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Progression of Atrial Fibrillation after Cryoablation or Drug Therapy

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ABSTRACT

BACKGROUND

Atrial fibrillation is a chronic, progressive disorder, and persistent forms of atrial fibrillation are associated with increased risks of thromboembolism and heart failure. Catheter ablation as initial therapy may modify the pathogenic mechanism of atrial fibrillation and alter progression to persistent atrial fibrillation.

METHODS

We report the 3-year follow-up of patients with paroxysmal, untreated atrial fibrillation who were enrolled in a trial in which they had been randomly assigned to undergo initial rhythm-control therapy with cryoballoon ablation or to receive antiarrhythmic drug therapy. All the patients had implantable loop recorders placed at the time of trial entry, and evaluation was conducted by means of downloaded daily recordings and in-person visits every 6 months. Data regarding the first episode of persistent atrial fibrillation (lasting ≥7 days or lasting 48 hours to 7 days but requiring cardioversion for termination), recurrent atrial tachyarrhythmia (defined as atrial fibrillation, flutter, or tachycardia lasting ≥30 seconds), the burden of atrial fibrillation (percentage of time in atrial fibrillation), quality-of-life metrics, health care utilization, and safety were collected.

RESULTS

A total of 303 patients were enrolled, with 154 patients assigned to undergo initial rhythm-control therapy with cryoballoon ablation and 149 assigned to receive antiarrhythmic drug therapy. Over 36 months of follow-up, 3 patients (1.9%) in the ablation group had an episode of persistent atrial fibrillation, as compared with 11 patients (7.4%) in the antiarrhythmic drug group (hazard ratio, 0.25; 95% confidence interval [CI], 0.09 to 0.70). Recurrent atrial tachyarrhythmia occurred in 87 patients in the ablation group (56.5%) and in 115 in the antiarrhythmic drug group (77.2%) (hazard ratio, 0.51; 95% CI, 0.38 to 0.67). The median percentage of time in atrial fibrillation was 0.00% (interquartile range, 0.00 to 0.12) in the ablation group and 0.24% (interquartile range, 0.01 to 0.94) in the antiarrhythmic drug group. At 3 years, 8 patients (5.2%) in the ablation group and 25 (16.8%) in the antiarrhythmic drug group had been hospitalized (relative risk, 0.31; 95% CI, 0.14 to 0.66). Serious adverse events occurred in 7 patients (4.5%) in the ablation group and in 15 (10.1%) in the antiarrhythmic drug group.

CONCLUSIONS

Initial treatment of paroxysmal atrial fibrillation with catheter cryoballoon ablation was associated with a lower incidence of persistent atrial fibrillation or recurrent atrial tachyarrhythmia over 3 years of follow-up than initial use of antiarrhythmic drugs. (Funded by the Cardiac Arrhythmia Network of Canada and others; EARLY-AF ClinicalTrials.gov number, NCT02825979.)

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A Quick Take is available at NEJM.org

Atrial fibrillation is a chronic and progressive disease that is characterized by exacerbations and remissions.[1] Although atrial fibrillation starts as an isolated electrical disorder, progressive electrical and structural remodeling of the heart leads to longer-lasting forms of atrial fibrillation.[2,3] The progression from paroxysmal atrial fibrillation (atrial fibrillation episodes lasting <7 continuous days) to persistent atrial fibrillation (atrial fibrillation episodes lasting ≥7 continuous days) has been observed to occur in 8 to 15% of patients over 12 months of follow-up and is associated with increasing rates of thromboembolism, heart failure, and health care utilization.[2,4-6]

Randomized, controlled trials have not shown a significant difference in cardiovascular outcomes when patients with established atrial fibrillation were treated with a strategy of ventricular rate control or pharmacologic rhythm control.[7] However, an initial strategy of rhythm control has been associated with a reduced risk of death from cardiovascular causes and with reduced rates of stroke among patients in whom atrial fibrillation had been diagnosed within the previous year.[8]

Catheter ablation has been shown to reduce arrhythmia recurrences, produce clinically meaningful improvements in quality of life, and reduce health care resource utilization.[9,10] Because catheter ablation is a tailored procedure that modifies the pathogenic mechanism leading to the onset and perpetuation of atrial fibrillation, it is postulated that intervention with ablation early in the natural history of atrial fibrillation may limit disease progression and improve clinical outcomes.

We previously conducted the Early Aggressive Invasive Intervention for Atrial Fibrillation (EARLY-AF) trial, a randomized trial involving patients with symptomatic, untreated atrial fibrillation in which treatment with catheter cryoballoon ablation was compared with use of antiarrhythmic drugs. The EARLY-AF trial showed that the initial treatment of symptomatic, paroxysmal atrial fibrillation with cryoablation resulted in a significantly lower recurrence of any atrial tachyarrhythmia (atrial fibrillation, atrial flutter, or atrial tachycardia) lasting 30 seconds or longer between 91 and 365 days after treatment initiation than antiarrhythmic drug therapy alone.[11] The main objective of the current follow-up analysis was to evaluate the effect of initial rhythm control on progression to persistent atrial fibrillation as assessed by an implantable continuous rhythm monitor.

Methods

Trial Design and Oversight

We conducted this investigator-initiated, multicenter, open-label, randomized trial with blinded end-point adjudication at 18 centers in Canada (see the Supplementary Appendix, available with the full text of this article at NEJM.org). The research program was designed as a pragmatic multiple-phase platform evaluating initial rhythm-control treatment in patients with symptomatic, previously untreated atrial fibrillation. The trial was designed to evaluate the effect of initial rhythm-control treatment on the recurrence of atrial tachyarrhythmia at 1 year of follow-up, which is the guideline-recommended end point for trials involving ablation for atrial fibrillation.[11,12] The trial also planned a 3-year follow-up to evaluate the effect of initial rhythm-control treatment on disease progression as assessed by an implantable continuous rhythm monitor.[12]

The trial protocol, which is available at NEJM.org, has been published previously[12]; additional information on the trial design is provided in the Supplementary Appendix. The trial design and conduct were overseen by an academic steering committee. The trial protocol was approved by the institutional review committee at each center. Data monitoring and collection and the primary analysis of the data were performed by the Cardiovascular Research Methods Centre (University of Ottawa) and the steering committee. The first author prepared the manuscript. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

The trial was funded by a peer-reviewed grant from the Cardiac Arrhythmia Network of Canada, by unrestricted grants from Medtronic and Baylis Medical, and by in-kind support from Medtronic and the University of British Columbia. The funders had no role in the trial design; the selection or monitoring of the participating centers; the selection or enrollment of patients; the collection, storage, or analysis of the data;

the interpretation of the data; the preparation of the manuscript; or the decision to submit the manuscript for publication.

TRIAL PARTICIPANTS AND RANDOMIZATION

Adults older than 18 years of age were eligible for enrollment if they had symptomatic paroxysmal atrial fibrillation and had had at least one electrocardiographically documented episode of atrial fibrillation within 24 months before randomization. Patients were excluded if they had a history of daily use of a class I or class III antiarrhythmic drug at therapeutic doses. All the patients provided written informed consent.

TRIAL PROCEDURES

After enrollment, all the patients underwent insertion of an implantable cardiac monitor (Reveal LINQ, Medtronic). The implantable cardiac monitor had an atrial fibrillation–detection algorithm to continuously analyze beat-to-beat variability of cardiac cycles and allow determination of the timing of occurrence of arrhythmia, as well as quantification of the atrial fibrillation burden (the percentage of time in atrial fibrillation).[13] The monitor, which was implanted no later than 24 hours after the initiation of antiarrhythmic drug therapy or the catheter ablation procedure, was programmed to standardized settings. The monitor remained in place throughout trial follow-up in all the patients.

Details regarding medical therapy and the ablation procedures have been published previously.[11,12] Oral anticoagulation was prescribed for patients who were older than 65 years of age or who had a $CHADS_2$ score of 1 or more (range, 0 to 6, with higher scores indicating a higher risk of stroke), as recommended by the Canadian Cardiovascular Society.[14] In addition, patients who had been randomly assigned to the ablation group received oral anticoagulation for a minimum of 3 months after ablation, regardless of stroke risk. Adherence to anticoagulation was strongly encouraged throughout the trial.

Patients were followed for at least 3 years after treatment initiation with a telephone call at 7 days and with in-person visits at 3, 6, and 12 months and then every 6 months thereafter. Automatic transmissions from the implantable cardiac monitor were obtained daily, with manual transmissions obtained weekly.

Survey data regarding quality of life (with the disease-specific Atrial Fibrillation Effect on Quality-of-Life survey [AFEQT] and the generic European Quality of Life-5 Dimensions [EQ-5D] survey) and atrial fibrillation symptoms (with the Canadian Cardiovascular Society Symptoms of Atrial Fibrillation [CCS-SAF] scale) were obtained at 6, 12, 24, and 36 months. The AFEQT survey is a disease-specific health-related quality-of-life instrument, with a score of 0 representing the worst and a score of 100 representing the best possible quality of life (i.e., no impairment due to atrial fibrillation). A change of at least 5 points in the AFEQT score is considered to be clinically meaningful.[15] The EQ-5D survey is a generic health-related quality-of-life instrument, with a score of 0 representing the worst and a score of 1.00 indicating the best possible health state. A change of at least 0.03 points in the EQ-5D score is considered to be clinically meaningful. The CCS-SAF scale ranges from 0 (asymptomatic) to 4 (atrial fibrillation resulting in severe impairment in quality of life and activities of daily living).[16] The AFEQT and EQ-5D questionnaires were completed without input from trial personnel.

During follow-up, patients were permitted to cross over to the alternate treatment strategy only after review by an independent committee to ensure that all the following criteria were met. First, the patient had to have had an atrial tachyarrhythmia event lasting 30 seconds or longer that occurred after the "blanking period" (the first 90 days after the initiation of treatment). Second, for patients in the antiarrhythmic drug group, the recurrence had occurred despite the receipt of a therapeutic dose of an antiarrhythmic drug (defined as >100 mg per day of flecainide, >160 mg per day of sotalol, >300 mg per day of propafenone, or 800 mg per day of dronedarone). Finally, the recurrence had been of sufficient clinical severity to warrant a change in therapy according to standard clinical practice. A change in treatment strategy during the blanking period or in the absence of documented atrial fibrillation was considered to be a protocol violation.

TRIAL END POINTS

The primary end point in the original trial was the first occurrence of any atrial tachyarrhyth-

mia (atrial fibrillation, atrial flutter, or atrial tachycardia) lasting 30 seconds or longer between 91 and 365 days after the initiation of an antiarrhythmic drug or the catheter ablation procedure. In the current analysis, our primary objective was to assess, in a time-to-event analysis, the first occurrence of persistent atrial fibrillation, which was defined as the first occurrence of an episode of continuous atrial tachyarrhythmia lasting 7 days or longer or lasting 48 hours to 7 days but necessitating cardioversion for termination. Three-year follow-up regarding recurrent atrial tachyarrhythmia is also presented. Secondary end points included arrhythmia burden (expressed as the percentage of time in atrial fibrillation); quality of life as assessed by the survey instruments; health care utilization as determined by emergency department visits, hospitalizations, cardioversion, or nonprotocol ablation; and serious adverse events. An adverse event was considered to be serious if it resulted in death or functional disability, use of an intervention, or new hospitalization or prolonged an existing hospitalization by more than 24 hours. All the safety end points were independently adjudicated by a clinical end-point committee whose members were unaware of the treatment assignments and patient identification.

STATISTICAL ANALYSIS

Analyses of the primary and secondary end points were based on the intention-to-treat principle. The intention-to-treat population included all the patients who had undergone randomization. Unadjusted survival curves were estimated with the Kaplan–Meier method and compared with the use of log-rank tests. Unadjusted hazard ratios and confidence intervals were derived from Cox proportional-hazards models. As an additional prespecified analysis, a multivariable Cox proportional-hazards model was used to test the consistency of the group effect. This model accounted for clinically important baseline characteristics, including trial site and patient's age, sex, weight, and duration of atrial fibrillation. The proportional-hazards assumption was assessed with the use of graphical tests (visual inspection of the log-minus-log plot) and numerical tests (test of the interaction term between treatment and time). Changes in quality-of-life scores at 12, 24, and 36 months after baseline are expressed as the least-squares mean differences with standard errors and were analyzed with the use of a linear mixed-effects model for repeated measures, including group, visit, and the interaction between group and visit.

The widths of the confidence intervals for the secondary end points have not been adjusted for multiplicity, so the intervals should not be used to infer definitive treatment effects. The analyses were performed with the use of SAS software, version 9.4 (SAS Institute).

RESULTS

PATIENTS AND FOLLOW-UP

A total of 303 patients were enrolled in the trial between January 17, 2017, and December 21, 2018, and were randomly assigned either to undergo cryoballoon ablation (154 patients) or to receive antiarrhythmic drug therapy (149 patients). The characteristics of the patients at baseline were balanced between the groups at randomization; the characteristics were also balanced among the 287 patients (94.7%) who completed 36 months of follow-up (Table S1 in the Supplementary Appendix). The enrolled population reflected the expected demographic characteristics of patients with early paroxysmal atrial fibrillation (Table S2).

Over 3 years of follow-up, 63 patients who had been initially randomly assigned to the antiarrhythmic drug group underwent catheter ablation after documented arrhythmia recurrence, and 27 patients who had been initially randomly assigned to the ablation group underwent repeat ablation. Two patients (1 in each group) died, and 14 patients (7 in each group) withdrew from the trial or were lost to follow-up (Fig. 1). Information on the prescribed drugs and the drug doses that were used in the antiarrhythmic drug group is provided in Table S3.

The median CHA_2DS_2-VASc score at baseline was 1 (interquartile range, 0 to 2); scores range from 0 to 9, with higher scores indicating a higher risk of stroke. All the patients with an indication for stroke prevention therapy received oral anticoagulation therapy (65.7% of the patients at baseline and 67.7% of those at final follow-up) (Table S4).

END POINTS

Over the 36-month follow-up period, a documented episode of persistent atrial fibrillation occurred in 3 of 154 patients (1.9%) in the ablation group and in 11 of 149 patients (7.4%) in the antiarrhythmic drug group (hazard ratio, 0.25; 95% confidence interval [CI], 0.09 to 0.70) (Fig. 2, Table 1, and Table S5). The median duration of the qualifying persistent atrial fibrillation episode was 15.8 days (interquartile range, 8.0 to 88.2), with the longest episode among these patients over the follow-up period lasting a median of 54.4 days (interquartile range, 11.4 to 163.8).

At 36 months, a documented recurrence of any atrial tachyarrhythmia lasting 30 seconds or longer had occurred in 87 patients in the ablation group (56.5%) and in 115 patients in the antiarrhythmic drug group (77.2%) (hazard ratio, 0.51; 95% CI, 0.38 to 0.67) (Fig. S1). A total of 89.1% of the episodes were adjudicated to be atrial fibrillation, and 10.9% were adjudicated to be atrial flutter or an atrial tachyarrhythmia.

The median number of daily transmissions from the implantable cardiac monitor that were received per patient was 1143 (interquartile range, 1084 to 1270). The median burden of atrial fibrillation (the percentage of time in atrial fibrillation) over the follow-up period was 0.00% (interquartile range, 0.00 to 0.12) in the ablation group and 0.24% (interquartile range, 0.01 to 0.94) in the antiarrhythmic drug group (Table 2 and Fig. S2).

The mean between-group difference in the AFEQT score was 8.0±2.2 points at 12 months, 9.0±2.3 points at 24 months, and 7.4±2.2 at 36 months after treatment initiation. Symptoms of atrial fibrillation had been reported by 14.9% patients in the ablation group and by 26.8% of those in the antiarrhythmic drug group at 12 months (relative risk, 0.56; 95% CI, 0.35 to 0.88); by 5.5% and 16.0%, respectively, at 24 months (relative risk, 0.34; 95% CI, 0.15 to 0.75); and by 4.8% and 17.1%, respectively, at 36 months (relative risk, 0.28; 95% CI, 0.13 to 0.61).

At 3 years, 5.2% of the patients in the ablation group and 16.8% of those in the antiarrhythmic drug group had been hospitalized (relative risk, 0.31; 95% CI, 0.14 to 0.66). Additional health care utilization outcomes are presented in Table 2.

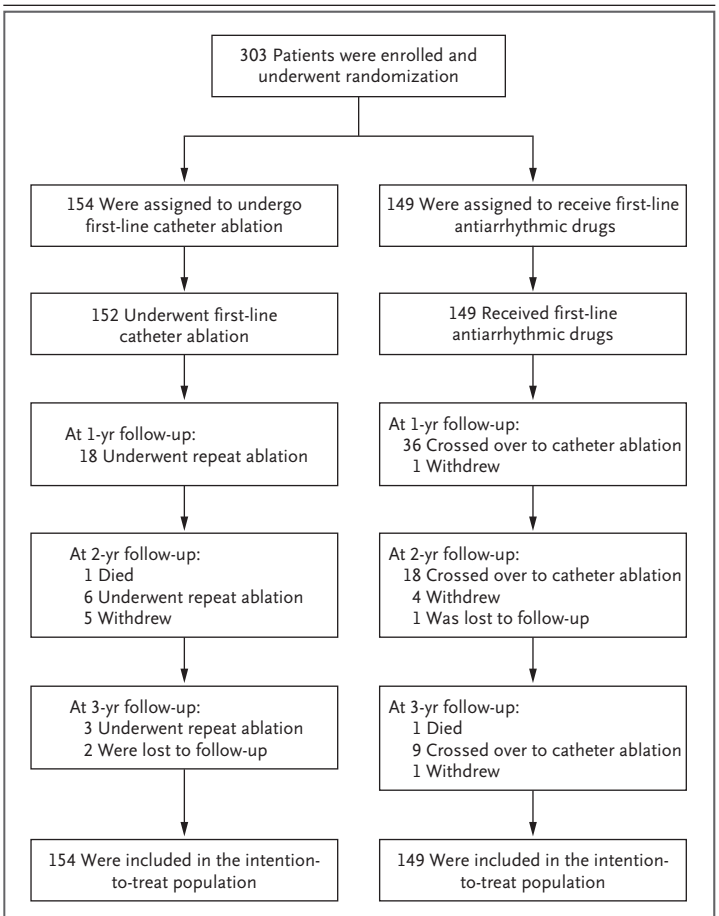

Figure 1. Randomization and Follow-up of the Patients.

SAFETY

At 36 months of follow-up, adverse events had occurred in 17 patients (11.0%) in the ablation group and in 35 patients (23.5%) in the antiarrhythmic drug group (Table 3). In the ablation group, these adverse events included one death, three cases of phrenic nerve palsy that resolved spontaneously, and two pacemaker implantations; in the antiarrhythmic drug group, these adverse events included one death, two cases of wide-complex tachycardia, two heart-failure exacerbations, three acute coronary syndromes, three neurologic events (two strokes and one transient ischemic attack, all in patients who were receiving oral anticoagulation at the time of event), three syncopal events, and four pacemaker implantations.

Table 1. Main End Points of Interest.*

End Point	Ablation Group (N=154)	Antiarrhythmic Drug Group (N=149)	Hazard Ratio (95% CI)
	number (percent)		
Progression to persistent atrial fibrillation from 91 days after treatment initiation to final follow-up	3 (1.9)	11 (7.4)	0.25 (0.09–0.70)
Recurrence of any atrial tachyarrhythmia			
From 91 days to 12 mo after treatment initiation†	66 (42.9)	101 (67.8)	0.48 (0.35–0.66)
From 91 days to 36 mo after treatment initiation	87 (56.5)	115 (77.2)	0.51 (0.38–0.67)

* Observed data are shown in the trial-group columns. The hazard ratio is a model-based effect estimate and was calculated with a Cox regression analysis. Because the statistical analysis plan did not include a provision for correcting for multiplicity when conducting tests for secondary or other outcomes, results are reported as point estimates and 95% confidence intervals. The widths of the confidence intervals have not been adjusted for multiplicity, so the intervals should not be used to infer definitive treatment effects for secondary outcomes.

† Data were previously reported by Andrade et al.[11]

DISCUSSION

In this 3-year follow-up of the EARLY-AF trial, we found that randomization to an initial strategy of catheter cryoballoon ablation was associated with a lower incidence of persistent atrial fibrillation, as determined by implantable cardiac devices capable of continuous rhythm monitoring, than pharmacologic rhythm control; the number needed to treat was 18. Catheter cryoballoon ablation was also associated with a lower burden of arrhythmia than antiarrhythmic drug therapy during the follow-up period.

Atrial fibrillation is initially an isolated electrical disorder that is initiated by sustained rapid firing from the pulmonary veins and maintained through secondary disorganization into fibrillatory waves or by induction of microreentrant circuits around the pulmonary venous–left atrial junction.[17,18] These repetitive pulmonary venous electrical discharges engender a maladaptive response, perpetuating atrial fibrillation by means of a combination of calcium-handling abnormalities, ion-channel dysfunction, structural remodeling, and autonomic dysregulation.[1,19,20] Collectively, atrial fibrillation–induced electrical, contractile, and structural remodeling promotes sustained arrhythmia and compels the progression from paroxysmal to persistent atrial fibrillation — a change that has been reported to occur in 8 to 15% of patients at 12 months of follow-up and in 22 to 36% of patients at 10 years of follow-up.[2-5]

Given the dynamic nature of these structural and electrical alterations, it has been postulated that early attempts to restore and maintain sinus rhythm may confer beneficial long-term outcomes.[8,20] Although electrical remodeling has been observed to reverse rapidly after sinus rhythm restoration, studies have suggested that antiarrhythmic drug therapy does not reverse the atrial structural remodeling or affect disease progression.[20,21] In contrast, catheter ablation is a tailored procedure that is designed to modify the pathogenic mechanism of atrial fibrillation initiation and perpetuation by means of a combination of pulmonary venous isolation (e.g., trigger elimination), autonomic nervous system modulation (by means of vagal denervation), and electroanatomical substrate modification (predominantly at the pulmonary venous–left atrial junction). Mechanistic studies have suggested that catheter ablation is associated with substantial reversal of the adverse structural remodeling.[21] These findings suggest that intervention early in the natural history of atrial fibrillation may affect disease progression.

The current long-term follow-up of the EARLY-AF trial builds on these observations by showing that initial catheter ablation was potentially disease-modifying. Using continuous cardiac monitoring, we observed that a lower percentage of patients who had been assigned to undergo first-line ablation than of those who had been assigned to receive initial antiarrhythmic drug therapy had progression to persistent atrial fi-

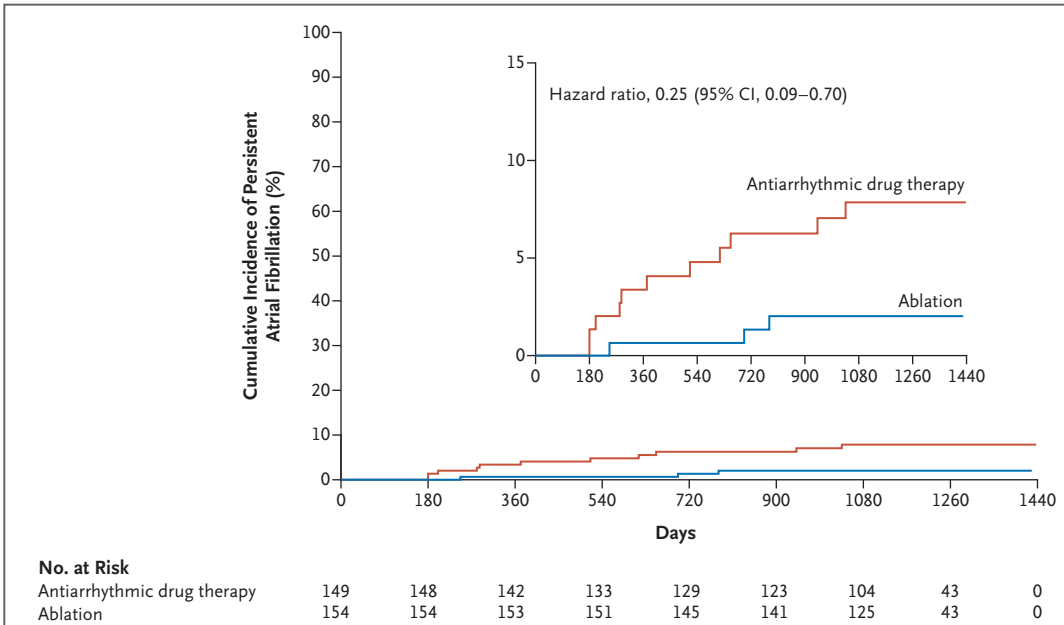

Figure 2. Cumulative Incidence of First Episode of Persistent Atrial Fibrillation.

Shown is a time-to-event analysis of the first occurrence of persistent atrial fibrillation, as documented by the implantable cardiac monitor between 91 days after the initiation of treatment (receipt of antiarrhythmic drug or catheter ablation) and final trial follow-up. The inset shows the same data on an enlarged y axis.

brillation over a median follow-up of 3 years. In addition, the improved arrhythmia outcomes with initial catheter ablation were associated with improvements in quality of life and a lower incidence of hospitalization during 3 years of follow-up. These latter findings are particularly relevant given that costs associated with the provision of atrial fibrillation–associated care are forecast to increase, from a current range of 1.0 to 2.5% of annual health care expenditures to more than 4% within the next two decades.[22,23]

These findings also build on the results of previous studies evaluating the effect of catheter ablation on disease progression, which have focused exclusively on patients at high risk for disease progression.[24,25] Although recently published results from the Atrial Fibrillation Progression Trial (ATTEST) showed significantly lower rates of disease progression after radiofrequency ablation, that trial exclusively enrolled patients in whom antiarrhythmic drugs were already proved to be ineffectual — a situation that weighted the therapeutic benefit toward ablation.[25] Routine surveillance for atrial arrythmias in ATTEST was performed by intermittent transtelephonic monitoring that was done once per week until 9 months after treatment initiation and once per month thereafter. In contrast, our trial was conducted in a population of a relatively young and healthy patients with untreated atrial fibrillation, used continuous cardiac monitoring for end-point detection, avoided antiarrhythmic drug use in the ablation group, and had relatively complete follow-up (94.7% of the trial population completed 36 months of follow-up). Despite enrolling a population of patients with relatively few coexisting conditions who were at low risk for progression of atrial fibrillation, we still found significant differences in the rates of disease progression with first-line ablation therapy as compared with antiarrhythmic drug use. The findings from our trial may also inform why previous trials of pharmacologic treatment, such as the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial,[7] did not show a difference in clinical outcomes, because the patients who were enrolled in these trials were predominantly later in their clinical course and the interventions that were used may not affect disease progression.

Table 2. Secondary End Points.*

End Point	Ablation Group (N = 154)	Antiarrhythmic Drug Group (N = 149)	Treatment Effect (95% CI)
Atrial fibrillation burden — % time in atrial fibrillation†			
From 91 days after treatment initiation to final follow-up			
Median (IQR)	0.00 (0.00–0.12)	0.24 (0.01–0.94)	
Mean	0.4±1.9	2.3±7.8	−1.9±0.7
At 91–365 days after treatment initiation‡			
Median (IQR)	0.00 (0.00–0.08)	0.13 (0.00–1.60)	
Mean	0.6±3.3	3.9±12.4	−3.3±1.0
At 366–730 days after treatment initiation			
Median (IQR)	0.00 (0.00–0.03)	0.03 (0.00–0.41)	
Mean	0.2±1.0	1.5±5.6	−1.3±0.5
At 731–1095 days after treatment initiation			
Median (IQR)	0.00 (0.00–0.04)	0.01 (0.00–0.18)	
Mean	0.3±2.3	1.4±8.3	−1.1±0.7
Quality-of-life end points§			
Change from baseline in AFEQT score¶			
At 12 mo‡	26.9±1.9	22.9±2.0	8.0±2.2
At 24 mo	29.7±2.0	24.7±2.0	9.0±2.3
At 36 mo	28.1±2.0	24.8±2.0	7.4±2.2
Change from baseline in EQ-5D score‖			
At 12 mo	0.06±0.01	0.01±0.01	0.05±0.02
At 24 mo	0.06±0.02	0.04±0.02	0.03±0.02
At 36 mo	0.06±0.02	0.01±0.02	0.05±0.02
Change from baseline in EQ-VAS score**			
At 12 mo‡	7.73±1.44	5.71±1.46	2.94±1.69
At 24 mo	7.44±1.56	6.53±1.55	1.87±1.85
At 36 mo	7.64±1.59	6.15±1.63	2.45±1.77
No symptoms — no. (%)†††‡‡			
At 12 mo‡	131 (85.1)	109 (73.2)	1.17 (1.05–1.30)
At 24 mo	121/128 (94.5)	110/131 (84.0)	1.13 (1.04–1.24)
At 36 mo	138/145 (95.2)	116/140 (82.9)	1.15 (1.06–1.26)
Secondary health care utilization end points‡‡			
Emergency department visit			
No. of patients with event (%)	40 (26.0)	46 (30.9)	0.84 (0.59–1.20)
No. of events	67	83	
Median no. of events per patient among those with an event (IQR)	1 (1–2)	1 (1–2)	
Hospitalization			
No. of patients with event (%)	8 (5.2)	25 (16.8)	0.31 (0.14–0.66)
No. of events	9	29	
Median no. of events per patient among those with an event (IQR)	1 (1–1)	1 (1–1)	

Table 2. (Continued.)

End Point	Ablation Group (N=154)	Antiarrhythmic Drug Group (N=149)	Treatment Effect (95% CI)
Cardioversion			
No. of patients with event (%)	14 (9.1)	20 (13.4)	0.68 (0.36–1.29)
No. of events	18	31	
Median no. of events per patient among those with an event (IQR)	1 (1–1)	1 (1–2)	
Nonprotocol ablation§§			
No. of patients with event (%)	27 (17.5)	63 (42.3)	0.41 (0.28–0.61)
No. of events	31	69	
Median no. of events per patient among those with an event (IQR)	1 (1–1)	1 (1–1)	
Safety end points — no. (%)‡‡			
Serious adverse event			
At 12 mo‡	5 (3.2)	6 (4.0)	0.81 (0.25–2.59)
At 36 mo	7 (4.5)	15 (10.1)	0.45 (0.19–1.05)
Any safety end-point event			
At 12 mo‡	14 (9.1)	24 (16.1)	0.59 (0.29–1.21)
At 36 mo	17 (11.0)	35 (23.5)	0.47 (0.28–0.79)

* Plus–minus values are means ±SE, except for atrial fibrillation burden, which is expressed as means ±SD. Observed data are shown in the trial-group columns, and treatment effects are model-based effect estimates. Because the statistical analysis plan did not include a provision for correcting for multiplicity when conducting tests for secondary or other outcomes, results are reported as point estimates and 95% confidence intervals. The widths of the confidence intervals have not been adjusted for multiplicity, so the intervals should not be used to infer definitive treatment effects for secondary outcomes. IQR denotes interquartile range.

† The between-group absolute difference in atrial fibrillation burden, expressed as the beta coefficient ±SE, was calculated with the use of a linear regression analysis.

‡ Data were previously reported by Andrade et al.[11]

§ Changes in quality-of-life scores from baseline at 12, 24, and 36 months are expressed as least-squares means ±SE and were analyzed with the use of a linear mixed-effects model for repeated measures, including group, visit, and an interaction between group and visit.

¶ Scores on the Atrial Fibrillation Effect on Quality of Life (AFEQT) survey, a disease-specific health-related quality-of-life instrument, range from 0 to 100, with higher scores indicating better health-related quality of life.

‖ Scores on the European Quality of Life–5 Dimensions (EQ-5D) survey, a generic health-related quality-of-life instrument, range from 0 to 1.00, with higher scores indicating better health-related quality of life.

** Scores on the European Quality of Life–Visual Analogue Scale (EQ-VAS), a vertical visual-analogue scale on which patients provide a global assessment of their health, range from 0 to 100, with higher scores indicating better health-related quality of life.

†† Scores on the Canadian Cardiovascular Society Severity of Atrial Fibrillation (CCS-SAF) semiquantitative scale range from 0 (asymptomatic) to 4 (atrial fibrillation resulting in severe impairment in quality of life and activities of daily living). Absence of symptoms was defined as a score of 0 or 1 (atrial fibrillation resulting in a minimal or no effect on the patient's quality of life).

‡‡ The treatment effect is expressed as the relative risk and 95% confidence interval.

§§ Nonprotocol ablation was defined as catheter ablation in patients who had been randomly assigned to the antiarrhythmic drug group or as repeat ablation in patients who had been randomly assigned to the ablation group.

Finally, the current trial evaluated one pillar of management of atrial fibrillation. In addition to control of rhythm, the comprehensive management of atrial fibrillation necessitates the management of coexisting cardiovascular conditions and stroke prevention by the provision of oral anticoagulation.[14] No prospective or randomized trials have been shown to support anticoagulation discontinuation after ablation, thus catheter ablation is not considered to be an alternative to oral anticoagulation therapy in patients at elevated risk for stroke. In our trial, all the patients with an indication for stroke-prevention therapy received oral anticoagulation therapy, even after catheter ablation.

Our trial has several limitations. Although we collected data regarding cardiovascular outcomes, such as thromboembolism, these end points can only be considered hypothesis-generating. Consistent with guideline recommendations and contemporary clinical practice, a number of patients crossed over from antiarrhythmic drug therapy to catheter ablation after failure of medical therapy to control their arrhythmia-related symptoms, although it is possible that the patients were undertreated. Because the trial was per-

Table 3. Adverse Events.

Event	Ablation Group (N = 154)	Antiarrhythmic Drug Group (N = 149)
Any safety end-point event		
No. of patients with event	17	35
No. of events	20	41
Death — no.	1*	1†
Cardiac event — no.		
Pericardial effusion or tamponade	0	1‡
Pericarditis	0	0
Exacerbation of heart failure	0	2
Syncope	1	3
Wide-complex tachycardia or proarrhythmic event	0	2
Bradycardia or arteriovenous block for which pacemaker insertion was warranted	2	4
Acute coronary syndrome	0	3
Neurologic event — no.¶		
Stroke	0	2
Transient ischemic attack	0	1
Vascular event — no.		
Arteriovenous fistula	0	0
Hematoma for which intervention was not warranted	1	0
Pseudoaneurysm for which intervention was warranted	0	0
Deep-vein thrombosis	1	0
Pulmonary event — no.		
Persistent phrenic nerve palsy§	3	0
Pneumonia	1	0
Self-limited hemoptysis	1	1
Gastrointestinal event — no.		
Esophageal injury or perforation	0	0
Gastrointestinal upset such as indigestion or diarrhea	2	2
Acute pancreatitis	1	0
Bleeding in lower gastrointestinal tract	0	1
Adverse drug reaction leading to dose modification or discontinuation — no.		
Prolongation of QT interval	0	1
Presyncope	0	5
Tremor	0	1
Visual disturbance	0	1
Mild cognitive impairment	0	1
Insomnia	0	1
Angioedema	1	0

Table 3. (Continued.)

Event	Ablation Group (N = 154)	Antiarrhythmic Drug Group (N = 149)
Other event — no.		
Erectile dysfunction	0	1
Rash	0	1
Epistaxis	2	0
Joint pain	0	2
Migraine	1	0
Sepsis	0	1
Mood disorder	2	0
Urinary retention	0	1
Arteritis	0	1
Nephrolithiasis	0	1

* Death was due to complications related to acute pancreatitis.
† Death was due to respiratory complications of amyotrophic lateral sclerosis.
‡ Cardiac tamponade for which intervention was warranted occurred in one patient in the antiarrhythmic drug group who underwent ablation after arrhythmia recurrence.
§ Persistent phrenic nerve palsy was defined as impairment in phrenic nerve function persisting beyond the end of the ablation procedure. All three phrenic nerve palsies resolved spontaneously within 1 month.
¶ One stroke occurred in a patient with a CHA_2DS_2-VASc score of 2 receiving rivaroxaban, one stroke occurred in a patient with a CHA_2DS_2-VASc score of 1 receiving apixaban, and one transient ischemic attack occurred in a patient with a CHA_2DS_2-VASc score of 3 receiving rivaroxaban. The CHA_2DS_2-VASc score is a clinical estimation of the risk of stroke in patients with atrial fibrillation, in which congestive heart failure, hypertension, an age of 65 years or older, diabetes, vascular disease, and female sex are given 1 point and an age of 75 years or older and stroke or transient ischemic attack are given 2 points.

formed with a single ablation technology, the observed outcomes may not be generalizable to other ablation energy sources.

In this 3-year follow-up of the EARLY-AF trial, the incidence of persistent atrial fibrillation or recurrent atrial tachyarrhythmias was lower among patients who had been assigned to undergo initial catheter cryoballoon ablation than among those who had been assigned to receive first-line antiarrhythmic drugs.

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APPENDIX

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