ORIGINAL ARTICLE

Cryoballoon or Radiofrequency Ablation for Paroxysmal Atrial Fibrillation

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ABSTRACT

BACKGROUND

Current guidelines recommend pulmonary-vein isolation by means of catheter ablation as treatment for drug-refractory paroxysmal atrial fibrillation. Radiofrequency ablation is the most common method, and cryoballoon ablation is the second most frequently used technology.

METHODS

We conducted a multicenter, randomized trial to determine whether cryoballoon ablation was noninferior to radiofrequency ablation in symptomatic patients with drug-refractory paroxysmal atrial fibrillation. The primary efficacy end point in a time-to-event analysis was the first documented clinical failure (recurrence of atrial fibrillation, occurrence of atrial flutter or atrial tachycardia, use of antiarrhythmic drugs, or repeat ablation) following a 90-day period after the index ablation. The noninferiority margin was prespecified as a hazard ratio of 1.43. The primary safety end point was a composite of death, cerebrovascular events, or serious treatment-related adverse events.

RESULTS

A total of 762 patients underwent randomization (378 assigned to cryoballoon ablation and 384 assigned to radiofrequency ablation). The mean duration of follow-up was 1.5 years. The primary efficacy end point occurred in 138 patients in the cryoballoon group and in 143 in the radiofrequency group (1-year Kaplan–Meier event rate estimates, 34.6% and 35.9%, respectively; hazard ratio, 0.96; 95% confidence interval [CI], 0.76 to 1.22; $P<0.001$ for noninferiority). The primary safety end point occurred in 40 patients in the cryoballoon group and in 51 patients in the radiofrequency group (1-year Kaplan–Meier event rate estimates, 10.2% and 12.8%, respectively; hazard ratio, 0.78; 95% CI, 0.52 to 1.18; $P=0.24$).

CONCLUSIONS

In this randomized trial, cryoballoon ablation was noninferior to radiofrequency ablation with respect to efficacy for the treatment of patients with drug-refractory paroxysmal atrial fibrillation, and there was no significant difference between the two methods with regard to overall safety. (Funded by Medtronic; FIRE AND ICE ClinicalTrials.gov number, NCT01490814.)

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According to a 2012 expert consensus statement, catheter ablation of drug-refractory paroxysmal atrial fibrillation is a class I level A indication,[1] and pulmonary-vein isolation is the standard approach.[1-3] The two most frequently used ablation technologies for pulmonary-vein isolation differ in the energy source and mode of application. The most common method is the use of radiofrequency current applied in a point-by-point mode, which leads to cellular necrosis by tissue heating; the other method is the use of cryogenic energy applied with a balloon in a single-step mode, which leads to necrosis by freezing (Fig. 1). Radiofrequency ablation for atrial fibrillation requires only limited use of fluoroscopy, because catheter guidance is achieved with the use of an electroanatomical mapping system,[1,4] but the approach demands extensive training.[1] The complexity of radiofrequency ablation technology has restricted ablation therapy for atrial fibrillation to a few specialized centers and has limited the availability of ablation therapy. Cryoablation for atrial fibrillation requires more extensive fluoroscopic guidance to position the balloon catheter at the pulmonary veins. The cryoballoon was developed to create a circular lesion around each pulmonary vein in a relatively simple manner.

Some small studies have compared the two types of ablation catheters.[5-10] The current study was designed to compare the performance of the rather complex yet well-established approach of radiofrequency ablation with that of the apparently simpler approach of cryoballoon ablation in a larger population of patients with paroxysmal atrial fibrillation.

Methods

Trial Design

The FIRE AND ICE trial was a multicenter, randomized, noninferiority, parallel-group, open-label trial, with blinded end-point assessment, in which cryoballoon ablation was compared with radiofrequency ablation. The trial was investigator-initiated; the steering committee was responsible for design, execution, and conduct of the study (see the Supplementary Appendix, available with the full text of this article at NEJM.org). Local ethics review committees at each center approved the study. A data and safety monitoring board reviewed interim results and monitored the safety of the patients. An end-point review committee, the members of which were unaware of the treatment-group assignments, adjudicated primary safety and efficacy events. All members of the steering committee approved the statistical analyses and interpretation of the data. The decision to publish the results and decisions regarding the contents of the manuscript were made by the steering committee. The authors attest to the accuracy of the data and of all analyses and to the fidelity of this report to the trial protocol, which is available at NEJM.org.

The trial was funded by Medtronic, with trial oversight by FGK Representative Service as legal sponsor. A contract research organization (the Institute for Clinical Cardiovascular Research, Munich, Germany) collected, monitored, maintained, and analyzed the data. During the trial, the contract research organization became insolvent. Legal sponsorship and trial oversight was transferred to Medtronic for completion of the trial, and a second contract research organization (Genae, Antwerp, Belgium) was hired. Data transfer between the two contract research organizations occurred without the sponsor handling the data, and blinding with regard to the treatment-group assignments was preserved.

Study Participants

Sixteen centers in eight countries participated in the trial (see the Supplementary Appendix for the list of investigators). Patients with symptomatic paroxysmal atrial fibrillation that was refractory to class I or class III antiarrhythmic drugs or beta blockers were enrolled. Patient eligibility was determined according to the inclusion and exclusion criteria listed in Tables S1 and S2 in the Supplementary Appendix.[4] All participants gave written informed consent. After enrollment, patients were randomly assigned, in a 1:1 ratio, to undergo ablation with pulmonary-vein isolation attempted with the use of a cryoballoon (cryoballoon group) or by means of radiofrequency current (radiofrequency group). Randomization was stratified according to center and age (≤65 vs. >65 years).

Interventions

The ablation methods are described in the Supplementary Appendix. In brief, in the cryoballoon group, operators attempted pulmonary-vein isolation by placing the device (with fluoroscopic guidance) at each pulmonary-vein antrum, advancing it toward the pulmonary vein to achieve

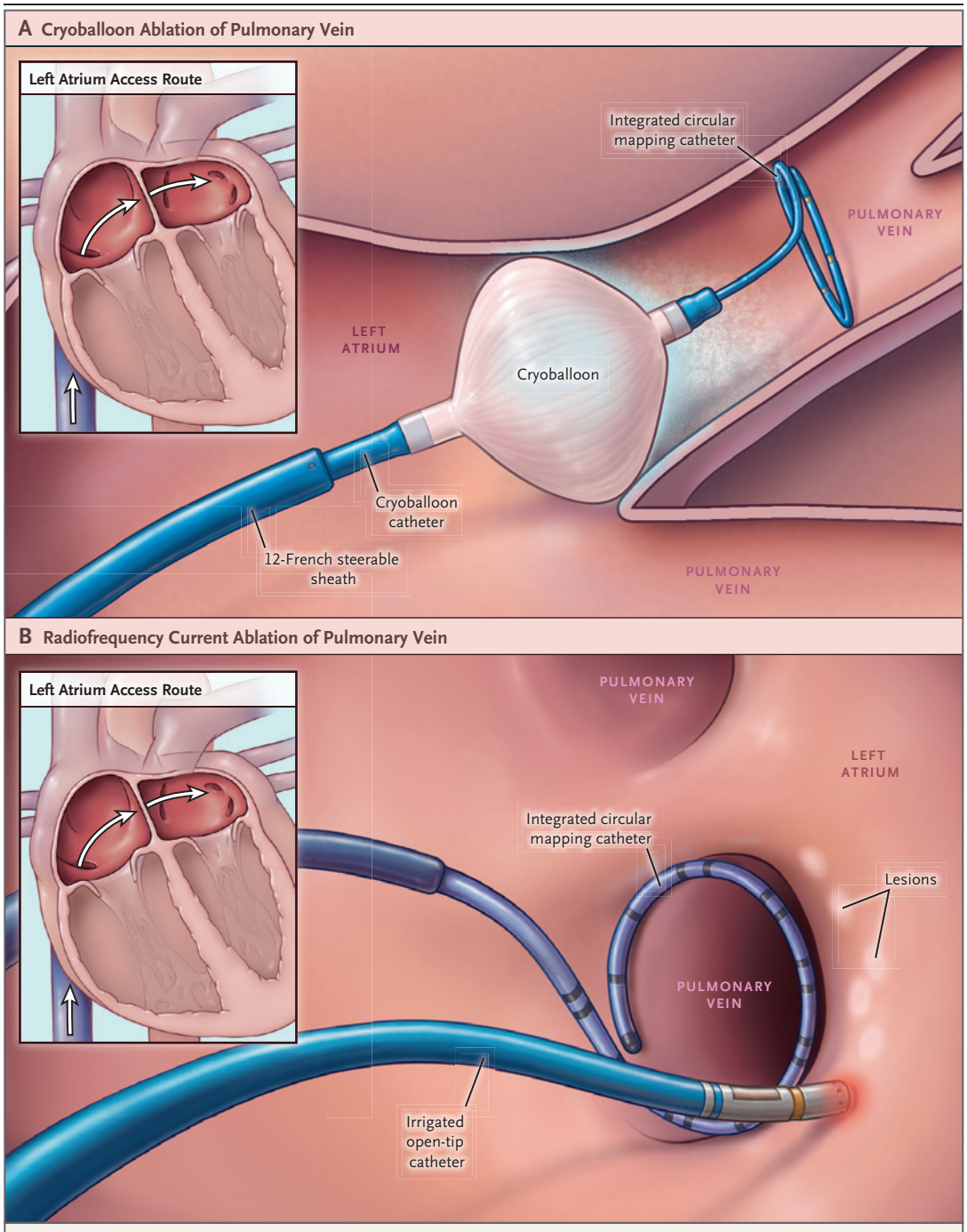

Figure 1. Catheter Ablation Methods.

Panel A shows the cryoballoon system, a single-step approach in which a balloon delivers subzero temperatures to the pulmonary-vein antra. Panel B shows the radiofrequency catheter ablation system, which uses heat-energy transfer to tissue and delivers a series of point-by-point connected lesions with assistance from a three-dimensional navigational system.

occlusion, and then cooling the tissue by filling the balloon with a liquid refrigerant. In the radiofrequency group, operators attempted pulmonary-vein isolation by creating a contiguous circular lesion around each pulmonary-vein antrum with point-by-point applications of radiofrequency energy, using electroanatomical navigation (Fig. 1).

STUDY FOLLOW-UP

After the index ablation procedure, in-office visits were scheduled at 3, 6, and 12 months and every 6 months thereafter (Fig. S1 in the Supplementary Appendix). At each visit, a medical history was obtained, a physical examination was performed, and a 12-lead electrocardiogram (ECG) and a 24-hour Holter monitor recording were obtained. A review of arrhythmia symptoms was conducted by telephone interview at 9 months and every 6 months thereafter. Patients were asked to provide a weekly transtelephonic ECG recording during the study and to transmit ECGs whenever symptoms of arrhythmia were felt. All follow-up assessments were performed by study personnel who were unaware of the treatment assignments.

END POINTS

The primary hypothesis was that catheter ablation with the use of the cryoballoon would be noninferior to radiofrequency ablation with respect to a prespecified efficacy criterion. This primary efficacy end point in a time-to-event analysis was the first documented clinical failure occurring more than 90 days after the index ablation procedure. Clinical failure was defined as documented recurrence of atrial fibrillation (lasting more than 30 seconds), documented occurrence of atrial flutter or atrial tachycardia, prescription of antiarrhythmic drugs (class I or III), or repeat ablation.

Recurrences of atrial fibrillation during the first 90 days after the index ablation (the so-called "blanking period") were not counted in the determination of the first clinical failure for the primary end point. Early recurrence of atrial fibrillation after ablation, resulting from inflammation or incomplete lesion healing, is common and may not predict long-term outcome.[1] Within the blanking period, recurrent arrhythmias could be managed with antiarrhythmic drugs (excluding amiodarone), cardioversion, or repeat ablation (with the same randomly assigned catheter type) without penalty with regard to the primary efficacy end point.

The prespecified secondary end points reported in this article include death from any cause, death from arrhythmia, total duration of the procedure, total fluoroscopy time, and first rehospitalization for cardiovascular causes. Additional prespecified secondary end points (for which results are not shown in this article) included the total number of hospitalizations for cardiovascular causes, time-to-event analyses of the components of the primary end point, time to recurrent atrial fibrillation, time to symptomatic atrial fibrillation, and quality of life.

The primary safety end point was a composite of death from any cause, stroke or transient ischemic attack from any cause, and serious adverse events. Serious adverse events included cardiac arrhythmias (apart from a recurrence of atrial fibrillation) that were causally related to the therapeutic intervention and procedure-related serious adverse events that were judged by the end-point review committee to be causally related to the treatment. All serious adverse events were prespecified. Physicians were required to report all adverse events.

STATISTICAL ANALYSIS

Assuming event-free 1-year survival rates of 70% in both groups and with a noninferiority margin of 10% (corresponding to a hazard ratio of 1.43), we calculated that 249 primary-end-point events would be required for the trial to have 80% power to test the noninferiority of cryoballoon ablation to radiofrequency ablation, at a one-sided alpha level of 0.025. A sample size of 549 patients was originally estimated. A prespecified blinded sample-size reestimation was performed before enrollment was fully complete. On the basis of the reestimation, we calculated that 768 patients would have to be enrolled to ensure that 249 primary-end-point events would be observed.

Two prespecified interim analyses and a final analysis were performed when 125, 187, and 249 primary-end-point events, respectively, had been observed. During the study, no early-stopping boundaries were met. Two analysis cohorts were prespecified (Fig. S2 in the Supplementary Appendix). The modified intention-to-treat cohort included all patients who underwent randomization and their randomly assigned catheter ablation procedure. The per-protocol cohort consisted of patients who were treated and did not have a major protocol deviation. A major protocol deviation was defined as a deviation that confounded the efficacy end point; such deviations included amiodarone use, undergoing an ablation with a non–study-specified catheter, and undergoing an ablation with a catheter that was not in accordance with the randomly assigned treatment group.

The primary efficacy end point was evaluated with the use of a noninferiority log-rank test.[11] In addition, a noninferiority test based on a Cox proportional-hazards model was performed. The corresponding hazard ratio and 95% confidence interval were estimated with a Cox proportional-hazards model, after confirmation of the proportional-hazards assumption. If noninferiority was met in both the modified intention-to-treat cohort and the per-protocol cohort, then superiority could be tested in the modified intention-to-treat cohort with the use of a log-rank test. Cox proportional-hazards regression was used to estimate hazard ratios in the primary analysis, subgroup analyses, and primary safety analysis. The Kaplan–Meier method was used to calculate 12-month event-rate estimates. For each subgroup analysis, a Wald test for interaction was performed. Four separate types of catheter were used during the study: the first-generation and second-generation cryoballoon catheters, the combined first-generation radiofrequency catheters (there were two types; see the Methods section in the Supplementary Appendix), and the advanced-generation radiofrequency catheter. A log-rank test was used to analyze the primary efficacy end point according to catheter type.

Because of the blanking period defined above, 90 days was selected as the landmark (starting time) of time-to-event analyses for the primary efficacy end point. Analyses were conducted with SAS software, version 9.4 (SAS Institute), and the R statistical package, version 3.2.2 (www.r-project.org). Mean values are presented with standard deviations.

RESULTS

PATIENTS

Enrollment of patients started on January 19, 2012, and was completed on January 27, 2015. A total of 769 patients were enrolled (Fig. S2 in the Supplementary Appendix). The modified intention-to-treat population included the 750 patients who were randomly assigned to a treatment group (376 in the radiofrequency group and 374 in the cryoballoon group) and received treatment. Of those patients, 352 in the radiofrequency group and 341 in the cryoballoon group did not have a major protocol violation reported; these patients comprised the per-protocol cohort. The characteristics of the patients at baseline were balanced between the two groups, with the exception of the prevalence of chronic kidney disease and diabetes (Table 1). During the procedure, complete isolation was achieved in 97.9% of pulmonary veins in the radiofrequency group and in 98.9% of pulmonary veins in the cryoballoon group.

A total of 85% of the scheduled follow-up visits in the radiofrequency group (2007 of a total of 2372 visits) and 87% of the scheduled follow-up visits in the cryoballoon group (2006 of 2317 visits) were attended (Table S3 in the Supplementary Appendix). Patients transmitted transtelephonic ECGs for a mean of 60% of the weeks in which they were followed in the radiofrequency group and for 58% of the weeks in which they were followed in the cryoballoon group. In the radiofrequency group, 4 patients were lost to follow-up, and 32 patients withdrew from the trial or were withdrawn by the investigator; in the cryoballoon group, 5 patients were lost to follow-up, and 37 patients withdrew from the trial or were withdrawn by the investigator. In both groups, the maximum follow-up time was 33 months, and the mean follow-up time was 1.5 years.

EFFICACY END POINTS

The number of end-point events required to test the primary efficacy hypothesis was achieved on September 17, 2015, and data freeze occurred on January 29, 2016. In the modified intention-to-treat analysis, after the 90-day blanking period, the primary efficacy end point occurred in 138 patients in the cryoballoon group and in 143 patients in the radiofrequency group (1-year Kaplan–Meier event-rate estimates, 34.6% and 35.9%, respectively; hazard ratio, 0.96; 95% confidence interval [CI], 0.76 to 1.22; $P<0.001$ for noninferiority) (Table 2 and Fig. 2A). In the per-protocol analysis, the primary efficacy end point occurred in 118 patients in the cryoballoon group and in 131 patients in the radiofrequency group (1-year Kaplan–Meier event-rate estimates, 31.9% and 35.0%, respectively; hazard ratio, 0.91; 95% CI, 0.71 to 1.17; $P<0.001$ for noninferiority). A prespecified superiority test performed for the primary efficacy end point did not indicate a significant difference between the treatment groups ($P=0.74$). Prespecified subgroup analyses of the primary efficacy end point revealed no significant interactions (Fig. S3 in the Supplementary Appendix). A prespecified comparison

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Radiofrequency Group (N=376)	Cryoballoon Group (N=374)
Age — yr	60.1±9.2	59.9±9.8
Age >65 yr — no. (%)	117 (31.1)	113 (30.2)
Male sex — no. (%)	236 (63)	221 (59)
Years since first PAF diagnosis	4.7±5.3	4.6±5.1
Body-mass index†	27.8±4.5	28.0±4.7
Left atrial diameter — mm	40.6±5.8	40.8±6.5
Systolic blood pressure — mm Hg	134.8±18.9	133.6±18.0
Diastolic blood pressure — mm Hg	78.9±10.6	78.8±11.5
CHA_2DS_2-VASc score‡		
Mean	1.8±1.3	1.9±1.4
Distribution — no. (%)		
0	67 (17.8)	58 (15.5)
1	109 (29.0)	108 (28.9)
2	97 (25.8)	95 (25.4)
3	62 (16.5)	60 (16.0)
4	33 (8.8)	40 (10.7)
5	7 (1.9)	10 (2.7)
6	1 (0.3)	3 (0.8)
NYHA classification — no. (%)§		
No heart failure	277 (73.9)	263 (70.3)
Class I	40 (10.7)	47 (12.6)
Class II	58 (15.5)	64 (17.1)
Medical history — no. (%)		
Previous DCCV	88 (23.4)	86 (23.0)
Previous stroke	4 (1.1)	5 (1.3)
Previous TIA	10 (2.7)	11 (2.9)
Previous myocardial infarction	9 (2.4)	9 (2.4)
Previous CABG	4 (1.1)	2 (0.5)
Previous PCI	16 (4.3)	24 (6.4)
Coronary artery disease	32 (8.5)	31 (8.3)
LV hypertrophy — no. (%)¶	2 (0.5)	1 (0.3)
Chronic kidney disease — no. (%)‖	4 (1.1)	13 (3.5)
Hypertension — no. (%)**	221 (58.8)	215 (57.5)
Hyperlipidemia — no. (%)††	106 (28.3)	115 (30.9)
Type 2 diabetes — no. (%)‖	22 (5.9)	37 (9.9)
Medication use — no. (%)		
Antiarrhythmic drug	225 (59.8)	236 (63.1)
ACE inhibitor	89 (23.7)	73 (19.5)
Beta-blocker	253 (67.3)	235 (62.8)
Anticoagulation drug	274 (72.9)	282 (75.4)

* Plus–minus values are means ±SD. ACE denotes angiotensin-converting enzyme, CABG coronary-artery bypass graft, DCCV direct current cardioversion, NYHA New York Heart Association, PAF paroxysmal atrial fibrillation, PCI percutaneous coronary intervention, and TIA transient ischemic attack.
† Body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ The CHA_2DS_2-VASc score is a clinical estimation of the risk of stroke in patients with atrial afibrillation; scores range from 0 to 9, with higher scores indicating a greater risk of stroke.
§ Data were missing for one patient in the radiofrequency group.
¶ Left ventricular (LV) hypertrophy was defined as an LV wall thickness greater than 15 mm.
‖ The difference between the treatment groups was significant ($P<0.05$).
** Hypertension was defined as blood pressure higher than 140/90 mm Hg.
†† Hyperlipidemia was defined as a total cholesterol value higher than 300 mg per deciliter (7.76 mmol per liter). Data were missing for two patients in the radiofrequency group and two patients in the cryoballoon group.

Table 2. Efficacy End Points.*

End Point	Radiofrequency Group (N=376)	Cryoballoon Group (N=374)	Hazard Ratio (95% CI)†	P Value
Primary efficacy end point — no. of patients (%)‡	143 (35.9)§	138 (34.6)§	0.96 (0.76–1.22)	<0.001¶
Components of the primary efficacy end point — no. of patients				
Recurrent atrial arrhythmia	87	80	—	—
Antiarrhythmic drug treatment	49	51	—	—
Repeat ablation	7	7	—	—
Secondary efficacy end points				
Death from any cause — no. of patients	0	2‖	—	0.25**
Death from arrhythmia — no. of patients	0	0	—	—
Total procedure duration — min	140.9±54.9	124.4±39.0	—	<0.001††
Left atrial dwell time — min‡‡	108.6±44.9	92.3±31.4	—	<0.001††
Total fluoroscopy time — min§§	16.6±17.8	21.7±13.9	—	<0.001††
Rehospitalization for cardiovascular causes — no. of patients (%)	55 (13.5)§	44 (9.4)§	0.78 (0.53–1.16)	0.28**

* Plus–minus values are means ±SD.
† Time-to-event analyses use radiofrequency group as the reference (a hazard ratio <1 favors cryoablation, and a hazard ratio >1 favors radiofrequency ablation).
‡ The primary end point was a composite of documented recurrence of atrial fibrillation (lasting more than 30 seconds), documented occurrence of atrial flutter or atrial tachycardia, prescription of antiarrhythmic drugs (class I or III), or repeat ablation.
§ This value is the Kaplan–Meier estimate at 1 year.
¶ This P value is for noninferiority assessed by the log-rank test.
‖ One death (at day 366) was of unknown cause; one death (at day 95) was associated with sepsis and was determined by autopsy to be a noncardiac-related death.
** This P value was calculated by Fisher's exact test.
†† This P value was calculated by Student's t-test.
‡‡ Left atrial dwell time was a post hoc (nonprespecified) procedural end point and represents the length of time catheters were present in the left atrium during the procedure. This end point was evaluated in 357 patients in the radiofrequency group and in 354 patients in the cryoballoon group.
§§ Total fluoroscopy time was evaluated in 373 patients in the radiofrequency group and in 371 patients in the cryoballoon group.

of the primary efficacy end point among the four separate types of catheters revealed no significant heterogeneity (P=0.25) (Fig. 2B).

Results regarding the secondary efficacy end points are shown in Table 2. There were two deaths in the cryoballoon group; one death (at day 366) was of unknown cause, and the other death (at day 95) was associated with sepsis and was determined by autopsy to be a noncardiac-related death. The mean total procedure time was shorter in the cryoballoon group than in the radiofrequency group (124 vs. 141 minutes, P<0.001), as was the left atrial dwell time (the length of time the catheter was present in the left atrium during the procedure), which was a post hoc end point (92 vs. 109 minutes, P<0.001). The mean total fluoroscopy time was shorter in the radiofrequency group than in the cryoballoon group (17 vs. 22 minutes, P<0.001). The time to first rehospitalization for cardiovascular causes did not differ significantly between the groups.

SAFETY END POINTS

The primary safety end point occurred in 40 patients in the cryoballoon group and in 51 patients in the radiofrequency group (1-year Kaplan–Meier event rate estimates, 10.2% and 12.8%, respectively; hazard ratio, 0.78; 95% CI, 0.52 to 1.18; P=0.24) (Fig. 2C and Table 3). The most common safety events were groin-site complications (16 in the radiofrequency group and 7 in the cryoballoon group) and phrenic-nerve injury (10 in the cryoballoon group) (Table 3). No atrioesophageal fistulae, pulmonary-vein stenoses, or procedure-related deaths were observed. A full list of postprocedural adverse events is provided in Table S4 in the Supplementary Appendix.

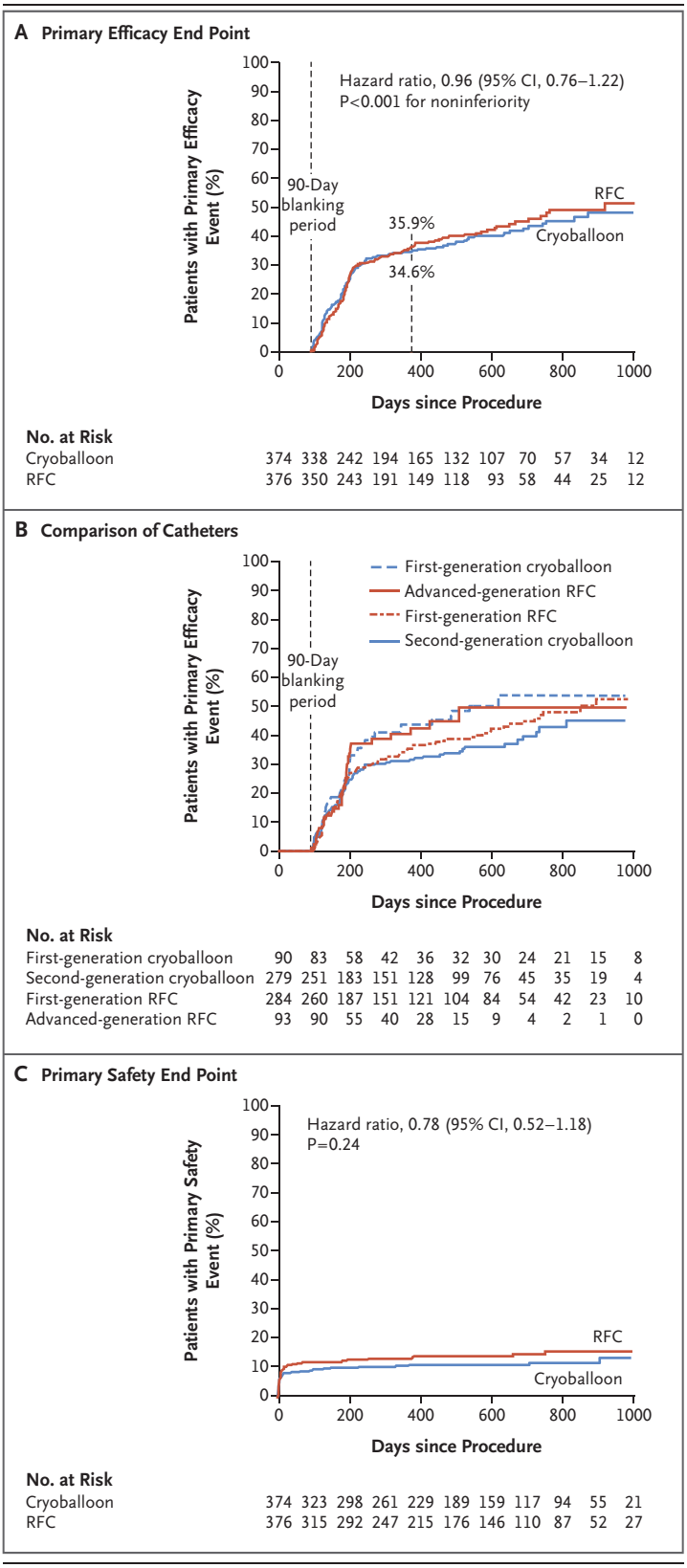

Figure 2. Event-free Survival for the Primary Efficacy and Safety End Points in the Modified Intention-to-Treat Cohort.

Panel A shows the 90-day landmark analysis of the primary efficacy end point. The trial confirmed the noninferiority of cryoballoon ablation to radiofrequency (RFC) catheter ablation. The first 90 days after the index ablation was the so-called "blanking period"; events during this period were not counted in the determination of clinical failure for the primary end point. Panel B shows the subgroup test of homogeneity across all four catheter categories; there was no significant difference among the catheters (P=0.25). The as-treated cohort was used for this analysis. Five patients were randomly assigned to the cryoballoon group but underwent radiofrequency ablation; they are included in the first-generation radiofrequency group; four patients who were randomly assigned to the radiofrequency group and were treated with nonstudy radiofrequency catheters are not included. Panel C shows the analysis of the primary safety end point. There was no significant difference between the cryoballoon and radiofrequency groups.

DISCUSSION

The FIRE AND ICE trial was a randomized evaluation of catheter ablation in patients with paroxysmal atrial fibrillation, in which we examined the efficacy, safety, and procedural profiles of the two most commonly used ablation technologies. The characteristics of the patients were consistent with those in other trials[5-10,12,13] and are representative of patients with paroxysmal atrial fibrillation.[1] Cryoballoon ablation was found to be noninferior to radiofrequency ablation with regard to the primary efficacy end point, and superiority was not achieved in either group. There was no significant difference among the four types of ablation catheters with regard to the primary efficacy end point. There was also no significant difference in the primary safety end point between the radiofrequency group and the cryoballoon group.

Phrenic-nerve injury was the most common safety event in the cryoballoon group, although the 2.7% rate in our trial was substantially lower than the 13.5% rate reported in the Sustained Treatment of Paroxysmal Atrial Fibrillation (STOP AF) trial.[12] The most common safety events in the radiofrequency group were groin-site complications, which were unusually frequent in this trial (4.3%). Some groin injuries

Table 3. Safety End Points.

End Point	Radiofrequency Group (N=376)	Cryoballoon Group (N=374)	P Value*
	no. of patients (%)		
Primary safety end point†	51 (12.8)‡	40 (10.2)‡	
Death from any cause§	0	2 (0.5)¶	0.50
Stroke or TIA from any cause§	2 (0.5)	2 (0.5)	1.00
Atrial arrhythmia§‖	13 (3.5)	8 (2.1)	0.38
Atrial flutter or atrial tachycardia	10 (2.7)	3 (0.8)	0.09
Non–arrhythmia-related serious adverse events§	36 (9.6)	28 (7.5)	0.36
Groin-site complication**	16 (4.3)	7 (1.9)	0.09
Unresolved phrenic nerve injury††			
At discharge	0	10 (2.7)	0.001
At 3 months	0	2 (0.5)	0.25
At >12 months	0	1 (0.3)	0.50
Cardiac tamponade or pericardial effusion	5 (1.3)	1 (0.3)	0.22
Pulmonary or bronchial complication	4 (1.1)	2 (0.5)	0.69
Transient neurologic complication	3 (0.8)	1 (0.3)	0.62
Dyspnea	2 (0.5)	1 (0.3)	1.00
Gastrointestinal complication	2 (0.5)	1 (0.3)	1.00
Other, nonarrhythmia cardiac complications‡‡	0	3 (0.8)	0.12
Anxiety	0	1 (0.3)	0.50
Contrast media reaction	1 (0.3)	0	1.00
Contusion	1 (0.3)	0	1.00
Esophageal ulcer	0	1 (0.3)	0.50
Hematuria	1 (0.3)	0	1.00
Local edema	1 (0.3)	0	1.00
Atrioesophageal fistula	0	0	—
Pulmonary vein stenosis	0	0	—

* The P values were calculated with Fisher's exact test.
† In the time to event analyses, radiofrequency group was used as the reference; the hazard ratio was 0.78 (95% CI, 0.52–1.18; P=0.24) (a hazard ratio <1 favors cryoablation, and a hazard ratio >1 favors radiofrequency ablation).
‡ This value is the Kaplan–Meier estimate at 1 year.
§ This end point was a component of the primary safety end point, which was a composite of death from any cause, stroke or transient ischemic attack from any cause, and serious adverse events.
¶ The deaths were not related to the treatment or device; one death (at day 366) was of unknown cause; one death (at day 95) was associated with sepsis and was determined by autopsy to be a noncardiac-related death.
‖ Atrial arrhythmia includes palpitations, presyncope, the sick sinus syndrome, supraventricular extrasystoles, and syncope.
** Groin-site complications include vascular pseudoaneurysm, arteriovenous fistula, device-related infection, hematoma, puncture-site hemorrhage, and groin pain.
†† Phrenic nerve injuries included eight injuries that resolved by 3 months, one that resolved at 6 months, and one that was unresolved more than 12 months after the procedure. Two additional nonserious events of phrenic nerve injury were reported, and both resolved before hospital discharge.
‡‡ Other cardiac complications include atrial septal defect, coronary artery disease, and pericarditis.

may be caused by the two-sheath system that is often used (a radiofrequency catheter and a separate circular mapping catheter).[1,13] Serious treatment-related adverse events of atrial arrhythmia occurred in 2.7% of the patients in the radiofrequency group and in 0.8% of the patients in the cryoballoon group (P=0.09). These new-onset arrhythmias may have been caused by incomplete pulmonary-vein isolation.

Six previous studies (which were smaller than the current trial, nonrandomized, or both) comparing radiofrequency ablation with cryoballoon ablation have been completed.[5-10] With regard to efficacy, four of these studies showed statistical equivalence between the two technologies,[5,6,9,10] whereas two studies showed a higher efficacy of cryoballoon ablation.[7,8] With regard to safety, five of the studies showed equivalent safety between the two technologies.[6-10] The FreezeAF trial showed a better safety profile with radiofrequency ablation; this result was driven by phrenic-nerve injuries associated with cryoballoon ablation.[5] However, the FreezeAF analysis included episodes of phrenic-nerve injury that resolved before discharge.[5] Also, the FreezeAF trial was primarily an examination of first-generation catheters.

In our trial, procedure duration and left atrial dwell time were shorter in the cryoballoon group, whereas fluoroscopy time was shorter in the radiofrequency group. Single-step circumferential ablations were probably key to the shorter duration of the cryoballoon procedure. Occlusion of the pulmonary vein by the cryoballoon is tested by means of contrast injection and fluoroscopic examination, and this testing contributed to prolonged fluoroscopy time. In contrast, radiofrequency ablation requires no occlusion angiography, and catheter steering is achieved by means of electroanatomical mapping.

The case-report form used in this trial did not record individualized secondary catheter performance characteristics. For the cryoballoon catheter, the study did not record pulmonary-vein occlusion scores, time to pulmonary-vein isolation, the duration of the freezing procedure, or the number of freezes. Similarly, in the radiofrequency catheter group, the study did not record application times, contact-force measurements, peak wattage, or three-dimensional mapping variables. During trial design, many of these catheter variables were not routinely reported.

The trial investigators attempted to plan and conduct this study so that the most advanced-generation catheters would be used on approximately the same date and at approximately equal distribution. However, because of an urgent field safety notice and voluntary field removal (i.e., recall by the manufacturer) in the European Union, the advanced-generation radiofrequency catheter became unavailable beginning in September 2013, with some reshipping started in January 2014. This interruption prohibited further statistical evaluation of efficacy according to individual catheter type.

Pulmonary-vein isolation is the cornerstone ablation strategy in the treatment of patients with paroxysmal atrial fibrillation.[1] However, achieving acute pulmonary-vein isolation does not guarantee long-term electrical isolation of the pulmonary veins.[14] The use of newer radiofrequency catheters with contact-force sensing has improved long-term pulmonary-vein isolation.[14-16] The second-generation cryoballoon catheter has also shown improvement in long-term pulmonary-vein isolation,[17] which may be attributable to the extensive wide-area circumferential ablation that is achieved.[18] Extensive wide-area circumferential ablation may have ablation-related benefits beyond pulmonary-vein isolation, including concomitant ganglionated plexus modification.[19] However, our trial was not powered to test the superiority of either the first-generation or the second-generation catheters.

In summary, in the FIRE AND ICE trial, we found that in the treatment of patients with drug-refractory paroxysmal atrial fibrillation, pulmonary-vein isolation by means of cryoballoon ablation was noninferior to pulmonary-vein isolation by radiofrequency ablation in terms of efficacy and safety.

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