Circulation: Arrhythmia and Electrophysiology

ORIGINAL ARTICLE

Repeat Ablation for Atrial Fibrillation Recurrence Post Cryoballoon or Radiofrequency Ablation in the FIRE AND ICE Trial

BACKGROUND: The FIRE AND ICE trial assessed efficacy and safety of pulmonary vein (PV) isolation using cryoballoon versus radiofrequency current (RFC) ablation in patients with drug refractory, symptomatic, paroxysmal atrial fibrillation (AF). The purpose of the current study was to assess index lesion durability as well as reablation strategy and outcomes in trial patients undergoing a reablation procedure.

METHODS: Patients with reablation procedures during FIRE AND ICE were retrospectively consented and enrolled at 13 trial centers. The first reablation for each patient was included in the analysis. Documented arrhythmias before reablation, number and location of reconnected PVs, lesions created during reablations, procedural characteristics, and acute as well as long-term outcomes were assessed.

RESULTS: Eighty-nine (36 cryoballoon and 53 RFC) patients were included in this study. Paroxysmal atrial fibrillation was the predominant recurrent arrhythmia (69%) before reablation. Reablations occurred at a median of 173 and 182 days (P=0.54) in the cryoballoon and RFC cohorts, respectively. The number of reconnected PVs was significantly higher in the RFC than the cryoballoon group (2.1±1.4 versus 1.4±1.1; P=0.010), which was driven by significantly more reconnected left superior PVs and markedly more reconnected right superior PVs. The number of (predominantly RFC) lesions applied during reablation was significantly greater in patients originally treated with RFC (3.3±1.3 versus 2.5±1.5; P=0.015) with no difference in overall acute success (P=0.70). After reablation, no differences in procedure-related rehospitalization or antiarrhythmic drug utilization were observed between cohorts.

CONCLUSIONS: At reablation, patients originally treated with the cryoballoon had significantly fewer reconnected PVs, which may reflect RFC catheter instability in certain left atrial regions, and thus required fewer lesions for reablation success. Repeat ablations were predominantly performed with RFC and resulted in similar acute success, duration of hospitalization, and antiarrhythmic drug prescription between the study cohorts.

CLINICAL TRIAL REGISTRATION: URL: https://www.clinicaltrials.gov. Unique identifier: NCT03314753.

VISUAL OVERVIEW: A visual overview is available for this article.

Karl-Heinz Kuck, MD
Jean-Paul Albenque, MD, PhD
K.R. Julian Chun, MD
Alexander Fürnkranz, MD
Mathias Busch, MD
Arif Elvan, MD
Michael Schlüter, PhD
Kendra M. Braegelmann, PhD
Fred J. Kueffer, MS
Lauren Hemingway, BS
Thomas Arentz, MD
Claudio Tondo, MD
Josep Brugada, MD
On behalf of the FIRE AND ICE Investigators*

*A list of all FIRE AND ICE study participants is given in the Appendix.

Key Words: atrial fibrillation ■ catheter ablation ■ hospitalization ■ pulmonary veins ■ randomized controlled trial

https://www.ahajournals.org/journal/circep

WHAT IS KNOWN?

- Durable pulmonary vein isolation is fundamental to freedom from atrial arrhythmia recurrence and is the primary goal when treating patients with paroxysmal atrial fibrillation via catheter ablation.
- In the FIRE AND ICE trial, a significantly higher rate of reablation was observed in patients treated with radiofrequency ablation than in patients treated with cryoballoon ablation (17.6% versus 11.8%, respectively, *P*=0.03).

WHAT THE STUDY ADDS?

- In patients who underwent a repeat ablation in FIRE AND ICE, significantly fewer pulmonary veins were reconnected in patients treated with the cryoballoon than in patients treated with radiofrequency current (1.4±1.1 versus 2.1±1.4; *P*=0.010). Accordingly, fewer lesion sets were applied during the reablation procedure in patients initially treated with the cryoballoon (2.5±1.5 versus 3.3±1.3; *P*=0.015), suggesting that cryoballoon lesions were more durable than radiofrequency lesions in this trial.
- The anatomic distribution of reconnected pulmonary veins differed between patients treated with cryoballoon versus radiofrequency ablation during the index procedure, which may suggest that the cryoballoon more aptly achieves the catheter stability required to achieve durable PVI in anatomically challenging areas such as the myocardial ridge separating the left-sided pulmonary veins from the left atrial appendage.

Durable pulmonary vein isolation (PVI) is fundamental to freedom from atrial arrhythmia recurrence and is the primary goal when treating patients with paroxysmal atrial fibrillation (AF) via catheter ablation.[1,2] PVI is either achieved by heating of cardiac tissue with a focal radiofrequency current (RFC) catheter or by freezing the tissue with a cryoballoon catheter.[1–3] The FIRE AND ICE trial is the largest, randomized, multinational comparative study of efficacy and safety of these 2 ablation modalities for the treatment of paroxysmal AF by way of PVI.[3] The trial established that cryoballoon ablation was noninferior to RFC ablation with respect to the primary efficacy and safety end points.[3] Yet, patients treated with the cryoballoon had significantly fewer repeat ablations, direct-current cardioversions, all-cause rehospitalizations, and cardiovascular rehospitalizations during follow-up.[4] Differences in lesion durability between the treatment cohorts are unknown.

Prospective evaluations of lesion durability are limited by the invasive, therapeutically unnecessary nature of a remapping procedure; therefore, insight into lesion durability has been gleaned during reablation procedures. While comparative evaluations of PVI durability have been conducted,[5–8] to our knowledge, the present analysis is the largest multicenter examination of reablation data from an originally randomized trial that compared RFC and cryoballoon catheter ablation. The purpose of the present analysis was to evaluate index PVI lesion durability among FIRE AND ICE trial patients who underwent a reablation procedure. Because there was a lower rate of reablation observed in the cryoballoon cohort, we hypothesized that index cryoballoon PVI was more durable than index RFC PVI in patients who ultimately underwent a reablation in this trial.

METHODS

The data that support the findings of this study are available from the corresponding author on reasonable request.

Study Design

The FIRE AND ICE Redo study was an observational, retrospective evaluation of patients who underwent a repeat ablation during the FIRE AND ICE trial to compare arrhythmia recurrence, number and anatomic pattern of reconnected PVs, and index PVI lesion durability in patients originally randomized to cryoballoon or RFC ablation. Of the 16 sites that participated in FIRE AND ICE, 13 sites in Europe (listed below) participated in this trial. The trial was approved by each site's ethics committee/institutional review board, registered, and conducted in accordance with the Declaration of Helsinki. Data to fulfill the predefined objectives about the index procedure, patient characteristics following the index, and the repeat ablation procedures were collected. An independent end point review committee (blinded to randomization) reviewed and adjudicated all repeat ablation study data.

Patient Cohort

Patients enrolled in the original trial were between the ages of 18 and 75 years old and had drug refractory, symptomatic, paroxysmal AF.[3] On average, these patients were followed 1.5±0.8 years post the index ablation and underwent a repeat procedure after evidence of arrhythmia recurrence was documented and at the discretion of the patient and operating physician. A total of 110 patients from the FIRE AND ICE modified intention to treat cohort collectively underwent a total of 119 repeat ablations during follow-up. Of the 119 reablations, 49 were performed in 44 subjects who had undergone an index cryoballoon ablation procedure, and 70 were performed in 66 subjects who had undergone an index RFC ablation procedure (Table 1).[4] Patients with a documented repeat ablation at any time during the original trial (regardless of the 90-day blanking period) were included in this evaluation after providing written informed consent; no new subjects were enrolled into this current evaluation. In patients who underwent multiple reablations, only the first reablation was included in this analysis. Patients who underwent a repeat procedure following an index cryoballoon ablation were denoted as

Table 1. Patient Disposition

	RFC Group	CB Group	Total Cohort
FIRE AND ICE trial			
Total FIRE AND ICE patients*	376	374	750
Number of patients with reablations	66	44	110
FIRE AND ICE Redo study			
FIRE AND ICE Repeat patients†	53	36	89
Repeat ablation with CB	0	13	13
Repeat ablation with RFC	53	23	76

CB indicates cryoballoon; and RFC, radiofrequency current.
*Modified intention to treat cohort.
†Reconsented patients with a reablation during FIRE AND ICE.

cryoballoon-Redo, and patients who underwent a repeat procedure following an index RFC ablation were denoted as RFC-Redo.

Patient Assessment Before Repeat Ablation

Baseline patient characteristics collected at the time of enrollment in FIRE AND ICE were compared between reablation cohorts. Data from the index ablation as well as the type of arrhythmia recurrence before the repeat ablation were collected. Documented arrhythmia recurrence before the reablation was categorized as paroxysmal or persistent AF, atrial tachycardia, and typical/atypical atrial flutter.

Repeat ablation procedures were performed at the same hospital center as the index ablation. Both PV and non-PV locations were evaluated for arrhythmic potential at the time of the reablation procedure. PVI was confirmed via bidirectional entrance and exit block. Information about the number and location of gaps in the PV lesions captured via a focal catheter or 3-dimensional electroanatomical mapping were documented as available. Spot gaps were predefined as 1 mm in size requiring a single application without catheter movement to reisolate the PV or cause a change in the PV activation sequence. A linear gap was defined as a gap that required multiple applications or dragging of the RFC catheter.

Repeat Ablation Protocol

If PV reconnection was observed, PV reisolation was performed and verified by entrance and exit block testing. It was recommended that the same energy source to which the patient was randomized in FIRE AND ICE for the index ablation be applied during the reablation; however, the ablation modality used during repeat ablation was ultimately left to the discretion of the operator. Cryoballoon and RFC ablation methods have been described in detail.[3] Additional ablation of substrate or potential focal AF triggers was allowed during the procedure at the discretion of the treating physician. Lesion sets applied during repeat ablation were classified as one of the following: (Re-) PVI, left atrial (LA) trigger, right atrial trigger, superior vena cava trigger, inferior vena cava trigger, cavotricuspid isthmus block, mitral valve isthmus line, left-sided roofline, complex fractionated atrial electrogram ablation, posterior wall line, atrioventricular nodal reentry tachycardia ablation, or other lesion sets that were not predefined. Acute procedural success was defined as reisolation of the PVs by entrance/exit block and the elimination of a trigger or a line of bidirectional conduction block when adjunctive ablations were performed. Reablation total procedure time, LA dwell time, and fluoroscopy time were recorded for each repeat procedure.

The length of the repeat ablation hospital stay from the time of admission to the time of discharge as well as prescription of antiarrhythmic drugs (Class 1 or III) at the time of discharge was assessed. Arrhythmia recurrence documentation was not collected during the FIRE AND ICE trial after the primary end point was met, but all-cause rehospitalizations and repeat ablations during follow-up after the first redo procedure were documented.

Statistical Analyses

Data analyses were conducted using the modified intent-to-treat study populations (consistent with previous publications comparing subjects randomized to cryoballoon or RFC). The type of atrial arrhythmia recurrence before reablation, the percent of patients with reconnected PVs, acute success, and the percent of patients prescribed antiarrhythmic drugs postreablation were compared between the cryoballoon-Redo and RFC-Redo cohorts using exact methods. The hospital length of stay and time to repeat ablation were compared using the Wilcoxon rank-sum test. The number of reconnected PVs and the number of ablation lesions performed during reablation were compared using a 2-sample *t* test. Freedom from rehospitalization and repeat reablation after the first redo procedure was assessed using the Kaplan-Meier method and the log-rank test.

Continuous variables are presented as mean±SD or median with interquartile range, as appropriate. Categorical variables are presented as absolute and relative frequencies. There were no adjustments for multiple testing, and a $P<0.05$ was considered statistically significant. All analyses were conducted using SAS software, version 9.4 (SAS Institute, Cary, NC) and R statistical package, version 3.2.2 (https://www.r-project.org).

RESULTS

Patient Population

A total of 89 patients, 36 patients with cryoballoon (cryoballoon-Redo) and 53 patients with RFC (RFC-Redo), from the FIRE AND ICE trial who underwent a repeat ablation were consented and enrolled (Table 1). The patients were 61±10 years old, 46% female, had a left ventricular ejection fraction of 62±7%, and an LA diameter of 41±7 mm at the time of enrollment into the original trial. There were no statistically significant differences in characteristics or comorbidities at the time of the index ablation between reablation cohorts (Table 2); however, there was a numerically higher percentage of women in the cryoballoon-Redo than in the RFC-Redo cohort (58% versus 38%, respectively; $P=0.08$). Most reablation patients, all originally treated

Table 2. Baseline Patient Demographics and Comorbidities for Repeat Ablation Subjects

Characteristic*	RFC-Redo (n=53)	CB-Redo (n=36)	*P* Value†
Age, y	60 ± 10	62 ± 11	0.48
Female sex	20 (38)	21 (58)	0.08
Diagnosed with PAF, y	4.5 (1.5–8.2)	3.7 (1.9–9.2)	0.86‡
Body mass index, kg/m^2	27±4	28±5	0.60
HATCH score	1.2±1.1	1.5±1.2	0.23
CHA_2DS_2-VASc score	2 (1–2)	2 (1–3)	0.07‡
LV ejection fraction, %	62±7	62±7	0.88
LA diameter, mm	41.6±5.7	39.4±7.9	0.16
LA volume, mL	73±35	62±41	0.64
History of AFL	11 (21)	6 (17)	0.79
Prior DCCV	15 (28)	8 (22)	0.63
Prior stroke/TIA	2 (4)	2 (6)	1.00
AAD at discharge	35 (66)	22 (61)	0.66
Coronary artery disease	3 (6)	1 (3)	0.64
Prior MI	1 (2)	0 (0)	1.00
Prior CABG	2 (4)	0 (0)	0.51
Prior PCI	2 (4)	0 (0)	0.51
Aortic stenosis	0 (0)	0 (0)	1.00
Hypertension	32 (60)	22 (61)	1.00
Hyperlipidemia	13 (25)	12 (33)	0.47
Diabetes mellitus (type I or II)	5 (9)	4 (11)	1.00
Peripheral artery disease	0 (0)	0 (0)	1.00

Values are mean±SD, median (25th percentile, 75th percentile), or n/N (%). AAD indicates antiarrhythmic drug; AFL, atrial flutter; CABG, coronary artery bypass graft; CB, cryoballoon; DCCV, direct current cardioversion; HATCH, hypertension, age ≥75 years, transient ischemic attack or stroke, chronic obstructive pulmonary disease, heart failure; LA, left atrium; LV, left ventricular; MI, myocardial infarction; PAF, paroxysmal atrial fibrillation; PCI, percutaneous coronary intervention; RFC, radiofrequency current; and TIA, transient ischemic attack.

*Baseline patient characteristics collected at enrollment in FIRE AND ICE, before the index ablation.

†Fisher exact test for categorical variables, 2-sample *t* test for continuous variables.

‡Wilcoxon rank-sum test.

for paroxysmal AF, recurred with paroxysmal AF (61/89, 69%); however, in 12/89 (13%) patients paroxysmal AF had progressed to persistent AF (Figure 1).

PV Reconnections at the Time of Reablation

The median time to first repeat ablation was not different between cryoballoon-Redo and RFC-Redo cohorts (173 and 182 days, respectively; *P*=0.54). Data on the number of reconnected PVs identified during reablation were available in 98% (52/53) of RFC-Redo patients and 89% (32/36) of cryoballoon-Redo patients. Most patients in the RFC-Redo and cryoballoon-Redo cohorts had ≥1 reconnected PV at the time of repeat

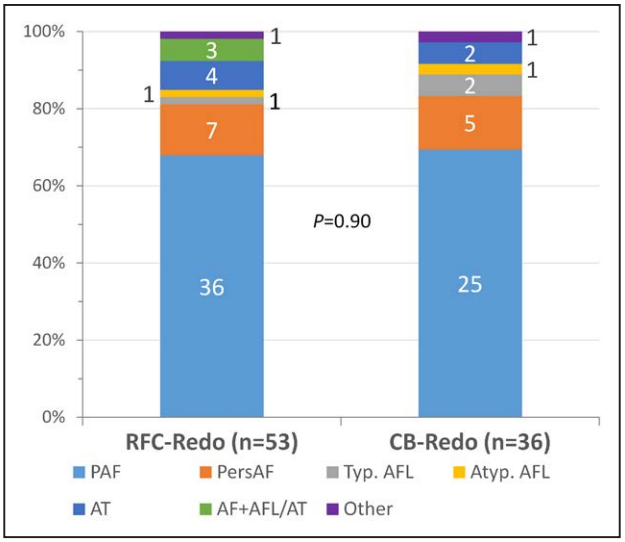

Figure 1. Recurrent arrhythmias before reablation. Paroxysmal atrial fibrillation (AF) was the most prevalent recurrent arrhythmia in both patient groups (68% in radiofrequency current [RFC]-Redo patients, 69% in cryoballoon [CB]-Redo patients). Seven patients (13%) in the RFC-Redo group and 5 patients (14%) in the CB-Redo group progressed from paroxysmal to persistent AF. There was no difference in the type of atrial arrhythmia recurrence before reablation between cohorts (*P*=0.09). Numbers in stacked columns denote numbers of patients. AFL indicates atrial flutter; AT, atrial tachycardia; Atyp, atypical; PAF, paroxysmal atrial fibrillation; PersAF, persistent atrial fibrillation; and Typ, typical.

ablation (43/52 [83%] versus 25/32 [78%], respectively; *P*=0.78). Overall, the mean number of reconnected PVs per patient was significantly higher in the RFC-Redo cohort (2.1±1.4) than in the cryoballoon-Redo cohort (1.4±1.1; *P*=0.010; Figure 2A). The number of reconnected PVs per patient in both patient cohorts is depicted in Figure 2B.

Specifically, in the cryoballoon-Redo cohort, there were significantly fewer reconnected left superior PVs (28% versus 60%; *P*=0.010) and a strong trend towards significantly fewer reconnected right superior PVs (29% versus 52%; *P*=0.07) than in the RFC-Redo cohort (Table 3). Left inferior PVs tended to reconnect less frequently after an index cryoballoon ablation than after an index RFC ablation (33% versus 50%, respectively; *P*=0.17). There was no apparent difference in the incidence of right inferior PV reconnections between index treatment modalities (52% in RFC-Redo and 50% in cryoballoon-Redo; Table 3). Data on the number and specific location of lesion gaps according to quadrants or octants of the PV circumference were available for too few patients to perform meaningful analyses.

Reablation Procedural Characteristics

RFC catheter ablation was used in 85% (76/89) of all repeat ablation procedures regardless of the index PVI ablation modality. Specifically, 23/36 (64%) of cryoballoon-Redo patients and 53/53 (100%) of RFC-Redo patients were retreated with RFC (Table 1). Of the

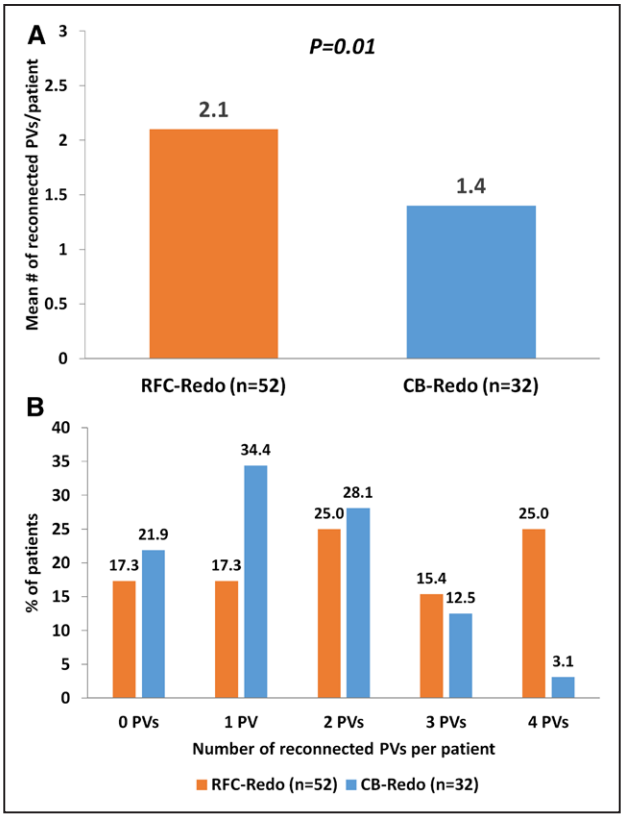

Figure 2. Pulmonary vein (PV) reconnections identified during repeat ablation.
A, Mean number of reconnected PVs according to patient group. In the radiofrequency current (RFC)-Redo cohort a significantly higher mean number of reconnected PVs per patient than in the cryoballoon (CB)-Redo cohort was observed during repeat ablation (*P*=0.01). **B**, Percentage of patients with 0 to 4 reconnected PVs per patient according to patient group.

patients treated with RFC at reablation, 6/23 (26%) and 16/53 (30%) of patients were treated with contact-force sensing RFC catheters in the cryoballoon-Redo and RFC-Redo arms, respectively. The total number of ablations (PVs treated and non-PVI lesions) delivered during the repeat procedure in the RFC-Redo cohort (3.3±1.3) was significantly higher than the number of ablations delivered during reablation in the cryoballoon-Redo cohort (2.5±1.5; *P*=0.015). While the mean number of PVs treated per patient in the RFC-Redo cohort had a tendency to be higher than in the cryoballoon-Redo cohort (2.4±1.4 versus 1.8±1.4; *P*=0.07), there was no statistical difference in the per-patient number of non-PVI ablations delivered during reablation (*P*=0.32; Table 4). Acute reisolation was achieved in all PVs except for one right superior PV treated with RFC during reablation. A total of 42 (47%) reablation patients underwent non-PV ablation. Non-PVI lesions were applied exclusively with RFC and were successful except for mitral valve isthmus lines (50% success) and cavotricuspid isthmus blocks (80% success; Table I in the Data Supplement). There were no differences in reablation procedural duration, LA dwell time, and fluoroscopy time between cohorts (Table 5).

Table 3. Reconnected PVs at Time of Reablation

	RFC-Redo (n=52)	CB-Redo (n=32)	*P* Values*
Total number of reconnected PVs			
Mean	2.1±1.4	1.4±1.1	0.010
Median	2	1	
LSPV	30/50 (60)	8/29 (28)	0.010
LIPV	25/50 (50)	10/30 (33)	0.17
LCPV	2/2 (100)	2/2 (100)	1.00
RSPV	27/52 (52)	9/31 (29)	0.07
RMPV	NA	NA	
RIPV	27/52 (52)	16/32 (50)	1.00

Values are mean±SD or n/N (%). CB indicates cryoballoon; LCPV, left common pulmonary vein; LIPV, left inferior pulmonary vein; LSPV, left superior pulmonary vein; NA, not applicable; PV, pulmonary vein; RFC, radiofrequency current; RIPV, right inferior pulmonary vein; RMPV, right middle pulmonary vein; and RSPV, right superior pulmonary vein.
*Fisher exact test for categorical variables, 2-sample *t* test for continuous variables.

Reablation Patient Follow-Up

The length of hospital stay following the first repeat ablation was not different between cryoballoon-Redo and RFC-Redo cohorts (median 2 [interquartile range, 1–3] nights in both groups; *P*=0.65). There was also no difference in the percentage of patients prescribed antiarrhythmic drugs at discharge following the repeat ablation: 31/53 (58%) of RFC-Redo patients versus 19/36 (53%) of cryoballoon-Redo patients (*P*=0.67). Patients in the cryoballoon-Redo and RFC-Redo cohorts were followed for 1.4±0.8 and 1.3±0.8 years after the first reablation, respectively. Kaplan-Meier estimates of 1-year freedom from all-cause rehospitalization after the first reablation in the cryoballoon-Redo and RFC-Redo

Table 4. PV and Non-PV Lesions Applied During Reablation

	RFC-Redo (n=53)	CB-Redo (n=36)	*P* Values*
Patients with >1 PV treated	47 (88.7)	28 (77.8)	0.24
Total ablation sets (PVs+non-PV)			
Mean	3.3±1.3	2.5±1.5	0.015
Median	3	2	
PVs treated per patient			
Mean	2.4±1.4	1.8±1.4	0.07
Median	2	2	
Patients with PVI-only ablations	24 (45.3)	23 (63.9)	0.13
Non-PV ablations per patient			
Mean	0.9±1.0	0.7±1.2	0.32
Median	1	0	

Values are mean±SD or n (%). CB indiates cryoballoon; PV, pulmonary vein; PVI, pulmonary vein isolation; and RFC, radiofrequency current.
*Fisher exact test for categorical variables, 2-sample *t* test for continuous variables.

Table 5. Repeat Ablation Procedure Times

	RFC-Redo (n=53)	CB-Redo (n=36)	*P* Values*
Total procedure time, min	115 (87–140); (n=23)	109 (82–120); (n=18)	0.38*
LA dwell time, min	84 (55–95); (n=11)	77 (67–110); (n=7)	1.00*
Fluoroscopy time, min	16.6±10; (n=45)	17.0±9.6; (n=33)	0.86†

Values are median (25th percentile–75th percentile) or mean±SD. CB indicates cryoballoon; LA, left atrium; and RFC, radiofrequency current.
*Wilcoxon rank-sum test.
†Two-sample *t* test.

cohorts were 81.8% (95% CI, 63.8%–91.4%) and 84.3% (95% CI, 69.7%–92.3%), respectively (*P*=0.66). Kaplan-Meier estimates of 1-year freedom from another reablation procedure were 97.0% (95% CI, 80.4%–99.6%) for cryoballoon-Redo and 92.8% (95% CI, 79.2%–97.6%) for RFC-Redo (*P*=0.98).

DISCUSSION

Main Findings

Main findings of this evaluation of PV lesion durability in patients who underwent repeat ablation after randomization to an index PVI using either the cryoballoon or RFC are as follows:

- Regardless of the index ablation modality, the recurrent arrhythmia before reablation was paroxysmal AF in 69% of cases and persistent AF in 13%.
- At the time of reablation, the number of reconnected PVs per patient was significantly lower in patients initially treated with the cryoballoon than in patients initially treated with RFC.
- Cryoballoon-Redo patients, compared with RFC-Redo patients, presented significantly less often with reconnected left superior PVs (28% versus 60%) and exhibited a tendency for fewer reconnected left inferior PVs (33% versus 50%) and right superior PVs (29% versus 52%).
- Although RFC was predominantly used during the reablation procedure for both cohorts, significantly fewer (PV and non-PV) ablation lesions were created per patient in the cryoballoon-Redo cohort. There was no difference between groups in the number of non-PV ablations applied per patient.

Reablation Patient Population

Overall, 15% of patients underwent a reablation during the trial period, which is comparable to a randomized comparison of RFC and cryoballoon catheter ablation that reported an overall 20% reablation rate at 12 months.[4,7] However, FIRE AND ICE showed that significantly fewer patients randomized to cryoballoon ablation underwent a repeat ablation (12% of patients with index cryoballoon) than patients randomized to RFC ablation (18% of patients with index RFC).[4] Along with differences in rehospitalization, this may suggest that although the average time to first AF recurrence was not different, the patient-felt burden of AF recurrence necessitated less reintervention following cryoballoon than RFC ablation.[9]

Baseline characteristics collected at the time of enrollment in the FIRE AND ICE trial were not statistically different between cryoballoon-Redo and RFC-Redo patients, which suggests that observed differences in the present study were likely because of the index ablation modality. While all patients presented with paroxysmal AF at the time of enrollment, ≈14% of these patients had progressed to persistent AF before the reablation procedure. The long history of AF (median of ≈4 years before index ablation) in this reablation population may have contributed to the observed disease progression.[10,11]

Index PVI Durability

This analysis demonstrated that at the time of repeat ablation, there were fewer reconnected PVs in patients whose index PVI was performed with the cryoballoon rather than RFC ablation, which is consistent with retrospective analyses that have identified a significantly lower PV reconnection rate in cryoballoon cohorts at repeat ablation than RFC reablation cohorts (18.8% versus 34.6%; 20.4% versus 36.1%; and 36.8% versus 58.1%; respectively; all $P<0.05$).[5–7] Specifically, significantly fewer superior PV reconnections in patients treated with cryoballoon compared with RFC ablation have consistently been reported.[5,6,8] These data may reflect differences in catheter stability in anatomically challenging locations. For example, significantly fewer reconnected left superior PVs were observed in the cryoballoon-Redo cohort. Stable, point-by-point RFC ablation, mandatory for creation of a contiguous and transmural ablation line, may not be readily achieved along the myocardial ridge separating the left-sided PVs from the LA appendage (which may be only a few millimeters in width particularly at the left superior PV[12]). In contrast, the cryoballoon only needs to be placed firmly in either PV ostium to achieve PVI in a single freeze; therefore, the myocardial ridge does not affect the ability of the cryoballoon to create durable lesions in this area. Similarly, the cryoballoon can ablate the right superior PV with relative ease compared with the difficulty of achieving RFC catheter stability at the posterosuperior aspect of the LA, particularly in situations of deep respiratory excursion.[8] There was no observed difference in right inferior PV reconnection rates between cryoballoon-Redo and RFC-Redo

cohorts. This may be because the inferior most aspect of the right inferior PV can be challenging to access (particularly if the site of transseptal puncture is too high in relation to the right inferior PV or if the PV is located too low in relation to the site of a proper transseptal puncture) with either ablation modality.[8] Measurement of contact force can provide a surrogate measure of catheter stability, but even an increase in power may not necessarily overcome inadequate lesion formation from RFC catheter instability leading to PV reconnection over time.[13] A randomized controlled trial is required to show whether the ablation index will lead to improved outcomes of PVI via point-by-point RFC ablation, as suggested in a recent observational study.[14]

Invasive and noninvasive investigations of PVI durability in all study patients have corroborated results from studies in reablation cohorts. The EFFICAS II trial identified that 63% of all 24 enrolled patients were free from PV lesion gaps during a remapping procedure 3 months after the index RFC PVI, while durable PVI was observed in 79% of the 21 patients evaluated 3 months after second-generation cryoballoon PVI in the SUPIR trial.[13,15] Gadolinium enhanced cardiac magnetic resonance imaging has been leveraged to noninvasively assess chronic lesion durability and identified that cryoballoon ablation resulted in fewer gaps in PV lesions 1 to 3 months following the index PVI compared with RFC ablation.[16] Together, these data suggest that cryoballoon ablation results in more durable PVI than RFC ablation regardless of whether patients ultimately required a repeat ablation.

Repeat Ablation Procedural Characteristics

This study demonstrated that fewer lesions at the time of repeat ablation were required to reisolate the PVs in patients initially treated with cryoballoon versus RFC. This is likely a consequence of fewer reconnected PVs in the cryoballoon-Redo cohort compared with the RFC-Redo cohort. However, a total of 47% of reablation patients were also treated with non-PV lesions during the repeat procedures in this study. The number of non-PV lesions applied during the repeat procedure did not differ between cohorts, which may suggest there was a similar contribution of non-PV triggers to AF recurrence between cryoballoon-Redo patients and RFC-Redo patients.

Although it was recommended to treat patients with the same ablation modality used in the index procedure, RFC was used in 85% of all repeat ablations in this trial. Therefore, procedural characteristics and freedom from rehospitalization and reablation were not different between cryoballoon-Redo and RFC-Redo cohorts. The rationale for the catheter selected during the reablation was not documented, but the tendency to use RFC during the repeat procedure may reflect a desire for flexibility to target tissue adjunctive to the PVs in the event the operator deems it necessary. However, studies that have investigated cryoballoon usage during a repeat ablation following an index intervention with either cryoballoon or RFC ablation report freedom from AF recurrence at 1 year in 60% to 70% and 83% of patients, respectively.[17–19] A randomized comparison of RFC versus cryoballoon ablation during repeat ablation did not identify a difference in freedom from AF at 1-year postreablation.[20] Together, these data suggest that the cryoballoon may be an underutilized tool for reablation procedures and warrant future studies to evaluate reablation success with the cryoballoon.

Limitations

Although patients in this study were prospectively randomized to either cryoballoon or RFC index PVI, the treatment that patients received during the repeat procedure was no longer randomized. Physicians were encouraged to use the same energy source in a repeat ablation as was used during the index procedure, but this guidance was not well adhered to outside the 90-day blanking period. This retrospective collection of data did not result in complete records to fulfill all study objectives from all patients, and the specific location(s) that initiated AF recurrence were not documented. Institutional variation in the information recorded during the repeat ablation and inconsistent definitions of study measurements prevented inclusion and analysis of all data. Some intended study objectives (eg, lesion gap information) were unable to be addressed because of insufficient information to perform meaningful statistics. Further, the original FIRE AND ICE protocol was not designed to document AF recurrence after the primary end point was met; therefore, the risk of AF recurrence after reablation cannot be reported in this analysis.

Conclusions

The FIRE AND ICE trial showed that patients treated with cryoballoon ablation required a repeat ablation less often than patients treated with RFC ablation. The present analysis demonstrated that of those patients who underwent reablation, cryoballoon-Redo patients had fewer reconnected PVs, particularly left superior PVs, with a strong trend observed in right superior PVs. These data may indicate that catheter stability mandatory to achieve durable PVI is more aptly achieved with the cryoballoon catheter than with RFC catheters. Accordingly, patients initially treated with cryoballoon PVI required fewer reablation lesions than patients initially treated with RFC PVI.

ARTICLE INFORMATION

Received January 31, 2019; accepted April 5, 2019.

The Data Supplement is available at https://www.ahajournals.org/doi/suppl/10.1161/CIRCEP.119.007247.

Correspondence

Karl-Heinz Kuck, MD, Department of Cardiology, Asklepios Klinik St Georg, Lohmühlenstr. 5, 20099 Hamburg, Germany. Email kuckkh@aol.com

Affiliations

Asklepios Klinik St Georg, Hamburg, Germany (K.-H.K., M.S.). Clinique Pasteur, Toulouse, France (J.-P.A.). Cardioangiologisches Centrum Bethanien, Frankfurt (K.R.J.C.). Universitätsklinikum Düsseldorf (A.F.). Universitätsmedizin, Greifswald, Germany (M.B.). Isala Klinieken, Zwolle, the Netherlands (A.E.). Medtronic, Inc, Minneapolis, MN (K.M.B., F.J.K., L.H.). University Heart Center Freiburg-Bad Krozingen, Germany (T.A.). Heart Rhythm Center at Centro Cardiologico Monzino, IRCCS Department of Clinical Sciences and Community Health, University of Milan, Italy (C.T.). Hospital Clínic de Barcelona, Spain (J.B.).

Acknowledgments

We would like to thank the FIRE AND ICE sites and staff for their valuable contributions to this study, and Ralf Meyer, Petra Kremer, and Bob Hokanson from Medtronic for support with the study and generation of this article.

Sources of Funding

The FIRE AND ICE Redo study was funded by Medtronic, Inc.

Disclosures

Dr Kuck reports personal fees from Medtronic and Biosense Webster during the conduct of the study and personal fees from St Jude Medical outside the submitted work. Dr Albenque reports personal fees from St Jude Medical and Biosense Webster outside the submitted work. Dr Chun reports grant support and personal fees from Medtronic during the conduct of the study and personal fees from Biosense Webster outside the submitted work. Dr Fürnkranz reports personal fees from Medtronic, both during the conduct of the study and outside the submitted work. Dr Braegelmann, F.J. Kueffer, and L. Hemingway are employees of Medtronic. Dr Arentz reports grant support and personal fees from Medtronic during the conduct of the study. The other authors report no conflicts.

APPENDIX

FIRE AND ICE Investigators: Karl-Heinz Kuck [PI], Andreas Metzner, Thomas Fink, Christine Lemes (Asklepios Klinik St. Georg, Hamburg, Germany); Julian Chun [PI], Shaojie Chen, Boris Schmidt, Fabrizio Bologna, Stefano Bordignon (Cardioangiologisches Centrum Bethanien, Frankfurt, Germany); Arif Elvan [PI], Mohamed Mouden (Isala Klinieken, Zwolle, The Netherlands); Thomas Arentz [PI], Björn Müller-Eschenborn, Amir Jadidi (University Heart Center Freiburg-Bad Krozingen, Bad Krozingen, Germany); Michael Kühne [PI], Christian Sticherling (Universitätsspital Basel, Switzerland); Mathias Busch [PI], Anne Krüger, Edison Abdiou (Universitätsmedizin Greifswald, Greifswald, Germany); Lluis Mont [PI], Eva Maria Benito Martín, Francisco Alarcón Sanz (Hospital Clinic de Barcelona, Barcelona, Spain); Petr Neuzil [PI], Libor Dujka (Nemocnice Na Homolce Praha, Prague, Czech Republic); Ricardo Ruiz-Granell [PI] (Hospital Clinico Universitario de Valencia, Valencia, Spain); Alberto Barrera [PI], Amalio Ruiz Salas (Hospital Clínico Universitario "Virgen de la Victoria", Malaga, Spain); Jean-Paul Albenque [PI], Serge Boveda (Clinique Pasteur Toulouse, France); Volker Kühlkamp [PI], Bogdan Stanciu (Herz-Zentrum Bodensee, Konstanz, Germany); Nicasio Pérez-Castellano [PI], Julián Pérez Villacastín, Victoria Canadas Godoy (Hospital Clinico San Carlos, Madrid (Spain).

REFERENCES

1. Calkins H, Hindricks G, Cappato R, Kim YH, Saad EB, Aguinaga L, Akar JG, Badhwar V, Brugada J, Camm J, Chen PS, Chen SA, Chung MK, Nielsen JC, Curtis AB, Davies DW, Day JD, d'Avila A, de Groot NMSN, Di Biase L, Duytschaever M, Edgerton JR, Ellenbogen KA, Ellinor PT, Ernst S, Fenelon G, Gerstenfeld EP, Haines DE, Haissaguerre M, Helm RH, Hylek E, Jackman WM, Jalife J, Kalman JM, Kautzner J, Kottkamp H, Kuck KH, Kumagai K, Lee R, Lewalter T, Lindsay BD, Macle L, Mansour M, Marchlinski FE, Michaud GF, Nakagawa H, Natale A, Nattel S, Okumura K, Packer D, Pokushalov E, Reynolds MR, Sanders P, Scanavacca M, Schilling R, Tondo C, Tsao HM, Verma A, Wilber DJ, Yamane T. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. *Heart Rhythm*. 2017;14:e275–e444. doi: 10.1016/j.hrthm.2017.05.012
2. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener HC, Heidbuchel H, Hendriks J, Hindricks G, Manolis AS, Oldgren J, Popescu BA, Schotten U, Van Putte B, Vardas P, Agewall S, Camm J, Baron Esquivias G, Budts W, Carerj S, Casselman F, Coca A, De Caterina R, Deftereos S, Dobrev D, Ferro JM, Filippatos G, Fitzsimons D, Gorenek B, Guenoun M, Hohnloser SH, Kolh P, Lip GY, Manolis A, McMurray J, Ponikowski P, Rosenhek R, Ruschitzka F, Savelieva I, Sharma S, Suwalski P, Tamargo JL, Taylor CJ, Van Gelder IC, Voors AA, Windecker S, Zamorano JL, Zeppenfeld K. 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Europace*. 2016;18:1609–1678. doi: 10.1093/europace/euw295
3. Kuck KH, Brugada J, Fürnkranz A, Metzner A, Ouyang F, Chun KR, Elvan A, Arentz T, Bestehorn K, Pocock SJ, Albenque JP, Tondo C; FIRE AND ICE Investigators. Cryoballoon or radiofrequency ablation for paroxysmal atrial fibrillation. *N Engl J Med*. 2016;374:2235–2245. doi: 10.1056/NEJMoa1602014
4. Kuck KH, Fürnkranz A, Chun KR, Metzner A, Ouyang F, Schlüter M, Elvan A, Lim HW, Kueffer FJ, Arentz T, Albenque JP, Tondo C, Kühne M, Sticherling C, Brugada J; FIRE AND ICE Investigators. Cryoballoon or radiofrequency ablation for symptomatic paroxysmal atrial fibrillation: reintervention, rehospitalization, and quality-of-life outcomes in the FIRE AND ICE trial. *Eur Heart J*. 2016;37:2858–2865. doi: 10.1093/eurheartj/ehw285
5. Ciconte G, Velagić V, Mugnai G, Saitoh Y, Irfan G, Hunuk B, Ströker E, Conte G, Sieira J, Di Giovanni G, Baltogiannis G, Brugada P, de Asmundis C, Chierchia GB. Electrophysiological findings following pulmonary vein isolation using radiofrequency catheter guided by contact-force and second-generation cryoballoon: lessons from repeat ablation procedures. *Europace*. 2016;18:71–77. doi: 10.1093/europace/euv224
6. Aryana A, Singh SM, Mugnai G, de Asmundis C, Kowalski M, Pujara DK, Cohen AI, Singh SK, Fuenzalida CE, Prager N, Bowers MR, O'Neill PG, Brugada P, d'Avila A, Chierchia GB. Pulmonary vein reconnection following catheter ablation of atrial fibrillation using the second-generation cryoballoon versus open-irrigated radiofrequency: results of a multicenter analysis. *J Interv Card Electrophysiol*. 2016;47:341–348. doi: 10.1007/s10840-016-0172-z
7. Buist TJ, Adiyaman A, Smit JJJ, Ramdat Misier AR, Elvan A. Arrhythmia-free survival and pulmonary vein reconnection patterns after second-generation cryoballoon and contact-force radiofrequency pulmonary vein isolation. *Clin Res Cardiol*. 2018;107:498–506. doi: 10.1007/s00392-018-1211-9
8. Ang R, Hunter RJ, Lim WY, Opel A, Ullah W, Providencia R, Baker V, Finlay MC, Dhinoja MB, Earley MJ, Schilling RJ. Long term outcome and pulmonary vein reconnection of patients undergoing cryoablation and/or radiofrequency ablation: results from the Cryo Versus RF trial. *J Atr Fibrillation*. 2018;11.
9. Kuck KH, Brugada J, Schlüter M, Braegelmann KM, Kueffer FJ, Chun KRJ, Albenque JP, Tondo C, Calkins H; FIRE AND ICE Trial Investigators. The FIRE AND ICE Trial: what we know, what we can still learn, and what we need to address in the future. *J Am Heart Assoc*. 2018;7:e010777. doi: 10.1161/JAHA.118.010777
10. Padfield GJ, Steinberg C, Swampillai J, Qian H, Connolly SJ, Dorian P, Green MS, Humphries KH, Klein GJ, Sheldon R, Talajic M, Kerr CR. Progression of paroxysmal to persistent atrial fibrillation: 10-year follow-up in the Canadian registry of atrial fibrillation. *Heart Rhythm*. 2017;14:801–807. doi: 10.1016/j.hrthm.2017.01.038
11. Proietti R, Hadjis A, AlTurki A, Thanassoulis G, Roux JF, Verma A, Healey JS, Bernier ML, Birnie D, Nattel S, Essebag V. A Systematic review on the progression of paroxysmal to persistent atrial fibrillation: shedding new light on the effects of catheter ablation. *JACC Clin Electrophysiol*. 2015;1:105–115. doi: 10.1016/j.jacep.2015.04.010
12. Schmidt B, Ernst S, Ouyang F, Chun KR, Broemel T, Bänsch D, Kuck KH, Antz M. External and endoluminal analysis of left atrial anatomy and the pulmonary veins in three-dimensional reconstructions of magnetic resonance angiography: the full insight from inside. *J Cardiovasc Electrophysiol*. 2006;17:957–964. doi: 10.1111/j.1540-8167.2006.00548.x

13. Kautzner J, Neuzil P, Lambert H, Peichl P, Petru J, Cihak R, Skoda J, Wichterle D, Wissner E, Yulzari A, Kuck KH. EFFICAS II: optimization of catheter contact force improves outcome of pulmonary vein isolation for paroxysmal atrial fibrillation. *Europace*. 2015;17:1229–1235. doi: 10.1093/europace/euv057
14. Phlips T, Taghji P, El Haddad M, Wolf M, Knecht S, Vandekerckhove Y, Tavernier R, Duytschaever M. Improving procedural and one-year outcome after contact force-guided pulmonary vein isolation: the role of interlesion distance, ablation index, and contact force variability in the 'CLOSE'-protocol. *Europace*. 2018;20(FI_3):f419–f427. doi: 10.1093/europace/eux376
15. Reddy VY, Sediva L, Petru J, Skoda J, Chovanec M, Chitovova Z, Di Stefano P, Rubin E, Dukkipati S, Neuzil P. Durability of pulmonary vein isolation with cryoballoon ablation: results from the Sustained PV Isolation with Arctic Front Advance (SUPIR) study. *J Cardiovasc Electrophysiol*. 2015;26:493–500. doi: 10.1111/jce.12626
16. Kurose J, Kiuchi K, Fukuzawa K, Mori S, Ichibori H, Konishi H, Taniguchi Y, Hyogo K, Imada H, Suehiro H, Nagamatsu YI, Akita T, Takemoto M, Hirata KI, Shimoyama S, Watanabe Y, Nishii T, Negi N, Kyotani K. The lesion characteristics assessed by LGE-MRI after the cryoballoon ablation and conventional radiofrequency ablation. *J Arrhythm*. 2018;34:158–166. doi: 10.1002/joa3.12025
17. Schade A, Langbein A, Spehl S, Barth S, Deneke T, Groschup G, Koller ML, Schumacher B. Recurrence of paroxysmal atrial fibrillation after cryoisolation of the pulmonary veins. Is a "redo" procedure using the cryoballoon useful? *J Interv Card Electrophysiol*. 2013;36:287–95; discussion 295. doi: 10.1007/s10840-012-9725-y
18. De Regibus V, Iacopino S, Abugattas JP, Mugnai G, Moran D, Ströker E, Coutino HE, Takarada K, Choudhury R, Paparella G, Umbrain V, Brugada P, de Asmundis C, Chierchia GB. Repeat procedures using the second-generation cryoballoon for recurrence of atrial fibrillation after initial ablation with conventional radiofrequency. *J Interv Card Electrophysiol*. 2017;49:119–125. doi: 10.1007/s10840-017-0236-8
19. Westra SW, van Vugt SPG, Sezer S, Evertz R, Hemels ME, Beukema RJ, de Asmundis C, Brouwer MA, Chierchia GB. Second-generation cryoballoon ablation for recurrent atrial fibrillation after an index cryoballoon procedure: a staged strategy with variable balloon size. *J Interv Card Electrophysiol*. 2019;54:17–24. doi: 10.1007/s10840-018-0418-z
20. Pokushalov E, Romanov A, Artyomenko S, Baranova V, Losik D, Bairamova S, Karaskov A, Mittal S, Steinberg JS. Cryoballoon versus radiofrequency for pulmonary vein re-isolation after a failed initial ablation procedure in patients with paroxysmal atrial fibrillation. *J Cardiovasc Electrophysiol*. 2013;24:274–279. doi: 10.1111/jce.12038