UNMET NEEDS IN THE MANAGEMENT OF HEART FAILURE

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HF is a complex syndrome involving multiple organ systems and is associated with high re-hospitalization and mortality rates

- HF is a chronic progressive condition, punctuated by acute episodes
- Each acute event results in further organ damage; myocardial and renal damage occurring during such episodes may contribute to progressive left ventricular and/or renal dysfunction
- Increasing frequency of acute events with disease progression leads to high rates of hospitalization and increased risk of mortality

Heart failure Mortality statistics

Mortality rates in heart failure are high even for patients compliant with the best available treatments

~50% DIE WITHIN 5 YEARS OF DIAGNOSIS

When heart failure symptoms are stabilised by current treatments, it may seem that patients are doing well, but the neurohormonal imbalance underlying heart failure is still silently occurring, resulting in disease progression.

The impact of heart failure on individuals is significant, and the worldwide prevalence is high


Evolution of heart failure therapy

Only the first approval time for each therapeutic class is shown.

a Recommended for AHF after stabilisation; b recommended for treatment of hypertension in patients with symptomatic HF (NYHA functional class II-IV) and LV systolic dysfunction; c Tolvaptan may be used to treat patients with resistant hyponatremia; d European Medical Agency has approved ivabradine for use in patients with a heart rate ≥75 bpm. May also be considered in patients with a contraindication to β-blockers.

ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; MRA: mineralocorticoid receptor antagonist; SNI: sinus node If channel inhibitor; VRA: vasopressin receptor antagonist

Have current treatments fulfilled all gaps in Heart failure management?

A. Yes
B. No
C. Not sure
Mortality in HFrEF remains high despite the introduction of new therapies that improve survival

- **Survival rates in chronic HF have improved with the introduction of new therapies**¹

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Reduction in relative risk of mortality vs placebo</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACEI*</td>
<td>16% (1.4% ARR; mean follow up of 41.4 months) SOLVD¹,²</td>
<td>1. McMurray et al. Eur Heart J 2012;33:1787–847; 2. SOLVD Investigators. N Engl J Med 1991;325:293–302; 3. ] [34% (6.0% ARR; mean follow up of 1.5 years) CIBIS-III²</td>
</tr>
<tr>
<td>MRA*</td>
<td>30% (11.0% ARR; mean follow up of 33.7 months) CHARMA-Alternative⁴</td>
<td></td>
</tr>
<tr>
<td>ARB*</td>
<td>17% (3.0% ARR; median follow up of 33.7 months) CHARMA-Alternative⁴</td>
<td></td>
</tr>
</tbody>
</table>

- **However, significant mortality remains — ~50% of patients die within 5 years of diagnosis**⁶⁻⁸

¹On top of standard therapy at the time of study (except in CHARMA-Alternative where background ACEI therapy was excluded). Patient populations varied between trials and as such relative risk reductions cannot be directly compared. SOLVD (Studies of Left Ventricular Dysfunction), CIBIS-II (Cardiac Insufficiency Bisoprolol Study II) and RALES (Randomized Aldactone Evaluation Study) enrolled chronic HF patients with LVEF ≤35%. CHARM-Alternative (Candesartan in Heart failure: Assessment of Reduction in Mortality and Morbidity) enrolled chronic HF patients with LVEF ≤40%.

ACEI=angiotensin-converting enzyme inhibitor; ARB=angiotensin receptor blocker; HF=heart failure; HFrEF=heart failure with reduced ejection fraction; LVEF=left ventricular ejection fraction; MRA=mineralocorticoid receptor antagonist

PHARMACOLOGICAL APPROACHES TO THE TREATMENT OF CHRONIC HF HAVE YET TO REALIZE THE POTENTIAL OF ENHANCING THE NATRIURETIC PEPTIDE SYSTEM
Decline in Systolic Function leads to Activation of Three Major Neurohormonal Systems

Natriuretic peptide system
- Vasodilation
- Blood pressure
- Sympathetic tone
- Natriuresis/diuresis
- Vasopressin
- Aldosterone
- Fibrosis
- Hypertrophy

Renin angiotensin aldosterone system
- Ang II
  - AT_1R
- Vasoconstriction
  - Blood pressure
  - Sympathetic tone
  - Aldosterone
  - Hypertrophy
  - Fibrosis

Sympathetic nervous system
- Epinephrine
- Noradrenaline
- α, β
  - β_1 receptors
- Vasoconstriction
  - RAAS activity
  - Vasoconstriction
  - Heart rate
  - Contractility

Evolution of pharmacologic approaches in HF: Neprilysin inhibition as a new therapeutic strategy in patients with HF1

NP system
- Vasodilation
- Blood pressure
- Sympathetic tone
- Natriuresis/diuresis
- Vasopressin
- Aldosterone
- Fibrosis
- Hypertrophy

NEP inhibitors: natriuretic and other vasoactive peptides enhancement

ACEI=angiotensin-converting enzyme inhibitor; Ang-angiotensin; ARB=angiotensin receptor blocker; AT_1=angiotensin type 1; HF=heart failure; MRA=mineralocorticoid receptor antagonist; NEP=neprilysin; NP=natriuretic peptide; NPR=natriuretic peptide receptor; RAAS=renin-angiotensin-aldosterone system; SNS=sympathetic nervous system

Natriuretic peptides have potential beneficial actions in HF

Release of ANP and BNP from heart and CNP in vasculature

↓ Sympathetic outflow
↓ Vasopressin
↓ Salt appetite and water intake

↑ Na⁺/H₂O loss
↓ Aldosterone
↓ Renin

↓ Hypertrophy
↓ Fibroblast proliferation

Vasodilation
↓ Systemic vascular resistance
↓ Pulmonary artery pressure
↓ Pulmonary capillary wedge pressure
↓ Right atrial pressure

Have there been treatment approaches to utilize the potential of enhancing the NP system?

A. Yes
B. No
C. Not sure
New Modalities in the treatment of Heart Failure patients

Approved HF agents

- Digitalis
- Diuretics
- Vasodilators
- Inotropes (dobutamine)
- MRA (spironolactone)
- ACEIs (captopril; enalapril)
- β-blockers (bisoprolol)
- If channel inhibitor (ivabradine)
- ACEIs (lisinopril; β-blockers/vasopril)
- ACEIs (ramipril; metoprolol)
- ARBs (candesartan; valsartan)
- MRA (eplerenone)
- H-ISDN (hydralazine and isosorbide dinitrate)

- Since the discovery of ANP in 1981, numerous agents have been adopted into clinical practice for treatment of chronic HF.
- Despite the known potential beneficial effects of the natriuretic peptide system, enhancing this system is not exploited by any currently approved chronic HF agents.

*Development terminated*

NOT ALL PHARMACOLOGICAL APPROACHES TO ENHANCE NP SYSTEM WERE SUCCESSFUL
WHAT ABOUT OTHER TREATMENT MODALITIES?
LCZ696 is a first-in-class angiotensin receptor neprilysin inhibitor (ARNI)

- **ARNI=angiotensin receptor neprilysin inhibitor; AT₁=angiotensin II type 1**
  - LCZ696 is a novel drug which delivers simultaneous neprilysin inhibition and AT₁ receptor blockade¹⁻³
  - LCZ696 is a salt complex that comprises the two active components²⁻³
    - sacubitril (AHU377) – a pro-drug; further metabolized to the neprilysin inhibitor LBQ657, and
    - valsartan – an AT₁ receptor blocker in a 1:1 molar ratio

². Andrew Yu, PhD, Sally Neel, PhD, Pury Chadbourn, PhD at All Translational and Pharmaceutical Affairs, LCZ696, a Novel Dual-Angiotensin Receptor-Neprilysin Inhibitor (ARNI), J Clin Pharmacol 2010;50:803–810

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**LCZ696 MECHANISM OF ACTION**
LCZ696 simultaneously inhibits nephrilysin (via LBQ657) and blocks AT₁ receptors (via valsartan)⁴⁻⁴

- Inactive fragments
- ANP, BNP, CNP, other vasoactive peptides

**Enhancing**
- Vasorelaxation
- Blood pressure
- Sympathetic tone
- Aldosterone levels
- Fibrosis
- Hypertrophy
- Natriuresis/diuresis

**Sacubitril (AHU377; pro-drug)**

**LBQ657 (NEP inhibitor)**

**Valsartan**

**RAAS**
- Angiotensinogen (liver secretion)
- Ang I
- Ang II
- AT₁ receptor

**Inhibiting**
- Vasoconstriction
- Blood pressure
- Sympathetic tone
- Aldosterone
- Fibrosis
- Hypertrophy

*Angiotensinogen liver secretion; Ang I; Ang II; AT₁ receptor


PARADIGM-HF STUDY
PROSPECTIVE COMPARISON OF ARNI WITH ACEI TO DETERMINE IMPACT ON GLOBAL MORTALITY AND MORBIDITY IN HEART FAILURE

A multicenter, randomized, double-blind, parallel-group, active-controlled study to evaluate the efficacy and safety of LCZ696 compared with enalapril on morbidity and mortality in patients with chronic HF and reduced ejection fraction.

PARADIGM-HF Study Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure
**PARADIGM-HF:**

- Is the first study to test the effect of LCZ696 on morbidity and mortality in patients with HFrEF
  
  - primarily evaluates whether simultaneous angiotensin receptor neprilysin inhibition with LCZ696 compared with enalapril, in addition to conventional HF treatment...
  
  - delays time to first occurrence of either CV death or HF hospitalization...
  
  - in patients with stable NYHA FC II–IV HF and reduced ejection fraction (LVEF ≤40%)

- Determined the place of the ARNI LCZ696 as an alternative to an ACEI (enalapril) in patients with chronic systolic HFrEF

- May change the approach to neurohormonal modulation in HFrEF

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**Paradigm study is comparing LCZ696 to ……………**

A. Placebo

B. Enalapril 10 mg bid

C. Not sure

- ARNI=angiotensin receptor neprilysin inhibitor;
- AT1=angiotensin II type 1
PARADIGM-HF: study design1-3

Randomization
n=8442

Double-blind Treatment period

Single-blind active run-in period

<table>
<thead>
<tr>
<th>Enalapril 10 mg BID*</th>
<th>LCZ696 100 mg BID</th>
<th>LCZ696 200 mg BID§</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 Weeks</td>
<td>1–2 Weeks</td>
<td>2–4 Weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LCZ696 200 mg BID§</td>
</tr>
<tr>
<td>Enalapril 10 mg BID#</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

On top of standard HFrEF therapy (excluding ACEIs and ARBs)

1. McMurray, Packer, Desai et al. Dual angiotensin receptor neprylisin inhibition as an alternative to angiotensin converting enzyme inhibition in patients with chronic systolic heart failure: rationale for and design of the Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF). Eur J Heart Fail 2013;15:1062-73

PARADIGM-HF: Key Inclusion Criteria

- Chronic HF NYHA FC II–IV with LVEF ≤40%*
- BNP (or NT-proBNP) levels as follows:
  - ≥150 (or ≥600 pg/mL), or
  - ≥100 (or ≥400 pg/mL) and a hospitalization for HFrEF within the last 12 months
- ≥4 weeks’ stable treatment with an ACEI or an ARB‡, and a β-blocker
- Aldosterone antagonist should be considered for all patients (with treatment with a stable dose for ≥4 weeks, if given)

*The ejection fraction entry criteria was lowered to ≤35% in a protocol amendment.
‡Dosage equivalent to enalapril ≥10 mg/day. ACEI=angiotensin-converting enzyme inhibitor; ARB=angiotensin receptor blocker; BNP=B-type natriuretic peptide; FC=functional class; HFrEF=heart failure; HFpEF=heart failure with preserved ejection fraction; NT-proBNP=N-terminal pro-B-type natriuretic peptide; NYHA=New York Heart Association; PARADIGM-HF=Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure.
Results

Overall 20% reduction in risk of CV death or unplanned HF hospitalization

<table>
<thead>
<tr>
<th>Days after randomization</th>
<th>Enalapril (n=4,212)</th>
<th>LCZ696 (n=4,187)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>HR: 0.80 (95% CI 0.73, 0.87)</td>
<td></td>
</tr>
<tr>
<td>180</td>
<td>p=0.0000002</td>
<td></td>
</tr>
</tbody>
</table>

At risk
Enalapril: 4,212 3,883 3,579 2,922 2,123 1,488 853 236
LCZ696: 4,187 3,922 3,863 3,018 2,257 1,544 896 249

1-sided p-value shown
CI=confidence interval; CV=cardiovascular; HR=hazard ratio


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Results
- Overall 20% reduction in risk of CV death alone and 21% reduction in risk of UHHF alone

1-sided p value shown
UHHF = unplanned hospitalization for heart failure

Results
- Overall 16% reduction in risk of all-cause death

1-sided p value shown
In patients who were alive, LCZ696 was also superior to enalapril in reducing ...

All of this while enalapril had:

i. fewer survivors, and
ii. greater intensification of therapy

SECONDARY ANALYSIS: CLINICAL PROGRESSION

Packer et al. Angiotensin receptor neprilysin inhibition compared with enalapril on the risk of clinical progression in surviving patients with HFrEF Circulation 2015;131:54–61
Lower proportion of HFrEF patients on LCZ696 were treated in the emergency department for worsening of HF (discharge without hospitalization)

- CI=confidence interval; HF=heart failure; HR=hazard ratio
- Packer M, McMurray JJ, Desai AS et al. Angiotensin receptor neprilysin inhibition compared with enalapril on the risk of clinical progression in surviving patients with heart failure Circulation 2015;131:54–61
Treatment with LCZ696 resulted in a lower likelihood of multiple hospitalizations for HF

<table>
<thead>
<tr>
<th>Number of admissions for HF</th>
<th>LCZ696 (N=4,187)</th>
<th>Enalapril (N=4,212)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>12.8%</td>
<td>8.8%</td>
</tr>
<tr>
<td>2</td>
<td>9.9%</td>
<td>7.9%</td>
</tr>
<tr>
<td>3</td>
<td>8.6%</td>
<td>6.9%</td>
</tr>
<tr>
<td>4+</td>
<td>3.9%</td>
<td>2.6%</td>
</tr>
</tbody>
</table>

29% fewer HFrEF patients were hospitalized more than once for HF with LCZ696 than with enalapril (n=170 and n=240, respectively; p=0.001)

CI=confidence interval; HF=heart failure; HFrEF=heart failure with reduced ejection fraction; HR=hazard ratio


The reduction in HF hospitalization with LCZ696 was evident within the first 30 days after randomization

<table>
<thead>
<tr>
<th>Number of patients at risk</th>
<th>Days after randomization</th>
</tr>
</thead>
<tbody>
<tr>
<td>LCZ696</td>
<td>Enalapril</td>
</tr>
<tr>
<td>4,187</td>
<td>N=4,212</td>
</tr>
<tr>
<td>4,174</td>
<td>4,192</td>
</tr>
<tr>
<td>4,153</td>
<td>4,166</td>
</tr>
<tr>
<td>4,140</td>
<td>4,143</td>
</tr>
</tbody>
</table>

HR 0.60 (95% CI: 0.38–0.94) p=0.027

CI=confidence interval; HF=heart failure; HR=hazard ratio

Lower proportion of patients treated with LCZ696 required intensification of outpatient HF therapy* (defined as treatment failure)

- Addition of a new drug for treatment of HF, intravenous therapy or increase in daily dose of diuretic for >1 month, prospectively defined as a treatment failure.

CI=confidence interval; HF=heart failure; HFrEF=heart failure with reduced ejection fraction; HR=hazard ratio

Packer M, McMurray JJ, Desai AS et al. Angiotensin receptor neprilysin inhibition compared with enalapril on the risk of clinical progression in surviving patients with heart failure Circulation 2015;131:54-61

PARADIGM-HF: POST-HOC ANALYSIS

Effects on quality of life (AHA congress, Orlando, FL, 07–11 Nov2015)
**Health-Related Quality of Life - Kansas City Cardiomyopathy Questionnaire**

- Health-related quality of life (HRQL) is a key target of therapy in the management of patients with CHF
- KCCQ: directly completed by the patient (patient-based); supplements NYHA Functional class (provider-based)

**HF Pathology**

- Oxygenation to tissues

**Signs & Symptoms**

- Fatigue
- Weakness
- Dyspnea

**Impacts**

- Decreased Physical abilities
- Worsening symptoms
- Social needs and self-help

**PRO**

- Kansas City Cardiomyopathy Questionnaire

**Concept**

- Physical Function
- Symptom domains
- Self efficacy/ social limitation

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**Between-treatment Analysis of Change* in KCCQ Summary Scores and all KCCQ Domains at 8 Months**

*Adjusted for baseline score and treatment

**LSM differences range from 0.79 – 1.69 favoring LCZ696 with p-values range from 0.05 to <0.001**

KCCQ – Kansas City Cardiomyopathy Questionnaire, LSM – Least squares mean, OS - Overall summary, CS- clinical summary

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Prospectively defined safety events

<table>
<thead>
<tr>
<th>Event, n (%)</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 SBP &lt;90 mmHg</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>139 (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/L</td>
<td>674 (16.1)</td>
<td>727 (17.3)</td>
<td>0.15</td>
</tr>
<tr>
<td>&gt;6.0 mmol/L</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 (adjudicated by a blinded expert committee)</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>Catecholamines or glucocorticoids without hospitalization</td>
<td>6 (0.1)</td>
<td>4 (0.1)</td>
<td>0.52</td>
</tr>
<tr>
<td>Hospitalized without 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>

Fewer patients in the LCZ696 group than in the enalapril group stopped their study medication because of an AE (10.7 vs 12.3%, p=0.03)

Adverse events leading to permanent study drug discontinuation

- Fewer patients in the LCZ696 group than in the enalapril group discontinued study drug due to an adverse event (10.7 vs 12.3%; p=0.03)
### Summary of results – safety

- The superiority of LCZ696 over enalapril was not accompanied by important safety concerns
- Fewer patients stopped their study medication because of an adverse event in the LCZ696 group than in the enalapril group
- There was no increase in the rate of discontinuation due to possible hypotension-related adverse effects, despite a higher rate of symptomatic hypotension in the LCZ696 group
- Fewer patients in the LCZ696 group developed renal impairment, hyperkalemia or cough than in the enalapril group
- The LCZ696 group had a higher proportion of patients with non-serious angioedema, but LCZ696 was not associated with an increase in serious angioedema

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### Conclusions from the PARADIGM-HF results publication

- “...angiotensin receptor-neprilysin inhibition with LCZ696 was superior to ACE inhibition alone in reducing the risks of death and of hospitalization for HF”
- “The magnitude of the beneficial effect of LCZ696, as compared with enalapril, on CV mortality was at least as large as that of long-term treatment with enalapril, as compared with placebo.”
- “This robust finding provides strong evidence that combined inhibition of the angiotensin receptor and neprilysin is superior to inhibition of the RAS alone in patients with chronic HF.”
- “...results are applicable to a broad spectrum of patients with HF, including those who are currently taking an ACE inhibitor or ARB or who are likely to be able to take such an agent without having unacceptable side effects.”
Commentary from the accompanying NEJM editorial

- “PARADIGM-HF may well represent a new threshold of hope for patients with HF”
- “Now, a novel drug, LCZ696, a dual inhibitor of angiotensin II receptor and neprilysin, may prove to be the first disruptive agent to the heart-failure treatment algorithm, which has remained essentially unchanged for a decade”
- “The beneficial results seen in PARADIGM-HF may apply to a wide spectrum of patients, even those who are currently receiving the best possible therapy”

HF=heart failure; PARADIGM-HF=Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure


THANK YOU