Cryoballoon versus Open Irrigated Radiofrequency Ablation in Patients With Paroxysmal Atrial Fibrillation: The Prospective, Randomised, Controlled, Non-Inferiority FreezeAF Study

**Running title:** Luik et al.; Cryoballoon vs. radiofrequency ablation in PAF

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**Journal Subject Codes:** Diagnostic testing:[106] Electrophysiology, Etiology:[5] Arrhythmias, clinical electrophysiology, drugs, Treatment:[22] Ablation/ICD/surgery
Abstract

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

Methods and Results—In a prospective, non-inferiority study 315 patients were randomly assigned to RF (n=159) or CB (n=156) ablation. The primary endpoint 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% vs. 2.6% CB; p=0.028). The primary endpoint 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 vs. 19.9% of CB; p=0.933). For the intention-to-treat (ITT) population, non-inferiority of CB was revealed for the pre-defined inferiority margin (risk difference [RD] 0.029; 95% confidence interval [CI] -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 non-inferiority was confirmed (RD 0.010; 95% CI -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).

Conclusions—This large, prospective, randomised, controlled study demonstrates non-inferiority of CB ablation versus RF ablation for treating patients with paroxysmal AF.

Clinical Trial Registration Information—clinicaltrials.gov. Identifier: NCT00774566.

Key words: arrhythmia, atrial fibrillation, catheter ablation, cryoballoon
Background

Atrial fibrillation (AF) is the most common form of cardiac arrhythmia, and 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 using electrical cardioversion; however, the rate of AF recurrence is high, even with administration of antiarrhythmic drugs (AAD).\(^3\) In combination with their relatively low efficacy, AADs have the additional 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 in comparison to drug therapy.\(^7\)\(^-\)\(^10\)

Incidences of PV stenosis, thromboembolic complications, cardiac perforations with pericardial tamponade, oesophageal fistulae, and phrenic nerve palsies (PNP) have been reported.\(^11\)\(^-\)\(^11\)

The more recently introduced strategy of employing a cryoballoon catheter (CB) for PV isolation has produced encouraging results in a number of trials. Neumann et al. 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.\(^12\) In a separate long-term study in patients with paroxysmal AF, freedom from AF recurrence was reported for 53% of patients after 5 years.\(^13\) There have been a number of studies comparing ablation with CB to that with RF for PV isolation. In general, the obtained data demonstrate equivalent efficacy and similar safety profiles for the two techniques, although CB has been associated with a trend for reduced incidences of cardiac perforations with pericardial tamponade, but with higher rates of phrenic nerve palsy in comparison to RF ablation.\(^14\)\(^-\)\(^17\)
Whilst these studies provided a wealth of information regarding the two ablation energy sources, the absence of randomisation in all but one of these trials is a significant drawback. The FreezeAF trial was designed to overcome such shortcomings by utilising a randomised, controlled, non-inferiority design to directly compare RF with CB for treating patients with paroxysmal AF (NCT00774566).

Methods

Study design

FreezeAF is a randomised, controlled, prospective, non-inferiority clinical trial designed to assess the efficacy and safety of PV isolation performed using either a cryoballoon or an irrigated RF ablation catheter. The main objective of the study was to determine whether cryoablation was not inferior to RF open irrigated tip ablation for treatment of paroxysmal AF. The total follow-up period was 12 months, with additional evaluation of the endpoints 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 15th 2008, and the study was carried out in accordance with the Declaration of Helsinki.

Patients

Patients aged 18–75 years 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 beta blockers. Patients were excluded if they had previously undergone left atrial (LA) ablation or surgery, if their LA was over 55 mm in diameter, or if there was evidence of LA
thrombus. Further exclusion criteria included unstable angina, myocardial infarction (MI) within the previous 3 months, cardiac surgery or percutaneous transluminal coronary angioplasty within the previous 3 months, an ejection fraction (EF) below 40%, heart failure grade III–IV (New York Heart Association criteria), stroke or transient ischaemic attack (TIA) within the previous 6 months, pregnancy, or a life expectancy of less than one year. A full list of inclusion and exclusion criteria has been previously published. Preprocedural, LA thrombi were excluded by transoesophageal echocardiography. Additionally, the patients underwent either computed tomography (CT) or magnetic resonance imaging (MRI) of the LA to determine physiological abnormalities and to exclude PV stenosis. Patients were assigned a CHA2DS2-VASc score to indicate the risk of thromboembolism, and a HAS-Bled score to indicate the risk of bleeding. After providing consent, patients were randomised with allocation ratio 1:1 to either the CB or RF procedure. Random numbers were generated using the SAS software (Cary, NC, USA), where block randomisation 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 using a circular mapping catheter. RF-mediated antral ablation was performed using a 3.5 mm irrigated tip catheter in conjunction with a 3D navigation system (Ensite NavX/Velocity, St. Jude Medical, St. Paul, USA; Carto-3, Biosense Webster, Inc., Diamond Bar, CA, USA). Cryoablation of the PV ostia was carried out using the Arctic Front Cryo Ablation Catheter System and FlexCath Steerable Sheath (Medtronic, Inc., MN, USA). The 28 mm cryoballoon was preferentially used; however, a switch to the 23 mm device was allowed if necessary, as were touch-ups with a conventional cryocatheter (Freezor
Max, Medtronic, Inc.). For each PV, at least 2 applications of cryoenergy 2x300sec with the first
generation cryo balloon and 2x240sec with second generation cryoballoons were employed
according to the manufacturer’s recommendation. Additional applications could be used if
deemed necessary.

All patients received anticoagulation therapy during the 4 weeks prior to and for at least 6
months after the index procedure. Periprocedural, the anticoagulation therapy was administered
uninterrupted, independent of the selected drug. A bridging regime with heparin s.c. was only
administered if the patients received phenprocoumon and the INR was < 2 at the time of the
procedure. Heparin was administered during the procedure to maintain an activated clotting time
of 250–350sec. All AADs were discontinued 4–5 half-life periods prior to the procedure. Beta
blockers were the only AAD administered afterwards. 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 employed. A further CT or MRI was carried out at the 3 month clinic
visit to evaluate the PVs. Furthermore, at least one 24 h Holter ECG was performed at the 3 and
9 month clinical visit 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 six months after the index procedure, exclusively using
the same energy source to which the patient had initially been randomised.

Outcomes

The primary endpoint was defined as absence of atrial arrhythmias in combination with absence
of persistent complications during the 6 and 12 month follow-up periods (co-primary endpoints).
Persistent complications were defined as any new PV stenosis, phrenic nerve palsy,
cerebrovascular accident (CVA), bleedings, or vascular complications that occur during and/or
within after 48h after the procedure. Data of patients that either died or denied a clinical follow-up with rhythm assessment were considered as missing. Adjudicators were not blinded to the group assignment upon the determination of AF recurrence. Each documented episode of an atrial arrhythmia > 30sec after the three months blanking period was considered as a failure. The 6 month follow-up was used to evaluate the outcome of the index procedure, while the 12 month visit additionally took into account any redo procedures. Secondary endpoints included procedural data, total radiation exposure, total procedure duration, and occurrence of adverse events, including phrenic nerve palsy (assessed using breathing or pacing manoeuvre at the physician discretion), pericardial effusion, and vascular complications. The assessment of quality of life was planned in the initial protocol version, but 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) requiring 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 endpoints was carried out for both the intention to treat (ITT) population and the per-protocol (PP) population. ITT analysis included all randomised patients who received study treatment which were evaluated in the group to which they were assigned, 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 prior to the 6 months follow up, cross over and LA ablation strategies other than PV isolation. Prior to 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 non-inferiority was formulated in terms of the rate of achievement of the primary endpoint 12 month after the CB procedure ($p_{CB}$) and after the RF procedure ($p_{RF}$), respectively, whereas the null hypothesis was defined as $H_0: p_{CB} - p_{RF} \leq -\delta$, with $\delta = 0.15$.$^{18}$

An analogous test problem was formulated for the related rates after 6 month follow-up, with this null hypothesis only tested if that for the 12 months follow-up was rejected; otherwise, both null hypotheses would be accepted. By applying 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 non-inferiority test for rates according to Farrington and Manning.$^{21}$ at a one-sided significance level of $\alpha = 2.5\%$. Multiple imputation was applied to deal with missing values for the primary endpoints. The multiple imputation by chained equations (MICE) algorithm$^{22,23}$ was used with a logistic regression model for the primary endpoints and the group assignment as covariable. In order to adequately reflect the variability due to imputed data, 100 imputed data sets were used. The results of the related analyses were pooled by Rubin’s 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 (SD), 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 using the two sided Wilcoxon rank sum test, while the two-sided chi-squared test...
was used to compare categorical variables. The statistical analysis was performed with R 3.13 with the package MICE, version 2.22, used for multiple imputation.\textsuperscript{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.\textsuperscript{3, 12} To reach a power of $1 - \beta = 80\%$ for the one-sided Farrington–Manning test at a level of $\alpha = 2.5\%$, the required sample size was $2 \times 122 = 244$ patients.\textsuperscript{21} Owing to the uncertainty regarding the assumption of an overall rate of 0.78, a blinded sample size recalculation was pre-specified in the protocol.\textsuperscript{18} The overall rate observed in March 2011 was 0.65 and thus smaller than the anticipated one. Employing this rate for both groups but leaving all other quantities of the initial sample size calculation (especially the non-inferiority margin) unchanged lead 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 knowing group assignment 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 for the PP analysis (Figure 1), respectively. There were more males than females undergoing the procedure (60.6\% male overall), with no significant difference in the proportions of each in the two groups (Table 1). In addition, the age of the patients did not vary between groups (p =
0.87). 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 being treated with a variety of anticoagulants, with the majority in both groups receiving phenprocoumon (74.0%; Table 2). A high proportion of patients in each group were being treated with beta blockers (89.5%), and a relevant number were receiving an angiotensin-converting enzyme (ACE) inhibitor (39.0%). Similar proportions of patients in each group were being treated with an angiotensin II type 1 (AT1) antagonist, a diuretic, or a statin. With the exception of apixaban (4 patients in CB group, 0 in RF), there were no significant differences between the two treatment groups with regards to any of the medications that were prescribed.

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

Physiological anomalies of the PVs, e.g. a common ostium of the left PVs or an additional right middle PV were equally distributed in both groups. An additional ablation of the cavitricuspid isthmus due to 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 4). Ablation of the cavitricuspid isthmus was always performed with either irrigated RF or non-irrigated RF energy.

**Primary endpoint**

The co-primary endpoints were defined as absence of atrial arrhythmias in combination with absence of persistent complications during the 6 and 12 month follow-up period. In the ITT
population, this was the case for 63.1% of patients in the RF group and 64.1% of patients in the CB group at 6 months and for 70.7% and 73.6% of patients, respectively, at 12 months. The increase in the rate of the primary endpoint was due to redo procedures that were only allowed after 6 months. There were 62 patients who underwent redo procedures, 31 in each group (19.5% RF vs. 19.9% CB; p=0.933).

Using the defined margin of $\delta = 0.15$, and a one-sided significance level of $\alpha = 2.5\%$ for the Farrington-Manning test for non-inferiority, the null hypothesis at 12 months could be rejected ($H_0: p_{CB} - p_{RF} \leq -0.15$; risk difference (RD) (95% Confidence Interval (CI)): 0.029 (-0.074 to 0.132); p < 0.001; Table 5). The analogous null hypothesis at 6 months was therefore tested, and it was found that it could also be rejected (RD (95% CI): 0.010 (-0.097 to 0.116); p = 0.002). A sensitivity analysis where missing values were imputed as failures confirmed these results (Supplemental Table 1).

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

**Secondary endpoints**

In 10 patients a second, different size cryoballoon catheter (23 and 28 mm) was needed to achieve PV isolation. None needed a touch-up with a conventional cryocatheter. The overall procedure time was about 13 minutes shorter in the CB group (p = 0.006). X-ray duration was
very similar in both groups (median 24 min in RF and 25.5 min 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, in 14 (4.4%) patients occurred major and in 13 (4.1%) patients minor events. 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). In detail: 13 (4.1%) vascular complications were reported with no
difference between groups and 9 of them being classified as major. Overall 5 (1.6%) pericardial
effusions 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 pulmonary vein (5.8% of those with CB). Symptomatic PNP
were classified as major events (3 out of 9). PNP resolved in 4 of the 9 cases during the hospital
stay, 2 before the 6 month and all before the 12 month follow up (all were followed throughout
12 months). Recovery was demonstrated via fluoroscopy. No PV stenosis occurred in either
group and no TIA / stroke were reported.

31 redo procedures were performed in either group (total of 62) and 3 major
complications were reported. In the RF group 1 PV stenosis requiring PV stenting and in the CB
group 1 pericardial effusion requiring pericardial drainage and 1 vascular complication requiring
additional compression therapy occurred. No PNP, TIA/Stroke were reported for the second
procedure.

Discussion
The randomised FreezeAF study was carried out to comprehensively evaluate non-inferiority of CB compared to 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 randomised to undergo PV isolation using one of the two 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 two treatment groups were well-matched in terms of gender and age, with similar rates of comorbidities. Furthermore, there were no significant differences in the proportions of patients concurrently receiving any of the anticoagulants, beta 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 CHA2DS2-VASc score of 1 or 2, indicating an intermediate risk of stroke within a year, while 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 0–2.20

A number of studies have demonstrated the efficacy and safety of CB ablation for treatment of AF12,13,26-28, however, it is still unclear how this strategy compares to the well-established RF method. Here, we demonstrated non-inferiority of PV isolation using CB ablation in comparison to that using RF for a primary endpoint of freedom from atrial arrhythmia combined with absence of persistent complications. At both 6 and 12 months, CB was shown to be non-inferior to RF within a margin of δ = 0.15. A margin of 15%, which might be considered being large, was deemed acceptable at the inception of the study given the advantages of CB with respect to dimensions other the primary endpoint. While this assessment was based on
multiple reports at the time of study initiation, a recent meta-analysis has summarized the potential advantages of CB over RF. They included a total of 14 articles and 1,104 patients and found the fluoroscopy time (weight mean difference [WMD] -14.23 min (95% CI -25.45 to -2.82)), the overall procedure time (WMD -29.65 min (95% CI -29.65; 95% CI -50.77 to -8.54)) to be significantly shorter, with a non-significant increase in the ablation time (WMD +11.66 min (95% CI -10.71 to 34.34). Furthermore cryoballoon was found to be associated with a trend for less major complications (OR 0.46; 95% CI 0.11 to 1.83). Finally there is also evidence that the learning curve for cryoballoon ablation was much shorter than for radiofrequency ablation.

Non-inferiority 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 non-randomised 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 phrenic nerve palsy. Recently, although not directly comparable, Malmborg et al. reported a small randomised study comparing cryoballoon with the circular multipolar duty-cycled radiofrequency-based pulmonary vein ablation catheter (PVAC) 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. reported on a single-centre 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 and 61.1% in the RF groups (p=0.93). Overall complication rates were equivalent; however, fewer cardiac perforations occurred with CB (0% vs 4%, P = 0.042).

In addition to efficacy, there are a number of other factors that should be taken into
account when selecting the most suitable approach to treating a patient. Safety is of paramount importance, both in terms of 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 dosage 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 dosage in the CB group is explained by the necessity of a higher resolution of the fluoroscopy image to prove the balloon’s occlusion. The overall procedure time was significantly shorter for the cryoenergy technique. This is a result that 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 non-significant trend for less complications with CB reported in the aforementioned meta-analysis.\textsuperscript{29} However, the events in our study were mainly influenced 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 phrenic nerve palsies had been resolved, and at 12 months, all had recovered, which is in agreement with other studies.\textsuperscript{26, 32, 34} PV stenoses on the other hand are recognised 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. No TIA/stroke occurred in either group.

**Conclusions**

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

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**Conflict of Interest Disclosures:** A. Luik has received consulting fees/honoraria from Medtronic, Inc., Boston Scientific Corp., Biosense Webster and St. Jude Medical. M. Merkel has received consulting fees/honoraria from Medtronic, Inc., CardioFocus, Inc., and Boston Scientific Corp. C. Schmitt has received consulting fees/honoraria from Pfizer, Inc., Bayer/Schering Pharma, Boehringer Ingelheim, and Medtronic, Inc. M. Kieser was a member of the Data and Safety Monitoring Board of the FIRE AND ICE study (ClinicalTrials.gov Identifier: NCT01490814). A. Radzewitz, M. Walter, P. Bramlage, T. Riexinger, N. Horn, M. Brinkmeier Theofanopoulou, K. Kunzmann, P. Hoermann, K. Schmidt, and G. Schymik have no conflicts of interest to declare.

**References:**


Table 1. Patient characteristics.

<table>
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<th>Total (N = 315)</th>
<th>RF (N = 159)</th>
<th>CB (N = 156)</th>
<th>p-value RF vs. CB</th>
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<tr>
<td>191 (60.6%)</td>
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<td>100 (64.1%)</td>
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<td>Age (years)*</td>
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<td>5 (3.1%)</td>
<td>4 (2.6%)</td>
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<td>3 vessels</td>
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<td>5 (3.1%)</td>
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<td>17 (10.7)</td>
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<td>(N = 134)</td>
<td>(N = 135)</td>
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<td>174 (64.7%)</td>
<td>80 (59.7%)</td>
<td>94 (69.6%)</td>
<td></td>
</tr>
<tr>
<td>Tricuspid valve regurgitation</td>
<td>(N = 303)</td>
<td>(N = 154)</td>
<td>(N = 149)</td>
<td>0.180</td>
</tr>
<tr>
<td>None</td>
<td>293 (97.0%)</td>
<td>151 (98.1%)</td>
<td>142 (95.3%)</td>
<td></td>
</tr>
<tr>
<td>Slight</td>
<td>10 (3.2%)</td>
<td>3 (1.9%)</td>
<td>7 (4.7%)</td>
<td></td>
</tr>
<tr>
<td>Multiple valvular defects</td>
<td>(N = 313)</td>
<td>(N = 159)</td>
<td>(N = 154)</td>
<td>0.312</td>
</tr>
<tr>
<td></td>
<td>45 (14.4%)</td>
<td>26 (16.4%)</td>
<td>19 (12.3%)</td>
<td></td>
</tr>
</tbody>
</table>

*Data given as median (p25, p75). †P-value calculated using two-sided Wilcoxon rank sum test. All other p-values calculated using two-sided chi-squared test.
Table 2. Prior medication.

<table>
<thead>
<tr>
<th></th>
<th>Total (N = 315)</th>
<th>RF (N = 159)</th>
<th>CB (N = 156)</th>
<th>p-value RF vs. CB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenprocoumon</td>
<td>233 (74.0%)</td>
<td>119 (74.8%)</td>
<td>114 (73.1%)</td>
<td>0.721</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>52 (16.5%)</td>
<td>25 (15.7%)</td>
<td>27 (17.3%)</td>
<td>0.705</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>25 (7.9%)</td>
<td>13 (8.2%)</td>
<td>12 (7.7%)</td>
<td>0.874</td>
</tr>
<tr>
<td>Apixaban</td>
<td>4 (1.3%)</td>
<td>0 (0.0%)</td>
<td>4 (2.6%)</td>
<td>0.042</td>
</tr>
<tr>
<td>Aspirin</td>
<td>33 (10.5%)</td>
<td>20 (12.6%)</td>
<td>13 (8.3%)</td>
<td>0.219</td>
</tr>
<tr>
<td>Platelet aggregation inhibitor other than Aspirin</td>
<td>9 (2.9%)</td>
<td>7 (4.6%)</td>
<td>2 (1.3%)</td>
<td>0.091</td>
</tr>
<tr>
<td>Beta blocker</td>
<td>282 (89.5%)</td>
<td>140 (89.2%)</td>
<td>142 (92.2%)</td>
<td>0.357</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>123 (39.0%)</td>
<td>65 (41.4%)</td>
<td>58 (37.7%)</td>
<td>0.500</td>
</tr>
<tr>
<td>AT1 antagonist</td>
<td>60 (19.0%)</td>
<td>30 (19.1%)</td>
<td>30 (19.5%)</td>
<td>0.934</td>
</tr>
<tr>
<td>Diuretics</td>
<td>77 (24.4%)</td>
<td>34 (21.8%)</td>
<td>43 (27.9%)</td>
<td>0.212</td>
</tr>
<tr>
<td>Statins</td>
<td>85 (27.0%)</td>
<td>41 (26.3%)</td>
<td>44 (28.6%)</td>
<td>0.651</td>
</tr>
</tbody>
</table>

ACE, angiotensin-converting enzyme; AT1, angiotensin II type 1. P-values calculated using two-sided chi-squared test.

Table 3. Risk indices.

<table>
<thead>
<tr>
<th></th>
<th>Total (N = 315)</th>
<th>RF (N = 159)</th>
<th>CB (N = 156)</th>
<th>p-value RF vs. CB</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHA2DS2-VASc</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>66 (21.0%)</td>
<td>31 (19.5%)</td>
<td>35 (22.4%)</td>
<td>0.278</td>
</tr>
<tr>
<td>1</td>
<td>92 (29.2%)</td>
<td>45 (28.3%)</td>
<td>47 (30.1%)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>83 (26.3%)</td>
<td>42 (26.4%)</td>
<td>41 (26.3%)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>50 (15.9%)</td>
<td>26 (16.4%)</td>
<td>24 (15.4%)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>18 (5.7%)</td>
<td>12 (7.5%)</td>
<td>6 (3.8%)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>4 (1.3%)</td>
<td>2 (1.3%)</td>
<td>2 (1.3%)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>2 (0.6%)</td>
<td>1 (0.6%)</td>
<td>1 (0.6%)</td>
<td></td>
</tr>
<tr>
<td>HAS-Bled</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>88 (27.9%)</td>
<td>43 (27.0%)</td>
<td>45 (28.8%)</td>
<td>0.253</td>
</tr>
<tr>
<td>1</td>
<td>114 (36.2%)</td>
<td>53 (33.3%)</td>
<td>61 (39.1%)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>86 (27.3%)</td>
<td>47 (29.6%)</td>
<td>39 (25.0%)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>23 (7.3%)</td>
<td>13 (8.2%)</td>
<td>10 (6.4%)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>4 (1.3%)</td>
<td>3 (1.9%)</td>
<td>1 (0.6%)</td>
<td></td>
</tr>
</tbody>
</table>

CHA2DS2-VASc score for predicting the 1 year risk of a thromboembolism; HAS-Bled score for predicting the 1 year risk of bleeding. P-values calculated using two-sided Wilcoxon rank sum test.
Table 4. Electrophysiology study of the heart.

<table>
<thead>
<tr>
<th></th>
<th>Total (N = 315)</th>
<th>RF (N = 159)</th>
<th>CB (N = 156)</th>
<th>p-value RF vs. CB</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTI ablation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(radiofrequency)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PV anomalies</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>239 (75.9%)</td>
<td>118 (74.2%)</td>
<td>121 (77.6%)</td>
<td>0.573</td>
</tr>
<tr>
<td>At least one (LPV or RMPV)</td>
<td>76 (24.1%)</td>
<td>41 (25.8%)</td>
<td>35 (22.4%)</td>
<td></td>
</tr>
</tbody>
</table>

PV, pulmonary vein; LPV, common ostium of left pulmonary veins; RMPV, right middle pulmonary vein; CTI, cavotricuspid isthmus; P-values calculated using two-sided chi-squared test.
**Table 5. Primary endpoint analysis.**

| ITT population | 6 months | Combined endpoint** | 99 / 157 (0.631) | 98 / 153 (0.641) | 0.010 (-0.097 to 0.116) | 0.002 |
|               | 12 months | Combined endpoint*** | 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  | 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 |

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; a significant p-value indicates that non-inferiority is met; * for ITT, CIs and p-values were calculated by applying multiple imputation to deal with missing data while 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.
Table 6. Secondary endpoints.

<table>
<thead>
<tr>
<th></th>
<th>Total median (p25, p75) (N = 315)</th>
<th>RF median (p25, p75) (N = 159)</th>
<th>CB median (p25, p75) (N = 156)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total procedure time (min)</td>
<td>170.0 (140.0, 202.0)</td>
<td>174.0 (146.5, 218.0)</td>
<td>161.0 (132.8, 193.2)</td>
<td>0.006</td>
</tr>
<tr>
<td>X-ray dose (Gy*cm²)</td>
<td>56.0 (30.0, 85.5)</td>
<td>50.0 ( )</td>
<td>61.5 (36.0, 95.5)</td>
<td>0.012</td>
</tr>
<tr>
<td>X-ray duration (min)</td>
<td>24.1 (17.1, 33.2)</td>
<td>24.0 (16.9, 37.2)</td>
<td>24.5 (17.5, 31.0)</td>
<td>0.632</td>
</tr>
</tbody>
</table>

p25, 25%-quartile; p75, 75%-quartile. P-values calculated using two-sided Wilcoxon rank sum test.

Table 7. Number of patients with periprocedural complications during index procedure.

<table>
<thead>
<tr>
<th></th>
<th>Total (N = 315)</th>
<th>RF (N = 159)</th>
<th>CB (n=156)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major events</td>
<td>13 (4.1%)</td>
<td>5 (3.1%)</td>
<td>8 (5.1%)</td>
<td>0.372</td>
</tr>
<tr>
<td>Minor events</td>
<td>9</td>
<td>3</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Minor events</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Pericardial effusion</td>
<td>5 (1.6%)</td>
<td>3 (1.9%)</td>
<td>2 (1.3%)</td>
<td>0.683</td>
</tr>
<tr>
<td>Major events</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Minor events</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>PV stenosis</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>n.a.</td>
</tr>
<tr>
<td>Major events</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Minor events</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Phrenic nerve palsy</td>
<td>9 (2.9%)</td>
<td>0 (0%)</td>
<td>9 (5.8%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Major events</td>
<td>3</td>
<td>0</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Minor events</td>
<td>6</td>
<td>0</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>TIA / stroke</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>n.a.</td>
</tr>
<tr>
<td>Total</td>
<td>27 (8.6%)</td>
<td>8 (5.0%)</td>
<td>19 (12.2%)</td>
<td>0.022</td>
</tr>
<tr>
<td>Major events</td>
<td>14 (4.4%)</td>
<td>3 (1.9%)</td>
<td>11 (7.1%)</td>
<td></td>
</tr>
<tr>
<td>Minor events</td>
<td>13 (4.1%)</td>
<td>5 (3.1%)</td>
<td>8 (5.1%)</td>
<td></td>
</tr>
</tbody>
</table>

P-values calculated using two-sided Wilcoxon rank sum test (comparison of total number of complications on ordinal scale: None < Minor < Major); n.a., not applicable.
Figure Legend:

**Figure 1.** Patient flow, including planned sample size recalculation. Patient flow, including planned sample size recalculation. *The initial sample size calculation resulted in 244 patients which was readjusted in March 2011 after a pre-specified blinded sample size recalculation (see methods). Patients withdrawing consent prior to treatment were unaware of the assignment and were excluded from the population. Patients that refused a 12 month follow-up were contacted by phone to verify that they were alive though no heart rhythm was obtained. RF = radiofrequency catheter ablation; CB = cryoballoon ablation; AAD = antiarrhythmic drug therapy; Tx = treatment.
Planned sample size* 
(n = 314)

Patients randomised 
(n = 322)

No tx, consent withdrawn; 
pts unaware of assignment 
(n = 2)

RF ablation 
(n = 159)

Death (n=1; suicide) 
Lost to FU (n=1) 
Major protocol violations (n=3)

Baseline 

CB ablation 
(n = 156)

Death (n=1; accident) 
Lost to FU (n=2) 
Major protocol violations (n=3)

ITT 
Population

PP 
Population 

Baseline 

RF ablation 
(n = 154)

Lost to FU (n=10) 
Major protocol violations (n=3)

6 months 

PP 
Population 

Baseline 

RF ablation 
(n = 141)

Lost to FU (n=9) 

12 months 

PP 
Population 

Baseline 

RF ablation 
(n = 154)

CB ablation 
(n = 150)

Lost to FU (n=2) 
Major protocol violations (n=3)

Death (n=1; suicide) 
Lost to FU (n=1) 
Major protocol violations (n=3)

Lost to FU (n=1)

Major protocol violations (n=3)
Cryoballoon versus Open Irrigated Radiofrequency Ablation in Patients With Paroxysmal Atrial Fibrillation: The Prospective, Randomised, Controlled, Non-Inferiority 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

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### Supplemental Table 1. Sensitivity analysis of primary endpoint

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

<table>
<thead>
<tr>
<th>PP population</th>
<th>RF</th>
<th>CB</th>
<th>RD (95% CI)*</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 months</td>
<td>Combined endpoint</td>
<td>99 / 154 (0.643)</td>
<td>98 / 150 (0.653)</td>
<td>0.010 (-0.096 to 0.117)</td>
</tr>
<tr>
<td>12 months</td>
<td>Combined endpoint</td>
<td>103 / 141 (0.730)</td>
<td>105 / 141 (0.745)</td>
<td>0.014 (-0.089 to 0.117)</td>
</tr>
</tbody>
</table>

**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

초록

배경
발작성 심방세동 환자에서 폐징맥 분리를 위한 치료법으로서, 개방순환(open irrigated) 라디오초단파(radiofrequency) 도자 절제술과 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 환병증 없이 심방성 부정맥이 발생하지 않는 것이었다. 두 군 간에는 라디오초단파 치료군에서 헤리혈관이 더 많은 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(제사술 후 성공률), 제사술은 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 임종되었다(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 비열등성

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