Heart Failure in the Elderly:
Reviewing the Evidence in 2016

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Disclosures

- Jan Basile, MD
  - Research Grants: NIH (SPRINT), Eli-Lilly
  - Consultant/Advisory Board: Amgen, Arbor, Janssen
  - Speaking Bureau: Arbor
Educational Objectives

- Understand the epidemiology of heart failure including its prevalence, increase with age, and ethnic disparities

- Describe the appropriate workup for patients with symptomatic heart failure including when and how to use Brain Natriuretic peptide (BNP) and Pro-B-type natriuretic peptide (NT-proBNP)

- Recognize the differing treatments for those with heart failure with preserved ejection fraction (HFpEF) vs heart failure with reduced ejection fraction (HFrEF)

- Recognize the newer treatments for (HFrEF) including LCZ696 (valsartan/sacubitril) and ivrabadine
On a scale of 1 to 5, please rate how confident you would be in the evaluation and management of patients with heart failure?

1. Not at all confident
2. Slightly confident
3. Moderately confident
4. Pretty much confident
5. Very confident
Case # 1

78 year old AA woman, for follow up visit

• History of non ischemic cardiomyopathy and hypertension
  - frequently has to rest during daily housework due to shortness of breath.
  - has 1 pillow orthopnea
  - was hospitalized 6 months ago for heart failure

• There is no history of CAD

• Echocardiogram 6 months ago: Dilated LV, EF 30%

• Medications: Valsartan 160 mg bid; Carvedilol 25 mg bid; Furosemide 40 mg bid, spironolactone 25 qd. She had a cough to enalapril.

• Physical Examination: BP 125/80, pulse 62/min; Weight 255lb No JVD; Lungs clear; cardiac regular rate; grade 2/6 systolic murmur; Abdomen soft non tender; Extremities 1+ edema
Case #1: 78 year old AA woman

Clinical Pearl #1

- Patient has NYHA Class III HF, and is moderately symptomatic
- Patient was recently hospitalized due to HF.
- During this follow up visit:
  - evaluate for ongoing/new symptoms
  - optimize evidence-based therapies
  - reduce recurrent hospitalization
  - improve survival
Epidemiology of Heart Failure (HF) in the United States

- 5.8 million patients in the US suffer from HF and 23 million worldwide\(^1\)
- As of 2012, 2.4% of the US population was reported to have HF\(^1\)
- The number with HF is estimated to surpass 10 million in the US by 2037\(^2\)
- HF is the leading cause for inpatient hospitalization in the U.S. \(^2\)
- The total cost of HF is projected to grow from $44.6 billion in 2015, to $97 billion by 2030 with 53% of the cost due to hospitalization\(^1\)
- About 20% of patients with HF die within the first year of the diagnosis while \(\sim 50\%\) of patients die within 5 years after diagnosis\(^3\)
- \(\sim 35\%\) with class IV HF die within 1 year\(^3\)

Prevalence of HF Increases With Age
(Men are always at a greater risk than women and the gap has widened)

AHA. Heart Disease and Stroke Statistics 2010 Update
Projected HF Prevalence By Race/Ethnicity
2012-2030

Blacks > Whites secondary to the risk from hypertension and HFpEF

Hypertension may be the single most important modifiable risk factor for heart failure in the US.

Hypertensive men and women have substantially greater risk for developing heart failure than normotensive men and women.
Case #1: 78 year old AA woman

Clinical Pearl #2

- Patient has symptoms of heart failure and recent echocardiogram during hospitalization revealed reduced ejection fraction (EF)

- **HFrEF** is distinct from **HFpEF**
  - **HFrEF** = heart failure with reduced EF
  - **HFpEF** = heart failure with preserved EF

- Evidence based treatment is different for **HFrEF** vs **HFpEF**
Definition of Heart Failure

- Heart failure (HF) is a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood.
- The cardinal manifestations of HF are dyspnea and fatigue, which may limit exercise tolerance and fluid retention, which may lead to pulmonary congestion and peripheral edema.
- HF pathology may affect heart size, wall thickness and ejection fraction.

AHA/ACC Heart Failure Stage

**Stage A:** High risk of developing HF but w/o sx or structural changes

Hypertension, Diabetes, Alcohol Abuse, Family history of cardiomyopathy

**Stage B:** Evidence of structural changes in the heart, but w/o signs or sx

**Stage C:** Prior or Current symptoms of HF

**Stage D:** Refractory Symptoms despite medical care

Yancy CW et al., J Am Coll Cardiol 2013 Oct 15; 62:e147
Heart Failure: Causal Mechanisms

- Smoking
- Dyslipidemia
- Diabetes

Hypertension

Obesity
- Diabetes

HFrEF

MI

Systolic Dysfunction

HFpEF

LVH

Diastolic Dysfunction

HF

Normal LV Structure and Function

LV Remodeling

Subclinical LV Dysfunction

Overt Heart Failure

ACC/AHA Stage A  ↔  Stage B  ↔  Stage C

Morphologic Changes of the Heart

- HF c Preserved EF-LVH
- Normal
- HF c Reduced EF

RV
LV
Heart Failure is Associated with Neurohormonal Excess and Nitric Oxide Insufficiency

Neurohormones (RAAS/SNS) → Endothelial Nitric Oxide

**Neurohormonal Antagonists**
- Beta Blockers (I-IV)
- Renin-Angiotensin Antagonists
  - ACE Inhibitors (I-IV)
  - ARBs (I-IV)
- Mineralocorticoid Receptor Antag (II-IV)

**Nitric Oxide Enhancemnt (NOE)**
- Fixed-dose combination ISDN/HYD
- Omapatrilat (Dual ACE and NEP inh)
- Angiotensin-Neprilysin Antagonist
2013 ACCF/AHA Guideline: Summary of Class I (Should be Performed) Recommendations for Initial Evaluation - Stage C-Symptomatic Patients

- History and physical examination
- Family history in patients with dilated cardiomyopathy
- Weight and volume status
- CBC, urinalysis, electrolytes, lipids, liver panel, and TSH
- Electrocardiogram
- Chest radiograph
- 2-dimensional echocardiogram with assessment of left ventricular (LV) systolic function.
- BNP or N-terminal BNP to assess likelihood of HF in those ambulatory with dyspnea or acute decompensation when the etiology for decompensation is uncertain
- Repeat measurement of LV function when a significant change in clinical status has occurred

Yancy CW et al., J Am Coll Cardiol 2013 Oct 15; 62:e147
Natriuretic Peptides: Diagnosis

In ambulatory patients with dyspnea, measurement of BNP or N-terminal pro-B-type natriuretic peptide (NT-proBNP) is useful to support clinical decision making regarding the diagnosis of HF, especially in the setting of clinical uncertainty.

Measurement of BNP or NT-proBNP is useful to support clinical judgment for the diagnosis of acutely decompensated HF, especially in the setting of uncertainty for the diagnosis.

Yancy CW et al., J Am Coll Cardiol 2013 Oct 15; 62:e147
Stages, Phenotypes, Prevention and Treatment of HF

**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

**THERAPY**
**Goals**
- Control symptoms
- Improve HRQOL
- Prevent hospitalization
- Prevent mortality

**Drugs**
- ACEI or ARB as appropriate
- Beta blockers as appropriate

**Strategies**
- Identification of comorbidities

**Treatment**
- Diuresis to relieve symptoms of congestion
- Follow guideline driven indications for comorbidities, e.g., HTN, AF, CAD, DM
- Revascularization or valvular surgery as appropriate

**In selected patients**
- ICD
- Revascularization or valvular surgery as appropriate

**Options**
- Advanced care measures
- Heart transplant
- Chronic inotropes
- Temporary or permanent MCS
- Experimental surgery or drugs
- Palliative care and hospice
- ICD deactivation

Yancy CW et al., J Am Coll Cardiol 2013 Oct 15; 62:e147
Case #1: 78 year old AA woman

Clinical Pearl #3

- Patient has persistent symptoms despite optimal neurohormonal blockade with Valsartan, Carvedilol, and spironolactone

- FDC I/H (Fixed Dose Combination Isosorbide Dinitrate and Hydralazine) should be added to treatment regimen

- FDC I/H is the only Evidence-based guideline treatment that is recommended at this time for this patient with NYHA Class III HFrEF
2013 ACC/AHA Guideline: HYD and ISDN

The combination of HYD and ISDN is recommended for African Americans with NYHA class III–IV HFrEF on GDMT – IA

A combination of HYD and ISDN can be useful with HFrEF who cannot be given ACE-Is or ARBs – IIA B

GDMT-Guideline Directed Management Therapy

Class I Pharmacologic Treatments for Stage C HFrEF

**HFrEF Stage C**
**NYHA Class I – IV**

*Treatment:*

- For NYHA class II-IV patients.
  - Provided estimated creatinine >30 mL/min and K+ <5.0 mEq/dL.

- For persistently symptomatic African Americans, NYHA class III-IV:
  - ACEI or ARB AND Beta Blocker
  - Add Hydral-Nitrates

- For NYHA class II-IV patients:
  - Add Aldosterone Antagonist

**Add**

- For all volume overload, NYHA class II-IV patients:
  - Loop Diuretics

Yancy CW et al., *J Am Coll Cardiol* 2013 Oct 15; 62:e147
### Medical Rx for Stage C HFrEF: Magnitude of Benefit Demonstrated in RCTs

<table>
<thead>
<tr>
<th>GDMT</th>
<th>RR Reduction in Mortality</th>
<th>NNT to Prevent 1 Death in 36 months</th>
<th>RR Reduction for HF Hospitalization</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitor or ARB</td>
<td>17%</td>
<td>26</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/nitrate</td>
<td>43%</td>
<td>7</td>
<td>33%</td>
</tr>
</tbody>
</table>

Yancy CW et al., *J Am Coll Cardiol* 2013 Oct 15; 62:e147
Combination of Isosorbide Dinitrate and Hydralazine in Blacks with Heart Failure

Anne L. Taylor, M.D., Susan Ziesche, R.N., Clyde Yancy, M.D., Peter Carson, M.D., Ralph D'Agostino, Jr., Ph.D., Keith Ferdinand, M.D., Malcolm Taylor, M.D., Kirkwood Adams, M.D., Michael Sabolinski, M.D., Manuel Worcel, M.D., and Jay N. Cohn, M.D., for the African-American Heart Failure Trial Investigators*

CONCLUSIONS
The addition of a fixed dose of isosorbide dinitrate plus hydralazine to standard therapy for heart failure including neurohormonal blockers is efficacious and increases survival among black patients with advanced heart failure.

BACKGROUND
We examined whether a fixed dose of both isosorbide dinitrate and hydralazine provides additional benefit in blacks with advanced heart failure, a subgroup previously noted to have a favorable response to this therapy.

METHODS
A total of 1050 black patients who had New York Heart Association class III or IV heart failure with dilated ventricles were randomly assigned to receive a fixed dose of isosorbide dinitrate plus hydralazine or placebo in addition to standard therapy for heart failure. The primary end point was a composite score made up of weighted values for death from any cause, a first hospitalization for heart failure, and change in the quality of life.

From the University of Minnesota (A.L.T., J.N.C.) and Minneapolis Veterans Affairs Hospital (S.Z.) — both in Minneapolis; University of Texas Southwestern Medical Center, Dallas (C.Y.); Veterans Affairs Medical Center, Washington, D.C. (P.C.); Wake Forest University, School of Medicine, Winston-Salem, N.C. (R.D.); Heartbeats Life Center and Xavier University, New Orleans (K.F.); Jackson Cardiology Associates, Jackson, Miss. (M.T.); Association of Black Cardiologists, Atlanta (M.T.); University of North Carolina, Chapel Hill (K.A.); and NitroMed, Lexington, Mass. (M.S., M.W.).
African American Heart Failure Trial (A-HeFT)

• Objective
  – Demonstrate the safety and efficacy of ISDN/HYD compared with placebo in African American patients with moderate to severe HF concurrently receiving standard HF treatment

• Inclusion Criteria
  – Patients self-identified as African American
  – NYHA class III or IV HF (> 3 months)
  – LVEF ≤ 35% (or ≤ 45% with dilated LV by echo)
  – Standard therapy for HF, including ACEI/ARB + BB (> 3 months)

A-HeFT Characteristics (Inclusion Criteria)

Standard Therapy Medications
(All Patients)

- Diuretics: 94%
- ACE inhibitors: 78%
- ARBs: 28%
- Beta-blockers: 87%
- Digoxin: 62%
- Spironolactone: 39%

A-HeFT: All-Cause Mortality

Primary Efficacy Endpoint – Composite score: All-Cause Mortality; First HF Hospitalization; Change in QoL at 6 months relative to baseline

Survival (%)

N=1050

Hazard ratio=0.57

P=0.01

Fixed Dose Isosorbide/Hydralazine

Placebo

43% Decrease

Days Since Baseline Visit Date

<table>
<thead>
<tr>
<th>Days Since Baseline Visit Date</th>
<th>Fixed-dose I/H</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>518</td>
<td>532</td>
</tr>
<tr>
<td>100</td>
<td>463</td>
<td>466</td>
</tr>
<tr>
<td>200</td>
<td>407</td>
<td>401</td>
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<tr>
<td>300</td>
<td>359</td>
<td>340</td>
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<td>400</td>
<td>313</td>
<td>285</td>
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<td>500</td>
<td>251</td>
<td>232</td>
</tr>
<tr>
<td>600</td>
<td>13</td>
<td>24</td>
</tr>
</tbody>
</table>

AHeFT: Trial Summary  N=1050

All-Cause Mortality (%)

- Placebo + Standard Therapies: 6.2 (n=32)
- FDC I/H + Standard Therapies: 10.2 (n=54)

P=0.012

First HF Hospitalization (%)

- Placebo + Standard Therapies: 24.4 (n=85)
- FDC I/H + Standard Therapies: 16.4 (n=130)

P<0.001

Patient Reported Functional Status

- Placebo + Standard Therapies: 0 (n=532)
- FDC I/H + Standard Therapies: -8 (n=518)

P<0.01

Case #1: 78 year old woman

**Clinical Pearl #4**

**Treatment with FDC I/H**

- Initiate and titrate as was done in the AHEFT Trial
  - 1 FDC tablet 3 times per day
    - Isosorbide dinitrate: 20mg
    - Hydralazine: 37.5 mg
  - Total dose
    - Isosorbide dinitrate: 60 mg/d
    - Hydralazine: 112.5mg/d

- Titration (after 4 weeks on initial dose)
  - Double the dose (2 FDC tablets)
    - Total dose: Isosorbide dinitrate: 120mg/d
      - Hydralazine: 225mg/d
Case # 2

56 year old white male here for follow up

History of dilated cardiomyopathy with EF of 28%
- Generally well but continues to have shortness of breath when climbing 2 flights of stairs.

• No history of CAD, he continues to have increasing orthopnea
• BP 110/70 HR 59; No JVD, lungs clear, No S3, No edema
• Medications: Lisinopril 40 mg qd; Carvedilol 12.5 mg bid;
  Spironolactone 25 mg qd, lasix 20 mg bid;

Physical Examination:
- BP 110/70, HR 59/min;
- No JVD; Lungs clear; cardiac regular rate and rhythm;
  Abdomen soft non tender; Extremities without edema
Question Case 2

Which of the following is the most reasonable approach?

1. Make no changes
2. Add Valsartan 40 mg bid
3. Add Ivabradine 5 mg bid
4. Add Digoxin 0.125 mg qd
5. Discontinue Lisinopril and add
   Sacubutril/Valsartan 49/51 mg qd in 36 hours
Any degree of uncertainty a physician may have relative to the condition of a patient can contribute to disparities in treatment. Smedley B. et al, IOM March 2002 McMurray J. et al. NEJM 2014;371(11):993-1004.
PARADIGM-HF

- Industry-supported, largest-ever, 5-year systolic HF trial (NYHA class II-IV) and EF’s ≤ 40% (later 35) involving 8,442 patients (mean age 64, 79% male, only 5% AA) at 1,043 study sites in 47 countries on stable dose of BB + ACEi or ARB for at least 4 wks

- Compared enalapril 10 mg bid vs LCZ696 200 mg bid (containing sacubutritel, a neprilysin inhibitor, that increases natriuretic peptides, and valsartan)

- Stopped early with median f/u 2+ years (27 months) with composite 1⁰ outcome of CV death or first hospitalization for HF both reduced by 20% (p<0.001) and improved QOL.

- Drug discontinuation less in the LCZ696 group

First-in-Class Angiotensin Receptor Neprilysin Inhibitor (ARNI)

First-in-Class Angiotensin Receptor Neprilysin Inhibitor (ARNI)

Mechanism of Action of LCZ696

Natriuretic peptide system
- Pro-BNP
- BNP
- NT-proBNP
  - ANP
  - Bradykinin
  - Substance P
  - Adrenomedullin
  - Angiotensin III

Inactive fragments

Renin-angiotensin system
- Angiotensinogen (liver secretion)
- Angiotensin I
- Angiotensin II
- AT$_1$ receptor

Vasodilation
- Blood pressure
- Sympathetic tone
- Aldosterone levels
- Fibrosis
- Hypertrophy
- Natriuresis/diuresis

Vasoconstriction
- Blood pressure
- Sympathetic tone
- Aldosterone
- Fibrosis
- Hypertrophy

AHU377 (Sacubitril)

**PARADIGM-HF: Cardiovascular Death or Heart Failure Hospitalization (Primary Endpoint)**

Kaplan-Meier Estimate of Cumulative Rates (%)

**Days After Randomization**

**Patients at Risk**

<table>
<thead>
<tr>
<th></th>
<th>LCZ696</th>
<th>Enalapril</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>4187</td>
<td>4212</td>
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<tr>
<td>180</td>
<td>3922</td>
<td>3883</td>
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<tr>
<td>360</td>
<td>3663</td>
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<td>540</td>
<td>3018</td>
<td>2922</td>
</tr>
<tr>
<td>720</td>
<td>2257</td>
<td>2123</td>
</tr>
<tr>
<td>900</td>
<td>1544</td>
<td>1488</td>
</tr>
<tr>
<td>1080</td>
<td>896</td>
<td>853</td>
</tr>
<tr>
<td>1260</td>
<td>249</td>
<td>236</td>
</tr>
</tbody>
</table>

**Enalapril**

(n=4212)

**LCZ696**

(n=4187)

HR = 0.80 (0.73-0.87)

P = 0.0000002

PARADIGM-HF: ANGIOTENSIN-NEPRILYSIN INHIBITION IN HFrEF

- 8,399 patients with class II (70%)-IV HFrEF received enalapril or sacubitril/valsartan (LCZ696) for 3.5 y in randomized, double-blinded fashion.¹

- A 55 yo would have a projected life expectancy of 11.6 y with enalapril and 12.9 y with sacubitril/valsartan (20% decrease in event rate).²

- FDA approved for class II-IV HFrEF in July 2015 based on these results.

PARADIGM: Relationship Between LVEF and Incident Outcomes Adjusted for Baseline Covariates

Solomon SD et al. Circ Heart Fail. 2016;9:e002744
PARADIGM: Treatment Effect of Sacubitril/Valsartan by Tertiles of LVEF For All Outcomes

Solomon SD et al. Circ Heart Fail. 2016;9:e002744
Sacubitril/Valsartan

• Comes in three strengths 24/26 mg; 49/51 mg; 97/103 mg
• To reduce the risk of death and hospitalization for HF in patients with NYHA Chronic Class II (70%)-IV (1%) HFrEF
• Should not be given in those with hx of angioedema from ACEI or ARB, concomitant ACEI, or Aliskerin in those with diabetes. It is a replacement and not add on for RAAS blockade.
• Start with 49/51 bid if on ACEI or ARB and after 2-4 weeks up-titrate to 97/103 mg bid maintainance dose, as tolerated.
• If not on ACEi/ARB or on low doses of ACEi/ARB, or eGFR < 30 cc/min, or moderate hepatic impairment (Child Pugh B)-start with 24/26 mg bid and double the dose q 2-4 weeks to the target dose of 97/103 mg bid, as tolerated.
• Switching from or to an ACEI allow 36 hour wash-out between the two drugs. Not as important with being on ARB.
Sacubitril/Valsartan

• Special populations:
  - increased risk of neonatal morbidity/death 2nd and 3rd TM
  - Not recommended:
    Nursing
    Pediatric Patients
    Severe Hepatic Impairment

• Follow:
  - creatinine ( not used if Cr Cl < 30 cc/min)
  - watch for hyperkalemia ( do not use if K+ > 5.2)
  - hypotension-reduce diuretic, salt replacement, etc-do not initiate if systolic BP < 100 mm Hg (< 90 during the run in)
Case # 3

75 year old white woman here for follow up History of diabetes, hyperlipidemia and hypertension

- Has mild shortness of breath when walking from car to church. Gained 15 pounds over the past year

• She was hospitalized due to poorly controlled hypertension and heart failure eight months ago. No history of CAD

  - 1 pillow orthopnea and frequent ankle swelling; Echocardiogram: Normal LV, EF 70%; LVH and atrial enlargement

• Medications: Amlodipine 5 mg daily; Atenolol 50 mg daily; Atorvastatin 20 mg daily; Aspirin 81 mg daily

• Physical Examination: BP 135/80, pulse 68/min; weight 285lb

  - No JVD; Lungs clear; cardiac regular rate and rhythm;

  Abdomen soft non tender; Extremities 2+ bilateral ankle edema
Case #3: 75 year old white woman

Clinical Pearl #3

- Dyspnea and edema in older woman
- Recent hospitalization for uncontrolled hypertension and heart failure
- Consider HFpEF and need for cautious diuretic therapy with potassium supplementation
Heart Failure: Causal Mechanisms

HF Prognosis in Women

- Women are more likely to have diastolic HF, as opposed to the systolic HF experienced in males
- Women are less likely than men to have coronary artery disease
- CAD increases mortality risk 2.5 times in women, and only 1.5 times in men
Diastolic Filling: Normal vs Left Ventricular Hypertrophy

\[ P = LV \text{ pressure} \]
\[ V = LV \text{ volume} \]

LV, left ventricular; LVH, left ventricular hypertrophy.
Why Do HFpEF Patients Decompensate?

- Excess salt
- Atrial fibrillation
- Medications: NSAIDs, CCBs,
- Inadequate diuretic Rx
- Worsening hypertension
- Myocardial ischemia
- Worsening renal function
- Iatrogenic volume overload
- Anemia
Morphologic Changes of the Heart
**Case #4**

**Clinical Pearl #4**

- Randomized clinical trials have not shown survival benefit with any particular drug therapy in patients with HFpEF

- Need to control BP, and careful diuresis to control symptoms of edema and/or shortness of breath
# Diuretics For Heart Failure

<table>
<thead>
<tr>
<th>Examples</th>
<th>Maximum Effect % of Filtered Na+ Load</th>
<th>Site of Action In Nephron</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Carbonic Anhydrous Inhibitors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acetazolamide</td>
<td>3-5%</td>
<td>Proximal Tubule</td>
</tr>
<tr>
<td><strong>Loop Diuretics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Furosemide</td>
<td>20-25%</td>
<td>Thick Ascending Limb of Loop of Henle</td>
</tr>
<tr>
<td>Bumetanide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Torsemide</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Thiazide Diuretics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCTZ</td>
<td>5-8%</td>
<td>Early Distal Tubule</td>
</tr>
<tr>
<td>Metolazone</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Potassium Sparing Diuretics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spironolactone</td>
<td>2-3%</td>
<td>Late Distal Tubule with Collecting Duct</td>
</tr>
<tr>
<td>Eplerenone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amiloride</td>
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</tr>
</tbody>
</table>
Conclusion

In patients with heart failure and a preserved ejection fraction, treatment with spironolactone did not significantly reduce the incidence of the primary composite outcome of death from cardiovascular causes, aborted cardiac arrest, or hospitalization for the management of heart failure.
HFpEF: Recommendations

- Control systolic and diastolic blood pressure
- Diuretics for relief of symptoms due to volume overload
- Coronary revascularization for patients with CAD or angina with myocardial ischemia
- Treat Atrial Fibrillation
- Use of beta-blocking agents, ACE inhibitors, and ARBs for hypertension in HFpEF
- ARBs might be considered to decrease hospitalizations in HFpEF

Case # 4

• 76 year old WM, history of CAD s/p CABG, Ischemic cardiomyopathy, EF 35%, Severe COPD with frequent use of inhalers, comes to see you following a recent hospitalization for decompensated heart failure

• Medications: Metoprolol 12.5 mg daily, Aspirin 81 mg daily, Atorvastatin 40 mg daily; Albuterol inhaler 2 puffs four times daily

• Physical Examination: BP 118/80, pulse 85/min; Weight 235lb No JVD; Lungs scattered wheezes; cardiac regular rate and rhythm; no murmurs or gallops; Abdomen soft non tender; Extremities no edema

• EKG: sinus rhythm, with nonspecific STT abnormality
Case #4

Clinical Pearl #5

• This patient has a relatively high resting heart rate and severe COPD

• The scattered wheezes are likely related to COPD and may be exacerbated by metoprolol

• What is the treatment option for this patient who may be intolerant of further dosage increase in beta blocker and has a high resting heart rate?
Ivabradine Approved for Systolic Heart Failure

- Ivabradine is an inhibitor of the If “funny channel” of the sinus node pacemaker lowering heart rate (HR) w/o affecting BP or other ionic currents. It is a pure heart rate reducing agent

- FDA approved on April 15, 2015 for patients with stable chronic heart failure with reduced EF(< 35%), a normal sinus rhythm and a resting HR of at least 70 beats per minute, and taking beta blockers at the guideline recommended or the highest dose the patient can tolerate.

- Ivabradine was studied in a clinical trial of 6,505 participants (SHIFT trial) on a background of evidence-based standard therapy including ACEI or ARB, Aldosterone antagonist (etc).
Ivabradine approved for Systolic Heart Failure

- Ivabradine reduced the time to first hospitalization for worsening heart failure compared to placebo but did not reduce overall mortality. HR lowering reduces O2 demand w/o affecting LV function.

- Most common side effects observed in clinical trial participants were bradycardia, hypertension, atrial fibrillation, and temporary vision disturbance (flashes of light) called phosphenes occurring within the first two months that usually resolve with continued use.
Ivabradine approved for Systolic Heart Failure

- Start at 5 mg bid and if pulse is > 60 after two weeks increase to 7.5 mg bid. Reduce to 2.5 mg bid if pulse < 50.
- Ivabradine should not be started in the hospital as it has not been studied in this setting. It is an outpatient medication (started and followed).
- It is only effective in those with normal sinus rhythm.
- Ivabradine costs $375/month.
- Monitor the pulse, especially when used with other rate limiting drugs such as digoxin and amiodarone. Also monitor heart rhythm as 1 in 100 patients can develop atrial fibrillation.
Systolic Heart failure treatment with the If inhibitor ivabradine Trial

Participating Countries

Europe
Belgium
Denmark
Finland
France
Germany
Greece
Ireland
Italy
The Netherlands
Portugal
Spain
Sweden
Turkey
UK
Bulgaria
Czech Republic
Estonia
Hungary
Latvia
Lithuania
Norway
Poland
Romania
Russia
Slovakia
Slovenia
Ukraine

North America
Canada

South America
Argentina
Brazil
Chili

Asia
China
Hong Kong
India
South Korea
Malaysia
Australia

6505 patients, 37 countries, 677 centers
Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Ivabradine 3241</th>
<th>Placebo 3264</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, y</td>
<td>60.7</td>
<td>60.1</td>
</tr>
<tr>
<td>Male, %</td>
<td>76</td>
<td>77</td>
</tr>
<tr>
<td>Ischemic etiology, %</td>
<td>68</td>
<td>67</td>
</tr>
<tr>
<td>NYHA II, %</td>
<td>49</td>
<td>49</td>
</tr>
<tr>
<td>NYHA III/IV, %</td>
<td>51</td>
<td>51</td>
</tr>
<tr>
<td>Previous MI, %</td>
<td>56</td>
<td>56</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>30</td>
<td>31</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>67</td>
<td>66</td>
</tr>
</tbody>
</table>

## Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Ivabradine (n=3241)</th>
<th>Placebo (n=3264)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean heart rate, bpm</td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td>Mean LVEF, %</td>
<td>29</td>
<td>29</td>
</tr>
<tr>
<td>Mean SBP, mm Hg</td>
<td>122</td>
<td>121</td>
</tr>
<tr>
<td>Mean DBP, mm Hg</td>
<td>76</td>
<td>76</td>
</tr>
<tr>
<td>eGFR, mL/min/1.73 m²</td>
<td>75</td>
<td>75</td>
</tr>
</tbody>
</table>

Primary composite endpoint (CV Mortality or HF Hospitalization)

Ivabradine n=793 (14.5%PY) Placebo n=937 (17.7%PY)

$HR = 0.82$ [95% CI 0.75-0.90] $p<0.0001$

Cumulative frequency (%)

Ivabradine n=514 (9.4%PY)  Placebo n=672 (12.7%PY)

\[ HR = 0.74 \quad [95\% CI 0.66-0.83] \quad p<0.0001 \]

Mean ivabradine dose: 6.4 mg bid at 1 month
6.5 mg bid at 1 year

• Heart failure with systolic dysfunction and elevated heart rate is associated with poor outcomes (primary composite endpoint in the placebo group is 18%/year)

• Ivabradine reduced primary endpoint (CV mortality or heart failure hospitalization) by 18% (p<0.0001). The absolute risk reduction was 4.2%

• This beneficial effect was mainly driven by a favorable effect on hospitalization for heart failure (RRR 26%)

• Overall, treatment with ivabradine was safe and well tolerated
Case #4

Clinical Pearl #6

• Based on data from SHIFT study, this patient should benefit from treatment with ivabradine.

• This drug was recently approved by the FDA

• Since patient was recently discharged following hospitalization for acute HF, it will be important to coordinate care with his cardiologist in order to determine optimum timing and dose of ivabradine
<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Mechanism of Action</th>
<th>Common Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiotensin converting enzyme inhibitors (ACEIs*)</td>
<td>Block excess activation of the renin-angiotensin system</td>
<td>Cough, lightheadedness</td>
</tr>
<tr>
<td>Angiotensin receptor blockers (ARBs)*</td>
<td>Block excess activation of the renin-angiotensin system</td>
<td>Lightheadedness</td>
</tr>
<tr>
<td>Aldosterone antagonists*</td>
<td>Block excess aldosterone; potassium-sparing diuretic</td>
<td>Increased urination, hyperkalemia, gynecomastia</td>
</tr>
<tr>
<td>Beta blockers (BBs)*</td>
<td>Block effect of excess norepinephrine release</td>
<td>Fatigue, lightheadedness</td>
</tr>
<tr>
<td>Diuretics</td>
<td>Reverse excessive water retention</td>
<td>Hypovolemia, hypokalemia</td>
</tr>
<tr>
<td>Isosorbide Dinitrate and Hydralazine (FDC I/H)*</td>
<td>Produces vasodilation by increasing nitric oxide</td>
<td>Headache, lightheadedness</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Increases cardiac contractility</td>
<td>Dysrhythmia</td>
</tr>
<tr>
<td>Ivabradine*</td>
<td>Funny channel blocker (SA node)</td>
<td>Bradycardia, hypertension, visual brightness</td>
</tr>
</tbody>
</table>
Class I Recommendations for Pharmacologic Treatment for Stage C HFrEF

HFrEF Stage C
NYHA Class I-IV
Treatment:

- **Class I, LOE A**
  - ACEI or ARB AND beta blocker

For all volume overload, NYHA Class II-IV patients
- **Class I, LOE C**
  - Loop diuretics

For persistently symptomatic African Americans, NYHA Class III-IV
- **Class I, LOE A**
  - Hydral-nitrates

For NYHA Class II-IV patients, if estimated creatinine >30 mL/min and K⁺ <5.0 mEq/dL
- **Class I, LOE A**
  - Aldosterone Antagonist

Place in therapy for sacubitril/valsartan? Ivabradine?

## Some Drugs for Heart Failure With Reduced Ejection Fraction

<table>
<thead>
<tr>
<th>Drug</th>
<th>Some Oral Formulations</th>
<th>Usual Initial Adult Dosage&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Usual Maximum Adult Dosage&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Cost&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Angiotensin-Converting Enzyme (ACE) Inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Captopril - generic</td>
<td>12.5, 25, 50, 100 mg tabs&lt;sup&gt;d&lt;/sup&gt;</td>
<td>6.25 mg tid</td>
<td>50 mg tid</td>
<td>$151.50</td>
</tr>
<tr>
<td>Enalapril - generic</td>
<td>2.5, 5, 10, 20 mg tabs</td>
<td>2.5 mg bid</td>
<td>20 mg bid</td>
<td>39.90</td>
</tr>
<tr>
<td>Vasotec (Valeant)</td>
<td></td>
<td></td>
<td></td>
<td>1311.60</td>
</tr>
<tr>
<td>Fosinopril - generic</td>
<td>10, 20, 40 mg tabs&lt;sup&gt;d&lt;/sup&gt;</td>
<td>5-10 mg once/d</td>
<td>40 mg once/d</td>
<td>10.40</td>
</tr>
<tr>
<td>Lisinopril - generic</td>
<td>2.5, 5, 10, 20, 40 mg tabs</td>
<td>2.5-5 mg once/d</td>
<td>40 mg once/d</td>
<td>2.70</td>
</tr>
<tr>
<td>Prinivil (Merck)</td>
<td>5, 10, 20 mg tabs</td>
<td></td>
<td></td>
<td>94.10</td>
</tr>
<tr>
<td>Zestril (Almatica)</td>
<td>2.5, 5, 10, 20, 30, 40 mg tabs</td>
<td></td>
<td></td>
<td>48.00</td>
</tr>
<tr>
<td>Perindopril erbumine&lt;sup&gt;e&lt;/sup&gt; - generic</td>
<td>2, 4, 8 mg tabs</td>
<td>2 mg once/d</td>
<td>16 mg once/d</td>
<td>37.30</td>
</tr>
<tr>
<td>Aceon (Symplmed)</td>
<td></td>
<td></td>
<td></td>
<td>196.20</td>
</tr>
<tr>
<td>Quinapril - generic</td>
<td>5, 10, 20, 40 mg tabs</td>
<td>5 mg bid</td>
<td>20 mg bid</td>
<td>23.60</td>
</tr>
<tr>
<td>Accupril (Pfizer)</td>
<td></td>
<td></td>
<td></td>
<td>185.10</td>
</tr>
<tr>
<td>Ramipril - generic</td>
<td>1.25, 2.5, 5, 10 mg caps</td>
<td>1.25-2.5 mg once/d</td>
<td>10 mg once/d</td>
<td>15.80</td>
</tr>
<tr>
<td>Altace (Merck)</td>
<td></td>
<td></td>
<td></td>
<td>186.20</td>
</tr>
<tr>
<td>Trandolapril - generic</td>
<td>1, 2, 4 mg tabs</td>
<td>1 mg once/d</td>
<td>4 mg once/d</td>
<td>16.20</td>
</tr>
<tr>
<td>Mavik (Abbvie)</td>
<td></td>
<td></td>
<td></td>
<td>59.10</td>
</tr>
<tr>
<td><strong>Angiotensin Receptor Blockers (ARBs)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azilsartan medoxomil&lt;sup&gt;f&lt;/sup&gt; - Edarbi (Arbor)</td>
<td>40, 80 mg tabs</td>
<td>40-80 mg once/d</td>
<td>80 mg once/d</td>
<td>162.60</td>
</tr>
<tr>
<td>Candesartan cilexetil - generic</td>
<td>4, 8, 16, 32 mg tabs</td>
<td>4-8 mg once/d</td>
<td>32 mg once/d</td>
<td>103.30</td>
</tr>
<tr>
<td>Atacand (AstraZeneca)</td>
<td></td>
<td></td>
<td></td>
<td>131.10</td>
</tr>
<tr>
<td>Losartan&lt;sup&gt;e&lt;/sup&gt; - generic</td>
<td>25, 50, 100 mg tabs</td>
<td>25-50 mg once/d</td>
<td>150 mg once/d</td>
<td>16.20</td>
</tr>
<tr>
<td>Cozaar (Merck)</td>
<td></td>
<td></td>
<td></td>
<td>297.40</td>
</tr>
<tr>
<td>Valsartan - generic</td>
<td>40, 80, 160, 320 mg tabs&lt;sup&gt;d&lt;/sup&gt;</td>
<td>20-40 mg bid</td>
<td>160 mg bid</td>
<td>52.40</td>
</tr>
<tr>
<td>Diovan (Novartis)</td>
<td></td>
<td></td>
<td></td>
<td>319.20</td>
</tr>
<tr>
<td><strong>Angiotensin-Receptor Neprilysin Inhibitor</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sacubitril/valsartan - Entresto (Novartis)</td>
<td>24/26, 49/51, 97/103 mg tabs</td>
<td>49/51 mg bid&lt;sup&gt;f&lt;/sup&gt;</td>
<td>97/103 mg bid</td>
<td>375.00&lt;sup&gt;g&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Abbreviations: ER, extended-release.

<sup>a</sup> A full version of this table appears in *The Medical Letter on Drugs and Therapeutics*. August 3, 2015;57(1474):107-109.

<sup>b</sup> Dosage adjustment may be needed for hepatic or renal impairment.

<sup>c</sup> Approximate WAC for 30 days’ treatment at the lowest usual maximum adult dosage. WAC = wholesaler acquisition cost or manufacturer’s published price to wholesalers; WAC represents a published catalogue or list price and may not represent an actual transactional price. Source: AnalySource<sup>®</sup> Monthly. July 5, 2015. Reprinted with permission by First Databank, Inc. All rights reserved. ©2015. http://www.fdbhealth.com/policies/drug-pricing-policy.

<sup>d</sup> Available as scored tablets.

<sup>e</sup> Not approved by the FDA for treatment of heart failure.

<sup>f</sup> For patients with an eGFR <30 mL/min/1.73 m<sup>2</sup> or for those with moderate hepatic impairment, the dose is 24/26 mg bid.

<sup>g</sup> WAC according to the manufacturer.
Summary Slide

• Heart Failure has a high morbidity and mortality.
• Current Rx of HFrEF is both empiric (Diuretics, Lifestyle) and evidence-based (ACEi’s, ARB’s, BB’s, and MRA’s).
• Newer Therapies including Ivabradine and Valsartin/sacubitril have been approved for HFrEF.
• In HFrEF current therapies remain empiric, with some evidence suggesting that MRA therapy may be helpful.
• Device therapy is used for specific subsets of patients including ICD for reduced HFrEF, CRT for HFrEF wide QRS/LBBB, and destination therapy with an LVAD as a bridge to transplantation or End Stage HF.
• The Paragon-HF trial is ongoing to look at the role of Valsartan/Sacubitril in those with HFpEF.
Post-test ARS Question 1

On a scale of 1 to 5, please rate how confident you would be in the evaluation and management of patients with heart failure?

1. Not at all confident
2. Slightly confident
3. Moderately confident
4. Pretty much confident
5. Very confident