Pharmacologic Pearls in Chronic Heart Failure

David Parra, Pharm.D., FCCP, BCPS
Clinical Pharmacy Specialist, Cardiology
West Palm Beach VAMC

Clinical Associate Professor
Department of Experimental and Clinical Pharmacology
College of Pharmacy, University of Minnesota

Presenter disclosure information

Financial Disclosure: I do not have a financial relationships with any commercial entity which may represent, in perception or reality, a conflict of interest in the context of this presentation

The views expressed in this presentation reflect those of the author, and not necessarily those of the Department of Veterans Affairs
Objectives

1. Outline the pharmacologic approach to chronic heart failure with reduced ejection fraction (HFrEF)
2. Discuss strategies for selection and optimization of specific pharmacologic therapy in patients with HFrEF
3. Review approaches to pharmacologic therapy of heart failure with preserved ejection fraction (HFpEF)

Background Facts

- **Incidence**
  - 825,000 new cases diagnosed yearly
  - 75% of cases have antecedent hypertension
- **Prevalence**
  - 5,100,000 people in the United States (2010)
  - Increases from < 1% in those < 40 years of age to > 11% in those 80 years of age or more
- **Economic burden**
  - > 1 million discharges per year 2000-2010
  - > 1.8 million office visits (primary diagnosis) in 2010
  - Total costs in 2012 of 30.7 million (68% direct medical)

Lifetime Risk

<table>
<thead>
<tr>
<th>Diseases</th>
<th>Remaining Lifetime Risk at Age 40 y</th>
<th>Remaining Lifetime Risk at Age 70 y</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
</tr>
<tr>
<td>Acute MI</td>
<td>2 in 3†</td>
<td>1 in 2†</td>
</tr>
<tr>
<td>CHD†</td>
<td>1 in 2</td>
<td>1 in 3</td>
</tr>
<tr>
<td>AF‡</td>
<td>1 in 4</td>
<td>1 in 4</td>
</tr>
<tr>
<td>CHF§</td>
<td>1 in 5</td>
<td>1 in 5</td>
</tr>
<tr>
<td>Stroke§</td>
<td>1 in 62</td>
<td>1 in 50</td>
</tr>
<tr>
<td>Dementia§</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Hip fracture§</td>
<td>1 in 20</td>
<td>1 in 6</td>
</tr>
<tr>
<td>Breast cancer§</td>
<td>...</td>
<td>1 in 8</td>
</tr>
<tr>
<td>Prostate cancer§</td>
<td>1 in 6</td>
<td>...</td>
</tr>
<tr>
<td>Lung cancer§</td>
<td>1 in 13</td>
<td>1 in 16</td>
</tr>
<tr>
<td>Colon cancer§</td>
<td>1 in 19</td>
<td>1 in 21</td>
</tr>
<tr>
<td>CMI§</td>
<td>1 in 3</td>
<td>1 in 3</td>
</tr>
<tr>
<td>Hypertension§</td>
<td>9 in 100</td>
<td>9 in 100</td>
</tr>
<tr>
<td>Obesity§</td>
<td>1 in 3</td>
<td>1 in 3</td>
</tr>
</tbody>
</table>

* = 45 years of age; © = 65 years of age; ‡ = 55 years of age; ... = not calculated


Comparative Burden of Disease

<table>
<thead>
<tr>
<th>Disease State</th>
<th>1-year mortality (men)</th>
<th>1-year mortality (women)</th>
<th>5-year mortality (men)</th>
<th>5-year mortality (women)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Failure*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1950-1969</td>
<td>30%</td>
<td>28%</td>
<td>70%</td>
<td>57%</td>
</tr>
<tr>
<td>1970-1979</td>
<td>41%</td>
<td>28%</td>
<td>75%</td>
<td>59%</td>
</tr>
<tr>
<td>1980-1989</td>
<td>33%</td>
<td>27%</td>
<td>65%</td>
<td>51%</td>
</tr>
<tr>
<td>1990-1999</td>
<td>28%</td>
<td>24%</td>
<td>59%</td>
<td>45%</td>
</tr>
<tr>
<td>All Cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>38%</td>
<td>37.3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast Cancer</td>
<td></td>
<td></td>
<td>14.1%</td>
<td></td>
</tr>
<tr>
<td>Prostate Cancer</td>
<td></td>
<td></td>
<td>2.4%</td>
<td></td>
</tr>
<tr>
<td>Colon Cancer</td>
<td></td>
<td></td>
<td>38.6%</td>
<td></td>
</tr>
</tbody>
</table>

*All values adjusted for age and reported in patients who survived the initial 30 days after the onset of heart failure (Framingham cohort). Cancer survival rates derived from Surveillance, Epidemiology, and End Results (SEER) program 1973-1998

Heart Failure (HF)

“HF is a complex clinical syndrome that results from any structural or functional impairment of ventricular filling or ejection of blood”

**Reduced Ejection Fraction (HFrEF)**
- Signs or symptoms of HF
- LVEF ≤ 40%

**Preserved Ejection Fraction (HFpEF)**
- Signs or symptoms of HF
- LVEF ≥ 50%
- + LV diastolic dysfunction
- + Dyspnea/Fatigue/Volume overload
- + Elevated BNP (NT-proBNP)

Subsets of HFpEF

- **HFpEF, borderline (LVEF 41-49%)**
  - Characteristics, treatment patterns, and outcomes are similar to those of HFpEF

- **HFpEF, improved (LVEF > 40%)**
  - Previously had HFrEF but have improved/recovered
  - May be clinically distinct than those with persistently preserved or reduced EF
  - Further research needed to better characterize

2013 ACCF/AHA Guideline for the Management of Heart Failure
Stages in the Development of HFrEF

Stages and NYHA Functional Classifications of HF

<table>
<thead>
<tr>
<th>ACOG/AHA Stages of HF</th>
<th>NYHA Functional Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>A: At high risk for HF but without structural heart disease or symptoms of HF</td>
<td>None</td>
</tr>
<tr>
<td>B: Structural heart disease but without signs or symptoms of HF</td>
<td>I: No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF.</td>
</tr>
<tr>
<td>C: Structural heart disease with prior or current symptoms of HF</td>
<td>III: Marked limitation of physical activity. Unable to carry on any physical activity without symptoms of HF or symptoms of HF at rest.</td>
</tr>
<tr>
<td>D: Refractory HF requiring specialized interventions</td>
<td>IV: Unable to carry on any physical activity without symptoms of HF, or symptoms of HF at rest.</td>
</tr>
</tbody>
</table>

2013 ACCF/AHA Guideline for the Management of Heart Failure
**HFrEF: Stage B* Treatment Approach**

*Structural heart disease but without (nor a history of) signs or symptoms of heart failure*

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>In patients with a history of MI and reduced EF, ACE inhibitors or ARBs should be used to prevent HF</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>In patients with MI and reduced EF, evidence-based beta blockers should be used to prevent HF</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>In patients with MI, statins should be used to prevent HF</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Blood pressure should be controlled to prevent symptomatic HF</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>ACE inhibitors should be used in all patients with a reduced EF to prevent HF</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Beta blockers should be used in all patients with a reduced EF to prevent HF</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>An ICD is reasonable in patients with asymptomatic ischemic cardiomyopathy who are at least 40 d post-MI have an LVEF ≤30%, and on GDMT</td>
<td>Ila</td>
<td>B</td>
</tr>
<tr>
<td>Nondihydropyridine calcium channel blockers may be harmful in patients with low LVEF</td>
<td>III, Harm</td>
<td>C</td>
</tr>
</tbody>
</table>

2013 ACCF/AHA Guideline for the Management of Heart Failure

---

**HFrEF: Stage C* Treatment Approach**

*Structural heart disease with prior or current signs or symptoms of heart failure*

2013 ACCF/AHA Guideline for the Management of Heart Failure
Renin-Angiotensin-Aldosterone System

**Non ACE Pathways**
- Angiotensinogen
  - Renin
- ACE
- Bradykinin
- Inactive Peptides

**ACE Pathways**
- Angiotensin I
  - Angiotensin II
  - AT1 Receptor
  - AT2 Receptors
  - Antihypertrophic, proapoptotic ??

**ACE-I**
- Beta-Blockers
- Cathepsin G
- CAGE
- Chymase

**All-Receptor Blockers**
- AT1 Receptor

**Non ACE Pathways**
- t-PA
- Sodium & Fluid Retention
- Sympathetic Activation
- Thirst Stimulation

**ACE Pathways**
- Angiotensin II
- AT2 Receptors
- Antihypertrophic, proapoptotic ??

**ACE-I**
- Beta-Blockers, Digoxin

**Outcome Trials of ACE Inhibitors in HFrEF**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patients</th>
<th>NYHA Class</th>
<th>Placebo Mortality</th>
<th>Hazard ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>V-HeFT II</td>
<td>1095</td>
<td>I-IV</td>
<td>154%</td>
<td>8.27</td>
</tr>
<tr>
<td>CONSENSUS I</td>
<td>2108</td>
<td>I-IV</td>
<td>88%</td>
<td>8.69</td>
</tr>
<tr>
<td>SOLVD Tx</td>
<td>1981</td>
<td>I-IV</td>
<td>88%</td>
<td>8.68</td>
</tr>
<tr>
<td>SOLVD Px</td>
<td>1975</td>
<td>I-IV</td>
<td>88%</td>
<td>8.63</td>
</tr>
<tr>
<td>SAVE</td>
<td>2790</td>
<td>I-IV</td>
<td>88%</td>
<td>8.81</td>
</tr>
<tr>
<td>ISIS-4</td>
<td>16,600</td>
<td>I-IV</td>
<td>88%</td>
<td>8.52</td>
</tr>
</tbody>
</table>
ARBs in Heart Failure

- ACEI does not produce long-term suppression of Angiotensin II (“escape phenomenon”)

- Angiotensin II can be generated by other pathways

- Circulating Ang II inhibition may not be equivalent to tissue Ang II inhibition

- 8-12% of patients cannot tolerate ACEI

ARB Trials in HFrEF

<table>
<thead>
<tr>
<th></th>
<th>ELITE I/II</th>
<th>ValHEFT</th>
<th>CHARM</th>
<th>OPTIMAAL</th>
<th>VALIANT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients (n)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1505</td>
<td></td>
<td>1010</td>
<td>1001</td>
<td>1001</td>
<td>1001</td>
</tr>
<tr>
<td><strong>Study Design</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Randomized</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>β-blocker</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metoprolol</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mortality</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N/A</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>HF Hosp</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N/A</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N/A</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
ARB Trials in HFrEF

<table>
<thead>
<tr>
<th>ELITE I/II</th>
<th>ValHEFT</th>
<th>CHARM</th>
<th>OPTIMAAL</th>
<th>VALIANT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>9656</td>
<td>9656</td>
<td>9656</td>
<td>9656</td>
</tr>
</tbody>
</table>

ARBs are Proven Alternatives to ACE Inhibitors

<table>
<thead>
<tr>
<th>Mortality</th>
<th>ELITE I/II</th>
<th>ValHEFT</th>
<th>CHARM</th>
<th>OPTIMAAL</th>
<th>VALIANT</th>
</tr>
</thead>
<tbody>
<tr>
<td>HF Hosp</td>
<td>ELITE I/II</td>
<td>ValHEFT</td>
<td>CHARM</td>
<td>OPTIMAAL</td>
<td>VALIANT</td>
</tr>
<tr>
<td>Other</td>
<td>ELITE I/II</td>
<td>ValHEFT</td>
<td>CHARM</td>
<td>OPTIMAAL</td>
<td>VALIANT</td>
</tr>
</tbody>
</table>

When to Use ARBs In HFrEF

- **Class I**
  - Alternative when ACEI not tolerated (LOE A)
    - Caution with angioedema

- **Class II**
  - Alternative to ACEI as first-line therapy especially if already taking for other indications (Class IIa, LOE A)
  - Added to an ACEI and BB if persistent HF symptoms and MRA is not indicated or tolerated (Class IIb, LOE A)

- **Class III (harm)**
  - Combination of ACE-I, ARB, Aldosterone antagonist (LOE C)

2013 ACCF/AHA Guideline for the Management of Heart Failure
How Important is Dose Titration?

ATLAS compared with SOLVD

<table>
<thead>
<tr>
<th>Treatments compared</th>
<th>Reduction in risk of death</th>
<th>Reduction in risk of death or hospitalization for HF</th>
</tr>
</thead>
<tbody>
<tr>
<td>High dose vs. placebo (SOLVD)</td>
<td>16%</td>
<td>26%</td>
</tr>
<tr>
<td>Low dose vs. placebo (not studied)</td>
<td>not known</td>
<td>not known</td>
</tr>
<tr>
<td>High dose vs. low dose (ATLAS)</td>
<td>8%</td>
<td>15%</td>
</tr>
</tbody>
</table>

Use of low dose ACE-I provides only about half of the benefit that can be achieved with high dose


How Important is Dose Titration?

HEAAL Trial design: Patients with heart failure and left ventricular ejection fraction \(\leq 40\%\) were randomized to high-dose losartan 150 mg daily (n = 1,927) vs. low-dose losartan 50 mg daily (n = 1,919). Median follow-up was 4.7 years.

How Important is Dose Titration?

<table>
<thead>
<tr>
<th>Disease State</th>
<th>1-year mortality (men)</th>
<th>1-year mortality (women)</th>
<th>5-year mortality (men)</th>
<th>5-year mortality (women)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Failure*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1950-1969</td>
<td>30%</td>
<td>28%</td>
<td>70%</td>
<td>57%</td>
</tr>
<tr>
<td>1970-1979</td>
<td>41%</td>
<td>30%</td>
<td>65%</td>
<td>55%</td>
</tr>
<tr>
<td>1980-1989</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1990-1999</td>
<td>33%</td>
<td>28%</td>
<td>59%</td>
<td>45%</td>
</tr>
</tbody>
</table>

*All values adjusted for age and reported in patients who survived the initial 30 days after the onset of heart failure (Framingham cohort). Cancer survival rates derived from Surveillance, Epidemiology, and End Results (SEER) program 1973-1998


Titrate as Tolerated to Doses Achieved in Clinical Trials

Breast Cancer 14.1%
Prostate Cancer 2.4%
Colon Cancer 38.6%

*All values adjusted for age and reported in patients who survived the initial 30 days after the onset of heart failure (Framingham cohort). Cancer survival rates derived from Surveillance, Epidemiology, and End Results (SEER) program 1973-1998

Audience Response Question

You initiate a patient with HFrEF who also has CKD on an ACEi. After one week the estimated GFR has decreased by 20%. You do the following?

A. Stop the ACEi, repeat labs in 1-2 weeks
B. Continue dose, repeat labs in 1-2 weeks
C. Reduce dose, repeat labs in 1-2 weeks
D. Refer the patient to nephrology
Monitoring Renal Function

Table 137. Changes in Management Based on Magnitude of Early Decrease in GFR

<table>
<thead>
<tr>
<th>Early decrease in estimated GFR (%)</th>
<th>0-15%</th>
<th>15-30%</th>
<th>30-50%</th>
<th>&gt;50%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosage adjustment for ACEI and ARB</td>
<td>None</td>
<td>None</td>
<td>Reduce</td>
<td>Discontinue</td>
</tr>
<tr>
<td>Recommended interval for monitoring GFR</td>
<td>As per GFR (previous table)</td>
<td>Once after 10-14 days. If repeat GFR remains within 15-30% of baseline value, resume monitoring schedule as per GFR (previous table)</td>
<td>Every 5-7 days until GFR is within 30% of baseline value</td>
<td>Every 5-7 days until GFR is within 15% of baseline value</td>
</tr>
<tr>
<td>Evaluate for causes of decreased GFR (including consideration of RAD, see Guideline 4)</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>


Monitoring Serum Potassium

Table 142. Recommendations for Prevention and Management of Hyperkalemia, According to Baseline Serum Potassium

<table>
<thead>
<tr>
<th>Baseline Serum Potassium (mEq/L)</th>
<th>≤4.5</th>
<th>4.5-5.0</th>
<th>5.1-5.5</th>
<th>&gt;5.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Education to avoid high potassium foods</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Measures to lower serum potassium</td>
<td>No</td>
<td>No</td>
<td>Simultaneous with initiation</td>
<td>Prior to initiation</td>
</tr>
<tr>
<td>Recommended interval for monitoring serum potassium after initiation or change in dose of antihypertensive therapy</td>
<td>4-12 weeks</td>
<td>2-4 weeks</td>
<td>≤2 weeks</td>
<td>≤2 weeks</td>
</tr>
</tbody>
</table>

How Do Beta Blockers Improve Heart Failure?

- Upregulation of beta receptors
- Improved coupling of beta receptors to secondary intracellular signals
- Alterations in myocardial metabolism
- Improved calcium transport
- Increased protein synthesis and message expression
- Inhibition of renin-angiotensin system
- Inhibition of endothelin and cytokine release

Unique Features of Select β-Blockers

- Metoprolol
  - 50- to 100-fold less β₂ antagonism than propranolol
- Bisoprolol:
  - Particularly long half-life
  - Highly β₁ selective
- Carvedilol
  - Antioxidant properties
  - Stereoselective metabolism
  - 10:1 ratio of β:α antagonism
- Nebivolol
  - Nitric oxide-potentiating vasodilatory effect
  - Most β₁ selective

The Failing Heart and Adrenergic Receptors

• Dominant receptor in normal human heart is Beta-1
• In the failing heart ratios change
  – 40% beta-2
  – 10% alpha-1 (up regulated)
  – 60% beta-1 (down regulated)


The Failing Heart and Adrenergic Receptors

However, you need to consider both selectivity of the neurohormones that stimulate these receptors and pathogenic consequences of specific receptor stimulation

– The signaling molecule that drives adrenergic receptors that is increased in the failing heart is norepinephrine
  • 20:1 affinity for beta-1 versus beta-2
  • 10:1 affinity for beta-1 versus alpha-1

– Myopathic potential appears much greater with beta-1 stimulation versus beta-2
  • 10x stimulation of beta-2 receptor to get the same degree of cardiomyopathy seen with stimulation of beta-1 receptor

**Beta-adrenergic Blocking Therapy**

**All-Cause Mortality in HFrEF**

<table>
<thead>
<tr>
<th>RR</th>
<th>CIBIS-II 1.3 years</th>
<th>MERIT-HF 12 months</th>
<th>COPERNICUS – 12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>34% $P = 0.0001$</td>
<td>placebo 228/1320 (17%) bisoprolol 156/1327 (12%)</td>
<td>placebo 217/2001 (11%) metoprolol-XL 145/1990 (7%)</td>
<td>Placebo 190/1133 (18.5%) carvedilol 130/1156 (11.4%)</td>
</tr>
<tr>
<td>34% $P = 0.0062$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>35% $P = 0.0014$</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Relative risk and 95% confidence intervals


---

**Are All Beta-blockers Effective in HFrEF?**

- **Bucindolol**
- **Metoprolol tartrate immediate release**

**Bottom Line:**

All dosage forms and all beta-blockers are not interchangeable in the treatment of HFrEF
**Beta-blockers with Proven Benefit in HFrEF**

<table>
<thead>
<tr>
<th>Beta-blocker</th>
<th>Initial Dose</th>
<th>Target Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisoprolol</td>
<td>1.25mg once daily</td>
<td>10mg once daily</td>
</tr>
<tr>
<td>Carvedilol immediate release</td>
<td>3.125mg twice daily</td>
<td>25mg twice daily*</td>
</tr>
<tr>
<td>Metoprolol succinate SA</td>
<td>12.5 to 25mg once daily</td>
<td>200mg once daily</td>
</tr>
<tr>
<td>Nebivolol (less robust evidence)</td>
<td>1.25mg once daily</td>
<td>10mg once daily</td>
</tr>
</tbody>
</table>

* 50mg twice daily if patient more than 85kg

---

**Initiation and Monitoring of Beta-Blockers**

- **Stable on ACE?** (i.e. no IV inotropes or s/sx’s of fluid)
  - **Initiate BB at lowest dose**
  - **Well tolerated?**
    - Yes: **Double dosage q 2 wks to achieve doses known to reduce mortality**
    - No: **Hypotension?**
      - ↓ vasodilator/ACEI/diuretic Space doses
    - **Worse HF? (edema, SOB)**
      - ↑ Diuretic/ACEI BB if necessary
    - **Bradycardia?**
      - ↓ to last tolerated BB dose Adjust other meds
    - **Other? (fatigue, impotence)**
      - Educate Adjust BB dose

*European Society of Cardiology. Task Force for the Dx and Txt of Heart Failure. Eur Heart J 2001;22:5127-1560*
Which Drug First?  
ACE-I vs. Beta Blocker

CIBIS III  
1010 pts, new dx HF  
NYHA II-III, EF<=35%  
Monotherapy for 6 mos, followed by combination rx  
• In ITT population, bisoprolol- first strategy was noninferior to enalapril-first

Diuretics

• Only drugs in heart failure that can effectively control fluid retention  
• Essential for symptomatic fluid overload  
• ACC/AHA Class I; LOE C for volume overloaded NYHA Class II-IV patients to improve symptoms  
• Have not demonstrated a survival benefit
Sodium Reabsorption Sites in the Nephron

- 70% Proximal Tubule
- 5% Distal Tubule
- 20% Loop of Henle
- 1-4% Collecting Tubule

Advantages: Loop Diuretics

- **Primary site of action: thick ascending limb**
  - Site of greatest Na⁺ capacity (25% of filtered Na⁺ load)
  - Nephron segments past this site do not possess reabsorptive capacity to reabsorb this rejectate
- **Effective despite low GFRs**
  - Basal level of fractional sodium reabsorption higher
  - Block tubuloglomerular feedback response (thiazides do not, and may enhance this at times)
Pharmacokinetic Considerations

• Bioavailability
  – Least for furosemide
  – Higher doses may be needed to achieve adequate serum concentrations in decompensated patients
  – Food interferes with absorption of furosemide and bumetanide, but not torsemide

• Half-Life/Metabolism
  – Relatively short, effect tends to decline before next dose administered
  – Enhanced sodium reabsorption by nephron between doses
  – More frequent dosing (e.g. BID) and dietary sodium and fluid restriction are often necessary

Loop Diuretic Pharmacodynamics

- Use adequate initial dose
- Avoid overdosing
- More frequent administration of effective doses
- Combination diuretic therapy for diuretic resistance
Chronic Diuretic Use in Heart Failure: A Concern?


Is it All Diuretics?

Furosemide vs. torsemide (TORIC Trial)

- Open label, non-randomized, post-marketing surveillance trial
- Not designed as a mortality study
- Torsemide 10 mg daily (n=778) vs. Furosemide 40 mg daily (n=527) or other (n=72)

Diuretics

• Initiation and Maintenance
  – Appropriate dose with titration until urine output increases, and weight decreases (generally by 0.5 to 1.0 kg daily)
  – Sodium and fluid restriction
  – May need to tolerate some degree of hypotension and/or renal insufficiency until fluid retention resolved
  – Reassess dose over time/patient participation

Digitalis Glycosides: Digoxin

• Inhibits Na\(^+\)-K\(^+\) ATPase pump in
  – Cardiac, non-cardiac, and renal cells
• Withdrawal in patients with HFrEF
  – Reduction in exercise tolerance and worsening of HF (RADIANCE, PROVED trials)
• DIG trial: Pivotal trial in HFrEF patients in normal sinus rhythm and NYHA Class II-III
  – No mortality benefit, reduction in combined endpoint of death and hospitalization
**DIG Trial: Survival Analysis Based on Serum Drug Concentration**

![Graph showing survival rates based on serum drug concentration]


**DIG Trial: Analysis of Digoxin Levels**

- Higher serum drug concentrations were associated with increased mortality rates ($p = 0.006$ for trend)
  - 0.5–0.8ng/mL, 29.9%; 0.9–1.1ng/mL, 38.8%;
  - $\geq 1.2$ng/mL, 48%
- Lower serum drug concentrations (not higher) had lower mortality than placebo group ($p < 0.05$)
  - 0.5–0.8ng/mL, 6.3% lower mortality
  - $\geq 1.2$ng/mL, 11.8% higher mortality


**Digoxin: Bottom Line**

- Doses targeted to traditional levels not warranted, and probably harmful; ideal serum drug range 0.5 to 0.9ng/mL
- Class IIa, LOE B recommendation that digoxin can be beneficial in patients with HFrEF to decrease hospitalizations for HF
- Conflicting data on mortality risks with digoxin use for atrial fibrillation with or without heart failure continue to accumulate

---

**Aldosterone Inhibitors**

- **Spironolactone**
  - Competitive antagonist of the aldosterone receptor (myocardium, arterial walls, kidney)

- **ALDOSTERONE**
  - Retention Na$^+$ → Edema
  - Retention H$_2$O
  - Excretion K$^+$ → Arrhythmias
  - Excretion Mg$^{2+}$
  - Collagen deposition
    - Fibrosis
      - myocardium
      - vessels
Pharmacologic Considerations with Aldosterone Antagonists

Selectivity
- Eplerenone 1000x less binding to androgen receptor, 100x less to progesterone receptor, and 10-20x less to mineralcorticoid receptor, yet still 50-75% as potent as spironolactone

Administration with food
- Eplerenone (no effect), spironolactone (increased absorption)

Metabolites
- Eplerenone (inactive), spironolactone (active + long half-life)

Metabolism/drug interactions
- Eplerenone (CYP 3A4 interactions)


Efficacy in HFrEF

RALES: Spironolactone reduced total mortality 30% (p < 0.0001) over 2 years in NYHA late III and IV patients with EF < 35%

EHPESUS: Eplerenone reduced total mortality 15% (p = 0.008) over 16 months in post MI(3-14 days) patients with EF ≤ 40% and symptoms of heart failure or diabetes

EMPHASIS-HF: Eplerenone reduced CV death/HF hospitalizations 37% (p < 0.001) over 21 months in NYHA Class II with EF < 30% (or 31-35% if QRS > 130ms)

Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms. New Eng J Med 2010; DOI:10.1056/NEJMoa1009492
Aldosterone Antagonists

• Class I
  – NYHA class II–IV HF with LVEF ≤ 35% (class II should have a history of prior CV hospitalization or elevated BNP/pro-BNP (LOE A)
  – Post MI with LVEF ≤ 40% with symptoms of HF or history of diabetes mellitus (LOE B)

• Class III (harm)
  – Inappropriate use if creatinine > 2.5 mg/dL in men or > 2.0 mg/women (or eGFR >30 mL/min/1.73 m2), and/or potassium > 5.0 mEq/L (LOE B)

2013 ACCF/AHA Guideline for the Management of Heart Failure

Aldosterone Antagonists

• Dosing

<table>
<thead>
<tr>
<th>eGFR (mL/min/1.73 m²)</th>
<th>≤50</th>
<th>30–49</th>
<th>≥50</th>
<th>30–49</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial dose (only if K+ ≤5 mEq/L)</td>
<td>25 mg once daily</td>
<td>25 mg once every other day</td>
<td>12.5 to 25.0 mg once daily</td>
<td>12.5 mg once daily or every other day</td>
</tr>
<tr>
<td>Maintenance dose (after 4 wk for K+ ≤5 mEq/L)</td>
<td>50 mg once daily</td>
<td>25 mg once daily</td>
<td>25 mg once or twice daily</td>
<td>12.5 to 25.0 mg once daily</td>
</tr>
</tbody>
</table>

• Creatinine and potassium monitoring
  – 3 days, 1 week post initiation, and one week post dose changes, and at least monthly for 1st 3 months and every 3 months thereafter
  – Risk of hyperkalemia increases with concomitant use of higher doses of ACEI (e.g. lisinopril ≥ 10mg)

2013 ACCF/AHA Guideline for the Management of Heart Failure
Hydralazine/ISDN

- Achievement of both arterial and venous vasodilation
  - Nitrates may also inhibit abnormal myocardial and vascular growth
  - Hydralazine may interfere with some biochemical and molecular mechanisms responsible for progressive HF
  - Hydralazine may inhibit development of nitrate tolerance

- Studies have suggested that African Americans
  - Less active renin–angiotensin system
  - Lower bioavailability of nitric oxide
  - Retrospective analyses of the databases of previous trials suggested a clinically significant response to the combination

A-HeFT

Trial design: 1,050 black patients who had New York Heart Association class III or IV heart failure with EF < 35% were randomly assigned to receive a fixed dose of isosorbide dinitrate plus hydralazine or placebo in addition to standard therapy for heart failure (target 225mg hydralazine; ISDN 120mg). Median follow-up 10 months.

Baseline Medications (% of patients)
- Diuretic ~90%; ACE inhibitor or ARB ~85%, Beta-blocker ~75%, Digoxin ~60%; Spironolactone ~40%

Hydralazine/ISDN

• Class I
  – To reduce morbidity and mortality in patients self described as African Americans with NYHA III-IV HFrEF receiving optimal therapy with BBs and ACEIs (LOE A)

• Class IIa
  – To reduce morbidity and mortality in patients with current or prior symptomatic HFrEF who cannot be given an ACEI (or ARB) because of drug intolerance, hypotension, or renal insufficiency (LOE B)

2013 ACCF/AHA Guideline for the Management of Heart Failure

Omega-3 polyunsaturated fatty acids (PUFA)

Trial design: 6,975 patients who had New York Heart Association class II-IV failure heart (irrespective of LVEF) were randomly assigned to receive n-3 PUFA 1 g daily. Median follow-up 3.9 years.

GISSI-HF investigators. Lancet 2008; Aug 29
Omega-3 polyunsaturated fatty acids (PUFA)

- **Class IIa**
  - Reasonable to use as adjunctive therapy in patients with NYHA class II–IV symptoms and HFrEF or HFpEF, unless contraindicated, to reduce mortality and cardiovascular hospitalizations (Level of Evidence B)

---

### Magnitude of Benefit
**Demonstrated in RCTs of HFrEF**

<table>
<thead>
<tr>
<th>GDMT</th>
<th>RR Reduction in Mortality</th>
<th>NNT for Mortality Reduction (Standardized to 36 mo)</th>
<th>RR Reduction in HF Hospitalizations</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitor or ARB</td>
<td>17%</td>
<td>26</td>
<td>31%</td>
</tr>
<tr>
<td>Beta blocker</td>
<td>34%</td>
<td>9</td>
<td>41%</td>
</tr>
<tr>
<td>Aldosterone antagonist</td>
<td>30%</td>
<td>6</td>
<td>35%</td>
</tr>
<tr>
<td>Hydralazine/nitrate</td>
<td>43%</td>
<td>7</td>
<td>33%</td>
</tr>
</tbody>
</table>

2013 ACCF/AHA Guideline for the Management of Heart Failure
Emerging Therapies

• **Ivabradine**
  - Selective sinus node inhibitor (If current)
  - SHIFT trial (n = 6558)
  - HFrEF (LVEF ≤ 35%), NSR, HR ≥ 70, admission for HF < 12 months, on GDMT
  - Median follow-up at ~ 2 years showed 18% decrease in CVD death or hospital admission for HF (24% vs. 29%, p< 0.0001)
  - Granted priority review by FDA August, 2014

Emerging Therapies

• **Angiotensin receptor-neprilysin inhibitor (ARNI)**
  - PARADIGM-HF trial (n = 8442)
  - HFrEF (LVEF ≤ 40%, later ≤ 35%), on GDMT
  - Median follow-up at 27 months showed 20% decrease in CVD death or hospital admission for HF (21.8% vs. 26.5%, p< 0.001), and improvement in HF symptoms
  - Total mortality was reduced 16% (17.0% vs. 19.8%, p < 0.001) and improved symptoms
  - More nonserious angioedema and symptomatic HOTN
Summary: Optimizing HFrEF Therapy

- Use loop diuretics at adequate dose to relieve congestion
- ACE inhibitors + Beta-blockers for all with EF ≤ 40%
- ARBs for ACE-inhibitor intolerant patients
- Use agents with demonstrated efficacy in clinical trials, titrate to maximally tolerated dose
- Aldosterone antagonists are increasingly the preferred ‘third’ agent
- Hydralazine/Isosorbide may be useful for select populations (ACE/ARB intolerant, African-American)
- Digoxin may still be useful, caution with dose

HFpEF: Treatment Recommendations

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic and diastolic blood pressure should be controlled according to published clinical practice guidelines</td>
<td>I</td>
<td>B (27, 91)</td>
</tr>
<tr>
<td>Diuretics should be used for relief of symptoms due to volume overload.</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Coronary revascularization for patients with CAD in whom angina or demonstrable myocardial ischemia is present despite GDMT</td>
<td>Ia</td>
<td>C</td>
</tr>
<tr>
<td>Management of AF according to published clinical practice guidelines for HFpEF to improve symptomatic HF</td>
<td>Ia</td>
<td>C</td>
</tr>
<tr>
<td>Use of beta-blocking agents, ACE inhibitors, and ARBs for hypertension in HFpEF</td>
<td>Ia</td>
<td>C</td>
</tr>
<tr>
<td>ARBs might be considered to decrease hospitalizations in HFpEF</td>
<td>IIb</td>
<td>B (589)</td>
</tr>
<tr>
<td>Nutritional supplementation is not recommended in HFpEF</td>
<td>IIa</td>
<td>C</td>
</tr>
</tbody>
</table>

ACE indicates angiotensin-converting enzyme; AF, atrial fibrillation; ARBs, angiotensin-receptor blockers; CAD, coronary artery disease; COR, Class of Recommendation; GDMT, guideline-directed medical therapy; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; and LOE, Level of Evidence.

2013 ACCF/AHA Guideline for the Management of Heart Failure