Treatment of HF and AF
Cross Specialty 1: Joint Symposium with Heart Failure
KHRS 2019
Dae In Lee
Mutual Promotion between HF and AF

HF

LA enlargement
↑ LA pressure
Functional MR

Fibrosis
Neurohormonal activation

↓ Cardiac output

AF
A meta-analysis of the prognostic significance of atrial fibrillation in chronic heart failure

Mamas A. Mamas.

<table>
<thead>
<tr>
<th>Author</th>
<th>Setting</th>
<th>Number</th>
<th>LV systolic function inclusion</th>
<th>Mean follow-up</th>
<th>% AF</th>
<th>Number (% of deaths)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carson et al.⁷</td>
<td>Y-HEFT I &amp; II</td>
<td>1427</td>
<td>LVEF &lt; 45%</td>
<td>2.5 years</td>
<td>19</td>
<td>480/1221 (39)</td>
<td>NS</td>
</tr>
<tr>
<td>Dries et al.⁶</td>
<td>SOLVD</td>
<td>6517</td>
<td>LVEF &lt; 35%</td>
<td>2.8 years</td>
<td>6</td>
<td>1395/8098 (23)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mathew et al.¹³</td>
<td>DIG</td>
<td>7788</td>
<td>All LVEF included</td>
<td>3.1 years</td>
<td>11</td>
<td>2231/6922 (32)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Crijns et al.¹⁵</td>
<td>PRIME II</td>
<td>409</td>
<td>LVEF &lt; 35%</td>
<td>3.4 years</td>
<td>21</td>
<td>153/325 (47)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Swedberg et al.¹⁶</td>
<td>COMET</td>
<td>3029</td>
<td>LVEF &lt; 35%</td>
<td>4.8 years</td>
<td>20</td>
<td>874/2429 (36)</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>Olsson et al.¹⁰</td>
<td>CHARM</td>
<td>7601</td>
<td>All LVEF included</td>
<td>3.1 years</td>
<td>15</td>
<td>1466/6451 (23)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pederson et al.¹⁴</td>
<td>DIAMOND</td>
<td>3587</td>
<td>LVEF &lt; 35%</td>
<td>N/A</td>
<td>24</td>
<td>1951/2661 (73)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Effect of AF on Mortality in HF

**Cons**

- **AF may affect mortality** in patients with HF
  - Hemodynamic effects
  - Thromboembolic effects
  - Side effects of drug
    (AADs, Anticoagulants…)

**Pros**

- AF and HF share many predisposing factors
- **AF may act as only a surrogate marker of more advanced heart failure**
Temporal Relations of Atrial Fibrillation and Congestive Heart Failure and Their Joint Influence on Mortality
The Framingham Heart Study

Thomas J. Wang, MD; Martin G. Larson, ScD; Daniel Levy, MD; Ramachandran S. Vasan, MD; Eric P. Leip, MS; Philip A. Wolf, MD; Ralph B. D’Agostino, PhD; Joanne M. Murabito, MD, ScM; William B. Kannel, MD; Emelia J. Benjamin, MD, ScM

Circulation. 2003;107:2920–2925

<table>
<thead>
<tr>
<th>Relation of incidence of AF and HF</th>
<th>HR (Effect on Mortality)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preexisting AF ➔ Subsequent HF</td>
<td>Men: 2.7, Women: 3.7</td>
</tr>
<tr>
<td>Preexisting HF ➔ Subsequent AF</td>
<td>Men: 1.6; Women: 2.7</td>
</tr>
<tr>
<td>Diagnosis HF and AF on same day</td>
<td>N.S</td>
</tr>
</tbody>
</table>

New onset of AF had negative effect on mortality in HF patients.

- Implantable cardioverter–defibrillator therapy and risk of congestive heart failure or death in MADIT II patients with atrial fibrillation
- Atrial fibrillation and mortality in heart failure: a community study
Early management of new onset AF is crucial in improving prognosis of HF patients.
AF Management

Anticoagulation

Rate Control

Rhythm control
AF, HFrEF and Anticoagulation

European guidelines (ESC guideline 2016)

Oral anticoagulants for any AF patient
with a CHA2DS2-VASc score of more than 1
with the exception of those whose only risk factor is female

ARISTOTLE STUDY (APIXABAN vs. Warfarin)

Stroke risk: HFrEF > HFmdEF > HFpEF
Anticoagulation of AF in HF

Atrial fibrillation and heart failure due to reduced versus preserved ejection fraction: A systematic review and meta-analysis of death and adverse outcomes

Incidence of Stroke: HFpEF = HFpEF
It is reasonable to support the recommendation of prescribing oral anticoagulants to patients with AF and HF irrespective of LVEF.
Rate Control: Strict or Lenient?

Lenient versus Strict Rate Control in Patients with Atrial Fibrillation

RACE II trial

Lenient (resting HR < 110 bpm) vs. Strict (resting HR < 80 bpm)

There was no difference in the primary composite end point

Cardiovascular causes, hospitalization of HF, Stroke, Systemic embolism, bleeding, life threatening arrhythmic events
Hazard ratio significantly increased only for HR >100 beats per minute (1.29; P=0.003). 

American College of Cardiology/American Heart Association guidelines

“Lenient rate control strategy may be reasonable (but only) in asymptomatic patients with preserved LV function.”

“Stricter rate control strategy may be reasonable in patients with HFrEF.”
Treatment strategy

- AV node ablation + RV pacing

  *Meta-analysis (Wood et al.) = significant improvement of LVEF*

- AV node ablation + CRT

- AF ablation
Pulmonary-Vein Isolation for Atrial Fibrillation in Patients with Heart Failure

AF + LVEF < 40% + NYHA II or III

Ablation was superior to CRT: Composite end point (EF, 6 minutes walk, life quality)

PV isolation (n = 41)

Vs.

AV node ablation + CRT (n=40)
The benefit of AF ablation is questionable in patients with AF (long duration, enlarged LA...
Poorly rate controlled AF → Tachycardia mediated cardiomyopathy (TMC)

Who is good responder for treatment in patients with TMC?

Sinus rhythm restores ventricular function in patients with cardiomyopathy and no late gadolinium enhancement on cardiac magnetic resonance imaging who undergo catheter ablation for atrial fibrillation.

Liang-Han Ling, MBBS, PhD, Andrew J. Taylor, MBBS, PhD, Andris H. Ellims, MBBS, Leah M. Iles, MBBS, Alex J.A. McLellan, MBBS, Geoffrey Lee, MBChB, PhD, Saurabh Kumar, BSc (Med)/ MBBS, PhD, Geraldine Lee, PhD, Andrew Teh, MBBS, PhD, Caroline Medi, B.Med, PhD, David M. Kaye, MBBS, PhD, Jonathan M. Kalman, MBBS, PhD, Peter M. Kistler, MBBS, PhD

Heart rhythm 2013
AF-CHF Trial (n=1376)

Subgroup analysis

Neither rhythm control nor presence of sinus was associated with any benefit in cardiovascular mortality.

<table>
<thead>
<tr>
<th></th>
<th>No. at Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhythm control</td>
<td>593</td>
</tr>
<tr>
<td>Rate control</td>
<td>604</td>
</tr>
</tbody>
</table>

Figure 2. Kaplan–Meier Estimates of Death from Cardiovascular Causes (Primary Outcome).
Rhythm control versus Rate control

**DIAMOND Study: Subgroup analysis**

Efficacy of Dofetilide in the Treatment of Atrial Fibrillation-Flutter in Patients With Reduced Left Ventricular Function: A Danish Investigations of Arrhythmia and Mortality ON Dofetilide (DIAMOND) Substudy

Maintenance of sinus rhythm was associated with significant reduction in mortality

(risk ratio [RR], 0.44; 95% CI, 0.30 to 0.64; \( P < 0.0001 \)).
However, these two trial did not included symptomatic deteriorated patients. For these patients, more aggressive attempts (eg. Ablation) might be needed.

**Last Question**

Is AF ablation beneficial for patients with HFrEF?
Rhythm control _Ablation

Observation Study

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Sample size</th>
<th>NICM, %</th>
<th>LVEF</th>
<th>Procedure success index</th>
<th>LVEF Improvement, %</th>
<th>Follow up, month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen, 2004</td>
<td>377</td>
<td>20</td>
<td>36</td>
<td>52</td>
<td>+5</td>
<td>14</td>
</tr>
<tr>
<td>Hsu, 2004</td>
<td>116</td>
<td>55</td>
<td>35</td>
<td>50</td>
<td>+22</td>
<td>12</td>
</tr>
<tr>
<td>Tondo, 2006</td>
<td>105</td>
<td>45</td>
<td>33</td>
<td>55</td>
<td>+22</td>
<td>14</td>
</tr>
<tr>
<td>Genslesk, 2007</td>
<td>366</td>
<td>82</td>
<td>42</td>
<td>55</td>
<td>+14</td>
<td>22</td>
</tr>
</tbody>
</table>

2007~2015: Author, Sample size, LVEF improvements
- Lumomsky: 70 pts, +10%
- Nademanee: 129 pts, +10%
- De Potter: 72 pts, +8%
- Choi: 30 pts, +13%
- Cha: 368 pts, +21%
- Anselmino: 196 pts, +10%
- Calvo: 658 pts, +12%
- Nedios: 138 pts, +15%
- Kosiuk: 83 pts, +4%
- Lobo: 31 pts, +14%

In most studies,

Patients with ischemic cardiomyopathy was not good responder for AF ablation.
## Randomized Trial (2008~2016)

<table>
<thead>
<tr>
<th>Comparators</th>
<th>Sample size</th>
<th>NICM, %</th>
<th>LVEF</th>
<th>Procedure success index</th>
<th>LVEF Improvement, %</th>
<th>Follow up, month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Khan, 2008</td>
<td>Vs. CRT</td>
<td>81</td>
<td>27</td>
<td>27</td>
<td>68</td>
<td>+8</td>
</tr>
<tr>
<td>MacDonald, 2011</td>
<td>Vs. rate control</td>
<td>41</td>
<td>37</td>
<td>36</td>
<td>40</td>
<td>+4</td>
</tr>
<tr>
<td>Jones, 2013</td>
<td>Vs. rate control</td>
<td>52</td>
<td>73</td>
<td>22</td>
<td>68</td>
<td>+11</td>
</tr>
</tbody>
</table>

Rate control may not be the ideal comparator because the patients seeking ablation are often those believed to be very symptomatic from their AF.

Small sample size, Hard-endpoint?
Catheter Ablation for Atrial Fibrillation with Heart Failure

CASTLE AF

outcomes in patients with heart failure.\textsuperscript{13-17} Nevertheless, the effectiveness of catheter ablation in improving rates of hard primary end points such as death or the progression of heart failure has not been tested in large, randomized, controlled trials, and guidelines provide no clear consensus regarding the best management approach.\textsuperscript{6,11,18,19}

We initiated the Catheter Ablation versus Standard Conventional Therapy in Patients with Left Ventricular Dysfunction and Atrial Fibrillation (CASTLE-AF) trial to address this issue.\textsuperscript{20}
Study Design CASTLE AF

AF ± ICD / CRT

Ablation (n=200)

Rate control (n=197)

PVI ± Line

60-80 bpm (resting)
90-115 bpm (exercise)

38 months f/up

Primary outcome: death + worsening HF
Primary Outcome CASTLE AF

A Death or Hospitalization for Worsening Heart Failure

- Probability of Survival Free of Hospital Admission
- Months of Follow-up
- No. at Risk
  - Ablation: 179, 141, 114, 76, 58, 22
  - Medical therapy: 184, 145, 111, 70, 48, 12

Hazard ratio, 0.62 (95% CI, 0.43–0.87)
- P=0.007 by Cox regression
- P=0.006 by log-rank test

P=0.006

71.5%

55.4%
### Table 2. Primary and Secondary Clinical End Points.

<table>
<thead>
<tr>
<th>End Point</th>
<th>Ablation (N=179)</th>
<th>Medical Therapy (N=184)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value Cox Regression</th>
<th>P Value Log-Rank Test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>number (percent)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Primary</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary†</td>
<td>51 (28.5)</td>
<td>82 (44.6)</td>
<td>0.62 (0.43–0.87)</td>
<td>0.007</td>
<td>0.006</td>
</tr>
<tr>
<td><strong>Secondary</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from any cause</td>
<td>24 (13.4)</td>
<td>46 (25.0)</td>
<td>0.53 (0.32–0.86)</td>
<td>0.01</td>
<td>0.009</td>
</tr>
<tr>
<td>Heart-failure hospitalization</td>
<td>37 (20.7)</td>
<td>66 (35.9)</td>
<td>0.56 (0.37–0.83)</td>
<td>0.004</td>
<td>0.004</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>20 (11.2)</td>
<td>41 (22.3)</td>
<td>0.49 (0.29–0.84)</td>
<td>0.009</td>
<td>0.008</td>
</tr>
<tr>
<td>Cardiovascular hospitalization</td>
<td>64 (35.8)</td>
<td>89 (48.4)</td>
<td>0.72 (0.52–0.99)</td>
<td>0.04</td>
<td>0.04</td>
</tr>
<tr>
<td>Hospitalization for any cause</td>
<td>114 (63.7)</td>
<td>122 (66.3)</td>
<td>0.99 (0.77–1.28)</td>
<td>0.96</td>
<td>0.96</td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>5 (2.8)</td>
<td>11 (6.0)</td>
<td>0.46 (0.16–1.33)</td>
<td>0.15</td>
<td>0.14</td>
</tr>
</tbody>
</table>
CASTLE AF

AF ablation > Rate control

In terms of hard endpoint

<table>
<thead>
<tr>
<th></th>
<th>Sinus rhythm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ablation</td>
<td>64%</td>
</tr>
<tr>
<td>Rate control</td>
<td>29%</td>
</tr>
</tbody>
</table>

CRT efficacy?
Conclusions

• Although AF and HF mutually interact each other, AF can be a surrogate marker of progressed HF.
• However, it is clear that early intervention of new onset AF in patients with HFrEF can improve survival.
• In terms of rate control, guideline suggest that stricter rate control in HF patients is preferred.
• CASTLE AF showed ablation may reduce the mortality in patients with AF + HF.
Thank you for your attention.