Catheter Ablation vs Antiarrhythmic Drug Therapy in Patients with Symptomatic Atrioventricular Nodal Reentrant Tachycardia: A Randomised, Controlled Trial

Demosthenes G. Katritsis, MD, PhD,[1,2] Theodoros Zografos, MD,[2] George D. Katritsis, MBChB, BSc,[3] Eleftherios Giazitzoglou, MD,[2] Vasilios Vachliotis, MD,[2] George Paxinos, MD,[2] A. John Camm, MD,[4] Mark E. Josephson, MD[1]

[1]*Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA*
[2] *Athens Euroclinic, Athens, Greece*
[3]*The Oxford University Clinical Academic Graduate School, Oxford, UK*
[4]*St George's University of London, London, UK*

Corresponding author: Dr D Katritsis, Division of Cardiology, Beth Israel Deaconess Medical Center, 185 Pilgrim Rd, Baker 4, Boston, MA 02215. E-mail address: dkatrits@bidmc.harvard.edu or dkatritsis@euroclinic.gr

Abstract

Aims To conduct a randomized trial in order to guide the optimum therapy of symptomatic atrioventricular nodal reentrant tachycardia (AVNRT).

Methods Patients with at least one symptomatic episode of tachycardia per month, and an electrophysiologic diagnosis of AVNRT, were randomly assigned to catheter ablation or chronic antiarrhythmic drug (AAD) therapy with bisoprolol (5 mg od) and/or diltiazem (120-300 mg od). All patients were properly educated to treat subsequent tachycardia episodes with autonomic maneuvers or a "pill in the pocket" approach. The primary end-point of the study was hospital admission for persistent tachycardia cardioversion, during a follow-up period of 5 years.

Results Sixty one patients were included in the study. In the ablation group, one patient was lost to follow-up, and 29 were free of arrhythmia or conduction disturbances at a 5-year follow-up. In the AAD group, 3 patients were lost to follow-up. Of the remainder, 10 patients (35.7%) continued with initial therapy, 11 patients (39.2%) remained on diltiazem alone, and 7 patients (25%) interrupted their therapy within the first 3 months following randomization, and subsequently developed an episode requiring cardioversion. During a follow-up of 5 years, 21 patients in the AAD group required hospital admission for cardioversion. Survival free from the study end-point was significantly higher in the ablation group compared to the AAD group (log-rank test, $P<0.001$).

Conclusions Catheter ablation is the therapy of choice for symptomatic AVNRT. AAD therapy is ineffective and not well tolerated.

Key Words: atrioventricular; nodal; ablation; tachycardia; antiarrhythmic drugs

Condensed abstract

Sixty-one patients with AVNRT, were randomly assigned to catheter ablation or chronic antiarrhythmic drug (AAD) therapy with bisoprolol (5 mg od) and/or diltiazem (120-300 mg od). During a follow-up of 5 years, survival free from hospital admission for persistent tachycardia cardioversion was significantly higher in the ablation group compared to the AAD group (log-rank test, $P<0.001$).

What's new?

- Catheter ablation is the treatment of choice for symptomatic patients with AVNRT, by substantially improving quality of life, and reducing costs.
- However, its potential superiority over antiarrhythmic drug administration or even watchful follow-up, has not been tested in a randomised trial.
- We present the first randomised, controlled study that proves the superiority of ablation to drug therapy in AVNRT.

Introduction

Although atrioventricular nodal re-entrant tachycardia (AVNRT) is the most common regular arrhythmia encountered in clinical practice, no randomised data exist to guide evidence-based therapy. Chronic administration of antiarrhythmic drugs decreases the frequency and the duration of AVNRT, but has a variable success in abolishing tachycardia episodes, ranging from 13 to 82%, and up to 20% of patients may discontinue therapy.[1-10] Furthermore, particular antiarrhythmic medication may result in rare, but life-threatening proarrhythmic effects.[7-10] There has been evidence that catheter ablation is the treatment of choice for symptomatic patients, by substantially improving quality of life,[11-13] and reducing costs.[14,15] However, its potential superiority over antiarrhythmic drug administration or even watchful follow-up,[16] has not been tested in a randomised trial.

We have, therefore, conducted a randomised, controlled trial, to compare catheter ablation therapy to chronic antiarrhythmic drug administration in patients with frequent (>1/month), symptomatic episodes of AVNRT. To the best of our knowledge this is the first randomised, controlled study of its kind to be published.

Methods

Patients

Adult patients, aged 18 to 65 years, with at least one symptomatic episode of tachycardia per month, at least one occasion of admission for cardioversion, and an electrophysiologic diagnosis of AVNRT at Athens Euroclinic, were recruited. AVNRT was diagnosed by fulfillment of established criteria during detailed atrial and ventricular pacing maneuvers. Exclusion criteria were concomitant structural heart disease, any degree of atrioventricular or intraventricular block on the 12-lead ECG, contraindications to beta blockers, pregnancy, or other comorbidity. The study received approval by our

institutional review board, and all patients provided a written, informed consent that had been fully explained prior to the electrophysiology procedure.

Randomization

Patients with a 12-lead ECG during tachycardia resembling AVNRT were invited to participate. If they consented and the diagnosis was confirmed, they were subjected to the randomization procedure. Immediately following electrophysiology study, consenting patients were randomly assigned to slow pathway catheter ablation by the same experienced operator (DGK), or to antiarrhythmic drug therapy. Patients who had provided an informed consent were allocated to treatment groups according to a computer-generated randomization procedure. The allocations were kept in sealed, opaque envelopes and treatment allocation was released to the study coordinator. In case of arrhythmia, patients were instructed to perform autonomic maneuvers (standing Valsalva, carotid sinus massage, or the diving reflex), and if this was not successful, and the patient had either abandoned drug medication or had been allocated to ablation, to take a single oral dose of diltiazem 120 mg and propranolol 80 mg.[4,17] If the tachycardia persisted for more than 60 min after maneuvers or the "pill in the pocket" approach, patients had to seek medical attention for cardioversion, and the end-point of the trial was reached. Cardioversion was accomplished with intravenous adenosine (bolus of 6 or 12 mg) as the treatment of choice, but IV verapamil (0.075-1.5 mg/kg) or diltiazem (0.15-0.45 mg/kg), were also allowed in the absence of hypotension, at the discretion of the attending physician.

Antiarrhythmic drug therapy

Antiarrhythmic therapy consisted of a low dose of oral bisoprolol (5 mg once daily) and slow-release diltiazem (120-300 mg once daily) was started in all patients. If this resulted in AV nodal conduction disturbances, hypotension, or other complications, the patient was given the option to abandon therapy or to remain on the lower dose of diltiazem alone.

Catheter ablation

Anatomical slow pathway ablation was performed according to standard techniques.[29,30] Initially a right-sided slow pathway ablation was attempted, with care to keep the ablating catheter below the ostium of the coronary sinus as visualized in the RAO projection; ablation was not performed at the mid or anterior septum. End-points for ablation termination were demonstration of energy-induced junctional rhythm conducted to the atria, and non-inducibility of tachycardia with isoprenaline challenge. If RF-induction of junctional rhythm or non-inducibility of tachycardia could not be accomplished from the right side of the septum, left-sided slow pathway ablation through a trans-septal puncture was undertaken, as described elsewhere.[18] Following successful ablation, patients were discharged from hospital within 24 hours on aspirin for one month, and no antiarrhythmic drugs.

Study end-points

The primary end-point of the study was admission to the hospital for tachycardia cardioversion following failure of the autonomic maneuvers or the pill in the pocket approach, where appropriate. All patients were followed-up for up to 5 years, unless if a study end-point occurred. Follow-up visits were scheduled at a 6-monthly basis. For patients referred from elsewhere, the referring physician was contacted.

Statistical analysis

Sample size was estimated assuming an efficacy rate of 60% for medical therapy and 95% for catheter ablation, according to previously published studies.[1-10,13] The required sample size to achieve 80% power when a=0.05 was 27 patients for each group. Continuous variables are presented as mean ± SD, and categorical variables are summarized as absolute and relative (%) frequencies. Freedom from the study end-point was determined using Kaplan-Meier analysis, and differences in free from the end-point survival were evaluated using the log rank test. All reported *P* values are based on two-sided tests and *P* <.05 was considered significant for all statistical determinations. All statistical calculations were performed using IBM SPSS Statistics version 22.0 (IBM Corp., Armonk, New York, USA). Power analysis was performed using MedCalc for Windows, version 14.8 (MedCalc Software, Ostend, Belgium).

Results

Patients

Out of 407 patients who were referred for electrophysiology testing, and were diagnosed with AVNRT at Athens Euroclinic during the period 2000-2009, 61 patients were recruited to the trial. The mean age of all patients was 39.6±7.5 years (range 24 to51), and 45 patients (74%) were female (Table 1).

Catheter ablation

All patients were subjected to conventional, right-sided ablation as described. In one patient a left-sided approach was successfully accomplished. No AV block was encountered, and no patient experienced AVNRT recurrence during the next 5 years following ablation (Figure 1). One patient was lost to follow-up.

Antiarrhythmic Drug Therapy

Three patients were lost to follow-up. Of the remainder, 10 patients (35.7%) continued with initial therapy until admission for cardioversion or completion of follow-up, 11 patients (39.2%) remained on diltiazem alone, and 7 patients (25%) interrupted their therapy within the first 3 months following randomization. They refused further drug therapy and, following admission for AVNRT, proceeded to ablation. At completion of follow-up, these patients remained free of sustained arrhythmia requiring cardioversion. Five of them had experienced tachycardia episodes that were either short-lived (<30 min) or interrupted by Valsalva maneuvers. One patient, female 48 years old, was admitted with AVNRT and hypotension that required fluid resuscitation following a single dose of diltiazem and propranolol. Within the next 1.7±1.8 years, 21 patients in the AAD group required hospital admission for cardioversion (Figure 1). Seven patients of the AAD group, 5 on bisoprolol and diltiazem, and 2 on diltiazem alone, remained free of arrhythmia. Survival free from the primary end-point was significantly higher in the catheter ablation group, compared to the antiarrhythmic drug therapy group (log-rank test, P<0.001)(Figure 2).

Discussion

Our data indicate that catheter ablation is the treatment of choice for patients with symptomatic AVNRT. Drug therapy, at least as administered in our study, is ineffective, and several of these, otherwise healthy, patients refuse to continue it.

Chronic administration of antiarrhythmic drugs for AVNRT has been tried in several previous trials. Verapamil has been mainly studied,[1,2] but diltiazem has similar effects on the AV node.[3] Beta blockers and digoxin are also probably of value but data are limited.[2] Long-term therapy with a combination of diltiazem and propranolol has been successfully tried.[4] Flecainide and propafenone are effective,[5] probably more than

verapamil,[6] but they are potentially proarrhythmic, and cases of ventricular tachycardia during prophylactic therapy of SVT have been reported both by the Propafenone PSVT and the FAPIS groups.[7,8] Sotalol,[9] and dofetilide[10] have been found effective but potential proarrhythmia due to QT prolongation makes these agents less attractive for long-term therapy. The long-term use of amiodarone in this setting is prohibited by its complications. We chose bisoprolol and diltiazem based on their safety and tolerability profile, but still 68% of our patients could not tolerate both of them. In accordance with previous studies, 25% of our patients refused to follow any long-term drug therapy after having experienced the initial months of treatment.

Catheter ablation for AVNRT has been reported to offer a success rate of 95% with no procedure-related mortality, is associated with a risk of 0.5-1% AV block, and has an approximately 4% recurrence rate.[13,19] With growing experience, these results can certainly improve. At Athens Euroclinic as well as Beth Israel Deaconess Medical Center, recurrence rate is less than 1.5%, and AV block is entirely preventable. This can be accomplished by avoiding an anterior approach and targeting only the anatomical area of the slow pathway either from the left or right septal side, avoiding the coronary sinus ostium, and terminating the energy delivery with the onset of a junctional rhythm, especially when not conducted to the atria.[20] One of our cases required a left-sided access that was accomplished following trans-septal access. Although a left-sided approach may also be performed via a retrograde, trans-aortic access, the trans-septal approach allows better exploration of the posterior septum.

Study limitations

The main limitation of our study is the small number of our patients. However, recruiting patients who were about to undergo an electrophysiology study and had the option of ad

hoc ablation was not an easy task, and this is also reflected in the long recruitment period. Other centers that had been invited to participate in order to increase our numbers had also expressed these reservations. Thus, recruited population does not necessarily represents the average patient with AVNRT. Second, our results of catheter ablation are derived from an experienced operator with a special interest in this arrhythmia and large experience on trans-septal puncture, and may not be valid for smaller volume centers. Finally, the combination of two safe but bradycardic drugs may have been responsible for the relatively high drop-out rate in the AAD group.

Conclusion

Patients with frequent, symptomatic episodes of AVNRT should be offered the option of catheter ablation. Chronic antiarrhythmic therapy, at least when restricted to drugs of known safety, is ineffective and not tolerated by a substantial number of patients.

Figure 1. Randomisation and follow-up results.

Figure 2. Arrhythmia-free survival during follow-up.

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Figure 1

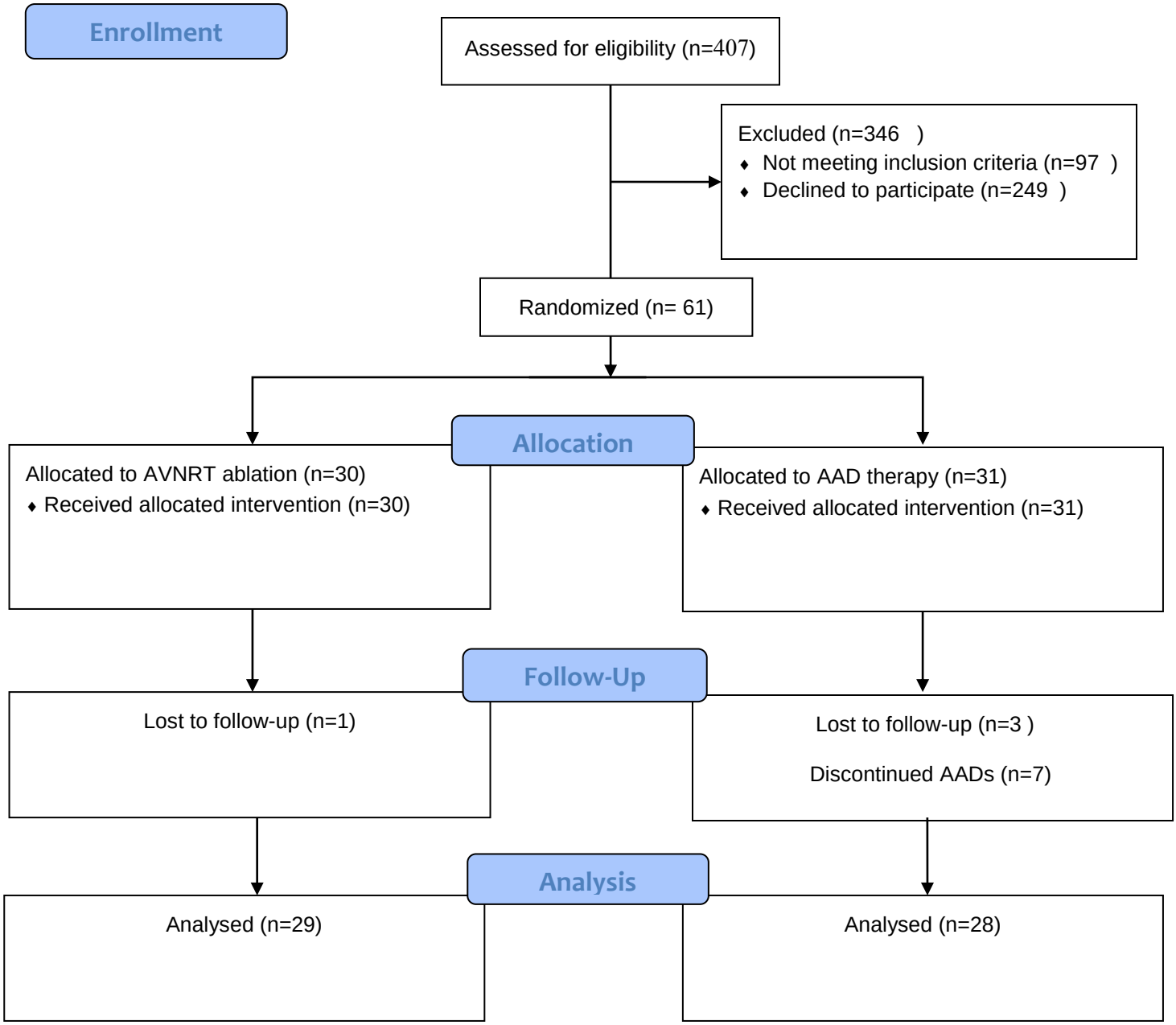
Enrollment
Assessed for eligibility (n=407)
Excluded (n=346)
♦ Not meeting inclusion criteria (n=97)
♦ Declined to participate (n=249)
Randomized (n= 61)
Allocation
Allocated to AVNRT ablation (n=30)
♦ Received allocated intervention (n=30)
Allocated to AAD therapy (n=31)
♦ Received allocated intervention (n=31)
Follow-Up
Lost to follow-up (n=1)
Lost to follow-up (n=3)
Discontinued AADs (n=7)
Analysis
Analysed (n=29)
Analysed (n=28)

Figure 2

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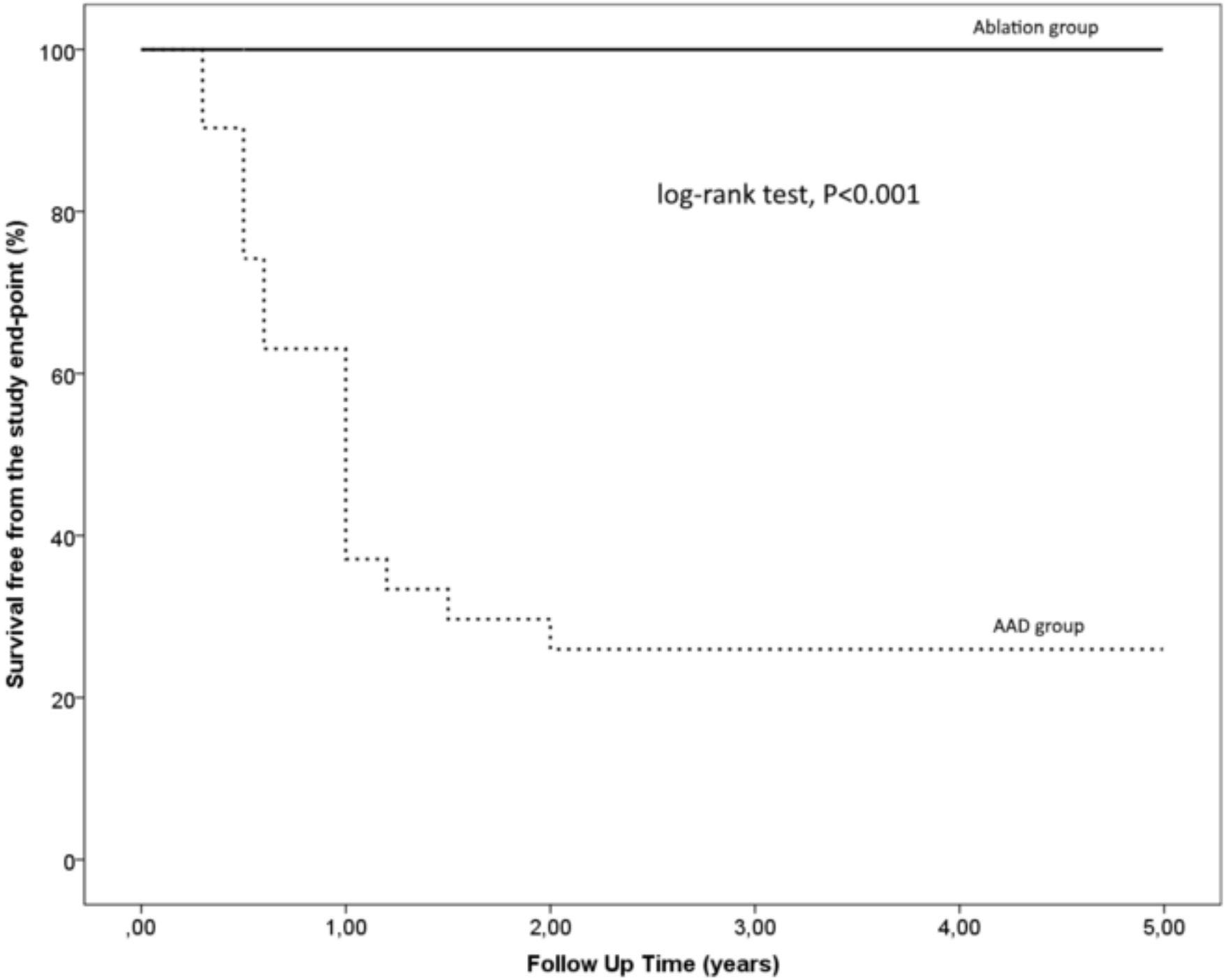

Table 1. Patient characteristics and clinical outcome

	Catheter ablation n =30	**Medical therapy n=31**	**P-value**
Age (years)	41.3±6.9	38.1±7.9	0.098
Female gender (%)	23 (77%)	22 (71%)	0.772
Tachycardia Cycle Length (ms)	330.3±44.9	321.0±32.0	0.355
Episodes per month	2.3±1.4	2.1±1.1	0.636