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An evaluation of the strategy of maintenance of sinus rhythm by antiarrhythmic drug therapy after ablation and pacing therapy in patients with paroxysmal atrial fibrillation

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Aims Permanent atrial fibrillation develops in many patients after ablation and pacing therapy. We compared a strategy that initially allowed patients to remain in atrial fibrillation with a strategy that initially attempted to restore and maintain sinus rhythm.

Methods and Results In this multicentre randomized controlled trial, 68 patients affected by severely symptomatic paroxysmal atrial fibrillation were assigned, after successful atrioventricular junction ablation and pacing treatment, to antiarrhythmic drug therapy with amiodarone, propafenone, flecainide or sotalol and were compared with 69 patients assigned, after successful AV junction ablation and pacing treatment, to no antiarrhythmic drug therapy. The patients were followed-up for 12 to 24 months (mean 16 ± 4). The drug arm patients had a 57% reduction in the risk of developing permanent atrial fibrillation (21% vs 37%, $P=0{\cdot}02$). Evaluation after 12 months revealed similar quality of life scores and echocardiographic parameters in the two groups, but the drug arm patients had more episodes of heart failure and hospitalizations ($P=0{\cdot}05$). The outcome was similar between the 40 patients who developed permanent atrial fibrillation and the 97 who did not.

Conclusion Conventional antiarrhythmic therapy reduces the risk of development of permanent atrial fibrillation after ablation and pacing therapy. The present data do not support the concept that the development of permanent atrial fibrillation is related to an adverse outcome when a perfect control of heart rate is obtained by ablation and pacing.

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Key Words: Catheter ablation, atrial fibrillation, pacemakers, antiarrhythmia agents, atrioventricular node.

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Introduction

In patients with paroxysmal atrial fibrillation that is not controlled by pharmacological therapy, ablation and pacing therapy has proved highly effective in controlling symptoms, though permanent atrial fibrillation develops in many patients shortly after ablation. For example, in one study[1] permanent atrial fibrillation was present, 1 and 2 years after ablation, in 22% and 40% of patients, respectively. In one randomized prospective study[2], antiarrhythmic drugs were able to prevent the development of permanent atrial fibrillation in the first 6 months after ablation. However, the long-term efficacy of antiarrhythmic drug therapy is unknown and the potential advantage of maintaining sinus rhythm with

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antiarrhythmic drugs must be weighed against the potential negative impact of these drugs on quality of life and cardiac performance.

The aim of this study was to evaluate the effect of antiarrhythmic drug therapy on long-term maintenance of normal sinus rhythm after ablation and pacing therapy and to evaluate its clinical efficacy. As it was expected that some patients would not be able to maintain sinus rhythm in the long-term, this study was actually an evaluation of a strategy that initially allowed patients to remain in atrial fibrillation versus a strategy that initially attempted to restore and maintain normal sinus rhythm.

Methods

Protocol

This was a prospective, randomized, multicentre trial comparing the effects of antiarrhythmic drug therapy with no antiarrhythmic drugs after successful atrioventricular junction ablation and DDDR mode-switching pacemaker treatment. Patients were followed-up for 12 to 24 months. Their quality of life and cardiac performance were compared after 12 months. The study protocol had been approved by the Ethics Committee of the hospitals participating in the study. The subjects enrolled gave their informed consent.

Assignment and blinding

Randomization was carried out centrally, blocking on study centres in order to minimize possible biases due to differences in patient characteristics between centres. The allocation of sequences was computer-generated and the intervention assignments were hidden from participants in the trial until the time of allocation.

End-points

The primary end-point was to test the hypothesis that antiarrhythmic drug therapy was able to prevent the development of permanent atrial fibrillation during long-term follow-up. Secondary end-points were to evaluate: (1) the effect of antiarrhythmic drug strategy on major clinical events, quality of life and cardiac performance and, therefore, to evaluate whether antiarrhythmic drug strategy yields any additional benefit to ablation and pacing therapy; (2) the impact of the development of permanent atrial fibrillation on the clinical outcome of patients; (3) the effect of antiarrhythmic drugs in reducing the total time during which the patient is in permanent atrial fibrillation; (4) the long-term effects of ablation and pacing therapy on quality of life and cardiac performance.

Patient eligibility

Consecutive patients affected by paroxysmal atrial fibrillation (electrocardiographically documented) who met all the following criteria were considered eligible for inclusion: (1) tachyarrhythmic episodes that caused severe symptoms, including palpitations, dyspnoea, easy fatigue and chest discomfort, that were intolerable for the patient on account of their frequency or as a manifestation of cardiac failure; (2) failure of three or more antiarrythmic drugs (including amiodarone) to maintain stable sinus rhythm or to control symptoms; (3) three or more episodes of paroxysmal tachyarrhythmia during the previous 12 months (an episode of paroxysmal tachyarrhythmia was defined as lasting more than 1 h); (4) duration of tachyarrhythmic episodes >1 year; (5) age >50 years.

Criteria for exclusion from the study were the following: (1) previous implantation of a pacemaker for other reasons; (2) the need for a pacemaker implant for symptomatic bradycardia; (3) intolerance to antiarrhythmic drugs; (4) acute clinical diseases during the previous 6 months; (5) associated severe general infections; (6) geographical impossibility to follow-up.

Study design

According to the randomization list, eligible patients were assigned to one of the two study arms if they had undergone successful atrioventricular junction ablation and pacemaker implantation, remained in sinus rhythm at least intermittently in the period of time between screening and randomization, and gave informed consent. The pacemaker could be implanted before or after ablation; ablation could be repeated if stable atrioventricular block was not achieved during the first session. A stabilization period of 1–7 days was required between the procedure and randomization.

Patients were seen at the outpatient clinic every 3 months until the end of the study or the patient's death. The follow-up examination included electrocardiogram to determine the underlying rhythm (sinus rhythm or atrial fibrillation), collection of data on clinical status, co-morbidities, symptoms, adherence to the study treatments, and interrogation of the pacemaker to retrieve data concerning pathological atrial rhythms, as defined by the pacemaker algorithm.

Moreover, on enrolment and at the 12-month examination, patients underwent echocardiographic evaluation and quality of life measurements contained in the Minnesota Living with Heart Failure questionnaire[3] and the Specific Symptom Scale[2]. These instruments have been demonstrated to discern changes in the symptoms of patients with atrial fibrillation both in sequential and in case-control studies[2,4,5].

Pacemaker implantation

All patients received a dual-chamber mode-switching rate-responsive pacemaker (Diamond or Selection, Vitatron). The ventricular lead was placed at the apex of

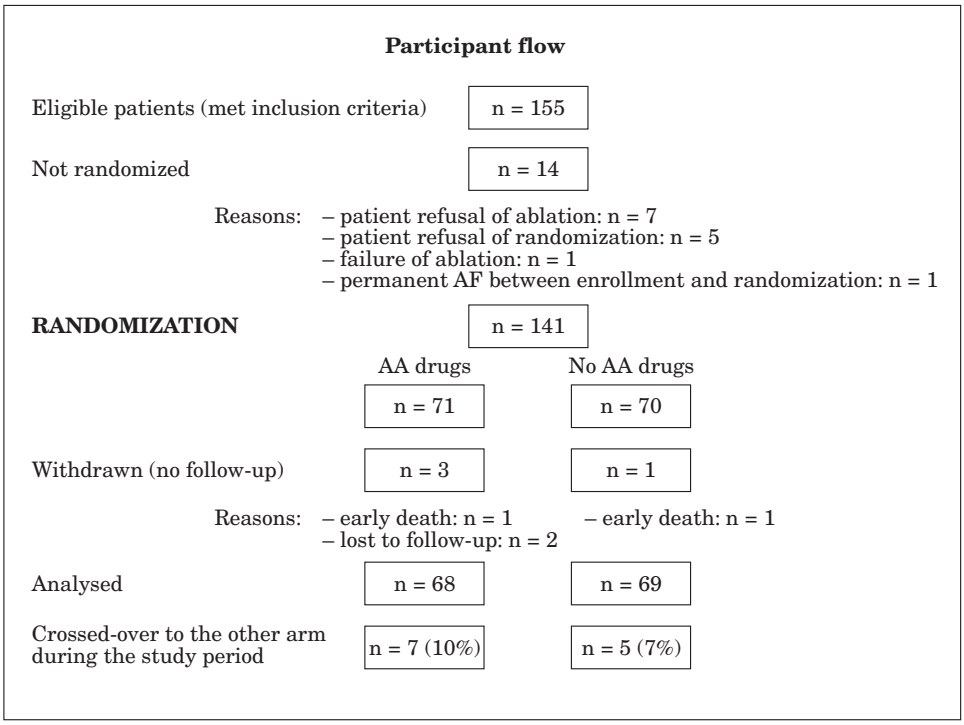

Figure 1 **Progress through the various stages of the trial, including flow of participants, withdrawals, cross-over and timing of outcome measurements.**

the right ventricle. The pacemaker was able to collect and store the total duration of follow-up (days) and the total duration of pathological atrial rhythm. These data were retrieved every 3 months so that the percentage of pathological atrial rhythm could be calculated. This percentage was considered to be representative of the total burden of episodes of atrial fibrillation of the patients. Unless otherwise indicated, devices were programmed to a lower rate of 70 beats . min^{-1}, an upper rate limit of 130 beats . min^{-1}, and an AV interval rate adaptive (medium).

Pharmacological therapy throughout the study period

In the drug-arm patients, amiodarone, propafenone, flecainide and sotalol were used. Amiodarone was recommended as first choice treatment. Propafenone and flecainide were discouraged in patients with heart failure. Apart from these recommendations, the choice of the antiarrhythmic drug was individualized for each patient at the discretion of the attending investigator in order to mimic their preference in clinical practice. Recommended dosages were: amiodarone (at a steady-state dose of 200 mg . day^{-1}), sotalol (120–240 mg . day^{-1}), propafenone (450–900 mg . day^{-1}), flecainide (100–200 mg . day^{-1}) and combinations of these. Therapists were allowed to change the drug or increase the dose, if deemed necessary in order to maintain sinus rhythm. Relapse into atrial fibrillation was not necessarily considered a failure of the strategy to maintain sinus rhythm. The patients assigned to the no drug arm had any antiarrhythmic drug therapy discontinued at the time of randomization. Electrical cardioversion was not allowed in either group.

Antithrombotic therapy was used in accordance with the published guidelines[6].

Definitions

Paroxysmal AF was defined as episodes lasting ≤ 3 days, self-terminating or pharmacologically-electrically terminated.

Atrial fibrillation was considered to have become permanent if it was present during two consecutive follow-up examinations and persisted during a further examination performed 1 month later. The date of onset of permanent atrial fibrillation was considered to be that of the first of the three examinations.

Heart failure was defined as the renewed onset or worsening of symptoms and signs of heart failure that required introduction or changes in the dose of digoxin, diuretics or angiotensin-converting enzyme inhibitors.

Statistics

Comparison between continuous variables was carried out by means of paired and unpaired Student's t-test or non-parametric Mann-Whitney's 'test U', as

Table 1 Baseline characteristics of the study population

	Drugs n=68	No drugs n=69
Age, years	67 ± 8	69 ± 8
Male sex	31 (46)	27 (39)
Structural heart disease		
Absent	24 (35)	25 (36)
Hypertensive	23 (34)	19 (28)
Ischaemic	11 (16)	11 (16)
Valvular	5 (7)	10 (14)
Other	5 (7)	4 (6)
Echocardiogram		
Left ventricular end-diastolic diameter >56 mm	13 (19)	8 (12)
Ejection fraction <50%	8 (12)	12 (17)
Left atrial diameter >40 mm	39 (57)	34 (49)
History of tachyarrhythmias		
Only atrial fibrillation	46 (68)	42 (61)
Atrial fibrillation and atypical atrial flutter	22 (32)	27 (39)
Duration of arrhythmia, years	8 ± 7	9 ± 7
Median no. of hospitalizations (interquartile range)	5 (3–8)	5 (3–7)
Median no. of episodes last year (interquartile range)	12 (7–46)	12 (6–40)
Heart rate during AF (standard electrocardiogram), beats . min^{-1}	132 ± 20	130 ± 23
Number of previous ineffective treatments	3·3 ± 1·3	3·0 ± 1·2
Holter recording		
AF persisting during the whole recording time	7 (10)	10 (14)
≥1 episode of atrial tachyarrhythmia >30 s	28 (41)	30 (43)
Mean heart rate (excluding patients with persistent AF), beats . min^{-1}	69 ± 10	70 ± 12
Heart failure requiring pharmacological treatment (digoxin, diuretics or angiotensin-converting enzyme inhibitors)	9 (13)*	18 (26)*
Anticoagulant therapy	32 (47)	32 (46)

*P=0·04.
Numbers indicated in brackets are percentages. Values are mean ± SD or number of patients.
AF=atrial fibrillation.

appropriate; comparison between proportions was made by Fisher's exact test. Moreover, the time to the onset of permanent atrial fibrillation was analysed by means of Kaplan–Meier survival curves and the curves were compared by means of the log-rank test.

The assumption for the sample size calculation was that, on the basis of previous studies[1,2] the drug group would have a 50% reduction in the development of permanent atrial fibrillation after 2 years (absolute decrease of permanent atrial fibrillation rate from 40% to 20%) compared with the no-drug arm. The sample size able to provide an 80% power to show a difference between groups, with a probability of 95%, is 150 patients.

Results

Participant flow and follow-up

Progress through the various stages of the trial, including flow of participants, withdrawals and cross-over are shown in Fig. 1. Two patients died and one was lost to follow-up before the first visit and no data could be obtained; another patient was lost to follow-up before the 6th month visit. Since the follow-up of these patients was not long enough to reach the primary end-point of the study (development of permanent atrial fibrillation as defined in the methods), they were withdrawn from the analysis. The resulting 68 patients in the drug arm and 69 patients in the no-drug arm were analysed according the intention-to-treat principle. Baseline characteristics of the study population are shown in Table 1. The ablation end-point was reached without complications in all but one patient. In four patients, atrioventricular conduction resumed after a few days and a second procedure was rapidly performed, which achieved persistent AV block.

Enrolment started in January 1998 and ended in April 1999. All the patients were followed-up for a minimum of 12 months and a maximum of 24 months (mean 16 ± 4). Follow-up was completed in April 2000.

Analysis

Primary end-points

Fewer patients assigned to the drug arm developed permanent atrial fibrillation during the study period, with a relative reduction rate of 57% (odds ratio 0·43 (95% CI interval 0·18–0·98)) (Table 2). The actuarial estimates of progression to permanent atrial fibrillation are shown in the Fig. 2. The difference between groups

Table 2 Clinical events during the study period

Event	Drugs n=68	No drugs n=69	*P*
History of AF			
Development of permanent AF	14 (21)	26 (37)	0·02
AF at the time of 3-monthly examinations			
number of exams with AF/total exams, %	84/347 (24)	138/359 (38)	0·000
Total burden of AF (derived from pacemaker Interrogation)			
median percentage of time in AF	10·4	19·6	0·04*
(interquartile range)	(1·9–35·4)	(3·0–79·6)	
median percentage of time in AF before the development of permanent AF	5·4	7·7	0·92
(interquartile range)	(0·9–14·6)	(1·1–18·6)	
Major clinical events			
Heart failure			
patients	15 (22)	7 (10)	0·05
total number of episodes	22	10	
Hospitalization for heart failure			
patients	12 (18)	5 (7)	0·05
total no. of hospitalizations	22	7	
Stroke	3 (4)	1 (1)	0·30
Acute myocardial infarction	1 (1)	2 (3)	0·51
Heart transplantation	1 (1)	0 (0)	0·50

Numbers indicated in brackets are percentages.
AF=atrial fibrillation.
*Comparison between percentage of time in atrial fibrillation was made using the non-parametric Mann–Whitney U-test.

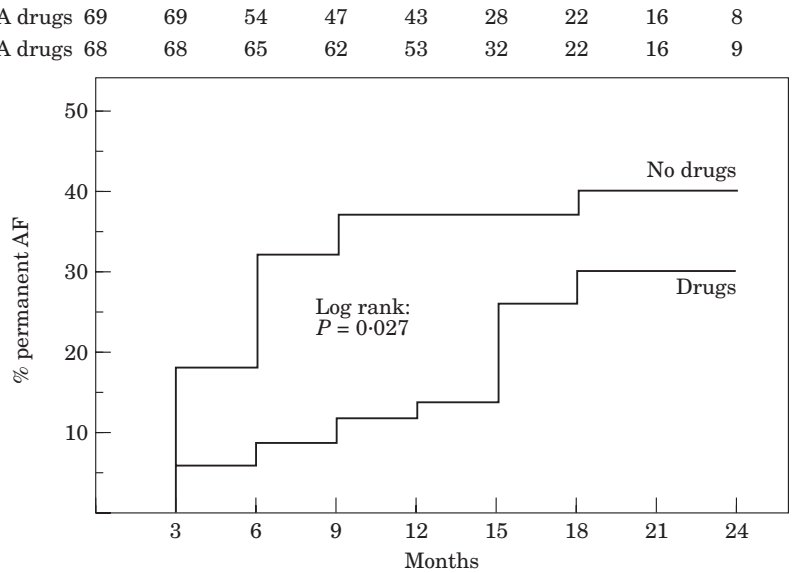

Figure 2 **Kaplan–Meyer estimates of probability of developing permanent atrial fibrillation in the patients assigned to the drug arm and in those assigned to the no-drug arm (by intention-to-treat). AF=atrial fibrillation.**

was high after 12 months (14% vs 36%); it diminished after 24 months (30% vs 40%).

Secondary end-points

As a consequence of ablation and pacing therapy, quality of life greatly improved after 12 months compared to pre-ablation evaluation in both groups (Table 3).

On 12-month evaluation, quality of life scores were similar in the two groups of patients (Table 3); echocardiographic data were also similar (Table 4). More episodes of heart failure and more hospitalizations due to heart failure occurred in the drug arm patients ($P=0·05$) (Table 2). As a consequence, in the drug arm there was 2·5-fold (CI interval 0·9–7·4) relative increase of heart failure and a 2·7-fold (CI interval 0·8–9·6)

Table 3 Results of quality of life measurements

Symptoms (score)	Enrolment (before ablation)			Month 12			Difference Enrolment/month 12			
	Drugs n=68	No drugs n=69	*P*	Drugs n=68	No drugs n=69	*P*	Drugs		No drugs	
							%	*P*	%	*P*
LHFQ questionnaire	43 ± 17	45 ± 18	0·51	20 ± 20	22 ± 18	0·54	− 53%	0·000	− 51%	0·000
Specific symptoms scale										
Palpitations	6·8 ± 2·8	7·3 ± 2·6	0·28	2·1 ± 2·4	1·7 ± 2·1	0·30	− 69%	0·000	− 77%	0·000
Effort dyspnoea	5·4 ± 2·9	5·0 ± 3·5	0·47	3·0 ± 2·9	3·0 ± 2·7	1	− 44%	0·000	− 40%	0·000
Rest dyspnoea	2·5 ± 2·7	3·1 ± 3·3	0·25	0·7 ± 1·7	0·8 ± 1·8	0·74	− 72%	0·000	− 74%	0·000
Exercise intolerance	6·3 ± 2·5	5·7 ± 3·3	0·23	3·3 ± 2·7	3·3 ± 2·8	1	− 48%	0·000	− 42%	0·000
Easy fatigue	3·9 ± 3·2	5·1 ± 3·4	0·03	1·6 ± 2·4	1·2 ± 2·0	0·29	− 41%	0·000	− 76%	0·000
Chest discomfort	1·9 ± 2·9	2·5 ± 3·2	0·25	1·4 ± 2·7	0·8 ± 1·7	0·12	− 26%	0·04	− 68%	0·000
NYHA class	2·0 ± 0·7	1·9 ± 0·7	0·40	1·6 ± 0·6	1·6 ± 0·6	1	− 20%	0·001	− 16%	0·000

Values are mean ± SD; LHFQ=Living with Heart Failure Questionnaire.

Table 4 Echocardiographic results at month 12 evaluation

	Drugs n=68	No drugs n=69
Left ventricular end-diastolic diameter, mm	53 ± 7	51 ± 5*
Left ventricular end-systolic diameter, mm	35 ± 8	33 ± 7
Fractional shortening, %	35 ± 8	35 ± 8
Ejection fraction, %	52 ± 11 (65)	55 ± 10 (62)
Left atrial diameter, mm	42 ± 6	42 ± 7
Mitral regurgitation (4-point scale score)	1·9 ± 0·8	2·0 ± 0·7

Values are mean ± SD; when the data were not available for all patients, the numbers of patients with data are indicated in brackets.
*$P<0·05$.

relative increase of hospitalizations due to heart failure. During the study, 40 patients developed permanent atrial fibrillation and 97 did not. The outcome, evaluated both as the occurrence of major clinical events and as a measurement of quality of life, was quite similar (Table 5).

In the drug arm, fewer episodes of atrial fibrillation were documented at the time of the 3-monthly follow-up examinations. Also the total burden of atrial fibrillation recorded by the pacemakers was lower, but when the periods of permanent atrial fibrillation were eliminated, the difference was no longer significant (Table 2).

In the drug arm, 21 patients were treated with amiodarone, 24 with propafenone or flecainide, 22 with sotalol and one with amiodarone plus flecainide. The study was not designed for the comparison between antiarrhythmic drugs, their assignement was not randomized and the power was too small to make any conclusion. However, we were unable to show any difference in regard to the rate of development of permanent atrial fibrillation and the clinical outcome among patients who had received amiodarone, propafenone/flecainide or sotalol.

Five patients died during the study period, including the two who were withdrawn from analysis. Causes of death were: sudden death (#2), stroke (#2) and heart failure (#1). Four of the five deaths occurred in patients assigned to the drug arm (difference not significant).

Discussion

Main findings

The results of the study show that ablation and pacing therapy were able to improve symptoms and functional capacity in both groups of patients. The main result is that conventional antiarrhythmic drug therapy was able to reduce the risk of development of permanent atrial fibrillation after ablation and pacing therapy for at least 2 years even in a selected population with frequent recurrences of paroxysmal atrial fibrillation that had been considered to be resistant to multiple pharmacological treatment.

Despite the higher percentage of patients who remained in sinus rhythm, we were unable to show any clinical benefit in patients treated with antiarrhythmic therapy in addition to that already obtained with ablation and pacing alone and, in contrast, in some patients, we observed serious adverse clinical events, as evidenced

Table 5 Comparison of the outcome of the patients who developed permanent atrial fibrillation during the study period with those who did not

Event	Permanent group n=40	No permanent group n=97	*P*
Major clinical events			
Heart failure			
patients	7 (17)	15 (15)	0·48
total number of episodes	12	20	
Hospitalization for heart failure			
patients	6 (15)	11 (11)	0·37
total no. of hospitalizations	11	18	
Stroke	1 (2)	3 (3)	0·67
Acute myocardial infarction	0 (0)	3 (3)	0·35
Heart transplantation	0 (0)	1 (1)	0·71
Quality of life measurements (month 12)*			
LHFQ questionnaire	21 ± 17	21 ± 20	1
Specific Symptoms Scale			
Palpitations	1·6 ± 1·9	2·0 ± 2·4	0·35
Effort dyspnoea	3·3 ± 2·8	2·9 ± 2·8	0·45
Rest dyspnoea	0·8 ± 1·6	0·7 ± 1·8	0·76
Exercise intolerance	3·3 ± 2·5	3·3 ± 2·9	1
Easy fatigue	1·4 ± 2·0	1·4 ± 2·3	1
Chest discomfort	1·1 ± 2·1	1·1 ± 2·3	1
NYHA class	1·6 ± 0·6	1·6 ± 0·6	1

Numbers indicated in brackets are percentages.
LHFQ=Living with Heart Failure Questionnaire.
*On month 12 evaluation, permanent atrial fibrillation was present in 36/40 of the permanent group and in 86/97 of the not permanent group patients.

by the higher number of episodes of heart failure and hospitalization. Thus, the perfect control of ventricular rhythm provided by ablation and pacing seems to be the most important objective to be obtained and probably minimizes the importance of preserving atrial contraction.

Permanent atrial fibrillation and outcome

Although there are many theoretical considerations as to why the presence and development of atrial fibrillation could be related to an adverse outcome, the present data do not support this notion as evaluated in terms of quality of life scores and the incidence of heart failure, hospitalizations, stroke and death (Table 5). Whether this is due to the perfect control of heart rate obtained by ablation and pacing is unclear. However, our results confirm those of the PIAF study[7], in which the control of heart rate had a similar effect on quality of life to the maintenance of sinus rhythm and caused fewer hospitalizations, and the results of the study by Tuinenburg *et al.*[8], who observed that serial electrical cardioversion did not prevent heart failure.

On the other hand, a substudy from the SOLVD[9] showed that the presence of atrial fibrillation at baseline was associated with an increased risk of pump failure and hospitalization compared to sinus rhythm. One recent trial[10] suggested that the development of permanent atrial fibrillation was associated with clinical and haemodynamic deterioration, and several reports documented improvement of left ventricular function and exercise capacity after successful cardioversion[11], though this latter observation leaves open whether the reduced rate or the restored regularity of ventricular contraction is more important for this effect of cardioversion. Even if not addressed in the present study, it is also controversial whether atrial fibrillation independently contributes to mortality[9–13].

Limitations

The study has some limitations. Firstly, owing to its open-label design, there is a potential for bias particularly for patient-perceived quality of life. Secondly, we included some patients who had persistent (non self-terminating) atrial fibrillation; the patients with persistent atrial fibrillation have more probability of development of permanent atrial fibrillation than those with paroxysmal (self-terminating) atrial fibrillation.

The long-term effect of ablation and pacing therapy.

The beneficial effect on quality of life lasted for at least 1 year and was of the same extent as that observed in previous short-term studies[2,14]. Moreover, we observed

fairly low rates of heart failure (especially in patients not treated with antiarrhythmic drugs), embolism and death. These findings are similar to those of other previous studies[15–17].

In conclusion, in paroxysmal atrial fibrillation, ablation and pacing is an efficacious and safe therapy whose benefits persist in the long-term without the need for any adjunctive antiarrhythmic therapy. After the procedure, there is a fairly low incidence of adverse clinical events. The development of permanent atrial fibrillation does not seem to modify the outcome and probably does not require treatment. The theoretical clinical benefit of the maintenance of sinus rhythm must be weighed against the potential deleterious effect of antiarrhythmic drugs.

Addendum

Concern is raised in the literature on the supposed long-term negative clinical effects from non-physiological pacing in the right ventricular apex. We were able to extend the follow-up of the clinical events from the end of the study (April 2000) to June 2001 in 134 patients. As consequence, the total follow-up period was extended to 34 ± 8 months (minimum 12, maximum 44 months). During the period of extension, 11 patients had episodes of heart failure (six in the drug and five in the no drug arm), seven had hospitalization for heart failure (four and three respectively). Two patients of the drug arm had other events (one acute mycordial infarction and one ventricular fibrillation); three patients in the no drug arm had other events (one episode of cerebral transient ischaemic attack, one ventricular fibrillation and one mitral valvular surgery). Three patients died (two in the drug and one in the no drug arm): the cause of death was heart failure in two and undefined in one case. Thus, overall 31% of patients in the drug arm and in 17% of patients in the no drug arm had heart failure ($P=0{\cdot}05$), 24% and 12% of patients were hospitalized for heart failure ($P=0{\cdot}05$), and 4% and 3% of patients had an episode of stroke; 65% and 77% of patients were free of clinical events during the long-term follow-up ($P=0{\cdot}08$). Therefore, the results of the present study were maintained also during the extended follow-up period and are consistent with those of the other studies[15–17]. The perfect control of heart rate seems to protect against the non-physiological pacing from the apex of the right ventricle.

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Appendix

PAF 2 Participating Centers and Investigators

The number of patients is given in parentheses

Ospedale S. Maria Nuova, Reggio Emilia: Menozzi C, Bottoni N, Lolli G (18)
Ospedali Riuniti, Lavagna: Brignole M, Gianfranchi L (15)
Istituto Humanitas, Milano: Gasparini M, Mantica M (13)
Ospedale Cisanello, Pisa: Bongiorni MG, Arena G (12)
Ospedale S. Anna, Como: Botto GL, Broffoni T, Sagone A (10)
Ospedale S. Bortolo, Vicenza: Ometto R, Bonanno C, Finocchi G (10)
Ospedale Civile, Cento: Alboni P, Paparella N, Fucà G (9)
Ospedale S Croce, Cuneo: Bruna C, Rossetti G, Vado A (9)
Ospedale S Gerardo, Monza: Vincenti A, Cirò A, De Ceglia S (9)
Ospedale Civile P. Cosma, Camposampiero: Verlato R, Turrini P (8)
Ospedale Maggiore della Carità, Novara: Occhetta E, Bortnik M (7)
Ospedale Civile, Mirano: Bertaglia E, D'Este D (7)
Casa di Cura Pederzoli, Peschiera del Garda: Vicentini A (6)
Ospedale SM Misericordia, Udine: Proclemer A, Facchin D (4)
Ospedale Umberto I, Mestre: Raviele A, Bonso A (2)
Presidio Ospedaliero Ca' Foncello, Treviso: Mantovan R (1)
Ospedale Civile, Imperia: Musso G (1)

Study Coordinators: Brignole M, Menozzi C

Analysis of data and statistics: Brignole M, Menozzi C

External Monitoring and Safety Committee: Gammage M, coordinator (Birmingham), Bertulla A (Genova), Rossi P (Novara)

Executive Committee: Brignole M, Menozzi C, Corbucci G (Vitatron)