Heart Failure Update
Hope or Hype?

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I HAVE NO POTENTIAL FINANCIAL CONFLICTS TO DISCLOSE
Pharmacy Technician Learning Objectives

- Identify the risk factors for heart failure
- Describe what constitutes a heart failure exacerbation
- Recognize drug therapies common to patients with heart failure
- List common drugs associated with heart failure exacerbations
Pharmacist Learning Objectives

• Describe how newly approved treatments for heart failure fit into current therapy
• Develop a rational treatment plan for a patient with decompensated heart failure
• Explain interventions to minimize the rate of readmission after a heart failure exacerbation
Heart Failure Overview

• Cardiac output cannot meet demands of body
  – Shortness of breath
  – Edema
  – Generalized fatigue/weakness

• Exacerbation
  – New onset heart failure
  – Deterioration of stable heart failure
Etiology

Myocardial Infarction | Aging | Atrial Fibrillation | Renal dysfunction

Smoking | Myocardial Cell death | NT-proBNP | Urinary albumin loss

HFrEF | Obesity | HFpEF

Men | Women

Unique Phenotype-Specific Risk Factors?

“Common HFpEF” phenotypes: (>1 may coexist in patient)
- Filling limitation (diastolic)
- Ejection limitation (systolic)
- Cardioacceleration (HR/autonomic)
- Vasoregulation (endothelial)
- Skeletal muscle
- Others?

“Non-HFpEF” etiologies:
- Valvular heart disease
- Hypertrophic cardiomyopathy
- Infiltrative cardiomyopathy
- Constrictive pericarditis
- High output heart failure
- Right ventricular myopathy

Etiology-specific Treatments (surgery, chemotherapy)

Unique Phenotype-specific Treatments?

Eur Heart J 2013;34:1393
Heart Failure Death 2000—2014

HF Cause of Death 2000—2014

Heart Failure Spectrum

- **HFrEF (systolic)**
  - Large dilated heart
  - Decreased ejection fraction (EF), cardiac output & tissue perfusion
  - Poor prognosis

- **HFpEF (diastolic)**
  - Normal or increased ejection fraction
  - Venous pooling
  - Prognosis better vs. systolic
Pathophysiology

• Compensation
  – Reaction to decreased pumping capacity
  – Increased preload
    • Attempt to increase CO
    • Na⁺ & H₂O retention
      – RAAS, AVP, SNS, BNP, ANP
      – Intended to be short term fix for acute reductions

• Persistent decline in CO
  – Long term activation contributes to disease progression
Heart Failure Compensation

- Systems activated to increase cardiac output
  - Renin angiotensin aldosterone system (RAAS) activation
  - Sympathetic activation
  - Increased vasopressin
  - Increased counter-regulatory hormones
    - ANP, BNP
HF Exacerbation

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

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

- Cardiotoxic substances
  - Ethanol
  - Doxorubicin, daunomycin, cyclophosphamide, trastuzumab, imatinib
  - Amphetamines
    - Cocaine, methamphetamine

- Na⁺ / H₂O retention
  - NSAIDs
  - Thiazolidinediones
  - Glucocorticoids
PHARMACOTHERAPY
Interventions

- Vasodilators
  - ACE inhibitors
  - ARB
  - Nitrates & hydralazine
- Beta-blockers
- Aldosterone antagonists
- Symptom control
  - Diuretics
  - ± digoxin
Vasodilation

• **ACE Inhibitors**
  – Improved hemodynamics & functional status
  – Improved survival

• **Angiotensin receptor blockers (ARBs)**
  – Benefit similar to ACE inhibitors; recommended if ACE intolerant

• **Long-acting nitrate plus hydralazine**
  – Add—on to standard therapy in African Americans
  – Non-African American intolerant of ACE inhibitor/ARB

Nat Rev Nephrol 2010;6,:319
Neprilysin

- Degrades vasoactive peptides
  - Natriuretic peptides, bradykinin, others
Neprilysin Inhibition

- Increases natriuretic peptides & opposes neurohormonal activity
PARADIGM-HF

• HFrEF
  – LCZ696 (valsartan & neprilysin inhibitor) vs. enalapril

• Methods
  – Double-blind RCT
    • N = 8442 class II-IV HF
    • EF ≤ 40%
  – Primary outcome
    • Composite of CV death or hospitalization for HF

N Engl J Med 2014;371;11
PARADIGM-HF

• Results
  – Trial stopped @ mean f/u 27 months
  – Primary outcome
    • LCZ696 = 914 (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

N Engl J Med 2014;371;11
PARADIGM-HF

• Conclusions
  – LCZ696 superior to enalapril in reducing risk of death & hospitalization for HF

N Engl J Med 2014;371;11
Sacubatril & Valsartan (Entresto®)

• Potential to replace ACE inhibitor
  – Contraindicated with ACEI
  – HFrEF NYHA class II-IV
    • LVEF ≤40%
    • Stable
      – Symptomatic despite optimal therapy

• Dosing
  – Sacubatril/valsartan
    • 24mg/26mg=50mg (~40mg valsartan)
    • 49mg/51mg=100mg (~80mg valsartan)
    • 97mg/103mg=200mg (~160mg valsartan)
Beta-Blockers

• Standard of care in stable HFrEF
  – Improved survival & decreased HF progression
    • Increase ejection fraction
  – Improve symptoms
  – Do not initiate if decompensated
    • Continue during hospitalization unless hemodynamically unstable

• Negative chronotrope
  – Decreased heart rate

• Tolerability
  – Asthma
  – Blood pressure
Heart Rate Control

- HFrEF patients
  - Elevated HR
    - Increase in morbidity & mortality

- Placebo group in SHIFT trial
  - Risk of CV death or HF hospitalization
    - 2.9% per 1BPM increase
    - 15.6% per 5BPM increase

- HR <60bpm vs. >75bpm
  - 32.4% decrease mortality & HF hospitalization

![Graph showing the relationship between heart rate and patients with primary composite endpoint over months. The graph indicates a significant decrease in patients with primary composite endpoint as heart rate increases from 70 to 87 bpm.](Lancet 2010;376:886)
HR Regulation

• SA node produces “pacemaker” impulses
  – Spreads to AV node triggering ventricular contraction

• $I_f$ current
  – Initiates diastolic depolarization of SA node
HR Regulation

- HCN channels
  - Hyperpolarization-activated cyclic nucleotide-gated channels
  - Regulate flow of $I_f$ current
Ivabradine

- **$I_f$ inhibitor**
  - Binds to HCN channels
    - “use dependent”

- **SA node (f channels)**
  - Carries $I_f$ current
    - prolongs diastolic time
    - Inhibition reduces heart rate

- **Retina (h channels)**
  - Carries $I_h$ current
    - Inhibition causes visual disturbances
Ivabradine

- Prolongs diastolic time
  - Inhibits $I_f$ current, reducing heart rate
- Increases stroke volume
  - Preserves myocardial contractility
  - BP

Nat Rev Drug Disc 2006;5:1034
Ivabradine

- HFrEF patients
  - Elevated HR
    - Increase in morbidity & mortality
- HR ≥ 87 BPM
  - >2X risk for CV death or hospitalization for HF vs. HR 70-72 BPM
    - Hazard ratio 2.34, 95% CI 1.84–2.98, p < 0.0001
- Elderly HFpEF patients had symptomatic improvement & HR reduction

Eur Heart J 2013;34:suppl 1
Circulation 2001;103:1428
Lancet 2010;376:886
Ivabradine (Corlanor®)

- Approved to reduce hospitalization from HF
  - Consider in HFrEF
    - LVEF ≤35%
    - Resting heart rate
      - ≥70 BPM
    - On max dose of BB
      - Or intolerant

- Titrate to resting HR
Aldosterone Antagonists

• Aldosterone effects
  – Na\(^+\) & H\(_2\)O retention
  – Myocardial hypertrophy, fibrosis, vascular remodeling

• Aldosterone blockade
  – Improved survival class III/IV HFrEF
    • Reduced pump failure & sudden cardiac death

• Benefit in early disease not as well established; consider if symptomatic on optimal therapy

Nat Rev Nephrol 2010;6;319
Digoxin

• Mild positive inotrope
  – Decreases sympathetic activation
    • Symptom control
      – Decreases hospitalization
        » Does NOT improve survival

• Symptomatic HFrEF on appropriate therapy
  – Low dose

• Mechanism
  – Inhibits myocardial Na\(^+\)K\(^+\) ATPase pump
    • Increased Ca\(^{++}\) influx via Na\(^+\)Ca\(^{++}\) exchanger
      – Increases cardiac contraction
Pipeline Therapy

• RAAS activation
  – Long term remodeling
    • ACEI, ARB, aldosterone antagonists have proven benefits
  – Acute effects on hemodynamics & renal function
    • ACEI, ARB, aldosterone antagonists not appropriate for use in acute heart failure

• TRV027
  – β-arrestin biased ligand AT$_1$R
    • Allows blockade of AT2
      – Vasoconstriction, H$_2$O, Na$^+$ retention
    • Stimulation of β-arrestin
      – Increased cardiac contractility

http://www.trevenainc.com/TRV027-how-it-works.php
JT—54 YO ♀

- 2nd hospitalization for HF exacerbation in 3 months
  - Past medical history
    - Developed HFREF after an MI in 2009 (LVEF <30%)
    - Hypothyroidism
    - Osteoarthritis
  - Outpatient medications
    - Metoprolol succinate, lisinopril, furosemide

- What else do you want to know?
Compensation in patients with HF is detrimental because long-term it can cause:

A. Sodium and water retention
B. Increased heart rate
C. Cardiac remodeling
D. All of the above
Patients who require hospitalization for HF are likely to show which of the following symptoms?

A. Shortness of breath
B. Fluid overload
C. Tachycardia
D. All of the above
Which of the following patients is likely to receive the most benefit from sacubitril/valsartan?

A. Clinically stable patient with HFpEF
B. Asymptomatic patient with HFrEF
C. Stable patient with HFrEF and symptoms despite optimal therapy
D. Patient with current HFrEF exacerbation despite optimal therapy
Which of the following patients might be expected to receive benefit from ivabradine?

A. 52 YO man with HFrEF and severe asthma
B. 63 YO woman with HFrEF, BP 92/58mmHg, HR 82BPM on optimal therapy
C. 49 YO man with acute decompensated HF
D. A & B only
E. All of the above
Summary

• Current standards of care
  – ACE inhibitors/ARB
    • Nitrates & hydralazine
  – Beta-blockers
  – Aldosterone antagonists
  – Symptom control
    • Diuretics
    • ± digoxin

• Newcomers
  – Sacubatril/valsartan
    • Symptomatic despite optimal therapy
    • Intolerant to ACEI/ARB
  – Ivadrabine
    • Elevated HR despite optimal BB therapy