Effect of a bigger cryoballoon on the total antral lesion size: Evaluation of POLARx FIT

BETTER-FIT

CLINICAL INVESTIGATION PLAN

This protocol contains confidential information for use by the Investigator and their designated representatives participating in this clinical investigation. The protocol should be held confidential and maintained in a secure location.

PROTOCOL TITLE 'Effect of a bigger cryoballoon on the total antral lesion size: evaluation of POLARx FIT'

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	**General Assessment and Registration form (ABR form), the application form that is required for submission to the accredited Ethics Committee; in Dutch: Algemeen Beoordelings- en Registratieformulier (ABR-formulier)**
ADE	**Adverse Device Effect**
AE	**Adverse Event**
AF	**Atrial Fibrillation**
CB	**Cryoballoon**
CCMO	**Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek**
DD	**Device Deficiency**
DMS	**Diaphragmatic Movement Sensor**
eCRF	**Electronic Case Report Form**
GDPR	**General Data Protection Regulation; in Dutch: Algemene Verordening Gegevensbescherming (AVG)**
IB	**Investigator's Brochure**
IC	**Informed Consent**
ICE	**Intracardiac Echocardiography**
IFU	**Instructions For Use**
METC	**Medical research ethics committee (MREC); in Dutch: medisch-ethische toetsingscommissie (METC)**
LA	**Left Atrium**
LAPW	**Left Atrial Posterior Wall**
PV	**Pulmonary Vein**
PVI	**Pulmonary Vein Isolation**
SADE	**Serious Adverse Device Effect**
SAE	**Serious Adverse Event**
Sponsor	**The sponsor is the party that commissions the organization or performance of the research, for example a pharmaceutical company, academic hospital, scientific organization, or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor but referred to as a subsidizing party.**
TTE	**Transthoracic Echocardiogram**

TTI	**Time-to-Isolation**
UAVG	**Dutch Act on Implementation of the General Data Protection Regulation; in Dutch: Uitvoeringswet AVG**
UHDx	**Ultrahigh-Density**
USADE	**Unanticipated Serious Adverse Device Effect**
WMO	**Medical Research Involving Human Subjects Act; in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**

SUMMARY

Effect of a bigger cryoballoon on the total antral lesion size: evaluation of POLARx FIT - BETTER-FIT

Rationale: The next generation POLARx™ cryoablation balloon (CB) catheter will have the option of to deliver cryotherapy with the current balloon size of 28 mm or a new, larger 31 mm size by changing the inner balloon pressure (POLARx™ FIT, Boston Scientific). Currently, there is no data on the extension of left atrial (LA) lesion formation with the 31 mm balloon size of the POLARx™ FIT cryoablation balloon catheter. The hypothesis is that a larger CB size results in a wide antral circumferential lesion.

Objective: The primary objective is to evaluate the antral lesion size using ultrahigh-density (UHDx) mapping pre- and post-cryoablation with the 31 mm balloon size CB. Secondary objectives are the proportion of pulmonary veins (PVs) where a 31 mm CB could be positioned to achieve a grade 4 occlusion and the single shot success rate with the 31 mm balloon size CB.

Study design: Single-center, single-arm, prospective study with pre- and post-PVI UHDx mapping.

Study population: Twenty adult patients with paroxysmal AF who are scheduled to undergo pulmonary vein isolation (PVI) with a CB.

Intervention: Patients will undergo pre- and post-ablation UHDx mapping (Orion™ catheter and Rhythmia™ 3D-mapping system, Boston Scientific) during the index procedure.

Main study parameters/endpoints: The primary endpoint is the extent of the antral lesion size. Secondary endpoints are the proportion of PVs with grade 4 occlusion with the 31 mm balloon size CB, the single shot success rate of the 31 mm balloon size CB, difference in proportion of achieving grade 4 occlusion in comparison to the standard (28 mm) size.

Nature and extent of the burden and risks associated with participation, benefit, and group relatedness: A UHDx mapping will be acquired before and after complete PVI. The procedures will be performed under deep sedation, which is standard practice for CB procedures in our institution. The risk of additional mapping is limited. LA mapping is a standard diagnostic method for patients undergoing PVI with radiofrequency ("standard-of-care"). In the current study, UHDx mapping will now be used in patients undergoing PVI with CB. The most important complication of additional intracardiac mapping is cardiac tamponade, but this risk is low (<0.5%).

1. INTRODUCTION AND RATIONALE

Pulmonary vein isolation (PVI) is the cornerstone of interventional treatment of symptomatic atrial fibrillation (AF). Among the different available single-shot devices, the cryoballoon has demonstrated to be as effective and safe as radiofrequency ablation for achieving PVI, while being associated with shorter procedure duration and longer fluoroscopy time.[1-6] Furthermore, cryoballoon ablation seems to be less operator-dependent than radiofrequency ablation.[7]

Mid 2020 a novel cryoballoon (CB) was introduced for the treatment of paroxysmal AF: the 28 mm POLARx™ catheter (Boston Scientific, Marlborough, MA, USA). The initial clinical results with POLARx™ have shown a similar acute procedural efficacy and safety profile as the fourth-generation 28 mm Artic Front Advance Pro™ (AFA-Pro) CB catheter (Medtronic, MN, USA).[8-17] In contrast to AFA-Pro, the POLARx™ CB operates with a constant inner balloon pressure allowing it to maintain a constant size throughout inflation and ablation. The procedure time, ablation time and fluoroscopy time are similar between POLARx™ and AFA-Pro.[8] One-year freedom from atrial arrhythmias was 77% with POLARx™ which is also comparable with AFA-Pro.[18]

The next generation POLARx™ CB (POLARx™ FIT) will allow each ablation to be performed with either the standard balloon size (28 mm) or an alternative larger size (31 mm). The POLARx™ FIT catheter will expand to the standard balloon size upon every inflation. After each inflation and prior to initiating ablation, the user can increase the balloon size using the console user interface. The larger size is enabled by increasing the inner balloon pressure from 2.5 psi to 7.5 psi (which is still lower than the balloon pressure during ablation with AFA-PRO). Currently, there is limited data on the extension of left atrial (LA) scar formation with the 31 mm balloon size of the POLARx™ FIT CB. Previous quantitative data have shown that the second-generation 28 mm AFA CB creates antral lesions.[19] Preliminary data demonstrated that a 31 mm balloon size will result in an antral shift in balloon position.[20] A wide antral lesion may potentially be beneficial for targeting ganglionic plexi and rotational activity near pulmonary vein (PV) ostia thereby potentially increasing long-term arrhythmia survival.[21] However, there is a lack of clinical data on the use of the larger balloon size, and the benefits and limitations of the larger balloon size on occluding different pulmonary veins. The primary aim of the present study is to evaluate the antral lesion size when performing a cryoablation with the 31 mm balloon size of the POLARx™ FIT CB catheter. The secondary aim is to evaluate the feasibility of achieving a grade 4 occlusion with this larger balloon size and the single shot success.

2. OBJECTIVES

The primary objective is to determine the antral lesion area after PVI with a 31 mm balloon size POLARx™ FIT cryoballoon.

The secondary objectives are to determine the proportion of achieving a grade 4 occlusion, the single shot success rate per PV with the 31 mm balloon size POLARx™ FIT CB and the difference in occlusion quality in comparison to the 28 mm balloon size.

3. STUDY DESIGN

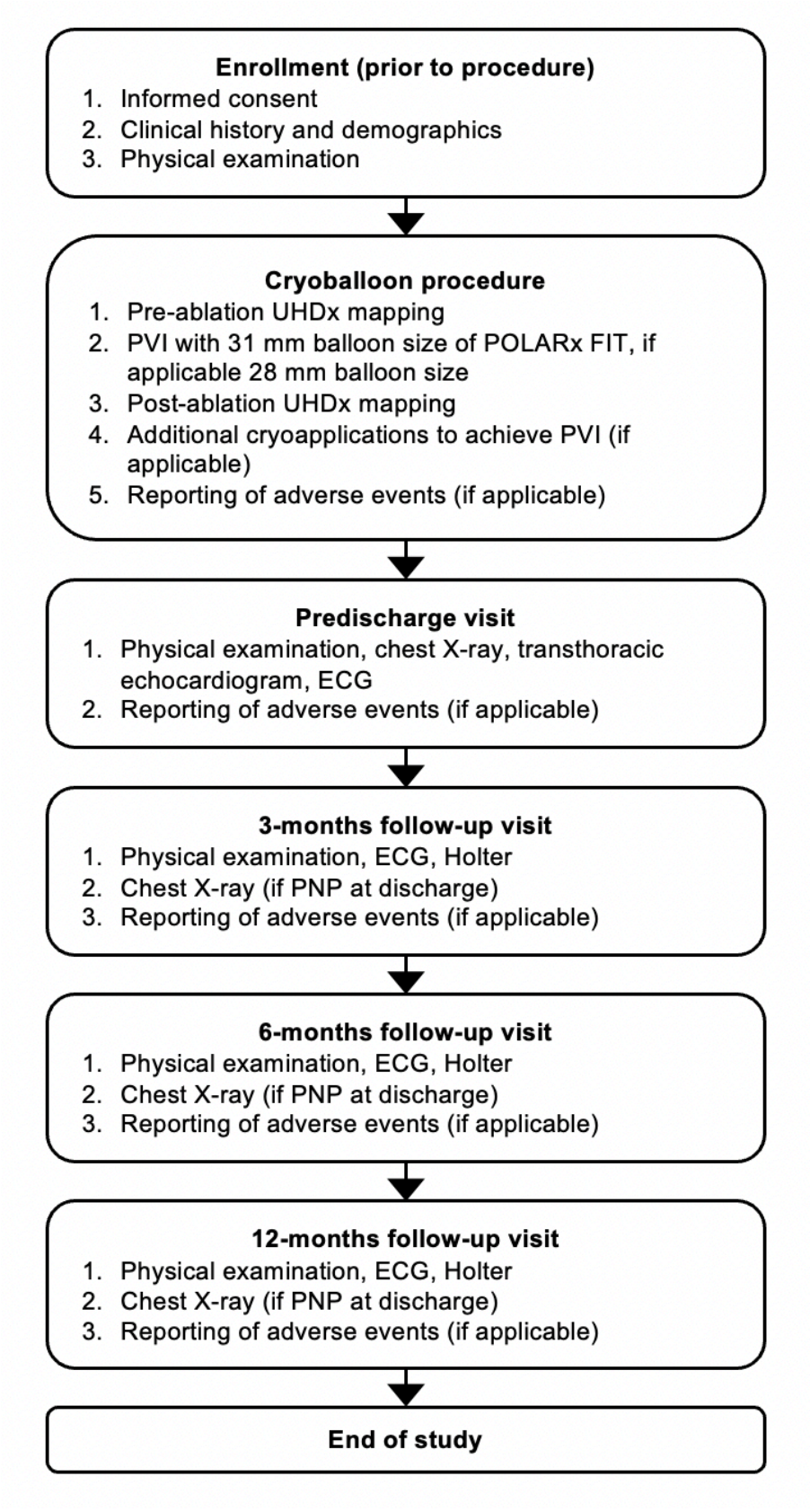
3.1 Study design

Investigator-initiated, single-center, open label, prospective, single-arm study evaluating the 31 mm balloon size of the POLARx™ FIT cryoballoon. Before and after complete PVI, a 3-dimensional ultrahigh-density (UHDx) map will be created. The study population will consist of 20 patients undergoing a first PVI with a normal PV anatomy (exclusion of large common ostium or supernumerary veins as determined by a preprocedural CT-scan) in the Erasmus MC, Rotterdam, the Netherlands. Patients will be seen at the outpatient clinic 3 (blanking), 6 and 12 months after the index ablation to assess potential adverse events and recurrence of atrial arrhythmias. After the 1-year visit the study will end for the individual patient. The study flowchart is depicted in Figure 3.1.1.

3.2 Estimated enrolment and study duration

Enrolment in the study is expected to take approximately 8 months. The last patient included will be followed for at least 12 months after the index procedure, thus, the total duration of the study is expected to be approximately 20 months.

Figure 3.1.1. Study flowchart



4. STUDY POPULATION

4.1 Population (base)

AF is the most common arrhythmia in the general population and is associated with an increased risk of stroke, heart failure and mortality. When patients have symptoms secondary to AF either a rate or rhythm control strategy is possible. Components of a rhythm control strategy consists of the use of antiarrhythmic medication, cardioversion, and catheter ablation. When patients have symptomatic AF despite the use of antiarrhythmic medication, they are candidates for a catheter ablation. PVI is the cornerstone of catheter ablation of AF. In the Erasmus MC, more than 300 patients with AF undergo PVI annually of whom approximately 100 patients with a cryoballoon. Most patients undergoing PVI with a cryoballoon has paroxysmal AF. This population is the target population of the ***BETTER-FIT*** study. A maximum of 20 patients will be enrolled in the study.

4.2 Inclusion criteria

To be eligible to participate in this study, a subject must meet all the following criteria:

1. History of symptomatic paroxysmal AF
2. Subjects who are indicated for a PVI according to the 2020 ESC guidelines for the diagnosis and management of AF[22]
3. Subjects who are willing and capable of providing informed consent
4. Subjects who are willing and capable of participating in all testing associated with this clinical investigation
5. Subjects whose age is 18 years or above

4.3 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

1. Any known contraindication to an AF ablation or anticoagulation
2. History of previous left atrial ablation or surgical treatment of AF, atrial flutter, or atrial tachycardia
3. AF secondary to electrolyte imbalance, thyroid disease, or any other reversible or non-cardiac cause
4. Significant structural heart disease as evidenced by:

a. Left ventricular ejection fraction <45% based on most recent transthoracic echocardiogram (TTE) performed <6 months prior to enrollment

b. LA diameter >55 mm based on most recent TTE performed <6 months prior to enrollment

c. Previous cardiac surgery

d. Previous cardiac valvular surgical or percutaneous procedure
e. Interatrial baffle, closure device, patch, or occluder
f. Unstable angina or ongoing myocardial ischemia
g. Moderate or severe valvular heart disease on most recent TTE performed <6 months prior to enrolment
h. Congenital heart disease
i. Left atrial thrombus
5. History of blood clotting or bleeding disease
6. Stroke or transient ischemic attack <3 months prior to enrollment
7. Active systemic infection
8. Common ostium PV >24 mm defined by CT-scan
9. Pregnant, lactating, or women of childbearing potential who are, or plan to become, pregnant during the time of the study
10. Subjects who are currently enrolled in another investigational study or registry that would directly interfere with the current study

4.4 Sample size calculation

With 20 patients we can provide a reliable estimate of the antral lesion area with the 31 mm balloon size of POLARx™ FIT. A recent study by Gunawardene et al. evaluated the antral lesion area in 20 patients who underwent pulmonary vein isolation with a different technique (i.e., pulsed field ablation).[23] The total circumferential antral lesion areas of the left and right sides were 20.5 ± 3.8 and 25.5 ± 5.7 cm^2, respectively. The precision achieved with 20 patients thus seems adequate to provide a reliable estimate of the antral lesion area. Furthermore, the percentage of technical successful placement of the larger balloon size and the single freeze success percentage are based on the number of PVs (approximately 80 PVs in 20 patients). It is expected that 20 patients will be enrolled in a period of 8 months (approximately 30% enrolment rate of target population), thus an estimated mean inclusion rate of 2.5 patients per month.

5. TREATMENT OF SUBJECTS

5.1 Investigational product/treatment

5.1.1 Periprocedural management

All patients will receive oral anticoagulation for at least 4 weeks before ablation. Direct acting oral anticoagulants are continued in the morning of the procedure. Vitamin K antagonists will be continued with a target INR between 2.0 and 2.5. To exclude left atrial

thrombi, all patients will undergo a transesophageal echocardiogram just before the procedure.

5.1.2 Transseptal puncture

Femoral vein punctures will be performed under ultrasound guidance. After placement of 2 short introducer sheaths (8F and 10F) in the femoral vein, a bolus of intravenous heparin (5000 IE) will be given. A transseptal puncture will be performed using a SL1-sheath (Swartz, Abbott, Abbott Park, IL) and RF transseptal needle (NRG, Bayliss Medical, Rouyn-Noranda, Canada) under guidance of intracardiac echocardiography (ICE) (ViewFlex Xtra, Abbott). The SL1 sheath will be replaced by the POLARSHEATH™ (Boston Scientific). The dilator and guidewire will be slowly pulled out and the sheath is flushed thoroughly before introduction of the cryoballoon catheter. After the transseptal puncture, the ICE catheter is replaced by a steerable decapolar diagnostic catheter (Inquiry™, 2-5-2 mm spacing, St. Jude Medical). The decapolar catheter is placed in the right ventricle (for vagal response) or in the vena cava superior (for phrenic nerve pacing).

5.1.3 Pre-ablation UHDx mapping

Mapping will be preferentially performed in sinus rhythm with prior cardioversion of AF if required. UHDx mapping will be performed with RHYTHMIA HDx™ mapping system and a 64-pole mini-basket mapping catheter (INTELLAMAP ORION™, Boston Scientific). LA voltage maps will be constructed with special point density in the antra of PVs.

5.1.4 Ablation procedure

After placement of the POLARMAP™ circular mapping catheter in the target PV, the cryoballoon is initially inflated to the standard 28 mm size. The most optimal PV occlusion with the 28 mm balloon size will be achieved and the grade of PV occlusion will be determined using a semi-quantitative grading (1 – rapid outflow of contrast medium from the PV to 4 – complete contrast retention with no observable leak).[24] Thereafter, the balloon will increase in size to 31 mm and the most optimal PV occlusion will be achieved. Again, the grade of PV occlusion will be determined using a semi-quantitative grading (grade 0 to 4).[24] After optimal PV occlusion with the 31 mm balloon size, a single 3-minutes cryoapplication will be delivered, irrespective of achieving PV isolation. The cryoapplication will be prematurely stopped when the inner balloon temperature is -69ºC. If PV isolation is not achieved after the first attempt, subsequent cryoapplications (3 or 4 minutes depending on TTI) are delivered until achieving isolation. The balloon size during subsequent applications can be adjusted according to the preferences of the operator.

The order of PVs will be left superior PV, left inferior PV, right inferior PV, and right superior PV. During cryoablation of the left-sided PVs, a diagnostic catheter will be placed in the right ventricle to provide ventricular pacing in case of a vagal response after cryoablation. During cryoablation of the right-sided PVs, high-output right phrenic nerve stimulation will be performed using a diagnostic catheter in the right subclavian vein or superior vena cava. Diaphragmatic excursion will be checked by a combination of manual palpitation and the use of the Diaphragmatic Movement Sensor (DMS). Whenever the diaphragmatic excursions decrease, cryoablation will be immediately terminated. The following parameters will be noted per cryoapplication: time from ablation till -40 ºC, TTI, balloon nadir temperature, thawing time till 0ºC.

5.1.5 Confirmation of complete PVI

Electrical isolation of a PV is demonstrated by entrance and exit block. Entrance block is defined as the absence of local potentials inside the vein as assessed by the POLARMAP™ circular mapping catheter. Exit block is defined as absence of atrial capture while pacing from inside the vein with the POLARMAP™ circular mapping catheter. If a PV shows reconnection, repeat cryoablation will be performed with the goal of achieving electrical isolation. This can be performed with the 28 mm or 31 mm balloon size per operator discretion. Complete PVI is defined as electrical isolation of all PVs. After complete PVI, post-ablation UHDx mapping will be performed.

5.1.6 Post-ablation UHDx mapping

After achieving complete PVI, the 64-pole mini-basket mapping catheter will be introduced through the POLARSHEATH for repeat mapping. Repeat mapping will be preferentially performed in sinus rhythm with prior cardioversion of AF if required. There will be no specified waiting time before remapping. LA voltage maps will be constructed with special point density in the antra of PVs. Post-ablation LA lesion surface area will be assessed as previously described.[23] The key parameters that will be collected are described in the Methods section. If conduction gaps or PV reconnections are found during UHDx mapping, the mapping catheter will be replaced by the POLARx™ cryoablation catheter and additional ablations will be performed to achieve complete PVI. Another UHDx map will be constructed after re-isolation.

5.1.7 Follow-up after index procedure

The day following the procedure, the groin will be inspected for groin hematoma and a transthoracic echocardiogram will be performed to rule out pericardial effusion. Patients will be scheduled for an outpatient visit 3, 6 and 12 months after the index procedure.

This follow-up schedule is standard of care in the Erasmus MC after a PVI. During these visits a physical examination, 12-lead ECG and Holter will be performed. If a PNP occurred during the index procedure, a chest X-ray will be performed during the outpatient clinic visit. The indication for a repeat AF ablation is according to the discretion of the treating physician. During a repeat ablation it is preferable to perform a bipolar voltage map to gain insight in the durability of the antral lesion size area.

5.1.8 Data collection schedule

Procedure	Enrollment (up to day -60)	Baseline (up to day -60)	Index procedure (day 0)	Month 3 follow-up (91±14 days)	Month 6 follow-up (180±30 days)	Month 12 follow-up (365±30 days)	Unscheduled visit
Informed consent	X						
Eligibility criteria	X	X	X				
Demographics		X					
Medical history		X					
Physical examination		X		X	X	X	X
PV anatomical assessment (CT)		X					
TTE		X					
Screening for LA thrombus			X				
Procedural data			X				
12-lead ECG		X	X	X	X	X	X
PNP assessment			X	(X)[1]	(X)[1]	(X)[1]	
Holter monitor				X	X	X	X
Documentation of repeat ablation				X	X	X	
Medications	Prior and current antiarrhythmic medications and anticoagulant therapy regimen from enrollment through end of visit study						
Protocol deviations	From enrollment through end of visit study						
Adverse event assessment	Continuous from enrollment through end of visit study						

[1] Assessment of follow-up visit is only applicable for subjects who had phrenic nerve palsy detected at the index procedure.

5.2 Use of co-intervention (if applicable)

N/A

5.3 Escape medication (if applicable)

N/A

6. INVESTIGATIONAL PRODUCT

6.1 Name and description of investigational product

The POLARx™ FIT cryoablation catheter is CE-marked and is indicated for the treatment of patients with symptomatic AF. In comparison to the previous generation of POLARx™ cryoablation catheter, the POLARx™ FIT cryoablation catheter can apply cryoablation treatment with either 28 mm or 31 mm balloon size per operator discretion. The POLARx™ FIT catheter will expand to the standard balloon size of 28 mm upon every inflation. After each inflation and prior to initiating ablation, the user can increase the balloon size using the console user interface. The larger size is enabled by increasing the inner balloon pressure from 2.5 psi to 7.5 psi. To ensure the freezing capability of the larger size balloon is consistent with the standard size balloon, the nitrous oxide flow rate during ablation is increased from 7800 sccm to 8700 sccm. All other aspects of the nitrous oxide delivery and control for POLARx™ FIT are unchanged from POLARx™. A detailed overview of the hardware components and connections of the POLARx™ FIT cryoablation system is provided in Figures 6.1.1. and 6.1.2. The individual devices within the cryoablation system and their UPN are listed in Table 6.1.1.

Figure 6.1.1. POLARx™ FIT cryoballoon

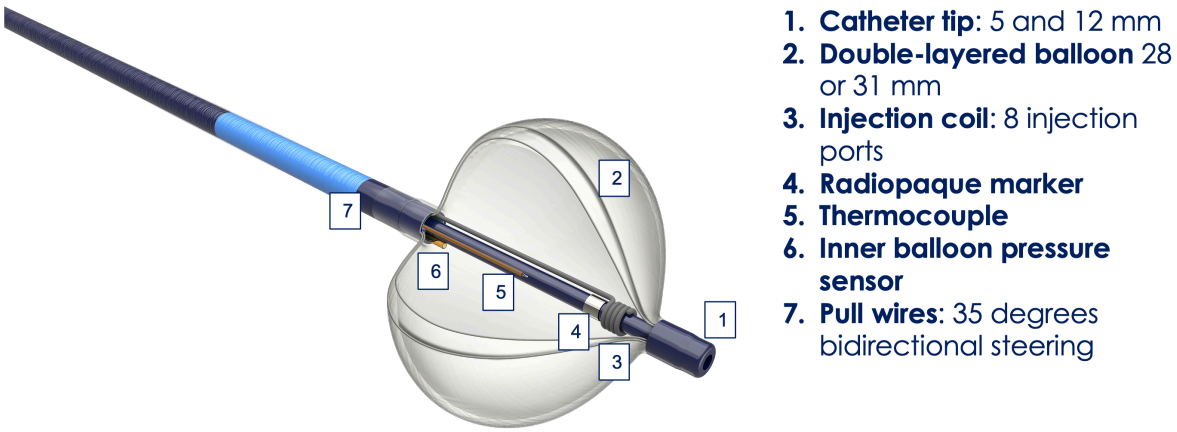


Figure 6.1.2. Overview of all connections of the POLARx™ FIT cryoablation system

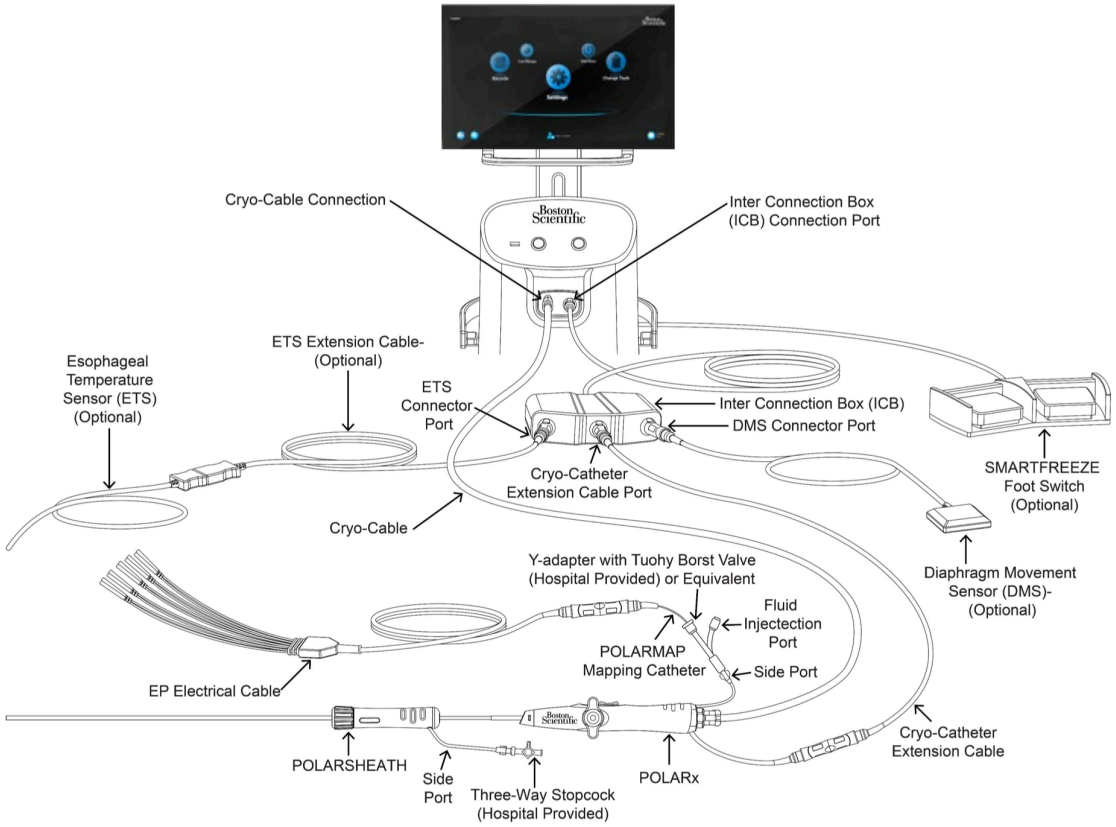


Table 6.1.1. Cryoablation devices used in the ***BETTER-FIT*** study

Product name	**Product description**	**UPN**
POLARx ST	POLARx Balloon Catheter ST 28mm	M004CRBS2000
POLARx LT	POLARx Balloon Catheter LT 28mm	M004CRBS2100
POLARSHEATH™	POLARSHEATH Steerable Sheath	M004CRBS3050
POLARMAP™	POLARMAP Mapping Catheter 20mm	M004CRBS7200
SMARTFREEZE™	SMARTFREEZE Cryo Console	M004CRBS4000
DMS Sensor	Diaphragm Movement Sensor	M004CRBS6110
Cryo Extension Cable	SMARTFREEZE Electrical Ext Cable	M004CRBS5100
Cryo Cable	Cryo Gas Cable	M004CRBS5200
POLARMAP EGM Pin Breakout Cable	POLARMAP EGM Pin Breakout Cable	M004CRBS6200
Interconnection Box	Interconnection Box	M004CRBS4110
Dual Foot Pedal Switch	Foot Switch	M004CRBS4200

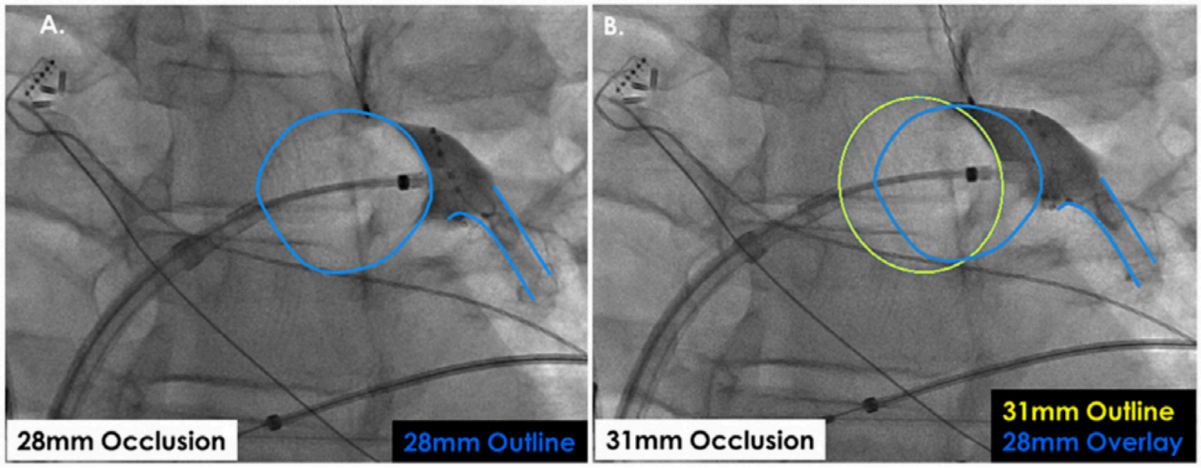
6.2 Summary of findings from non-clinical studies

The *Instructions For Use* (IFU) of the POLARx™ FIT cryoablation catheter is attached as supplement material. Because the device is CE marked, available on the market and the device is used within its indications, we have not requested a new IB for this study.

6.3 Summary of findings from clinical studies

FROZEN-AF (NCT 041331680) was a multi-center, open label, prospective, single arm study to document the safety and performance of Boston Scientific's Cryoablation System (IDE trial) which started in June 2020. As a substudy, the efficacy and safety of the POLARx™ FIT cryoablation catheter was evaluated in 50 patients.[20] Acute isolation was achieved in all 50 patients. The novel 31 mm configuration was used in 65% of ablations. In the 198 ablations performed at 31mm, 80.8% achieved a grade 4 occlusion. In PVs where the first ablation was performed at 31mm the single shot isolation rate was significantly higher than in PVs where the first ablation was performed at 28mm (62.1% versus 35.3%). Notably, there was only 1 instance of transient phrenic nerve paralysis which resolved prior to discharge. Preliminary landmark-based analysis of a subset of veins suggests that inflation to 31mm results in a marked antral shift of balloon position.

Figure 6.3.1. Antral shift of balloon position.[20]



6.4 Summary of known and potential risks and benefits

Cryoballoon ablation is a safe and effective tool for the treatment of AF with a high rate of durable PVI. A recent large Netherlands Heart Registration (n=13,823) demonstrated that CB ablation was associated with less cardiac tamponades (0.3% versus 0.8%) and less vascular complications (1.3% versus 1.7%) compared to radiofrequency ablation.[25] In contrast, CB ablation was associated with a higher risk of phrenic nerve palsy (1.5% versus 0.1%). These data are mainly based on the use of the second-generation CB (Arctic Front Advance).

There is limited data on the incidence of periprocedural complications when using the POLARx™ cryoablation catheter. Studies have shown that the risk of PNP is similar

to Arctic Front Advance Pro™.[8] Real-world data from 372 patients in the POLAR-ICE registry (NCT 04250714) have demonstrated the following complications (Table 9.4.1.). It is expected that the POLARx™ FIT cryoablation catheter will have a similar safety profile as the POLARx™ cryoablation catheter. As can be appreciated from Table 6.4.1., most complications are related to the procedure and not the device itself.

Table 6.4.1. Periprocedural complications in the POLAR-ICE registry (n=388)

Complication	Number of patients (%)
Phrenic nerve palsy	9 (2.3%)
Serious vascular access complications	6 (1.5%)
Cardiac tamponade	2 (0.5%)
Air embolism	2 (0.5%)
Persistent gastroparesis	1 (0.3%)
Myocardial infarction	1 (0.3%)
Stroke	1 (0.3%)

Abstract at EHRA 2022, Tilz et al.

6.5 Description and justification of route of administration and dosage

N/A

6.6 Dosages, dosage modifications and method of administration

N/A

6.7 Preparation and labelling of Investigational Medicinal Product

N/A

6.8 Drug accountability

N/A

7. NON-INVESTIGATIONAL PRODUCT

N/A. The study doesn't include a non-investigational product.

7.1 Name and description of non-investigational product(s)

7.2 Summary of findings from non-clinical studies

7.3 Summary of findings from clinical studies

7.4 Summary of known and potential risks and benefits

7.5 Description and justification of route of administration and dosage

7.6 Dosages, dosage modifications and method of administration

7.7 Preparation and labelling of Non Investigational Medicinal Product

7.8 Drug accountability

8. METHODS

8.1 Study parameters/endpoints

8.1.1 Main study parameter/endpoint

- *Extent of antral lesion size* (continuous variable) directly after cryoablation with a 31 mm balloon size POLARx™ FIT cryoablation catheter. Measures of antral lesion size are described in paragraph 8.3.1. and Table 8.3.1.1.

8.1.2 Secondary study parameters/endpoints (if applicable)

- *Proportion of grade 4 occlusion* (continuous variable, expressed as %) with a 31 mm balloon size POLARx™ FIT cryoablation catheter (on PV level) during cryoballoon procedure.
- *Single shot success rate* (continuous variable, expressed as %) with a 31 mm balloon size POLARx™ FIT cryoablation catheter (on PV level) during cryoballoon procedure.
- *Difference in proportion of grade 4 occlusion with a 28 mm or 31 mm balloon size* (continuous variable, expressed as %) POLARx™ FIT cryoablation catheter (on PV level) during cryoballoon procedure.

8.1.3 Other study parameters (if applicable)

The cumulative 1-year freedom from atrial arrhythmias after cryoballoon ablation will be described using Kaplan-Meier method using a blanking period of 3 months.

8.2 Randomisation, blinding, and treatment allocation

N/A

8.3 Study procedures

8.3.1 Assessment of antral lesion size

In the pre- and post-ablation UHDx-map, bipolar voltage will be assess using a scar-cutoff <0.3 mV.[23] The following spatial measurements will be made consistent with a previously published method by Gunawardene et al.[23]: (1) the surface areas of the posterior left- and right-sided PV antral isolation, (2) the LAPW surface area with voltage pre- and post-ablation, and (3) the distance between the ipsilateral, antral levels of isolation at superior, middle and inferior latitudes of the LAPW (Figures 8.3.1.A,B and D). The surface area of each PV ostium and the area of the circular antral ablation lesion was measured around each ipsilateral PV pair (Figure

8.3.1.C). Low-voltage areas will be quantified using a bipolar voltage <0.3 mV. The scale on the maps will be set from 0.1 to 0.3 mV. The purple region represents unablated tissue with a bipolar voltage >0.3 mV. The scar-border zone will be represented by bipolar voltages between 0.1-0.3 mV. The PV ostium is located by the steep angle between the LA wall and the tubular aspect of the PV.

Figure 8.3.1. Methods for measurements of surface areas and distances in pre- and postablation UHDx maps. (A) Pre-ablation UHDx voltage map and measurement of LAPW surface area (indicated by the white dots) and pre-ablation superior, middle, and inferior line. (B) Postablation UHDx voltage map and measurement of the non-ablated LAPW surface area (indicated by the white dots) and postablation superior, middle, and inferior line. (C) Measurement of the PV ostia sizes of the LSPV and LIPV and the area of the circumferential antral ablation along the ipsilateral lateral PV pair (indicated by the whit dots). (D) Measurements of the posterior surface areas of the left- and right-sided pulmonary vein antral isolation areas. Modified from Gunawardene et al.[23]

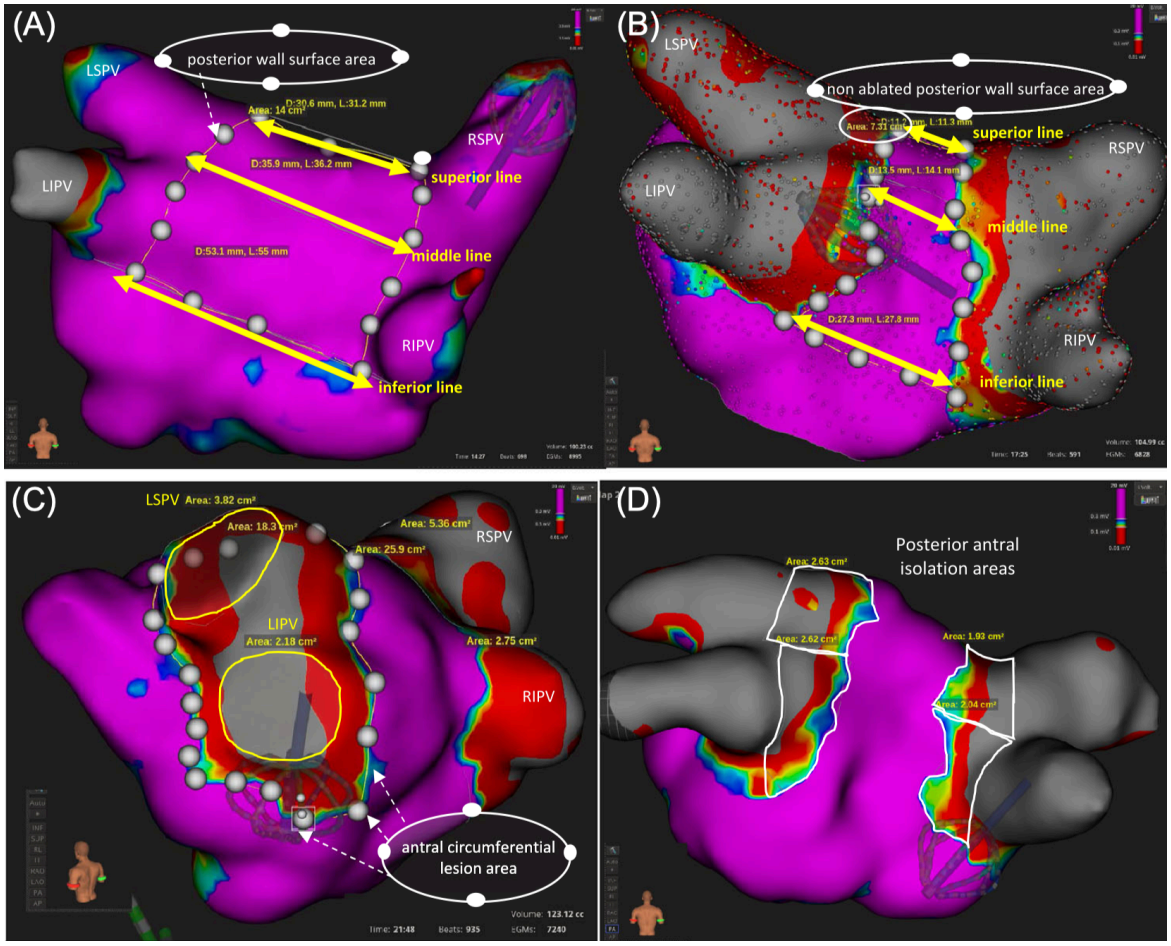


Table 8.3.1.1. provides an overview of the key parameters assessing the extent of the antral lesion size.

Table 8.3.1.1. UHDx measurements

Measurement	Preablation	Postablation
Nonablated LAPW surface area (cm^2)	X	X
Superior line (mm)	X	X
Middle line (mm)	X	X
Inferior line (mm)	X	X
Total LPV ostia (cm^2) - LSPV ostia (cm^2) - LIPV ostia (cm^2) - LCV ostia (cm^2), if applicable	-	X
Total RPV ostia (cm^2) - RSPV ostia (cm^2) - RIPV ostia (cm^2) - RCV ostia (cm^2), if applicable	-	X
Left-sided circumferential antral lesion area (cm^2)	-	X
Right-sided circumferential antral lesion area (cm^2)	-	X
Posterior PV antral isolation area - LSPV (cm^2) - LIPV (cm^2) - RSPV (cm^2) - RIPV (cm^2) - LCV (cm^2), if applicable - RCV (cm^2), if applicable	-	X

Abbreviations: LAPW, left atrial posterior wall; LCV, left common pulmonary vein; LIPV, left inferior pulmonary vein; LPV, left pulmonary vein; LSPV, left superior pulmonary vein; RCV, right common pulmonary vein; RIPV, right inferior pulmonary vein; RPV, right pulmonary vein; RSPV, right superior pulmonary vein.

8.3.2 Proportion of grade 4 occlusion

In this study we will evaluate the proportion of grade 4 occlusion (i.e., contrast stasis) of the 28 mm and 31 mm balloon size POLARx™ FIT cryoablation catheter. Therefore, cine acquisitions of contrast vein occlusions will be analyzed. Occlusion will be categorized by using a previously described scale (1—rapid outflow of contrast medium from the PV to 4—complete contrast retention with no observable leak).[24] Two experienced observers blinded to vein outcome will assess recorded venograms.

8.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

8.4.1 Specific criteria for withdrawal (if applicable)

N/A

8.5 Replacement of individual subjects after withdrawal

Enrolled subjects who decide to leave the study before the index procedure will be replaced by new subjects.

8.6 Follow-up of subjects withdrawn from treatment

Subjects who are withdrawn from the study will continue their follow-up in agreement with local practice.

8.7 Premature termination of the study

N/A

9. SAFETY REPORTING

9.1 Temporary halt for reasons of subject safety

In accordance with section 10, subsection 4 of the Medical Research Involving Human Subjects Act (*in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen,* WMO), the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardize subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

9.2 Adverse Events and Device Deficiencies

During the clinical investigation, undesired medical events can occur in participating patients, which are called adverse events (AEs) in the following. Furthermore, device deficiencies (DD) may also be observed. All AEs and DDs of the investigational device shall be assessed by the investigator and shall be documented and reported throughout the clinical investigation within the timelines defined below (Figure 9.2.1.). According to ISO 14155:2020 (third edition) events will be classified based on the definitions below. The investigator will report all reportable events to the sponsor without undue delay but not later than 3 calendar days after obtaining knowledge of the event (including assessment of causal relationship with device or investigational procedure). Reportable events are:

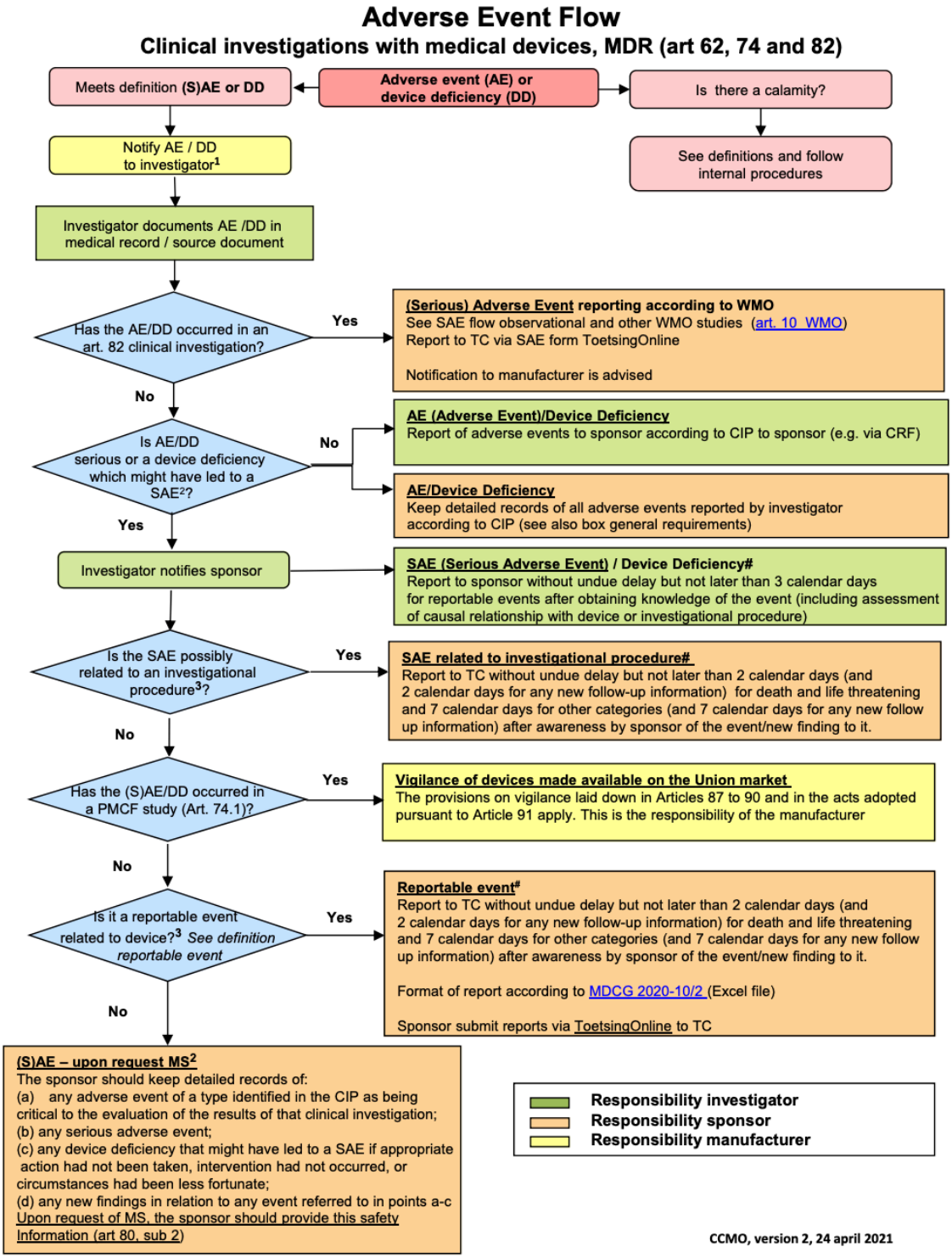
a) Any SAE that has a causal relationship with the investigational device, the comparator, or the investigation procedure or where such causal relationship is reasonably possible
b) Any DD that might have led to a SAE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate
c) Any new findings in relation to any event referred in point (a) and (b)

The sponsor will report reportable events through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 2 calendar days of first knowledge for SAEs that result in death or are life threatening. All other SAEs will be reported within a period of maximum 7 calendar days after the sponsor has first knowledge of the SAE. All SAE will be reported and will be categorized as related to the device (SADE) or not.

The sponsor will report expedited unanticipated serious adverse device effects (USADEs) through the web portal *ToetsingOnline* to the METC. The expedited reporting of USADEs through the web portal *ToetsingOnline* is sufficient as notification to the competent authority. The expedited reporting will occur not later than 15 days after the sponsor has first knowledge of the adverse reactions. For fatal or life-threatening cases,

the term will be maximal 7 days for a preliminary report with another 8 days for completion of the report.

Figure 9.2.1. Adverse events flow



9.2.1 Definition of Adverse Device Effects (ADE)

An adverse device effect (ADE) (see ISO 14155:2020 3.1) is an adverse event (AE) that is related to the use of an investigational medical device. This includes any AE resulting from insufficient or inadequate instructions for use or the deployment, implantation, installation, or operation, or any malfunctioning of the investigational medical device and any event resulting from use error or from intentional misuse of the investigational medical device. This includes comparator if the comparator is a medical device.

9.2.2 Definition of Adverse Events (AE)

An AE is defined (see ISO 14155:2020 3.2) as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users, or other persons whether or not related to the investigational medical device, and whether anticipated or unanticipated. This includes:

- Events related to the investigational medical device or the comparator
- Events related to the procedures involved
- For users or other persons, this definition is restricted to events related to the use of investigational medical devices or comparators

9.2.3 Causality Assessment

The relationship between the use of the investigational medical device (including the medical-surgical procedure) and the occurrence of each AE shall be assessed and categorized, considering the presence of confounding factors, such as concomitant medication and treatment, the natural history of the underlying disease, other concurrent illness, or risk factors. Each AE will be classified according to five different levels of causality. The investigator will use the following definitions to assess the relationship of the (serious) AE to the investigational medical device or procedures and the sponsor will review the investigators categorization:

- ***Not related***: the relationship to the medical device or procedure can be excluded
- ***Unlikely***: the relationship with the use of the medical device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.
- ***Possible***: the relationship with the use of the investigational medical device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g., an underlying or concurrent illness/clinical condition or/and an effect of another device, drug or treatment). Cases where relatedness cannot be

assessed, or no information has been obtained should also be classified as possible.

- ***Probable***: the relationship with the use of the investigational medical device seems relevant and/or the event cannot be reasonably explained by another cause, but additional information may be obtained.
- ***Causal relationship***: the (serious) event is associated with the investigational medical device or with procedures beyond reasonable doubt.

The investigators will distinguish between the AEs related to the investigational medical device and those related to the device procedures (any procedure specific to the investigational device). Procedure related events refers to the procedure related to the application of the investigational medical device only and therefore not to any other procedure for other devices and not to any other procedures or treatments applied later throughout the clinical investigation, for instance to treat (serious) AEs.

An AE can be related both to the procedure and the investigational medical device. Complications of procedures are considered not related if the said procedures would have been applied to the patients also in the absence of investigational medical device use or application.

9.2.4 Definition of Device Deficiency (DD)

Device deficiency (DD) (see ISO 14155:2020 3.19) is defined as inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety, or performance, including malfunctions, use errors and inadequacy in the information supplied by the manufacturer including labelling. This definition includes DD related to investigation medical device or the comparator.

DDs of the investigational medical device shall be documented throughout the study. DDs which caused an AE are reported on the respective adverse event form. In case the DD did not cause an adverse event, the provided DD form shall be used to document this “non-medical” event.

If a DD could have led to a SADE,

- If either suitable action had not been taken,
- If intervention had not been made, or
- If circumstances had been less fortunate,

The DD is classified as an DD with a SADE potential.

9.2.5 Definition of Serious Adverse Events (SAE)

AEs are classified as serious (see ISO 14155:2020 3.45) if one or more of the following consequences are fulfilled:

a) Led to death
b) Led to serious deterioration in the health of the subject, users, or other persons as defined by one or more of the following:
    1) A life-threatening illness or injury, or
    2) A permanent impairment of a body structure or a body function including chronic diseases, or
    3) In-patient or prolonged hospitalization, or
    4) Medical or surgical intervention to prevent life-threatening illness or injury, or permanent impairment to a body structure or a body function.
c) Led to fetal distress, fetal death or a congenital abnormality or birth defect including physical or mental impairment.

Note: planned hospitalization for a pre-existing condition, or a procedure required by the clinical investigation plan (CIP), without serious deterioration in health is not considered a SAE. In-patient hospitalization is defined as at least one overnight stay (change of date) in a hospital. In case, a patient is only for some hours in the hospital (without change of date), this event will not be documented as serious, unless one or more other seriousness criteria are fulfilled.

9.2.6 Definition of Serious Adverse Device Effect (SADE)

An ADE (see ISO 14155:2020 3.44) that resulted in any of the consequences characteristic of a SAE is considered serious.

9.2.7 Definition of Unanticipated Serious Adverse Device Effects (USADE)

SADEs (see ISO 14155:2020 3.51) are defined as unanticipated if by their nature, incidence, severity, or outcome they have not been identified in the current risk assessment. These events must be reported to the sponsor immediately.

9.3 Annual safety report

An annual safety report will be submitted to the METC of the Erasmus MC.

9.4 Follow-up of adverse events

All SAEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist. SAEs need to be reported till end of study within the Netherlands, as defined in the protocol.

9.5 Data Safety Monitoring Board (DSMB) / Safety Committee

A DSMB will not be established given low-risk character of the study and the well-established safety of the catheters. The principal investigator will be responsible for registering and reporting any ADEs, SADE or USADEs to the METC.

10. STATISTICAL ANALYSIS

10.1 Primary study parameters

The primary study parameter is the extent of the antral lesion size. The antral lesion size will be established using the parameters as detailed in Table 8.3.1.1. The antral lesioin size will be described as absolute and relative measures. Absolute measures include nonablated LAPW, superior line, mid line, inferior line, circumferential antral lesion area, and posterior PV antral lesion area. Relative measures include the difference between the pre- and post-ablation maps regarding the absolute measures expressed as a percentage.

10.2 Secondary study parameters

The secondary study parameters are the proportion of grade 4 occlusion and the single shot success rate. Both will be determined per PV and expressed as frequency and percentage (N, %). The difference in the proportion of grade 4 occlusion between the 28 mm and 31 mm balloon size will be compared using the McNemar test for paired nominal data.

10.3 Other study parameters

N/A

10.4 Interim analysis (if applicable)

N/A

11. ETHICAL CONSIDERATIONS

11.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki (version 2013), ISO 14155: 2020, WMO and other regional and local laws.

11.2 Recruitment and consent

Patients who are referred to the study center for a PVI are always seen by a physician on a dedicated outpatient clinic to inform them on the procedure, efficacy, and risks of a PVI. If the patient is a suitable patient for a PVI with a cryoballoon and the patient gives consent for the procedure, they are considered potential study candidates. If they fulfil the in- and exclusion criteria as defined in chapter 4, then they will be approached by a member of the study team (not treating physician) to explain the study and obtain informed consent if the patient is eligible and willing to participate in the study. Informed consent will be obtained and documented in writing before a subject is enrolled in the clinical study. It is the responsibility of the investigator to ensure that a written informed consent is obtained from the subject (or legally acceptable representative) before any activity or procedure is undertaken that is not part of routine care.

11.3 Objection by minors or incapacitated subjects (if applicable)

N/A

11.4 Benefits and risks assessment, group relatedness

The hypothesis is that the larger balloon size of POLARx™ FIT cryoablation catheter will result in a larger antral lesion size. This may have a beneficial effect by reducing the risk of recurrence of AF after the index procedure. In general, cryoballoon procedures are associated with less periprocedural risks compared to PVI using RF. It is expected that the larger balloon size (31 mm versus 28 mm) will not result in a significant increase in periprocedural complications. Catheter handling will not change due to the larger balloon size. One of the most common complications due to CB procedures is right-sided PNP. It is expected that a larger balloon size will have a beneficial effect on the risk of PNP because the larger balloon size will prevent placement of the CB too deep in the right-sided PVs. By having a more antral position of the CB the risk of PNP is decreased.

11.5 Compensation for injury

The sponsor has a liability insurance which is in accordance with article 7 of the WMO. The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study. The insurance applies to

the damage that becomes apparent during the study or within 4 years after the end of the study.

11.6 Incentives (if applicable)

Patients included in the study will not receive any financial compensation. Travel costs reimbursement is possible (if visits are not part of the routine clinical care).

12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

12.1 Handling and storage of data and documents

Data will be handled confidentially and encoded. A subject identification code will be used to be able to trace data to an individual subject. This code will not be based on the patient initials and birthdate. The key to the code will be safeguarded by the investigator. The handling of personal data will comply with the EU General Data Protection Regulation (GDPR) and the Dutch Act on Implementation of the General Data Protection Regulation (*in Dutch: Uitvoeringswet AVG, UAVG*). Electronic Case Report Forms (eCRFs) will be utilized. Site staff will enter the information required by the protocol onto eCRFs using a validated software/ database that conforms to requirements for electronic data capture. The subsidiary party, whose headquarters is located in the United States, can only access the fully anonymized data upon request.

12.2 Monitoring and Quality Assurance

According to the NFU table the risk classification regarding patient risk is considered moderate. The risk classification regarding scientific quality is considered negligible. Based on this assessment, the frequency of monitoring will be 2 visits per year. For details of the monitoring plan, we refer to the local rules in the Erasmus MC for research with moderate risk (*in Dutch: onderzoek met matig risico*).

12.3 Amendments

A 'substantial amendment' is defined as an amendment to the terms of the METC application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any intervention used in the trial.

All substantial amendments will be notified to the METC. Non-substantial amendments will not be notified to the accredited METC but will be recorded and filed by the sponsor.

12.4 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

12.5 End of study report

The sponsor will notify the accredited METC of the end of the study within a period of 90 days. The end of the study is defined as the last patient's last visit. The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action. In case the study is ended prematurely, the sponsor will notify the accredited METC within 15 days, including the reasons for the premature termination. Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

12.6 Public disclosure and publication policy

The basic principles of the CCMO's position on the disclosure/ publication of trial results obtained from studies involving human subjects will be respected. The results of the study will be submitted for publication to peer-reviewed scientific journals independent of the subsidiary party. The investigator shall ensure by its best efforts that confidentiality interests of the subsidiary party shall be respected. Therefore, the investigator shall forward a manuscript of the planned publication at least 30 days prior publication to the subsidiary party. The subsidiary party is entitled to examine the manuscript and to make comments on it.

To provide transparency and discourage publication bias, the study is registered in the www.clinicaltrials.gov before the first inclusion.

13. STRUCTURED RISK ANALYSIS

13.1 Potential issues of concern

N/A (see paragraph 13.2)

13.2 Synthesis

The POLARx™ FIT is a CE-marked device and will be used within the registered indication for use. Therefore, paragraph 13.1 was skipped. In general, PVI using a cryoballoon is considered safer than radiofrequency ablation. This is related that CB ablation is associated with lower interoperator variability, shorter learning curve and faster procedure times. Our center has extensive experience with cryoballoon procedures and have been using the Arctic Front cryoballoon (Medtronic) since 2005. Since 2019 we started cryoablation using the novel POLARx™ cryoablation system as part of the CE mark study.[18] After the POLARx™ cryoablation system obtained the CE mark in 2020, we have compared the safety of the POLARx™ to the Arctic Front Advance Pro™ cryoablation system in a real-world population and showed no differences in the rate of periprocedural complications.[13] We also conducted a meta-analysis in 2021 and did not show a difference in periprocedural complications between both cryoablation systems.[8] The second generation POLARx™ cryoablation catheter, POLARx™ FIT, is identical to its predecessor from the perspective of catheter design. The major difference is that POLARx™ FIT can be used as either a standard sized balloon (28 mm) or a slightly larger sized (31 mm) balloon. This small increase in balloon size will most likely have no impact on periprocedural complications but may have a small effect on positioning of the balloon at the antral part of the PVs. This effect is evaluated in the current study. The larger balloon may even have a beneficial effect on the risk of PNP because the larger balloon size prevents that the balloon will be positioned too deep in the PV. A deeper position in the PV is associated with a higher risk of PNP. Finally, in this study we will perform pre- and postablation 3D mapping with a 64-pole mini-basket Orion™ catheter. 3D mapping is standard in RF procedures and mapping is not associated with a high risk of cardiac perforation. Because the Orion™ catheter is introduced through the 15.9F POLARSHEATH™ steerable sheath, specific attention will be paid to the risk of air ingress because the risk of air ingress is increased when using a smaller catheter in the POLARSHEATH™. We believe that the increased risk for the subjects in this study is negligible.

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