Cryoballoon ablation vs. antiarrhythmic drugs: first-line therapy for patients with paroxysmal atrial fibrillation

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Aims
Treatment guidelines for patients with atrial fibrillation (AF) suggest that patients should be managed with an antiarrhythmic drug (AAD) before undergoing catheter ablation (CA). This study evaluated whether pulmonary vein isolation employing cryoballoon CA is superior to AAD therapy for the prevention of atrial arrhythmia (AA) recurrence in rhythm control naive patients with paroxysmal AF (PAF).

Methods and results
A total of 218 treatment naive patients with symptomatic PAF were randomized (1:1) to cryoballoon CA (Arctic Front Advance, Medtronic) or AAD (Class I or III) and followed for 12 months. The primary endpoint was > 1 episode of recurrent AA (AF, atrial flutter, or atrial tachycardia) > 30 s after a prespecified 90-day blanking period. Secondary endpoints included the rate of serious adverse events (SAEs) and recurrence of symptomatic palpitations (evaluated via patient diaries). Freedom from AA was achieved in 82.2% of subjects in the cryoballoon arm and 67.6% of subjects in the AAD arm (HR = 0.48, P = 0.01). There were no group differences in the time-to-first episode of recurrent AA (AF, atrial flutter, or atrial tachycardia) > 30 s after a prespecified 90-day blanking period. Secondary endpoints included the rate of serious adverse events (SAEs) and recurrence of symptomatic palpitations (evaluated via patient diaries). Freedom from AA was achieved in 82.2% of subjects in the cryoballoon arm and 67.6% of subjects in the AAD arm (HR = 0.48, P = 0.01). There were no group differences in the time-to-first episode of recurrent AA (AF, atrial flutter, or atrial tachycardia) > 30 s after a prespecified 90-day blanking period. Secondary endpoints included the rate of serious adverse events (SAEs) and recurrence of symptomatic palpitations (evaluated via patient diaries). Freedom from AA was achieved in 82.2% of subjects in the cryoballoon arm and 67.6% of subjects in the AAD arm (HR = 0.48, P = 0.01). There were no group differences in the time-to-first episode of recurrent AA (AF, atrial flutter, or atrial tachycardia) > 30 s after a prespecified 90-day blanking period.

Conclusions
Cryoballoon CA was superior to AAD therapy, significantly reducing AA recurrence in treatment naive patients with PAF. Additionally, cryoballoon CA was associated with lower symptom recurrence and a similar rate of SAEs compared with AAD therapy.

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Introduction

Treatment guidelines for patients with atrial fibrillation (AF) suggest that patients should be first managed with an antiarrhythmic drug (AAD). When a patient becomes AAD-refractory (intolerant or non-responsive), catheter ablation (CA) by pulmonary vein isolation (PVI) is recommended in those patients with recurrent symptomatic paroxysmal AF (PAF). Importantly, early rhythm control with AADs or ablation is associated with a reduction in adverse cardiovascular outcomes. Additionally, a shortened duration from AF diagnosis until CA has been shown to improve long-term rhythm control. To date, three randomized studies (RAAFFT-1, RAAFFT-2, and MANTRA-PAF) have compared radiofrequency current (RFC) CA to AAD therapy in treatment naïve patients with PAF. In summary, RFC CA can be more effective in younger (otherwise healthy) patients compared with AAD therapy, but RFC CA might also yield a higher incidence of adverse events.

The FIRE AND ICE trial demonstrated non-inferiority of cryoballoon compared with RFC CA with regards to the primary safety and efficacy endpoints in patients with drug-refractory symptomatic paroxysmal AF (PAF). Cryoballoon ablation was superior to antiarrhythmic drug therapy for the prevention of atrial arrhythmia recurrence over 12 months and was associated with lower arrhythmia symptom recurrence. There was no difference in the rate of serious adverse events between groups. These findings suggest that cryoballoon ablation is an effective first-line treatment strategy in drug naïve patients with symptomatic paroxysmal atrial fibrillation pursuing rhythm control therapy.

What’s new?

• This prospective, randomized global study evaluated cryoballoon catheter ablation vs. antiarrhythmic drug therapy as an initial, first-line rhythm control strategy in patients with symptomatic paroxysmal atrial fibrillation.
• Cryoballoon ablation was superior to antiarrhythmic drug therapy for the prevention of atrial arrhythmia recurrence over 12 months and was associated with lower arrhythmia symptom recurrence.
• There was no difference in the rate of serious adverse events between groups.
• These findings suggest that cryoballoon ablation is an effective first-line treatment strategy in drug naïve patients with symptomatic paroxysmal atrial fibrillation pursuing rhythm control therapy.

Keywords

Antiarrhythmic drug • Catheter ablation • Atrial fibrillation • Cryoballoon • First-line treatment • Randomized study
cryoballoon CA was superior to AAD for preventing atrial arrhythmia (AA) recurrence over 12 months. Moreover, serious procedure-related complications were uncommon.10,11 Here, we report the primary trial results of the randomized, global Cryo-FIRST study that evaluated cryoballoon CA vs. AAD therapy in patients undergoing first-line rhythm control treatment for symptomatic PAF.

Methods

Trial design

Detailed methods of the Cryo-FIRST trial (ClinicalTrials.gov Identifier: NCT01803438) have been previously published.12 In brief, this was a multicentre, prospective, open blind-endpoint controlled randomized (1:1) study to compare cryoballoon CA against AAD therapy in treatment naive patients with symptomatic, recurrent PAF. The steering and publication committees were composed of physicians who assumed a leadership role in the conduct of the study. This study complied with the Declaration of Helsinki and ISO 14155. Local ethics review committees approved the study at each participating centre. The study was sponsored by Medtronic. Data were inputted by each participating centre into an internet-based data collection system (Oracle Clinical) and an independent adverse event committee and Holter core laboratory were used to insure impartial classification of the study events. The final analysis was conducted by the sponsor; all authors take explicit responsibility for the accuracy and fidelity of the analyses performed by the corporate sponsor that are reported in this manuscript. The decision to publish the results and final decisions regarding the contents of the manuscript were made by the publication committee.

Study participants

Twenty centres in Europe, Australia, and Latin America participated in this trial (Supplementary material online, Table S1). This study enrolled patients 18 to 75 years old with a normal ECG (QRS width <120 ms; QTc <440 ms; PQ <210 ms), structurally normal heart (left ventricular ejection fraction ≥50%, thickness of the inter-ventricular septum ≤12 mm and left atrium diameter (short axis) ≤46 mm) and recurrent symptomatic PAF who were drug naive (had not previously received a Class I or III AAD for >48 h).12 All patients provided written informed consent prior to participation. After enrollment, patients were randomly assigned 1:1 to undergo cryoballoon CA or AAD therapy. A full list of inclusion and exclusion criteria has been previously published.12

Cryoballoon catheter ablation

The cryoballoon CA procedure has been previously described in detail.8,9,12–14 In brief, a 28- or 23-mm second-generation cryoballoon (Arctic Front Advance Cardiac Cryoablation Catheter, Medtronic) was delivered using a transseptal puncture and an over-the-wire delivery technique. The balloon was placed at each pulmonary vein (PV). Acute PVI was confirmed by entrance block (and where assessable, exit block) testing using a dedicated inner lumen, circular diagnostic mapping catheter (Achieve Mapping Catheter, Medtronic). Continuous phrenic nerve pacing with intervals of 1000–3000 was required during cryoballoon ablation of the right-sided PVs. Ablation was immediately stopped in the event of significantly altered movement of the diaphragm. In the case of incomplete electrical isolation of the PV or identification of focal triggers, additional freeze applications with the focal catheter (Freezor MAX Cardiac Cryoablation Catheter, Medtronic) or the alternative-sized cryoballoon were permitted. Patients were discharged and maintained on systemic anticoagulation therapy for a minimum of 3 months. Re-ablation and use of AADs were allowed during the first 90 days after the index procedure. After the 90-day blanking period, all AADs were discontinued except for β-blockers and calcium channel blockers, and repeat ablations were defined as primary endpoint failures.

Antiarrhythmic drug therapy

Subjects randomized to the AAD therapy arm received a Class I or III AAD in accordance with each hospital’s clinical practice and the 2012 ESC guidelines for the management of AF.15 However, amiodarone was discouraged due to its potential extracardiac toxicity. The use of other AADs was not allowed except for β-blockers. Drug, dose, and schedule changes were permitted during the first 90 days to optimize AAD therapy in case of inefficacy. Oral anticoagulation and use of calcium channel blockers were not governed by the study protocol.

Study follow-up

Scheduled follow-up visits took place at baseline, 1, 3, 6, 9, and 12 months, and included a 12-lead ECG and 7-day Holter. A patient diary was used to evaluate the occurrence of symptomatic palpitations. After the 90-day blanking period, prescription of AAD in the CA arm and CA in the AAD therapy arm was considered treatment crossover events.

End points

The primary study endpoint was freedom from any AA recurrence (at least one episode of AF, atrial flutter, or atrial tachycardia) lasting >30 s at 12 months documented by 7-day Holter ECG or any other ECG recording outside of the 90-day blanking period. Cardioversion and repeat CA for AA recurrence outside of the 90-day blanking period were also counted towards a primary endpoint failure event, as it was assumed that these procedures were conducted due to AA recurrence >30 s. Prespecified secondary endpoints reported here include the rate of serious adverse events (SAEs) and recurrence of patient-reported symptomatic palpitations. Serious adverse events include by definition events that led to death or serious deterioration in the health of the subject resulting in: a life-threatening illness or injury, a permanent impairment of a body structure or a body function, inpatient or prolonged hospitalization, or medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function. Atrial arrhythmia recurrence was classified as a SAE if it resulted in inpatient or prolonged hospitalization per the above SAE definition.

Statistical analysis

It was assumed that 10% of subjects would withdraw from the study. Consequently, a sample size of 218 was chosen to achieve 80% power to detect a 20% reduction in the freedom from AA recurrence at 12-months with CA vs. AAD therapy at an alpha-level of 5% (two-sided Type I error).12 The primary analysis was based on the intention-to-treat (ITT) cohort. A sensitivity analysis was performed in a per-protocol cohort that included all subjects randomized until the point of crossover. Survival curves for the time-to-first primary endpoint and time-to-first SAEs were estimated by the Kaplan–Meier method and evaluated for statistical difference using the log-rank test. Differences in the rate of SAEs and recurrent symptomatic palpitations were estimated and compared between groups by means of the mixed Poisson model. No adjustments for multiple comparisons were performed, and missing data were not imputed.
Results

Patients
A total of 220 patients were enrolled between April 2014 and October 2018. The ITT cohort consisted of 107 patients randomized to cryoballoon CA and 111 patients randomized to AAD therapy. Subject baseline characteristics are presented in Table 1. Enrolment, randomization, and follow-up of study participants are summarized in Figure 1. Compliance with 7-day Holter monitoring was 87.1% in the cryoballoon group and 84.4% in the AAD group.

Treatment characteristics
For the cryoballoon arm, procedural details are available in Supplementary material online, Tables S2 and S3. During the index procedure complete isolation of all PVs was achieved in all 96 patients (100%). There were six re-ablations for AA recurrence(s) in six subjects assigned to cryoballoon, four of which occurred during the blanking period. Antiarrhythmic drug therapy was discontinued by the end of the blanking in all subjects that underwent cryoballoon CA and was not reinitiated during follow-up.

Two subjects never started AAD therapy, one was non-compliant and the other subject’s medical condition did not allow it. Drug and dosing information for the 103 subjects who initiated treatment in the AAD arm is available in Table 2. Antiarrhythmic drug therapy was discontinued in 20 patients due to patient non-compliance (n = 1), patient withdrawal from the study (n = 1), crossover to cryoballoon CA (n = 17 out of 19 AAD patients who crossed over) and physician discretion secondary to the development of side effects (n = 1). In subjects who did not cross over to cryoballoon CA, two had a change in dose after blanking; one of these subjects also had a change in AAD medication post-blanking.

Crossovers
Crossovers occurred in 20 subjects (9%). One subject in the cryoballoon arm chose not to undergo an ablation procedure and instead used AAD therapy. This subject experienced a primary endpoint event (documented AA recurrence outside of the 90-day blanking period). Additionally, 19 subjects in the AAD arm had a crossover event, electing to have a cryoballoon CA during the study. Of these, seven had documented AA recurrence after the blanking period and were considered primary endpoint failures (AA recurrence before crossover: n = 3; and AA recurrence after crossover: n = 4). There were 12 subjects who crossed over from AAD to cryoballoon CA that did not have a primary endpoint event. Of these 12 subjects, four subjects had a crossover within the 90-day blanking period (among which, two subjects had not started AAD therapy).

Primary endpoint
In the ITT analysis, freedom from any AA was achieved in 82.2% of subjects in the cryoballoon arm and 67.6% of subjects in the AAD arm (HR = 0.48, 95% CI: 0.26–0.86; P = 0.013) as illustrated in Figure 2. Reasons for primary endpoint failure through 12 months in the ITT analysis are listed in Table 3. Study findings were similar in the per-protocol analysis, with freedom from any AA achieved in 83.1% of subjects in the cryoballoon arm and 67.2% of subjects in the AAD arm (HR = 0.44, 95% CI: 0.24–0.82; P = 0.008). Single procedure success of cryoballoon CA at 12 months was 80.2% (95% CI: 70.4–87.1%). Atrial fibrillation burden during Holter monitoring at each follow-up visit is presented in Supplementary material online, Table S4 and Figure S1.

Secondary endpoints
During follow-up, there were 42 SAEs in 26 subjects in the cryoballoon arm and 56 SAEs in 37 subjects in the AAD arm [incidence rate ratio (IRR)=0.79; 95% CI: 0.51–1.22; P = 0.28, Table 4]. Atrial
Arrhythmia recurrence that met the definition of a SAE occurred in 11 subjects in the cryoballoon arm and 28 subjects in the AAD arm. There were 11 procedure-related SAEs in the cryoballoon arm, including one case of transient ischaemic attack on the same day of cryoballoon CA; this patient was taking warfarin at the time of the procedure. Additionally, one subject randomized to AAD experienced transient phrenic nerve palsy after undergoing CA. There was no difference in time-to-first SAE in either the ITT (HR = 0.76, 95% CI: 0.46–1.26; P = 0.28, Figure 3) or per-protocol analyses (HR = 0.79, 95% CI: 0.48–1.32; P = 0.37). Additionally, there was no death, atri-oesophageal fistula, pericardial tamponade, or stroke reported during the study, and there was no phrenic nerve injury present at the time of hospital discharge.

Throughout follow-up, the incidence rate of patient-reported days with symptomatic palpitations was lower in the cryoballoon arm (7.61 days/year) compared with the AAD arm (18.96 days/year, IRR = 0.40, 95% CI: 0.24–0.69; P < 0.001). At 12 months, 77 of 89 subjects (86.5%) in the cryoballoon arm and 69 of 98 subjects (70.4%) in the AAD arm were without AF-related symptoms (EHRA score 1; P = 0.017). The annualized rate of hospital or emergency service access due to symptoms caused by AA recurrence was 0.23 in the cryoballoon and 0.35 in the AAD group (IRR: 0.67, 95% CI: 0.41–1.10; P = 0.11).

Discussion

This was a global randomized study evaluating cryoballoon CA vs. AAD therapy as a first-line treatment in patients with recurrent symptomatic PAF. Cryoballoon CA was superior to AAD treatment for the prevention of AA recurrence over 12 months, and accordingly was associated with lower symptom recurrence. Moreover, a comparable safety profile was observed between both treatment strategies, with no significant group differences in the time-to-first SAE or the overall rate of SAEs throughout follow-up. Together these findings suggest that cryoballoon CA is an effective first-line treatment strategy in patients with symptomatic PAF.

Most comparisons between CA and AAD therapy have been completed in patients deemed as ‘AAD-refractory’ before study enrolment. These studies have consistently demonstrated that CA is...
superior to AADs for the reduction of AA recurrence and the avoidance of AF disease progression. Accordingly, the use of CA has received a Class I recommendation in patients with symptomatic, drug-refractory PAF in current guidelines. However, the safety and efficacy of CA vs. AADs as a first-line treatment has not been as extensively investigated in large randomized trials (especially when considering cryoballoon CA), and consequently, the usage of CA as a first-line treatment has received a Class IIa recommendation.

Historically, three randomized studies (RAAFT-1, RAAFT-2, and MANTRA-PAF) have evaluated RFC CA vs. AAD therapy for preventing AF recurrence in treatment naive patients with PAF. A meta-analysis of the 491 patients enrolled in these trials observed a 37% reduction in AF recurrence with CA. However, these studies were

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**Table 2** Antiarrhythmic drug therapy and dosing

| Drug       | Daily dose (mg) | Therapy start (n = 101)a | Month 3 (n = 97)b | Month 12 (n = 94)c |
|------------|-----------------|--------------------------|------------------|-------------------|
| Flecainide | 50              | 3 (2.9%)                 | 2 (2.1%)         | 2 (2.1%)          |
|            | 80              | 1 (1.0%)                 | 0 (0%)           | 0 (0%)            |
|            | 100             | 23 (22.3%)               | 12 (12.4%)       | 10 (10.6%)        |
|            | 120             | 0 (0%)                   | 1 (1.0%)         | 0 (0%)            |
|            | 150             | 10 (9.7%)                | 15 (15.5%)       | 11 (11.7%)        |
|            | 200             | 24 (23.3%)               | 13 (13.4%)       | 12 (12.8%)        |
| Propafenone| 300             | 14 (13.6%)               | 9 (9.3%)         | 9 (9.6%)          |
|            | 375             | 0 (0%)                   | 0 (0%)           | 1 (1.1%)          |
|            | 450             | 13 (12.6%)               | 13 (13.4%)       | 10 (10.6%)        |
|            | 600             | 6 (5.8%)                 | 6 (6.2%)         | 6 (6.4%)          |
| Sotalol    | 40              | 0 (0%)                   | 1 (1.0%)         | 0 (0%)            |
|            | 80              | 3 (2.9%)                 | 7 (7.2%)         | 4 (4.3%)          |
|            | 160             | 1 (1.0%)                 | 4 (4.1%)         | 2 (2.1%)          |
|            | 240             | 1 (1.0%)                 | 0 (0%)           | 0 (0%)            |
| Dronedarone| 800             | 2 (1.9%)                 | 5 (5.2%)         | 4 (4.3%)          |
| Amiodarone | 200             | 0 (0%)                   | 2 (2.1%)         | 1 (1.1%)          |
|            | 400             | 0 (0%)                   | 1 (1.0%)         | 0 (0%)            |
| Stopped AAD therapyd | NA | 0 (0%)                   | 6 (6.2%)         | 22 (23.4%)        |

Values are n (%).

*dDosing information was not available for one patient who was treated with flecainide and one patient treated with sotalol at therapy start. These patients are not included in the table.

*bPatients with available data. At 3 months, six patients had exited the study or missed the follow-up; these patients are not included in the table.

*cPatients with available data. At 12 months, nine patients had exited the study or missed the follow-up; these patients are not included in the table.

dThis category includes patients who crossed over to CA.

AAD, antiarrhythmic drug; CA, catheter ablation.

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**Table 3** Reason for primary endpoint failure through 12 months

| Primary endpoint failure event | Cryoballoon CA | AAD |
|-------------------------------|---------------|-----|
| Total                         | 16            | 33  |
| Atrial arrhythmia recurrence  | 15            | 33  |
| Atrial fibrillation           | 12            | 23  |
| Atrial flutter                | 0             | 1   |
| Atrial tachycardia            | 3             | 7   |
| Atrial fibrillation, atrial flutter | 0          | 1   |
| Atrial fibrillation, atrial flutter, and atrial tachycardia | 0 | 1 |
| Reablation                    | 1             | 0   |
| Cardioversion                 | 0             | 0   |

AAD, antiarrhythmic drug; CA, catheter ablation.

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**Figure 2** Time to first atrial arrhythmia recurrence in the intention-to-treat cohort.
limited by a small sample size or a relatively high rate of repeat ablation procedures. In our study, cryoballoon CA was associated with more than a 50% reduction in AA recurrence over 12 months. Importantly, in the present study, CA was found to be superior to AAD therapy despite cross-over events in 17% of patients randomized to AAD therapy. Overall, eight crossovers from the AAD to CA arm did not count as primary endpoint failure events due to the absence of documented AA recurrence outside of the blanking period. However, these events would likely be viewed as AAD treatment failure in clinical practice.

The procedural success observed with cryoballoon CA in this trial is generally aligned with that previously reported in three observational studies in treatment naive populations. In these studies, freedom from arrhythmia recurrence ranged from 71% to 89% over a follow-up period of 12–28 months. More recently, two randomized studies (EARLY-AF and STOP AF First) have specifically evaluated cryoballoon CA vs. AAD therapy as a first-line treatment strategy in patients with symptomatic AF. Similar to the present investigation, both studies demonstrated that cryoballoon CA was superior to AAD therapy for preventing AA recurrence over 12 months. A strength of these trials was the use of more robust cardiac monitoring during follow-up; however, enrolment was limited to Canada and the USA. Cryo-First extends findings from these studies to new geographies including Europe, Australia, and South America.

A primary concern around the use of any CA as a first-line therapy is safety, considering the serious albeit uncommon complications associated with CA. In the present investigation, safety was comprehensively evaluated by collecting all SAEs. Importantly, the rate of SAEs was similar between groups. While more SAEs were adjudicated to be procedure-related compared with drug-related, there were more patients in the AAD arm who experienced AA recurrence leading to hospitalization. Moreover, AADs were discontinued in 20 patients randomized to AAD therapy. Importantly, there were no occurrences of death, atrio-oesophageal fistula, stroke, pericardial tamponade, or chronic phrenic nerve injury within the CA cohort.

### Table 4: Serious adverse events

| Adverse event, events (subjects) | Cryoballoon CA (n = 107) | AAD (n = 111) |
|----------------------------------|--------------------------|----------------|
|                                  | All | Procedure related | System related | All | Drug related | Procedure related (cross over) |
|----------------------------------|-----|--------------------|----------------|-----|------------|-----------------------------|
| Total                            | 42  | 11 (9)             | 2 (1)          | 56  | 4 (4)      | 1 (1)                       |
| Acute coronary syndrome          | 0   | 0                  | 0              | 1   | 0          | 0                           |
| Acute kidney injury              | 0   | 0                  | 0              | 1   | 0          | 0                           |
| Adverse drug reaction            | 0   | 0                  | 0              | 3   | 2 (2)      | 0                           |
| Arteriospasm coronary            | 1   | 1 (1)              | 0              | 0   | 0          | 0                           |
| Atrial arrhythmia recurrence     | 15  | 1 (1)              | 0              | 34  | 2 (2)      | 0                           |
| AVNRT                            | 1   | 0                  | 0              | 0   | 0          | 0                           |
| Bronchitis                       | 1   | 0                  | 0              | 0   | 0          | 0                           |
| Chest pain                       | 1   | 0                  | 0              | 0   | 0          | 0                           |
| Gastrointestinal pain            | 1   | 0                  | 0              | 0   | 0          | 0                           |
| Impaired gastric emptying        | 1   | 1 (1)              | 0              | 1   | 0          | 0                           |
| Impaired healing                 | 0   | 0                  | 0              | 1   | 0          | 0                           |
| Lung disorder/infected           | 4   | 1 (1)              | 0              | 0   | 0          | 0                           |
| Non-sustained ventricular tachycardia | 0   | 0                  | 0              | 1   | 0          | 0                           |
| Oedema peripheral                | 0   | 0                  | 0              | 1   | 0          | 0                           |
| Orthostatic hypotension          | 0   | 0                  | 0              | 1   | 0          | 0                           |
| Palpitations                     | 0   | 0                  | 0              | 1   | 0          | 0                           |
| Pericardial disorder             | 3   | 3 (3)              | 1 (1)          | 0   | 0          | 0                           |
| Phrenic nerve paralysis          | 0   | 0                  | 0              | 1   | 0          | 1 (1)                       |
| Pneumonia                        | 1   | 0                  | 0              | 0   | 0          | 0                           |
| Procedural failure               | 1   | 1 (1)              | 0              | 0   | 0          | 0                           |
| Pyrexia                          | 1   | 1 (1)              | 0              | 0   | 0          | 0                           |
| Syncope                          | 0   | 0                  | 0              | 1   | 0          | 0                           |
| Transient ischaemic attack       | 1   | 1 (1)              | 1 (1)          | 0   | 0          | 0                           |
| Vascular access site haemorrhage | 1   | 1 (1)              | 0              | 0   | 0          | 0                           |
| Other                            | 9   | 9 (9)              | 0              | 9   | 7 (7)      | 0                           |

Atrial arrhythmia recurrence was only classified as a serious adverse event if it resulted in hospitalization.

aNone of these events resulted in cardiac tamponade.
bTransient phrenic nerve palsy was experienced by one subject randomized to AAD who underwent CA.
cFailure of the transseptal puncture was observed in one subject randomized to cryoballoon; a second procedure was successful.

AAD, antiarrhythmic drug; AVNRT, atrioventricular nodal reentry tachycardia; CA, catheter ablation.
safely performed by experienced operators.16,17,22 Support a growing body of literature demonstrating that CA can be
apy,20 and a lower rate of symptomatic AA recurrence with cryoballoon CA have together demonstrated a trend towards a reduction in
early in the AF disease process. In congruence, these findings are gen-
lower in the cryoballoon arm, suggesting that CA is superior to AAD therapy for symptom reduction, even in patients who are relatively
patients in the cryoballoon CA arm were without symptoms at present study population, which was relatively young and healthy
clinical challenge of long-term AAD therapy. Rather than specifying a
AAD to CA pose a challenge for extended follow-up periods.

Conclusions
Cryoballoon CA was superior to AAD therapy, significantly reducing AA recurrence in relatively young, treatment naive patients with current symptomatic PAF and a structurally normal heart. Moreover, CA was associated with lower symptom recurrence and a similar rate of SAEs compared with AAD treatment. Our findings suggest that cryoballoon CA using the Arctic Front Advance Cardiac Cryoablation Catheter is effective as a first-line therapy in relatively young otherwise healthy patients with symptomatic PAF.

Supplementary material
Supplementary material is available at Europace online.

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Data availability

The data underlying this article cannot be shared publicly due to privacy of the individuals that participated in the study.

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