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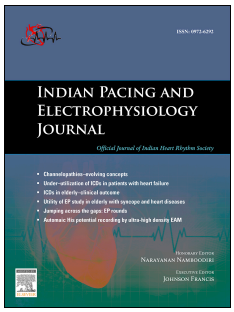

Cryoballoon Ablation for the Treatment of Atrial Fibrillation in Kazakhstan: One Year Outcome From the Cryo Global Registry

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PII: S0972-6292(25)00090-7

DOI: https://doi.org/10.1016/j.ipej.2025.06.008

Reference: IPEJ 686

To appear in: *Indian Pacing and Electrophysiology Journal*

Received Date: 11 February 2025

Revised Date: 8 May 2025

Accepted Date: 18 June 2025

Please cite this article as: Abdrakhmanov A, Nuralinov O, Rashbayeva G, Tursunbekov A, Bagibayev S, Bakytzhanuly A, Esilbayev Z, Chinybayeva A, Abdrakhmanova Z, Salustri A, Suleymen Z, Kirkimbayeva R, Cryoballoon Ablation for the Treatment of Atrial Fibrillation in Kazakhstan: One Year Outcome From the Cryo Global Registry, *Indian Pacing and Electrophysiology Journal*, https://doi.org/10.1016/j.ipej.2025.06.008.

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Conflicts of Interest and Source of Funding: Study was sponsored and funded by Medtronic. All authors (or their institutions) received research support from Medtronic to conduct this study. In addition, Ayan Abdrakhmanov received from Company Medtronic salary.

Role of Funding Source*:* The study was sponsored and funded by Medtronic, which contributed to the study design, data collection and analysis. The lead author (Ayan Abdrakhmanov) had full access to all study data and final responsibility for the decision to submit for publication. The authors were not paid to write this article by the sponsor or any other agency.

Word Count: 2828.

Acknowledgements: Biostatistical analysis was provided by Matt Johnson of Medtronic (XXX, United States). Medical writing support was provided by Ilaria Pietta of Medtronic (Milan, Italy) in accordance with Good Publication Practice guidelines.

Disclosures: The authors declare that they have no competing interests (financial, professional, or personal) relevant to this manuscript. We have read and understood the journal policy on the declaration of interests and have no interests to declare.

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Abstract

Introduction: Atrial fibrillation (AF) is a prevalent and potentially serious cardiac rhythm disorder. Cryoballoon ablation using the Arctic Front catheter offers a modern treatment approach. This subanalysis evaluates the safety, efficacy, and impact on quality of life for patients undergoing t this procedure in Kazakhstan. The Cryo AF Global Registry (NCT02752737) is an ongoing prospective, multi-center observational post-market registry collecting global data on CBA procedures conducted with the Arctic Front™ Family of Cardiac Cryoablation Catheters.

Methods: The study included patients aged 18 and older with paroxysmal, persistent, and long-standing persistent AF. Key safety endpoints included serious adverse events related to the device or procedure. Efficacy was measured by the absence of AF, atrial flutter (AFL), and/or atrial tachycardia (AT) after a 90-day period of discontinuing antiarrhythmic medications.

Results: No injuries to the phrenic nerve or serious complications were reported. Three serious adverse events occurred, but these were not related to the procedure. At 12 months, the Kaplan-Meier analysis showed a 92.9% rate of freedom from AF or other atrial arrhythmias after the 90-day blanking period. Two repeat ablations (2.9%) were needed for AF.

Conclusion: This analysis supports the conclusion that cryoballoon ablation is both safe and effective for treating AF in Kazakhstan, resulting in significant improvements in patients' quality of life.

Registration Number: NCT02752737

Key Words: Cryoballoon Ablation, Kazakhstan, Cryo Registry, Arctic Front

Abbreviations:

AF - atrial fibrillation

PAF - paroxysmal atrial fibrillation

PsAF - persistent atrial fibrillation

AADs - antiarrhythmic drugs

CA - catheter ablation

RFA - radiofrequency ablation

CBA - cryoballon ablation

QoL - quality of life

AFL - atrial flutter

CTI - additional cavotricuspid isthmus

AT - Atrial tachycardia

NYHA - New York Heart Association

CI - confidence intervals

CMAP - Compound Motor Action Potential.

EQ-5D-3L- EQ-5D three-level version

ICE - Intracardiac echocardiography

Introduction

Atrial fibrillation (AF) is a common cardiac arrhythmia characterized by ineffective atrial contraction due to uncoordinated electrical activation; it represents a leading cause of cardiovascular morbidity [1].

When symptomatic (in both the paroxysmal AF (PAF) and persistent AF (PsAF) forms) and refractory to antiarrhythmic drugs (AADs), AF is usually treated by catheter ablation (CA) for pulmonary vein isolation (PVI), which has shown to be effective in alleviating symptoms and preventing recurrency [1].

PVI can either be achieved by radiofrequency ablation (RFA) or cryoballon ablation (CBA). The latter is an ablation technique for PVI performed with the Arctic Front Advance catheter (Medtronic, Minneapolis); compared to RFA, this technique has shown to be associated with a lower risk of AF recurrence and lower procedural time, being a single shot procedure [2].

Safety and efficacy of the CBA procedure have been extensively demonstrated globally in previous trials on patients with either RFA or PsAF who are refractory to AADs [3, 4], prior to AAD failure [3] or as a first-line treatment [5].

In Kazakhstan, where AF has a prevalence/incidence of that is reflective of global trends in cardiovascular diseases, the incidence rate has not been widely documented, CBA has been adopted since 2015. However, the published evidence is limited [1].

The Cryo AF Global Registry is an ongoing study designed to assess the safety and clinical performance of Arctic Front™ Family of Cardiac Cryoablation Catheters (Medtronic, USA) in a broad patient population treated according to local real-world practice [3, 6].

This sub-analysis of the Cryo AF Global Registry aims to assess the safety and efficacy of CBA and the post-intervention quality of life (QoL) in patients with symptomatic AF treated according to standards of care in Kazakhstan.

Methods

Study design

The Cryo AF Global Registry (NCT02752737) is an ongoing prospective, multi-center observational post-market registry collecting global data on CBA procedures conducted with the Arctic Front™ Family of Cardiac Cryoablation Catheters. The study is being conducted in accordance with the Declaration of Helsinki, and a global steering committee is responsible for overseeing data quality and analyses.

At a local level in Kazakhstan, the study was conducted in compliance with all local regulatory requirements. The protocol was approved by the institutional review board of the participating site, and all enrolled subjects provided written informed consent.

This sub-analysis aimed to assess safety, efficacy and patient-reported QoL for CBA procedures conducted according to the local standard of care in Kazakhstan.

Patient population

Participants aged ≥ 18 years having a planned CBA procedure with an Arctic Front™ catheter were eligible for inclusion into the Cryo AF Global Registry. There were no exclusion criteria based on pre-existing characteristics or medical conditions.

This sub-analysis is based on a study cohort of subjects presenting with either PAF (AF episodes terminating spontaneously or within 7 days of onset), PsAF (AF episodes presenting continuously beyond 7 days and ≤12 months) and long-standing PsAF (continuous AF episodes since more than 12 months) and mostly with previous AAD failure.

All subjects were enrolled at the National Research Cardiac Surgery Center in Astana between November 2018 and September 2021. None of the subjects had previous CBA experience. Detailed demographic and baseline characteristics, including age, sex, body mass index, AF type and duration, comorbidities (hypertension, diabetes, coronary artery disease, prior stroke/TIA), left atrial diameter, left ventricular ejection fraction, baseline medication use (antiarrhythmics and anticoagulants), and geographic region of enrollment, are provided in Supplementary Table S1 (Demographics and Baseline Characteristics Summary).

Cryoballoon ablation procedure

Per the Cryo AF Global Registry protocol, all CBA procedures were conducted as extensively described previously [3, 4, 7, 8] and according to the local standard of care.

Access to the left atrium (LA) was achieved with a transseptal puncture. Then, a dedicated 15-F outer diameter steerable sheath (FlexCath or FlexCath Advance Steerable Sheath; Medtronic, Inc) was used to introduce a 28 mm cryoballoon ablation catheter (Arctic Front; Arctic Front Advance; Arctic Front Advance – ST; Arctic Front Advance Pro; Medtronic, Inc) into the LA. Both the catheter and the sheath were subsequently guided to the target pulmonary vein (PV) using either a J-tip guidewire or a dedicated inner-lumen octopolar/decapolar circular mapping catheter (Achieve or Achieve Advance, Medtronic, Inc).

The cryoapplication was then initiated, with the physicians determining number and duration of cryoapplications per PV. Typically, cryoapplications were halted upon detection of a decrease in diaphragmatic response. Our methodology involved a minimum of three or more applications to each vein from different angles. Following the ablation, PVI was confirmed according to the method chosen by the physician. We used the Achieve® mapping catheter (integrated with the cryoballoon) to monitor pulmonary vein potentials during ablation. Complete disappearance of intracardiac potentials on the Achieve catheter was required to declare acute isolation of each vein. After initial isolation was attained, we delivered at least 1-2 additional cryothermal applications per vein, adjusting the balloon position to different angulations for each freeze.

Per protocol, sites were recommended to monitor phrenic nerve function during right-sided PVI using pacing and one adjunctive method for diaphragmatic function monitoring.

Intraprocedural esophageal temperature monitoring, procedural imaging, ablation tools and adjunctive ablations were operator determined and documented. Also, post ablation testing, periprocedural anticoagulation, and post-procedure AAD initiation or continuation was left to the discretion of the operators.

Participants were discharged based on local standard-of-care policies.

Patient Follow up

Participants were followed up for 12 months according to local standard practice. A standard of care visit was planned within about 6 months post-procedure, and an in-person or telephone visit at 12 months follow-up was required per Cryo AF Global Registry protocol. Arrhythmia recurrence was monitored by any of the following methods: electrocardiogram, Holter monitor, trans-telephonic monitor, insertable cardiac monitor, pacemaker, and/or implantable cardioverter defibrillator.

During the follow-up visit, additional information collected included cardiovascular medications and adverse events. QoL was assessed by the EQ-5D three-level version (EQ-5D-3L) questionnaire [9], which was distributed to participants at baseline and at 12 months follow up.

Objectives and endpoints

The primary efficacy objective was freedom from AF, atrial flutter (AFL) and/or, atrial tachycardia (AT) following a 90-day blanking period. Such period is meant to allow healing of the cardiac tissue and atrial remodeling after CBA [5]; thus, arrhythmias occurring within this 90-days timeframe were not considered for primary efficacy evaluation.

The related primary efficacy endpoints were i) AF/AFL/AT events following a 90-day blanking period as reported after standard of care visit or in the annual visit case report form; ii) repeat ablation for AF/AFL/AT post 90-day blanking period.

Ancillary efficacy objectives for this sub-analysis were assessment of post-procedure variations in AADs intake, freedom from hospitalization (all causes and cardiovascular-related) and QoL improvements. The related endpoints were, respectively, compared AAD prescription at baseline and at 12 months, all-cause and cardiovascular-related hospitalization events and compared QoL evaluation at baseline and at 12 months.

Primary safety endpoints were all serious device- or procedure-related adverse events. Seriousness of adverse events was defined based on the definition in the ISO 14155 standard. Per

protocol, all adverse events were followed until resolved, unresolved with no further actions or subject exit from the study.

Statistical analysis

All subjects from the Cryo AF Global Registry with data collected at the Kazakhstan site were included in the data analysis. Data were summarized using descriptive statistics, with counts and percentages for categorical variables, and mean, standard deviation, median, quartiles and minimum and maximum for continuous variables. Change from baseline was calculated at 12 months and analyzed using a two-sided T-test to determine if there was evidence of a change (not equal to zero) at a significance level of 0.05. Safety events were both listed and summarized overall and by relationship to procedure and system and seriousness using number of events and number and percentage of subjects. Freedom from AF and from hospitalization endpoints were analyzed using Kaplan-Meier curves and estimates, with log-log transformed 95% confidence intervals (CI). Subjects' dates of event (including AF recurrence, repeat ablation and hospitalization) were at the first instance, if multiple, or were censored at date of study exit (Month 12). Data analyses were performed by Medtronic-employed statisticians. A validated statistical software package (SAS version 9.4) was used to analyze the study results.

Results

Baseline characteristics

The cohort for this Kazakhstan sub-analysis of the Cryo AF Global Registry consisted of 70 adult participants (mean ± standard deviation 59.7 ± 9.9 years old, range 21 – 77 years, 54.3% females).

Subjects had been diagnosed with AF (PAF 64.3%, PsAF 21.4% and long-standing PsAF 14.3%) for a mean of 2.8 ± 3.3 years.

The diameter of the left atrium was on average 39.5 ± 5.1 mm (range 29-52 mm) and the mean left ventricular ejection fraction was 58.5% ± 5.8%.

All participants were receiving AADs at baseline, with a mean of 1.3 ± 0.5 failed AADs prior to CBA, and 1 subject (1.4%) receiving CBA without prior AAD failure.

Heart failure was reported according to the New York Heart Association (NYHA) classification for 64 subjects (31.4% with class I NYHA, 54.3% with class II and 5.7% with class III). Two subjects (2.9%) did not have heart failure reported, while for 4 subjects (5.7%) the NYHA classification was not available.

Sixty-six (94.3%) participants had a mean Congestive Heart Failure or Left Ventricular Dysfunction (CHA2DS2-VASc) score of 2.7 ± 1.2.

History of prior AFL was reported in 5 subjects (8.1%) and history of AT in 3 (4.3%). Five participants (7.1%) had prior atrial flutter ablation and 2 (2.9%) had prior PVI.

Additional baseline information is reported in Table 1.

Procedural characteristics

The 28-mm Arctic Front Advance cryoballoon was used to perform CBA in all the 70 patients.

Mean durations for the overall procedure (time from venous access to last cryocatheter removal), left atrial dwell (time from first cryocatheter insertion to last cryocatheter removal) and fluoroscopy were, respectively, 54.7 ± 12.4, 33.4 ± 9.1 and 10.1 ± 4.5 minutes. In the majority of the cases (80%) the procedure was conducted with the subjects in conscious state; general anesthesia was used in 13 subjects (18.6%), while deep/moderate sedation was used in a single patient (1.4%).

Mapping and navigation throughout the procedures were mainly performed using fluoroscopy (100%) and PV venography (91.4%).

Intracardiac echocardiography (ICE) was also used as a mapping/navigational tool in 31 subjects (44.3%) and in other 16 patients (22.9%) for esophageal monitoring.

The phrenic nerve was monitored in all patients by pacing or palpation, diaphragm stimulation and Compound Motor Action Potential (CMAP).

PV occlusion was mainly determined using fluoroscopy (98.6%), EP pressure monitoring (88.6%) or ICE (45.7%). No drug challenge was conducted to verify PVI.

For 66 patients the investigators reported on effective isolation of the targeted PVs; acute PVI success was reported in 65 cases (98.5%).

Additional cavotricuspid isthmus (CTI) ablation was performed in one subject (1.4%). Left and right atrium AF Trigger ablation were also performed in 61 (87.1%) and 49 (70%) patients respectively. Further details related to the procedural characteristics are presented in Table 2.

Overall, 280 PVs were treated with the 28 mm Arctic Front Advance device, with a total of 314 cryoapplications (4.5 ± 0.8 applications per subject, range 4 – 8 and 1.1 ± 0.3 applications per vein, range 1 – 2). Each cryoapplication lasted on average 234.9 ± 25.3 seconds, with an average coldest temperature of -50.1 ± 6.9 Celsius.

In most of the cases (82.8%) PVI was not verified.

Additional details reporting cryoapplication outcomes for each of the four PVs are reported in Table 3.

Safety

At procedure discharge, no phrenic nerve injuries, vascular complications, pericardial effusion, cardiac tamponade or major bleedings were reported.

Three safety events occurred in the analyzed cohort, as reported in Table 4. All events were classified as serious and not related to either the index procedure or the Arctic Front device. Two patients experienced the first episode of AFL recurrency within the blanking period; in both cases, hospitalization and AAD treatment was needed. Repeat ablation (by RFA) was performed within the blanking period for one patient and afterwards for the second one. Another patient experienced an episode of AF recurrence after the blanking period that required an RFA procedure for repeat RSPV isolation. All adverse events were followed until resolved.

Efficacy

Primary Efficacy Endpoints

At 12 months follow up, the Kaplan-Meier estimate for freedom from AF or other atrial arrhythmias after a 90-days blanking period was 92.9% (95% CI 83.7 - 97.0), as shown in Figure 1.

As mentioned, two (2.9%) repeat ablations for AF following the 90-day blanking period were required.

Ancillary Efficacy Endpoints

AAD prescription data prior to study, at baseline, at procedure discharge and at 12 months post-procedure are presented in Table 5. At the end of the follow up period, a decrease of 67.1% AAD prescription from baseline is observed.

Figure 1 and Figure 2 show the Kaplan-Meier estimate at 12 months follow up for freedom from hospitalization (all cause and cardiovascular related respectively).

Quality of life

QoL evaluation outcomes as reported by the study participants in an EQ-5D three-level version (EQ-5D-3L) questionnaire are presented in Table 6. A score of 1 in the questionnaire represents the higher QoL level and a score of 3 represents the lower. All 70 (100%) participants in the cohort completed the questionnaire at both baseline and 12 months follow up.

When compared to baseline, results at 12 months follow up show statistically significant post-procedure improvements in all QoL areas.

Discussion

Our study provides the first Kazakhstan-specific data on cryoballoon ablation (CBA) outcomes, demonstrating high success rates and low complication rates. These findings align with previous

research, such as the study by Baimbetov et al., which compared the effectiveness and safety of CBA versus radiofrequency ablation (RFA) in patients with persistent atrial fibrillation (AF). Their study concluded that both methods had comparable primary efficacy, with RFA showing a non-significant trend toward superiority in the long-term, and no significant differences in overall safety between the two approaches. Our results contribute to the growing body of evidence supporting the use of the Arctic Front Cardiac Cryoablation System for managing AF in real-world practice.

Summary of main findings

This sub-analysis of the Cryo AF Global Registry involved data collected on 70 adult subjects enrolled for a CBA procedure at the National Research Cardiac Surgery Center in Astana (Kazakhstan).

The CBA procedure in the analyzed cohort of patients with PAF, PsAF or long-standing PsAF was completed safely, with a total adverse events rate of 4.3% and no procedure- or device-related adverse events reported.

Of the 3 serious adverse events reported, two were AFL episodes occurring during the 90-days blanking period, when arrhythmias events typically have higher chances to occur due to the healing process of the cardiac tissue and atrial remodeling after CBA [5]. Per protocol, these events were not considered for primary efficacy analysis. Both AFL episodes led to hospitalization and repeat ablation (in one case performed after the blanking period and thus accounted for primary efficacy evaluation).

One additional subject underwent repeat ablation during the follow up period, due to recurring AF.

Freedom from AF and all atrial arrhythmias was estimated at 92.9% (95% CI: 83.7, 97.0), while freedom from hospitalization (both all causes and cardiovascular-related) was 97.1% (95% CI: 89.1, 99.3) at 12 months follow up. Our results were comparable with those of the global registry, which is supported by the published experience of South Africa, which reports 97.4%

freedom from arrhythmia [11]. Our findings may be attributed to several factors, including meticulous patient selection, standardized procedural protocols, and the extensive experience of our team. Notably, our methodology involved applying a minimum of three applications to each vein from different angles, which was a distinctive feature of our approach.

At one-year follow up, a decrease of 67.1% AAD prescription from baseline and 65.7% from discharge was observed; further, QoL evaluation reported significant improvement ($p \leq 0.01$) at 12 months post-procedure.

Comparison to other Cryo Registry sub-analyses

When compared to recent global [3] and local [10, 11] sub-analyses of the Cryo AF Global Registry data, similarities and differences can be highlighted. Mean subjects age in these cohorts was highly aligned (59.7 ± 9.9 years in the Kazakhstan study, 61 ± 12 in the global analysis [3], 60 ± 11 and 60 ± 12 in the Korean [10] and South-African [11] sub-analyses respectively).

While all participants in the Kazakhstan cohort were taking AADs at baseline (despite previous AAD failures), the comparative studies included subjects who had suspended AADs due to prior failures and "first-line" patients (non-drug refractory and not taking AADs at baseline).

Interestingly, this sub-analysis shows reduced overall procedure time (54.7 ± 12.4 minutes vs 82 ± 34 [3], 76 ± 21 [10] and 82 ± 27 minutes [11] respectively) and reduced number of cryoapplications per vein time (1.1 ± 0.3 vs 1.5 ± 0.9 [3], 1.5 ± 1.0 [10] and 1.6 ± 0.7 [11]) when compared to the cited reference studies.

This may be explained by the consistent use of conscious sedation (80% participants in the Kazakhstan cohort), which has been reported to lead to shorter procedure times [3, 12], by the reduced use of adjunctive equipment or PVI testing methods, and by the longer duration of each cryoapplication in the Kazakhstan cohort (234.9 ± 25.3 seconds vs 185 ± 53 [3], 167 ± 54 [10] and 223 ± 56 seconds [11] respectively).

None of the procedure- or device-related serious adverse events reported in the reference literature (supraventricular arrhythmia recurrences [3], events related to the puncture site for catheter access [3, 10, 11], phrenic nerve injuries [3, 11], cardiac tamponade or pericardial effusion, stroke or transient ischemic attacks, deaths [3]) occurred in this study.

Comment on freedom from AF & all atrial arrhythmias

There was an important reduction in AAD prescription at 12 months as compared to discharge (-65.7%) in the Kazakhstan cohort, higher than what reported in other sub-analyses of the Cryo AF Global Registry (- 26% in the global analysis [3] and -37.6% in the Korean subanalysis [10]).

The Kazakhstan freedom from hospitalization rates (all cause: 97.1%, (95% CI 89.1, 99.3); cardiovascular-related: 97.1% (95% CI 89.1, 99.3)) was aligned with the South-African sub-analysis (all cause and cardiovascular-related: 97.5%, (95% CI 83.5, 99.6) in PAF subjects and 100% in PsAF subjects) [11] and higher than in the Korean sub-analysis (all cause: 88.7% (95% CI 84.5, 91.8%); cardiovascular-related: 89.7% (95% CI 84.6, 92.7%) in all subjects) [10].

QoL improvements at 12 months reported in the Kazakhstan cohort were aligned to those reported in similar sub-analyses ($p \leq 0.1$ in the global study [3], $p \leq 0.001$in both the Korean [10] and South-African [11] analyses). Specifically, for example, persistent forms of atrial fibrillation became the focus of targeted investigation in evaluating the efficacy and safety of low-dose amiodarone in patients with persistent atrial fibrillation following catheter ablation

Limitations

This sub-analysis has some limitations. First of all, the observational non-randomized study design and the limited number of participants enrolled in a single center do not allow generalization of the results. However, as discussed above, the CBA efficacy data appear in alignment with those reported in other recent local sub-analyses of the Cryo AF Global Registry, with shorter average procedure time.

- Due to the limited dimension of the cohort, an efficacy comparison in PAF and PsAF subjects was not performed.
- We did not use implantable cardiac monitors (ICMs), which may have led to missed asymptomatic episodes of AF.

Conclusions

This Kazakhstan sub-analysis of the Cryo AF Global Registry data confirms that CBA in patients with PAF, PsAF and long-standing PsAF presenting AAD failure is performed safely and effectively according to the local standard of care with few adjunctive tools.

The high rates of freedom from recurrence of arrhythmia episodes reflect in significant improvement in the QoL evaluation assessed at 12 months post-procedure as compared to baseline evaluation.

This study provides the first data on cryoablation outcomes in Kazakhstan with high success rates and low complication rates in real-world practice.

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Table 1 - Demographics and Baseline Characteristics

Subject Characteristics	Kazakhstan cohort, total subjects with an Index Procedure (N=70, unless noted otherwise)
Age (years)	59.7 ± 9.9
Female Sex	32 (45.7%)
Body Mass Index (kg/m^2)	29.5 ± 3.6
Diagnosed with AF (years)	2.8 ± 3.3 [N = 68]
Type of AF	
Long-standing persistent	10 (14.3%)
Paroxysmal	45 (64.3%)
Persistent	15 (21.4%)
Left Atrial Diameter (mm)	39.5 ± 5.1 [N = 69]
Left Ventricular Ejection Fraction (%)	58.5 ± 5.8 [N = 69]
Systolic Blood Pressure (mmHg)	126.3 ± 12.4
Diastolic Blood Pressure (mmHg)	80.5 ± 6.5
Number of Previously Failed AADs	1.3 ± 0.5
0	1 (1.4%)
1	49 (70%)
2	20 (28.6%)
Subjects taking AADs at baseline	70 (100%)
Baseline NYHA	
Class I	22 (31.4%)
Class II	38 (54.3%)
Class III	4 (5.7%)
NYHA classification not available	4 (5.7%)
No heart failure	2 (2.9%)
CHA2DS2-VASc (Score)	2.7 ± 1.2
CHA2DS2-VASc (Category)	
Not reported	4 (5.7%)
0	1 (1.5%)
1	10 (15.2%)
2	15 (22.7%)
3	23 (34.8%)
4	13 (19.7%)
5	4 (6.1%)
Hypertension	53 (75.7%)
Prior Myocardial Infarction	3 (4.3%)

Subject Characteristics	Kazakhstan cohort, total subjects with an Index Procedure (N=70, unless noted otherwise)
Diabetes	5 (7.1%)
History of Thromboembolism	1 (1.4%)
Prior Stroke	2 (2.9%)
Prior Transient Ischemic Attack	0 (0%)
History of Atrial Tachycardia	3 (4.3%)
History of Atrial Flutter	5 (8.1%) [N = 62]
Pulmonary Value Stenosis	0 (0%)
History of Vascular Diseases	6 (8.6%)
History of Coronary Artery Disease	11 (15.7%)
Sleep Apnea	0 (0%)
Prior Atrial Flutter Ablation	5 (7.1%)
Prior PVI	2 (2.9%)
Prior Cardiac Device	2 (3.3%) [N = 61]

All values are presented as number (%) or mean ± standard deviation.
AF: atrial fibrillation; AADs: antiarrhythmic drugs; NYHA: New York Heart Association; CHA2DS2-VASc: Congestive heart failure or left ventricular dysfunction; PVI: Pulmonary Vein Isolation

Table 2 - Procedural Characteristics

Procedural characteristics	Kazakhstan cohort, total subjects with an Index Procedure (N=70)
Total Laboratory Occupancy Time (min)	95.8 ± 24.2
Total Procedure Time (min)	54.7 ± 12.4
Total Fluoroscopy Time (min)	10.1 ± 4.5
Total Cryo Fluoroscopy Time (min)	6.3 ± 2.9
Left Atrial Dwell Time (min)	33.4 ± 9.1
Fluoroscopy Dose (mSv)	29.7 ± 33.4
Total Contrast Used (cc)	61.4 ± 22.4
Sedation Method	
Conscious	56 (80%)
General	13 (18.6%)
Deep/Moderate	1 (1.4%)
Mapping/Navigational Tool	
Fluoroscopy	70 (100%)
Pulmonary Vein Venography	64 (91.4%)

ICE	31 (44.3%)
Rotational Angiography	7 (10%)
CT	3 (4.3%)
Esophageal Monitoring	
Not Done	53 (75.7%)
Temperature Probe	1 (1.4%)
ICE	16 (22.9%)
Phrenic Nerve Monitoring	70 (100%)
Pacing / Palpation	70 (100%)
Diaphragm Stimulation	69 (98.6%)
CMAP	70 (100%)
Other	0 (0%)
Method for Determining PV Occlusion	
Fluoroscopy	69 (98.6%)
EP Pressure Monitoring	62 (88.6%)
ICE	32 (45.7%)
All Targeted PVs Isolated (Investigator)	
Not reported	4 (5.7%)
Yes	65 (98.5%)
No	1 (1.5%)
Drug Challenge to Verify Vein Isolation	0 (0%)
Non-PVI ablations	
Cavotricuspid Isthmus (CTI)	1 (1.4%)
Left Atrial AF Trigger	61 (87.1%)
Right Atrial AF Trigger	49 (70%)
AVNRT	0 (0%)
Superior Vena Cava Vein Trigger	0 (0%)
Inferior Vena Cava Vein Trigger	0 (0%)
Mitral Valve Isthmus or Line	0 (0%)
Left Sided Roofline	0 (0%)
Left Sided Posterior Wall Isolation	0 (0%)
Left Atrial Appendage	0 (0%)
Complex Fractionate Atrial Electrograms (CFAE)	0 (0%)
Rotor	0 (0%)

CardioInsight Detection	0 (0%)
Other	0 (0%)

All values are presented as number (%) or mean ± standard deviation.
ICE: intracardiac echocardiography; CMAP: Compound Motor Action Potential; PVs: pulmonary veins; PVI: Pulmonary Vein Isolation; AF: atrial fibrillation; AVNRT: Atrio-Ventricular Nodal Reentrant Tachycardia.

Table 3 - Cryoapplications

Cryoapplications								
Applications per Subject (mean ± SD)	4.5 ± 0.8							
	Number of Pulmonary Veins Treated (N)	**Applications per Vein (mean ± SD)**	**Number of Applications (N)**	**Application Duration (s), (mean ± SD)**	**Coldest Temperature (Celsius), (mean ± SD)**	**Time to Isolation (s)*, (mean ± SD)**	**PV Isolation Outcome**	
Overall	280	1.1 +/- 0.3	314	234.9 +/- 25.3	-50.1 +/- 6.9	68.1 +/- 36.1	Yes	49 (15.6%)
							Not verified	260 (82.8%)
							No	5 (1.6%)
Left Superior PV	70	1.1 +/- 0.3	79	238.2 +/- 13.4	-50.1 +/- 7.1	67.5 +/- 35.3	Yes	13 (16.5%)
							Not verified	64 (81%)
							No	2 (2.5%)
Left Inferior PV	70	1.2 +/- 0.4	83	232.5 +/- 30.6	-47.7 +/- 6.8	69.9 +/- 31.9	Yes	14 (16.9%)
							Not verified	68 (81.9%)
							No	1 (1.2%)
Right Superior PV	70	1.1 +/- 0.3	75	235.4 +/- 23.3	-52 +/- 6	60.4 +/- 26.1	Yes	10 (13.3%)

							Not verified	64 (85.3%)
							No	1 (1.3%)
Right Inferior PV	70	1.1 +/- 0.3	77	233.4 +/- 29.9	-50.9 +/- 6.9	73 +/- 49.6	Yes	12 (15.6%)
							Not verified	64 (83.1%)
							No	1 (1.3%)

* Time to isolation has only been reported when PV Isolation Outcome = "Yes"

Table 4 - Adverse Events in the Kazakhstan Cohort

	Number of Events (Number, % Subjects) in the Kazakhstan cohort (N=70)	
Adverse Event Classifications	**All Adverse Events**	**Serious Adverse Events**
Total Adverse Events	3 (3, 4.3%)	3 (3, 4.3%)
Relationship to Index Procedure		
Number of events during or after index procedure before any repeat ablation	3 (3, 4.3%)	3 (3, 4.3%)
Not related	3 (3, 4.3%)	3 (3, 4.3%)
Related	0 (0, 0%)	0 (0, 0%)
Number of events during or after any repeat ablation	0 (0, 0%)	0 (0, 0%)
Relationship to System		
Not related	3 (3, 4.3%)	3 (3, 4.3%)
Related	0 (0, 0%)	0 (0, 0%)

Table 5 - Antiarrhythmic Drug Prescription

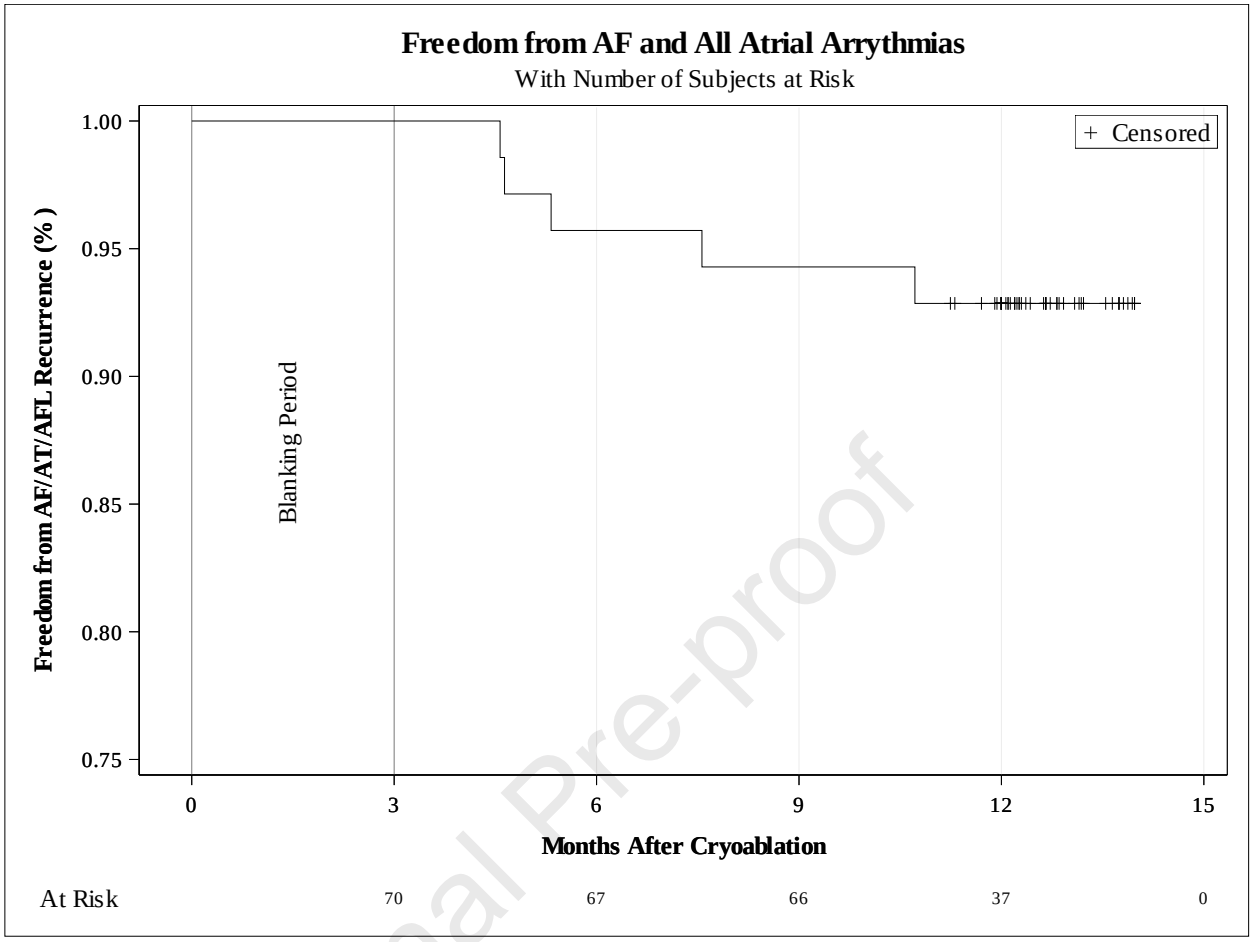
Subjects Taking Class I or III AAD	
Timepoint	**Kazakhstan cohort, total subjects with an Index Procedure (N=70)**
Prior to Study	
No	1 (1.4%)
Yes	69 (98.6%)

Subjects Taking Class I or III AAD	
Timepoint	**Kazakhstan cohort, total subjects with an Index Procedure (N=70)**
Baseline	
No	0 (0%)
Yes	70 (100%)
Procedure Discharge	
No	1 (1.4%)
Yes	69 (98.6%)
Month 12	
No	47 (67.1%)
Yes	23 (32.9%)

Table 6 - Quality of Life Analysis, as measured by the EQ-5D-3L questionnaire

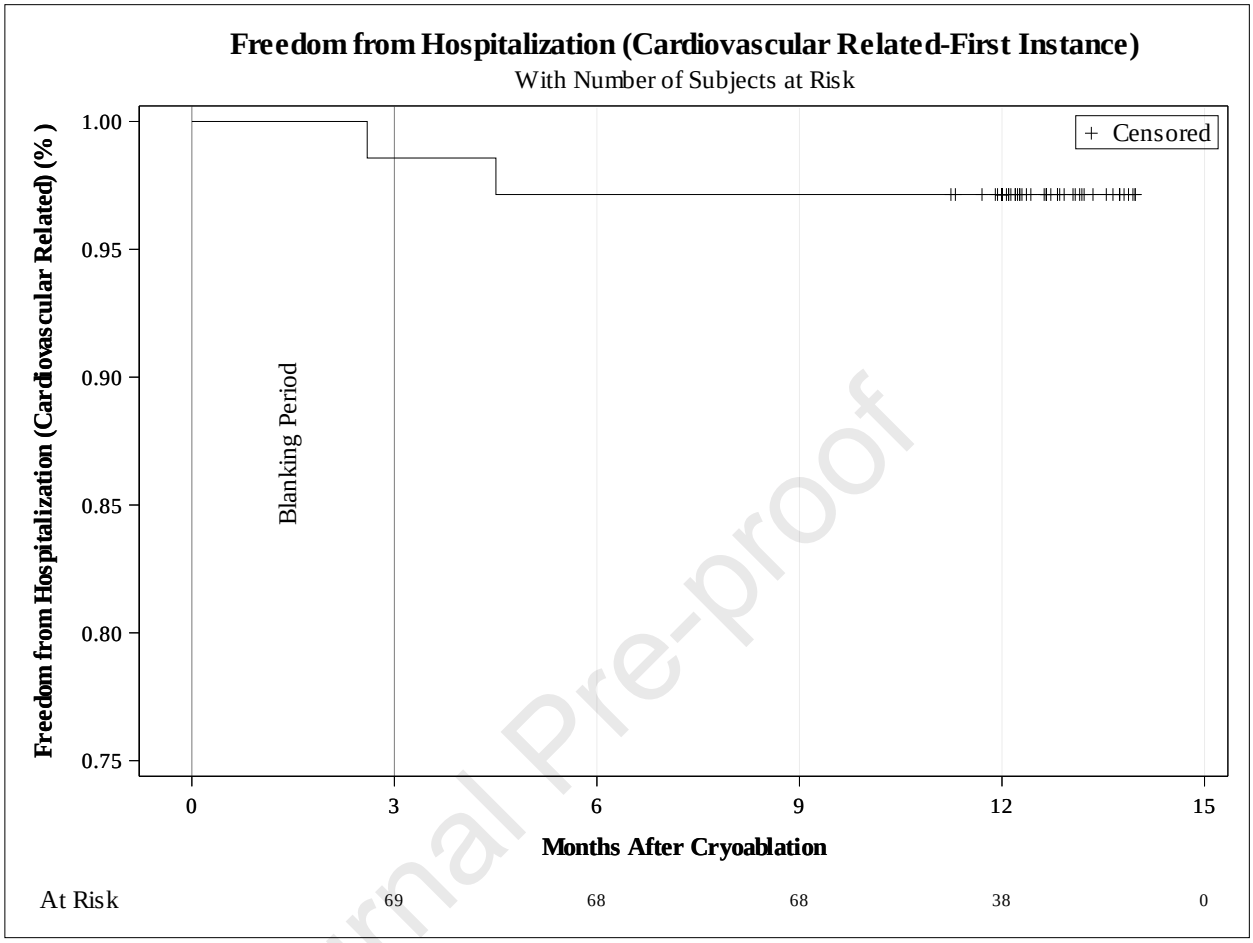
			Change from Baseline	
Question	**Baseline**	**Month 12**	**Change**	**P-Value (T-test)**
Mobility	1.5 +/- 0.5	1.1 +/- 0.2	-0.4 +/- 0.5	<0.01
Self-Care	1.2 +/- 0.4	1 +/- 0.2	-0.1 +/- 0.4	<0.01
Usual Activities	1.4 +/- 0.5	1.1 +/- 0.3	-0.3 +/- 0.6	<0.01
Pain/Discomfort	1.6 +/- 0.5	1.1 +/- 0.3	-0.5 +/- 0.6	<0.01
Anxiety/Depression	1.6 +/- 0.5	1.3 +/- 0.5	-0.2 +/- 0.7	0.01
Visual Analogue Score: Your Own Health State Today	78.5 +/- 12.8	93.4 +/- 5.5	14.9 +/- 14.4	<0.01
EQ-5D-3L Score	0.9 +/- 0.1	1 +/- 0	0.1 +/- 0.1	<0.01

Figure 1 - Primary Efficacy Analysis - Freedom from AF & All Atrial Arrhythmias (Kaplan-Meier estimate)



Endpoint	Kazakhstan cohort, total subjects with an Index Procedure (N=70)
Freedom from AF and All Atrial Arrhythmias after 90-days blanking period	
No	5 (7.1%)
Yes	65 (92.9%)
Kaplan-Meier Estimate (95% CI)	92.9% (83.7, 97.0)

Figure 2 - Efficacy Analysis - Freedom from Hospitalization - Cardiovascular Related (First Instance) (Kaplan-Meier estimate)



First Cardiovascular Hospitalization	
Endpoint	**Kazakhstan cohort, total subjects with an Index Procedure (N=70)**
Freedom from Hospitalization	
No	2 (2.9%)
Yes	68 (97.1%)
Kaplan-Meier Estimate (95% CI)	97.1% (89.1, 99.3)

Declaration of interests

☐ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☒ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Ayan reports financial support was provided by Medtronic. Omirbek reports financial support was provided by Medtronic. Azat reports financial support was provided by Medtronic. Serik reports financial support was provided by Medtronic. Abay reports financial support was provided by Medtronic. Zhandos reports financial support was provided by Medtronic. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.