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The Australian Intervention Randomized Control of Rate in Atrial Fibrillation Trial (AIRCRAFT)

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OBJECTIVES The Australian Intervention Randomized Control of Rate in Atrial Fibrillation Trial was a multicenter trial of atrioventricular junction ablation and pacing (AVJAP) compared with pharmacologic ventricular rate control (medication [MED]) in patients with mild to moderately symptomatic permanent atrial fibrillation (AF).

BACKGROUND There have been very few prospective randomized trials, undertaken in highly symptomatic patients, comparing AVJAP with pharmacologic methods of ventricular rate control for patients with permanent AF.

METHODS There were 99 patients (70 men, mean age 68 ± 8.6 years) at five centers. Forty-nine patients were randomized to AVJAP while 50 patients were randomized to pharmacologic control. The primary end point was cardiac function measured by echocardiography and exercise tolerance. The secondary end points were ventricular rate control, evaluated by 24-h ambulatory electrocardiographic monitoring, and quality of life. Data were collected at randomization and then at one month, six months, and 12 months post-randomization.

RESULTS At 12 months follow-up there was no significant difference in left ventricular ejection fraction (AVJAP: 54 ± 17%; MED: 61 ± 13% [p = ns]) or exercise duration on treadmill testing (AVJAP: 4.1 ± 2 min; MED: 4.6 ± 2 min [p = ns]); however, the peak ventricular rate was lower in the AVJAP group during exercise (112 ± 17 beats/min vs. 153 ± 36 beats/min, $p < 0.05$) and activities of daily life (117 ± 16 beats/min vs. 152 ± 37 beats/min, $p < 0.05$). The CAST quality-of-life questionnaire revealed that patients in the AVJAP group had fewer symptoms at six months ($p = 0.003$) and at 12 months ($p = 0.004$). The observed relative risk reduction in symptoms at 12 months was 18%. Global subjective semiquantitative measurement of quality of life using the "ladder of life" revealed that the AVJAP group reported a 6% better quality of life at six months ($p = 0.011$).

CONCLUSIONS In this trial, AVJAP for patients with mild to moderately symptomatic permanent AF did not worsen cardiac function during long-term follow-up, and quality of life was improved. (J Am Coll Cardiol 2003;41:1697–702i) © 2003 by the American College of Cardiology Foundation

Atrial fibrillation (AF) is the most common chronic tachyarrhythmia, affecting 5% of people over the age of 60 (1). Ventricular rate control is a major treatment aim for patients with permanent AF. Although several studies have compared atrioventricular junction ablation and pacing (AVJAP) with pharmacologic ventricular rate control in AF, earlier studies were not randomized (2–4), and the few published randomized prospective studies comparing the two treatment options have included very symptomatic patients with a mean left ventricular ejection fraction (LVEF) <50 (5,6).

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The Australian Intervention Randomized Control of Rate in Atrial Fibrillation Trial (AIRCRAFT) was a multicenter, prospective randomized trial of AVJAP versus pharmacologic treatment for ventricular rate control and was undertaken in patients with permanent AF who had mild to moderate symptoms, preserved LVEF, and a ventricular rate that was controlled pharmacologically. AVJAP has not been compared to pharmacologic therapy in this population, which represents the great majority of patients with permanent AF.

The primary end point was cardiac function measured by echocardiography and exercise tolerance. The secondary end points included ventricular rate control, evaluated by 24-h ambulatory electrocardiographic monitoring, and quality of life (QoL).

METHODS

Study protocol. The study protocol was approved by the ethics committees of all participating hospitals. The study was completely explained to each prospective patient before

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Abbreviations and Acronyms

AF	= atrial fibrillation
AQoL	= Assessment of Quality of Life Questionnaire
AIRCRAFT	= Australian Intervention Randomized Control of Rate in Atrial Fibrillation Trial
AVJAP	= atrioventricular junction ablation and pacing
ECG	= electrocardiogram
HR	= heart rate
LVEF	= left ventricular ejection fraction
MED	= medication
QoL	= quality of life
SIP	= Sickness Impact Profile

he or she consented, in writing, to participate in any study-related procedures. Ethics committee approval for the study was obtained in May 1998 and the first patient was enrolled in June 1998. The last patient completed follow-up in July 2001.

The study inclusion criteria were: 1) age >40 years, 2) symptomatic permanent AF (>12 months or with failed cardioversion or medication therapy) with uncontrolled ventricular rate in which a good rate control (defined as rest heart rate [HR] <80 and exercise HR <150) could be achieved by drugs during a three-month screening period, 3) ability to give informed consent, and 4) ability to perform a treadmill test.

The exclusion criteria were: 1) clinical indication for ablation and pacing; 2) the likelihood of surgery or transcatheter valvuloplasty within 12 months of enrollment; 3) untreated resting mean ventricular rate <80 beats/min (averaged over 1 min on three separate occasions) and <150 beats/min during maximum exercise (averaged over 1 min during a treadmill test using the modified Bruce protocol); 4) unstable angina pectoris; 5) Wolff-Parkinson-White syndrome; 6) severe tricuspid valvular regurgitation (by echo criteria) or tricuspid prosthetic valve; 7) New York Heart Association functional class IV despite pharmacologic treatment; 8) unwillingness or inability to cooperate or to give informed consent; 9) any other serious medical condition (such as terminal illness) that, in the opinion of the investigator, would preclude optimal participation in the study; 10) an occupation or hobby that precluded permanent pacing; and 11) inability to travel to the study center for follow-up.

Upon entry into the trial all patients had intensive medical therapy directed by a cardiologist for three months before randomization in an attempt to maximize pharmacologic ventricular rate control. Successful ventricular rate control was arbitrarily defined as a resting mean ventricular rate <80 beats/min (measured during a period of 1 min on three separate occasions) and <150 beats/min during maximum tolerated exercise (during a treadmill test using a modified Bruce protocol). Randomization was conducted independently by the biostatistical consulting service of the University of Western Australia. Patients were stratified according to echocardiographic estimation LVEF >45% or <45% at the end of the initial three-month observation period. The randomization code was computer generated and was balanced within each site as well as for LVEF >45% or <45%. Patients were randomized regardless of the clinical results of the period of intensive medical management, and the randomization code was hidden from the treating cardiologist until the time of allocation.

Pharmacologic treatment. In the pharmacologic treatment group, drugs were prescribed to achieve satisfactory control of the ventricular rate. Drugs used for ventricular rate control included digoxin, metoprolol, atenolol, verapamil, and diltiazem either alone or in combination. The choice of drugs was at the discretion of the treating clinician. Patient compliance was monitored by patient interview at each visit.

Catheter ablation and pacing. In the AVJAP group patients underwent a combined ablation and pacemaker insertion procedure. For atrioventricular junction ablation a deflectable tip ablation catheter was positioned across the tricuspid annulus to record atrial and ventricular electrograms and a His bundle potential. Radiofrequency energy was then delivered with power and duration determined by impedance response or catheter tip temperature monitoring as well as observed response. The end point of the ablation procedure was the development of complete heart block.

The pacemaker implanted was a Pacesetter Trilogy SR model 2250L (Pacesetter Inc., Sylmar, California) programmed VVIR, with rate-response functions optimized for each patient. The minimum pacing rate was 80 to 90 beats/min for one month after ablation, with reprogramming to a lower rate determined by the treating cardiologist thereafter.

Concomitant medication. Patients continued all noncardiovascular medications unchanged. Use of warfarin or antiplatelet agents was not altered by involvement in the trial. Patients randomized to the AVJAP group ceased ventricular rate-controlling drugs following the procedure. Where patients were on beta-blockers, calcium channel blockers, or digoxin for reasons other than ventricular rate control, these drugs were continued.

Patient evaluation at each visit. At baseline (at the end of the three-month lead-in period), patients had an exercise (treadmill) test, 24-h ambulatory electrocardiogram (ECG), and echocardiogram. One month after randomization, patients had an exercise test and 24-h ambulatory ECG. Six and 12 months after randomization patients had an exercise test, 24-h ambulatory ECG, and echocardiogram. A modified Bruce protocol, more aggressive in terms of slope and speed increments than a standard Bruce protocol, was used for exercise testing in order to determine the peak exercise heart rate in an efficient way. Complete two-dimensional color Doppler echocardiography was performed. Left ventricular volumes and ejection fraction were calculated using

Table 1. Baseline Characteristics of Study Population

	MED n = 50	AVJAP n = 49	p Value	Global Population n = 99
Age, yrs	67.9 ± 9	68 ± 8.5	0.973	68 ± 8.7
Male gender	72%	69%	0.775	71%
Ischemic heart disease	38%	43%	0.622	40%
Dilated cardiomyopathy	2%	6%	0.362	4%
Valvular heart disease	31%	35%	0.667	33%
Hypertension	38%	51%	0.192	44%
Diabetes	18%	10%	0.266	14%
Duration of AF (months)	78 ± 131	58 ± 66	0.322	68 ± 104
Symptom frequency/month	4 ± 5.3	3.5 ± 0.92	0.352	4 ± 3.8
Warfarin treatment	76%	78%	0.855	77%
Aspirin treatment	28%	35%	0.942	34%

AF = atrial fibrillation; AVJAP = atrioventricular junction ablation and pacing; MED = medication.

Teicholz formula. The mean of 10 consecutive cardiac cycles was used for patients in AF and three cardiac cycles for patients in paced rhythm.

Quality-of-life assessment (Appendix). Patients completed health-related QoL questionnaires at baseline, six months, and 12 months. The following questionnaires were administered: the Assessment of Quality of Life Questionnaire (AQoL) (7), the CAST Quality of Life Questionnaire (8), and the Sickness Impact Profile (SIP) (9).

Statistical analysis. Independent statistical analysis was undertaken by the biostatistical consulting service of the University of Western Australia (demographic, cardiac function, and ventricular rate data) and the Centre for Health Program Evaluation (QoL data). Data were analyzed using the SAS software package. The intent-to-treat principle was used for all analyses. Continuous variables were compared using the *t* test and categorical variables were compared using Fisher's exact test. The QoL questionnaires were scored according to rules of the original authors. The QoL data were analyzed using the Mann-Whitney *U* test (2-sided) for nonparametric independent samples; because a large number of statistical tests were performed, only p values <0.01 were considered statistically significant. For all data other than the QoL data, a p value <0.05 was considered statistically significant. A parametric two-sample *t* test was used at each time point to compare the mean values for medication (MED) group versus AVJAP group. The hypothesis we were testing was that there was no difference in the mean values for the two groups at each time point.

RESULTS

Study population (Table 1). After randomization, 49 patients were allocated to the AVJAP group and 50 to the MED group. As outlined in Table 1, the two groups were well matched for age, gender ratio, structural heart disease, ischemic heart disease, hypertension, symptom frequency, and duration of AF.

Patient flow (Fig. 1). The majority of patient withdrawals were among the AVJAP group before the ablation procedure; the most common reason for withdrawal was the patients "felt too well." Two patients in the MED group had AVJAP three and six months following randomization. In both cases, the reason for crossover was "troublesome symptoms in addition to a mean resting heart rate >80 beats/min or >150 beats/min during maximum exercise."

Pharmacologic treatment. In the MED group the proportion of patients on single ventricular rate-control agents and combinations remained constant during the study. In contrast, 21 of 34 (62%) of the AVJAP group were not on any ventricular rate-controlling drugs or combinations following the ablation procedure. Hypertension and ischemic heart disease were the most common reasons for AVJAP patients to continue ventricular rate-controlling drugs.

Catheter ablation and pacemaker insertion. All patients in the AVJAP group had successful ablation of the AV junction at the initial procedure, with a median of two applications of radiofrequency energy at 30 to 50 W using the right heart approach. One patient developed a large groin hematoma immediately following the procedure and two patients developed pacemaker pocket hematomas; none had any long-term adverse sequelae.

Echocardiographic evaluation of LVEF (Table 2). No significant change in echocardiographically measured LVEF was observed in either group during the study.

Treadmill test. The total exercise time did not improve with ablation and pacing (Table 2). At one month post-randomization, the AVJAP group had a higher resting heart rates and lower maximum heart rates than the medical treatment group. At six months post-randomization, the AVJAP group had lower resting and maximum heart rates than the MED group, whereas at 12 months post-randomization, the AVJAP group had similar resting heart rates and lower maximum heart rates than the medical treatment group.

Holter monitor (Table 2). At one month post-randomization, the AVJAP group had a higher minimum and mean heart rates and lower maximum heart rates than the MED group. At six months post-randomization, the AVJAP group had a higher minimum and lower maximum heart rate, whereas at 12 months post-randomization, the

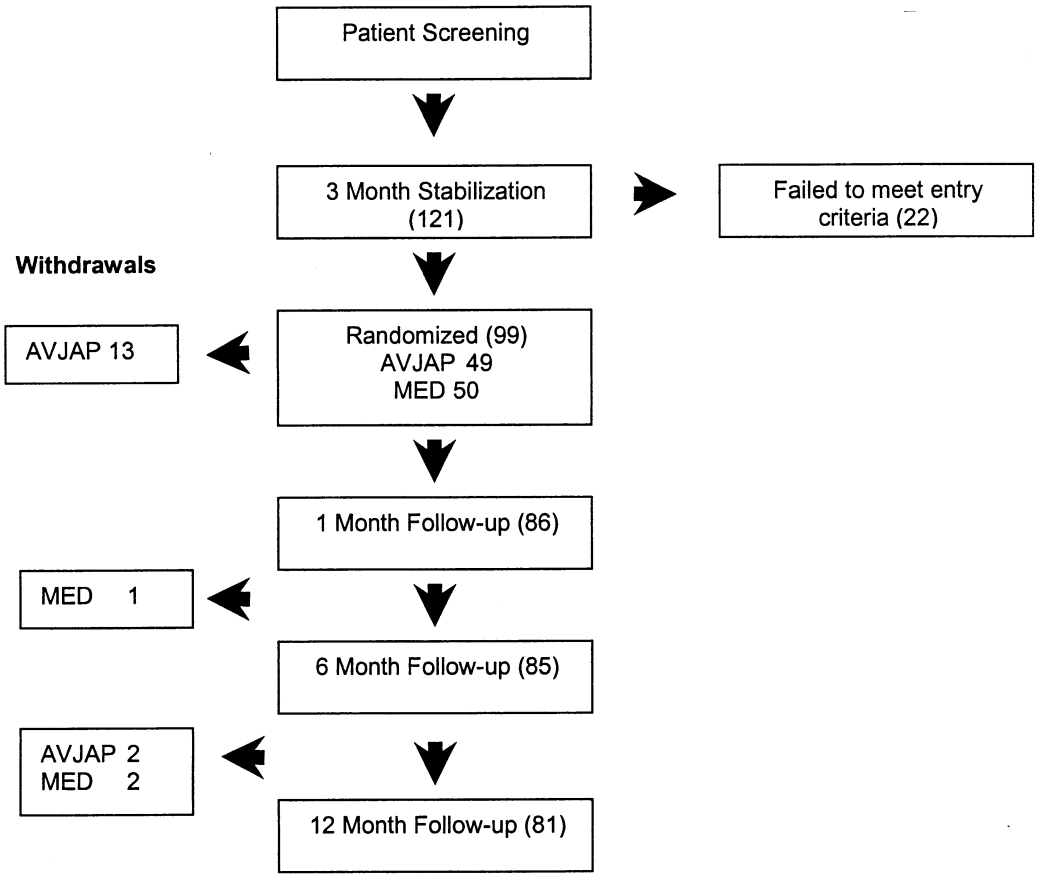

Figure 1. Patient flow. AVJAP = atrioventricular junction ablation and pacing; MED = medication.

AVJAP group had higher lower and mean heart rates and lower maximum heart rates than the MED group.

Quality of life (Table 2). Even though the results of the AQoL and SIP QoL questionnaires were not significantly different for the two treatment groups, analysis of the CAST QoL questionnaire data revealed that the AVJAP group had significant improvements in quality of life. The CAST QoL "symptom scale" ranges from 9 to 54, and the AVJAP group had a reduction of 8 units on this scale at six months whereas the medical treatment group had a reduction of 0.4 units (<1% change). The reduction in symptoms in the AVJAP group was maintained at 12 months, when there was a 6.6-point reduction compared to baseline. The observed relative risk reduction in symptoms at 12 months was 18% ($p = 0.004$). Global subjective semiquantitative assessment of QoL using the "ladder of life" revealed that

Table 2. Echocardiographic LVEF, Treadmill Test, and Holter Results

	Baseline		1 Month		6 Months		12 Months	
Number of Patients	MED 50	AVJAP 49	MED 50	AVJAP 36	MED 49	AVJAP 36	MED 47	AVJAP 34
Echocardiogram								
LV ejection fraction (%)	57 ± 14	55 ± 16	—	—	56 ± 19	54 ± 14	61 ± 13	54 ± 17
Treadmill test								
Exercise time (min)	4.3 ± 3	4.2 ± 2.1	4.3 ± 2.3	4.4 ± 1.9	4.3 ± 2	5.2 ± 4	4.6 ± 2	4.1 ± 2
Exercise rest HR (beats/min)	79 ± 23	82 ± 25	81 ± 16	87 ± 8*	82 ± 17	74 ± 8*	77 ± 19	75 ± 8
Exercise maximum HR (beats/min)	151 ± 45	158 ± 33	154 ± 31	115 ± 14*	159 ± 32	112 ± 19*	153 ± 36	112 ± 17*
Holter								
Minimum HR (beats/min)	41 ± 12	41 ± 17	44 ± 14	80 ± 12*	42 ± 12	70 ± 7*	39 ± 9	70 ± 9*
Mean HR (beats/min)	77 ± 13	79 ± 20	76 ± 12	87 ± 9*	76 ± 17	77 ± 6	71 ± 11	76 ± 7*
Maximum HR (beats/min)	154 ± 37	152 ± 41	147 ± 44	117 ± 14*	150 ± 39	116 ± 19*	152 ± 37	117 ± 16*
QoL								
AQoL utility score	0.64 ± 0.24	0.71 ± 0.22			0.64 ± 0.16	0.71 ± 0.22	0.66 ± 0.18	0.75 ± 0.18
SIP total score	7.13 ± 5.81	7.43 ± 8.91			7.46 ± 5.12	9.98 ± 5.38	6.76 ± 4.63	8.89 ± 8.32

*$p < 0.05$. Values are mean ± SD

AQoL = Assessment of Quality of Life Questionnaire; HR = heart rate; LV = left ventricular; LVEF = left ventricular ejection fraction; SIP = Sickness Impact Profile. Other abbreviations as in Table 1.

Table 3. Adverse Events

	MED	AVJAP	p
Death	1	2	0.617
Acute MI	1	2	0.617
Unstable angina	1	4	0.204
Hematoma	0	3	0.117
Pulmonary embolism	0	1	0.495
Drug reaction	3	0	0.242
Total	6	12	0.125

MI = myocardial infarction. Other abbreviations as in Table 1.

the AVJAP group reported a 6% better QoL at six months and 12 months than the MED group ($p = 0.01$).

Patients with baseline LVEF <45%. Nine patients in the MED group and 10 patients in the AVJAP group had an LVEF ≤45% at baseline. Predefined subgroup analysis revealed no differences in LVEF, exercise tolerance, or heart rates on treadmill testing or Holter monitoring for LVEF ≤45% patients.

Adverse events. Adverse events seen during the study are outlined in Table 3. Comparing the two treatment groups, there was no significant difference in the occurrence of any adverse event. Two patients in the AVJAP group died during the study. Both deaths were sudden out-of-hospital events and occurred six months postablation in patients with low LVEF. One patient in the MED group had a sudden out-of-hospital event one month post-randomization.

DISCUSSION

Our study addresses the question posed by Wood et al. (10): "what is the role of ablation and pacing therapy in the wider population of patients with less symptomatic AF?" The main findings of AIRCRAFT were that, in this patient population, AVJAP had a neutral effect on cardiac function measured by echocardiography or treadmill testing and QoL was improved.

It is well established that, for patients with highly symptomatic medically refractory permanent AF, AVJAP provides superior symptom relief compared with pharmacologic management (2–6,10). Early nonrandomized studies suggested that AVJAP also improves cardiac function (2–4), and the reasons suggested for this improvement were reversal of tachycardia-related cardiomyopathy (11,12) as well as the favorable hemodynamic effects of a regular ventricular rhythm (13). Two prospective randomized trials (5,6) reported results while the present study was underway. Brignole et al. (5) showed a neutral effect on LVEF following AVJAP in highly symptomatic permanent AF patients with congestive heart failure, whereas Ueng et al. (6) showed a modest improvement in the LVEF of patients with a mean baseline LVEF of 44% and previously well-controlled ventricular rates.

The AIRCRAFT patient population is unique because it includes patients with mild to moderate symptoms. The exclusion and inclusion criteria were chosen to determine if there is a benefit of AVJAP in the wider population of patients with permanent AF because AVJAP has not previously been compared to pharmacologic ventricular rate control in a controlled prospective manner in this population. Subgroup analysis of patients with baseline LVEF ≤45 was prespecified in the study protocol because earlier studies suggested that patients with impaired LVEF were most likely to have improvement of LVEF following AVJAP (2–4).

Analysis of the prespecified subgroup of patients with LVEF ≤45% failed to show any benefit of AVJAP on echocardiographically measured LVEF. There were, however, very few patients in this subgroup, so these results must be interpreted with caution. These findings contrast with those of Twidale et al. (2), Edner et al. (3), and the "Ablate and Pace" trial (4). In an uncontrolled study Twidale et al. studied 14 patients with a mean LVEF of 42 ± 3% and found that this improved to 49 ± 4% ($p < 0.02$) following AVJAP during a mean of nine months follow-up (2). The study of Edner et al. lacked a control treatment arm, and only post-hoc analysis of those patients with baseline LVEF <50% showed a significant improvement in LVEF (from 32 ± 11% to 45 ± 11%, $p < 0.001$) a mean of 216 days following AVJAP (3). The larger "Ablate and Pace" trial, which was also nonrandomized, similarly showed an improvement in LVEF by post-hoc analysis of the patients, with a baseline LVEF < 45% (from 30 ± 9% to 45 ± 11%, $p < 0.01$) during one-year follow-up (4). The patient populations in these studies were different in terms of symptoms and ventricular rate control to the present AIRCRAFT study. The prospective randomized study of Ueng et al. (6) was smaller than AIRCRAFT and showed an improvement in acute hemodynamic variables as well as LVEF. A possible reason for the difference in results between our study and that of Ueng et al. (6) is the difference in baseline LVEF of the two patient populations.

There has been recent interest in the importance of synchrony of cardiac contraction in patients with impaired LVEF. Patients who undergo AVJAP (with a right ventricular apical pacing lead position) have iatrogenic cardiac dyssynchrony that may counteract the beneficial effects of rate and rhythm regulation. In patients with impaired LVEF and permanent AF a biventricular pacing system may be superior; this has not been studied in a controlled prospective manner (14,15), however.

The mean ventricular rate measured by ambulatory electrocardiography was higher in the AVJAP group at one month because the minimum ventricular pacing rate was set at 80 to 90 beats/min for one month following ablation. This has been reported to reduce the risk of sudden cardiac death (16). The ventricular rate during times of physical activity was significantly better controlled in the AVJAP group because, following ablation, the peak ventricular rate and rate response function are programmable. Excessive control of ventricular rate during exertion may result in chronotropic incompetence, but this was not seen in the

AIRCRAFT trial, as evidenced by the fact that the exercise duration by treadmill testing at six and 12 months follow-up was not significantly different from the MED group.

The improvement in QoL was only apparent from analysis of the CAST quality-of-life questionnaire data. This questionnaire was chosen for the study because it was designed for patients with arrhythmias. The AQoL and SIP questionnaires are not disease specific and provide a global impression of health-related QoL. It is apparent from our study that the improvement in QoL following AVJAP is due to symptom control, which was sensitively measured by the CAST QoL questionnaire but not by the AQoL or SIP questionnaires. It is unlikely that the improvement in QoL was due to a placebo effect of having an invasive procedure, as the results were durable during 12 months follow-up.

There was no significant difference in the mortality rate in the two groups, although the study was not sufficiently powered to examine this as an end point. There have been concerns about sudden death following AVJAP (16,17), possibly due to bradycardia-dependent QT prolongation leading to ventricular fibrillation (16,17), but recent publications have reported that AVJAP is not associated with increased risk of sudden cardiac death (18,19).

In summary, AVJAP is a safe and effective means of controlling ventricular rate in permanent AF. In the wider population of patients with permanent AF, having mild to moderate symptoms, our study supports the use of this treatment strategy when symptom control and improved QoL are the primary goals. This strategy does not cause deterioration of cardiac function.

Conclusions. In this trial, AVJAP for patients with mild to moderately symptomatic permanent AF did not worsen cardiac function during long-term follow-up and QoL was improved.

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APPENDIX

QUALITY OF LIFE QUESTIONNAIRES USED IN AIRCRAFT

1. The Assessment of Quality of Life Questionnaire (AQoL) (7). This questionnaire was designed using a sample from the population of the state of Victoria (Australia) as well as a sample from inpatients of a major public teaching hospital in Melbourne (7). The AQol has been validated by comparison with other established QoL questionnaires. AQoL consists of 12 questions and can be completed within 10 min. The AQoL provides an overall score for health-related quality of life, with a score of 1.0 representing the best possible quality of life and a score of 0 representing the worst possible quality of life.

2. The CAST QoL questionnaire (8). This questionnaire was developed for use in the cardiac arrhythmia suppression trial (CAST). The questionnaire comprises 21 questions obtained from established scales and has been shown to be sensitive for measuring quality of life in cardiac patients. It is relevant to the results of the AIRCRAFT study in that this is the only questionnaire used that measures typical arrhythmia symptoms (dizziness, irregular heartbeats, chest pain, shortness of breath). The presence or absence and frequency of specific symptoms are scored to give a "symptom scale" with a higher number representing greater symptoms and, therefore, worse QoL. The CAST questionnaire also has a "Ladder of Life" question, which is a subjective, semiquantitative assessment by the patient of his/her overall life satisfaction, with a score of 10 representing the best possible life and a score of 1 representing the worst possible life. An example of the questionnaire is provided in the appendix accompanying reference 8.

3. The Sickness Impact Profile (SIP) (9). The SIP is a relatively complex and cumbersome QoL measurement tool requiring 20 to 30 min to complete. As for the AQoL, this questionnaire is not disease specific. The SIP total score is a measure of overall health-related quality of life, with a higher score representing better quality of life. The validation of the SIP is discussed in detail in reference 9.