Heart Failure
Medical and Surgical Treatment

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Burden of Heart Failure

Prevalence  5.7 million Americans >20-years old
            Lifetime risk at age 40 - 1:9 men, 1:6 women

Incidence  >825,000 new cases/year

Morbidity  12-15 million office visits
            6.5 million hospital days annually
            More than 1 million hospital discharges
            Most frequent cause of hospitalization (>65 yrs)
            $9 billion hospital costs (71% total health expen)

Mortality  20% 10-year survival in patients with symptoms
            50% diagnosed die within 5 years
            11% 30-day inpatient hospital mortality

American Heart Association. 2015  Heart Disease and Stroke Statistics Update
Risk Factors for Heart Failure

- Coronary Artery Disease
- Hypertension
- Diabetes
- Age
- Gender and Ethnicity
- Obesity
- Arrhythmias
Treatment
Lifestyle modification

- Risk factor modification
- Diet
- Fluid Limitation
- Monitoring weight daily
- Exercise
Treatment
Medications shown to improve survival

- hydralazine plus isosorbide dinitrate
- angiotensin converting enzyme (ACE) inhibitors
- β-Blockers (carvedilol, metoprolol succinate, bisoprolol)
- spironolactone
- angiotensin receptor blocker (ARB)
- sacubitril-valsartan (Entresto) *

* Limited Data
Neprilysin, a neutral endopeptidase, degrades several endogenous vasoactive peptides, including natriuretic peptides, bradykinin, and adrenomedullin.

Inhibition of neprilysin increases the levels of these substances, countering the neurohormonal over-activation that contributes to vasoconstriction, sodium retention, and maladaptive Angiotensin-Neprilysin Inhibition.

Vardeny et al. JACC: Heart Failure 2014;2(6):664
Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure

John J.V. McMurray, M.D., Milton Packer, M.D., Akshay S. Desai, M.D., M.P.H., Jianjian Gong, Ph.D., Martin P. Lefkowitz, M.D., Adel R. Rizkala, Pharm.D., Jean L. Rouleau, M.D., Victor C. Shi, M.D., Scott D. Solomon, M.D., Karl Swedberg, M.D., Ph.D., and Michael R. Zile, M.D., for the PARADIGM-HF Investigators and Committees*

ABSTRACT

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

A. Primary End Point

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

B. Death from Cardiovascular Causes

Hazard ratio, 0.80 (95% CI, 0.71–0.89)
P < 0.001

McMurray et al. NEJM 2014
PARADIGM-HF

C Hospitalization for Heart Failure

D Death from Any Cause

Hazard ratio, 0.79 (95% CI, 0.71–0.89)  
P<0.001

Hazard ratio, 0.84 (95% CI, 0.76–0.93)  
P<0.001

No. at Risk

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Days since Randomization</th>
</tr>
</thead>
<tbody>
<tr>
<td>LCZ696</td>
<td>0  180  360  540  720  900  1080  1260</td>
</tr>
<tr>
<td>Enalapril</td>
<td>4212  3883  3579  2922  2123  1488  853  236</td>
</tr>
<tr>
<td>LCZ696</td>
<td>4187  3922  3663  3018  2257  1544  896  249</td>
</tr>
<tr>
<td>Enalapril</td>
<td>4212  3883  3579  2922  2123  1488  853  236</td>
</tr>
</tbody>
</table>

McMurray et al. NEJM 2014
Dosage of LCZ696 (Entresto)

• ENTRESTO is contraindicated with concomitant use of an angiotensin-converting enzyme (ACE) inhibitor. If switching from an ACE inhibitor to ENTRESTO allow a washout period of 36 hours between administration of the two drugs.

• Patients previously taking an ACE inhibitor or ARB: The recommended starting dose of ENTRESTO is 49/51 mg twice-daily.

• Patients not taking an ACE inhibitor or ARB or previously taking low Doses of these agents: The recommended starting dose of ENTRESTO is 24/26 mg twice-daily.

• Double the dose of ENTRESTO after 2 to 4 weeks to the target maintenance dose of 97/103 mg twice daily, as tolerated.
<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>ACE: A</td>
<td>The clinical strategy of inhibition of the renin-angiotensin system with ACE inhibitors (Level of Evidence: A) (9-14), OR ARBs (Level of Evidence: A) (15-18), OR ARNI (Level of Evidence: B-R) (19) in conjunction with evidence-based beta blockers (20-22), and aldosterone antagonists in selected patients (23, 24), is recommended for patients with chronic HFREF to reduce morbidity and mortality.</td>
</tr>
<tr>
<td>I</td>
<td>ARNI: B-R</td>
<td>In patients with chronic symptomatic HFREF NYHA class II or III who tolerate an ACE inhibitor or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality (19).</td>
</tr>
<tr>
<td>III: Harm</td>
<td>B-R</td>
<td>ARNI should not be administered concomitantly with ACE inhibitors or within 36 hours of the last dose of an ACE inhibitor (31, 32).</td>
</tr>
<tr>
<td>III: Harm</td>
<td>C-EO</td>
<td>ARNI should not be administered to patients with a history of angioedema.</td>
</tr>
</tbody>
</table>
Treatment
Medications shown to improve symptoms

• diuretics
• digoxin
• ivabradine (Corlanor) *

* Limited Data
Ivabradine (Corlanor)
Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study

Karl Swedberg, Michel Komajda, Michael Böhm, Jeffrey S Borer, Ian Ford, Ariane Dubost-Brama, Guy Lerebours, Luigi Tavazzi, on behalf of the SHIFT Investigators*

**Ivabradine** is a specific inhibitor of the $I_f$ current in the sinoatrial node

Symptomatic heart failure and a left-ventricular ejection fraction of 35% or lower, were in sinus rhythm with heart rate 70 beats per min or higher, had a hospitalization for HF within the previous 12 months and were on stable background therapy including a beta-blocker when tolerated

Mean heart rate during the study in the total study population

Kaplan-Meier cumulative event curves for the primary composite endpoint of cardiovascular death or hospital admission for worsening heart failure

- Placebo (937 events)
- Ivabradine (793 events)

HR 0.82 (95% CI 0.75–0.90), p<0.0001

RR 18%
Kaplan-Meier cumulative event curves for (A) death from heart failure and (B) all-cause death


RR 26%
Effect of Ivabradine on LV Remodeling and Function

LVESVI ml/m²

Ivabradine

Placebo

Baseline

8 mos

Baseline

8 mos

7.0 ml/m²

p=0.0002

Tardif et al. ESC EHJ 2011
Effect of Ivabradine on LV Remodeling and Function

Baseline

8 mos

Ivabradine

Placebo

LVEF %

35
34.5
34
33.5
33
32.5
32
31.5
31
30.5
30
29.5

2.4
p=0.0003

Tardif et al. ESC EHJ 2011
### Recommendation for Ivabradine

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendation</th>
</tr>
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<tbody>
<tr>
<td>IIa</td>
<td>B-R</td>
<td>Ivabradine can be beneficial to reduce HF hospitalization for patients with symptomatic (NYHA class II-III) stable chronic HFrEF (LVEF ≤35%) who are receiving GDEM, including a beta blocker at maximum tolerated dose, and who are in sinus rhythm with a heart rate of 70 bpm or greater at rest (37-40).</td>
</tr>
</tbody>
</table>
Treatment
Device Treatment

- Continuous positive airway pressure (CPAP) for sleep apnea
- Implantable cardioverter defibrillator (ICD)
- Biventricular pacing
  Resynchronization Therapy (CRT)
Treatment
Surgical Treatment

• Mitral Valve Repair
• Other valvular replacement
• Coronary Artery Bypass Grafting
• Left Ventricular Assist Device (LVAD)
• Cardiac Transplantation
Heart Transplant: Gold-Standard

SURVIVAL (Years)

1967 (1 week)

Dr. Shumway

Dr. Barnard

Louis Washkanski
Adult and Pediatric Heart Transplants

Kaplan-Meier Survival
(Transplants: January 1982 – June 2015)

Median survival = 10.7 years;
Median survival conditional on surviving to 1 year = 13.3 years

N = 118,788
Adult and Pediatric Heart Transplants
Recipient Age Distribution by Era

- 1982-1998 (N=57,185)
- 1999-2008 (N=40,500)
- 2009-6/2015 (N=28,210)

p<0.0001
Limited Donors For Heart Transplantation

Patients on Transplant Wait List

Patients Transplanted

Number of Wait List Additions

Number of Heart Transplants

Adapted from: http://optn.transplant.hrsa.gov/latestData
Adult Heart Transplants

% of Patients Bridged with Mechanical Circulatory Support*
(Transplants: January 2000 – December 2014)

% of Patients

Year of Transplant


2016

* LVAD, RVAD, TAH, ECMO
HeartMate II

HeartWare
LVAD Function

Pulsatile LVADs
Continuous flow LVADs
Pump Function
Actuarial Survival
INTERMACS 2013

INTERMACS 2008-2013

- CF LVAD
  - 80%
  - 68 ± 4%
  - 55 ± 7%

- PF LVAD
  - 69%
  - 58 ± 5%

REMATCH, Medical Arm: 25%

IMPROVEMENTS with:
- DEVICES
- MANAGEMENT
LESS ADVANCED Illness (Patient Selection)

INTERMACS 2013 Annual Report
Definitions for Advanced Heart Failure

HF Association of European Society of Cardiology

- Severe HF symptoms (NYHA Class III/IV)
- Episodes of volume overload and/or low resting CO
- Objective evidence of myocardial dysfunction
  - Echo, cath, BNP/NT-proBNP
- Poor objective function capacity
  - Inability to exercise
  - 6 minute walk test <300m
  - Peak VO2<12-14 ml/kg/min
- More than one HF hospitalization in past 6 months
- Persistence of above despite optimal medical therapy
Conclusions

• Landscape of Advanced HF has changed due to emerging therapies

• Transplant remains the gold-standard therapy

• VAD therapies are undergoing increased implementation as device technology improves

• Increasing evidence that placement of VAD earlier in advanced heart failure is associated with better outcomes

• Simple clues to identify advanced HF
  • > 1 rehospitalization/ED visit within 6 months of admission
  • Unable to tolerate evidence based heart failure therapy (ACE/BBL)
  • Low SBP, renal insufficiency
  • Persistent congestion, dyspnea, NYHA Class III/IV symptoms
Thank you
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(904) 956-3272
Questions & Discussion