In-Sync:
Heart Failure and Atrial Fibrillation
Guideline-Based Management

M. McDonald, E. O’Meara
HF Update, 2019
Disclosures

• **Michael McDonald**
  – Honoraria: Novartis, Servier
  – Clinical Trials: None

• **Eileen O’Meara**
  – Honoraria: Amgen, Novartis, Pfizer-BMS, Servier
  – Clinical Trials: Amgen, Bayer, Luitpold, National Institutes of Health, Novartis, Merck
Objectives: Co-existing HF and AF

• Define the clinical significance and risk profile in this population

• Recognize rate, rhythm and device considerations in HF and AF

• Discuss the impact of recent clinical trial data relevant to these patients
Common Comorbidities Associated with HF

<table>
<thead>
<tr>
<th>Cardiovascular Comorbidities</th>
<th>Non-cardiovascular comorbidities</th>
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</thead>
<tbody>
<tr>
<td>• HTN 48%</td>
<td>• COPD 35%</td>
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<td>• A fib 44%</td>
<td>• Anemia 30%</td>
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<td>• MI 26%</td>
<td>• CKD 27%</td>
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<td>• Valve disease 24%</td>
<td>• Diabetes 25%</td>
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<td>• Stroke 24%</td>
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Patients typically have multiple comorbidities: Mean 4.7 comorbidities per pt
Does it matter?

- Meta analysis of 7 RCTs in HF
- 30,248 patients
  - 14% had AF
  - 86% in sinus rhythm
- Presence of AF in HF associated with increase risk of death
  - OR 1.40
  - Not influenced by LVEF

Mamas et al, Eur J Heart Fail 2009
Consider:

70 F, ischemic CMP
NYHA 3
EF 30% on optimal medical Rx
ICD in situ

What is her predicted survival with and without atrial fibrillation?

AF is associated with worse survival at all time points

Alba et al, J Cardiac Fail, 2018
Same Patient:
70 F, EF 30% on optimal medical Rx, ICD in situ, NYHA 3 sx, unknown duration of persistent AF
What is the optimal strategy in this scenario?

A. Target rate control

B. Rhythm control

C. Upgrade ICD to CRT-D
AF CHF Trial

1376 patients, persistent or paroxysmal AF
LVEF <35%, NYHA II-IV

Randomized to rate control (HR <80 at rest) vs rhythm control (cardioversion +/- antiarrhythmics drugs)

Mean f/u 37 months – higher % of patients in sinus rhythm at all time points in rhythm control group

No significant difference in death due to CV causes or any secondary outcomes
Rate control approach may be a reasonable first line strategy

• Rate control is not associated with worse outcomes for most patients

• Can assess clinical response

• Avoids procedures, hospitalization and AAD
What heart rate should be targeted?

- RACE II Trial
- 614 patients, permanent AF
- Randomized to one of two rate control strategies
- Followed 2-3 years; approx. 10bpm difference between groups at all time points
- No significant difference in cumulative incidence of CV death, HF, stroke/embolism, bleeding, serious arrhythmia

BUT... NOT a HF Trial
~10% patients had a history of HF

Van Gelder et al, NEJM 2010
Heart rate targets for AF in HF patients?

**A** All-cause mortality: Atrial fibrillation

- Post hoc patient-level analysis of combined AF-CHF and AFFIRM trials
- 5164 patients; 4848 AF and 2311 sinus rhythm
- Mean f/u 40.8 months
- 36% of patients had LVEF <40%

**B** All-cause mortality: Sinus rhythm

- Baseline HR predicts mortality in sinus rhythm patients but NOT in AF patients
- *AF with HR > 114 bpm was associated with more hospitalizations vs HR < 114 bpm*

Andrade et al, Heart Rhythm, 2016
Recommendations: Rate Control

We recommend in patients with HF and AF that the ventricular rate be controlled at rest and during exercise (Strong Recommendation; Moderate-Quality Evidence).

We recommend β-blockers for rate control particularly in those with HFrEF (Strong Recommendation; Moderate-Quality Evidence).

We recommend rate-limiting CCBs be considered for rate control in HFpEF (Weak Recommendation; Low-Quality Evidence).
Values and preferences

These recommendations are on the basis of an understanding that the management of patients with HF with AF should be individualized with respect to the need to identify precipitating factors, to assess the risk of therapy such as the development of bradycardia and pro-arrhythmia with antiarrhythmic agents, and the bleeding risk of systemic anticoagulation.

In patients with HF with AF, for whom a rate control strategy is used, the heart rate treatment target remains unclear. Retrospective analyses of large RCTs suggest that rates > 110-115 bpm might be associated with worse outcomes.
Back to the case

- Still symptomatic, HR 110-120 on max beta blocker
- Is there a role for digoxin?
Dig Trial:
6800 patients, history of HF, EF <45%
Digoxin (med. dose 0.25mg/d) vs placebo
NB: pre beta blocker, MRA era

Overall mortality

Death or HF Hospitalization

Digoxin: friend or foe?

- Dig Trial: post hoc analysis
- Mortality with digoxin relates to serum dig levels rather than sex
- Low dig levels (<1.0 ng/mL) associated with lower risk of HF hospitalization
In DIG, patients did NOT have Afib!
Digoxin: safety in AF?
Ongoing controversy

Digoxin Use and Subsequent Outcomes Among Patients in a Contemporary Atrial Fibrillation Cohort

Larry A. Allen, MD, MHS,* Gregg C. Fonarow, MD, Deluan Xia, MD, PhD,† Laine E. Thomas, PhD,‡ Lucas N. Marzec, MD,* Sean D. Pekonne, MD, MBA,‡ Bernard J. Gersh, MD, FACC, DP,PPAT, Alan S. Go, MD,‡ Elaine M. Hylek, MD, MPH,§ Peter R. Kowey, MD,§ Kenneth W. Mahaffey, MD,§ Paul Chang, MD,§ Eric D. Peterson, MD, MPH,† Jonathan P. Picciano, MD, MHS,§ for the ORBIT-AF Investigators
JACC 2015

Increased Mortality Associated With Digoxin in Contemporary Patients With Atrial Fibrillation
Findings From the TREAT-AF Study

Mintu P. Tushka, MD, MAS,* Pasquale Santangeli, MD,† Wolfgang C. Winkelmayr, MD, MPH, ScD,§ Xiangyan Xu, MS,* Aditya J. Ullal, BA,* Claire T. Than, MPH,* Susan Schmitt, PhD,* Tyson H. Holmes, PhD,§ Susan M. Frayne, MD, MPH,§ Claran S. Philbin, PhD,* Felix Yang, MD,§ Donald D. Hoang, BA,* F. Michael Ho, MD, PhD,†† Paul A. Heidenreich, MD, MS††
JACC 2014

Meta-Analysis of Digoxin Use and Risk of Mortality in Patients With Atrial Fibrillation

Ai-Jun Ouyang, PhD,* Yun-Ni Lv, PhD, Hai-Li Zhong, PhD, Xin-Hua Wen, PhD, Xiao-Hua Wei, Hong-Wei Peng, PhD, Jian Zhou, PhD, and Li-Li Liu, PhD
Am J Cardiol 2015

Digoxin and Risk of Death in Adults With Atrial Fibrillation
The ATRIA-CVRN Study

James V. Freeman, MD, MPH, MS; Kristi Reynolds, PhD; Margaret Fang, MD, MPH; Natalia Udaltsova, PhD; Anthony Steinle, MD, MPH; Niela K. Pomerantz, BA; Leila H. Borowski, MPH, Teresa N. Harrison, SM; Daniel E. Singer, MD; Alan S. Go, MD
Circ Arrhythm Electrophysiol 2015

Digoxin use in patients with atrial fibrillation and adverse cardiovascular outcomes: a retrospective analysis of the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF)

Jeffry R Wahren, Susanna R Steams, Yolga Lohkrygs, Jonathan L Haspelin, Gorden Brettbrand, Daniel E. Singer, Kenneth W Mahaffey, Graeme H Huxley, Scott D Berelowitz, Christopher G Issel, Keith A A Fox, Robert M Califf, Jonathan P Picciano, Marthin J Paul, for the ROCKET AF Steering Committee and Investigators
Lancet 2015
Digoxin for Rate Control of AF

HF Guidelines

We recommend the additional use of digoxin in patients with HFrEF and chronic AF and poor control of ventricular rate and/or persistent symptoms despite optimally tolerated β-blocker therapy, or when β-blockers cannot be used (Strong Recommendation; Low-Quality Evidence).

AF Guidelines

We suggest that digoxin can be considered as a therapeutic option to achieve rate control in patients with AF and symptoms caused by rapid ventricular rates whose response to β-blockers and/or calcium channel blockers is inadequate, or in whom such rate-controlling drugs are contraindicated or not tolerated (Conditional Recommendation, Moderate-Quality Evidence).

No specific recommendation for digoxin in HF population
Values and preferences. Digoxin is considered a second-line agent because although some published cohort, retrospective, and subgroup studies show no harm, there are others that suggest possible harm.

Practical tips.
- Dosing should be adjusted according to renal function and potential drug interactions
- Maximum trough digoxin serum concentration of 1.2 ng/mL would be prudent
- In the setting of reduced EF, digoxin use should be dictated by the recommendations of the CCS Heart Failure Clinical Guidelines
Back to the case

• HR 70-80bpm, persistent AF, now NYHA II-III symptoms
• One hospitalization in past 6 months
• Meds:
  – Bisoprolol 10mg q am, 5mg qpm
  – Sacubitril-Valsartan 100mg bid
  – Eplerenone 25mg/d
  – Digoxin 0.125mg/d
• Next Move?
• Rhythm control?
• CRT upgrade?
CRT: CCS Recommendations

CRT is recommended for patients in sinus rhythm with NYHA II-IV symptoms, and:

- LVEF < 35%
- QRS duration > 130ms due to LBBB

*Strong recommendation, good quality of evidence*

Weak recommendations for:

- Patients with atrial fibrillation who are otherwise suitable candidates for CRT
- Patients with QRS >150ms and non-LBBB who are otherwise suitable candidates for CRT
Case: CRT-ICD follow-up

• After reviewing options with the patient, a decision is made to proceed with CRT-D implant
  – Uncomplicated procedure

• 6 month follow up:
  – Feels about the same but struggling with intermittent fluid retention
  – No ICD shocks
  – Lead thresholds all fine
  – BiV paced 75%
What would you like to do next?

A) Increase digoxin 0.25mg/d
B) Ablate AV node
C) Cardioversion +/- add amiodarone
D) AF ablation
Opportunities for optimization
Targeting 100% BiV pacing in AF

ALTITUDE Study
>36,000 patient database

Greatest difference in survival observed with BiV pacing >98%

Worsening HF associated with BiV pacing <98%

Dichotomy seen for both sinus rhythm and AF patients
Systematic Review: Effects of AV nodal ablation on permanent AF patients with CRT

Meta-analysis of observational studies

- >1200 patients with permanent (mostly) AF and CRT
- Comparison: AVN ablation versus no AVN ablation strategy
- BiV pacing: 100% AVN ablation group 82-95% no-AVN ablation group
- Signal toward reduced all-cause (A) and cardiovascular (B) mortality

Yin et al, Clin Cardiol 2014
Back to the case

- Continues to have NYHA III symptoms; low output and congestive features

- Persistent AF
  - Avg. HR 70-80 bpm
  - Cardioverted x 2, unsuccessful
  - BiV pacing 80%

- Not happy with his quality of life

- Referred for AV node ablation...
Another Case: 59 F

- Presented with acute pulmonary edema and atrial fibrillation
- LVEF 35-40%, normal valves
- Normal coronaries
- Started on HF medical therapy, improved but still NYHA II-III sx
59 F

- Outpatient monitoring
  - Rhythm alternated between sinus and AF
- Meds
  - Perindopril, metoprolol, spironolatone
  - Started amiodarone
- Initially long periods of sinus rhythm (months)
  - Improved LVEF (>50%)
- After 2 years, increasing frequency of paroxysmal/persistent AF, worsened HF symptoms and drop in LVEF (~40%)
- Wished to pursue rhythm control
Rate vs Rhythm Control in AF

Algorithm for Rate vs Rhythm Control for Patients With Symptomatic AF

**SYMPTOMATIC AF**

- ATTEMPT RATE CONTROL:
  - β-blocker
  - Calcium channel blocker

**SYMPTOMS RESOLVE**

- YES
  - CONTINUE RATE CONTROL

- NO
  - MODIFY RATE CONTROL
  - CONSIDER RHYTHM CONTROL

**Paroxysmal AF**

- Low burden recurrence
  - Pill in pocket antiarrhythmic therapy
- High burden recurrence
  - Maintenance anti-arrhythmic therapy
  - Catheter ablation

**Persistent AF**

- Consider cardioversion
  - Symptoms improve, but AF recurs
  - Symptoms improve, and patient maintains sinus rhythm
  - Symptoms do not change in sinus rhythm and AF recurs

Special circumstances in which to consider early rhythm control:

- Highly symptomatic
- Multiple recurrences
- Extreme impairment in QOL
- Arrhythmia-induced cardiomyopathy

Canadian Cardiovascular Society
Leadership, Knowledge, Community.
Recommendations: Rhythm Control

We recommend the use of antiarrhythmic therapy to achieve and maintain sinus rhythm; if rhythm control is indicated, it should be restricted to amiodarone (Strong Recommendation; Moderate-Quality Evidence).

We recommend that restoration and maintenance of sinus rhythm in chronic HF not be performed routinely, but individualized on the basis of patient characteristics and clinical status (Strong Recommendation; High-Quality Evidence).
AF Ablation: Contemporary Evidence in HF

- Multicentre, open label RCT
- 363 patients with paroxysmal/persistent AF
- LVEF <35%, NYHA II-IV, ICD in situ
- Failed antiarrhythmic drugs
- Randomized to catheter ablation vs medical management (rate or rhythm control)
- Primary endpoint: death or HF hospitalization

Marrouche et al, N Engl J Med 2018
Catheter ablation improved primary endpoint, LVEF, HF symptoms

3013 patients screened
Mean f/u 38 months
84% of ablation group received an ablation (1.3 +/- 0.5 procedures per pt)
10% of medical therapy group crossed over to receive ablation
50% of patients in ablation group had recurrence of AF
We suggest catheter ablation of AF be considered as a therapeutic strategy to achieve and maintain sinus rhythm if rhythm control is indicated and antiarrhythmic therapy has failed or the patient is unable to tolerate antiarrhythmic therapy (Weak Recommendation; Low-Quality Evidence).
Atrial fibrillation ablation in practice: assessing CABANA generalizability

Peter A. Noseworthy, Bernard J. Gersh, David M. Kent, Jonathan P. Piccini, Douglas L. Packer, Nilay D. Shah, and Xiaoxi Yao

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Aims

The Catheter Ablation vs. Antiarrhythmic Drug Therapy for Atrial Fibrillation (CABANA) trial aimed to assess the impact of ablation on morbidity and mortality. This observational study was conducted in parallel to CABANA to assess trial generalizability.
CABANA Trial and Generalizability

**Table 2**: Outcomes in overall propensity score-weighted patients (N = 183,760)

<table>
<thead>
<tr>
<th>Drug treated (N = 171,728)</th>
<th>Ablated (N = 120,032)</th>
<th>Absolute reduction in event rate (95% CI)</th>
<th>Hazard ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of events</td>
<td>Person years</td>
<td>Event rate</td>
<td>Number of events</td>
<td>Person years</td>
</tr>
<tr>
<td>Composite</td>
<td>848</td>
<td>13,972</td>
<td>6.07</td>
<td>672</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>520</td>
<td>14,522</td>
<td>3.58</td>
<td>369</td>
</tr>
<tr>
<td>Ischaemic stroke</td>
<td>135</td>
<td>14,347</td>
<td>0.94</td>
<td>83</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>286</td>
<td>14,133</td>
<td>2.02</td>
<td>310</td>
</tr>
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**Take home figure**: Hazard ratio for primary outcome stratified by potential trial eligibility in the overall population (N = 183,760).
Back to our case....

• Patient amenable to catheter ablation

• Underwent uncomplicated PVI
  – 2 procedures over 18 months

• Sinus rhythm documented in follow up at all time points after 2\textsuperscript{nd} ablation (2 year f/u)

• Rare palpitations, NYHA 1

• LVEF 55%
The consideration of patients with structural heart disease as an appropriate ablation candidate does represent a philosophical shift in practice because these patients were previously discouraged from ablation because of concerns regarding potential inefficacy and harm.
Finally, don’t forget the basics

We suggest that non-vitamin K antagonist oral anticoagulants should be the agent of choice for stroke prophylaxis in patients with HF and nonvalvular AF, and that the treatment dose be guided by patient-specific characteristics including age, weight, and renal function (Weak Recommendation; Moderate-Quality Evidence).

We suggest the application of evidence-based therapies for HFrEF, per CCS HF guidelines, for primary prevention of AF (Weak Recommendation; Moderate-Quality Evidence).
Thank you!