Advances in the Treatment of Atrial Fibrillation

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Treatment Goals in Atrial Fibrillation

AF Diagnosis

Manage AF

- Ablation
- Pacing
- Drugs for Rhythm & Rate Control

Manage AF Related Stroke Risk

- Warfarin (Coumadin®)
- New Drugs: Dabigatran, Apixaban, Rivaroxaban, Edoxaban
- Intervention: Ligation, Clips, LAA Closure Devices
Topics

1. Atrial Fibrillation (AF) Overview
2. Stroke Risk Reduction
   – Drugs
   – Left Atrial Appendage Occlusion
3. Cryoablation for the Treatment of Paroxysmal Atrial Fibrillation for control of symptoms
Atrial Fibrillation (AF) & Stroke Risk Reduction
Pharmacologic Treatment for Stroke Risk Reduction
Atrial Fibrillation & Stroke Risk

AF is the most common cardiac arrhythmia

AF increases risk of stroke

Blood clots form in the left atrial appendage

Many patients are unprotected

> 33M people with AF Worldwide¹

5x greater risk of stroke with AF²

>90% of stroke-causing clots that come from the left atrium in non-valvular AF are formed in the LAA³

~45% of patients eligible for warfarin are untreated (tolerance/adherence)⁴

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• Assess stroke risk with CHA$_2$DS$_2$-VASc score
  – Score 1: Annual stroke risk 1%, oral anticoagulants or aspirin may be considered
  – Score ≥2: Annual stroke risk 2%-15%, oral anticoagulants are recommended

• Higher CHADS$_2$ score predicts worse outcomes (stroke, major bleeding & vascular mortality)$^1$

• Balance benefit vs. bleeding risk
Warfarin is an effective means of stroke reduction in patients with AF but can present challenges:

- Many patients spend a significant amount of time outside of the therapeutic range.

- Warfarin tops the list for emergency hospitalizations for adverse drug events in older Americans\(^2\)

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Stroke Treatment Option: warfarin (Coumadin®)

- INR control is difficult with warfarin treatment & impacts stroke & bleeding risk
- Only ~½ of patients on warfarin are at goal anticoagulation intensity

Patients outside the therapeutic range are at an increased risk of ischemic and hemorrhagic stroke

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1 Glazer NL, Arch Intern Med (2007)
2 Shen AY, J Am Coll Cardiol (2007)
3 Go AS, JAMA (2003)
Warfarin Use by CHADS$_2$ Score

- Medicare claims data, 2006-2007$^1$
  - Warfarin use less than 60% in high-risk patients

Stroke Treatment Option: Novel Oral Anticoagulants (NOACs)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Study Drug Discontinuation Rate</th>
<th>Major Bleeding (rate/year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivaroxaban¹</td>
<td>24%</td>
<td>3.6%</td>
</tr>
<tr>
<td>Apixaban²</td>
<td>25%</td>
<td>2.1%</td>
</tr>
<tr>
<td>Dabigatran³ (150 mg)</td>
<td>21%</td>
<td>3.3%</td>
</tr>
<tr>
<td>Edoxaban⁴ (60 mg / 30 mg)</td>
<td>33 % / 34%</td>
<td>2.8% / 1.6%</td>
</tr>
<tr>
<td>Warfarin¹-⁴</td>
<td>17 – 28%</td>
<td>3.1 – 3.6%</td>
</tr>
</tbody>
</table>

There is an unmet need of stroke risk reduction for patients with AF who are seeking an alternative to long-term OACs

This chart is not based on a head-to-head trial and is not intended to suggest head-to-head comparisons of the separate trials or the therapies under study.

Non-Pharmacologic Treatment for Stroke Risk Reduction
Stroke Treatment Option: LAA Ligation

- Surgical approaches to thromboembolic prophylaxis have been explored since the 1940s
- LAA closure or obliteration has most often been considered as an adjunct to other cardiac procedures such as mitral valvotomy or cardiac bypass surgery
- Studies on patients undergoing LAA closure have shown a trend toward reduction in embolic events

- A review of the literature on LAA closure prior to 2010 found closure rates of 10%-73%¹

A need exists for a less invasive approach that can consistently close the LAA

² Kanderian et al. JACC 2008, 52:924–9
**LAA Closure (LAAC) Devices**

<table>
<thead>
<tr>
<th>PLAATO</th>
<th>WATCHMAN™ Device</th>
<th>ACP</th>
</tr>
</thead>
<tbody>
<tr>
<td>• First LAAC device (2001)</td>
<td>• Only LAAC device with 2 Randomized Controlled Trials</td>
<td>• US Trial halted in 2013</td>
</tr>
<tr>
<td>• Device no longer available</td>
<td>• FDA approved with specific indication to reduce the risk of thromboembolism ClinicalTrials.gov identifiers: NCT00129545 (PROTECT AF) NCT01182441 (PREVAIL)</td>
<td>• AMPLATZER™ Cardiac Plug Clinical Trial</td>
</tr>
</tbody>
</table>

**LAA Clip**

**EXCLUDE** Trial (completed)

- AtriClip Device was FDA approved in 2010 for LAA closure
  - No specific indication for Stroke Reduction

ClinicalTrials.gov identifier: NCT00779857

**Surgical Ligation**

“Safety and Efficacy of Left Atrial Appendage Occlusion Devices”

Observational Study (retrospective)

- To compare LARIAT® vs. WATCHMAN™
- LARIAT currently does not have a specific indication for LAA Closure or Stroke Reduction

ClinicalTrials.gov identifier: NCT01695564
Left Atrial Appendage Closure (LAAC) Description

- Device alternative to oral anticoagulation therapy in patients with non-valvular AF
- Designed to reduce the risk of thromboembolism by closing off the left atrial appendage (LAA), which is believed to be the source of a majority of stroke-causing blood clots in people with non-valvular AF
- Over time, patients may be able to stop taking oral anticoagulants

WATCHMAN™ Left Atrial Appendage Closure (LAAC) Device Overview

**Nitinol Frame**
- Radially expands to maintain position in LAA
- Available sizes:
  - 21, 24, 27, 30, 33 mm (diameter)
- 10 Active fixation anchors around device perimeter engage LAA tissue for stability and retention
- Features an intra-LAA design to avoid contact with Left Atrial wall

**160 Micron Membrane**
- Polyethylene terephthalate (PET) cap
- Designed to block emboli from exiting the LAA

*Designed specifically for the left atrial appendage*
WATCHMAN™ Left Atrial Appendage Closure (LAAC) Device Procedure

• One-time implant that does not need to be replaced
• Performed in a cardiac cath lab/EP suite, does not need hybrid OR
• Performed by a Heart Team
  • EP/IC or EP&IC, TEE, General Anesthesia, Surgical Back-up, WATCHMAN Clinical Specialist
• Transfemoral Access: Catheter advanced to the LAA via the femoral vein (Does not require open heart surgery)
• General anesthesia (typical)
• 1 hour procedure (typical)
• 1-2 day hospital stay (typical)
**Indications for Use**

The WATCHMAN Device is indicated to reduce the risk of thromboembolism from the left atrial appendage in patients with non-valvular atrial fibrillation who:

- Are at increased risk for stroke and systemic embolism based on CHADS\(_2\) or CHA\(_2\)DS\(_2\)-VASc scores and are recommended for anticoagulation therapy;
- Are deemed by their physicians to be suitable for warfarin; and
- Have an appropriate rationale to seek a non-pharmacologic alternative to warfarin, taking into account the safety and effectiveness of the device compared to warfarin.

The WATCHMAN Access System is intended to provide vascular and transseptal access for all WATCHMAN Left Atrial Appendage Closure Devices with Delivery Systems.

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*Please refer to product DFU for more specific details on patient selection.*
WATCHMAN™ Device Patient Selection

Specific factors may include one or more of the following:
• history of major bleeding while taking anticoagulation therapy
• patient’s prior experience with OAC (if applicable):
  – inability to maintain stable INR
  – inability to comply with regular INR monitoring and unavailability of an approved alternative OAC
• medical condition, occupation, or lifestyle placing patient at high risk of major bleeding secondary to trauma
• presence of indication(s) for long-term warfarin use, other than non-valvular atrial fibrillation (e.g. mechanical heart valve, hypercoagulable states, recurrent deep venous thrombosis)

Specific factors that need to be considered for the WATCHMAN Device and implantation procedure include:
• overall medical status, including conditions which might preclude the safety of a percutaneous, transcatheter procedure
• suitability for percutaneous, trans-septal procedures, including considerations of:
  – cardiac anatomy relating to LAA size and shape
  – vascular access anatomy
  – ability to tolerate general or local anesthesia
  – ability to undergo required imaging
  – ability to comply with recommended post-WATCHMAN Device implant pharmacologic regimen
    • warfarin plus aspirin for at least 45 days post-device implantation
    • clopidogrel and aspirin through 6 months post-procedure
    • aspirin indefinitely

* Please refer to product DFU for more specific details on patient selection
WATCHMAN™ Device Clinical Studies & Results
Favorable Procedural Safety Profile: 7-Day Safety Events

- PROTECT AF
  - 1st Half: 9.9%
  - 2nd Half: 4.8%

- CAP
  - n=566: 4.1%

- PREVAIL
  - n=269: 4.1%

- CAP2
  - n=579: 3.8%

All Device and/or procedure-related serious adverse events within 7 Days

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~50% New Operators in PREVAIL
Implant success defined as deployment and release of the device into the left atrial appendage

PROTECT AF
Implant success 91%

CAP
Implant success 94%

PREVAIL
Implant success 95%

p = 0.04

Warfarin Cessation

<table>
<thead>
<tr>
<th>Study</th>
<th>45-day</th>
<th>12-month</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROTECT AF</td>
<td>87%</td>
<td>&gt;93%</td>
</tr>
<tr>
<td>CAP</td>
<td>96%</td>
<td>&gt;96%</td>
</tr>
<tr>
<td>PREVAIL</td>
<td>92%</td>
<td>&gt;99%</td>
</tr>
</tbody>
</table>

PREVAIL Implant Success
No difference between new and experienced operators

Experienced Operators
• n=26
• 96%

New Operators
• n=24
• 93%  p = 0.28

Most Studied LAAC Device. Only One with Long-Term Clinical Data

<table>
<thead>
<tr>
<th></th>
<th>PROTECT AF</th>
<th>CAP Registry</th>
<th>PREVAIL</th>
<th>CAP2 Registry</th>
<th>Totals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrolled</td>
<td>800</td>
<td>566</td>
<td>461</td>
<td>579</td>
<td>2406</td>
</tr>
<tr>
<td>Randomized</td>
<td>707</td>
<td>---</td>
<td>407</td>
<td>---</td>
<td>1114</td>
</tr>
<tr>
<td>WATCHMAN: warfarin (2:1)</td>
<td>463 : 244</td>
<td>566</td>
<td>269 :138</td>
<td>579</td>
<td>1877:382</td>
</tr>
<tr>
<td>Mean Follow-up (years)</td>
<td>4.0</td>
<td>3.7</td>
<td>2.2</td>
<td>0.58</td>
<td>N/A</td>
</tr>
<tr>
<td>Patient-years</td>
<td>2717</td>
<td>2022</td>
<td>860</td>
<td>332</td>
<td>5931</td>
</tr>
</tbody>
</table>

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## Patient Risk Factors Across Trials

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>PROTECT AF N=707</th>
<th>CAP N=566</th>
<th>PREVAIL N=407</th>
<th>CAP2 N=579</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHADS₂ Score</td>
<td>2.2 ± 1.2</td>
<td>2.4 ± 1.2</td>
<td>2.6 ± 1.0</td>
<td>2.7 ± 1.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CHADS₂ Risk Factors (%) of Patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHF</td>
<td>26.9</td>
<td>23.3</td>
<td>19.1</td>
<td>27.1</td>
<td>0.004</td>
</tr>
<tr>
<td>Hypertension</td>
<td>89.8</td>
<td>91.4</td>
<td>88.8</td>
<td>92.5</td>
<td>0.15</td>
</tr>
<tr>
<td>Age ≥ 75</td>
<td>43.1</td>
<td>53.6</td>
<td>51.8</td>
<td>59.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>26.2</td>
<td>32.4</td>
<td>24.9</td>
<td>33.7</td>
<td>0.001</td>
</tr>
<tr>
<td>Stroke/TIA</td>
<td>18.5</td>
<td>27.8</td>
<td>30.4</td>
<td>29.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CHA₂DS₂-VASc</td>
<td>3.5 ± 1.6</td>
<td>3.9 ± 1.5</td>
<td>4.0 ± 1.2</td>
<td>4.5 ± 1.3</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Majority of Patients at High Stroke Risk, All Eligible for Anti-coagulation

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Majority of Patients in the Trial were at Moderate to High Bleeding Risk

1. Estimated HAS BLED score. Labile INR and liver function were not collected and given a score of zero
Source: Holmes DR, et al. Holmes, DR et al. JACC 2015;
WATCHMAN™ Met Criteria for both Noninferiority and Superiority for the Primary Composite Endpoint Compared to Warfarin

### Table 2. Intention-to-Treat Primary Efficacy and Safety Outcomes According to Treatment Group by Bayesian Model

<table>
<thead>
<tr>
<th>Event</th>
<th>Device Group (n = 463)</th>
<th>Warfarin Group (n = 244)</th>
<th>Device/Warfarin Rate Ratio (95% Credible Interval)</th>
<th>Posterior Probabilities, %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Events/Patient-Years</strong></td>
<td>Events/Patient-Years</td>
<td>Observed Rate(^a)</td>
<td>Events/Patient-Years</td>
<td>Observed Rate(^a)</td>
</tr>
<tr>
<td><strong>Primary efficacy endpoint</strong></td>
<td>39/1720.2</td>
<td>2.3 (1.7-3.2)</td>
<td>34/900.8</td>
<td>3.8 (2.5-4.9)</td>
</tr>
<tr>
<td><strong>Stroke</strong></td>
<td>26/1720.7</td>
<td>1.5 (1.0-2.2)</td>
<td>20/900.9</td>
<td>2.2 (1.3-3.1)</td>
</tr>
<tr>
<td><strong>Ischemic</strong></td>
<td>24/1720.8</td>
<td>1.4 (0.9-2.1)</td>
<td>10/904.2</td>
<td>1.1 (0.5-1.7)</td>
</tr>
<tr>
<td><strong>Hemorrhagic</strong></td>
<td>3/1774.2</td>
<td>0.2 (0.0-0.4)</td>
<td>10/916.2</td>
<td>1.1 (0.5-1.8)</td>
</tr>
<tr>
<td><strong>Disabling</strong>(^c)</td>
<td>8/1771.3</td>
<td>0.5 (0.2-0.8)</td>
<td>11/912.7</td>
<td>1.2 (0.6-1.9)</td>
</tr>
<tr>
<td><strong>Nondisabling</strong>(^c)</td>
<td>18/1723.7</td>
<td>1.0 (0.7-1.7)</td>
<td>9/907.7</td>
<td>1.0 (0.4-1.7)</td>
</tr>
<tr>
<td><strong>Systemic embolization</strong></td>
<td>3/1773.6</td>
<td>0.2 (0.0-0.4)</td>
<td>0/919.5</td>
<td>0</td>
</tr>
<tr>
<td><strong>Cardiovascular or unexplained death</strong></td>
<td>17/1774.3</td>
<td>1.0 (0.6-1.5)</td>
<td>22/919.4</td>
<td>2.4 (1.4-3.4)</td>
</tr>
<tr>
<td><strong>Primary safety endpoint</strong></td>
<td>60/1666.2</td>
<td>3.6 (2.8-4.6)</td>
<td>27/878.2</td>
<td>3.1 (2.0-4.3)</td>
</tr>
</tbody>
</table>

**Abbreviation:** NA, not applicable.

\(^a\) Events per 100 patient-years (95% credible interval).

\(^b\) Primary efficacy defined as composite of stroke, systemic embolization, or cardiovascular/unexplained death.

\(^c\) Disabling or fatal strokes were those with a Modified Rankin Score of 3-6 after the stroke. Nondisabling strokes were those with Modified Rankin Scores of 0-2 after the stroke.

\(^d\) Safety defined as procedure-related events (pericardial effusion requiring intervention or prolonged hospitalization, procedure-related stroke, or device embolization) and major bleeding (intracranial or bleeding requiring transfusion).
**Watchman™ Protect AF Study Overview**

**Long-Term, Final 5-Year Results**

<table>
<thead>
<tr>
<th>Study Design &amp; Objective</th>
<th>Prospective, randomized (2:1), non-inferiority trial of LAA closure vs. warfarin in non-valvular AF patients for prevention of stroke</th>
</tr>
</thead>
</table>
| Primary Endpoint         | **Efficacy:** Composite end point of stroke, cardiovascular death or systemic embolization  
**Safety:** Major bleeding, device embolization or pericardial effusion |
| Statistical Plan         | All analyses by intention-to-treat  
Bayesian (stratified for CHADS₂ score) : Primary Efficacy and Safety endpoints  
Cox Proportional: All Secondary Analyses |
| Patient Population       | n = 707  
Mean CHADS₂ = 2.2, CHA₂DS₂-VASc = 3.5 |
| Key Inclusion Criteria   | Paroxysmal / Persistent / Permanent AF  
CHADS ≥ 1 (93% had a CHA₂DS₂-VASc Score ≥2)  
Eligible for long-term warfarin therapy |
| Mean Follow-Up           | 2,717 patient-years, 48 months |
| Number of Sites          | 59 in the United States and Europe  
Enrollment Feb 2005 – June 2008 |
### PROTECT AF: Final, 5-Year Primary Efficacy Events Consistent with 4-Year Results

<table>
<thead>
<tr>
<th>Event Rate</th>
<th>Rate Ratio (95% Crl)</th>
<th>Posterior Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>WATCHMAN</td>
<td>Warfarin</td>
</tr>
<tr>
<td>Primary efficacy</td>
<td>2.2</td>
<td>3.7</td>
</tr>
<tr>
<td>Stroke (all)</td>
<td>1.5</td>
<td>2.2</td>
</tr>
<tr>
<td>Systemic embolism</td>
<td>0.2</td>
<td>0.0</td>
</tr>
<tr>
<td>Death (CV/unexplained)</td>
<td>1.0</td>
<td>2.3</td>
</tr>
</tbody>
</table>

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Meta-Analysis Shows Comparable Primary Efficacy Results to Warfarin

<table>
<thead>
<tr>
<th>Event</th>
<th>Hazard Ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All stroke or SE</td>
<td>1.02 (0.94-1.09)</td>
<td>0.94</td>
</tr>
<tr>
<td>Ischemic stroke or SE</td>
<td>1.95 (1.80-2.12)</td>
<td>0.05</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>0.22 (0.07-0.69)</td>
<td>0.004</td>
</tr>
<tr>
<td>Ischemic stroke or SE &gt;7 days</td>
<td>1.56 (1.38-1.76)</td>
<td>0.21</td>
</tr>
<tr>
<td>CV/unexplained death</td>
<td>0.48 (0.38-0.61)</td>
<td>0.006</td>
</tr>
<tr>
<td><strong>All-cause death</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major bleed, all</td>
<td>1.00 (0.84-1.19)</td>
<td>0.98</td>
</tr>
<tr>
<td>Major bleeding, non procedure-related</td>
<td>0.51 (0.37-0.72)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Source: Holmes DR, et al. Holmes, DR et al. JACC 2015; In Press. Combined data set of all PROTECT AF and PREVAIL WATCHMAN patients versus chronic warfarin patients SH-230506-AD June15
WATCHMAN™ Device Reduced Ischemic Stroke Over No Therapy

**Imputation based on published rate with adjustment for CHA$_2$DS$_2$-VASc score (3.0); Olesen JB. Thromb Haemost (2011)**

*SH-230506-AD June15*
Implant – 45 day
Warfarin: dosage to achieve INR 2.0-3.0
Aspirin: 81 mg while on warfarin
Clopidogrel: No

LAA Seal per 45 Day TEE

45 day – 6 Months
Warfarin: No
Aspirin: 325 mg*
Clopidogrel: Yes

45 day – 6 Months*
Warfarin: Yes
Aspirin: 81 mg while on warfarin
Clopidogrel: No

6 Months – 5 Years
Warfarin: No
Aspirin: 325 mg*
Clopidogrel: No

6 Months – 5 Years
Warfarin: Discontinued when seal is adequate
Aspirin:
On warfarin - 81 mg
Off warfarin - 325 mg* indefinitely
Clopidogrel: No

*Cessation of warfarin is at physician discretion provided that any peri-device flow demonstrated by TEE is ≤ 5mm. Before 6 months, when seal is adequate, patients can cease warfarin and should begin clopidogrel 75 mg daily and increase aspirin dosage to 300-325 mg daily. This regimen should continue until a total of 6 months have elapsed after implantation.
PROTECT AF/PREVAIL Pooled Analysis: Less Bleeding with WATCHMAN™ Device 6 Months Post-Implant

**Definition of bleeding:** Serious bleeding event that required intervention or hospitalization according to adjudication committee

Price, MJ. Avoidance of Major Bleeding with WATCHMAN Left Atrial Appendage Closure Compared with Long-Term Oral Anticoagulation: Pooled Analysis of the PROTECT-AF and PREVAIL RCTs. TCT 2014 (abstract)

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Management of Atrial Fibrillation with Cryoablation
Atrial Fibrillation: Fibrillation of the Muscles of the Atria of the Heart

Normal sinus rhythm

Abnormal electrical pathways

Normal electrical pathways

Sinus (SA) node

Atrioventricular (AV) node

Normal sinus rhythm

Abnormal electrical pathways

Atrial fibrillation
Anatomical Cryoballoon PVI

RF Ablation Catheter

Cryoballoon Ablation Catheter

Ablation Lesion

LEFT ATRIAL ANATOMY

RA

RSPV

RIPV

LIPV

LSPV

CS
Properties of Cryoablation

• Removes heat from the tissue
• Ablates at the point of balloon contact
Lesion histology

**Cryo**
- Minimal Thrombus
- Endocardium Intact
- Fibrosis Complete
- Well Demarcated

**RF**
- Disrupted Endocardium
- Thrombus Present
- Hemorrhage Still Present
- Fibrosis Started

Cryolesion at 1 Week (canine model)
-75°C • 1 x 4 minutes

RF Lesion at 1 Week (canine model)
+70°C • 50 W • 60 seconds
Ablation Safety and Efficacy
STOP AF PAS Results

Arctic Front Advance™ Cryoballoon - Second Generation

- 82.1% freedom from AF at 12 months (n=345)
- Low 2.3% (8/345) repeat ablation rate during the 90 day blanking period
- 5.8% (20/345) adverse event rate
- 3.2% (11/345) PNI unresolved at hospital discharge, 0.9% (3/345) ongoing ≥12 months post ablation

Single Procedure Freedom from AF, AT and AFL

Arctic Front Advance™ Cryoballoon Single Center Published Studies

Arrhythmia monitoring methods and definition of procedure success (Freedom from AF Only or AF/AT/AFL) varied between studies.

FIRE AND ICE Trial
Primary Endpoints
Cryoballoon Met Non-Inferiority Safety Endpoint

Primary Safety Endpoint Results
RFC group 51 vs. 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 a serious (e.g. hospitalization) and casually related to the therapeutic intervention (e.g. ablation-induced or drug-induced)
***0.5% PNI ongoing after 3 months

Thank You