onset AF lasting < 24 h were included. Atrial fibrillation was confirmed by 12-lead electrocardiogram (ECG) in all patients. Only the patients with well-defined onset of arrhythmia were considered eligible. The time limit was set up to avoid prolonged anticoagulation therapy, which is necessary before cardioversion of AF lasting > 48 h. The study treatment was therefore tailored not to exceed 20 h, leaving at least 4 h for alternative methods of cardioversion that were left to the discretion of the attending physician. Detailed exclusion criteria were as follows: (1) Age < 18 years; (2) premenopausal women not using adequate birth control; (3) AF causing significant heart failure (New York Heart Association [NYHA] class > II) or anginal chest pain; (4) acute coronary event during the previous 3 weeks (myocardial infarction, unstable angina, percutaneous transluminal coronary angioplasty, or coronary artery bypass graft); (5) hemodynamically significant valvular heart disease; (6) contraindications to immediate rhythm reversion, such as history of an embolic event in a patient not receiving anticoagulation therapy; (7) Wolff-Parkinson-White syndrome; (8) sick sinus syndrome; (9) baseline systolic blood pressure < 100 mmHg or diastolic blood pressure > 110 mmHg; (10) contraindications to amiodarone: Mean heart rate during AF < 80/min, atrioventricular block, thyroid function disorders (currently treated thyroid disease or clinical symptoms), iodine hypersensitivity/allergy, porphyria, pregnancy, pulmonary fibrosis; (11) amiodarone therapy or prolonged antiarrhythmic therapy with another agent; (12) history of proarrhythmia following administration of drugs prolonging QT interval; (13) electrolyte imbalance (serum potassium < 3.5 mmol/l or/and serum magnesium < 1.7 mg/dl; (14) renal or liver insufficiency, suprarenal gland insufficiency, myasthenia gravis; and (15) insulin-dependent diabetes.

Protocol

After screening for inclusion/exclusion criteria, written informed consent was obtained and patients were randomly assigned to the amiodarone group or to the control group in 2:1 fashion. Randomization was performed by central telephone assignment in the coordinating center. Amiodarone hydrochloride (Cordarone®, Sanofi Winthrop, Gentilly-Cedex, France) was given at an initial dose of 5 mg/kg body weight in 50 ml of saline (infusion rate 100 ml/h) followed by a continuous infusion of amiodarone at a dose of 10 mg/kg diluted in 1000 ml of 10% glucose with 20 IU of human rapid-action insulin with 80 mEq of potassium chloride and 8.0 g of magnesium sulphate (GIKM) at a rate of 51 ml/h. Patients allocated to the control group received 1000 ml of GIKM alone. The study treatment was administered through either the peripheral or the central vein and was maintained up to 20 h independent of sinus rhythm restoration. The data on underlying diseases were completed based on documented medical history.

The patients were observed in the Coronary Care Unit with continuous ECG monitoring. Blood pressure was measured every 60 min. Hypotension was considered as a symptomatic drop in systolic blood pressure < 90 mmHg or > 30 mmHg compared with baseline.

Serious side effects were defined as study treatment-induced supra- or ventricular arrhythmia, bradycardia < 50/min, or symptomatic hypotension requiring termination of treatment or decreasing the rate of infusion.

The study complies with the Declaration of Helsinki. The Local Ethics Committee approved the study protocol and written informed consent was obtained from each patient prior to study entry.

Statistics

Statistical analysis was performed using MEDISTAT v2.0 software. The study sample was calculated to detect the effect of amiodarone, assuming its efficacy 25% more than the spontaneous conversion rate, which is estimated to be 50%.[10] Qualitative variables were compared by chi-square test, and the differences in continuous variables were analyzed using the Student's *t*-test. Univariate analysis was performed to assess the possible influence of underlying diseases, concomitant medication, and other factors on the rate of conversion in both groups. For all comparisons, a p value of < 0.05 was required for statistical significance.

Results

Patient Characteristics

Of the 160 patients enrolled, 147 had an underlying cardiac disease (hypertension, n = 84; coronary artery disease, n = 43; symptoms of mild heart failure up to NYHA class II, n = 20), whereas 13 patients had idiopathic AF.

Thirty patients (19%) had a history of paroxysmal (self-terminating) AF, whereas the remaining patients had a history of persistent AF, requiring intervention for restoration of sinus rhythm. In 40 (25%) patients, the index AF episode was the first AF attack, whereas the remaining patients had at least one AF attack in the past. Patients in both arms of the study showed a similar distribution of baseline characteristics (Table I).

TABLE I Patients baseline characteristics

	Amiodarone group n = 106	Control group n = 54
Age (years)	61.7 ± 13.8	61.4 ± 10.8
Males (%)	59 (56)	30 (54)
Duration of AF (h)	19.6 ± 8.1	20.3 ± 10.2
Ventricular rate (beats/min)	118.9 ± 20.2	115.7 ± 19.4
Systolic pressure (mmHg)	135 ± 19	130 ± 24
History of any AF attack (%)	82 (77)	38 (70)
History of paroxysmal, self-terminating AF only (%)	19 (18)	11 (20)
Underlying disease		
Hypertension (%)	55 (52)	29 (54)
CAD (%)	29 (27)	14 (26)
Heart failure (%)		
NYHA I/II	14 (13)	6 (11)
Lone atrial fibrillation (%)	8 (7)	5 (9)
Concomitant medication		
Beta blockers (%)	33 (31)	17 (32)
Diuretics (%)	17 (16)	8 (15)
ACE inhibitors (%)	39 (37)	22 (40)
Calcium antagonists (%)	18 (17)	10 (19)
Digoxin (%)	5 (5)	4 (7)
Left atrial size (mm) [a]	42 ± 8	41 ± 9
LVEF (%) [a]	60 ± 25	58 ± 19

[a] Data available in 93 patients in the amiodarone group and in 47 patients in the control group.

All differences between the amiodarone and control group were not significant.

Abbreviations: AF = atrial fibrillation, CAD = coronary artery disease, ACE = angiotensin-converting enzyme, LVEF = left ventricular ejection fraction, NYHA = New York Heart Association.

Conversion to Sinus Rhythm

Twenty hours after initiation of therapy, sinus rhythm was restored in 88 (83%) patients of the amiodarone group and in 24 (44%) patients of the control group ($p < 0.0001$). The mean time to conversion was 8.2 ± 6.2 and 7.2 ± 4.9, respectively (NS). The dose of amiodarone administered to rhythm conversion was 740 ± 296 mg.

During the first 3 h of the study, treatment conversion of sinus rhythm was obtained in 24 (23%) patients of the amiodarone group and 7 (13%) patients of the control group (NS). Up to 8 h after initiation of treatment, restoration of sinus rhythm was achieved in 53 (50%) patients receiving amiodarone and 14 (26%) controls ($p < 0.05$) (Fig. 1). Mean dose of amiodarone at that point of time was 531 ± 208 mg.

In the whole study group, left atrial size was the only predictor of sinus rhythm restoration, whereas the presence or type of underlying disease or previous antiarrhythmic drug therapy did not affect the conversion rate (Table II). When the data from responders and nonresponders in the amiodarone and control groups were analyzed separately, left atrial size remained as a predictor of conversion to sinus rhythm only in the amiodarone group (Table III). Responders in the amiodarone group and the control group did not differ significantly with respect to analyzed parameters (Table III).

Adverse Reactions

There were two serious adverse reactions requiring termination of the study treatment, both in the amiodarone group. In one patient, severe bradycardia followed by 7 s of asystole was observed before sinus rhythm restoration in 15 h of treatment after receiving 1100 mg of amiodarone. In the second patient, prolonged asystole with cardiac arrest occurred in 2 h of treatment after receiving 390 mg of amiodarone. Hemodynamically stable rhythm (AF) was restored in this patient after short-lasting external chest compression, without other intervention, and the sinus rhythm returned thereafter. In other six (5.6%) patients in the amiodarone group, bradycardia < 50/min was observed with no clinical symptoms, and those patient received the total scheduled dose of the drug. No other serious side effects were seen.

Discussion

The present study has shown that intravenous amiodarone is effective and relatively safe in the termination of recent-onset AF. These results are based on one of the largest reported number of patients with short-lasting AF treated with intravenous amiodarone, given as the only antiarrhythmic medication for restoration of sinus rhythm.

Conversion Rate

Although intravenous amiodarone has been used for several years in clinical practice, its usefulness in restoration of sinus rhythm in patients with recent-onset AF has not yet been fully evaluated. Actually, there are only four controlled studies

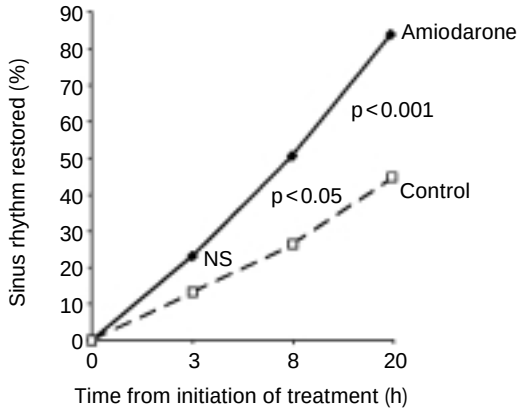

FIG. 1 Proportion of patients successfully converted to sinus rhythm at 3, 8, and 20 h after initiation of the study medication. NS = not significant.

TABLE II Predictors of conversion (univariate analysis) in the whole study group

	Conversion to sinus rhythm		
	Yes (n = 112)	No (n = 48)	p Value
Age (years)	60.6 ± 12.7	59.4 ± 11.8	NS
Males (%)	63 (56)	26 (54)	NS
Duration of AF (h)	15.4 ± 7.2	18.3 ± 11.2	NS
Ventricular rate (beats/min)	116.8 ± 19.2	113.7 ± 17.8	NS
Systolic pressure (mmHg)	133 ± 18	129 ± 23	NS
Underlying disease			
Hypertension	56 (50)	28 (58)	NS
CAD	29 (26)	14 (29)	NS
Heart failure (NYHA I/II) (%)	15 (13)	5 (10)	NS
Lone atrial fibrillation (%)	12 (11)	1 (2)	NS
Concomitant medication			
Beta blockers (%)	35 (31)	15 (31)	NS
Diuretics (%)	18 (16)	7 (15)	NS
ACE inhibitors (%)	43 (38)	18 (38)	NS
Left atrial size (mm) [a]	40 ± 7	42 ± 5	0.05

[a] Data available in 93 patients in the amiodarone group and in 47 patients in the control group.
Abbreviation: NS = not significant. Other abbreviations as in Table I.

TABLE III Predictors of conversion in the amiodarone and control groups

	Amiodarone			Control		
	Responders n = 88	Nonresponders n = 18	p Value	Responders n = 24	Nonresponders n = 30	p Value
Age (years)	58.5 ± 12.6	62.5 ± 14.8	NS	62.2 ± 10.5	60.5 ± 11.4	NS
Males (%)	51 (58)	8 (44)	NS	12 (50)	18 (60)	NS
Duration of AF (h)	18.5 ± 6.4	20.1 ± 8.0	NS	18.5 ± 9.1	20.6 ± 11.4	NS
Ventricular rate (beats/min)	116.5 ± 20.2	120.1 ± 18.8	NS	113.5 ± 20.1	117.2 ±18.0	NS
Systolic pressure (mmHg)	133 ± 16	137 ± 20	NS	129 ± 20	131 ± 26	NS
Underlying disease						
Hypertension (%)	46 (52)	9 (50)	NS	10 (42)	19 (63)	NS
CAD (%)	22 (25)	7 (39)	NS	7 (29)	7 (23)	NS
Heart failure (NYHA I/II) (%)	12 (14)	2 (11)	NS	3 (12)	3 (10)	NS
Lone atrial fibrillation (%)	8 (9)	0 (0)	NS	4 (16)	1 (3)	NS
Concomitant medication						
Beta blockers (%)	25 (28)	8 (44)	NS	10 (42)	7 (23)	NS
Diuretics (%)	12 (14)	5 (28)	NS	2 (8)	6 (20)	NS
ACE inhibitors (%)	30 (34)	9 (50)	NS	9 (37)	13 (43)	NS
Left atrial size (mm) [a]	40 ± 8	43 ± 5	0.05	41 ± 8	42 ± 6	NS

[a] Data available in 77 responders and 16 nonresponders in the amiodarone group and in 20 responders and 27 nonresponders in the control group.
P value = comparison between responders and nonresponders in the amiodarone group and in the control group.
Differences between responders in the amiodarone group and in the responders in the control group were NS.
Abbreviations as in Tables I and II.

(summarized in Table IV) that comprised patients with AF lasting < 48–72 h; thus, they are comparable to our study group. The results of these studies are discordant: the efficacy rate varies from only 59% to as much as 92%.

The remaining published studies[11–16] dealt either with patients with longer AF duration or oral loading of amiodarone. Also, in other studies that comprised patients with AF lasting < 7–10 days, the results regarding amiodarone efficacy were inconsistent.[11–14]

These discrepancies, perhaps, may occur by chance, as the study groups were small. The differences in patients' baseline characteristics, duration of index AF episode, and mode of

TABLE IV Intravenous amiodarone in cardioversion of atrial fibrillation: Results of controlled trials

Author/Ref. No.	Number of patients		AF duration	Efficacy assessed after (h)	Conversion rate (%)			Dosage of amiodarone
	AMIO	Control			AMIO	Control	p Value	
Donovan *et al.* (6)		32				56	NS	7 mg/kg/8h
	32	PL	< 72 h	8	59	PL		
		34				68	NS	
		FLE				FLE		
Kochiadakis *et al.* (7)		46				78	NS	300 mg/h and then
	48	PFN	< 48 h	24	83	PFN		20 mg/kg/24 h
		49				55		
		PL				PL	0.02	
Cotter *et al.* (8)							0.0017	125 mg/h
	50	50	< 48 h	24	92	64		(total 3 g/24 h)
		PL				PL		
Martinez-Marcos *et al.* (9)		50				72		
	50	PFN	< 48 h	12	64	PFN	NS	5 mg/kg/20 min bolus
		50				90	0.002	and then 50 mg/h/12 h
		FLE				FLE		
Present study	106	54	< 24 h	20	83	44	0.0001	5mg/kg/30 min and then 10 mg/kg/20 h

Abbreviations: AMIO = intravenous (IV) amiodarone, Contr. = control group, PL = placebo, PFN = IV proAFenone, FLE = IV flecainide, NS = not significant.

amiodarone infusion, as well as the time from initiation of treatment to assessment of amiodarone efficacy may also contribute to the differences in the obtained results.

Of the above-mentioned parameters, the duration of therapy with intravenous amiodarone is probably the most important factor influencing the efficacy rate. It has been shown in other studies that the efficacy of amiodarone in the termination of AF of different duration is significantly lower than that of class Ic drugs when assessed within the first 3 h of treatment.[6, 11, 14]

In our study, the difference between efficacy of amiodarone and control treatment started to be significant after 8 h of treatment, when 50% of patients receiving amiodarone were converted to sinus rhythm. This is not surprising because intravenous amiodarone exerts different electrophysiologic effects than oral formulation. Initially, intravenous amiodarone shows only antiadrenergic and calcium-channel blocking properties, whereas antiarrhythmic effects attributable to class III—that is, prolongation of refractoriness—begins to occur much later, at least after 30 min and maybe even as late as 6 h from the initiation of infusion.[17, 18] In some other reports, the conversion rate in the amiodarone-treated patients assessed within 8 h of therapy was similar and did not exceed 59%.[6, 9, 14] Lack of difference between efficacy of amiodarone and control treatment during the first 8 h of therapy may be explained in part by the above-mentioned delayed onset of amiodarone class III antiarrhythmic action, and in part by the well-known fact that the highest rate of spontaneous termination of AF is seen within the first 8 h of AF.[14, 19]

Dosage Regimen

The initial and total dose as well as the rate of intravenous infusion of amiodarone differs from study to study. Clearly, there is no standard regimen that can be recommended; however, the higher the total dose of the drug, and the longer duration of treatment, the better the efficacy (see Table IV). The mean total dose of amiodarone in our study was 1200 ± 209 mg, which was slightly less than that in the study of Kochiadakis *et al.*,[7] who reported the same efficacy of the drug as in our study, and much less than in the study of Cotter *et al.*,[8] in which the efficacy reached 92% following the total 24-h dose of 3.0 g of amiodarone. In our study the mean dose of amiodarone administered up to rhythm conversion was 740 ± 296 mg.

Thus, the results of all studies dealing with intravenous amiodarone indicate the time- and dose-dependent mechanism of the rhythm conversion in patients with AF, but no optimal dose of the drug has been recommended. Our regimen, with a relatively low dose of amiodarone, proved to be effective. It may be hypothesized that the smaller dose is safer (we observed two cases of asystole), a fact that should be tested prospectively in order to establish the lowest effective dose of intravenous amiodarone in termination of AF.

Role of Organic Heart Disease

Similar to variations in AF duration, the differences in patients' characteristics may also account for divergent results of

the studies on efficacy of antiarrhythmic treatment. It has been shown that the spontaneous conversion rate within 8 h of admission was 27% in patients with hypertension, 17% in patients with structural heart disease, and 56% in patients with none of these conditions.[19]

When the responders and nonresponders were analyzed according to the underlying disease, no significant differences in the conversion rate between the two treatment groups were observed (Table III). The presence of structural heart disease seemed not to influence adversely the antiarrhythmic efficacy of amiodarone. These results suggest that amiodarone may be equally effective (and also relatively safe) in patients with or without organic heart disease and, therefore, may be administered in patients who have relative contraindications to class I antiarrhythmic drugs. Left atrial size was the predictor of conversion to sinus rhythm only in the amiodarone group, although the difference was small and of borderline significance. This result is in line with findings of another study, which demonstrated higher efficacy of antiarrhythmic drugs in patients without left atrial enlargement.[7]

The results of some other studies also suggest that intravenous amiodarone may be a drug of choice in the restoration of sinus rhythm in the setting of organic heart disease.

In the study published by Cotter *et al.*,[8] the number of patients with underlying cardiovascular disease and mean left atrial diameter was much greater than that in our study, and a significant proportion of the study group had reduced left ventricular ejection fraction. However, in their study, the overall amiodarone efficacy after 24 h was close to that obtained in our report and reached 92%.

Lack of differences between amiodarone and control treatment efficacy in lone AF may be explained by a very high spontaneous conversion rate in these patients. In our study population, only 8% of patients had lone AF, and in 92% of these patients sinus rhythm was achieved (100% in amiodarone group and 80% in controls).

It may be speculated that the most cost-effective approach in lone AF may be to institute no treatment for at least 8 h from the onset of arrhythmia (when the spontaneous conversion rate is the highest) and administration of antiarrhythmic drugs only when a patient remains in atrial AF over this period of time.

Adverse Reactions

The adverse effects of amiodarone in our study occurred in 7.5% of patients. The fact that there were two cases of asystole (1.8%) indicates that amiodarone must be administered intravenously only in patients in whom cardiac rhythm is continuously monitored and resuscitation facilities are available. There were no cases of other symptomatic proarrhythmic effects such as ventricular tachycardia or atrioventricular conduction disturbances, and no clinically significant hypotension was documented.

Cotter *et al.*, who used a total dose of 3.0g/24 h, observed nonsymptomatic bradycardia < 50/min in 10% of patients and no single case of proarrhythmia.[8] Kochiadakis *et al.*[7] and Martinez-Marcos *et al.*[9] also observed no proarrhythmic effects of amiodarone and severe hypotension; the incidence of allergic reactions in both studies was 2%. Contrary to other studies, in our large study group we did observe the serious adverse events mentioned above, and therefore amiodarone should not be considered as a safe drug to be given outside of resuscitation facilities. Moreover, the differences in dosage in the comparable studies suggest that the risk of adverse events caused by intravenous amiodarone may not be dose dependent.

In the majority of our patients, amiodarone was administered through peripheral vein; however, phlebitis was not observed.

Study Limitations

The study was not designed as double-blind; however, the endpoint (rhythm conversion) should not been influenced by this fact. In the control group, GIKM infusion, not saline, was given. The GIKM infusion is our first-line routine therapy in AF due to the well-known fact that electrolyte imbalance often leads to cardiac arrhythmias. Magnesium sulfate was used in both study groups; thus, amiodarone efficacy can be accurately assessed. Comparison with studies using saline in the control group may, however, be limited. Since we included only the patients with NYHA I or II class, the role of amiodarone in patients with AF and severely depressed left ventricular function has not been addressed in this study and needs to be further elucidated.

The study group included patients with a history of paroxysmal as well as persistent AF. These two groups of patient may respond differently to antiarrhythmic therapy. However, in our study, both groups were equally represented in both treatment arms and therefore should not have influenced the results of our study.

Conclusions

Amiodarone administered intravenously is effective in the termination of AF lasting < 24 h. In general, it is also safe; however, during the treatment, heart rhythm should be continuously monitored and intensive care facilities should be immediately available. The antiarrhythmic efficacy of amiodarone was not influenced by underlying cardiovascular disease and, therefore, this agent may be particularly useful in patients with organic heart disease in whom class I antiarrhythmic agents are generally contraindicated.

Appendix: List of Participating Centers and Investigators

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