

# First-line catheter ablation of paroxysmal atrial fibrillation: outcome of radiofrequency vs. cryoballoon pulmonary vein isolation

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Received 22 April 2015; accepted after revision 15 July 2015; online publish-ahead-of-print 25 October 2015

## Aims

First-line ablation prior to antiarrhythmic drug (AAD) therapy is an option for symptomatic paroxysmal atrial fibrillation (PAF); however, the optimal ablation technique, radiofrequency (RF), or cryoballoon (CB) has to be determined.

## Methods and results

The FREEZE Cohort Study compares RF and CB ablation. Treatment-naïve patients were documented in the FREEZE-plus Registry. Periprocedural data and outcome were analysed. From 2011 to 2014, a total of 373/4184 (8.9%) patients with PAF naïve to AAD were identified. Pulmonary vein isolation (PVI) was performed with RF ( $n = 180$ ) or CB ( $n = 193$ ). In the RF group, patients were older (65 vs. 61 years,  $P < 0.01$ ) compared with the CB group. The procedure time was significantly shorter and radiation exposure higher in the CB group. Major adverse events occurred in 1.6% (CB) and 3.7% (RF) of patients ( $P = 0.22$ ). AF/atrial tachycardia (AT) recurrence until discharge was 4.5% (RF) and 8.5% (CB,  $P = 0.2$ ). Follow-up (FU)  $\geq 12$  months was available in 99 (RF) and 107 (CB) patients. After 1.4 years of FU, freedom from AF/atrial tachycardia (AT) was 61% (RF) and 71% (CB,  $P = 0.11$ ). In the RF group, more patients underwent cardioversion, and a trend for more repeat ablations was observed. Persistent phrenic nerve palsy was observed in one patient treated by CB.

## Conclusion

First-line ablation for PAF is safe and effective with either RF or CB. The procedure was faster with the CB, but the radiation exposure was higher. Although there was a trend for more recurrences and complications in the RF group, a more favourable risk profile in patients undergoing CB ablation might have biased the results.

**ClinicalTrials.gov** identifier NCT01360008.

## Keywords

Paroxysmal atrial fibrillation • First-line • Catheter ablation • Cryoballoon • Radiofrequency ablation • Clinical outcome • Efficacy • Safety

### What's new?

- Catheter ablation as a first-line treatment prior to AAD is an alternative strategy which is covered by current guidelines.
- The CB ablation procedure was shorter and less complex compared with RF.
- There was a non-significant trend for a higher rate of freedom from AF/AT in the CB group compared with the RF group; however, it remained unknown if this difference was attributed to a difference in methods or a difference in patient baseline characteristics.
- Cryoballoon ablation seems to be safe when compared with RF ablation as fewer major adverse events occurred in the CB group, although this difference was statistically not significant.
- A prospective randomized study comparing RF and CB ablation for first-line treatment of paroxysmal AF has to confirm our observations.

## Introduction

Catheter ablation (CA) for symptomatic drug-refractory, paroxysmal atrial fibrillation (PAF) is a Class I/A treatment indication in the current guidelines.<sup>1,2</sup> The effect of CA prior to the use of antiarrhythmic drug (AAD) was evaluated in the pilot RAAFT trial, which randomized 70 patients to either pulmonary vein isolation (PVI) or an AAD treatment.<sup>3</sup> At 12 months, 63% of patients randomized to the AAD arm and only 13% of patients in the PVI arm had at least one recurrence of symptomatic AF ( $P < 0.001$ ). Later, in the randomized multicentre RAAFT-2 trial, Morillo *et al.*<sup>4</sup> demonstrated that RF CA compared with AAD resulted in a lower rate of recurrent AF/atrial tachycardia (AT) at 2 years (AAD 72.1% vs. RF 54.5%,  $P = 0.02$ ); however, recurrence was frequently observed in both groups. By comparison, Cosedis Nielsen *et al.*<sup>5</sup> found no significant difference between first-line CA and AAD therapy in the cumulative burden of AF over a 2-year period in the randomized MANTRA-PAF trial. Consequently, current guidelines indicate that CA prior to AAD therapy is a Class IIa/B option for those patients suffering from symptomatic PAF, preferring interventional treatment or for those with contraindications for AAD with a low-risk profile for periprocedural complications.<sup>1,2</sup>

When CA is necessary, PVI is the cornerstone of ablation for PAF and RF CA is the traditional method of ablation.<sup>6</sup> However, more recently, the use of the cryoballoon (CB) CA technique has increased significantly.<sup>7</sup> In 2012, the second-generation CB was introduced which demonstrated a superior efficacy compared with the predecessor design without compromise to the safety profile.<sup>8,9</sup> Interestingly, the 1-year outcome data with the new CB published by different groups showed a consistently high rate of freedom from AF in the range of 78–83.6%<sup>10–12</sup> and a durable PVI.<sup>13</sup> In contrast, 12-month data for RF CA of PAF vary from 56 to 89%.<sup>14</sup> Until now, comparative studies have not demonstrated significant differences for efficacy and safety of AF ablation with either CB or RF ablation.<sup>15</sup> More recently, two important studies comparing RF and CB ablation are being conducted. The FIRE&ICE Trial (NCT01490814) is a randomized study of 767 patients comparing RF and CB ablation

in patients with symptomatic drug-refractory PAF, and the FREEZE Cohort Study (NCT01360008) is a large ( $n = 4000$ ) prospective comparative-effectiveness multicentre cohort trial.<sup>16</sup>

With regard to first-line therapy by CB CA, the Cryo-FIRST (NCT01803438) study is an ongoing randomized trial comparing AAD therapy and CB ablation for patients with symptomatic PAF naïve to AAD treatment. However, it is still unknown if point-by-point RF or CB ablation is superior for patients undergoing first-line CA for symptomatic PAF.

## Methods

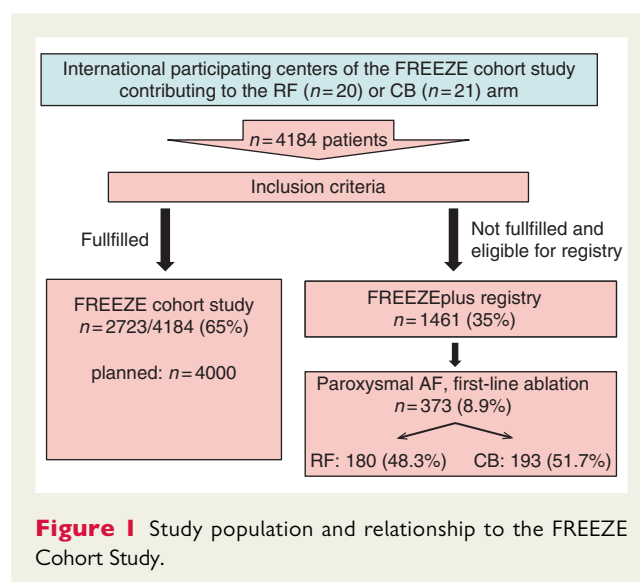
### Objectives

The primary aim of the present FREEZEplus Substudy was to compare the safety and efficacy of point-by-point RF CA and CB ablation in patients undergoing initial CA of symptomatic AF prior to AAD therapy. The following study goals were established: (i) to obtain information on the current practice and frequency of first-line CA in experienced centres participating in the FREEZE Cohort Study; (ii) to compare the periprocedural safety and efficacy of both CA techniques (RF and CB) in this first-line cohort; and (iii) to compare freedom from AF/AT after 1-year follow-up (FU) between both cohorts.

### Study population

From April 2011 to December 2014, a total of 4184 patients were prospectively included in the FREEZE Cohort Study ( $n = 2723$ )<sup>16</sup> or the FREEZEplus Registry ( $n = 1461$ ) worldwide in 41 participating centres (see Supplementary material online for details) from six different countries (Austria, Germany, Greece, South Africa, Spain, and USA). The inclusion/exclusion criteria of the FREEZE Cohort Study are provided in the Supplementary material online.

As a prerequisite, each centre had to announce (prior to study site initiation) if they were enrolling patients that had CA by either RF or CB. Before enrolment,  $\geq 50$  AF ablation procedures had to be performed with the chosen catheter technique prior to the beginning of recruitment. For this current prospective comparative-analysis study, all patients that were included for evaluation from the FREEZEplus Registry were naïve to AAD therapy and had confirmed PAF (Figure 1).



**Figure 1** Study population and relationship to the FREEZE Cohort Study.

At each centre, local ethics committees have approved the study, and an informed consent was obtained from all patients. The study complies with the Declaration of Helsinki, and data were collected prospectively.

### Ablation procedure protocol

Prior to the procedure baseline characteristics were assessed by the recruiting centres. Pulmonary vein isolation was the primary approach for the CA of these patients, and it was performed with commercially available catheters. In the RF arm, 3.5–4.0 mm cooled tip catheters were used from a variety of different manufacturers. It was not a prerequisite to use a three-dimensional (3D)-mapping system or contact force sensing catheters in any procedure. Phased RF circular pulmonary ablation catheter (PVAC), laser, or mesh ablations were not considered in this study. In the CB cohort, treatment with the 23 mm, 28 mm, or both balloons was allowed, and CB selection was based on the discretion of the treating physician. Focal-RF touch-up ablations were allowed if PVI was not achieved with the CB alone. Additional lesions could be applied if deemed necessary in both RF and CB procedures. Unfractionated heparin was used for intraprocedural anticoagulation, and the administration was controlled by measuring activated clotting time with a target range of 300–400 s. Postprocedural management of anticoagulation was left on the discretion of the treating physician.

### Follow-up

Echocardiography was performed after the procedure to rule out pericardial effusion, and during the hospital stay, all patients were monitored for the first 24–48 h (post-procedure) with electrocardiograms (ECGs) and/or Holter studies. Additional ECGs and Holter studies were conducted up to 7 days in patients with continued AF symptoms. All complications were prospectively monitored during the hospital stay. Additional FU was performed with the assistant of an independent clinical research organization [Stiftung Institut fuer Herzinfarktforschung (a.k.a. IHF Foundation), Ludwigshafen, Germany] and scheduled at 12 months post-ablation. A structured telephone interview was performed by trained study assistants to assess any additional adverse events and complications during the FU period. Symptoms of AF recurrence after discharge and symptom severity score were evaluated, and in cases with documented AF by a Holter study or ECG, the information was obtained and added to the database. In addition, a structured FU was allowed to be performed by the participating centres, but it was not a prerequisite as the primary objective was the patient's perception to arrhythmias as only highly symptomatic patients were included. If patients were not available at FU, the general practitioner was asked to provide additional contact information or the civil registry office was involved.

### Statistical analysis

Categorical variables are expressed as numbers and percentages, and continuous variables are expressed as means with standard deviations (SDs) or as medians with quartiles. For comparison of categorical data between both groups, the  $\chi^2$  test was used, and for continuous variables, statistical testing was conducted using the Mann–Whitney–Wilcoxon test. Reported *P*-values were calculated using two-tailed tests, and statistical significance was defined as  $P < 0.05$ . All analyses were performed using SAS© software, version 9.3 (Cary, NC, USA).

## Results

### Baseline characteristics and preprocedural findings

In the FREEZEplus Registry, a total of 373 patients were included from 2011 until 2014. These patients had symptomatic PAF and

were naïve to AAD therapy at the time of their initial AF ablation procedure. Amongst all FREEZE Cohort patients with signed informed consent, treatment-naïve PAF was documented in 373/4184 (8.9%) patients (Figure 1).

Pulmonary vein isolation was performed using CB ( $n = 193$ , 51.7%) or RF ablation ( $n = 180$ , 48.3%). Baseline characteristics and preprocedural findings are summarized in Tables 1 and 2, respectively. Hypertension and peripheral artery disease (PAD) were less prevalent, and patients were younger in the CB cohort compared with the RF group. As a result, the CHA<sub>2</sub>DS<sub>2</sub>-VASc score was significantly lower in the CB group compared with the RF group ( $1.8 \pm 1.5$  vs.  $2.3 \pm 1.5$ ,  $P < 0.01$ ). In 97.1 and 89.4% of patients, the European Heart Rhythm Association (EHRA) symptom score was  $\geq$  II in the CB and RF groups ( $P < 0.001$ ), respectively. At the time of the procedure, normal sinus rhythm was more often present in the CB group (91.1%) compared with the RF group (82.0%),  $P < 0.05$ . The left atrium (LA) was mildly enlarged in both groups (41 vs. 41 mm,  $P = 0.98$ ). There was a statistically significant difference between the groups with regard to the mean left ventricular ejection fraction (LVEF) (CB 60.0 (IQR 55, 60) vs. RF 60.0 (IQR 58, 60)%,  $P < 0.01$ ); however, this difference was no longer significant when analysing patients with LVEF  $\leq$  40%.

### Procedural results

The procedural endpoint (PVI) was achieved in  $\geq$ 98% of pulmonary veins in both groups without statistical difference (see Supplementary material online, Appendix for details). In the RF group, 3D mapping systems were used in 98.9% of procedures and PV angiographies in 61% of the cases. Most of the CB procedures were guided by PV angiography (89.5%), and intracardiac echocardiography (ICE) was used in 33.5% of the CB procedures. Focal touch-ups with either RF or cryofocal catheters were rarely used to achieve acute PVI (1.1%) in CB procedures, and the alternative balloon size as an additional balloon during the same CB procedure was applied in 8.3% of patients (Table 3). The median procedure time of the CB cohort compared with RF group was significantly shorter (112 vs. 180 min,  $P < 0.0001$ ), as well as the LA catheter dwell time. In addition, fewer catheters were placed in the LA with the CB procedure compared with the RF procedure ( $1.3 \pm 0.5$  vs.  $2.0 \pm 0.2$ ,  $P < 0.0001$ ). No difference was found for the fluoroscopy time between the groups. With CB CA, radiation exposure was significantly higher compared with RF CA (2663 vs. 2067 cGy cm<sup>2</sup>,  $P < 0.05$ ).

### Periprocedural complications

In the study, there were two instances of Major Adverse Cardiac or Cerebrovascular Events, defined as death, stroke, or myocardial infarction (Table 4). One stroke occurred in both groups. Non-significant trends were observed for a higher incidence of pericardial tamponade requiring drainage in the RF group, and more phrenic nerve palsy (PNP) in the CB group. Major adverse events occurred in 1.6 and 3.7% of patients in the CB and RF groups ( $P = 0.22$ ), respectively. Minor adverse event rates were similar in the CB (7.4%) and RF (7.3%) groups,  $P = 0.99$ .

### Freedom from arrhythmia until discharge

Atrial fibrillation recurrence until discharge occurred in the CB (6.9%) and RF (3.7%) groups without significant difference ( $P =$

**Table 1** Baseline characteristics of patients with symptomatic PAF prior to AAD therapy (not including  $\beta$ -blocker) who underwent initial CA for PVI

	CB	RF	P-Value
Number of patients	193 (52)	180 (48)	–
Age	60.5 (52.0, 69.0)	65.0 (54.0, 72.0)	<0.01
EHRA $\geq$ II	189 (97.1)	161 (89.4)	<0.0001
Female sex category	80 (41)	74 (41)	0.98
Height (cm)	175 (168, 183)	174.5 (168, 182)	0.53
BMI (kg/m <sup>2</sup> )	26.4 (24.2, 29.1)	26.2 (24.3, 29.8)	0.79
Previous non-AF ablation	14 (7.3)	16 (8.9)	0.56
CAD	19 (9.8)	29 (16.1)	0.07
Valve disease	11 (5.7)	18 (10)	0.12
Cardiomyopathy	1 (0.5)	4 (2.2)	0.15
Hypertensive heart disease	53 (27.5)	37 (20.6)	0.12
Hypertension	113 (58.5)	133 (73.9)	<0.01
Diabetes	12 (6.2)	15 (8.3)	0.43
Renal failure, GFR < 60 mL/min	3 (1.6)	6 (3.3)	0.26
Chronic obstructive pulmonary disease	5 (2.6)	8 (4.4)	0.33
PAD	0 (0)	7 (3.9)	<0.01
Previous stroke	9 (4.7)	7 (3.9)	0.71
Previous TIA	2 (1.0)	6 (3.3)	0.13
CHA <sub>2</sub> DS <sub>2</sub> -VASc score	1.8 $\pm$ 1.5	2.3 $\pm$ 1.5	<0.01
CHA <sub>2</sub> DS <sub>2</sub> -VASc score $\geq$ 2	93 (50.3)	105 (62.9)	<0.05

n (%), mean  $\pm$  SD, or median (IQR).

CAD, coronary artery disease; GFR, glomerular filtration rate; PAD, peripheral artery disease; TIA, transitory ischemic attack.

**Table 2** Preprocedural findings

	CB (n = 193)	RF (n = 180)	P-Value
Heart rate (b.p.m.)	64 (57, 74)	63 (58, 73)	0.96
Sinus rhythm	174/191 (91.1)	146/178 (82.0)	<0.05
No. AV conduction block	185/192 (96.4)	165/178 (92.7)	0.12
QRS duration (ms)	90 (83, 100)	90 (80, 100)	0.76
LVEF (%)	60.0 (55, 60)	60.0 (58, 60)	<0.01
LVEF $\leq$ 40%	4/186 (2.2)	3/168 (1.8)	0.81
LA diameter (mm)	41 (38, 45)	41 (38, 45)	0.98
LA diameter >45 mm	40/190 (21.1)	28/171 (16.4)	0.26
PV anatomy determined	140/191 (73.3)	116/177 (65.5)	0.11
Normal PV anatomy	140/191 (89.3)	94/116 (81.0)	0.06
Left common os	13/140 (9.3)	12/116 (10.3)	0.78
S-creatinine (mg/dL)	0.9 (0.8, 1.0)	0.9 (0.8, 1.0)	0.59

n (%), mean  $\pm$  SD, or median (IQR).

0.19). After PVI, AT, or atrial flutter was rarely documented until discharge in the CB and RF groups (1.6 vs. 1.2%,  $P = 0.78$ ). At discharge, fewer patients were taking AAD Class I/III in the CB cohort (10.6%) compared with the RF group (16%,  $P = 0.14$ ).

## Follow-up

In the study, 206/373 patients (55.2%) were eligible for the scheduled 12-month FU. In the CB and the RF groups, FU was performed in 107/193 (55.4%) and in 99/180 (55.0%) of patients, respectively

**Table 3** Procedural results

	CB (n = 193)	RF (n = 180)	P-Value
Anaesthesia	190/192 (99.0)	174/175 (99.4)	0.62
Total number of catheters	2.5 ± 0.9	3.3 ± 0.7	<0.0001
Number of catheters transseptal in LA	1.3 ± 0.5	2.0 ± 0.2	<0.0001
3D mapping system	1/187 (0.5)	173/175 (98.9)	<0.0001
Irrigated RF catheter	–	160/174 (92)	–
Robotic control of RF catheter	–	3/174 (1.7)	–
PV angiography performed	171/191 (89.5)	107/175 (61.1)	<0.0001
ICE	64/191 (33.5)	7/175 (4)	<0.0001
Second-generation CB <sup>a</sup>	164/191 (85.9)	–	–
Additional usage of the alternate CB size	16/193 (8.3)	–	–
Number of cryoballoons	1.1 ± 0.3	–	–
Focal touch-up applications	2/188 (1.1)	–	–
Duration of all applications (min)	32.0 (28.0, 37.7)	37.9 (31.3, 53.6)	<0.001
LA catheter dwell time (min)	80.0 (66.0, 100.0)	137.5 (102.5, 180.0)	<0.0001
Total procedure time (min)	112.0 (93.5, 130.0)	180.0 (135.0, 210.0)	<0.001
Fluoroscopy time (min)	16.0 (13.0, 23.0)	16.0 (11.0, 28.0)	0.95
Dose area product (cGy cm <sup>2</sup> )	2663 (1646, 3958)	2067 (1426, 2593)	<0.05

n (%), mean ± SD, or median (IQR).

ICE, intracardiac echocardiography.

<sup>a</sup>Cryoballoon Arctic Front Advance™, Medtronic Inc., MA, USA.

**Table 4** Procedural complications

	CB	RF	P-Value
MACCE	1/188 (0.5)	1/163 (0.6)	0.92
Death	0	0	–
Myocardial infarction	0	0	–
Stroke	1/188 (0.5)	1/163 (0.6)	0.92
Pericardial tamponade requiring drainage	1/188 (0.5)	4/162 (2.5)	0.13
Severe bleeding	0/188 (0)	1/164 (0.6) <sup>a</sup>	0.28
PNP	3/187 (1.6)	1/159 (0.6)	0.40
Resolved at discharge <sup>b</sup>	2/3 (67)	1/1 (100)	0.50
Major adverse events	3/189 (1.6)	6/164 (3.7)	0.22
Inguinal haematoma	7/186 (3.8)	9/157 (5.7)	0.39
AV fistula or spurious aneurysm	6/189 (3.2)	3/164 (1.8)	0.42
Infection at puncture side	1/189 (0.5)	0/164 (0)	0.35
Minor adverse events	14/189 (7.4)	12/164 (7.3)	0.99
Total adverse events	17/189 (9.0)	18/164 (11.0)	0.54

n (%), mean ± SD, or median (IQR).

AV, arteriovenous; MACCE, Major Adverse Cardiac and Cerebrovascular Event; PNP, phrenic nerve palsy.

<sup>a</sup>Patient received three blood units.

<sup>b</sup>PNP not counted as a major adverse event if resolved until discharge.

( $P = 0.93$ ). Median FU duration since intervention was 511 (IQR 428.0, 533.0) days in the CB group and 518 (IQR 462.0, 532.0) days in the RF group,  $P = 0.32$ . For evaluation of arrhythmia

recurrence patients underwent Holter studies (84 vs. 84%,  $P = 0.96$ ), event recordings (6 vs. 7%,  $P = 0.92$ ) or at least resting ECGs (10 vs. 9%,  $P = 0.89$ ) in the CB and the RF groups, respectively.

At 12-month FU, freedom from any AF/AT  $\geq 30$  s after the initial procedure was 76/107 (71.0%) in the CB group and 60/99 (60.6%) in the RF group,  $P = 0.11$ . We did perform comparisons between the first and second generation of the CB. Owing to the small number of patients treated with CBG1,  $n = 27$  (14.1% of patients in the CB group, see Table 3), we did not see any statistical differences in parameters describing clinical outcome. European Heart Rhythm Association symptom score improved in both groups, and 76.3% of patients in the CB group and 72.8% of patients in the RF group were classified as EHRA I (no symptoms). Cardioversion during FU was performed in the CB group in 1.2% and in the RF group in 11.0% of patients,  $P < 0.01$ . Patients were readmitted during FU in 28.2% of patients in the CB group and in 50% of patients in the RF group ( $P < 0.01$ ). The reason for re-hospitalization was AF in 33.3 and 30.2% of patients in the CB and RF groups, respectively. Repeat ablation during FU was performed in 6.0 and 14.6% of patients in the CB and RF groups, respectively ( $P = 0.07$ ).

Of all the patients, only one patient reported a persistent PNP at FU, this PNP had occurred during CB ablation. The rate of persistent PNP in the CB group was 1/107 (0.9%). No other interventional complications (induced persistent problems) were reported, and importantly, there were no reports of atrio-oesophageal fistula. Adverse events during the FU period after discharge were reported in both groups and could not be attributed to the procedure itself. In the CB group, one patient suffered from a non-procedural stroke, and two patients experienced unexplained syncope. In the RF group,



one patient was treated because of moderate bleeding, and one patient reported an unexplained syncope event.

Lastly, patients rated the procedure as 'overall successful' in 56.4% in the CB group and 47.9% in the RF group,  $P = 0.24$ . Patients assigned the procedure as 'partially successful' in 22.2% in the CB group and 14.6% in the RF group,  $P = 0.17$ . From the survey, almost all patients would return to the same clinic in both groups (CB: 92.7 and RF: 95.0%,  $P = 0.54$ ).

## Discussion

To the best of our knowledge, this study is the first prospective, international, multicentre registry trial evaluating RF or CB ablation in first-line therapy. Specifically, the study examines the preferred ablation method for PVI as a first-line treatment strategy in symptomatic PAF patients naïve to AAD therapy. A major advantage of this study is that during the initiation process each participating centre had to declare if they wanted to contribute either to the RF or to the CB arm of the FREEZE Cohort Study. This may have reduced the risk that participating centres were more experienced (or only experienced) in one ablation catheter category (RF or CB). Prior experience and learning curve are potential bias problems in randomized trials when performing two different techniques at one institution.

The current guidelines indicate first-line PAF ablation as a Class IIa/B indication for those symptomatic patients preferring interventional treatment or for those with contraindications for AAD treatment with a low-risk profile for periprocedural complications.<sup>1,2</sup> Conclusively, only 8.9% (Figure 1) of the total number of patients screened for the FREEZE Cohort Study were identified as first-line PAF patients undergoing AF ablation even in experienced interventional EP centres. This group of patients were examined in this study from the FREEZEplus cohort.

At 1-year FU, 71% of patients on antiarrhythmic medication for the maintenance of normal sinus rhythm developed recurrent AF.<sup>14</sup> Compared with a pharmacological treatment strategy, PVI results in a significantly increased freedom from AF at 1 year.<sup>14</sup> However, CA as an invasive strategy bears a procedural risk of up to 4.5% for major complications<sup>17</sup> compared with the cumulative risk of side-effects of AADs (e.g. proarrhythmias in the case of long-term treatment with AADs<sup>18</sup>). Our data demonstrate that first-line CA for PAF can safely be performed with either RF or CB technology. Major adverse events occurred infrequently in both groups with a trend for more major adverse events in the RF group (1.6 vs. 3.7%,  $P = 0.22$ ). The main contributor for the higher incidence observed in the RF group were the four cases of pericardial tamponades. It is unclear from this study, if point-by-point RF CA itself has a higher risk for complications, or if an older patient population in the RF group with a longer mean LA dwell time and with more catheters in LA increased the risk of the RF procedures. Nevertheless, the major adverse event rate in the RF group is still in-line with the reported 4.5% complication rate reported by Cappato *et al.*<sup>17</sup> in the worldwide survey. Fortunately, persistent problems induced by CA were rarely observed in the entire study, and only one PNP persisted  $\geq 12$  months after CB ablation (0.9%). The combined rate of freedom from AF after the initial ablation with CB or RF ablation was 136/206 (66%) in this study with a median FU of 1.4 years.

This is a reasonable result when compared with the interventional arm of the MANTRA-PAF trial where 85% of patients were free from any AF after a mean of 1.6 ablation procedures at 24 months. Also, in RAAFT-2, the rate of freedom from AF was 45.5% after a mean of 1.14 procedures at 24 months.<sup>4</sup>

In the CB group of our study, there was a non-significant trend for a higher rate of freedom from AF compared with RF (71 vs. 61%,  $P = 0.11$ ). In addition, during FU there were significantly more cardioversions and repeat ablations performed in the RF group compared with the CB group. Taken together, these observations could be interpreted as a potential higher success rate in the CB group. However, 1-year single-centre outcome data with the new CB in paroxysmal drug-refractory AF demonstrate even a higher success rate in the range of 78–83.6%.<sup>10–12</sup> Our results must be taken with caution as we observed some differences in the baseline clinical characteristics of the non-randomized cohorts. Although the LA diameter was without difference between the groups, the older age, a higher prevalence of hypertension and PAD resulted in a higher CHA<sub>2</sub>DS<sub>2</sub>-VASc score in the RF group compared with the CB group. The CHA<sub>2</sub>DS<sub>2</sub>-VASc score is an independent predictor for recurrences after ablation of PAF.<sup>19</sup> Thus, the differences in AF substrate between the groups might partly explain the outcome differences in our study. However, contact force-sensing RF catheters are an evolution of ablation of AF. The initial published results of the TOCCATA study<sup>20</sup> using a contact force-sensing catheter in 2012 and data from the recently published EFFICAS II study support the concept that contact force is the missing link to create durable PVI when using RF point-by-point ablation for AF.<sup>21</sup> The FREEZE Cohort Study is a multicentre study and started the enrolment in April 2011. The electronic case report form do not differentiate between irrigated tip catheters with and without determination of contact force. This is why we cannot provide information about the usage of those catheters in the FREEZE Cohort Study.

However, beside the difference in freedom from AF we demonstrated highly significant differences between the groups with respect to items representative for the complexity of the ablation procedure although the procedural endpoint, PVI, was identical in both arms. More catheters were necessary in the LA with RF (CB:  $1.3 \pm 0.5$  vs. RF:  $2.0 \pm 0.2$ ,  $P < 0.0001$ ). Most RF investigators used double transseptal punctures for the Lasso catheter and the irrigated RF catheter; whereas, CB ablation can be performed with a single transseptal puncture in an over-the-wire technique with the CB combined with an inner-lumen spiral mapping catheter (Achieve™ catheter, Medtronic Inc., MN, USA). The catheter dwell time in the LA was significantly shorter with CB compared with RF CA. There are several reasons for this observation. With RF ablation, an electroanatomic shell of the LA needs to be created using a 3D mapping system. Some investigators use additional PV angiographies to determine the optimal antral position of the ablation catheter. These preparations are sometimes time consuming. In contrast, with CB ablation, the procedure is more straightforward. Immediately after transseptal puncture and positioning of the sheath with the CB in the LA, the left superior PV is targeted with the spiral mapping catheter and the balloon is advanced until optimal occlusion is visualized by PV angiography and/or ICE. In many cases, with one- or two-cryothermal deliveries one PV can be isolated in contrast to RF CA where several point-by-point RF lesions are

necessary to create a circumferential PVI. A fast procedure is preferable for the patient, the investigator, and the medical technical assistance.

By comparison, with CB ablation, the radiation dose was significantly higher compared with RF CA (2663 vs. 2067 cGy cm<sup>2</sup>,  $P < 0.05$ ). In CB CA, PV angiographies are necessary for demonstrating occlusion with the CB. However, the radiation exposure is comparable with percutaneous coronary intervention and complex ablation procedures.<sup>22</sup> Even in the RF group, the amount of radiation was high although most of the procedures were performed with a 3D mapping systems. This might be explained by the finding that many RF investigators also used PV angiography to facilitate exact localization of the PV ostium when performing a wide antral circumferential ablation line. In the treatment of patients suffering from symptomatic AF with RF or CB ablation, the key principle of radiation protection needs to receive better attention. Each patient should get the right imaging exam, at the right time. Radiation doses should be as low as reasonable achievable<sup>22</sup> but not at the expense of patient safety or efficacy.

In the future, more and more patients will be suffering from symptomatic AF. Today, RF ablation is still the most widespread ablation method, but the use of CB steadily increases.<sup>7</sup> Our results indicate that the CB has the potential to be an important tool to treat AF in the future, including in patients undergoing first-line ablation.

## Limitations

A major limitation of this prospective observational registry study is the potential selection bias within the non-randomized groups with older patients in the RF group. Another limitation is the methodology of the 12-month FU performed by trained assistants over the telephone. Although most of the patients underwent Holter studies, no data are available on the exact number of Holters used for each patient. As the study is an ongoing study, only 206/373 (55%) of patients were eligible for 12-month FU, diminishing the overall impact of the outcome results.

## Conclusion

The treatment of patients with symptomatic PAF with CA prior to AAD therapy is an option in a significant number of patients and seems to be safe and effective with RF or CB. By comparison, the CB procedure was significantly faster and less complex, which are important considerations when evaluating the preferred ablation method. The radiation exposure was higher in the CB group but remained in a reasonable range when compared with RF cohort.

Although there was a trend for more AF/AT recurrences and adverse events in the RF group, methodological limitations and a more favourable risk profile in patients undergoing CB ablation might have biased our findings on outcome parameters. More data are necessary to determine the preferred energy source for first-line CA of AF. At the moment (when comparing RF and CB usage), the recommended strategy should be to use the preferred technique (ablation catheter) by the local operator, as learning curve and catheter proficiency are proven factors to a successful CA.

## Supplementary material

Supplementary material is available at *Europace* online.

## Acknowledgements

FREEZE Cohort Study is an investigator-initiated trial, principle investigator E.H., conducted by the Stiftung Institut für Herzinfarktforschung (IHF) foundation in Ludwigshafen, Germany, and supported by Medtronic Inc., Minneapolis, MN, USA.

## Funding

The FREEZE Cohort Study was supported by Medtronic Inc., Minneapolis, MN, USA.

**Conflict of interest:** F.S. and U.D. received honoraria for lectures and educational support from Medtronic, and honoraria for lectures from Bristol Meyer Squibb. G.N. received consulting fees and honoraria from Medtronic, St Jude Medical, Biosense Webster, and Biotronik. M.K. received travel expenses, honoraria for lectures, advisory board activities, and proctoring from Medtronic. K.R.J.C. received educational honoraria and travel support from Medtronic. J.T. received consulting fees and honoraria from Medtronic. R.T. received research grants from St Jude Medical, Hansen Medical, and Sentreheart, and honoraria for lecture from Biotronik, Topera Medical, Pfizer Inc., Bristol Meyers Squibb, Bayer/Schering Pharma, Sanofi Aventis, and Biosense Webster. K.H.K. received research grants from Biosense Webster, Medtronic, St Jude Medical, and Boston Scientific, and consulting honoraria from St Jude Medical, Stereotaxis, and Edwards Lifescience. J.S. discloses contracted research with Medtronic. E.H. received honoraria for lectures from Boehringer Ingelheim, Boston Scientific, MSD SHARP&DOHME GmbH, research funding from Biotronik, Edwards Corp, Medtronic, Philips, St Jude Medical, Braun AG, and Stentys Inc.

## References

1. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC Jr. et al. AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol* 2014;**64**:e1–76.
2. Camm AJ, Lip GY, De Caterina R, Savelieva I, Atar D, Hohnloser SH et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation—developed with the special contribution of the European Heart Rhythm Association. *Europace* 2012;**14**:1385–413.
3. Wazni OM, Marrouche NF, Martin DO, Verma A, Bhargava M, Saliba W et al. Radiofrequency ablation vs antiarrhythmic drugs as first-line treatment of symptomatic atrial fibrillation: a randomized trial. *JAMA* 2005;**293**:2634–40.
4. Morillo CA, Verma A, Connolly SJ, Kuck KH, Nair GM, Champagne J et al. Radiofrequency ablation vs antiarrhythmic drugs as first-line treatment of paroxysmal atrial fibrillation (RAAFT-2): a randomized trial. *JAMA* 2014;**311**:692–700.
5. Cosedis Nielsen J, Johannessen A, Raatikainen P, Hindricks G, Walfridsson H, Kongstad O et al. Radiofrequency ablation as initial therapy in paroxysmal atrial fibrillation. *N Engl J Med* 2012;**367**:1587–95.
6. Calkins H, Kuck KH, Cappato R, Brugada J, Camm AJ, Chen SA et al. HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation: recommendations for patient selection, procedural techniques, patient management and follow-up, definitions, endpoints, and research trial design. *Europace* 2012;**14**:528–606.
7. Schmidt M, Dorwarth U, Andresen D, Brachmann J, Kuck KH, Kuniss M et al. Cryoballoon versus RF ablation in paroxysmal atrial fibrillation: results from the German Ablation Registry. *J Cardiovasc Electrophysiol* 2014;**25**:1–7.
8. Straube F, Dorwarth U, Schmidt M, Wankel M, Ebersberger U, Hoffmann E. Comparison of the first and second cryoballoon: high-volume single-center safety and efficacy analysis. *Circ Arrhythm Electrophysiol* 2014;**7**:293–9.
9. Straube F, Dorwarth U, Vogt J, Kuniss M, Heinz Kuck K, Tebbenjohanns J et al. Differences of two cryoballoon generations: insights from the prospective multicentre, multinational FREEZE Cohort Substudy. *Europace* 2014;**16**:1434–42.

10. Furnkranz A, Bordignon S, Dugo D, Perotta L, Gunawardene M, Schulte-Hahn B *et al*. Improved 1-year clinical success rate of pulmonary vein isolation with the second-generation cryoballoon in patients with paroxysmal atrial fibrillation. *J Cardiovasc Electrophysiol* 2014;**25**:840–4.
11. Chierchia GB, Di Giovanni G, Ciconte G, de Asmundis C, Conte G, Sieira-Moret J *et al*. Second-generation cryoballoon ablation for paroxysmal atrial fibrillation: 1-year follow-up. *Europace* 2014;**16**:639–44.
12. Metzner A, Reissmann B, Rausch P, Mathew S, Wohlmuth P, Tilz R *et al*. One-year clinical outcome after pulmonary vein isolation using the second-generation 28-mm cryoballoon. *Circ Arrhythm Electrophysiol* 2014;**7**:288–92.
13. Reddy VY, Sediva L, Petru J, Skoda J, Chovanec M, Chitovova Z *et al*. Durability of pulmonary vein isolation with cryoballoon ablation: results from the Sustained PV Isolation with Arctic Front Advance (SUPIR) Study. *J Cardiovasc Electrophysiol* 2015;**26**:493–500.
14. Piccini JP, Lopes RD, Kong MH, Hasselblad V, Jackson K, Al-Khatib SM. Pulmonary vein isolation for the maintenance of sinus rhythm in patients with atrial fibrillation: a meta-analysis of randomized, controlled trials. *Circ Arrhythm Electrophysiol* 2009;**2**:626–33.
15. Cheng X, Hu Q, Zhou C, Liu LQ, Chen T, Liu Z *et al*. The long-term efficacy of cryoballoon vs irrigated radiofrequency ablation for the treatment of atrial fibrillation: a meta-analysis. *Int J Cardiol* 2014;**181C**:297–302.
16. Hoffmann E, Dorwarth U, Kuck KH, Vogt J, Kuniss M, Schneider S *et al*. Design and baseline patient characteristics of the prospective, observational, multicenter and multinational cohort study comparing radiofrequency with cryoablation for pulmonary vein isolation in patients with atrial fibrillation—The Freeze Cohort Study. *Int J Clin Med* 2014;**5**:1161–72.
17. Cappato R, Calkins H, Chen SA, Davies W, Iesaka Y, Kalman J *et al*. Updated worldwide survey on the methods, efficacy, and safety of catheter ablation for human atrial fibrillation. *Circ Arrhythm Electrophysiol* 2010;**3**:32–8.
18. Camm AJ. Safety considerations in the pharmacological management of atrial fibrillation. *Int J Cardiol* 2008;**127**:299–306.
19. Letsas KP, Efremidis M, Giannopoulos G, Deftereos S, Lioni L, Korantzopoulos P *et al*. CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc scores as predictors of left atrial ablation outcomes for paroxysmal atrial fibrillation. *Europace* 2014;**16**:202–7.
20. Reddy VY, Shah D, Kautzner J, Schmidt B, Saoudi N, Herrera C *et al*. The relationship between contact force and clinical outcome during radiofrequency catheter ablation of atrial fibrillation in the TOCCATA study. *Heart Rhythm* 2012;**9**:1789–95.
21. Kautzner J, Neuzil P, Lambert H, Peichl P, Petru J, Cihak R *et al*. EFFICAS II: optimization of catheter contact force improves outcome of pulmonary vein isolation for paroxysmal atrial fibrillation. *Europace* 2015;**17**:1229–35.
22. Picano E, Vano E, Rehani MM, Cuocolo A, Mont L, Bodi V *et al*. The appropriate and justified use of medical radiation in cardiovascular imaging: a position document of the ESC Associations of Cardiovascular Imaging, Percutaneous Cardiovascular Interventions and Electrophysiology. *Eur Heart J* 2014;**35**:665–72.