Disclosures

- Novartis: Consultant, Speaker's Bureau

Objectives

- Describe pharmacologic properties of two recently approved drugs for HF-rEF
  - An angiotensin receptor neprilysin inhibitor
  - A selective sinus node If channel inhibitor
- Discuss use of newer agents in conjunction with other HF-rEF medications to improve quality of life and survival, and reduce rehospitalization
Definition & Pathology of Heart Failure

- A clinical syndrome; it results from any structural or functional impairment of ventricular filling or ejection of blood

**Pathophysiology of HFrEF**

- Cardiomyopathy
- Cardiac overload
- Coronary disease

Left ventricular dysfunction

- Vasoconstriction
- Neurohormonal activation

- Peripheral organ blood flow
- Skeletal Blood flow
- RBF, Na retention
- LV dilatation
- LV hypertrophy
- Arrhythmias

Symptoms, fluid retention, death

**Heart Failure Pharmacotherapy Reduces Death**

Percentage of Deaths in Heart Failure and Reduced Ejection Fraction (HFrEF) Clinical Trials Caused by Cardiovascular Disease, 1985-2014

How Should Novel Medications Be Incorporated into the Pharmacotherapy of Heart Failure Patients?

A 32 year old female without significant PMH is flown to your center in refractory cardiogenic shock one week after delivering a healthy baby boy. She has been newly diagnosed with non-ischemic dilated cardiomyopathy.

Case Presentation

• Developed progressive shock and multi-organ dysfunction
• ECMO initiated
• After 4 days, clinical status improved
  • ECMO is successfully weaned
  • Remained hospitalized for an additional 2 weeks.
• NOW: 1 month post discharge and you are seeing her in clinic
• Current pharmacotherapies:
  • Furosemide and warfarin for LV thrombus
  • Low dose carvedilol
  • Low dose lisinopril
• She tells you she feels her life has been turned upside down and is frightened about her and baby’s future.

What is the optimal pharmacotherapy plan?

ECMO, extracorporeal membrane oxygenation; LV, left ventricular
**Pharmacologic Treatment for Stage C HFrEF**

- **NYHA Class I-IV patients, if estimated creatinine >30 mL/min and K+ <5.0 mEq/dL**
- For persistently symptomatic African Americans, NYHA Class III-IV
- For persistently symptomatic / volume overload, NYHA Class III-IV patients
- For persistently symptomatic / African Americans, NYHA Class III-IV

- **Treatment:**
  - **ACEI or ARB AND beta blocker**
  - **Loop diuretics**
  - **Hydralazine - nitrates**
  - **Aldosterone Antagonist**

---

**Pooled Analysis: 32 RCT of ACEi**

- **All-cause mortality in 5 pooled trials:** OR 0.80 (95% CI, 0.74-0.87; *p*<0.0001)*

  Treatment of 100 patients could prevent 7 major events (death/CHF readmission/MI)*


---

**Clinical Effects of ARBs on HF**

- **CHARM-Alternative**
  - Proportion of pts with CV death or hospital admission for CHF

- **Val-HeFT**
  - Probability of freedom from combined endpoint

Risk-Treatment Mismatch in HF: Major Clinical Challenge

Guideline Recommendations and Medications in HF: 2 Issues

#1. “Medications don’t work in patients who don’t take them”
C. Everett Koop

Teach Back

NEW CONCEPT: Health information, advice, instructions, or change in management

Assess patient comprehension / Ask patient to demonstrate
Clarify & tailor explanation
Re-assess recall and comprehension / Ask patient to demonstrate

Adherence / Error reduction

Shared Decision Making

Guideline Recommendations and Medications in HF: 2 Issues

#1. “Medications don’t work in patients who don’t take them” C. Everett Koop

#2. Health care providers who fail to order AND who under dose HF medications are not serving their patients best interest

Patients who Survived 1st HF Hospitalization and Claimed a RASI, β-B or Spironolactone Prescription in 3 mos. (statin, 6 mos) of Discharge

Majority <50% of target dose with little dose escalation over time

Mineralocorticoid Receptor Antagonism

Mineralocorticoid receptor expressed in renal tubular cells
- Associated with sodium retention and K+ loss
- Also expressed in vascular smooth muscle cells, endothelial cells, myocardium, brain, kidney, and other tissues (i.e., eyes)

Vicious Cycle of MR Activation

Mineralocorticoid Receptor Antagonism Evidence

- **RALES**\(^1\): Spironolactone in advanced NYHA FC III-IV [10% on beta-blocker (BB)]
  - 24-month 30% \(\text{↓}\) all-cause mortality; 30% \(\text{↓}\) in HF hospitalization

- **EPHESUS**\(^2\): Eplerenone in early post-AMI (3-14 days) with LVSD/HF and/or DM [85% on BB]
  - 16 month 13% \(\text{↓}\) all-cause mortality; \(\text{↓}\) in combo CV mortality and HF hospitalization

- **EMPHASIS-HF**\(^3\): chronic stable HF/NYHA class II + Hx CV hospitalization within the past 6 months
  - 21 month 37% \(\text{↓}\) total mortality and total hospitalizations

---

Stage C HFrEF Tx: Mineralocorticoid Receptor Antagonists

<table>
<thead>
<tr>
<th>GDMT</th>
<th>RR Reduction in Mortality</th>
<th>NNT to 5% Mortality (Standardized to 36 months)</th>
<th>RR Reduction in HF Hospitalization</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACEi / 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>MRA</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>


Contemporary Use of MRA Based on Guideline Recommendations

- Registry- or survey-based studies
- Prescribing rates of ACEi, ARBs, BBs and MRAs among HFREF patients
- Published in 2000-2015
- 23 reports and 83,605 patients

<table>
<thead>
<tr>
<th>Medication</th>
<th>Prescribed, %</th>
<th>Treatment Gap, %</th>
<th>≥ 50% Target Dose, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACEi/ARB</td>
<td>79.8</td>
<td>13.1</td>
<td>72, ACEi / 51, ARB</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>81.4</td>
<td>3.9</td>
<td>49</td>
</tr>
<tr>
<td>MRA</td>
<td>36.4</td>
<td>16.8</td>
<td>83</td>
</tr>
</tbody>
</table>


Stage C HFrEF Tx: Mineralocorticoid Receptor Antagonists

Recommended for patients w NYHA class II-IV and
- LVEF of ≤ 35%, unless contraindicated
- If NYHA class II:
  - History of prior cardiovascular hospitalization or
  - Elevated plasma BNP
  - Creatinine ≤ 2.5 mg/dL, men // ≤ 2.0 mg/dL, women or
  - eGFR ≥30 mL/min/1.73m2
  - Potassium < 5.0 mEq/L
  - Monitor K+, renal function, & diuretic dosing
  - To minimize risk of hyperkalemia and renal insufficiency

Stage C HF\textsubscript{r}EF MRA Use; AHA/ACC Guidelines

Recommended to \(6\) morbidity and mortality after AMI if LVEF \(\leq 40\%\) who develop symptoms of HF or Hx diabetes mellitus, unless contraindicated

Inappropriate use \textit{is potentially harmful}

- Life-threatening hyperkalemia
  - If potassium > 5.0 mEq/L
- Renal insufficiency when:
  - Sr. creatinine \(>2.5\) mg/dL/men
  - or \(>2.0\) mg/dL/women
  - or eGFR <30 mL/min/1.73m²


Mortality in HF-\(r\)-EF

\begin{table}
\centering
\begin{tabular}{|c|c|c|c|}
\hline
 & ACEI* & β-Blocker* & MRA* & ARB* \\
\hline
SOLVD & 16\% &  &  &  \\
CIBIS-II & 34\% &  &  &  \\
RALES & 30\% &  &  &  \\
CHARM-ALT & 17\% &  &  &  \\
\hline
\end{tabular}
\end{table}

* Standard therapies at the time of the study (except CHARM-Alternative, where background ACE-I was excluded)

Although survival rates improved with new therapies, mortality remains at 50% within 5 years of diagnosis

2016 ACC/AHA/HFSA Heart Failure Guideline Update

- Released May 20, 2016
- Focus: Pharmacological Treatment for Stage C HF-\(r\)-EF recommendations
  - Renin-angiotensin system inhibition with:
    - Angiotensin converting enzyme inhibitor (ACEI)
    - Angiotensin receptor blocker (ARB)
    - Angiotensin receptor neprilysin inhibitor (ARNI)
  - Ivabradine

How Does an ARNI fit into HF-rEF Treatment?

- Angiotensin receptor blocker
- Neprilysin Inhibitor
  - Degrades many endogenous vasoactive peptides

Endogenous vasoactive peptides
  (natriuretic peptides, adrenomedullin, bradykinin, substance P, calcitonin gene-related peptide)

Neprilysin

Inactive metabolites

Neprilysin Inhibitor

Endogenous vasoactive peptides
  (natriuretic peptides, adrenomedullin, bradykinin, substance P, calcitonin gene-related peptide)

Neprilysin

Neprilysin inhibition

 inactive metabolites

Renin Angiotensin System

Angiotensin I

ACE

ANG II

ATIR

Neprilysin

Neprilysin inhibition

Aldosterone

Sodium retention

Volume expansion

Vascular smooth muscle cell growth

Vasoconstriction

LV dysfunction

Myocardial fibrosis, hypertrophy

 inactive metabolites

ACE

ANG II

ATIR

Neprilysin

 inactive metabolites

Sodium retention

Volume expansion

Vascular smooth muscle cell growth

Vasoconstriction

LV dysfunction

Myocardial fibrosis, hypertrophy

 inactive metabolites
Mechanisms of Progression in Heart Failure

- Myocardial or vascular stress or injury
- \( \uparrow \) activity or response to maladaptive mechanisms
- \( \downarrow \) activity or response to adaptive mechanisms
- Evolution and progression of heart failure

Mechanisms of Progression in Heart Failure

- Myocardial or vascular stress or injury
- \( \uparrow \) activity or response to maladaptive mechanisms
- \( \downarrow \) activity or response to adaptive mechanisms
- Angiotensin receptor blocker
- Neprilysin inhibitor
- Evolution and progression of heart failure

Angiotensin Receptor Neprilysin Inhibition

- LCZ696- Valsartan / Sacubitril
- Angiotensin receptor blocker
- Inhibition of neprilysin
Aim of the PARADIGM-HF Trial

Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure trial (PARADIGM-HF)

- LCZ696 400 mg daily
- Enalapril 20 mg daily

Designed to replace current use of ACEi and ARB as the cornerstone of the treatment of heart failure

PARADIGM-HF: Entry Criteria

- NYHA class II-IV heart failure
- LV ejection fraction ≤ 40% → 35%
- BNP ≥ 150 (or NT-proBNP ≥ 600 pg/mL), but 1/3 lower if hospitalized for heart failure within 12 months
- Any use of ACEi or ARB, but able to tolerate stable dose equivalent to at least enalapril 10 mg/daily for at least 4 weeks
- Guideline recommended use of β-blocker and MRA
- Systolic BP ≥ 95 mmHg, eGFR ≥ 30 ml/min/1.73 m² and serum K ≤ 5.4 mEq/L at randomization


PARADIGM-HF: Entry Criteria

- Not entered:
  - Patients with a history of angioedema related to previous ACEi or ARB therapy
  - Patients taking ACEi concurrently
  - Patients with diabetes on aliskiren concurrently
- Excluded if:
  - Current acute decompensated HF
  - Hx Severe pulmonary disease

PARADIGM-HF: Study Design

Randomization

Single-blind run-in period

Double-blind period

- Enalapril 10 mg BID
- LCZ696 200 mg BID

(1:1 randomization)


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


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

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

Kaplan-Meier Estimate of Cumulative Rates (%)

Enalapril (n=4212)

LCZ696 (n=4187)

HR = 0.80 (0.73-0.87)
P = 0.0000002
Number needed to treat = 21

PARADIGM-HF: Cardiovascular Death

Kaplan-Meier Estimate of Cumulative Rates (%)

Enalapril (n=4212)

PARADIGM-HF: Cardiovascular Death

Kaplan-Meier Estimate of Cumulative Rate (%)
**PARADIGM-HF: Cardiovascular Death**

- **Enalapril** (n=4212)
  - HR = 0.80 (0.71-0.89)
  - Number need to treat = 32

- **LCZ696** (n=4187)

**Kaplan-Meier Estimate of Cumulative Rates (%)**

<table>
<thead>
<tr>
<th>Days After Randomization</th>
<th>LCZ696</th>
<th>Enalapril</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>360</td>
<td>720</td>
</tr>
<tr>
<td></td>
<td>1080</td>
<td>180</td>
</tr>
<tr>
<td></td>
<td>1260</td>
<td>240</td>
</tr>
</tbody>
</table>

**PARADIGM-HF: Effect of LCZ696 vs Enalapril on Primary Endpoint and Its Components**

<table>
<thead>
<tr>
<th></th>
<th>LCZ696 (n=4187)</th>
<th>Enalapril (n=4212)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary endpoint</strong></td>
<td>914 (21.8%)</td>
<td>1117 (26.5%)</td>
<td>0.80 (0.73-0.87)</td>
<td>0.000002</td>
</tr>
<tr>
<td><strong>Cardiovascular death</strong></td>
<td>558 (13.3%)</td>
<td>693 (16.5%)</td>
<td>0.80 (0.71-0.89)</td>
<td>0.00004</td>
</tr>
<tr>
<td><strong>Hospitalization for heart failure</strong></td>
<td>537 (12.8%)</td>
<td>658 (15.6%)</td>
<td>0.79 (0.71-0.89)</td>
<td>0.00004</td>
</tr>
</tbody>
</table>

**Effects on Primary Endpoint & Cardiovascular Death, by Subgroups**

**PARADIGM-HF: All-Cause Mortality**

![Graph showing mortality rates for Enalapril and LCZ696](image)

HR = 0.84 (0.76-0.93) P<0.0001

**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>Prospectively identified adverse events</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>Discontinuation for adverse event</td>
<td>449</td>
<td>516</td>
<td>0.02</td>
</tr>
<tr>
<td>For hypotension</td>
<td>36</td>
<td>29</td>
<td>NS</td>
</tr>
<tr>
<td>For hyperkalemia</td>
<td>11</td>
<td>15</td>
<td>NS</td>
</tr>
<tr>
<td>For renal impairment</td>
<td>29</td>
<td>59</td>
<td>0.001</td>
</tr>
<tr>
<td>Angioedema (adjudicated)</td>
<td>16</td>
<td>9</td>
<td>NS</td>
</tr>
<tr>
<td>Medications, no hospitalization</td>
<td>3</td>
<td>1</td>
<td>NS</td>
</tr>
<tr>
<td>Hospitalized; no airway compromise</td>
<td>0</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Airway compromise</td>
<td>0</td>
<td>0</td>
<td>NS</td>
</tr>
</tbody>
</table>

**Paradigm-HF; Outcomes by Age**

8399 patients aged 18-96 years

- Line of unity
- LCZ696 to Enalapril Hazard Ratio; grey shading, 95% CI

![Graph showing outcomes by age](image)
≥ 5-point Fall (Deterioration) in KCCQ at 8 months by Age & Tx

Favorable benefit-risk profile in all age groups

PARADIGM-HF: Benefit with Dose Reduction?

- Dose reduction post randomization:
  - Enalapril: \( \frac{1792}{4212} = 42.5\% \)
  - Sacubitril/valsartan: \( \frac{1755}{4187} = 41.9\% \)
  - Overall: \( \frac{3547}{8442} = 42.0\% \)

- Those w dose reduction had more severe HF at baseline and were:
  - Older
  - More Ischemic CM
  - More diabetes
  - Higher NT-proBNP
  - Higher NYHA FC III
  - Less use: BB & MRA
  - Higher creatinine
  - Lower systolic BP
  - Higher diuretic use
  - Higher CRT/ICD use

Vardeny et al. J Card Fail. 2015;21(8); Suppl S9.

<table>
<thead>
<tr>
<th>LCZ696, mg</th>
<th>Enalapril, mg</th>
<th>Events (N)</th>
<th>HR (95% CI)</th>
<th>RRR</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>200</td>
<td>10</td>
<td>1262</td>
<td>0.79 (0.71, 0.88)</td>
<td>21%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>100-200</td>
<td>5-10</td>
<td>541</td>
<td>0.80 (0.67, 0.94)</td>
<td>20%</td>
<td>0.008</td>
</tr>
<tr>
<td>&lt; 100 mg</td>
<td>&lt; 5 mg</td>
<td>225</td>
<td>0.76 (0.58, 0.99)</td>
<td>24%</td>
<td>0.043</td>
</tr>
</tbody>
</table>

Vardeny et al. J Card Fail. 2015;21(8); Suppl S9.
PARADIGM-HF: Summary of Findings

In HF-REF, when compared with recommended doses of enalapril:

LCZ696 was more effective than enalapril in...

- the risk of CV death and HF hospitalization
- the risk of CV death by incremental 20%
- the risk of HF hospitalization by incremental 21%
- all-cause mortality by incremental 16%
- incrementally symptoms and physical limitations

LCZ696 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 in discontinuations
- Not more likely to cause serious angioedema

ARNI Doubles Effect on Cardiovascular Death of Current Inhibitors of the RAS

![Graph showing % Decrease in Mortality](image)

ACC/AHA/HFSA Guideline Update

Recommendations for RAS Inhibition with ACEi or ARB or ARNI (Stage C-HF/REF)

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>ACEi: A</td>
<td>Inhibition of the RAS with ACEi OR ARB OR ARNI in conjunction with evidence-based beta blocker, and aldosterone antagonist in selected patients, is recommended for patients with chronic HF/REF to morbidity and mortality</td>
</tr>
<tr>
<td></td>
<td>ARB: A</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ARNI: B-R</td>
<td></td>
</tr>
</tbody>
</table>

COR= class of recommendation (Strength); green, I recommended (Strong)
LOE= level of evidence (Quality); A, high quality evidence; B, moderate quality; randomized

ACC/AHA/HFSA Guideline Update
Recommendations for RAS Inhibition with
ACEi or ARB or ARNI (Stage C-HFrEF)

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>ACEi: A</td>
<td>Use of ACEi is beneficial for patients with prior or current symptoms of chronic HFrEF to ↓ morbidity and mortality</td>
</tr>
<tr>
<td>I</td>
<td>ARB: A</td>
<td>The use of ARB to ↓ 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</td>
</tr>
<tr>
<td>II</td>
<td>ARNI: B-R</td>
<td>In patients with chronic symptomatic HFrEF NYHA class II or III who tolerate an ACEi or ARB, replacement by ARNI is recommended to further ↓ morbidity and mortality</td>
</tr>
</tbody>
</table>

COR= class of recommendation (Strength); green, IS recommended (Strong)
LOE= level of evidence (Quality); A, high qual evidence; B, moderate qual; randomized


ACC/AHA/HFSA Guideline Update
Recommendations for RAS Inhibition with
ACEi or ARB or ARNI (Stage C-HFrEF)

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>III</td>
<td>B-R</td>
<td>ARNI should not be administered concomitantly with ACEi or within 36 hours of the last dose of an ACEi</td>
</tr>
<tr>
<td>III</td>
<td>C-EO</td>
<td>ARNI should not be administered to patients with a history of angioedema</td>
</tr>
</tbody>
</table>

COR= class of recommendation (Strength); red, IS HARM
LOE= level of evidence (Quality); B, moderate quality; 1 or more randomized trial
C-EO, Expert opinion, based on clinical experience


Heart Rate as a Predictor of Death and/or HF Hospitalizations in Chronic HF (SHIFT placebo group)

Increase in risk by 2.9% per 1 bpm ↑; 15.6% per 5 bpm ↑

**SHIFT: Baseline Heart Rate Analysis**

![Heart Rate Analysis Diagram](image)


---

**Heart Rate and Pathophysiology of HF (All Cause)**

- Elevated heart rate directly affects progression of coronary atherosclerosis
  - 
  
  - Oxygen demand / Oxygen supply

  **Short term:**
  - ↓ LV function, ↑ heart failure

  **Long term:**
  - ↑ Death (Heart Failure and Sudden)

---

**Heart Rate Control**

![Heart Rate Control Diagram](image)


---

**If**, a hyperpolarization-activated pacemaker current; Slows diastolic depolarization in the SA node
Hyperpolarization-activated Cyclic Nucleotide-gated (HCN4) Channels

Sino-atrial node: 80% HCN4

Ivabradine (Iv): Inhibiting HCN4 (i.e. If current) → ↓iNa⁺ → ↓iCa²⁺

ICa²⁺, intracellular calcium; iNa⁺, intracellular sodium

SHIFT Study

• Hypothesis:
  • Therapeutic slowing of HR will reduce the risk of cardiovascular outcomes and symptoms (QoL) in patients with
  • NYHA functional class II – IV HF
  • Systolic dysfunction (EF ≤ 35%)
  • HR ≥ 70 bpm in NSR
  • Receiving GDMT including maximally tolerated β-B

Heart rate is not just a risk marker but a modifiable “risk factor” in heart failure


SHIFT Study Design

SHIFT Study Design

Patients and follow-up

7411 screened
6558 randomized

3268 to ivabradine 3290 to placebo

Excluded: 27 Excluded: 26

3241 analyzed 3264 analyzed
2 lost to follow-up 1 lost to follow-up

Study duration:
Median: 22.9 months; Maximum: 41.7 months


SHIFT (Time to first event); N=6505
CV Death or Hospitalization for HF

Number needed to treat for 1 year = 26


SHIFT (Time to first event); N=6505
Hospitalization for HF

Number needed to treat for 1 year = 26

**SHIFT** (*Time to first event*); N=6505

Death from HF

![Graph showing cumulative incidence of HF deaths with and without Ivabradine]


---

**SHIFT**: Cumulative incidence of HF Hospitalizations (first and repeated)

![Graph showing cumulative incidence of HF hospitalizations with and without Ivabradine]


---

**Heart Rate as a Predictor of Death and/or HF Hospitalizations in Chronic HF (SHIFT based on Day 28 in the Ivabradine group)**

![Graph showing heart rate distribution and hospitalization rates]

SHIFT: Other benefits of HR slowing with ivabradine (from pre-specified protocol sub-studies)

- Significantly greater improvement in HF related QoL by KCCQ with ivabradine than with placebo
  - Clinically meaningful with ivabradine; not with placebo
  - Magnitude of HQoL improvement was directly related to magnitude of HR reduction

Conclusions - Implications

- In patients with chronic HF-REF (≤35%) in NSR with HR ≥70 bpm and already receiving guideline-suggested Tx, isolated HR reduction improves outcomes in addition to those achievable with β-blockade, including
  - δ in CV death or HF hospitalizations
  - ↑ in LV function
  - δ in total hospitalizations
  - ↑ HQoL
- Benefits occur when ivabradine was ADDED to current recommended therapy
ACC/AHA/HFSA Guideline Update

Recommendations for Ivabradine (Stage C-HFrEF)

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIa</td>
<td>B-R</td>
<td>Ivabradine can be beneficial to reduce HF hospitalization for pts. with symptomatic (NYHA class II-III), stable chronic HFrEF (LVEF ≤35%) who are receiving GDEM, inc. β-blocker at maximum tolerated dose, and who are in NSR with a heart rate of 70 bpm or &gt; at rest</td>
</tr>
</tbody>
</table>

COR= class of recommendation (Strength); yellow, is reasonable/useful (Moderate)
LOE= level of evidence (Quality); B, moderate quality; 1 or more randomized trials;
GDEM: Guideline-directed evaluation and management


Guideline-Recommended Pharmacologic Treatments

<table>
<thead>
<tr>
<th>NYHA Class</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitor, ARB</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>ARNI</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td>Beta-blocker</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td>Aldosterone antagonist (MRA)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td>Diuretics</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td>Digoxin</td>
<td>✓</td>
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<td>Ivabradine</td>
<td>✓</td>
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<tr>
<td>Hydralazine / isosorbide dinitrate</td>
<td>✓</td>
<td>✓</td>
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</tbody>
</table>

(✓) For select patients
ARNI, angiotensin receptor neprilysin inhibitor; MRA, mineralocorticoid receptor antagonist


Case 1: Relatively Stable Patient

Presentation
- 65-year-old woman with chronic HF due to dilated cardiomyopathy
  - NYHA FC II, no HF hospitalizations within last year, EF 35%

Examination Notes
- Euvolemic, BP 115/75 mmHg, heart rate 67 bpm

Laboratory Results
- Cr 1.5
- K 4.5
- NT-proBNP 1,200 pg/mL

<table>
<thead>
<tr>
<th>Medications</th>
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<tbody>
<tr>
<td>Lisinopril 10 mg 1x daily</td>
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<tr>
<td>Carvedilol 12.5 mg 2x daily</td>
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<tr>
<td>Spironolactone 25 mg 1x daily</td>
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<tr>
<td>Furosemide 40 mg 2x daily</td>
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Would you continue with patient’s current medications or switch to a different treatment?
What strategies would you implement to reduce HF hospitalization?
Case 2: Higher Risk Patient With HF

Presentation
- 72-year-old man with chronic HF due to ischemic heart disease
  - NYHA FC III, hospitalized twice for HF in past 6 months, EF 25%

Examination Notes
- JVP 2 cm above clavicle, BP 112/65 mmHg, heart rate 79 bpm

Laboratory Results
- Cr 1.9
- K 4.9
- NT-proBNP 3,200 pg/mL

Medications
- Valsartan 80 mg 2x daily
- Carvedilol 3.125 mg 2x daily
- Unable to tolerate MRA due to concerns about hyperkalemia
- Furosemide 80 mg 2x daily

Would you continue current medications or switch to different Tx?
Which methods should we use to decongest patient prior to discharge?

Case 3: Putting it All Together

74 yr old AA male with HF/EF
- Complaint: “I can’t catch my breath sometimes”
- Med Hx: Type 2 DM, HTN, CAD, hyperlipidemia, qout, previous anterior wall MI (ejection fraction [EF] 15% post MI); 2 stents; obesity [BMI 32 kg/m2]
- HF/EF Dx: 5 years ago; just moved to your town
  - EF currently 30%; NYHA FC III; stable
  - Today’s VS: BP 102/68, HR 86 bpm; Resp 22 bpm
- X-Ray: Marked prominence of pulmonary vascular shadows (bilateral), increased haziness and decreased radiolucency of the lung parenchyma (bilateral), increased transverse diameter of the heart
- Objective assessment: apical pulse at 5th ICS; S1 and 2 diminished; S3 at apex; JVP ~12 cm at 90°; firm abdomen; grade 3 systolic murmur; strongest at apex and radiates toward base

Serum labs
- Glucose 132mg/dL (non-fasting)
- BUN 33mg/dL
- Creatinine 1.6mg/dL
- Albumin 3.1g/dL
- Sodium 132mEq/L
- Potassium 4.0mEq/L
- eGFR 48

Current Medications
- Lisinopril 40 mg/d
- Carvedilol 25 mg 2x/d
- Furosemide 60 mg/d
- ASA 81 mg/d
- Clopidogrel 75 mg/d
- Metformin 500 mg 2x/d
- Atorvastatin 40 mg/d
- Allopurinol 200 mg/d

APN medication changes? If yes, what?
Putting it All Together

Self management
• Diet
• Exercise/activity
• Flu shot
• ETOH/smoking cessation
• Weight loss
• Caution w non-prescription/OTC medications
• Follow-up
• Comorbidities

Medication adherence
• Consider lifestyle
• Discuss value
• Provide resources