Atrial Fibrillation and Heart Failure: Fire and Fury

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Heart Failure and Atrial Fibrillation, Like Fire and Fury

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Atrial Fibrillation and Heart Failure: Fire and Fury

Lecture Outline:

1. What constitutes “Fire and Fury”?
2. Prognostic Implications
3. How do they impact on Guidelines-based treatment for each other?
4. Unanswered questions?
Atrial Fibrillation and Heart Failure: Fire and Fury

Shared etiology and risk factors between the two entities leading to a situation where each entity:

a) Promotes the development of the other

b) Contributes to adverse hemodynamic and neuroendocrine consequences of the other

c) Worsens morbidity and mortality of each other
Epidemiology of AF and HF

- AF and HF, individually, affect 1-2% of the population: common problems, 3-5 million have AF and 4-6 million HF

- Annual incidence of:
  - HF in AF patients: 3.3%
  - AF in HF patients: 5.8%

- Both share common etiologies
  - CAD, CM, valvular disease, HTN, DM, sleep Apnoea

- Bidirectional pathophysiologic relationship
  - AF prevalence increases with HF severity
  - HF prevalence increases with AF duration
Pathophysiologic Interaction Between AF and HF

↑ filling pressure
Dysregulation of Intracellular Ca++
Neurohormonal activation
fibrosis
↓ Cardiac output
↑ LA size

HF

AF

1. Rapid ventricular rate
2. Irregular rate
3. Loss of atrial systole
4. Increased MR, TR

Tachycardia-related myopathy

Anter, E. et al., Circulation. 2009;119:2516-2525
AF Prevalence and Adverse events in HF with different ranges of LVEF

Sartipy et al., *JACC-HF* 2017;5:565-574. Swedish Heart Failure Registry
Prevalence of AF in CHF Trials

AF (%)

Class I

Class II

Class II-III

Class III

Class IV

SOLVD-P

SOLVD-T

US CARVD

ATLAS

CONSENSUS
Framingham Heart Study participants from 1980-2012
1737 had new onset AF and 1166 had new onset HF
Cumulative Incidence of AF and HF

AF Incidence in HF

- Prevalent HF
- No HF

Log rank P<0.001

HF Incidence in AF

- Incident HFpEF
- Incident HFpEF
- Incident HFpEF
- Incident HFpEF

Log rank P<0.001 (comparing prevalent AF vs no AF for both HF subtypes)

Number at Risk
- Prevalent HF: 90, 64, 51, 34, 25
- No HF: 14774, 14395, 13847, 13237, 12613

Number at Risk
- Prevalent AF: 403, 3534, 293, 247, 209
- No AF: 14800, 14478, 14004, 13477, 12934

Santhanakrishnan R, et al., *Circulation* 2016; 133:484-492
### Outcome in ORBIT Registry of AF Patients With and Without HF

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. HF (6309 pts)</th>
<th>HF (236 pts)</th>
<th>Adjusted HR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cause death</td>
<td>3.35%</td>
<td>8.24%</td>
<td>1.84</td>
<td>0.023</td>
</tr>
<tr>
<td>Stroke/TIA/SE</td>
<td>1.32%</td>
<td>3.09%</td>
<td>1.53</td>
<td>0.4</td>
</tr>
</tbody>
</table>
| All-cause Hospitalization| 26.4%             | 90%          | 3.35        | 0.0001  

Pcendey et al., JACC Heart Failure 2017;5:44-52
AF in HF: Independent Risk of Poor Outcome or just a Bystander?

- Meta-analysis of 53,969 patients in 16 HF trials:
  - Hazard ratio for ↑ mortality: 1.40
  - Independent effect (Mamas et al., *Eur J Heart Fail*. 2009;11:676-683)

- Incident AF (new onset) has more impact than prevalent (pre-existent) AF
  - ↓ Functional class, VO₂max, cardiac output
  - More mitral and tricuspid regurgitation
  - (Pozzoli et al., *JACC*. 1998;32:197-204)

- New onset AF in MADIT II: All-cause mortality increased
  - Hazard ratio (2.7)
  - Hospitalization increased two-fold
Effect on Mortality of New Onset AF in pts with HFrEF or HFpEF

Santhanakrishnan et al., Circulation 2016;133:484-492
<table>
<thead>
<tr>
<th>All-cause Mortality in:</th>
<th>Predictor</th>
<th>Hazard Ratio</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All HF (n=598)</td>
<td>Prevalent AF</td>
<td>1.25</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>Interim AF</td>
<td>1.89</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>-only HFrEF (n=289)</td>
<td>Prevalent AF</td>
<td>1.18</td>
<td>0.23</td>
</tr>
<tr>
<td></td>
<td>Interim AF</td>
<td>2.03</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>only HFpEF (n=309)</td>
<td>Prevalent AF</td>
<td>1.33</td>
<td>0.08</td>
</tr>
<tr>
<td></td>
<td>Interim AF</td>
<td>1.58</td>
<td>0.02</td>
</tr>
</tbody>
</table>
Tachycardia-induced Cardiomyopathy in AFib: Potentially reversible subset of HF

Therapeutic Approach to Patients with AF and HF

- Identify and optimize management of underlying etiologic/risk factors: obesity, HTN, sleep apnea, etc.
- Delineate time course of AF and HF
- Oral anticoagulation in all, except when contraindicated
- Optimize standard HF Rx
  - ACE inhibitors: ↓ atrial stretch/fibrosis
  - Aldosterone antagonists: neurohormonal modulation
  - Beta-blockers: rate control, neurohormonal modulation
All shown to ↓ incident AF in HF patients
Guidelines based Therapeutic Approach to Patients with AF and HF

- Optimize ventricular rate control
  - Resting HR ~ 80 bpm
  - 6 min walk rate: < 110 bpm

- Beta-blockers, digoxin, and amiodarone
  - Recommended in HFrEF
  - Ca++ blockers only in HFpEF
  - Data on beta-blockers less convincing for AF + HF patients

- AV node ablation + Biventricular pacing when pharmacologic rate control suboptimum

- Identify subsets where rhythm control preferable
  - Pharmacologic vs RF catheter ablation?
Meta-Analysis of 11 RCTs – Beta Blockers in HF Collaborative Group

Kotecha et al., JACC 2017;69:2885-96
### 2014 Guidelines for Rate Control in HF Patients with AF

**Heart failure**

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Level</th>
<th>Grade</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>A combination of digoxin and beta blocker (or a nondihydropyridine calcium channel antagonist with HFrEF) is reasonable to control resting and exercise heart rate with AF</td>
<td>IIa</td>
<td>B</td>
<td>(267,503)</td>
</tr>
<tr>
<td>It is reasonable to perform AV node ablation with ventricular pacing to control heart rate when pharmacological therapy is insufficient or not tolerated</td>
<td>IIa</td>
<td>B</td>
<td>(269,508,509)</td>
</tr>
<tr>
<td>IV amiodarone can be useful to control heart rate with AF when other measures are unsuccessful or contraindicated</td>
<td>IIa</td>
<td>C</td>
<td>N/A</td>
</tr>
<tr>
<td>With AF and RVR causing or suspected of causing tachycardia-induced cardiomyopathy, it is reasonable to achieve rate control by AV nodal blockade or a rhythm-control strategy</td>
<td>IIa</td>
<td>B</td>
<td>(51,307,510)</td>
</tr>
<tr>
<td>In patients with chronic HF who remain symptomatic from AF despite a rate-control strategy, it is reasonable to use a rhythm-control strategy</td>
<td>IIa</td>
<td>C</td>
<td>N/A</td>
</tr>
<tr>
<td>Amiodarone may be considered when resting and exercise heart rate cannot be controlled with a beta blocker (or a nondihydropyridine calcium channel antagonist with HFrEF) or digoxin, alone or in combination</td>
<td>IIb</td>
<td>C</td>
<td>N/A</td>
</tr>
<tr>
<td>AV node ablation may be considered when rate cannot be controlled and tachycardia-mediated cardiomyopathy is suspected</td>
<td>IIb</td>
<td>C</td>
<td>N/A</td>
</tr>
<tr>
<td>AV node ablation should not be performed without a pharmacological trial to control ventricular rate</td>
<td>III: Harm</td>
<td>C</td>
<td>N/A</td>
</tr>
<tr>
<td>For rate control, IV nondihydropyridine calcium channel antagonists, IV beta blockers, and dronedarone should not be given with decompensated HF</td>
<td>III: Harm</td>
<td>C</td>
<td>N/A</td>
</tr>
</tbody>
</table>

January et al., *JACC* Vol. 64, No. 21, 2014
• No evidence that rhythm control by AADs improves survival, stroke risk, CV hospitalization, QOL or LV dysfunction

• Routine use of rhythm-control strategy not recommended and rate control with anticoagulation preferred strategy

• Rhythm control indicated when:
  - symptoms persist despite rate control
  - rate control difficult to achieve
  - tachycardia-related CM suspected

• Catheter ablation role not adequately defined or studied
RF Catheter Ablation of AF

- First introduced in late 1990
- Cures AF by eliminating and/or modifying AF sources in one or both atria
- Guidelines endorsed 1st or 2nd line Rx in symptomatic AF
- Success 3-4 fold higher in sinus restoration vs AADS:
  - 80-90% paroxysmal
  - 70-80% recent persistent AF
  - 50-70% long lasting persistent AF
- Not associated with adverse effects of AADs
- Serious complications infrequent (1-2%)
# Potentially Serious Complications of RF Catheter Ablation

<table>
<thead>
<tr>
<th>Complication</th>
<th>Frequency</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Air embolism during procedure</td>
<td>&lt; 0.5%</td>
<td>Acute MI, AV block cardiac arrest</td>
</tr>
<tr>
<td>2. Atrial-esophageal fistula</td>
<td>&lt;1 in 5,000 cases</td>
<td>Usually 1-4 weeks later – fever, polymicrobial endocarditis, high fatality</td>
</tr>
<tr>
<td>3. Cardiac tamponade</td>
<td>0.5 - 1.0%</td>
<td>Hypertension, Pericardiocentesis/surgery</td>
</tr>
<tr>
<td>4. Phrenic Nerve Palsy</td>
<td>0.1 – 0.5%</td>
<td>SOB, Partial collapse of lung</td>
</tr>
<tr>
<td>5. Gastric motility disorder</td>
<td>&lt;0.3%</td>
<td>Nausea, vomiting</td>
</tr>
<tr>
<td>6. Pulmonary vein stenosis</td>
<td>&lt;1%</td>
<td>SOB, fatigue</td>
</tr>
<tr>
<td>7. Acute CVA/TIA</td>
<td>0.2 – 0.5%</td>
<td>Usually mild neurological deficit</td>
</tr>
<tr>
<td>8. Death</td>
<td>0.1 – 0.3%</td>
<td>Multifactorial</td>
</tr>
<tr>
<td>9. Vascular site complications</td>
<td>1 – 3%</td>
<td>Pseudo-aneurysm, AV-fistulas, Hematomas</td>
</tr>
</tbody>
</table>
## Recent Randomized Trials of AF Catheter Ablation in Heart Failure

<table>
<thead>
<tr>
<th>RCT</th>
<th>Year Published</th>
<th>Addressed Question</th>
</tr>
</thead>
<tbody>
<tr>
<td>AATAC</td>
<td>2016</td>
<td>Is RF ablation superior to amiodarone?</td>
</tr>
<tr>
<td>CAMERA-MRI</td>
<td>2017</td>
<td>Does LV function improve with RF catheter ablation?</td>
</tr>
<tr>
<td>CASTLE-AF</td>
<td>2018</td>
<td>What is the effect on mortality and morbidity in HF?</td>
</tr>
<tr>
<td>CABANA*</td>
<td>2018</td>
<td>What is the effect on mortality with catheter ablation vs AADs?</td>
</tr>
</tbody>
</table>

*15% of 2204 patients had HF*
Freedom from AF (ICD documented)
in AATACH

DiBiase et al., Circ. 2016;133:1637-1644
Other Outcome Analysis in AATACH

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Catheter Ablation</th>
<th>Amiodarone</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-yr Mortality, %</td>
<td>8</td>
<td>18</td>
<td>0.037</td>
</tr>
<tr>
<td>All-cause Hospitalization, %</td>
<td>31</td>
<td>57</td>
<td>0.001</td>
</tr>
<tr>
<td>LVEF, Δ, %</td>
<td>8</td>
<td>6</td>
<td>0.02</td>
</tr>
<tr>
<td>QoL (MLFHQ score)</td>
<td>↓ 11</td>
<td>↓ 6</td>
<td>0.04</td>
</tr>
</tbody>
</table>

DiBiase et al., Circ. 2016;133:1637-1644
Catheter Ablation vs Medical Rate Control in AF and Systolic Dysfunction – The CAMERA-MRI Study

- Prospective, multi-center, parallel group. Open label randomized trial (2013-2016)
- **Inclusion Criteria**: Unexplained HF with persistent AF and EF <45% (Ischemic/valvular etiologies excluded)
- 4-week phase-in to control rate and optimize Rx
- Cardiac MRI (Gadolinium) at baseline and 6 months
- **Primary endpoint**: ΔLVEF at 6 months
- **Secondary endpoints**: MRI detected scar, BNP, 6 min walk, AF burden

*Prabhu et al., JACC 2017; 70:1949-1961*
CAMERA-MRI
Outcomes at 6 Months

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Catheter Ablation</th>
<th>Med Rx</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Endpoint</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Δ MRI-LVEF, %</td>
<td>18</td>
<td>4</td>
<td>0.0001</td>
</tr>
<tr>
<td><strong>Secondary Endpoints</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Δ Echo-LVEF, %</td>
<td>↑ 18</td>
<td>↑ 9</td>
<td>0.01</td>
</tr>
<tr>
<td>Δ Functional class</td>
<td>↓ 1.2</td>
<td>↓ 0.4</td>
<td>0.0001</td>
</tr>
<tr>
<td>Δ BNP</td>
<td>↓ 168</td>
<td>↓ 9</td>
<td>0.0006</td>
</tr>
<tr>
<td>Normal LVEF at 6 months, %</td>
<td>58</td>
<td>9</td>
<td></td>
</tr>
</tbody>
</table>
AF Catheter Ablation in HF
CAMERA-MRI

Prabhu et al., JACC 2017; 70:1949-1961
AF Catheter Ablation in HF
CAMERA-MRI

Prabhu et al., JACC 2017; 70:1949-1961
Summary Statements of the CAMERA- MRI Study

- Persistent AF is an under-recognized cause of otherwise unexplained sys HF (AF mediated CM) in a significant proportion of such pts

- Sinus restoration with Catheter Ablation is associated with an improved LVEF, cardiac remodeling and functional capacity

- Absence of MRI detected fibrosis identifies “Super Responders” to Catheter ablation
Catheter Ablation vs. Standard Therapy in Patients with LV Dysfunction and Atrial Fibrillation – CASTLE-AF

- Multi-center, open-label, randomized trial (2008-2016)

- **Inclusion Criteria:**
  - HF patients, with symptomatic paroxysmal/persistent AF
  - LVEF ≤35%, HF class II-IV
  - Implanted ICD/CRT (Biotronic)

- 5 weeks of phase-in period to adjust HF meds before randomizing 1:1 to catheter ablation vs med Rx

- **Primary endpoint:** Composite of all-cause mortality and HF-related hospitalizations

- **Secondary endpoints:** CVA, AF freedom, all-cause hospitalization

- Median F/U: 38 months

*Morrouche et al., NEJM 2018;378:417-427*
Survival Curve for Primary Endpoint in CASTLE-AF

B  Death from Any Cause

C  Hospitalization for Worsening Heart Failure

Morrouche et al., NEJM 2018;378:417-427
## Primary and Secondary Endpoints In CASTLE-AF

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Treatment Type</th>
<th>Hazard Ratio</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ablation</td>
<td>Medical Rx</td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>28%</td>
<td>45%</td>
<td>0.62</td>
</tr>
<tr>
<td>Secondary</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>13%</td>
<td>25%</td>
<td>0.53</td>
</tr>
<tr>
<td>HF hospital</td>
<td>21%</td>
<td>36%</td>
<td>0.56</td>
</tr>
<tr>
<td>CV deaths</td>
<td>11%</td>
<td>22%</td>
<td>0.49</td>
</tr>
<tr>
<td>CVA</td>
<td>3%</td>
<td>6%</td>
<td>0.46</td>
</tr>
<tr>
<td>Other outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEF Δ over 5 yrs</td>
<td>8% (2-19%)</td>
<td>0.2% (-3 – 16%)</td>
<td>—</td>
</tr>
<tr>
<td>AF freedom</td>
<td>63%</td>
<td>22%</td>
<td></td>
</tr>
</tbody>
</table>

*Morrouche et al., NEJM 2018;378:417-427*
AF and HF:
Summary Statements and Implications

- RF catheter ablation restores sinus with 60-70% success rate
- Efficacy superior than amiodarone and maintained over long-term follow up
- Sinus restoration associated with total mortality, LVEF, HF-related hospitalizations
- Non-ischemic etiology of HF, absence of MRI-detected scar and shorter AF duration predicts greater improvement in LVF and normalization of LV dysfunction in a select subset
## Recommendation for Catheter Ablation in HF

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>RECOMMENDATION</th>
</tr>
</thead>
</table>
| IIb | B-R  | 1. AF catheter ablation may be reasonable in selected patients with symptomatic AF and HF with reduced left ventricular (LV) ejection fraction (HFrEF) to potentially lower mortality rate and reduce hospitalization for HF *(S6.3.4-1, S6.3.4-2)*.  
   **NEW:** New evidence, including data on improved mortality rate, has been published for AF catheter ablation compared with medical therapy in patients with HF. |
Potentially Reversible subsets of AFib-induced HF

<table>
<thead>
<tr>
<th>Tachycardia-induced Cardiomyopathy</th>
<th>AF-mediated Cardiomyopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>• In the setting of persistently elevated heart rate with AF</td>
<td>• AFib history precedes onset of HF and not dependent on ventricular rate</td>
</tr>
<tr>
<td>• Mechanism-related to low cardiac output and impaired Ca^{++} regulation</td>
<td>• Mechanism-related to irregularity of cardiac cycles, impaired Ca^{++} regulation, increased MR/TR</td>
</tr>
<tr>
<td>• Exact incidence unknown ~ 5% of AF and HF patients</td>
<td>• Exact incidence unknown</td>
</tr>
<tr>
<td>• Largely reversible if recognized early and treated appropriately</td>
<td>• Reversible if recognized early and sinus restored</td>
</tr>
</tbody>
</table>
Factors that Predict HF Improvement with Restoration of Sinus Rhythm

- Tachycardia-related CM
- AF that precedes or concurrent with the diagnosis of HF
- New onset HF in a patient with AF
- Absence of known chemical etiologic factors for HF (e.g., no valvular/coronary disease)
- Absence of late Gadolinium enhancement on cardiac MRI
- Improvement in LVEF/HF symptoms after cardioversion
Clinical Situations where AF ablation not desireable

- Elderly with multiple co morbidities
- Long standing persistent AF
- Advanced late class 111 and class 1V functional class HF
- Well tolerated AF without any symptoms or hemodynamic compromise
- Ischemic CM with significant fibrosis/akinesia/ dyskinesia
Unanswered Questions for Concomitant HF and AF

1. What defines symptomatic AF in HF patients?
2. First-line rhythm control therapy in HF
   – Amiodarone/dofetilide?
   – Catheter ablation of AF?
3. How best to identify responders to RF catheter ablation for AF? (e.g., cardioversion trial after amiodarone?)
4. Which strategies can prevent HF in patients with AF?
5. What is the optimal rate control in AF-HF?
6. Is catheter ablation effective in HFpEF?
Catheter Ablation of AF in HF with preserved or reduced EF

Black-Meier et al., Heart Rhythm 2018; 15:651-657
RF Catheter Ablation of AF in HF

Black-Meier et al., *Heart Rhythm* 2018; 15:651-657
RF Catheter Ablation of AF in HF

Black-Meier et al., Heart Rhythm 2018; 15:651-657