AF Ablation in HFrEF and HFpEF
Patient Selection, Expected Results, and Prevention of Recurrences

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AF Catheter Ablation in HF

Lecture Outline:

- Epidemiologic and prognostic considerations
- Time to revisit equivalence of rate vs. rhythm analysis
- Review RCT data on catheter ablation for HFrEF and HFpEF
- Guideline-based patient selection criteria
- Unmet needs and future directions
AF and HF: Epidemiological and Prognostic Considerations

• Common problems: US Prevalence of AF: 5 million of HF: 6 million
• Frequently coexist: AF in 10-60% of HF pts HF in 20-30% of AF pts
• Shared etiology and make each other’s pathophysiology worse
• AF equally prevalent in HFrEF and HFpEF - prevalence ↑ with worsening NYHA class
• AF ↑ mortality risk by (30-50%), ↑ HF hospitalization by 50% and impairs functional class/QOL

AF-induced Mechanisms of Cardiac Dysfunction in HF Patients

Reddy et al., Circulation 2022;146:339-357
Outcome in Relation to Type of AF at Randomization in PARADIGM-HF and ATMOSPHERE (15415 pts with HFpEF)

## Overview of Rate vs. Rhythm Analysis for AF and HF Before the Ablation Era

- Average proportion of sinus 36-83% for rhythm control and 10-60% for rate control

<table>
<thead>
<tr>
<th>Trial</th>
<th>No. Pts.</th>
<th>Inclusion Criteria</th>
<th>Endpoint</th>
<th>Comparator</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>DIAMOND-CHF</td>
<td>1518</td>
<td>III/IV and EF &lt; 35%</td>
<td>Mortality</td>
<td>Dofetilide</td>
<td>No effect</td>
</tr>
<tr>
<td>AF-CHF</td>
<td>1376</td>
<td>EF &lt; 35%</td>
<td>CV death</td>
<td>Amiodarone</td>
<td>No effect</td>
</tr>
<tr>
<td>AFFIRM-HF</td>
<td>788</td>
<td>EF &lt; 50%</td>
<td>Mortality</td>
<td>Rate vs. rhythm</td>
<td>No effect</td>
</tr>
<tr>
<td>RACE-HF</td>
<td>261</td>
<td>II/III</td>
<td>Mortality + Hospitalization</td>
<td>Rate vs. rhythm</td>
<td>No effect</td>
</tr>
</tbody>
</table>
Rhythm Control vs. Rate Control: Perspective a Decade Ago

- Despite ~30% superiority in restoring and maintaining sinus, AADs do not improve CV outcomes in pts with or without HF

- Potential Explanations: AF presence just a bystander, late intervention, proarrhythmic, negative hemodynamic and cellular EP effects of long-term AADs, and declining AADs efficacy over long-term F/U

- Similarly discouraging results of AADs in RCTs in other patient populations: CAST, SWORD, and ALIVE

- Rate Control Strategy became Guidelines (2014) endorsed Standard of Rx: rhythm control strategy only for persistent symptom despite rate control (used only in 10-15% patients in multiple registries)
Catheter Ablation for Rhythm Control

- Targets sources of Afib (PV isolation/substrate modification) and potentially a curative modality
- **Rapid adoption** over last two decades as second or first-line therapy for AF: Endorsed by national/international Guidelines
- High success: 70-80% for paroxysmal
  60-80% for recent persistent
- **Low** short-term complications
  < 1-2% serious complications
  Mortality risk < 0.5%
- **Long-term safety** well established
- Superior to AADs as first-line therapy (RAAFT)
- Early observational studies in HF showed similar effectiveness and low complications

Need to re-assess its effects on CV outcomes in HF population??
## RCTs of AF Ablation in HF Population

<table>
<thead>
<tr>
<th>Study</th>
<th>No. Pts.</th>
<th>Pt. Characteristics</th>
<th>Comparator</th>
<th>F/U</th>
<th>Primary Endpoint</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>PABA-CHF (2008)</td>
<td>81</td>
<td>≤ 40</td>
<td>II - III</td>
<td>6 mos.</td>
<td>LVEF, 6 min WD, QOL</td>
<td>Abl superior</td>
</tr>
<tr>
<td>MacDonald (2010)</td>
<td>41</td>
<td>≤ 35</td>
<td>II - IV</td>
<td>6 mos.</td>
<td>LVEF Δ</td>
<td>No significant difference</td>
</tr>
<tr>
<td>ARC-HF (2013)</td>
<td>52</td>
<td>≤ 35</td>
<td>II - IV</td>
<td>12 mos.</td>
<td>Peak VO₂</td>
<td>Abl superior</td>
</tr>
<tr>
<td>CAMTAF (2014)</td>
<td>50</td>
<td>≤ 50</td>
<td>II - IV</td>
<td>12 mos.</td>
<td>LVEF Δ</td>
<td>Abl superior</td>
</tr>
<tr>
<td>AATAC (2016)</td>
<td>203</td>
<td>≤ 40</td>
<td>II - III</td>
<td>36 mos.</td>
<td>AF recurrence</td>
<td>Abl superior</td>
</tr>
<tr>
<td>CAMERA-MRI (2017)</td>
<td>68</td>
<td>≤ 45</td>
<td>II - IV</td>
<td>6 mos.</td>
<td>LVEF Δ</td>
<td>Abl superior</td>
</tr>
<tr>
<td>AMICA (2019)</td>
<td>202</td>
<td>≤ 35</td>
<td>II - III</td>
<td>12 mos.</td>
<td>LVEF Δ</td>
<td>No significant difference</td>
</tr>
<tr>
<td>RAFT (2023)</td>
<td>411</td>
<td>No cutoff</td>
<td>II - III</td>
<td>37 mos.</td>
<td>Mortality + HF events</td>
<td>Non-significant trend for abl superiority</td>
</tr>
</tbody>
</table>
Success for Sinus Maintenance for AF Ablation Trials in HF Patients

Mulder et al., *Heart* 2022; 108:422-428
Forest Plots Displaying Mean $\Delta$ in LVEF and 6MWT

Patient Population in CASTLE-AF

Sohns, C., et al., Circ Arrhythm Electrophysiol 2020;13:e008461
Survival Curve for Primary Endpoint in CASTLE-AF

Morrouche et al., NEJM 2018;378:417-427
Primary Endpoint* Impact in Relation to NYHA Class and Low EF in CASTLE-AF

* Primary endpoint: All cause mortality and HF hospitalization.
Sohns et al., Circ EP, 2020
CABANA HF Trial: Outcomes for Ablation vs. Drug Therapy in Heart Failure Subset

Primary Outcome*

All Cause Mortality

*All cause mortality, disabling stroke, serious bleeding, or cardiac arrest

Packer D., et al., *Circulation*, 2021;143:1377-1390
AF Recurrence and QOL Outcomes in CABANA-HF

AF Recurrence

*Mayo AF specific symptoms inventory (MAFS1) Scoring

Packer D., et al., Circulation, 2021;143:1377-1390
RAFT-AF Trial: Study Design

- Multicenter, prospective, randomized trial

- Eligible patients: High burden paroxysmal AF/persistent AF with reduced (<45%) or preserved EF, HF Class II or III and high BNP

- Randomized to rate control or catheter ablation

- Primary Outcome: Composite of time to death and HF events

- Secondary Outcomes: Δ LVEF, NT-pro BNP, 6 min walk, QOL at 12/24 months

- Sample Size Calculated: 600 pts: 300 in each area

- Recruitment stopped in Sept 2017 by Data Monitoring Committee due to low enrollment, low event rate, and perceived futility for outcome (363 pts with 19 months F/u)

Parkash R., et al., Circulation, 2022;145:1693-1704
Primary Endpoint (Mortality + HF Event) in RAFT-AF Trial

# Efficacy Outcomes by LVEF Stratification I
## RAFT-AF Trial

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Treatment Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LVEF ≤ 45% (n=240)</td>
</tr>
<tr>
<td>All cause mortality + HF Event</td>
<td>0.63 (0.39 to 1.02)</td>
</tr>
<tr>
<td></td>
<td>( p: 0.059 )</td>
</tr>
<tr>
<td>6 min walk distance (meters)</td>
<td>( \uparrow 41 \ (9 \text{ to } 73) )</td>
</tr>
<tr>
<td></td>
<td>( p: 0.02 )</td>
</tr>
<tr>
<td>( \Delta \text{NT-pro BNP, %} )</td>
<td>-44 (\text{-6 to 23})</td>
</tr>
<tr>
<td></td>
<td>( p &lt; 0.0001 )</td>
</tr>
<tr>
<td>( \Delta \text{LVEF, %} )</td>
<td>6.3 (2.7 to 9.9)</td>
</tr>
<tr>
<td></td>
<td>( p: 0.019 )</td>
</tr>
</tbody>
</table>

Forest Plots of Metanalysis of AF Ablation in HF Patients

All-cause mortality

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Ablation</th>
<th>Drugs</th>
<th>Weight</th>
<th>M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
<td></td>
</tr>
<tr>
<td>AATAC 2016 [19]</td>
<td>8</td>
<td>102</td>
<td>18</td>
<td>101</td>
</tr>
<tr>
<td>AMICA 2019 [13]</td>
<td>8</td>
<td>100</td>
<td>8</td>
<td>95</td>
</tr>
<tr>
<td>ARC-HF 2013 [21]</td>
<td>1</td>
<td>24</td>
<td>0</td>
<td>26</td>
</tr>
<tr>
<td>CABANA 2021 [17]</td>
<td>23</td>
<td>378</td>
<td>37</td>
<td>400</td>
</tr>
<tr>
<td>CAMERA-MRI 2017 [24]</td>
<td>0</td>
<td>33</td>
<td>0</td>
<td>33</td>
</tr>
<tr>
<td>CAMTAF 2014 [20]</td>
<td>0</td>
<td>26</td>
<td>1</td>
<td>24</td>
</tr>
<tr>
<td>CASTLE-AF 2018 [18]</td>
<td>24</td>
<td>179</td>
<td>46</td>
<td>184</td>
</tr>
<tr>
<td>RAFT-AF 2022 [14]</td>
<td>29</td>
<td>214</td>
<td>34</td>
<td>197</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>1056</td>
<td>1060</td>
<td>100.0%</td>
<td>0.65 [0.51, 0.82]</td>
</tr>
<tr>
<td>Total events</td>
<td>93</td>
<td>144</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.00; Chi² = 4.15, df = 6 (p = 0.66); I² = 0%

Test for overall effect: Z = 3.51 (p = 0.0005)

Forest Plots of Metaanalysis of AF Ablation in HF Patients
AF Mediated Cardiomyopathy (AMC)

- **Definition**: AF either as the sole cause for ventricular dysfunction, or exacerbating ventricular dysfunction in patients with pre-existent CM/HF

- **Diagnosis**: difficult due to variable clinical presentations and insidious clinical course

- **Supportive Evidence**:
  a) Temporal correlation between AF onset/increasing burden and HF status
  b) Severity of ventricular dysfunction disproportional to the severity of SHD
  c) Relatively quick recovery of HF after successful rhythm (or rate) control

- Timely diagnosis and early intervention are critical to optimize clinical outcomes

- True prevalence unknown but likely underestimated
AF Catheter Ablation in HF CAMERA-MRI
6 month F/U

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

- Data relevant largely to HFrEF and supports its effectiveness and safety
- One (CASTLE-AF) of the 2 RCTs met primary endpoint of decreased all cause mortality + HF hospitalizations
- Cumulative data, however, overwhelmingly favorable
  - 46% ↓ all cause mortality
  - 45% ↓ in HF hospitalizations
  - Absolute 5% ↑ in LVEF
  - 54% ↓ in long-term AF recurrence
- Inclusion criteria restrictive and results may not be generalizable to all patients with HF
- Significant heterogeneity in beneficial response among study populations and paucity of long term follow up
## Summary of Current Guidelines on AF Catheter Ablation in Patients with HF

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Recommendation</th>
<th>Class</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>2019 AHA/ACC/HRS Update on 2014 Guidelines</td>
<td>May be reasonable in selected HFrEF patients with symptoms to improve survival and reduce HF hospitalizations</td>
<td>IIb</td>
<td>B-R</td>
</tr>
<tr>
<td>2020 ESC AF Guidelines for dx and Rx in collaboration with EACTS</td>
<td>Recommended when tachycardia-induced CM highly probable, independent of symptom status</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>Should be considered in selected AF and HFrEF to improve survival/reduce HF hospitalizations</td>
<td>IIa</td>
<td>B</td>
</tr>
</tbody>
</table>
# AF Catheter Ablation in HFrEF

## Likely to Benefit
- AF mediated CM suspected
- NYHA Class I/II HF
- Paroxysmal and early persistent AF
- Younger patients (<80 years)
- No significant ventricular scar on LGE-MRI
- None/mild LA fibrosis

## Less Likely to Benefit
- NYHA III/IV HF
- Longstanding persistent AF
- Severe LA cardiomyopathy
- Advanced age
- Significant ventricular scar
- Advanced comorbidities

AHA Scientific Statement on Managing AF in Patients with HFrEF. Gopinathannak et al., *Circulation*, 2021
Atrial Scar Quantification by MRI

Utah stage 1

Utah stage 2

Utah stage 3

Utah stage 4

Syros et al., *Innovations in Cardiac Rhythm Management*, Advances in Imaging to Assist Atrial Fibrillation Ablation
AHA Scientific Statement for Managing AF in HFrEF

Modified from Gopinathannak et al., Circulation, 2021
Status of Catheter Ablation of AF in Patients with HFpEF

• May be less efficacious than in HFrEF
  – concomitant LA myopathy
  – substrate modification may add to more fibrosis and LA dysfunction

• Likely more beneficial for high burden paroxysmal/early persistent AF

• Inconclusive RCT based data

• Two ongoing pilot studies
  – AMPERE
  – TAP-CHF

Parkash R., et al., Circulation, 2022;145:1693-1704
AF Catheter Ablation in HF
Unmet Needs and Future Directions

• Do patients with HFpEF benefit?
  - RCTs needed (AMPERE, TAP-CHF)

• Long-term durability of benefit?

• Ablation success: <30 sec recurrent AF episodes (as endorsed by HRS) or by significant (50-70%?) AF burden reduction

• Optimum Ablation Strategy: PV isolation done or with substrate modification

• Optimum timing of catheter ablation after diagnosis
AF Burden Reduction in Relation to Clinical Outcomes in CASTLE-AF

A. Primary Endpoint

B. All-Cause Mortality

C. wHF Hospitalization

* 152 non-ablated and 128 ablated patients

AF Management in HFrEF and HFpEF: Concluding Statements

• AF develops in about half of HF patients and carries adverse prognostic significance

• Catheter ablation represents an effective and safe modality to restore and maintain sinus in HF pts with paroxysmal or early persistent AF

• Available data relevant largely for HFrEF and dedicated RCTs needed for HFpEF

• Unlike AADs, catheter ablation improves all cause mortality and HF hospitalizations in “select” group of HFrEF (Class IIa/IIb recommendation)

• AV node ablation and CRT should be considered when rate control difficult and patients not candidates for catheter ablation

• Earlier intervention with ablation likely to be more beneficial for recently diagnosed AF in HF patients