Improving Outcomes in Patients with Heart Failure: Closing the Gaps
Scope of Heart Failure (HF)

- 6.5 million Americans ≥20 years of age have HF
- 960,000 new cases of HF are diagnosed annually
- 5-year survival rate for HF is ~50%

Annual new HF events per 1000 person years

- Age 65-74y: 9.2
- Age 75-84y: 22.3
- Age 85y and older: 43.0

Hospital Discharges for HF

## Classification of HF

<table>
<thead>
<tr>
<th>Classification</th>
<th>Ejection Fraction</th>
<th>Description</th>
</tr>
</thead>
</table>
| I. HF with reduced ejection fraction  | ≤40%              | - Also referred to as systolic HF  
- Typically enrolled in clinical trials for HF treatments                                                                                     |
| (HFrEF)                                |                   |                                                                                                                                             |
| II. HF with preserved ejection fraction| ≥50%              | - Also referred to as diastolic HF  
- Challenging diagnosis (exclusion)  
- No efficacious therapies have been identified to date                                                                                      |
| (HFpEF)                                |                   |                                                                                                                                             |
| a. HFpEF, borderline                   | 41% to 49%        | - Characteristics, treatment patterns, and outcomes are similar to those of patients with HFpEF                                              |
| b. HFpEF, improved                     | >40%              | - May represent a subset of patients that previously had HFrEF and demonstrated improvement or recovery in EF                                |

## HF Staging and Therapeutic Goals

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>Treatment Goals</th>
</tr>
</thead>
</table>
| A     | Patients at high risk for HF but without structural heart disease or symptoms of HF | - Heart-healthy lifestyle  
- Prevent vascular and coronary disease  
- Prevent LV structural abnormalities  
- Improve survival |
| B     | Patients with structural heart disease but without signs or symptoms of HF | - Prevent HF symptoms  
- Prevent further cardiac remodeling  
- Improve survival |
| C     | Patients with structural heart disease with prior or current symptoms of HF | - Control symptoms  
- Patient education  
- Improve HRQOL  
- Prevent hospitalization/mortality  
- Improve survival |
| D     | Patients with refractory HF | - Control symptoms  
- Improve HRQOL  
- Prevent hospital readmissions  
- Establish end-of-life goals  
- Improve survival |

Hospitalized HF
Case

• 72-year-old male with a history of ischemic cardiomyopathy with an EF of 20% presents with a 2-week history of progressive exertional dyspnea followed by peripheral edema and the need to sleep on 3 pillows
• For the past 2 nights he has had paroxysmal nocturnal dyspnea (PND)
• Has avoided mowing the lawn for past 4 months due to shortness of breath (SOB)
Case (cont’d.)

• Past medical history:
  – 3-vessel bypass (9 years ago)
  – Type 2 diabetes
    ▪ No end-organ complications
  – ICD

• Medications:
  – Carvedilol 12.5 mg twice daily
  – Lisinopril 40 mg daily
  – Spironolactone 25 mg daily
  – Furosemide 40 mg twice daily

• Physical exam:
  – HR 102 bpm, BP 102/74 mmHg
  – RR 18 breaths per minute
  – Lungs clear
  – Cor with PMI to left axillary line
  – JVP to angle of jaw, S3
  – Abd with tender liver
  – Ext with 2+ edema; feet are cool

• EKG notable for:
  – Sinus tachycardia
  – New LBBB

• Labs notable for:
  – Na 136 mEq/L
  – K 5.1 mEq/L
  – CO2 28 mmol/L
  – BUN 62 mg/dL
  – Creatinine 2.3 mg/dL (baseline 1.5)
  – proBNP 2365 pg/mL

Next steps:
• Admit to the hospital
• Change furosemide to IV, start at 80 mg IV BID

ICD = implantable cardioverter-defibrillator
PMI = point of maximal impulse
JVP = jugular venous pressure
LBBB = left bundle branch block
Acute HF Treatment Goals

- Improve symptoms, especially congestion and low-output symptoms
- Optimize volume status
- Identify etiology
- Identify precipitating factors
- Optimize diuretic therapy; minimize side effects
- Identify who might benefit from revascularization
- Educate patients regarding medication and HF self-assessment
- Consider enrollment in a disease management program

Question

- What do you do with the carvedilol (beta blocker)?
  - Keep dose the same
  - Lower the dose
  - Discontinue
Question

- What do you do with spironolactone (ACE inhibitor)?
  - Keep dose the same
  - Lower the dose
  - Discontinue
Question

• What do you do with lisinopril (aldosterone antagonist)?
  – Keep dose the same
  – Lower the dose
  – Discontinue
<table>
<thead>
<tr>
<th>Perfusion</th>
<th>Congestion</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Dry, Warm</td>
<td></td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>Dry, Cold</td>
<td></td>
<td>L</td>
<td>C</td>
</tr>
</tbody>
</table>

**A**
- RR 18 bpm
- JVP to angle of jaw, S3
- Abd with tender liver
- Ext with 2+ edema
- proBNP 2365

**B**
- BP 102/74 mmHg
- feet are cool
- Creat 2.3

ACCF/AHA 2013 Guidelines for Hospitalized (Acute) HF

- IV diuretics for fluid overload
- Continue guideline-directed medical therapy (GDMT) for HFrEF patients
  - Except in cases of hemodynamic instability or where contraindicated
- Initiate beta blockers (low-dose) following volume status optimization/IV discontinuation
  - Initiate at low dose in stable patients only
  - Use caution in patients who have required inotropes during their hospital course
- Thromboembolism prophylaxis during stay
- Inotropes in very select circumstances

ACCF/AHA 2013 Guidelines for Hospitalized (Acute) HF (cont’d.)

- When diuresis is inadequate:
  - Higher doses of IV loop diuretics, or
  - Add a second diuretic (eg, thiazide)
- The following may be considered:
  - Low-dose dopamine infusion in addition to loop diuretic therapy to improve diuresis and better preserve renal function and renal blood flow
  - Ultrafiltration for patients with refractory congestion not responding to medical therapy
  - If symptomatic hypotension is absent, IV nitroglycerin, nitroprusside, or nesiritide as an adjuvant to diuretic therapy for relief of dyspnea
  - Vasopressin antagonists to improve serum sodium concentration in hypervolemic, hyponatremic states

Question

• Would you recommend a biventricular pacemaker for this patient?
  – Yes
  – No
Question

- Would you evaluate this patient for ischemia?
  - Yes
  - No
Question

• Is this patient a candidate for advanced therapies?
  – Yes
  – No
Discharge and Transition
Case (cont’d.)

- He diureses 8.9 kg over the course of 5 days and feels well; able to walk the floors without difficulty
- Appears euvolemic on exam
- Creatinine improves to 1.5 mg/dL
- Cardiac catheterization with no change in his coronary anatomy
Hospital Readmission

• 30-day hospital readmission is a quality of care measure

• The median 30-day hospital readmission rate for HF patients between 2009 and 2012 was 23%

• Predictors of rehospitalization/mortality (OPTIMIZE-HF Trial):

<table>
<thead>
<tr>
<th>Increase risk</th>
<th>Decrease risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Admission serum creatinine</td>
<td>• ACE/ARB at discharge</td>
</tr>
<tr>
<td>• COPD</td>
<td>• Decrease in admission SBP of 10 mm Hg</td>
</tr>
<tr>
<td>• HF hospitalization within 6 mo</td>
<td>• Cath performed</td>
</tr>
<tr>
<td>• Vent</td>
<td>• ICD placed</td>
</tr>
<tr>
<td>• Digoxin</td>
<td>• Hgb &gt; 10 g/dL</td>
</tr>
<tr>
<td>• Admission serum creatinine</td>
<td></td>
</tr>
</tbody>
</table>
HF Rehospitalization Predicts Mortality

Median survival (years) among HF patients following 1\textsuperscript{st}, 2\textsuperscript{nd}, 3\textsuperscript{rd}, and 4\textsuperscript{th} hospitalization

## Factors Associated with Higher Risk

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Measured outcome</th>
<th>High-risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fonarow et al, 2005</td>
<td>37,772</td>
<td>In-hospital mortality</td>
<td>- High blood urea nitrogen (≥43 mg/dL)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Low admission systolic blood pressure (≤115 mmHg)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- High levels of serum creatinine (≥2.75 mg/dL)</td>
</tr>
<tr>
<td>Stiell et al, 2013</td>
<td>559</td>
<td>Serious adverse events</td>
<td>- Serum CO2 &gt;35 mmol/L</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Prior intubation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Acute ischemic changes on ECG</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Troponin I or T elevated ≥MI level</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Heart rate ≥110 beats/min on ED arrival</td>
</tr>
<tr>
<td>Lee et al, 2012</td>
<td>7,433</td>
<td>Mortality within 7 days of presentation</td>
<td>- Higher triage heart rate</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Higher creatinine concentration</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Lower triage systolic blood pressure</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Initial oxygen saturation</td>
</tr>
<tr>
<td>Lassus et al, 2013</td>
<td>5,306</td>
<td>30-day and 1-year mortality</td>
<td>- Presence of biomarkers (ST2, MR-proADM, CRP, NT-proBNP, BNP, MR-proANP)</td>
</tr>
</tbody>
</table>

Follow-Up Care – HF

• Utilize effective systems of care coordination with special attention to care transitions
• Ensure each patient has a clear, detailed, and evidence-based plan of care
  – Achievement of GDMT goals
  – Effective management of comorbid conditions
  – Timely follow-up with health care team
  – Appropriate lifestyle interventions
  – Compliance w/secondary prevention guidelines for CVD
• Utilize palliative and supportive care in symptomatic advanced HF

<table>
<thead>
<tr>
<th>Drug prescription</th>
<th>No. (%) of Patients</th>
<th>At Hospital Discharge (All Patients age ≤79 y)</th>
<th>90 Days Post-discharge (Patients age 66-79 y)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low Risk</td>
<td>Average Risk</td>
<td>High Risk</td>
</tr>
<tr>
<td>No. of patients</td>
<td>784</td>
<td>473</td>
<td>161</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>635 (81)</td>
<td>346 (73)</td>
<td>96 (60)</td>
</tr>
<tr>
<td>ACE inhibitor or ARB</td>
<td>677 (86)</td>
<td>380 (80)</td>
<td>105 (65)</td>
</tr>
<tr>
<td>Beta blocker</td>
<td>314 (40)</td>
<td>154 (33)</td>
<td>38 (24)</td>
</tr>
<tr>
<td>No ACE inhibitor, ARB, or beta blocker</td>
<td>76 (10)</td>
<td>73 (15)</td>
<td>43 (27)</td>
</tr>
<tr>
<td>Observed 1-y mortality rate, %</td>
<td>13.9</td>
<td>26.4</td>
<td>47.2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug prescription, excluding limiting comorbidities</th>
<th>No. (%) of Patients</th>
<th>At Hospital Discharge (All Patients age ≤79 y)</th>
<th>90 Days Post-discharge (Patients age 66-79 y)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low Risk</td>
<td>Average Risk</td>
<td>High Risk</td>
</tr>
<tr>
<td>No. of patients</td>
<td>693</td>
<td>306</td>
<td>74</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>559 (81)</td>
<td>222 (73)</td>
<td>40 (54)</td>
</tr>
<tr>
<td>ACE inhibitor or ARB</td>
<td>599 (86)</td>
<td>243 (79)</td>
<td>45 (61)</td>
</tr>
<tr>
<td>Beta blocker</td>
<td>292 (42)</td>
<td>97 (32)</td>
<td>16 (22)</td>
</tr>
<tr>
<td>No ACE inhibitor, ARB, or beta blocker</td>
<td>64 (9)</td>
<td>47 (15)</td>
<td>24 (32)</td>
</tr>
<tr>
<td>Observed 1-y mortality rate, %</td>
<td>14.0</td>
<td>26.5</td>
<td>46.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>Therapeutic Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>- See next slide</td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td>- Adapt treatment for compromised renal function, particularly for drugs affecting the RAAS system</td>
</tr>
<tr>
<td>Chronic pulmonary disease</td>
<td>- Can complicate diagnosis of HF</td>
</tr>
<tr>
<td></td>
<td>- May lead to prescription of beta blockers</td>
</tr>
<tr>
<td>Diabetes</td>
<td>- Prescribe certain hypoglycemic medications with caution (metformin, TZDs)</td>
</tr>
<tr>
<td>Atrial fibrillation or flutter</td>
<td>- Improve QOL and diminish thromboembolic risk</td>
</tr>
<tr>
<td></td>
<td>- Consider rhythm or rate control</td>
</tr>
<tr>
<td>Sleep apnea</td>
<td>- Optimally manage HF</td>
</tr>
<tr>
<td></td>
<td>- Encourage weight loss</td>
</tr>
<tr>
<td></td>
<td>- See next slide</td>
</tr>
<tr>
<td>Angina</td>
<td>- Avoid medications contraindicated in HF</td>
</tr>
<tr>
<td>Systemic arterial hypertension</td>
<td>- See next slide</td>
</tr>
<tr>
<td>Rheumatic disease</td>
<td>- Avoid medications contraindicated in HF</td>
</tr>
<tr>
<td>Depression</td>
<td>- Avoid medications contraindicated in HF</td>
</tr>
<tr>
<td>Malignancy</td>
<td>- Chemotherapy can be cardiotoxic; carefully monitor cardiac function</td>
</tr>
</tbody>
</table>

Management of Comorbidities (cont’d.)

• Anemia
  – Independently associated with HF disease severity, reduced exercise capacity
  – Consider IV iron replacement to improve functional status and QOL in patients with NYHA class II/III HF and iron deficiency
  – Erythropoietin-stimulating agents should not be used (III: No Benefit)

• Sleep apnea
  – Consider sleep assessment in NYHA class II-IV HF and suspicion of sleep disordered breathing or excessive daytime sleepiness
  – Consider CPAP
  – In NYHA class II-IV HFrEF and central sleep apnea, adaptive servo-ventilation causes harm (III: Harm)

• Hypertension
  – Goal of <130/80 mmHg
  – Titrate GDMT to attain goal in both HFrEF and HFpEF

Individualizing Discharge/Transition Plans

- Discharge instructions
- Scheduling follow-up within 7-14 days post-discharge
- Communication between inpatient and outpatient team members
- Coordination of care among multidisciplinary and multispecialty providers (social workers, other specialty consultations, HF specialists, etc)
Patient Education and Self-Care

- Patient education improves knowledge, self-monitoring, medication adherence, time to hospitalization, and days in the hospital.
- Important teaching points:
  - How to monitor symptoms and weight fluctuations
  - How to restrict sodium intake
  - How to take medications as prescribed
    - Function and importance of medications
  - How to stay physically active

Case (cont’d.)

- Reinitiate spironolactone at 25 mg/day
- Plan to upgrade to biventricular pacemaker
- Schedule follow-up at 4 days
Chronic HF in Outpatient Setting
Case (cont’d.)

• You see him back in a month…
  – He had the biventricular pacemaker placed 2 weeks ago and feels well
  – Able to start mowing his lawn a bit but admits that it is only with the tractor

• Physical examination:
  – HR 80 bpm, BP 140/72 mmHg RR 14 breaths per minute
  – Lungs are clear
  – JVP of 6 cm at the clavicle
  – RRR with no S3
  – No edema

• Medications:
  – Carvedilol 6.25 mg twice daily
  – Lisinopril 20 mg per day
  – Spironolactone 25 mg per day
  – Furosemide 80 mg twice daily

• Labs:
  – Na 138 mEq/L
  – K 4.3 mEq/L
  – CO2 28 mmol/L
  – BUN 25 mg/dL
  – Creatinine 1.5 mg/dL
Follow-Up Visits: Clinical Considerations

• Is patient’s heart failure progressing?
  – Activity
  – Symptoms
  – Weight
• Is patient compliant with diet and medications?
• Is there anything else that can/should be done?
Question

• Would you consider additional GDMT?
  – Yes
  – No
Question

• Would you consider hydralazine or isosorbide mononitrate for this patient?
  – Yes
  – No
Question

• Would you consider digoxin for this patient?
  – Yes
  – No
Question

• Would you consider ivabradine for this patient?
  – Yes
  – No
Question

- Would you consider sacubitril/valsartan for this patient?
  - Yes
  - No
Individualizing Chronic HF Management

• Treat according to etiology
• Sequence of therapy initiation may differ for each patient
• Precision and targeted therapies are as important as GDMT
• Toxicity and tolerance may differ for each patient
• Adjust treatment based on patient preference
  – Shared decision making
General Measures

• **Lifestyle Modifications**
  - Weight reduction
  - Discontinue smoking
  - Avoid alcohol and other cardiotoxic substances
  - Exercise

• **Medical Considerations**
  - Treat hypertension, hyperlipidemia, diabetes, arrhythmias
  - Coronary revascularization
  - Anticoagulation
  - Immunization
  - Sodium restriction
  - Daily weights
  - Close outpatient monitoring
ACCF/AHA 2013/2017 Guidelines: Overview of GDMT

**Stage A**
- ACEI or ARB in appropriate patients for vascular disease or diabetes
- Statins as appropriate

**Stage B**
- ACEI or ARB as appropriate
- Beta blockers as appropriate

*In select patients:*
- ICD
- Revascularization or valvular surgery as appropriate

**Stage C**

*HFpEF*
- Diuresis
- Guideline-driven indications for comorbidities

*HFrEF*
- Diuretics
- ACEI or ARB
- Beta blockers
- Aldosterone antagonists
- Ivabradine
- Sacubitril/valsartan

*In select patients:*
- Hydralazine/isosorbide dinitrate
- ACEI or ARB
- Digitalis
- CRT
- ICD
- Revascularization or valvular surgery as appropriate

**Stage D**
- Advanced care measures
- Heart transplant
- Chronic inotropes
- Temporary or permanent MCS
- Experimental surgery or drugs
- Palliative care and hospice
- ICD deactivation

ACEI = angiotensin-converting enzyme inhibitor
ARB = angiotensin-receptor blocker
CRT = cardiac resynchronization therapy
ICD = implantable cardioverter-defibrillator
MCS = mechanical circulatory support

ACCF/AHA 2017 Guidelines: Stage C Treatment

Step 1
Establish Dx of HFrEF; assess volume; initiate GDMT

Step 2
Consider the following patient scenarios

- NYHA class II-IV, provided est. CrCl >30 mL/min & K+ <5.0 mEq/L
- NYHA class II-III HF: Adequate BP on ACEI or ARB; No CI to ARB or sacubitril
- NYHA class III-IV, in black patients
- NYHA class II-III, LVEF ≤35%; (caveat: >1 y survival, >40 d post MI)
- NYHA class II-IV, LVEF ≤35%, NSR & QRS ≥150 ms with LBBB pattern
- NYHA class II-III, NSR, heart rate ≥70 bpm on maximally tolerated dose beta blocker

Step 3
Implement indicated GDMT. Choices are not mutually exclusive, and no order is inferred

- Aldosterone antagonist (COR I)
- Discontinue ACEI or ARB; initiate ARNI (COR I)
- Hydral-Nitrates (COR I)
- ICD (COR I)
- CRT or CRT-D (COR I)
- Ivabradine (COR Ia)

Step 4
Reassess symptoms

Step 5
Consider additional therapy

- Palliative care (COR I)
- Transplant (COR I)
- LVAD (COR IIa)
- Investigational studies

Continue GDMT with serial reassessment & optimized dosing/adherence

ACEIs in Stage C HF

• ACEIs reduce morbidity and mortality in HFrEF with mild, moderate, or severe symptoms of HF with or without CAD
• No difference among available ACEIs
• Start at low dose and titrate upward
  – If maximal doses are not tolerated, intermediate doses should be attempted
• Abrupt withdrawal of ACEIs can lead to clinical deterioration and should be avoided
• ACEIs may produce angioedema
  – Use caution in patients with low systolic BP, renal insufficiency, elevated serum potassium
• ACEIs inhibit kininase and increase bradykinin
  – May induce cough

Beta Blockers in Stage C HF

- Beta blockers (bisoprolol, carvedilol, or metoprolol succinate sustained-release) recommended for all patients with current or prior symptoms of HFrEF, unless contraindicated, to reduce morbidity and mortality
  - Initiate as soon as HFrEF is diagnosed
    - Even when symptoms are mild or improve with other treatments
  - Beta blockers may be added to low-dose ACEI therapy
  - Prescribe with diuretics in patients with a current or recent history of fluid retention
  - May be considered in patients with reactive airway disease
    - Use with caution

Beta Blockers in Stage C HF (cont’d.)

- Initiate at very low doses and increase gradually (with monitoring) to target dose
- Watch for adverse events (AEs)
  - Fluid retention and worsening HF
    - Intensify conventional therapy
  - Fatigue
    - Consider/treat other causes
  - Bradycardia or heart block
    - Consider decreasing dose
  - Hypotension
    - Administer beta blocker and ACEI at different times during the day
    - Consider decreasing diuretic dose
    - Decrease dose or discontinue beta blocker upon evidence of hypoperfusion

Mineralocorticoid Receptor Antagonists (MRAs) in Stage C HF

• Indication:
  – NYHA class II-IV HF who have LVEF of ≤35%, unless contraindicated
  – Following acute MI in patients with LVEF ≤40% who develop HF symptoms or who have a history of diabetes mellitus
  – Creatinine should be:
    ▪ ≤2.5 mg/dL in men
    ▪ ≤2.0 mg/dL in women
  – Potassium should be <5.0 mEq/L
• Monitor potassium, renal function, and diuretic dosing to minimize risk of hyperkalemia
  – Inappropriate use of MRAs is potentially harmful due to life-threatening hyperkalemia or renal insufficiency when serum creatinine is >2.5 mg/dL in men or >2.0 mg/dL in women

Treatment of HF: What’s New?

- Angiotensin receptor-neprilysin inhibitor (ARNI)
  - Sacubitril/valsartan
    - Approved July 2015 for the treatment of HF
- PARADIGM-HF trial (N=8,442 NYHA class II-IV, EF <40%, later reduced to <35%)
  - Open-label run-in, first with enalapril, then sacubitril/valsartan (if tolerated), then randomized
  - Pro BNP ≥600/BNP >150 or HF hospitalization in the last year
  - Primary endpoint: Composite death from CV causes or hospitalization for HF
  - Secondary endpoint: Time to death, KCCQ, time to new atrial fibrillation, renal function

KCCQ = Kansas City Cardiomyopathy Questionnaire

PARADIGM-HF Exclusion Criteria

- Symptomatic hypotension
- Systolic BP <100 mmHg at screening or 95 mmHg at randomization
- eGFR <30 ml/min/1.73 m² or decrease in the eGFR >35% between screening and randomization
- Serum potassium >5.2 mmol/L at screening or >5.4 mmol/L at randomization
- History of angioedema or unacceptable side effects during receipt of ACEI or ARB

Paradigm-HF: Primary Endpoint of CV Death or HF Hospitalization

Hazard ratio, 0.80 (95% CI, 0.73–0.87)
P<0.001

Cumulative Probability

Days since Randomization

No. at Risk
Sac/Val
4187 3922 3663 3018 2257 1544 896 249
Enalapril
4212 3883 3579 2922 2123 1488 853 236

## Paradigm-HF: Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Sacubitril/valsartan N (%)</th>
<th>Enalapril N (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary composite outcome</td>
<td>914 (21.8%)</td>
<td>1117 (26.5%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>711 (17%)</td>
<td>835 (19.8%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death from CV cause</td>
<td>558 (13.3%)</td>
<td>693 (16.5%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>First hospitalization for worsening HF</td>
<td>537 (12.8%)</td>
<td>658 (15.6%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

### Sacubitril/Valsartan vs Enalpril on Primary Endpoints and on CV Death by Subgroup

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Sac/Val No.</th>
<th>Enalpril No.</th>
<th>Primary Endpoint</th>
<th>Death from Cardiovascular Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hazard Ratio (95% CI)</td>
<td>P Value for Interaction</td>
</tr>
<tr>
<td>All Patients</td>
<td>4187</td>
<td>4212</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 years</td>
<td>2111</td>
<td>2168</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥65 years</td>
<td>2076</td>
<td>2044</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>3308</td>
<td>3259</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>879</td>
<td>953</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NYHA Class</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I or II</td>
<td>3187</td>
<td>3130</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III or IV</td>
<td>1002</td>
<td>1076</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estimated GFR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60 mL/min/1.73 m²</td>
<td>1541</td>
<td>1520</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥60 mL/min/1.73 m²</td>
<td>2646</td>
<td>2692</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ejection fraction</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤35%</td>
<td>3715</td>
<td>3722</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;35%</td>
<td>472</td>
<td>489</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NT-proBNP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤Median</td>
<td>2079</td>
<td>2116</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;Median</td>
<td>2103</td>
<td>2087</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1218</td>
<td>1241</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2969</td>
<td>2971</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior use of ACE inhibitor</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>921</td>
<td>946</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>3266</td>
<td>3266</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior use of aldosterone antagonist</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1916</td>
<td>1812</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2271</td>
<td>2400</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior hospitalization for heart failure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1580</td>
<td>1545</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2607</td>
<td>2667</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

# PARADIGM-HF: Adverse Events

<table>
<thead>
<tr>
<th>Prospectively identified AEs</th>
<th>Sac/Val (n=4187)</th>
<th>Enalapril (n=4212)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic hypotension</td>
<td>14.0%</td>
<td>9.2%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum potassium &gt;6.0 mmol/L</td>
<td>4.3%</td>
<td>5.6%</td>
<td>0.007</td>
</tr>
<tr>
<td>Serum creatinine ≥2.5 mg/dL</td>
<td>3.3%</td>
<td>4.5%</td>
<td>0.007</td>
</tr>
<tr>
<td>Cough</td>
<td>11.3%</td>
<td>14.3%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Discontinuation for AE</th>
<th>10.7%</th>
<th>12.3%</th>
<th>0.03</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinuation for hypotension</td>
<td>0.9%</td>
<td>0.7%</td>
<td>0.38</td>
</tr>
<tr>
<td>Discontinuation for hyperkalemia</td>
<td>0.3%</td>
<td>0.4%</td>
<td>0.56</td>
</tr>
<tr>
<td>Discontinuation for renal impairment</td>
<td>0.7%</td>
<td>1.4%</td>
<td>0.002</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Angioedema (adjudicated)</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Medications, no hospitalization</td>
<td>6 (0.1%)</td>
<td>4 (0.1%)</td>
<td>0.52</td>
</tr>
<tr>
<td>Hospitalized, no 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>

Influence of Sacubitril/Valsartan on Readmission Rates After HF Hospitalization: PARADIGM-HF

PARADIGM-HF: Summary of Findings

In HF with reduced ejection fraction, when compared with recommended doses of enalapril:

Sacubitril/valsartan was more effective than enalapril in...
- Reducing the risk of CV death and HF hospitalization by incremental 20%
- Reducing the risk of CV death by incremental 20%
- Reducing the risk of HF hospitalization by incremental 21%
- Reducing all-cause mortality by incremental 16%
- Incrementally improving symptoms and physical limitations

Sacubitril/valsartan was better tolerated than enalapril ...
- Less likely to cause cough, hyperkalemia, or renal impairment
- Less likely to be discontinued due to an AE
- More hypotension, but no increase in discontinuations
- Not more likely to cause serious angioedema

FDA-Approved Sacubitril/Valsartan

<table>
<thead>
<tr>
<th>Indication</th>
<th>The fixed-dose combination of the neprilysin inhibitor sacubitril and the ARB valsartan is indicated to reduce the risk of CV death and HF hospitalization in patients with HFrEF.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosage</td>
<td>Start with 49/51 mg twice daily. Double the dose after 2 to 4 weeks as tolerated to maintenance dose of 97/103 mg twice daily.</td>
</tr>
<tr>
<td>Renal/hepatic impairment</td>
<td>For patients not currently taking an ACEI or ARB, or for those with severe renal impairment (eGFR &lt;30 mL/min/1.73 m²) or moderate hepatic impairment, start with 24/26 mg twice daily.</td>
</tr>
<tr>
<td>Switching from an ACE inhibitor</td>
<td>Stop ACE inhibitor for 36 hours before starting treatment.</td>
</tr>
<tr>
<td>Contraindications</td>
<td>History of angioedema related to previous ACE inhibitor or ARB, concomitant use of ACE inhibitors, concomitant use of aliskiren in patients with diabetes. WARNING – pregnancy, hyperkalemia.</td>
</tr>
<tr>
<td>Side effects</td>
<td>Hypotension, hyperkalemia, cough, dizziness, renal failure, and angioedema (0.5% sac/val vs 0.2% enalapril).</td>
</tr>
</tbody>
</table>
2017 ACC/AHA/HFSA Update on New Pharmacological Therapy: ARNI

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Cor</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renin-angiotensin inhibition with ACEIs or ARBs or <strong>ARNI</strong> in conjunction with evidence-based beta blockers and aldosterone antagonists in selected patients</td>
<td>I</td>
<td>ACE: A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ARB: A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ARNI: B-R</td>
</tr>
<tr>
<td>ACEIs are beneficial in patients with prior or current symptoms of chronic HFrEF to reduce morbidity and mortality</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>ARBs are recommended to reduce morbidity and mortality in patients with prior or current symptoms of chronic HFrEF who are intolerant to ACEIs due to cough or angioedema</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>In patients with chronic symptomatic HFrEF NYHA class II or III who tolerate an ACEI or ARB, replacement by an <strong>ARNI</strong> is recommended to further reduce morbidity and mortality</td>
<td>I</td>
<td>B-R</td>
</tr>
<tr>
<td><strong>ARNI</strong> should not be administered concomitantly or within 36 hours of the last dose of ACEI</td>
<td>III: Harm</td>
<td>B-R</td>
</tr>
<tr>
<td><strong>ARNI</strong> should not be administered to patients with a history of angioedema</td>
<td>III: Harm</td>
<td>C-EO</td>
</tr>
</tbody>
</table>

Treatment of HF: What’s New?

• Sinoatrial node modulator
  – Ivabradine
    ▪ Approved April 2015 to reduce hospitalization from worsening chronic HFrEF
• SHIFT trial: n=6558 randomized to ivabradine vs placebo
  – **Inclusion criteria**: HF (LVEF ≤35%), sinus rhythm with HR ≥70 bpm, hospital admission within the previous year, stable background, treatment including beta blocker if tolerated
  – **Exclusion criteria**: Recent (<2 months) MI, ventricular or atrioventricular pacing operative for ≥40% of the day, atrial fibrillation or flutter, symptomatic hypotension
SHIFT Study: Mean Heart Rate

Mean ivabradine dose: 6.4 mg twice daily at 1 month; 6.5 mg twice daily at 1 year

HR reduction: Ivabradine ↓ HR 10.9 bpm at day 28, 9.1 bpm at 1 year, and 8.1 at study end vs placebo

SHIFT Study: Primary Endpoint of CV Death or Hospitalization for Worsening HF

Placebo
937 events (29%)

Ivabradine
793 events (24%)

Patients with Primary Endpoint (%)

HR 0.82 (95% CI, 0.75–0.90) \( P < 0.0001 \)
ARR = 5%, NNT = 20

SHIFT Study: Effect of Ivabradine on Outcomes

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Ivabradine (n=3241)</th>
<th>Placebo (n=3264)</th>
<th>HR</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary endpoint</td>
<td>24%</td>
<td>29%</td>
<td>0.82</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>16%</td>
<td>17%</td>
<td>0.90</td>
<td>0.092</td>
</tr>
<tr>
<td>Death from HF</td>
<td>3%</td>
<td>5%</td>
<td>0.74</td>
<td>0.014</td>
</tr>
<tr>
<td>All-cause hospitalization</td>
<td>38%</td>
<td>42%</td>
<td>0.89</td>
<td>0.003</td>
</tr>
<tr>
<td>Any CV hospitalization</td>
<td>30%</td>
<td>34%</td>
<td>0.85</td>
<td>0.0002</td>
</tr>
<tr>
<td>CV death, hospitalization for worsening HF, or hospitalization for non-fatal MI</td>
<td>25%</td>
<td>30%</td>
<td>0.82</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

SHIFT Study: Incidence of Selected AEs

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Ivabradine (n=3241)</th>
<th>Placebo (n=3264)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All serious AEs</td>
<td>45% (1450)</td>
<td>48% (1553)</td>
<td>0.025</td>
</tr>
<tr>
<td>All AEs</td>
<td>75% (2439)</td>
<td>74% (2423)</td>
<td>0.303</td>
</tr>
<tr>
<td>Heart failure</td>
<td>25% (804)</td>
<td>29% (937)</td>
<td>0.0005</td>
</tr>
<tr>
<td>Symptomatic bradycardia</td>
<td>5% (150)</td>
<td>1% (32)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Asymptomatic bradycardia</td>
<td>6% (184)</td>
<td>1% (48)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>9% (306)</td>
<td>8% (251)</td>
<td>0.012</td>
</tr>
<tr>
<td>Phosphenes</td>
<td>3% (89)</td>
<td>1% (17)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>1% (17)</td>
<td>&lt;1% (7)</td>
<td>0.042</td>
</tr>
</tbody>
</table>

Phosphenes are luminous phenomena; bradycardia is defined here as resting heart rate lower than 50 bpm or the patient had signs or symptoms related to bradycardia. Swedberg K, et al. Lancet. 2010;376(9744):875-885.
**FDA-Approved Ivabradine**

<table>
<thead>
<tr>
<th><strong>Ivabradine</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indication</strong></td>
</tr>
<tr>
<td>To reduce the risk of hospitalization for worsening HF in patients with stable, symptomatic chronic HF with LVEF ≤35% who are in sinus rhythm with resting HR ≥70 bpm and either are on maximally tolerated doses of beta blockers or have a contraindication to beta blocker use.</td>
</tr>
<tr>
<td><strong>Dosage</strong></td>
</tr>
<tr>
<td>Start with 5 mg twice daily. After 2 weeks of treatment, adjust dose based on HR. Max is 7.5 mg twice daily. In patients with conduction defects or in whom bradycardia could lead to hemodynamic compromise, start with 2.5 mg twice daily.</td>
</tr>
<tr>
<td><strong>Contraindications</strong></td>
</tr>
<tr>
<td>Acute decompensated HF; BP &lt;90/50 mmHg; sick sinus syndrome or third-degree AV block, unless a functioning demand pacemaker is present; resting HR &lt; 60 bpm prior to treatment; severe hepatic impairment; pacemaker dependence. WARNING – fetal toxicity.</td>
</tr>
<tr>
<td><strong>Adverse events</strong></td>
</tr>
<tr>
<td>Occurring in ≥1% of patients are bradycardia, hypertension, atrial fibrillation, and luminous phenomena (phosphenes).</td>
</tr>
</tbody>
</table>

*Ivabradine Prescribing Information, 2017.*
Ivabradine can be beneficial to reduce HF hospitalization for patients with symptomatic (NYHA class II-III) stable chronic HFrEF (LVEF ≤35%) who are receiving guideline-directed evaluation and management, 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.
### ACCF/AHA 2013/2017 Guidelines: Class III (Harm)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Drug(s)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td><strong>Nondihydropyridine calcium channel blockers</strong></td>
<td>- Nondihydropyridine calcium channel blockers with negative inotropic effects may be harmful in asymptomatic patients with low LVEF and no symptoms of HF after MI</td>
</tr>
<tr>
<td>C</td>
<td><strong>ACEI + ARB + aldosterone antagonist</strong></td>
<td>- Routine combined use of an ACEI, ARB, and aldosterone antagonist is potentially harmful for patients with HFrEF</td>
</tr>
<tr>
<td>C</td>
<td><strong>Antiarrhythmic drugs, calcium channel-blocking drugs (except amlodipine), NSAIDS, thiazolidinediones</strong></td>
<td>- Drugs known to adversely affect the clinical status of patients with HFrEF are potentially harmful and should be avoided or withdrawn</td>
</tr>
<tr>
<td>C</td>
<td><strong>Infused positive inotropic drugs</strong></td>
<td>- Long-term use of an infusion of a positive inotropic drug is not recommended and may be harmful except as palliation</td>
</tr>
</tbody>
</table>
| C     | **Angiotensin receptor-neprilysin inhibitor (ARNI)**                    | - ARNI should not be administered concomitantly with ACEIs or within 36 hours of the last dose of an ACEI  
- ARNI should not be administered in patients with a history of angioedema                                                                 |
| D     | **Infused positive inotropic drugs**                                   | - Routine intravenous use, either continuous or intermittent, is potentially harmful in stage D HF  
- Short-term intravenous use in hospitalized patients without evidence of shock or threatened end-organ performance is potentially harmful                              |

ACCF/AHA 2013 Guidelines: Stage D Treatment

**Stage D Options**
- Heart transplant
- Chronic inotropes
- Temporary or permanent mechanical circulatory support
- Experimental surgery or drugs
- Palliative care and hospice
- ICD deactivation

---

**Recommendations**

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inotropic support</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiogenic shock pending definitive therapy or resolution</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>BTT or MCS in stage D refractory to GDMT</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>Short-term support for threatened end-organ dysfunction in hospitalized patients with stage D and severe HF/EF</td>
<td>IIb</td>
<td>B</td>
</tr>
<tr>
<td>Long-term support with continuous infusion palliative therapy in select stage D HF</td>
<td>IIb</td>
<td>B</td>
</tr>
<tr>
<td>Routine intravenous use, either continuous or intermittent, is potentially harmful in stage D HF</td>
<td>III: Harm</td>
<td>B</td>
</tr>
<tr>
<td>Short-term intravenous use in hospitalized patients without evidence of shock or threatened end-organ performance is potentially harmful</td>
<td>III: Harm</td>
<td>B</td>
</tr>
</tbody>
</table>

**MCS**

- MCS is beneficial in carefully selected patients with stage D HF in whom definitive management (e.g., cardiac transplantation) is anticipated or planned
- Nondurable MCS is reasonable as a “bridge to recovery” or “bridge to decision” for carefully selected patients with HF and acute profound disease
- Durable MCS is reasonable to prolong survival for carefully selected patients with stage D HF/EF

Cardiac transplantation

- Evaluation for cardiac transplantation is indicated for carefully selected patients with stage D HF despite GDMT, device, and surgical management

---

## ACCF/AHA 2017 Guidelines for HFpEF

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendation</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>B</td>
<td>Systolic and diastolic BP should be controlled in accordance with published clinical practice guidelines to prevent morbidity</td>
<td>2013 recommendation remains current</td>
</tr>
<tr>
<td>I</td>
<td>C</td>
<td>Diuretics should be used for relief of symptoms due to volume overload</td>
<td>2013 recommendation remains current</td>
</tr>
<tr>
<td>IIa</td>
<td>C</td>
<td>Coronary revascularization is reasonable in patients with CAD in whom symptoms (angina) or demonstrable myocardial ischemia is judged to be having an adverse effect despite GDMT</td>
<td>2013 recommendation remains current</td>
</tr>
<tr>
<td>IIa</td>
<td>C</td>
<td>Management of AF according to published clinical practice guidelines in patients with HFpEF is reasonable to improve symptoms</td>
<td>2013 recommendation remains current</td>
</tr>
<tr>
<td>IIa</td>
<td>C</td>
<td>The use of beta-blocking agents, ACEIs, and ARBs in patients with hypertension is reasonable to control BP</td>
<td>2013 recommendation remains current</td>
</tr>
<tr>
<td>IIb</td>
<td>B-R</td>
<td>In appropriately selected patients with HFpEF (with EF ≥45%, elevated BNP, or HF admission within 1 yr, eGFR &gt;30 mL/min, Cr &lt;2.5 mg/dL, potassium &lt;5.0 mEq/L), aldosterone receptor antagonists might be considered to decrease hospitalizations</td>
<td>NEW: Current recommendation reflects new RCT data</td>
</tr>
</tbody>
</table>

Case (cont’d.)

- You see the patient 6 months later and he has NYHA class I symptoms
- Carvedilol is successfully increased back to 25 mg twice daily
- Switched to sacubitril/valsartan
- HR 62 bpm, BP 108/68 mmHg, RR 14 breaths per minute
Conclusions

• Acute assessment and management
  – Goals
    ▪ Improve symptoms
    ▪ Identify etiology/precipitating factors
    ▪ Optimize volume status and chronic oral treatment
  – Look for factors associated with increased risk
    ▪ ↑ SCR, ↓ BP, presence of biomarkers, etc

• Discharge and transition
  – Ensure adequate (and timely!) follow-up
  – Provide patient education
  – Utilize care coordination, multidisciplinary care, and shared decision making
Conclusions (cont’d.)

• Chronic management
  – Utilize GDMT
    ▪ New 2017 recommendations include…
      – **Ivabradine** can be beneficial in symptomatic (NYHA class II-III) stable chronic HFrEF (LVEF ≤35%) patients who are receiving guideline-directed evaluation and management
      – **Sacubitril/valsartan**: ACEI, ARB, OR ARNI recommended in patients with HFrEF
    ▪ Avoid:
      – Calcium channel blockers (stage B)
      – ACEI + ARB + aldosterone antagonist (stage C)
      – ACEI + ARNI (stage C)
      – Chronic infusion of inotropes as an outpatient, except for palliation (stage D)
  – Uptitrate slowly
  – Monitor patients carefully
  – Educate patients on potential AEs
  – Manage comorbidities appropriately