Cryoballoon Versus Open Irrigated Radiofrequency Ablation in Patients With Paroxysmal Atrial Fibrillation: The Prospective, Randomized, Controlled, Noninferiority FreezeAF Study

Armin Luik, MD; Andrea Radzewitz, PsyD; Meinhard Kieser, ScD; Marlene Walter; Peter Bramlage, MD; Patrick Hörmann, MD; Kerstin Schmidt, MD; Nicolas Horn, MD; Maria Brinkmeier-Theofanopoulou, MD; Kevin Kunzmann, MSc; Tobias Riiexinger, MD; Gerhard Schymik, MD; Matthias Merkel, MD; Claus Schmitt, MD

Background—There is a lack of data on the comparative efficacy and procedural safety of open irrigated radiofrequency (RF) and cryoballoon catheter (CB) ablation for pulmonary vein isolation in patients with paroxysmal atrial fibrillation.

Methods and Results—In a prospective, noninferiority study, 315 patients were randomly assigned to RF (n=159) or CB (n=156) ablation. The primary end point was freedom from atrial arrhythmia with absence of persistent complications. Patients were largely comparable between groups with more vascular disease in the RF group (8.2% versus 2.6% for CB; P=0.028). The primary end point at 12 months was achieved by 70.7% with RF and 73.6% with CB (multiple procedure success), including 31 redo procedures in each group (19.5% of RF versus 19.9% of CB; P=0.933). For the intention-to-treat population, noninferiority of CB was revealed for the predefined inferiority margin (risk difference, 0.029; 95% confidence interval, −0.074 to 0.132; P<0.001). Rates at 6 months were 63.1% and 64.1% for the RF and CB groups (single procedure success), and noninferiority was confirmed (risk difference, 0.010; 95% confidence interval, −0.097 to 0.116; P=0.002). Periprocedural complications for the index procedure were more frequent in the CB group (5.0% RF, 12.2% CB; P=0.022) with a significant difference in phrenic nerve palsies (0% RF, 5.8% CB; P=0.002).

Conclusion—This large, prospective, randomized, controlled study demonstrates noninferiority of CB ablation versus RF ablation for treating patients with paroxysmal atrial fibrillation.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00774566.

Key Words: arrhythmias, cardiac ■ atrial fibrillation ■ catheter ablation

Atrial fibrillation (AF), the most common form of cardiac arrhythmia, is associated with a risk of associated complications such as stroke and heart failure, in addition to a higher rate of mortality.1,2 Sinus rhythm can often be restored with electric cardioversion; however, the rate of AF recurrence is high, even with administration of antiarrhythmic drugs (AADs).3 In addition to their relatively low efficacy, AADs have the disadvantage of causing adverse events, often leading to discontinuation.4,5 Catheter ablation is a well-established technique for treating paroxysmal AF via pulmonary vein (PV) isolation, with a variety of energy sources used, most commonly radiofrequency (RF) or cryoenergy.6 RF ablation has been shown to be a highly effective first- or second-line treatment for AF; however, it is associated with more immediate and severe complications compared with drug therapy.7–10 Incidences of PV stenosis, thromboembolic complications, cardiac perforations with pericardial tamponade, esophageal fistulas, and phrenic nerve palsies (PNPs) have been reported.7–11

Clinical Perspective on p 1319

The more recently introduced strategy of using a cryoballoon catheter (CB) for PV isolation has produced encouraging results in a number of trials. Neumann et al12 documented maintained sinus rhythm over a median follow-up period of 12 months in 74% of patients with mainly paroxysmal or persistent AF who underwent the procedure. In a separate long-term study in patients with paroxysmal AF, freedom from AF
recurrence was reported for 53% of patients after 5 years.\textsuperscript{13} A number of studies have compared ablation with CB with ablation with RF for PV isolation. In general, the obtained data demonstrate equivalent efficacy and similar safety profiles for the 2 techniques, although CB has been associated with a trend for reduced incidences of cardiac perforations with pericardial tamponade but with higher rates of PNP compared with RF ablation.\textsuperscript{14–17}

Although these studies have provided a wealth of information on the 2 ablation energy sources, the absence of randomization in all but 1 of these trials is a significant drawback. The FreezeAF trial was designed to overcome this shortcoming by using a randomized, controlled, noninferiority design to directly compare RF with CB for treating patients with paroxysmal AF (http://www.clinicaltrials.gov; NCT00774566).

Methods

Study Design

FreezeAF is a randomized, controlled, prospective, noninferiority clinical trial designed to assess the efficacy and safety of PV isolation performed with either a CB or an irrigated RF ablation catheter.\textsuperscript{14} The main objective of the study was to determine whether cryoablation was not inferior to RF open irrigated tip ablation for the treatment of paroxysmal AF. The total follow-up period was 12 months, with additional evaluation of the end points carried out at 6 months after the index procedure.

All patients enrolled in the study provided written, informed consent. Furthermore, the trial protocol was approved by the ethics committee of the University of Freiburg on September 15, 2008, and the study was carried out in accordance with the Declaration of Helsinki.

Patients

Patients 18 to 75 years of age who had experienced at least 2 episodes of AF within the last 3 months were consecutively enrolled in the study. Further eligibility criteria were at least 1 episode of AF confirmed by ECG and documentation of at least 1 ineffective AAD treatment, including â-blockers. Patients were excluded if they had previously undergone left atrial (LA) ablation or surgery, if their LA was >55 mm in diameter, or if there was evidence of LA thrombus. Further exclusion criteria included unstable angina, myocardial infarction within the previous 3 months, cardiac surgery or percutaneous transluminal coronary angioplasty within the previous 3 months, an ejection fraction <40%, heart failure grade III to IV (New York Heart Association criteria), stroke or transient ischemic attack within the previous 6 months, pregnancy, or a life expectancy of <1 year. A full list of inclusion and exclusion criteria has previously been published.\textsuperscript{18} Preprocedurally, LA thrombi were excluded by transesophageal echocardiography. Additionally, the patients underwent either computed tomography or magnetic resonance imaging of the LA to determine physiological abnormalities and to exclude PV stenosis. Patients were assigned a CHA\textsubscript{2}DS\textsubscript{2}-VASc score to indicate the risk of thromboembolism and a HAS-Bled score to indicate the risk of bleeding.\textsuperscript{19,20} After providing consent, patients were randomly assigned with an allocation ratio of 1:1 to either the CB or RF procedure. Random numbers were generated with SAS software (Cary, NC) in which block randomization with randomly selected block sizes was applied.

Ablation Procedures

For both groups of patients, a single or double transseptal puncture was performed after arterial and venous access had been achieved. PV angiography and measurement of PV potentials were carried out both before and after PV isolation with the use of a circular mapping catheter. RF-mediated antral ablation was performed with a 3.5-mm irrigated tip catheter in conjunction with a 3-dimensional navigation system (Ensite NavX/Velocity, St. Jude Medical, St. Paul, MN; Carto-3, Biosense Webster, Inc, Diamond Bar, CA). Cryoablation of the PV ostia was carried out with the Arctic Front Cryo Ablation Catheter System and FlexCath Steerable Sheath (Medtronic, Inc, Minneapolis, MN). The 28-mm CB was preferentially used; however, a switch to the 23-mm device was allowed if necessary, as were touchups with a conventional cryoablation catheter (Freezor Max, Medtronic, Inc). For each PV, at least 2 applications of cryoenergy for 300 seconds with first-generation CBs and 2 times for 240 seconds with second-generation CBs were used according to the manufacturer’s recommendation. Additional applications could be used if deemed necessary.

Outcomes

The primary end point was defined as the absence of atrial arrhythmias in combination with absence of persistent complications during the 6- and 12-month follow-up periods (coprimary end points). Persistent complications were defined as any new PV stenosis, PNP, cerebrovascular, or bleeding or vascular complications that occurred during or within 48 hours after the procedure. Data of patients who either died or declined a clinical follow-up with rhythm assessment were considered missing. Adjudicators were not blinded to the group assignment on the determination of AF recurrence. Each documented episode of an atrial arrhythmias >30 seconds after the 3-month blanking period was considered a failure. The 6-month follow-up was used to evaluate the outcome of the index procedure; the 12-month visit additionally took into account any redo procedures. Secondary end points included procedural data, total radiation exposure, total procedure duration, and occurrence of adverse events, including PNP (assessed with breathing or pacing maneuvers at the discretion of the physician), pericardial effusion, and vascular complications. The assessment of quality of life was planned in the initial protocol version but was not further pursued. Major bleeding was defined as any bleeding or vascular complication requiring additional therapy. Minor bleeding was defined as any bleeding or vascular complication (hematoma, pseudoaneurysm, atriovenous fistula) that required prolonged hospitalization but could be managed conservatively. Detailed definitions of the components of each of the primary and secondary outcomes have been previously published.\textsuperscript{18}

Statistical Analysis

Analysis of the primary end points was carried out for both the intention-to-treat (ITT) population and the per-protocol (PP) population. ITT analysis included all randomized patients who received study treatment who were evaluated in the group to which they were assigned, regardless of whether or not they completely adhered to the study protocol. Patients with major protocol violations were excluded from the PP analysis. Major protocol deviations were defined as AAD treatment after the ablation procedure, redo procedures before the 6-month follow-up, crossover, and LA ablation strategies other than PV isolation. Before the analysis, each patient was assigned to the appropriate population according to the occurrence of protocol
deviations. For the purpose of statistical analysis, patients with protocol deviations during the 6-month follow-up were additionally excluded from the 12-month PP analysis set.

The test problem for the assessment of noninferiority was formulated in terms of the rate of achievement of the primary end point 12 months after the CB procedure \((p_{CB})\) and after the RF procedure \((p_{RF})\), whereas the null hypothesis was defined as follows: \(H_0: p_{CB} - p_{RF} \leq -\delta\), where \(\delta=0.15\). An analogous test problem was formulated for the related rates after the 6-month follow-up, with this null hypothesis tested only if that for the 12-month follow-up was rejected; otherwise, both null hypotheses were accepted. As a result of the application of this multiple testing procedure, the experiment-wise type I error rate was controlled in the strong sense. The tests were carried out by applying the noninferiority test for rates according to Farrington and Manning\(^{21}\) at a 1-sided significance level of \(\alpha=2.5\%\). Multiple imputation was applied to deal with missing values for the primary end points. The multiple imputation by chained equations algorithm\(^{22,23}\) was used with a logistic regression model for the primary end points and the group assignment as the covariable. To adequately reflect the variability caused by imputed data, 100 imputed data sets were used. The results of the related analyses were pooled by the Rubin rule.\(^{24}\) An additional sensitivity analysis was performed, imputing all missing data sets as failures.

Descriptive statistics were used to describe the secondary variables, with means and standard deviations, medians and first and third quartiles, or absolute and relative frequencies given as appropriate. \(P\) values for these variables are not adjusted for multiplicity. For ordinal and continuous variables, the \(P\) values for treatment group comparisons were determined with the 2-sided Wilcoxon rank-sum test, whereas the 2-sided \(\chi^2\) test was used to compare categorical variables. Statistical analysis was performed with R 3.13, with the multiple imputation by chained equations version 2.22 used for multiple imputation.\(^{25}\)

Sample Size Calculation

The originally planned sample size was calculated assuming equal rates of 0.78 for achieving the primary outcome, which was based on the findings of previous studies and experience with the procedures.\(^3,12\) To reach a power of \(1-\beta = 80\%\) for the 1-sided Farrington-Manning test at a level of \(\alpha=2.5\%\), the required sample size was \(2 \times 122=244\) patients.\(^{21}\) Owing to the uncertainty about the assumption of an overall rate of 0.78, a blinded sample size recalculation was prespecified in the protocol.\(^{18}\) The overall rate observed in March 2011 was 0.65, smaller than the anticipated rate. Using this rate for both groups but leaving all other quantities of the initial sample size calculation (especially the noninferiority margin) unchanged led to an increase in sample size to a total of \(2 \times 157=314\) patients.

Results

Patients

A total of 322 patients were included, with 7 not receiving treatment as part of the trial because of a withdrawal of consent but without their group assignment known, leaving 315 patients randomly assigned. This resulted in a final ITT population of 315 patients, 159 allocated to receive RF ablation and 156 allocated to receive CB ablation. Eleven patients had protocol deviations at 6 months (5 in RF, 6 in CB) and 33 at 12 months (18 in RF, 15 in CB), leaving 304 and 282 patients, respectively, for the PP analysis (Figure). More male than female patients underwent the procedure (60.6% male overall), with no significant difference in the proportions of each in the 2 groups (Table 1). In addition, the age of the patients did not vary between groups \((P=0.871)\). In terms of comorbidities, there were no significant differences in the proportions of patients who presented with coronary artery disease, hypertension, diabetes mellitus, stroke, aortic insufficiency, mitral regurgitation, tricuspid valve insufficiency, or multiple valvular defects. There was a slightly lower proportion of patients with vascular disease in the CB group \((P=0.028)\).

Patients were treated with a variety of anticoagulants, with the majority in both groups receiving phenprocoumon.

---

**Figure.** Patient flow, including planned sample size recalculation. *The initial sample size calculation resulted in 244 patients, which was readjusted in March 2011 after a prespecified blinded sample size recalculation (see Methods). Patients (pts) withdrawing consent before treatment (tx) were unaware of the assignment and were excluded from the population. Patients who refused a 12-month follow-up were contacted by phone to verify that they were alive although no heart rhythm was obtained. CB indicates cryoballoon ablation; FU, follow-up; ITT, intention to treat; PP, per protocol; and RF, radiofrequency catheter ablation.
A high proportion of patients in each group were being treated with β-blockers (89.5%), and a relevant number were receiving an angiotensin-converting enzyme inhibitor (39.0%). Similar proportions of patients in each group were being treated with an angiotensin II type 1 antagonist, a diuretic, or a statin. Except for apixaban (4 patients in CB group, 0 in RF), there were no significant differences between the 2 treatment groups with regard to any of the prescribed medications.

In terms of risk for thromboembolism and bleeding, the CHA2DS2-VASc and HAS-Bled indexes, respectively, were comparable for both treatment groups (Table 3).

Physiological anomalies of the PVs, for example, a common ostium of the left PVs or an additional right middle PV, were distributed equally in both groups. An additional ablation of the cavotricuspid isthmus as a result of documented typical atrial flutter before or during the procedure was less frequent in the CB group (13.5% versus 23.9% in RF; \(P=0.018\)).

### Table 1. Patient Characteristics

| Comorbidities                      | Total (n=315), n (%) | RF (n=159), n (%) | CB (n=156), n (%) | \(P\) Value, RF vs CB |
|------------------------------------|----------------------|------------------|------------------|-----------------------|
| Male sex                           | 191 (60.6)           | 91 (57.2)        | 100 (64.1)       | 0.212                 |
| Age, y*                            | 61 (54, 67)          | 60 (54, 67)      | 61 (54, 66)      | 0.871†                |
| Coronary artery disease            |                      |                  |                  |                       |
| None                               | 276 (87.6)           | 139 (84.7)       | 137 (87.8)       |                       |
| 1 Vessel                           | 23 (7.3)             | 10 (6.3)         | 13 (8.3)         |                       |
| 2 Vessels                          | 9 (2.9)              | 5 (3.1)          | 4 (2.6)          |                       |
| 3 Vessels                          | 7 (2.2)              | 5 (3.1)          | 2 (1.3)          |                       |
| Hypertension                       | 199 (64.2)           | 103 (66.0)       | 96 (62.3)        | 0.498                 |
| Diabetes mellitus                  | 31 (9.8)             | 17 (10.7)        | 14 (9.0)         | 0.609                 |
| Stroke                             | 24 (7.6)             | 12 (7.5)         | 12 (7.7)         | 0.961                 |
| Vascular disease                   | 17 (5.4)             | 13 (8.2)         | 4 (2.6)          | 0.028                 |
| Mitral regurgitation               | 269                  | 134              | 135              | 0.065†                |
| None                               | 88 (32.7)            | 51 (38.1)        | 37 (27.4)        |                       |
| Slight                             | 174 (64.7)           | 80 (59.7)        | 94 (69.6)        |                       |
| Moderate                           | 7 (2.6)              | 3 (2.2)          | 4 (3.0)          |                       |
| Tricuspid valve regurgitation      | 303                  | 154              | 149              | 0.180                 |
| None                               | 293 (97.0)           | 151 (98.1)       | 142 (95.3)       |                       |
| Slight                             | 10 (3.2)             | 3 (1.9)          | 7 (4.7)          |                       |
| Multiple valvular defects          | 313                  | 159              | 154              | 0.312                 |
|                                    | 45 (14.4)            | 26 (16.4)        | 19 (12.3)        |                       |

*Data given as median (25th, 75th percentiles).
†\(P\) value calculated with the 2-sided Wilcoxon rank-sum test. All other \(P\) values calculated with the 2-sided \(\chi^2\) test.

### Table 2. Prior Medication

| Medication                          | Total (n=315), n (%) | RF (n=159), n (%) | CB (n=156), n (%) | \(P\) Value, RF vs CB |
|-------------------------------------|----------------------|------------------|------------------|-----------------------|
| Phenprocoumon                       | 233 (74.0)           | 119 (74.8)       | 114 (73.1)       | 0.721                 |
| Dabigatran                          | 52 (16.5)            | 25 (15.7)        | 27 (17.3)        | 0.705                 |
| Rivaroxaban                         | 25 (7.9)             | 13 (8.2)         | 12 (7.7)         | 0.874                 |
| Apixaban                            | 4 (1.3)              | 0 (0.0)          | 4 (2.6)          | 0.042                 |
| Aspirin                             | 33 (10.5)            | 20 (12.6)        | 13 (8.3)         | 0.219                 |
| Platelet aggregation inhibitor other than aspirin | 9 (2.9)              | 7 (4.6)          | 2 (1.3)          | 0.091                 |
| β-Blocker                           | 282 (89.5)           | 140 (89.2)       | 142 (92.2)       | 0.357                 |
| ACE inhibitor                       | 123 (39.0)           | 65 (41.4)        | 58 (37.7)        | 0.500                 |
| AT1 antagonist                      | 60 (19.0)            | 30 (19.1)        | 30 (19.5)        | 0.934                 |
| Diuretics                           | 77 (24.4)            | 34 (21.8)        | 43 (27.9)        | 0.212                 |
| Statins                             | 85 (27.0)            | 41 (26.3)        | 44 (28.6)        | 0.651                 |

\(P\) values calculated with the 2-sided \(\chi^2\) test. ACE indicates angiotensin-converting enzyme; and AT1, angiotensin II type 1.
Ablation of the cavotricuspid isthmus was always performed with either irrigated RF or nonirrigated RF energy.

**Primary End Point**

The coprimary end points were defined as absence of atrial arrhythmias in combination with absence of persistent complications during the 6- and 12-month follow-up periods. In the ITT population, the coprimary end points were reached in 63.1% of patients in the RF group and 64.1% of patients in the CB group at 6 months and in 70.7% and 73.6% of patients, respectively, at 12 months. The increase in the rate of the primary end point was attributable to redo procedures, which were allowed only after 6 months. Sixty-two patients underwent redo procedures, 31 in each group (19.5% RF versus 19.9% CB; \( P = 0.933 \)).

With the use of the defined margin of \( \delta = 0.15 \) and a 1-sided significance level of \( \alpha = 2.5\% \) for the Farrington-Manning test for noninferiority,²¹ the null hypothesis at 12 months could be rejected (risk difference, 0.029; 95% confidence interval [CI], −0.074 to 0.132; \( P < 0.001 \); Table 5). We therefore tested the analogous null hypothesis at 6 months and found that it could also be rejected for this end point (risk difference, 0.010; 95% CI, −0.096 to 0.117; \( P = 0.002 \)). A sensitivity analysis in which missing values were imputed as failures confirmed these results (Table I in the online-only Data Supplement).

At the 12-month follow-up, the PP population comprised 141 patients in both the RF and CB treatment groups. At 6 months, there were 154 in the RF group and 150 in the CB group. With the same noninferiority margin of \( \delta = 0.15 \) and the same 1-sided significance level of \( \alpha = 2.5\% \), the null hypothesis at 12 months could be rejected (risk difference, 0.014; 95% CI, −0.089 to 0.117; \( P < 0.001 \); Table 5). Subsequent analysis of primary end-point achievement at 6 months revealed that the null hypothesis could also be rejected for this end point (risk difference 0.010; 95% CI, −0.096 to 0.117; \( P = 0.002 \)).

**Secondary End Points**

In 10 patients, a second CB of a different size (23 and 28 mm) was needed to achieve PV isolation. None needed a touchup with a conventional cryocatheter. The overall procedure time was about 13 minutes shorter in the CB group (\( P = 0.006 \)). The x-ray duration was very similar in both groups (median, 24 minutes in RF and 25.5 minutes in CB; \( P = 0.632 \)), although the median of the total x-ray dosage was 11.5 Gy·cm² higher for the CB procedure (\( P = 0.012 \); Table 6) with an overall median x-ray dose of 56.0 Gy·cm².

**Complications**

Few adverse events occurred during the index procedure in either treatment group (Table 7). Overall, major events

Table 4). Ablation of the cavotricuspid isthmus was always performed with either irrigated RF or nonirrigated RF energy.

### Table 3. Risk Indexes

| CHA2DS2-VASc | Total (n=315), n (%) | RF (n=159), n (%) | CB (n=156), n (%) | \( P \) Value, RF vs CB |
|-------------|---------------------|------------------|------------------|------------------------|
| 0           | 66 (21.0)           | 31 (19.5)        | 35 (22.4)        | 0.278                  |
| 1           | 92 (29.2)           | 45 (28.3)        | 47 (30.1)        |                        |
| 2           | 83 (26.3)           | 42 (26.4)        | 41 (26.3)        |                        |
| 3           | 50 (15.9)           | 26 (16.4)        | 24 (15.4)        |                        |
| 4           | 18 (5.7)            | 12 (7.5)         | 6 (3.8)          |                        |
| 5           | 4 (1.3)             | 2 (1.3)          | 2 (1.3)          |                        |
| 6           | 2 (0.6)             | 1 (0.6)          | 1 (0.6)          |                        |

| HAS-Bled | Total (n=315), n (%) | RF (n=159), n (%) | CB (n=156), n (%) | \( P \) Value, RF vs CB |
|----------|---------------------|------------------|------------------|------------------------|
| 0        | 88 (27.9)           | 43 (27.0)        | 45 (28.8)        | 0.253                  |
| 1        | 114 (36.2)          | 53 (33.3)        | 61 (39.1)        |                        |
| 2        | 86 (27.3)           | 47 (29.6)        | 39 (25.0)        |                        |
| 3        | 23 (7.3)            | 13 (8.2)         | 10 (6.4)         |                        |
| 4        | 4 (1.3)             | 3 (1.9)          | 1 (0.6)          |                        |

CHA2DS2-VASc score for predicting the 1-year risk of a thromboembolism; HAS-Bled score for predicting the 1-year risk of bleeding.²⁰ \( P \) values calculated with the 2-sided Wilcoxon rank-sum test.

### Table 4. Electrophysiological Study of the Heart

| CTI ablation (RF) | Total (n=315), n (%) | RF (n=159), n (%) | CB (n=156), n (%) | \( P \) Value, RF vs CB |
|-------------------|---------------------|------------------|------------------|------------------------|
| None              | 239 (75.9)          | 118 (74.2)       | 121 (77.6)       | 0.573                  |
| At least 1 (LPV or RMPV) | 76 (24.1)       | 41 (25.8)        | 35 (22.4)        |                        |

\( P \) values calculated with the 2-sided \( \chi^2 \) test. CTI indicates cavotricuspid isthmus; LPV, common ostium of left pulmonary veins; PV, pulmonary vein; RF, radiofrequency; and RMPV, right middle pulmonary vein.
Patients with paroxysmal AF were enrolled and randomized to undergo PV isolation with 1 of the 2 energy sources. Patient characteristics were similar to other reports of patients with paroxysmal AF with a low mean age and a low degree of comorbidity. The 2 treatment groups were well matched in terms of sex and age and had similar rates of comorbidity. The 2 treatment groups were well matched in terms of the 1-year risk score for predicting a major bleed, with the majority of individuals in both groups being assigned a score of 0 to 2.19 There were also no differences in terms of the 1-year risk score for predicting a major bleed, with the majority of individuals in both groups being assigned a score of 0 to 2.20

A number of studies have demonstrated the efficacy and safety of CB ablation for the treatment of AF.21,13,26–28; however, it is still unclear how this strategy compares with the well-established RF method. Here, we demonstrated noninferiority of PV isolation with CB ablation compared with using RF for a primary end point of freedom from atrial arrhythmia combined with the absence of persistent complications. At both 6 and 12 months, CB was shown to be noninferior to RF within a margin of δ = 0.15. A margin of 15%, which might be considered large, was deemed acceptable at the inception of the study, given the advantages of CB with respect to dimensions other than the primary end point. Although this assessment was based on multiple reports at the time of study initiation,

| ITT population | RF | CB | RD (95% CI)* | P Value* |
|----------------|----|----|-------------|---------|
| At 6 mo Combined end point† | 99/157 (0.631) | 98/153 (0.641) | 0.010 (−0.097 to 0.116) | 0.002 |
| At 12 mo Combined end point‡ | 104/147 (0.707) | 106/144 (0.736) | 0.029 (−0.074 to 0.132) | <0.001 |

P values (1 sided) and CIs were calculated with the Farrington-Manning method; a significant P value indicates that noninferiority is met. CB indicates cryoballoon catheter; CI, confidence interval; ITT, intention to treat; PP, per protocol; RD, rate difference (cryoballoon minus radiofrequency); and RF, radiofrequency.

*For ITT, CIs and P values were calculated by applying multiple imputation to deal with missing data, whereas no missing data occurred for PP.
†Equals the number of patients with single procedure success at 6 months.
‡Equals the number of patients with multiple procedure success at 6 months; persistent complications at 6 months in the CB group (n=3) and RF group (n=0); no persistent complications at 12 months; numbers equal rhythm control rate at 12 months.

Discussion

The randomized FreezeAF study was carried out to comprehensively evaluate noninferiority of CB compared with RF ablation in terms of absence of atrial arrhythmias and persistent complications during a follow-up period of 12 months. Patients with paroxysmal AF were enrolled and randomized to undergo PV isolation with 1 of the 2 energy sources. Patient characteristics were similar to other reports of patients with paroxysmal AF with a low mean age and a low degree of comorbidity. The 2 treatment groups were well matched in terms of sex and age and had similar rates of comorbidity. The 2 treatment groups were well matched in terms of the 1-year risk score for predicting a major bleed, with the majority of individuals in both groups being assigned a score of 0 to 2.20

A number of studies have demonstrated the efficacy and safety of CB ablation for the treatment of AF.21,13,26–28; however, it is still unclear how this strategy compares with the well-established RF method. Here, we demonstrated noninferiority of PV isolation with CB ablation compared with using RF for a primary end point of freedom from atrial arrhythmia combined with the absence of persistent complications. At both 6 and 12 months, CB was shown to be noninferior to RF within a margin of δ = 0.15. A margin of 15%, which might be considered large, was deemed acceptable at the inception of the study, given the advantages of CB with respect to dimensions other than the primary end point. Although this assessment was based on multiple reports at the time of study initiation,

### Table 5. Primary End-Point Analysis

| ITT population | RF | CB | RD (95% CI)* | P Value* |
|----------------|----|----|-------------|---------|
| At 6 mo Combined end point† | 99/157 (0.631) | 98/153 (0.641) | 0.010 (−0.097 to 0.116) | 0.002 |
| At 12 mo Combined end point‡ | 104/147 (0.707) | 106/144 (0.736) | 0.029 (−0.074 to 0.132) | <0.001 |

**Table 6. Secondary End Points**

| Total, Median (25th, 75th percentiles) (n=315) | RF, Median (25th, 75th percentiles) (n=159) | CB, Median (25th, 75th percentiles) (n=156) | P Value |
|-----------------------------------------------|---------------------------------------------|---------------------------------------------|---------|
| Total procedure time, min                     | 170.0 (140.0, 202.0)                        | 174.0 (146.5, 218.0)                        | 161.0 (132.8, 193.2) | 0.006 |
| X-ray dose, Gy·cm²                            | 56.0 (30.0, 85.5)                           | 50.0 (          )                           | 61.5 (36.0, 95.5)  | 0.012 |
| X-ray duration, min                           | 24.1 (17.1, 33.2)                           | 24.0 (16.9, 37.2)                           | 24.5 (17.5, 31.0)  | 0.632 |

P values calculated with 2-sided Wilcoxon rank-sum test.
a recent meta-analysis has summarized the potential advantages of CB over RF.\textsuperscript{29} This meta-analysis, which included a total of 14 articles and 1104 patients, found fluoroscopy time (weight mean difference, $-14.23$ minutes; 95% CI, $-25.45$ to $-2.82$) and overall procedure time (weight mean difference, $-29.65$ minutes; 95% CI, $-50.77$ to 8.54) to be significantly shorter, with a nonsignificant increase in ablation time (weight mean difference, $11.66$ minutes; 95% CI, $-10.71$ to 34.34). Furthermore, CB was found to be associated with a trend for fewer major complications (odds ratio, 0.46; 95% CI, 0.11–1.83). Finally, there is also evidence that the learning curve for CB ablation was much shorter than for RF ablation.\textsuperscript{30}

Noninferiority was demonstrated for both the ITT and PP populations. Furthermore, the overall rate of complications was 8.6% with no persistent complications at 12 months. Previous nonrandomized trials have indicated that CB PV isolation is equivalent to RF in terms of achieving freedom from atypical atrial flutter and tachycardia in patients with paroxysmal AF but with a higher rate of PNP.\textsuperscript{14,17,31} Recently, although not directly comparable, Malmborg et al\textsuperscript{16} reported a small, randomized study comparing CB with the circular multipolar duty-cycled RF-based PV ablation catheter in patients with persistent or paroxysmal AF. They demonstrated freedom from AF in 52% and 38% of CB and duty-cycled RF patients, respectively, after 6 months ($P=0.13$), with values of 46% and 34%, respectively, at 12 months ($P=0.21$). Wasserlauf et al\textsuperscript{17} reported a single-center, prospective, cohort study in patients undergoing catheter ablation for paroxysmal AF using CB (n=101) or RF (n=100). Freedom from AF at 1 year was 60.3% in the CB group and 61.1% in the RF group ($P=0.93$). Overall complication rates were equivalent; however, fewer cardiac perforations occurred with CB (0% versus 4%; $P=0.042$).

In addition to efficacy, a number of other factors should be taken into account in the selection of the most suitable approach to treating a patient. Safety is of paramount importance, in terms of both periprocedural factors and complications identified during follow-up. Here, we found that the mean x-ray duration was equal in both groups, whereas the x-ray dose was slightly greater for the patients who underwent the CB procedure. Previous studies have found both longer\textsuperscript{14,31} and shorter\textsuperscript{16,17} fluoroscopy times for the CB procedure. The higher amount of the x-ray dose in the CB group is explained by the need for a higher resolution of the fluoroscopy image to prove balloon occlusion. The overall procedure time was significantly shorter for the cryoenergy technique. This result has been replicated in a number of other studies.\textsuperscript{17,32,33}

Rates of adverse events were low in both treatment groups, making it difficult to draw definitive conclusions. In this study, periprocedural complications were lower in the RF group, which is in potential disagreement with the nonsignificant trend for fewer complications with CB reported in the aforementioned meta-analysis.\textsuperscript{29} However, the events in our study were influenced mainly by the number of (transient) PNP in the CB group. By the time of the 6-month follow-up period, all but 3 cases of PNP had been resolved, and at 12 months, all patients with PNP had recovered, which is in agreement with other studies.\textsuperscript{36,32,34} PV stenoses, on the other hand, are recognized as complications associated with RF ablation.\textsuperscript{6,35,36} In the present study, there was a single PV stenosis in a redo procedure with RF energy. Vascular complications and pericardial effusion were comparable in both groups, although the pericardial effusions in the CB group needed to be drained.

### Conclusions

In response to a need for more conclusive data on the efficacy and safety of CB for PV isolation, we carried out a randomized noninferiority study comparing the technique with...
the well-established RF ablation method. At both the 6- and 12-month follow-up, CB was demonstrated to be noninferior to RF in terms of freedom from AF and an absence of persistent complications.

### Funding Source

This is an investigator-initiated study. The study was supported with 20,000 EUR to acquire Holter monitor devices by CryoCath/Medtronic.

### Disclosures

Dr Liuk has received consulting fees/honoraria from Medtronic, Inc, Boston Scientific Corp, Biosense Webster, and St. Jude Medical. Dr Merkel has received consulting fees/honoraria from Medtronic, Inc, CardioFocus, Inc, and Boston Scientific Corp. Dr Schmitt has received consulting fees/honoraria from Pfizer, Inc, Bayer/Schering Pharma, Boehringer Ingelheim, and Medtronic, Inc. Dr Kieser was a member of the Data and Safety Monitoring Board of the FIRE AND ICE study (http://www.clinicaltrials.gov; identifier: NCT01490814). The authors report no conflicts.

### References

1. Benjamin EF, Wolf PA, D’Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. *Circulation* 1998;98:946–952. doi: 10.1161/01.CIR.98.10.946.
2. Stewart S, Hart CL, Hole DJ, McMurray JJ. A population-based study of the long-term risks associated with atrial fibrillation: 20-year follow-up of the Renfrew/Paisley study. *Am J Med.* 2002;113:359–364. doi: 10.1016/S0002-9343(02)01236-8.
3. Van Gelder IC, Crijns HJ, Tieleman RG, Brugemann J, De Kam PJ, Gosselin AF, Verheugt FW, Loe KL. Chronic atrial fibrillation: success of serial cardioversion therapy and safety of oral anticoagulation. *Arch Intern Med.* 1996;156:2585–2592. doi: 10.1001/archinte.1996.00440210109011.
4. Laiinen-LaFuentbe C, Longos-Tejero MA, Bergmann JF, Belmin J. Antiarrhythmics for maintaining sinus rhythm after cardioversion of atrial fibrillation. *Cochrane Database Syst Rev.* 2012;1:CD005049. doi: 10.1002/14651858.CD005049.pub3.
5. Hollands JM, Gowan M, Riney JN, Deal EN, Kates AM. Role of new drugs for management of atrial fibrillation. *Ann Pharmacother.* 2012;46:1656–1670. doi: 10.1345/aph.1R155.
6. Cappato R, Calkins H, Chen SA, Davies W, Haysakaer M, Catheter ablation versus antiarrhythmic drugs for atrial fibrillation: results from the AF-COR study. *J Am Coll Cardiol.* 2014;63:1587–1595. doi: 10.1016/j.jacc.2012.09.033.
7. Morillo CA, Cappato R, Calkins H, Chen SA, Da-Castello MA, Bergmann JF, Belmin J. Role of new drugs in the treatment of atrial fibrillation: state of the art. *Minerva Cardioangiol.* 2010;58:257–264. doi: 10.1007/s41006-009-0004-1.
8. Krahn J, Heintze J, Gutleben KJ, Muntean B, Horstkotte D, Nölker G. Long-term outcomes after cryoballoon pulmonary vein isolation: results from the North American Arctic Front (STOP AF) pivotal trial. *J Am Coll Cardiol.* 2013;61:1723–1732. doi: 10.1016/j.jacc.2012.11.064.
9. Mogi T, Hara S, Hasegawa H. Cryoballoon ablation preferable to radiofrequency ablation for treatment of atrial fibrillation with increased risk of pulmonary vein stenosis. *J Am Coll Cardiol.* 2003;42:752–758.
10. Malmberg H, Lönnerholm S, Blomström P, Blomström-Lundqvist C. Ablation of atrial fibrillation with cryoballoon or duty-cycled radiofrequency pulmonary vein ablation catheter: a randomized controlled study comparing the clinical outcome and safety; the AF-COR study. *Eur Heart J.* 2013;15:1152–1159. doi: 10.1093/eurheartj/eut021.
11. Knecht S, Sticherling C, von Felten S, Conen D, Schaer B, Ammann P, Altman D, Osswald S, Kühne M. Long-term comparison of cryoballoon and radiofrequency ablation of paroxysmal atrial fibrillation: a propensity score matched analysis. *Int J Cardiol.* 2014;176:645–650. doi: 10.1016/j.ijcard.2014.06.038.
12. Tse HF, Reek S, Timmermans C, Lee KL, Geller JC, Rodríguez LM, Ghaye B, Ayers GM, Crijns HJ, Klein HU, Lau CP. Pulmonary vein isolation using transvenous catheter cryoablation for treatment of atrial fibrillation without risk of pulmonary vein stenosis. *J Am Coll Cardiol.* 2003;42:752–758.
13. Liuk A, Merkel M, Hoeren D, Riezinger T, Kieser M, Schmitt C. Rationale and design of the FreezeAF trial: a randomized controlled noninferiority trial comparing isolation of the pulmonary veins with the cryoballoon catheter versus open irrigated radiofrequency ablation in patients with paroxysmal atrial fibrillation. *Am Heart J.* 2010;159:555–560.e1. doi: 10.1016/j.ahj.2010.01.008.
14. Lip GYF, Nieuwlaat R, Pisters R, Lane DA, Crijns HJJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the Euro Heart Survey on Atrial Fibrillation. *Chest.* 2010;137:263–272. doi: 10.1378/chest.09-1584.
15. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJJ, Lip GYF. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest.* 2010;138:1093–1100. doi: 10.1378/chest.10-0134.
16. Harrington CP, Manning G. Test statistics and sample size formulae for comparative binomial trials with null hypothesis of non-zero risk difference or non-unity relative risk. *Stat Med.* 1990;9:1447–1454.
17. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and practice for Clinical and Epidemiological Studies. *Stat Med.* 2011;30:377–399. doi: 10.1002/sim.4067.
18. van Buuren S, Groothuis-Oudshoorn K. mice: Multivariate Imputation by Chained Equations in R. *J Stat Software.* 2011;45:1-67.
19. Rubin DB. *Multiple Imputation for Nonresponse in Surveys.* 1987.
20. R Core Team. *R: A LANGUAGE and Environment for Statistical Computing.* Vienna, Austria: R Foundation for Statistical Computing; 2013.
21. Klein G, Oswald H, Gardiwal A, Lüsbrink U, Lissel C, Yu H, Drexler H. Efficacy of pulmonary vein isolation by cryoballoon ablation in patients with paroxysmal atrial fibrillation. *Heart Rhythm.* 2008;5:802–806. doi: 10.1016/j.hrthm.2008.02.014.
22. Packer DL, Kowal RC, Wheeler KR, Irwin JM, Champagne J, Guerra PG, Dubuc M, Reddy V, Nelson L, Holcomb RG, Lehmann JW, Ruskin JN. STOP AF Cryoablation Investigators. 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;61:1713–1723. doi: 10.1016/j.jacc.2012.11.064.
23. Vogt J, Heintze J, Gutleben JK, Muntean B, Horstkotte D, Nöller G. Long-term outcomes after cryoballoon pulmonary vein isolation: results from a prospective study in 605 patients. *J Am Coll Cardiol.* 2013;61:1707–1712. doi: 10.1016/j.jacc.2012.09.033.
24. Xu X, Huang Y, Cai H, Ouyang J, Niu S, Shen W, Lin J, Peng F, Niu W. Is cryoballoon ablation preferable to radiofrequency ablation for treatment of atrial fibrillation by pulmonary vein isolation? A meta-analysis. *PLoS One.* 2014;9:e90323. doi: 10.1371/journal.pone.0090323.
25. Klein G, Gardiwal A, Oswald H. Catheter-based cryoablation of atrial fibrillation: state of the art. *Minerva Cardioangiol.* 2008;56:623–633.
26. Schmidt M, Dorwarth U, Andresen D, Brachmann J, Kaech KH, Kuniss M, Lewalter T, Spitzer S, Willems S, Senges J, Jünger C, Hoffmann E, Alders T, Osswald S, Kühne M. Catheter-based cryoablation of atrial fibrillation: state of the art. *Minerva Cardioangiol.* 2008;56:623–633.
Cryoballoon versus RF ablation in paroxysmal atrial fibrillation: results from the German Ablation Registry. J Cardiovasc Electrophysiol. 2014;25:1–7. doi: 10.1111/jce.12267.

32. Mugnai G, Chierchia GB, de Asmundis C, Sieira-Moret J, Conte G, Capulzini L, Wauters K, Rodriguez-Mahero M, Di Giovanni G, Baldi G, Ciccone G, Saitoh Y, Julià J, Brugada P. Comparison of pulmonary vein isolation using cryoballoon versus conventional radiofrequency for paroxysmal atrial fibrillation. Am J Cardiol. 2014;113:1509–1513. doi: 10.1016/j.amjcard.2014.01.425.

33. Herrera Siklódy C, Arentz T, Minners J, Jesel L, Stratz C, Valina CM, Weber R, Katuschke D, Toti F, Morel O, Trenk D. Cellular damage, platelet activation, and inflammatory response after pulmonary vein isolation: a randomized study comparing radiofrequency ablation with cryoablation. Heart Rhythm. 2012;9:189–196. doi: 10.1016/j.hrthm.2011.09.017.

34. Chun KR, Schmidt B, Metzner A, Tilz R, Zerm T, Köster I, Fürnkranz A, Koekterek B, Konstantinidou M, Antz M, Ouyang F, Kuck KH. The ‘single big cryoballoon’ technique for acute pulmonary vein isolation in patients with paroxysmal atrial fibrillation: a prospective observational single centre study. Eur Heart J. 2009;30:699–709. doi: 10.1093/eurheartj/ehn570.

35. Yu WC, Hsu TL, Tai CT, Tsai CF, Hsieh MH, Lin WS, Lin YK, Tsao HM, Ding YA, Chang MS, Chen SA. Acquired pulmonary vein stenosis after radiofrequency catheter ablation of paroxysmal atrial fibrillation. J Cardiovasc Electrophysiol. 2001;12:887–892.

36. Saad EB, Marrouche NF, Saad CP, Ha E, Bash D, White RD, Rhodes J, Prieto L, Martin DO, Saliba WI, Schweikert RA, Natale A. Pulmonary vein stenosis after catheter ablation of atrial fibrillation: emergence of a new clinical syndrome. Ann Intern Med. 2003;138:634–638. doi: 10.7326/0003-4819-138-8-200304150-00010.

**CLINICAL PERSPECTIVE**

This is the first large, randomized trial demonstrating that the cryoballoon technique is noninferior to the current gold standard of radiofrequency catheter ablation for pulmonary vein isolation in patients with paroxysmal atrial fibrillation. Unlike the radiofrequency catheter ablation technique, cryoballoon is a single-shot device that does not require specially trained operators and an additional 3-dimensional mapping system. This leads to a shortening of the procedure time. However, cryoballoon was associated with the occurrence of phrenic nerve palsies, which completely resolved during the 12 months after the intervention.
Cryoballoon Versus Open Irrigated Radiofrequency Ablation in Patients With Paroxysmal Atrial Fibrillation: The Prospective, Randomized, Controlled, Noninferiority FreezeAF Study

Armin Luik, Andrea Radzewitz, Meinhard Kieser, Marlene Walter, Peter Bramlage, Patrick Hörmann, Kerstin Schmidt, Nicolas Horn, Maria Brinkmeier-Theofanopoulou, Kevin Kunzmann, Tobias Riexinger, Gerhard Schymik, Matthias Merkel and Claus Schmitt

_Circulation_. 2015;132:1311-1319; originally published online August 17, 2015;
doi: 10.1161/CIRCULATIONAHA.115.016871

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2015 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/132/14/1311
Free via Open Access

Data Supplement (unedited) at:
http://circ.ahajournals.org/content/suppl/2015/08/17/CIRCULATIONAHA.115.016871.DC1
http://circ.ahajournals.org/content/suppl/2016/12/26/CIRCULATIONAHA.115.016871.DC2

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org/subscriptions/
**Supplemental Table 1.** Sensitivity analysis of primary endpoint

| ITT population | 6 months | Combined endpoint** | RF | CB | RD (95% CI)* | p-value* |
|----------------|----------|---------------------|----|----|--------------|----------|
|                |          | 99 / 157 (0.631)    | 98 / 153 (0.641) | 0.006 (-0.100 to 0.112) | 0.002    |
| 12 months      | Combined endpoint*** | 104 / 147 (0.707) | 106 / 144 (0.736) | 0.025 (-0.078 to 0.129) | < 0.001  |
|                | Only single procedure | 90 / 147 (0.612) | 87 / 144 (0.604) | - | - |

| PP population | 6 months | Combined endpoint | 99 / 154 (0.643) | 98 / 150 (0.653) | 0.010 (-0.096 to 0.117) | 0.002 |
| 12 months     | Combined endpoint | 103 / 141 (0.730) | 105 / 141 (0.745) | 0.014 (-0.089 to 0.117) | < 0.001 |

*Legend: ITT, intention to treat; PP, per-protocol; RD, rate difference (CB-RF); CI, confidence interval. P-values (one-sided) and confidence intervals were calculated using the Farrington-Manning method; * for ITT, CIs and p-values were calculated by imputing missing data as „failure“ (no missing data occurred for PP); ** equals the number of patients with single procedure success at 6 months; *** equals the number of patients with multiple procedure success at 12 months; persistent complications at 6 months in CB group (n=3) and RF group (n=0); no persistent complications at 12 months; numbers equal rhythm control rate at 12 months.*
발작성 심방세동 환자에서 냉동풍선 치료법도 라디오초단파 도자절제술과 비슷한 치료효과를 보였다: Freeze AF 연구

최 기 준 교수 서울아산병원 심장내과

초 록

배경
발작성 심방세동 환자에서 폐전맥 분리를 위한 치료법으로서, 개방순환(open irrigated) 라디오초단파(radiofrequency) 도자절제술과 냉동풍선 치료법(cryoballoon ablation)의 시술 안전성 및 치료효과를 비교한 자료는 거의 없다.

방법 및 결과
본 연구는 전향적, 비열등성 연구로, 315명의 대상 환자들을 라디오초단파 치료군 159명과 냉동풍선 치료군 156명으로 무작위 배정하였다. 일차 종료점은 지속적인 합병증 없이 심방성 부정맥이 발생하지 않는 것이었다. 두 군 간에는 라디오초단파 치료군에서 혈관질환이 더 많다는 점(라디오초단파 치료군 8.2% vs. 냉동풍선 치료군 2.6%; P=0.028) 외에 큰 차이가 없었다. 치료 12개월 후 일차 종료점에 도달한 환자들은 라디오초단파 치료군에서 70.7%, 냉동풍선 치료군에서 73.6%였고(재시술 후 성공률), 재시술은 두 군에서 31명의 환자에서 시행되었다(라디오초단파 치료군 19.5% vs. 냉동풍선 치료군 19.9%; P=0.933).

Intention-to-treat 분석에서 냉동풍선 치료법의 비열등성은 연구 시작 시 설정한 열등성 기준으로 볼 때 임증되었다(risk difference, 0.029; 95% CI, -0.074 to 0.132; P<0.001). 첫 시술 후 6개월 성공률 역시 각 군에서 63.1%와 64.1%로 비열등성에 임증되었다(risk difference, 0.010; 95% CI, -0.097 to 0.116; P=0.002). 처음 시술과 연관된 시술 관련 합병증은 냉동풍선 치료군에서 더 많았다(라디오초단파 치료군 5.0% vs. 냉동풍선 치료군 12.2%; P=0.022). 특히, 황격신경(phrenic nerve) 마비는 라디오초단파 치료군에서는 발생하지 않았지만, 냉동풍선 치료군에서 5.8%가 발생하여 두각한 차이를 보였다(P=0.002).

결론
이번 대규모, 전향적, 무작위 배정, 비교연구는 라디오초단파 치료법과 비교하여 발작성 심방세동 환자의 치료 시 냉동풍선 치료법의 비열등성을 입증하였다.