Applying the Latest Advances and Evidence of Clinical Outcomes to Individualize Heart Failure Treatment: A Case Based Discussion
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Disclosures

- **Ola Akinboboye, MD, MPH, MBA** - As per the American Board of Internal Medicine, Dr. Akinboboye will not present content that will have any direct link with the Cardiovascular Board Exam.

- **Jan Basile, MD** serves on the grant/research support team for The National Heart, Lung, and Blood Institute (Sprint). Dr. Basile also serves as a consultant and the grant/research support for the National Heart, Lung, and Blood Institute (Sprint) and Eli-Lilly (Rewind). He is also on the speaker’s bureau for Arbor, Amgen and Janssen.

- **Phillip B. Duncan, MD** serves on the advisory board for Arbor. Dr. Duncan is also on the speakers bureau for Novartis.

- **Brent M. Egan, MD** serves on the advisory committee for AstraZeneca and Valencia as well as a speaker for Medtronic. Dr. Egan serves on the Clinical Evaluation and Treatment team for Up-To-Date.

- **Keith C. Ferdinand, MD, FACC** serves as a consultant for Boehringer Ingelheim, Sanofi, Amgen and Eli Lilly.
Disclosures

- **Icilma V. Fergus, MD, FACC** has no relationships to disclose.

- **Robert L. Gillespie, MD, FACC, FASE, FASNC** serves as an investor for Relypsa.

- **Barbara Hutchinson, MD, PhD, FACC** has no relationships to disclose.

- **Elizabeth Ofili, MD, MPH, FACC** serves on the grant/Research support team for the National Institute of Health. Dr. Ofili also serves as a consultant/advisory board member for Bristol-Myers Squibb, Novartis, Arbor, Merck & Co., Janssen Research and Development.

- **Anekwe Onwuanyi, MD** serves as a speaker for Novartis.
Disclosures

- Priscilla E. Pemu, MD, MSCR, FACP serves as an Employee for Morehouse School of Medicine, Piedmont Medical Care Corporation.

- David N. Smith, MD serves as a speaker for Arbor and CardioDx.

- Kevin L. Thomas, MD serves as a Consultant for BMS and Pfizer.

- Mark A. Thompson, MD serves as a speaker/training member for Novartis.

- Laurence O. Watkins, MD, MPH, FACC is involved in the patient care at Healthy Heart Center, Inc.

- Karol E. Watson, MD, PhD serves as a consultant for Amgen, GSK, Merck and Quest.
Educational Objectives

• Know the risk factors for heart failure and the role of biomarkers in diagnosis and treatment

• Describe pathophysiologic factors contributing to increased risk of heart failure among African Americans and other ethnic minorities

• Identify approaches to facilitate early recognition of heart failure

• Manage heart failure using the most recent clinical evidence
Projected HF Prevalence: Race/Ethnicity 2012-2030

African Americans Have a Higher Lifetime Risk and Earlier Onset of Developing Heart Failure

• The lifetime risk of HF in adults over 45 years old is\(^1\)
  – 32.8% (95% confidence interval [CI]: 27.4-36.1) or 1 in 3 for AAs
  – 25.9% (95% CI: 22.7-28.0) or 1 in 4 for whites

• The likelihood of developing HF before age 50 is 20-fold higher (\(P=0.001\)) among AAs vs whites\(^2\)

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Why Are African Americans More at Risk for Heart Failure?

- Mechanism of HF and responses to pharmacologic therapy among AAs may differ from those among other races\(^1\-^3\)

<table>
<thead>
<tr>
<th>Modifiable risk factors</th>
<th>Hypertension, diabetes, obesity, LVH, smoking, and chronic kidney disease are more common in AAs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurohormonal imbalances and endothelial dysfunction</td>
<td>Derangements in the renin-angiotensin-aldosterone and adrenergic axes as well as impaired endothelial function are more common in AAs</td>
</tr>
<tr>
<td>Genetic polymorphisms</td>
<td>Racial disparity may be the result of several polymorphisms associated with the risk of HF (beta 1 adrenergic receptor, alpha 2c receptor, aldosterone synthase, G protein, transforming growth factor beta, nitric oxide [NO] synthase, and transthyretin)</td>
</tr>
<tr>
<td>Socioeconomic factors and quality of care</td>
<td>Low socioeconomic status and discrimination from health care providers serve as barriers to attaining treatment goals in AAs</td>
</tr>
</tbody>
</table>


2013 ACCF/AHA Guidelines: Prevention and Treatment of HF

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

A 60-year-old white female presents for a checkup
- Evaluated in Urgent Care Center 4 weeks ago for cough without fever. Lisinopril discontinued and valsartan started
- Over past 2 weeks, dry hacking cough resolving
- Moderate SOB after walking 1 block

Medical history:
- Diagnosed with HF 1 year ago, LV EF 38%
- CAD treated with stent in RCA
- Hypertension, T2DM, and dyslipidemia

Medications:
- Metoprolol succinate 200 mg qd, valsartan 160 mg bid, furosemide 40 mg bid, ASA 81 mg qd, atorvastatin 80 mg qd, clopidogrel 75 mg qd
Case #1 (cont’d)

Physical examination:
- BP 135/80 mmHg, pulse 70 bpm, resp. 18 bpm, afebrile
- Trace pedal edema
- Weight has been stable
- Otherwise unremarkable

Blood tests:
- CBC: WNL
- Metabolic panel: WNL
- Cardiac troponin: 0.04 ng/mL  (normal < 0.04ng/ml)
ARS Question

What was the most likely cause of her dry cough?

1. Decompensated HF
2. Lisinopril side effect
3. Pulmonary infection
4. None of the above
Patient is moderately SOB with exertion. What change, if any, would you make to her medication regimen?

1. No change
2. Add aldosterone antagonist
3. Add isosorbide dinitrate/hydralazine
4. Stop valsartan and start sacubitril/valsartan
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


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**Table 1. Characteristics of the Patients at Baseline.**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>LCZ696 (N = 4187)</th>
<th>Enalapril (N = 4212)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age — yr</td>
<td>63.8±11.5</td>
<td>63.8±11.3</td>
</tr>
<tr>
<td>Female sex — no. (%)</td>
<td>879 (21.0)</td>
<td>953 (22.6)</td>
</tr>
<tr>
<td>Race or ethnic group — no. (%)†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>2763 (66.0)</td>
<td>2781 (66.0)</td>
</tr>
<tr>
<td>Black</td>
<td>213 (5.1)</td>
<td>215 (5.1)</td>
</tr>
<tr>
<td>Asian</td>
<td>759 (18.1)</td>
<td>750 (17.8)</td>
</tr>
<tr>
<td>Other</td>
<td>452 (10.8)</td>
<td>466 (11.1)</td>
</tr>
<tr>
<td>Region — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>North America</td>
<td>310 (7.4)</td>
<td>292 (6.9)</td>
</tr>
<tr>
<td>Latin America</td>
<td>713 (17.0)</td>
<td>720 (17.1)</td>
</tr>
<tr>
<td>Western Europe and other‡</td>
<td>1026 (24.5)</td>
<td>1025 (24.3)</td>
</tr>
<tr>
<td>Central Europe</td>
<td>1393 (33.3)</td>
<td>1433 (34.0)</td>
</tr>
<tr>
<td>Asia–Pacific</td>
<td>745 (17.8)</td>
<td>742 (17.6)</td>
</tr>
</tbody>
</table>
First-in-Class Angiotensin Receptor Neprilysin Inhibitor (ARNI)

**Mechanism of Action of LCZ696**

- **Natriuretic peptide system**
  - Pro-BNP
  - BNP
  - NT-proBNP

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

- **Neprilysin**
  - AHU377 (Sacubitril)
  - LBQ657
  - Valsartan

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

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

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

Kaplan-Meier Estimate of Cumulative Rates (%)

<table>
<thead>
<tr>
<th>Days After Randomization</th>
<th>LCZ696 (n=4187)</th>
<th>Enalapril (n=4212)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>180</td>
<td>180</td>
</tr>
<tr>
<td></td>
<td>360</td>
<td>360</td>
</tr>
<tr>
<td></td>
<td>540</td>
<td>540</td>
</tr>
<tr>
<td></td>
<td>720</td>
<td>720</td>
</tr>
<tr>
<td></td>
<td>900</td>
<td>900</td>
</tr>
<tr>
<td></td>
<td>1080</td>
<td>1080</td>
</tr>
<tr>
<td></td>
<td>1260</td>
<td>1260</td>
</tr>
</tbody>
</table>

HR = 0.80 (0.73-0.87)
P = 0.0000002

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>
</tr>
<tr>
<td>180</td>
<td>3922</td>
<td>3883</td>
</tr>
<tr>
<td>360</td>
<td>3663</td>
<td>3579</td>
</tr>
<tr>
<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>336</td>
</tr>
</tbody>
</table>

Packer M., et al. For PARADIGM Investigators
Sacubitril/valsartan: Approved and Recommended

• **FDA Approved** to reduce the risk of cardiovascular death and hospitalization in chronic heart failure patients (NYHA Class II-IV) and reduced EF

• **2016 ACC/AHA/HFSA Guidelines:**
  - Recommend sacubitril/valsartan for patients with:
    - NYHA class II or III HF and reduced EF
    - who tolerate an ACE inhibitor or ARB
  - Replacement of ACE/ARB with ARNI recommended to further reduce morbidity/mortality
  - Close surveillance of serum potassium and creatinine (LOE I-BR)

Yancy, CW, et al. 2016 Heart Failure Focused Update on Pharmacologic Therapy
Medication changes:

- Sacubitril/valsartan 49/51 mg started
- Titrated to 97/103 mg 4 weeks later
- Patient reports good exercise tolerance (NYHA class II)
Case #1 (cont’d)

1 week later, presents to ER with chest pain

- Denies dyspnea, PND, orthopnea

Physical examination:
- BP 120/72 mmHg, pulse 68 bpm, resp. 16 bpm, afebrile
- Otherwise unremarkable

Labs:
- CBC, metabolic panel: WNL
- Cardiac troponin X: WNL
- BNP: 600 pg/mL (normal ≤ 100 pg/ml)
- Chest X-ray: cardiomegaly but no pulmonary congestion
ARS Question

Why is BNP elevated in this patient?

1. Exacerbation of HF
2. Myocardial infarction
3. Expected effect of sacubitril/valsartan
4. None of the above
<table>
<thead>
<tr>
<th>Therapy</th>
<th>Effect on BNP/NT-proBNP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuresis</td>
<td>↓</td>
</tr>
<tr>
<td>ACE-I/ARB</td>
<td>↓</td>
</tr>
<tr>
<td>β blockers</td>
<td>↓</td>
</tr>
<tr>
<td>Aldosterone antagonists</td>
<td>↓</td>
</tr>
<tr>
<td>BiV pacing</td>
<td>↓</td>
</tr>
<tr>
<td>Exercise</td>
<td>↓</td>
</tr>
<tr>
<td>Rate control of AF</td>
<td>↓</td>
</tr>
<tr>
<td>NP infusions</td>
<td>↓</td>
</tr>
<tr>
<td>Serelaxin</td>
<td>↓</td>
</tr>
<tr>
<td><strong>LCZ696</strong></td>
<td>↓ NT-proBNP, ↑ BNP</td>
</tr>
<tr>
<td>Neuregulin</td>
<td>↑</td>
</tr>
</tbody>
</table>
## PARADIGM-HF: Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>LCZ696 (n=4187)</th>
<th>Enalapril (n=4212)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prospectively identified adverse events</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptomatic hypotension</td>
<td>588</td>
<td>388</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Serum potassium &gt; 6.0 mmol/l</td>
<td>181</td>
<td>236</td>
<td>0.007</td>
</tr>
<tr>
<td>Serum creatinine ≥ 2.5 mg/dl</td>
<td>139</td>
<td>188</td>
<td>0.007</td>
</tr>
<tr>
<td>Cough</td>
<td>474</td>
<td>601</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td><strong>Discontinuation for adverse event</strong></td>
<td>449</td>
<td>516</td>
<td>0.02</td>
</tr>
<tr>
<td>Discontinuation for hypotension</td>
<td>36</td>
<td>29</td>
<td>NS</td>
</tr>
<tr>
<td>Discontinuation for hyperkalemia</td>
<td>11</td>
<td>15</td>
<td>NS</td>
</tr>
<tr>
<td>Discontinuation for renal impairment</td>
<td>29</td>
<td>59</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Angioedema (adjudicated)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medications, no hospitalization</td>
<td>16</td>
<td>9</td>
<td>NS</td>
</tr>
<tr>
<td>Hospitalized; no airway compromise</td>
<td>3</td>
<td>1</td>
<td>NS</td>
</tr>
<tr>
<td>Airway compromise</td>
<td>0</td>
<td>0</td>
<td>----</td>
</tr>
</tbody>
</table>

Packer M., et al. For PARADIGM Investigators
PARADIGM-HF Adverse Events

- The most common side effects were hypotension, hyperkalemia, and renal impairment.
- Angioedema was also reported with black patients and patients with a prior history of angioedema having a higher risk.
Case #2
A 68-year-old Caucasian man presents for a checkup after visiting multiple specialists

- Disabled, poor sleep, no energy, SOB walking to mail box
- Smokes 1 ppd, drink 2-3 beers per day
- Gained 10 lbs since last visit

Medical history:
- Hypertension, T2DM, dyslipidemia, obesity, CAD, COPD, CKD, GERD, osteoarthritis, depression
- HF with LV EF 65%, LV hypertrophy, mild mitral regurgitation
Case #2 (cont’d)

Review of consultant notes revealed:

- **Cardiologist:**
  - Decided SOB was largely pulmonary

- **Nephrologist:**
  - Reduced furosemide to 40 mg bid from 80mg bid, because of reduced kidney function (BUN 40 mg/dL, creatinine 1.5 mg/dL)

- **Pulmonologist:**
  - Decided SOB was largely cardiac
  - Scheduled sleep study for OSA

- **Endocrinologist:**
  - Strongly advised starting insulin; patient resisted
  - Sitagliptin initiated instead
Case #2

Medications:

- furosemide 40 mg bid
- lisinopril 40 mg
- carvedilol 25 mg bid
- amlodipine 10 mg qd
- aspirin 81 mg qd
- metformin 850 mg bid
- glipizide 10 mg qd
- sitagliptin 100 mg qd
- fluoxetine 40 mg qd
- naproxen 500 mg bid prn
- omeprazole 40 mg qd
- budesonide/formoterol 160/4.5 mcg 2 inhalations bid
Case #2 (cont’d)

Today’s Physical examination:

- BP 154/78 mmHg, pulse 68 bpm, resp. 20 bpm, afebrile
- Carotid bruit bilateral, JVD at 45°, bibasilar rales, PMI AAL, S3, S4, abdominal bruit, +3 pretibial edema, trace pedal pulses

Studies:

- Na⁺ 134 mg/dL, K⁺ 4.7 mEq/L
- Creatinine 1.8 mg/dL, eGFR 41 mL/min/1.73m²
- Fasting blood glucose 186 mg/dL, A1C 9.4%
- Albumin:creatinine ratio 489 mcg/mg
- BNP 380 ng/dL
- FEV₁ 2.5L, FEV₁/FVC 0.5 (0.65 with bronchodilator)
ARS Question

In your opinion, what is the most important issue for this patient today?

1. Stage 3B CKD
2. Volume overload
3. COPD with reactive component
4. Uncontrolled hypertension and T2DM
5. All of the above
Case #2 (cont’d)

Management:

- Increase furosemide to 80 mg bid
- Stop metformin and glipizide and start insulin glargine at night and repaglinide with meals
- Refer to Certified Diabetes Educator
- Stop naproxen, start acetaminophen
- Recommend smoking cessation counseling

2 months later: Doing better

- Lost 10 lbs, walks ¼ mile with no SOB
- No rales, trace edema
- BP 128/74 mmHg, K⁺ 4.4 mEq/L, creatinine 2.3 mg/dL, eGFR 30 mL/min/1.73m², BNP 76 ng/mL, FBG ~150 mg/dL
Patients with HFpEF may decompensate for any of the following reasons, EXCEPT:

1. Hypertension
2. Atrial fibrillation
3. Inadequate diuretic dose
4. Worsening renal function
5. Persistent hyperglycemia
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
- Unsuspected OSA
- Anemia
Morphologic Changes of the Heart

HF c Preserved EF-LVH

Normal

HF c Reduced EF

RV

LV
Case # 2: Need for Care Coordination

- Randomized clinical trials have not shown survival benefit with any particular drug therapy in patients with HFpEF
- Control BP and diabetes, stop smoking, careful diuresis to improve symptoms of shortness of breath and edema
- Patient has multiple comorbidities and risk factors, sees multiple physicians
- With new onset atrial fibrillation, will need rate control (adjust beta blocker) and addition of anticoagulation
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 I
- Diuretics for relief of symptoms due to volume overload I
- Coronary revascularization for patients with CAD or angina with myocardial ischemia IIa
- Treat Atrial Fibrillation IIa
- Use of beta-blocking agents, ACE inhibitors, and ARBs for hypertension in HFpEF IIa
- ARBs might be considered to decrease hospitalizations in HFpEF IIb

Case #3

A 58-year-old African American man presents for a checkup

- Reports moderate SOB while playing golf
- Mild orthopnea (“1 pillow”)
- Asks about “powerful new drug” for HF
Case #3

Medical history:
- Hypertension, non-ischemic cardiomyopathy, LV EF 36%, LV hypertrophy, left atrial enlargement, mild mitral regurgitation
- Hospitalized 6 months ago for HF

Medications:
- valsartan 160 mg bid, carvedilol 25 mg bid, furosemide 40 mg bid

Physical examination:
- BP 140/80 mmHg, pulse 68 bpm, weight 185 lbs
- No JVD, lungs clear, normal rate and rhythm, grade 2/6 systolic murmur
- Extremities +1 edema
ARS Question

Which of the following actions for this patient is supported by evidence and guidelines?

1. Add ivabradine
2. Add aldosterone antagonist
3. Add isosorbide dinitrate/hydralazine
4. Stop valsartan and start sacubitril/valsartan
• Patient has persistent symptoms despite optimal neurohormonal blockade with valsartan and carvedilol

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

• FDC I/H is the Evidence-based guideline treatment recommended at this time for this patient with NYHA Class III HFrEF
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

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.
A-HeFT: Trial Summary N=1050

- **All-Cause Mortality (%)**
  - Placebo + Standard Therapies: 6.2%
  - FDC I/H + Standard Therapies: 10.2%
  - P=0.012

- **First HF Hospitalization (%)**
  - Placebo + Standard Therapies: 16.4%
  - FDC I/H + Standard Therapies: 24.4%
  - P<0.001

- **Patient Reported Functional Status**
  - Placebo + Standard Therapies: n=532
  - FDC I/H + Standard Therapies: n=518
  - P<0.01

Case #3 (cont’d)

Treatment with FDC I/H

• Initiate and titrate as was done in A-HEFT 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
Disparities in Heart Failure: Ten Years After A-HEFT, Have We Advanced Health Equity?

Use of Hydralazine-Isosorbide Dinitrate Combination in African American and Other Race/Ethnic Group Patients With Heart Failure and Reduced Left Ventricular Ejection Fraction

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**Background**—Hydralazine-isosorbide dinitrate (H-ISDN) therapy is recommended for African American patients with moderate to severe heart failure with reduced ejection fraction (<40%) (HFrEF), but use, temporal trends, and clinical characteristics associated with H-ISDN therapy are unknown.

**Conclusions**—Overall, few potentially eligible patients with HFrEF are treated with H-ISDN, and among African-Americans fewer than one-fourth of eligible patients received guideline-recommended H-ISDN therapy. Improved ways to facilitate use of H-ISDN therapy in African American patients with HFrEF are needed. ([J Am Heart Assoc. 2013;2:e000214 doi: 10.1161/JAHA.113.000214])

**Key Words:** guideline adherence • heart failure • quality • race/ethnicity • registry

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Heart failure (HF) results in substantial morbidity, mortality, and healthcare expenditures.1–3 African Americans are at increased risk for developing HF and experience worse outcomes post-HF development.4,6 Beyond angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), beta-blockers, and aldosterone antagonists use in patients with heart failure with reduced ejection fraction (HFrEF),6–13 clinical trials have established...
Case #4

A 72-year-old Asian female

- Reports frequent wheezing
- Previously treated with carvedilol, but reported pulmonary symptoms when dose titrated to 6.25 mg bid
- Switched to bisoprolol; wheezing returned when dose increased to 5 mg qd
- Reduced dose to 2.5 mg qd after phone consult
- Wheezing still interfering with her sleep and when she walks up stairs
Case #4 (cont’d)

Medical History:
- Stage C, NYHA class II HF; LV EF 30%; NSTEMI 3 years ago; hypertension; dyslipidemia; non smoker

Physical examination:
- BP 108/64 mmHg, heart rate 84 bpm, resp. 18 bpm, afebrile
- Normal sinus rhythm; wheezing without rales or crackles; trace peripheral edema

Medications:
- Lisinopril 20 mg qd, furosemide 80 mg qd, eplerenone 50 mg qd, bisoprolol 2.5 mg qd, atorvastatin 80 mg qd, aspirin 81 mg qd

Labs:
- creatinine 2.0 mg/dL, eGFR 34 mL/min/1.73m²
ARS Question

What course would you follow at this time?

1. Switch from bisoprolol to metoprolol
2. Discontinue bisoprolol and initiate ivabradine
3. Discontinue bisoprolol and maintain other current medications
4. None of the above
Ivabradine Approved for Systolic Heart Failure

- Ivabradine is an inhibitor of the $I_f$ or “funny channel” of the sinus node pacemaker.
  - Pure heart rate-reducing agent
  - Lowers heart rate without affecting BP or other ionic currents.

- Ivabradine evaluated in SHIFT trial:
  - 6,505 participants with HFrEF on Guidelines-Directed Medical Therapy
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

Ivabradine Placebo

Cumulative frequency (%) - 18%

**Race:** Ivabradine appeared to be similarly effective in whites and Asians.

**Because of the small number of Black patients in the trial, differences in response for Blacks could not be determined.**

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<table>
<thead>
<tr>
<th>Race</th>
<th>Number of Patients</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>5771</td>
<td>88.7%</td>
</tr>
<tr>
<td>Black or African American</td>
<td>75</td>
<td>1.2%</td>
</tr>
<tr>
<td>Asian</td>
<td>532</td>
<td>8.2%</td>
</tr>
<tr>
<td>Other</td>
<td>127</td>
<td>2.0%</td>
</tr>
</tbody>
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Ivabradine-Associated Risk Reductions are Related to HR Achieved and Magnitude of HR Reduction

- In HF in sinus rhythm with HR $\geq 75$ bpm, heart rate reduction with ivabradine improved outcomes, including all-cause death and cardiovascular death
- Ivabradine-associated risk reductions were related to both HR achieved and magnitude of HR reduction
- Patients achieving $<60$ bpm or with $>10$ bpm reduction had the best prognosis

Case #4 (cont’d)

- Based on data from SHIFT study, ivabradine dose should be titrated for optimum heart rate reduction, starting at 5mg bid

- Prognosis was best when treatment reduced heart rate by 10 bpm or more from baseline, or when achieved heart rate was less than 60 bpm

- Monitor rhythm while on therapy - discontinue if patient develops atrial fibrillation
SHIFT: Adverse Drug Reactions with rate ≥1% Higher on Ivabradine than Placebo

<table>
<thead>
<tr>
<th></th>
<th>Ivabradine N=3260</th>
<th>Placebo N=3278</th>
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</thead>
<tbody>
<tr>
<td>Bradycardia</td>
<td>10%</td>
<td>2.2%</td>
</tr>
<tr>
<td>Hypertension, BP increased</td>
<td>8.9%</td>
<td>7.8%</td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>8.3%</td>
<td>6.6%</td>
</tr>
<tr>
<td>Phosphenes, visual brightness*</td>
<td>2.8%</td>
<td>0.5%</td>
</tr>
</tbody>
</table>

** Regularly monitor cardiac rhythm. Discontinue ivabradine if atrial fibrillation develops

*Onset is generally within the first 2 months of treatment, after which they may occur repeatedly. Phosphenes were generally reported to be of mild to moderate intensity and led to treatment discontinuation in < 1% of patients; most resolved during or after treatment.
Conclusions

• HFrEF with heart rate >70 bpm despite maximally tolerated beta blocker therapy is associated with poor outcomes. These patients may benefit from ivabradine.

• Sacubitril/valsartan may be appropriate for patients with HFrEF
  • Small sample size of African Americans in PARADIGM study may limit use in this population

• Recognize the impact of health disparities and apply the best clinical trial evidence to support the treatment of HF in African Americans and other ethnic minorities
POST-TEST QUESTIONS
Post-test ARS Question 1

Which of the following was the most prevalent modifiable risk factor for heart failure among predominantly African American patients admitted with a primary diagnosis of heart failure?

1. Hypertension
2. Hyperglycemia
3. Current smoking
4. Hypercholesterolemia
In the SHIFT trial, the use of ivabradine was associated with reductions in cardiovascular mortality or heart failure hospitalization compared to placebo in all patients, EXCEPT those treated with maximum tolerated dose beta blockers.

1. True

2. False
Post-test ARS Question 3

A 69-year-old white woman presents with a history of NYHA class III/ stage C heart failure with left ventricular ejection fraction 30%, CAD, hypertension, and dyslipidemia. She reports shortness of breath when climbing stairs, but no other symptoms. BP 109/71 mmHg, HR 64 bpm, potassium 4.5 mEq/L, and eGFR 33 mL/min/1.73m².

Meds: furosemide 40 mg bid, metoprolol succinate 200 mg qd, lisinopril 20 mg qd, eplerenone 50 mg qd, and atorvastatin 80 mg qd.

Which of the following might be appropriate at this time?

1. Patient is stable; maintain current regimen
2. Discontinue metoprolol and initiate ivabradine
3. Discontinue eplerenone based on serum potassium levels
4. Discontinue lisinopril and initiate sacubitril/valsartan after 36 hours
Post-test ARS Question 4

How often will you consider changes to medical therapy for patients with heart failure and a heart rate $\geq 70$ bpm as a result of this lecture?

1. Never
2. Rarely
3. Sometimes
4. Often
5. Always
A 61-year-old African American man, NYHA class II/stage C heart failure and left ventricular ejection fraction 30%, obesity (BMI 32.4 kg/m²), hypertension, and dyslipidemia presents for a checkup. He reports shortness of breath when he walks more than 100 feet, but no other symptoms. BP today is 120/78 mmHg, HR 66 bpm, eGFR 41 mL/min/1.73m², and potassium 4.7 mEq/L.

Meds: metoprolol SR 100 mg qd, furosemide 40 mg bid, valsartan 160 mg bid, atorvastatin 80 mg qd, eplerenone 50 mg qd, aspirin 81 mg qd

After reviewing the brief scenario above, please rate each of the statements as consistent with or not consistent with best clinical practice for management of heart failure:

Initiate isosorbide dinitrate/hydralazine.

1. Yes, it is consistent
2. No, it is not consistent
Post-test ARS Question 6

61 y/o AA male, NYHA Class II/stage C, SOB walking 100 feet

- EF 30%
- VS: 120/78, HR 66
- Labs: eGFR 41, K 4.7 mEq/L
Meds: metoprolol SR 100 mg qd, furosemide 40 mg bid, valsartan 160 mg bid, atorvastatin 80 mg qd, eplerenone 50 mg qd, ASA 81 mg qd.

After reviewing the brief scenario above, please rate each of the statements as consistent with or not consistent with best clinical practice for management of heart failure:

Consider switching from valsartan to lisinopril/hydrochlorothiazide.

1. Yes, it is consistent
2. No, it is not consistent
Post-test ARS Question 7

61 y/o AA male, NYHA Class II/stage C, SOB walking 100 feet

- EF 30%
- VS: 120/78, HR 66
- Labs: eGFR 41, K 4.7 mEq/L
  Meds: metoprolol SR 100 mg qd, furosemide 40 mg bid, valsartan 160 mg bid, atorvastatin 80 mg qd, eplerenone 50 mg qd, ASA 81 mg qd.

After reviewing the brief scenario above, please rate each of the statements as consistent with or not consistent with best clinical practice for management of heart failure:

**Discontinue eplerenone based on serum potassium levels.**

1. Yes, it is consistent
2. No, it is not consistent
Post-test ARS Question 8

61 y/o AA male, NYHA Class II/stage C, SOB walking 100 feet

- EF 30%
- VS: 120/78, HR 66
- Labs: eGFR 41, K 4.7 mEq/L
- Meds: metoprolol SR 100 mg qd, furosemide 40 mg bid, valsartan 160 mg bid, atorvastatin 80 mg qd, eplerenone 50 mg qd, ASA 81 mg qd.

After reviewing the brief scenario above, please rate each of the statements as **consistent** with or **not consistent** with best clinical practice for management of heart failure:

**Initiate ivabradine.**

1. Yes, it is consistent
2. No, it is not consistent
Post-test ARS Question 9

61 y/o AA male, NYHA Class II/stage C, SOB walking 100 feet

- EF 30%
- VS: 120/78, HR 66
- Labs: eGFR 41, K 4.7 mEq/L
Meds: metoprolol SR 100 mg qd, furosemide 40 mg bid, valsartan 160 mg bid, atorvastatin 80 mg qd, eplerenone 50 mg qd, ASA 81 mg qd.

After reviewing the brief scenario above, please rate each of the statements as consistent with or not consistent with best clinical practice for management of heart failure:

Switch patient from valsartan to sacubitril/valsartan.

1. Yes, it is consistent
2. No, it is not consistent
Post-test ARS Question 10

Please rate your confidence in your ability to manage patients with heart failure in accordance with current guidelines and evidence:

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