UPDATES IN MANAGEMENT OF HF

Jennifer R Brown MD, MS
Heart Failure Specialist
Medstar Cardiology Associates

DC ACP Meeting
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Disclosures:

speaker bureau for novartis

speaker bureau for actelion

I will not discuss off-label use of any products
Forecasting the Impact of Heart Failure in the United States

Projected Prevalence

Projected Cost Increases

Heidenreich PA et al. Circ Heart Fail. 2013;6(3):606-19
Heart Failure Hospitalizations Remain Common

Coronary Heart Disease

Heart Failure

Improvement in Heart Failure Assessment and Management is Needed

- Direct and indirect cost estimates for HF up to $56 billion USD annually
- Average HF Admission costs between $7,000 - $13,000 USD/admission
- Re-hospitalization rate: 50% within 6 months
- ACA has made HF readmission a major focus for improvement

Berkowitz et al Lippincotts Case Manag. 2005
Schlendorf et al Curr Treat Options in Cardiovasc Med 2011
AHF MORTALITY RATES

- ~4% of patients with AHF die during hospitalization\(^{10}\)
- 10% of patients die within 30 days following hospitalization for AHF\(^{9}\)
- >20% of patients die within 180 days of an acute HF event\(^{7,8}\)
- ~30% of patients die within 1 year of an acute HF event\(^{5,8}\)
In patients with heart failure:

≥24% die within 1 year of diagnosis\(^3\)

~50% die within 5 years of diagnosis\(^4\)
Main challenges: heart failure hospitalization

- Annual hospitalizations in both the United States and Europe: >1 million
- Heart failure hospitalizations as a percentage of total hospital admissions: 1-4%
- Hospitalized due to worsening chronic heart failure as compared with de novo heart failure: Up to 9/10 patients
- Average length of hospital stay: 5-10 days
- Nearly 1 out of 2 patients (46%) are rehospitalized for heart failure within the 60-day post discharge period
- Almost 1 out of 4 hospitalized patients (24%) are rehospitalized for heart failure within the 30-day post discharge period

References:
2017 ACC/AHA/HFSA

Focused Update Guideline for the Management of Heart Failure
Biomarkers:

For prevention:

The 2017 Focused Update gives a Class IIa recommendation (Level of Evidence: B-R) for utilizing natriuretic peptide biomarker-based screening for those at risk of developing HF, followed by team-based care including a cardiovascular specialist optimizing guideline-directed medical therapy (GDMT), to prevent the development of left ventricular dysfunction (systolic or diastolic) or new-onset HF.
For *diagnosis*:

The 2017 Focused Update gives a Class I recommendation (Level of Evidence: A) for measurement of natriuretic peptide biomarkers in patients presenting with dyspnea, to support a diagnosis or exclusion of HF.
For *prognosis or added risk stratification*:
The 2017 Focused Update gives a:

- Class I recommendation (Level of Evidence: A) for measurement of B-type natriuretic peptide (BNP) or N-terminal (NT)-proBNP for establishing prognosis or disease severity in chronic HF.
- Class I recommendation (Level of Evidence: A) for measurement of baseline natriuretic peptide biomarkers and/or cardiac troponin on admission to the hospital to establish a prognosis in acutely decompensated HF.
- Class IIa recommendation (Level of Evidence: B-NR) for measurement of a predischarge natriuretic peptide level during a HF hospitalization, to establish a post-discharge prognosis.
- Class IIa recommendation (Level of Evidence: B-NR) for measurement of other clinically available tests, such as biomarkers of myocardial injury or fibrosis, in patients with chronic HF for additive risk stratification.
ST2 plays a role in reducing cardiomyocyte hypertrophy and fibrosis

Abnormalities in ST2 experimentally result in severe cardiac remodeling and heart failure

Intact sST2

sST2 knock out
Value of various markers for prognosis in acute dyspnea

AUC

<table>
<thead>
<tr>
<th>Marker</th>
<th>AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>ST2</td>
<td>0.80</td>
</tr>
<tr>
<td>MR-proADM</td>
<td>0.78</td>
</tr>
<tr>
<td>NT-proBNP/</td>
<td>0.76</td>
</tr>
<tr>
<td>MR-proANP</td>
<td>0.75</td>
</tr>
<tr>
<td>Galectin-3</td>
<td>0.73</td>
</tr>
<tr>
<td>BUN</td>
<td>0.70</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>0.69</td>
</tr>
<tr>
<td>Creatinine clearance</td>
<td>0.67</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.65</td>
</tr>
<tr>
<td>cTnT</td>
<td>0.54</td>
</tr>
<tr>
<td>Eotaxin</td>
<td>0.52</td>
</tr>
<tr>
<td>Apelin-1</td>
<td></td>
</tr>
</tbody>
</table>
Using ST2 can reduce 30-day rehospitalization rates.

Normal readmission rates:

- Hospitalization: 17.3%
- Death: 17.6%

After using ST2:...
**st2 in the heart failure guidelines:**
The role of st2 is as a useful additive biomarker to BNP and nt pro-bnp as detailed below:

<table>
<thead>
<tr>
<th>Biomarker, Application</th>
<th>Setting</th>
<th>COR</th>
<th>LOE</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natriuretic peptides</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnosis or exclusion of HF</td>
<td>Ambulatory, Acute</td>
<td>I</td>
<td>A</td>
<td>212, 217–223, 245–250</td>
</tr>
<tr>
<td>Prognosis of HF</td>
<td>Ambulatory, Acute</td>
<td>I</td>
<td>A</td>
<td>222, 224–229, 248, 251–258</td>
</tr>
<tr>
<td>Achieve GDMT</td>
<td>Ambulatory</td>
<td>IIa</td>
<td>B</td>
<td>230–237</td>
</tr>
<tr>
<td>Guidance for acutely decompensated HF therapy</td>
<td>Acute</td>
<td>IIb</td>
<td>C</td>
<td>259, 260</td>
</tr>
<tr>
<td>Biomarkers of myocardial injury</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Additive risk stratification</td>
<td>Acute, Ambulatory</td>
<td>I</td>
<td>A</td>
<td>238–241, 248, 253, 256–267</td>
</tr>
<tr>
<td>Biomarkers of myocardial fibrosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Additive risk stratification</td>
<td>Ambulatory</td>
<td>IIb</td>
<td>B</td>
<td>242–244</td>
</tr>
<tr>
<td></td>
<td>Acute</td>
<td>IIb</td>
<td>A</td>
<td>248, 253, 256, 258–260, 262, 264–267</td>
</tr>
</tbody>
</table>

COR indicates Class of Recommendation; GDMT, guideline-directed medical therapy; HF, heart failure; and LOE, Level of Evidence.
Stage C HF With Preserved EF (HFpEF):
The 2017 Focused Update gives the following:

- Class IIa recommendation (Level of Evidence: B-R) for use of aldosterone antagonists in appropriately selected patients with HFpEF (with EF ≥45%, elevated BNP or HF admission within 1 year, estimated glomerular filtration rate >30 and creatinine <2.5 mg/dl, potassium <5.0 mEq /L), to decrease hospitalizations.

- Class III recommendation (Level of Evidence: B-R) for routine use of nitrates or phosphodiesterase-5 inhibitors to increase activity or quality of life (QoL) in patients with HFpEF, as there is no benefit.

- Class III recommendation (Level of Evidence: B-C) for routine use of nutritional supplements in patients with HFpEF, as there is no benefit.
Anemia:
The 2017 Focused Update gives a:

- Class IIb recommendation (Level of Evidence: B-R) for intravenous iron replacement in patients with New York Heart Association (NYHA) class II and III HF and iron deficiency (ferritin <100 ng/ml or 100-300 ng/ml if transferrin saturation <20%), to improve functional status and QoL.

- Class III recommendation (Level of Evidence: B-R) that erythropoietin stimulating agents should not be used in patients with HF and anemia to improve morbidity and mortality, as there is no benefit.
Hypertension:
The 2017 Focused Update gives a:

- ▶ Class I recommendation (Level of Evidence: B-R) for targeting an optimal blood pressure (BP) of <130/80 mm Hg in those with hypertension and at increased risk (stage A HF).

- ▶ Class I recommendation (Level of Evidence: C-EO) for titration of GDMT to attain systolic BP (SBP) <130 mm Hg in patients with HFrEF and hypertension.

- ▶ Class I recommendation (Level of Evidence: C-LD) for titration of GDMT to attain SBP <130 mm Hg in patients with HFpEF and persistent hypertension after management of volume overload.
Sleep-Disordered Breathing:
The 2017 Focused Update gives a:

- Class IIa recommendation (Level of Evidence: C-LD) for a formal sleep assessment in patients with NYHA class II–IV HF and suspicion of sleep-disordered breathing or excessive daytime sleepiness.
- Class IIb recommendation (Level of Evidence: B-R) for utilization of continuous positive airway pressure in patients with cardiovascular disease and obstructive sleep apnea, to improve sleep quality and daytime sleepiness.
- Class III recommendation: Harm (Level of Evidence: B-R) for use of adaptive servo-ventilation in patients with NYHA class II–IV HFrEF and central sleep apnea, as it causes harm.
Ivabradine and outcomes in chronic heart failure (SHIFT)

**Background**
Chronic heart failure is associated with high mortality and morbidity. Raised resting heart rate is a risk factor for adverse outcomes. We aimed to assess the effect of heart-rate reduction by the selective sinus-node inhibitor ivabradine on outcomes in heart failure.

**Findings**
6558 patients were randomly assigned to treatment groups (3268 ivabradine, 3290 placebo). 793 (24%) patients in the ivabradine group and 937 (29%) of those taking placebo had a primary endpoint event (HR 0.82, 95% CI 0.75–0.90, p<0.0001). The effects were driven mainly by hospital admissions for worsening heart failure (672 [21%] placebo vs 514 [16%] ivabradine; HR 0.74, 0.66–0.83; p<0.0001) and deaths due to heart failure (151 [5%] vs 113 [3%]; HR 0.74, 0.58–0.94, p=0.014).

The results support the importance of heart-rate reduction with ivabradine for improvement of clinical outcomes in heart failure and confirm the important role of heart rate in the pathophysiology of this disorder.
SHIFT (Systolic Heart Failure Treatment with the If Inhibitor Ivabradine Trial)

M Komajda (Groupe Hospitalier Pitié-Salpêtrière, Paris, France)
European Society of Cardiology 2010 Congress

• Background:
  Ivabradine is a selective inhibitor of a sodium-potassium channel highly expressed in the sinoatrial node, on which it has a mild dampening effect

• Population and treatment:
  >6500 patients with NYHA class 2–4 heart failure, an LVEF <35%, a resting heart rate >70 bpm, and HF hospitalization within the previous year

  Randomized to placebo or ivabradine at a starting dose of 5 mg twice daily, with adjustments to achieve a resting HR of 50 to 60 bpm; all patients were on standard HF medications according to guidelines

• Primary outcome:
  Composite of CV death or HF hospitalization
Heart Rate: A Prognostic Risk Factor in Heart Failure

Patients with CAD and EF < 40%

Cardiovascular Death

Heart Rate ≥70 bpm

Heart Failure Hospitalization

Heart Rate ≥70 bpm

Heart Rate Reduction and Mortality in Heart Failure

- Major criticism of COMET (carvedilol vs metoprolol)

Kjekshus J. Eur Heart J 1999.
Ivabradine selectively inhibits the “funny” current in the sinus node.

Slows HR independent of BB effect “less negative inotropy”

Implications for patients with impaired stroke volume.
Systolic Heart failure treatment with the If inhibitor ivabradine Trial

To evaluate whether the $I_f$ inhibitor ivabradine improves cardiovascular outcomes in patients with
1. Moderate to severe chronic HF
2. Left ventricular EF $\leq 35\%$
3. Heart rate $\geq 70$ bpm and
4. Recommended therapy
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

Median study duration: 22.9 months; maximum: 41.7 months
Mean heart rate reduction

Mean ivabradine dose: 6.4 mg bid at 1 month

6.5 mg bid at 1 year

Heart rate (bpm)

Ivabradine
Placebo

80
75
64
67

0 2 weeks 1 4 8 12 16 20 24 28 32
Months
Primary Composite Endpoint: CV Death + HF hospitalization

Cumulative frequency (%)

HR = 0.82 [95% CI 0.75-0.90]

ARR = 4.2%
NNT = 24

- 18%

Ivabradine

P<0.0001
Cardiovascular Death

Ivabradine n=449 (7.5%PY)  Placebo n=491 (8.3%PY)

Cumulative frequency (%)  

HR = 0.91  p=0.128

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Months

0  6  12  18  24  30

0  10  20  30
Hospitalization for heart failure

Ivabradine n=514 (9.4%PY) Placebo n=672 (12.7%PY)

Cumulative frequency (%)  HR = 0.74 [95% CI 0.66-0.83] p<0.0001

- 26%

Ivabradine
SHIFT: Results

- Significant 18% reduction in HR for CV death or hospitalization for worsening HF with ivabradine vs control group—driven by significant 26% HR reductions for the individual secondary end points of death from HF and hospitalization for worsening HF

### Primary and secondary end points\(^a\)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Ivabradine (n=3241), %</th>
<th>Placebo (n=3264), %</th>
<th>HR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary end point</td>
<td>24</td>
<td>29</td>
<td>0.82 (0.75–0.90)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death from HF</td>
<td>3</td>
<td>5</td>
<td>0.74 (0.58–0.94)</td>
<td>0.014</td>
</tr>
<tr>
<td>HF hospitalization</td>
<td>16</td>
<td>21</td>
<td>0.74 (0.66–0.83)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CV death, HF hospitalization, or admission for nonfatal MI</td>
<td>25</td>
<td>30</td>
<td>0.82 (0.74–0.89)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

\(^a\) Mean follow-up of 23 months
\(^b\) HR=hazard ratio
# Ivabradine Guideline Recommendations

## 2016 ACC/AHA/HFSA Heart Failure Update

### Recommendation for Ivabradine

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ila</td>
<td>B-R</td>
<td>Ivabradine can be beneficial to reduce HF hospitalization for patients with symptomatic (NYHA class II-III) stable chronic HF/EF (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 (37-40).</td>
</tr>
</tbody>
</table>

Yancy CW, et al. JACC 2016

## 2012 European HF Guidelines

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>2012 European HF Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ila</td>
<td>Should be considered to reduce the risk of HF hospitalization in patients in sinus rhythm with an EF ≤ 35%, a heart rate remaining ≥ 70 bpm, and persisting symptoms (NYHA class II-IV) despite treatment with an evidence-based dose of beta-blocker (or maximum tolerated dose below that), ACE inhibitor (or ARB), and an MRA (or ARB)²</td>
</tr>
<tr>
<td>IIb</td>
<td>May be considered to reduce the risk of HF hospitalization in patients in sinus rhythm with an EF ≤ 35% and a heart rate ≥ 70 bpm who are unable to tolerate a beta-blocker. Patients should also receive an ACE inhibitor (or ARB) and an MRA (or ARB)²</td>
</tr>
</tbody>
</table>

McMurray JJV, et al. EHJ 2012
LCZ-696
Dual Effects of Sacubitril/Valsartan

- Diuresis
- Natriuresis
- Vasodilatation
- Decreased myocardial remodeling

Heart Failure

Angiotensinogen

Renin

Ang I

ACE

Ang II

AT1R

Sodium retention
- Volume expansion
- VSMC growth
- Vasoconstriction
- LV dysfunction
- Myocardial fibrosis
- Myocardial hypertrophy

Neprilysin

Sacubitril/valsartan

Inactive metabolites

Aldosterone

Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure: Paradigm Trial

BACKGROUND
We compared the angiotensin receptor–neprilysin inhibitor LCZ696 with enalapril in patients who had heart failure with a reduced ejection fraction. In previous studies, enalapril improved survival in such patients.

RESULTS
The trial was stopped early, after a median follow-up of 27 months, because of the benefit with LCZ696. The primary outcome occurred in 914 patients (21.8%) in the LCZ696 group and 1117 patients (26.5%) in the enalapril group (hazard ratio in the LCZ696 group, 0.80; 95% confidence interval [CI], 0.73 to 0.87; P<0.001). A total of 711 patients (17.0%) receiving LCZ696 and 835 patients (19.8%) receiving enalapril died. As compared with enalapril, LCZ696 also reduced the risk of hospitalization for heart failure by 21% (P<0.001) and decreased the symptoms and physical limitations of heart failure (P=0.001).

CONCLUSIONS
LCZ696 was superior to enalapril in reducing the risks of death and of hospitalization for heart failure.
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

SPECIFICALLY DESIGNED TO REPLACE CURRENT USE OF ACE INHIBITORS AND ANGIOTENSIN RECEPTOR BLOCKERS AS THE CORNERSTONE OF THE TREATMENT OF HEART FAILURE
Angiotensin Receptor Neprilysin Inhibition (ARNI): LCZ696

LCZ696

sacubitril

valsartan

Natriuretic peptides
- BK, ADM
- Subs-P, VIP, CGRP

Angiotensin II

- Vasodilation
- Natriuresis
- Diuresis
- Inhibition of pathologic growth/fibrosis

Neprilysin

Degradation products

AT₁ Receptor

- Vasoconstriction
- Sodium/water retention
- Fibrosis/hypertrophy
PARADIGM-HF
Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial

- Age ≥18 years. NYHA class II-IV. LVEF ≤0.40 (amended to ≤0.35).
- BNP ≥150 pg/ml (NTpro-BNP ≥600 pg/ml) or if HF hosp. within 12 mo. BNP ≥100 pg/ml (NTpro-BNP ≥400 pg/ml)
- Background RAS blocker therapy equivalent to enalapril ≥10 mg/d
- Beta-blocker and MRA as recommended by guidelines
- SBP ≥100 mmHg run-in/ ≥95 mmHg at randomization
- eGFR ≥30 ml/min/1.73m²/no decrease >25% (amended to 35%)
- Potassium ≤5.2 mmol/l run-in/ ≤5.2 mmol/l at randomization

Single-blind period:
- Enalapril 5-10 mg bid
- LCZ 100 mg bid
- LCZ 200 mg bid

Double-blind period:
- LCZ696 200 mg BID (n=4187)
- Enalapril 10 mg BID (n=4212)
- N = 8442 (1:1 randomization)

1-2 weeks → 2 weeks
Outcome driven (CV death): Stopped early for benefit
Median follow-up = 27 months
PARADIGM-HF
Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial

**Single-blind period**
- Enalapril 5-10 mg bid
- S/V200 mg bid
- S/V100 mg bid

**Double-blind period**
- Sacubitril/Valsartan 200 mg BID (n=4187)
- Enalapril 10 mg BID (n=4212)

Outcome driven (CV death): median follow-up = 27 months

Prior ACEi/ARB use discontinued
- 10,513 patients
- 9,419 (90%) patients
- 8,442 (80%) patients

Age: 64 years. Female: 22%. Black: 5.1%.
NYHA class II 70% (class III 24%). Mean LVEF 29%.
NT pro BNP: 1613 pg/ml. eGFR 68 ml/min/1.73m². A-Fib 37%.
Diuretic use 80%, β-blocker 93%, MRA 56%. ICD15%. CRT 7%.
PARADIGM-HF
Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial

Primary composite outcome
HR: 0.80 (0.73, 0.87) p = 0.0000004

Death from CV causes
20% risk reduction

HF hospitalization
21% risk reduction

McMurray, Packer et al. NEJM 2014
PARADIGM-HF
Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial

Death from any cause
16% risk reduction

HR: 0.84 (0.76, 0.93)
P = 0.0009

Cumulative Proportion of Patients Who Died from Any Cause (%)

Days after Randomization

Enalapril (n=4212)
835
711
LCZ696 (n=4187)
Sacubitril/valsartan doubles the survival benefit of current renin-angiotensin inhibitors.

% Decrease in Mortality

- 0%
- 10%
- 20%
- 30%
- 40%

- ARB
- ACE inhibitor
- Sacubitril/valsartan

Nephrilysin inhibition 16%

Effect of ACE inhibitor vs placebo derived from SOLVD-Treatment trial.
Effect of ARB vs placebo CHARM-Alternative and CHARM-Added.
Effect of LCZ696 vs ACE inhibitor derived from PARADIGM-HF trial.
CV mortality: Baseline ICD use (post hoc analysis)

Cardiovascular death
HR 0.80 (0.71, 0.89); p < 0.0001

<table>
<thead>
<tr>
<th></th>
<th>Enalapril</th>
<th>LCZ696</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICD - No</td>
<td>HR 0.80 (0.71, 0.90)*</td>
<td></td>
</tr>
<tr>
<td>ICD - Yes</td>
<td>HR 0.76 (0.55, 1.05)*</td>
<td></td>
</tr>
</tbody>
</table>

*Interaction p = 0.92
Table 3. Adverse Events during Randomized Treatment.*

<table>
<thead>
<tr>
<th>Event</th>
<th>LCZ696 (N = 4187)</th>
<th>Enalapril (N = 4212)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension</td>
<td>no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptomatic</td>
<td>588 (14.0)</td>
<td>388 (9.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Symptomatic with systolic blood pressure &lt;90 mm Hg</td>
<td>112 (2.7)</td>
<td>59 (1.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Elevated serum creatinine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥2.5 mg/dl</td>
<td>139 (3.3)</td>
<td>188 (4.5)</td>
<td>0.007</td>
</tr>
<tr>
<td>≥3.0 mg/dl</td>
<td>63 (1.5)</td>
<td>83 (2.0)</td>
<td>0.10</td>
</tr>
<tr>
<td>Elevated serum potassium</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;5.5 mmol/liter</td>
<td>674 (16.1)</td>
<td>727 (17.3)</td>
<td>0.15</td>
</tr>
<tr>
<td>&gt;6.0 mmol/liter</td>
<td>181 (4.3)</td>
<td>236 (5.6)</td>
<td>0.007</td>
</tr>
<tr>
<td>Cough</td>
<td>474 (11.3)</td>
<td>601 (14.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Angioedema†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No treatment or use of antihistamines only</td>
<td>10 (0.2)</td>
<td>5 (0.1)</td>
<td>0.19</td>
</tr>
<tr>
<td>Use of catecholamines or glucocorticoids without hospitalization</td>
<td>6 (0.1)</td>
<td>4 (0.1)</td>
<td>0.52</td>
</tr>
<tr>
<td>Hospitalization without airway compromise</td>
<td>3 (0.1)</td>
<td>1 (&lt;0.1)</td>
<td>0.31</td>
</tr>
<tr>
<td>Airway compromise</td>
<td>0</td>
<td>0</td>
<td>—</td>
</tr>
</tbody>
</table>

* Shown are results of the analyses of prespecified safety events at any time after randomization. The numbers of patients who permanently discontinued a study drug were as follows: for hypotension, 36 (0.9%) in the LCZ696 group and 29 (0.7%) in the enalapril group (P = 0.38); for renal impairment, 29 (0.7%) and 59 (1.4%), respectively (P = 0.002); and for hyperkalemia, 11 (0.3%) and 15 (0.4%), respectively (P = 0.56).

† Angioedema was adjudicated in a blinded fashion by an expert committee.
PARADIGM-HF: Adverse events leading to permanent study drug discontinuation

- **Enalapril**
  - Any adverse event: 516
  - Hypotension: 449
  - Renal reasons: 29
  - Any angioedema: 10

- **Sacubitril/valsartan**
  - Any adverse event: 36
  - Hypotension: 29
  - Renal reasons: 59
  - Any angioedema: 19

\( p = 0.03 \) for any adverse event, \( p = 0.38 \) for hypotension, \( p = 0.002 \) for renal reasons.
### Recommendations for Renin-Angiotensin System Inhibition With ACE Inhibitor or ARB or ARNI

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>ACE: A</td>
<td>The clinical strategy of inhibition of the renin-angiotensin system with ACE inhibitors <em>(Level of Evidence: A)</em>, <strong>OR</strong> ARBs <em>(Level of Evidence: A)</em>, <strong>OR</strong> ARNI <em>(Level of Evidence: B-R)</em> in conjunction with evidence-based beta blockers, and aldosterone antagonists 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>
</tr>
<tr>
<td>COR</td>
<td>LOE</td>
<td>Recommendations</td>
</tr>
<tr>
<td>-----</td>
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<td>---------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>I</td>
<td>ARNI:B-R</td>
<td>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.</td>
</tr>
</tbody>
</table>
### Highlighting Key Recommendations

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>The clinical strategy of inhibition of the renin-angiotensin system with ACE inhibitors or ARBs or ARNI, in conjunction with evidence-based β-blockers and aldosterone antagonists in selected patients, is recommended for patients with chronic HFrEF to reduce morbidity and mortality.</td>
<td>I</td>
<td>ACE: A; ARB: A; ARNI: B-R</td>
</tr>
<tr>
<td>The use of ACE inhibitors is beneficial for patients with prior or current symptoms of chronic HFrEF to reduce morbidity and mortality.</td>
<td>I</td>
<td>ACE: A</td>
</tr>
<tr>
<td>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.</td>
<td>I</td>
<td>ARB: A</td>
</tr>
<tr>
<td>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.</td>
<td>I</td>
<td>ARNI: B-R</td>
</tr>
<tr>
<td>ARNI should not be administered concomitantly with ACE inhibitors or within 36 hours of the last dose of an ACE inhibitor.</td>
<td>III: Harm</td>
<td>B-R</td>
</tr>
<tr>
<td>ARNI should not be administered to patients with a history of angioedema.</td>
<td>III: Harm</td>
<td>C-EO</td>
</tr>
<tr>
<td>Ivabradine can be beneficial to reduce heart failure hospitalization for patients with symptomatic (NYHA class II-III) stable chronic HFrEF (LVEF ≤35%) who are receiving GDEM, including a β-blocker at maximum tolerated dose, and who are in sinus rhythm with a heart rate of 70 bpm or greater at rest.</td>
<td>IIA</td>
<td>B-R</td>
</tr>
</tbody>
</table>

**Abbreviations:** ARB, angiotensin receptor blockers; ARNI, angiotensin receptor-neprilysin inhibitor; COR, class of recommendation; GDEM, guideline-directed evaluation and management; HFrEF, heart failure with reduced ejection fraction; LOE, level of evidence; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

**Source:** Adapted from: Yancy C, et al. *Circulation.* 2016 May 20 [Epub ahead of print].
How do you switch from ace-I to arni?

- 36 hour wash out period

- if on equivalent of < 10 mg PO BID enalapril, start low dose ARNI (24/26 mg PO BID), then up-titrate every 2-4 weeks

- If on equivalent of > 10 mg PO BID enalapril, start mid dose arni (49/51 mg PO bid), then up-titrate every 2-4 weeks
How do you switch from an aRB to arni?

- no wash out period

- if on equivalent of < 160 mg PO losartan, start low dose ARNI (24/26 mg PO BID), then up-titrate every 2-4 weeks

- If on equivalent of > 160 mg PO losartan, start mid dose arni (49/51 mg PO bid), then up-titrate every 2-4 weeks
Heart transplants worldwide

Years of survival after a heart transplant

- The most frequent cause of death in the first 30 days is donor heart failure due to shock or trauma or narrow blood vessels in the recipient's lungs.
- Leading cause of death in the first year is rejection of the donor heart by immune system that sees the new heart as a foreign object and attacks it.

In the years following surgery, the walls of the coronary arteries can become thick, hard and less stretchy, reducing blood circulation in the new heart and causing serious damage.

Source: International Society for Heart & Lung Transplantation; National Heart Lung and Blood Institute
Heart Mate II

The VAD is a surgically implanted artificial heart pump used to treat patients with advanced congestive heart failure.
HeartMate II LVAS Survival Rates vs. Optimal Medical Management (OMM)\textsuperscript{5,12*}

- HeartMate II Bridge to Transplant (BTT) - 85%
- HeartMate II Destination Therapy (DT) - 73%
- OMM (Rematch NEJM, 2001) - 25%
- 2 Years - 63%
- 1 Year - 25%
- 0 - 85%
Improvement in NYHA functional class
Heartmate II DT LVAD trial

Joseph G. Rogers, Keith D. Aaronson, Andrew J. Boyle, Stuart D. Russell, Carmelo A. Milano, Francis D. Pagani...
Continuous Flow Left Ventricular Assist Device Improves Functional Capacity and Quality of Life of Advanced Heart Failure Patients
Journal of the American College of Cardiology Volume 55, Issue 17 2010 1826 - 1834
The MOMENTUM 3 U.S. IDE Clinical Trial is a prospective, multi-center, unblinded randomized study comparing the HeartMate 3 Left Ventricular Assist System (LVAS) to the HeartMate II LVAS in advanced stage heart failure patients.

Learn more
Expanding HF Choices & Decisions

1989
• Digoxin
• Diuretics
• Vasodilators

2017
• ACE inhibitors/ARBs
• Beta-blockers
• Aldosterone antagonists
• ARB/Neprilysin Inhibitor
• Hydralazine/Nitrates
• Ivabradine
• ICD and CRT
• Mechanical circulatory support
• CardioMEMS
• Disease management
• Palliative care
Applying Evidence to Health Care Delivery

It takes an average of 17 years for new knowledge generated by randomized controlled trials to be incorporated into practice, and even then application is highly uneven.
Conclusions

• The prevalence of heart failure is increasing though HFpEF is becoming more common

• Exciting time to be caring for patients with HFReEF with multiple new therapeutic options

• New challenges to implementation of evidence-based chronic medical therapies