Κρυοθεραπεία.
Σε ποιους ασθενείς;

Χάρης Κοσσυβάκης
Καρδιολογικό Τμήμα
Γ.Ν.Α. «Γ. ΓΕΝΝΗΜΑΤΑΣ»
Background

- Atrial fibrillation (AF) is the most common arrhythmia with prevalence > 33 million\(^1\)

- Catheter ablation is a Class I Level A recommendation for treatment of symptomatic paroxysmal AF (PAF) refractory or intolerant to ≥1 Class I or III antiarrhythmic drug (AAD)\(^5\)

- Pulmonary vein isolation (PVI) is the cornerstone of AF ablation strategy\(^6\)

\(^2\) Medtronic internal estimates taking into account of clinical and economic exclusion
\(^3\) Wyse, et al. Circ. 1996; 93:1262-1277
Pulmonary Vein Isolation is the Cornerstone of Paroxysmal AF Ablation

2012 HRS Consensus Statement

“... point-by-point RF energy and Cryoballoon ablation are the two standard ablation systems used for catheter ablation of AF today ...”
Cryoballoon Has Experienced Rapid Growth in Worldwide Adoption and Clinical Experience
The CB-2G **significantly** improved the efficacy of PVI with high rates of single-shot isolation when compared to the CB-1G.
Single Procedure Freedom from AF, AT and AFL
Arctic Front Advance Cryoballoon Single Center Published Studies

Single Procedure Freedom From AF, most off AAD

PV Lesion Durability with RF and Cryoballoon

STUDIES EVALUATING PV RE-CONDUCTION USING REPEAT ELECTROPHYSIOLOGY AND MAPPING AFTER THE INDEX PROCEDURE

% of Patients without Gaps During Remapping Procedure

- RF
- RF: Contact Sensing
- Arctic Front™ Cryoballoon
- Arctic Front Advance™ Cryoballoon

<table>
<thead>
<tr>
<th>Patients (n)</th>
<th>Follow-up**</th>
<th>GAP-AF</th>
<th>Willems</th>
<th>Jiang</th>
<th>EFFICAS I</th>
<th>EFFICAS II*</th>
<th>Ahmed</th>
<th>SUPIR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>n=117</td>
<td>n=40</td>
<td>n=75</td>
<td>n=75</td>
<td>n=24</td>
<td>n=12</td>
<td>n=21</td>
</tr>
<tr>
<td>3 Months</td>
<td>3 Months</td>
<td>30%</td>
<td>23%</td>
<td>8%</td>
<td>35%</td>
<td>63%</td>
<td>67%</td>
<td>78%</td>
</tr>
</tbody>
</table>

* Calculated rate from manuscript data reporting 9/24 patients with gaps.
**Time between index procedure and re-mapping procedure. All patients were evaluated regardless of clinical symptoms.

1. Late Breaking Clinical Trials session I at the EHRA EUROPACE 2013 meeting in Athens, Greece
Results from a multicentre comparison of cryoballoon vs. radiofrequency ablation for paroxysmal atrial fibrillation: is cryoablation more reproducible?

freedom from AF 68–80%

freedom from AF 46–79%

✓ Lower inter-operator and inter-centre variability with Cryoballoon ablation regarding freedom from AF

Providencia et al, Europace 2015
cryoballoon ablation seems to perform equally well, with a less-pronounced impact of centre or operator experience
shorter learning curve and higher reproducibility of this technique.

In centres which were performing cryoballoon ablation for only a few months before the beginning of the FrenchAF survey, cryoballoon ablation performed better (Centre C) or was non-inferior to RF (Centres A and E), which had been in use for 10 years in those centres.
Cryoballoon ablation

- Symptomatic Paroxysmal AF
  - Drug refractory
  - First line therapy
- Persistent AF
Symptomatic Paroxysmal AF

drug refractory

First line therapy
RFC Ablation ("FIRE") vs Cryoballoon Ablation ("ICE")

Primary Efficacy Endpoint Met

Modified ITT analysis
- Non-inferiority hypothesis met
- HR [95% CI] = 0.96 [0.76-1.22]; p = 0.0004
- Superiority test: p = 0.74
**Primary Safety Endpoint Met**

12.8% RFC vs 10.2% CRYO

**Modified ITT analysis**

HR [95% CI] = 0.78 [0.52-1.18]; p = 0.24

<table>
<thead>
<tr>
<th>Safety Event Type</th>
<th>RFC (n=376)</th>
<th>Cryoballoon (n=374)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause death*</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>All-cause stroke/TIA</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Arrhythmia-related SAE</td>
<td>13</td>
<td>8</td>
</tr>
<tr>
<td>Non-arrhythmia-related SAE</td>
<td>36</td>
<td>28</td>
</tr>
<tr>
<td>Total</td>
<td>51</td>
<td>40</td>
</tr>
</tbody>
</table>

*Unrelated to treatment/device*

## Treatment-Related Serious Adverse Events

<table>
<thead>
<tr>
<th>Event (N, %)</th>
<th>RFC (n=376)</th>
<th>Cryoballoon (n=374)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Groin Site Complication*</td>
<td>16 (4.3%)</td>
<td>7 (1.9%)</td>
</tr>
<tr>
<td>Atrial Flutter/Atrial Tachycardia**</td>
<td>10 (2.7%)</td>
<td>3 (0.8%)</td>
</tr>
<tr>
<td>Phrenic Nerve Injury unresolved at discharge</td>
<td>0 (0%)</td>
<td>10 (2.7%)***</td>
</tr>
<tr>
<td>Unresolved at 3 months</td>
<td>0 (0%)</td>
<td>2 (0.5%)</td>
</tr>
<tr>
<td>Unresolved at &gt; 12 months</td>
<td>0 (0%)</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>Cardiac Tamponade/Pericardial Effusion</td>
<td>5 (1.3%)</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>Stroke/TIA</td>
<td>2 (0.5%)</td>
<td>2 (0.5%)</td>
</tr>
<tr>
<td>Atrial Septal Defect</td>
<td>1 (0.3%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Esophageal Ulcer</td>
<td>0 (0%)</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>Pericarditis</td>
<td>0 (0%)</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>Atrioesophageal Fistula</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Pulmonary Vein Stenosis</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

* Includes vascular pseudoaneurysm, AV fistula, device-related infection, hematoma, puncture site hemorrhage, groin pain
** Serious (e.g., hospitalization) and causally related to the therapeutic intervention (e.g., ablation-induced or drug-induced)
*** 8 resolved by 3 month visit, 1 resolved by 6 months visit, 1 unresolved after 12 month visit

Procedural Characteristics

Shorter, More Consistent* Procedure Times with the 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.

Freedom From Cardiovascular Hospitalization

Modified ITT Analysis

Cryo: 139 events in 89 subjects (89/374; 23.8%)
RFC: 203 events in 135 subjects (135/376; 35.9%)

Kuck KH, et al. The FIRE AND ICE Trial Looking Beyond the Primary Safety and Efficacy Endpoints. Late-breaking Clinical Trial Presentation at Cardiostim 2016 June 8-10; Nice, France. (Abstract)
Freedom From Repeat Ablation

Modified ITT Analysis

Cryo: 49 events in 44 subjects (44/374; 11.8%)

RFC: 70 events in 66 subjects (66/376; 17.6%)

Event Free Survival

Log-Rank p-value = 0.03

Number at Risk

<table>
<thead>
<tr>
<th></th>
<th>CRYOBALLOON</th>
<th>RFC</th>
</tr>
</thead>
<tbody>
<tr>
<td>At Risk</td>
<td>374</td>
<td>376</td>
</tr>
<tr>
<td>Events</td>
<td>343</td>
<td>341</td>
</tr>
<tr>
<td>Subjects</td>
<td>301</td>
<td>302</td>
</tr>
</tbody>
</table>

Days Since Index Ablation

Kuck KH, et al. The FIRE AND ICE Trial Looking Beyond the Primary Safety and Efficacy Endpoints. Late-breaking Clinical Trial Presentation at Cardiostim 2016 June 8-10; Nice, France. (Abstract)
Quality-of-life improved during follow-up in both groups and was maintained throughout 30 months.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>6 Months</th>
<th>∆</th>
<th>P-Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cryoballoon</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mental</td>
<td>47.1±10.3</td>
<td>51.1±8.9</td>
<td>4.0±9.8</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Physical</td>
<td>43.7±9.1</td>
<td>47.0±9.1</td>
<td>3.2±8.2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>RFC</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mental</td>
<td>48.9±9.8</td>
<td>50.8±8.8</td>
<td>1.9±9.9</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Physical</td>
<td>44.5±9.5</td>
<td>47.6±8.6</td>
<td>3.1±8.6</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

* t-test

Kuck KH, et al. The FIRE AND ICE Trial Looking Beyond the Primary Safety and Efficacy Endpoints. Late-breaking Clinical Trial Presentation at Cardiostim 2016 June 8-10; Nice, France. (Abstract)
The CB ablation procedure was shorter and less complex compared with RF.

non-significant trend for a higher rate of freedom from AF/AT in the CB group compared with the RF group
### 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Level</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Catheter ablation of symptomatic paroxysmal AF is recommended to improve AF symptoms in patients who have symptomatic recurrences of AF on antiarrhythmic drug therapy (amiodarone, dronedarone, flecainide, propafenone, sotalol) and who prefer further rhythm control therapy, when performed by an electrophysiologist who has received appropriate training and is performing the procedure in an experienced centre.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Catheter ablation of AF should be considered as first-line therapy to prevent recurrent AF and to improve symptoms in selected patients with symptomatic paroxysmal AF as an alternative to antiarrhythmic drug therapy, considering patient choice, benefit, and risk.</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>Catheter ablation should target isolation of the pulmonary veins using radiofrequency ablation or cryotherapy balloon catheters.</td>
<td>IIa</td>
<td>B</td>
</tr>
</tbody>
</table>
Persistent AF

- advanced structural and electrical remodelling

<table>
<thead>
<tr>
<th>Persistent AF</th>
<th>AF that lasts longer than 7 days, including episodes that are terminated by cardioversion, either with drugs or by direct current cardioversion, after 7 days or more.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long-standing persistent AF</td>
<td>Continuous AF lasting for ≥1 year when it is decided to adopt a rhythm control strategy.</td>
</tr>
</tbody>
</table>
Continuous AF Induces Cardiac Remodeling

*Atrial Fibrillation can initiate irreversible fibrosis at many cardiac sites.*

Pulmonary Vein Isolation is the Cornerstone of Most AF Ablation Procedures

2012 consensus recommendation: “operators should consider more extensive ablation based on linear lesions or complex fractionated electrograms” for ablation of persistent AF.

Emerging evidence challenges the current AF catheter ablation consensus recommendations of persistent AF ablation.

linear lesions

CFAE
Additional CFE or Lines ablation increased procedural time (may increase risk).

![Procedural Characteristics](chart.png)

<table>
<thead>
<tr>
<th></th>
<th>PVI</th>
<th>PVI+CFE</th>
<th>PVI+LINES</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procedure time (min)</td>
<td>166.95 ± 54.83</td>
<td>229.16 ± 83.20</td>
<td>222.56 ± 89.37</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mapping time (min)</td>
<td>13.89 ± 6.64</td>
<td>18.75 ± 14.01</td>
<td>14.38 ± 7.68</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Fluoroscopy time (min)</td>
<td>29.35 ± 16.21</td>
<td>42.11 ± 21.70</td>
<td>40.91 ± 24.97</td>
<td>0.0003</td>
</tr>
</tbody>
</table>

STAR AF II: In Ablation of Persistent AF “Less May be More”

PVI-only ablation is significantly more effective in achieving Freedom from Atrial Fibrillation and Atrial Arrhythmia than PVI + Lines ablation, PVI +CFAEs after a single procedure without AADs.

Arctic front advance can provide safe and effective procedure in patients suffering from persistent AF

Single Procedure Freedom From AF at 12 Months

- Lemes et al. (n=49) 69%
- Ciconte et al. (n=50) 60%
- Koektuerk et al. (n=100) 67%
- Guhl et al. (n=61) 62%
- Straube et al. (n=157) 82%
- Perrotta et al. (n=21) 71%

Cryoballoon Advance is significantly faster than Contact Force RF with equivalent outcomes in Persistent AF!

- 100 consecutive patients with drug-refractory persistent AF (CB-Adv: 50; Contact Force RF: 50).
- CB-Adv: PVI only with AFA 28mm with 240sec cryo applications.
- Contact Force RF:
  - PVI with Thermocool® SmartTouchTM, BSW & Tacticath® Endosense, SJM.
  - Contact Force RF target: 10g (max. 50g) with perpendicular vector to the tissue.
- 1 cardiac tamponade occurred in the Contact Force RF group. Transient PN injury with complete resolution by end of the procedure occurred in 2 patients in the AFA group.

<table>
<thead>
<tr>
<th></th>
<th>CB-Adv (n = 50)</th>
<th>RFCA (n = 50)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procedure duration, minutes</td>
<td>90.5 ± 41.7</td>
<td>140.2 ± 46.9</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Fluoroscopy duration, minutes</td>
<td>14.5 ± 6.6</td>
<td>19.8 ± 6.8</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Predictors of afib recurrences

For each additional month of persistent AF, the risk of arrhythmia recurrence increased by 1.6 times!!!
Two years outcome in patients with persistent atrial fibrillation after pulmonary vein isolation using the second-generation 28-mm cryoballoon

- 50 patients
- Single procedure success rate after 2-year follow-up.
- Clinical success rate of 56% comparable with the results of conventional RF ablation.
- No major complications occurred.
### Extent of Posterior Wall Ablation with Arctic Front and Arctic Front Advance Cryoballoon

#### POST PROCEDURE VOLTAGE MAPS

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>4</td>
<td>43</td>
</tr>
<tr>
<td>Balloon and Application Time</td>
<td>CB1 28 mm, 5 min</td>
<td>CB2 28 mm, 3 min</td>
</tr>
<tr>
<td>Extent of posterior wall ablation</td>
<td>40%</td>
<td>73%</td>
</tr>
<tr>
<td>6 month Freedom from AF</td>
<td>75%</td>
<td>95%</td>
</tr>
</tbody>
</table>

73% of posterior wall ablated with Arctic Front Advance Cryoballoon

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ANATOMY OF THE AUTONOMIC GANGLIA
Persistent AF

Sequence of ablation targets for persistent AF

1\textsuperscript{st} PROCEDURE
pulmonary vein isolation
(target complete isolation)

2\textsuperscript{nd} PROCEDURE
verify isolation of all pulmonary veins

3\textsuperscript{rd} PROCEDURE
additional ablation

PVI incomplete: complete PVI
consider additional ablation*

PVI complete: additional ablation
Linear lesions (verify block)**
- roof line
- mitral isthmus
- posterior LA box

Consider (depending on local expertise**)
coronary sinus isolation
vena cava isolation
targeting “rotors”, “breakthroughs”, or “drivers” of AF

Habitual cardiovascular conditions promoting recurrent AF
prevented by lifestyle changes and medical therapy

Calkins et al, European Heart Journal July, 2016
third-generation cryoballoon

- higher rate of real-time electrical PV recordings

- a 40% shorter distal tip, facilitating proximal positioning of the Achieve-catheter and an increased rate of PV signal recordings.
CONCLUSIONS

✓ Cryoballoon ablation represents an effective and safe alternative therapy regarding symptomatic, drugs refractory paroxysmal atrial fibrillation
✓ First line therapy for symptomatic paroxysmal atrial fibrillation

- prospective randomized study comparing antiarrhythmic drugs and CB ablation as first-line treatment (Cryo-First trial)

✓ New evidence support PVI as first stand-alone procedure in patients with persistent AF, opening the possibility of cryoballoon use in these patients.

- Need for multicenter, prospective, randomized studies to confirm the impact of cryoballoon in persistent AF