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Cryoballoon Versus Open Irrigated Radiofrequency Ablation in Patients With Paroxysmal Atrial Fibrillation

The Prospective, Randomized, Controlled, Noninferiority FreezeAF Study

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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.

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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]

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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 al[12] 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

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recurrence was reported for 53% of patients after 5 years.[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.[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.[18] 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 β-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.[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_2DS_2-VASc score to indicate the risk of thromboembolism and a HAS-BLED score to indicate the risk of bleeding.[19,20] After providing consent, patients were randomized 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 cryocatheter (Freezor Max, Medtronic, Inc). For each PV, at least 2 applications of cryoenergy 2 times 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.

All patients received anticoagulation therapy during the 4 weeks before and for at least 6 months after the index procedure. Periprocedurally, administration of the anticoagulation therapy was uninterrupted, regardless of the selected drug. A bridging regimen with subcutaneous heparin was administered only if the patients received phenprocoumon and the international normalized ratio was <2 at the time of the procedure. Heparin was administered during the procedure to maintain an activated clotting time of 250 to 350 seconds. All AADs were discontinued 4 to 5 half-lives before the procedure. β-Blockers were the only AAD administered afterward. Patients were monitored during the hospital stay and at clinic visits at 3, 6, 9, and 12 months after the ablation procedure. A blanking period of 3 months was used. A further computed tomography or magnetic resonance imaging was carried out at the 3-month clinic visit to evaluate the PVs. Furthermore, at least one 24-hour Holter ECG was performed at the 3- and 9-month clinical visits to check for atrial arrhythmias. At 6 and 12 months, a 7- to 14-day Holter ECG was carried out to test for long-term recurrences. In the case of observed AF, a second ablation procedure was allowed starting 6 months after the index procedure, exclusively using the same energy source to which the patient had initially been randomized.

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 accident, bleedings, or vascular complications that occurred during or within after 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 arrhythmia >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.[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 $\delta=0.15$.[18]

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 χ^2 test was used to compare categorical variables. Statistical analysis was performed with R 3.13, with the multiple imputation by chained equations package 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 $2\times122=244$ 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 $2\times157=314$ 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

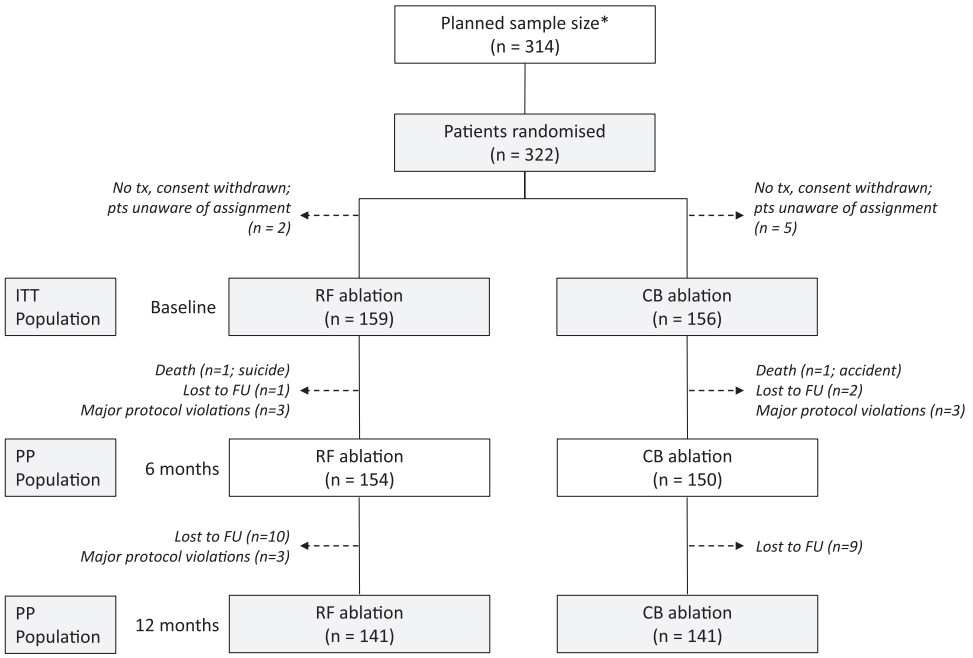

Figure. Patient flow, including planned sample size recalculation. *The initial sample size calculation resulted in 244 patients, which was readjusted in March 2011 after a prespecified blinded sample size recalculation (see Methods). Patients (pts) withdrawing consent before treatment (tx) were unaware 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.

Table 1. Patient Characteristics

	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†
Comorbidities				
Coronary artery disease				0.847†
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 χ^2 test.

(74.0%; Table 2). 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 CHA_2DS_2-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 2. Prior 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 χ^2 test. ACE indicates angiotensin-converting enzyme; and AT1, angiotensin II type 1.

Table 3. Risk Indexes

	Total (n=315), n (%)	RF (n=159), n (%)	CB (n=156), n (%)	*P* Value, RF vs CB
CHA_2DS_2-VASc				
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				
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)	

CHA_2DS_2-VASc score for predicting the 1-year risk of a thromboembolism[19]; 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). 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 δ=0.15 and a 1-sided significance level of α=2.5% for the Farrington-Manning test for noninferiority,[21] the null hypothesis at 12 months could be rejected (H_0: $p_{CB}-p_{RF}\leq -0.15$; 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 (risk difference, 0.010; 95% CI, −0.097 to 0.116; *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 δ=0.15 and the same 1-sided significance level of α=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 ≈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·cm^2 higher for the CB procedure (*P*=0.012; Table 6) with an overall median x-ray dose of 56.0 Gy·cm^2.

Complications

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

Table 4. Electrophysiological Study of the Heart

	Total (n=315), n (%)	RF (n=159), n (%)	CB (n=156), n (%)	*P* Value, RF vs CB
CTI ablation (RF)	59 (18.7)	38 (23.9)	21 (13.5)	0.018
PV anomalies				0.573
None	239 (75.9)	118 (74.2)	121 (77.6)	
At least 1 (LPV or RMPV)	76 (24.1)	41 (25.8)	35 (22.4)	

P values calculated with the 2-sided χ^2 test. CTI indicates cavotricuspid isthmus; LPV, common ostium of left pulmonary veins; PV, pulmonary vein; RF, radiofrequency; and RMPV, right middle pulmonary vein.

Table 5. Primary End-Point Analysis

		RF	CB	RD (95% CI)*	*P* Value*
ITT population					
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
	Only single procedure	90/147 (0.612)	87/144 (0.604)	…	…
PP population					
At 6 mo	Combined end point	99/154 (0.643)	98/150 (0.653)	0.010 (–0.096 to 0.117)	0.002
At 12 mo	Combined end point	103/141 (0.730)	105/141 (0.745)	0.014 (–0.089 to 0.117)	<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 12 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.

occurred in 14 patients (4.4%), and minor events occurred in 13 patients (4.1%). The periprocedural complication rate was higher in the CB group (5.0% in the RF and 12.2% in the CB group; *P*=0.022). Specifically, 13 vascular complications (4.1%) were reported with no difference between groups, and 9 of them were classified as major. Overall, 5 pericardial effusions (1.6%) occurred. The 2 major events occurred in the CB group and needed pericardial drainage. All resolved without the need for surgery. In 9 patients, right PNP was observed during cryoablation of the right superior PV (5.8% of those with CB). Symptomatic PNPs were classified as major events (3 of 9). PNPs resolved in 4 of the 9 patients during the hospital stay, 2 before the 6-month follow-up and all before the 12-month follow-up (all were followed up throughout the 12 months). Recovery was demonstrated via fluoroscopy. No PV stenosis occurred in either group, and no transient ischemic attack/stroke was reported.

Thirty-one redo procedures were performed in each group (total of 62), and 3 major complications were reported. In the RF group, 1 PV stenosis requiring PV stenting occurred, and in the CB group, 1 pericardial effusion requiring pericardial drainage and 1 vascular complication requiring additional compression therapy occurred. No PNP or transient ischemic attack/stroke was reported for the second procedure.

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 comorbidities. Furthermore, there were no significant differences in the proportions of patients concurrently receiving any of the anticoagulants, β-blockers, or other cardiovascular-related medications. Electrophysiology studies revealed that patients undergoing the CB procedure had a slightly lower incidence of typical atrial flutter. Therefore, the rate of an additional ablation of the tricuspid isthmus was lower. The majority of patients in both groups were assigned a CHA_2DS_2-VASc score of 1 or 2, indicating an intermediate risk of stroke within a year, whereas a small proportion were at major risk.[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[12,13,26–28]; 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 the primary end point. Although this assessment was based on multiple reports at the time of study initiation,

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·cm^2	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.

Table 7. Number of Patients with Periprocedural Complications During the Index Procedure

	Total (n=315), n (%)	RF (n=159), n (%)	CB (n=156), n (%)	*P* Value
Vascular	13 (4.1)	5 (3.1)	8 (5.1)	0.372
Major events	9	3	6	
Minor events	4	2	2	
Pericardial effusion	5 (1.6)	3 (1.9)	2 (1.3)	0.683
Major events	2	0	2	
Minor events	3	3	0	
PV stenosis	0	0	0	NA
Major events	0	0	0	
Minor events	0	0	0	
Phrenic nerve palsy	9 (2.9)	0 (0)	9 (5.8)	0.002
Major events	3	0	3	
Minor events	6	0	6	
TIA/stroke	0	0	0	NA
Total	27 (8.6)	8 (5.0)	19 (12.2)	0.022
Major events	14 (4.4)	3 (1.9)	11 (7.1)	
Minor events	13 (4.1)	5 (3.1)	8 (5.1)	

P values calculated with 2-sided Wilcoxon rank-sum test (comparison of total number of complications on ordinal scale: none<minor<major). PV indicates pulmonary vein; and TIA, transient ischemic attack.

a recent meta-analysis has summarized the potential advantages of CB over RF.[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.[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.[14,17,31] Recently, although not directly comparable, Malmborg et al[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[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[14,31] and shorter[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.[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.[29] However, the events in our study were influenced mainly by the number of (transient) PNPs in the CB group. By the time of the 6-month follow-up period, all but 3 cases of PNPs had been resolved, and at 12 months, all patients with PNPs had recovered, which is in agreement with other studies.[26,32,34] PV stenoses, on the other hand, are recognized as complications associated with RF ablation.[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. No transient ischemic attack/stroke occurred in either group.

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.

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Disclosures

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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.