Turning Heart Failure into Heart Success:
A review of new pharmacotherapeutic approaches
to heart failure management

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Disclosures

» Speaker has no conflicts of interest to disclose
Objectives

- Review the pathophysiology of heart failure as it related to neurohormonal pathways
- Identify pharmacotherapeutic treatment options for heart failure (HF) and tailor use based upon individualized patient characterizations
- Adjust treatment plans for HF patients to improve morbidity and mortality, as well as reduce hospitalizations

Where Do We Stand

<table>
<thead>
<tr>
<th>Prevalence</th>
<th>5.7 Million Americans</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence</td>
<td>&gt;800,000 new cases/year (2011)</td>
</tr>
<tr>
<td>Morbidity</td>
<td>&gt;1 million hospitalizations annually (1)</td>
</tr>
<tr>
<td></td>
<td>5-10% of all admissions</td>
</tr>
<tr>
<td></td>
<td>Most frequent cause of hospitalization in the elderly</td>
</tr>
<tr>
<td>Mortality</td>
<td>&gt;250,000 deaths/year</td>
</tr>
<tr>
<td>Cost</td>
<td>$31 billion annually (2012)</td>
</tr>
</tbody>
</table>

Adapted from AHA Heart and Stroke Facts Statistical Update, 2015.
The Cost is Rising

- HF accounts for 1-2% of overall healthcare spending
- In the US, HF consumes more Medicare dollars than ANY other diagnosis
- 77% of lifetime costs are accrued during hospitalizations

Average Costs

Total Estimated Life Time Costs - $109,541/person
Hospitalizations: $83,980/person

While Survival Continues to Decline

Survival

Preserved ejection fraction
Reduced ejection fraction

P=0.03

Year
Classifying Heart Failure

Heart Failure

Preserved Ejection Fraction
HFrEF

Reduced Ejection Fraction
HFpEF

Hypertension
Ischemia
Valvular Disease
Arrhythmia

NYHA Classification System

**New York Heart Association (NYHA)**

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>Cardiac disease without limitations on physical activity</td>
</tr>
<tr>
<td>Class II</td>
<td>Cardiac disease with slight limitation of physical activity</td>
</tr>
<tr>
<td>Class III</td>
<td>Cardiac disease with marked limitation of physical activity</td>
</tr>
<tr>
<td>Class IV</td>
<td>Cardiac disease with inability to carry on physical activity without discomfort</td>
</tr>
</tbody>
</table>
ACC/AHA Staging

<table>
<thead>
<tr>
<th>Stage A</th>
<th>Patients at high risk of heart failure (ex. cardiotoxic medications)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage B</td>
<td>Structural heart disease, no signs or symptoms</td>
</tr>
<tr>
<td>Stage C</td>
<td>Structural heart disease with current or previous signs or symptoms</td>
</tr>
<tr>
<td>Stage D</td>
<td>Refractory heart failure requiring specialized interventions</td>
</tr>
</tbody>
</table>

Meet EF

EF is a 72yo F who presents to your office for follow up. She has been increasingly more short of breath when she takes her daily walk and she frequently gets winded folding the laundry. She also mentions feeling significantly worse following her son’s Labor Day cookout.

**PMH:** Hyperlipidemia, Heart Failure (EF 30%), DMII, Gout

**Vitals:** HR 108 BP 138/55 RR 20 Tmax 37C o2 sat 95% RA

**PE:** A&O x 3, Warm Extremities, Bilateral crackles, 2+ pitting edema & JVD

**Pertinent Labs:** Na 131, K 3.8, BUN 22, SCr 1.2 (baseline), LFTs WNL, BNP 2780, Trop 0.01
EF Continued

**Home Meds:**
- Aspirin 81mg QD
- Carvedilol 6.25mg BID
- Digoxin 0.125mcg QD
- Furosemide 40mg QD
- Insulin SS
- Lantus 10 units QHS
- Lipitor 40mg QD
- Lisinopril 40mg QD
- Metformin 500mg BID
- Colchicine PRN

**ECG:** Sinus Tachycardia HR 102

**Repeat Echo:** Global hypokinesis; EF 25%

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**What ACC/AHA Stage is EF**

A) **Stage A:** Patients at high risk of heart failure

B) **Stage B:** Structural heart disease, no signs or symptoms

C) **Stage C:** Structural heart disease with current or previous signs or symptoms

D) **Stage D:** Refractory heart failure requiring specialized interventions
Which NYHA Class is EF

A) Class I: Cardiac disease without limitations on physical activity
B) Class II: Cardiac disease with slight limitation of physical activity
C) Class III: Cardiac disease with marked limitation of physical activity
D) Class IV: Cardiac disease with inability to carry on physical activity without discomfort

Heart Failure Progression: Neurohormonal Activation Hypothesis

Acute or Chronic Myocardial injury → Decreased LV performance, ↑ wall stress → Activation of RAAS and SNS → LV Remodeling, progressive LV dysfunction → Interstitial Fibrosis, Myocyte hypertrophy and apoptosis (cell death). → Peripheral vasoconstriction, Hemodynamic alterations → Heart failure symptoms

ACE-inhibitors/ARBs, ß-Adrenergic Blockers, Aldosterone Antagonists → Morbidity and mortality, Arrhythmias, Pump failure
**History of HF Pharmacotherapy**

<table>
<thead>
<tr>
<th>Loop Diuretics &amp; Digoxin</th>
<th>Aldosterone Antagonists</th>
<th>Beta Blockers</th>
<th>ARNi* &amp; Ivabradine</th>
</tr>
</thead>
</table>

- **ACE Inhibitors/ Angiotensin II Receptor Blockers**
  - 1987

- **Omapatrilat**
  - 2001

- **Hydralazine/ Isosorbide Dinitrate**
  - 2004

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**Loop Diuretics**

- Recommended in patients with HFrEF with fluid retention
  - Class I; Level C
- Physiological Benefits:
  - Decrease Preload
- Mortality Benefits
  - NONE. Higher doses may be associated with increased mortality

<table>
<thead>
<tr>
<th>Equipotent Dosing</th>
<th>Bumetanide</th>
<th>Torsemide</th>
<th>Furosemide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative Potency</td>
<td>1mg</td>
<td>20mg</td>
<td>40mg</td>
</tr>
<tr>
<td>IV:PO Conversion</td>
<td>1:1</td>
<td>1:1</td>
<td>1:2</td>
</tr>
<tr>
<td>Initial Dosing</td>
<td>0.5-1mg QDay/BID</td>
<td>10-20mg QDay</td>
<td>20-40mg QDay/BID</td>
</tr>
</tbody>
</table>
Managing Diuretic Resistance

- Rule out non-adherence to medications and/or diet and salt restriction
- Higher dose of same diuretic
  - Increase amount to urinary site of action
- Switch to another loop diuretic
  - Bumetanide: bioavailability 80-95%
  - Torsemide: longer T ½ (6 hours in HF pts)
- Increase frequency
- Sequential nephron blockade
  - Addition of metolazone to block the distal tubule

Digoxin

- May be beneficial in patients with HFrEF
  - LOE: Class IIa; Level B
- Decreases Hospitalizations (28%)
- No reduction in mortality
Clinical Evidence

<table>
<thead>
<tr>
<th>Study</th>
<th>Eligibility</th>
<th>Drug Regimen</th>
<th>Primary Outcome</th>
<th>Main Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>DIG (1997)</td>
<td>LVEF ≤ 45%, normal sinus, receiving diuretics and ACEi</td>
<td>Digoxin (dose titrated to serum level 0.5 – 2.0) vs. placebo</td>
<td>Mortality</td>
<td>Mortality was unaffected HR 0.99 (0.91 – 1.07) p = 0.80</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Decreased hospitalization overall and due to HF 0.72 (0.66 – 0.79) p&lt;0.001</td>
</tr>
<tr>
<td>DIG Sub Study</td>
<td>Men enrolled in DIG trial, LVEF ≤ 45%, normal sinus rhythm</td>
<td>Digoxin (serum levels): 0.5 – 0.8 ng/mL 0.9 – 1.1 ng/mL ≥ 1.2 ng/mL vs. placebo</td>
<td>All-cause mortality within 37 months</td>
<td>Serum drug level mortality %: 0.5 – 0.8 ng/mL (29.9%); 6.3% Lower 0.9 – 1.1 ng/mL (38.8%); No benefit ≥ 1.2 ng/mL (48.0%); 11.8% Higher Decreased mortality in serum drug level 0.5 - 0.8 (95% CI 2.1% - 10.5%)</td>
</tr>
</tbody>
</table>

ACE Inhibitors

- Cornerstone of Heart Failure Pharmacotherapy
- Use in all patients with HFrEF
  - LOE: Class I; Level A
- Physiologic Benefits:
  - Decrease Preload & Afterload; Prevents ventricular remodeling
  - Decrease mortality (16-27%)
  - Decrease hospitalizations
  - Slow disease progression
## ACE Inhibitors – Key Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Eligibility</th>
<th>Treatment Arms</th>
<th>Primary Outcome</th>
<th>Results</th>
</tr>
</thead>
</table>
| Consensus (1987) | NYHA Class IV; Cardiomegaly | Enalapril 20mg BID vs Placebo | All cause mortality | 27% reduction in all cause mortality  
40% reduction in 6months (p=0.002)                                      |
| SOLVD (1991)   | NYHA Class I-IV; LVEF ≤35%   | Enalapril 10mg BID vs Placebo | All cause mortality | 16% reduction in all cause mortality (p=0.0036)  
Fewer HF related hospitalizations                                        |
| Aire (1993)    | Acute MI w/in 3-5days with clinical evidence of HF | Ramipril 5mg BID vs Placebo | All cause mortality | 27% reduction in all cause mortality (p=0.002)  
Significant reduction in severe HF, MI and stroke                          |
| VHEFT-II (1991)| NYHA Class II - IV           | Enalapril vs Hydralazine/ISDN | All cause mortality | 34% reduction in mortality after 1yr; 28% after 2yrs  
44% reduction in hospitalizations                                          |

### Impact on Renal Function

Data from CONSENSUS Trial – Enalapril vs Placebo  
(EF ≤ 35%, NYHA Class IV)

Patients with the greatest rise in creatinine (99% increase on average) had lower MAP & higher doses of furosemide.  
This effect was independent of the ACEi dose.

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Use in Chronic Kidney Disease

![Graph showing serum creatinine levels over time with comparison between Benazepril and Placebo.]


**ARB - Key Trials**

<table>
<thead>
<tr>
<th>Study</th>
<th>Eligibility</th>
<th>Treatment Arms</th>
<th>Primary Outcome</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>ELITE II (2000)</td>
<td>NYHA Class II-IV Age &gt;60 LVEF&lt;40%</td>
<td>Losartan 50mg QD vs Captopril 50mg TID</td>
<td>All cause mortality</td>
<td>NS difference in mortality (p=0.16) Trend favored captopril Fewer pts discontinued ARB</td>
</tr>
<tr>
<td>CHARM (2003)</td>
<td>LVEF &lt;40% with or without ACEi; LVEF&gt;40%</td>
<td>Candesartan 32mg vs Placebo</td>
<td>All cause mortality</td>
<td>10% reduction in overall mortality Adjusted HR 0.9 (0.82-0.99)</td>
</tr>
<tr>
<td>VALIANT (2003)</td>
<td>LVEF &lt;35-40%, post-MI within 0.5-10d, SBP&gt;100mmHG</td>
<td>Valsartan 160mg BID vs Captopril 50mg TID</td>
<td>All cause mortality</td>
<td>Non-inferior to captopril HR 1.0 (0.9-1.11) Combination of ACEi/ARB increases adverse events without survival benefit</td>
</tr>
</tbody>
</table>
Practical Considerations

- RAAS inhibition is essential
- ARBs can be used as an alternative to ACEi in patients who can't tolerate ACEi
- Abnormal baseline renal function is not a contraindication to initiation
- Caution if potassium rises >5.5mEq/L or the creatinine is >3.0mg/dL
- Don’t be intimidated by asymptomatic hypotension – consider decreasing loop diuretic doses first.

Aldosterone Antagonists

- Use in patients with NYHA Class II-IV HF with EF<35%
  - LOE: Class I; Level A
- Physiologic Benefits:
  - Decrease Preload; Prevent cardiac fibrosis
  - Decrease mortality (15-30%)
  - Decrease hospitalizations
  - Slow disease progression
Aldosterone Antagonists – Key Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Eligibility</th>
<th>Treatment Arms</th>
<th>Primary Outcome</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RALES</strong></td>
<td>NYHA Class III-IV, LVEF&lt;35%, treatment with ACEi/Loop</td>
<td>Spironolactone 25mg vs Placebo</td>
<td>All cause mortality</td>
<td>30% reduction in all cause mortality ARR 11% Decreased hospitalizations</td>
</tr>
<tr>
<td><strong>(1999)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>EPHESUS</strong></td>
<td>Acute MI w/in 3-14d, LVEF &lt;40%, DM, signs of HF</td>
<td>Eplerenone 50mg vs Placebo</td>
<td>All cause mortality</td>
<td>15% reduction in all cause mortality Decrease in death from or hospitalization for CV causes</td>
</tr>
<tr>
<td><strong>(2003)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>EMPHASIS-HF</strong></td>
<td>NYHA Class II, LVEF&lt;35%, on current recommended treatment</td>
<td>Eplerenone 50mg vs Placebo</td>
<td>Composite of death from CV causes or hospitalization for HF</td>
<td>37% reduction in the composite endpoint Reduced risk of death and hospitalization</td>
</tr>
<tr>
<td><strong>(2011)</strong></td>
<td></td>
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</tr>
</tbody>
</table>
Practical Considerations

- Review prior labs for any episodes of hyperkalemia
- If a regimen contains potassium supplementation, stop it if reasonable. Instruct on low potassium diet
- Abnormal baseline renal function is not a contraindication. Caution if creatinine >3 mg/dL
- Be observant of the symptomatic response for a given patient. If the drug significantly improves signs and symptoms, do everything possible to continue its use
- If potassium rises >5.5mEq/L, consider back titration

Omapatrilat

- The “super ACE inhibitor”
- Combined both ACE inhibition and neutral endopeptidase (neprilysin)
  - Promoted vasodilitation, natriuresis, inhibition of SNS and RAAS
- Denied approval by the FDA
  - 3.1x higher risk of angioedema due to greater potentiation of bradykinin
### β - Blockers

- Recommended for all stable patients to decrease mortality
  - LOE: Class I; Level A
- Physiologic Benefits:
  - Suppress sympathetic nervous system
  - Decrease Preload, decrease contractility
- Decreased mortality (35%)
- Decreased hospitalizations
- Improved functional class & Improved LVEF

### Beta Blockers – Key Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Eligibility</th>
<th>Treatment Arms</th>
<th>Primary Outcome</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>US Carvedilol HF Study (1996)</td>
<td>NYHA Class II-IV, LVEF ≤ 35</td>
<td>Carvedilol 25-50mg BID vs Placebo</td>
<td>All cause mortality</td>
<td>35% reduction in all cause mortality (p&lt;0.001), decreased hospitalizations</td>
</tr>
<tr>
<td>CIBIS-II (1999)</td>
<td>Stable NYHA Class II-IV, LVEF ≤ 35</td>
<td>Bisoprolol 10mg QDay vs Placebo</td>
<td>All cause mortality</td>
<td>34% reduction in all cause mortality (p&lt;0.001), decreased SCD, decreased hospitalizations</td>
</tr>
<tr>
<td>MERIT-HF (1999)</td>
<td>Stable NYHA Class II-IV, LVEF ≤ 40</td>
<td>Metoprolol Succinate 200mg QDay vs Placebo</td>
<td>All cause mortality</td>
<td>34% reduction in all cause mortality (p=0.00062); decreased SCD and death from HF exacerbation</td>
</tr>
<tr>
<td>COPERNICUS (2003)</td>
<td>NYHA Class III-IV, LVEF ≤ 25%</td>
<td>Carvedilol 25mg BID vs Placebo</td>
<td>All cause mortality</td>
<td>35% reduction in all cause mortality (p=0.0014), decreased risk of death and hospitalization</td>
</tr>
</tbody>
</table>
COMET Trial

Decrease All Cause Mortality  
34% vs. 40%; P = 0.0017  
Relative Risk Reduction:  
17%

Number at Risk:  
Metoprolol  
1,518  
1,359  
1,234  
1,105  
933  
352  
Carvedilol  
1,511  
1,366  
1,259  
1,155  
1,002  
383  

Mortality (%)  
0  
10  
20  
30  
40  

Time (years)  
0  
1  
2  
3  
4  
5

Hydralazine – Isosorbide Dinitrate

- Recommended for African Americans with NYHA Class III – IV HFrEF on guideline-directed therapy
  - Decreased mortality (43%)
  - LOE: Class I; Level A
- Combination can be useful in patients with HFrEF who cannot be given ACE inhibitors or ARBs
  - LOE: Class IIa; Level B
- Physiologic Benefits:
  - Reduction in preload and afterload → Arterial and Venous vasodilation
  - Nitric oxide donor, protective effects
Hydralazine-ISDN – Key Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Eligibility</th>
<th>Treatment Arms</th>
<th>Primary Outcome</th>
<th>Results</th>
</tr>
</thead>
</table>
| V-HEFT I   | Men 18-75yrs, LVEF <45%, reduced exercise tolerance on Dig & Diuretics | ISDN+hydralazine vs. prazosin vs. placebo | All cause mortality | 34% reduction in all cause mortality (p< 0.028)  
LVEF significantly increased compared to placebo (p < 0.001)  
No significant differences placebo vs. prazosin |
| VHEFT-II   | NYHA Class II - IV                                     | Enalapril vs Hydralazine/ISDN   | All cause mortality | 34% reduction in mortality after 1yr;  
28% after 2yrs  
44% reduction in hospitalizations |
| AHEFT      | NYHA class III-IV, age ≥18, self-identified black, LVEF ≤ 45%, on Standard HF therapy | ISDN 40 mg + hydralazine 75 mg TID vs. placebo | Composite endpoint: Death from any cause, HF Hospitalization, Change in QOL | 43% reduction in rate of death from any cause (p = 0.01)  
Mean primary composite score improved (p = 0.01)  
33% relative reduction in rate of first HF-related hospitalization (p=0.001)  
Improved QOL (p=0.02) |

Back To EF...

- After listening to her story you review her medications to ensure she is on the best regimen to optimize outcomes
- Current HF Medications:
  - Carvedilol 6.25mg BID
  - Digoxin 0.125mcg QD
  - Furosemide 40mg QD
  - Lisinopril 40 mg QD

Is this the best we can do?
New Developments in HF Pharmacotherapy

- **Valsartan/Sacubitril (Entresto®)** – combination of an ARB with a neprilysin inhibitor
  - Class referred to as ARNI
  - Neprilysin is a protease (aka neutral endopeptidase) that degrades many biologically active circulating peptides such as the natriuretic peptides (ANP, BNP), bradykinin, angiotensin II, and adrenomedullin

- **Ivabradine (Corlanor®)** – Novel heart rate slowing agent acting solely on the sinus node.

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**ARNI Dual Mechanism (Entresto®)**

[Diagram showing the dual mechanism of ARNI (Angiotensin Receptor Neprilysin Inhibitor) with annotations for NP system and RAAS pathways.]

PARADIGM HF

- Multicenter, prospective, randomized, comparative trial
- N=8,399
- 1,043 centers in 47 countries
- Median follow-up: 27 months (stopped early)
- Intention-to-treat
- Primary outcome
  - CV mortality or HF hospitalization

Inclusion/Exclusion Criteria

<table>
<thead>
<tr>
<th>INCLUSION</th>
<th>EXCLUSION</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA class II-IV symptoms</td>
<td>Symptomatic hypotension</td>
</tr>
<tr>
<td>LVEF ≤40% until 2010 at which point this was reduced to ≤35%</td>
<td>SBP &lt;100 mmHg at screening or &lt;95 mmHg at randomization</td>
</tr>
<tr>
<td>If no HF hospitalizations in prior year: BNP ≥150 pg/mL or NT proBNP ≥600 pg/mL</td>
<td>eGFR &lt;30 mL/min/1.73 m²</td>
</tr>
<tr>
<td>If a HF hospitalization in prior year: BNP ≥100 pg/mL or NT proBNP ≥400 pg/mL</td>
<td>K &gt;5.2 mmol/L at screening or &gt;5.4 mmol/L at randomization</td>
</tr>
<tr>
<td>ACEi or ARB therapy with stable dose for prior 4 weeks, equivalent to enalapril ≥ 10 mg/day</td>
<td>Acute coronary event in the last 3 months</td>
</tr>
<tr>
<td>Beta blocker with stable dose for prior 4 weeks</td>
<td>Severe pulmonary disease, hepatic impairment</td>
</tr>
<tr>
<td></td>
<td>History of angioedema</td>
</tr>
<tr>
<td></td>
<td>&quot;Unacceptable side effects&quot; with ACE-inhibitors or ARBs</td>
</tr>
</tbody>
</table>
Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age</td>
<td>64</td>
</tr>
<tr>
<td>Sex</td>
<td>79% Male</td>
</tr>
<tr>
<td>Race</td>
<td>White 66%, Black 5%, Asian 18%, other 11%</td>
</tr>
<tr>
<td>PMH</td>
<td>HF hospitalization 62%, HTN 71%, MI 43%, DM 35%, AF 36%, Stroke 9%</td>
</tr>
<tr>
<td>HF</td>
<td>ICM 60%; NYHA class: I 4%, II 72%, III 23%, IV 0.8%, unknown &lt;1%</td>
</tr>
<tr>
<td>Lab Data</td>
<td>Creatinine 1.13 mg/dL, NT proBNP 1,631 pg/mL</td>
</tr>
<tr>
<td>Medications</td>
<td>ACEi 78%, ARB 22% (no ACEi or ARB 20 patients, ACEi+ARB 45 patients), Diuretic 80%, Digitalis 29%, Beta Blocker 93%, Aldosterone Antagonist 52%</td>
</tr>
</tbody>
</table>

PARADIGM HF – Study Design

Note: 24/26 mg, 49/51 mg, and 97/103 mg doses of ENTRESTO were referred to as 50 mg, 100 mg, and 200 mg, respectively
Outcomes

- **Primary Outcome**
  - CV mortality or HF hospitalization 21.8% vs. 26.5%
    - (HR 0.80; 95% CI 0.73-0.87; P<0.001; **NNT 21**)

- **Secondary Outcomes**
  - CV mortality 13.3% vs. 16.5%
    - (HR 0.80; 95% CI 0.71-0.89; P<0.001; **NNT 31**)
  - HF hospitalization 12.8% vs. 15.6%
    - (HR 0.79; 95% CI 0.71-0.89 P<0.001; **NNT 36**)
  - All-cause mortality 17.0% vs. 19.8%
    - (HR 0.84; 95% CI 0.76-0.93; P=0.001; **NNT 36**)
  - Renal function decline ESRD, decrease in eGFR ≥50% or decrease in eGFR≥30mL/min 2.2% vs. 2.6% (HR 0.86; 95% CI 0.65-1.13; P=0.28)
**Results Similar to SOLVD**

- **Relative Risk Reduction**: 16%
- **p-value**: 0.0036

![Graph showing mortality rates over follow-up months for Placebo and Enalapril](graph.png)

**PARADIGM HF – Adverse Events**

<table>
<thead>
<tr>
<th>Event</th>
<th>LCZ696 (N=4,187)</th>
<th>Enalapril (N=4,212)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension</td>
<td></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>119 (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>
</tbody>
</table>

*McMurray et al. NEJM August 30, 2014*
PARADIGM HF Critiques

- Change in inclusion criteria mid-study to go from $\text{EF} \leq 40\%$ to $\text{EF} \leq 35\%$
- Comparator Arm should have included ARB
- Target doses of ACEi weren’t maximized
- Black population under represented (5%)
- Few severely symptomatic patients
- Unknown long term effects of beta amyloid breakdown
  - Follow up on cognitive outcomes is needed

PARADIGM HF – Conclusions

- This trial led to Valsartan/Sacubitril (Entresto®) being approved by the FDA July 2015
- The mortality benefits vs. Enalapril are comparable to those observed in the SOLVD treatment trial (Enalapril vs. Placebo)
- ARNI therapy will likely replace ACE inhibitors and ARBs in the management of HFrEF
- **Note:** Because sacubitril inhibits breakdown of BNP, serum BNP levels will be unreliable. Recommend checking NT-PRO BNP when clinically indicated
ACEI and ARB (for ACEI intolerant patients) still have a Class I recommendation (*Level of Evidence: A*), **AND NOW** angiotensin receptor–neprilysin inhibitors (ARNI) do as well

Class I recommendation for ARNI to replace an ACE inhibitor or ARB in selected patients with chronic symptomatic HFrEF (NYHA class II/III) with an adequate blood pressure who are *already tolerating* a reasonable dose of ACE inhibitor or ARB

Class III (HARM) recommendation for use of ARNI concomitantly with ACE inhibitors or within 36 hours of the last dose of an ACE inhibitor

Class III (HARM) recommendation for use of ARNI in patients with a history of angioedema

### Valsartan/Sacubitril Dosing

<table>
<thead>
<tr>
<th>Current treatment with ACEI</th>
<th>Current treatment with ARB</th>
<th>No treatment with ACEI/ARB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose ≤10mg Enalapril or Equivalent</td>
<td>Dose ≤160mg Valsartan or Equivalent</td>
<td>Start Val/Sac 24/26mg BID</td>
</tr>
<tr>
<td>Dose &gt;10mg Enalapril or Equivalent</td>
<td>Dose &gt;160mg Valsartan or Equivalent</td>
<td>Start Val/Sac 24/26mg BID</td>
</tr>
<tr>
<td><strong>Stop ACEI 36 hours prior to ARNI initiation</strong></td>
<td>Start Val/Sac 24/26mg BID</td>
<td>Start Val/Sac 24/26mg BID</td>
</tr>
<tr>
<td>Start Val/Sac 24/26mg BID</td>
<td>Start Val/Sac 49/51mg BID</td>
<td>Start Val/Sac 49/51mg BID</td>
</tr>
<tr>
<td>Double doses every 2-4 weeks to reach target dose 97/103mg BID</td>
<td>Double doses every 2-4 weeks to reach target dose 97/103mg BID</td>
<td>Double doses every 2-4 weeks to reach target dose 97/103mg BID</td>
</tr>
</tbody>
</table>
Ivabradine (Corlanor®)

- Inhibits the “funny” inward current ($I_f$) of sino-atrial myocytes
- Binds the HCN4 membrane ion channel in these cells and modulates the $I_f$ current to decrease heart rate without affecting contractility
- Utilized to explore the effect of more intensive heart rate reduction in the management of both heart failure and/or ischemic heart disease

SHIFT Trial

- Double Blind, Placebo Controlled
- Ivabradine (5mg titrated to 7.5mg bid) vs. placebo
- 6558 patients included with:
  - Symptomatic heart failure
  - LVEF $\leq$ 35%
  - Sinus rhythm with heart rate $\geq$ 70 BPM
  - Hospitalization for heart failure within the previous year
  - Stable background treatment including a β blocker if tolerated
- Primary Endpoint: CV Death and HF Hospitalization
**SHIFT Trial – Results**

**CV Death or Hospital Admission for Worsening HF**

- Relative Risk Reduction: 18%

**Cumulative Frequency (%)**

- **Placebo**
- **Ivabradine**

**MONTHS**

**SHIFT Trial – Results**

<table>
<thead>
<tr>
<th></th>
<th>Ivabradine group (n=2344)</th>
<th>Placebo group (n=2364)</th>
<th>HR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary endpoint</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CV death or hospital admission for worsening heart failure</td>
<td>752 (32%)</td>
<td>957 (40%)</td>
<td>0.82 (0.75-0.90)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mortality endpoints</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>503 (21%)</td>
<td>592 (25%)</td>
<td>0.90 (0.82-0.98)</td>
<td>0.0692</td>
</tr>
<tr>
<td>Hospitalization for worsening heart failure</td>
<td>481 (20%)</td>
<td>481 (20%)</td>
<td>0.90 (0.82-1.01)</td>
<td>0.1383</td>
</tr>
<tr>
<td>Death from heart failure</td>
<td>130 (5%)</td>
<td>181 (8%)</td>
<td>0.74 (0.55-0.98)</td>
<td>0.0434</td>
</tr>
<tr>
<td>Other endpoints</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any cause hospital admission</td>
<td>1231 (52%)</td>
<td>1255 (54%)</td>
<td>0.99 (0.93-1.05)</td>
<td>0.5698</td>
</tr>
<tr>
<td>Hospitalization for worsening heart failure</td>
<td>534 (23%)</td>
<td>672 (28%)</td>
<td>0.74 (0.65-0.85)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Any cause hospital admission</td>
<td>977 (41%)</td>
<td>2225 (94%)</td>
<td>0.43 (0.27-0.69)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CV death or hospital admission for worsening heart failure or hospitalization for worsening heart failure</td>
<td>325 (37%)</td>
<td>879 (50%)</td>
<td>0.61 (0.37-0.98)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Data are number of first events (%), hazard ratios (HR), 95% CI, and p values.

Table 3: Effects on primary and major secondary endpoints.
## SHIFT Trial – Adverse Events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Ivabradine Group (n= 3232)</th>
<th>Placebo Group (n= 3260)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>2439 (75%)</td>
<td>2423 (74%)</td>
<td>0.303</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>804 (25%)</td>
<td>937 (29%)</td>
<td>0.0005</td>
</tr>
<tr>
<td>Symptomatic Bradycardia</td>
<td>150 (5%)</td>
<td>32 (1%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Asymptomatic Bradycardia</td>
<td>184 (6%)</td>
<td>48 (1%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>306 (9%)</td>
<td>251 (8%)</td>
<td>0.012</td>
</tr>
<tr>
<td>Blurred Vision</td>
<td>17 (1%)</td>
<td>7 (&lt;1%)</td>
<td>0.042</td>
</tr>
</tbody>
</table>


## SHIFT Trial – Beta Blocker Effect

<table>
<thead>
<tr>
<th>BB category (% of target dose)</th>
<th>Placebo event rate (%)</th>
<th>Hazard ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEP (CV death, HF hospitalisation)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No β-blocker</td>
<td>39.3</td>
<td>0.71</td>
<td>0.55-0.93</td>
</tr>
<tr>
<td>BB, 25%</td>
<td>40</td>
<td>0.74</td>
<td>0.59-0.92</td>
</tr>
<tr>
<td>BB, 25% to &lt;50%</td>
<td>30.8</td>
<td>0.81</td>
<td>0.68-0.98</td>
</tr>
<tr>
<td>BB, 50% to &lt;100%</td>
<td>24.8</td>
<td>0.88</td>
<td>0.72-1.07</td>
</tr>
<tr>
<td>BB, ≥100%</td>
<td>20.1</td>
<td>0.99</td>
<td>0.79-1.24</td>
</tr>
<tr>
<td>HF hospitalisation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No β-blocker</td>
<td>29</td>
<td>0.62</td>
<td>0.45-0.85</td>
</tr>
<tr>
<td>BB, 25%</td>
<td>29</td>
<td>0.68</td>
<td>0.52-0.89</td>
</tr>
<tr>
<td>BB, 25% to &lt;50%</td>
<td>22</td>
<td>0.74</td>
<td>0.59-0.93</td>
</tr>
<tr>
<td>BB, 50% to &lt;100%</td>
<td>18</td>
<td>0.83</td>
<td>0.65-1.05</td>
</tr>
<tr>
<td>BB, ≥100%</td>
<td>14</td>
<td>0.84</td>
<td>0.63-1.11</td>
</tr>
</tbody>
</table>

Ivabradine – Points to Consider

- Indicated for the management of patients with HF, LVEF ≤ 35%, and resting heart rates greater than 70 in SR on **optimal medical therapy**
- May be particularly useful in patients truly intolerant of beta-adrenergic blockers
- This drug is not considered an alternative to beta-blockade in patients with LV systolic dysfunction.

Concerns:
- Poly-pharmacy
- Shouldn’t we just more aggressively titrate beta-blockers further upward?
- Possible adverse effects in patients with chronic angina.

HF 2016 Guideline Updates

- Class IIa recommendation to reduce HF hospitalization in patients with symptomatic (NYHA class II-III) stable chronic HF/EF (LVEF ≤35%) 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
What should we recommend for EF?

Vitals: HR 92 BP 138/55 RR 20 Tmax 37C o2 sat 95% RA
PE: Warm extremities, Bilateral crackles, 2+ pitting edema & JVD
Pertinent Labs: Na 131, K 3.8, BUN 22, SCr 1.2 (baseline), BNP 2780 Trop 0.01

A) Maintain her current regimen and follow up in a week
B) Continue Lisinopril, Stop Furosemide initiate Bumex 0.5mg QD and Valsartan/Sacubitril 51/49mg BID
C) Stop Lisinopril and Carvedilol, increase Furosemide to 40mg BID, initiate Valsartan/Sacubitril 51/49mg BID and Ivabradine 5mg QD in 36h
D) Stop Lisinopril, increase Furosemide to 40mg BID, initiate Valsartan/Sacubitril 51/49mg in 36h, consider up titration of Carvedilol
E) Admit her for acute decompensated heart failure exacerbation

Conclusions

- Heart Failure is prevalent, costly, and the incidence will rise
- Therapies for Heart failure with reduced LVEF are well established and proven
- Loop diuretics while often necessary have not been shown to improve survival
- The ARB/Neprilysin inhibitor, Sacubitril/Valsartan will likely replace ACE-inhibitors as the cornerstone of vasodilator therapy for most patients
- The primary utility of Ivabradine (Corlanor) may be in those truly intolerant to beta-blockers
Questions?