Disclosures

- Novartis: Consultant, Speaker’s Bureau
- Amgen: Speaker’s Bureau

2016 ACC/AHA/HFSA Heart Failure Guideline Update

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

Pooled Analysis: 32 RCT of ACEi

- Total mortality: Placebo 21.9%, ACEI 15.8%, P<0.01
- Death due to CHF mortality: Placebo 10.5%, ACEI 6.5%, P<0.001
- Death or hospitalization due to CHF: Placebo 32.6%, ACEI 22.5%, P<0.001


Clinical Effects of ACEIs on HF

Overview of 5 Trials
(SAVE, AIRIE, TRACE, SOLVD prevention, SOLVD treatment)

- All cause mortality, OR 0.80 (95% CI 0.74-0.87)

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:
    - Placebo: 3.0%
    - Carvedilol: 2.0%
    - HR 0.68 (95% CI 0.42-1.11)

- Val-HeFT
  - Probability of freedom from combined endpoint:
    - Placebo: 49.2%
    - Carvedilol: 62.8%
    - HR 0.77 (95% CI 0.63-0.94)

Mortality in HF-rEF

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

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

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


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

Neprilysin Inhibitor

Neurohormonal activation
Vascular tone
Cardiac fibrosis, hypertrophy
Sodium retention

Inactive metabolites
Renin Angiotensin System

Angiotensin I

ACE

ANG II

ATIR

Neprilysin

Inactive metabolites

Neprilysin inhibition

Aldosterone

Sodium retention

Volume expansion

Vascular smooth muscle cell growth

Vasoconstriction

LV dysfunction

Myocardial fibrosis, hypertrophy

Mechanisms of Progression in Heart Failure

Myocardial or vascular stress or injury

† activity or response to maladaptive mechanisms

‡ activity or response to adaptive mechanisms

Evolution and progression of heart failure

Mechanisms of Progression in Heart Failure

Myocardial or vascular stress or injury

† activity or response to maladaptive mechanisms

‡ 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

LCZ696 200 mg BID

(1:1 randomization)


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

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Patients at Risk
LCZ696 (n=4187)
Enalapril (n=4212)

Kaplan-Meier Estimate of Cumulative Rates (%)


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

Patients at Risk
LCZ696 (n=4187)
Enalapril (n=4212)

Kaplan-Meier Estimate of Cumulative Rates (%)

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


PARADIGM-HF: Cardiovascular Death

Patients at Risk
LCZ696 (n=4187)
Enalapril (n=4212)

Kaplan-Meier Estimate of Cumulative Rates (%)

**PARADIGM-HF: Cardiovascular Death**


**PARADIGM-HF: Cardiovascular Death**


**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>Primary endpoint</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>Cardiovascular death</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>Hospitalization for heart failure</td>
<td>537 (12.8%)</td>
<td>658 (15.6%)</td>
<td><strong>0.79 (0.71-0.89)</strong></td>
<td><strong>0.00004</strong></td>
</tr>
</tbody>
</table>

Effects on Primary Endpoint & Cardiovascular Death, by Subgroups

PARADIGM-HF: All-Cause Mortality

PARADIGM-HF: Adverse Events
**Paradigm-HF; Outcomes by Age**

8399 patients aged 18-96 years

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


**≥ 5-point Fall (Deterioration) in KCCQ at 8 months by Age & Tx**

Favorable benefit-risk profile in all age groups


**Effects of LCZ696 vs Enalapril by Age- Primary End Point**

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

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 . . .**

• Decreased the risk of CV death and HF hospitalization
• Decreased the risk of CV death by incremental 20%
• Decreased the risk of HF hospitalization by incremental 21%
• Decreased all-cause mortality by incremental 16%
• Incrementally decreased 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 increase in discontinuations
• Not more likely to cause serious angioedema
**ARNI Doubles Effect on Cardiovascular Death of Current Inhibitors of the RAS**

<table>
<thead>
<tr>
<th>% Decrease in Mortality</th>
<th>Angiotensin receptor blocker</th>
<th>ACE inhibitor</th>
<th>Angiotensin receptor neprilysin inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>0%</td>
<td>10%</td>
<td>15%</td>
<td>18%</td>
</tr>
<tr>
<td>10%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20%</td>
<td></td>
<td></td>
<td>20%</td>
</tr>
<tr>
<td>30%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40%</td>
<td></td>
<td></td>
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Effect of ARB vs placebo derived from CHARM-Alternative trial  
Effect of ACEI vs placebo derived from SOLVD-Treatment trial  
Effect of ARNI vs ACE inhibitor derived from PARADIGM-HF trial

**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>
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<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 HFrEF to reduce 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>
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**ACC/AHA/HFSA Guideline Update**

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<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 reduce morbidity and mortality</td>
</tr>
<tr>
<td></td>
<td>ARB: A</td>
<td>The use of ARB 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</td>
</tr>
<tr>
<td></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 reduce morbidity and mortality</td>
</tr>
</tbody>
</table>

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

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<tr>
<th>COR</th>
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<th>Recommendations</th>
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<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 ▼

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

- Acetylcholine
- Norepinephrine
- Muscarinic receptor
- PKA
- cAMP
- Beta receptor
- I Ca,L
- K Ca,T
- I K
- I f
- Sinus node cell


I f, a hyperpolarization-activated pacemaker current; Slows diastolic depolarization in the SA node

Ivabradine

- Ivabradine selectively inhibits the I f current in the sinus node
- Sinus node
- The pacemaker of the heart

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

Patients and follow-up

**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


SHIFT (Time to first event); N=6505
Death from HF


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

IRR (95% CI), 0.75 (0.65;0.87)
P=0.0002

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

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 ↑ outcomes in addition to those achievable with β-blockade, including
  - ↓ in CV death or HF hospitalizations
  - ↑ in LV function
  - ↓ in total hospitalizations
  - ↑ HrQoL
- 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