FIRE AND ICE

AF Ablation Clinical Trial

Establishing a New Gold Standard in AF Ablation

Arctic Front Advance™ Cryoballoon
Improving outcomes that matter to Patients, Clinicians, and the Healthcare System
The FIRE AND ICE Trial (NCT01490814) is the largest multicenter, controlled, prospective, 1:1 randomized, non-inferiority, parallel-group, open, and blinded endpoints assessment study to date comparing the efficacy and safety of pulmonary vein isolation using Arctic Front™ catheters versus THERMOCOOL® point-by-point radiofrequency catheters with CARTO® 3D mapping system in patients with paroxysmal atrial fibrillation.

**Study Population**
- 762 patients randomized 1:1 at 16 sites in 8 countries
- Key inclusion criteria:
  - Symptomatic paroxysmal atrial fibrillation (PAF) with ≥ 2 episodes and ≥ 1 episode documented within the last 12 months
  - Documented treatment failure of ≥ 1 antiarrhythmic drug (class I or III AAD)
- Key exclusion criteria:
  - Previous LA ablation or surgery PCI, MI within 3 months of enrollment
  - Stroke/TIA within 6 months of enrollment
  - LVEF < 35%
  - LA diameter > 55 mm

**Efficacy Endpoints**
- Time to first documented recurrence of atrial fibrillation (AF) > 30 sec/atrial tachycardia (AT)/atrial flutter (AFL) or prescription of AAD or repeat ablation, whichever comes first (a blanking period of 3 months was maintained after the index procedure)

**Safety Endpoints**
- Primary safety outcome parameter: a composite of all-cause death, all-cause stroke/transient ischemic attack (TIA) and serious treatment related adverse events

**Secondary Analyses**
- Procedure and fluoroscopy time*
- Sites reported time to first and number of all-cause hospitalization, including: Cardiovascular-related hospitalizations† (including AF hospitalizations†), repeat ablations,* and direct current cardioversions (DCCV)
  - Hospitalizations defined as a prolonged stay of ≥ 2 nights post index ablation or in-patient stay not concurrent with index procedure of ≥ 1 calendar day
- Quality of life* was assessed every 6 months using the SF-12 and EQ-5D-3L

*Protocol defined secondary outcome
† Not predefined but included in analyses

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**TRIAL DESIGN**

**Weekly and Symptomatic Tele-ECG Monitoring**
- In-Office Visit with 24h Holter
- Telephone Follow-up
- Quality of Life Questionnaire

Follow-up continues for patients through a maximum of 33 months.
PRIMARY EFFICACY ENDPOINT ACHIEVED

NON-INFERIORITY STUDY DESIGN WITH THE CRYOBALLOON MEETING THE PRIMARY ENDPOINTS

Rigorous composite efficacy endpoint measured time to first documented:
- Recurrent atrial arrhythmia (AF > 30s/AT/AFL)
- AAD prescription
- Repeat ablation

Freedom From Primary Failure Event

Homogeneity test across all groups: $p = 0.25$

Number at Risk

<table>
<thead>
<tr>
<th></th>
<th>Number at Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arctic Front Advance</td>
<td>279 251 183 151 128 99 76 45 35 19 4</td>
</tr>
<tr>
<td>THERMOCOOL®/THERMOCOOL SF®</td>
<td>284 260 187 151 121 104 84 54 42 23 10</td>
</tr>
<tr>
<td>THERMOCOOL SMARTTOUCH®</td>
<td>93 90 55 40 28 15 9 4 2 1 0</td>
</tr>
<tr>
<td>Arctic Front</td>
<td>90 83 58 42 36 32 30 24 21 15 8</td>
</tr>
</tbody>
</table>

One-year Kaplan-Meier estimates: Arctic Front Advance 69%
THERMOCOOL SMARTTOUCH 60%
**SHORTER, MORE CONSISTENT* PROCEDURE TIMES WITH CRYOBALLOON**

<table>
<thead>
<tr>
<th>TIME MEASUREMENT (minutes)</th>
<th>RFC (n = 376)</th>
<th>CRYOBALLOON (n = 374)</th>
<th>P-VALUE**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procedure Time***</td>
<td>140.9 ± 54.9</td>
<td>124.4 ± 39.0</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>LA Dwell Time***</td>
<td>108.6 ± 44.9</td>
<td>92.3 ± 31.4</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Fluoroscopy Time</td>
<td>16.6 ± 17.8</td>
<td>21.7 ± 13.9</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

*Standard deviations were smaller in the cryoballoon group for all three procedure time measures, indicating more consistent times with less variation from the mean.

**t-test

***Protocol required 30 min. waiting period after last application to assess PV isolation.

**LOW OVERALL INCIDENCE OF SERIOUS TREATMENT-RELATED ADVERSE EVENTS**

Most Frequently Observed Treatment-related SAEs

<table>
<thead>
<tr>
<th>SAE</th>
<th>RFC (n = 376)</th>
<th>Cryoballoon (n = 374)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Groin Site Complication*</td>
<td>4.3%</td>
<td>1.9%</td>
</tr>
<tr>
<td>Atrial Flutter/ Atrial Tachycardia†</td>
<td>2.7%</td>
<td>0.8%</td>
</tr>
<tr>
<td>PNI Unresolved at Discharge**</td>
<td>0%</td>
<td>2.7%</td>
</tr>
<tr>
<td>Cardiac Tamponade/ Pericardial Effusion</td>
<td>1.3%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Stroke/TIA</td>
<td>0.5%</td>
<td>0.5%</td>
</tr>
</tbody>
</table>

Primary Safety Endpoint Achieved:

- RFC group 51
- Cryoballoon group 40 (HR = 0.78; 95% CI = 0.52–1.18; p = 0.24)

One-year Kaplan-Meier event rate estimates 10.2% Cryoballoon and 12.8% RFC

*Includes vascular pseudoaneurysm, AV fistula, device-related infection, hematoma, puncture site hemorrhage, groin pain

†Adjudicated as serious (e.g., hospitalization) and causally related to the therapeutic intervention (e.g., ablation-induced or drug-induced)

**0.5% PNI ongoing after 3 months
Significantly Fewer All-cause Hospitalizations and Cardiovascular (CV) Hospitalizations with Cryoballoon Compared to Radiofrequency

**Freedom From All-cause Hospitalizations**

- **Cryoballoon**: 210 in 122 patients (122/374; 32.6%)
- **RFC**: 267 in 156 patients (156/376; 41.5%)

- **Log-Rank p-value**: 0.01

**Freedom From Cardiovascular Hospitalizations**

- **Cryoballoon**: 139 in 89 patients (89/374; 23.8%)
- **RFC**: 203 in 135 patients (135/376; 35.9%)

- **Log-Rank p-value**: < 0.01
Freedom from Cardiovascular Hospitalization Subgroup Analysis of Patient Baseline

In a subgroup analysis, patients treated with Cryoballoon were less likely to have a cardiovascular-related hospitalization independent of baseline DC cardioversion history.

Trend favors Cryoballoon across all subgroups

Statistically significant differences in CHA₂DS₂-VASc score and prior DC cardioversion

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Level</th>
<th>N of Patients</th>
<th>HR (2-Sided 95% CI)</th>
<th>P-Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>≤ 65</td>
<td>520</td>
<td>Favors Cryoballoon</td>
<td>0.15</td>
</tr>
<tr>
<td></td>
<td>&gt; 65</td>
<td>230</td>
<td>Favors RFC</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>Female</td>
<td>293</td>
<td>0.43</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>457</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHA₂DS₂-VASc Score:</td>
<td>0-1</td>
<td>342</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2-5</td>
<td>408</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HATCH Score:</td>
<td>0</td>
<td>232</td>
<td>0.18</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1-3</td>
<td>518</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First PAF Diagnosis:</td>
<td>&lt; 2.69 years</td>
<td>374</td>
<td>0.69</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥ 2.69 years</td>
<td>374</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LA Diameter:</td>
<td>≤ 41 mm</td>
<td>287</td>
<td>0.22</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt; 41 mm</td>
<td>297</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AAD at Discharge:</td>
<td>No AAD use</td>
<td>371</td>
<td>0.93</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AAD use</td>
<td>379</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior (History of) DCCV:</td>
<td>Yes</td>
<td>174</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>576</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All Patients</td>
<td></td>
<td>750</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*P-Value from interaction term in Cox regression model
CI = confidence interval; HR = hazard ratio; PAF = paroxysmal atrial fibrillation

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>N of Patients</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cryoballoon: No Prior DCCV</td>
<td>71/288 (24.7%)</td>
<td>P &lt; 0.01</td>
</tr>
<tr>
<td>RFC: No Prior DCCV</td>
<td>92/288 (31.9%)</td>
<td></td>
</tr>
<tr>
<td>Cryoballoon: Prior DCCV</td>
<td>18/86 (20.9%)</td>
<td>P = 0.05</td>
</tr>
<tr>
<td>RFC: Prior DCCV</td>
<td>43/88 (48.9%)</td>
<td></td>
</tr>
</tbody>
</table>

Number at Risk

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Number at Risk</th>
<th>Days Since Index Ablation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cryoballoon: No Prior DCCV</td>
<td>288</td>
<td>000 200 400 600 800 1000</td>
</tr>
<tr>
<td>Cryoballoon: Prior DCCV</td>
<td>86</td>
<td>000 200 400 600 800 1000</td>
</tr>
<tr>
<td>RFC: No Prior DCCV</td>
<td>288</td>
<td>000 200 400 600 800 1000</td>
</tr>
<tr>
<td>RFC: Prior DCCV</td>
<td>88</td>
<td>000 200 400 600 800 1000</td>
</tr>
</tbody>
</table>
Significantly Fewer Repeat Ablations with Cryoballoon Compared to Radiofrequency

**Freedom From Repeat Ablation**

- **CRYOBALLOON**: 49 in 44 patients (44/374; 11.8%)
- **RFC**: 70 in 66 patients (66/376; 17.6%)

**Log-Rank p-value = 0.03**

- **CRYOBALLOON**
- **RFC**

**Significantly Fewer DC Cardioversions with Cryoballoon Compared to Radiofrequency**

**Freedom From DC Cardioversion Post Index Ablation**

- **CRYOBALLOON**: 13 in 12 patients (12/374; 3.2%)
- **RFC**: 28 in 24 patients (24/376; 6.4%)

**Log-Rank p-value = 0.04**

Number at Risk

- **CRYOBALLOON**: 374, 343, 301, 221, 149, 84, 20
- **RFC**: 376, 341, 302, 213, 135, 72, 22

**Number at Risk**

- **CRYOBALLOON**: 374, 321, 247, 170, 100, 24
- **RFC**: 376, 320, 235, 162, 96, 30

33% Fewer Repeat Ablations

50% Fewer DC Cardioversions
Establishing a New Gold Standard in AF Ablation

For more info visit: FIREANDICEtrial.com

References

Brief Statement
Arctic Front™ and Arctic Front Advance™ Cardiac CryoAblation Catheter Systems

Indications: The Arctic Front and Arctic Front Advance Cardiac CryoAblation Catheter Systems are indicated for the treatment of drug refractory recurrent symptomatic paroxysmal atrial fibrillation.

Contraindications: Use of either Arctic Front or Arctic Front Advance cryoballoon catheters is contraindicated:
1. In the ventricle because of the danger of catheter entrapment in the chordae tendineae.
2. In patients with one or more pulmonary vein stents.
3. In patients with cryoglobulinemia.
4. In patients with active systemic infections.
5. In conditions where the manipulation of the catheter within the heart would be unsafe (e.g., intracardiac mural thrombus).

Warnings/Precautions: Do not re-sterilize this device for purpose of reuse. Use only the 12 Fr FlexCath™ Steerable Sheath family with the Arctic Front Advance cryoballoon because using another sheath may damage the catheter or balloon segment. Do not inflate the balloon inside the sheath. Always verify with fluoroscopy or by using the proximal shaft visual marker that the balloon is fully outside the sheath before inflation to avoid catheter damage. Do not position the cryoballoon catheter within the tubular portion of the pulmonary vein to minimize phrenic nerve injury and pulmonary vein stenosis. Do not connect the cryoballoon to a radiofrequency (RF) generator or use it to deliver RF energy because this may cause catheter malfunction or patient harm.

The catheter contains pressurized refrigerant during operation; release of this gas into the circulatory system due to equipment failure or misuse could result in gas embolism, which can occlude vessels and lead to tissue infarction with serious consequences. Always advance and withdraw components slowly to minimize the risk of air embolism.

Do not pull on the catheter, sheath, umbilical cables or console while the catheter is frozen to the tissue; this may lead to tissue injury.

Do not advance the balloon beyond the guide wire to reduce the risk of tissue damage.

Do not pass the catheter through a prosthetic heart valve (mechanical or tissue) to avoid damage to the valve, valvular insufficiency or premature failure of the prosthetic valve.

Always inflate the balloon in the atrium then position it at the pulmonary vein ostium to avoid vascular injury.

Do not ablate in the tubular portion of the pulmonary vein. Use continuous phrenic nerve pacing throughout each cryoablation application in the right pulmonary veins. To avoid nerve injury, place a hand on the abdomen in the location of the diaphragm to assess for changes in the strength of the diaphragmatic contraction or loss of capture. In case of no phrenic nerve capture, frequently monitor diaphragmatic movement using fluoroscopy. Stop ablation immediately if phrenic nerve impairment is observed.

The Arctic Front and Arctic Front Advance cryoballoons were not studied for safety of changes in anticoagulation therapy in patients with paroxysmal atrial fibrillation. This equipment should be used only by or under the supervision of physicians trained in left atrial cryoablation procedures. Cryoablation procedures should be performed only in a fully equipped facility.

Potential Complications: Potential complications/ adverse events from cardiac catheterization and ablation include, but are not limited to the following: Anemia; Anxiety; Atrial flutter; Back pain; Bleeding from puncture sites; Blurred vision; Bradycardia; Bronchitis; Bruising; Cardiac tamponade; Cardiopulmonary arrest; Cerebral vascular accident; Chest discomfort/pain/pressure; Cold feeling; Cough; Death; Diarrhea; Dizziness; Esophageal damage (including esophageal fistula); Fatigue; Fever/Headache; Hemoptysis; Hypotension/ Hypertension; Light headedness; Myocardial infarction; Nausea/vomiting; Nerve injury; Pericardial effusion; Pulmonary vein stenosis; Shivering; Shortness of breath; Sore throat; Tachycardia; Transient ischemic attack; Urinary infection; Vasovagal reaction; Visual changes.

Refer to the device technical manual for detailed information regarding the procedure, indications, contraindications, warnings, precautions, and potential complications/adverse events. For further information, please call Medtronic at 1-800-328-2518 and/or consult the Medtronic website at www.medtronic.com.

Caution: Federal Law (USA) restricts this device to sale by or on the order of a physician.