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CIRCA-DOSE: Methods and Rationale

ABSTRACT

Introduction: Pulmonary vein (PV) isolation (PVI) is an effective therapy for paroxysmal atrial fibrillation (AF), but has limitations. The two most significant recent advances have centered on the integration of real-time quantitative assessment of catheter contact force into focal radiofrequency (RF) ablation catheters, and the development of dedicated ablation tools capable of achieving PVI with a single ablation lesion (Arctic Front™ cryoballoon, Medtronic, Minneapolis, MN). While each of these holds promise for improving the clinical success of catheter ablation of AF, there has not been a rigorous comparison of these advanced ablation technologies. Moreover the optimal duration of cryablation (freezing time) has not been determined.

Methods and Analysis: Patients undergoing a first PVI procedure for paroxysmal AF will be recruited. Patients will be randomized 1:1:1 between contact force irrigated RF ablation, short duration cryoballoon ablation (2 minute applications) and standard duration cryoballoon ablation (4 minute applications). The primary outcome is time to first documented AF recurrence on implantable loop recorder. With a sample size of 111 per group and a two-sided 0.025 significance level (to account for the two main comparisons), the study will have 80% power (using a log rank test) to detect a difference of 20% between contact force RF catheter ablation and either of the two cryoballoon ablation groups. Factoring in a 4% loss to follow-up, 116 patients per group should be randomized and followed for a year (total study population of 348).

Ethics and Dissemination: The study was approved by the University of British Columbia Office of Research (Services) Ethics Clinical Research Ethics Board. Results of the study will be submitted for publication in a peer-reviewed journal.

Trial Registration number: ClinicalTrials.gov **NCT01913522**

AUTHORS CONTRIBUTIONS:

JA, MD, and PK conceived the study. JA, ASLT, AV, LM, PK, MD, MWD, GAW were involved in the drafting of the peer-reviewed grant, the study protocol, and the manuscript. MB, JC, PLS, PN, JFR, JS, AV served on the steering committee for the trial, and have provided critical revision of the manuscript.

STRENGTHS AND LIMITATIONS OF THE STUDY

- The CIRCA-DOSE is the first large multicenter randomised trial evaluating modern ablation technologies (contact force guided RF ablation compared to second-generation cryoballoon ablation)
- In addition the trial will also evaluate the optimal cryoablation duration for patients undergoing cryoballoon ablsatiom, potentially improving procedural access and minimising the risk of recurrence.
- The trial uses continuous arrhythmia monitoring via implantable cardiac devices, and thus represents one of the most robust AF ablation trials performed to date.
- In addition to the dichotomous endpoint of arrhythmia recurrence, the CIRCA-DOSE trial will be able to evaluate the effect of ablation on arrhythmia burden.

INTRODUCTION

Atrial fibrillation (AF) is a common chronic progressive disease, characterized by exacerbations and remissions. Over the past 10-15 years, multiple large-scale observational studies and randomized controlled trials have demonstrated that catheter ablation is superior to AAD therapy in maintaining sinus rhythm.(1-10) In addition, catheter ablation has been shown to be superior to anti-arrhythmic drugs (AADs) for the improvement of symptoms, exercise capacity, and quality of life.(4,11-13) Unfortunately, the results of ablation are limited by arrhythmia recurrence, which is most often due to a failure to effectuate a lasting contiguous circumferential transmural myocardial lesion around the PV ostia.(1,3-10,14,15) In response considerable effort has been directed towards developing technologies to achieve safer and more durable PV isolation (PVI). The two most significant advances in the last few years have centered on the integration of real-time quantitative assessment of catheter contact force into focal radiofrequency (RF) ablation catheters, and the development of dedicated ablation tools capable of achieving PVI with a single ablation lesion, the most mature of which is the Arctic Front™ cryoballoon (Medtronic, Minneapolis, MN).

While each of these advances holds promise for improving the clinical success of catheter ablation of AF, there has not been a rigorous comparison of the current generations of contact-force assisted RF ablation versus the use of the second-generaton cryoballoon. Moreover, many technical aspects of the use of each technology have yet to be fully elucidated. Specifically, in

the case of the cryoballoon the optimal cryoablation duration has not been determined.(16) The CIRCA-DOSE trial has been designed to evaluate these two questions. The CIRCA-DOSE study is a multi-center randomised trial designed to rigorously evaluate the effectiveness of contact-force assisted RF PVI versus PVI performed with the second-generaton cryoballoon, as well as evaluate the optimal cryoablation duration.

Contact Force Ablation

Ablation electrode-tissue contact is an important determinant of lesion size, and ultimately durability of conduction block. Conventionally, this has been assessed by the operator using a combination of fluoroscopic imaging of the catheter tip motion, tactile feedback and local electrogram attenuation, as well as impedance reductions during energy delivery. While widely used, the accuracy of these surrogate measures is poor. Contact force sensing is a newly developed technology that allows for real-time estimation of the contact force between the tip of the catheter and target myocardium, thus providing the operator with an accurate quantitative assessment of tissue contact.

Recent data suggest that incorporating real-time contact force assessment results in a reduction in procedure time, ablation time and total energy delivery, with a comparable safety profile to that observed with standard irrigated RF.(17,18) However, the two largest multicenter trials evaluating this technology demonstrated a one-year success of 68% (TactiCath, TOCCASTAR) and 74% (SmartTouch, SMART-AF).(19,20) In the case of the former the success was no different from that observed with standard non-contact force RF ablation. Interestingly, post-hoc analyses of these studies suggested that the outcomes were improved when the procedure was performed with adequate contact-force parameters (84% one-year freedom from AF in the 47% of patients in whom ablation was in the target range ≥80% of the time in SMART-AF, and 76% one-year freedom from AF in the 57% of patients in whom ≥90% of the lesions were >10 g in TOCCASTAR). No differences in the incidence of complications have been reported between patients undergoing ablation with contact force vs. non-contact force sensing RF ablation catheters.(19,21,22)

Cryoballoon Ablation

Recent studies have examined short- and long-term success with the second-generation cryoballoon. Studies of planned re-mapping procedures have demonstrated that the durability of PVI at three months post index ablation procedure was improved at 91% with the second generation cryoballoon, compared to 67% of PVs with standard (non-contact force) RF, and 88% of PVs with the first generation cryoballoon.(18,23-27) Clinically this has translated into a one-year freedom from recurrent AF of 82% with the second generation cryoballoon (11 studies; 1725 patients), which was significantly improved compared to the first generation cryoballoon in a separate comparative meta-analysis (odds ratio of arrhythmia recurrence 0.34 [0.26-0.45] when compared to first-generation cryoballoon; 10 studies, 2310 patients).(28) From a safety standpoint there were significantly more phrenic nerve palsies (transient and persistent) observed with the first generation cryoballoon.

Contact Force Ablation vs. Cryoballoon Ablation

There is limited data directly comparing contact-force guided RF ablation to cryoballoon ablation. Since the inception of the CIRCA-DOSE study, three observational studies have reported comparable safety and efficacy between contact-force guided RF ablation and cryoballoon ablation for paroxysmal (2 studies) and persistent (1 study) AF. Specifically, Jourda et al. reported a single-centre experience with 150 consecutive patients undergoing PVI for paroxysmal AF with the second generation cryoballoon (75 patients), and contact-force guided irrigated RF ablation (SmartTouch, 75 patients).(29) In this non-randomised study the one-year freedom from recurrent AF (as detected by Holter monitoring at 1, 3, 6, 9, and 12 months) was 85% in the cryoballoon group and 88% in the contact-force group (P=0.988). Squara et al. reported a similar 1-year freedom from recurrent paroxysmal AF (73% in the cryoballoon group and 76% in the contact-force group [SmartTouch and Tacticath]; P=0.63) in their ambidirectional (combined prospective and retrospective enrolment) multi-centre cohort study of 4 participating centres (2 centers performed both cryoballoon and RF ablation; 1 centre performed exclusively cryoballoon ablation; and 1 performed exclusively RF ablation).(30) Lastly, Ciconte et al. reported a single-centre experience with 100 consecutive patients undergoing PVI for persistent AF with the second generation cryoballoon (50 patients), and contact-force guided irrigated RF ablation (SmartTouch and Tacticath, 50 patients).(31) In this

non-randomised study the one-year freedom from recurrent AF (as detected by Holter monitoring at 1, 3, 6, and 12 months) was 60% in the cryoballoon group and 56% in the contact-force group (P=0.78).

The multicenter, randomized FIRE and ICE trial was designed to determine whether cryoballoon ablation was non-inferior to RF ablation in symptomatic patients with drug-refractory paroxysmal AF.(32) Patients were randomised to Arctic Front-based cryoballoon ablation (374 patients), vs. irrigated RF ablation (376 patients). The primary efficacy endpoint (documented recurrence of AF/AT/AFL >30s, AAD prescription, or re-ablation) occurred in 138 patients in the cryoballoon group and in 143 in the RF group (1-year Kaplan–Meier event rate estimates, 34.6% and 35.9%, respectively; hazard ratio, 0.96; 95% confidence interval [CI], 0.76 to 1.22; P<0.001 for noninferiority). However, despite reporting recently it is important to note that the study was not an exclusive comparison of advanced technologies, with the majority of patients receiving non-contact force irrigated RF ablation (284/376 in the RF group) and a significant proportion (90 of 374 patients) receiving first generation cryoballoon ablation. As such the relative safety and efficacy of these new technologies remains unknown.

Data Supporting Shorter Freeze Durations

The optimal duration of freezing, that is, how long the tissue should be kept in the frozen state, is not well established. Current recommendations are for cryoablation dosing at 240 seconds for each application, which is based on studies of an early focal cryocatheter. In these studies, it was observed that the effect of a cryoablation lesion reached a plateau of three-minutes after the onset of ablation. Thereafter "prolongation of exposure time beyond 3 minutes did not result in any further increase in lesion dimension or volume."(33,34) Since then, the cryocatheter has evolved from a rigid focal catheter to a semi-compliant balloon, which necessitated a redesign of the cryorefrigerant delivery mechanisms. Moreover, the refrigerant itself has changed from slow-cooling to more efficacious gases (i.e., nitrous oxide).

Information regarding the safety and efficacy of shorter cryoballoon ablation durations are limited to 3 minute lesions, which have been suggested in several non-randomised studies to be of comparable efficacy to longer duration cryolesions.(35,36) We recently completed a

randomized pre-clinical study examining the immediate and delayed effects of shorter ablation time on PVI efficacy.(37) In our study, thirty-two mongrel dogs underwent cryoballoon ablation with a 23-mm cryoballoon catheter. PVI procedures were randomized to a single 2-minute vs. 4-minute cryoballoon application. Although 4-minute lesions were associated with a thicker neointima than 2-minute lesions (223.8µm vs. 135.6µm; p=0.007), no differences were observed in the rates of procedural PVI, or the achievement of complete circumferentially transmural lesions at 30 days (78% overall; 86.2% for 2-min vs. 70% for 4-min; P=0.285).

Arrhythmia Monitoring

While from a patient perspective the freedom from symptoms related to AF may be the most important clinical endpoint, contemporary evidence suggests that there is a poor correlation between symptoms and AF burden.(38,39) Moreover the presence or absence of symptoms does not affect the prognosis and complications of the AF.(40) As such any evaluation of treatment efficacy must include protocol-determined arrhythmia monitoring. Given that paroxysmal AF is by definition a disease of clusters, studies have shown that the detection of AF recurrence is proportional to the duration of monitoring.(41) Specifically, Kottkamp et al. demonstrated an increased detection of arrhythmia recurrences post AF ablation for highly symptomatic AF in a group undergoing serial 7-day ECG monitoring versus those undergoing only intermittent ECG monitoring (26% vs. 12% documented recurrence).(42) Unfortunately, while non-invasive intermittent rhythm monitoring remains the most widely utilised method of ascertaining ablation efficacy it often fail to detect AF recurrence. Specifically the sensitivity (31-71%) and negative predictive value (21-39%) are significantly inferior to continuous monitoring techniques.(43) This imprecision associated with intermittent arrhythmia monitoring confers a significant risk of Type II error, which makes it inappropriate for outcome ascertainment in a trial designed to evaluate the efficacy of different therapeutic interventions.

As such, a major strength of the current study is the reliance on continuous cardiac monitoring for the determination of arrhythmia outcomes. All participants in the CIRCA-DOSE trial will have an implantable cardiac monitor with an automated AF detection algorithm (REVEAL LINQ) inserted a minimum of 1 month prior to ablation. This subcutaneous implantable cardiac

monitor continuously analyzes the beat-to-beat variability of cardiac cycles leading to an accurate determination of the timing of arrhythmia recurrence, as well as an accurate quantification of atrial fibrillation burden (hours in AF per day, and percentage of overall time in AF). With respect to this latter point, the use of AF burden allows for a more detailed examination of the relatively efficacy of the three-different treatment approaches, beyond which can be obtained with dichotomous event analyses such as "time-to-first-AF recurrence." Unfortunately, intermittent rhythm monitoring techniques are unable to accurately quantify AF burden.(43)

METHODS AND ANALYSIS

Study Design

The CIRCA-DOSE study (ClinicalTrials.gov #**NCT01913522**) is a multicentre prospective randomized clinical trial. The study will be conducted at 8 clinical centres in Canada. Patients with symptomatic paroxysmal and early persistent AF refractory to at least one AAD and referred for first percutaneous catheter ablation will be enrolled (**Figure 1**). At least 1 episode of AF must be documented on 12-lead electrocardiogram (ECG), transtelephonic monitor (TTM), or Holter monitor within 24 months of randomization (Inclusion and exclusion criteria are detailed in **Supplementary Table 1)**.(44)

All patients will undergo the implantation of an implantable cardiac monitor (ICM) with an AF detection algorithm a minimum of 30 days prior to the index ablation for the purpose of arrhythmia monitoring (Reveal LINQ, Medtronic). The ICM analyzes beat-to-beat variability of cardiac cycles on a 2-minute ECG strip and stores the tracing for independent adjudication. The device is also capable of quantifying the amount of AF per day, and the overall AF burden (percentage of the observed time that a patient is in AF). Additionally, the patient can activate the device manually to facilitate analysis of heart rhythm during symptomatic events. ICM programmed parameters are summarized in **Supplementary Table 2**.

Patients will be assigned in a 1:1:1 ratio using permuted block randomization stratified by site to: 1) Standard RF ablation guided by tissue-contact force; 2) Short cryoballoon ablation

duration (2-minute cryoapplications); and 3) Standard cryoballoon ablation duration (4-minute cryoapplications). Patients will be blinded to their randomization assignment.

Catheter Ablation Procedure

Effective anticoagulation with oral vitamin K antagonists (target INR between 2-3), low molecular weight heparin, or dabigatran/apixaban/rivaroxaban for at least one month and/or the exclusion of a left atrial (LA) thrombus by transesophageal echocardiography (TEE; <48 hours pre-ablation) is mandated prior to ablation.(45) Antiarrhythmic drugs will be discontinued five half-lives before the procedure, except for amiodarone, which will be discontinued 8 weeks prior to ablation. Interventions will be performed on patients in the fasting state under conscious sedation or general anesthesia, per local practice.

For each of the three treatment arms, patients will undergo pulmonary vein isolation (PVI) according to standard clinical practice.(45-48) No prophylactic LA linear ablation lesions, or ablation of complex fractionated atrial electrograms (CFAE) will be permitted in addition to PV isolation. In the event of documented right atrial cavotricuspid isthmus dependent flutter, cavotricuspid isthmus ablation is permitted (with irrigated RF or focal cryoablation).

Contact-Force Guided Radiofrequency Ablation

For patients randomized to RF catheter ablation a three-dimensional, non-fluoroscopic mapping system (CARTO3, Biosense Webster) will be used for anatomic reconstruction. Through one transseptal access, a circular mapping catheter (decapolar or duo-decapolar) will be advanced into the LA. The circular mapping catheter will be placed sequentially within each PV to record baseline electrical activity (PV potentials; PVPs). Via a second transseptal access, an irrigated-tip contact-force sensing RF ablation catheter (Thermocool SmartTouch or SmartTouch Surround Flow, Biosense Webster) will be positioned in the LA. Circumferential ablation lesions will be placed via the ablation catheter 1-2 cm from the PV ostia to electrically isolate the PV, as per standard practice.(44) RF energy will be delivered at 20-35 Watts to a maximum temperature of 43°C. The contact force targeted prior to lesion delivery will be 20 g (acceptable range 10-40 g), with a minimum individual target lesion duration of 400 gram-

seconds force-time integral (FTI). Circumferential lesions around the veins will be considered complete when the procedural endpoint has been reached (see below).

Cryoballoon Ablation

For patients randomized to cryoballoon ablation the transseptal sheath will be exchanged over a guidewire with a steerable 15-Fr sheath (**FlexCath, Medtronic**). Before introducing the balloon catheter (**Arctic Front Advance, Medtronic)** in the sheath a 15 or 20 mm diameter circular mapping catheter (CMC) will be inserted in the central lumen of the cryoballoon. A 23 or 28 mm cryoballoon will be advanced through the steerable sheath into the LA with the CMC used as a guidewire. While use of the larger (28-mm) cryoballoon is preferred, the 23-mm cryoballoon may be used based on physician judgment for PV diameters <20 mm.(49-51) Before ablation, the CMC will be positioned in the venous ostium to record baseline electrical activity. The CMC will then be advanced more distally for support. The cryoballoon will be positioned in the venous ostium and the degree of occlusion will be tested through the injection of 1:1 diluted contrast material. Vessel occlusion will be evaluated according to a semi-quantitative grading (**Supplementary Table 3**). Prior to ablation of right-sided PVs, a catheter will be placed in the superior vena cava cranial to the right superior PV in order to pace the right phrenic nerve (10-20 mA at 1.0-2.0 msec pulse width at a cycle length of 1000 msec). Ablation will be immediately terminated upon any perceived reduction in the strength of diaphragmatic contraction or a 30% reduction in the diaphragmatic compound motor action potential (CMAP) amplitude as measured via diaphragmatic electromyography.(52) If the procedure is performed under general anesthesia, paralytic agents will be discontinued at least 30 minutes prior to phrenic nerve pacing.

a) **Patients randomized to standard cryoballoon ablation** will undergo cryoablation with target duration of 4 minutes. Once PVI is achieved a single additional application of 4 minute cryoapplication will be delivered after the rewarming phase (to +20^{o}C).

b) **Patients randomized to short cryoballoon Ablation** will undergo cryoablation with target duration of 2 minutes. Once PVI is achieved a single additional 2 minute cryoapplication will be delivered after the rewarming phase (to +20^{o}C).

Ineffectual cryolesions: Excepting common ostia, cryoablation lesions that fail to isolate the vein (if real-time PV potential monitoring is feasible) or fail to achieve a temperature colder than minus 35°C after 60 seconds of ablation onset will be considered ineffectual and be terminated. Thereafter, the balloon and/or guidewire should be repositioned and a new lesion delivered.

Inability to Isolate: Should the operator fail to isolate the PV (excluding common ostia) after a minimum of 3 attempted cryoballoon applications, then focal ablation with the 8 mm cryocatheter (Freezor Max) targeted to sites of LA-PV breakthrough will be permitted at operator discretion.

Procedural Endpoint

For all three treatment arms the ablation procedure will be considered successful when PVI, as confirmed by bidirectional conduction block between PV and LA, has been achieved in accordance with the 2012 HRS/EHRA/ECAS consensus document.(44) Bidirectional conduction block is defined as the combination of entrance block (the stable absence of conduction into the PV from the LA) and exit block (the stable absence of conduction from the PV into the LA, either spontaneous or during pacing from the circular mapping catheter positioned at the PV ostium). Patients remaining in AF at the end of the procedure will be electrically or chemically cardioverted back to sinus rhythm. Remapping of all PVs post cardioversion will be performed to the procedural endpoint.

Evaluation of Spontaneous Reconnection and Dormant Conduction

For all three treatment arms a 20-minute observation period (beginning at the end of the last ablation lesion) will be used to assess spontaneous recovery of conduction.(44) If spontaneous reconnection occurs, the reconnected PVs will be re-isolated according to the randomised protocol.

Dormant conduction will be assessed with the use of a circular catheter in each PV by intravenous injection of 6 mg or more of adenosine to obtain at least 1 blocked P wave or a sinus pause ≥3 seconds. Dormant conduction will be defined by reappearance of PV conduction

for ≥1 beat. If there is no dormant conduction in any PV, then the procedure will be considered complete. If dormant conduction is elicited, the patient will undergo additional targeted ablation according to the randomised protocol until dormant conduction is abolished (i.e. adenosine fails to induce reconnection in any PV).

Post-ablation follow-up

Barring complications, patients will be discharged within 24 hours after the ablation procedure. All patients will remain anticoagulated for ≥3 months post procedure. While discontinuation of oral anticoagulation during the study period is strongly discouraged, in patients with a CHA_2DS_2VaSC score of <2, aspirin alone may be considered at treating physician discretion. Arrhythmia recurrence during the first 3 months post-ablation may be treated with cardioversion and/or antiarrhythmic drugs (except amiodarone). Where possible, repeat ablation procedures will be deferred until after the 3-month blanking period due to the potential for delayed cure (as per standard practice and in accordance with HRS/ECAS/EHRA recommendations).(44) If antiarrhythmic drugs (except amiodarone) are used in the first 3 months post ablation, they will be discontinued 5 half-lives before the end of the 3-month blanking period.(44) Scheduled follow-up visits will occur at 3, 6, and 12 months from the first ablation procedure (within a 2-week margin). A 24-hour Holter and 12-lead ECG will be performed at 3, 6, and 12 months. Automatic transmissions from the ICM will be obtained on a daily basis via CareLink. Patients will be instructed to record symptomatic episodes via use of the patient activator.

STUDY OUTCOMES

Primary endpoint is time to first recurrence of symptomatic or asymptomatic AF, atrial flutter, or atrial tachycardia (AF/AFL/AT) documented by 12-lead ECG, surface ECG rhythm strips, 24-hour ambulatory ECG (Holter) monitor, or on ILR between days 91 and 365 post ablation, or a repeat ablation procedure between days 0 and 365 post ablation. AF or atrial flutter/tachycardia will qualify as an arrhythmia recurrence after ablation if it lasts 30 seconds or longer (on surface ECG rhythm strips, 24-hour ambulatory Holter monitor) or 120 seconds or longer on ICM (the minimum programmable episode interval). All tracings will be

independently adjudicated by a committee blinded to treatment allocation. The primary end point and the 3-month blanking period adhere to the Heart Rhythm Society recommendations for reporting outcomes in AF ablation trials.(44)

Secondary endpoints are listed in Table 4 of the Supplementary Appendix.

SAMPLE SIZE

The sample size was determined based on the primary endpoints for the two main comparisons of interest: cryoablation with a 4-minute application vs. contact force guided RF catheter ablation, and cryoablation with a 2-minute application vs. RF catheter ablation. Overall event-free survival at one year is estimated to be 65%. With a sample size of 111 per group and a two-sided 0.025 significance level (to account for the two main comparisons), the study will have 80% power (using a log rank test) to detect a relative difference of 20% between contact force RF catheter ablation and either of the two cryoballoon ablation groups. Factoring in a 4% loss to follow-up, 116 patients per group should be randomized, for a total study population of 348. Power calculations are based on the log-rank test for equality of survival curves (nQuery, version 6.01), using simulated data.

STATISTICAL ANALYSES

Analysis of the primary and secondary endpoints will be based on the intention-to-treat principle according to the initial allocated strategy. Survival curves will be estimated by the Kaplan-Meier method and compared by the log rank test. The two main comparisons will be cryoablation with a 4-minute application vs. RF catheter ablation, and cryoablation with a 2-minute application vs. RF catheter ablation. The comparison between the two cryoablation groups will be considered secondary.

A Cox proportional hazards model will also be used to test the consistency of the group effect while accounting for clinically important baseline characteristics, which will include: ablation site, age, gender, race, weight, LA size, structural heart disease, AF duration, and number of AADs used in the past. The proportional hazard assumption will be assessed by visual inspection of the log-negative-log plot and through a formal test of the interaction term “group x time” at

α=0.05. Should this assumption fail, a stratified Cox model will be fitted in order to correct for non-proportional hazards if possible or, if ineffective, time-dependent variables will be introduced. Should these corrective techniques fail, logistic regression will be used instead.

Secondary endpoints expressed as time-to-event will be analyzed similarly using Kaplan-Meier survival curves and a log rank test. For all dichotomous qualitative variables, Chi-Square tests will be performed to assess group differences. Continuous variables, such as arrhythmia burden, will be analyzed using an analysis of variance (ANOVA). If the data are not normally distributed, then the non-parametric Wilcoxon Signed Rank test will be used. Health-related quality of life scores will be compared by analysis of covariance, adjusting for baseline values to reduce the error mean squares. In the event of missing data, a multiple imputation approach using SAS procedures PROC MI and PROC MIANALYZE will be considered. All tests will be conducted at an alpha level of 0.05 with the exception of the two main comparisons that will be conducted at an alpha level of 0.025. Similarly, hazard ratios for these two comparisons will be presented with 97.5% confidence intervals.

ETHICS AND DISSEMINATION:

Enrolment in the trial is predicated on assumption that patients have already made the decision to undergo a catheter ablation procedure for drug-refractory AF. The catheter ablation procedure used in this study is the same as the standard treatment method for AF and is not experimental. The risks of participation are therefore the same as those of standard atrial fibrillation ablation and independent of trial enrolment participants in the study would have accepted these risks. Institutional review board approval

The dissemination plan for the trial encompasses multiple modalities and strategies including an integrated and an end of project KT strategy. The integrated approach of the program benefits from the involvement of non-profit organizations with a mandate of end-user engagement and education (the Heart and Stroke Foundation), patients (the end-user), and healthcare professionals. The involvement of these groups from the planning phase through to completion represents an optimal strategy for engagement and empowerment, essentially creating invested champions at each level. Post project KT will leverage the involvement of

these groups to optimize the ability to reach the end-users. The information derived herein (whether positive, or negative) will be disseminated through established channels such as peer-reviewed publication, national and international meetings, webinars, and through social media. The involvement of Medtronic CryoCath, will facilitate dissemination of the findings to end users through their established educational infrastructure (Medtronic Academy website, large scale technology “user meetings”, to small group interactive conferences through their clinical specialist network). The end result of this KT plan will be the delivery of the optimal tailored treatment strategy to the individual patient at the optimal time.

CONCLUSIONS:

The CIRCA-DOSE study is the first multicenter prospective randomised clinical trial comparing cryoballoon-based PVI to irrigated contact-force guided RF energy, and cryoablation duration, with an endpoint based on continuous cardiac monitoring.

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Footnotes

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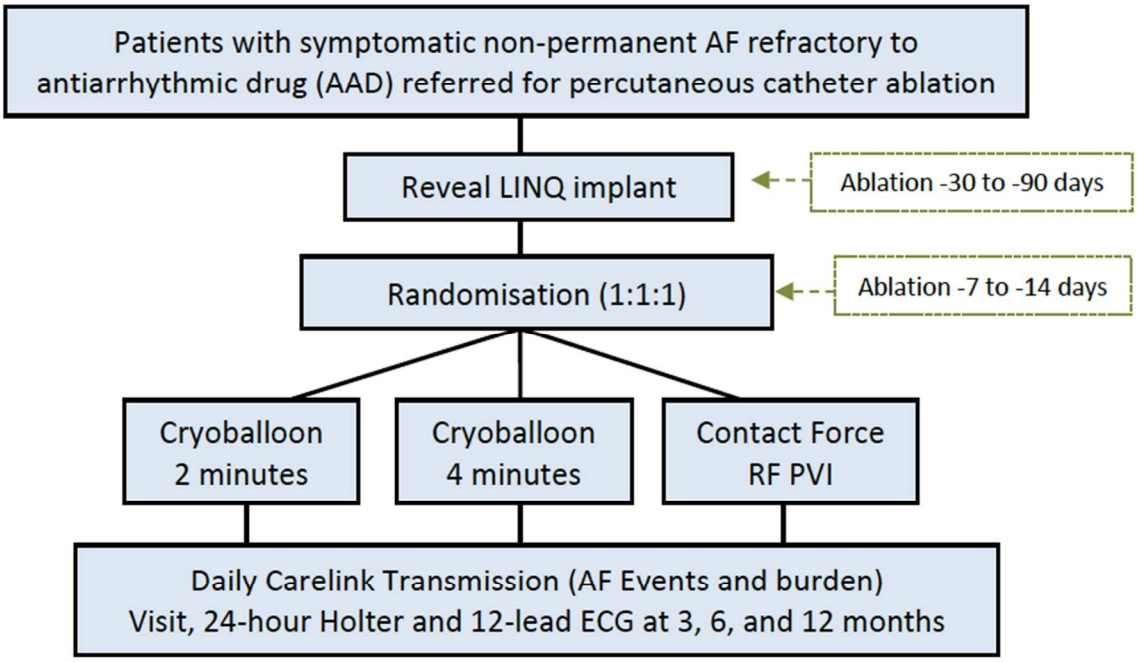
Ethics Approval: University of British Columbia Office of Research (Services) Ethics Clinical Research Ethics Board, as well as the local institutional review boards for each of the participating sites.

CIRCA-DOSE: Methods and Rationale

Figure 1: Study Flow diagram



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CIRCA-DOSE: Methods and Rationale

Supplementary Table 1: ***Inclusion and Exclusion Criteria***

INCLUSION CRITERIA
• Non-permanent atrial fibrillation documented on a 12 lead ECG, Trans Telephonic Monitoring (TTM) or Holter monitor within the last 24 months (Episodes of AF must be >30 seconds in duration to qualify as an inclusion criterion) • Age of 18 years or older on the date of consent • Candidate for ablation based on AF that is symptomatic and refractory (ineffective or intolerant) to at least one class 1 or 3 antiarrhythmic. • Continuous anticoagulation with warfarin (INR 2-3), low molecular weight heparin, or a direct oral antithrombotic (dabigatran, apixaban, rivaroxaban) for ≥4 weeks prior to the ablation; or a TEE that excludes LA thrombus ≤48 hours before ablation
EXCLUSION CRITERIA
• Previous left atrial (LA) ablation or LA surgery • AF due to reversible cause (e.g. hyperthyroidism, cardiothoracic surgery) • Intracardiac Thrombus • Pre-existing pulmonary vein stenosis or PV stent • Pre-existing hemidiaphragmatic paralysis • Contraindication to anticoagulation or radiocontrast materials • Anteroposterior LA diameter greater than 5.5 cm by TTE • Cardiac valve prosthesis • Clinically significant (moderately-severe, or severe) mitral valve regurgitation or stenosis • Myocardial infarction, PCI / PTCA, or coronary artery stenting during the 3-month period preceding the consent date • Cardiac surgery during the three-month interval preceding the consent date • Significant congenital heart defect (including atrial septal defects or PV abnormalities but not including PFO) • NYHA class III or IV congestive heart failure • Left ventricular ejection fraction (LVEF) less than 35% • Hypertrophic cardiomyopathy (Wall thickness >1.5 cm) • Significant Chronic Kidney Disease (CKD - eGFR <30 µMol/L) • Uncontrolled hyperthyroidism • Cerebral ischemic event (strokes or TIAs) during the six-month interval preceding the consent date • Pregnancy • Life expectancy less than one (1) year • Currently participating or anticipated to participate in any other clinical trial of a drug, device or biologic during the duration of this study • Unwilling or unable to comply fully with study procedures and follow-up

Supplementary Table 2: Implantable cardiac monitor programming

AF detection threshold	Balanced Sensitivity
Ectopy rejection	Nominal
Episode storage threshold	All (Record ECG of 2 minutes)

These parameters were chosen to optimise detection of AF (reported sensitivity of 96.1% with a positive predictive valve [PPV] of 73%), however al arrhythmia episodes will be independently adjudicated.[18, 19]

CIRCA-DOSE: Methods and Rationale

Supplementary Table 3: Gradation of pulmonary venous occlusion during cryoballoon ablation
Grade 1 – negligible occlusion with immediate rapid outflow from the PV
Grade 2 – mild backflow into the atrium
Grade 3 – minimal backflow into the atrium
Grade 4 – total contrast retention with no backflow into the atrium.

Supplementary Table 4: Secondary Endpoints

1) Time to first recurrence of symptomatic documented AF/AFL/AT between days 91 and 365 after ablation or a repeat ablation procedure between days 0 and 365 post ablation
2) Arrhythmia burden (daily AF burden - hours/day; overall AF burden - % time in AF)
3) Proportion of patients experiencing an acute or adenosine provoked PV reconnection during the index ablation procedure
4) Proportion of patients requiring a repeat ablation procedure because of documented recurrence of symptomatic AF/AFL/AT
5) Proportion of patients prescribed AADs because of documented recurrence of symptomatic AF/AFL/AT; 6) Proportion of patients with AF/AFL/AT during the first 90 days post ablation
7) Emergency visit or hospitalization >24h in a health-care facility
8) Major complications including death, stroke, TIA, Myocardial Infarction or systemic thromboembolism, PV stenosis, phrenic nerve palsy, pericarditis, pericardial effusion, cardiac perforation or tamponade, hematoma, AV fistula, pseudoaneurysm, esophageal injury and atrio-esophageal fistulae (both individually and as a composite endpoint)*
9) Overall and disease specific quality of life
10) Single and multiple procedure success (freedom from symptomatic or asymptomatic electrocardiographically documented AF/AFL/AT) after the first and last ablation procedure respectively
11) Single and multiple procedure success (freedom from symptomatic electrocardiographically documented AF/AFL/AT) after the first and last ablation procedure respectively.

*Complication definition as per 2012 HRS/EHRA/ECAS recommendations. Acute peri-procedural complications will be defined as occurring within 30 days of ablation, with delayed complications occurring 31-365 days after ablation

CIRCA-DOSE: Methods and Rationale

A major complication is a complication that results in permanent injury or death, requires intervention for treatment, or prolongs or requires hospitalization for more than 48 hours.Because early recurrences of AF/AFL/AT are to be expected following AF ablation, recurrent AF/AFL/AT within 3 months that requires or prolongs a patient's hospitalization should not be considered to be a major complication of AF ablation.

CIRCA-DOSE: Methods and Rationale

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	3
	2b	Specific objectives or hypotheses	4
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	9
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	n/a
Participants	4a	Eligibility criteria for participants	8
	4b	Settings and locations where the data were collected	8
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	9
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	12
	6b	Any changes to trial outcomes after the trial commenced, with reasons	n/a
Sample size	7a	How sample size was determined	13
	7b	When applicable, explanation of any interim analyses and stopping guidelines	n/a
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	9
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	9
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	9
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	9
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	13

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	n/a
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	13
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	14
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	n/a
	13b	For each group, losses and exclusions after randomisation, together with reasons	n/a
Recruitment	14a	Dates defining the periods of recruitment and follow-up	n/a
	14b	Why the trial ended or was stopped	n/a
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	n/a
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	n/a
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	n/a
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	n/a
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	n/a
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	n/a
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	n/a
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	n/a
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	n/a
Other information			
Registration	23	Registration number and name of trial registry	2, 8
Protocol	24	Where the full trial protocol can be accessed, if available	This submission
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	1

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

BMJ Open

A Randomized Clinical Trial of Cryoballoon vs. Irrigated Radiofrequency Catheter Ablation for Atrial Fibrillation: The effect of Double Short vs. Standard Exposure Cryoablation Duration During Pulmonary Vein Isolation (CIRCA-DOSE) - Methods and Rationale

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Keywords:	atrial fibrillation, ablation, cryoablation

A Randomized Clinical Trial of Cryoballoon vs. Irrigated Radiofrequency Catheter Ablation for Atrial Fibrillation: The effect of Double Short vs. Standard Exposure Cryoablation Duration During Pulmonary Vein Isolation (CIRCA-DOSE) - Methods and Rationale

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CIRCA-DOSE: Methods and Rationale

ABSTRACT

Introduction: Pulmonary vein (PV) isolation (PVI) is an effective therapy for paroxysmal atrial fibrillation (AF), but has limitations. The two most significant recent advances have centered on the integration of real-time quantitative assessment of catheter contact force into focal radiofrequency (RF) ablation catheters, and the development of dedicated ablation tools capable of achieving PVI with a single ablation lesion (Arctic Front™ cryoballoon, Medtronic, Minneapolis, MN). While each of these holds promise for improving the clinical success of catheter ablation of AF, there has not been a rigorous comparison of these advanced ablation technologies. Moreover, the optimal duration of cryablation (freezing time) has not been determined.

Methods and Analysis: Patients undergoing a first PVI procedure for paroxysmal AF will be recruited. Patients will be randomized 1:1:1 between contact force irrigated RF ablation, short duration cryoballoon ablation (2 minute applications) and standard duration cryoballoon ablation (4 minute applications). The primary outcome is time to first documented AF recurrence on implantable loop recorder. With a sample size of 111 per group and a two-sided 0.025 significance level (to account for the two main comparisons), the study will have 80% power (using a log rank test) to detect a difference of 20% between contact force RF catheter ablation and either of the two cryoballoon ablation groups. Factoring in a 4% loss to follow-up, 116 patients per group should be randomized and followed for a year (total study population of 348).

Ethics and Dissemination: The study was approved by the University of British Columbia Office of Research (Services) Ethics Clinical Research Ethics Board. Results of the study will be submitted for publication in a peer-reviewed journal.

Trial Registration number: ClinicalTrials.gov **NCT01913522**

AUTHORS CONTRIBUTIONS:

JA, MD, and PK conceived the study. JA, ASLT, AV, LM, PK, MD, MWD, GAW were involved in the drafting of the peer-reviewed grant, the study protocol, and the manuscript. MB, JC, PLS, PN, JFR, JS, AV served on the steering committee for the trial, and have provided critical revision of the manuscript.

STRENGTHS AND LIMITATIONS OF THE STUDY

- The CIRCA-DOSE is the first large multicenter randomised trial evaluating modern ablation technologies (contact force guided RF ablation compared to second-generation cryoballoon ablation)
- In addition, the trial will also evaluate the optimal cryoablation duration for patients undergoing cryoballoon ablation, potentially improving procedural access and minimising the risk of recurrence.
- The trial uses continuous arrhythmia monitoring via implantable cardiac devices, and thus represents one of the most robust AF ablation trials performed to date.
- In addition to the dichotomous endpoint of arrhythmia recurrence, the CIRCA-DOSE trial will be able to evaluate the effect of ablation on arrhythmia burden.

CIRCA-DOSE: Methods and Rationale

INTRODUCTION

Atrial fibrillation (AF) is a common chronic progressive disease, characterized by exacerbations and remissions. Over the past 10-15 years, multiple large-scale observational studies and randomized controlled trials have demonstrated that catheter ablation is superior to AAD therapy in maintaining sinus rhythm.[1-10] In addition, catheter ablation has been shown to be superior to anti-arrhythmic drugs (AADs) for the improvement of symptoms, exercise capacity, and quality of life.[4 11-13] Unfortunately, the results of ablation are limited by arrhythmia recurrence, which is most often due to a failure to effectuate a lasting contiguous circumferential transmural myocardial lesion around the PV ostia.[1 3-10 14 15] In response considerable effort has been directed towards developing technologies to achieve safer and more durable PV isolation (PVI). The two most significant advances in the last few years have centered on the integration of real-time quantitative assessment of catheter contact force into focal radiofrequency (RF) ablation catheters, and the development of dedicated ablation tools capable of achieving PVI with a single ablation lesion, the most mature of which is the Arctic Front™ cryoballoon (Medtronic, Minneapolis, MN).

While each of these advances holds promise for improving the clinical success of catheter ablation of AF, there has not been a rigorous comparison of the current generations of contact-force assisted RF ablation versus the use of the second-generation cryoballoon. Moreover, many technical aspects of the use of each technology have yet to be fully elucidated. Specifically, in the case of the cryoballoon the optimal cryoablation duration has not been determined.[16] The CIRCA-DOSE trial has been designed to evaluate these two questions. The CIRCA-DOSE study is a multi-center randomised trial designed to rigorously evaluate the effectiveness of contact-force assisted RF PVI versus PVI performed with the second-generation cryoballoon, as well as evaluate the optimal cryoablation duration.

Contact Force Ablation

Ablation electrode-tissue contact is an important determinant of lesion size, and ultimately durability of conduction block. Conventionally, this has been assessed by the operator using a combination of fluoroscopic imaging of the catheter tip motion, tactile feedback and local

electrogram attenuation, as well as impedance reductions during energy delivery. While widely used, the accuracy of these surrogate measures is poor. Contact force sensing is a newly developed technology that allows for real-time estimation of the contact force between the tip of the catheter and target myocardium, thus providing the operator with an accurate quantitative assessment of tissue contact.

Recent data suggest that incorporating real-time contact force assessment results in a reduction in procedure time, ablation time and total energy delivery, with a comparable safety profile to that observed with standard irrigated RF.[17 18] However, the two largest multicenter trials evaluating this technology demonstrated a one-year success of 68% (TactiCath, TOCCASTAR) and 74% (SmartTouch, SMART-AF).[19 20] In the case of the former the success was no different from that observed with standard non-contact force RF ablation. Interestingly, post-hoc analyses of these studies suggested that the outcomes were improved when the procedure was performed with adequate contact-force parameters (84% one-year freedom from AF in the 47% of patients in whom ablation was in the target range ≥80% of the time in SMART-AF, and 76% one-year freedom from AF in the 57% of patients in whom ≥90% of the lesions were >10 g in TOCCASTAR). No differences in the incidence of complications have been reported between patients undergoing ablation with contact force vs. non-contact force sensing RF ablation catheters.[19 21 22]

Cryoballoon Ablation

Recent studies have examined short- and long-term success with the second-generation cryoballoon. Studies of planned re-mapping procedures have demonstrated that the durability of PVI at three months post index ablation procedure was improved at 91% with the second generation cryoballoon, compared to 67% of PVs with standard (non-contact force) RF, and 88% of PVs with the first generation cryoballoon.[18 23-27] Clinically this has translated into a one-year freedom from recurrent AF of 82% with the second generation cryoballoon (11 studies; 1725 patients), which was significantly improved compared to the first generation cryoballoon in a separate comparative meta-analysis (odds ratio of arrhythmia recurrence 0.34 [0.26-0.45] when compared to first-generation cryoballoon; 10 studies, 2310 patients).[28] From a safety

standpoint there were significantly more phrenic nerve palsies (transient and persistent) observed with the second generation cryoballoon.

Contact Force Ablation vs. Cryoballoon Ablation

There is limited data directly comparing contact-force guided RF ablation to cryoballoon ablation. Since the inception of the CIRCA-DOSE study, three observational studies have reported comparable safety and efficacy between contact-force guided RF ablation and cryoballoon ablation for paroxysmal (2 studies) and persistent (1 study) AF. Specifically, Jourda et al. reported a single-centre experience with 150 consecutive patients undergoing PVI for paroxysmal AF with the second generation cryoballoon (75 patients), and contact-force guided irrigated RF ablation (SmartTouch, 75 patients).[29] In this non-randomised study the one-year freedom from recurrent AF (as detected by Holter monitoring at 1, 3, 6, 9, and 12 months) was 85% in the cryoballoon group and 88% in the contact-force group (P=0.988). Squara et al. reported a similar 1-year freedom from recurrent paroxysmal AF (73% in the cryoballoon group and 76% in the contact-force group [SmartTouch and Tacticath]; P=0.63) in their ambidirectional (combined prospective and retrospective enrolment) multi-centre cohort study of 4 participating centres (2 centers performed both cryoballoon and RF ablation; 1 centre performed exclusively cryoballoon ablation; and 1 performed exclusively RF ablation).[30] Lastly, Ciconte et al. reported a single-centre experience with 100 consecutive patients undergoing PVI for persistent AF with the second generation cryoballoon (50 patients), and contact-force guided irrigated RF ablation (SmartTouch and Tacticath, 50 patients).[31] In this non-randomised study the one-year freedom from recurrent AF (as detected by Holter monitoring at 1, 3, 6, and 12 months) was 60% in the cryoballoon group and 56% in the contact-force group (P=0.78). While none of these studies demonstrated a significant difference in the incidence of complications a recent meta-analysis observed a lower incidence of pericardial effusion (OR 0.44; 95%CI 0.28-0.69; P<0.01) and tamponade (OR 0.31; 95%CI 0.15-0.64; P<0.01) with cryoballoon ablation in comparison to contact-force guided RF ablation, whereas transient phrenic nerve palsy was more frequent after cryoballoon (OR 7.40; 95%CI 2.56–21.34; P<0.01).[32]

The multicentre, randomized FIRE and ICE trial was designed to determine whether cryoballoon ablation was non-inferior to RF ablation in symptomatic patients with drug-refractory paroxysmal AF.[33] Patients were randomised to Arctic Front-based cryoballoon ablation (374 patients), vs. irrigated RF ablation (376 patients). The primary efficacy endpoint (documented recurrence of AF/AT/AFL >30s, AAD prescription, or re-ablation) occurred in 138 patients in the cryoballoon group and in 143 in the RF group (1-year Kaplan–Meier event rate estimates, 34.6% and 35.9%, respectively; hazard ratio, 0.96; 95% confidence interval [CI], 0.76 to 1.22; P<0.001 for noninferiority). However, despite reporting recently it is important to note that the study was not an exclusive comparison of advanced technologies, with the majority of patients receiving non-contact force irrigated RF ablation (284/376 in the RF group) and a significant proportion (90 of 374 patients) receiving first generation cryoballoon ablation. As such the relative safety and efficacy of these new technologies remains unknown.

Data Supporting Shorter Freeze Durations

The optimal duration of freezing, that is, how long the tissue should be kept in the frozen state, is not well established. Current recommendations are for cryoablation dosing at 240 seconds for each application, which is based on studies of an early focal cryocatheter. In these studies, it was observed that the effect of a cryoablation lesion reached a plateau of three-minutes after the onset of ablation. Thereafter "prolongation of exposure time beyond 3 minutes did not result in any further increase in lesion dimension or volume."[34 35] Since then, the cryocatheter has evolved from a rigid focal catheter to a semi-compliant balloon, which necessitated a redesign of the cryorefrigerant delivery mechanisms. Moreover, the refrigerant itself has changed from slow-cooling to more efficacious gases (i.e., nitrous oxide).

Information regarding the safety and efficacy of shorter cryoballoon ablation durations are limited to 3 minute lesions, which have been suggested in several non-randomised studies to be of comparable efficacy to longer duration cryolesions.[36 37] We recently completed a randomized pre-clinical study examining the immediate and delayed effects of shorter ablation time on PVI efficacy.[38] In our study, thirty-two mongrel dogs underwent cryoballoon ablation

with a 23-mm cryoballoon catheter. PVI procedures were randomized to a single 2-minute vs. 4-minute cryoballoon application. Although 4-minute lesions were associated with a thicker neointima than 2-minute lesions (223.8µm vs. 135.6µm; p=0.007), no differences were observed in the rates of procedural PVI, or the achievement of complete circumferentially transmural lesions at 30 days (78% overall; 86.2% for 2-min vs. 70% for 4-min; P=0.285), however a reduction in late PV strictures was observed in the 2 minute group (6/30 PVs with strictures in the 4-minute freeze duration vs. 0/29 PVs with strictures in the 2-minute freeze duration; p=0.024).

Arrhythmia Monitoring

While from a patient perspective the freedom from symptoms related to AF may be the most important clinical endpoint, contemporary evidence suggests that there is a poor correlation between symptoms and AF burden.[39 40] Moreover the presence or absence of symptoms does not affect the prognosis and complications of the AF.[41] As such any evaluation of treatment efficacy must include protocol-determined arrhythmia monitoring. Given that paroxysmal AF is by definition a disease of clusters, studies have shown that the detection of AF recurrence is proportional to the duration of monitoring.[42] Specifically, Kottkamp et al. demonstrated an increased detection of arrhythmia recurrences post AF ablation for highly symptomatic AF in a group undergoing serial 7-day ECG monitoring versus those undergoing only intermittent ECG monitoring (26% vs. 12% documented recurrence).[43] Unfortunately, while non-invasive intermittent rhythm monitoring remains the most widely utilised method of ascertaining ablation efficacy it often fail to detect AF recurrence. Specifically the sensitivity (31-71%) and negative predictive value (21-39%) are significantly inferior to continuous monitoring techniques.[44] This imprecision associated with intermittent arrhythmia monitoring confers a significant risk of Type II error, which makes it inappropriate for outcome ascertainment in a trial designed to evaluate the efficacy of different therapeutic interventions.

As such, a major strength of the current study is the reliance on continuous cardiac monitoring for the determination of arrhythmia outcomes. All participants in the CIRCA-DOSE trial will have an implantable cardiac monitor with an automated AF detection algorithm (REVEAL LINQ)

inserted a minimum of 1 month prior to ablation. This subcutaneous implantable cardiac monitor continuously analyses the beat-to-beat variability of cardiac cycles leading to an accurate determination of the timing of arrhythmia recurrence, as well as an accurate quantification of atrial fibrillation burden (hours in AF per day, and percentage of overall time in AF). With respect to this latter point, the use of AF burden allows for a more detailed examination of the relatively efficacy of the three-different treatment approaches, beyond which can be obtained with dichotomous event analyses such as "time-to-first-AF recurrence." Unfortunately, intermittent rhythm monitoring techniques are unable to accurately quantify AF burden.[44]

METHODS AND ANALYSIS

Study Design

The CIRCA-DOSE study (ClinicalTrials.gov #**NCT01913522**) is a multicentre prospective randomized clinical trial. The study will be conducted at 8 clinical centres in Canada. Patients with symptomatic paroxysmal and early persistent AF refractory to at least one AAD and referred for first percutaneous catheter ablation will be enrolled (**Figure 1**). At least 1 episode of AF must be documented on 12-lead electrocardiogram (ECG), transtelephonic monitor (TTM), or Holter monitor within 24 months of randomization (Inclusion and exclusion criteria are detailed in **Supplementary Table 1)**.[45]

All patients will undergo the implantation of an implantable cardiac monitor (ICM) with an AF detection algorithm a minimum of 30 days prior to the index ablation for the purpose of arrhythmia monitoring (Reveal LINQ, Medtronic). The ICM analyzes beat-to-beat variability of cardiac cycles on a 2-minute ECG strip and stores the tracing for independent adjudication. The device is also capable of quantifying the amount of AF per day, and the overall AF burden (percentage of the observed time that a patient is in AF). Additionally, the patient can activate the device manually to facilitate analysis of heart rhythm during symptomatic events. ICM programmed parameters are summarized in **Supplementary Table 2**.

Patients will be assigned in a 1:1:1 ratio using permuted block randomization stratified by site to: 1) Standard RF ablation guided by tissue-contact force; 2) Short cryoballoon ablation duration (2-minute cryoapplications); and 3) Standard cryoballoon ablation duration (4-minute cryoapplications). Patients will be blinded to their randomization assignment.

Catheter Ablation Procedure

Effective anticoagulation with oral vitamin K antagonists (target INR between 2-3), low molecular weight heparin, or dabigatran/apixaban/rivaroxaban for at least one month and/or the exclusion of a left atrial (LA) thrombus by transesophageal echocardiography (TEE; <48 hours pre-ablation) is mandated prior to ablation.[46] Antiarrhythmic drugs will be discontinued five half-lives before the procedure, except for amiodarone, which will be discontinued 8 weeks prior to ablation. Interventions will be performed on patients in the fasting state under conscious sedation or general anesthesia, per local practice.

For each of the three treatment arms, patients will undergo pulmonary vein isolation (PVI) according to standard clinical practice.[46-49] No prophylactic LA linear ablation lesions, or ablation of complex fractionated atrial electrograms (CFAE) will be permitted in addition to PV isolation. In the event of documented right atrial cavotricuspid isthmus dependent flutter, cavotricuspid isthmus ablation is permitted (with irrigated RF or focal cryoablation).

Contact-Force Guided Radiofrequency Ablation

For patients randomized to RF catheter ablation a three-dimensional, non-fluoroscopic mapping system (CARTO3, Biosense Webster) will be used for anatomic reconstruction. Through one transseptal access, a circular mapping catheter (decapolar or duo-decapolar) will be advanced into the LA. The circular mapping catheter will be placed sequentially within each PV to record baseline electrical activity (PV potentials; PVPs). Via a second transseptal access, an irrigated-tip contact-force sensing RF ablation catheter (Thermocool SmartTouch or SmartTouch Surround Flow, Biosense Webster) will be positioned in the LA. Circumferential ablation lesions will be placed via the ablation catheter 1-2 cm from the PV ostia to electrically isolate the PV, as per standard practice.[45] RF energy will be delivered at 20-35 Watts to a

maximum temperature of 43°C. The contact force targeted prior to lesion delivery will be 20 g (acceptable range 10-40 g), with a minimum individual target lesion duration of 400 gram-seconds force-time integral (FTI). Circumferential lesions around the veins will be considered complete when the procedural endpoint has been reached (see below).

Cryoballoon Ablation

For patients randomized to cryoballoon ablation the transseptal sheath will be exchanged over a guidewire with a steerable 15-Fr sheath (**FlexCath, Medtronic**). Before introducing the balloon catheter (**Arctic Front Advance, Medtronic)** in the sheath a 15 or 20 mm diameter circular mapping catheter (CMC) will be inserted in the central lumen of the cryoballoon. A 23 or 28 mm cryoballoon will be advanced through the steerable sheath into the LA with the CMC used as a guidewire. While use of the larger (28-mm) cryoballoon is preferred, the 23-mm cryoballoon may be used based on physician judgment for PV diameters <20 mm.[50-52] Before ablation, the CMC will be positioned in the venous ostium to record baseline electrical activity. The CMC will then be advanced more distally for support. The cryoballoon will be positioned in the venous ostium and the degree of occlusion will be tested through the injection of 1:1 diluted contrast material. Vessel occlusion will be evaluated according to a semi-quantitative grading (**Supplementary Table 3**). Prior to ablation of right-sided PVs, a catheter will be placed in the superior vena cava cranial to the right superior PV in order to pace the right phrenic nerve (10-20 mA at 1.0-2.0 msec pulse width at a cycle length of 1000 msec). Ablation will be immediately terminated upon any perceived reduction in the strength of diaphragmatic contraction or a 30% reduction in the diaphragmatic compound motor action potential (CMAP) amplitude as measured via diaphragmatic electromyography.[53] If the procedure is performed under general anesthesia, paralytic agents will be discontinued at least 30 minutes prior to phrenic nerve pacing.

a) **Patients randomized to standard cryoballoon ablation** will undergo cryoablation with target duration of 4 minutes. Once PVI is achieved a single additional application of 4 minute cryoapplication will be delivered after the rewarming phase (to +20°C).

b) **Patients randomized to short cryoballoon Ablation** will undergo cryoablation with target duration of 2 minutes. Once PVI is achieved a single additional 2 minute cryoapplication will be delivered after the rewarming phase (to +20°C).

Ineffectual cryolesions: Excepting common ostia, cryoablation lesions that fail to isolate the vein (if real-time PV potential monitoring is feasible) or fail to achieve a temperature colder than minus 35°C after 60 seconds of ablation onset will be considered ineffectual and be terminated. Thereafter, the balloon and/or guidewire should be repositioned and a new lesion delivered.

Inability to Isolate: Should the operator fail to isolate the PV (excluding common ostia) after a minimum of 3 attempted cryoballoon applications, then focal ablation with the 8 mm cryocatheter (Freezor Max) targeted to sites of LA-PV breakthrough will be permitted at operator discretion.

Procedural Endpoint

For all three treatment arms the ablation procedure will be considered successful when PVI, as confirmed by bidirectional conduction block between PV and LA, has been achieved in accordance with the 2012 HRS/EHRA/ECAS consensus document.[45] Bidirectional conduction block is defined as the combination of entrance block (the stable absence of conduction into the PV from the LA) and exit block (the stable absence of conduction from the PV into the LA, either spontaneous or during pacing from the circular mapping catheter positioned at the PV ostium). Patients remaining in AF at the end of the procedure will be electrically or chemically cardioverted back to sinus rhythm. Remapping of all PVs post cardioversion will be performed to the procedural endpoint.

Evaluation of Spontaneous Reconnection and Dormant Conduction

For all three treatment arms a 20-minute observation period (beginning at the end of the last ablation lesion) will be used to assess spontaneous recovery of conduction.[45] If spontaneous reconnection occurs, the reconnected PVs will be re-isolated according to the randomised protocol.

Dormant conduction will be assessed with the use of a circular catheter in each PV by intravenous injection of 6 mg or more of adenosine to obtain at least 1 blocked P wave or a sinus pause ≥3 seconds. Dormant conduction will be defined by reappearance of PV conduction for ≥1 beat. If there is no dormant conduction in any PV, then the procedure will be considered complete. If dormant conduction is elicited, the patient will undergo additional targeted ablation according to the randomised protocol until dormant conduction is abolished (i.e. adenosine fails to induce reconnection in any PV).

Post-ablation follow-up

Barring complications, patients will be discharged within 24 hours after the ablation procedure. All patients will remain anticoagulated for ≥3 months post procedure. While discontinuation of oral anticoagulation during the study period is strongly discouraged, in patients with a CHA_2DS_2VaSC score of <2, aspirin alone may be considered at treating physician discretion. Arrhythmia recurrence during the first 3 months post-ablation may be treated with cardioversion and/or antiarrhythmic drugs (except amiodarone). Where possible, repeat ablation procedures will be deferred until after the 3-month blanking period due to the potential for delayed cure (as per standard practice and in accordance with HRS/ECAS/EHRA recommendations).[45] If antiarrhythmic drugs (except amiodarone) are used in the first 3 months post ablation, they will be discontinued 5 half-lives before the end of the 3-month blanking period.[45] Scheduled follow-up visits will occur at 3, 6, and 12 months from the first ablation procedure (within a 2-week margin – Table 1). A 24-hour Holter and 12-lead ECG will be performed at 3, 6, and 12 months. Automatic transmissions from the ICM will be obtained on a daily basis via CareLink. Patients will be instructed to record symptomatic episodes via use of the patient activator.

STUDY OUTCOMES

Primary endpoint is time to first recurrence of symptomatic or asymptomatic AF, atrial flutter, or atrial tachycardia (AF/AFL/AT) documented by 12-lead ECG, surface ECG rhythm strips, 24-hour ambulatory ECG (Holter) monitor, or on ILR between days 91 and 365 post ablation, or a repeat ablation procedure between days 0 and 365 post ablation. AF or atrial

flutter/tachycardia will qualify as an arrhythmia recurrence after ablation if it lasts 30 seconds or longer (on surface ECG rhythm strips, 24-hour ambulatory Holter monitor) or 120 seconds or longer on ICM (the minimum programmable episode interval). All tracings will be independently adjudicated by a committee blinded to treatment allocation. The primary end point and the 3-month blanking period adhere to the Heart Rhythm Society recommendations for reporting outcomes in AF ablation trials.[45]

Secondary endpoints are listed in Table 4 of the Supplementary Appendix.

Event Adjudication: The clinical events committee will be composed of a Chairman, and six (6) reviewers with expertise in clinical event adjudication. The CEC is responsible for review and adjudication of all primary and secondary end-points, which include serious adverse events and major complications. Two reviewers will be assigned to review each endpoint and major complication. If both reviewers agree, the Chairman will be provided with the Reviewer's Forms and he will ratify the adjudication by completing the Final Adjudication Form. If the reviewers are in disagreement, the Chairman will review the event and will serve as the third reviewer. If there is still disagreement between all three reviewers, a meeting will be scheduled to discuss the event.

SAMPLE SIZE

The sample size was determined based on the primary endpoints for the two main comparisons of interest: cryoablation with a 4-minute application vs. contact force guided RF catheter ablation, and cryoablation with a 2-minute application vs. RF catheter ablation. Overall event-free survival at one year is estimated to be 65%. With a sample size of 111 per group and a two-sided 0.025 significance level (to account for the two main comparisons), the study will have 80% power (using a log rank test) to detect a relative difference of 20% between contact force RF catheter ablation and either of the two cryoballoon ablation groups. Factoring in a 4% loss to follow-up, 116 patients per group should be randomized, for a total study population of 348. Power calculations are based on the log-rank test for equality of survival curves (nQuery, version 6.01), using simulated data.

STATISTICAL ANALYSES

Analysis of the primary and secondary endpoints will be based on the intention-to-treat principle according to the initial allocated strategy. Survival curves will be estimated by the Kaplan-Meier method and compared by the log rank test. The two main comparisons will be cryoablation with a 4-minute application vs. RF catheter ablation, and cryoablation with a 2-minute application vs. RF catheter ablation. The comparison between the two cryoablation groups will be considered secondary.

A Cox proportional hazards model will also be used to test the consistency of the group effect while accounting for clinically important baseline characteristics, which will include: ablation site, age, gender, race, weight, LA size, structural heart disease, AF duration, and number of AADs used in the past. The proportional hazard assumption will be assessed by visual inspection of the log-negative-log plot and through a formal test of the interaction term "group x time" at α=0.05. Should this assumption fail, a stratified Cox model will be fitted in order to correct for non-proportional hazards if possible or, if ineffective, time-dependent variables will be introduced. Should these corrective techniques fail, logistic regression will be used instead.

Secondary endpoints expressed as time-to-event will be analyzed similarly using Kaplan-Meier survival curves and a log rank test. For all dichotomous qualitative variables, Chi-Square tests will be performed to assess group differences. Continuous variables, such as arrhythmia burden, will be analyzed using an analysis of variance (ANOVA). If the data are not normally distributed, then the non-parametric Wilcoxon Signed Rank test will be used. Health-related quality of life scores will be compared by analysis of covariance, adjusting for baseline values to reduce the error mean squares. In the event of missing data, a multiple imputation approach using SAS procedures PROC MI and PROC MIANALYZE will be considered. All tests will be conducted at an alpha level of 0.05 with the exception of the two main comparisons that will be conducted at an alpha level of 0.025. Similarly, hazard ratios for these two comparisons will be presented with 97.5% confidence intervals.

ETHICS AND DISSEMINATION:

CIRCA-DOSE: Methods and Rationale

Enrolment in the trial is predicated on assumption that patients have already made the decision to undergo a catheter ablation procedure for drug-refractory AF. The catheter ablation procedure used in this study is the same as the standard treatment method for AF and is not experimental. The risks of participation are therefore the same as those of standard atrial fibrillation ablation and independent of trial enrolment participants in the study would have accepted these risks. Institutional review board approval will be obtained at the sponsor institution, as well as at each participating site.

The dissemination plan for the trial encompasses multiple modalities and strategies including an integrated and an end of project KT strategy. The integrated approach of the program benefits from the involvement of non-profit organizations with a mandate of end-user engagement and education (the Heart and Stroke Foundation), patients (the end-user), and healthcare professionals. The involvement of these groups from the planning phase through to completion represents an optimal strategy for engagement and empowerment, essentially creating invested champions at each level. Post project KT will leverage the involvement of these groups to optimize the ability to reach the end-users. The information derived herein (whether positive, or negative) will be disseminated through established channels such as peer-reviewed publication, national and international meetings, webinars, and through social media. The involvement of Medtronic CryoCath, will facilitate dissemination of the findings to end users through their established educational infrastructure (Medtronic Academy website, large scale technology “user meetings”, to small group interactive conferences through their clinical specialist network). The end result of this KT plan will be the delivery of the optimal tailored treatment strategy to the individual patient at the optimal time.

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Footnotes

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Ethics Approval: University of British Columbia Office of Research (Services) Ethics Clinical Research Ethics Board, as well as the local institutional review boards for each of the participating sites.

CIRCA-DOSE: Methods and Rationale

FIGURE LEGENDS

Figure 1: Study Flow diagram. Legend: AAD – Antiarrhythmic drugs; AF – atrial fibrillation; PVI – pulmonary vein isolation; RF - radiofrequency

CIRCA-DOSE: Methods and Rationale

Table 1: Schedule of enrolment, interventions, and assessments. Legend – CT – computed tomography; MRI – magnetic resonance imaging; QOL – quality of life

	STUDY PERIOD						
	Enrolment	Ablation	Follow-up				Close-out
TIMEPOINT**	>30 days prior to ablation	0	*Hospital discharge*	*1 week*	*3 months*	*6 months*	*12 months*
Eligibility screen	X						
Informed consent	X						
Clinical examination	X		X		X	X	X
Telephone Interview				X			
Laboratory investigations		X					
12-lead ECG	X	X	X		X	X	X
Echocardiography	X						
24 hour Holter	X				X	X	X
QOL questionnaire	X					X	X
Cardiac CT or MRI*							
Loop recorder implantation	X						
Loop recorder interrogation	◆—	—	—	—	—	—	—◆

*if performed

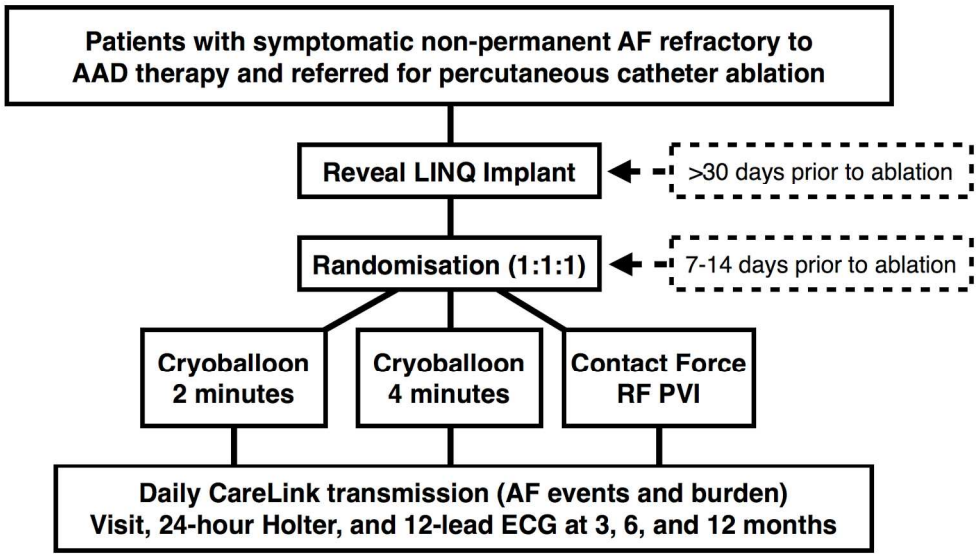

Figure 1: Study Flow diagram. Legend: AAD – Antiarrhythmic drugs; AF – atrial fibrillation; PVI – pulmonary vein isolation; RF - radiofrequency

299x168mm (300 x 300 DPI)

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CIRCA-DOSE: Methods and Rationale

Supplementary Table 1: ***Inclusion and Exclusion Criteria***

INCLUSION CRITERIA
• Non-permanent atrial fibrillation documented on a 12 lead ECG, Trans Telephonic Monitoring (TTM) or Holter monitor within the last 24 months (Episodes of AF must be >30 seconds in duration to qualify as an inclusion criterion) • Age of 18 years or older on the date of consent • Candidate for ablation based on AF that is symptomatic and refractory (ineffective or intolerant) to at least one class 1 or 3 antiarrhythmic. • Continuous anticoagulation with warfarin (INR 2-3), low molecular weight heparin, or a direct oral antithrombotic (dabigatran, apixaban, rivaroxaban) for ≥4 weeks prior to the ablation; or a TEE that excludes LA thrombus ≤48 hours before ablation
EXCLUSION CRITERIA
• Previous left atrial (LA) ablation or LA surgery • AF due to reversible cause (e.g. hyperthyroidism, cardiothoracic surgery) • Intracardiac Thrombus • Pre-existing pulmonary vein stenosis or PV stent • Pre-existing hemidiaphragmatic paralysis • Contraindication to anticoagulation or radiocontrast materials • Anteroposterior LA diameter greater than 5.5 cm by TTE • Cardiac valve prosthesis • Clinically significant (moderately-severe, or severe) mitral valve regurgitation or stenosis • Myocardial infarction, PCI / PTCA, or coronary artery stenting during the 3-month period preceding the consent date • Cardiac surgery during the three-month interval preceding the consent date • Significant congenital heart defect (including atrial septal defects or PV abnormalities but not including PFO) • NYHA class III or IV congestive heart failure • Left ventricular ejection fraction (LVEF) less than 35% • Hypertrophic cardiomyopathy (Wall thickness >1.5 cm) • Significant Chronic Kidney Disease (CKD - eGFR <30 µMol/L) • Uncontrolled hyperthyroidism • Cerebral ischemic event (strokes or TIAs) during the six-month interval preceding the consent date • Pregnancy • Life expectancy less than one (1) year • Currently participating or anticipated to participate in any other clinical trial of a drug, device or biologic during the duration of this study • Unwilling or unable to comply fully with study procedures and follow-up

CIRCA-DOSE: Methods and Rationale

Supplementary Table 2: Implantable cardiac monitor programming

AF detection threshold	Balanced Sensitivity
Ectopy rejection	Nominal
Episode storage threshold	All (Record ECG of 2 minutes)

These parameters were chosen to optimise detection of AF (reported sensitivity of 96.1% with a positive predictive valve [PPV] of 73%), however al arrhythmia episodes will be independently adjudicated.[18, 19]

Supplementary Table 3: Gradation of pulmonary venous occlusion during cryoballoon ablation
Grade 1 – negligible occlusion with immediate rapid outflow from the PV
Grade 2 – mild backflow into the atrium
Grade 3 – minimal backflow into the atrium
Grade 4 – total contrast retention with no backflow into the atrium.

CIRCA-DOSE: Methods and Rationale

Supplementary Table 4: Secondary Endpoints

1) Time to first recurrence of symptomatic documented AF/AFL/AT between days 91 and 365 after ablation or a repeat ablation procedure between days 0 and 365 post ablation
2) Arrhythmia burden (daily AF burden - hours/day; overall AF burden - % time in AF)
3) Proportion of patients experiencing an acute or adenosine provoked PV reconnection during the index ablation procedure
4) Proportion of patients requiring a repeat ablation procedure because of documented recurrence of symptomatic AF/AFL/AT
5) Proportion of patients prescribed AADs because of documented recurrence of symptomatic AF/AFL/AT; 6) Proportion of patients with AF/AFL/AT during the first 90 days post ablation
7) Emergency visit or hospitalization >24h in a health-care facility
8) Major complications including death, stroke, TIA, Myocardial Infarction or systemic thromboembolism, PV stenosis, phrenic nerve palsy, pericarditis, pericardial effusion, cardiac perforation or tamponade, hematoma, AV fistula, pseudoaneurysm, esophageal injury and atrio-esophageal fistulae (both individually and as a composite endpoint)*
9) Overall and disease specific quality of life
10) Single and multiple procedure success (freedom from symptomatic or asymptomatic electrocardiographically documented AF/AFL/AT) after the first and last ablation procedure respectively
11) Single and multiple procedure success (freedom from symptomatic electrocardiographically documented AF/AFL/AT) after the first and last ablation procedure respectively.

CIRCA-DOSE: Methods and Rationale

*Complication definition as per 2012 HRS/EHRA/ECAS recommendations. Acute peri-procedural complications will be defined as occurring within 30 days of ablation, with delayed complications occurring 31-365 days after ablation

A major complication is a complication that results in permanent injury or death, requires intervention for treatment, or prolongs or requires hospitalization for more than 48 hours. Because early recurrences of AF/AFL/AT are to be expected following AF ablation, recurrent AF/AFL/AT within 3 months that requires or prolongs a patient's hospitalization should not be considered to be a major complication of AF ablation.

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	3
	2b	Specific objectives or hypotheses	4
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	9
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	n/a
Participants	4a	Eligibility criteria for participants	8
	4b	Settings and locations where the data were collected	8
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	9
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	12
	6b	Any changes to trial outcomes after the trial commenced, with reasons	n/a
Sample size	7a	How sample size was determined	13
	7b	When applicable, explanation of any interim analyses and stopping guidelines	n/a
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	9
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	9
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	9
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	9
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	13

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	n/a
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	13
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	14
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	n/a
	13b	For each group, losses and exclusions after randomisation, together with reasons	n/a
Recruitment	14a	Dates defining the periods of recruitment and follow-up	n/a
	14b	Why the trial ended or was stopped	n/a
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	n/a
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	n/a
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	n/a
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	n/a
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	n/a
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	n/a
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	n/a
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	n/a
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	n/a
Other information			
Registration	23	Registration number and name of trial registry	2, 8
Protocol	24	Where the full trial protocol can be accessed, if available	This submission
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	1

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

BMJ Open

A Randomized Clinical Trial of Cryoballoon vs. Irrigated Radiofrequency Catheter Ablation for Atrial Fibrillation: The effect of Double Short vs. Standard Exposure Cryoablation Duration During Pulmonary Vein Isolation (CIRCA-DOSE) - Methods and Rationale

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Keywords:	atrial fibrillation, ablation, cryoablation

A Randomized Clinical Trial of Cryoballoon vs. Irrigated Radiofrequency Catheter Ablation for Atrial Fibrillation: The effect of Double Short vs. Standard Exposure Cryoablation Duration During Pulmonary Vein Isolation (CIRCA-DOSE) - Methods and Rationale

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CIRCA-DOSE: Methods and Rationale

ABSTRACT

Introduction: Pulmonary vein (PV) isolation (PVI) is an effective therapy for paroxysmal atrial fibrillation (AF), but has limitations. The two most significant recent advances have centred on the integration of real-time quantitative assessment of catheter contact force into focal radiofrequency (RF) ablation catheters, and the development of dedicated ablation tools capable of achieving PVI with a single ablation lesion (Arctic Front™ cryoballoon, Medtronic, Minneapolis, MN). While each of these holds promise for improving the clinical success of catheter ablation of AF, there has not been a rigorous comparison of these advanced ablation technologies. Moreover, the optimal duration of cryoablation (freezing time) has not been determined.

Methods and Analysis: Patients undergoing a first PVI procedure for paroxysmal AF will be recruited. Patients will be randomized 1:1:1 between contact force irrigated RF ablation, short duration cryoballoon ablation (2 minute applications) and standard duration cryoballoon ablation (4 minute applications). The primary outcome is time to first documented AF recurrence on implantable loop recorder. With a sample size of 111 per group and a two-sided 0.025 significance level (to account for the two main comparisons), the study will have 80% power (using a log rank test) to detect a difference of 20% between contact force RF catheter ablation and either of the two cryoballoon ablation groups. Factoring in a 4% loss to follow-up, 116 patients per group should be randomized and followed for a year (total study population of 348).

Ethics and Dissemination: The study was approved by the University of British Columbia Office of Research (Services) Ethics Clinical Research Ethics Board. Results of the study will be submitted for publication in a peer-reviewed journal.

Trial Registration number: ClinicalTrials.gov **NCT01913522**

AUTHORS CONTRIBUTIONS:

JA, MD, and PK conceived the study. JA, ASLT, AV, LM, PK, MD, MWD, GAW were involved in the drafting of the peer-reviewed grant, the study protocol, and the manuscript. MB, JC, PLS, PN, JFR, JS, AV served on the steering committee for the trial, and have provided critical revision of the manuscript.

STRENGTHS AND LIMITATIONS OF THE STUDY

- The CIRCA-DOSE is the first large multicentre randomised trial exclusively evaluating modern ablation technologies (contact force guided RF ablation compared to second-generation cryoballoon ablation).
- A major strength of the trial is the use rigor to which arrhythmia outcomes will be evaluated. In addition to continuous arrhythmia monitoring all arrhythmia events will be independently adjudicated by a committee blinded to treatment allocation, and thus it represents one of the most robust AF ablation outcome trials performed to date
- The trial is designed to evaluate outcomes beyond dichotomous arrhythmia recurrence, including AF burden (which is impossible to quantify with intermittent rhythm monitoring techniques), and quality of life metrics.
- The inclusion criteria were designed to mimic the patients seen in clinical practice (including the inclusion of patients with persistent AF) in order to ensure that the trial is externally valid and generalizable.
- While powered for arrhythmia recurrence outcomes, the relatively limited sample size will limit future sub-analyses.

CIRCA-DOSE: Methods and Rationale

INTRODUCTION

Atrial fibrillation (AF) is a common chronic progressive disease, characterized by exacerbations and remissions. Over the past 10-15 years, multiple large-scale observational studies and randomized controlled trials have demonstrated that catheter ablation is superior to AAD therapy in maintaining sinus rhythm.[1-10] In addition, catheter ablation has been shown to be superior to anti-arrhythmic drugs (AADs) for the improvement of symptoms, exercise capacity, and quality of life.[4 11-13] Unfortunately, the results of ablation are limited by arrhythmia recurrence, which is most often due to a failure to effectuate a durable contiguous circumferential transmural myocardial lesion around the PV ostia.[1 3-10 14 15] In response considerable effort has been directed towards developing technologies to achieve safer and more durable PV isolation (PVI). The two most significant advances in the last few years have centred on the integration of real-time quantitative assessment of catheter contact force into focal radiofrequency (RF) ablation catheters, and the development of dedicated catheters capable of achieving PVI with a single ablation lesion, the most mature of which is the Arctic Front™ cryoballoon (Medtronic, Minneapolis, MN).

While each of these advances holds promise for improving the clinical success of catheter ablation of AF, there has not been a rigorous comparison of the contact-force assisted RF ablation versus the second-generation cryoballoon. The CIRCA-DOSE trial has been designed to evaluate these two questions. The CIRCA-DOSE study is a multi-centre randomised trial designed to rigorously evaluate the effectiveness of contact-force assisted RF PVI versus PVI performed with the second-generation cryoballoon, as well as evaluate the optimal cryoablation duration.[16]

Contact Force Ablation

Ablation electrode-tissue contact is an important determinant of lesion size, and ultimately durability of conduction block. Conventionally, this has been assessed by the operator using a combination of fluoroscopic imaging of the catheter tip motion, tactile feedback and local electrogram attenuation, as well as impedance reductions during energy delivery. While widely used, the accuracy of these surrogate measures is poor. Contact force sensing is a recent

innovation that allows for real-time estimation of the contact force between the tip of the catheter and target myocardium, thus providing the operator with an accurate quantitative assessment of tissue contact.

Recent data suggest that incorporating real-time contact force assessment results in a reduction in procedure time, ablation time, and total energy delivery, with a comparable safety profile to that observed with standard irrigated RF.[17 18] However, the two largest multicentre trials evaluating this technology demonstrated a one-year success of 68% (TactiCath, TOCCASTAR) and 74% (SmartTouch, SMART-AF).[19 20] In the case of the former the success was no different from that observed with standard non-contact force RF ablation. Interestingly, post-hoc analyses of these studies suggested that the outcomes were improved when the procedure was performed with adequate contact-force parameters (84% one-year freedom from AF in the 47% of patients in whom ablation was in the target range ≥80% of the time in SMART-AF, and 76% one-year freedom from AF in the 57% of patients in whom ≥90% of the lesions were >10 g in TOCCASTAR). No differences in the incidence of complications have been reported between patients undergoing ablation with contact force vs. non-contact force sensing RF ablation catheters.[19 21 22]

Cryoballoon Ablation

Recent studies have examined short- and long-term success with the second-generation cryoballoon. Studies of planned re-mapping procedures have demonstrated that the durability of PVI at three months post index ablation procedure was improved at 91% with the second-generation cryoballoon, compared to 67% of PVs with standard (non-contact force) RF, and 88% of PVs with the first generation cryoballoon.[18 23-27] Clinically this has translated into a one-year freedom from recurrent AF of 82% with the second generation cryoballoon (11 studies; 1725 patients), which was significantly improved compared to the first generation cryoballoon in a separate comparative meta-analysis (odds ratio of arrhythmia recurrence 0.34 [0.26-0.45] when compared to first-generation cryoballoon; 10 studies, 2310 patients).[28] From a safety standpoint there were significantly more phrenic nerve palsies (transient and persistent) observed with the second-generation cryoballoon.

Contact Force Ablation vs. Cryoballoon Ablation

There is limited data directly comparing contact-force guided RF ablation to cryoballoon ablation. Since the inception of the CIRCA-DOSE study, three observational studies have reported comparable safety and efficacy between contact-force guided RF ablation and cryoballoon ablation for paroxysmal (2 studies) and persistent (1 study) AF. Specifically, Jourda et al. reported a single-centre experience with 150 consecutive patients undergoing PVI for paroxysmal AF with the second-generation cryoballoon (75 patients), and contact-force guided irrigated RF ablation (SmartTouch, 75 patients).[29] In this non-randomised study the one-year freedom from recurrent AF (as detected by Holter monitoring at 1, 3, 6, 9, and 12 months) was 85% in the cryoballoon group and 88% in the contact-force group (P=0.988). Squara et al. reported a similar 1-year freedom from recurrent paroxysmal AF (73% in the cryoballoon group and 76% in the contact-force group [SmartTouch and Tacticath]; P=0.63) in their ambidirectional (combined prospective and retrospective enrolment) multi-centre cohort study of 4 participating centres (2 centres performed both cryoballoon and RF ablation; 1 centre performed exclusively cryoballoon ablation; and 1 performed exclusively RF ablation).[30] Lastly, Ciconte et al. reported a single-centre experience with 100 consecutive patients undergoing PVI for persistent AF with the second-generation cryoballoon (50 patients), and contact-force guided irrigated RF ablation (SmartTouch and Tacticath, 50 patients).[31] In this non-randomised study the one-year freedom from recurrent AF (as detected by Holter monitoring at 1, 3, 6, and 12 months) was 60% in the cryoballoon group and 56% in the contact-force group (P=0.78). While none of these studies demonstrated a significant difference in the incidence of complications a recent meta-analysis observed a lower incidence of pericardial effusion (OR 0.44; 95%CI 0.28-0.69; P<0.01) and tamponade (OR 0.31; 95%CI 0.15-0.64; P<0.01) with cryoballoon ablation in comparison to contact-force guided RF ablation, whereas transient phrenic nerve palsy was more frequent after cryoballoon (OR 7.40; 95%CI 2.56–21.34; P<0.01).[32]

CIRCA-DOSE: Methods and Rationale

The multicentre, randomized FIRE and ICE trial was designed to determine whether cryoballoon ablation was non-inferior to RF ablation in symptomatic patients with drug-refractory paroxysmal AF.[33] Patients were randomised to Arctic Front-based cryoballoon ablation (374 patients), vs. irrigated RF ablation (376 patients). The primary efficacy endpoint (documented recurrence of AF/AT/AFL >30s, AAD prescription, or re-ablation) occurred in 138 patients in the cryoballoon group and in 143 in the RF group (1-year Kaplan–Meier event rate estimates, 34.6% and 35.9%, respectively; hazard ratio, 0.96; 95% confidence interval [CI], 0.76 to 1.22; P<0.001 for noninferiority). However, despite reporting recently it is important to note that the study was not an exclusive comparison of advanced technologies, with the majority of patients receiving non-contact force irrigated RF ablation (284/376 in the RF group) and a significant proportion (90 of 374 patients) receiving first generation cryoballoon ablation. As such the relative safety and efficacy of these new technologies remains unknown.

Data Supporting Shorter Freeze Durations

The optimal duration of freezing, that is, how long the tissue should be kept in the frozen state, is not well established. Current recommendations are for cryoablation dosing at 240 seconds for each application, which is based on studies of an early focal cryocatheter. In these studies, it was observed that the effect of a cryoablation lesion reached a plateau of three-minutes after the onset of ablation. Thereafter "prolongation of exposure time beyond 3 minutes did not result in any further increase in lesion dimension or volume."[34 35] Since then, the cryocatheter has evolved from a rigid focal catheter to a semi-compliant balloon, which necessitated a redesign of the cryorefrigerant delivery mechanisms. Moreover, the refrigerant itself has changed from slow-cooling to more efficacious gases (i.e., nitrous oxide).

Information regarding the safety and efficacy of shorter cryoballoon ablation durations are limited to 3 minute lesions, which have been suggested in several non-randomised studies to be of comparable efficacy to longer duration cryolesions.[36 37] We recently completed a randomized pre-clinical study examining the immediate and delayed effects of shorter ablation time on PVI efficacy.[38] In our study, thirty-two mongrel dogs underwent cryoballoon ablation with a 23-mm cryoballoon catheter. PVI procedures were randomized to a single 2-minute vs.

4-minute cryoballoon application. Although 4-minute lesions were associated with a thicker neointima than 2-minute lesions (223.8µm vs. 135.6µm; p=0.007), no differences were observed in the rates of procedural PVI, or the achievement of complete circumferentially transmural lesions at 30 days (78% overall; 86.2% for 2-min vs. 70% for 4-min; P=0.285), however a reduction in late PV strictures was observed in the 2 minute group (6/30 PVs with strictures in the 4-minute freeze duration vs. 0/29 PVs with strictures in the 2-minute freeze duration; p=0.024).

Arrhythmia Monitoring

While from a patient perspective the freedom from symptoms related to AF may be the most important clinical endpoint, contemporary evidence suggests that there is a poor correlation between symptoms and AF burden.[39 40] Moreover the presence or absence of symptoms does not affect the prognosis and complications of the AF.[41] As such any evaluation of treatment efficacy must include protocol-determined arrhythmia monitoring. Given that paroxysmal AF is by definition a disease of clusters, studies have shown that the detection of AF recurrence is proportional to the duration of monitoring.[42] Specifically, Kottkamp et al. demonstrated an increased detection of arrhythmia recurrences post AF ablation for highly symptomatic AF in a group undergoing serial 7-day ECG monitoring versus those undergoing only intermittent ECG monitoring (26% vs. 12% documented recurrence).[43] Unfortunately, while non-invasive intermittent rhythm monitoring remains the most widely utilised method of ascertaining ablation efficacy it often fails to detect AF recurrence. Specifically, the sensitivity (31-71%) and negative predictive value (21-39%) are significantly inferior to continuous monitoring techniques.[44] This imprecision associated with intermittent arrhythmia monitoring confers a significant risk of Type II error, which makes it inappropriate for outcome ascertainment in a trial designed to evaluate the efficacy of different therapeutic interventions.

As such, a major strength of the current study is the reliance on continuous cardiac monitoring for the determination of arrhythmia outcomes. All participants in the CIRCA-DOSE trial will have an implantable cardiac monitor with an automated AF detection algorithm (REVEAL LINQ) inserted a minimum of 1 month prior to ablation. This subcutaneous implantable cardiac

monitor continuously analyses the beat-to-beat variability of cardiac cycles leading to an accurate determination of the timing of arrhythmia recurrence, as well as an accurate quantification of atrial fibrillation burden (hours in AF per day, and percentage of overall time in AF). With respect to this latter point, the use of AF burden allows for a more detailed examination of the relatively efficacy of the three-different treatment approaches, beyond which can be obtained with dichotomous event analyses such as "time-to-first-AF recurrence." Unfortunately, intermittent rhythm monitoring techniques are unable to accurately quantify AF burden.[44]

METHODS AND ANALYSIS

Study Design

The CIRCA-DOSE study (ClinicalTrials.gov #**NCT01913522**) is a multicentre prospective randomized clinical trial. The study will be conducted at 8 clinical centres in Canada. Patients with symptomatic paroxysmal and early persistent AF refractory to at least one AAD and referred for first percutaneous catheter ablation will be enrolled (**Figure 1**). At least 1 episode of AF must be documented on 12-lead electrocardiogram (ECG), transtelephonic monitor (TTM), or Holter monitor within 24 months of randomization (Inclusion and exclusion criteria are detailed in **Supplementary Table 1)**.[45]

All patients will undergo the implantation of an implantable cardiac monitor (ICM) with an AF detection algorithm a minimum of 30 days prior to the index ablation for the purpose of arrhythmia monitoring (Reveal LINQ, Medtronic). The ICM analyses beat-to-beat variability of cardiac cycles on a 2-minute ECG strip and stores the tracing for independent adjudication. The device is also capable of quantifying the amount of AF per day, and the overall AF burden (percentage of the observed time that a patient is in AF). Additionally, the patient can activate the device manually to facilitate analysis of heart rhythm during symptomatic events. ICM programmed parameters are summarized in **Supplementary Table 2**.

Patients will be assigned in a 1:1:1 ratio using permuted block randomization stratified by site to: 1) Standard RF ablation guided by tissue-contact force; 2) Short cryoballoon ablation duration (2-minute cryoapplications); and 3) Standard cryoballoon ablation duration (4-minute cryoapplications). Patients will be blinded to their randomization assignment.

Catheter Ablation Procedure

Effective anticoagulation with oral vitamin K antagonists (target INR between 2-3), low molecular weight heparin, or dabigatran/apixaban/rivaroxaban for at least one month and/or the exclusion of a left atrial (LA) thrombus by transesophageal echocardiography (TEE; <48 hours pre-ablation) is mandated prior to ablation.[46] Antiarrhythmic drugs will be discontinued five half-lives before the procedure, except for amiodarone, which will be discontinued 8 weeks prior to ablation. Interventions will be performed on patients in the fasting state under conscious sedation or general anaesthesia, per local practice.

For each of the three treatment arms, patients will undergo pulmonary vein isolation (PVI) according to standard clinical practice.[46-49] No prophylactic LA linear ablation lesions, or ablation of complex fractionated atrial electrograms (CFAE) will be permitted in addition to PV isolation. In the event of documented right atrial cavotricuspid isthmus dependent flutter, cavotricuspid isthmus ablation is permitted (with irrigated RF or focal cryoablation).

Contact-Force Guided Radiofrequency Ablation

For patients randomized to RF catheter ablation a three-dimensional, non-fluoroscopic mapping system (CARTO3, Biosense Webster) will be used for anatomic reconstruction. Through one transseptal access, a circular mapping catheter (decapolar or duo-decapolar) will be advanced into the LA. The circular mapping catheter will be placed sequentially within each PV to record baseline electrical activity (PV potentials; PVPs). Via a second transseptal access, an irrigated-tip contact-force sensing RF ablation catheter (Thermocool SmartTouch or SmartTouch Surround Flow, Biosense Webster) will be positioned in the LA. Circumferential ablation lesions will be placed via the ablation catheter 1-2 cm from the PV ostia to electrically isolate the PV, as per standard practice.[45] RF energy will be delivered at 20-35 Watts to a

maximum temperature of 43°C. The contact force targeted prior to lesion delivery will be 20 g (acceptable range 10-40 g), with a minimum individual target lesion duration of 400 gram-seconds force-time integral (FTI). Circumferential lesions around the veins will be considered complete when the procedural endpoint has been reached (see below).

Cryoballoon Ablation

For patients randomized to cryoballoon ablation the transseptal sheath will be exchanged over a guidewire with a steerable 15-Fr sheath (**FlexCath, Medtronic**). Before introducing the balloon catheter (**Arctic Front Advance, Medtronic)** in the sheath a 15 or 20 mm diameter circular mapping catheter (CMC) will be inserted in the central lumen of the cryoballoon. A 23 or 28 mm cryoballoon will be advanced through the steerable sheath into the LA with the CMC used as a guidewire. While use of the larger (28-mm) cryoballoon is preferred, the 23-mm cryoballoon may be used based on physician judgment for PV diameters <20 mm.[50-52] Before ablation, the CMC will be positioned in the venous ostium to record baseline electrical activity. The CMC will then be advanced more distally for support. The cryoballoon will be positioned in the venous ostium and the degree of occlusion will be tested through the injection of 1:1 diluted contrast material. Vessel occlusion will be evaluated according to a semi-quantitative grading (**Supplementary Table 3**). Prior to ablation of right-sided PVs, a catheter will be placed in the superior vena cava cranial to the right superior PV in order to pace the right phrenic nerve (10-20 mA at 1.0-2.0 msec pulse width at a cycle length of 1000 msec). Ablation will be immediately terminated upon any perceived reduction in the strength of diaphragmatic contraction or a 30% reduction in the diaphragmatic compound motor action potential (CMAP) amplitude as measured via diaphragmatic electromyography.[53] If the procedure is performed under general anaesthesia, paralytic agents will be discontinued at least 30 minutes prior to phrenic nerve pacing.

a) **Patients randomized to standard cryoballoon ablation** will undergo cryoablation with target duration of 4 minutes. Once PVI is achieved a single additional application of 4-minute cryoapplication will be delivered after the rewarming phase (to +20°C).

b) **Patients randomized to short cryoballoon Ablation** will undergo cryoablation with target duration of 2 minutes. Once PVI is achieved a single additional 2-minute cryoapplication will be delivered after the rewarming phase (to +20°C).

Ineffectual cryolesions: Excepting common ostia, cryoablation lesions that fail to isolate the vein (if real-time PV potential monitoring is feasible) or fail to achieve a temperature colder than minus 35°C after 60 seconds of ablation onset will be considered ineffectual and be terminated. Thereafter, the balloon and/or guidewire should be repositioned and a new lesion delivered.

Inability to Isolate: Should the operator fail to isolate the PV (excluding common ostia) after a minimum of 3 attempted cryoballoon applications, then focal ablation with the 8 mm cryocatheter (Freezor Max) targeted to sites of LA-PV breakthrough will be permitted at operator discretion.

Procedural Endpoint

For all three treatment arms the ablation procedure will be considered successful when PVI, as confirmed by bidirectional conduction block between PV and LA, has been achieved in accordance with the 2012 HRS/EHRA/ECAS consensus document.[45] Bidirectional conduction block is defined as the combination of entrance block (the stable absence of conduction into the PV from the LA) and exit block (the stable absence of conduction from the PV into the LA, either spontaneous or during pacing from the circular mapping catheter positioned at the PV ostium). Patients remaining in AF at the end of the procedure will be electrically or chemically cardioverted back to sinus rhythm. Remapping of all PVs post cardioversion will be performed to the procedural endpoint.

Evaluation of Spontaneous Reconnection and Dormant Conduction

For all three treatment arms a 20-minute observation period (beginning at the end of the last ablation lesion) will be used to assess spontaneous recovery of conduction.[45] If spontaneous reconnection occurs, the reconnected PVs will be re-isolated according to the randomised protocol.

Dormant conduction will be assessed with the use of a circular catheter in each PV by intravenous injection of 6 mg or more of adenosine to obtain at least 1 blocked P wave or a sinus pause ≥3 seconds. Dormant conduction will be defined by reappearance of PV conduction for ≥1 beat. If there is no dormant conduction in any PV, then the procedure will be considered complete. If dormant conduction is elicited, the patient will undergo additional targeted ablation according to the randomised protocol until dormant conduction is abolished (i.e. adenosine fails to induce reconnection in any PV).

Post-ablation follow-up

Barring complications, patients will be discharged within 24 hours after the ablation procedure. All patients will remain anticoagulated for ≥3 months post procedure. While discontinuation of oral anticoagulation during the study period is strongly discouraged, in patients with a CHA_2DS_2VASc score of <2, aspirin alone may be considered at treating physician discretion. Arrhythmia recurrence during the first 3 months post-ablation may be treated with cardioversion and/or antiarrhythmic drugs (except amiodarone). Where possible, repeat ablation procedures will be deferred until after the 3-month blanking period due to the potential for delayed cure (as per standard practice and in accordance with HRS/ECAS/EHRA recommendations).[45] If antiarrhythmic drugs (except amiodarone) are used in the first 3 months post ablation, they will be discontinued 5 half-lives before the end of the 3-month blanking period.[45] Scheduled follow-up visits will occur at 3, 6, and 12 months from the first ablation procedure (within a 2-week margin – Table 1). A 24-hour Holter and 12-lead ECG will be performed at 3, 6, and 12 months. Automatic transmissions from the ICM will be obtained on a daily basis via CareLink. Patients will be instructed to record symptomatic episodes via use of the patient activator.

STUDY OUTCOMES

Primary endpoint is time to first recurrence of symptomatic or asymptomatic AF, atrial flutter, or atrial tachycardia (AF/AFL/AT) documented by 12-lead ECG, surface ECG rhythm strips, 24-hour ambulatory ECG (Holter) monitor, or on ILR between days 91 and 365 post ablation, or a repeat ablation procedure between days 0 and 365 post ablation. AF or atrial

flutter/tachycardia will qualify as an arrhythmia recurrence after ablation if it lasts 30 seconds or longer (on surface ECG rhythm strips, 24-hour ambulatory Holter monitor) or 120 seconds or longer on ICM (the minimum programmable episode interval). All tracings will be independently adjudicated by a committee blinded to treatment allocation. The primary end point and the 3-month blanking period adhere to the Heart Rhythm Society recommendations for reporting outcomes in AF ablation trials.[45]

Secondary endpoints are listed in Table 4 of the Supplementary Appendix.

Event Adjudication: The clinical events committee will be composed of a Chairman, and six (6) reviewers with expertise in clinical event adjudication. The CEC is responsible for review and adjudication of all primary and secondary end-points, which include serious adverse events and major complications. Two reviewers will be assigned to review each endpoint and major complication. If both reviewers agree, the Chairman will be provided with the Reviewer's Forms and he will ratify the adjudication by completing the Final Adjudication Form. If the reviewers are in disagreement, the Chairman will review the event and will serve as the third reviewer. If there is still disagreement between all three reviewers, a meeting will be scheduled to discuss the event.

SAMPLE SIZE

The sample size was determined based on the primary endpoints for the two main comparisons of interest: cryoablation with a 4-minute application vs. contact force guided RF catheter ablation, and cryoablation with a 2-minute application vs. RF catheter ablation. Overall event-free survival at one year is estimated to be 65%. With a sample size of 111 per group and a two-sided 0.025 significance level (to account for the two main comparisons), the study will have 80% power (using a log rank test) to detect a relative difference of 20% between contact force RF catheter ablation and either of the two cryoballoon ablation groups. Factoring in a 4% loss to follow-up, 116 patients per group should be randomized, for a total study population of 348. Power calculations are based on the log-rank test for equality of survival curves (nQuery, version 6.01), using simulated data.

STATISTICAL ANALYSES

Analysis of the primary and secondary endpoints will be based on the intention-to-treat principle according to the initial allocated strategy. Survival curves will be estimated by the Kaplan-Meier method and compared by the log rank test. The two main comparisons will be cryoablation with a 4-minute application vs. RF catheter ablation, and cryoablation with a 2-minute application vs. RF catheter ablation. The comparison between the two cryoablation groups will be considered secondary.

A Cox proportional hazards model will also be used to test the consistency of the group effect while accounting for clinically important baseline characteristics, which will include: ablation site, age, gender, race, weight, LA size, structural heart disease, AF duration, and number of AADs used in the past. The proportional hazard assumption will be assessed by visual inspection of the log-negative-log plot and through a formal test of the interaction term "group x time" at α=0.05. Should this assumption fail, a stratified Cox model will be fitted in order to correct for non-proportional hazards if possible or, if ineffective, time-dependent variables will be introduced. Should these corrective techniques fail, logistic regression will be used instead.

Secondary endpoints expressed as time-to-event will be analysed similarly using Kaplan-Meier survival curves and a log rank test. For all dichotomous qualitative variables, Chi-Square tests will be performed to assess group differences. Continuous variables, such as arrhythmia burden, will be analysed using an analysis of variance (ANOVA). If the data are not normally distributed, then the non-parametric Wilcoxon Signed Rank test will be used. Health-related quality of life scores will be compared by analysis of covariance, adjusting for baseline values to reduce the error mean squares. In the event of missing data, a multiple imputation approach using SAS procedures PROC MI and PROC MIANALYZE will be considered. All tests will be conducted at an alpha level of 0.05 with the exception of the two main comparisons that will be conducted at an alpha level of 0.025. Similarly, hazard ratios for these two comparisons will be presented with 97.5% confidence intervals.

ETHICS AND DISSEMINATION:

CIRCA-DOSE: Methods and Rationale

Enrolment in the trial is predicated on assumption that patients have already made the decision to undergo a catheter ablation procedure for drug-refractory AF. The catheter ablation procedure used in this study is the same as the standard treatment method for AF and is not experimental. The risks of participation are therefore the same as those of standard atrial fibrillation ablation and independent of trial enrolment participants in the study would have accepted these risks. Institutional review board approval will be obtained at the sponsor institution, as well as at each participating site.

The dissemination plan for the trial encompasses multiple modalities and strategies including an integrated and an end of project knowledge-translation (KT) strategy. The integrated approach of the program benefits from the involvement of non-profit organizations with a mandate of end-user engagement and education (the Heart and Stroke Foundation of Canada), patients (the end-user), and healthcare professionals. The involvement of these groups from the planning phase through to completion represents an optimal strategy for engagement and empowerment, essentially creating invested champions at each level. Post project KT will leverage the involvement of these groups to optimize the ability to reach the end-users. The information derived herein (whether positive, or negative) will be disseminated through established channels such as peer-reviewed publication, national and international meetings, webinars, and through social media. The involvement of Medtronic CryoCath, will facilitate dissemination of the findings to end users through their established educational infrastructure (Medtronic Academy website, “user meetings”, to small group interactive conferences through their clinical specialist network). The end result of this KT plan will be the delivery of the optimal tailored treatment strategy to the individual patient at the optimal time.

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CIRCA-DOSE: Methods and Rationale

FOOTNOTES

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Role of the Funding source: The funding sources had no role in the design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results.

Ethics Approval: University of British Columbia Office of Research (Services) Ethics Clinical Research Ethics Board, as well as the local institutional review boards for each of the participating sites.

CIRCA-DOSE: Methods and Rationale

FIGURE LEGENDS

Figure 1: Study Flow diagram. Legend: AAD – Antiarrhythmic drugs; AF – atrial fibrillation; PVI – pulmonary vein isolation; RF - radiofrequency

CIRCA-DOSE: Methods and Rationale

Table 1: Schedule of enrolment, interventions, and assessments. Legend – CT – computed tomography; MRI – magnetic resonance imaging; QOL – quality of life

	STUDY PERIOD						
	Enrolment	Ablation	Follow-up				Close-out
TIMEPOINT**	>30 days prior to ablation	0	*Hospital discharge*	*1 week*	*3 months*	*6 months*	*12 months*
Eligibility screen	X						
Informed consent	X						
Clinical examination	X		X		X	X	X
Telephone Interview				X			
Laboratory investigations		X					
12-lead ECG	X	X	X		X	X	X
Echocardiography	X						
24 hour Holter	X				X	X	X
QOL questionnaire	X					X	X
Cardiac CT or MRI*	X						
Loop recorder implantation	X						
Loop recorder interrogation	◆—	—	—	—	—	—	—◆

*if performed

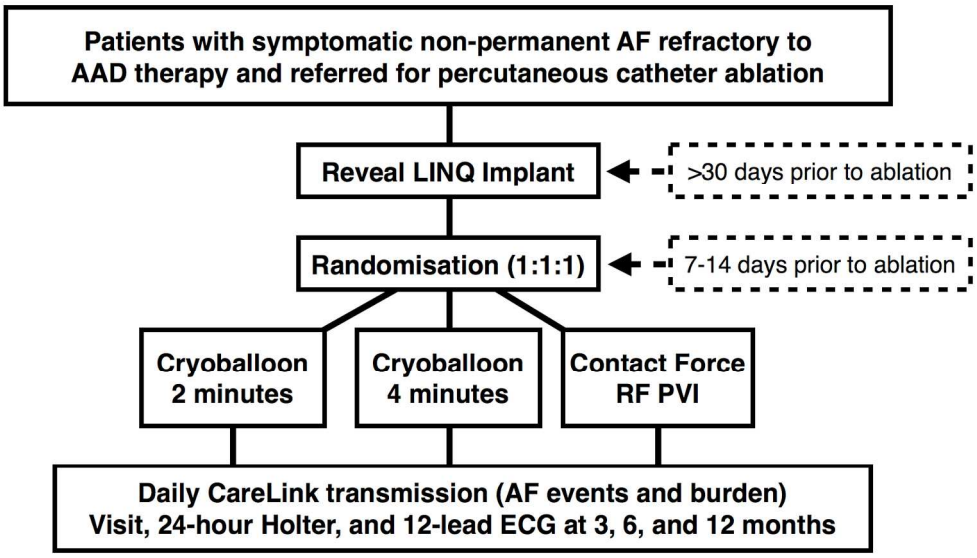

Figure 1: Study Flow diagram. Legend: AAD – Antiarrhythmic drugs; AF – atrial fibrillation; PVI – pulmonary vein isolation; RF - radiofrequency

299x168mm (300 x 300 DPI)

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CIRCA-DOSE: Methods and Rationale

Supplementary Table 1: ***Inclusion and Exclusion Criteria***

INCLUSION CRITERIA
• Non-permanent atrial fibrillation documented on a 12 lead ECG, Trans Telephonic Monitoring (TTM) or Holter monitor within the last 24 months (Episodes of AF must be >30 seconds in duration to qualify as an inclusion criterion) • Age of 18 years or older on the date of consent • Candidate for ablation based on AF that is symptomatic and refractory (ineffective or intolerant) to at least one class 1 or 3 antiarrhythmic. • Continuous anticoagulation with warfarin (INR 2-3), low molecular weight heparin, or a direct oral antithrombotic (dabigatran, apixaban, rivaroxaban) for ≥4 weeks prior to the ablation; or a TEE that excludes LA thrombus ≤48 hours before ablation
EXCLUSION CRITERIA
• Previous left atrial (LA) ablation or LA surgery • AF due to reversible cause (e.g. hyperthyroidism, cardiothoracic surgery) • Intracardiac Thrombus • Pre-existing pulmonary vein stenosis or PV stent • Pre-existing hemidiaphragmatic paralysis • Contraindication to anticoagulation or radiocontrast materials • Anteroposterior LA diameter greater than 5.5 cm by TTE • Cardiac valve prosthesis • Clinically significant (moderately-severe, or severe) mitral valve regurgitation or stenosis • Myocardial infarction, PCI / PTCA, or coronary artery stenting during the 3-month period preceding the consent date • Cardiac surgery during the three-month interval preceding the consent date • Significant congenital heart defect (including atrial septal defects or PV abnormalities but not including PFO) • NYHA class III or IV congestive heart failure • Left ventricular ejection fraction (LVEF) less than 35% • Hypertrophic cardiomyopathy (Wall thickness >1.5 cm) • Significant Chronic Kidney Disease (CKD - eGFR <30 µMol/L) • Uncontrolled hyperthyroidism • Cerebral ischemic event (strokes or TIAs) during the six-month interval preceding the consent date • Pregnancy • Life expectancy less than one (1) year • Currently participating or anticipated to participate in any other clinical trial of a drug, device or biologic during the duration of this study • Unwilling or unable to comply fully with study procedures and follow-up

CIRCA-DOSE: Methods and Rationale

Supplementary Table 2: Implantable cardiac monitor programming

AF detection threshold	Balanced Sensitivity
Ectopy rejection	Nominal
Episode storage threshold	All (Record ECG of 2 minutes)

These parameters were chosen to optimise detection of AF (reported sensitivity of 96.1% with a positive predictive valve [PPV] of 73%), however al arrhythmia episodes will be independently adjudicated.[18, 19]

CIRCA-DOSE: Methods and Rationale

Supplementary Table 3: Gradation of pulmonary venous occlusion during cryoballoon ablation
Grade 1 – negligible occlusion with immediate rapid outflow from the PV
Grade 2 – mild backflow into the atrium
Grade 3 – minimal backflow into the atrium
Grade 4 – total contrast retention with no backflow into the atrium.

CIRCA-DOSE: Methods and Rationale

Supplementary Table 4: Secondary Endpoints

1) Time to first recurrence of symptomatic documented AF/AFL/AT between days 91 and 365 after ablation or a repeat ablation procedure between days 0 and 365 post ablation
2) Arrhythmia burden (daily AF burden - hours/day; overall AF burden - % time in AF)
3) Proportion of patients experiencing an acute or adenosine provoked PV reconnection during the index ablation procedure
4) Proportion of patients requiring a repeat ablation procedure because of documented recurrence of symptomatic AF/AFL/AT
5) Proportion of patients prescribed AADs because of documented recurrence of symptomatic AF/AFL/AT; 6) Proportion of patients with AF/AFL/AT during the first 90 days post ablation
7) Emergency visit or hospitalization >24h in a health-care facility
8) Major complications including death, stroke, TIA, Myocardial Infarction or systemic thromboembolism, PV stenosis, phrenic nerve palsy, pericarditis, pericardial effusion, cardiac perforation or tamponade, hematoma, AV fistula, pseudoaneurysm, esophageal injury and atrio-esophageal fistulae (both individually and as a composite endpoint)*
9) Overall and disease specific quality of life
10) Single and multiple procedure success (freedom from symptomatic or asymptomatic electrocardiographically documented AF/AFL/AT) after the first and last ablation procedure respectively
11) Single and multiple procedure success (freedom from symptomatic electrocardiographically documented AF/AFL/AT) after the first and last ablation procedure respectively.

*Complication definition as per 2012 HRS/EHRA/ECAS recommendations. Acute peri-procedural complications will be defined as occurring within 30 days of ablation, with delayed complications occurring 31-365 days after ablation

A major complication is a complication that results in permanent injury or death, requires intervention for treatment, or prolongs or requires hospitalization for more than 48 hours. Because early recurrences of AF/AFL/AT are to be expected following AF ablation, recurrent AF/AFL/AT within 3 months that requires or prolongs a patient's hospitalization should not be considered to be a major complication of AF ablation.

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	3	Date and version identifier –	1.0 June 27, 2014
Funding	4	Sources and types of financial, material, and other support	21
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	2
	5b	Name and contact information for the trial sponsor	1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	21
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	14

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	____4_____
	6b	Explanation for choice of comparators	_____10_____
Objectives	7	Specific objectives or hypotheses	_____4_____
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	9 _____
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	____9_____
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	_supplement___
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	___10-13_____
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	___n/a_____
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	___8_____
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	____13_____
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	_____13_____
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	___9, 23_____

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	___14_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	___n/a_____
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	___10_____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	_____10_____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	___10_____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	____10, 14_____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	____n/a_____
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	_____13_____
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	_n/a_____

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	__n/a_____
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	_____15_____
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	_____15_____
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	15 _____
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	___14_____
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	____14_____
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	____14_____
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	____14_____
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	____16_____
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	_____n/a_____

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	9
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	n/a
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	21
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	2
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	none
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	16
	31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	3
	2b	Specific objectives or hypotheses	4
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	9
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	n/a
Participants	4a	Eligibility criteria for participants	8
	4b	Settings and locations where the data were collected	8
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	9
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	12
	6b	Any changes to trial outcomes after the trial commenced, with reasons	n/a
Sample size	7a	How sample size was determined	13
	7b	When applicable, explanation of any interim analyses and stopping guidelines	n/a
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	9
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	9
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	9
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	9
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	13

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	n/a
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	13
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	14
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	n/a
	13b	For each group, losses and exclusions after randomisation, together with reasons	n/a
Recruitment	14a	Dates defining the periods of recruitment and follow-up	n/a
	14b	Why the trial ended or was stopped	n/a
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	n/a
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	n/a
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	n/a
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	n/a
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	n/a
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	n/a
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	n/a
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	n/a
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	n/a
Other information			
Registration	23	Registration number and name of trial registry	2, 8
Protocol	24	Where the full trial protocol can be accessed, if available	This submission
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	1

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

BMJ Open

A Randomized Clinical Trial of Cryoballoon vs. Irrigated Radiofrequency Catheter Ablation for Atrial Fibrillation: The effect of Double Short vs. Standard Exposure Cryoablation Duration During Pulmonary Vein Isolation (CIRCA-DOSE) - Methods and Rationale

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Secondary Subject Heading:	Cardiovascular medicine, Pharmacology and therapeutics
Keywords:	atrial fibrillation, ablation, cryoablation

A Randomized Clinical Trial of Cryoballoon vs. Irrigated Radiofrequency Catheter Ablation for Atrial Fibrillation: The effect of Double Short vs. Standard Exposure Cryoablation Duration During Pulmonary Vein Isolation (CIRCA-DOSE) - Methods and Rationale

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Running Title: CIRCA-DOSE: Rationale and Methods

Key words: Atrial fibrillation, Ablation, Cryoablation, Pulmonary Vein Isolation

CIRCA-DOSE: Methods and Rationale

ABSTRACT

Introduction: Pulmonary vein (PV) isolation (PVI) is an effective therapy for paroxysmal atrial fibrillation (AF), but has limitations. The two most significant recent advances have centred on the integration of real-time quantitative assessment of catheter contact force into focal radiofrequency (RF) ablation catheters, and the development of dedicated ablation tools capable of achieving PVI with a single ablation lesion (Arctic Front™ cryoballoon, Medtronic, Minneapolis, MN). While each of these holds promise for improving the clinical success of catheter ablation of AF, there has not been a rigorous comparison of these advanced ablation technologies. Moreover, the optimal duration of cryoablation (freezing time) has not been determined.

Methods and Analysis: Patients undergoing a first PVI procedure for paroxysmal AF will be recruited. Patients will be randomized 1:1:1 between contact force irrigated RF ablation, short duration cryoballoon ablation (2 minute applications) and standard duration cryoballoon ablation (4 minute applications). The primary outcome is time to first documented AF recurrence on implantable loop recorder. With a sample size of 111 per group and a two-sided 0.025 significance level (to account for the two main comparisons), the study will have 80% power (using a log rank test) to detect a difference of 20% between contact force RF catheter ablation and either of the two cryoballoon ablation groups. Factoring in a 4% loss to follow-up, 116 patients per group should be randomized and followed for a year (total study population of 348).

Ethics and Dissemination: The study was approved by the University of British Columbia Office of Research (Services) Ethics Clinical Research Ethics Board. Results of the study will be submitted for publication in a peer-reviewed journal.

Trial Registration number: ClinicalTrials.gov **NCT01913522**

AUTHORS CONTRIBUTIONS:

JA, MD, and PK conceived the study. JA, ASLT, AV, LM, PK, MD, MWD, GAW were involved in the drafting of the peer-reviewed grant, the study protocol, and the manuscript. MB, JC, PLS, PN, JFR, JS, AV served on the steering committee for the trial, and have provided critical revision of the manuscript.

STRENGTHS AND LIMITATIONS OF THE STUDY

- The CIRCA-DOSE is the first large multicentre randomised trial exclusively evaluating modern ablation technologies (contact force guided RF ablation compared to second-generation cryoballoon ablation).
- A major strength of the trial is the use rigor to which arrhythmia outcomes will be evaluated. In addition to continuous arrhythmia monitoring all arrhythmia events will be independently adjudicated by a committee blinded to treatment allocation, and thus it represents one of the most robust AF ablation outcome trials performed to date
- The trial is designed to evaluate outcomes beyond dichotomous arrhythmia recurrence, including AF burden (which is impossible to quantify with intermittent rhythm monitoring techniques), and quality of life metrics.
- The inclusion criteria were designed to mimic the patients seen in clinical practice (including the inclusion of patients with persistent AF) in order to ensure that the trial is externally valid and generalizable.
- While powered for arrhythmia recurrence outcomes, the relatively limited sample size will limit future sub-analyses.

CIRCA-DOSE: Methods and Rationale

INTRODUCTION

Atrial fibrillation (AF) is a common chronic progressive disease, characterized by exacerbations and remissions. Over the past 10-15 years, multiple large-scale observational studies and randomized controlled trials have demonstrated that catheter ablation is superior to AAD therapy in maintaining sinus rhythm.[1-10] In addition, catheter ablation has been shown to be superior to anti-arrhythmic drugs (AADs) for the improvement of symptoms, exercise capacity, and quality of life.[4 11-13] Unfortunately, the results of ablation are limited by arrhythmia recurrence, which is most often due to a failure to effectuate a durable contiguous circumferential transmural myocardial lesion around the PV ostia.[1 3-10 14 15] In response considerable effort has been directed towards developing technologies to achieve safer and more durable PV isolation (PVI). The two most significant advances in the last few years have centred on the integration of real-time quantitative assessment of catheter contact force into focal radiofrequency (RF) ablation catheters, and the development of dedicated catheters capable of achieving PVI with a single ablation lesion, the most mature of which is the Arctic Front™ cryoballoon (Medtronic, Minneapolis, MN).

While each of these advances holds promise for improving the clinical success of catheter ablation of AF, there has not been a rigorous comparison of the contact-force assisted RF ablation versus the second-generation cryoballoon. The CIRCA-DOSE trial has been designed to evaluate these two questions. The CIRCA-DOSE study is a multi-centre randomised trial designed to rigorously evaluate the effectiveness of contact-force assisted RF PVI versus PVI performed with the second-generation cryoballoon, as well as evaluate the optimal cryoablation duration.[16]

Contact Force Ablation

Ablation electrode-tissue contact is an important determinant of lesion size, and ultimately durability of conduction block. Conventionally, this has been assessed by the operator using a combination of fluoroscopic imaging of the catheter tip motion, tactile feedback and local electrogram attenuation, as well as impedance reductions during energy delivery. While widely used, the accuracy of these surrogate measures is poor. Contact force sensing is a recent

innovation that allows for real-time estimation of the contact force between the tip of the catheter and target myocardium, thus providing the operator with an accurate quantitative assessment of tissue contact.

Recent data suggest that incorporating real-time contact force assessment results in a reduction in procedure time, ablation time, and total energy delivery, with a comparable safety profile to that observed with standard irrigated RF.[17 18] However, the two largest multicentre trials evaluating this technology demonstrated a one-year success of 68% (TactiCath, TOCCASTAR) and 74% (SmartTouch, SMART-AF).[19 20] In the case of the former the success was no different from that observed with standard non-contact force RF ablation. Interestingly, post-hoc analyses of these studies suggested that the outcomes were improved when the procedure was performed with adequate contact-force parameters (84% one-year freedom from AF in the 47% of patients in whom ablation was in the target range ≥80% of the time in SMART-AF, and 76% one-year freedom from AF in the 57% of patients in whom ≥90% of the lesions were >10 g in TOCCASTAR). No differences in the incidence of complications have been reported between patients undergoing ablation with contact force vs. non-contact force sensing RF ablation catheters.[19 21 22]

Cryoballoon Ablation

Recent studies have examined short- and long-term success with the second-generation cryoballoon. Studies of planned re-mapping procedures have demonstrated that the durability of PVI at three months post index ablation procedure was improved at 91% with the second-generation cryoballoon, compared to 67% of PVs with standard (non-contact force) RF, and 88% of PVs with the first generation cryoballoon.[18 23-27] Clinically this has translated into a one-year freedom from recurrent AF of 82% with the second generation cryoballoon (11 studies; 1725 patients), which was significantly improved compared to the first generation cryoballoon in a separate comparative meta-analysis (odds ratio of arrhythmia recurrence 0.34 [0.26-0.45] when compared to first-generation cryoballoon; 10 studies, 2310 patients).[28] From a safety standpoint there were significantly more phrenic nerve palsies (transient and persistent) observed with the second-generation cryoballoon.

Contact Force Ablation vs. Cryoballoon Ablation

There is limited data directly comparing contact-force guided RF ablation to cryoballoon ablation. Since the inception of the CIRCA-DOSE study, three observational studies have reported comparable safety and efficacy between contact-force guided RF ablation and cryoballoon ablation for paroxysmal (2 studies) and persistent (1 study) AF. Specifically, Jourda et al. reported a single-centre experience with 150 consecutive patients undergoing PVI for paroxysmal AF with the second-generation cryoballoon (75 patients), and contact-force guided irrigated RF ablation (SmartTouch, 75 patients).[29] In this non-randomised study the one-year freedom from recurrent AF (as detected by Holter monitoring at 1, 3, 6, 9, and 12 months) was 85% in the cryoballoon group and 88% in the contact-force group (P=0.988). Squara et al. reported a similar 1-year freedom from recurrent paroxysmal AF (73% in the cryoballoon group and 76% in the contact-force group [SmartTouch and Tacticath]; P=0.63) in their ambidirectional (combined prospective and retrospective enrolment) multi-centre cohort study of 4 participating centres (2 centres performed both cryoballoon and RF ablation; 1 centre performed exclusively cryoballoon ablation; and 1 performed exclusively RF ablation).[30] Lastly, Ciconte et al. reported a single-centre experience with 100 consecutive patients undergoing PVI for persistent AF with the second-generation cryoballoon (50 patients), and contact-force guided irrigated RF ablation (SmartTouch and Tacticath, 50 patients).[31] In this non-randomised study the one-year freedom from recurrent AF (as detected by Holter monitoring at 1, 3, 6, and 12 months) was 60% in the cryoballoon group and 56% in the contact-force group (P=0.78). While none of these studies demonstrated a significant difference in the incidence of complications a recent meta-analysis observed a lower incidence of pericardial effusion (OR 0.44; 95%CI 0.28-0.69; P<0.01) and tamponade (OR 0.31; 95%CI 0.15-0.64; P<0.01) with cryoballoon ablation in comparison to contact-force guided RF ablation, whereas transient phrenic nerve palsy was more frequent after cryoballoon (OR 7.40; 95%CI 2.56–21.34; P<0.01).[32]

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The multicentre, randomized FIRE and ICE trial was designed to determine whether cryoballoon ablation was non-inferior to RF ablation in symptomatic patients with drug-refractory paroxysmal AF.[33] Patients were randomised to Arctic Front-based cryoballoon ablation (374 patients), vs. irrigated RF ablation (376 patients). The primary efficacy endpoint (documented recurrence of AF/AT/AFL >30s, AAD prescription, or re-ablation) occurred in 138 patients in the cryoballoon group and in 143 in the RF group (1-year Kaplan–Meier event rate estimates, 34.6% and 35.9%, respectively; hazard ratio, 0.96; 95% confidence interval [CI], 0.76 to 1.22; P<0.001 for noninferiority). However, despite reporting recently it is important to note that the study was not an exclusive comparison of advanced technologies, with the majority of patients receiving non-contact force irrigated RF ablation (284/376 in the RF group) and a significant proportion (90 of 374 patients) receiving first generation cryoballoon ablation. As such the relative safety and efficacy of these new technologies remains unknown.

Data Supporting Shorter Freeze Durations

The optimal duration of freezing, that is, how long the tissue should be kept in the frozen state, is not well established. Current recommendations are for cryoablation dosing at 240 seconds for each application, which is based on studies of an early focal cryocatheter. In these studies, it was observed that the effect of a cryoablation lesion reached a plateau of three-minutes after the onset of ablation. Thereafter "prolongation of exposure time beyond 3 minutes did not result in any further increase in lesion dimension or volume."[34 35] Since then, the cryocatheter has evolved from a rigid focal catheter to a semi-compliant balloon, which necessitated a redesign of the cryorefrigerant delivery mechanisms. Moreover, the refrigerant itself has changed from slow-cooling to more efficacious gases (i.e., nitrous oxide).

Information regarding the safety and efficacy of shorter cryoballoon ablation durations are limited to 3 minute lesions, which have been suggested in several non-randomised studies to be of comparable efficacy to longer duration cryolesions.[36 37] We recently completed a randomized pre-clinical study examining the immediate and delayed effects of shorter ablation time on PVI efficacy.[38] In our study, thirty-two mongrel dogs underwent cryoballoon ablation with a 23-mm cryoballoon catheter. PVI procedures were randomized to a single 2-minute vs.

4-minute cryoballoon application. Although 4-minute lesions were associated with a thicker neointima than 2-minute lesions (223.8µm vs. 135.6µm; p=0.007), no differences were observed in the rates of procedural PVI, or the achievement of complete circumferentially transmural lesions at 30 days (78% overall; 86.2% for 2-min vs. 70% for 4-min; P=0.285), however a reduction in late PV strictures was observed in the 2 minute group (6/30 PVs with strictures in the 4-minute freeze duration vs. 0/29 PVs with strictures in the 2-minute freeze duration; p=0.024).

Arrhythmia Monitoring

While from a patient perspective the freedom from symptoms related to AF may be the most important clinical endpoint, contemporary evidence suggests that there is a poor correlation between symptoms and AF burden.[39 40] Moreover the presence or absence of symptoms does not affect the prognosis and complications of the AF.[41] As such any evaluation of treatment efficacy must include protocol-determined arrhythmia monitoring. Given that paroxysmal AF is by definition a disease of clusters, studies have shown that the detection of AF recurrence is proportional to the duration of monitoring.[42] Specifically, Kottkamp et al. demonstrated an increased detection of arrhythmia recurrences post AF ablation for highly symptomatic AF in a group undergoing serial 7-day ECG monitoring versus those undergoing only intermittent ECG monitoring (26% vs. 12% documented recurrence).[43] Unfortunately, while non-invasive intermittent rhythm monitoring remains the most widely utilised method of ascertaining ablation efficacy it often fails to detect AF recurrence. Specifically, the sensitivity (31-71%) and negative predictive value (21-39%) are significantly inferior to continuous monitoring techniques.[44] This imprecision associated with intermittent arrhythmia monitoring confers a significant risk of Type II error, which makes it inappropriate for outcome ascertainment in a trial designed to evaluate the efficacy of different therapeutic interventions.

As such, a major strength of the current study is the reliance on continuous cardiac monitoring for the determination of arrhythmia outcomes. All participants in the CIRCA-DOSE trial will have an implantable cardiac monitor with an automated AF detection algorithm (REVEAL LINQ) inserted a minimum of 1 month prior to ablation. This subcutaneous implantable cardiac

monitor continuously analyses the beat-to-beat variability of cardiac cycles leading to an accurate determination of the timing of arrhythmia recurrence, as well as an accurate quantification of atrial fibrillation burden (hours in AF per day, and percentage of overall time in AF). With respect to this latter point, the use of AF burden allows for a more detailed examination of the relatively efficacy of the three-different treatment approaches, beyond which can be obtained with dichotomous event analyses such as "time-to-first-AF recurrence." Unfortunately, intermittent rhythm monitoring techniques are unable to accurately quantify AF burden.[44]

METHODS AND ANALYSIS

Study Design

The CIRCA-DOSE study (ClinicalTrials.gov #**NCT01913522**) is a multicentre prospective randomized clinical trial. The study will be conducted at 8 participating clinical centres in Canada. The protocol has been developed in accordance with Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines.

Participants

Patients aged >18 years with symptomatic paroxysmal and early persistent AF that is refractory to at least one AAD, and who have been referred for first percutaneous catheter ablation will be screened for eligibility. At least 1 episode of AF must be documented on 12-lead electrocardiogram (ECG), transtelephonic monitor (TTM), or Holter monitor within 24 months of randomization. Inclusion and exclusion criteria are detailed in **Supplementary Table 1**.[45]

Screening and Selection

Patients referred for catheter ablation of symptomatic AAD-refractory AF and meeting the eligibility criteria will be offered the opportunity to participate in the trial (**Figure 1**). Informed consent and baseline clinical data will be obtained by the physician investigator.

Randomisation

Patients who meet eligibility criteria and give informed consent will be assigned in a 1:1:1 ratio using permuted block randomization according to a computer-generated sequence, with a block size of 6 and 12 per site to: 1) Standard RF ablation guided by tissue-contact force; 2) Short cryoballoon ablation duration (2-minute cryoapplications); and 3) Standard cryoballoon ablation duration (4-minute cryoapplications). An independent, blinded statistician will generate the block randomisation scheme. Patients will be blinded to their randomization assignment.

Loop Recorder Implant

Patients who meet eligibility criteria and give informed consent will undergo the implantation of an implantable cardiac monitor (ICM) a minimum of 30 days prior to the index ablation for the purpose of arrhythmia monitoring (Reveal LINQ, Medtronic). The ICM has an AF detection algorithm that analyses beat-to-beat variability of cardiac cycles on a 2-minute ECG strip. Arrhythmia events meeting these criteria are stored for independent adjudication. The device is also capable of quantifying the amount of AF per day, and the overall AF burden (percentage of the observed time that a patient is in AF). Additionally, the patient can activate the device manually to facilitate analysis of heart rhythm during symptomatic events. ICM programmed parameters are summarized in **Supplementary Table 2**.

Catheter Ablation Procedure

Effective anticoagulation with oral vitamin K antagonists (target INR between 2-3), low molecular weight heparin, or dabigatran/apixaban/rivaroxaban for at least one month and/or the exclusion of a left atrial (LA) thrombus by transesophageal echocardiography (TEE; <48 hours pre-ablation) is mandated prior to ablation.[46] Antiarrhythmic drugs will be discontinued five half-lives before the procedure, except for amiodarone, which will be discontinued 8 weeks prior to ablation. Interventions will be performed on patients in the fasting state under conscious sedation or general anaesthesia, per local practice.

For each of the three treatment arms, patients will undergo pulmonary vein isolation (PVI) according to standard clinical practice.[46-49] No prophylactic LA linear ablation lesions, or

ablation of complex fractionated atrial electrograms (CFAE) will be permitted in addition to PV isolation. In the event of documented right atrial cavotricuspid isthmus dependent flutter, cavotricuspid isthmus ablation is permitted (with irrigated RF or focal cryoablation).

Contact-Force Guided Radiofrequency Ablation

For patients randomized to RF catheter ablation a three-dimensional, non-fluoroscopic mapping system (CARTO3, Biosense Webster) will be used for anatomic reconstruction. Through one transseptal access, a circular mapping catheter (decapolar or duo-decapolar) will be advanced into the LA. The circular mapping catheter will be placed sequentially within each PV to record baseline electrical activity (PV potentials; PVPs). Via a second transseptal access, an irrigated-tip contact-force sensing RF ablation catheter (Thermocool SmartTouch or SmartTouch Surround Flow, Biosense Webster) will be positioned in the LA. Circumferential ablation lesions will be placed via the ablation catheter 1-2 cm from the PV ostia to electrically isolate the PV, as per standard practice.[45] RF energy will be delivered at 20-35 Watts to a maximum temperature of 43°C. The contact force targeted prior to lesion delivery will be 20 g (acceptable range 10-40 g), with a minimum individual target lesion duration of 400 gram-seconds force-time integral (FTI). Circumferential lesions around the veins will be considered complete when the procedural endpoint has been reached (see below).

Cryoballoon Ablation

For patients randomized to cryoballoon ablation the transseptal sheath will be exchanged over a guidewire with a steerable 15-Fr sheath (**FlexCath, Medtronic**). Before introducing the balloon catheter (**Arctic Front Advance, Medtronic)** in the sheath a 15 or 20 mm diameter circular mapping catheter (CMC) will be inserted in the central lumen of the cryoballoon. A 23 or 28 mm cryoballoon will be advanced through the steerable sheath into the LA with the CMC used as a guidewire. While use of the larger (28-mm) cryoballoon is preferred, the 23-mm cryoballoon may be used based on physician judgment for PV diameters <20 mm.[50-52] Before ablation, the CMC will be positioned in the venous ostium to record baseline electrical activity. The CMC will then be advanced more distally for support. The cryoballoon will be positioned in the venous ostium and the degree of occlusion will be tested through the injection of 1:1

diluted contrast material. Vessel occlusion will be evaluated according to a semi-quantitative grading (**Supplementary Table 3**). Prior to ablation of right-sided PVs, a catheter will be placed in the superior vena cava cranial to the right superior PV in order to pace the right phrenic nerve (10-20 mA at 1.0-2.0 msec pulse width at a cycle length of 1000 msec). Ablation will be immediately terminated upon any perceived reduction in the strength of diaphragmatic contraction or a 30% reduction in the diaphragmatic compound motor action potential (CMAP) amplitude as measured via diaphragmatic electromyography.[53] If the procedure is performed under general anaesthesia, paralytic agents will be discontinued at least 30 minutes prior to phrenic nerve pacing.

a) **Patients randomized to standard cryoballoon ablation** will undergo cryoablation with target duration of 4 minutes. Once PVI is achieved a single additional application of 4-minute cryoapplication will be delivered after the rewarming phase (to +20°C).

b) **Patients randomized to short cryoballoon Ablation** will undergo cryoablation with target duration of 2 minutes. Once PVI is achieved a single additional 2-minute cryoapplication will be delivered after the rewarming phase (to +20°C).

Ineffectual cryolesions: Excepting common ostia, cryoablation lesions that fail to isolate the vein (if real-time PV potential monitoring is feasible) or fail to achieve a temperature colder than minus 35°C after 60 seconds of ablation onset will be considered ineffectual and be terminated. Thereafter, the balloon and/or guidewire should be repositioned and a new lesion delivered.

Inability to Isolate: Should the operator fail to isolate the PV (excluding common ostia) after a minimum of 3 attempted cryoballoon applications, then focal ablation with the 8 mm cryocatheter (Freezor Max) targeted to sites of LA-PV breakthrough will be permitted at operator discretion.

Procedural Endpoint

For all three treatment arms the ablation procedure will be considered successful when PVI, as confirmed by bidirectional conduction block between PV and LA, has been achieved in

accordance with the 2012 HRS/EHRA/ECAS consensus document.[45] Bidirectional conduction block is defined as the combination of entrance block (the stable absence of conduction into the PV from the LA) and exit block (the stable absence of conduction from the PV into the LA, either spontaneous or during pacing from the circular mapping catheter positioned at the PV ostium). Patients remaining in AF at the end of the procedure will be electrically or chemically cardioverted back to sinus rhythm. Remapping of all PVs post cardioversion will be performed to the procedural endpoint.

Evaluation of Spontaneous Reconnection and Dormant Conduction

For all three treatment arms a 20-minute observation period (beginning at the end of the last ablation lesion) will be used to assess spontaneous recovery of conduction.[45] If spontaneous reconnection occurs, the reconnected PVs will be re-isolated according to the randomised protocol.

Dormant conduction will be assessed with the use of a circular catheter in each PV by intravenous injection of 6 mg or more of adenosine to obtain at least 1 blocked P wave or a sinus pause ≥3 seconds. Dormant conduction will be defined by reappearance of PV conduction for ≥1 beat. If there is no dormant conduction in any PV, then the procedure will be considered complete. If dormant conduction is elicited, the patient will undergo additional targeted ablation according to the randomised protocol until dormant conduction is abolished (i.e. adenosine fails to induce reconnection in any PV).

Post-ablation follow-up

Barring complications, patients will be discharged within 24 hours after the ablation procedure. Scheduled follow-up visits will occur at 3, 6, and 12 months from the first ablation procedure (within a 2-week margin – Table 1). A 24-hour Holter and 12-lead ECG will be performed at 3, 6, and 12 months. Automatic transmissions from the ICM will be obtained on a daily basis via CareLink. Patients will be instructed to record symptomatic episodes via use of the patient activator.

All patients will remain anticoagulated for ≥3 months post procedure. While discontinuation of oral anticoagulation during the study period is strongly discouraged, in patients with a CHA_2DS_2VASc score of <2, aspirin alone may be considered at treating physician discretion. Arrhythmia recurrence during the first 3 months post-ablation may be treated with cardioversion and/or antiarrhythmic drugs (except amiodarone). Where possible, repeat ablation procedures will be deferred until after the 3-month blanking period due to the potential for delayed cure (as per standard practice and in accordance with HRS/ECAS/EHRA recommendations).[45] If antiarrhythmic drugs (except amiodarone) are used in the first 3 months post ablation, they will be discontinued 5 half-lives before the end of the 3-month blanking period.[45]

STUDY OUTCOMES

Primary endpoint is time to first recurrence of symptomatic or asymptomatic AF, atrial flutter, or atrial tachycardia (AF/AFL/AT) documented by 12-lead ECG, surface ECG rhythm strips, 24-hour ambulatory ECG (Holter) monitor, or on ILR between days 91 and 365 post ablation, or a repeat ablation procedure between days 0 and 365 post ablation. AF or atrial flutter/tachycardia will qualify as an arrhythmia recurrence after ablation if it lasts 30 seconds or longer (on surface ECG rhythm strips, 24-hour ambulatory Holter monitor) or 120 seconds or longer on ICM (the minimum programmable episode interval). All tracings will be independently adjudicated by a committee blinded to treatment allocation. The primary end point and the 3-month blanking period adhere to the Heart Rhythm Society recommendations for reporting outcomes in AF ablation trials.[45]

Secondary endpoints are listed in Table 4 of the Supplementary Appendix.

Event Adjudication: The clinical events committee will be composed of a cardiac electrophysiologist as Chairperson, and six (6) cardiologist reviewers with expertise in clinical event adjudication. Two reviewers will be assigned to review each endpoint and SAE with disagreement resolved by the Chairperson or entire CEC (as outlined below).

SAMPLE SIZE

The sample size was determined based on the primary endpoints for the two main comparisons of interest: cryoablation with a 4-minute application vs. contact force guided RF catheter ablation, and cryoablation with a 2-minute application vs. RF catheter ablation. Overall event-free survival at one year is estimated to be 65%. With a sample size of 111 per group and a two-sided 0.025 significance level (to account for the two main comparisons), the study will have 80% power (using a log rank test) to detect a relative difference of 20% between contact force RF catheter ablation and either of the two cryoballoon ablation groups. Factoring in a 4% loss to follow-up, 116 patients per group should be randomized, for a total study population of 348. Power calculations are based on the log-rank test for equality of survival curves (nQuery, version 6.01), using simulated data.

DATA MANAGEMENT

A unique subject number not derived from personal identifiers will be utilized for subject identification. Study information using this unique subject number will be collected using case report forms, which will be entered into a secure online platform (InForm 6.0). All electronic data are encrypted, password protected and stored on a secure network within the coordinating centre. The coordinating centre will perform regular evaluations of data integration and quality, management and resolution of data discrepancies, tracking of adverse event information, database quality control, and generate reports for principal and co-applicants, study sites and for committee meetings. At the conclusion of the study the coordinating center will lock the clinical data and perform the final analysis of the trial results.

STATISTICAL ANALYSES

Analysis of the primary and secondary endpoints will be based on the intention-to-treat principle according to the initial allocated strategy. Survival curves will be estimated by the Kaplan-Meier method and compared by the log rank test. The two main comparisons will be cryoablation with a 4-minute application vs. RF catheter ablation, and cryoablation with a 2-minute application vs. RF catheter ablation. The comparison between the two cryoablation groups will be considered secondary.

A Cox proportional hazards model will also be used to test the consistency of the group effect while accounting for clinically important baseline characteristics, which will include: ablation site, age, gender, race, weight, LA size, structural heart disease, AF duration, and number of AADs used in the past. The proportional hazard assumption will be assessed by visual inspection of the log-negative-log plot and through a formal test of the interaction term "group x time" at α=0.05. Should this assumption fail, a stratified Cox model will be fitted in order to correct for non-proportional hazards if possible or, if ineffective, time-dependent variables will be introduced. Should these corrective techniques fail, logistic regression will be used instead.

Secondary endpoints expressed as time-to-event will be analysed similarly using Kaplan-Meier survival curves and a log rank test. For all dichotomous qualitative variables, Chi-Square tests will be performed to assess group differences. Continuous variables, such as arrhythmia burden, will be analysed using an analysis of variance (ANOVA). If the data are not normally distributed, then the non-parametric Wilcoxon Signed Rank test will be used. Health-related quality of life scores will be compared by analysis of covariance, adjusting for baseline values to reduce the error mean squares. In the event of missing data, a multiple imputation approach using SAS procedures PROC MI and PROC MIANALYZE will be considered. All tests will be conducted at an alpha level of 0.05 with the exception of the two main comparisons that will be conducted at an alpha level of 0.025. Similarly, hazard ratios for these two comparisons will be presented with 97.5% confidence intervals.

DATA MONITORING AND CLINICAL EVENTS COMMITTEE

A seven-member clinical events committee (CEC) will be composed of a cardiac electrophysiologist as Chairperson, and six (6) cardiologist reviewers with expertise in clinical event adjudication. The CEC members are independent from the sponsor and investigators, blinded to the study allocation, and have no conflicts of interest relevant to the trial. The CEC is responsible for review and adjudication of all primary and secondary arrhythmia end-points, which include serious adverse events (SAE) and major complications. Information about the occurrence of any SAE is sought at all scheduled visits. For all adverse events source documentation will be obtained prior to CEC review. Two reviewers will be assigned to review

each endpoint and SAE. If both reviewers agree, the Chairperson will be provided with the Reviewer's Forms and he will ratify the adjudication by completing the final adjudication form. If the reviewers are in disagreement, the Chairperson will review the event and will serve as the third reviewer. If there is still disagreement between all three reviewers, a meeting will be scheduled to discuss the event.

ETHICS AND DISSEMINATION:

Enrolment in the trial is predicated on assumption that patients have already made the decision to undergo a catheter ablation procedure for drug-refractory AF. The catheter ablation procedure used in this study is the same as the standard treatment method for AF and is not experimental. The risks of participation are therefore the same as those of standard atrial fibrillation ablation and independent of trial enrolment participants in the study would have accepted these risks. Full ethics approval has already been obtained at all the participating sites.

The dissemination plan for the trial encompasses multiple modalities and strategies including an integrated and an end of project knowledge-translation (KT) strategy. The integrated approach of the program benefits from the involvement of non-profit organizations with a mandate of end-user engagement and education (the Heart and Stroke Foundation of Canada), patients (the end-user), and healthcare professionals. The involvement of these groups from the planning phase through to completion represents an optimal strategy for engagement and empowerment, essentially creating invested champions at each level. Post project KT will leverage the involvement of these groups to optimize the ability to reach the end-users. The information derived herein (whether positive, or negative) will be disseminated through established channels such as peer-reviewed publication, national and international meetings, webinars, and through social media. The involvement of Medtronic CryoCath, will facilitate dissemination of the findings to end users through their established educational infrastructure (Medtronic Academy website, "user meetings", to small group interactive conferences through their clinical specialist network). The end result of this KT plan will be the delivery of the optimal tailored treatment strategy to the individual patient at the optimal time.

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FOOTNOTES

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Role of the Funding source: The funding sources had no role in the design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results.

Ethics Approval: University of British Columbia Office of Research (Services) Ethics Clinical Research Ethics Board, as well as the local institutional review boards for each of the participating sites.

CIRCA-DOSE: Methods and Rationale

FIGURE LEGENDS

Figure 1: Study Flow diagram. Legend: AAD – Antiarrhythmic drugs; AF – atrial fibrillation; PVI – pulmonary vein isolation; RF - radiofrequency

Table 1: Schedule of enrolment, interventions, and assessments. Legend – CT – computed tomography; MRI – magnetic resonance imaging; QOL – quality of life

	STUDY PERIOD						
	Enrolment	Ablation	Follow-up				Close-out
TIMEPOINT**	**>30 days prior to ablation**	**0**	***Hospital discharge***	***1 week***	***3 months***	***6 months***	***12 months***
Eligibility screen	X						
Informed consent	X						
Clinical examination	X		X		X	X	X
Telephone Interview				X			
Laboratory investigations		X					
12-lead ECG	X	X	X		X	X	X
Echocardiography	X						
24 hour Holter	X				X	X	X
QOL questionnaire	X					X	X
Cardiac CT or MRI*	X						
Loop recorder implantation	X						
Loop recorder interrogation	◆—	—	—	—	—	—	—◆

*if performed

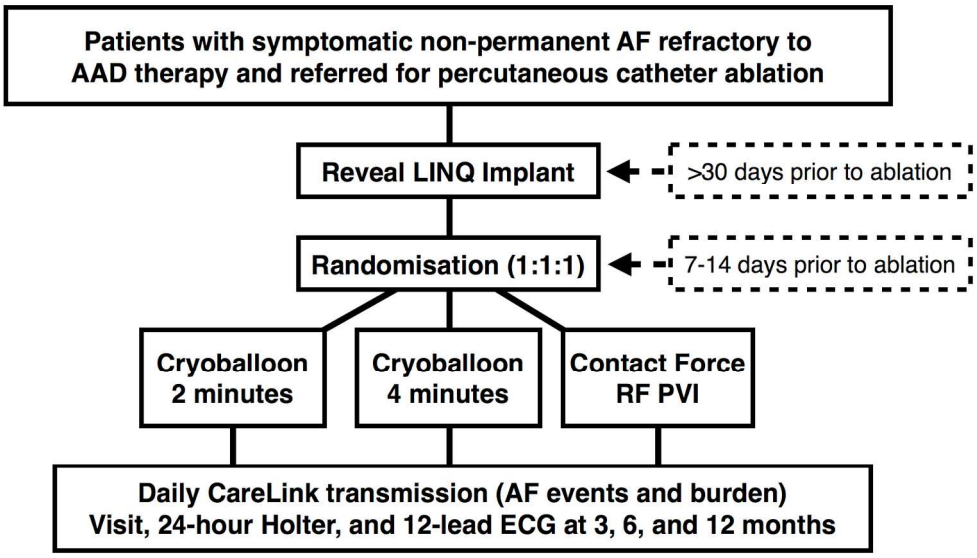

Figure 1: Study Flow diagram. Legend: AAD – Antiarrhythmic drugs; AF – atrial fibrillation; PVI – pulmonary vein isolation; RF - radiofrequency

299x168mm (300 x 300 DPI)

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CIRCA-DOSE: Methods and Rationale

Supplementary Table 1: ***Inclusion and Exclusion Criteria***

INCLUSION CRITERIA
• Non-permanent atrial fibrillation documented on a 12 lead ECG, Trans Telephonic Monitoring (TTM) or Holter monitor within the last 24 months (Episodes of AF must be >30 seconds in duration to qualify as an inclusion criterion) • Age of 18 years or older on the date of consent • Candidate for ablation based on AF that is symptomatic and refractory (ineffective or intolerant) to at least one class 1 or 3 antiarrhythmic. • Continuous anticoagulation with warfarin (INR 2-3), low molecular weight heparin, or a direct oral antithrombotic (dabigatran, apixaban, rivaroxaban) for ≥4 weeks prior to the ablation; or a TEE that excludes LA thrombus ≤48 hours before ablation
EXCLUSION CRITERIA
• Previous left atrial (LA) ablation or LA surgery • AF due to reversible cause (e.g. hyperthyroidism, cardiothoracic surgery) • Intracardiac Thrombus • Pre-existing pulmonary vein stenosis or PV stent • Pre-existing hemidiaphragmatic paralysis • Contraindication to anticoagulation or radiocontrast materials • Anteroposterior LA diameter greater than 5.5 cm by TTE • Cardiac valve prosthesis • Clinically significant (moderately-severe, or severe) mitral valve regurgitation or stenosis • Myocardial infarction, PCI / PTCA, or coronary artery stenting during the 3-month period preceding the consent date • Cardiac surgery during the three-month interval preceding the consent date • Significant congenital heart defect (including atrial septal defects or PV abnormalities but not including PFO) • NYHA class III or IV congestive heart failure • Left ventricular ejection fraction (LVEF) less than 35% • Hypertrophic cardiomyopathy (Wall thickness >1.5 cm) • Significant Chronic Kidney Disease (CKD - eGFR <30 µMol/L) • Uncontrolled hyperthyroidism • Cerebral ischemic event (strokes or TIAs) during the six-month interval preceding the consent date • Pregnancy • Life expectancy less than one (1) year • Currently participating or anticipated to participate in any other clinical trial of a drug, device or biologic during the duration of this study • Unwilling or unable to comply fully with study procedures and follow-up

Supplementary Table 2: Implantable cardiac monitor programming

AF detection threshold	Balanced Sensitivity
Ectopy rejection	Nominal
Episode storage threshold	All (Record ECG of 2 minutes)

These parameters were chosen to optimise detection of AF (reported sensitivity of 96.1% with a positive predictive valve [PPV] of 73%), however al arrhythmia episodes will be independently adjudicated.[18, 19]

CIRCA-DOSE: Methods and Rationale

Supplementary Table 3: Gradation of pulmonary venous occlusion during cryoballoon ablation
Grade 1 – negligible occlusion with immediate rapid outflow from the PV
Grade 2 – mild backflow into the atrium
Grade 3 – minimal backflow into the atrium
Grade 4 – total contrast retention with no backflow into the atrium.

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Supplementary Table 4: Secondary Endpoints

1) Time to first recurrence of symptomatic documented AF/AFL/AT between days 91 and 365 after ablation or a repeat ablation procedure between days 0 and 365 post ablation
2) Arrhythmia burden (daily AF burden - hours/day; overall AF burden - % time in AF)
3) Proportion of patients experiencing an acute or adenosine provoked PV reconnection during the index ablation procedure
4) Proportion of patients requiring a repeat ablation procedure because of documented recurrence of symptomatic AF/AFL/AT
5) Proportion of patients prescribed AADs because of documented recurrence of symptomatic AF/AFL/AT; 6) Proportion of patients with AF/AFL/AT during the first 90 days post ablation
7) Emergency visit or hospitalization >24h in a health-care facility
8) Major complications including death, stroke, TIA, Myocardial Infarction or systemic thromboembolism, PV stenosis, phrenic nerve palsy, pericarditis, pericardial effusion, cardiac perforation or tamponade, hematoma, AV fistula, pseudoaneurysm, esophageal injury and atrio-esophageal fistulae (both individually and as a composite endpoint)*
9) Overall and disease specific quality of life
10) Single and multiple procedure success (freedom from symptomatic or asymptomatic electrocardiographically documented AF/AFL/AT) after the first and last ablation procedure respectively
11) Single and multiple procedure success (freedom from symptomatic electrocardiographically documented AF/AFL/AT) after the first and last ablation procedure respectively.

CIRCA-DOSE: Methods and Rationale

*Complication definition as per 2012 HRS/EHRA/ECAS recommendations. Acute peri-procedural complications will be defined as occurring within 30 days of ablation, with delayed complications occurring 31-365 days after ablation

A major complication is a complication that results in permanent injury or death, requires intervention for treatment, or prolongs or requires hospitalization for more than 48 hours. Because early recurrences of AF/AFL/AT are to be expected following AF ablation, recurrent AF/AFL/AT within 3 months that requires or prolongs a patient's hospitalization should not be considered to be a major complication of AF ablation.

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	_____1_____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	_____2_____
	2b	All items from the World Health Organization Trial Registration Data Set	_____2_____
Protocol version	3	Date and version identifier –	1.0 June 27, 2014
Funding	4	Sources and types of financial, material, and other support	_____22_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	_____2_____
	5b	Name and contact information for the trial sponsor	_____1_____
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	_____22_____
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	__3, 14, 15.____

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	____4_____
	6b	Explanation for choice of comparators	__6, 9, 10, 11___
Objectives	7	Specific objectives or hypotheses	_____4_____
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	9, 10
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	____9, 1_____
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	_9, supplement___
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	___10-13_____
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	___n/a, _____
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	___8-9_____
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	____14_____
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	14, supplement

Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	_9, 13, 14, 24___
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	___14-15_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	___n/a_____
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	___10_____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	_____10_____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	___10_____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	____10, 14, 15___
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	____n/a_____
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	___8,10,13,24__

	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	____n/a_____
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	__15_____
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	_____15-16____
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	_____16_____
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	15-16 _____
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	___16_____
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	____14_____
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	____14, 16_____
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	____14_____
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	____16_____

Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	n/a
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	9
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	15
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	22
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	3
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	none
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	17
	31b	Authorship eligibility guidelines and any intended use of professional writers	3
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	uploaded
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	3
	2b	Specific objectives or hypotheses	4
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	9
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	n/a
Participants	4a	Eligibility criteria for participants	8
	4b	Settings and locations where the data were collected	8
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	9
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	12
	6b	Any changes to trial outcomes after the trial commenced, with reasons	n/a
Sample size	7a	How sample size was determined	13
	7b	When applicable, explanation of any interim analyses and stopping guidelines	n/a
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	9
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	9
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	9
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	9
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	13

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	n/a
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	13
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	14
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	n/a
	13b	For each group, losses and exclusions after randomisation, together with reasons	n/a
Recruitment	14a	Dates defining the periods of recruitment and follow-up	n/a
	14b	Why the trial ended or was stopped	n/a
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	n/a
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	n/a
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	n/a
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	n/a
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	n/a
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	n/a
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	n/a
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	n/a
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	n/a
Other information			
Registration	23	Registration number and name of trial registry	2, 8
Protocol	24	Where the full trial protocol can be accessed, if available	This submission
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	1

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.