An Investigator Initiated, Controlled, Prospective, Non-Inferiority, Parallel-Group, randomised, Interventional, Open, Blinded Outcome Assessment (PROBE-Design), Multi-centre Trial, Comparing Efficacy and Safety of Isolation of the Pulmonary Veins with a Cryoballoon Catheter Versus a Radiofrequency Ablation with a ThermoCool Catheter in Patients with Paroxysmal Atrial Fibrillation

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Comparing efficacy and safety of isolation of the pulmonary veins (PV) using a Cryoballoon catheter versus a radiofrequency ablation with a ThermoCool catheter in patients with paroxysmal atrial fibrillation (AF).

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Cardiac arrhythmias
Study type	Interventional

Summary

ID

NL-OMON39146

Source
ToetsingOnline

Brief title
FIRE AND ICE Trial

Condition

- Cardiac arrhythmias

Synonym
irregular heart beat, Paroxysmal atrial fibrillation

Research involving
Human

Sponsors and support

Primary sponsor: FGK Representative Service GmbH
Source(s) of monetary or material Support: Industry,Medtronic

Intervention

Keyword: atrial fibrillation, Cryoballoon Catheter, Multi-centre Trial, Radiofrequency Ablation

Outcome measures

Primary outcome

Time to first documented recurrence of atrial arrhythmias (a blanking period of three months will be maintained after the initial procedure).

Secondary outcome

Several secondary outcomes will be assessed in the trial population.

Key secondary outcomes: Procedural data (total procedural duration, time of fluoroscopy and duration of hospital stay), quality of life, sedation, flutter ablation and survival time.

Assessment of safety: serious adverse events during the observation period with special emphasis on complications due to interventions as well as phrenic nerve palsy and PV stenosis.

Study description

Background summary

Atrial fibrillation (AF) is a common and disabling cardiac arrhythmia, affecting 1-2% of the population in Europe and 1-2 million US-Americans. In addition to hemodynamic compromise and higher mortality rates, AF causes an increased risk of systemic emboli arising from the left atrium (LA). The risk of stroke in patients with non-valvular AF is five to seven times higher than that in comparable patients without AF; overall, 20-25% of ischemic strokes are due to cardiac emboli, of which half arise in patients with non-valvular AF1,2. In addition to such proven mortality and morbidity risks, AF is associated with a substantial burden of symptoms, stemming from the arrhythmia itself, exacerbation of comorbid conditions such as congestive heart failure, and associated anxiety over possible sequelae as well as the substantial burden of adverse effects from antiarrhythmic drugs (AADs)3.
Currently available treatments are unsatisfactory for many reasons. Antiarrhythmic drug therapy has a relatively low efficacy even in patients with paroxysmal atrial fibrillation (PAF), with frequent recurrence and a high incidence of intolerable drug adverse effects3. Isolation of pulmonary veins (PVs) using radiofrequency (RF) energy has shown considerable clinical success in the treatment of PAF. Success rates vary from 60-86%4-9. However, RF ablation has also been associated with serious complications, including PV stenosis, thromboembolic complications, cardiac perforation with pericardial tamponade, and rarely phrenic nerve palsy or esophageal fistulae5,10,11. Furthermore, RF energy effects are rapidly irreversible and cannot be used to temporarily alter and reversibly assess the electrophysiologic functions of the cardiac conduction tissue adjacent to the ablating catheter. Use of RF energy can be painful, whereas freezing with cryotherapy may be pain free.
Medtronic CryoCath Technologies (Montreal, Quebec, Canada) has developed the ArcticFront® Cardiac CryoAblation Catheter System (with the FlexCath Steerable Sheath) to allow the rapid formation of continuous cryoablation lesions at the PV ostia. Pre-clinical data have demonstrated long-term effectiveness of balloon cryoablation for permanent electrical isolation of the PVs. Results from these preclinical studies suggest that no pulmonary venous stenosis and no thromboembolic incidents have occurred12,13. The most frequent complications were right-sided phrenic nerve palsy12,14,15. Current experience with the cryoablation technique in humans is based on a feasibility trial14 and a non-randomised clinical trial16. In this non-randomised clinical trial, 346 consecutive patients have undergone a successful cryoablation therapy. PV isolation was achieved in 97%, whereas freedom from documented PAF was achieved in 74% after a median follow-up of 12 months. No death and no PV narrowing occurred. In 26 patients (7.7%), a phrenic nerve palsy could be observed. The majority of the patients recovered within six months; all patients recovered within 12 months16.
The STOP-AF pivotal trial demonstrated the safety and efficacy of the

ArcticFront® System in treating and eradicating paroxysmal atrial fibrillation. In this multi-centre randomised clinical trial 245 patients were enrolled (82 to drug treatment, 163 to cryoablation). The trial showed that 69.9% of patients treated with ArcticFront® were free from atrial fibrillation at one year, compared to 7.3% of patients treated with drug therapy only. The trial also demonstrated that treatment with the device is safe, with limited procedure-related adverse events (3.1%), and patients enrolled in the trial displayed a significant reduction of symptoms, a decrease in the use of drug therapy and substantial improvements in both physical and mental quality-of-life factors23.
Based on these encouraging results, this randomised clinical trial has been designed to provide valid scientific evidence on the safety and effectiveness of the ArcticFront® Cardiac CryoAblation Catheter System (with a FlexCath Steerable Sheath) (referred to as *cryoballoon* in the following text) to electrically isolate PVs in patients with PAF by comparing it with radiofrequency (RF) energy (using NaviStar® ThermoCool® Irrigated Tip Ablation Catheter in combination with 3D mapping system CARTO), which represents the most widely accepted and used energy form in AF ablation procedures.

Study objective

Comparing efficacy and safety of isolation of the pulmonary veins (PV) using a Cryoballoon catheter versus a radiofrequency ablation with a ThermoCool catheter in patients with paroxysmal atrial fibrillation (AF).

Study design

Controlled, prospective, non-inferiority, parallel-group, randomised, interventional, open, blinded outcome assessment (PROBE-design), multi-centre trial.

Intervention

Electrical isolation of the pulmonary veins in patients with PAF either with a cryoballoon ablation (ArcticFront® Cardiac CryoAblation Catheter System with the FlexCath Steerable Sheath) or radiofrequency ablation technique using the NaviStar® ThermoCool® Irrigated Tip Ablation Catheter in combination with 3D mapping system CARTO.

Study burden and risks

It is likely that the trial patients will benefit from the structured, well-controlled application of guideline-conform patient management in both trial groups due to close supervision during the study.
There are no recommendations how to differentiate the two ablation procedures. Therefore the risk of the participating patients appears small given the fact

that all therapies are approved, used in clinical routine and applied in-line with current recommendations and guidelines, for details about risk of ablation procedures see 3.1 of the trial protocol.
In addition to the therapeutic benefit this trial will further enhance the pathophysiological understanding of AF.
Telemetric ECG screening is used as a consistent monitoring tool in both treatment groups and may help to prevent future strokes in a patient population at potential risk for stroke9,20, reflecting the spreading notion that asymptomatic AF is a common first manifestation of stroke18.
As all treatments in FIRE AND ICE are in-line with clinical practice and recommended by guidelines, adverse events are expected to occur in similar clinical manifestations and at a comparable rate as the known adverse events of the approved therapies applied in the trial.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

DI1. Symptomatic PAF with at least two episodes within the last three months and at least one episode documented (30 seconds episode length).
I2. Documented treatment failure for effectiveness of at least one anti-arrhythmic drug (AAD Type I or III, excluding *-blocker and AAD intolerance).
I3. * 18 and * 75 years of age.
I4. Patients who are mentally and linguistically able to understand the aim of the trial and to show sufficient compliance in following the trial protocol.
I5. Patient is able to verbally acknowledge and understand the associated risks, benefits, and treatment alternatives to therapeutic options of this trial: cryoballoon ablation system or standard RF ablation technique. The patients, by providing informed consent, agree to these risks and benefits as stated in the patient informed consent document. All the details have been presented to him and he has signed the informed consent form for the trial.

Exclusion criteria

E1. Any disease that limits life expectancy to less than one year.
E2. Participation in another clinical trial (of a drug, device or biologic), either within the past two months or ongoing.
E3. Pregnant women or women of childbearing potential not on adequate birth control: only women with a highly effective method of contraception [oral contraception or intra-uterine device (IUD)] or sterile women can be randomised.
E4. Breastfeeding women.
E5. Substance misuse.
E6. Active systemic infection.
E7. Cryoglobulinaemia.
E8. Previous participation in this clinical trial.
E9. Patients with prosthetic valves.
E10. Employment by the sponsor or by the department of any of the investigators.
E11. Close relatives of any of the investigators.
E12. Any previous LA ablation or surgery.
E13. Any cardiac surgery or percutaneous coronary intervention (PCI) within three months prior to enrolment.
E14. Unstable angina pectoris.
E15. Myocardial infarction within three months prior to enrolment.
E16. Symptomatic carotid stenosis.
E17. Chronic obstructive pulmonary disease with detected pulmonary hypertension.
E18. Any condition contraindicating chronic anticoagulation.
E19 Stroke or transient ischemic attack within six months prior to enrolment.
E20. Any significant congenital heart defect corrected or not (including atrial septal defects or PV abnormalities) but not including patent foramen ovale.
E21. New York Heart Association (NYHA) class III or IV congestive heart failure.
E22. EF < 35 % (determined by echocardiography within 60 days of enrolment as

documented in patient medical history).
E23. Anteroposterior LA diameter > 55 mm (by trans-thoracic echocardiography (TTE) within three months to prior enrolment).
E24. LA thrombus (TEE diagnostic performed on admission).
E25. Intracardiac thrombus.
E26. PV diameter > 26 mm in right sided PVs.
E27. Mitral prosthesis.
E28. Hyperthrophic cardiomyopathy.
E29. 2° (Type II) or 3° atrioventricular block.
E30. Brugada syndrome or long QT syndrome.
E31. Arrhythmogenic right ventricular dysplasia.
E32. Sarcoidosis.
E33. PV stent.
E34. Myxoma.
E35. Thrombocytosis (platelet count > 600,000 / µl), thrombocytopenia (platelet count < 100,000 / µl).
E36. Any untreated or uncontrolled hyperthyroidism or hypothyroidism.
E37. Severe renal dysfunction (stage V, requiring or almost requiring dialysis, glomerular filtration rate (GFR) < 15 ml / min).

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Parallel
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	07-05-2013
Enrollment:	114
Type:	Actual

Ethics review

Approved WMO Date:	26-11-2012
Application type:	First submission
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	21-01-2013
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	05-02-2013
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	06-02-2014
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	24-03-2014
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	20-10-2014
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	01-06-2015
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
Other	NCT01490814
CCMO	NL41175.075.12