Heart Failure
CTSHP Fall Seminar
Laurajo Ryan, PharmD, MSc, BCPS, CDE

Pharmacist Learning Objectives
- Outline the pathophysiology of heart failure
- List triggers for decompensated heart failure
- Describe current options for treating heart failure
- Identify how current and future therapy options can impact the course of disease in heart failure
- Devise an appropriate pharmacotherapy regimen for a patient with heart failure

Pharmacy Technician Objectives
- Define heart failure
- Describe the epidemiology of heart failure
- List triggers for decompensated heart failure
- Identify common adverse events associated with heart failure

“A CONDITION IN WHICH BECAUSE OF A CARDIAC ABNORMALITY, THE HEART FAILS TO PUMP BLOOD AT A RATE THAT MEETS THE NEEDS OF THE BODY WHILE MAINTAINING LOW FILLING PressURES”

“A COMPLEX CLINICAL SYNDROME RESULTING FROM A STRUCTURAL OR FUNCTIONAL CARDIAC DISORDER THAT IMPAIRS VENTRICULAR FILLING OR EJECTION”

Heart Failure Population
- ~5 million patients in the U.S.
  - Numbers rising
  - Aging population
  - MI survival
  - Mortality
    - 5 year survival ~50%
  - Factors affecting prognosis
    - Age
    - Gender
    - LV EF
    - Renal function
    - Blood pressure
    - HF etiology
    - Drug or device therapy
  - Medicare
    - Most common diagnosis
    - Most costly diagnosis
    - Age > 65
      - Most common reason for hospitalization
    - Age > 75
      - ~10%

Heart Failure Consequences
- Impaired cardiac pumping ability
  - Cannot keep up with oxygen demand
  - Dyspnea & fatigue
  - Decreased exercise tolerance
  - Fluid retention
    - Pulmonary congestion
    - Peripheral edema
**Systolic vs. Diastolic**

- **Systolic (HFrEF)**
  - Decreased
  - Cardiac output
  - Tissue perfusion
  - Large dilated heart
  - BP low/normal
  - L EF
  - S₃ gallop
  - Poor prognosis

- **Diastolic (HFpEF)**
  - Pooling of blood in the venous system
  - Small LV, concentric hypertrophy
  - Women > men
  - Normal or increased EF
  - S₄ gallop
  - Treatment not well established
  - Prognosis better vs. systolic

**Etiology**

- **“Congestive” Heart Failure**
  - Syndrome
    - Numerous etiologies
    - Common set of symptoms
    - Common physiological adaptations
    - Abnormal ventricular function
    - Neurohormonal regulation
      - Contraction (systole)
      - Relaxation (diastole)
  - Treatment not well established
    - Exacerbate symptoms
    - Reduce survival

**Clinical Presentation**

- Asymptomatic → cardiogenic shock
  - Jugular venous pressure
  - Heart sounds, murmurs
  - Lower extremity edema
  - Plasma BNP
  - Dyspnea, particularly on exertion
  - Pulmonary rales, crackles
  - Orthopnea
  - Paroxysmal nocturnal dyspnea
  - Exercise intolerance
  - Tachypnea
  - Cough
  - Hemoptysis
  - Fatigue
  - Nocturia
  - Ascites
  - Abdominal pain
  - Anorexia
  - Nausea, bloating
  - Poor appetite
  - Early satiety
  - Mental status changes

**Treatment Goals**

- Goals
  - Improve quality of life
  - Relieve/reduce symptoms
  - Prevent, minimize hospitalization
  - Slow disease progression
  - Prolong survival

- Current standards
  - Diuretics
  - ACE inhibitor or ARB
  - β-blocker
  - ± spironolactone
  - ± digoxin
11/4/2014

Key advances in the past 10 years of HF research

Pathophysiology

Pathophysiology—Decreased Perfusion

- Cardiac system senses decreased perfusion
  - Increased cardiac muscle mass
    - Hypertrophy
      - Changes myocardium at molecular & cellular levels
    - Major focus for therapeutic interventions
      - Reverse modeling, decrease mortality, slow disease progression

- Adaptive responses become harmful
  - Contribute to disease progression

Compensation

- Reaction to decreased pumping capacity
  - Compensation to maintain CO
    - Intended to be short term fix for acute reductions
      - BP or renal perfusion
  - Persistent decline in CO
    - Long term activation of compensatory responses
      - Functional, structural, biochemical, molecular changes
  - Mechanisms lead to Na+ & H2O retention
    - Preload to CO
      - Less effect on SV in HF than normal heart
RAAS Activation

- Increases aldosterone release
  - ↑ Na+ retention
  - Interstitial cardiac fibrosis
  - Other target organ fibrosis, vascular remodeling, pro-inflammatory state, oxidative stress
  - ↑ risk of arrhythmias
  - Aldosterone antagonists reduce mortality

- Angiotensin II
  - Arterial & venous vasoconstriction
  - Na+ & water retention
  - Maintains perfusion pressure in severe HF
  - Stimulates ventricular hypertrophy & remodeling
  - ACE-inhibitors / ARBs prolong survival

Increased AVP

- Vasopressin release
  - Arterial vasoconstriction
  - Venous vasoconstriction
  - Na+ & water retention
  - Initially beneficial
    - Restores hemodynamic stability
  - Eventual cardiac tolerance
    - Decreased vagal tone
    - Decreased HR variability

Autonomic System Activation

- Dysfunctional response to stressors
  - ↑ heart rate at rest
  - Contractile stimulation
  - Increased peripheral vascular resistance
    - Arterial vasoconstriction
    - Venous vasoconstriction
  - Vasotocin
    - Tachyure
    - Attempt to redistribute blood flow
      - Coronary & cerebral vessels
    - Leads to ↓ CO
  - Tachycardia & increased contractility
    - Norepinephrine
    - Abnormal baroreceptor responses

- Decreased cardiac response
  - Inotropic stimulation
    - ↓ & desensitized β1 receptors
    - Contributes to exercise intolerance
    - Contractile dysfunction
    - Reduced response to inotropic agents in acute HF
    - Metoprolol upregulates the β1 receptors
  - Hypertrophied myocardial cells
    - Shortened lifespan
    - Slower contraction/relaxation
    - Leads to diastolic failure

Counter-regulatory Hormones

- Atrial-natriuretic peptide & brain-natriuretic peptide
  - Enhance natriuresis & diuresis
    - Reduce right atrial pressure
    - ↓ systemic vascular resistance
    - ↓ aldosterone secretion
    - ↓ sympathetic activation
    - ↓ systemic resistance
    - ↓ hypotrophy
    - Vasodilation

- Elevated BNP
  - Marker for increased mortality, risk of sudden death, symptoms, hospitalization
  - BNP assays
    - BNP or N-terminal pro-BNP
    - Help with HF diagnosis
  - Recombinant human BNP (nesiritide)
    - Short-term hemodynamic & symptom improvement
      - Acute HF

HF Exacerbation

- Causes
  - Non-adherence
    - Na+ & H2O restrictions
  - Medication
    - Noncompliance
    - Inappropriate/inadequate therapy
    - Medication
  - Cardiac events
    - MI/ischemia
    - CAD
    - Atrial fibrillation
  - Anemia
  - Infection

WARNING

MEDICATION MAY CAUSE SEVERE SIDE EFFECTS SUCH AS HEADACHE, DIZZINESS, AND DEATH. TAKE AS PRESCRIBED.

HF EXACERBATION
HF Exacerbation

- Negative inotropes
  - Antiarrhythmics
  - β-blockers
  - Calcium channel blockers
    - Verapamil
    - Diltiazem
- Antifungals
  - Itraconazole
  - Terbenafoine

- Cardiotoxic
  - Ethanol
  - Doxorubicin
  - Daunorubicin
  - Cyclophosphamide
  - Trastuzumab
  - Imatinib
  - Amphetamines
    - Cocaine
    - Methamphetamine

HF Management

- Control risk factors
  - Alcohol & smoking cessation
  - Treat CAD, myocardial ischemia
  - Treat HTN, DM, lipids & thyroid

- Treatment
  - ACEI or ARB
  - Spironolactone if warranted

- Symptom treatment
  - Diuretic
  - Na+ restriction +/- digoxin

- Follow-up
  - Patient education
  - Patient self-care
  - Phone or electronic follow-up

The Interventions

DIURETICS

Loop Diuretics

- Symptomatic treatment of fluid retention
  - ↓ symptoms
  - ↓ hospitalizations
  - ↑ exercise tolerance
  - ↑ quality of life
- No evidence of ↑ survival
- Adverse effects
  - Volume depletion
  - ↓ renal perfusion
  - Hypokalemia
  - Hyponatremia

Loop Diuretics

- Most potent diuretics
  - Efficacy maintained in impaired renal function
  - Reduced effect with dietary Na+
- Electrolyte abnormalities
- Dosing strategies
  - Dose increase
  - Addition of thiazide
  - Bolus vs. CI
Thiazide Diuretics

• Weak diuretics alone
  – Combine with loop
  – Improved diuresis
• Comparable effects
  – Metolazone ↑ potent
  – Even with ↓ renal function

VASODILATORS

ACE Inhibitors

• Standard of care
  – Improved hemodynamics
    • ↓ SVR (afterload)
    • ↑ stroke volume • CO
    • ↓ pulmonary wedge pressure
  – Improved functional status
    • ↑ exercise tolerance
    • ↓ symptoms
  – Improved survival
    • 20—30% vs. placebo
• Adverse events
  – Cough
  – Hypotension
  – Renal insufficiency
    • Drop in GFR
  – Hyperkalemia
  – Angioedema
• Contraindications
  – Angioedema
  – Pregnancy

Angiotensin Receptor Blockers

• Similar benefit to ACE inhibitors
  – Theoretical advantage over ACE inhibitors
    • Block receptor vs. production
• Well tolerated—no cough
  – No effect on bradykinin
• Less drug interactions
  – Not metabolized by cytochrome P-450
• Recommended if ACE intolerant
  – Cough
  – Angioedema cross reaction—use extreme caution

Nitrates & Hydralazine

• Nitrates
  – Venodilation
  – ↓ preload
• Hydralazine
  – Direct vasodilator
    • ↓ SVR, ↑ SV & CO
• Combination long-acting nitrate & hydralazine
  – Add-on to standard therapy in African Americans
    • 43% decrease in all-cause mortality
  – Non-African American patients intolerant of ACE inhibitor/ARB

BETA-BLOCKERS
β-Blockers

- Stable patients with ↓LVEF
  - Add—on therapy
  - Improve survival
  - Decrease HF progression
  - Increase ejection fraction
  - Improve symptoms
  - Numerous large clinical trials support benefit
    - Carvedilol (Coreg®)
    - Metoprolol succinate (Toprol XL®)
    - Bisoprolol (Zebeta®)
  - Positive effects NOT a class effect

- Initiate low dose
  - Titrate slowly (over weeks)
  - Adverse effects—particularly with too fast titration
    - Bradycardia
    - Hypotension
    - Fatigue
    - Worsening HF
  - Continue during hospitalization unless hemodynamically unstable

Aldosterone Antagonists

- Aldosterone
  - Na⁺ & H₂O retention
  - Myocardial hypertrophy
  - Myocardial fibrosis
  - Vascular remodeling

- Aldosterone blockade
  - Inhibit Na⁺ reabsorption
  - Inhibit K⁺ excretion
  - Improved survival
    - Pump failure
    - Sudden cardiac death

- Spironolactone (Aldactone®)
  - Gynecomastia

- Eplerenone (Inspra™)
  - Selective mineralocorticoid receptor blocker
  - No gynecomastia

- Recommended
  - Stage C & D (B with major risk factors)
  - Benefit in early disease not as well established

MISCELLANEOUS AGENTS

Digoxin

- Does NOT improve survival
- Improves symptoms
  - ↑ exercise tolerance
  - ↑ CO
  - ↓ hospitalization
- Mild positive inotrope
  - Decreased sympathetic activation
    - Sensitizes baroreceptors

- Withdrawal
  - Risk of worsening HF
    - ~30% in subsequent 3—5 months

- Predictors of efficacy (symptomatic patients)
  - S₃
  - Longer duration of HF
  - LV dilation
  - LVEF depression

- Low dose
  - >1.0ng/mL associated with ↑ mortality

Antiarrhythmic Drugs

- Sudden cardiac death
  - 40—50% HF mortality
    - Ventricular tachyarrhythmias

- Empiric antiarrhythmic therapy
  - No benefit in HF
  - Pro-arrhythmic

- Amiodarone (Cordarone®, Pacerone®)
  - Destabilizing ventricular tachycardia, fibrillation or sudden death
    - Prevents excessive defibrillator shocks
Anticoagulation

- Thromboembolism is common
  - Especially with very low EF
- Should all HF patients be anticoagulated?
  - Controversial
    - Absence of atrial fibrillation
    - Trials have significant overlap

Seven Major Classes of Biomarkers Contributing to the Biomarker Profile in HF

Neprilysin Inhibition

- HFrEF
  - Angiotensin receptor–neprilysin inhibitor
    - LCZ696 vs. enalapril
- Methods
  - Double-blind randomized controlled trial
  - N = 8442 class II–IV heart failure & EF ≤ 40%
  - Primary outcome
    - Composite of CV or hospitalization for HF
- Results
  - Trial stopped @ mean f/u 27 months
  - Primary outcome
    - LCZ696 = 514 (21.8%) vs. enalapril = 1117 (26.5%)
    - Hazard ratio 0.80; 95% CI, 0.73 to 0.87; P<0.001
  - LCZ696 group
    - > hypotension, non-serious angioedema
    - < renal impairment, hyperkalemia, cough
- Conclusions
  - LCZ696 superior to enalapril in reducing risk of death & hospitalization for HF
Non-Pharmacologic

![Image of LVAD and heart](image)

**Cardiac Stem Cells**

- **Homing mechanism**
  - Migrate to heart after injection

**Heart Failure**

- **Common deadly disease**
  - Numerous compensatory mechanisms
  - HFrEF vs HfPEF
    - Treatment differences
  - Current therapies
  - Up & coming therapies