End-Stage Cardiac Disease: Medication Use and Symptom Management

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Disclosure

- I have no relevant financial relationships with manufacturers of any commercial products and/or providers of commercial services discussed in this presentation.
- This discussion will include the use of medications for off-label indications.

Objectives

- Describe the common symptoms of end-stage heart failure
- Discuss the drug classes used to treat heart failure
- Formulate a strategy to manage symptoms associated with end-stage heart failure
Epidemiology of Heart Failure (HF)

- 5.7 million patients in the United States
- About 900,000 new heart failure cases annually
- One in 9 deaths with heart failure mentioned on death certificate
  - Underlying cause of death in 65,120 patients

Types of HF

**Reduced Ejection Fraction**
- AKA: systolic dysfunction
- Poor contractile function
- Decreased ability for the heart to adequately pump blood
- Left ventricular ejection fraction (EF) ≤ 40%

**Preserved Ejection Fraction**
- AKA: diastolic dysfunction
- Normal or preserved contractile function
- Decreased ability for the heart to relax
- Left ventricular ejection fraction (EF) >40%
Systemic and pulmonary hypertension
• Atherosclerotic disease
• Valvular disease
• Cardiomyopathy
• Congenital heart disease
• Endocarditis/myocarditis
• Diabetes
• Anemia

Etiology

Neurohormonal Activity in HF

Right-Sided Dysfunction

| Symptomatic nervous system | Norepinephrine |

| Renin Angiotensin Aldosterone System | Angiotensin II |
|                                      | Aldosterone |

Clinical Presentation

| Symptomatic nervous system | Norepinephrine |

| Renin Angiotensin Aldosterone System | Angiotensin II |
|                                      | Aldosterone |

| Peripheral edema | Abdominal pain | Nausea | Biliousing | | Ascites | Jugular venous distension | Hepatomegaly |

| Pulmonary edema | Dyspnea on exertion | Orthopnea | Tachypnea | Cough | Paroxysmal nocturnal dyspnea | Bibasilar rales | Cheyne-Stokes respirations | S3 gallop | Pleural effusion |

| Fatigue | Weakness | Nocturia | Tachycardia | Pallor | Cyanosis of digits | Altered mental status | Sleep disorders | Anxiety | Anorexia/cachexia |
### New York Heart Association (NYHA) Functional Classification

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>I</td>
<td>Asymptomatic patients</td>
</tr>
<tr>
<td>II</td>
<td>No symptoms at rest, symptoms with ordinary physical activity</td>
</tr>
<tr>
<td>III</td>
<td>No symptoms at rest, symptoms with minimal physical activity</td>
</tr>
<tr>
<td>IV</td>
<td>Symptoms at rest, symptoms with any physical activity</td>
</tr>
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</table>

### ACCF/AHA Stages of Heart Failure

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
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<tbody>
<tr>
<td>A</td>
<td>High risk for developing HF, but no structural heart disease</td>
</tr>
<tr>
<td>B</td>
<td>Structural heart disease, but asymptomatic</td>
</tr>
<tr>
<td>C</td>
<td>Typical HF symptoms</td>
</tr>
<tr>
<td>D</td>
<td>Refractory HF symptoms at rest despite maximal therapy</td>
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ACCF/AHA = American College of Cardiology Foundation/American Heart Association

### Hospice Eligibility Criteria for Cardiovascular Disease

- Poor response to optimal guideline-directed medical therapy
- Declined or not a candidate for surgical procedure
- NYHA Class IV
- Supporting factors:
  - Ejection fraction ≤ 20%
  - Treatment-resistant symptomatic supraventricular or ventricular arrhythmias
  - Unexplained or cardiac-related syncope
  - Stroke due to cardiac embolism
  - Cardiac arrest or resuscitation
  - HIV disease
Mr. HF

- HF is a 71 yo male with end-stage heart disease. He has been hospitalized 4 times over the past 6 months for CHF exacerbations. During his last hospitalization, his furosemide dose was doubled. Frequently becomes short of breath with casual conversation. He states that he is tired of going to the hospital and would like to remain at home.
- PMH: CHF with LVEF 15%, HTN, s/p MI (8 years ago), OA
- Uncontrolled symptoms: dyspnea at rest, edema in legs (3-4+ pitting), fatigue
- BP 144/76, HR 62, O₂ sats 98% on RA, NKDA
- Medications:
  - Lisinopril 40 mg PO once daily
  - Metoprolol succinate ER 100 mg once daily
  - Furosemide 40 mg PO twice daily
  - KCl 20 mEq PO once daily
  - Atorvastatin 40 mg PO once daily
  - Aspirin 81 mg PO once daily
  - Celecoxib 200 mg PO once daily PRN
  - NTG 0.4 mg sublingual PRN

Medications Used for the Treatment of Heart Failure

HF Goals of Therapy

<table>
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<tr>
<th>Stage A</th>
<th>Stage B</th>
<th>Stage C</th>
<th>Stage D</th>
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<tbody>
<tr>
<td>• Heart healthy lifestyle</td>
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<td></td>
</tr>
<tr>
<td>• Prevent HF symptoms</td>
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<td></td>
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<tr>
<td>• Prevent further cardiac remodeling</td>
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<td></td>
<td></td>
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<tr>
<td>• Control symptoms</td>
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<td></td>
<td></td>
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<tr>
<td>• Improve quality of life</td>
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<td></td>
<td></td>
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<tr>
<td>• Prevent hospitalization</td>
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<td></td>
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<tr>
<td>• Prevent mortality</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>• Control symptoms</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>• Improve quality of life</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>• Reduce hospital admissions</td>
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<td></td>
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<tr>
<td>• Establish patient’s end-of-life goals</td>
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Adapted from 2013 ACCF/AHA Guideline for the Management of Heart Failure
### Guideline-Directed Medical Therapy (GDMT)

<table>
<thead>
<tr>
<th>Reduced Ejection Fraction</th>
<th>Preserved Ejection Fraction</th>
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<tr>
<td>- Angiotensin-Converting Enzyme Inhibitors (ACE-I)</td>
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<tr>
<td>- Angiotensin-Receptor Blockers (ARB)</td>
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<tr>
<td>- Beta Blockers</td>
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<tr>
<td>- Aldosterone Antagonists</td>
<td>- Non-Dihydropyridine Calcium Channel Blockers</td>
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<tr>
<td>- Diuretics</td>
<td>-</td>
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**Angiotensin-Receptor Blockers (ARBs)**

- **HF with reduced EF**
  - Who are unable to tolerate ACE-I (e.g., cough)
  - Caution if patient had angioedema with ACE-I
- **Efficacy** – similar to ACE-I
- **End-stage HF**
  - May initiate or continue ARBs
  - Consider dose reduction or discontinuation if patient has symptomatic hypotension
- **Adverse reactions**
  - Hypotension, hyperkalemia, angioedema (less common than ACE-I), rash, taste disturbances
- **Examples:**
  - Losartan (Cozaar®)
  - Valsartan (Diovan®)
  - Irbesartan (Avapro®)

**Beta-blockers**

- **Stable HF with reduced EF**
- **Efficacy:**
  - Decrease morbidity and mortality
  - Decrease HF hospitalizations
  - Decrease symptoms
  - Slow disease progression
  - Improve quality of life
- **Use with caution in patients with:**
  - Asthma, reactive airway disease (use beta-1 selective blocker, e.g., metoprolol)
  - Diabetes (mask signs/symptoms of hypoglycemia)

**Beta-blockers**

- **End-stage HF**
  - Typically not initiated in hospice
  - May continue if patient is already taking
  - Consider dose reduction or discontinuation if symptomatic bradycardia or symptomatic hypotension
  - Do not abruptly discontinue: withdraw slowly
- **Adverse Effects**
  - Hypotension, bradycardia, fatigue, fluid retention, dizziness, lightheadedness
- **Beta-blockers that have been proven to be effective**
  - Bisoprolol (Zebeta®)
  - Carvedilol (Coreg®, Coreg CR®)
  - Metoprolol succinate (Toprol XL®)
- **Other beta-blockers have not demonstrated the same benefit in HF**
Metoprolol Succinate (Toprol XL®) vs. Metoprolol Tartrate (Lopressor®)

Metoprolol succinate is an extended-release formulation that should not be crushed; however, these tablets may be cut in half.

Metoprolol tartrate is an immediate-release formulation and these tablets may be crushed or cut in half.

Aldosterone Antagonists

- HF with reduced EF
  - Who are already on a beta-blocker and ACE-I (or ARB)
- Efficacy
  - Decrease morbidity and mortality
  - Decrease HF hospitalizations
  - Decreases symptoms
- End-stage HF
  - May continue, but consider dose reduction or discontinuation if patient has renal insufficiency or hyperkalemia
- Adverse effects
  - hyperkalemia, gynecomastia, breast pain, sexual dysfunction
- Examples:
  - Spironolactone (Aldactone®)
  - Eplerenone (Inspra®)

Take Note!

Aldosterone Antagonists

If spironolactone or eplerenone is added to a patient’s HF regimen (that includes a loop diuretic and potassium chloride), remember to discontinue or reduce dose of potassium supplementation.

Take Note!
Loop Diuretics

- Site of action: loop of Henle
- Use in patients to manage fluid retention
- Efficacy
  - Decrease fluid retention
  - Decrease symptoms
  - Reduce preload
  - Have not been shown to decrease morbidity and mortality
- Loop diuretics are more potent than other classes of diuretics
- Caution in patients with true sulfa allergy (except ethacrynic acid)

Loop Diuretics

- End-stage HF
  - May initiate or continue to manage fluid retention
- Monitor patient closely to avoid over-diuresis as this may cause hypotension and worsen renal function
- Adverse effects
  - Electrolyte disturbances (hypokalemia, hyponatremia, hypomagnesemia, hypocalcemia), hypotension, dehydration
- Examples:
  - Bumetanide (Bumex®)
  - Furosemide (Lasix®)
  - Torsemide (Demadex®)
  - Ethacrynic acid (Edecrin®)

Thiazide and Thiazide-Like Diuretics

- Site of action: distal tubule (+/- proximal tubule)
- Efficacy:
  - Decrease fluid retention
  - Decrease symptoms
  - Improve exercise tolerance
  - Have not been shown to decrease morbidity and mortality in HF
- Typically used in combination with a loop diuretic to overcome diuretic resistance
- Caution using thiazide diuretics in patients with true sulfa allergy
- Examples:
  - Metolazone (Zaroxolyn®)
  - Hydrochlorothiazide (Microzide®)
  - Chlorothiazide (Diuril®)
Digoxin

- HF with reduced EF
  - Symptomatic despite use of ACE-I (or ARB), beta-blocker, diuretic, and aldosterone antagonist

- Efficacy
  - Decrease HF hospitalizations, decrease symptoms, improve exercise tolerance
  - Has not been shown to decrease mortality

- End-stage HF
  - Risks often outweigh the benefits in hospice and palliative care
  - Consider discontinuing if renal insufficiency

- Adverse effects
  - Nausea, vomiting, confusion, anorexia, arrhythmias, visual disturbances

- Factors that increase the risk of toxicity:
  - Renal insufficiency, low lean body mass, hypokalemia, hypomagnesemia, hypothyroidism, interacting medications (clarithromycin, erythromycin, tetracycline, amiodarone, dronedarone, tricyclic antidepressants, verapamil, quinidine)

Hydralazine and Isosorbide Dinitrate

- HF with reduced EF
  - An alternative for patients who do not tolerate ACE-I, ARB, or beta-blocker
  - Who are symptomatic despite ACE-I (or ARB), beta-blocker, and aldosterone antagonists

- Efficacy
  - Decrease mortality
  - Decrease HF hospitalizations
  - Improve exercise tolerance
  - Reduce preload (isosorbide) and afterload (hydralazine)

- Adverse effects
  - Headache, dizziness, flushing, hypotension, gastrointestinal complaints

- Examples:
  - Fixed-dose combination of hydralazine/isosorbide dinitrate (BiDil®)
  - Also available as separate agents
  - Dosing: TID – QID

Sacubitril/valsartan (Entresto®)

- Neprilysin inhibitor (sacubitril) + ARB (valsartan)
  - Inhibition of neprilysin = vasodilation and decreased sodium/water retention

- HF with reduced EF
  - NYHA class II-III who do not tolerate an ACE-I or ARB

- Efficacy
  - PARADIGM-HF study
  - Decrease in HF hospitalizations, cardiovascular death, and all-cause mortality
  - Reduces clinical progression?
  - Shown to be more effective than enalapril alone

- Do not use with an ACE-I or within 36 hours of the last ACE-I dose

- Adverse effects
  - Hypotension, hyperkalemia, cough, angioedema

- Cost $8.10 per tablet (all strengths)
  - Twice daily dosing - $16.20 per day
  - Available strengths (sacubitril-valsartan): 24-26 mg, 49-51 mg, 97-103 mg
Ivabradine (Corlanor®)

- Decreases heart rate by selective inhibition of the I_f current in the sinoatrial node
- Stable HF with reduced EF
  - NYHA class II-III who are receiving GDMT
  - Beta-blocker should be at the maximum tolerated dose
  - Sinus rhythm with a heart rate of ≥70 bpm at rest
- Efficacy: reduces HF hospitalizations, HF death
- Adverse effects
  - Bradycardia, hypertension, atrial fibrillation, luminous phenomena (visual brightness)
- Cost $7.80 per tablet (all strengths)
  - Twice daily dosing - $15.60 per day
  - Available strengths: 5 mg, 7.5 mg

HF with Preserved EF

- Manage blood pressure
  - Specific blood pressure targets not established
  - ACE-I or ARB
- Theoretically promote relaxation and diastolic filling
  - Beta-blockers
  - Non-dihydropyridine calcium channel blockers
    - Diltiazem (Cardizem®, Tiazac®)
    - Verapamil (Calan®, Verelan®)
  - Adverse effects: bradycardia, hypertension, peripheral edema, constipation
- Loop diuretics for fluid overload

Considerations in Hospice

<table>
<thead>
<tr>
<th>Symptomatic Benefit in HF?</th>
<th>Drug Classes</th>
</tr>
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<tbody>
<tr>
<td>Likely</td>
<td>ACE-I, ARB, Beta-Blockers, Loop Diuretics</td>
</tr>
<tr>
<td>Possibly</td>
<td>Aldosterone Antagonists, Thiazide and Thiazide-like Diuretics, Hydralazine + Nitrates</td>
</tr>
<tr>
<td>Limited</td>
<td>Digoxin, Calcium-Channel Blockers, Sacubitril/Valsalan, Ivabradine</td>
</tr>
</tbody>
</table>

Adapted from Palliative Care Consultant, 4th Edition
Medications to Avoid in HF

- Non-steroidal anti-inflammatory drugs (NSAIDs)
  - ibuprofen (Motrin®, Advil®), naproxen (Aleve®), meloxicam (Mobic®)
- Cyclooxygenase-2 (COX-2) inhibitors
  - Celecoxib (Celebrex®)
- Corticosteroids
  - Exceptions: dexamethasone
- Thiazolidinediones
  - Pioglitazone (Actos®), rosiglitazone (Avandia®)
- Non-dihydropyridine calcium channel blockers (HF with reduced EF)
  - Diltiazem, verapamil
- Antiarrhythmics
  - Exceptions: amiodarone, dofetilide

Symptom Management in End-Stage HF

General Supportive Agents

- Oxygen therapy
  - Correction of hypoxemia (<90% on room air)
  - Indications
    - Acute chest pain due to ischemia
    - Suspected hypoxemia of any cause
    - Cardiopulmonary arrest
General Supportive Agents

- Opioids
  - Management of dyspnea, pain, chest pain
  - Morphine sulfate typically first-line
  - Possible mechanisms:
    - Causes vasodilation
    - Suppresses respiratory awareness
    - Decreases oxygen consumption
    - Decreases myocardial oxygen requirements

Symptom Management – Dyspnea

- Non-pharmacologic interventions
  - Positioning to an upright position
  - Promote air movement using a fan or opening a window
  - Relaxation techniques

- Pharmacologic therapy
  - Opioids
    - Morphine 2.5-5 mg PO/SL every hour PRN
  - Diuretics for fluid overload
  - Oxygen if hypoxic
  - Benzodiazepines
    - Lorazepam 0.5 mg PO/SL every 4 hours PRN
  - Bronchodilators (e.g., albuterol)
  - Inotropic agents

Inotropic Agents

- Intravenous inotropic agents: milrinone, dobutamine

- Benefits
  - Effective for refractory symptoms of HF
  - May decrease hospitalizations
  - Allows patients with advanced HF to be discharged home

- Risks
  - Does not increase survival
  - Risk of arrhythmias, hypotension, tachycardia, IV line complications, sudden death
  - Patients with defibrillators may be at an increased risk of shocks
  - Requires specialized home care and training
  - Patients and family members should be involved in the decision-making process
Symptom Management – Fluid Overload/Edema

- Loop diuretics are first-line therapy
- Non-pharmacological therapy
  - Dietary sodium and fluid restriction if appropriate
  - Elevate legs, support stockings
- Monitoring
  - Target fluid weight loss = 0.5-1 kg/day
  - Symptomatic hypotension, renal dysfunction, dehydration
  - Electrolyte disturbances (e.g., hypokalemia)

Diuretic Resistance

- Several mechanisms proposed
  - Worsening renal function
  - Chronic diuretic use may cause rebound sodium retention
  - Renal adaptation – hypertrophy and hyperfunction of distal tubule cells
  - Decreased absorption of the diuretic due to hypoperfusion or bowel edema
  - Post-diuretic effect
  - Braking phenomenon
- Rule out:
  - Noncompliance with medication regimen
  - Medications that may cause/worsen edema

Overcoming Diuretic Resistance

- Increase loop diuretic dose and/or frequency
- Change loop diuretic to a different loop diuretic
  - Furosemide 40 mg = torsemide 20 mg = bumetanide 1 mg
- Switch from oral administration to intravenous administration
- Add a diuretic with a different mechanism of action
  - Metolazone (Zaroxolyn®) 2.5-10 mg PO once daily
  - Hydrochlorothiazide (Microzide®) 25-100 mg PO once twice daily
  - Chlorothiazide (DiaP®) 500-1000 mg IV once daily
  - Spironolactone (Aldactone®) 12.5-25 mg PO once daily
Symptom Management – Pain

- Up to 78% of patients with end-stage disease
- Can be multifactorial – myocardial ischemia, angina, bowel ischemia, comorbid conditions
- Opioids
  - Morphine 2.5-5 mg PO/SL every hour PRN
- Angina/chest pain
  - Isosorbide dinitrate, isosorbide mononitrate, nitroglycerin
  - Ranolazine (Ranexa®)
    - For angina pain refractory to nitrates, beta-blockers, calcium channel blockers
    - Extended-release tablet
    - May increase the risk of arrhythmias (prolong QT interval)
- Avoid NSAIDs for pain
  - Contribute to fluid retention, renal dysfunction, hypertension

Symptom Management – Fatigue

- Due to cardiac insufficiency, loss of muscle mass, deconditioning, comorbid conditions, medications
- If tolerated, optimize HF medications to improve cardiac performance
  - May need to decrease dose of beta-blocker
- Encourage regular exercise if appropriate
- May benefit from a stimulant (e.g., methylphenidate)
  - Keep in mind adverse effects: tachycardia, palpitations, insomnia, anxiety, anorexia

Symptom Management – Depression/Anxiety

- Depression can occur in 30-35% of patients with HF
  - Prevalence increases with worsening functional class
  - Associated with higher symptom burden, increased cardiac events, hospitalizations, death
- Psychosocial support
  - Cognitive behavioral therapy, support groups, spiritual support
- Antidepressant therapy
  - Selective serotonin-reuptake inhibitors
  - Methylphenidate
- Benzodiazepines for anxiety
  - Lorazepam 0.5 mg PO/SL every 4 hours PRN
Mr. HF

- HF is a 71 yo male with end-stage heart disease. He has been hospitalized 4 times over the past 6 months for CHF exacerbations. During his last hospitalization, his furosemide dose was doubled. Frequently becomes short of breath with casual conversation. He states that he is tired of going to the hospital and would like to remain at home.

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  - Aspirin 81 mg PO once daily
  - Celecoxib 200 mg PO once daily PRN
  - NTG 0.4 mg sublingual PRN

Edema
- Increase furosemide dose to 60 mg PO BID
- Change furosemide to either bumetanide 1 mg BID or torsemide 20 mg BID
- Add metolazone 2.5 mg PO once daily or spironolactone 12.5 mg PO once daily
- If add spironolactone, consider discontinuing potassium

Dyspnea
- Add morphine 2.5 mg PO/SL every hour PRN
- Decreasing edema may help improve dyspnea
- No need for oxygen (no hypoxia)

Fatigue
- Consider decreasing dose of metoprolol succinate ER to 75 mg PO once daily
- Discontinue celecoxib

Key Points

- Patients with end-stage heart disease have symptoms at rest and are unable to carry on minimal physical activity or exertion without symptoms
- Use of guideline-directed medical therapy (e.g., ACE-Is, beta-blockers, aldosterone antagonists, diuretics) in hospice and palliative care may become limited due to hypotension and declining renal function
- Opioids are effective for managing dyspnea, pain, chest pain
- Consider diuretic resistance in patients with persistent or worsening fluid overload
Questions?

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References

- Goldbinder (Corlanor) for heart failure. Medical Letter. May 2015;57(1469):75-76.
References