Atrial Fibrillation and Heart Failure: A Cause or a Consequence?

Nancy M. Albert PhD, CCNS, CHFN, CCRN, NE-BC, FAHA, FCCM, FAAN
Associate Chief Nursing Officer-Research and Innovation and Clinical Nurse Specialist - Kaufman Center for Heart Failure
Disclosures

- Title: Atrial Fibrillation and Heart Failure: A Cause or a Consequence?
- Author: Dr. Nancy M. Albert
- Disclosures: None related to this presentation
  - Consultant to:
    - Novartis
Objectives

- Describe the factors that precipitate:
  - AF in HF
  - HF in AF
- Discuss the effects of coexisting AF and HF
- State a global management plan for HF-rEF and AF
Major Risk Factors for AF in the Atherosclerosis Risk in Communities Study

Prevalence of Atrial Fibrillation

Prevalence of Diagnosed AF by Age and Sex

Projected Number of Adults with AF in the US, 1995-2030

AF Cost Estimates- Inpatient & Outpatient Encounter Dx.

Background on Heart Failure

<table>
<thead>
<tr>
<th>Year</th>
<th>Prevalence, Age ≥ 20 yrs.</th>
<th>Incidence, Age ≥ 55 yrs.</th>
<th>Mortality/Any Mention</th>
<th>Hospital Discharges, 2010, All ages</th>
<th>Cost, 2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011-2014</td>
<td>6,500,000 (2.5%)</td>
<td>960,000 / Yr.</td>
<td>68,626/308,976</td>
<td>1,023,000</td>
<td>$30.7 billion</td>
</tr>
</tbody>
</table>

Projected costs of HF in US

Cost: ~$244 for every US adult

Total $, Billions

Atrial Fibrillation & HF

• 2 epidemics of the century
  - Close and complex relationship
    • Both are age-related
    • Frequently in the context of multiple comorbid conditions
• AF and HF can directly and independently lead to the development of the other
AF-HF Complex

Aging
Hypertension
Metabolic Syndrome
Diabetes
Obesity
Valve Dis.
Cardio-
myopathy
Coronary Dis.
Thyroid Dis.
Sleep Apnea
Alcohol
Genetics
Pulmonary Dis.
Inflammation
Smoking

Luong C, et al.  
*Curr Heart Fail Rep.*  
Multi-morbidity

- 1430 patients with AF, Olmsted Ct, MN
- 19 comorbidities studied
  - Largest attributable risk of AF were:
    - Hypertension (25.4%)
    - Coronary artery disease (17.7%)
    - Heart failure (13.3%)
  - Along with obesity and smoking, the 5 morbidities explained 51.4% of AF

? ↓ in prevalence with CV preventive measures

Atrial Fibrillation Leads to HF

- Tachycardia induced cardiomyopathy
- Hemodynamic changes
- Atrial enlargement / stretch
- L type Ca++ channel down-regulation
- Electrical-contractile remodeling
- Neuroendocrine stimulation
- Atrial-ventricular fibrosis
- Atrial-ventricular remodeling
- Pro-inflammatory state

LV remodeling leads to more LV remodeling

HF “begets” HF

Silent Atrial Fibrillation

Clinical Consequences

- Cryptogenic Stroke
- Ischemic Stroke
- Heart Failure
- Early mortality
- Cognitive Decline
- Dementia

Clinical Challenges

- Detection of silent AF
- Quantification of AF burden
- Prevention of the progression to the permanent form of AF
- Prevention of thromboembolic phenomena
- Prevention of cardiomyopathy

Dilaveris PE, Kennedy HL. Clin Cardiol 2017; Mar 8 ePub ahead of print
Heart Failure Leads to AF

LV systolic and diastolic dysfunction…

• Increased LV filling pressures
• Atrial enlargement/stretch
• Ventricular remodeling
• Atrial-ventricular fibrosis
• Neuroendocrine activation
• Sympathetic activation
• Apoptosis, altered gene expression
• Oxidative stress
• Calcium cycling
• Electrical remodeling

AF “begets” AF

Hypothesis for AF in HF

- In HF, ↑ end-diastolic pressure is transmitted through the intercommunicated system
  - LV-LA-Pulmonary Veins-Alveolar Capillaries
  - Causing ↑ PAWP and potential pulmonary edema
- End-diastolic pressure is the sum of:
  - LV diastolic pressure + LA systolic pressure
- Stopping LA mechanical systole can ↓ pressure in the system in HF

Hypothesis for AF in HF

• AF stops mechanical systole of the LA and \( \downarrow \) intercommunicating pressure and PAWP
• It is possible that AF is a mechanism for protection from \( \uparrow \) LVEDP and PAWP, and prevents the danger of pulmonary edema
• Mechanical systole in RA is also terminated, leads to \( \downarrow \) RVEDP
  - At the end of diastole when the TV is open, pressure of systemic venous inflow into the heart is decreased, decreasing preload

Shared and Synergistic Mechanisms of AF & HF

Loss of atrial systole
Decreased diastolic filling interval
Decreased cardiac output
Increased end-diastolic pressure
RAAS/neurohormonal activation

Tachycardia
Irregular conduction

Cycle of interdependence between HF and AF

Left atrial stretch
Increased atrial pressure
Increased atrial size
Atrial fibrosis

Increased focal triggers
Conduction slowing
Shortened atrial effective refractory period
Increased action potential duration heterogeneity

Incidence of Events 5 Years After Diagnosis of Atrial Fib.

N=186,461

Events in 5 Years after Diagnosis of Atrial Fibrillation

## In-Hospital Worsening HF
N=63,727

### Patient Comorbidities; n (%)

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>Worsening HF</th>
<th>Complicated Hosp.</th>
<th>Uncomp. Presentation</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>4245 (60.4)</td>
<td>7997 (52.1)</td>
<td>22,165 (53.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>2380 (35.3)</td>
<td>5117 (33.3)</td>
<td>14,957 (36.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>3036 (43.2)</td>
<td>5332 (34.7)</td>
<td>9415 (22.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>COPD or asthma</td>
<td>2210 (31.4)</td>
<td>4606 (30.0)</td>
<td>12,358 (29.9)</td>
<td>0.03</td>
</tr>
<tr>
<td>Diabetes</td>
<td>3223 (45.8)</td>
<td>6695 (43.6)</td>
<td>15,921 (38.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>2712 (38.6)</td>
<td>5969 (38.9)</td>
<td>14,031 (33.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>5233 (74.4)</td>
<td>11,468 (74.7)</td>
<td>30,343 (73.4)</td>
<td>0.005</td>
</tr>
<tr>
<td>Peripheral vascular dis.</td>
<td>1645 (23.4)</td>
<td>3153 (20.5)</td>
<td>7304 (17.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prior MI</td>
<td>2381 (33.9)</td>
<td>5459 (35.5)</td>
<td>11,765 (28.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoker, former</td>
<td>2717 (38.6)</td>
<td>5713 (37.3)</td>
<td>14,459 (35.0)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
AF in Decompensated HF

- Brazilian study
- AF prevalence, 40% in 659 consecutive cases
  - Permanent type AF, 73.5%
- In multivariate model, AF was associated with:
  - Advanced age, $p<0.0001$
  - Non-ischemic etiology, $p=0.02$
  - RV dysfunction, $p=0.03$
  - Lower systolic BP, $p=0.02$
  - Higher ejection fraction, $p<0.0001$
  - Enlarged left atrium, $p<0.0001$

Mendes, FD et al. *Arq Bras Cardiol.* 2014;Aug ePub.
AF in Patients with HF and ICD

- Single center study of ICM patients who received ICD for primary prevention
- 197 pts; 85.8% male, median age, 66.8 years
- Median FU, 2.8 years, 44.2% developed AF
- Factors associated with AF development:

<table>
<thead>
<tr>
<th>Univariate; $p&lt;0.05$</th>
<th>Multivariable; $p&lt;0.05$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>--</td>
</tr>
<tr>
<td>NYHA FC</td>
<td>--</td>
</tr>
<tr>
<td>Renal impairment (eGFR &lt; 60 ml/min/1.73 m2)</td>
<td>Renal impairment: HR: 2.04 (CI: 1.10-3.79)</td>
</tr>
</tbody>
</table>

Campbell, NG et al. *Int J Cardiol.* 2014;175:328-332.
Events in 5 Years after Diagnosis of Atrial Fibrillation Based on Setting Where Diagnosed

N=74,364

N=112,097

For all-cause mortality:
- 1.17 (95% CI, 1.11 – 1.23)
  • Moderate heterogeneity between studies
    ($I^2 = 44.5\%, \ P = 0.017$)

For cardiovascular mortality:
- 1.15 (95% CI, 0.98 – 1.34, $P = 0.08$)
  • Non-sign. heterogeneity between studies

Prognostic Significance of Atrial Fibrillation in HFP EF & HFr EF

Prognostic Significance of Atrial Fibrillation and Heart Failure

Cardiovascular Health Study – 5,673 community dwelling adults ≥ 65 years; followed for 13 years

- 116 patients had AF
- 219 patients had HF
- 39 patients had both AF and HF
- 5,263 had neither AF or HF

Pt characteristics:
- Mean age: 73 ± 6 years; 58% women
- 15% African American

Prognostic Significance of Atrial Fibrillation and Heart Failure

Cardiovascular Health Study – 5,673 community dwelling adults ≥ 65 years; followed for 13 years

- All-cause mortality occurred in:
  - 43% of patients with neither AF or HF
  - 66% of patients with AF only
  - 74% of patients with HF only
  - 85% of patients with both AF and HF

Prognostic Significance of Atrial Fibrillation and Heart Failure

Cardiovascular Health Study - All-Cause Mortality

Both HF and AF
HR=3.04 (95% CI, 2.15–4.29)

HF without AF
HR=2.31 (95% CI, 1.97–2.71)

AF without HF
HR=1.36 (95% CI, 1.08–1.72)

Neither (Reference)

Follow-up in years

All-cause mortality

Prognostic Significance of Atrial Fibrillation and Heart Failure

Cardiovascular Health Study – 5,673 community dwelling adults ≥ 65 years; followed for 13 years

• Adjusted HR (95% CIs) for CV mortality:
  - AF only vs. neither, 1.85 (1.35 - 2.54), *p*<0.001
  - HF only vs. neither, 3.20 (2.58 - 3.98), *p*<0.001
  - AF & HF vs. neither, 5.21 (3.43 - 7.90), *p*<0.001

• Adjusted HR (95% CIs) for non-CV mortality:
  - HF only vs neither: 1.72 (1.35 - 2.18), *p*<0.001

Prognostic Significance of Atrial Fibrillation and Heart Failure

Cardiovascular Health Study – 5,673 community dwelling adults ≥ 65 years; followed for 13 years

• Adjusted HR (95% CIs) for HF only vs. AF only
  - All-cause mortality: 1.69 (1.29 to 2.23)
  - CV mortality: 1.73 (1.20 to 2.51)
  - Non-CV mortality: 1.64 (1.09 to 2.46)

• Compared with HF alone, those with both conditions had greater CV but not all-cause mortality

## Atrial Fibrillation in Heart Failure - Effects

<table>
<thead>
<tr>
<th>Causes of Death in Heart Failure, by Heart Rhythm</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NSR; N=2,237</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>126 (6%)</td>
</tr>
<tr>
<td>Sudden death</td>
<td>927 (41%)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>539 (24%)</td>
</tr>
<tr>
<td>Cardiac (not heart failure)</td>
<td>59 (3%)</td>
</tr>
<tr>
<td>Stroke</td>
<td>43 (2%)</td>
</tr>
<tr>
<td>Vascular (not stroke)</td>
<td>99 (4%)</td>
</tr>
<tr>
<td>Non-cardiovascular</td>
<td>180 (8%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>264 (12%)</td>
</tr>
</tbody>
</table>

Priorities in Management: AF + HFrEF

CAN-TREAT

Initial Management Algorithm

For NEWLY diagnosed HFrEF and AF

Atrial Fibrillation in Heart Failure – Effects of Beta Blockers

Atrial Fibrillation in Heart Failure – *Effects of Beta Blockers*

**CARDIOVASCULAR HOSPITAL ADMISSION**
Normal Sinus Rhythm | Atrial Fibrillation

Atrial Fibrillation in Heart Failure – **Effects of Beta Blockers**

<table>
<thead>
<tr>
<th>All Cause Mortality in Patients with Atrial Fib.</th>
<th>HR (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDC\textsuperscript{25}</td>
<td>1.00 (0.34–2.95)</td>
<td>2.3%</td>
</tr>
<tr>
<td>CIBIS \textsuperscript{12}\textsuperscript{2}</td>
<td>1.14 (0.46–2.83)</td>
<td>3.2%</td>
</tr>
<tr>
<td>US-HF\textsuperscript{28}</td>
<td>1.14 (0.65–2.03)</td>
<td>1.9%</td>
</tr>
<tr>
<td>ANZ\textsuperscript{18}</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Conclusion:** Do not expect prognostic benefit from b-blockers in HFrEF with concomitant AF

- Researchers are exploring whether the variance in efficacy was due to heart rate, LVEF, or other fundamental differences in how AF patients respond to b-blockers

## Rate Control of AF in HFrEF

<table>
<thead>
<tr>
<th>Guidelines</th>
<th>Agent</th>
<th>Safety</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommended</td>
<td>$\beta$-Blockers</td>
<td>Individual patient data sub-group meta-analysis of RCTs suggests no safety concerns.</td>
<td>Individual patient data sub-group meta-analysis of RCTs shows no impact on mortality or hospitalization in concomitant HFrEF and AF.</td>
</tr>
<tr>
<td>Recommended as second line</td>
<td>Digoxin</td>
<td>Systematic review suggests no increase in mortality in concomitant HF and AF; higher mortality in AF patients in observational studies is likely due to residual confounding.</td>
<td>No RCTs vs. placebo in AF patients, combined therapy with $\beta$-blockers improves LVEF.</td>
</tr>
<tr>
<td>Avoid/use caution</td>
<td>Non-dihydropyridine calcium channel blockers</td>
<td>Limited sub-group data in post-MI patients only; suggestive of increased death, re-infarction, and HF.</td>
<td>None demonstrated.</td>
</tr>
</tbody>
</table>
CRT in Advanced HFrEF and Atrial Fibrillation

NoAF / AFL group (n = 887):
- Compared to optimal pharma. therapy (OPT), CRT + OPT groups had ↓ in
  - Death or hospitalization: HR 0.73, \( p = 0.002 \)
  - Death or HF hospitalization: HR 0.53, \( p < 0.001 \)

Intermittent AF / AFL group (n = 293):
- CRT did not improve outcomes vs. OPT
  - Death or hospitalization: HR 1.16, \( p = 0.38 \)
  - Death or HF hospitalization: HR 0.97, \( p = 0.88 \)

Catheter Ablation vs. Medical Treatment of AF in HF

- In persistent AF, symptomatic HF and LVEF < 50%, randomized to:
  - Medical treatment
  - Catheter ablation
- Outcome: LV EF% at 6 months
  - Baseline EF
    - Ablation group: 32 ± 8% (n=26)
    - Medical group: 34 ± 12% (n=24)

Freedom From Arrhythmia

![Graph showing survival free from atrial fibrillation (AF) or atrial tachycardia (AT) over time.](image)

### Survival Characteristics

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Ablation</th>
<th>Medical Tx</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 months</td>
<td>19/26 (73%)</td>
<td>7/26 (27%)</td>
<td>0.015</td>
</tr>
<tr>
<td>6 months</td>
<td>21/26 (81%)</td>
<td>5/26 (19%)</td>
<td></td>
</tr>
</tbody>
</table>

### LVEF (%)

<table>
<thead>
<tr>
<th>6-Month</th>
<th>Ablation</th>
<th>Medical Tx</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF%</td>
<td>40 ± 12%</td>
<td>31 ± 13%</td>
<td>0.015</td>
</tr>
</tbody>
</table>

---

Hx AF in HFpEF: Risk of Stroke

Sub-study; Irbesartan in HF w Preserved EF Trial:

• Hx AF at baseline, 1209 (29.7%)
  - 557 (13.5%) had Hx of AF alone
  - 670 (16.2%) had Hx AF and AF on ECG

• No differences in risk of stroke between groups with Hx AF or Hx AF and AF on ECG

Sub-study; Irbesartan in HF w Preserved EF Trial:

- During 53 month (median) follow-up
  - Fatal or nonfatal stroke occurred in:
    - 6.5% (79/1209) pts with Hx AF
    - 3.9% (114/2901) with no AF
  - Hazard ratio of stroke if Hx AF vs no Hx of AF
    - HR: 2.2; 95% CI, 1.6-3.2; \( P<0.0001 \)

AF and SCD: Relevance of HF

- Case-control study;
  - Cases - SCD; Controls - age and sex matched patients with CAD
- Assessed association between AF and SCD
- Cases - more likely to have:
  - History of AF; $p < 0.0001$
  - Myocardial infarction, $p = 0.007$
  - HF, $p < 0.0001$
  - Stroke, $p < 0.0001$
  - Diabetes, $p < 0.0001$

AF and SCD: Relevance of HF

- In multivariate analysis without considering HF
  - AF was a significant predictor of SCD
    - OR: 1.6; 95% CI: 1.2 to 2.0; $p = 0.002$
- In multivariate analysis that included CHF
  - AF-SCD association was not significant
    - OR: 1.1; 95% CI: 0.8 to 1.5; $p = 0.45$
  - HF was a predictor of SCD
    - OR: 3.1; 95% CI: 2.4 to 4.1; $p < 0.0001$

Non-valvular AF, NOACs & Stroke/SE

NOACs, Non-Vitamin K Antagonist Oral Anticoagulants; SE, systemic embolism

Non-valvular AF, NOACs & Major Bleeding

Is Heart Rate Important in Chronic HF and AF?

2,039 outpatients with chronic HF-rEF (≤50%)

- Baseline, 488 (24%) AF -- 1 year, 184 (22%) AF
- Median survival:
  - AF was 6.1 years (IQR, 5.3-6.9 years)
  - NSR was 7.3 years (IQR, 6.5-8.1 years)
  - After covariate adjustment, no difference in survival
- No association between HR (in 10 bpm increments) and survival in patients in AF
- In NSR, higher HR had worse survival

New Onset AF Predicts HF Progression

BAF, Baseline AF
NAF, New-onset AF

New Onset AF pts:
• ~4.5-fold ↑ in all-cause or HF hospitalization days/pt
  - both \( P < .0001 \)

Atrial Fibrillation in Heart Failure - Effects

- 187 HF patients completed neuropsychological testing & trans-cranial Doppler ultrasonography
  - Cerebral blood flow velocity (CBF-V) of the middle cerebral artery (cerebral perfusion)
- Results: 32.1% of patients w HF had AF
- If HF & AF - worse: Effects remained controlling for HF severity, demographic and medical factors
  - Global cognition
  - Memory
  - CBF-V

Conclusions

• In AF and HF
  - AF begets AF … and may beget HF
  - HF begets HF; hypothesis: HF begets AF
  - Patients had higher mortality risk
  - Beta blockers not effective in reducing mortality
  - Patients had higher stroke risk
  - HF increased risk of SCD
  - Heart rate was not a factor in survival
  - AF in HF may worsen cognition
Conclusions

- In AF and HF
  - New onset AF worsened HF
    - Higher hospitalization and mortality
  - Patients with AF may not be on GDMT
  - Cardiac resynchronization is ineffective
  - Catheter ablation effective in improving EF% at 6months

AHA Get With The Guidelines – AF Will help answer questions & enhance GDMTs