Guideline-Based Management of Heart Failure and Arrhythmic Complications

Jo E. Rodgers, Pharm.D., BCPS, FCCP, FNAP, FHFS, FAHA
Clinical Associate Professor, UNC Eshelman School of Pharmacy

James E. Tisdale, Pharm.D., BCPS, FCCP, FAPhA, FNAP, FAHA
Professor, Purdue University College of Pharmacy
Disclosure

Jo Rodgers

Novartis: Advisory Board, Research Support

All other planners, presenters, and reviewers of this session report no financial relationships relevant to this activity.
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Learning Objectives

• Given a description of a specific patient with heart failure and reduced ejection fraction (HFrEF), develop a medication regimen that reflects guideline-directed medical therapy based on current evidence-based guidelines.

• Given a description of a specific patient with heart failure and preserved ejection fraction (HFpEF), develop a medication regimen that reflects guideline-directed medical therapy based on current evidence-based guidelines.
Projected Prevalence and Cost

**Prevalence**

Projected number of patients with HF in the US will increase by 46% by 2030.

Projected number of patients diagnosed with HF in the US will rise to 8 million in 2030, one in every 33 people.

**Cost**

Projected doubling of costs in the US from $31 billion in 2013 to $70 billion in 2030.

80% of costs related to hospitalization.

*Circ Heart Fail. 2013;6:606-619*
### Classification of Recommendation and Level of Evidence

<table>
<thead>
<tr>
<th>CLASS I (STRONG)</th>
<th>CLASS IIa (MODERATE)</th>
<th>CLASS IIb (WEAK)</th>
<th>CLASS III: NO BENEFIT (MODERATE)</th>
<th>CLASS III: HARM (STRONG)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benefit &gt;&gt;&gt; Risk</td>
<td>Benefit &gt;&gt; Risk</td>
<td>Benefit &gt; Risk</td>
<td>Benefit = Risk</td>
<td>Risk &gt; Benefit</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>LEVEL A</th>
<th>Level B-R</th>
<th>Level B-NR</th>
<th>Level C-LD</th>
<th>Level C-EO</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-quality evidence (&gt;1 RCT)</td>
<td>Moderate-quality evidence (&gt;1 RCT)</td>
<td>Well-designed, non-randomized (&gt;1 study)</td>
<td>Studies with limitations of design or execution</td>
<td>Expert Opinion</td>
</tr>
</tbody>
</table>

### Biomarkers Indications for Use

<table>
<thead>
<tr>
<th>ACC/AHA Stage A/B HF</th>
<th>ACC/AHA Stage C/D HF</th>
<th>ACC/AHA Acute/Hospitalized HF</th>
</tr>
</thead>
<tbody>
<tr>
<td>At risk for HF</td>
<td>Ambulatory pts with new-onset dyspnea</td>
<td>NYHA class II-IV</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acute dyspnea to ED</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hospitalized for ADHF</td>
</tr>
</tbody>
</table>

#### Prevention
- BNP or NT-proBNP (COR IIa)

#### Diagnosis
- BNP or NT-proBNP (COR I)

#### Prognosis or added risk stratification
- BNP or NT-proBNP (COR I)
- BNP or NT-proBNP, and cardiac troponin (COR I)
- Other biomarkers of myocardial injury/fibrosis (COR IIb)
- Other biomarkers of myocardial injury/fibrosis (COR IIb)
- Predischarge BNP or NT-proBNP (COR IIa)
GUIDE-IT Trial

- Prospective, randomized, multicenter clinical trial
- High-risk heart failure patients with HFrEF (n=1,100)
- Biomarker-guided therapy (goal NT-proBNP level <1,000 pg/ml) vs usual care
- Composite endpoint: time to CV death or first HF hospitalization
- Trial ended 18 months early due to no benefit

**Therapy for Stage C HFrEF: Magnitude of Benefit Demonstrated in RCTs**

<table>
<thead>
<tr>
<th>GDMT</th>
<th>Relative Risk Reduction in Mortality</th>
<th>Number Needed to Treat for Mortality *</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitor or ARB</td>
<td>17%</td>
<td>26</td>
</tr>
<tr>
<td>Beta blocker</td>
<td>34%</td>
<td>9</td>
</tr>
<tr>
<td>Aldosterone antagonist</td>
<td>30%</td>
<td>6</td>
</tr>
<tr>
<td>Hydralazine/nitrate</td>
<td>43%</td>
<td>7</td>
</tr>
</tbody>
</table>

*Standardized to 36 months

Treatment of HFrEF Stage C and D

**Step 1**
HFrEF NYHA class I-IV (Stage C)

ACEi/ARB AND GDMT beta blocker; diuretics as needed (COR I)

**Step 2**

- NYHA class II-III HF
  - Adequate BP on ACEi or ARB; no C/I to ARB or sacubitril

- NYHA class II-IV; provided est. CrCl > 30 mL/min & K⁺<5.0 mEq/L

- NYHA class III-IV, in black patients

**Step 3**

- Discontinue ACEi or ARB; initiate ARNI (COR I)
  - Aldosterone antagonist (COR I)

- NYHA class II-III, NSR, heart rate ≥70 bpm on maximally tolerated dose BB

- Hydral-Nitrates (COR I)

**Step 4**

- Refractory NYHA class III-IV (Stage D)

**Step 5**

- Palliative care (COR I);
  - Transplant (COR I);
  - LVAD (COR IIa);
  - Investigational studies

Neprilysin Inhibitor/AT₁ Receptor Blocker

**Natriuretic Peptide System**
- pro-BNP
- BNP
- NT-pro BNP

**Renin Angiotensin System**
- Angiotensinogen (liver secretion)
- Angiotensin I
- Angiotensin II

**Neprilysin**
- **X**
- Inactive fragments
  - vasodilation
  - blood pressure
  - sympathetic tone/aldosterone
  - fibrosis/hypertrophy
  - natriuresis/diuresis

**LCZ696**

**AHU377**

**Valsartan**

**AT₁ receptor**
- **X**
- Vasoconstriction
- blood pressure
- sympathetic tone/aldosterone
- fibrosis/hypertrophy

*J Am Coll Card HF 2014; 2:663-70*
### Inclusion Criteria

- Age $\geq 18$ yrs
- NYHA Class II-IV
- LVEF $\leq 35\%$
- BNP $\geq 150$ pg/mL or NT-proBNP $\geq 600$ pg/mL
- Stable dose (4 wks) BB and ACEI/ARB equivalent to $\geq$ enalapril 10 mg/day

### Exclusion Criteria

- Symptomatic hypotension
- SBP $< 100$ mmHg
- eGFR $< 30$ mL/min/1.73 m$^2$
- Serum K$^+$ $> 5.2$ mmol/L
- Hx of angioedema
- Unacceptable side effects with ACEI/ARB

PARADIGM-HF Trial: Study Design

Randomization

Single-blind run-in period
- Enalapril
- LCZ696

Double-blind period
- LCZ696 200 mg BID
- Enalapril 10 mg BID

(1:1 randomization)

Dosages:
- Enalapril: 10 mg BID, 100 mg BID, 200 mg BID
- LCZ696: 200 mg BID

PARADIGM-HF: Primary Endpoint

Cardiovascular Death or Heart Failure Hospitalization (%)

Days After Randomization

Enalapril
(n=4212)

Sacubitril/Valsartan
(n=4187)

1117 (26.5%)
914 (21.8%)

HR = 0.80 (0.73-0.87)
P = 0.0000004
Number needed to treat = 21

**PARADIGM-HF: Adverse Events**

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Ernesto (n=4187)</th>
<th>Enalapril (n=4212)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic hypotension</td>
<td>588 (14%)</td>
<td>388 (9.2%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Serum potassium &gt; 6.0 mmol/l</td>
<td>181 (4.3%)</td>
<td>236 (5.6%)</td>
<td>0.007</td>
</tr>
<tr>
<td>Serum creatinine ≥ 2.5 mg/dl</td>
<td>139 (3.3%)</td>
<td>188 (4.5%)</td>
<td>0.007</td>
</tr>
<tr>
<td>Cough</td>
<td>474 (11.3%)</td>
<td>601 (14.2%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Angioedema</td>
<td>19 (0.4%)</td>
<td>10 (0.3%)</td>
<td>NS</td>
</tr>
</tbody>
</table>
Guideline Update: Sacubitril/Valsartan

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Guideline Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>B-R</td>
<td>ACEi or ARB or ARNi in conjunction with beta-blockers + MRA (where appropriate) is recommended for patients with chronic HFrEF to reduce morbidity and mortality.</td>
</tr>
<tr>
<td>I</td>
<td>B-R</td>
<td>In patients with chronic, symptomatic HFrEF NYHA class II or III who tolerate and ACE inhibitor or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality</td>
</tr>
</tbody>
</table>

## Sacubitril/Valsartan Dosing

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Initial Dose</th>
<th>Target Dose (Maximum)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most patients</td>
<td>49/51 mg twice daily</td>
<td>97/103 mg twice daily</td>
</tr>
</tbody>
</table>

- **Special populations**
  - Not on ACEI or ARB
  - On low doses of ACEI or ARB
  - eGFR <30 mL/min/1.73 m²
  - Moderate hepatic impairment

  |                               | 24/26 mg twice daily | 97/103 mg twice daily |

- **Do NOT** administer within 36 hours of ACEI administration

Entresto™ (Sacubitril/Valsartan) Package Insert 2017
Ivabradine: Selective $I_f$ Inhibitor

$I_f$ inhibition reduces diastolic depolarization slope, thereby lowering HR

*Br J Pharmacol.* 1994;112:37-42
SHIFT Trial: Entry Criteria/Study Design

6558 patients with NYHA II-IV HF, LVEF ≤ 35%, prior HF hospitalization (within 12 months) and HR ≥ 70 bpm in NSR

Ivabradine 7.5/5/2.5 mg bid
Target HR 50-60 bpm

Median study duration: 22.9 months; maximum: 41.7 months

Lancet 2010; 376:875-885
SHIFT Trial: Impact on Heart Rate

Mean dose (1 yr) 6.5 mg twice daily
70% on Ivabradine 7.5 mg bid

At study end, HR difference 8.1 bpm (95% CI 7.5–8.7).

Lancet 2010; 376:875-885
## SHIFT Trial: Endpoints

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Ivabradine (n=3241)</th>
<th>Placebo (n=3264)</th>
<th>HR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death or HF hospitalization</td>
<td>793 (24%)</td>
<td>937 (29%)</td>
<td>0.82 (0.75–0.90)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CV death</td>
<td>449 (14%)</td>
<td>491 (15%)</td>
<td>0.91 (0.80–1.03)</td>
<td>0.128</td>
</tr>
<tr>
<td>HF hospitalization</td>
<td>514 (16%)</td>
<td>672 (21%)</td>
<td>0.74 (0.66–0.83)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*Lancet* 2010; 376:875-885
# SHIFT Trial: Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>Ivabradine N=3232, n (%)</th>
<th>Placebo N=3260, n (%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All adverse events</td>
<td>2439 (75%)</td>
<td>2423 (74%)</td>
<td>0.303</td>
</tr>
<tr>
<td>Heart failure</td>
<td>804 (25%)</td>
<td>937 (29%)</td>
<td>0.0005</td>
</tr>
<tr>
<td>Symptomatic bradycardia</td>
<td>150 (5%)</td>
<td>32 (1%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Asymptomatic bradycardia</td>
<td>184 (6%)</td>
<td>48 (1%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>306 (9%)</td>
<td>251 (8%)</td>
<td>0.012</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>130 (4%)</td>
<td>178 (5%)</td>
<td>0.007</td>
</tr>
<tr>
<td>Phosphenes</td>
<td>89 (3%)</td>
<td>17 (1%)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*Lancet 2010; 376:875-885*
Guideline Update: Ivabradine

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIa</td>
<td>B-R</td>
<td>Ivabradine can be beneficial to reduce HF hospitalization for patients with symptomatic (NYHA class II-III), stable, chronic HFrEF (LVEF&lt;=35%) who are receiving GDMT, including a beta-blocker at maximally tolerated dose, and who are in sinus rhythm with a HR&gt;=70 bpm at rest</td>
</tr>
</tbody>
</table>

Ivabradine Dosing

Starting dose: 5 mg twice daily with meals
- At 2 weeks, adjust dose to achieve a resting HR 50-60 bpm
- Thereafter, adjust dose as needed based on resting HR and tolerability
- Max dose 7.5 mg twice daily
- If history of conduction defects, or other patients in whom bradycardia could lead to hemodynamic compromise, initiate at 2.5 mg twice daily
BC is a 63 year old Caucasian female with HF (LVEF 32%, NYHA class III) who presents for her routine clinic visit.

**Medications**: furosemide 40 mg twice daily, lisinopril 20 mg daily, metoprolol XL 150 mg daily, digoxin 0.125 mg MWF.

**PE/Vitals/Labs**: No signs/symptoms of volume overload, BP 122/76 mmHg, HR 62 bpm, RR 14, K⁺ 5.2 mmol/L, BUN 45 mg/dL, sCr 2.2 mg/dL, and SDC 0.7 ng/mL

How should BC’s HF regimen be optimized?
1. Add spironolactone 25 mg daily
2. Increase to metoprolol XL 200 mg daily
3. Add ivabradine
4. Change lisinopril to sacubitril/valsartan
## Therapy for Stage C HFrEF

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic and diastolic BP control</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Diuretics for relief of volume overload</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Coronary revascularization for patients with CAD</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>Management of atrial fibrillation</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>Use of beta-blockers, ACEIs, and ARBs for HTN</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>ARBs might be considered to reduce hospitalizations</td>
<td>IIb</td>
<td>B</td>
</tr>
<tr>
<td>Nutritional supplementation is not recommended</td>
<td>III: No Benefit</td>
<td>C</td>
</tr>
</tbody>
</table>

## Therapy for Stage C HFpEF

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
<th>Comment/Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIb</td>
<td>B-R</td>
<td>In appropriately selected* patients with HFpEF (elevated BNP or HF admission within 1 yr), ARAs might be considered to reduce hospitalizations.</td>
<td>NEW: Current recommendation reflects new RCT data.</td>
</tr>
<tr>
<td>III: No Benefit</td>
<td>B-R</td>
<td>Routine use of nitrates or phosphodiesterase-5 inhibitors to increase activity or QoL in patients with HFpEF is ineffective.</td>
<td>NEW: Current recommendation reflects new data from RCTs.</td>
</tr>
</tbody>
</table>

* eGFR > 30 mL/min, sCr < 2.5 mg/dL, K < 5 mEq/L

TOPCAT Trial

- Spironolactone vs placebo in HFpEF
- **Primary endpoint:** CV death, cardiac arrest, or HF hospitalization
  - HR 0.89 (95% CI, 0.77-1.04); p = 0.14

<table>
<thead>
<tr>
<th>Region (n)</th>
<th>Spironolactone</th>
<th>Placebo</th>
<th>HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Americas (1767)</td>
<td>242 (27.3%)</td>
<td>280 (31.8%)</td>
<td>0.82 (0.69-0.98)</td>
<td>0.026</td>
</tr>
<tr>
<td>Russia/Georgia (1678)</td>
<td>78 (9.3%)</td>
<td>71 (8.4%)</td>
<td>1.10 (0.79-1.51)</td>
<td>0.058</td>
</tr>
</tbody>
</table>

Regional differences: p < 0.001

_Circ_ 2015; 131:34-42
## Treating Hypertension in HFrEF and HFpEF

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
<th>Comment/Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C-EO (HFrEF)</td>
<td>Patients with HFrEF and HFpEF and HTN should be prescribed GDMT titrated to attain SBP &lt; 130 mm Hg.</td>
<td><strong>NEW</strong>: Recommendation has been adapted from recent clinical trial data but not specifically tested per se in a randomized trial of patients with HF.</td>
</tr>
<tr>
<td></td>
<td>C-LD (HFpEF)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**SPRINT Trial**

- > 50 YO, SBP 130-180 mm Hg and increased risk of CV events
- Intensive Trt: SBP < 120 mmHg vs Standard Trt: SBP < 140 mmHg
- **Primary Endpoint**: MI, other ACS, stroke, HF or death from CV causes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Intensive Trt (n=4678)</th>
<th>Standard Trt (n=4683)</th>
<th>HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome</td>
<td>243 (5.2%)</td>
<td>319 (6.8)</td>
<td>0.75 (0.64-0.89)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Heart failure</td>
<td>62 (1.3)</td>
<td>100 (2.1)</td>
<td>0.62 (0.45-0.84)</td>
<td>0.002</td>
</tr>
<tr>
<td>CV death</td>
<td>37 (0.8)</td>
<td>65 (1.4)</td>
<td>0.57 (0.38-0.85)</td>
<td>0.005</td>
</tr>
<tr>
<td>All-cause death</td>
<td>155 (3.3)</td>
<td>210 (4.5)</td>
<td>0.73 (0.6-0.9)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

RT is a 47 year old African American male with HFpEF (LVEF 55-60%) who presents for his routine clinic visit.

Medications: bumetanide 2 mg twice daily, lisinopril 20 mg daily, amlodipine 10 mg daily, HCTZ 25 mg daily, HYD 75 mg three times daily.

PE/Vitals/Labs: No signs/symptoms of volume overload, BP 167/89 mmHg, HR 72 bpm, RR 14, K⁺ 4.2 mmol/L, BUN 27 mg/dL, sCr 1.2 mg/dL

How should RT’s HF regimen be optimized?
1. Increase to lisinopril 40 mg daily
2. Increase to amlodipine 20 mg daily
3. Add ISMN 30 mg daily
4. Add spironolactone 25 mg daily
<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
<th>Comment/Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIb</td>
<td>B-R</td>
<td>In patients with NYHA class II-III HF and iron deficiency*, IV iron might be reasonable to improve functional status and QoL.</td>
<td><strong>NEW</strong>: New evidence consistent with therapeutic benefit.</td>
</tr>
</tbody>
</table>

*Ferritin < 100 ng/mL or 100 to 300 ng/mL if transferrin saturation is <20%
Key Takeaways

• Key Takeaway #1
  – Sacubitril-valsartan and ivabradine should be incorporated into GDMT for patients with HFrEF.

• Key Takeaway #2
  – Spironolactone may be considered to reduce hospitalizations in select patients with HFpEF.

• Key Takeaway #3
  – Patients with HFrEF and HFpEF and HTN should be prescribed GDMT titrated to attain SBP < 130 mm Hg.

• Key Takeaway #4
  – In patients with NYHA class II-III HF and iron deficiency, IV iron might be reasonable to improve functional status and QoL.
Guideline-Based Management of Heart Failure and Arrhythmic Complications

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James E. Tisdale, Pharm.D., BCPS, FCCP, FAPhA, FNAP, FAHA
Professor, Purdue University College of Pharmacy
Learning Objectives

• Given a description of a specific patient with heart failure and atrial fibrillation, develop a medication regimen that reflects guideline-directed medical therapy based on current evidence-based guidelines.

• Given a description of a specific patient with heart failure and ventricular tachycardia, develop a medication regimen that reflects guideline-directed medical therapy based on current evidence-based guidelines.
Epidemiology of Atrial Fibrillation in Heart Failure

• ~ 40% of patients with HF develop AF
• 51% of Medicare beneficiaries with AF also have HF
• 59% of Medicaid beneficiaries with AF also have HF

J Am Coll Cardiol 2014;64:e1-e76.
Epidemiology of Atrial Fibrillation in Heart Failure

<table>
<thead>
<tr>
<th>NYHA Functional Class</th>
<th>Prevalence of AF</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>4%</td>
</tr>
<tr>
<td>II-III</td>
<td>10-15%</td>
</tr>
<tr>
<td>III-IV</td>
<td>26-30%</td>
</tr>
<tr>
<td>IV</td>
<td>50%</td>
</tr>
</tbody>
</table>

Am J Cardiol 2003;91 (suppl):2D-8D.
Impact of Atrial Fibrillation on Heart Failure Mortality

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>2.7 (1.9-3.7) (Framingham)</td>
</tr>
<tr>
<td></td>
<td>1.3 (1.2-2.1) (Meta-analysis)</td>
</tr>
</tbody>
</table>

Circulation 2003;107:2920.
Mechanisms by Which Heart Failure Can Cause Atrial Fibrillation and Vice Versa

<table>
<thead>
<tr>
<th>How HF Can Cause AF</th>
<th>How AF can Cause HF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Promotes heterogeneity of atrial conduction by:</td>
<td>Reduces cardiac output by:</td>
</tr>
<tr>
<td>• Increasing atrial filling pressures</td>
<td>• Tachycardia-induced cardiomyopathy</td>
</tr>
<tr>
<td>• Neurohormonal activation</td>
<td>• Loss of AV synchrony</td>
</tr>
<tr>
<td>• Ion channel dysregulation (I_{Na}, I_{kr}, I_{ks}, I_{Ca,L})</td>
<td>• Absent atrial contraction</td>
</tr>
<tr>
<td>• Atrial fibrosis</td>
<td></td>
</tr>
<tr>
<td>Promotes atrial remodeling</td>
<td>Increases left ventricular end diastolic pressure</td>
</tr>
<tr>
<td>Increases pulmonary vein automaticity</td>
<td>Promotes mitral and tricuspid regurgitation</td>
</tr>
<tr>
<td></td>
<td>Neurohormonal activation</td>
</tr>
</tbody>
</table>

Goals of Therapy of Atrial Fibrillation in Patients with Heart Failure

- Prevention of stroke & systemic thromboembolism
- Ventricular rate control
- Conversion to sinus rhythm
- Maintenance of sinus rhythm
Goals of Therapy of Atrial Fibrillation in Patients with Heart Failure

- Prevention of stroke & systemic thromboembolism
- Ventricular rate control
- Conversion to sinus rhythm
- Maintenance of sinus rhythm
Prevention of Stroke and Thromboembolism in Patients with Atrial Fibrillation and Heart Failure

<table>
<thead>
<tr>
<th>Components of Score</th>
<th>CHA$_2$DS$_2$-VASc Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Age $&gt;$ 75 years</td>
<td>2</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td>History of stroke, TIA, or thromboembolism</td>
<td>2</td>
</tr>
<tr>
<td>Vascular disease (prior MI, PAD, or aortic plaque)</td>
<td>1</td>
</tr>
<tr>
<td>Age 65-74 years</td>
<td>1</td>
</tr>
<tr>
<td>Sex category (female sex)</td>
<td>1</td>
</tr>
<tr>
<td>Maximum score</td>
<td>9</td>
</tr>
</tbody>
</table>

J Am Coll Cardiol 2014;64:e1-e76.
Prevention of Stroke and Thromboembolism in Patients with Atrial Fibrillation and Heart Failure

Heart Failure as a Risk Factor for Stroke in Patients with AF

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>HF definition</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Am J Cardiol 1990;65:1112-6.</td>
<td>272</td>
<td>Cardiomyopathy</td>
<td>0.037</td>
</tr>
<tr>
<td>Ann Intern Med 1992;116:6-12.</td>
<td>568</td>
<td>LV dysfunction</td>
<td>0.03</td>
</tr>
<tr>
<td>Arch Intern Med 1994;154:1449-57.</td>
<td>1593</td>
<td>HF</td>
<td>NS</td>
</tr>
<tr>
<td>J Stroke Cerebrovasc Dis 1995;5:147-57.</td>
<td>854</td>
<td>LV fractional shortening &lt; 25%</td>
<td>0.2</td>
</tr>
<tr>
<td>JAMA 1998;279:1273-7.</td>
<td>892</td>
<td>HF</td>
<td>NS</td>
</tr>
<tr>
<td>Am J Cardiol 1998;82:119-21.</td>
<td>312</td>
<td>LVEF &lt; 50%</td>
<td>0.03</td>
</tr>
<tr>
<td>Arch Intern Med 1998;158:1316-20.</td>
<td>1066</td>
<td>LV dysfunction (moderate-severe)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Prevention of Stroke and Thromboembolism in Patients with Atrial Fibrillation and Heart Failure

Efficacy of Non-Vitamin K Anticoagulants in Patients with Heart Failure

Dabigatran vs Warfarin

p=0.39

Apixaban vs Warfarin

p=0.21

Rivoxaban better

p=0.62

Edoxaban vs Warfarin

p=0.97

Prevention of Stroke and Thromboembolism in Patients with Atrial Fibrillation and Heart Failure

<table>
<thead>
<tr>
<th>CHA$_2$DS$_2$-VASc Score</th>
<th>Recommended Strategy for Prevention of Stroke and Systemic Thromboembolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Antithrombotic therapy not recommended</td>
</tr>
<tr>
<td>1</td>
<td>No antithrombotic therapy, or Treatment with an oral anticoagulant or aspirin may be considered</td>
</tr>
<tr>
<td>≥ 2</td>
<td>Oral anticoagulation recommended. Options include: Warfarin (INR 2.0-3.0) Apixaban Dabigatran Rivaroxaban Edoxaban</td>
</tr>
</tbody>
</table>

J Am Coll Cardiol 2014;64:e1-e76.
Goals of Therapy of Atrial Fibrillation in Patients with Heart Failure

- Prevention of stroke & systemic thromboembolism
- Ventricular rate control
- Conversion to sinus rhythm
- Maintenance of sinus rhythm
# Ventricular Rate Control in Patients with Atrial Fibrillation and Heart Failure (HFrEF)

## Drug Therapy Recommendations

<table>
<thead>
<tr>
<th>Drug Therapy</th>
<th>HFrEF</th>
<th>HFpEF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-blockers</td>
<td>✓ *</td>
<td>✓</td>
</tr>
<tr>
<td>CCB (Diltiazem or verapamil)</td>
<td>X</td>
<td>✓</td>
</tr>
<tr>
<td>Digoxin</td>
<td>✓ †</td>
<td>X</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>✓ †</td>
<td>✓</td>
</tr>
<tr>
<td>Dronedarone</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

*Caution in ADHF
† First-line therapy for acute rate control in patients with ADHF, but not for long-term oral therapy

J Am Coll Cardiol 2014;64:e1-e76.
Ventricular Rate Control in Patients with Atrial fibrillation and Heart Failure

Dronedarone in High Risk Permanent Atrial Fibrillation (PALLAS)

Primary and Secondary Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Dronedarone (n=1619)</th>
<th>Placebo (n=1617)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke, MI, SE, CV death</td>
<td>HR 2.29 (95% CI 1.34-3.94, p=0.002)</td>
<td>HR 1.95 (95% CI 1.45-2.62, p=0.002)</td>
</tr>
<tr>
<td>Unplanned CV hospitalization or death</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Terminated prematurely; median follow-up 3.5 months

Ventricular Rate Control in Patients with Atrial Fibrillation and HFrEF

Acute Ventricular Rate Control

HFrEF

→

IV Digoxin
or

IV Amiodarone

→

IV Beta-blocker
Ventricular Rate Control in Patients with Atrial Fibrillation and HFpEF

Acute Ventricular Rate Control

HFpEF

↓

IV Beta-blocker

or

IV CCB (Diltiazem, verapamil)

↓

IV Amiodarone

J Am Coll Cardiol 2014;64:e1-e76.
Ventricular Rate Control in Patients with Atrial Fibrillation and HFrEF

Long Term Ventricular Rate Control

HFrEF

↓

Oral Beta-blocker

↓

Oral Beta-blocker plus Digoxin

↓

Oral Amiodarone

J Am Coll Cardiol 2014;64:e1-e76.
Long Term Ventricular Rate Control

HFpEF

→ Oral Beta-blocker

or

→ Oral CCB

→ Add Digoxin

→ Oral Amiodarone
### Recommended Heart Rate Targets

<table>
<thead>
<tr>
<th>Type of patient</th>
<th>Heart rate target</th>
<th>Class of recommendation</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>HFrEF or symptomatic HFpEF</td>
<td>Strict (&lt; 80 bpm)</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>Asymptomatic and preserved LV systolic function</td>
<td>Lenient (&lt; 100 bpm)</td>
<td>IIb</td>
<td>B</td>
</tr>
</tbody>
</table>

J Am Coll Cardiol 2014;64:e1-e76.
### Digoxin and Mortality in Patients with AF and HF

Meta-analysis of digoxin and mortality in AF and HF

- **n=16 studies of patients with AF**
- **n=111,978 digoxin users**
- **N=389,643 non-digoxin users**

<table>
<thead>
<tr>
<th></th>
<th>All patients HR (95% CI)</th>
<th>Patients with AF &amp; no HF HR (95% CI)</th>
<th>Patients with AF &amp; HF HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All-cause mortality</strong></td>
<td>1.27 (1.19-1.36)</td>
<td>1.47 (1.25-1.73)*</td>
<td>1.21 (1.07-1.36)*</td>
</tr>
<tr>
<td><strong>CV mortality</strong></td>
<td>1.21 (1.12-1.30)</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

*Interaction p = 0.06

Cardiol J 2016;23:333-343.
BC is a 63 year old Caucasian female with HF (LVEF 32%, NYHA class III) who presents to the Emergency Department complaining of dizziness and feeling heart her “fluttering.”

**Medications:** furosemide 40 mg twice daily, lisinopril 20 mg daily, metoprolol XL 150 mg daily, digoxin 0.125 mg MWF.

**PE/Vitals/Labs:** No signs/symptoms of volume overload, BP 112/72 mmHg, HR 132 bpm, RR 14, K⁺ 5.2 mmol/L, BUN 45 mg/dL, sCr 2.2 mg/dL, and SDC 0.7 ng/mL. ECG reveals atrial fibrillation.

How should BC’s ventricular rate be controlled?
1. IV amiodarone 300 mg over 1 hour, then 20 mg/hour infusion
2. IV digoxin 0.25 mg every 4 hours to max dose of 1.5 mg over 24 hours
3. IV diltiazem 0.25 mg/kg bolus over 2 min, then 10 mg/hour infusion
4. IV esmolol 50 mcg bolus then 50 mcg/kg/min infusion
Goals of Therapy of Atrial Fibrillation in Patients with Heart Failure

- Prevention of stroke & systemic thromboembolism
- Ventricular rate control
- Conversion to sinus rhythm
- Maintenance of sinus rhythm
Conversion to Sinus Rhythm in Patients with Atrial fibrillation and Heart Failure

Cardioversion is known to be safe (AF < 48 hours or negative TEE or therapeutically anticoagulated for ≥ 3 weeks)

Consider DCC

If DCC unfeasible, undesirable, or unsuccessful

Amiodarone
Dofetilide
Ibutilide*

*Avoid if LVEF < 30%
BC is a 63 year old Caucasian female with HF (LVEF 32%, NYHA class III) who presents to the Emergency Department complaining of dizziness and feeling heart her “fluttering.” She was admitted to hospital and now her ventricular rate is controlled.

**Medications:** furosemide 40 mg twice daily, lisinopril 20 mg daily, metoprolol XL 150 mg daily, digoxin 0.125 mg MWF.

**PE/Vitals/Labs:** No signs/symptoms of volume overload, BP 122/76 mmHg, HR 75 bpm, RR 14, K⁺ 5.2 mmol/L, BUN 45 mg/dL, sCr 2.2 mg/dL, and SDC 0.7 ng/mL. ECG reveals atrial fibrillation.

How should BC’s AF be terminated?
1. Immediate direct current cardioversion
2. IV ibutilide 1 mg over 10 minutes
3. Oral dofetilide 125 mcg twice daily
4. TEE then direct current cardioversion if no LA clot
Goals of Therapy of Atrial Fibrillation in Patients with Heart Failure

• Prevention of stroke & systemic thromboembolism
• Ventricular rate control
• Conversion to sinus rhythm
• Maintenance of sinus rhythm
Maintenance of Sinus Rhythm in Patients with Atrial Fibrillation and Heart Failure

Rhythm Control vs Rate Control in Patients with Heart Failure

- Total mortality
  - Rhythm control (n=682)
  - Rate control (n=694)
  - p=0.68

- CV death
  - Rhythm control (n=682)
  - Rate control (n=694)
  - p=0.53

## Maintenance of Sinus Rhythm in Patients with Atrial Fibrillation and Heart Failure

### Treatment Recommendations

<table>
<thead>
<tr>
<th>Drug Therapy</th>
<th>HFrEF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone</td>
<td>✓</td>
</tr>
<tr>
<td>Dofetilide</td>
<td>✓</td>
</tr>
<tr>
<td>Catheter ablation</td>
<td>✓</td>
</tr>
<tr>
<td>Dronedarone</td>
<td>x</td>
</tr>
<tr>
<td>Flecainide</td>
<td>x</td>
</tr>
<tr>
<td>Propafenone</td>
<td>x</td>
</tr>
<tr>
<td>Sotalol</td>
<td>x</td>
</tr>
</tbody>
</table>

J Am Coll Cardiol 2014;64:e1-e76.
Maintenance of Sinus Rhythm in Patients with Atrial Fibrillation and Heart Failure

Dronedarone in Severe Heart Failure (hospitalized with symptomatic LVEF < 35%)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Dronedarone (n=310)</th>
<th>Placebo (n=317)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary (death from any cause or hospitalization for worsening HF)</td>
<td>HR 1.38 (0.92-2.09, (p=0.12))</td>
<td>HR 2.13 (1.07-4.25, (p=0.03))</td>
</tr>
<tr>
<td>Death from any cause</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BC was discharged home on her heart failure meds and dabigatran 150 mg twice daily. Her AF recurred intermittently, and she was symptomatic despite treatment with her beta-blocker and digoxin.

**Medications:** furosemide 40 mg twice daily, lisinopril 20 mg daily, metoprolol XL 150 mg daily, digoxin 0.125 mg MWF.

**PE/Vitals/Labs:** No signs/symptoms of volume overload, BP 122/76 mmHg, HR 75 bpm, RR 14, K⁺ 5.2 mmol/L, BUN 45 mg/dL, sCr 2.2 mg/dL, and SDC 0.7 ng/mL. ECG reveals atrial fibrillation.

Which of the following is the optimal therapy for reducing the frequency of recurrence of BC’s AF episodes?

1. Amiodarone 400 mg orally daily for 2 weeks, then 200 mg once daily
2. Dronedarone 400 mg orally twice daily
3. Flecainide 150 mg orally every 12 hours
4. Sotalol 80 mg orally once daily
Prevention of Atrial Fibrillation in Patients with Heart Failure

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Class of recommendation</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>An ACE inhibitor or ARB is reasonable for primary prevention of new-onset AF in patients with HFrEF</td>
<td>IIa</td>
<td>B</td>
</tr>
</tbody>
</table>

J Am Coll Cardiol 2014;64:e1-e76.
## RAS Inhibition for Prevention of AF in Patients with HF

Meta-analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOLVD (n=374)</td>
<td>0.18 (0.09-0.37)</td>
</tr>
<tr>
<td>CHARM (n=6,379)</td>
<td>0.81 (0.66-1.00)</td>
</tr>
<tr>
<td>Val-HeFT (n=4,395)</td>
<td>0.63 (0.49-0.80)</td>
</tr>
<tr>
<td><strong>Total (n=11,148)</strong></td>
<td><strong>0.52 (0.31-0.87)</strong></td>
</tr>
</tbody>
</table>

Epidemiology of Ventricular Arrhythmias in Heart Failure

• ~20% of patients with HF die of sudden cardiac death annually
• Roughly half of HF deaths are due to arrhythmias
Acute Management of Hemodynamically Stable Ventricular Tachycardia in Heart Failure

- VT
  - HFrEF
    - IV amiodarone
  - HFP EF or normal LV function
    - IV procainamide
    - IV amiodarone or sotalol

Circulation 2010;122(suppl 3):S729-S767.
## ICD Recommendations for Secondary Prevention of SCD in HF

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survivors of cardiac arrest due to VF or hemodynamically unstable VT</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Spontaneous sustained VT, hemodynamically stable or unstable</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Syncope of undetermined origin with sustained VT or VF induced during EP study</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Nonsustained VT due to prior MI, LVEF $\leq$ 40% and inducible VF or sustained VT during EP study</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Unexplained syncope, significant LV dysfunction and nonischemic DCM</td>
<td>IIa</td>
<td>C</td>
</tr>
</tbody>
</table>

**Circulation** 2013; 127: e283-e352
## ICD Recommendations for Primary Prevention in Stage C HF

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary prevention of SCD to reduce total mortality in selected patients ≥ 40 days post-MI with LVEF ≤ 30% and NYHA class I symptoms on GDMT with expected meaningful survival &gt; 1 year</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Primary prevention of SCD to reduce total mortality in selected patients with nonischemic DCM or IHD ≥ 40 days post-MI with LVEF ≤ 35% and NYHA class II or III symptoms on GDMT with expected meaningful survival &gt; 1 year</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>An ICD is of uncertain benefit to prolong meaningful survival in patients with high risk of nonsudden death such as frequent hospitalizations, frailty or severe comorbidities</td>
<td>IIb</td>
<td>B</td>
</tr>
</tbody>
</table>

ICD vs Amiodarone for Primary Prevention of SCD in HF

Patients with NYHA class II or III HF & LVEF ≤ 35%

Amiodarone vs placebo: HR 1.06 (0.86-1.30, p=0.56)
ICD vs placebo: HR 0.77 (0.62-0.96, p=0.007)

Key Takeaways

• Key Takeaway #1
  o Atrial fibrillation is common in patients with heart failure and is associated with increased mortality

• Key Takeaway #2
  o Specific antiarrhythmic drugs should be avoided in patients with HFrEF due to negative inotropic activity, increased risk of drug-induced arrhythmias, and/or increased mortality:
    • CCBs (diltiazem, verapamil)
    • Dronedarone
    • Flecainide
    • Propafenone
    • Sotalol

• Key Takeaway #3
  o IV amiodarone is the preferred drug for hemodynamically stable VT in patients with HFrEF

• Key Takeaway #4
  o Many patients with heart failure require ICD implantation to reduce the risk of sudden cardiac death