Learning Objectives

- Review the definition, prevalence, and pathophysiology of heart failure (HF)
- Describe the recommendations in the 2016 focused guideline update on pharmacologic therapy for HF
- Summarize the impact of updated guideline recommendations on HF management
- Describe the rationale for individualization of medical therapy in the patient with HF

Heart Failure – Definition

- Heart failure – Defined in the most simplistic terms as the myocardium’s inability to meet the metabolic demands of the body
- Typically a primary defect in myocardial function leading to a decrease in cardiac output
- Syndrome is characterized by a pattern of signs and symptoms
- HF is stratified into distinct clinical patterns according to left ventricular ejection fraction (EF):
  - HF with reduced EF (HFrEF) – systolic dysfunction
  - HF with preserved EF (HFP EF) – diastolic dysfunction
  - HF with mid-range or borderline EF (HFmrEF)
  - HF with improved EF (EF improves after index event)
Heart Failure – Definition

- HFrEF (EF ≤ 40%) primarily results from systolic HF
- HFpEF (EF ≥ 50%) primarily results from diastolic HF
  - Diagnosis of HFpEF is challenging - exclude other potential noncardiac causes of symptoms suggestive of HF
- HFmEF (EF 41% to 49%) - characteristics, treatment patterns, and outcomes appear similar to patients with HFpEF
- HFimpEF with an improved EF (>40) who previously had HFrEF represents a clinically distinct subgroup of patients
- Mortality benefit with drug therapy based on randomized controlled trials (RCTs) - only in HFrEF
- RCTs not able to demonstrate mortality benefit with drug therapy in HFpEF
- No RCTs conducted specifically in HFmEF or HF with improved EF

Prevalence of Heart Failure in the U.S.

- 5.7 million American adults have heart failure (based on data from 2009–2012)
  - Incidence increases with age and is higher in African Americans than Hispanics or whites
  - May reflect higher prevalence of hypertension, diabetes, and low socioeconomic status
- Heart failure – underlying cause of death in > 65,000 patients in 2013
  - Contributing factor in > 300,000 deaths in 2013

Prevalence of Heart Failure in the U.S.

- Heart failure – 1st listed hospital discharge diagnosis among 1,023,000 patients in 2010
- In 2012, 1,774,000 physician office visits for heart failure
- In 2011, 553,000 emergency department visits for heart failure
- Heart failure costs in 2012 - $30.7 billion per year
  - 68% for direct medical costs (hospitalizations were the largest proportion of these costs)
Pathophysiology of Heart Failure

Alteration in Myocardial Function
- LV dysfunction
- LV Remodeling
- Hemodynamic compromise
- Neurohormonal activation
- HF syndrome
- Symptoms
- Morbidity
- Death
- Vasoconstriction


Heart Failure Stages (2013 ACC/AHA/HFSA Guidelines)

- **Stage A**: Risk factors for HF
- **Stage B**: Presence of structural heart disease (e.g., MI, LV dysfunction, valve disease) without symptoms of HF
- **Stage C**: Structural heart disease and current or prior symptoms of HF
- **Stage D**: HF refractory to conventional treatment; consider ventricular assist device, transplantation or palliative care

New York Heart Association (NYHA) Heart Failure Classification

- **Class I**: No symptoms
- **Class II**: Symptoms with ordinary physical activity
- **Class III**: Symptoms with less than normal activity
- **Class IV**: Symptoms at rest

### Chronic Heart Failure Treatment

<table>
<thead>
<tr>
<th>Drug/Drug Class</th>
<th>ACC/AHA Stage B</th>
<th>ACC/AHA Stage C</th>
<th>ACC/AHA Stage D</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitors*</td>
<td>Yes (or ARB)</td>
<td>Yes (or ARB)</td>
<td>Yes</td>
</tr>
<tr>
<td>β-adrenergic blockers*</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Diuretics</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Digoxin</td>
<td>No</td>
<td>Consider</td>
<td>Consider</td>
</tr>
<tr>
<td>Aldosterone receptor antagonists*</td>
<td>No</td>
<td>Consider</td>
<td>Yes</td>
</tr>
<tr>
<td>Hydralazine/nitrate*‡</td>
<td>No</td>
<td>Consider</td>
<td>Consider</td>
</tr>
</tbody>
</table>

*Drug/drug class shown to improve survival in HF
+ Mortality benefit in African American patients

#### 2016 ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure

<table>
<thead>
<tr>
<th>Applying Class of Recommendation and Level of Evidence to Treatments in Patient Care</th>
<th>Class (Strength) of Recommendation</th>
<th>Benefit &gt;&gt; Risk</th>
<th>Class (Strength) of Recommendation</th>
<th>Benefit &gt;&gt; Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Class I (strong)</td>
<td>Benefit &gt;&gt;&gt; Risk</td>
<td>Level A</td>
<td>High quality evidence from &gt; 1 randomized trial Meta-analysis of high quality randomized trials</td>
</tr>
<tr>
<td></td>
<td>Class IIa (moderate)</td>
<td>Benefit &gt;&gt; Risk</td>
<td>Level B</td>
<td>Moderate quality evidence from ≥ 1 randomized trials</td>
</tr>
<tr>
<td></td>
<td>Class IIb (weak)</td>
<td>Benefit ≥ Risk</td>
<td>Level B-RR</td>
<td>Moderate quality evidence from ≥1 well-designed, well-executed non-randomized, observational, or registry trials</td>
</tr>
<tr>
<td></td>
<td>Class III No Benefit (moderate)</td>
<td>Not recommended</td>
<td>Level C-RR</td>
<td>Randomized or non-randomized observational or registry trials with design or analytic limitations Psychosocial or randomized studies in patients</td>
</tr>
<tr>
<td></td>
<td>Class III Harm (strong)</td>
<td>Harmful</td>
<td>Level C-EQ</td>
<td>Consensus of expert opinion based on clinical experience</td>
</tr>
</tbody>
</table>

‡ Hydralazine/nitrate with evidence of benefit in patients with conditions associated with excess mortality/mortality.
2016 ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure

Recommendations for Renin-Angiotensin System Inhibition With ACE Inhibitor or ARB or ARNI

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>A</td>
<td>The primary strategy of inhibition of the renin-angiotensin system with ACE inhibitors (Grade of Evidence: A; Level of Evidence: B; LOE: B) or ARBs (Grade of Evidence: A; Level of Evidence: C; LOE: C) or a combination with evidence-based beta blockers (Grade: B; Level of Evidence: C; LOE: B) should be considered for all patients with heart failure.</td>
</tr>
<tr>
<td>E</td>
<td>B</td>
<td>In patients with chronic symptomatic HF-REF NYHA class II or III who tolerate an ACE inhibitor or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality (Grade: C; Level of Evidence: C; LOE: C).</td>
</tr>
</tbody>
</table>

First FDA-Approved Angiotensin Receptor/Neprilysin Inhibitor (ARNI) (LCZ696)

Angiotensin Receptor Blocker (Valsartan)

Nephrilysin Inhibitor (Sacubitril)

Endogenous vasoactive peptides
- Natriuretic peptides
- Adrenomedullin
- Bradykinin, substance P, angiotensin II, calcitonin gene-related peptide

Neprilysin

Inactive metabolites

Neurohormonal activation
- Vascular tone
- Cardiac fibrosis, hypertrophy
- Sodium retention
Angiotensin Receptor/Nephrilysin Inhibitor

- 1:1 molar ratio of sacubitril and valsartan (ARB) which dissociate after ingestion
- Sacubitril is a prodrug which is rapidly converted to the active nephrilysin inhibitor LBQ657 by plasma esterases
- Available as 24/26 mg (50 mg), 49/51 (100 mg) and 97/103 (200 mg) fixed-dose combination tablets
- The 26 mg, 51 mg, and 103 mg of valsartan is bioequivalent to 40 mg, 80 mg, and 160 mg of valsartan in the Diovan® tablet
- This increase in bioavailability is thought to be due to differences in the manufacturing process

PARADIGM-HF – Study Design

Multicenter, randomized, parallel-group, double-blind, active control
Primary Outcome: Death from CV cause + 1st HF hospitalization

- Age >18 years
- NYHA function class II–IV
- LV ejection fraction <40%
- BNP >150 pg/mL
- NTproBNP >600 pg/mL
- sBP < 100 mmHg
- eGFR < 30 mL/min/1.73m²
- K+ >5.2 mmol/L
- Prior history of angioedema with ACEI

Enalapril “run-in”
N = 10,513

~2 weeks

Sacubitril/Valsartan
200 mg fixed dose

Randomization
N = 8,442

Sacubitril/Valsartan
300 mg fixed dose

Enalapril
10 mg BID

~4-6 weeks

PARADIGM-HF Baseline Characteristics

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>ACEI 78%</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>ARB 23%</td>
</tr>
<tr>
<td>Race</td>
<td>Beta-blocker 23%</td>
</tr>
<tr>
<td>Hispanic</td>
<td>Diuretic 83%</td>
</tr>
<tr>
<td>Gender</td>
<td>Digoxin 30%</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>Aldosterone antagonist 54%</td>
</tr>
<tr>
<td>Heart rate</td>
<td>CRT 7%</td>
</tr>
<tr>
<td>CHF</td>
<td>ICD 16%</td>
</tr>
<tr>
<td>Prior history</td>
<td>CRT 7%</td>
</tr>
<tr>
<td>ACEI</td>
<td>CRT 7%</td>
</tr>
<tr>
<td>ARB</td>
<td>CRT 7%</td>
</tr>
</tbody>
</table>
PARADIGM-HF – Outcomes

![Graph of PARADIGM-HF Outcomes]

PARADIGM-HF – Adverse Events

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Enalapril</th>
<th>ARNI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension</td>
<td>9.2%</td>
<td>14.0%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Symptomatic + SBP &lt; 90 mmHg</td>
<td>1.4%</td>
<td>2.7%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum creatinine ≥ 2.5 mg/dL</td>
<td>4.5%</td>
<td>3.3%</td>
<td>0.007</td>
</tr>
<tr>
<td>Serum potassium ≥ 5.5 mmol/L</td>
<td>17.3%</td>
<td>16.1%</td>
<td>0.15</td>
</tr>
<tr>
<td>Cough</td>
<td>14.3%</td>
<td>11.3%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Angioedema</td>
<td>0.1%</td>
<td>0.2%</td>
<td>0.31</td>
</tr>
<tr>
<td>Discontinuation for AEs due to study medication</td>
<td>12.3%</td>
<td>10.7%</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Considerations With Use of ARNI

- History of hypersensitivity to any component (ARB or sacubitril)
- Patients on ACE inhibitors: 36-hour washout with ARNI dose titration based on size of ACE inhibitor dose
  - 2013 HF guidelines: Abrupt withdrawal of treatment with an ACE inhibitor can lead to clinical deterioration and should be avoided
  - Dose titration: 24mg/26mg → 47mg/51mg → 97mg/103mg
- Patients not on ACE inhibitor or ARB: guidelines and PI differ on management strategy
- ARNI may be started in patients not receiving an ACE inhibitor or ARB
- Guidelines suggest patients should be sympotmatic on an ACE inhibitor or ARB prior to switching to ARNI (valsartan/sacubitril)
Angiotensin Receptor/Neprilysin Inhibitor – Challenges with Use

- QOL data based on the KC Cardiomyopathy Questionnaire – favors ARNI over enalapril
- No data available on changes in exercise capacity in PARADIGM-HF
- AWAKE-HF – study in progress evaluating activity and sleep as well as other QOL parameters
- Does not appear to include an evaluation of 6 minute walk test or treadmill time
- Almost all data in patients with NYHA Class II/III HF
  - Essentially no data in Class IV patients (not indicated in NYHA Class I)
  - Little published data using ARNI in African American patients
  - No published data on the use of ARNI in patients receiving nitrates/hydralazine
  - Theoretical concerns with ARNI and cognitive function:
    - Neprilysin is one of several enzymes that metabolizes amyloid-beta protein linked to plaque formation in patients with Alzheimer’s disease
    - No adverse neurocognitive effects reported in PARADIGM-HF, but testing not performed
    - Initiation of ARNI represents a challenge (based on PARADIGM protocol)
      - Washout and dose titration requires planning
      - Single-blind run-in period artificially improved tolerability
      - Excluded ACS in last 3 months, severe pulmonary disease, CrCL < 30 mL/min
    - Cost may be a concern (~$12 per day)
      - Patients may be reluctant to switch

Angiotensin Receptor/Neprilysin Inhibitor – Benefits

- ARNI was more effective than enalapril:
  - Reduced the risk of CV death and HF hospitalization
  - Reduced the relative risk of CV death by 20%
  - Reduced the relative risk of HF hospitalization by 21%
  - Reduced the relative risk of all-cause mortality by 16%
  - Improvement in QOL
- ARNI was better tolerated than enalapril:
  - Less likely to cause cough, hyperkalemia or renal impairment
  - Less likely to be discontinued due to an adverse event
  - More hypotension, but no increase in rate of discontinuation
  - No more likely to cause serious angioedema
Impact of Elevated Heart Rate on Mortality

- High heart rates have been associated with increased mortality
  - General adult population
  - Hypertension
  - Stable coronary artery disease
  - Diabetes mellitus
  - Heart failure

- Explains (at least in part) the mechanism of benefit of beta-blockers in reducing mortality

- Achievement of heart rate thresholds with beta-blockers may produce mortality benefit similar to that seen with "target" doses of beta-blockers

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2016 ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure

<table>
<thead>
<tr>
<th>Recommendation for Diuretics</th>
<th>CON</th>
<th>LOE</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Fraternal can be beneficial to reduce HF hospitalization for patients with NYHA class II-II, stable chronic HF (NYHA class II) who are receiving DHFA, including a beta blocker at maximum tolerated dose, and who are in sinus rhythm with a heart rate of 70 bpm or greater at rest (27-48).</td>
</tr>
</tbody>
</table>

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Ivabradine – Reduces Heart Rate

- **MOA:** selectively blocks the hyperpolarization-activated cyclic nucleotide-gated (If) channels in a concentration-dependent manner.
- **Active** when If channels are open.
- **Greatest activity occurs** when open-close cycling of the If channel is most rapid, hence it exhibits greatest effect when sinus rates are highest.
- **Works exclusively** by reducing sinus rate.
- **Typical** HR is ~10 bpm at rest and during exercise.
- **No effect on** cardiac contractility.
- **Reduces myocardial oxygen demand**.
- **Prolongs diastole** – increases myocardial perfusion and coronary flow.

**INDICATIONS**
- Age >18 years
- **Moderate**- to **severe** HF for at least 4 months duration
- LV ejection fraction ≤35%
- Recent HF admission (1 year)

**CONTRAINDICATIONS**
- HR <70 bpm
- Recent MI (<2 months)
- Symptomatic hypotension
- AV pacing for >40% day
- AFib/flutter

**Ivabradine 5 mg BID**

**Enrollment**
- **N = 6,558**
- **Placebo (N = 3,264)**

**Target dose was 7.5 mg BID**
- HR was < 60 bpm

**Baseline Characteristics – SHIFT Trial**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Ivabradine (n = 3,241)</th>
<th>Placebo (n = 3,264)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>60.7 ± 11.2</td>
<td>60.1 ± 11.7</td>
</tr>
<tr>
<td><strong>Gender (% male)</strong></td>
<td>76%</td>
<td>77%</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>2879 (89%)</td>
<td>2892 (89%)</td>
</tr>
<tr>
<td>Asian</td>
<td>266 (8%)</td>
<td>264 (8%)</td>
</tr>
<tr>
<td>Other</td>
<td>94 (3%)</td>
<td>108 (3%)</td>
</tr>
<tr>
<td><strong>Heart rate (bpm)</strong></td>
<td>79.7 ± 9.5</td>
<td>80.1 ± 9.8</td>
</tr>
<tr>
<td><strong>Systolic BP (mmHg)</strong></td>
<td>122.0 ± 16.1</td>
<td>121.4 ± 15.9</td>
</tr>
<tr>
<td><strong>Diastolic BP (mmHg)</strong></td>
<td>75.7 ± 9.6</td>
<td>75.6 ± 9.4</td>
</tr>
<tr>
<td><strong>EF (%)</strong></td>
<td>50.0 ± 5.1</td>
<td>50.0 ± 5.3</td>
</tr>
<tr>
<td><strong>NYHA</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1822 (56%)</td>
<td>1584 (49%)</td>
</tr>
<tr>
<td>2</td>
<td>1605 (50%)</td>
<td>1618 (50%)</td>
</tr>
<tr>
<td>3</td>
<td>55 (2%)</td>
<td>61 (2%)</td>
</tr>
<tr>
<td><strong>Ischemic Etiology</strong></td>
<td>2215 (68%)</td>
<td>2202 (67%)</td>
</tr>
<tr>
<td><strong>SCD/CRT</strong></td>
<td>120 (4%)</td>
<td>159 (5%)</td>
</tr>
</tbody>
</table>
### Effect of Ivabradine on Outcomes According to HR

- **Subgroup analysis of ivabradine-treated patients in the SHIFT trial**

- HR achieved at 28 days after start of therapy correlated with reductions in primary outcome at 2 years
  - Patients with ivabradine-treated HR ≥ 75 bpm – primary endpoint occurred in just over 30% of these patients
  - Patients with ivabradine-treated HR < 60 bpm – primary endpoint occurred in less than 20% of these patients
  - Linear relationship between HR reductions at 28 days and primary endpoint at 2 years

- **Magnitude of reduction in HR at 28 days also correlated with reductions in composite primary outcome at 2 years**
  - Ivabradine-treated patients with HR reductions > 10 bpm had greater reductions in primary outcomes compared to patients with no HR decrease and those with a HR decrease of 0 to 10 bpm

### Background Beta-Blocker Therapy in the SHIFT Trial

- **Patients (%)**
  - At least 50% target daily dose
  - Target daily dose

- **89 ± 89**
  - **Ivabradine**
  - **Placebo**

- **56 ± 56**
  - **Ivabradine**
  - **Placebo**

- **26 ± 26**
  - **Ivabradine**
  - **Placebo**
### Reasons for Failure to Reach Target Beta Blocker Doses in the SHIFT Trial*

<table>
<thead>
<tr>
<th>Reason</th>
<th>Ivabradine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension</td>
<td>933 (44%)</td>
<td>952 (45%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>676 (32%)</td>
<td>670 (32%)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>284 (14%)</td>
<td>302 (14%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>267 (13%)</td>
<td>245 (12%)</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>134 (6%)</td>
<td>125 (6%)</td>
</tr>
<tr>
<td>Other</td>
<td>199 (9%)</td>
<td>219 (10%)</td>
</tr>
</tbody>
</table>

*More than one reason may have been given.

---

### Reasons for Patients Not Taking Beta Blockers in SHIFT

<table>
<thead>
<tr>
<th>Reason</th>
<th>Ivabradine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>COPD</td>
<td>126 (37%)</td>
<td>109 (32%)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>59 (17%)</td>
<td>68 (20%)</td>
</tr>
<tr>
<td>Asthma</td>
<td>35 (10%)</td>
<td>39 (11%)</td>
</tr>
<tr>
<td>Cardiac decompensation</td>
<td>23 (7%)</td>
<td>31 (9%)</td>
</tr>
<tr>
<td>Dizziness or bradycardia</td>
<td>24 (7%)</td>
<td>17 (5%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>17 (5%)</td>
<td>20 (6%)</td>
</tr>
<tr>
<td>Raynaud or PAD</td>
<td>16 (5%)</td>
<td>20 (6%)</td>
</tr>
<tr>
<td>Other</td>
<td>44 (13%)</td>
<td>37 (11%)</td>
</tr>
<tr>
<td>Total</td>
<td>344 (11%)</td>
<td>340 (10%)</td>
</tr>
</tbody>
</table>

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### SHIFT – Adverse Events

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Placebo</th>
<th>Ivabradine</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event</td>
<td>74%</td>
<td>75%</td>
<td>0.303</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>48%</td>
<td>45%</td>
<td>0.025</td>
</tr>
<tr>
<td>Heart failure</td>
<td>29%</td>
<td>25%</td>
<td>0.0005</td>
</tr>
<tr>
<td>Symptomatic bradycardia</td>
<td>1%</td>
<td>5%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Asymptomatic bradycardia</td>
<td>1%</td>
<td>6%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>6%</td>
<td>9%</td>
<td>0.012</td>
</tr>
<tr>
<td>Phosphenes</td>
<td>1%</td>
<td>3%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>&lt;1%</td>
<td>1%</td>
<td>0.042</td>
</tr>
</tbody>
</table>
Ivabradine Pharmacokinetics

- Rapid absorption (tmax = 0.75–1.5 hours) – bioavailability of 37% to 49%
- Should be taken with meals. Food delays absorption by 1 hour, increases plasma concentrations by 20% to 40%
- Extensive Vd with 70% plasma protein binding
- Extensively metabolized – cytochrome P450 3A4 to several metabolites (major metabolite is N-dimethyl ivabradine)
- t1/2 of ivabradine is 6 hours
- Drug interactions primarily involve 3A4 inhibitors and inducers
  - Inhibitors:azole antifungals, macrolide antibiotics, HIV protease inhibitors, non-dihydropyridine calcium channel blockers, grapefruit juice
  - Inducers: 1st generation anticonvulsants, rifampin, St. John’s Wort
- Pharmacodynamic interactions: beta blockers, non-dihydropyridine calcium channel blockers, digoxin, amiodarone

Ivabradine Dosing

<table>
<thead>
<tr>
<th>Initiation of Therapy</th>
<th>After 2 weeks check heart rate</th>
<th>After another 2 weeks recheck heart rate; re-evaluate every 4 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ivabradine 5 mg BID</td>
<td>If &gt; 60 bpm, dose to 7.5 mg BID or 5 mg BID if initial dose was 2.5 mg BID.</td>
<td>Target dose is 7.5 mg BID if HR is &gt; 50-60 bpm.</td>
</tr>
<tr>
<td>2.5 mg BID if risk of bradycardia</td>
<td>If 50-60 bpm maintain dose</td>
<td>2.5 or 5 mg BID are acceptable doses based on HR response.</td>
</tr>
<tr>
<td>At 30 days after randomization, 63% of patients on 7.5 mg BID, 26% on 5 mg BID, and 8% on 2.5 mg BID.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Ivabradine Precautions/Contraindications

Precautions
- ICD and CRT therapy is not contraindicated
- History of atrial fibrillation or conduction disturbances
- Elderly: >75 yrs consider a lower starting dose (2.5 mg BID)
- Renal Impairment:
  - No dose adjustment – CrCl >15 ml/min
  - No data are available in patients with CrCl <15 ml/min
- Hepatic Impairment:
  - No dose adjustment – moderate hepatic impairment
  - Caution – severe hepatic impairment

Contraindications
- Hypotension
- HR < 60 bpm prior to treatment
- Sinus node dysfunction
diseases or conduction disease
- Acute decompensated heart failure
- Severe hepatic impairment
- Pacer dependence with threshold rate ≤ 60 bpm
- Concomitant use of strong CYP 3A4 inhibitors
Ivabradine Summary

**Indication**
- Patients with stable, symptomatic (NYHA II-IV), chronic HF with EF ≤ 35%
  who are in sinus rhythm with a resting heart rate ≥ 70 bpm
- Dosing twice daily with food

**Benefits**
- Reduces HF hospitalizations and HF mortality
- CV mortality reduction, but not statistically significant
- Fewer serious adverse events (primarily due to fewer HF exacerbations)

**Risks**
- Bradycardia
- Atrial fibrillation
- Phosphenes
- Potential for adverse events with strong CYP3A4 inhibitors

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Ivabradine Summary

**Challenges with ivabradine use**
- Maximizing beta-blocker use and dosing
- Type and dose of beta blocker not randomized or standardized
- Almost no data in NYHA Class IV patients
- No available data in African American patients
- No available data in patients receiving nitrates/hydralazine
- Estimated proportion of HF patients eligible for ivabradine ~ 12%
- Cost ~ $12/day
- NNT to achieve the primary composite outcome (HF hospitalization) is 26
  - Annual cost of ivabradine is ~$4,400
  - Cost to prevent one hospital admission for HF is ~$14,000
- Formal cost-effectiveness analyses are needed

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**Case #1**

SL is a 68-year-old African American female who presents to her primary care provider's office with a 4-day history of worsening shortness of breath, fatigue, and cough that occurs with less than usual activity.

**Patient History:** Hypertension, dyslipidemia, mild aortic stenosis, and heart failure. Echocardiogram 3 months ago showed EF 35%, no evidence of diastolic dysfunction, and aortic valve area of 1.5 cm².

**Medication History:** SL takes metoprolol-XL 50 mg/d, lisinopril 5 mg/d, amlodipine 5 mg/d, atorvastatin 20 mg/d, and furosemide 20 mg/d.

After talking to the nurse in her physician's office 2 days ago, SL was advised to increase her dose of furosemide to 20 mg BID.
Case #1, Continued

**Examination:** Other information collected at this visit:
- Body weight: 92 kg
- Height: 5'6"
- BP: 148/78 mmHg
- Rales at bases of both lungs
- + pitting edema in both ankles
- Laboratory: serum creatinine: 1.2 mg/dL, K+: 3.5 mEq/L, NT-proBNP: 1489 pg/mL
- 12-lead ECG shows sinus rhythm with a rate of 78 bpm

**Questions:**
1. What changes would you recommend to SL's therapy?
2. Would SL be a candidate for ivabradine or ARNI (valsartan/sacubitril)?
3. If medication changes are made, how would you initiate and monitor such therapy?

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Case #2

CJ is a 56-year-old white male who presents to the heart failure clinic for routine follow-up. CJ has a 5-year history of HF with a known EF of 30% secondary to a MI.

CJ indicates he has been feeling well and is still able to walk for 15 minutes at 2.5 mph on his home treadmill. He is primarily concerned about getting his PT/INR checked for his warfarin, which he takes for permanent atrial fibrillation.

**Physical exam findings:**
- CHA2DS2-VASC score of 4 (HF, HTN, type 2 DM, MI)
- Weight: 98 kg, BP: 150/88 mmHg, pulse: 66 bpm

**Medication history:**
- Furosemide 20 mg BID, lisinopril 20 mg QD, carvedilol 25 mg BID, warfarin 6 mg QD, ASA 81 mg/d, rosuvastatin 20 mg/d, allopurinol 300 mg/d for gout

Laboratory findings at this visit:
- INR: 2.6
- serum creatinine 1.1 mg/dL
- K+: 4.0 mEq/L
- NT-proBNP: 398 pg/mL
- uric acid 3.8 mg/dL

**Questions:**
1. What changes would you recommend to CJ's therapy?
2. Would CJ be a candidate for ivabradine or ARNI therapy?
3. If so, how would you initiate and monitor such therapy?