



**HAL**  
open science

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

Malte Kuniss, Nikola Pavlovic, Vedran Velagic, Jean Sylvain Hermida, Stewart Healey, Giuseppe Arena, Nicolas Badenco, Christian Meyer, Jian Chen, Saverio Iacopino, et al.

### ► To cite this version:

Malte Kuniss, Nikola Pavlovic, Vedran Velagic, Jean Sylvain Hermida, Stewart Healey, et al.. Cryoballoon ablation vs. antiarrhythmic drugs: first-line therapy for patients with paroxysmal atrial fibrillation. *EP-Europace*, 2021, 23 (7), pp.1033 - 1041. 10.1093/europace/euab029 . hal-03346324

**HAL Id: hal-03346324**





**<https://hal.sorbonne-universite.fr/hal-03346324>**

Submitted on 16 Sep 2021

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

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

Malte Kuniss <sup>1\*</sup>, Nikola Pavlovic <sup>2</sup>, Vedran Velagic<sup>3</sup>, Jean Sylvain Hermida<sup>4</sup>, Stewart Healey<sup>5</sup>, Giuseppe Arena<sup>6</sup>, Nicolas Badenco<sup>7</sup>, Christian Meyer <sup>8</sup>, Jian Chen<sup>9</sup>, Saverio Iacopino<sup>10</sup>, Frédéric Anselme <sup>11</sup>, Douglas L. Packer<sup>12</sup>, Heinz-Friedrich Pitschner<sup>1</sup>, Carlo de Asmundis<sup>13</sup>, Stephan Willems<sup>14</sup>, Fabio Di Piazza<sup>15</sup>, Daniel Becker<sup>16</sup>, and Gian-Battista Chierchia<sup>13</sup>; for the Cryo-FIRST Investigators

<sup>1</sup>Kerckhoff Heart Center, Benekestrasse 2-8, 61231 Bad Nauheim, Germany; <sup>2</sup>Sestre Milosrdnice University Hospital Centre, Zagreb, Croatia; <sup>3</sup>University Hospital Centre Zagreb, Zagreb, Croatia; <sup>4</sup>Centre Hospitalier Universitaire d'Amiens-Picardie, Amiens, France; <sup>5</sup>Monash Health, Clayton, Australia; <sup>6</sup>Ospedale Apuane, Massa Carrara, Italy; <sup>7</sup>AP-HP Sorbonne Université, ICAN Institute, Hopital Pitié-Salpêtrière, Paris, France; <sup>8</sup>University Heart Center, Hamburg, Cardiac Neuro- and Electrophysiology Research Consortium, EVK Düsseldorf, Düsseldorf, Germany; <sup>9</sup>Haukeland University Hospital, University of Bergen, Bergen, Norway; <sup>10</sup>Maria Cecilia Hospital, GVM Care&Research, Cotignola, Italy; <sup>11</sup>CHU de Rouen, Rouen, France; <sup>12</sup>Mayo Clinic Hospital—St. Mary's Campus, Rochester, MN, USA; <sup>13</sup>Heart Rhythm Management Centre, Universitair Ziekenhuis Brussel, Postgraduate program in Cardiac Electrophysiology and Pacing, European Reference Networks Guard-Heart, Vrije Universiteit Brussel, Brussels, Belgium; <sup>14</sup>University Heart Center, Hamburg, Asklepios Klinik St. Georg, Hamburg, Germany; <sup>15</sup>Medtronic, Core Clinical Solutions, Study and Scientific Solutions, Rome, Italy; and <sup>16</sup>Medtronic, Meerbusch, Germany

Received 4 November 2020; editorial decision 21 January 2021; accepted after revision 25 January 2021; online publish-ahead-of-print 17 March 2021

## 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  $\geq 1$  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 (HR = 0.76,  $P = 0.28$ ) or overall incidence [incidence rate ratio (IRR) = 0.79,  $P = 0.28$ ] of SAEs. The incidence rate of symptomatic palpitations was lower in the cryoballoon (7.61 days/year) compared with the AAD arm (18.96 days/year; IRR = 0.40,  $P < 0.001$ ).

## Conclusions

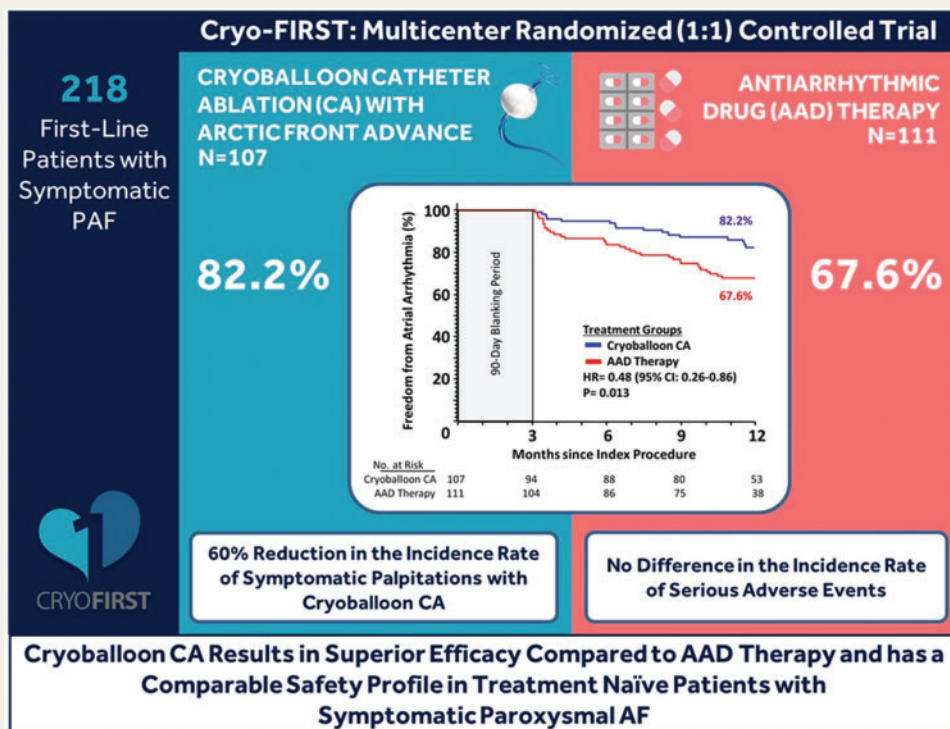
Cryoballoon CA was superior to AAD therapy, significantly reducing AA recurrence in treatment naive patients with PAF. Additionally, cryoballoon CA was associated with lower symptom recurrence and a similar rate of SAEs compared with AAD therapy.

\* Corresponding author. Tel: +49 6032 996 0; fax: +49 6032 996 2236. E-mail address: m.kuniss@kerckhoff-klinik.de

© The Author(s) 2021. Published by Oxford University Press on behalf of the European Society of Cardiology.

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

## Graphical Abstract



## Keywords

Antiarrhythmic drug • Catheter ablation • Atrial fibrillation • Cryoballoon • First-line treatment • Randomized study

## 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.

## Introduction

Treatment guidelines for patients with atrial fibrillation (AF) suggest that patients should be first managed with an antiarrhythmic drug

(AAD).<sup>1</sup> 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).<sup>1</sup> Importantly, early rhythm control with AADs or ablation is associated with a reduction in adverse cardiovascular outcomes.<sup>2</sup> Additionally, a shortened duration from AF diagnosis until CA has been shown to improve long-term rhythm control.<sup>3,4</sup> To date, three randomized studies (RAAFT-1, RAAFT-2, and MANTRA-PAF) have compared radiofrequency current (RFC) CA to AAD therapy in treatment naïve patients with PAF.<sup>5-7</sup> 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.<sup>5-7</sup>

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 PAF<sup>8</sup>; however, cryoballoon CA-treated patients had significantly fewer repeat ablations, direct-current cardioversions, all-cause rehospitalizations, and cardiovascular rehospitalizations during the study period.<sup>9</sup> More recently, two randomized studies conducted in North America evaluated initial rhythm-control therapy with cryoballoon CA vs. AAD treatment and found that first-line treatment with

cryoballoon CA was superior to AAD for preventing atrial arrhythmia (AA) recurrence over 12 months. Moreover, serious procedure-related complications were uncommon.<sup>10,11</sup> 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.<sup>12</sup> 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  $\leq 120$  ms; QTc  $< 440$  ms; PQ  $\leq 210$  ms), structurally normal heart [left ventricular ejection fraction  $\geq 50\%$ , thickness of the inter-ventricular septum  $\leq 12$  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).<sup>12</sup> All patients provided written informed consent prior to participation. After enrolment, 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.<sup>12</sup>

### Cryoballoon catheter ablation

The cryoballoon CA procedure has been previously described in detail.<sup>8,9,12–14</sup> 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  $\beta$ -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.<sup>15</sup> However, amiodarone was discouraged due to its potential extracardiac toxicity. The use of other AADs was not allowed except for  $\beta$ -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).<sup>12</sup> 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

**Table 1** Baseline subject characteristics

	Cryoballoon CA (n = 107)	AAD (n = 111)
Demographics and echocardiographic characteristics		
Age (years)	50.5 (13.1)	54.1 (13.4)
Sex, male	76 (71.0%)	72 (64.9%)
Time from first ECG-documented AF to enrolment (years)	0.7 (1.5)	0.8 (2.1)
Left atrial diameter (short axis) (mm)	37.0 (5.9)	38.0 (4.9)
Left atrial diameter (long axis) (mm)	46.8 (8.2)	47.7 (6.3)
Left ventricular ejection fraction (%)	62.8 (5.4)	63.7 (5.4)
EHRA class		
Class I	0 (0.0%)	0 (0.0%)
Class II	75 (70.1%)	83 (74.8%)
Class III	30 (28.0%)	25 (22.5%)
Class IV	2 (1.9%)	1 (0.9%)
Medical history		
Hypertension	33 (30.8%)	40 (36.0%)
Diabetes	1 (0.9%)	4 (3.6%)
Hyperlipidaemia	23 (21.5%)	25 (22.5%)
Myocardial infarction	2 (1.9%)	0 (0.0%)
Coronary artery disease	2 (1.9%)	1 (0.9%)
Congestive heart failure	0 (0.0%)	0 (0.0%)
Stroke	0 (0.0%)	0 (0.0%)
Transient ischaemic attack	0 (0.0%)	1 (0.9%)
Valve dysfunction	3 (2.8%)	2 (1.8%)
CHA <sub>2</sub> DS <sub>2</sub> -VASc score		
0	49 (45.8%)	38 (34.2%)
1	33 (30.8%)	40 (36.1%)
2	13 (12.2%)	15 (13.5%)
3	4 (3.7%)	10 (9.0%)
4	3 (2.8%)	2 (1.8%)
Baseline medications		
Anticoagulant	38 (35.5%)	49 (44.1%)
Acetylsalicylic acid	5 (4.7%)	7 (6.3%)
β-Blocker	54 (50.5%)	56 (50.5%)
Calcium channel blocker	9 (8.4%)	15 (13.5%)

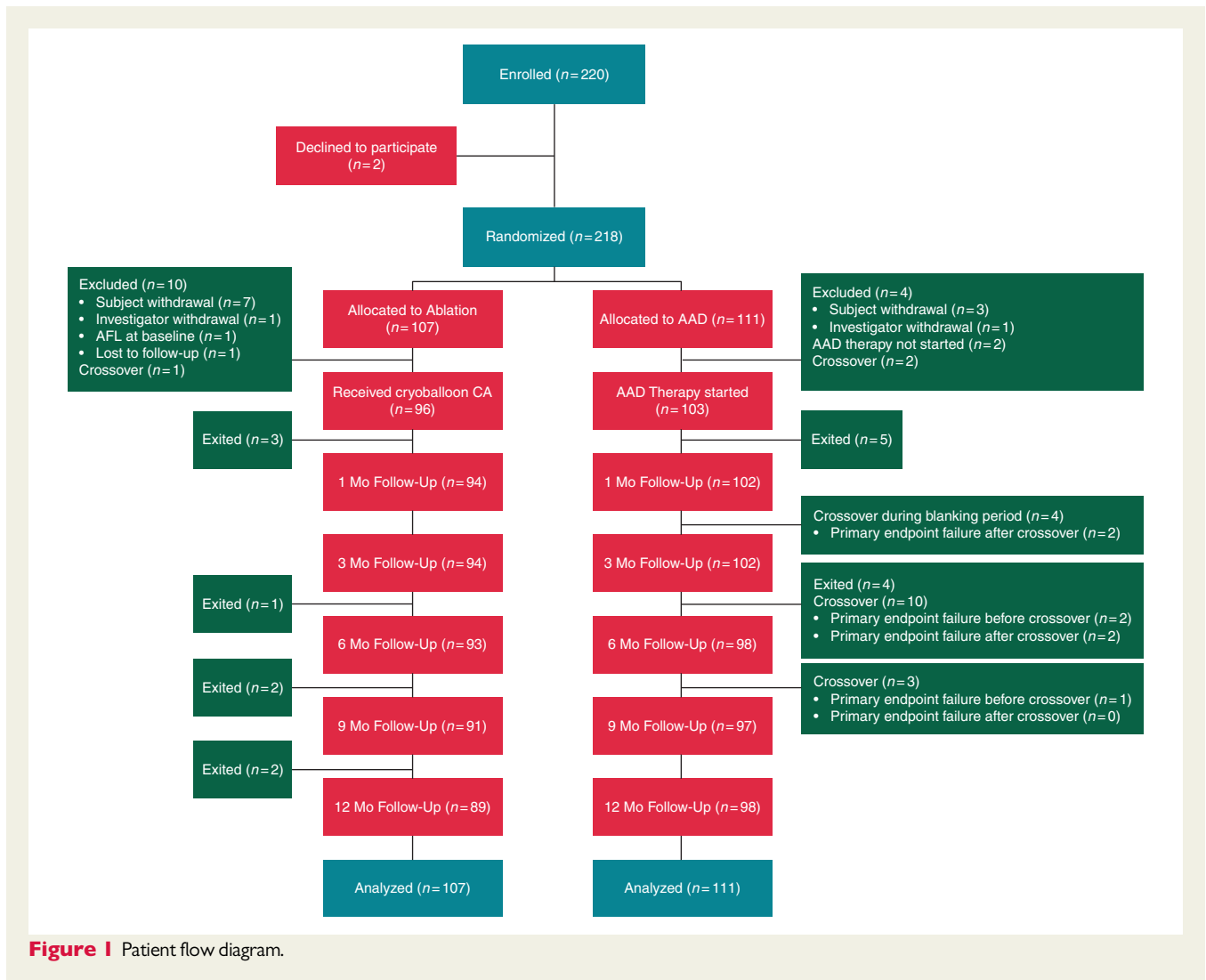
Values are n (%) or mean (standard deviation).

AAD, antiarrhythmic drug; AF, atrial fibrillation; CA, catheter ablation; EHRA, European Heart Rhythm Association score.

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, atrio-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

**Table 2** Antiarrhythmic drug therapy and dosing

Drug	Daily dose (mg)	Therapy start (n = 101) <sup>a</sup>	Month 3 (n = 97) <sup>b</sup>	Month 12 (n = 94) <sup>c</sup>
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%)
	800	0 (0%)	0 (0%)	0 (0%)
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%)
Dronedaron	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 therapy <sup>d</sup>	NA	0 (0%)	6 (6.2%)	22 (23.4%)

Values are n (%).

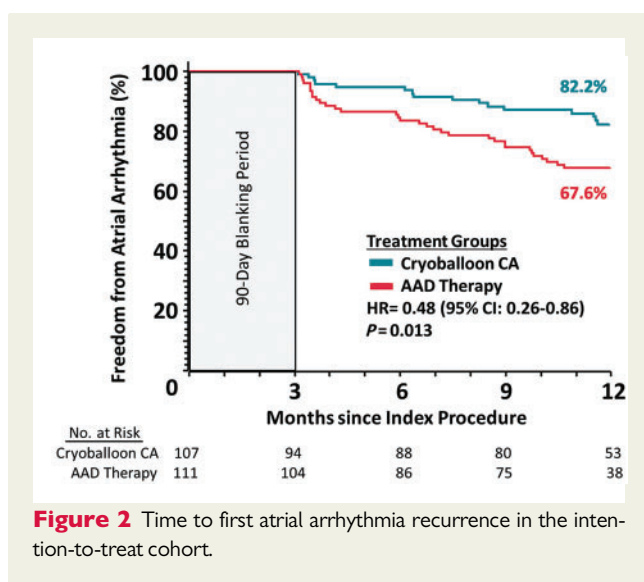
<sup>a</sup>Dosing information was not available for one patient who was treated with flecainide and one patient treated with sotalol at therapy start. These patients are not included in the table.

<sup>b</sup>Patients 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.

<sup>c</sup>Patients 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.

<sup>d</sup>This category includes patients who crossed over to CA.

AAD, antiarrhythmic drug; CA, catheter ablation.



**Figure 2** Time to first atrial arrhythmia recurrence in the intention-to-treat cohort.

superior to AADs for the reduction of AA recurrence and the avoidance of AF disease progression.<sup>16–19</sup> Accordingly, the use of CA has received a Class I recommendation in patients with symptomatic, drug-refractory PAF in current guidelines.<sup>1</sup> 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

**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.

considering cryoballoon CA), and consequently, the usage of CA as a first-line treatment has received a Class IIa recommendation.<sup>1</sup>

Historically, three randomized studies (RAAFT-1, RAAFT-2, and MANTRA-PAF)<sup>5–7</sup> 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.<sup>20</sup> However, these studies were

**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 (26)	11 (9)	2 (1)	56 (37)	4 (4)	1 (1)
Acute coronary syndrome	0	0	0	1 (1)	0	0
Acute kidney injury	0	0	0	1 (1)	0	0
Adverse drug reaction	0	0	0	3 (3)	2 (2)	0
Arteriospasm coronary	1 (1)	1 (1)	0	0	0	0
Atrial arrhythmia recurrence	15 (11)	1 (1)	0	34 (28)	2 (2)	0
AVNRT	1 (1)	0	0	0	0	0
Bronchitis	1 (1)	0	0	0	0	0
Chest pain	1 (1)	0	0	0	0	0
Gastrointestinal pain	1 (1)	0	0	0	0	0
Impaired gastric emptying	1 (1)	1 (1)	0	1 (1)	0	0
Impaired healing	0	0	0	1 (1)	0	0
Lung disorder/infection	4 (1)	1 (1)	0	0	0	0
Non-sustained ventricular tachycardia	0	0	0	1 (1)	0	0
Oedema peripheral	0	0	0	1 (1)	0	0
Orthostatic hypotension	0	0	0	1 (1)	0	0
Palpitations	0	0	0	1 (1)	0	0
Pericardial disorder <sup>a</sup>	3 (3)	3 (3)	1 (1)	0	0	0
Phrenic nerve paralysis	0	0	0	1 (1) <sup>b</sup>	0	1 (1)
Pneumonia	1 (1)	0	0	0	0	0
Procedural failure <sup>c</sup>	1 (1)	1 (1)	0	0	0	0
Pyrexia	1 (1)	1 (1)	0	0	0	0
Syncope	0	0	0	1 (1)	0	0
Transient ischaemic attack	1 (1)	1 (1)	1 (1)	0	0	0
Vascular access site haemorrhage	1 (1)	1 (1)	0	0	0	0
Other	9 (9)	0	0	9 (7)	0	0

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

<sup>a</sup>None of these events resulted in cardiac tamponade.

<sup>b</sup>Transient phrenic nerve palsy was experienced by one subject randomized to AAD who underwent CA.

<sup>c</sup>Failure of the transeptal 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.

limited by a small sample<sup>7</sup> size or a relatively high rate of repeat ablation procedures.<sup>5,6</sup>

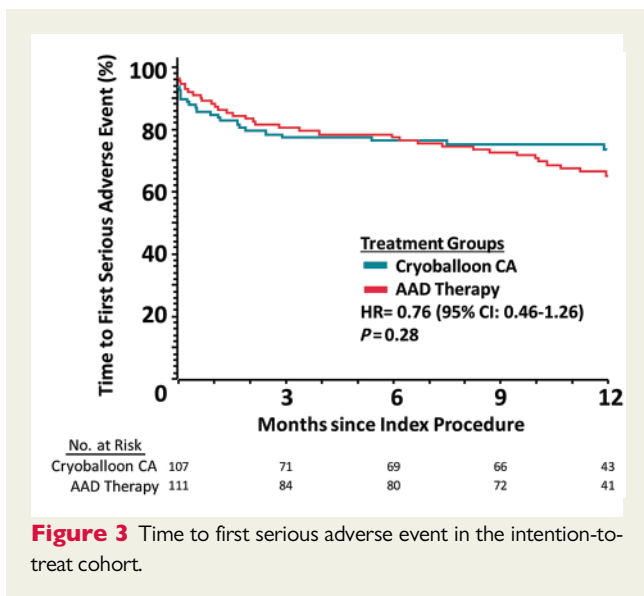
In our study, cryoballoon CA was associated with more than a 50% reduction in AA recurrence over 12 months. Importantly, in the present study, CA was found to be superior to AADs despite cross-over events in 17% of patients randomized to AAD therapy. Overall, eight crossovers from the AAD to CA arm did 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.<sup>13,14,21</sup> More recently, two randomized studies (EARLY-AF<sup>10</sup> and STOP AF First<sup>11</sup>) 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<sup>10</sup> and the USA.<sup>11</sup> 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.<sup>1,17</sup> 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 in





**Figure 3** Time to first serious adverse event in the intention-to-treat cohort.

the present trial. Overall, these findings align with those recently reported in STOP AF First and EARLY-AF; both of these studies observed SAEs in a similar proportion of patients randomized to first-line cryoballoon CA as AAD therapy.<sup>10,11</sup> Moreover, these results support a growing body of literature demonstrating that CA can be safely performed by experienced operators.<sup>16,17,22</sup>

A primary objective of restoring sinus rhythm in patients with recurrent PAF is to reduce symptoms.<sup>1</sup> This is especially true in the present study population, which was relatively young and healthy with a low risk of embolic events. In our investigation, 87% of the patients in the cryoballoon CA arm were without symptoms at 12 months compared with 70% in the AAD arm. Moreover, the incidence of days with patient-reported symptomatic palpitations was lower in the cryoballoon arm, suggesting that CA is superior to AAD therapy for symptom reduction, even in patients who are relatively early in the AF disease process. In congruence, these findings are generally aligned with results from previous randomized first-line studies that have together demonstrated a trend towards a reduction in symptomatic AF recurrence with RFC CA compared with AAD therapy,<sup>20</sup> and a lower rate of symptomatic AA recurrence with cryoballoon CA vs. AAD therapy.<sup>10</sup>

## Limitations

Our trial has some limitations. There were 31 patients (14%) who exited the study early, of which 14 patients (6%) exited before initiating therapy. This could have introduced bias in the randomization. Also, crossovers occurred in 9% of patients, primarily from the AAD to cryoballoon arm. However, this rate is similar or lower than previously reported in ablation trials,<sup>6,17,23</sup> and the per-protocol sensitivity analysis could not show any impact of crossovers on the study results. Moreover, the high rate of crossover further highlights the clinical challenge of long-term AAD therapy. Rather than specifying a specific AAD regimen, drug choice and dosing decisions were left to the discretion of individual investigators according to the 2012 ESC guidelines. While this adds variability, it also allows the AAD arm to reflect contemporary clinical practice. Some patients did receive

doses of AAD drugs that were lower than recommended by the 2012 ESC guidelines, which may reflect intolerance to higher doses. Importantly, some of the lower AAD doses observed (including 100 mg of flecainide and 80 mg of sotalol) are in-line with the AHA/ACC/HRS guidelines for the management of patients with AF.<sup>24,25</sup> Nevertheless, it is possible that undertreatment of the AAD group may have led to a higher rate of AA recurrence, and an overestimation of the benefit of ablation. Routine and symptom-based event recording was not required in this study. Consequently, we were not able to evaluate symptom-rhythm correlation. It is also possible that freedom from AA recurrence was overestimated. However, this was a randomized study and both groups completed the same robust Holter monitoring protocol with similar compliance. As such, it is unlikely that the absence of event recorders biased the group difference in AA recurrence observed. For centres to participate in this study, they were required to perform 100 ablation procedures per year, and to have performed a minimum of 50 cryoballoon ablation procedures before the start of the study. Although the outcomes of cryoballoon CA have been shown to be less dependent on operator experience than RFC ablation,<sup>26</sup> the safety and efficacy results observed in the present study may not be generalizable to less experienced centres. Similarly, the study population was relatively young and healthy, and findings from this study may not be applicable to other populations. Lastly, patients were only followed for 12 months. While additional studies are needed to determine the longer term safety and efficacy of CA as a first-line treatment, frequent crossovers from 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 recurrent 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.

## Acknowledgements

The authors would like to thank the Cryo-FIRST sites and staff for their valuable contributions to this study. Also, the authors thank Prof. Thomas Neumann and Christine Scheld for their contributions to the Holter Core Lab, and Ralf Meyer, Rachele Kaplon, Kelly van Bragt, Laura Manotta, Hae Lim, Federica Fonti, and Alessandra Gentili from Medtronic for support with the study.

## Funding

This work was supported by Medtronic.

**Conflict of interest:** M.K. reports speaker fees from Abbott and Medtronic; proctoring, consultancy, and advisory board services for Medtronic; research grants from Medtronic and Biosense Webster. N.P.

reports speaker's honoraria from Medtronic and Biosense Webster; proctoring fees from Medtronic and Biosense Webster. V.V. reports speaker fees and proctoring honoraria for Medtronic, travel grants from Biotronik, Biosense-Webster, and Medtronic. J.S.H. reports honoraria for inclusion of patients and realization of the study. S.H., C.A., and G.-B.C. report speaker fees for Medtronic, Biotronik, Biosense Webster, and Abbott; teaching honoraria from Medtronic and Biotronik; proctoring honoraria from Medtronic. G.A. reports research support on Holter monitors. N.B. reports consultancy fees from Biosense Webster, Boston Scientific SAS, and Medtronic. C.M. reports consultancy and speaker fees from Biosense Webster and Boston Scientific. J.C. reports a research grant from Medtronic. F.A. reports consultant for and lecture fees from Boston Scientific, Medtronic, and Microport CRM. D.L.P. in the past 12 months has provided consulting services for Abbott \$0, Biosense Webster \$0, Inc., Biotronik <\$5000, Boston Scientific \$0, CardioFocus \$0, Johnson & Johnson \$0, MediaSphere Medical, LLC <\$5000, Medtronic \$0, St. Jude Medical \$0, and Siemens \$0, SigNum Preemptive Healthcare, Inc. \$0, Spectrum Dynamics \$0, and Themedical \$0. He receives research funding from the Abbott, Biosense Webster, Boston Scientific/EPT, Cardiolsight, CardioFocus, Endosense, German Heart Foundation, Hansen Medical, Medtronic, NIH, Robertson Foundation, St. Jude Medical, Siemens, and Themedical. Mayo Clinic and D.L.P. and R. Robb have a financial interest in mapping technology. In accordance with the Bayh-Dole Act, this technology has been licensed to St. Jude Medical, and Mayo Clinic and D.L.P. and Robb have received annual royalties >\$10 000, the federal threshold for significant financial interest. Mayo Clinic and Dr R. Robb have a financial interest in Analyze-AVW technology that may have been used to analyse some of the heart images in this research. In accordance with the Bayh-Dole Act, this technology has been licensed to commercial entities, and both Mayo Clinic and Dr Robb have received royalties >\$10 000, the federal threshold for significant financial interest. In addition, Mayo Clinic holds an equity position in the company to which the AVW technology has been licensed. D.L.P. and Mayo Clinic jointly have equity in a privately held company, External Beam Ablation Medical Devices. Royalties from Wiley & Sons, Oxford, and St. Jude Medical. S.V. reports Speakers bureau/study funding from Abbott and Boston Scientific; speakers bureau from Boehringer Ingelheim, Bristol Myers Squibb, Bayer Vital, and Daiichi -Sankyo. F.D.P. and D.B. are employed by and stockholders of Medtronic. S.I. and H.-F.P. reports no conflict of interest.

## Data availability

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

## References

- Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomstrom-Lundqvist C et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2021;**42**:373–498.
- Kirchhof P, Camm AJ, Goette A, Brandes A, Eckardt L, Elvan A et al. Early rhythm-control therapy in patients with atrial fibrillation. *N Engl J Med* 2020;**383**: 1305–16.
- Bunch TJ, May HT, Bair TL, Johnson DL, Weiss JP, Crandall BG et al. Increasing time between first diagnosis of atrial fibrillation and catheter ablation adversely affects long-term outcomes. *Heart Rhythm* 2013;**10**:1257–62.
- Lunati M, Arena G, Iacopino S, Verlato R, Tondo C, Curnis A et al. Is the time between first diagnosis of paroxysmal atrial fibrillation and cryoballoon ablation a predictor of efficacy? *J Cardiovasc Med* 2018;**19**:446–52.
- 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.
- 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.
- 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.
- Kuck KH, Brugada J, Furnkranz A, Metzner A, Ouyang F, Chun KR et al. Cryoballoon or radiofrequency ablation for paroxysmal atrial fibrillation. *N Engl J Med* 2016;**374**:2235–45.
- Kuck KH, Furnkranz A, Chun KR, Metzner A, Ouyang F, Schluter M et al. Cryoballoon or radiofrequency ablation for symptomatic paroxysmal atrial fibrillation: reintervention, rehospitalization, and quality-of-life outcomes in the FIRE AND ICE trial. *Eur Heart J* 2016;**37**:2858–65.
- Andrade JG, Wells GA, Deyell MW, Bennett M, Essebag V, Champagne J et al. Cryoablation or drug therapy for initial treatment of atrial fibrillation. *N Engl J Med* 2020;
- Wazni OM, Dandamudi G, Sood N, Hoyt R, Tyler J, Durrani S et al. Cryoballoon ablation as initial therapy for atrial fibrillation. *N Engl J Med* 2020;
- Hermida JS, Chen J, Meyer C, Iacopino S, Arena G, Pavlovic N et al. Cryoballoon catheter ablation versus antiarrhythmic drugs as a first-line therapy for patients with paroxysmal atrial fibrillation: rationale and design of the international Cryo-FIRST study. *Am Heart J* 2019;**222**:64–72.
- Akkaya E, Berkowitsch A, Zaltsberg S, Greiss H, Hamm CW, Sperzel J et al. Second-generation cryoballoon ablation as a first-line treatment of symptomatic atrial fibrillation: two-year outcome and predictors of recurrence after a single procedure. *Int J Cardiol* 2018;**259**:76–81.
- Namdar M, Chierchia GB, Westra S, Sorgente A, Meir ML, Bayrak F et al. Isolating the pulmonary veins as first-line therapy in patients with lone paroxysmal atrial fibrillation using the cryoballoon. *Europace* 2012;**14**:197–203.
- Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Europace* 2010; **12**:1360–420.
- Khan AR, Khan S, Sheikh MA, Khuder S, Grubb B, Moukarbel GV. Catheter ablation and antiarrhythmic drug therapy as first- or second-line therapy in the management of atrial fibrillation: systematic review and meta-analysis. *Circ Arrhythm Electrophysiol* 2014;**7**:853–60.
- Packer DL, Mark DB, Robb RA, Monahan KH, Bahnon TD, Poole JE, for the CABANA Investigators et al. Effect of catheter ablation vs antiarrhythmic drug therapy on mortality, stroke, bleeding, and cardiac arrest among patients with atrial fibrillation: the CABANA randomized clinical trial. *JAMA* 2019;**321**: 1261–74.
- Wilber DJ, Pappone C, Neuzil P, De Paola A, Marchlinski F, Natale A et al. Comparison of antiarrhythmic drug therapy and radiofrequency catheter ablation in patients with paroxysmal atrial fibrillation: a randomized controlled trial. *JAMA* 2010;**303**:333–40.
- Kuck KH, Lebedev DS, Mikhaylov EN, Romanov A, Geller L, Kalesj O et al. Catheter ablation or medical therapy to delay progression of atrial fibrillation: the randomized controlled atrial fibrillation progression trial (ATTEST). *Europace* 2020;
- Hakalahti A, Biancari F, Nielsen JC, Raatikainen MJ. Radiofrequency ablation vs. antiarrhythmic drug therapy as first line treatment of symptomatic atrial fibrillation: systematic review and meta-analysis. *Europace* 2015;**17**:370–8.
- Straube F, Dorwarth U, Ammar-Busch S, Peter T, Noelker G, Massa T et al. First-line catheter ablation of paroxysmal atrial fibrillation: outcome of radiofrequency vs. cryoballoon pulmonary vein isolation. *Europace* 2016;**18**:368–75.
- Muthalaly RG, John RM, Schaeffer B, Tanigawa S, Nakamura T, Kapur S et al. Temporal trends in safety and complication rates of catheter ablation for atrial fibrillation. *J Cardiovasc Electrophysiol* 2018;**29**:854–60.
- Packer DL, Kowal RC, Wheelan KR, Irwin JM, Champagne J, Guerra PG et al. Cryoballoon ablation of pulmonary veins for paroxysmal atrial fibrillation: first results of the North American Arctic Front (STOP AF) pivotal trial. *J Am Coll Cardiol* 2013;**61**:1713–23.
- January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC, Jr. et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. *Circulation* 2014;**130**:2071–104.
- January CT, Wann LS, Calkins H, Field ME, Chen LY, Furie KL et al. 2019 AHA/ACC/HRS Focused Update of the 2014 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 Clinical Practice Guidelines and the Heart Rhythm Society. *Heart Rhythm* 2019;**16**: e66–e93.
- Providencia R, Defaye P, Lambiasi PD, Pavin D, Cebron JP, Halimi F et al. Results from a multicentre comparison of cryoballoon vs. radiofrequency ablation for paroxysmal atrial fibrillation: is cryoablation more reproducible? *Europace* 2017; **19**:48–57.