

ORIGINAL ARTICLE

Cryoablation or Drug Therapy for Initial Treatment of Atrial Fibrillation

Jason G. Andrade, M.D., George A. Wells, Ph.D., Marc W. Deyell, M.D., Matthew Bennett, M.D., Vidal Essebag, M.D., Ph.D., Jean Champagne, M.D., Jean-Francois Roux, M.D., Derek Yung, M.D., Allan Skanes, M.D., Yaariv Khaykin, M.D., Carlos Morillo, M.D., Umjeet Jolly, M.D., Paul Novak, M.D., Evan Lockwood, M.D., Guy Amit, M.D., Paul Angaran, M.D., John Sapp, M.D., Stephan Wardell, M.D., Sandra Lauck, Ph.D., Laurent Macle, M.D., and Atul Verma, M.D., for the EARLY-AF Investigators*

ABSTRACT

BACKGROUND

Guidelines recommend a trial of one or more antiarrhythmic drugs before catheter ablation is considered in patients with atrial fibrillation. However, first-line ablation may be more effective in maintaining sinus rhythm.

METHODS

We randomly assigned 303 patients with symptomatic, paroxysmal, untreated atrial fibrillation to undergo catheter ablation with a cryothermy balloon or to receive antiarrhythmic drug therapy for initial rhythm control. All the patients received an implantable cardiac monitoring device to detect atrial tachyarrhythmia. The follow-up period was 12 months. The primary end point was the first documented recurrence of any atrial tachyarrhythmia (atrial fibrillation, atrial flutter, or atrial tachycardia) between 91 and 365 days after catheter ablation or the initiation of an antiarrhythmic drug. The secondary end points included freedom from symptomatic arrhythmia, the atrial fibrillation burden, and quality of life.

RESULTS

At 1 year, a recurrence of atrial tachyarrhythmia had occurred in 66 of 154 patients (42.9%) assigned to undergo ablation and in 101 of 149 patients (67.8%) assigned to receive antiarrhythmic drugs (hazard ratio, 0.48; 95% confidence interval [CI], 0.35 to 0.66; $P < 0.001$). Symptomatic atrial tachyarrhythmia had recurred in 11.0% of the patients who underwent ablation and in 26.2% of those who received antiarrhythmic drugs (hazard ratio, 0.39; 95% CI, 0.22 to 0.68). The median percentage of time in atrial fibrillation was 0% (interquartile range, 0 to 0.08) with ablation and 0.13% (interquartile range, 0 to 1.60) with antiarrhythmic drugs. Serious adverse events occurred in 5 patients (3.2%) who underwent ablation and in 6 patients (4.0%) who received antiarrhythmic drugs.

CONCLUSIONS

Among patients receiving initial treatment for symptomatic, paroxysmal atrial fibrillation, there was a significantly lower rate of atrial fibrillation recurrence with catheter cryoballoon ablation than with antiarrhythmic drug therapy, as assessed by continuous cardiac rhythm monitoring. (Funded by the Cardiac Arrhythmia Network of Canada and others; EARLY-AF ClinicalTrials.gov number, NCT02825979.)

From Vancouver General Hospital (J.G.A., M.B.), the University of British Columbia (J.G.A., M.W.D., M.B., S.L.), and the Centre for Cardiovascular Innovation (J.G.A., M.W.D.), Vancouver, Montreal Heart Institute, Université de Montréal (J.G.A., L.M.) and McGill University Health Centre (V.E.), Montreal, the University of Ottawa Heart Institute, Ottawa (G.A.W.), Université Laval, Quebec, QC (J.C.), Université de Sherbrooke, Sherbrooke, QC (J.-F.R.), Rouge Valley Centenary Hospital, Scarborough, ON (D.Y.), Western University, London, ON (A.S.), Southlake Regional Health Centre, University of Toronto, Newmarket, ON (Y.K., A.V.), Libin Cardiovascular Institute, University of Calgary, Calgary, AB (C.M.), St. Mary's General Hospital, Kitchener, ON (U.J.), Royal Jubilee Hospital, Victoria, BC (P.N.), Royal Alexandra Hospital, Edmonton, AB (E.L.), McMaster University, Hamilton, ON (G.A.), St. Michael's Hospital, University of Toronto, Toronto (P.A.), Dalhousie University, Halifax, NS (J.S.), and the University of Saskatchewan, Saskatoon, SK (S.W.) — all in Canada. Address reprint requests to Dr. Andrade at Vancouver General Hospital, Rm. 9159, 9th Fl. Cardiology, 2775 Laurel St., Vancouver, BC V5Z 1M9, Canada, or at jason.andrade@vch.ca.

*A list of the EARLY-AF committee members and investigators is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on November 16, 2020, at NEJM.org.

DOI: [10.1056/NEJMoa2029980](https://doi.org/10.1056/NEJMoa2029980)

Copyright © 2020 Massachusetts Medical Society.

ATRIAL FIBRILLATION, THE MOST COMMON cardiac arrhythmia, affects approximately 1 to 2% of the overall population.¹ Without preventative treatment, atrial fibrillation will recur in 90% of patients.² Guidelines recommend the use of antiarrhythmic drugs as initial therapy for the maintenance of sinus rhythm in symptomatic patients.³⁻⁵ However, these medications have somewhat limited efficacy^{6,7} and have substantial side effects.^{8,9}

Catheter ablation is superior to antiarrhythmic drugs in maintaining sinus rhythm and improving quality of life in patients in whom drugs have already failed.¹⁰⁻¹² However, catheter ablation as first-line treatment may be better than antiarrhythmic drugs in preventing the recurrence of atrial tachyarrhythmia, reducing the atrial fibrillation burden, and improving patient well-being. Previous trials of early catheter ablation with radiofrequency energy have not been conclusive and have been limited by a high incidence of recurrent arrhythmia, complications, and crossover.¹³⁻¹⁵

We conducted the randomized Early Aggressive Invasive Intervention for Atrial Fibrillation (EARLY-AF) trial of initial rhythm control in patients with symptomatic, untreated atrial fibrillation. We compared the use of catheter cryoballoon ablation with antiarrhythmic drugs to prevent the recurrence of atrial tachyarrhythmia, as assessed by an implantable continuous rhythm monitor.

METHODS

TRIAL DESIGN AND OVERSIGHT

This investigator-initiated, multicenter, open-label, randomized trial with blinded end-point adjudication was conducted at 18 centers in Canada (listed in the Supplementary Appendix, available with the full text of this article at NEJM.org). The trial protocol has been described previously¹⁶ and is provided with the statistical analysis plan at NEJM.org. An academic steering committee oversaw the trial design and conduct. The trial protocol was approved by the institutional review committee at each center.

Data monitoring and collection and the primary data analysis 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, unrestricted grants from Medtronic and Baylis Medical, and 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 the patients; the data collection, storage, or analysis; the interpretation of the data; the preparation of the manuscript; or the decision to submit the manuscript for publication.

TRIAL PARTICIPANTS AND RANDOMIZATION

We enrolled adults (>18 years of age) who had symptomatic atrial fibrillation and at least one episode of atrial fibrillation detected on electrocardiography within 24 months before randomization. Patients were excluded if they had a history of regular (daily) use of a class I or class III antiarrhythmic drug at therapeutic doses. Further inclusion and exclusion criteria are detailed in Table S1 in the Supplementary Appendix. All the patients provided written informed consent.

Eligible patients were randomly assigned in a 1:1 ratio to an initial strategy of catheter cryoballoon ablation or antiarrhythmic drug therapy. Randomization was performed with concealed allocation, according to a computer-generated allocation sequence, with permuted blocks of four and eight. Randomization was stratified according to center with the use of Web-based software.

TRIAL PROCEDURES

After enrollment, all the patients underwent insertion of an implantable cardiac monitor (Reveal LINQ, Medtronic). This 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).¹⁷ 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 (Table S2). Data on potential arrhythmia events detected by the device were stored for adjudication by an independent clinical end-point committee whose members were unaware of the trial-group assignments.

The patients who were assigned to receive an-

tiarrhythmic drug therapy were prescribed daily therapy within 1 week after randomization. The choice of antiarrhythmic drug for each patient was determined according to local practice. During the 3-month titration phase, the drug was progressively adjusted to the maximum dose that was associated with an acceptable side-effect profile, according to protocols detailed in the Supplementary Appendix, with the goal of complete suppression of atrial fibrillation as detected by the implanted monitor. In the event of inefficacy or unacceptable side effects during the first 90 days, a switch to a second or third agent was prespecified.

The cryoablation procedure was detailed previously¹⁶ and is described in the Supplementary Appendix. Patients who were randomly assigned to catheter ablation underwent pulmonary-vein isolation with the use of a 23-mm or 28-mm cryoballoon (Arctic Front Advance, Medtronic). The procedural end point was bidirectional conduction block of all pulmonary veins after a 20-minute observation period. If reconnection of a pulmonary vein was observed, repeat ablation was performed until the block was achieved.

In accordance with the 2017 expert consensus statement on catheter ablation, recurrences of atrial tachyarrhythmia during the first 90 days after the index ablation (the “blinking period”) were not counted in the determination of the first clinical failure for the primary end point.¹⁸ The rationale for the postablation blinking period is that early recurrences of atrial tachyarrhythmia are not necessarily predictive of later treatment failure. A similar blinking period in the patients assigned to antiarrhythmic drug therapy allowed for adjustment to the maximum doses that had an acceptable side-effect profile. Periablation use of antiarrhythmic drugs (excluding amiodarone) was permitted as long as these agents were discontinued five half-lives before the end of the blinking period.

The patients were followed for 1 year after the initiation of treatment with a telephone call at 7 days and visits at 3, 6, and 12 months. Automatic transmissions from the implantable cardiac monitor were obtained on a daily basis, and manual transmissions were obtained at least weekly. The patients were also instructed to record episodes of symptomatic arrhythmia with a patient-controlled handheld telemetry device. Data for measures of quality of life were collected at

6 and 12 months. These measures included the disease-specific Atrial Fibrillation Effect on Quality-of-Life survey (AFEQT) and the generic European Quality of Life–5 Dimensions (EQ-5D) survey. Symptoms of atrial fibrillation were measured on the Canadian Cardiovascular Society Severity of Atrial Fibrillation (CCS-SAF) scale.

The patients were permitted to cross over from antiarrhythmic drug therapy to ablation only after independent review to ensure that three criteria were met. First, an atrial tachyarrhythmia event had to have occurred after the blanking period (a primary end-point event). Second, the recurrence had to have been of sufficient clinical severity to warrant a change in therapy. Third, the recurrence had to have occurred despite the use of a therapeutic dose of an antiarrhythmic drug, which was defined as flecainide at a dose of more than 100 mg per day, sotalolol at a dose of more than 160 mg per day, propafenone at a dose of more than 300 mg per day, or dronedarone at a dose of 800 mg per day. In order for patients to cross over from ablation to antiarrhythmic drug therapy, only the first and second criteria were applied. A patient who switched treatment from drug therapy to ablation was encouraged to undergo ablation after the conclusion of the trial. A change in treatment strategy within the blanking period or in the absence of documented atrial fibrillation was a protocol violation and was considered to be a primary end-point event.

TRIAL END POINTS

The primary end point was the first recurrence of any atrial tachyarrhythmia (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. Repeat ablation during the blanking period was not permitted, and performance of repeat ablation was considered to be a primary end-point event. The secondary end points were the first recurrence of symptomatic atrial tachyarrhythmia between 91 and 365 days after the initiation of treatment, the arrhythmia burden (expressed as a percentage of time in atrial fibrillation), the success of multiple ablation procedures, quality of life, health care utilization, and serious adverse events. An adverse event was considered to be serious if it resulted in death or functional disability, warranted an intervention, or resulted in or prolonged hospital-

ization of more than 24 hours. All the efficacy and safety end points were independently adjudicated by a clinical end-point committee whose members were unaware of the trial-group assignments and the identity of the patients.

STATISTICAL ANALYSIS

We estimated the sample size for a two-sample time-to-event comparison using the log-rank test. We assumed a 1-year recurrence-free survival of 70% in the ablation group.¹³⁻¹⁵ Using a two-tailed alpha of 0.05, we estimated that 88 independent

events would be needed to achieve 90% power to show a 20-percentage-point difference between the ablation group and the antiarrhythmic drug group in the incidence of recurrence.¹⁴ Assuming a 15% crossover or loss to follow-up, we estimated that 298 patients (149 in each group) would need to be enrolled.

Analyses of the primary and secondary end points were based on the intention-to-treat principle. Unadjusted survival curves were estimated with the Kaplan–Meier method and compared with the use of log-rank tests. Unadjusted hazard ratios

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Ablation Group (N=154)	Antiarrhythmic Drug Group (N=149)
Age — yr	57.7±12.3	59.5±10.6
Male sex — no. (%)	112 (72.7)	102 (68.5)
BMI†	30.9±14.2	29.7±9.3
Obesity — no. (%)‡	56 (36.4)	53 (35.6)
Tobacco use	8 (5.2)	10 (6.7)
Blood pressure — mm Hg		
Systolic	129.1±18.1	129.3±15.7
Diastolic	78.4±10.6	78.0±9.8
Median yr since diagnosis of atrial fibrillation (IQR)	1 (0–3)	1 (0–4)
Paroxysmal atrial fibrillation — no. (%)	147 (95.5)	140 (94.0)
Symptomatic atrial fibrillation episodes/mo — median (IQR)	3 (1–10)	3 (1–10)
Previous cardioversion — no. (%)	56 (36.4)	63 (42.3)
Quality-of-life scores		
AFEQT score§	61.4±19.7	57.4±20.6
EQ-5D score¶	0.77±0.26	0.75±0.26
EQ-VAS score	75.4±14.5	74.4±16.5
CCS-SAF score of 3 or 4 — no. (%)**	84 (54.5)	84 (56.4)
CHA ₂ DS ₂ -VASc score††	1.9±1.0	1.9±1.1
Medications — no. (%)		
Beta-blocker	85 (55.2)	92 (61.7)
Nondihydropyridine calcium-channel blocker	11 (7.1)	10 (6.7)
ACE inhibitor	24 (15.6)	21 (14.1)
Angiotensin II receptor blocker	20 (13.0)	18 (12.1)
HMG-CoA reductase inhibitor	38 (24.7)	39 (26.2)
Mineralocorticoid-receptor antagonist	1 (0.6)	1 (0.7)
Previous use of class I or class III antiarrhythmic drug — no. (%)‡‡	40 (26.0)	44 (29.5)
Oral anticoagulation — no. (%)		
Warfarin	5 (3.2)	9 (6.0)
Non-vitamin K antagonist oral anticoagulant	98 (63.6)	87 (58.4)

Table 1. (Continued.)		
Characteristic	Ablation Group (N = 154)	Antiarrhythmic Drug Group (N = 149)
Concomitant cardiovascular conditions — no. (%)		
Hypertension	57 (37.0)	55 (36.9)
Ischemic heart disease	12 (7.8)	7 (4.7)
Sleep apnea	32 (20.8)	32 (21.5)
Previous stroke or transient ischemic attack	4 (2.6)	5 (3.4)
Stable heart failure ^{§§}	14 (9.1)	14 (9.4)
Left atrial diameter — mm	39.5±5.0	38.1±6.5
Left atrial volume — ml/m ²	35.6±15.2	35.4±12.5
Left ventricular ejection fraction — %	59.6±7.0	59.8±7.6

* Plus-minus values are means ±SD. ACE denotes angiotensin-converting enzyme, HMG-CoA 3-hydroxy-3-methylglutaryl-coenzyme A, and IQR interquartile range.

† The body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters.

‡ Obesity was defined as a BMI greater than 30.

§ 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 a 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 a 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 a 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 (severe effect of symptoms on quality of life and activities of daily living).

†† Scores on CHA₂DS₂-VASc, a clinical estimation of the risk of stroke among patients with atrial fibrillation, range from 0 to 9, with higher scores indicating a higher risk of stroke.

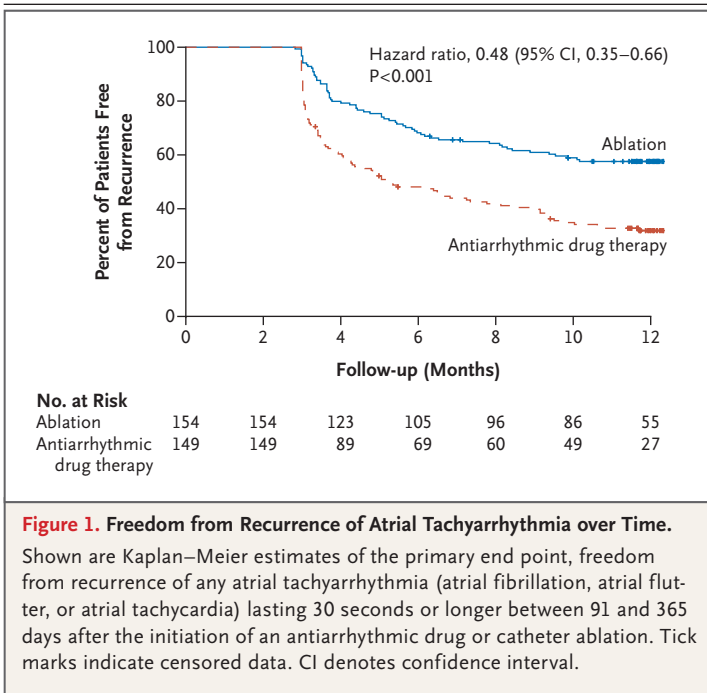
‡‡ The trial inclusion criteria permitted enrollment if a patient had received a Vaughan Williams class I or III antiarrhythmic drug in the remote past (i.e., he or she had received a trial of the drug and discontinued it with a washout period of >6 months), recently (within the past 6 months, but the dose was below the therapeutic threshold [i.e., <100 mg per day for flecainide, <300 mg per day for propafenone, <160 mg per day for sotalol, and <800 mg per day for dronedarone]), or temporarily (at a therapeutic dose for <4 weeks). However, enrollment was not allowed if the patient had had antiarrhythmic drug failure (adverse drug effects or frequent episodes of atrial fibrillation).

§§ Stable heart failure was defined as New York Heart Association class II or a left ventricular ejection fraction of less than 50%.

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, age, sex, weight, and the duration of atrial fibrillation. The proportional-hazards assumption was assessed with graphical tests (i.e., visual inspection of the log-minus-log plot) and numerical tests (i.e., tests of the interaction term between treatment and time, as described in the Supplementary Appendix). Changes in quality-of-life scores at 6 and 12 months from baseline were expressed as least-squares means ±SE and were analyzed with the use of a linear mixed-effects model for repeated measures, in-

cluding group, visit, and the interaction between group and visit. Prespecified subgroup analyses included the ablation volume according to center (procedure volume above or below the median), left atrial size (either enlarged with a left atrial diameter of ≥41 mm, a left atrial volume ≥59 ml, or a left atrial volume index ≥29 ml per square meter or not enlarged), and the duration of time since the diagnosis of atrial fibrillation (≥1 year or <1 year).

All tests were conducted at an alpha level of 0.05. 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 the secondary end points. The analyses were performed with the use of SAS software, version 9.4 (SAS Institute).



RESULTS

PATIENTS AND FOLLOW-UP

Between January 17, 2017, and December 21, 2018, a total of 303 patients were enrolled and were randomly assigned either to undergo cryoablation (154 patients) or to receive antiarrhythmic drug therapy (149 patients) (Fig. S1). The baseline characteristics were balanced in the two groups (Table 1). The median time from randomization to the initiation of treatment was 1 day (interquartile range, 0 to 9) in the antiarrhythmic drug group and 50 days (interquartile range, 41 to 64) in the ablation group. After the initiation of treatment, the median number of daily transmissions from the implantable cardiac monitor received per patient was 365 (interquartile range, 365 to 365). None of the patients crossed over from their assigned strategy before the occurrence of a primary end-point event.

TREATMENT CHARACTERISTICS

In the ablation group, complete pulmonary-vein isolation was confirmed in all 152 patients who underwent the procedure. The median duration of the procedure was 106 minutes (interquartile range, 89 to 131), with a fluoroscopy time of 18.9 minutes (interquartile range, 12.6 to 27.0). Additional details about ablation are provided in Ta-

ble S3. One repeat ablation was performed during the blanking period and was considered to be a primary end-point event. During follow-up, 26 patients who were randomly assigned to undergo ablation received an antiarrhythmic drug after a primary end-point event. Of these 26 patients, 17 underwent a second ablation procedure at a median of 213 days (interquartile range, 160 to 287) after the index ablation procedure.

Information on drugs and dosing used in the antiarrhythmic drug group is provided in Table S4. Flecainide (median dose, 200 mg per day) was the most frequently prescribed antiarrhythmic drug. Most patients (103 of 149 patients [69.1%]) received one drug. None of the patients in the antiarrhythmic drug group underwent ablation during the blanking period or before the occurrence of a primary end-point event. During follow-up, 36 of 149 patients (24.2%) underwent ablation after a documented primary end-point event at a median of 192 days (interquartile range, 151 to 253) after the initiation of antiarrhythmic drug therapy.

END POINTS

At 1 year, a documented recurrence of atrial tachyarrhythmia had occurred in 66 of the 154 patients assigned to undergo cryoablation (42.9%) and in 101 of the 149 patients assigned to receive antiarrhythmic drugs (67.8%) (hazard ratio, 0.48; 95% confidence interval [CI], 0.35 to 0.66; $P < 0.001$) (Fig. 1 and Table 2). The hazard ratio and 95% confidence interval were similar in an analysis of the primary end point that was adjusted for clinically important baseline characteristics (Table S5). The treatment effect for the primary end point was consistent across prespecified subgroups, as shown in Figure S2.

Symptomatic atrial tachyarrhythmia recurred in 17 of the 154 patients (11.0%) assigned to undergo ablation, as compared with 39 of the 149 patients assigned to receive antiarrhythmic drugs (26.2%) (hazard ratio, 0.39; 95% CI, 0.22 to 0.68) (Fig. S3). The median atrial fibrillation burden (the percentage of total time in atrial fibrillation) was 0% (interquartile range, 0 to 0.08) in patients assigned to undergo catheter ablation and 0.13% (interquartile range, 0 to 1.60) in those assigned to receive antiarrhythmic drugs (Fig. 2 and Table 2). At 1 year, the least-squares mean (\pm SE) change from baseline in the AFEQT survey score was 26.9 ± 1.9 in patients assigned to

Table 2. Primary and Secondary End Points.*

End Point	Ablation Group (N=154)	Antiarrhythmic Drug Group (N=149)	Treatment Effect (95% CI)
Primary end point: recurrence of symptomatic or asymptomatic atrial tachyarrhythmia with 90-day blanking period — no. (%)	66 (42.9)	101 (67.8)	0.48 (0.35–0.66)†
Secondary arrhythmia end points			
Recurrence of symptomatic atrial tachyarrhythmia, with 90-day blanking period — no. (%)	17 (11.0)	39 (26.2)	0.39 (0.22–0.68)†
Recurrence of symptomatic or asymptomatic atrial tachyarrhythmia after multiple ablation procedures — no. (%)	52 (33.8)	101 (67.8)	0.38 (0.27–0.53)†
Recurrence of symptomatic atrial tachyarrhythmia after multiple ablation procedures — no. (%)	11 (7.1)	39 (26.2)	0.26 (0.13–0.51)†
Atrial fibrillation burden — % time in atrial fibrillation			
Median (IQR)	0 (0–0.08)	0.13 (0–1.60)	
Mean	0.6±3.3	3.9±12.4	–3.3±1.0‡
Secondary quality-of-life end points§			
Change from baseline in AFEQT score¶			
At 6 mo	24.4±1.6	17.9±1.6	10.5±2.2
At 12 mo	26.9±1.9	22.9±2.0	8.0±2.2
Change from baseline in EQ-5D score			
At 6 mo	0.08±0.02	0.07±0.02	0.03±0.03
At 12 mo	0.12±0.02	0.06±0.02	0.07±0.03
Change from baseline in EQ-VAS score**			
At 6 mo	6.10±1.17	4.97±1.19	2.05±1.68
At 12 mo	7.73±1.44	5.71±1.46	2.94±1.69
No symptoms — no. (%)††			
At 6 mo	129 (83.8)	90 (60.4)	1.34 (1.17–1.55)‡‡
At 12 mo	131 (85.1)	109 (73.2)	1.17 (1.05–1.30)‡‡
Secondary health care utilization end points — no. (%)			
Emergency department visits	28 (18.2)	30 (20.1)	0.90 (0.57–1.44)‡‡
Hospitalization >24 hr	5 (3.2)	13 (8.7)	0.37 (0.14–1.02)‡‡
Nonprotocol ablation procedures — no. (%)			
Ablation during 90-day blanking period	1 (0.6)	0	NA
Ablation after recurrence of atrial tachyarrhythmia	17 (11.0)	36 (24.2)	0.46 (0.27–0.78)‡‡
Secondary safety end points — no. (%)			
Any serious adverse event related to the trial regimen	5 (3.2)	6 (4.0)	0.81 (0.25–2.59)‡‡
Any safety end-point event	14 (9.1)	24 (16.1)	0.59 (0.29–1.21)‡‡

* Plus–minus values are means ±SE, except for atrial fibrillation burden, which is expressed as means ±SD. Data in columns 2 and 3 are observed data, and data in column 4 are model-based effect estimates. The 95% confidence intervals for the secondary end points were not adjusted for multiplicity, and inferences drawn may not be reproducible. NA denotes not applicable.

† The treatment effect is expressed as the hazard ratio and 95% confidence interval, which were calculated with the use of Cox regression.

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

§ Changes in quality-of-life scores at 6 months and 12 months from baseline 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 interaction between group and visit.

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

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

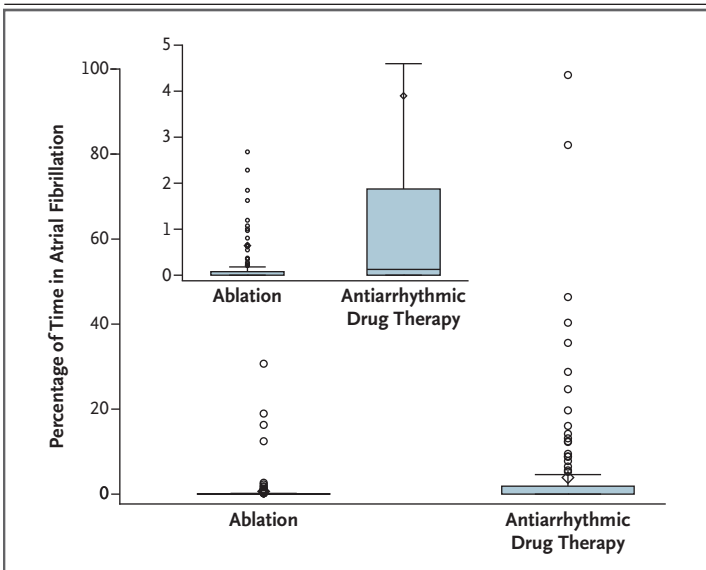


Figure 2. Atrial Fibrillation Burden in the Ablation and Antiarrhythmic Drug Groups.

Shown are box and whisker plots of atrial fibrillation burden expressed as the percentage of time in atrial fibrillation. The inset plots show the data on an expanded y axis. The upper whisker indicates the 90th percentile, the top of the blue box the 75th percentile, the horizontal line within the blue box the 50th percentile, and the bottom of the blue box the 25th percentile. The bottom whisker is too compressed to be shown but is meant to indicate the 10th percentile (0% in both groups). The circles beyond the upper whisker are individual data points for individual patients and are the outliers (beyond the 90th percentile). The diamond indicates the mean atrial fibrillation burden for the treatment group.

undergo ablation and 22.9 ± 2.0 in patients assigned to receive antiarrhythmic drugs (scores range from 0 to 100, with higher scores indicating better quality of life). Additional secondary end points are listed in Table 2.

Serious adverse events occurred in 5 of the 154 patients (3.2%) in the ablation group and in 6 of the 149 patients (4.0%) in the antiarrhythmic drug group. These events included three cases of phrenic-nerve palsy in the ablation group and two cases of wide-complex tachycardia, one case of syncope, and one case of exacerbation of heart failure in the antiarrhythmic drug group; each group also had two cases of symptomatic bradycardia for which pacemaker implantation was warranted. Adverse events are listed in Table 3 and Table S6.

DISCUSSION

In this trial involving patients with symptomatic, paroxysmal atrial fibrillation, we found that

arrhythmia recurred significantly less often with an initial strategy of catheter cryoballoon ablation than with an initial strategy of antiarrhythmic drug therapy, with a number needed to treat of 4. The use of implantable recorders that were capable of continuous monitoring also enabled the trial to show that ablation resulted in a lower burden of arrhythmia.

Atrial fibrillation is a progressive disease.¹⁹ Early in its course, atrial fibrillation is triggered by one or more ectopic foci that most commonly arise from the pulmonary veins.²⁰ Intervention early in the natural history of atrial fibrillation may limit disease progression by interrupting progressive pathophysiological changes and may improve clinical outcomes.¹⁹⁻²¹ Recently published trial results showed that early rhythm control, predominantly with antiarrhythmic drugs, reduced the risk of adverse cardiovascular outcomes, including stroke.²²

Most trials of catheter ablation of atrial fibrillation have compared ablation with antiarrhythmic drugs in patients in whom drug therapy has already failed, so the benefit is weighted toward ablation.^{10,11} Fewer trials have compared ablation with antiarrhythmic drugs as first-line therapy.¹³⁻¹⁵ These trials did not show a difference in arrhythmia or cardiovascular outcomes,¹³ showed only minor differences in arrhythmia recurrence,¹⁴ or were too small to be conclusive.¹⁵ The results were also limited by intermittent rhythm monitoring and high crossover from antiarrhythmic drugs to ablation, so the ability to detect a difference between treatment groups was blunted.¹³⁻¹⁵

The current trial restricted crossover between the groups. Furthermore, continuous rhythm monitoring, which is more sensitive in detecting paroxysmal atrial fibrillation than intermittent monitoring, was used.^{23,24} Continuous monitoring also allows for the assessment of atrial fibrillation burden, which may be more relevant to patient-centered outcomes than binary measures of arrhythmia recurrence. In a previous trial, the 53% ablation success measured in a time-to-first event analysis corresponded to a relative reduction in the atrial fibrillation burden that was greater than 99%.²⁵ In the current trial, the between-group difference in the percentage of patients with recurrence of atrial tachyarrhythmia was 24.9 percentage points, but the absolute between-group mean difference in atrial fibrillation burden was -3.3 percentage points.

Table 3. Adverse Events.

Event	Ablation Group (N=154)	Antiarrhythmic Drug Group (N=149)
Any serious adverse event related to the trial regimen — no. of patients (%) [*]	5 (3.2)	6 (4.0)
Any safety end-point event — no.		
Patients	14	24
Events	15	27
Death — no.	0	0
Cardiac event — no.		
Pericardial effusion for which drainage was warranted or tamponade	0	1 [†]
Pericardial effusion for which drainage was not warranted	0	0
Pericarditis	0	0
Exacerbation of heart failure	0	1
Syncope	1	2
Wide-complex tachycardia or proarrhythmic event	0	2
Bradycardia or atrioventricular block for which pacemaker insertion was warranted	2	2
Acute coronary syndrome	0	2
Neurologic event — no.		
Stroke	0	0
Transient ischemic attack	0	1
Vascular event — no.		
Arteriovenous fistula	0	0
Hematoma for which intervention was warranted	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	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
Other event — no.		
Erectile dysfunction	0	1
Rash	0	1
Epistaxis	2	0
Joint pain	0	2
Migraine	1	0

^{*} Details regarding the 11 serious adverse events adjudicated by the independent clinical end-point committee to be related to the assigned ablation or antiarrhythmic drug therapy are provided in Table S6 in the Supplementary Appendix.

[†] Cardiac tamponade for which intervention was warranted occurred in 1 patient who had been randomly assigned to antiarrhythmic drug therapy and who underwent ablation after the recurrence of arrhythmia (the primary end point).

[‡] Persistent phrenic-nerve palsy was defined as impairment in phrenic-nerve function persisting after the end of the ablation procedure. All 3 cases of phrenic-nerve palsy resolved within 1 month.

Safety is an important consideration with the early use of ablation in the treatment of atrial fibrillation. In our trial, the incidence of adverse events was similar in the two treatment groups. There were no procedural deaths or thromboembolic complications, and the most common periprocedural complication was self-limited phrenic-nerve palsy.²⁶ However, although antiarrhythmic drugs are not benign, we acknowledge that an invasive procedure is associated with more up-front risk than medical therapy, and the between-group difference in total atrial fibrillation burden in our trial was small.

Our trial has several limitations. Although the primary end point — recurrence of atrial arrhythmia — is an important benchmark for ablation trials,¹⁸ the trial did not have the power for us to examine cardiovascular outcomes. The trial was also performed with a single ablation technology, so our clinical outcomes may not be generalizable to the use of other ablation energy sources. The length of follow-up in the current trial was limited to 1 year, so we were unable to determine the longer-term effect of early ablation on progression of atrial fibrillation, health care utilization, and cost-effectiveness. The cardiac

monitor was implanted when treatment was initiated, so we could not evaluate the change in atrial fibrillation burden from baseline. Finally, we did not keep screening logs, so we cannot comment on the size of the patient pool screened to obtain the trial participants.

In this randomized trial involving patients with untreated paroxysmal atrial fibrillation, catheter cryoballoon ablation resulted in a significantly lower rate of recurrence of atrial tachyarrhythmia, as assessed by continuous cardiac rhythm monitoring, than antiarrhythmic drug therapy.

Supported by a peer-reviewed grant (SRG-15-P15-001) from the Cardiac Arrhythmia Network of Canada, which is a Network of Centres of Excellence program funded from a joint initiative of the Natural Sciences and Engineering Research Council, the Social Sciences and Humanities Research Council, the Canadian Institutes of Health Research, Industry Canada, and Health Canada; by unrestricted grants from Medtronic and Baylis Medical; and by in-kind support from Medtronic (implantable cardiac monitors) and the University of British Columbia.

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.

We thank the patients who participated in the trial, Patricia Theoret-Patrick and Janine Ryan for coordinating the trial, My-Linh Tran for data management, Li Chen of the Cardiovascular Research Methods Centre for statistical expertise, and Jody Swift of the University of British Columbia for administrative support.

REFERENCES

- Andrade J, Khairy P, Dobrev D, Nattel S. The clinical profile and pathophysiology of atrial fibrillation: relationships among clinical features, epidemiology, and mechanisms. *Circ Res* 2014;114:1453-68.
- Simantirakis EN, Papakonstantinou PE, Kanoupakis E, Chlouverakis GI, Tzeis S, Vardas PE. Recurrence rate of atrial fibrillation after the first clinical episode: a prospective evaluation using continuous cardiac rhythm monitoring. *Clin Cardiol* 2018;41:594-600.
- Andrade JG, Aguilar M, Atzema C, et al. The 2020 Canadian Cardiovascular Society/Canadian Heart Rhythm Society comprehensive guidelines for the management of atrial fibrillation. *Can J Cardiol* 2020 October 22 (Epub ahead of print).
- Hindricks G, Potpara T, Dagres N, et al. 2020 ESC guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2020 August 29 (Epub ahead of print).
- January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society in collaboration with the Society of Thoracic Surgeons. *Circulation* 2019;140(2):e125-e151.
- Roy D, Talajic M, Dorian P, et al. Amiodarone to prevent recurrence of atrial fibrillation. *N Engl J Med* 2000;342:913-20.
- Singh SN, Singh BN, Reda DJ, et al. Comparison of sotalol versus amiodarone in maintaining stability of sinus rhythm in patients with atrial fibrillation (Sotalol-Amiodarone Fibrillation Efficacy Trial [Safe-T]). *Am J Cardiol* 2003;92:468-72.
- Roden DM. Mechanisms and management of proarrhythmia. *Am J Cardiol* 1998;82:491-571.
- Doyle JF, Ho KM. Benefits and risks of long-term amiodarone therapy for persistent atrial fibrillation: a meta-analysis. *Mayo Clin Proc* 2009;84:234-42.
- Wilber DJ, Pappone C, Neuzil P, et al. Comparison of antiarrhythmic drug therapy and radiofrequency catheter ablation in patients with paroxysmal atrial fibrillation: a randomized controlled trial. *JAMA* 2010;303:333-40.
- Packer DL, Kowal RC, Wheelan KR, et al. Cryoballoon ablation of pulmonary veins for paroxysmal atrial fibrillation: first results of the North American Arctic Front (STOP AF) pivotal trial. *J Am Coll Cardiol* 2013;61:1713-23.
- Andrade JG, Macle L, Verma A, et al. Quality of life and health care utilization in the CIRCA-DOSE study. *JACC Clin Electrophysiol* 2020;6:935-44.
- Cosedis Nielsen J, Johannessen A, Raatikainen P, et al. Radiofrequency ablation as initial therapy in paroxysmal atrial fibrillation. *N Engl J Med* 2012;367:1587-95.
- Morillo CA, Verma A, Connolly SJ, et al. Radiofrequency ablation vs antiarrhythmic drugs as first-line treatment of paroxysmal atrial fibrillation (RAAFT-2): a randomized trial. *JAMA* 2014;311:692-700.
- Wazni OM, Marrouche NF, Martin DO, et al. Radiofrequency ablation vs antiarrhythmic drugs as first-line treatment of symptomatic atrial fibrillation: a randomized trial. *JAMA* 2005;293:2634-40.
- Andrade JG, Champagne J, Deyell MW, et al. A randomized clinical trial of early invasive intervention for atrial fibrillation (EARLY-AF) — methods and rationale. *Am Heart J* 2018;206:94-104.
- Sanders P, Pürerfellner H, Pokushalov

- E, et al. Performance of a new atrial fibrillation detection algorithm in a miniaturized insertable cardiac monitor: results from the Reveal LINQ Usability Study. *Heart Rhythm* 2016;13:1425-30.
18. Calkins H, Hindricks G, Cappato R, et al. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. *Heart Rhythm* 2017;14(10):e275-e444.
19. Padfield GJ, Steinberg C, Swampillai J, et al. Progression of paroxysmal to persistent atrial fibrillation: 10-year follow-up in the Canadian Registry of Atrial Fibrillation. *Heart Rhythm* 2017;14:801-7.
20. Nattel S, Guasch E, Savelieva I, et al. Early management of atrial fibrillation to prevent cardiovascular complications. *Eur Heart J* 2014;35:1448-56.
21. Andrade JG, Deyell MW, Verma A, et al. Association of atrial fibrillation episode duration with arrhythmia recurrence following ablation: a secondary analysis of a randomized clinical trial. *JAMA Netw Open* 2020;3(7):e208748.
22. Kirchhof P, Camm AJ, Goette A, et al. Early rhythm-control therapy in patients with atrial fibrillation. *N Engl J Med* 2020;383:1305-16.
23. Charitos EI, Ziegler PD, Stierle U, et al. Atrial fibrillation burden estimates derived from intermittent rhythm monitoring are unreliable estimates of the true atrial fibrillation burden. *Pacing Clin Electrophysiol* 2014;37:1210-8.
24. Ziegler PD, Koehler JL, Mehra R. Comparison of continuous versus intermittent monitoring of atrial arrhythmias. *Heart Rhythm* 2006;3:1445-52.
25. Andrade JG, Champagne J, Dubuc M, et al. Cryoballoon or radiofrequency ablation for atrial fibrillation assessed by continuous monitoring: a randomized clinical trial. *Circulation* 2019;140:1779-88.
26. Andrade JG, Dubuc M, Ferreira J, et al. Histopathology of cryoballoon ablation-induced phrenic nerve injury. *J Cardiovasc Electrophysiol* 2014;25:187-94.

Copyright © 2020 Massachusetts Medical Society.