ORIGINAL ARTICLE

Cryoballoon Ablation as Initial Therapy for Atrial Fibrillation

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ABSTRACT

BACKGROUND

In patients with symptomatic paroxysmal atrial fibrillation that has not responded to medication, catheter ablation is more effective than antiarrhythmic drug therapy for maintaining sinus rhythm. However, the safety and efficacy of cryoballoon ablation as initial first-line therapy have not been established.

METHODS

We performed a multicenter trial in which patients 18 to 80 years of age who had paroxysmal atrial fibrillation for which they had not previously received rhythm-control therapy were randomly assigned (1:1) to receive treatment with antiarrhythmic drugs (class I or III agents) or pulmonary vein isolation with a cryoballoon. Arrhythmia monitoring included 12-lead electrocardiography conducted at baseline and at 1, 3, 6, and 12 months; patient-activated telephone monitoring conducted weekly and when symptoms were present during months 3 through 12; and 24-hour ambulatory monitoring conducted at 6 and 12 months. The primary efficacy end point was treatment success (defined as freedom from initial failure of the procedure or atrial arrhythmia recurrence after a 90-day blanking period to allow recovery from the procedure or drug dose adjustment, evaluated in a Kaplan–Meier analysis). The primary safety end point was assessed in the ablation group only and was a composite of several procedure-related and cryoballoon system–related serious adverse events.

RESULTS

Of the 203 participants who underwent randomization and received treatment, 104 underwent ablation, and 99 initially received drug therapy. In the ablation group, initial success of the procedure was achieved in 97% of patients. The Kaplan–Meier estimate of the percentage of patients with treatment success at 12 months was 74.6% (95% confidence interval [CI], 65.0 to 82.0) in the ablation group and 45.0% (95% CI, 34.6 to 54.7) in the drug-therapy group ($P<0.001$ by log-rank test). Two primary safety end-point events occurred in the ablation group (Kaplan–Meier estimate of the percentage of patients with an event within 12 months, 1.9%; 95% CI, 0.5 to 7.5).

CONCLUSIONS

Cryoballoon ablation as initial therapy was superior to drug therapy for the prevention of atrial arrhythmia recurrence in patients with paroxysmal atrial fibrillation. Serious procedure-related adverse events were uncommon. (Supported by Medtronic; STOP AF First ClinicalTrials.gov number, NCT03118518.)

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In patients with symptomatic paroxysmal atrial fibrillation that does not respond to drug treatment, catheter ablation is superior to antiarrhythmic drug therapy for preventing recurrence of atrial arrhythmias.[1,2] Accordingly, ablation has become a well-accepted strategy for long-term rhythm control in this population.[3-5] Previous studies have suggested a benefit to intervention with ablation before drug failure, because a shorter "diagnosis-to-ablation" time is associated with lower rates of arrhythmia recurrence or repeat procedures and fewer hospitalizations.[6-10] Recently, the Early Treatment of Atrial Fibrillation for Stroke Prevention Trial (EAST-AFNET 4) showed that early rhythm control resulted in better cardiovascular outcomes than usual care.[11] Rhythm control with ablation may also decrease progression to persistent atrial fibrillation,[12] which is more difficult to manage.

Previous randomized trials evaluating ablation as compared with drug treatment as initial therapy have used point-by-point radiofrequency current ablation.[13-15] Together, these trials have shown a modestly lower risk of atrial fibrillation recurrence with radiofrequency ablation than with antiarrhythmic drug therapy.[16] However, a relatively high rate of repeat procedures was observed, and ablation was associated with more severe adverse events. Our goal was to evaluate the efficacy and safety of cryoballoon ablation as compared with drug therapy as an initial treatment strategy in patients with symptomatic paroxysmal atrial fibrillation.

Methods

Trial Design

We conducted this multicenter, randomized (1:1) trial (STOP AF First: Cryoballoon Catheter Ablation in Antiarrhythmic Drug Naive Paroxysmal Atrial Fibrillation) to evaluate cryoballoon ablation as compared with drug therapy as an initial treatment for patients with symptomatic paroxysmal atrial fibrillation. The institutional review board at each center approved the trial, and all patients provided written informed consent before participating. Medtronic sponsored the trial, was responsible (with steering committee oversight) for development of the final protocol and statistical analysis plan (available with the full text of this article at NEJM.org), and reviewed the manuscript that was submitted. A contract research organization (NAMSA) performed database development, data review, and site monitoring. An independent clinical events committee and a core laboratory were used to classify primary end-point events. Statistical analyses were conducted by an author who was an employee of the sponsor and were independently validated by one of the academic authors. The first author and the last four authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. The final content of the article that was submitted and publication decisions were determined by academic authors.

Trial Participants

Patients who were 18 to 80 years of age and had recurrent symptomatic paroxysmal atrial fibrillation were enrolled at 24 centers in the United States. Key exclusion criteria included previous treatment with an antiarrhythmic drug (class I or III) for 7 or more days, an enlarged left atrial diameter (>5 cm), or a previous left atrial ablation or left atrial surgical procedure. (Additional inclusion and exclusion criteria are provided in Table S1 in the Supplementary Appendix, available at NEJM.org.)

Cryoballoon Catheter Ablation

Patients who were randomly assigned to the ablation group underwent pulmonary vein isolation within 30 days after randomization. This procedure has been described previously[17]; additional details are provided in the Supplementary Appendix. A second-generation cryoballoon (Arctic Front Advance Cardiac Cryoablation Catheter, Medtronic) was inserted with the use of a transseptal puncture and an over-the-wire delivery technique. Two cryoballoon applications, each 3 minutes in duration, were recommended for each pulmonary vein. Pulmonary vein isolation was confirmed by entrance block (and where assessable, exit block). Treatment with class I or III antiarrhythmic drugs (excluding amiodarone) was permitted for up to 80 days after the procedure to allow complete washout by the end of the 90-day blanking period (designed to allow procedural recovery and drug dose adjustments) and to decrease the risk of a protocol violation. Anticoagulation was administered for at least 2 months. Given its long half-life, amiodarone was excluded in the ablation group to avoid confounding data regarding arrhythmia recurrences.

DRUG THERAPY

Treatment with a class I or III antiarrhythmic drug was initiated within 30 days after randomization and was conducted in accordance with the 2014 guidelines from the American College of Cardiology, American Heart Association, and Heart Rhythm Society (Table S2).[5] Drug dosing and schedule changes were allowed for 90 days after initiation, after which further changes were discouraged (details are provided in the Supplementary Appendix). Use of beta-blockers, calcium-channel blockers, or both was permitted in both groups.

TRIAL FOLLOW-UP

In-office visits were planned at 1, 3, 6, and 12 months. Arrhythmia monitoring included 12-lead electrocardiography (ECG) at each follow-up visit and patient-activated telephone monitoring weekly and when symptoms developed after the blanking period. At 6 and 12 months, 24-hour ambulatory ECG monitoring was also performed.

END POINTS

The primary efficacy end point was treatment success at 12 months, defined as freedom from the following events: initial failure of the procedure; any subsequent atrial fibrillation surgery or ablation in the left atrium (including those performed during the blanking period); or atrial arrhythmia recurrence (documented atrial fibrillation, atrial tachycardia, or atrial flutter for ≥30 seconds during ambulatory monitoring or for ≥10 seconds on a 12-lead ECG), cardioversion, or use of class I or III antiarrhythmic drugs (ablation group only) outside the 90-day blanking period.

The primary safety end point was evaluated in the ablation group only and was a composite of the following prespecified procedure-related or cryoballoon system–related serious adverse events: development of a clinically significant pericardial effusion within 30 days; symptomatic pulmonary vein stenosis or atrial–esophageal fistula within 12 months; unresolved phrenic nerve injury at 12 months; and transient ischemic attack, stroke, myocardial infarction, major vascular complication, or major bleeding within the first 7 days (additional details, including an explanation of the blanking period, are provided in the Supplementary Appendix).

Prespecified secondary end points included quality of life, which was assessed in the ablation group only (with the use of the Atrial Fibrillation Effect on Quality-of-Life [AFEQT] and European Quality of Life–5 Dimensions [EQ-5D] questionnaires, with scores compared between baseline and 12 months), and health care utilization, which was compared between the treatment groups. Other end points included serious adverse events, initial success of the procedure, and procedural characteristics (Table S3).

STATISTICAL ANALYSIS

In the calculations of sample size, we assumed that 45.0% of the patients in the drug-therapy group and 69.9% of the patients in the ablation group would have treatment success and that 4.0% of the patients in the ablation group would have a primary safety end-point event within 12 months (a description of the basis of these assumptions is provided in the Supplementary Appendix). On the basis of these assumptions and an expected 10% attrition, a sample size of 210 was calculated to be sufficient to provide at least 90% power for the analysis of the primary efficacy end point and 80% power for the analysis of the primary safety end point.

All analyses were conducted in a modified intention-to-treat population that included all patients who underwent randomization and in whom treatment was initiated. The primary efficacy end point was evaluated with Kaplan–Meier analysis and the log-rank test. Time 0 was defined as the date of ablation or the initiation of drug therapy, and data were censored at the patients' 12-month follow-up or exit from the trial. The start date for assessing atrial arrhythmia was 91 days after time 0. Because few events occurred during the blanking period (as expected), the proportional hazards assumption was not met and therefore a hazard ratio is not reported. The standard error for each percentage of patients with an event within 12 months was approximated with Greenwood's formula, and two-sided 95% log–log confidence intervals were constructed.

The primary safety end point was analyzed with the use of Kaplan–Meier survival analysis and was evaluated against a prespecified performance goal (upper boundary of the 95% confidence interval for the percentage of patients with a safety event, <12%) at 12 months. Kaplan–Meier analysis and the log-rank test were used to evaluate group differences in health care utilization. To account for missing data, a prespeci-

Table 1. Characteristics of the Patients.*

Characteristic	Ablation (N=104)	Drug Therapy (N=99)
Age — yr	60.4±11.2	61.6±11.2
Male sex — no. (%)	63 (61)	57 (58)
Time since paroxysmal atrial fibrillation onset — yr	1.3±2.5†	1.3±2.3‡
Left atrial diameter — mm	38.7±5.7	38.2±5.4‡
Left ventricular ejection fraction — %	60.9±6.0	61.1±5.9‡
Medical characteristics — no. (%)		
Hypertension	58 (56)	57 (58)
Diabetes	15 (14)	17 (17)
Myocardial infarction	4 (4)	2 (2)
Coronary artery disease	13 (12)	12 (12)
Congestive heart failure	1 (1)	3 (3)
Stroke	0	3 (3)
Transient ischemic attack	2 (2)	0
Cardiac valve dysfunction	8 (8)	9 (9)
Chronic obstructive pulmonary disease	5 (5)	6 (6)
Sleep apnea	26 (25)	20 (20)
Renal dysfunction	1 (1)	2 (2)
CHA_2DS_2-VASc score — no. (%)§		
0	20 (19)	16 (16)
1	28 (27)	28 (28)
2	33 (32)	19 (19)
3	12 (12)	22 (22)
>3	11 (11)	14 (14)
Baseline medications		
Anticoagulant	72 (69)	68 (69)
Aspirin	21 (20)	13 (13)
Beta-blocker	6 (6)	9 (9)
Calcium-channel blocker	10 (10)	4 (4)
Cardioversions in the previous 12 mo		
Electrical	19 (18)	15 (15)
Pharmacologic	8 (8)	14 (14)
Median time from randomization to initiation of treatment (IQR) — days	24 (16–28)	2 (0–8)

* Plus–minus values are means ±SD. IQR denotes interquartile range.
† Data were available for 102 patients.
‡ Data were available for 98 patients.
§ CHA_2DS_2-VASc scores range from 0 to 9, with higher scores indicating a greater risk of stroke. (The highest score observed in this trial was 6.)

fied tipping-point analysis was performed for each primary end point. Changes in quality of life in the ablation group were evaluated with a paired t-test. Adjustment for multiple comparisons in secondary analyses was performed with the use of the Hochberg procedure. All analyses were conducted with SAS software, version 9.4 (SAS Institute). (Additional details regarding the statistical analyses are provided in the Supplementary Appendix.)

RESULTS

PATIENTS

We enrolled 225 patients from June 2017 through May 2019. A total of 203 received either ablation (104 patients) or drug therapy (99 patients) and were included in the modified intention-to-treat population. Overall, 193 of the 203 patients (95%) completed 12 months of follow-up (Fig. S1 and Tables S4 and S5). Baseline characteristics were similar in the two groups (Table 1). Adherence to 24-hour ambulatory monitoring was 91% complete in the ablation group and 84% complete in the drug-therapy group. Adherence to weekly telephone monitoring was 80% complete in the ablation group and 82% complete in the drug-therapy group.

TREATMENT CHARACTERISTICS

Antiarrhythmic drug treatment and dosing are summarized in Table 2. During the blanking period, nine patients stopped taking antiarrhythmic drugs because of side effects. After the blanking period, three additional patients discontinued drug therapy. In the ablation group, the mean (±SD) procedure time was 139±74 minutes, the mean left atrial dwell time (i.e., the time during which the catheter was inside the left atrium) was 60±24 minutes, the mean fluoroscopy duration was 18.2±11.8 minutes, and the mean duration of cryoballoon application was 20.9±7.8 minutes.

PRIMARY EFFICACY END POINT

The percentage of patients with treatment success at 12 months was 74.6% (95% confidence interval [CI], 65.0 to 82.0) in the ablation group and 45.0% (95% CI, 34.6 to 54.7) in the drug-therapy group (P<0.001 by log-rank test) (Fig. 1). The primary end-point events are listed in Table 3. Initial failure of the procedure occurred in 3 of 104 patients (3%) in the ablation group, owing to ablation of a nonpulmonary vein site in the left atrium with a nontrial ablation catheter

(1 patient) and an inability to isolate all targeted pulmonary veins (owing to development of phrenic nerve injury in 1 patient and to pericardial effusion in 1 patient). There were 15 patients in the drug-therapy group who had a primary efficacy end-point event due to crossover to ablation; the reasons for crossover were documented antiarrhythmic drug side effects in 10 patients, ongoing symptoms in 4 patients, and atrial arrhythmia detected on cardiac monitoring conducted outside of the trial protocol in 3 patients (2 of the patients who crossed over had more than one reason). Another 19 patients in the drug-therapy group underwent ablation after having a primary efficacy end-point event. No patient in either treatment group underwent repeat ablation during the trial. In a post hoc analysis involving the 78 patients in the drug-therapy group who were taking a therapeutic dose of an antiarrhythmic drug throughout the trial (Table 2), treatment success was observed in 40 patients (51%) at 12 months.

A worst-case analysis accounting for early exits from the trial still showed significantly higher success rates with ablation (see the Supplementary Appendix). Results for prespecified subgroups are shown in Table S6.

Table 2. Antiarrhythmic Drug Dosing in the Drug-Therapy Group.*

Drug and Total Daily Dose	At End of Blanking Period (N=94)	At Treatment Failure, 12 Months, or Exit (N=94)
	no. of patients (%)	
Flecainide		
50 mg†	2 (2)	2 (2)
100 mg	22 (23)	21 (22)
150 mg	0	1 (1)
200 mg	28 (30)	27 (29)
300 mg	3 (3)	2 (2)
375 mg	1 (1)	1 (1)
As needed†	2 (2)	2 (2)
Propafenone		
450 mg	6 (6)	7 (7)
650 mg	1 (1)	1 (1)
Dronedarone E-4031		
800 mg	11 (12)	10 (11)
Sotalol		
80 mg	1 (1)	1 (1)
160 mg	6 (6)	6 (6)
Amiodarone		
200 mg	1 (1)	0
400 mg	1 (1)	1 (1)
Not taking a class I or III antiarrhythmic drug	9 (10)	12 (13)

* This table does not include three patients who requested withdrawal and two patients who were lost to follow-up before the end of the blanking period.
† These doses are not in accordance with the 2014 guideline for the management of atrial fibrillation from the American College of Cardiology, American Heart Association, and Heart Rhythm Society.[5]

PRIMARY SAFETY END POINT

Two primary safety end-point events occurred in the ablation group: development of a clinically significant pericardial effusion within 30 days and a myocardial infarction within 7 days after the procedure. The Kaplan–Meier estimate of the percentage of patients with a primary safety end-point event within 12 months was 1.9% (95% CI, 0.5 to 7.5). Because the upper boundary of the two-sided 95% confidence interval was less than 12%, the prespecified performance objective for the primary safety end point was met ($P<0.001$). One patient who had been randomly assigned to drug therapy had a major vascular complication after a subsequent cryoballoon ablation; this event was not included in the primary safety analysis. Results for prespecified subgroups and the tipping-point analysis are shown in Tables S7 and S8, respectively.

SERIOUS ADVERSE EVENTS

A serious adverse event occurred in 14% of the patients in the ablation group and in 14% of the patients in the drug-therapy group (Table 4). There were no cases of pulmonary vein stenosis. Table S9 shows overall adverse events.

SECONDARY END POINTS

Quality of life in the ablation group, as assessed with both the AFEQT and the EQ-5D, was found to have improved significantly from baseline to 12 months in an analysis in which the Hochberg method was used to account for multiple comparisons (Table S10). Overall, 31 of 104 patients in the ablation group and 43 of 99 patients in the drug-therapy group reported at least one cardiovascular-related health care utilization event. In the ablation group, there were 13 hospitalizations, 10 emergency-department visits, and 44 unscheduled office visits. In the drug-therapy

Table 3. Primary Efficacy End-Point Events within 12 Months.*

Event	Ablation (N=104)	Drug Therapy (N=99)
	no. of patients	
Primary efficacy end-point event	26	51
Initial failure of the procedure	3	—
Left atrial nonpulmonary vein isolation ablation	1†	—
Inability to isolate all accessible targeted pulmonary veins	2	—
Use of a nontrial device in the left atrium	1†	—
Documented atrial fibrillation, atrial tachycardia, or atrial flutter after 90 days	21	35
Ablation in left atrium‡	0	15
Cardioversion after 90 days	0	1
Class I or III antiarrhythmic drug use after 90 days	2	—

* The primary end point was treatment success at 12 months, defined as freedom from any of the following events: initial failure of the procedure; any subsequent atrial fibrillation surgery or ablation in the left atrium; or atrial arrhythmia recurrence, cardioversion, or use of class I or III antiarrhythmic drugs (ablation group only) outside the 90-day blanking period.

† One participant had treatment failure due to both left atrial nonpulmonary vein isolation ablation and the use of a nontrial device in the left atrium.

‡ In the ablation group, any ablation other than the index ablation indicated treatment failure; in the drug-therapy group, any ablation indicated treatment failure.

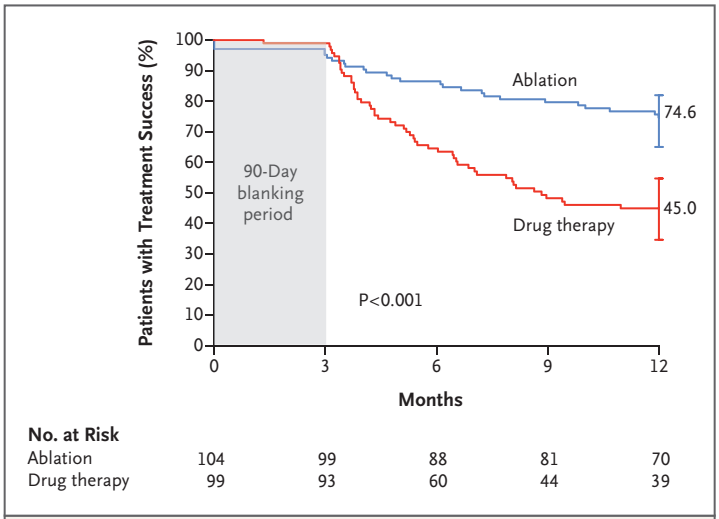

Figure 1. Treatment Success at 12 Months.

Treatment success was defined as freedom from any of the following events: initial failure of the procedure; any subsequent atrial fibrillation surgery or ablation in the left atrium; or atrial arrhythmia recurrence, cardioversion, or use of class I or III antiarrhythmic drugs (ablation group only) outside the 90-day blanking period. The median time from randomization to treatment initiation was 24 days in the ablation group and 2 days in the drug-therapy group. During the blanking period, three patients in the ablation group had treatment failure as a result of initial failure of the procedure, and one patient in the drug-therapy group had treatment failure because the patient underwent an ablation. Because the assumption of proportional hazards was not met, a hazard ratio is not presented. I bars indicate 95% confidence intervals.

group, there were 32 hospitalizations, 17 emergency-department visits, and 39 unscheduled office visits. Three of the 104 patients (3%) in the ablation group underwent a total of five cardioversions, and 7 of the 99 patients (7%) in the drug-therapy group underwent a total of eight cardioversions. In Kaplan–Meier analyses with the Hochberg method used to control for multiple testing, we found no significant differences at 12 months between the two groups in the percentages of patients free from a cardiovascular health care utilization event (69.9% and 53.5%, respectively) or free from cardioversion (97.1% and 92.4%, respectively).

DISCUSSION

In this randomized, multicenter trial, the initial use of cryoballoon ablation was superior to drug therapy for the prevention of atrial arrhythmia recurrence, with 75% of patients in the cryoballoon group and 45% of patients in the drug-therapy group having treatment success at 12 months. In the ablation group, 1.9% of patients had a primary safety end-point event within 12 months. A third of the patients in the drug-therapy group subsequently underwent ablation as a result of drug-related side effects or recurrence of arrhythmia.

Table 4. Serious Adverse Events.*

Serious Adverse Event	Ablation (N=104)		Drug Therapy (N=99)	
	no. of events	*no. of patients (%)*	*no. of events*	*no. of patients (%)*
Any serious adverse event	22	15 (14)	16	14 (14)
Acute myocardial infarction	2	1 (1)	0	0
Angina unstable	0	0	1	1 (1)
Atrial fibrillation	3	2 (2)	1	1 (1)
Bradycardia	0	0	1	1 (1)
Chest pain	1	1 (1)	1	1 (1)
Fluid overload	0	0	1	1 (1)
Heart rate increase	1	1 (1)	0	0
Hypertension	1	1 (1)	0	0
Hypotension	1	1 (1)	0	0
Muscle hemorrhage	1	1 (1)	0	0
Palpitations	0	0	1	1 (1)
Pericardial effusion	1	1 (1)	0	0
Pericarditis	0	0	1	1 (1)
Presyncope	0	0	1	1 (1)
Pulmonary embolism	0	0	1	1 (1)
Syncope	0	0	2	2 (2)
Ventricular tachyarrhythmia	1	1 (1)	0	0
Other	10†	9 (9)	5‡	5 (5)

* A serious adverse event was defined as an adverse event that led to death; that led to a serious deterioration in health resulting in a life-threatening illness or injury, permanent impairment of a body structure or a body function, inpatient hospitalization, prolonged hospitalization (>24 hours), or medical or surgical intervention to prevent life-threatening illness, injury, or permanent impairment to a body structure or a body function; or that led to fetal distress, fetal death, or a congenital abnormality or birth defect.

† Other includes appendicitis, cardiac sarcoidosis, encephalopathy, hepatic cyst, migraine, nephrolithiasis, noncardiac chest pain, and obesity (in 1 patient each) and osteoarthritis (in 2 patients).

‡ Other includes chronic obstructive pulmonary disease, influenza, osteoarthritis, rotator cuff syndrome, and spinal stenosis (in 1 patient each).

The recently published results of EAST-AFNET 4 showed that early rhythm control with either drug therapy or ablation resulted in better cardiovascular outcomes than usual care at a median 5.1 years of follow-up.[11] Increasing evidence suggests that earlier intervention with ablation is associated with a higher likelihood of freedom from atrial arrhythmia recurrence[6-10] and may prevent progression to persistent atrial fibrillation.[12] However, current guidelines and consensus statements recommend treatment with antiarrhythmic medications before undergoing ablation,[3-5] resulting in a delay from diagnosis to ablation.

In our trial, we enrolled patients without marked left atrial enlargement who were relatively early in the atrial fibrillation disease process, with a mean time from onset to enrollment of 1.3 years. Patients randomly assigned to cryoballoon ablation were much less likely than those who received drug therapy to have treatment failure within 12 months. A meta-analysis of three previous randomized, controlled trials (involving 491 patients in total) comparing point-by-point radiofrequency ablation with drug therapy[13-15] showed a modestly lower risk of atrial fibrillation recurrence with ablation than with drug therapy,[16] supporting the class IIa recommendation of catheter ablation as a first-line treatment in current guidelines.[4,5] However, a relatively high incidence of repeat ablation and antiarrhythmic drug use was observed in the ablation groups in two of these three trials.[13,14]

Our trial provides additional evidence support-

ing the use of ablation as an initial first-line treatment. We used a stringent definition of treatment success in which we classified subsequent ablation at any time as a primary end-point event in both treatment groups. Ablation was the reason for treatment failure in 15 patients in the drug-therapy group. Despite our stringent definition of treatment success, we observed a high percentage of patients (75%) in the ablation group who had treatment success after a single procedure without concomitant use of antiarrhythmic drugs. These findings are consistent with recent observations that the efficacy of ablation has improved over the past decade[18,19]; they are also consistent with findings in observational studies involving patients who had not received rhythm-control therapy previously, in which high percentages of patients were found to have freedom from atrial arrhythmia recurrence after cryoballoon ablation (71 to 89% over a follow-up period of 12 to 28 months).[20-22]

The safety profile of cryoballoon ablation has been established in patients whose condition does not respond to drug therapy, with complications occurring in approximately 6% of patients during follow-up periods of 14 to 34 months.[23,24] The present trial similarly showed that serious complications of cryoballoon ablation were uncommon among patients who had not previously received rhythm-control therapy, with only two patients in the ablation group having a primary safety end-point event. We observed no cases of stroke, death, atrial–esophageal fistula, unresolved phrenic nerve injury at 12 months, or symptomatic pulmonary vein stenosis at 12 months; however, the sample size may not have been large enough to allow detection of these uncommon outcomes.

Although antiarrhythmic drug therapy is recommended before ablation in current guidelines, drug therapy fails to prevent atrial fibrillation recurrence in 43 to 67% of patients[25] and has been associated with potentially serious proarrhythmic and extracardiac adverse effects.[4,5] In the present trial, treatment success was achieved in only 45% of the patients who had been randomly assigned to drug therapy. However, many of the adverse events that had previously been associated with antiarrhythmic drug use were not observed, a finding similar to that reported in EAST-AFNET 4.[11] The percentage of patients with a serious adverse event was similar between the treatment groups in the present trial. Among the patients who had been randomly assigned to drug therapy, 13% discontinued treatment within 12 months and 34% underwent ablation within a year after randomization. These findings highlight the clinical challenges associated with drug therapy for long-term rhythm control.

Our trial has some limitations. Follow-up was limited to 1 year; additional studies are needed to characterize the longer-term efficacy of first-line cryoballoon ablation. This trial allowed the use of class I and III drugs in accordance with current guidelines (Table 2). This introduces variability, and some patients may have been undertreated, which could have increased the relative benefit of ablation. Missed rhythm monitoring and the use of intermittent rather than continuous monitoring may have resulted in an overestimation of treatment success in both groups. However, adherence to monitoring was generally similar in the two groups and was similar to that in previous trials.[14,17] The unblinded nature of the trial may have contributed to the observed benefits of ablation, including the improvement in the quality of life. The only prespecified analysis of quality-of-life data was a comparison between baseline and 12 months in the ablation group; a comparison of quality-of-life end points between the groups was not prespecified because it was anticipated that changes in quality of life in the drug-therapy group would not necessarily reflect 12 months of drug therapy, as a result of patients having crossed over to ablation. Lastly, the trial was not powered to evaluate cardiovascular outcomes.

In this randomized, multicenter trial, cryoballoon ablation was superior to antiarrhythmic drug therapy for the prevention of atrial arrhythmia recurrence in patients with paroxysmal atrial fibrillation who had not previously received rhythm-control therapy. Serious procedure-related adverse events were uncommon.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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