Innovation in Heart Failure Treatment

Lynne Sylvia, PharmD
Vincent Willey, PharmD, BCACP

Supporter

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Disclosures

• Lynne Sylvia: declares no conflicts of interest, real or apparent, and no financial interests in any company, product, or service mentioned in this program, including grants, employment, gifts, stock holdings, and honoraria.

• Vincent Willey: declares no personal conflicts of interest, real or apparent, and no financial interests in any company, product, or service mentioned in this program, including grants, employment, gifts, stock holdings, and honoraria. His employer, HealthCore, does perform research studies that are funded by multiple pharmaceutical companies.

The American Pharmacists Association is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.

Learning Objectives

1. Explain the pathophysiology of heart failure, including the effects of neurohormones on the progression of disease.
2. Apply clinical trial data regarding the risks and benefits of current and newly approved treatments for heart failure to patient cases.
3. Describe the mechanisms of action and role of newly approved pharmacologic treatments for the management of heart failure.
4. Formulate an individualized care plan for a patient with heart failure that emphasizes self-care.
5. Apply patient education skills to promote adherence to therapy to prevent heart failure complications.
What are the evidence-based cornerstone medications for treatment of heart failure?

A. ACE inhibitor + beta-blocker + digoxin
B. ACE inhibitor + beta-blocker + aldosterone antagonist
C. Digoxin + furosemide
D. ACE inhibitor + beta-blocker + furosemide

Which of the following is TRUE about heart failure therapies?

A. Furosemide is the preferred oral diuretic due to its high bioavailability
B. All beta-blockers have been shown to be equal in effectiveness
C. Digoxin decreases hospitalization rates but not mortality
D. All of the above

Besides taking HF medications as directed, what is the most important action that a patient should take to control HF and prevent hospitalizations?

A. Weighing him/herself each day
B. Monitoring how much fluid he/she takes in each day
C. Reading food labels to limit salt intake
D. Taking his/her blood pressure twice a week

Which of the following statements regarding new HF therapies is true?

A. Sacubitril/valsartan is a neprilysin agonist and angiotensin receptor antagonist
B. Sacubitril/valsartan increases B-type natriuretic peptides (BNP), angiotensin II and bradykinin levels
C. Ivabradine has both negative chronotropic (rate) and inotropic (force) effects
D. Ivabradine’s main effects are on the atrioventricular node

Which of the following is true with regards to the Paradigm-HF trial which studied sacubitril-valsartan (S/V)?

A. S/V reduced death from CV causes and hospitalizations from HF compared with an ACE-I
B. S/V reduced death from CV causes and hospitalizations from HF compared with placebo
C. Death from any cause was not different between the study treatment arms
D. Approximately 70% of patients enrolled in the trial had NYHA class III and IV HF

Which of the following patients is most appropriate for ivabradine therapy?

A. A 60 y/o male with HF & HTN, LVEF = 30%, HR = 64 bpm who is taking an ACE-I and beta-blocker
B. A 55y/o female with HF & A Fib, LVEF = 35%, HR = 80 bpm who is taking an ACE-I but can’t tolerate a beta-blocker
C. A 65 y/o female with HF & HTN, LVEF = 40%, HR = 68 bpm who is taking an ACE-I and beta-blocker
D. A 58 y/o male with HF & DM, LVEF = 30%, HR = 76 bpm who is taking an ACE-I and beta-blocker
Heart Failure Management: Redefining the Role of the Pharmacist

Clinical Pharmacy Specialist – Cardiology

Meet Tom

• Tom is a 21 year old college student – resident assistant (RA), self-described ‘foodie’ who is studying photography and videography at a rural campus.
• He presents to clinic with shortness of breath and a 30 pound weight gain over the last 6 months, despite poor appetite
• He reports having a mild productive cough, feeling winded after coughing; he requires two extra pillows for sleeping.
• His family history includes father with nonischemic cardiomyopathy diagnosed in his 40s.

The work-up

• Test results –
  – Left ventricle is severely dilated
  – Left ventricular systolic function is severely reduced
  – Ejection fraction (LVEF) is 10% with global hypokinesis
  – No significant valvular disease

  – Acute kidney injury (Scr 1.44 versus baseline of 0.72)

The Discussion

• Diagnosis:
  – Nonischemic, dilated cardiomyopathy (idiopathic)
  – NYHA Class 3 (Stage C) heart failure

• Options (and Advanced Therapies):
  – Medication Management:
    • oral therapies and home IV infusions
  – Mechanical Management:
    • implantable heart pump
  – Heart Transplantation

The Face of Heart Failure

• Approximately 6 million people in USA
• 500,000 people newly diagnosed yearly
• One in 5 lifetime risk; risk increases with age
• Total cost of care in the USA in 2009 was $37.2 billion, the largest single Medicare expenditure
• One month readmission rate of 25%

Advanced therapies: extend life expectancy, present new opportunities and responsibilities to the health care team

After this session, you will be able to:

• Adapt your practice to the changing face of heart failure
  • Explain the pathophysiology of heart failure, particularly the effects of neurohormones on the progression of disease
  • Provide evidence-based recommendations for treatment of chronic heart failure
  • Design an individualized action-based plan for a patient that emphasizes self care
  • Counsel a patient to enact their self-care plan
What is heart failure?

- In simplest terms... pump failure
- Results from any disorder that affects the heart’s ability to contract (systolic function) or fill/relax (diastolic function)

Tissues/organs are not perfused adequately to meet body demands

Types of Heart Failure as a Cup

Systolic heart failure: The cup (ventricle) is full. The person drinking from the cup can only take sips from the cup. The person remains thirsty. The body tissues remain thirsty.

Diastolic heart failure: The cup (ventricle) can only be filled half way. The person drinking from the cup can take a big gulp. But, the person remains thirsty. The body tissues remain thirsty.

Classification of HF

ACC/AHA Classes A through D

- A: At high risk for HF but without structural heart disease or symptoms of HF (e.g., patients with HTN, DM, CAD or metabolic syndrome)
- B: Structural heart disease but without signs or symptoms of HF (e.g., MI)
- C: Structural heart disease with prior or current symptoms of HF (e.g., dyspnea)
- D: Refractory HF requiring specialized interventions (e.g., at rest)

NYHA Classes I - IV

- I: Asymptomatic
- II: Symptomatic with moderate exertion
- III: Symptomatic with minimal exertion
- IV: Symptomatic at rest

The Syndrome that is Heart Failure

Initial insult:

- Ischemic cardiomyopathy
- Post-MI
- Nonischemic myopathy
  - Genetic disorders
  - Alcohol-induced
  - Adriamycin-induced
  - Viral disorders
  - Valvular disease – stenosis (pressure) or regurgitation (volume)

Adaptive and maladaptive state:

- Adapt to low CO by release of neurohormones
- Chronic neurohormone release leads to maladaptation (remodeling of ventricular and vascular tissue)
- Progressive Syndrome

Physiologic response to low CO

CO = SV x HR

- Increased norepinephrine
- Increased angiotensin II

- Increased afterload
- Increased aldosterone
- Increased vasopressin and endothelin-1

Increased CO and BP

Which of the following is the single most important modifiable risk factor for heart failure in the USA?

A. high cholesterol
B. high blood pressure
C. diabetes
D. obesity
Neurohormones – Maladaptive Responses

<table>
<thead>
<tr>
<th>Neurohormone</th>
<th>Maladaptive Responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norepinephrine</td>
<td>Down regulation of the beta-receptor; Arrhythmias</td>
</tr>
<tr>
<td>Angiotensin II</td>
<td>Loss of flow-mediated vasodilation; Increased afterload</td>
</tr>
<tr>
<td>Aldosterone</td>
<td>Mechanical stress on the heart from too much preload; Apoptosis of endothelial cells</td>
</tr>
<tr>
<td>Endothelin</td>
<td>Hypertrophy of smooth muscle cells in vasculature; Fibrotic changes</td>
</tr>
</tbody>
</table>

End result = Myocardial remodeling

What are the evidence-based cornerstone medications for treatment of heart failure?

A. ACE inhibitor + beta-blocker + digoxin
B. ACE inhibitor + beta-blocker + aldosterone antagonist
C. Digoxin + furosemide
D. ACE inhibitor + beta-blocker + furosemide

Guideline-directed Medical Therapy

• Magnitude of Benefit demonstrated in RCTs - systolic HF

<table>
<thead>
<tr>
<th>Medication</th>
<th>RR reduction in Mortality*</th>
<th>RR reduction in hospitalizations*</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACEI or ARB</td>
<td>17%</td>
<td>31%</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>34%</td>
<td>41%</td>
</tr>
<tr>
<td>Aldosterone antagonist</td>
<td>30%</td>
<td>30%</td>
</tr>
</tbody>
</table>

*RR = relative risk

Back to Tom

• Medications on Admission
  – Furosemide 40 mg po once daily
  – Valsartan 60 mg po daily
  – Carvedilol 12.5 mg po BID
  – Digoxin 0.125 mg po daily
  – Magnesium 400 mg po TID
  – KCl 20 mEq po daily

• Why taking an ARB and not an ACEI?
• Why not on an aldosterone antagonist?
• What is the role of digoxin?
• Is furosemide the best diuretic for Tom?

What Matters about ACEIs and ARBs?

Recommended for prevention and treatment of HF

• No differences seen among the available ACE inhibitors
• Cautions:
  – Cough – 20% of patients experience dry cough
  – Angioedema – Life-threatening edema of face, throat and airway
  – Monitor Potassium and Renal Function (Scr)

Benefits seen in patients with mild, moderate or severe symptoms

When is an ARB indicated?

Tom’s regimen: Valsartan 60 mg po QD

“ARBs are recommended in patients with systolic HF with current or prior symptoms who are ACE inhibitor intolerant to reduce morbidity and mortality.” Evidence A
  – not associated with cough
  – can cause angioedema (lower risk than that of ACEIs)
  – need to monitor K and Scr
What about oral nitrates and hydralazine?

- Combination is recommended to reduce morbidity and mortality for self-described African Americans with NYHA Classes III-IV receiving optional therapy with ACEI and beta-blocker unless contraindicated (Evidence A)
  - May be considered in non-African American patients with HF and reduced LVEF who remain symptomatic despite optimized standard therapies. (Evidence C)
  - Also used in place of an ACEI or ARB in intolerant patients or those with significant renal dysfunction precluding use of an ACEI/ARB.

Which beta-blocker is best?

- Beta-blockers (bisoprolol, carvedilol or sustained release metoprolol succinate) should be used in all patients with a reduced LVEF (systolic HF) to prevent symptomatic HF (Evidence A)

<table>
<thead>
<tr>
<th>Carvedilol</th>
<th>Metoprolol succinate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonselective beta-blocker with alpha receptor blockade</td>
<td>Selective beta-1 blocker</td>
</tr>
<tr>
<td>Take with food</td>
<td>XL form releases the drug over 20 hours</td>
</tr>
<tr>
<td>May increase digoxin levels</td>
<td>May be preferred if BP is marginal</td>
</tr>
</tbody>
</table>

Is Tom an appropriate candidate for an aldosterone antagonist such as spironolactone?

A. Yes
B. No
C. I don't know

Aldosterone Antagonists

- “Recommended in patients with NYHA Class II to IV HF with systolic HF (LVEF < 35%) unless contraindicated” (Evidence A)
  - Spironolactone and Eplerenone

- Will antagonize the effects of aldosterone on ventricular remodeling; NOT used as diuretics

- Cautions:
  - Renal impairment – Scr should be 2.5 mg/dL or less in men; 2.0 mg/dL or less in women
  - Potassium should be less than 5 mEq/L

What is the role of digoxin in HF?

- “Can be beneficial in patients with systolic HF to decrease hospitalizations for HF (Evidence B)”
  - No effect on all cause mortality at 2 years
  - Reduced hospitalization rate (26.8% versus 34.7%; RR 0.72 (0.66-0.79))
  - Most beneficial in patients in Classes III and IV with lower EFs


- Can be added to an optimized regimen

What matters with Diuretics?

- “Recommended in patients with systolic HF and evidence of fluid retention to improve symptoms” (Evidence C)

- Not all patients are congested!
- Loop diuretics are the gold standard
- Thiazide diuretics (hydrochlorothiazide, metolazone) may be added to loop diuretics for “diuretic resistance”
- Pharmacists – Check for adequate potassium and magnesium replacement therapies!
Reminders: Diuretics

Loop diuretics are not equal! They differ in potency, oral bioavailability and duration of effect.

<table>
<thead>
<tr>
<th>Agent</th>
<th>Equivalent Dose</th>
<th>Bioavailability</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Furosemide</td>
<td>40 mg</td>
<td>40% to 70%</td>
<td>4 to 6 hrs</td>
</tr>
<tr>
<td>Bumetanide</td>
<td>1 mg</td>
<td>80% to 95%</td>
<td>6 to 8 hrs</td>
</tr>
<tr>
<td>Torsemide</td>
<td>20 mg</td>
<td>85% to 95%</td>
<td>12 to 16 hrs</td>
</tr>
<tr>
<td>Metolazone (thiazide-like)</td>
<td>2.5 mg to 10 mg 1 to 3 times a week</td>
<td>Half-life of 18 h</td>
<td>Bioavailability of 40% to 60%</td>
</tr>
</tbody>
</table>

Which of the following is TRUE about heart failure therapies?

A. Furosemide is the preferred oral diuretic due to its high po bioavailability
B. All beta-blockers have been shown to be equal in effectiveness
C. Digoxin decreases hospitalization rates but not mortality
D. All of the above

Back to Tom

- 30 pound weight gain over 6 months, SOB, cough and 2 pillow orthopnea, poor appetite
- Is he a candidate for a diuretic?
- Where does he wear his heart failure?

Tom’s Goals at time of Discharge

- Get back to independent living (back to school)
- Maintain his “dry” weight
- Work out a system for taking his medications yet maintain a ‘decent life-style’
- Eat healthy (but still be a college student)
- Limit hospitalizations as he waits for transplant

Besides taking HF medications as directed, what is the most important action that a patient should take to control HF and prevent hospitalizations?

A. Weighing him/herself each day
B. Monitoring how much fluid he/she takes in each day
C. Reading food labels to limit salt intake
D. Taking his/her blood pressure twice a week
Pharmacy’s Role in Helping Tom

- Multidisciplinary Teams have been shown to decrease readmission rates by 56% (NEJM 1995;333:1190-5)
- How can we help?
  - Medication Management including smoking cessation
  - Fluid management
  - Diet management (and reinforcement)
  - Supportive Care

Goal is to facilitate self-care

Self-Care: Recognizing Triggers

- Since your last refill or doctor visit...
  - Have you had a change in weight greater than 5 pounds?
  - Do you have shortness of breath?
  - Do you wake up short of breath at night?
  - How many pillows do you sleep on? Has this increased?

Findings – 66% of patients had warning signs of HF that prompted doctor visits

Medication Management – Diuretics

- Weight diaries
- Diuretic Sliding Scales
  - Take metolazone when...
  - Take 60 mg of Lasix when...
- Compression stocking
- Leg elevation

The Action Zones – Green, Yellow, Orange, RED

Insert “dry” or best weight

Reinforce Diet Compliance

<table>
<thead>
<tr>
<th>EAT THIS …</th>
<th>NOT THIS …</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fish, low salt tuna, grilled meats</td>
<td>Cured meats, bacon, cold cuts, sausage, hot dogs</td>
</tr>
<tr>
<td>Raw or fresh vegetables</td>
<td>Canned vegetables, baked beans, pickles</td>
</tr>
<tr>
<td>Low salt cheese such as mozzarella</td>
<td>High salt cheeses and processed cheese</td>
</tr>
<tr>
<td>Lite salad dressing</td>
<td>Regular salad dressings</td>
</tr>
<tr>
<td>Homemade soups</td>
<td>Canned soups</td>
</tr>
<tr>
<td>Herbs without salt (Mrs. Dash), low salt ketchup</td>
<td>Salt, spices with salt, Teriyaki sauce, Steak sauce, Relish, Soy sauce</td>
</tr>
<tr>
<td>Low salt tomato sauce</td>
<td>Tomato puree, tomato juice, tomato sauce</td>
</tr>
</tbody>
</table>

Read food labels; Limit sodium intake to maximum of 2000 mg a day
Drugs to Avoid

**Absolute Avoidance:**
- Nonsteroidal anti-inflammatory Drugs (NSAIDs)

**Conditional Avoidance:**
- Glitazones - increase peripheral edema
- Pregabalin - increase peripheral edema
- Nondihydropyridine CCBs – are negative inotropes (caution in patients with systolic HF)

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**Tom’s Self-Care Plan**

<table>
<thead>
<tr>
<th>Management Item</th>
<th>Action Plan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medication timing was leading to a missed dose in the afternoon</td>
<td>Take Torsemide in AM with breakfast; Take second dose at 6 PM (up until after 12 midnight)</td>
</tr>
<tr>
<td>Salt intake (cold cuts, crockpot meals; Reads labels)</td>
<td>Buy low salt turkey; avoid bologna, salami (minimize pickles)</td>
</tr>
<tr>
<td>Snacks (Chips)</td>
<td>No salt popcorn, low or no salt chips</td>
</tr>
<tr>
<td>Fluids – Monitors intake of fluids and limits to 2200 mL/day</td>
<td>Continue with fluid management; Avoid sugar-based fluids (soda)</td>
</tr>
<tr>
<td>Always thirsty</td>
<td>Use lip balm to keep lips moist; Carry hard sugar-free candies / gum</td>
</tr>
</tbody>
</table>

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**Advanced Therapy – Left Ventricular Assist Device (LVAD)**

http://www.nhlbi.nih.gov/health/health-topics/topics/vad/

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**Role in advanced therapies**

- Anticoagulation monitoring and management
  - Patients are routinely taking aspirin plus warfarin to prevent clot formation in the device
  - Home enoxaparin therapy, if INR falls below target INR

- Prevention and management of drive-line infections
  - Antibiotic dosing and access to antibiotics (e.g., linezolid, home infusions of vancomycin)

- Prevention of drug interactions with warfarin
  - Counseling on signs of bleeding
  - Working with cardiologists on drug interaction management

- Patient and family support

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**Where Can I get More Information?**

- Education Materials:
  - iBook – "Learning to Live with Heart Failure" – by UNC practitioners
  - http://www.cardiosmart.org (ACC Patient page)
  - www.mylvad.com

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**Key Points**

- Guideline-based drug therapy for heart failure reduces disease progression and mortality.
- Self-care education reduces hospital readmissions. Ask questions of your patients to facilitate self-care.
- Community pharmacists are in a unique position to affect the health and wellness of patients with heart failure. Listen, ask questions and guide your patients using all of your available tools.
Care-giving

“Every patient has their own story. We have information about our health that you don’t have. Instead of just telling me about my medications, listen to what I have to say. Ask me questions, then listen. To me, taking time to listen and valuing what I have to say are the most important things that a pharmacist can do”

Heart Failure
New Therapies

Patient Case

- AB is a 66 year old WM with newly diagnosed systolic HF
- Symptoms include SOB with minimal activity, ankle swelling and feeling bloated in his stomach
- History of MI, dyslipidemia and hypertension
- Ejection fraction = 30%
- Medications
  - Atorvastatin 80mg po daily
  - Atenolol 100mg po daily
  - HCTZ 25mg po daily
  - Aspirin 81mg po daily

OF COURSE YOU ALWAYS START AN ACE-I IN HEART FAILURE, DON’T YOU?

ACE-I Guideline Recommendations

“ACE inhibitors are recommended in patients with reduced ejection fraction heart failure and current or prior symptoms, unless contraindicated, to reduce morbidity and mortality”

Class I, level of evidence: A


ARB Guideline Recommendations

“ARBs are recommended in patients with reduced ejection fraction heart failure and current or prior symptoms who are ACE inhibitor intolerant, unless contraindicated, to reduce morbidity and morality”

Class I, level of evidence: A

ARB Guideline Recommendations

“ARBs are reasonable to reduce morbidity and mortality as alternatives to ACE inhibitors as first-line therapy for patients with reduced ejection fraction heart failure, especially for patients already taking ARBs for other indications, unless contraindicated.”

Class IIa, level of evidence: A


Medication Benefits in Systolic HF

<table>
<thead>
<tr>
<th>Medication</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>20</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/nitrates</td>
<td>43</td>
<td>7</td>
<td>33</td>
</tr>
</tbody>
</table>

ACE indicates angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; GDMT, guideline-directed medical therapy; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; NNT, number needed to treat; RCTs, randomized controlled trials; and RR, relative risk.


Heart Failure Compensatory Mechanisms

http://www.learntheheart.com/cardiology/systolic-congestive-heart-failure/

RAAS Medications


ANGIOTENSIN RECEPTOR NEPRILYSIN INHIBITORS (ARNIs)

A New Class of Heart Failure Medications

Natriuretic Peptides

- Atrial and B-type natriuretic peptides (ANP and BNP)
  - BNP secreted by ventricles in response to wall stress
    - May be used to detect the presence of or worsening of HF
    - Overall levels increased in HF
    - My reflect reduction in mature BNP levels and increased levels of less biologically active BNP
  - The N-terminal chain of BNP prohormone (NT-proBNP) may also be monitored in HF
- Promote natriuresis and diuresis
- Multiple other beneficial effects in HF patients
  - Vasodilation

Neprilysin

- Responsible for breaking down natriuretic peptides (NPs) into inactive fragments
  - Except for NT-proBNP
- Inhibiting neprilysin increases BNP concentrations
  - Also increases bradykinin and substance P
  - All vasodilatory substances
- Also breaks down angiotensin II
  - Vasoconstrictor
  - Need to combine RAAS inhibition with neprilysin inhibition
- Increased bradykinin levels → angioedema?


MOA of ARNIs

Sacubitril/Valsartan

- Brand name - Entresto™
  - LCZ696 in development
- Sacubitril
  - Neprilysin inhibitor
- Valsartan
  - Angiotensin II receptor blocker
- Indication
  - Patients with NYHA Class II-IV chronic heart failure
  - Reduce the risk of CV death and hospitalization for heart failure


Sacubitril/Valsartan Dosage

- Starting dose = 49/51mg po BID
- Target maintenance dose = 97/103mg po BID
  - Titrated up in 2 to 4 weeks
- Reduced starting dose = 24/26mg po BID
  - No prior ACE-I or ARB or prior low dose
  - Severe renal impairment
    - eGFR < 30 mL/min/1.73m²
  - Moderate hepatic impairment
    - Child-Pugh B classification
  - Goal still to achieve target dose


Sacubitril/Valsartan Contraindications

- Hypersensitivity
- History of angioedema related to prior ACE-I or ARB therapy
- Concomitant ACE-I therapy
  - Do not administer within 36 hours of an ACE-I
  - Due to risk of angioedema
- Concomitant use of aliskiren in patients with diabetes

Sacubitril/Valsartan Warnings
- Angioedema
- Hypotension
- Impaired renal function
- Hyperkalemia
- Fetal toxicity

Sacubitril/Valsartan Drug Interactions
- Minimal CYP450 metabolism
- Dual blockade of the renin-angiotensin aldosterone system
  - ACE-I – increased risk of angioedema
  - ARB – already contained in the formulation
  - Renin inhibitors
- Potassium-sparing diuretics/aldosterone antagonists
  - Hyperkalemia
- NSAIDs and Cox-2 inhibitors
  - May result in worsening renal function
- Lithium
  - Increased lithium levels

PARADIGM-HF Trial
Angiotensin-neprilysin inhibition versus enalapril in heart failure

PARADIGM-HF Trial - Methods
- Randomized, double blind, active controlled trial
  - Sacubitril/valsartan 97/103 (200) mg po BID
  - Enalapril 10mg po BID
  - Run-in period utilizing both drugs
- Inclusion criteria
  - NYHA Class II, III or IV heart failure
  - Ejection fraction ≤ 40% (decreased to ≤ 35% during trial)
- Primary outcome - composite
  - Death from CV causes
  - Hospitalization for heart failure
  - Designed to detect a difference in rates of CV deaths

PARADIGM-HF Trial - Results
- 8,442 patients
- Trial stopped early for overwhelming benefit
  - Prespecified stopping rules
- Median follow-up of 27 months
- Mean age ~ 64 years
- Mostly male (~ 80%)
- Race
  - ~2/3 White
  - ~20% Asian
  - ~5% Black
- < 10% of patients in trial from North America
- Mean ejection fraction ~ 30%
- Predominately NYHA class II (~70%)
- Study drug doses
  - Sacubitril/valsartan 375mg daily
  - Enalapril 19mg daily
- Treatments at randomization
  - Beta-blockers (~93%)
  - Mineralocorticoid antagonist (~55%)
PARADIGM-HF Trial – Efficacy Results

**A. Primary End Point**

- Hazard ratio, 0.80 (95% CI, 0.73–0.87) P<0.001

<table>
<thead>
<tr>
<th>Days since Randomization</th>
<th>LCZ2096 (No. at Risk)</th>
<th>Enalapril (No. at Risk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>4187</td>
<td>4212</td>
</tr>
<tr>
<td>180</td>
<td>3922</td>
<td>3883</td>
</tr>
<tr>
<td>270</td>
<td>3431</td>
<td>3450</td>
</tr>
<tr>
<td>360</td>
<td>3018</td>
<td>3018</td>
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<tr>
<td>450</td>
<td>2257</td>
<td>2232</td>
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<td>540</td>
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</tbody>
</table>

- LCZ = 21.8% vs. Enal = 26.5%

**B. Death from Cardiovascular Causes**

- Hazard ratio, 0.80 (95% CI, 0.71–0.89) P<0.001

<table>
<thead>
<tr>
<th>Days since Randomization</th>
<th>LCZ2096 (No. at Risk)</th>
<th>Enalapril (No. at Risk)</th>
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<td>994</td>
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<tr>
<td>720</td>
<td>280</td>
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</tbody>
</table>

- LCZ = 13.1% vs. Enal = 16.5%

**C. Hospitalization for Heart Failure**

- Hazard ratio, 0.79 (95% CI, 0.71–0.89) P<0.001

<table>
<thead>
<tr>
<th>Days since Randomization</th>
<th>LCZ2096 (No. at Risk)</th>
<th>Enalapril (No. at Risk)</th>
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<tr>
<td>720</td>
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</tr>
</tbody>
</table>

- LCZ = 12.5% vs. Enal = 15.6%

**D. Death from Any Cause**

- Hazard ratio, 0.84 (95% CI, 0.76–0.93) P<0.001

<table>
<thead>
<tr>
<th>Days since Randomization</th>
<th>LCZ2096 (No. at Risk)</th>
<th>Enalapril (No. at Risk)</th>
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<tbody>
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<td>994</td>
</tr>
<tr>
<td>720</td>
<td>280</td>
<td>279</td>
</tr>
</tbody>
</table>

- LCZ = 17.0% vs. Enal = 19.8%

PARADIGM-HF Trial – Safety Results

- 12% of patients withdrew during run-in period due to AEs
  - Cough, hyperkalemia, renal dysfunction, hypotension
- Double blind portion of the trial
  - Symptomatic hypotension
    - More common in ARNI arm (14.0 vs. 9.2%; P<0.001)
    - Elevated serum creatinine and potassium and cough higher in ACE-I arm
  - Angioedema
    - 19 ARNI patients vs. 10 ACE-I patients (P<0.13)

PARADIGM-HF Trial – Limitations

- Comparator used – enalapril
  - Valsartan/ARB
  - If ACE-I, lisinopril?
- Run-in period
- Minimal representation of patients from North America as well as Black patients
- Minimal patients with implantable cardioverter/defibrillators (ICDs)
Which of the following is true with regards to the Paradigm-HF trial which studied sacubitril-valsartan (S/V)?

A. S/V reduced death from CV causes and hospitalizations from HF compared with an ACE-I
B. S/V reduced death from CV causes and hospitalizations from HF compared with placebo
C. Death from any cause was not different between the study treatment arms
D. Approximately 70% of patients enrolled in the trial had NYHA class III and IV HF

So what should we recommend for AB?

Take Home Points

- Sacubitril/Valsartan shown more effective than guideline based ACE-I therapy for HF patients
  - New mechanism of action
  - Hard endpoints data against active comparator available
    - Including CV death and death overall
- Hypotension, hyperkalemia and angioedema AEs
- BID dosing
- Current data for reduced ejection fraction/systolic HF
  - Study ongoing for preserved ejection fraction/diastolic HF
- Expensive - current therapies generic
- Place in guidelines?

Patient Case

- JO is a 60 year old WM with NYHA class III systolic HF
- Significant SOB but stable for the last 3 months; was hospitalized for HF prior to that
- Ejection fraction = 25%; heart rate = 80 bpm
- HF Medications
  - Lisinopril 40 mg po daily
  - Metoprolol XL 50 mg po daily
  - Eplerenone 50 mg po daily
  - Furosemide 40 mg po daily

Heart Rate and Heart Failure

- Resting baseline heart rate appears to be associated with morbidity and mortality in patients with HF
- Epidemiologic studies as well as sub-analyses of RCTs
  - Need to always question internal validity
- Most seem to look at heart rate of above/below 70 bpm
- Main question
  - Disease marker vs. modifiable risk factor
Heart Rate and Heart Failure

Composite endpoint include CV death and hospitalization for worsening heart failure


Don’t be frightened!
… but this may bring back bad memories!

Cardiac Conduction Physiology

Cardiac Muscle Cell

http://people.eku.edu/ritchisong/301notes5.htm

Cardiac Conduction Physiology

Pacemaker Cardiac Cell

http://www.cvphysiology.com/Arrhythmias/A004.htm

Ivabradine MOA


Which of the following statements regarding new HF therapies is true?

A. Sacubitril/valsartan is a neprilysin agonist and angiotensin receptor antagonist
B. Sacubitril/valsartan increases B-type natriuretic peptides (BNP), angiotensin II and bradykinin levels
C. Ivabradine has both negative chronotropic (rate) and inotropic (force) effects
D. Ivabradine’s main effects are on the atrioventricular node
Ivabradine

- Brand name - Corlanor

- Indication
  - Reduce the risk of hospitalization for worsening heart failure in patients with stable, symptomatic chronic heart failure
  - Left ventricular ejection fraction (LVEF) ≤ 35%
  - Sinus rhythm
  - Resting heart rate ≥ 70 bpm
  - On maximally tolerated beta-blocker dose or contraindication

Ivabradine Dosage

- Starting dose = 5 mg po BID with meals
- Target – resting heart rate of 50-60 bpm
  - Assess after 2 weeks
- Maximum dose = 7.5 mg po BID
  - Titrated up in 2 to 4 weeks
- Reduced starting dose = 2.5 mg po BID
  - History of conduction defects
  - Bradycardia could lead to hemodynamic compromise

<table>
<thead>
<tr>
<th>Heart Rate</th>
<th>Dose Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 60 bpm</td>
<td>Increase dose by 2.5 mg (given twice daily) up to a maximum dose of 7.5 mg twice daily</td>
</tr>
<tr>
<td>50-60 bpm</td>
<td>Maintenance</td>
</tr>
<tr>
<td>&lt; 50 bpm or</td>
<td>Decrease dose by 2.5 mg (given twice daily); if current dose is 2.5 mg twice daily, discontinue therapy*</td>
</tr>
<tr>
<td>symptoms of</td>
<td></td>
</tr>
<tr>
<td>bradycardia</td>
<td></td>
</tr>
</tbody>
</table>

Ivabradine Contraindications

- Acute decompensated heart failure
- BP < 90/50 mmHg
- Sick sinus syndrome, sinoatrial block or 3rd degree AV block
- Resting heart rate < 60 bpm
- Severe hepatic impairment
  - Child-Pugh C classification
- Pacemaker dependence
- Concomitant use of strong CYP3A4 inhibitors

Ivabradine Warnings/Adverse Events

- Atrial fibrillation
  - Increases risk
  - D/C if A Fib develops
- Bradycardia/conduction disturbances
- Fetal toxicity
- Phosphenes
  - Visual disturbances
  - Enhanced brightness, halos, color bright lights, image decomposition

Ivabradine Drug Interactions

- Primarily CYP450 metabolism
- Strong CYP3A4 inhibitors contraindicated
  - Azole antifungals
  - Macrolides
  - HIV protease inhibitors
- Moderate CYP3A4 inhibitors should be avoided
  - Diltiazem, verapamil, grapefruit juice
- CYP3A4 inducers should be avoided
  - St. John’s wort, rifampin, phenytoin
- Negative chronotropes
  - Digoxin, amiodarone
BEAUTIFUL Trial
Ivabradine for patients with stable coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): a randomized, double-blind, placebo-controlled trial

BEAUTIFUL Trial - Methods
➢ Randomized, double blind, placebo controlled trial
  o Ivabradine 5 mg po BID
  o Titrated to 7.5 mg po BID if heart rate ≥ 60 bpm
➢ Inclusion criteria
  o CAD and LVEF < 40%
  o Resting heart rate ≥ 60 bpm
➢ Primary outcome – composite of the following
  o CV death
  o Acute MI
  o Hospitalization for new-onset or worsening heart failure
➢ Prespecified subanalysis - baseline heart rate ≥ 70 bpm

BEAUTIFUL Trial - Results
➢ 10,917 patients overall
➢ Median follow-up of 19 months
➢ Mean age ~ 65 years
➢ Mostly male (~ 83%)
➢ Mean heart rate ~ 72 bpm
➢ Heart failure NYHA classifications
  o Class I = 15%
  o Class II = 61%
  o Class III = 23%
➢ Mean ejection fraction ~ 32%
➢ Study drug doses
  o Almost half (47%) of ivabradine pts increased dose to 7.5mg po BID
  o Mean dose of 6.2 mg po BID
➢ Treatments at randomization
  o Beta-blockers (~84%)
  o ACE-I/ARB (~90%)
  o Mineralocorticoid antagonist (~30%)

BEAUTIFUL Trial – Efficacy Results

Composite endpoint results in the total study population

HR (95% CI) = 1.00 (0.91-1.10)
BEAUTIFUL Trial – Efficacy Results

Composite endpoint results in the heart rate ≥ 70 bpm subpopulation

HR (95% CI) = 0.91 (0.81-1.04)


BEAUTIFUL Trial – Efficacy Results

Acute MI endpoint results in the heart rate ≥ 70 bpm subpopulation

HR (95% CI) = 0.64 (0.49-0.84)


BEAUTIFUL Trial – Safety Results

- Total study population
  - 28% D/C in ivabradine group vs. 16% in placebo group
    - Bradycardia accounted for difference

- Subpopulation with heart rate ≥ 70 bpm
  - 23% D/C in ivabradine group vs. 16% in placebo group
    - Bradycardia much less in ivabradine group vs. total population

- Visual symptoms and psychiatric disorders rare but more frequent in ivabradine group


SHIFT Trial

Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study

SHIFT Trial - Methods

- Randomized, double blind, placebo controlled trial
  - Ivabradine 5 mg po BID
  - Titrated to 7.5 mg po BID if heart rate ≥ 80 bpm
  - Could down titrate to 2.5 mg po BID if heart rate < 50 bpm

- Inclusion criteria
  - Stable symptomatic chronic heart failure
  - Hospitalization for worsening heart failure in prior 12 months
  - LVEF ≤ 35%
  - Resting heart rate ≥ 70 bpm

- Primary outcome – composite
  - CV death
  - Hospitalization for worsening heart failure


SHIFT Trial - Results

- 6,505 patients overall
- Median follow-up of 23 months
- Mean age ~ 60 years
- Mostly male (~ 76%)
- Mean heart rate ~ 80 bpm
- Heart failure NYHA classifications
  - Class II = 49%
  - Class III = 50%
  - Class IV = 2%

SHIFT Trial - Results

- Mean ejection fraction ~ 29%
- Study drug doses
  - Mean dose of 6.4 mg po BID
- Treatments at randomization
  - Beta-blockers (~90%)
    - 26% of patients at target dose
    - 56% of patients at ≥ 50% of target dose
  - ACE-I/ARB (~92%)
  - Mineralocorticoid antagonist (~60%)


SHIFT Trial – Efficacy Results

- Composite endpoint
  - Hospitalization for worsening heart failure


SHIFT Trial – Efficacy Results

- Death from heart failure


SHIFT Trial – Results

- Less marked findings in the subgroup taking ≥ 50% of target Beta-blocker doses
  - Only statistically significant finding was for reduced hospitalization for worsening heart failure
  - Lower overall event rate in this subgroup – reduced power
- Safety
  - 21% D/C in ivabradine group vs. 19% in placebo group
  - Serious AEs occurred less in the ivabradine
  - Bradycardia
  - Visual disturbances

**SHIFT Trial – Limitations**

- Relatively young heart failure population
- Beta-blocker use
  - High percentage using
  - Poor adherence to guideline targeted doses
  - No significant benefit in patients taking ≥ 50% targeted doses
- No US patients in the trial
- Minimal patients with implantable cardioverter/defibrillators (ICDs)

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**So what should we recommend for JO?**

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**Take Home Points**

- Seems to be effective in stable heart failure patients with a heart rate ≥ 70 bpm taking multiple therapies
  - ACE-I/ARB, Beta-blockers, and mineralocorticoid antagonist
- Beta-blocker dosing
  - True intolerance
  - Maximally tolerated doses
  - Beta-blocker target doses vs. ivabradine
- BID dosing
- Expensive
- Place in guidelines?

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**Which of the following patients is most appropriate for ivabradine therapy?**

A. A 60 y/o male with HF & HTN, LVEF = 30%, HR = 64 bpm who is taking an ACE-I and beta-blocker
B. A 55y/o female with HF & A Fib, LVEF = 35%, HR = 80 bpm who is taking an ACE-I but can’t tolerate a beta-blocker
C. A 65 y/o female with HF & HTN, LVEF = 40%, HR = 68 bpm who is taking an ACE-I and beta-blocker
D. A 58 y/o male with HF & DM, LVEF = 30%, HR = 76 bpm who is taking an ACE-I and beta-blocker