Pharmacotherapy of Heart Failure
Guidelines Review, Therapeutic Update, and the Pharmacist’s Role

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Learning Objectives

• Discuss generally-accepted treatment guidelines for heart failure with reduced ejection fraction

• Discuss the impact of guideline adherence and effective transitions-of-care on patient outcomes

• Discuss new evidence and treatment modalities since publication of accepted treatment guidelines, most notably ivabradine

• Synthesize a treatment plan, given a patient diagnosed with heart failure with reduced ejection fraction
Pathophysiology & Classification

Neurohormonal Pathophysiology of Heart Failure
## Stages of Heart Failure & NYHA Classification

<table>
<thead>
<tr>
<th>Stages of Heart Failure</th>
<th>NYHA Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>None</td>
</tr>
<tr>
<td>B</td>
<td>I</td>
</tr>
<tr>
<td>C</td>
<td>II</td>
</tr>
<tr>
<td>D</td>
<td>III</td>
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<tr>
<td></td>
<td>IV</td>
</tr>
</tbody>
</table>

### Stages of Heart Failure

- **Stage A**: At high risk for HF but without structural heart disease or symptoms of HF.
- **Stage B**: Structural heart disease but without signs or symptoms of HF.
- **Stage C**: Structural heart disease with prior or current symptoms of HF.
- **Stage D**: Refractory HF requiring specialized interventions.

### NYHA Classification

- **Stage I**: No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF.
- **Stage II**: Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in symptoms of HF.
- **Stage III**: Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes symptoms of HF.
- **Stage IV**: Unable to carry on any physical activity without symptoms of HF, or symptoms of HF at rest.
Classification Based Left Ventricular Dysfunction

**HFrEF**
- Systolic Dysfunction
- Impaired Ventricular Contraction
- Ejection Fraction < 40%

**HFpEF**
- Diastolic Dysfunction
- Impaired Ventricular Relaxation
- Ejection Fraction > 50%


Approaches to Therapy
European Society of Cardiology Stepwise Approach

**Pharmacotherapy at Each Stage of Heart Failure**

**Stage A**
- HTN, Lipid Management
- Comorbidity Management
- Avoid Cardiotoxic Agents

**Stage B**
- ACEI or ARB (if rEF)
- Beta Blocker (if rEF)
- Statin
- Stage A Therapy

**Stage C**
- Stage B Therapy
- Aldosterone Antagonists
- Loop Diuretics (volume overload)
- ISNI (African Americans)

**Stage D**
- Stage C Therapy
- Acute Management
- Chronic Inotropes
- Palliative Care

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Pharmacotherapy for Stage C HFrEF

ACEI or ARB and Beta Blocker

NYHA II-IV
K < 5 mEq/dL
CrCl > 30 mL/min

NYHA III-IV
African American

Aldosterone Antagonist

Volume Overload

Hydralazine/Nitrate

Loop Diuretic

Neurohormonal Active Agents

- Angiotensin Converting Enzyme Inhibitors
- Angiotensin Receptor Blockers
- Beta Blockers
- Aldosterone Antagonists

ACE Inhibitors & Angiotensin Receptor Blockers

- Agents studied (mean dose used)
  - ACEI
    - Captopril (40.9 mg three times daily)
    - Enalapril (8.3 mg twice daily)
    - Lisinopril (35 mg daily)
  - ARB
    - Candesartan (24 mg daily)
    - Losartan (129 mg daily)
    - Valsartan (127 mg twice daily)

Mortality RRR 17%
Hospital Admission RRR 31%

Dosing Recommendations for ACEI/ARB

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial dosing</th>
<th>Target dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Captopril</td>
<td>6.25 mg three times daily</td>
<td>50 mg three times daily</td>
</tr>
<tr>
<td>Enalapril</td>
<td>2.5 mg twice daily</td>
<td>10 to 20 mg twice daily</td>
</tr>
<tr>
<td>Fosinopril</td>
<td>5 to 10 mg daily</td>
<td>40 mg daily</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>2.5 to 5 mg daily</td>
<td>20 to 40 mg daily</td>
</tr>
<tr>
<td>Perindopril</td>
<td>2 mg daily</td>
<td>8 to 16 mg daily</td>
</tr>
<tr>
<td>Quinapril</td>
<td>5 mg twice daily</td>
<td>20 mg twice daily</td>
</tr>
<tr>
<td>Ramipril</td>
<td>1.25 to 2.5 mg daily</td>
<td>10 mg daily</td>
</tr>
<tr>
<td>Trandolapril</td>
<td>1 mg daily</td>
<td>4 mg daily</td>
</tr>
<tr>
<td>Candesartan</td>
<td>4 to 8 mg daily</td>
<td>32 mg daily</td>
</tr>
<tr>
<td>Losartan</td>
<td>25 to 50 mg daily</td>
<td>50 to 150 mg daily</td>
</tr>
<tr>
<td>Valsartan</td>
<td>20 to 40 mg twice daily</td>
<td>160 mg twice daily</td>
</tr>
</tbody>
</table>
Beta Blockers

- Agents used (mean dosing)
  - Bisoprolol (8.6 mg daily)
  - Carvedilol (18.5 mg twice daily)
  - Metoprolol succinate (159 mg daily)

Mortality RRR 34%
Hospital Admission RRR 41%


Dosing Recommendations for Beta Blockers

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<thead>
<tr>
<th>Drug</th>
<th>Initial dosing</th>
<th>Target dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisoprolol</td>
<td>1.25 mg daily</td>
<td>10 mg daily</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>3.125 mg twice daily</td>
<td>25 mg twice daily</td>
</tr>
<tr>
<td>Carvedilol CR</td>
<td>10 mg daily</td>
<td>80 mg daily</td>
</tr>
<tr>
<td>Metoprolol succinate</td>
<td>12.5 to 25 mg daily</td>
<td>200 mg daily</td>
</tr>
</tbody>
</table>

Aldosterone Antagonists

- Agents studied (mean dosing)
  - Spironolactone (26 mg per day)
  - Eplerenone (42.6 mg daily)
- Special Indication
  - EF ≤ 35% and NYHA Class II-IV
  - EF ≤ 40% and previous MI
- Contraindications
  - SCR > 2.5 mg/dL (men), SCR > 2 mg/dL (women)
  - CrCl > 30 mL/min
  - Potassium > 5 mEq/dL
- Monitoring
  - Potassium
  - Renal function
  - Adjustment of diuretic dose

Mortality RRR 30%
Hospital Admission RRR 35%


Dosing Recommendations for Aldosterone Antagonists

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial dosing</th>
<th>Target dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spironolactone</td>
<td>12.5 to 25 mg daily</td>
<td>25 mg once or twice daily</td>
</tr>
<tr>
<td>Eplerenone</td>
<td>25 mg daily</td>
<td>50 mg daily</td>
</tr>
</tbody>
</table>

Hydralazine/Nitrates

• Agents studied (mean dosing)
  • Hydralazine/Isosorbide Dinitrate (175/90mg per day)
• Special Indications
  • NYHA III or IV \textit{and}
  • EF \leq 40\% \textit{and}
  • Patient self-identifies as African American

Mortality RRR 43%
Hospital Admission RRR 33%


Dosing Recommendations for Hydralazine/Nitrates

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial dosing</th>
<th>Target dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fixed Dose Combination</td>
<td>37.5 mg (HYDRAL), 20 mg (ISDN) three times daily</td>
<td>75 mg (HYDRAL), 40 mg (ISDN) three times daily</td>
</tr>
<tr>
<td>Hydralazine + Isosorbide Dinitrate</td>
<td>25 to 50 mg three to four times daily 20 to 30 mg three to four times daily</td>
<td>300 mg total daily dose 120 mg total daily dose</td>
</tr>
</tbody>
</table>

Adherence to Guidelines

General Practitioner Adherence to Chronic Heart Failure Guidelines

- ACEI/ARB: 87%
- Beta blocker: 84%
- MRA: 18%
- Overall Adherence: 56%

All Practitioner Adherence to Chronic Heart Failure Guidelines

- ACEI/ARB: 79%
- Beta blocker: 69%
- MRA: 29%
- Dual therapy: 58%
- Triple therapy: 19%


Does Guideline Adherence Matter?

Patient Outcomes Associated with Adherence at 1 year

- Readmission: Poor Adherence 43.6% vs. Good Adherence 37.7%
- Mortality: Poor Adherence 10.2% vs. Good Adherence 5.3%

Recent Approvals

Ivabradine (Corlanor®)

- FDA Approval 2015
- Included on ESC 2012 guidelines
- Indication
  - Stable, chronic management
  - EF ≤ 35%
  - HR ≥ 70 with maximum beta blocker dosing
- Mechanism of Action
  - Funny channel blocker
  - Decreases cardiac pacemaker electrical activity
- Dosing
  - Initial 5 mg twice daily; May titrate to 7.5 mg twice daily

Hospital Admission
RRR 24%

Corlanor® prescribing information. Amgen; 2015.
Sacubitril/Valsartan (Entresto®) - Snapshot

- **Angiotensin Receptor Blocker + Neprilysin Inhibitor (ARNI)**
- **Mechanism of action**
  - Pro-drug that is metabolized to an active metabolite
  - Active metabolite selective inhibits neprilysin
  - Increases availability of naturetic peptides
- **NOT TO BE USED IN COMBINATION WITH ACEI or ARB**
  - 36 hour washout period is mandatory for patients previously on ACEI
- **Formulations**
  - Sacubitril/valsartan 24mg/26mg (50mg) twice daily
  - Sacubitril/valsartan 49mg/51mg (100mg) twice daily
  - Sacubitril/valsartan 97mg/103mg (200mg) twice daily

Entresto® prescribing information. Novartis; 2015.

Sacubitril/Valsartan (Entresto®) – Dosing

- **Enalapril-equivalent ACEI dose > 10mg daily or Valsartan-equivalent ARB dose > 160mg**
  - Entresto® 100mg twice daily
  - Double dose every 2-4 weeks up to 200mg twice daily as tolerated

- **Enalapril-equivalent ACEI dose ≤ 10mg daily or Valsartan-equivalent ARB dose ≤ 160mg**
  - Entresto® 50mg twice daily
  - Double dose every 2-4 weeks up to 200mg twice daily as tolerated

- **CrCl < 30 mL/min/1.73 m² or Child-Pugh Class B**
  - Entresto® 50mg twice daily
  - Double dose every 2-4 weeks up to 200mg twice daily as tolerated

Entresto® prescribing information. Novartis; 2015.
Sacubitril/Valsartan (Entresto®) - Benefits & Risks

• Compared to Enalapril 10 mg twice daily
  • Cardiovascular death
    • ARR 3.2%
    • RRR 19%
    • HR 0.80 (CI 0.71 to 0.89)
  • Hospitalization
    • ARR 2.8%
    • RRR 18%
    • HR 0.79 (CI 0.71 to 0.89)
  • All cause mortality
    • ARR 2.8%
    • RRR 14%
    • HR 0.84 (CI 0.76 to 0.91)

• Concerns
  • Neprilisyn inhibition increases circulating amyloid-beta peptide → Pathophysiologic Alzheimer’s Disease?
  • FDA is requiring an evaluation from Novartis by 2022
  • Possible connection to macular degeneration found in mice


Pharmacist Involvement
Specific Pharmacist Roles

• Intensive Care Unit/Cardiac Care Unit
• Discharge (Transition of Care)
• Post-discharge Clinic
• Medication Therapy Management

Drug-related Problems Encountered in Heart Failure

<table>
<thead>
<tr>
<th>Drug-related problem</th>
<th>Example in HF</th>
</tr>
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<tbody>
<tr>
<td>Untreated indications</td>
<td>Omission of ACEI from discharge med list in a patient with reduced LVEF and no contraindication</td>
</tr>
<tr>
<td>Improper drug selection</td>
<td>Patient with acute decompensated HF receiving Dronedarone</td>
</tr>
<tr>
<td>Subtherapeutic dosage</td>
<td>BP &gt; 135/85; HR &gt; 75 on Lisinopril 5mg daily and Carvedilol 6.25mg twice daily</td>
</tr>
<tr>
<td>Failure to receive medications</td>
<td>Patient unable to fill prescribed drugs after discharge</td>
</tr>
<tr>
<td>Overdosage</td>
<td>Digoxin trough 1.7</td>
</tr>
<tr>
<td>Adverse drug reactions</td>
<td>Increased edema in presence of HF after initiation of Pioglitzone for T2DM</td>
</tr>
<tr>
<td>Drug interactions</td>
<td>Worsening renal function after combined ACEI and NSAID use</td>
</tr>
<tr>
<td>Drug without indication</td>
<td>Continuation of DVT prophylaxis post-discharge</td>
</tr>
</tbody>
</table>

McNeely EB. J Pharm Pract. 2016 [ePub ahead of print].
Incidence of Drug-Related Problems in an Outpatient Clinic (per 100 patients)

Dempsey JT. J Pharm Prac. 2016 [ePub ahead of print].

Prominent Factors Impeding Transition of Care in Chronic Heart Failure

Albert NM. Circ Heart Fail. 2015;8:384-409.
Components of Successful Transition of Care Program for Patients with Heart Failure

- Medication reconciliation
- Very early post-discharge contact and communication
- Early office follow-up within first week post-discharge
- Patient education on chronic HF self-care, including recognizing early warning symptoms
- Communication of patient health record with patient and post-discharge healthcare providers
- Integrated, interdisciplinary collaboration and coordination
- A framework that ensures that education is initiated in the hospital before day of discharge AND continues during initial community-based care

Albert NM. Circ Heart Fail. 2015;8:384-409.

Patient Cases & Discussion
Questions & Answers