

FIRE AND ICE Clinical Trial Backgrounder

FIRE AND ICE is the largest multi-center, prospective, randomized, non-inferiority study to compare cryoballoon catheter ablation to point-by-point radiofrequency (RF) catheter ablation in the treatment of paroxysmal atrial fibrillation (PAF). This landmark, head-to-head study, published in *The New England Journal of Medicine*, weighed the overall effectiveness and safety of Medtronic's Arctic Front™/Arctic Front Advance™ Cryoballoon Catheter Family against Biosense Webster's CARTO® System Guided ThermoCool®/ThermoCool® SF/ThermoCool® SmartTouch® RF catheters when isolating the pulmonary veins for the treatment of PAF.

The robust findings from the FIRE AND ICE trial clinically validate cryoballoon ablation as a safe, effective, straightforward option compared to the current standard of care RF therapy. Given that half of all diagnosed AF patients fail drug therapy¹, FIRE AND ICE has the potential to impact clinical treatment guidelines for this largely underserved patient population.

Study Design

- FIRE AND ICE was a controlled, prospective, parallel-group, randomized, open, blinded outcome assessment (PROBE-Design), multi-center study.
- The components that made up the primary efficacy endpoint were time to arrhythmia recurrence, the need for antiarrhythmic drug therapy and/or re-ablation.
- The primary safety outcome was a composite of all-cause death, all-cause stroke/transient ischemic attack and treatment-related serious adverse events.
- The trial utilized a non-inferiority study design, which is often used to demonstrate that a newer technology is comparable to the currently accepted and existing technology.
- Predefined secondary endpoints included cardiovascular-related hospitalizations, repeat ablations, and quality of life.
- Procedural data, sedation, flutter ablation and survival times also were examined.

Patient Selection and Follow-Up

FIRE AND ICE is an important addition to the growing body of clinical evidence highlighting the benefits of the Arctic Front Advance System in treating a large-scale PAF patient population.

- The study randomized 769 patients to ablation with either Arctic Front™ Cryoballoon catheter ablation systems or ThermoCool RF catheter ablation systems.
- All study patients were diagnosed with drug refractory symptomatic PAF.
- Main selection criteria included symptomatic PAF with two or more episodes and one or more episodes documented within 12 months from study enrollment.
- Patients had documented treatment failure of one or more anti-arrhythmic drug (class I or III AAD).
- Ranging in age 18 to 75 years of age, trial participants were from 16 medical centers throughout Europe.
- FIRE AND ICE had a solid representation of female patients.
 - In the cryoballoon ablation arm, 41 percent of the subjects were female.
 - In the RF ablation arm, 37 percent of the subjects were female.
- Rigorous patient follow-up was guideline-driven, and included regular in-office visits, weekly and symptomatic monitoring, telephone follow up and participation in a quality-of-life questionnaire.

Effectiveness:

- The trial met its primary efficacy endpoint of showing non-inferiority for the Arctic Front Cryoballoon catheters compared to ThermoCool RF ablation catheters ($p=0.0004$) in reducing arrhythmia recurrence and the need for antiarrhythmic drug therapy and/or re-ablation.

Safety:

- FIRE AND ICE met its primary safety endpoint of time to first all-cause death, all-cause stroke/TIA, or treatment-related serious adverse events ($p=0.24$);

Efficiency:

- The Arctic Front Cryoballoons consistently demonstrated shorter total procedure times compared to the RF ablation treatment arm ($p=0.0001$).
 - The Cryoballoon uses coolant to create contiguous, circumferential lesions to achieve PVI. It does not require 3D mapping, reducing procedural complexity.
 - RF ablation uses heat and requires 3D mapping as well as point-by-point application to achieve PVI

Secondary Analyses

Predefined secondary endpoints presented at Cardiostim 2016 included cardiovascular-related hospitalizations, repeat ablations, and quality of life. Other analyses of interest focused on all-cause hospitalizations and direct current cardioversion.

Cardiovascular-Related Hospitalizations:

- 139 cardiovascular-related hospitalizations occurred in 89 patients (23.8 percent) in the Cryoballoon group, and by comparison, 203 cardiovascular-related hospitalizations occurred in 135 patients (35.9 percent) in the RF catheter group ($p<0.01$).

Repeat Ablations:

- 49 repeat ablations were performed in 44 patients (44/374; 11.8 percent) in the Cryoballoon group; 70 repeat ablations were performed in 66 patients (66/376; 17.6 percent) in the RF catheter group ($p=0.03$).

Quality of Life:

- Patient quality of life was assessed at baseline and every six months after the index ablation procedure for up to 30 months. The study showed an improvement in mental and physical quality of life for patients in both treatment groups at six months, which was maintained throughout the follow-up period.

All-Cause Hospitalizations:

- In the Cryoballoon group, there were 210 all-cause hospitalizations in 122 patients (32.6 percent) compared to 267 all-cause hospitalizations in 156 patients (41.5 percent) treated with RF ablation ($p=0.01$).

Direct Current Cardioversion:

- The rate of direct current cardioversion (DCCV) after the index procedure was higher for patients treated by the RF catheter (6.4 percent) as compared to patients treated by the Cryoballoon (3.2 percent) ($p=0.04$).

About Atrial Fibrillation

Atrial fibrillation is the most common and one of the most undertreated heart rhythm disorders. It is estimated that half of all diagnosed atrial fibrillation patients fail drug therapy¹ and if left untreated, patients have up to a five times higher risk of stroke and an increased chance of developing heart failure.² Paroxysmal atrial fibrillation occurs when irregular heartbeats in the upper chambers start and stop suddenly on their own, usually for minutes or days at a time.

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¹ Wyse, et al. *Circulation*. 1996; 93:1262-1277.

² Fuster, et al. *Journal of the American College of Cardiology*. 2006; 48:854-906.