

ORIGINAL ARTICLE

Pulmonary-Vein Isolation for Atrial Fibrillation in Patients with Heart Failure

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ABSTRACT

BACKGROUND

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*PABA-CHF denotes the Pulmonary Vein Antrum Isolation versus AV Node Ablation with Bi-Ventricular Pacing for Treatment of Atrial Fibrillation in Patients with Congestive Heart Failure study.

N Engl J Med 2008;359:1778-85.
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Pulmonary-vein isolation is increasingly being used to treat atrial fibrillation in patients with heart failure.

METHODS

In this prospective, multicenter clinical trial, we randomly assigned patients with symptomatic, drug-resistant atrial fibrillation, an ejection fraction of 40% or less, and New York Heart Association class II or III heart failure to undergo either pulmonary-vein isolation or atrioventricular-node ablation with biventricular pacing. All patients completed the Minnesota Living with Heart Failure questionnaire (scores range from 0 to 105, with a higher score indicating a worse quality of life) and underwent echocardiography and a 6-minute walk test (the composite primary end point). Over a 6-month period, patients were monitored for both symptomatic and asymptomatic episodes of atrial fibrillation.

RESULTS

In all, 41 patients underwent pulmonary-vein isolation, and 40 underwent atrioventricular-node ablation with biventricular pacing; none were lost to follow-up at 6 months. The composite primary end point favored the group that underwent pulmonary-vein isolation, with an improved questionnaire score at 6 months (60, vs. 82 in the group that underwent atrioventricular-node ablation with biventricular pacing; $P < 0.001$), a longer 6-minute-walk distance (340 m vs. 297 m, $P < 0.001$), and a higher ejection fraction (35% vs. 28%, $P < 0.001$). In the group that underwent pulmonary-vein isolation, 88% of patients receiving antiarrhythmic drugs and 71% of those not receiving such drugs were free of atrial fibrillation at 6 months. In the group that underwent pulmonary-vein isolation, pulmonary-vein stenosis developed in two patients, pericardial effusion in one, and pulmonary edema in another; in the group that underwent atrioventricular-node ablation with biventricular pacing, lead dislodgment was found in one patient and pneumothorax in another.

CONCLUSIONS

Pulmonary-vein isolation was superior to atrioventricular-node ablation with biventricular pacing in patients with heart failure who had drug-refractory atrial fibrillation. (ClinicalTrials.gov number, NCT00599976.)

TRIALS OF ABLATION FOR ATRIAL FIBRILLATION have shown the procedure to be efficacious in reducing morbidity, improving the quality of life and functional capacity, and, in a retrospective analysis comparing ablation and antiarrhythmic medications, reducing mortality.¹⁻⁷ Increasingly, patients with heart failure have atrial fibrillation as well, and studies have shown that the efficacy rates for ablation are similar in this population with a low ejection fraction and among patients with heart failure alone.⁸⁻¹⁰ Atrioventricular-node ablation has been used to treat symptomatic atrial fibrillation with poor rate control, although few patients in these studies had a low ejection fraction.¹¹ Recently, biventricular pacing was found to be superior to right ventricular pacing after atrioventricular-node ablation.¹² Thus, the Pulmonary Vein Antrum Isolation versus AV Node Ablation with Bi-Ventricular Pacing for Treatment of Atrial Fibrillation in Patients with Congestive Heart Failure (PABA-CHF) study was undertaken to compare pulmonary-vein isolation with atrioventricular-node ablation and biventricular pacing with an implantable cardioverter-defibrillator (ICD) (atrioventricular-node ablation with biventricular pacing) in patients with a low ejection fraction and symptomatic atrial fibrillation.

METHODS

The PABA-CHF study was a multicenter, randomized, controlled trial comparing pulmonary-vein isolation with atrioventricular-node biventricular pacing. We studied patients with symptomatic atrial fibrillation and symptoms of New York Heart Association (NYHA) class II or III heart failure, despite the use of antiarrhythmic medications. Patients were included if they had an ejection fraction of 40% or less; had a medication regimen of beta-blockers and angiotensin-converting-enzyme inhibitors and, in patients with NYHA class III heart failure, spironolactone; were able to complete a 6-minute walk test; and were 18 years of age or older. The institutional review board at each participating center reviewed and approved the study.

Exclusion criteria were reversible causes of atrial fibrillation and heart failure; postoperative atrial fibrillation; previous maze or maze-like surgery; previous left atrial ablation; a life expectancy of 2 years or less; a high probability of undergoing cardiac transplantation within the next 12 months; a contraindication to antiarrhythmic or anticoagu-

lation medications; severe pulmonary disease; a documented intraatrial thrombus, tumor, or other abnormality that precludes catheter placement; or cardiac surgery, myocardial infarction, or percutaneous coronary intervention within the previous 3 months.

Randomization was computer-generated. After providing written informed consent, patients were randomly assigned to undergo either pulmonary-vein isolation or atrioventricular-node ablation with biventricular pacing, with follow-up at 3 and 6 months that consisted of a clinical assessment, 6-minute walk test, echocardiographic study, and completion of the Minnesota Living with Heart Failure (MLWHF) questionnaire. The questionnaire consists of 21 questions regarding patients' perception of the effects of heart failure on their daily lives; the score for each question ranges from 0 to 5, producing a total score of 0 to 105, with a higher score indicating a worse quality of life.

Crossover of patients from the assigned group to the other treatment group was discouraged during the study period, although patients assigned to the group undergoing pulmonary-vein isolation were permitted to undergo implantation of an ICD for primary or secondary prophylaxis against sudden death from cardiac causes. In addition, after the study period, patients were allowed to cross over to the other treatment.

The primary end point was a composite of ejection fraction, distance on the 6-minute walk test, and MLWHF score. The primary end point of the trial was reached if all three end points had a P value of less than 0.05 for the comparison between baseline, if two end points had a P value of less than 0.025, or if one end point had a P value of less than 0.017 (similar to the composite end point used in the Multicenter InSync Randomized Clinical Evaluation [MIRACLE] and the Multicenter InSync ICD Randomized Clinical Evaluation [MIRACLE ICD] trials).¹³⁻¹⁵ Both patients and physicians were made aware of the treatment assignments; however, collection of results of the 6-minute walk test, echocardiographic measurements, and MLWHF scores was performed without knowledge of the treatment assignments.

Follow-up was performed with the use of a loop event monitor that patients wore at months 2 through 6 after the procedure. Patients were instructed to record any symptoms and to record at least two or three transmissions weekly even if they were asymptomatic. Episodes were recorded if the duration was longer than 30 seconds. All

but one patient in the group that underwent pulmonary-vein isolation sent transmissions through month 6. One patient stopped sending transmissions 4 months after randomization, but he did follow up at month 6. All transmissions up to month 4 revealed sinus rhythm. Four patients in the group that underwent atrioventricular-node ablation with biventricular pacing stopped sending transmissions after it was clear that they had persistent atrial fibrillation; device interrogation at 6 months confirmed the persistence of atrial fibrillation.

PULMONARY-VEIN ISOLATION

Details of the pulmonary-vein-isolation procedure have been described previously.^{3,4,7} The ablation and circular-mapping catheters were advanced to the left atrium through sheaths from the right femoral vein after double transseptal puncture was performed with guidance from intracardiac echocardiography. Intravenous heparin was given with a target activated clotting time of 350 to 400 seconds.

The goal of the procedure was isolation of all pulmonary-vein antra with the aid of the circular-mapping catheter and the use of an ablation catheter with a tip 8 mm in length. Additionally, intracardiac echocardiography or venography was used to locate the pulmonary veins. Isolation was complete when no further pulmonary-vein potentials were recorded in the pulmonary-vein antra or no dissociated firing was seen. Ablation of additional linear lesions and the sources of complex fractionated electrograms was performed according to the preference of the center.

Warfarin was started after completion of the pulmonary-vein isolation and was continued for 3 months with target international normalized ratio of 2 or 3. Antiarrhythmic medications were discontinued after 2 months. The antiarrhythmic medications could be restarted at the discretion of the treating physician after 2 months. All re-initiations of antiarrhythmic medications were noted. After 3 and 6 months, warfarin was continued at the discretion of the treating physician. All patients were monitored for pulmonary-vein stenosis at 3 months and, if a second procedure was performed, at 6 months. A second pulmonary-vein isolation procedure or a procedure for atrial flutter could be performed at 3 months if atrial fibrillation or atrial flutter recurred. If patients underwent a second ablation, they were followed

for a total of 6 months after the last ablation, and the 6-month analysis was done using these follow-up data. All patients underwent computed tomography at baseline and at 3 months after ablation to assess for pulmonary-vein stenosis.

ATRIOVENTRICULAR-NODE ABLATION WITH BIVENTRICULAR PACING

Patients assigned to atrioventricular-node ablation with biventricular pacing underwent atrioventricular-node ablation and placement of a biventricular ICD. Ablation of the bundle of His was targeted with an ablation catheter to achieve complete atrioventricular block. Subsequently, a biventricular ICD system with an atrial lead was implanted. With the aid of venography, placement of the coronary sinus lead in a posterolateral or lateral branch was preferred if permitted by the coronary venous anatomy. Defibrillation-threshold testing was done to ensure a safety margin of at least 10 J. The type and settings of the device and the atrioventricular and venoventricular timing were chosen by the physician.

STATISTICAL ANALYSIS

The primary end point was a composite of the ejection fraction, distance on the 6-minute walk test, and MLWHF score at 6 months. For this composite end point, the difference between the study groups was considered to be significant if all three components had P values of less than 0.05, if two components had P values of less than 0.025, or if one component had a P value of less than 0.017. The secondary end points were freedom from atrial fibrillation and left atrial internal diameter at 6 months; for each of these end points, the difference between the groups was considered to be significant if the associated P value was less than 0.05. We estimated that 40 patients per group would be needed to detect differences of 35 m in the distance on the 6-minute walk test, 6% in the ejection fraction, and 15 points in the MLWHF score (for a statistical power of 80% with a two-sided alpha of 0.017). All end points were examined by means of an intention-to-treat analysis. All reported P values are two-sided. All categorical variables were compared with Fisher's exact test. Continuous variables were expressed as means (\pm SD) and were compared with the use of the Wilcoxon rank-sum and signed-rank tests.

For recurrence of atrial fibrillation, data for the first 2 months in each group were censored, since

early recurrence after pulmonary-vein isolation does not correlate with recurrence during a longer follow-up period and may reflect inflammation due to the procedure. All other recordings were used to classify the patient's rhythm status. Any recording of atrial fibrillation for more than 30 seconds was considered to be recurrent atrial fibrillation. If a second pulmonary-vein-isolation procedure was performed, data were censored for an additional month after the procedure.

RESULTS

CHARACTERISTICS OF THE PATIENTS

Between November 2002 and June 2006, a total of 177 patients were screened, of whom 81 were eligible for and consented to participate in the study. In all, 41 patients were randomly assigned to undergo pulmonary-vein isolation and 40 to undergo atrioventricular-node ablation with biventricular pacing (Fig. 1). No patients were lost to follow-up. The baseline characteristics of the study population are shown in Table 1. The distances on the 6-minute walk, ejection fractions, and MLWHF scores were similar to those in previous trials in-

volving patients with heart failure.^{13,15} At baseline, in the pulmonary-vein isolation group, 33 patients were receiving amiodarone, and 8 were receiving class III antiarrhythmic medications. In the group that underwent atrioventricular-node ablation with biventricular pacing, 36 patients were receiving amiodarone, and 4 patients were receiving class III antiarrhythmic medications.

FREEDOM FROM ATRIAL FIBRILLATION

All patients undergoing atrioventricular-node ablation with biventricular pacing had continuation of atrial fibrillation at 3 and 6 months. Among patients undergoing pulmonary-vein isolation, 78% were free from atrial fibrillation at 3 months, with or without the use of antiarrhythmic medications (Fig. 2). At 6 months, there had been eight repeat procedures for recurrent atrial fibrillation (in four patients) and atrial flutter or atrial tachycardia (in four other patients), and 88% of patients in the pulmonary-vein isolation group had freedom from atrial fibrillation with or without the use of antiarrhythmic medications. At 6 months, 71% of those patients were free from atrial fibrillation and from antiarrhythmic medications. All patients had symp-

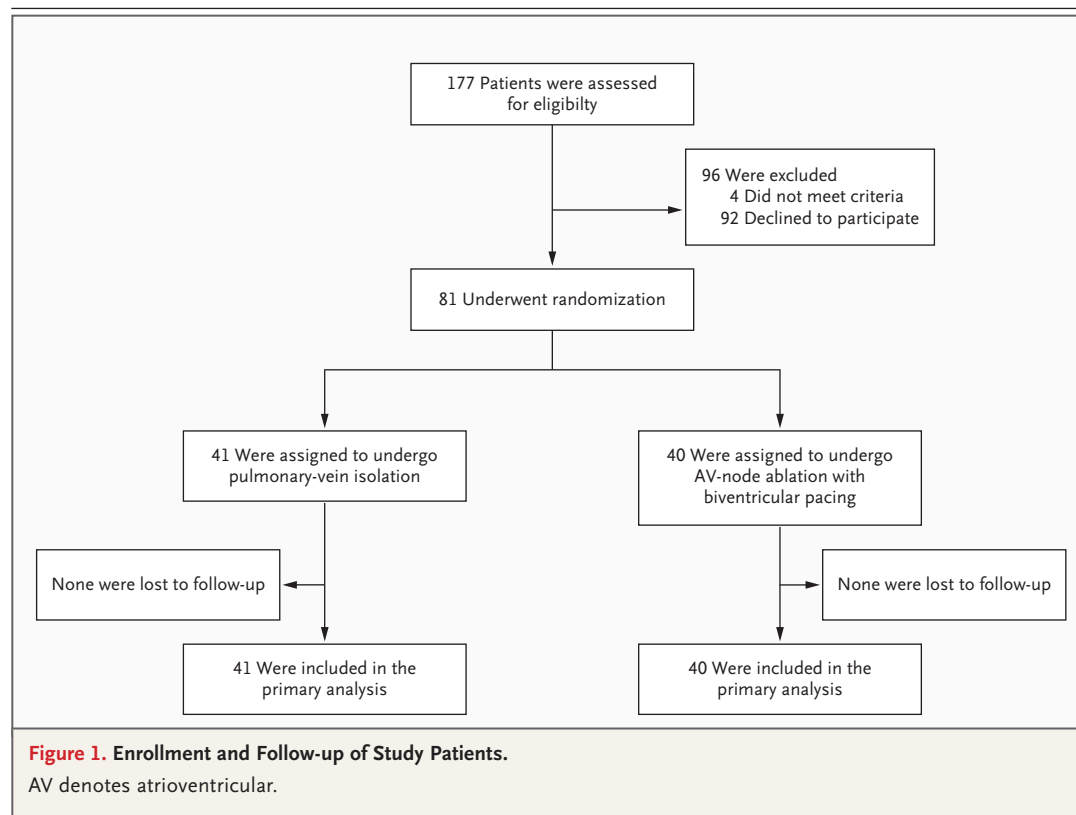


Table 1. Baseline Characteristics of the Patients.*

Characteristic	Pulmonary-Vein Isolation (N=41)	AV-Node Ablation with Biventricular Pacing (N=40)
Age (yr)	60±8	61±8
Male sex (%)	95	88
Coronary artery disease (%)	73	68
Type of atrial fibrillation (%)		
Paroxysmal	49	54
Persistent or long-standing persistent	51	46
Duration of atrial fibrillation (yr)	4.0±2.4	3.9±2.8
Ejection fraction (%)	27±8	29±7
Left atrial internal diameter (cm)	4.9±0.5	4.7±0.6
Heart rate (beats/min)	80±12	82±11
Duration of QRS interval (msec)	92±9	90±10
Distance on 6-minute walk test (m)	269±54	281±44
MLWHF score†	89±12	89±11

* Plus–minus values are means ±SD. The P values for all comparisons were not significant. AV denotes atrioventricular.
 † The Minnesota Living with Heart Failure questionnaire (MLWHF) measures patients' perception of the effects of heart failure on their daily lives; the total score ranges from 0 to 105, with a higher score indicating a worse quality of life.

tomatic recurrence of atrial fibrillation or atrial tachycardia, except for two patients in the group that underwent pulmonary-vein isolation.

MORPHOLOGIC CHANGES ON ECHOCARDIOGRAPHY

Ejection fraction and left atrial internal diameter were measured with the use of echocardiography. At 6 months, the difference in the mean ejection fraction between the two groups was significant: 35±9% for pulmonary-vein isolation, as compared with 28±6% for atrioventricular-node ablation with biventricular pacing (P<0.001) (Fig. 3A). The mean absolute change in the ejection fraction was an increase of 8±8% with pulmonary-vein isolation as compared with a decrease of 1±4% with atrioventricular-node ablation with biventricular pacing (P<0.001). The ejection fraction improved in 76% of patients who underwent pulmonary-vein isolation but only in 25% of patients who underwent atrioventricular-node ablation with biventricular pacing.

Left atrial internal diameter decreased in the group that underwent pulmonary-vein isolation, from 4.9±0.5 cm at baseline to 4.5±0.4 cm at 6 months, whereas left atrial internal diameter increased slightly in the group that underwent atrioventricular-node ablation with biventricular pacing, from 4.7±0.6 cm to 4.9±0.6 cm (P<0.001

for the comparison of the two groups at 6 months). The mean change in left atrial internal diameter was a reduction of 0.4±0.3 cm with pulmonary-vein isolation as compared with an increase of 0.1±0.2 cm with atrioventricular-node ablation with biventricular pacing (P<0.001). There was improvement in left atrial internal diameter in 80% of patients undergoing pulmonary-vein isolation but in only 15% of patients undergoing atrioventricular-node ablation with biventricular pacing.

FUNCTIONAL CAPACITY AND QUALITY OF LIFE

Functional capacity was measured as distance on the 6-minute walk test. In the group that underwent pulmonary-vein isolation, the distance increased from 269±54 m at baseline to 340±49 m at 6 months, as compared with 281±44 m to 297±36 m at 6 months in the group that underwent atrioventricular-node ablation with biventricular pacing (P<0.001) (Fig. 3B).

The quality of life was measured as the score on the MLWHF questionnaire, on which a lower score indicates a better quality of life. In the group that underwent pulmonary-vein isolation, the mean score improved, with a reduction from 89±12 at baseline to 60±8 at 6 months (Fig. 3C). In the group that underwent atrioventricular-node ablation with biventricular pacing, scores also im-

proved, though not as much: a reduction from 89 ± 11 at baseline to 82 ± 14 at 6 months ($P<0.001$ for the comparison between the two groups at 6 months).

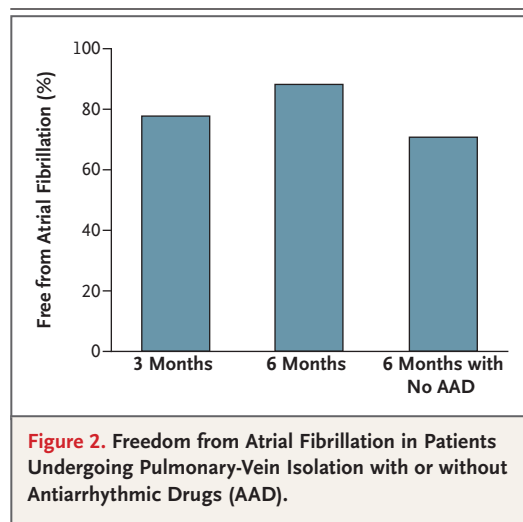
PRIMARY END POINT

The criteria for significant differences between the groups with respect to the primary end point were met, since the differences at 6 months for all three components (ejection fraction, distance on 6-minute walk, and MLWHF score) had P values of less than 0.017, thus satisfying any one of the three criteria. For pulmonary-vein isolation as compared with atrioventricular-node ablation with biventricular pacing, at 6 months the ejection fraction was significantly higher ($35\pm 9\%$ vs. $28\pm 6\%$, $P<0.001$), the 6-minute walking distance significantly longer (340 ± 49 m vs. 297 ± 36 m, $P<0.001$), and the MLWHF scores significantly better (60 ± 8 vs. 82 ± 14 , $P<0.001$).

TYPE OF ATRIAL FIBRILLATION AND PROGRESSION

Patients were classified as having atrial fibrillation that was paroxysmal, persistent, or long-standing persistent. Progression of atrial fibrillation was defined as atrial fibrillation that was becoming more advanced, and regression as atrial fibrillation that was becoming less advanced or disappearing. Progression was found in none of the patients who underwent pulmonary-vein isolation but in 30% of patients who underwent atrioventricular-node ablation with biventricular pacing ($P<0.001$). Conversely, the type of atrial fibrillation improved from nonparoxysmal to paroxysmal in 100% of patients in the group that underwent pulmonary-vein isolation as compared with 5% in the group that underwent atrioventricular-node ablation with biventricular pacing ($P<0.001$). At 6 months, more patients were receiving antiarrhythmic medications in the group that underwent atrioventricular-node ablation with biventricular pacing (14 patients receiving amiodarone and 1 receiving class III agents) than in the group that underwent pulmonary-vein isolation (5 patients receiving amiodarone, 4 receiving class III agents, and 1 receiving class IC agents).

We investigated whether the improvement in morphologic and functional variables in the group that underwent pulmonary-vein isolation occurred predominantly in patients with paroxysmal atrial fibrillation or in those with nonparoxysmal atrial fibrillation. Although the ejection fraction had in-



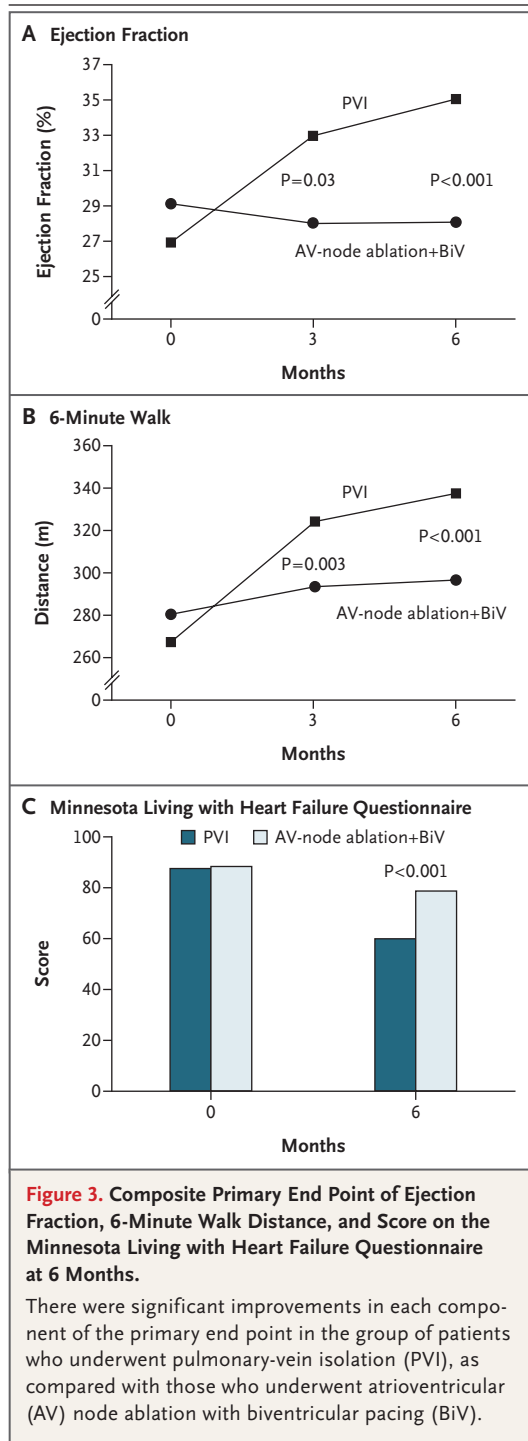
creased by 3 ± 3 percentage points at 6 months in the subgroup of patients with paroxysmal atrial fibrillation, the increase among patients with nonparoxysmal atrial fibrillation was 12 ± 10 percentage points ($P<0.001$). Similarly, there was greater improvement in the nonparoxysmal subgroup than in the paroxysmal subgroup in the 6-minute walking distance (an increase of 99 ± 66 m vs. 43 ± 23 m, $P=0.002$), the MLWHF score (a decrease of 33 ± 14 points vs. 24 ± 8 points, $P=0.001$), and the left atrial internal diameter (an increase of 0.6 ± 0.3 cm vs. 0.2 ± 0.2 cm, $P<0.001$).

COMPLICATIONS

There were no significant differences in the number of complications between the two groups. In the group that underwent pulmonary-vein isolation, three patients had groin bleeding, one had pericardial effusion, and another had pulmonary edema. There were also two patients with mild, asymptomatic stenosis of a single pulmonary vein. In the group that underwent atrioventricular-node ablation with biventricular pacing, two patients had left ventricular-lead dislodgment, two had a high left ventricular threshold, two had pocket hematoma, and one had pneumothorax. No patients died during the procedure or during follow-up.

DISCUSSION

This randomized, controlled trial compared pulmonary-vein isolation with the combination of atrioventricular-node ablation and biventricular



pacing for patients with symptomatic atrial fibrillation and an ejection fraction of 40% or less. The significance criteria for the composite primary end point were met, favoring pulmonary-vein isolation, with significant improvements in the ejection fraction, 6-minute walk distance, and

MLWHF score. In the group that underwent pulmonary-vein isolation, freedom from atrial fibrillation at 6 months was seen in 88% of patients regardless of the use of antiarrhythmic medications and in 71% without the use of antiarrhythmic medications and with the use of at least one repeat procedure.

It has been argued that the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial (ClinicalTrials.gov number, NCT00000556) favors rate-control therapy over a rhythm-control approach.¹⁶ In fact, atrioventricular-node ablation with biventricular pacing can be considered an extreme form of the rate-control strategy and of rate regularization. However, limitations of AFFIRM included the exclusion, at the discretion of the participating centers, of patients who were symptomatic or thought to benefit from rhythm control. In fact, a subsequent analysis of the AFFIRM data has shown that restoration of sinus rhythm is related to survival and that rhythm control with the use of antiarrhythmic medications does not have a high success rate.¹⁷ However, our study has shown that pulmonary-vein isolation (a form of rhythm control) has a high success rate and that, as compared with the best possible rate-control and rate-regularization strategy (atrioventricular-node ablation with biventricular pacing), pulmonary-vein isolation provides superior morphologic and functional improvements. The rationale for using atrioventricular-node ablation with biventricular pacing in patients with mean heart rates of less than 100 beats per minute derives from data showing that not only does cardiac function improve with regularization of the ventricular rate in patients with symptomatic atrial fibrillation who have normal ventricular rates, but symptoms also improve.^{18,19} In addition, patients undergoing atrioventricular-node ablation have improved 6-minute walk distances and feel better when a biventricular ICD is implanted, as compared with a right ventricular ICD alone.¹⁰

An unexpected observation was the high incidence of progression of atrial fibrillation associated with atrioventricular-node ablation with biventricular pacing. This finding makes atrioventricular-node ablation with biventricular pacing a less appealing option in centers where experienced atrial-fibrillation ablationists are available to perform pulmonary-vein isolation, a more definitive ablation procedure.

A subgroup analysis showed that, as compared

with patients with paroxysmal atrial fibrillation, those with nonparoxysmal atrial fibrillation derived more benefit from pulmonary-vein isolation in terms of the ejection fraction, 6-minute walking distance, quality-of-life score, and left atrial internal diameter. These data may contradict the conventional wisdom that patients with persistent or long-standing persistent atrial fibrillation are thought to have such an advanced form of atrial fibrillation as to preclude pulmonary-vein isolation.

The study has several limitations. Pulmonary-vein isolation was performed at centers with experienced ablationists, and the results thus may not be reproducible in all centers. In addition, the results might vary with longer follow-up. Also, the study was not blinded, and cost-effectiveness was not addressed.

In this study of symptomatic patients with atrial fibrillation and an ejection fraction of 40% or less, an ablation strategy involving pulmonary-vein isolation was found to be superior to atrioventricular-node ablation with implantation of a biventricular ICD, in terms of morphologic, functional, and quality-of-life variables. In addition,

the pulmonary-vein-isolation strategy resulted in high rates of freedom from both atrial fibrillation and antiarrhythmic medications. In such a population, pulmonary-vein isolation should be strongly considered at experienced centers.

Supported by a grant (257-2) from the Ministry of Education, Youth, and Sports of the Czech Republic and by a St. Jude Medical Educational Grant.

Dr. Khan reports receiving lecture fees from Boston Scientific; Dr. Jais, consulting fees from St. Jude Medical, Sorin Medical, and Biosense Webster; Dr. Cummings, consulting fees from St. Jude Medical and lecture fees from Boston Scientific, Medtronic, Corazon, Biosense Webster, and Siemens; Dr. Sanders, consulting fees from Medtronic and St. Jude Medical and lecture fees from St. Jude Medical, Biosense Webster, and Bard Electrophysiology; Dr. Kautzner, consulting and lecture fees from Boston Scientific, Biosense Webster, Medtronic, and St. Jude Medical; Dr. Wazni, lecture fees from St. Jude Medical; Dr. Schweikert, lecture fees from Medtronic, Biotronik, St. Jude Medical, Boston Scientific, Reliant Pharmaceuticals, Biosense Webster, and Siemens; and Dr. Saliba, lecture fees from Medtronic, Boston Scientific, and St. Jude Medical. Dr. Wang reports receiving consulting fees from Lifewatch, lecture fees from Boston Scientific, Medtronic, and St. Jude, and research support from Boston Scientific and having equity interest in Hansen Medical. Dr. Starling reports receiving consulting fees from Medtronic and BioControl and research support from Medtronic and having equity interest in Cardiomeas. Dr. Haïssaguerre reports receiving lecture fees from Biosense Webster and Bard Electrophysiology and research support from Boston Scientific. No other potential conflict of interest relevant to this article was reported.

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