DESIGN PAPER

A randomized controlled trial of the size-adjustable cryoballoon vs conventional cryoballoon for paroxysmal atrial fibrillation: The CONTRAST-CRYO II trial rationale and design

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BACKGROUND Pulmonary vein isolation (PVI) with cryoballoon technology is a well-established therapy for treatment of atrial fibrillation (AF). Recently, a size-adjustable cryoballoon (POLARx™ FIT) that enables delivery in a standard 28-mm or an expanded 31-mm size was introduced.

OBJECTIVE The purpose of this study was to perform a randomized clinical trial to evaluate the safety and efficacy of this novel cryoballoon compared to the conventional cryoballoon.

METHODS The CONTRAST-CRYO II trial is a multicenter, prospective, open-label, randomized controlled trial in which 214 patients with paroxysmal AF will be randomized 1:1 to cryoballoon ablation with either a conventional cryoballoon (Arctic Front Advance™ Pro) or a size-adjustable cryoballoon (POLARx FIT). The study was approved by the Institutional Review Boards at all investigational sites and has been registered in the UMIN Clinical Trials Registry (UMIN000052500).

RESULTS The primary endpoint of this study will be the incidence of phrenic nerve injury. Secondary endpoints include procedural success, chronic success through 12 months, procedure-related adverse events, biophysiological parameters during applications for each pulmonary vein (PV), total procedural and fluoroscopy times, level of PVI and isolation area, and probability of non-PV foci initiating AF.

CONCLUSION The CONTRAST-CRYO II trial is a multicenter, prospective, randomized controlled trial designed to assess the safety and efficacy of the POLARx FIT vs the Arctic Front Advance Pro. The findings from this trial will provide additional utility data on the efficacy of the size-adjustable cryoballoon for isolating PVs in patients with paroxysmal AF.

KEYWORDS Atrial fibrillation; Catheter ablation; Complication; Cryoballoon; Phrenic nerve injury

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Introduction

Pulmonary vein isolation (PVI) with cryoballoon technology is a safe and effective therapy for patients with atrial fibrillation (AF).[1] For more than a decade, the Arctic Front Advance Pro™ (AFA-Pro; Medtronic, Minneapolis, MN) has been the only available cryoballoon, so our understanding of cryoballoon technology is based predominantly on this system. Although the system underwent an evolutional modification, complete pulmonary vein (PV) occlusion still can be challenging in some patients

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KEY FINDINGS

- A novel POLARx FIT cryoballoon is more pliable and allows for expansion from a 28-mm size to 31-mm size, whereas a conventional Arctic Front cryoballoon has a fixed 28-mm size.
- The increased balloon size facilitates wide pulmonary vein antral lesion creation, and there is potential for reduced risk of phrenic nerve injury by avoiding a deep cannulation.
- Data from studies in which the performance of the POLARx FIT is prospectively evaluated and compared with the Arctic Front cryoballoon are limited, and to date no randomized clinical trials have compared the safety and efficacy of the POLARx FIT against the Arctic Front.
- The CONTRAST-CRYO II trial is a multicenter, prospective, open-label, randomized controlled trial to evaluate the novel cryoballoon compared with the conventional cryoballoon for pulmonary vein isolation in patients with paroxysmal atrial fibrillation.

because of anatomic variations (eg, early branching and a sharp axis configuration of the right inferior pulmonary vein [PV] or an oval shape of the PV ostium).[2] To overcome this issue, a novel compliant cryoballoon (POLARx™ FIT, Boston Scientific, Marlborough, MA) with its compatible sheath (POLARSHEATH™), which can achieve a greater deflection angle, has been introduced. Several observational studies have reported the comparative safety and effectiveness of this alternative to the conventional cryoballoon with variations in the biophysiological parameters between the 2 cryoballoon systems.[3–6] To elucidate the characteristics of the compliant cryoballoon, we previously proposed the protocol of a randomized controlled trial comparing the 2 technologies—CONTRAST-CRYO (Characteristics of Two Different Cryoballoon Systems for Treatment of Paroxysmal Atrial Fibrillation II)—and completed patient enrollment.[7]

One of the limitations of the 2 systems is the limited choice of balloon size. The AFA-Pro has 2 available sizes (23 and 28 mm), whereas the POLARx only has a fixed 28-mm size that is not adjustable during the procedure. Recently, a size-adjustable cryoballoon (POLARx FIT, Boston Scientific), which enables delivery in a standard 28-mm or an expanded 31-mm size without exchanging the catheter, has been developed. The increased size of the balloon not only facilitates better contact with PVs that have wide ostia but also enhances a larger isolation area. Furthermore, the risk of phrenic nerve injury (PNI) potentially is reduced by avoiding deep cannulation; however, no randomized studies have evaluated the safety and feasibility of the size-adjustable cryoballoon compared to the conventional cryoballoon.

Methods

Trial design

The CONTRAST-CRYO II trial is a multicenter, prospective, open-label, randomized controlled trial in which 214 patients with paroxysmal AF (PAF) will be randomized 1:1 to cryoballoon ablation with either a conventional AFA-Pro (28 mm, 8-mm tip) or a size-adjustable POLARx FIT (28 and 31 mm, 5-mm tip) using a permuted block randomization (Figure 1). Randomization will be stratified by the institution, and the outcome of the randomization will not be blinded to the operators, patients, or attending physicians. This study will be performed under ethical principles consistent with the Declaration of Helsinki. The CONTRAST-CRYO II trial has been registered in the UMIN (University hospital Medical Information Network) Clinical Trials Registry (Identification Number: UMIN000052500). Institutional Review Board approval was obtained at all investigational sites. Recruitment began in December 2023 and is expected to be completed by the end of December 2024. Informed written consent will be obtained from all trial participants before enrollment and randomization. No funding was used to support this work.

Study population

Study subjects will be eligible for entry into this trial if they are 20 years of age or older and have documented PAF within 12 months before randomization. The exclusion criteria prohibit persistent (lasting >7 days) or secondary AF, before catheter ablation of AF or cardiac surgery, pre-existing phrenic nerve palsy, history of a stroke or transient ischemic attack within the past 6 months, intracardiac thrombi, pregnancy, severe valvular disease, and a distinct contraindication for anticoagulation. All patients will be followed for at least 12 months.

Ablation procedure

All participants will receive therapeutic anticoagulation at least 3 weeks before the procedure according to the 2023 American Heart Association/American College of Cardiology/Heart Rhythm Society and 2021 Japanese Circulation Society/Japanese Heart Rhythm Society guidelines for nonpharmacotherapy of cardiac arrhythmia.[8,9] Transesophageal echocardiography and/or contrast computed tomography will be performed to exclude any intracardiac thrombi and evaluate PV anatomy before the procedure. Oral anticoagulation will be continued or minimally interrupted during the periprocedural period. All patients without contraindications will be maintained on anticoagulation therapy for at least 2 months after the index procedure.

The details of the anesthesia method will be left to the discretion of each facility. Esophageal monitoring via a thermocouple probe will be performed throughout the procedure. Activated clotting times will be maintained at a minimum of 300 seconds using intravenous heparin bolus or continuous infusion. After each PV isolated, entrance block will be

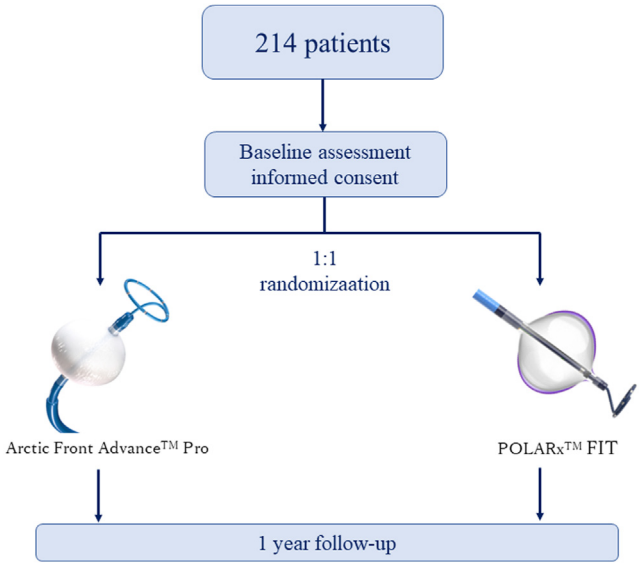

Figure 1 Study flow diagram.

confirmed after a 20-minute waiting period. Postablation 3=dimensional voltage maps will be obtained using any approved mapping system to evaluate the level of the PVI lines and area of the isolation. Non-PV arrhythmia foci will be identified by an isoproterenol infusion and/or electrical cardioversion. Additional procedures (cavotricuspid isthmus ablation, superior vena cava isolation, non-PV trigger ablation, or treatment-emergent left atrial flutter/atrial tachycardia ablation) will be performed at the discretion of the operators.

Size-adjustable cryoballoon

Two inflation modes are available in a size-adjustable cryoballoon during the procedure (28-mm or 31-mm mode). The bigger balloon size can be achieved by increasing the intraballoon pressure (2.5 to 7.5 PSIG). Regardless of the size difference, the minimum temperature on the balloon surface during freezing is similar for the 2 inflation modes. In addition to the size adjustability, the POLARx FIT has several properties different from the AFA-Pro (Table 1). It has a shorter tip and uses an insulated circular mapping catheter to improve the PV potential detection during freezing to provide a better time to isolation (TTI) identification. In addition, the POLARx FIT system has a novel diaphragmatic movement sensor (DMS^{TM}), which utilizes an accelerometer placed on the right costal cartilage for continuous monitoring of phrenic nerve activation.

Cryoballoon ablation protocol

The cryoballoon ablation procedure was detailed previously.[7] After a transseptal puncture, a steerable sheath (Flexcath Advance, Medtronic; or POLARSHEATH, Boston Scientific) was inserted into the left atrium. A spiral mapping catheter (Achieve, Medtronic; or POLARMAP^{TM}, Boston Scientific) was used as a guidewire and for mapping. In the size-adjustable balloon cohort, the 31-mm mode will be the first choice for each PV. The 28-mm mode can be used if a complete occlusion is difficult or PVI is not achieved with a bigger balloon size. After optimal occlusion of the PVs is confirm, freezing will be initiated and continued according to the protocol same as the CONTRAST-CRYO trial (Figure 2). A bonus freezing beyond the protocol is not recommended.[10,11]

Table 1 Characteristics of the two cryoballoon study systems

	Study catheter	
	Arctic Front Advance Pro	POLARx FIT
Balloon size (mm)	28	31
Change in balloon size during freezing	Slight enlargement	Stable
Sheath size (F)	15.0	15.9
Sheath deflection	135° at maximum	155° at maximum
Sheath character	Stiff	Soft and tapered
Freezing effect	Beyond the equator	Up to the equator
Distal tip length (mm)	8	5

The phrenic nerve will be continuously monitored by diaphragmatic electromyography along with tactile feedback of the diaphragmatic contraction during right-sided cryoballoon applications. The freezing will be double-stopped if a reduction in either diaphragmatic computed motor action potential (CMAP) or DMS reaches >30% or >40%, respectively. In addition, cryoballoon ablation will be aborted when the esophageal temperature drops to <15°C, or if the nadir balloon temperature of the AFA-Pro and POLARx falls to <−60°C and −70 °C, respectively. Biophysiological parameters including the application number required for PVI, total application number, freezing duration, TTI, rate of cooling (temperature at 30 seconds and 60 seconds) and its nadir temperature, time to reach −40°C, minimum esophageal temperature, and presence of touch-up ablation will be collected during the procedure.

Study endpoints

The primary endpoint of this study will be the incidence of PNI. Symptomatic PNI is defined as a proven PNI with dyspnea. Secondary endpoints include procedural success, chronic success through 12 months, freedom from redo procedures, freedom from electrical cardioversion, procedure-related adverse events, biophysiological parameters during applications for each PV, total procedural and fluoroscopy times, impact of the operators' experience on procedural and clinical outcomes, level of the PVI and area of the isolation, probability of non-PV foci initiating AF, ablation details for non-PV foci, rate of using the 31-mm mode in each vein, and PVI durability during redo procedures. Procedural success is defined as the demonstration of entrance block into each PV without touch-up ablation. Chronic success is defined as freedom from any recurrent atrial arrhythmia

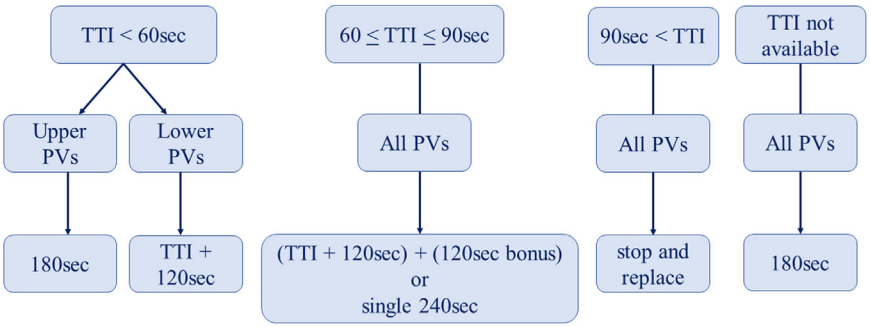

Figure 2 Cryoablation dosing protocol. Cryoballoon ablation will be initiated and continued according to the following protocol with both cryoballoon ablation systems after optimal occlusion of the pulmonary veins (PVs) is confirmed. (1) If the time to isolation (TTI) is <60 seconds, 180 seconds of freezing for the upper PVs and the TTI plus 120 seconds of freezing for the lower PVs will be applied. (2) If the TTI is between 60 and 90 seconds, either the TTI plus 120 seconds of freezing followed by a bonus 120 seconds if freezing or a single 240 seconds of freezing will be applied. (3) If the isolation is not achieved within 90 seconds, freezing will be abandoned, and different application methods to achieve an optimal occlusion will be attempted. (4) If the TTI is not detectable by the mapping catheter, freezing for 180 seconds will be applied.

lasting >30 seconds without antiarrhythmic drugs after a 90-day blanking period. Procedure-related adverse events are defined as any complications that occur within 30 days of the procedure. These events include death, stroke, transient ischemic attack, cardiac tamponade, major bleeding, vascular access complication, hemopneumothorax, gastroesophageal motility disorder, pericarditis, pleuritis, hospitalization for heart failure, and air embolism. In addition, atrioesophageal fistulas and PV stenosis are considered procedure-related adverse events at any timepoint during the 12-month follow-up.

Follow-up

A proton pump inhibitor is mandated until 1 month after the procedure. Patients will be followed after the procedure with in-office visits at 1, 3, 6, 9, and 12 months (Table 2). At each visit, medical history, arrhythmic symptoms, physical examination, and 12-lead electrocardiogram will be obtained by electrophysiologists. A 24-hour to 7-day Holter electrocardiogram also will be performed between 3 and 6 months and 12 months after the procedure. To enhance monitoring accuracy, patients will be encouraged to use a commercially available hemomanometer or photoplethysmography (Apple Watch, Apple Inc., Cupertino, CA), or to check palpitations by themselves. Additional monitoring such as patient-activated event recorders for 1 month (HCG 801, Omron, Kyoto, Kyoto) and/or 7- to 14-day autotriggered event recorders (SpiderFlash, ELA Medical, Minneapolis, MN) will be used to enhance monitoring if necessary. All patients with PNI will be scheduled for chest radiography at each in-office visit until complete recovery of the PNI. Computed tomographic or magnetic resonance imaging will be considered 1 year after the procedure to evaluate the incidence of PV narrowing. Antiarrhythmic drugs may be used within the blanking period at the operator's discretion. Per protocol, the drugs will be discontinued before the end of the blanking period.

Sample size calculation

Calculation of sample size is based on statistical consideration for the primary outcome. Previous studies reported that the incidence of PNI, including transient PNI, is approximately 10% with a conventional cryoballoon catheter.[12–14] However, with a larger-size balloon, the risk of PNI will be significantly reduced by avoiding deep cannulation. Therefore, we assumed the incidence of PNI would be 10% for the AFA-Pro and 1% for the POLARx FIT. Accordingly, a sample size of 107 patients per group is required for 1:1 randomization to provide 80% power and significance level of .05 (2-sided).

Table 2 Follow-up protocol

	Baseline	Procedure	Predischarge	Month 1	Month 3	Month 6	Month 12
Informed consent	X						
Baseline assessment	X						
AF symptom assessment	X			X	X	X	X
Clinical examination	X			X	X	X	X
Twelve-lead ECG	X			X	X	X	X
Holter 24 h to 7 d					X		X
Chest radiography	X		X				
Adverse event	X	X	X	X	X	X	X
Cardiac CT/MRI	X						X

AF = atrial fibrillation; CT = computed tomography; ECG = electrocardiography; MRI = magnetic resonance imaging.

Statistical analysis

Continuous variables are given as mean ± SD or median [interquartile range]. Categorical variables are given as count (percentage). Continuous variables will be compared between groups using the Student t test or Mann-Whitney U test, and categorical variables by χ^2 analysis or Fisher exact test, as appropriate. The primary endpoint will be evaluated with the Fisher exact test. Survival curves for arrhythmia recurrence will be expressed Kaplan-Meier analysis, and comparison of the time to recurrence rate after the ablation procedure between the 2 groups will be performed with a log-rank test. Multivariate Cox regression analysis will be performed to assess the risk factors of arrhythmia recurrence. $P < .05$ will be considered significant.

Discussion

This multicenter, prospective, randomized controlled trial will evaluate a novel size-adjustable cryoballoon (POLARx FIT) compared with a conventional cryoballoon (Arctic Front Advance Pro) for PVI in patients with PAF. Since the introduction of the cryoballoon system, innumerable AF patients have been treated by cryoballoon ablation, and numerous publications have demonstrated its efficacy and safety. However, the data regarding the procedural workflow, cryoablation metrics, intraprocedural targets, and outcomes are predominantly based on the AFA-Pro cryoballoon system. The POLARx FIT is a novel, size-adjustable cryoballoon that enables further expansion from 28 to 31 mm by increasing intraballoon pressure. In addition to adjustability of the balloon size, the POLARx FIT inherits several unique features from the POLARx cryoballoon system, including a freezing system, deflectable sheath, mapping catheter, console, and balloon platform. Although positive initial outcomes with this cryoballoon catheter have been reported, no randomized clinical trials have compared the safety and efficacy of the size-adjustable cryoballoon against the conventional cryoballoon.[15,16]

PNI

Although cryoballoon ablation is a well-established therapy for patients with PAF, procedure-related complications continue to occur. Of these complications, PNI is the most common with cryoballoon ablation, even after establishment of monitoring of diaphragmatic CMAP and double-stop techniques. Although most PNI resolves within 12 months and is asymptomatic even if it occurs, the latest registry data demonstrated that 2.4%–3.0% of PNI persists for >12 months, and 8.3%–16.4% are symptomatic.[17,18] Furthermore, insufficient freezing time due to PNI is related to a high rate of PV reconnections in the chronic phase.[19,20]

Deep cryoballoon cannulation has been reported to be associated with PNI because the right phrenic nerve most frequently runs anterolateral to the distal right PVs, and tissue thickness in the distal PV is thinner than that of the left atrium.[21,22] Therefore , a proximal-seal technique is widely implemented to avoid a deep position of the balloon.[23] The POLARx FIT with the 31-mm mode combined with the proximal-seal technique potentially reduces the risk of PNI by avoiding a deep cannulation. In addition, the POLARx FIT system is equipped with a DMS, which utilizes an accelerometer placed on the right costal cartilage for continuous monitoring of phrenic nerve activation. In conjunction with monitoring the diaphragmatic CMAP and standard tactile feedback of the diaphragmatic contraction, the DMS will allow early detection of PNI.

PV stenosis

Because radiofrequency ablation (RFA) inside the PVs results in a high incidence of PV stenosis, circumferential antral ablation is widely performed for PVI ablation.[24] Besides the circumferential ablation, cryothermal energy itself is considered to confer a lower risk of PV stenosis compared to radiofrequency energy, as it induces distinct inflammatory reactions and healing processes in the tissue.[25,26] However, significant numbers of PV stenosis still have been reported after cryoballoon ablation.[27] Although the incidence of severe PV stenosis seems to be low, it is potentially underestimated because most patients with moderate-to-severe PV stenosis remain asymptomatic, and limited patients undergo systematic evaluation of the PV stenosis with imaging modalities. At this point, prevention of PV stenosis is crucial. Although the mechanism of PV stenosis after cryoballoon ablation is unclear, deep cannulation or noncoaxial placement of the balloon might play a role. The CONTRAST-CRYO II trial will provide the difference in the incidence of PV stenosis using a sequential imaging evaluation and its severity between the size-adjustable cryoballoon and the conventional cryoballoon.

Area of PVI lesion

The CONTRAST-CRYO II trial will also provide critical data regarding the level of PVI and area of the isolation. Although cryoballoon ablation provides a simpler procedural workflow and shorter procedural compared to RFA, the level of PVI is dependent on PV anatomy and the left atrium, and the isolation area is smaller than that of RFA.[28] A larger isolation area is thought to result in a lower AF recurrence; however, a narrow corridor on the posterior wall potentially becomes a substrate of macroreentrant atrial tachycardias.[29,30] A 31-mm balloon theoretically creates a larger area of isolation than does a 28-mm balloon, but no comparative studies have been conducted to clarify the difference in the level of the PVI and area of the isolation between the 2 sizes of cryoballoons. A previous study demonstrated that non-PV foci were situated at the left superior PV antrum just outside the cryoballoon isolated area.[28] To compare the prevalence of non-PV foci between the 2 different cryoballoon systems, AF induction will be performed with infusion of isoproterenol and cardioversion of spontaneous and/or induced AF after PVI to elicit any non-PV foci.[31]

Biophysiological parameters

Previous studies have reported several differences in biophysiological parameters between the POLARx and AFA-Pro, including the nadir temperature during cryoballoon ablation, TTI, and temperature drop speed.[3–6] However, the data on biophysiological parameters with the POLARx FIT system are scarce. In this trial, each cryoablation parameter, including the number of freezes required for PVI, total number of freezes, freezing duration, TTI, balloon temperature at 30 and 60 seconds and its nadir, time to reach −40°C, minimum esophageal temperature, and presence of touch-up ablation will be collected during the procedure. The data will provide valuable insights to improve the procedural workflow and outcomes with the POLARx FIT.

Conclusion

The CONTRAST-CRYO II trial is a multicenter, prospective, randomized controlled trial designed to assess the safety and efficacy of the POLARx FIT compared to AFA-Pro. The findings from this trial will provide additional utility data on the efficacy of the size-adjustable cryoballoon for isolating PVs in patients with PAF.

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Authorship: All authors attest they meet the current ICMJE criteria for authorship.

Patient Consent: Informed written consent will be obtained from all trial participants before enrollment and randomization

Ethics Statement: Institutional Review Board approval was obtained at all investigational sites. This study will be performed under ethical principles consistent with the Declaration of Helsinki.

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