Advances in Heart Failure Management
MSMA Conference 2018

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Disclosures

- Salary support
  - Heart Failure Network (NHLBI) < 5%
Outline

- Heart failure epidemiology
- Heart failure with *reduced* ejection fraction
  - Current and emerging medical therapies
  - Device-based therapies
  - End-stage therapies
- Heart failure with *preserved* ejection fraction
  - Current and emerging medical therapies
  - Device-based therapies
- Heart failure hospitalization
EPIDEMIOLOGY OF HEART FAILURE
Who has heart failure?

Epidemiology and Natural History of HF

- Prevalence 5.7 million in US
- Hospitalization > 1 million/year in US
- Cost ~ $30.7 billion/year in US

(Circ Cardiovasc Qual Outcomes. 2010;3:573-580.)
Demographics

- Incidence rate per 1000 person-year
  - African American = 4.6
  - Hispanic = 3.5
  - White = 2.4
  - Chinese = 1.0
- Male > female
Heart Disease Death Rates, 2013-2015
All Ages 35+, by County

Rates are spatially smoothed to enhance the stability of rates in counties with small populations.

Data Source:
National Vital Statistics System
National Center for Health Statistics
## Risk Factors for Heart Failure

<table>
<thead>
<tr>
<th>Condition</th>
<th>RR</th>
<th>PAR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary artery disease</td>
<td>8.1</td>
<td>62%</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>1.6</td>
<td>17%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.4</td>
<td>10%</td>
</tr>
<tr>
<td>Obesity</td>
<td>1.3</td>
<td>8%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.9</td>
<td>3%</td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td>1.5</td>
<td>2%</td>
</tr>
</tbody>
</table>

NHANES data (Arch Intern Med. 2001;161(7):996.)
Heart Failure Prevention

How to Prevent Heart Failure

1 in 5 adults develop HEART FAILURE

Ways to reduce risk of developing heart failure

Lifestyle factors
- Regular physical activity
- Healthy weight
- No smoking
- Healthy eating

Medical conditions
- Treat high blood pressure
- Control diabetes
- Maintain healthy cholesterol levels
- Take heart protective medications as prescribed

doi:10.1001/jamacardio.2016.3394
# Pharmacotherapy and HF Prevention

<table>
<thead>
<tr>
<th>Condition</th>
<th>Agent</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic LV dysfunction</td>
<td>ACEi</td>
<td>SAVE</td>
</tr>
<tr>
<td></td>
<td>β-blocker</td>
<td>SOLVD</td>
</tr>
<tr>
<td>Stable CAD</td>
<td>ACEi</td>
<td>EUROPA</td>
</tr>
<tr>
<td>Prior MI</td>
<td>Statin</td>
<td>4S</td>
</tr>
<tr>
<td>NSTEMI</td>
<td>Clopidogrel</td>
<td>CURE</td>
</tr>
<tr>
<td>Diabetes + HTN</td>
<td>Tight control (ACEi, β-blocker)</td>
<td>UKPDS</td>
</tr>
<tr>
<td>Diabetes + Nephropathy</td>
<td>ARB</td>
<td>RENAAL, IDNT</td>
</tr>
<tr>
<td>Diabetes + Vascular disease</td>
<td>ACEi</td>
<td>HOPE</td>
</tr>
</tbody>
</table>
CHARACTERISATION OF HEART FAILURE
Heart failure
Congestion
Dyspnea
Edema
Fatigue
Elevated LAP
Elevated RAP
Elevated BNP
Left Ventricular Ejection Fraction

- Relatively reproducible
- Differentiates physiology (esp remodeling)
- Enrollment criterion for landmark trials
How does the LV really work?
## HFpEF vs HFrEF

<table>
<thead>
<tr>
<th></th>
<th>HFpEF</th>
<th>HFrEF</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF</td>
<td>≥ 50%</td>
<td>&lt; 40%</td>
</tr>
<tr>
<td>AKA</td>
<td>Diastolic HF</td>
<td>Systolic HF</td>
</tr>
<tr>
<td>LV Volume</td>
<td>Nondilated</td>
<td>Dilated</td>
</tr>
<tr>
<td>LV Mass</td>
<td>Concentric hypertrophy</td>
<td>Eccentric hypertrophy</td>
</tr>
<tr>
<td>Diastolic function</td>
<td>Abnormal</td>
<td>Often abnormal</td>
</tr>
<tr>
<td>GDMT</td>
<td>Limited</td>
<td>Numerous</td>
</tr>
<tr>
<td>% of HF Hosp</td>
<td>50%</td>
<td>50%</td>
</tr>
<tr>
<td>Mechanisms</td>
<td>Metabolic dysregulation, Endothelial dysfunction</td>
<td>Myocyte injury, neurohormonal activation</td>
</tr>
<tr>
<td>Mechanics</td>
<td>Elevated EDPVR slope</td>
<td>Reduced ESPVR slope</td>
</tr>
</tbody>
</table>
HFREF TREATMENT PARADIGM
Therapies for Systolic Heart Failure

1987
- Digoxin
- Diuretics
- Vasodilators
- Transplant

2017
- ACE-inhibitors/ARBs
- Beta blockers
- Aldosterone antagonists
- Hydralazine/Nitrates
- ARNIs
- Ivabradine
- Digoxin
- Diuretics
- ICD/CRT
- CardioMEMS
- LVAD
- Transplant
Risk Reduction with GDMT in HFrEF

<table>
<thead>
<tr>
<th>Agent</th>
<th>Rel Risk Mortality</th>
<th>NNT Mortality*</th>
<th>Rel Risk HF Hosp</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACEi / ARB</td>
<td>17%</td>
<td>77</td>
<td>31%</td>
</tr>
<tr>
<td>B-blocker</td>
<td>34%</td>
<td>28</td>
<td>41%</td>
</tr>
<tr>
<td>MRA</td>
<td>30%</td>
<td>18</td>
<td>35%</td>
</tr>
<tr>
<td>HZN / IDN</td>
<td>43%</td>
<td>21</td>
<td>33%</td>
</tr>
</tbody>
</table>

* Standardized to 12 mos


JACC HF. 2014;2(5):545-548
Survival

- Approximately 50% at 5 years after diagnosis
- Long term HF survival rates increased 45% from 1995 to 2005
Targets for Therapy: HFrEF

- Renin-Angiotensin-Aldosterone System (RAAS)
- Sympathetic Nervous System (SNS)
- Natriurietic Peptide System (NPS)
- Afterload conditions and vascular tone
- Preload conditions and blood volume
- Heart rate
- Electrical Dyssynchrony
- Contractility
Simplified GDMT for HFrEF ~ 2013

ACE Inhibitor + Beta Blocker +/- Diuretic

- GFR > 30 ml/min, K < 5 mEq/dl

- + Mineralocorticoid Receptor Antagonist

- African American

- + Isosorbide Dinitrate / Hydralazine
NEWER MEDICAL THERAPIES: HFREF
Neprilysin Inhibition

ProBNP
NTproBNP

Other Peptides*
BNP

Neprilysin

* ANP, CNP, Adrenomedullin, Substance P, Bradykinin

Natriuresis / diuresis
Vasodilation
Decrease SNS
Anti-proliferative

Sacubitril
# Substrates of Neprilysin

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Substrates of neprilysin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vasoactive peptides</strong></td>
<td>Mitogenesis and angiogenesis</td>
</tr>
<tr>
<td>Adrenomedullin</td>
<td>Bombesin-like peptides</td>
</tr>
<tr>
<td>Angiotensin I</td>
<td>Fibroblast growth</td>
</tr>
<tr>
<td>Angiotensin II</td>
<td></td>
</tr>
<tr>
<td>Natriuretic peptides</td>
<td>Hypothalamic-pituitary axis</td>
</tr>
<tr>
<td>(ANP, BNP, CNP, urodilatin)</td>
<td>Adrenocorticotropic hormone</td>
</tr>
<tr>
<td>Bradykinin</td>
<td>Gonadotropin-releasing hormone</td>
</tr>
<tr>
<td>Kallidin</td>
<td>α-melanocyte stimulating hormone</td>
</tr>
<tr>
<td>Endothelin</td>
<td>Oxytocin</td>
</tr>
<tr>
<td>Neurokinin A</td>
<td>Digestion and metabolism</td>
</tr>
<tr>
<td>Neuropeptide Y</td>
<td>Cholecystokinin</td>
</tr>
<tr>
<td>Substance P</td>
<td>Gastrin-releasing peptide</td>
</tr>
<tr>
<td>Peptides in neurologic processes</td>
<td>Glucagon</td>
</tr>
<tr>
<td>Amyloid β</td>
<td>Glucagon-like peptides</td>
</tr>
<tr>
<td>Galanin</td>
<td>Insulin-B chain</td>
</tr>
<tr>
<td>Neurotensin</td>
<td></td>
</tr>
<tr>
<td>Peptide YY</td>
<td></td>
</tr>
<tr>
<td>Pain and Inflammation</td>
<td></td>
</tr>
<tr>
<td>Calcitonin gene-related peptide</td>
<td></td>
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<tr>
<td>Dynorphin</td>
<td></td>
</tr>
<tr>
<td>β endorphin</td>
<td></td>
</tr>
<tr>
<td>Enkephalins</td>
<td></td>
</tr>
<tr>
<td>Neurokinin A</td>
<td></td>
</tr>
<tr>
<td>Vasoactive intestinal peptide</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Campbell, *Nature Reviews Cardiology*
PARADIGM

- Predominantly NYHA II (70%) & III (24%)
- Mean SBP 122 mmHg
- Mean LVEF ~ 30%
- Mean Age ~ 64 years
- 93% on Beta blockers
- 55% on MRAs
- Minority (16%) with ICDs

<table>
<thead>
<tr>
<th></th>
<th>LCZ696 (n=4187)</th>
<th>Enalapril (n=4212)</th>
<th>Hazard Ratio (95% CI)</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV Death or HF hospitalization</td>
<td>914 (21.8%)</td>
<td>1117 (26.5%)</td>
<td>0.80 (0.73-0.87)</td>
<td>21</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>558 (13.3%)</td>
<td>693 (16.5%)</td>
<td>0.80 (0.71-0.89)</td>
<td>32</td>
</tr>
<tr>
<td>Hospitalization for heart failure</td>
<td>537 (12.8%)</td>
<td>658 (15.6%)</td>
<td>0.79 (0.71-0.89)</td>
<td>36</td>
</tr>
<tr>
<td>All-cause Death</td>
<td>711</td>
<td>835</td>
<td>0.84 (0.76-0.93)</td>
<td>36</td>
</tr>
</tbody>
</table>
Questions

- Adequate dose of ACEi
  - Enalapril = 18.9 mg/d
  - Highest ever in an RCT

- Run-in
  - Failures c/w:
    - eGFR < 60
    - lower SBP
    - higher NTproBNP
    - ischemic etiology

- Amyloid Beta
  - ↑ CSF soluble Aβ 1-38
  - ↔ Aβ 1-42, Aβ 1-40

- Endpoint selection
  - Adding ED visits and intensified therapies - same benefit

- Quality of life impact
  - Small (2 point) mitigation of KCCQ decline
Questions

- **Mode of death**
  - ↓ SCD (HR 0.80)
  - ↓ HF death (HR 0.79)

- **Tolerability**
  - More D/C with enalapril

- **Remodeling**
  - Serial echo data unavailable.
  - PA pressure, Biomarkers, Aortic stiffness?

- **Age**
  - No interaction

- **Background therapy**
  - No interaction with:
    - Diuretics
    - Digoxin
    - Beta blockers
    - MRAs
    - ICD +/-
    - Coronary revascularization
Questions

- Benefit relative to HF severity
  - Benefit similar with/without recent hospitalization
  - Benefit shown across MAGGIC and EMPHASIS scores
  - Influence of LVEF? Yes, but no interaction
  - Low dose achieved?
    - Higher risk population
    - Favored Sac/Val at similar HR (wider CI)
  - **Few Class IIIB/IV patients included** (n=60, 0.7%)
<table>
<thead>
<tr>
<th>Trial name</th>
<th>NCT/ISDNI</th>
<th>Population</th>
<th>Primary endpoint</th>
<th>Subjects</th>
<th>Duration</th>
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</thead>
<tbody>
<tr>
<td>PIONEER-HF</td>
<td>NCT02554890</td>
<td>Recent AHF (HFrEF)</td>
<td>Δ NT-proBNP</td>
<td>736</td>
<td>8 weeks</td>
</tr>
<tr>
<td>TRANSITION</td>
<td>NCT02661217</td>
<td>Inpatient AHF (HFrEF)</td>
<td>% taking max dose sac/val at 10 weeks</td>
<td>1000</td>
<td>26 weeks</td>
</tr>
<tr>
<td>HFN-LIFE</td>
<td>NCT02816736</td>
<td>NYHA Class IV HFrEF</td>
<td>Δ NT-proBNP</td>
<td>400</td>
<td>24 weeks</td>
</tr>
<tr>
<td>PROVE-HF</td>
<td>NCT02887183</td>
<td>NYHA Class II–IV HFrEF</td>
<td>Remodeling parameters</td>
<td>830</td>
<td>52 weeks</td>
</tr>
<tr>
<td>EVALUATE-HF</td>
<td>NCT02874794</td>
<td>NYHA Class I–III with hypertension</td>
<td>Δ aortic impedance</td>
<td>432</td>
<td>12 weeks</td>
</tr>
<tr>
<td>PARENT</td>
<td>NCT02788656</td>
<td>NYHA Class II–III HFrEF</td>
<td>Δ mean PA pressure</td>
<td>20</td>
<td>32 weeks</td>
</tr>
<tr>
<td>PARADISE-MI</td>
<td>NCT02924727</td>
<td>Post-MI LVEF ≤40% with risk factors</td>
<td>Time to CV death, HF hospitalization, or outpatient HF</td>
<td>4650</td>
<td>156 weeks</td>
</tr>
<tr>
<td>PARAGON-HF</td>
<td>NCT01920711</td>
<td>HFrpEF with elevated NTproBNP, structural heart disease</td>
<td>Rate of CV death and total HF hospitalizations</td>
<td>4600</td>
<td>57 months</td>
</tr>
<tr>
<td>UK HARP-III</td>
<td>ISRCTN 11958993</td>
<td>CKD with an eGFR between 20 and 60 mL/min/1.73 m2</td>
<td>Δ GFR</td>
<td>400</td>
<td>12 months</td>
</tr>
<tr>
<td>PERSPECTIVE</td>
<td>NCT02884206</td>
<td>HFrpEF with elevated NTproBNP, structural heart disease</td>
<td>Δ global cognitive composite score</td>
<td>520</td>
<td>36 months</td>
</tr>
<tr>
<td>AWAKE-HF</td>
<td>NCT02970669</td>
<td>NYHA Class II–IV HFrEF</td>
<td>Δ daily actigraphy</td>
<td>136</td>
<td>16 weeks</td>
</tr>
<tr>
<td>ENTRESTO-SAS</td>
<td>NCT02916160</td>
<td>LVEF ≤45%</td>
<td>Δ apnea–hypopnea index</td>
<td>100</td>
<td>3 months</td>
</tr>
<tr>
<td>Peripheral Arterial Disease Trial</td>
<td>NCT02636283</td>
<td>No HF. Claudication with ankle-brachial index ≤0.90 NYHA II–III, HFrEF</td>
<td>Treadmill walk until pain initiated % tolerating max dose</td>
<td>40</td>
<td>8 weeks</td>
</tr>
<tr>
<td>PARASAIL (Post-approval study)</td>
<td>NCT02690974</td>
<td>NYHA II–III, HFrEF</td>
<td>Combined clinical outcome</td>
<td>360</td>
<td>52 weeks</td>
</tr>
<tr>
<td>Pediatric trial</td>
<td>NCT02678312</td>
<td>Age &lt;18, NYHA II–IV, HFrEF</td>
<td>Combined clinical outcome</td>
<td>360</td>
<td>52 weeks</td>
</tr>
<tr>
<td>Japanese trial</td>
<td>NCT02468232</td>
<td>Same as PARADIGM</td>
<td>Time to CV death or HF hospitalization</td>
<td>220</td>
<td>40 months</td>
</tr>
<tr>
<td>PARABLE</td>
<td>NCT02682719</td>
<td>LVEF &gt;50%, elevated BNP, LAVI &gt;8 mL/m2</td>
<td>Δ left atrial volume index</td>
<td>250</td>
<td>18 months</td>
</tr>
<tr>
<td>PRIME</td>
<td>NCT02687932</td>
<td>LVEF 25–50% with secondary MR (EROA &gt;0.1 cm²)</td>
<td>Δ EROA</td>
<td>118</td>
<td>12 months</td>
</tr>
</tbody>
</table>
## Guidelines Update

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Class</th>
<th>LoE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use ACEi, ARB, <strong>OR ARNI</strong> in HFrEF to reduce mortality</td>
<td>I</td>
<td>B-R</td>
</tr>
<tr>
<td>Replace ACEi/ARB with ARNI in chronic HFrEF (NYHA II/III) with an adequate</td>
<td>I</td>
<td>B-R</td>
</tr>
<tr>
<td>blood pressure who are already tolerating a reasonable dose of ACE inhibitor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>or ARB.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do not administer ARNI within 36 hrs of ACEi</td>
<td>III</td>
<td>B-R</td>
</tr>
<tr>
<td>Do not administer ARNI in patients with history of angioedema</td>
<td>III</td>
<td>C-EO</td>
</tr>
</tbody>
</table>
Valsartan/Sacubitril Take Home Points

- 20% relative ↓ mortality c/w enalapril (NNT 36)
- Predominantly studied in NHYA II, III
- Guidelines recommend considering a switch
- Renders BNP less accurate (NTproBNP better)*
- Side effects: angioedema, hypotension
Heart Rate Lowering

- Increased HR tracks with mortality in HFrEF
  - $\uparrow$ oxygen demand
  - $\downarrow$ ventricular efficiency
  - $\downarrow$ ventricular relaxation / $\uparrow$ ischemia

- Beta blockers have inotropic and chronotropic effects in addition to remodeling effects

- Many patients are intolerant to beta blockers
  - Reactive airways
  - Hypotension with fatigue
HR Reduction and Outcomes

- Meta-regression data
  - Achieved HR reduction more strongly associated with mortality than beta blocker dose is

- HF ACTION
  - Inverse relationship between beta blocker dose and mortality as well as HR and mortality
  - Appears to be more beta blocker dose than HR

Am J Cardiol 2008;101:865–869
JACC Vol. 60, No. 3, 2012
JACC: HEART FAILURE VOL. 4, NO. 2, 2016
Ivabradine

Na$^+$

K$^+$

[Diagram showing the effect of Ivabradine on sodium and potassium ions]
SHIFT

- Ivabradine (up to 7.5 mg/d) vs. Placebo
- 6505 subjects, median f/u 22.9 mos
- Characteristics
  - NYHA II-IV
  - HF hospitalization within the past 12 mos
  - LVEF ≤ 35%
  - Sinus rhythm, HR ≥ 70 bpm

- Only 25% of SHIFT subjects were on optimal beta blocker dose
- Titration schedule between ivabradine and beta blockers not defined
- Raises systolic blood pressure (neutral on myocardial oxygen demand?)

NNT = 26 for HF hospitalization
ACC/AHA Guidelines Update

Use ivabradine to reduce HF hospitalization in patients:
- NYHA II-III HFrEF (LVEF ≤35%)
- On GDMT including a β-blocker at max tolerated dose
- Sinus rhythm with HR > 70 bpm or greater at rest

Ivabradine Take Home Points
- Reduced HF hospitalization, not mortality
- Raises BP (unique among HF drugs)
- Augments, but should not replace beta blockade
FUTURE MEDICAL THERAPY: HFREF
Treating Iron Deficiency

- Anemia and iron deficiency
  - Common in HF and associated with worse outcomes
  - Serum ferritin relatively elevated c/w inflammation

- Ferric carboxymaltose (IV) may improve quality of life and HF performance status (Class IIb)
  - Ferritin < 100 ng/ml or 100-300 ng/ml with Tsat < 20%
  - Independent of hemoglobin

- Oral iron replacement failed to improve VO2

- ESAs not recommended – thrombotic events (Class III)
Potassium Binders

**NEW TREATMENTS FOR HYPERKALEMIA:**
Patiromer (RLY5016) and Sodium zirconium cyclosilicate (ZS-9)

<table>
<thead>
<tr>
<th>Positive effects:</th>
<th>Side Effects:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Normalizes and maintains potassium levels</td>
<td>• Drug-drug interactions</td>
</tr>
<tr>
<td>• Efficacy in heart failure</td>
<td>• Edema (at high doses of ZS-9)</td>
</tr>
<tr>
<td>• Reduces aldosterone levels and blood pressure</td>
<td>• Constipation, diarrhea, flatulence, nausea</td>
</tr>
<tr>
<td></td>
<td>• Hypomagnesemia</td>
</tr>
<tr>
<td></td>
<td>• Hypokalemia</td>
</tr>
</tbody>
</table>

**Evidence gaps:**

- *Prevention* of hyperkalemia
- Limitation of RAASi optimization due to hypotension or worsening renal function
- Safety and efficacy of RAASi optimization in patients excluded from previous trials
- Safety and efficacy of RAASi use at higher doses than used in previous trials

No HF outcomes trials to date

SGLT-2 Inhibitors

A) Normal TGF
   - Appropriate afferent arteriole tone
   - Normal GFR
   - Appropriate Na+/glucose reabsorption

B) Impaired TGF
   - Elevated GFR
   - Afferent arteriole vasodilation
   - Increased Na+/glucose reabsorption

C) Restored TGF
   - Afferent arteriole constriction
   - Normalization of GFR
   - Increased Na+ delivery to macula densa
   - Glucosuria

Normal physiology
Hyperfiltration in early stages of diabetic nephropathy
SGLT-2 inhibition reduces hyperfiltration via TGF
SGLT-2 Inhibitors

- EMPAREG and CANVAS – reduced HF events
- Await outcomes trials of SGLT2 in HFpEF, HFrEF
## SGLT-2 and HF: More to Come

<table>
<thead>
<tr>
<th>Large randomized controlled clinical trials in patients with HF</th>
<th></th>
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</thead>
<tbody>
<tr>
<td><strong>DEFINE-HF (Dapagliflozin Effect on Symptoms and Biomarkers in Diabetes Patients With Heart Failure)</strong></td>
<td>Double-blind, placebo-controlled RCT (phase 4)</td>
<td>Dapagliflozin 10 mg daily vs placebo</td>
<td>12 wk</td>
<td>250 patients with HF (≥19 y)</td>
</tr>
<tr>
<td><strong>PRESERVED HF (Dapagliflozin in Type 2 Diabetes or Pre-diabetes, and Preserved Ejection Fraction Heart Failure)</strong></td>
<td>Double-blind, placebo-controlled RCT (phase 4)</td>
<td>Dapagliflozin 10 mg daily vs placebo</td>
<td>12 wk</td>
<td>320 patients with HF (≥19 y)</td>
</tr>
<tr>
<td><strong>DAPA-HF (Study to Evaluate the Effect of Dapagliflozin on Incidence of Worsening Heart failure or Cardiovascular Death in Patients with CHF)</strong></td>
<td>Double-blind, placebo-controlled RCT (phase 3)</td>
<td>Dapagliflozin 10 mg daily vs placebo</td>
<td>36 mo</td>
<td>4500 patients with HFrEF (≥18 y)</td>
</tr>
<tr>
<td><strong>EMPEROR-Preserved (Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction)</strong></td>
<td>Double-blind, placebo-controlled RCT (phase 3)</td>
<td>Empagliflozin 10 mg daily vs placebo</td>
<td>38 mo</td>
<td>4126 patients with HFrEF (≥18 y)</td>
</tr>
<tr>
<td><strong>EMPEROR-Reduced (Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction)</strong></td>
<td>Double-blind, placebo-controlled RCT (phase 3)</td>
<td>Empagliflozin 10 mg daily vs placebo</td>
<td>38 mo</td>
<td>2850 patients with HFrEF (≥18 y)</td>
</tr>
</tbody>
</table>

*Circulation. 2017;136:1643–1658. DOI: 10.1161/CIRCULATIONAHA.117.030012*
Empagliflozin

- Consider empagliflozin or liraglutide in patients with **established cardiovascular disease** to reduce the risk of mortality
- In patients with long-standing suboptimally controlled type 2 diabetes and **established atherosclerotic cardiovascular disease**, empagliflozin or liraglutide should be considered...to reduce cardiovascular and all-cause mortality when added to standard care.
Omecamtiv mecarbil

Trial data

- **COSMIC – Phase II**
  - 150 pts, NYHA II-III
  - Increased
    - Stroke volume
    - Systolic ejection time
  - Decreased
    - LVESD/LVEDD
    - HR
    - NTproBNP

- **GALACTIC – Phase III**
  - 8000 patients, NYHA II-IV
  - Time to death/HF

Lancet 2016; 388: 2895–903
DEVICE BASED THERAPIES FOR HF
ICD AND CRT
ICD and CRT Guidelines

Patient with cardiomyopathy on GDMT for ≥3 mo or on GDMT and ≥40 d after MI, or with implantation of pacing or defibrillation device for special indications

LVEF ≤35%

Evaluate general health status

Comorbidities and/or frailty limit survival with good functional capacity to <1 y

Continue GDMT without implanted device

Acceptable noncardiac health

Evaluate NYHA clinical status

NYHA class I
- LVEF ≤30%
- QRS ≥150 ms
- LBBB pattern
- Ischemic cardiomyopathy
- QRS ≤150 ms
- Non-LBBB pattern

NYHA class II
- LVEF ≤35%
- QRS ≥150 ms
- LBBB pattern
- Sinus rhythm
- LVEF ≤35%
- QRS 120-149 ms
- LBBB pattern
- Sinus rhythm
- LVEF ≤35%
- QRS ≤150 ms
- Non-LBBB pattern
- Sinus rhythm
- QRS ≤150 ms
- Non-LBBB pattern

NYHA class III & Ambulatory class IV
- LVEF ≤35%
- QRS ≥150 ms
- LBBB pattern
- Sinus rhythm
- LVEF ≤35%
- QRS 120-149 ms
- LBBB pattern
- Sinus rhythm
- LVEF ≤35%
- QRS ≤150 ms
- Non-LBBB pattern
- Sinus rhythm
- LVEF ≤35%
- QRS 120-149 ms
- Non-LBBB pattern
- Sinus rhythm

Special CRT Indications
- Anticipated to require frequent ventricular pacing (>40%)
- Atrial fibrillation, if ventricular pacing is required and rate control will result in near 100% ventricular pacing with CRT
DANISH at a glance

- 1116 subjects with nonischemic CM assigned to ICD or no ICD. CRT was allowed.
- Sudden cardiac death HR 0.50 (95% CI 0.21-0.82)
- All cause mortality HR 0.87 (95% CI 0.68 – 1.12)
- Curves merge ~ 7 years follow-up
- Younger (<59 y/o) subjects benefitted
Maybe we’re doing a good job?

Figure 1. Trends in the Rate of Sudden Death across Trial Groups over Time.

N Engl J Med 2017; 377:1793-1795
Subcutaneous ICDs

Pro:
- Avoids vascular space
- Avoids leads in heart

Con:
- No pacing capability
- Can’t incorporate CRT

Consider in:
- Younger
- At risk for bacteremia
- Vascular access issues
Multipoint Pacing

- Anatomic and electrophysiologic variability limits success of CRT
- Multi-point pacing may offer improvement
  - Improved LV hemodynamic performance
  - Improved dyssynchrony on echo
  - Await large outcomes trials
Decompensated Heart Failure

↑ PA Pressure

↑ RA Pressure
Abdominal Congestion
Cardio-renal Syndrome
Peripheral Edema

↓ Output
Confusion
ATN / HIH
Lactatemia

↑ LA Pressure
Dyspnea
Orthopnea / PND
Pulmonary Edema
The Problem

Pathophysiology of congestion

- Filling pressure increase
- Intrathoracic impedance changes
- Autonomic adaptation
- Weight change
- Symptoms
- Hospitalization

Limitations to other methods

- Telemonitoring (weights, symptoms) is ineffective – several RCTs, SRMA
- Intrathoracic impedance too sensitive (PPV < 20%)
- Exam accuracy limited (PPV/NPV range 40-60%)
- Serial BNP monitoring under-studied
CHAMPION Clinical Trial:


NNT = 4
Implantable Hemodynamic Monitoring

- Consider for reduction of HF hospitalization in patients with NYHA Class III patients hospitalized within the past year
  - To reduce subsequent HF hospitalization
  - Irrespective of LVEF
- Subgroup analysis demonstrates effective in:
  - HFpEF and HFrEF
  - COPD
  - CKD
THERAPIES FOR END STAGE HF
NYHA Class I

- ACEI, ARB’s, beta blocker. Diuretics if volume overload
- Treat hypertension, diabetes mellitus, coronary artery disease, dyslipidemia. Use ACE inhibitor (ACEI) or angiotensin receptor blocker (ARB)

NYHA Class II-III

- Refer for cardiac rehabilitation
- Mineralocorticoid receptor antagonist
- Hydralazine-nitrates in African Americans
- Evaluate for iron deficiency

NYHA Class III - IV

- Consider implantable monitoring device
- Consider ivabradine
- Consider sacubitril/valsartan (LCZ696)

NYHA Class IV

- End of life discussions
- Ventricular assist device
- Transplant
- Palliative care

Risk factor reduction, patient and family education
Triggers for Referral to HF specialist

- **I**: IV inotropes
- **N**: NYHA IIIB/IV or persistent elevated BNP
- **E**: End-organ dysfunction (Cr ≥ 1.8, BUN ≥ 43)
- **E**: Ejection fraction ≤ 35%
- **D**: Defibrillator shocks
- **H**: Hospitalizations > 1
- **E**: Edema despite escalating diuretics
- **L**: Low BP (≤ 90 mmHg), high HR
- **P**: Prognostic med changes (reduction in GDMT)
Advanced HF Options

- Heart Transplant
- Durable Mechanical Circulatory Support
- Palliation +/- IV Inotropes
- Medical optimization / valve interventions / clinical trials
Mortality in Advanced Heart Failure

Heart Transplant Eligibility

- Age up to 70
- Sufficient disease severity
  - Requirement for mechanical circulatory support
  - Requirement for intravenous inotropes
  - Severe functional limitation (low VO2 max)
  - High predicted mortality by risk models
- Acceptable end organ function
- Psychosocial stability
- Not very obese (BMI < 35 kg/m²)
Adult and Pediatric Heart Transplants
Number of Transplants by Year and Location
Adult and Pediatric Heart Transplants
Kaplan-Meier Survival by Age Group
(Transplants: January 1982 – June 2015)

Median survival (years): Adult=10.7; Conditional=13.2; Pediatric=16.1; Conditional=20.9

p<0.0001

Adult (N=113,758)
Pediatric (N=12,995)
Estimated “Opportunity” for Advanced HF

Figure 2  Current Estimate of the Number of Advanced HF Patients

This represents approximate number of potential VAD candidates. Data from Miller (3). HF = heart failure.
Heart Pumps
LVAD Eligibility

- Bridge to Transplant (BTT)
  - Satisfies transplant eligibility
  - Requires prolonged support to wait for transplant

- Destination Therapy (DT)
  - Ineligible for transplant
    - Reversible risk factors
    - Age
  - Satisfactory renal, right ventricular, liver function
LVAD Use

Chart 21-5. Number of patients receiving left ventricular assist devices in the United States, 2006 to 2014. Data derived from Kirklin et al. [77]
LVAD and Survival

Median survival on LVAD support is 4 years

Figure 9 Actuarial survival curves stratified by implant strategy and era. BTT, bridge to transplant; DT, destination therapy. The depiction is as shown in Figure 6.
LVAD Complications

Continuous Flow LVAD/BiVAD Implants: 2008 – 2013, n = 9372

Instantaneous Death Rate (Hazard) for selected causes

Causes of Death
- Infection
- Bleeding
- RHF
- Neurological
- Device Malfunction
- MSOF

Deaths/Month vs. Months post implant

Infection
- MSOF
- Device Malfunction
- RHF
- Bleeding
- Neurological
Contrasting Summary of Options

Life with an LVAD

How long might I live?
Patients usually live longer with an LVAD. After 1 year, about 8 out of 10 patients who got an LVAD are still alive.¹

80%

Alive  Dead

How might I feel?
Of those patients who get through surgery, many feel big improvements in heart failure symptoms—less shortness of breath, less swelling, and more energy.¹ Most survivors say they can do more.

Life without an LVAD

How long might I live?
Patients usually do not live as long without an LVAD. After 1 year, almost 2 out of 10 patients who did not get an LVAD are still alive.

17%

Alive  Dead

How might I feel?
What complications might occur?
1 year after surgery, about¹:
- 5 to 6 patients out of 10 are readmitted to the hospital. 55%
- 1 in 10 patients have a disabling stroke. 10%
- 2 in 10 develop a device-related infection. 20%
- 2 in 10 have a serious bleed that requires medical attention. 20%
- Nearly 1 in 10 need surgery again to replace the LVAD pump. 5%

What might occur if I don’t get an LVAD?
Most likely, patients will not be alive at 1 year.
- Patients will not have to be dependent on a machine to live.
- Patients can often leave the hospital earlier and spend their remaining time at home.
- Patients often decide to only take medicine to help with pain and other symptoms.
- Palliative care and hospice are available, but without an LVAD, patients might need these services sooner (see description on next page).

Present numbers in a digestible way
NEWER MEDICAL THERAPIES: HFPEF
Failed Agents in HFpEF

- Aldosterone Antagonists*
- ARB
- ACEi
- Sildenafil
- Isosorbide
TOPCAT...a tale of international intrigue

Figure 2. Kaplan–Meier Plots of Two Components of the Primary Outcome.
Nitric Oxide Signaling – Not Dead Yet

LUNGS
- Pulmonary arterial vasodilation
- ↑ PA compliance
- ↓ PCWP

HEART
- Coronary vasodilation
- ↑ Lusitropy
- ↓ Hypertrophy and Fibrosis

VASCULAR/MUSCLE
- Peripheral arterial vasodilation
- Improved oxygen delivery
- Δ Skeletal muscle metabolism

Inorganic sodium Nitrite

Lungs

Nitrites

Acidosis/hypoxia in skeletal and cardiac muscle

(Metalloproteins)

Nitric Oxide

Soluble Guanylate Cyclase

cGMP

HFpEF patient

Inorganic Nitrate

Salivary gland and oral bacteria

L-Arginine

oxygen

(Nitric oxide synthases)
ARNI

- PARAGON-HF
  - Sacubitril/Valsartan vs. Valsartan for HFpEF
  - N=4300
  - Cumulative CV death or HF hospitalization
  - Anticipated 2019
HFpEF Phenomapping

- **Group 1**
  - Exercise-induced
  - Dynamic studies (RHC)

- **Group 2**
  - Volume overload
  - Hospitalizations

- **Group 3**
  - Pulmonary HTN
  - RV dysfunction
HFpEF Device Therapy
HFpEF Summary of the Current Evidence

- Treat comorbidities
  - Hypertension
  - Atrial fibrillation
  - Metabolic disorders (Diabetes, Hyperlipidemia)
  - Coronary artery disease

- Treat volume overload with judicious diuretics

- Encourage exercise and weight loss

- Consider MRAs to reduce hospitalization

- Do not use nitrates or PDE5 inhibitors

- Consider PA pressure monitoring to reduce hospitalization
HEART FAILURE HOSPITALIZATION
The target – unnecessary readmission

- Hospital admissions are prognostically unfavorable and expensive
- Rising rate of HF readmission across the 1990s and early 2000s
- Desire to contain costs, improve outcomes

*JAMA.* 2010;303(21):2141-2147.
Medicare's Hospital Readmission Reduction Program

- Established by ACA in 2010, effective Oct 2012
- Age > 65 CMS population (HF, AMI, COPD, PNA)
- Excessive readmission as weighed against risk-standardized readmission ratio (RSRR)
  - RSRR fails to account for: race, SES, hospital mix
  - May penalizes hospitals serving the underserved
  - Risk standardized readmission and mortality rates correlated poorly
- Penalized for ALL CMS admissions
Hospitalization and Mortality

- Overall improving
- Racial disparities

---

**Admission**

Delta in trend in 2005 = -2.4 (95% CI: -4.4, -0.39); p=0.02

Delta in trend in 2009 = -1.0 (95% CI: -2.3, 0.30); p=0.14

**Mortality**

Delta in trend in 2005 = 0.41 (95% CI: -1.3, 2.1); p=0.64

Delta in trend in 2009 = 3.2 (95% CI: 1.9, 5.4); p=0.002

---

*Circ Cardiovasc Qual Outcomes. 2017;10:e003552 (J Am Heart Assoc. 2017;6:e006955. DOI: 10.1161/JAHA.117.006955.).*
Readmission Prediction

- **Patient Risk Factors for Readmission**
  - Modest predictive accuracy of multivariable models
  - Residual congestion
  - Cognitive dysfunction
  - Poor health literacy

- **Hospital Risk Factors for High Readmission Rate**
  - Low SES service areas
  - Lower hospital volume
  - Less extensive CV service line
Thank You
<table>
<thead>
<tr>
<th>Trial</th>
<th>Drug (mg)</th>
<th>Comparator (mg)</th>
<th>N</th>
<th>Year</th>
<th>All Death</th>
<th>HF/CV Death</th>
<th>HF/CV Hosp</th>
<th>Combined</th>
<th>Adverse Events</th>
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<tbody>
<tr>
<td>NETWORK</td>
<td>Enal. 10, 20</td>
<td>Enal. 5</td>
<td>1532</td>
<td>1998</td>
<td>Neutral</td>
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<td>N/A</td>
<td>N/A</td>
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<td>ATLAS</td>
<td>Lis. ~ 35</td>
<td>Lisin. ~ 5</td>
<td>3164</td>
<td>2000</td>
<td>Neutral</td>
<td>Neutral</td>
<td>24% RRR</td>
<td>12% RRR</td>
<td>HR 0.87 (0.76-0.98) ↓(NNT 31)</td>
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<tr>
<td>HEAAL</td>
<td>Los. 150</td>
<td>Los. 50</td>
<td>3846</td>
<td>2009</td>
<td>NS</td>
<td>N/A</td>
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<td></td>
<td>Cr ↑ (NNH 27), K ↑ (NNH 37)</td>
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<tr>
<td>CHARM-Added</td>
<td>Cand.</td>
<td>ACEi Alone</td>
<td>2548</td>
<td>2003</td>
<td>Neutral</td>
<td>↓ (NNT 28)</td>
<td>↓ (NNT 26)</td>
<td>↓ (NNT 23)</td>
<td>ARF, Dizziness</td>
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<td>ACEi Alone</td>
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<td>HypoTN, ARF</td>
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<td>1639</td>
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<td>Neutral</td>
<td>Harm in DM</td>
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<td>No Harm in DM</td>
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<td>Recommendation</td>
<td>Class</td>
<td>Level of Evidence</td>
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<tr>
<td>When there is a clear indication for an ICD but there is transient contraindication (e.g.: infection).</td>
<td>IIA</td>
<td>C</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>As bridge to definitive therapy such (e.g.: transplantation)</td>
<td>IIA</td>
<td>C</td>
<td></td>
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<tr>
<td>Temporizing in expectation of LV improvement, (e.g.: ischemic CM with recent revascularization, newly diagnosed nonischemic dilated cardiomyopathy in patients starting GDMT, secondary cardiomyopathy being treated).</td>
<td>IIb</td>
<td>C</td>
<td></td>
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</tr>
<tr>
<td>As bridging therapy in situations where ICDs have been shown to reduce SCD but not overall survival such as within 40 d of MI</td>
<td>IIb</td>
<td>C</td>
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<tr>
<td>Do not use when nonarrhythmic risk is expected to significantly exceed arrhythmic risk, particularly in patients who are not expected to survive &gt;6 mo</td>
<td>III</td>
<td>C</td>
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Piccini et al. Circulation 2016