Heart Failure: Advances in Treatment

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Disclosures: None

Facts about Heart Failure

<table>
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</thead>
<tbody>
<tr>
<td>Both Sexes</td>
<td>6.5 million</td>
<td>1 million</td>
<td>75, 251</td>
<td>900,000</td>
<td>30.7 Billion</td>
</tr>
<tr>
<td>Males</td>
<td>2.9</td>
<td>495,000</td>
<td>33,667</td>
<td></td>
<td></td>
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<tr>
<td>Females</td>
<td>3.6</td>
<td>505,000</td>
<td>41,584</td>
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E Benjamin, AHA Statement 2018 Heart and Stroke Disease Statistics

Evolution of Drugs for Heart failure

Drugs and Devices
PARADIGM – HF

McMurray et al. NEJM Aug 30, 2014
Symptomatic hypotension (14% versus 9.2%)
Discontinuation due to hypotension (non-significant)
Angioedema (19 vs. 10)
Hyperkalemia (>6)
Increased Creatinine (>2.5)
Cough
Discontinuation due to renal dysfunction

Cost effectiveness

<table>
<thead>
<tr>
<th>TABLE 2 Cost Inputs</th>
<th>Value</th>
<th>Range</th>
<th>Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medications, 3 months (71)</td>
<td>70</td>
<td>18-84</td>
<td>Gamma</td>
</tr>
<tr>
<td>Sacubitril-valsartan</td>
<td>1,140</td>
<td>889-1,435</td>
<td>Gamma</td>
</tr>
<tr>
<td>Hospitalization, per event (14)</td>
<td>10,698, 5,190-26,985</td>
<td>11,347, 4,732-22,994</td>
<td>Gamma</td>
</tr>
</tbody>
</table>

Values are in 2015 U.S. dollars. HF = heart failure.

LCZ696
Enalapril

Cost effectiveness

$45,017 per quality-adjusted life-year gained in the United States
**Current Guidelines:**

Angiotensin receptor - neprilysin inhibitor

- **I** - ARNI BR
- **II** - ARNI
- **III** - C-LO

In patients with chronic symptomatic HF-REF NYHA class II or III who tolerate an ACE inhibitor or ARB replacement by an ARNI; recommended to further reduce morbidity and mortality (13%).

ARNI should not be administered concomitantly with ACE inhibitors or within 36 hours of the last dose of an ACE inhibitor (31, 32).

ARNI should not be administered to patients with a history of angioedema.


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**Word of Caution:**

**Neprilysn and Alzheimer Disease**

- Neprilysn and Alzheimer Disease

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

A multicenter, randomized, double-blind, active-controlled trial to evaluate the effects of Entresto compared to valsartan on cognitive function as assessed by comprehensive neurocognitive battery and PET imaging in patients with chronic heart failure with preserved ejection fraction.

http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2015/207620Orig1s000ltr.pdf

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**Neprilysn and Alzheimer Disease**

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The timetable you submitted on July 6, 2015, states that you will conduct this trial according to the following schedule:

- Draft Protocol Submission: November 2015
- Final Protocol submission: April 2016
- Trial Completion: October 2021
- Final Report Submission: March 2022

http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2015/207620Orig1s000ltr.pdf

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**Heart Rate and Chronic Heart Failure**

- Individual studies do not show association of HR and outcomes
- Meta-analysis shows HR correlates with all-cause mortality and remodeling (Ann Intern Med. 2009;150:784-794)
- HF-ACTION results – β blocker dose (not HR) and improved mortality (J Am Coll Cardiol HF 2016;4:109–15)
**SHIFT trial**

- 6505 patients randomized to ivabradine vs. placebo

**Inclusion:**
- Stable for 4 weeks
- LVEF ≤ 35%
- Sinus rhythm
- Hospitalization for HF in last 12 months
- Guideline based therapy – special emphasis on uptitration of beta blockers

**SHIFT trial: points to ponder**

- 18% significant reduction in CVD death and first hospitalization
- 26% significant reduction in first hospitalization
- 9% non-significant reduction in CVD death

**SHIFT**

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- 9% non-significant reduction in CVD death

**SHIFT trial: points to ponder**

- 1% CRT, and 3% patients with ICD
- 75% on β blocker therapy, 26% on target dose and only 56% on >50% of target dose
- Subgroup analyses with baseline HR <75bpm – no effect; baseline HR >75 had 3% absolute risk reduction in all-cause mortality
- Subgroup of patients on <50% of target β blocker doses showed statistically significant reduction in CVD death or HF hospitalization with ivabradine

_Circulation. 2016;133:2066-2075_
Ivabradine - Contraindications

• Acute HF
• BP <90/50
• Sick sinus syndrome, sinoatrial block, 2nd or 3rd degree AV block
• Pacemaker dependence
• Atrial fibrillation
• Severe Hepatic disease
• Pregnancy
• CYP3A4 inhibitors (diltiazem, Verapamil, Grapefruit juice)

Current guidelines: Ivabradine

• Approved by FDA in 2015 for ≥70 beats/min for reduction in hospitalization alone
• Approved in Europe for ≥ 75 beats/min for reduction in CVD death and hospitalization

CardioMEMS - Management of Heart Failure

Advanced Therapies for HF

• Optimal medical therapy
• Cardiac Resynchronization Therapy (CRT)
• IV Inotropes
• VAD – ventricular assist device
• Transplant
• Palliative care
Advanced HF therapy Evaluation

CHAMPION trial – CardioMEMS

Eligible patients
- NYHA class III

Contraindication
- Infection, DVT/PE, eGFR <25 or dialysis
- Congenital or right sided mechanical valves
- CRT in the past 3 months
- Unable to take anticoagulants/dual antiplatelets
- BMI >35; chest circumference >165 cm

Heart Transplants in US

Heart Transplants:
Number of Transplants by Year and Location

NOTE: This figure includes only the heart transplants that were reported to the ISHLT Transplant Registry. As such, the presented data may not mirror the changes in the number of heart transplants performed worldwide.
Adult Heart Transplants
% of Patients Bridged with Mechanical Circulatory Support* (Transplants: January 2005 – December 2015)

LVAD: Left Ventricular Assist Device

Evolution of LVAD

Future VAD

Heartmate XVE

Synergy

Heartmate II

HeartWare

Heartmate III
Indications for LVAD

Indications: combination of the following:
- Frequent hospitalizations for heart failure
- NYHA class III-IV functional limitations despite maximal therapy
- Intolerance of neurohormonal antagonists
- Increasing diuretic requirement
- Symptomatic despite CRT
- Inotropic dependence
- Low peak VO₂ (<14-16)
- End-organ dysfunction attributable to low cardiac output

AHA statement. Circulation 2017

Supplemental Figure 6

Continuous Flow LVAD/BiVAD implants: 2008 – 2016, n=17633

Are you Glad to Have a VAD?

EQ5D Dimension: Self Care

Implant Era
Severe Problems
Mild Problems

Pre-Implant 3 mths
6 mths
12 mths
18 mths
24 mths

Continuous Flow LVAD/BiVAD implants: 2008 – 2016, n=17633

% with Problems

EQ5D Dimension: Self Care

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Supplemental Figure 9

35

24.6%
26.3%
22.4%
21.5%
20.9%
23.0%
29.7%
7.0%
4.2%
3.8%
4.0%
3.4%
0.0%
10.0%
20.0%
30.0%
40.0%
50.0%
60.0%
70.0%
80.0%
90.0%
100.0%

% with Problems

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Natural History of HF

Thank You!

University of Wisconsin Hospital and Clinics