NO DISCLOSURES
OBJECTIVES

• Review Class I pharmacological recommendations from the 2013 ACCF/AHA Guideline for Management of Heart Failure

• Discuss the clinical implementation of Angiotensin Receptor Neprilysin Inhibitor (PARADIGM-HF Trial)

• Discuss the clinical implementation of ivabradine (SHIFT Trial)

• Review the 2017 ACC/AHA/HFSA Focused Update on Heart Failure Management
At Risk for Heart Failure

STAGE A
At high risk for HF but without structural heart disease or symptoms of HF
- e.g., Patients with:
  - HTN
  - Atherosclerotic disease
  - DM
  - Obesity
  - Metabolic syndrome or
  Patients
  - Using cardiotoxins
  - With family history of cardiomyopathy

THERAPY
- Goals:
  - Heart healthy lifestyle
  - Prevent vascular, coronary disease
  - Prevent LV structural abnormalities
- Drugs:
  - ACEI or ARB in appropriate patients for vascular disease or DM
  - Statins as appropriate

STAGE B
Structural heart disease but without signs or symptoms of HF
- e.g., Patients with:
  - Pre-HTN
  - Pre-MI
  - Left ventricular hypertrophy

THERAPY
- Goals:
  - Prevent hospitalization
  - Reduce hospital readmissions
  - Mortality
- Drugs:
  - ACEI or ARB in appropriate patients
  - Beta blockers
  - Aldosterone antagonists

STAGE C
Structural heart disease with prior or current symptoms of HF
- e.g., Patients with:
  - Marked HF symptoms at rest
  - Recurrent hospitalizations despite GDMT

THERAPY
- Goals:
  - Control symptoms
  - Improve HROQL
  - Reduce hospital readmissions
  - Establish patient’s end-of-life goals
- Options:
  - Advanced care measures
  - Heart transplant
  - Chronic inotropes
  - Temporary or permanent MCS
  - Experimental surgery or drugs
  - Palliative care and hospice
  - ICD deactivation

Heart Failure

STAGE D
Refractory HF
- e.g., Patients with:
  - Refractory symptoms of HF at rest, despite GDMT

THERAPY
- Goals:
  - Impress symptoms
  - Reduce hospital readmissions
  - Establish patient’s end-of-life goals
- Options:
  - Advanced care measures
  - Heart transplant
  - Chronic inotropes
  - Temporary or permanent MCS
  - Experimental surgery or drugs
  - Palliative care and hospice
  - ICD deactivation

Structural heart disease
CLINICAL EVALUATION

General Appearance:
- mentation
- respiratory status
- skin color and temp

Pulmonary Findings:
- bilateral rales or rhonchi
- Cheyne-Stokes respiration
- bibasilar dullness

Cardiac Findings:
- cardiomegaly (PMI)
- (+) S3
- murmur (TR or MR)
- tachycardia
- parasternal lift

Neck:
- JVD
- elevated JVP
- thready pulse

Kidney Findings:
- reduced urine output

Lower Extremity Findings:
- pedal edema
- chronic venous stasis changes
- cool and/or mottled extremities

Abdominal Findings:
- hepatomegaly
- hepatojugular reflex
- ascites
- weight gain

Genital Findings
- scrotal edema
# Classification of Heart Failure

<table>
<thead>
<tr>
<th>ACCF/AHA Stages of HF</th>
<th>NYHA Functional Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>A  At high risk for HF but without structural heart disease or symptoms of HF.</td>
<td>None</td>
</tr>
<tr>
<td>B  Structural heart disease but without signs or symptoms of HF.</td>
<td>I No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF.</td>
</tr>
<tr>
<td>C  Structural heart disease with prior or current symptoms of HF.</td>
<td>I No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF.</td>
</tr>
<tr>
<td></td>
<td>II Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in symptoms of HF.</td>
</tr>
<tr>
<td></td>
<td>III Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes symptoms of HF.</td>
</tr>
<tr>
<td></td>
<td>IV Unable to carry on any physical activity without symptoms of HF, or symptoms of HF at rest.</td>
</tr>
</tbody>
</table>
### IMPORTANT HEART FAILURE TRIALS

<table>
<thead>
<tr>
<th>Trial</th>
<th>Year</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>V-HeFT &amp; A-HeFT</td>
<td>1986, 2004</td>
<td>1986 and 2004 trials showing the benefit of ISDN/hydralazine in HFrEF and ultimately in African American patients</td>
</tr>
<tr>
<td>CONSENSUS Trial</td>
<td>1987</td>
<td>1987: Enalapril in severe HFrEF. Enalapril improves survival in NYHA class IV HFrEF when added to standard therapy</td>
</tr>
<tr>
<td>SOLVD Trial</td>
<td>1991</td>
<td>1991: Enalapril in mod-severe HFrEF (EF &lt;35%). Enalapril reduces 4-year mortality by 16% and reduces HF hospitalization</td>
</tr>
<tr>
<td>MERIT-HF Trial</td>
<td>1999</td>
<td>Mortality benefit with the following beta blocker therapy: Metoprolol XL, Bisoprolol, and Carvedilol</td>
</tr>
<tr>
<td>CIBIS II Trial</td>
<td>2003</td>
<td>1999: Spironolactone in HFrEF (EF &lt;35%, NYHA III-IV)</td>
</tr>
<tr>
<td>COPERNICUS Trial</td>
<td>2011</td>
<td>2011: Eplerenone in HFrEF (EF &lt;35%, NYHA II)</td>
</tr>
<tr>
<td>RALES Trial</td>
<td>2003</td>
<td>2003: Candesartan in HFrEF (EF &lt;40%, NYHA II-IV)</td>
</tr>
<tr>
<td>EMPHASIS-HF Trial</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHARM Trial</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
INTRODUCTION

Current Drugs That Reduce Mortality in HF With Reduced EF

ACE-I cornerstone of treatment for HFrEF for nearly 25 years.
ARBs are reasonable to reduce M&M as alternatives to ACE-I
GDMT includes optimal doses of ACE-I/ARB in addition to beta blocker (BB) and mineralocorticoid receptor antagonists (MRA)
All target maladaptive elements of HF.
SNS S

RAAS

ASOCONSTRICTION

ARRHYTHMIA

RAAS ACTIVATION

Na+ & H2O RETENTION

ALDOSTERONE SECRETION

SNS TIMULATION
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 IIHV patients
Add
Class I, LOE C
Loop Diuretics

For persistently symptomatic
African Americans
NYHA class IIHV
Add
Class I, LOE A
Hydral-Nitrates

For NYHA class IIHV patients
Provided estimated creatinine
>30 mL/min and K+ < 5.0 mEq/dL
Add
Class I, LOE A
Aldosterone
Antagonist
<table>
<thead>
<tr>
<th>I</th>
<th>ACE-I: A</th>
</tr>
</thead>
<tbody>
<tr>
<td>The use of ACE inhibitors is beneficial for patients with prior or current symptoms of chronic HFrEF to reduce morbidity and mortality (128-133, 143).</td>
<td></td>
</tr>
</tbody>
</table>

- Shown in large RCTs to reduce morbidity and mortality in patients with HFrEF
- No difference among available ACE inhibitors
- Start at low doses and titrate upward. If maximal doses are not tolerated, intermediate doses should be tried
- Caution in patients with hypotension, renal insufficiency, or hyperkalemia
- May cause angioedema or cough
- Contraindicated in pregnant women or anticipated pregnancy
**Angiotensin Receptor Blocker**

<table>
<thead>
<tr>
<th>I</th>
<th>ARB: A</th>
</tr>
</thead>
</table>

The use of ARBs to reduce morbidity and mortality is recommended in patients with prior or current symptoms of chronic HFrEF who are intolerant to ACE inhibitors because of cough or angioedema (134-137, 145, 146).

- Shown in large RCTs to **reduce morbidity and mortality** in patients with HFrEF
- Unlike ACE-I, ARBs do not inhibit kininase and are associated with a much lower incidence of cough and angioedema
- Caution in patients with hypotension, renal insufficiency, or hyperkalemia
- Good alternative if patient intolerant to ACE-I
**Beta Blockers**

- Use of 1 of the 3 BBs proven to **reduce morbidity and mortality** in patients with current or prior symptoms of HFrEF
  - Carvedilol
  - Sustained-release metoprolol succinate
  - Bisoprolol
- Patients need not take high doses of ACE-I before initiation of beta blocker therapy
- In patients taking a low dose of an ACE-I, the addition of a beta blocker produces greater improvement than an isolated increase in ACE-I dose
ALDOSTERONE RECEPTOR ANTAGONISTS

• Recommended in patients with **NYHA II-IV** and **LVEF ≤35%** to reduce morbidity and mortality

• Creatinine should be ≤2.5 mg/dL in men or ≤2.0 mg/dL in women

• Potassium should be <5 mEq/L

• Careful monitoring of potassium and renal function should be performed at initiation and closely followed thereafter to minimize risk of hyperkalemia and renal insufficiency

• Recommended for **acute MI in patient who have LVED ≤40% or who have a history of diabetes mellitus**
HYDRALAZINE AND ISOSORBIDE DINITRATE

- Recommended to **reduce morbidity and mortality** for patients self-described as **African American with NYHA class III-IV HFrEF**

- Used as adjunct therapy for African American patients with HFrEF who remain symptomatic despite optimal and concomitant use of ACE inhibitors, beta blockers, and aldosterone antagonists

- Combination therapy useful in patients who cannot be given an ACE-I or ARB due to drug intolerance or renal insufficiency (Class IIa Recommendation)

- Poor adherence due to frequency of administration and large number of tablets
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A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America

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BIOMARKERS

• Both BNP and NT-proBNP used to assist in the diagnosis or exclusion of HF but absolute values and cutoffs are NOT interchangeable
  • BNP >100 pg/mL
  • NT-proBNP >900 pg/mL

• Elevated plasma levels of natriuretic peptide biomarkers are associated with a wide variety of cardiac and noncardiac causes
  • Obesity associated with lower natriuretic peptide
  • Angiotensin Receptor Neprilysin Inhibitor (ARNI) increases BNP levels
BIOMARKERS: 2017 UPDATE

• Measurement of baseline levels of natriuretic peptide biomarkers on admission to the hospital is useful to establish a prognosis in acutely decompensated HF (Class IA)

• During a HF hospitalization, a pre-discharge natriuretic peptide level can be useful to establish a post-discharge prognosis (Class IIa)

• For patients at risk of developing HF, natriuretic peptide biomarker screening followed by team-based care can be useful to prevent new-onset HF (Class IIa)
Cardiac
  HF, including RV syndromes
  Acute coronary syndromes
  Heart muscle disease, including LVH
  Valvular heart disease
  Pericardial disease
  Atrial fibrillation
  Myocarditis
  Cardiac surgery
  Cardioversion
  Toxic-metabolic myocardial insults, including cancer chemotherapy

Noncardiac
  Advancing age
  Anemia
  Renal failure
  Pulmonary: obstructive sleep apnea, severe pneumonia
  Pulmonary hypertension
  Critical illness
  Bacterial sepsis
  Severe burns
ANGIOTENSIN RECEPTOR–NEPRILYSIN INHIBITOR (ARNI)
STUDY OBJECTIVE:
Examine whether the long-term effects of LCZ696 on morbidity and mortality were superior to those of ACE inhibition with enalapril in patients with chronic heart failure and a reduced ejection fraction.
WHAT IS LCZ696?

Valsartan + AHU377 = ARNI
WHAT IS NEPRILYSIN?

Natriuretic Vasoactive Peptides

Neprilysin inhibition counteracts neurohormonal overactivation that triggers decompensated heart failure.

Promotes sodium excretion
Increases vasodilatation
Decreases cardiac fibrosis
Decreases cardiac hypertrophy

Neprilysin

Inactive Metabolites

AHU377
STUDY PROCEDURES

- **Enalapril 10mg BID** for 2 weeks
- **LCZ 100mg BID** for 1-2 weeks
- **LCZ 200mg BID** for 2-4 weeks

**Single blind run in period**

**Double blind period**

1:1 Randomization

Evaluated Q2-8 wks for first 4mo, and Q4mo thereafter

- **LCZ 696 200mg BID**
• **LCZ696 (ARNI)** COMPARED TO ENALAPRIL:
  
  ❖ **MORE EFFECTIVE IN REDUCING THE RISK OF DEATH FROM CARDIOVASCULAR CAUSES AND HOSPITALIZATION FROM HEART FAILURE**
  
  ❖ **SUPERIOR IN REDUCING SYMPTOMS AND PHYSICAL LIMITATIONS OF HEART FAILURE**
  
  ❖ **CLINICALLY AND STATISTICALLY SIGNIFICANT BECAUSE SHOWN TO REDUCE MORTALITY COMPARED TO DOSE OF ENALAPRIL**
  
  ❖ **BENEFIT SEEN IN PATIENT WHO WERE ALREADY RECEIVING ALL OTHER DRUGS KNOWN TO IMPROVE SURVIVAL IN HF**
TRIAL RESULTS

• ADVERSE EFFECTS
  • LCZ696 ASSOCIATED WITH A HIGHER RATE OF SYMPTOMATIC HYPOTENSION DUE TO ITS GREATER VASODILATORY EFFECT BUT FEWER PATIENTS STOPPED THE MEDICATION COMPARED TO ENALAPRIL
  • NO DIFFERENCE IN RENAL PERFUSION AND SERUM CREATININE LEVELS

• Beneficial effect of LCZ696 on cardiovascular mortality was at least as large as that of long-term enalapril
PRIMARY ENDPOINT
Death from cardiovascular cause or first hospitalization for heart failure

Hazard ratio, 0.80 (95% CI, 0.73–0.87)
P<0.001
Number needed to treat=21

No. at Risk
LCZ696 4187 3922 3663 3018 2257 1544 896 249
Enalapril 4212 3883 3579 2922 2123 1488 853 236
ENTRESTO (SACUBITRIL/VALSARTAN)

• DOSAGE
  • ENTRESTO 50 MG = SACUBITRIL 24 MG/VALSARTAN 26 MG
  • ENTRESTO 100 MG = SACUBITRIL 49 MG/VALSARTAN 51 MG
  • ENTRESTO 200 MG = SACUBITRIL 97 MG/VALSARTAN 103 MG

• RECOMMENDED STARTING DOSE OF ENTRESTO IS 49/51 MG TWICE DAILY

• DOUBLE THE DOSE OF ENTRESTO AFTER 2-4 WEEKS TO THE TARGET MAINTENANCE OF 97/103 MG BID

• STARTING DOSE OF 24/26 MG BID RECOMMENDED FOR THOSE WITH NO PRIOR EXPOSURE TO ACE-I OR ARB
ENTRESTO (SACUBITRIL/VALSARTAN)

- ARNI **CONTRAINDICATED** with concomitant use of an ACE-I
- If switching from an ACE-I to ARNI (or vice versa), allow a washout period of **36 hours** between administration of the two drugs
- Dose Adjustment for Severe Renal (eGFR <30) and Hepatic Impairment (Child-Pugh B classification)
  - STARTING DOSE OF 24/26 MG BID
  - GOAL DOSE 97/103 MG BID
<table>
<thead>
<tr>
<th><strong>Angiotensin-converting enzyme inhibitor (ACEi)</strong></th>
<th><strong>Angiotensin II receptor blocker (ARB)</strong></th>
<th><strong>Not on ACEi or ARB</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients receiving a total daily dose of &gt;10 mg of enalapril or therapeutically equivalent doses of another ACEi, for example:</strong></td>
<td><strong>Patients receiving a total daily dose of &gt;160 mg of valsartan or therapeutically equivalent doses of another ARB, for example:</strong></td>
<td><strong>Not currently taking ACEis or ARBs</strong></td>
</tr>
</tbody>
</table>
|  - Lisinopril >10 mg  
  - Ramipril >5 mg |  - Losartan >50 mg  
  - Olmesartan >10 mg | |
| **Stop ACEi 36 hours before starting ENTRESTO** | **Start ENTRESTO at the recommended dose of 24/26 mg twice daily** | **Start ENTRESTO at the recommended dose of 24/26 mg twice daily** |
| | **Stop ACEi 36 hours before starting ENTRESTO** | **Start ENTRESTO at the recommended dose of 24/26 mg twice daily** |
| | **Start ENTRESTO at the recommended dose of 49/51 mg twice daily** | **Start ENTRESTO at the recommended dose of 24/26 mg twice daily** |
| | **Double the dose after 2 to 4 weeks to 49/51 mg twice daily, as tolerated by the patient** | **Double the dose after 2 to 4 weeks to 49/51 mg twice daily, as tolerated by the patient** |
| | | **Double the dose after 2 to 4 weeks to 49/51 mg twice daily, as tolerated by the patient** |

**Note:**
- Double the dose of ENTRESTO after 2 to 4 weeks, as tolerated by the patient, to reach the target maintenance dose of 97/103 mg twice daily.
Sinoatrial Node Modulator (Ivabradine)
SHIFT TRIAL

IVABRADINE AND OUTCOMES IN CHRONIC HEART FAILURE: A RANDOMIZED PLACEBO-CONTROLLED STUDY

STUDY OBJECTIVE:
Evaluate the effect of ivabradine in addition to guideline-based treatment on cardiovascular outcomes, symptoms, and quality of life in patients with chronic heart failure and systolic dysfunction.
WHAT IS IVABRADINE?

• I_f is a mixed Na^+-K^+ ionic current that regulates intrinsic pacemaker activity

• I_f channel is highly expressed in the sinoatrial node and is influenced by the autonomic nervous system

• Ivabradine selectively inhibits the I_f current in a dose-dependent manner which reduces cardiac pacemaker activity and lowers heart rate

• Unlike BBs or CCBs, ivabradine selectively reduces heart rate without loss of contractility
HCN channel
Mixed sodium and potassium channel that carries the $I_f$ current

$I_f$ current
Inward flow of positively charged ions that initiates the spontaneous diastolic depolarization phase, modulating heart rate

Corlanor®
Within the SA node, selectively blocks the HCN channel, inhibits the $I_f$ current, and lowers heart rate
STUDY PROCEDURES

7411 patients assessed

7106 selected*

305 excluded because of non-compliance with study criteria

548 excluded
- 349 non-compliance with study criteria
- 125 withdrew consent
- 68 adverse event
- 5 missing
- 1 no randomisation call

6558 randomised

3268 assigned Ivabradine

27 excluded
- 2 study drug not dispensed
- 25 patients from removed centres

3241 analysed (including 2 lost to follow-up and 73 who withdrew consent for study participation)

3290 assigned placebo

26 excluded
- 5 study drug not dispensed
- 21 patients from removed centres

3264 analysed (including 1 lost to follow-up and 58 who withdrew consent for study participation)
TRIAL RESULTS

• **IVABRADINE** reduced major risks associated with heart failure when added to guideline-based treatment:
  - **Relative Risk** of the primary endpoint fell by 18% compared with placebo.
  - Benefits became apparent within 3 months of initiation of treatment and were maintained throughout the course of the trial.
  - Greatest benefit seen in patients with **systolic heart failure** and **HR ≥70 BPM** which supports the idea that HR plays an important role in the pathophysiology of heart failure.
TRIAL RESULTS

• ADVERSE EFFECTS
  • ASSOCIATED WITH BRADYCARDIA BUT OVERALL WELL TOLERATED
  • NO IMPACT ON LABORATORY VALUES

• Benefits of adjunctive ivabradine therapy when target doses of beta blocker cannot be tolerated and HR remains ≥70 bpm
PRIMARY ENDPOINTS

A

- Placebo (372 events)
- Ixabradine (293 events)

HR 0.82 (95% CI 0.75-0.90), p=0.0001

B

- Placebo (673 events)
- Ixabradine (514 events)

HR 0.74 (95% CI 0.66-0.81), p=0.0001

C

- Placebo (491 events)
- Ixabradine (449 events)

HR 0.91 (95% CI 0.80-1.03), p=0.128

Number at risk
Placebo group Ixabradine group
0 3264 3241
6 2868 2928
12 2489 2600
18 2061 2173
24 1089 1191
30 439 447

Number at risk
Placebo group Ixabradine group
0 3264 3241
6 3094 3085
12 2817 2818
18 2391 2428
24 1318 1362
30 534 531

The Lancet 2010 376, 875-885 DOI: (10.1016/S0140-6736(10)61198-1)
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## RECOMMENDED STARTING DOSE

| 5 mg 2x/day | OR | 2.5 mg 2x/day | 7.5 mg 2x/day |

For patients in whom bradycardia could lead to hemodynamic compromise or with a history of conduction defects.

## AFTER 2 WEEKS, CHECK RESTING HEART RATE

<table>
<thead>
<tr>
<th>&gt; 60 bpm</th>
<th>Increase dose by 2.5 mg 2x/day up to a max of 7.5 mg 2x/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>TARGET RANGE 50-60 bpm</td>
<td>Maintain dose</td>
</tr>
<tr>
<td>&lt; 50 bpm OR SYMPTOMS OF BRADYCARDIA</td>
<td>Decrease dose by 2.5 mg 2x/day</td>
</tr>
</tbody>
</table>

- No dosage adjustment is required for patients with moderate to severe renal impairment (CrCl 15 to 60 mL/min)
IVABRADINE SAFETY INFORMATION

• CONTRAINdications:
  • Acute decompensated heart failure
  • Blood pressure <90/50 mmHg
  • Sick sinus syndrome
  • Resting HR <60 bpm prior to treatment
  • Severe hepatic impairment
  • Pacemaker-dependence

• May cause **fetal toxicity** when administered to pregnant women
• Increased risk of **atrial fibrillation**
• **Bradycardia and conduction disturbance**
2017 FOCUSED UPDATE:
MANAGEMENT OF HEART FAILURE
2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure

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**ANGIOTENSIN RECEPTOR – NEPRILYSIN INHIBITOR**

<table>
<thead>
<tr>
<th>I</th>
<th>ARNI: B-R</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>In patients with chronic symptomatic HFrEF NYHA class II or III who tolerate an ACE inhibitor or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality (138).</strong></td>
</tr>
</tbody>
</table>

- Hospitalization and mortality were significantly decreased compared to enalapril
- Approved for **symptomatic HFrEF** and intended to be substituted for ACE-I or ARBs
- Use of an ARNI is associated with hypotension and a low-frequency incidence of angioedema
- **Target dose** used in the trial was 97/103 mg twice daily

**NEW:** New clinical trial data necessitated this recommendation.
### Warning

<table>
<thead>
<tr>
<th>III: Harm</th>
<th>B-R</th>
<th>ARNI should not be administered concomitantly with ACE inhibitors or within 36 hours of the last dose of an ACE inhibitor (148, 149).</th>
<th>NEW: Available evidence demonstrates a potential signal of harm for a concomitant use of ACE inhibitors and ARNI.</th>
</tr>
</thead>
<tbody>
<tr>
<td>III: Harm</td>
<td>C-EO</td>
<td>ARNI should not be administered to patients with a history of angioedema.</td>
<td>NEW: New clinical trial data.</td>
</tr>
</tbody>
</table>
**IVABRADINE**

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendation</th>
<th>Comment/Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIa</td>
<td>B-R</td>
<td>Ivabradine can be beneficial to reduce HF hospitalization for patients with symptomatic (NYHA class II-III) stable chronic HFrEF (LVEF ≤35%) who are receiving GDEM*, 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 (154-157).</td>
<td>NEW: New clinical trial data.</td>
</tr>
</tbody>
</table>

- Selectively inhibits the If current in the sinoatrial node, providing heart rate reduction
- Optimize Class I guideline-directed management therapy before considering ivabradine
- Reduced HF hospitalization
- Strict parameters: NYHA II-IV, LVEF ≤35%, Sinus Rhythm HR ≥70bpm
THANK YOU