Guidelines and Beyond: New Drug Therapy for Heart Failure with Reduced Ejection Fraction

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Heart Failure Patients Are Difficult To Manage

50% of heart failure patients die within 5 years from diagnosis

20% of all cardiac admissions in Singapore

Most common cause of hospitalization and readmissions in patients > 65 years old

1 in 3 readmitted within 1 year

The vast majority of HF patients has 3 or more comorbidities
Effect of Vasodilator Therapy on Mortality in Chronic CHF Results of a Veterans Administration Cooperative Study (V-HEFT I)

- Multicenter, randomized, double-blind, placebo-controlled trial
- 642 men followed for an average of 2.3 years
- Patient History:
  - Men with impaired cardiac function and reduced exercise tolerance
  - All patients were taking digoxin and diuretics
- In addition to mortality, the follow-up data included EF, exercise tolerance and echocardiography

2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)

Developed with the special contribution of the Heart Failure Association (HFA) of the ESC

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What’s New In The 2016 Guideline?

- New term for patients with HF and a left ventricular ejection fraction (LVEF) that ranges from 40 to 49% — ‘HF with mid-range EF (HFmrEF)’
- Clear recommendations on the diagnostic criteria for HF with reduced EF (HFrEF), HFmrEF and HF with preserved EF (HFpEF);
- New algorithm for the diagnosis of HF in the non-acute setting
- Indications for the class of angiotensin receptor neprilysin inhibitors (ARNIs)
- Modified indications for cardiac resynchronization therapy (CRT)
- Recommendations aimed at prevention/delay of the development of overt HF
- New algorithm for diagnosis & treatment approach of acute HF based on the presence/absence of congestion/hypoperfusion
Definition of Heart Failure in 2016

HF is a clinical syndrome characterized by **typical symptoms** (e.g. breathlessness, ankle swelling and fatigue) that **may be accompanied by signs** (e.g. elevated jugular venous pressure, pulmonary crackles and peripheral oedema) **caused by a structural and/or functional cardiac abnormality**, resulting in a reduced cardiac output and/or elevated intracardiac pressures at rest or during stress.
Before: The 2 Faces of Heart Failure

Systolic Heart Failure

Diastolic Heart Failure
Increased prevalence of heart failure with normal EF

A. A large study of patients (n=4596) hospitalized with HF at a single institution over a 15 year period demonstrated that the percentage of patients who have a normal EF has increased over time

B. This was the result of an increased number of admissions for HF with a normal EF; the number of admissions for HF with reduced EF remained stable
HFpEF and HFrEF are associated with similarly high levels of mortality

• Survival rate among patients with a discharge diagnosis of HF in the USA was slightly higher among patients with HFpEF than those with HFrEF between 1987–2001\textsuperscript{1}
  
  - respective mortality rates were 29% and 32% at 1 year and 65% and 68% at 5 years

![Graph showing survival rates for HFrEF (LVEF <50%) and HFpEF (LVEF ≥50%) over 5 years.](image)

  - Survival rates for HFrEF (LVEF <50%) decrease more rapidly than for HFpEF (LVEF ≥50%), with a statistically significant difference (p=0.03)

• HFpEF is associated with significant morbidity and mortality, despite having a slightly higher survival rate compared with HFrEF\textsuperscript{2,3}

HF: heart failure; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; LVEF: left ventricular ejection fraction; USA: United States of America

Euroheart Failure
Distribution of LVEF in Hospital-diagnosed cases of HF across Europe

Percentage of patients

Left Ventricular Ejection Fraction (%)

11,015 pts in 115 hospitals in 24 countries

Cleland et al. Euroheart Survey EHJ 2003
## Current: HFpEF, HFmrEF & HFrEF

<table>
<thead>
<tr>
<th>Type of HF</th>
<th>HFrEF</th>
<th>HFmrEF</th>
<th>HFpEF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Criteria</td>
<td>Symptoms ± Signs</td>
<td>Symptoms ± Signs</td>
<td>Symptoms ± Signs</td>
</tr>
<tr>
<td>LVEF &lt;40%</td>
<td>LVEF 40-49%</td>
<td>LVEF ≥50%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1. Elevated levels of natriuretic peptides (BNP &gt;35 pg/ml and/or NT-proBNP &gt;15 pg/ml)</td>
<td>1. Elevated levels of natriuretic peptides (BNP &gt;35 pg/ml and/or NT-proBNP &gt;15 pg/ml)</td>
<td></td>
</tr>
</tbody>
</table>
|           | 2. At least one additional criterion:  
  • Relevant structural heart disease (LVH and/or LAE)  
  • Diastolic dysfunction | 2. At least one additional criterion:  
  • Relevant structural heart disease (LVH and/or LAE)  
  • Diastolic dysfunction |

* Signs may not be present in the early stages of HF (esp in HFpEF) and in patients treated with diuretics.
The Middle Child Syndrome

HFrEF

HFmrEF

HFpEF

Definite HFrEF (LVEF <40%)

Uncertain (40% ≤ LVEF <50%)

Definite HFpEF (LVEF ≥50%)

<table>
<thead>
<tr>
<th>Proportion of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>0%</td>
</tr>
<tr>
<td>50%</td>
</tr>
</tbody>
</table>
PATIENT WITH SUSPECTED HF
(non-acute onset)

ASSESSMENT OF HF PROBABILITY

1. Clinical history:
   - History of CAD (MI, revascularization)
   - History of arterial hypertension
   - Exposition to cardiotoxic drug/radiation
   - Use of diuretics
   - Orthopnoea / paroxysmal nocturnal dyspnoea

2. Physical examination:
   - Rales
   - Bilateral ankle oedema
   - Heart murmur
   - Jugular venous dilatation
   - Laterally displaced/broadened apical beat

3. ECG:
   - Any abnormality

All absent

Assessment of natriuretic peptides not routinely done in clinical practice

≥1 present

NATRIURETIC PEPTIDES

- NT-proBNP ≥125 pg/mL
- BNP ≥35 pg/mL

No

Yes

Normal

ECHOCARDIOGRAPHY

If HF confirmed (based on all available data):
determine aetiology and start appropriate treatment

HF unlikely: consider other diagnosis
Objectives of Pharmacological Therapy in HFrEF

• Reduce mortality

• Improve
  – clinical status
  – functional capacity
  – quality of life, prevent hospital admission

• Preventing HF hospitalization and improving functional capacity are important benefits to be considered in chronic heart failure
Landmark trials in patients with HFrEF


Percentages are relative risk reductions vs comparator

ACEI: angiotensin-converting-enzyme inhibitor; ARB: angiotensin receptor blocker; ARNI: angiotensin receptor neprilysin inhibitor; BB: beta blocker; CV: cardiovascular; HF: heart failure; HFrEF: heart failure with reduced ejection fraction; MRA: mineralocorticoid receptor antagonist. See notes for definitions of study names.
Pharmacological Therapy in HFrEF

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>An ACE-Id is recommended, in addition to a beta-blocker, for symptomatic patients with HFrEF to reduce the risk of HF hospitalization and death.</td>
<td>1</td>
<td>A</td>
</tr>
<tr>
<td>A beta-blocker is recommended, in addition an ACE-Id, for patients with stable, symptomatic HFrEF to reduce the risk of HF hospitalization and death.</td>
<td>1</td>
<td>A</td>
</tr>
<tr>
<td>An MRA is recommended for patients with HFrEF, who remain symptomatic despite treatment with an ACE-I and a beta-blocker, to reduce the risk of HF hospitalization and death.</td>
<td>1</td>
<td>A</td>
</tr>
</tbody>
</table>
Pharmacological Therapy in HFrEF

• ACEIs, MRAs and beta-blockers have been shown to improve survival and are recommended for the treatment of every patient.
• The use of diuretics should be modulated according to the patient’s clinical status.
• Beta-blockers and ACEIs are complementary, and can be started together as soon as the diagnosis of HFrEF is made.
• There is no evidence favouring the initiation of treatment with a beta-blocker before an ACEI has been started.
Mortality in HFrEF remains high despite 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>
</tr>
</thead>
<tbody>
<tr>
<td>ACEI(^*)</td>
<td>16% (4.5% ARR; mean follow up of 41.4 months)</td>
</tr>
<tr>
<td>\beta-blocker(^*)</td>
<td>34% (5.5% ARR; mean follow up of 1.3 years)</td>
</tr>
<tr>
<td>MRA(^*)</td>
<td>30% (11.0% ARR; mean follow up of 24 months)</td>
</tr>
<tr>
<td>ARB(^*)</td>
<td>17% (3.0% ARR; median follow-up of 33.7 months)</td>
</tr>
</tbody>
</table>

Drugs that inhibit the renin-angiotensin system have modest effects on survival

- However, significant mortality remains: ~50% of patients die within 5 years of diagnosis\(^6\)–\(^8\)

\(^*\)On top of standard therapy at the time of study (except in CHARM-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%.

Are Existing Neurohormonal Strategies Adequate?

NO!
Despite improvements in medical therapy, symptomatic HF still confers a 20-25% risk of premature death in the first 2.5 yrs after diagnosis, and 50% of these premature deaths are SCD (VT/VF).
Although it can be said that a heart failure patient in NYHA class II may have a higher risk of SCD, their relative annual risk of dying is less than the other NYHA classes.
Patient with symptomatic HFrEF

Therapy with ACE-I and beta-blocker (Up-titrated to maximum tolerated evidence-based doses)

Still symptomatic and LVEF ≤35%

Add MR antagonist (up-titrated to maximum tolerated evidence-based dose)

Still symptomatic and LVEF ≤35%

Able to tolerate ACEI (or ARB)

Sinus rhythm, QRS duration ≥130 msec

Sinus rhythm, HR ≥70 bpm

ARNI to replace ACE-I

Evaluate need for CRT

Ivabradine

These above treatments may be combined if indicated

Resistant symptoms

Yes

Consider digoxin or H-ISDN or LVAD, or heart transplantation

No

No further action required Consider reducing diuretic dose
Overactivation of the RAAS and SNS is detrimental in HFrEF and underpins the basis of therapy


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**Natriuretic peptide system**

- NPRs → NPs
- Vasodilation
  - Blood pressure ↓
  - Sympathetic tone ↓
  - Natriuresis/利尿
  - Vasopressin ↓
  - Aldosterone ↓
  - Fibrosis ↓
  - Hypertrophy ↓

**Sympathetic nervous system**

- Epinephrine
  - Norepinephrine
- α₁, β₁, β₂ receptors
- Vasoconstriction
  - RAAS activity ↑
  - Vasopressin ↑
  - Heart rate ↑
  - Contractility ↑

**Renin-angiotensin-aldosterone-system**

- Ang II → AT₁R
- Vasoconstriction
  - Blood pressure ↑
  - Sympathetic tone ↑
  - Aldosterone ↑
  - Hypertrophy ↑
  - Fibrosis ↑

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- The crucial importance of the RAAS is supported by the beneficial effects of ACEIs, ARBs and MRAs
- Benefits of β-blockers indicate that the SNS also plays a key role

ACEI: angiotensin-converting-enzyme inhibitor; Ang: angiotensin; ARB: angiotensin receptor blocker; AT₁R: angiotensin II type 1 receptor; MRA: mineralocorticoid receptor antagonist; NPs: natriuretic peptides; NPRs: natriuretic peptide receptors; RAAS: renin-angiotensin-aldosterone system; SNS: sympathetic nervous system
Natriuretic peptides have potential beneficial actions in heart failure

- Predominantly present in the heart and circulates in plasma
- Expression increases in the atrium and ventricle in cardiac hypertrophy

ANP

- Predominantly present in the heart and circulates in plasma
- Expression increases in the atrium and ventricle in cardiac hypertrophy
- Ventricular synthesis regulated by volume overload

BNP

- Predominantly present in the central nervous system (CNS) and vasculature
- Does not behave as a cardiac hormone – levels extremely low in circulation

CNP

Hemodynamic Effects of Nesiritide in HF Patients
A Randomized, Double-Blind, Placebo-Controlled Trial

Abraham WT et al. *J Cardiac Failure* 1998;4:37-44
One Enzyme — Neprilysin — Degrades Many Endogenous Vasoactive Peptides

Endogenous vasoactive peptides

(natriuretic peptides, adrenomedullin, bradykinin, substance P, calcitonin gene-related peptide)

Neprilysin

Inactive metabolites
Neprilysin Inhibition Potentiates Actions of Endogenous Vasoactive Peptides That Counter Maladaptive Mechanisms in Heart Failure

**Endogenous vasoactive peptides**
(natriuretic peptides, adrenomedullin, bradykinin, substance P, calcitonin gene-related peptide)

**Neprilysin**
Inactive metabolites

**Neprilysin inhibition**

- Neurohormonal activation
- Vascular tone
- Cardiac fibrosis, hypertrophy
- Sodium retention
The “Story” of augmentation of natriuretic peptides as a therapeutic strategy in HF


Stand-alone Neprilysin inhibition

- Tested enhancing the effects of natriuretic peptides by reducing their breakdown through neprilysin inhibition
  - E.g. candoxatril, thiorphan
  - Ultimately not developed for clinical use in heart failure

Omapatrilat (Neprilysin & ACE inhibition)

- Omapatrilat developed to both inhibit neprilysin and suppress the RAAS, via ACE inhibition
- Demonstrated a trend towards reduced morbidity and mortality in HFrEF
- Development was halted due to increased frequency of angioedema
LCZ696: Enhances natriuretic and other vasoactive peptides, & Suppress RAAS simultaneously

**ANP, BNP, CNP, other vasoactive peptides***

![](Image)

**Neprilysin**

Inactive fragments

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

**LBQ657** (NEP inhibitor)

**Valsartan**

**LCZ696**

**RAAS**

Angiotensinogen (liver secretion)

- Ang I
- Ang II

**AT₁ receptor**

**Enhancing**

- Vasorelaxation
- ↓ Blood pressure
- ↓ Sympathetic tone
- ↓ Aldosterone levels
- ↓ Fibrosis
- ↓ Hypertrophy
- ↑ Natriuresis/diuresis

*Neprilysin substrates listed in order of relative affinity for neprilysin: ANP, CNP, Ang II, Ang I, adrenomedullin, substance P, bradykinin, Endothelin-1, BNP

Natriuretic peptides have potential beneficial actions in HF

Heart failure: a state of “neurohumoral imbalance”

Endothelin
Aldosterone
Angiotensin II
Vasopressin

A paradigm shift: from “neurohumoral inhibition” to “neurohumoral modulation”

ANP
BNP
NO
Bradykinin
Prostacyclin

Endothelin
Aldosterone
Angiotensin II
Vasopressin

Vasoconstrictor/anti-natriuretic/pro-mitotic mediators
Vasodilator/natriuretic/anti-mitotic mediators

Vasoconstrictor/anti-natriuretic/pro-mitotic mediators
Vasodilator/natriuretic/anti-mitotic mediators
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 design**

**Randomization**
- **n=8442**

**Single-blind active run-in period**
- **Enalapril 10 mg BID**
- **LCZ696 100 mg BID**
- **LCZ696 200 mg BID**

**Double-blind Treatment period**
- **(1:1 randomization)**
  - **Enalapril 10 mg BID**
  - **LCZ696 200 mg BID**

**2 Weeks**
- **1–2 Weeks**
- **2–4 Weeks**

**Median of 27 months’ follow-up**

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*Enalapril 5 mg BID (10 mg TDD) for 1–2 weeks followed by enalapril 10 mg BID (20 mg TDD) as an optional starting run-in dose for those patients who are treated with ARBs or with a low dose of ACEI; 1200 mg TDD; 400 mg TDD; 20 mg TDD. McMurray et al. Eur J Heart Fail. 2013;15:1062–73; McMurray et al. Eur J Heart Fail. 2014;16:817–25; McMurray, et al. N Engl J Med 2014;*
Enalapril was chosen as the comparator to LCZ696 as the only ACEI shown to reduce mortality in a broad spectrum of HFrEF patients

- SOLVD-T showed enalapril benefit in NYHA class I–IV HFrEF
- Enalapril significantly reduced the risk of mortality vs placebo in this broad spectrum of patients with HFrEF

SOLVD-T trial

- NYHA I–IV, LVEF ≤35%, standard therapy
- Randomization
- Enalapril* 2.5–20 mg QD n=1285
- Placebo* n=1284
- Primary endpoint: All-cause mortality at follow-up

*On top of standard therapy for HF

Enalapril 10 mg BID was chosen as the appropriate comparator dose

- Enalapril 10 mg BID is the regulatory ‘gold-standard’ ACEI based upon CONSENSUS and SOLVD-T trial data\(^1\)–\(^3\)
  - The target dose in PARADIGM-HF was 10 mg BID, a dose comparable with that achieved in major HF trials using enalapril\(^3\)
  - The mean daily dose achieved in CONSENSUS and SOLVD-T was 18.4 and 16.6 mg, respectively\(^1,2\)

### Key HF trials with enalapril\(^*\)

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Target dose (mg)</th>
<th>Mean daily dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONSENSUS</td>
<td>127</td>
<td>20 BID</td>
<td>18.4</td>
</tr>
<tr>
<td>SOLVD-T</td>
<td>1285</td>
<td>10 BID</td>
<td>16.6</td>
</tr>
<tr>
<td>SOLVD-P</td>
<td>2111</td>
<td>10 BID</td>
<td>16.7</td>
</tr>
<tr>
<td>V-HeFT II</td>
<td>403</td>
<td>10 BID</td>
<td>15.0</td>
</tr>
<tr>
<td>OVERTURE</td>
<td>2884</td>
<td>10 BID</td>
<td>17.7</td>
</tr>
<tr>
<td>CARMEN</td>
<td>190</td>
<td>10 BID</td>
<td>16.8</td>
</tr>
</tbody>
</table>


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
PARADIGM-HF: Key exclusion criteria

- History of angioedema
- eGFR <30 mL/min/1.73 m² at screening, end of enalapril run-in or randomization, or a >35% decrease in eGFR between screening and end of enalapril run-in or between screening and randomization
- Serum potassium >5.2 mmol/L at screening OR >5.4 mmol/L at the end of the enalapril run-in or end of the LCZ696 run-in
- Requirement for treatment with both ACEI and ARBs
- Symptomatic hypotension, SBP <100 mmHg at screening, OR SBP <95 mmHg at end of enalapril run-in or at randomization
- Current acute decompensated HF
- History of severe pulmonary disease
- Acute coronary syndrome, stroke, transient ischemic attack, cardiac, carotid, or other major CV surgery, PCI, or carotid angioplasty within the 3 months prior to screening

PARADIGM-HF: Primary & Secondary objectives

- To evaluate the effect of LCZ696 200 mg BID compared with enalapril 10 mg BID, in addition to conventional HFrEF treatment, in delaying **time to first occurrence** of either **CV death** or **HF hospitalization**\(^1\)

- To assess whether LCZ696 was superior to enalapril in:
  - Improving quality of life (assessed by KCCQ score)
  - Delaying time to all-cause mortality
  - Delaying time to new-onset atrial fibrillation
  - Delaying time to decline of renal function as defined by:
    - 50% decline in eGFR from baseline, or
    - >30 mL/min/1.73 m\(^2\) decline in eGFR relative to baseline and to a value of <60 mL/min/1.73 m\(^2\) (indicating the development of moderate renal dysfunction), or
    - development of end-stage renal disease

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## PARADIGM-HF: Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>LCZ696 (n=4187)</th>
<th>Enalapril (n=4212)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>$63.8 \pm 11.5$</td>
<td>$63.8 \pm 11.3$</td>
</tr>
<tr>
<td>Women (%)</td>
<td>21.0%</td>
<td>22.6%</td>
</tr>
<tr>
<td>Ischemic cardiomyopathy (%)</td>
<td>59.9%</td>
<td>60.1%</td>
</tr>
<tr>
<td>LV ejection fraction (%)</td>
<td>$29.6 \pm 6.1$</td>
<td>$29.4 \pm 6.3$</td>
</tr>
<tr>
<td>NYHA functional class II / III (%)</td>
<td>71.6% / 23.1%</td>
<td>69.4% / 24.9%</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>122 ± 15</td>
<td>121 ± 15</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>72 ± 12</td>
<td>73 ± 12</td>
</tr>
<tr>
<td>N-terminal pro-BNP (pg/ml)</td>
<td>1631 (885-3154)</td>
<td>1594 (886-3305)</td>
</tr>
<tr>
<td>B-type natriuretic peptide (pg/ml)</td>
<td>255 (155-474)</td>
<td>251 (153-465)</td>
</tr>
<tr>
<td>History of diabetes</td>
<td>35%</td>
<td>35%</td>
</tr>
<tr>
<td>Digitalis</td>
<td>29.3%</td>
<td>31.2%</td>
</tr>
<tr>
<td>Beta-adrenergic blockers</td>
<td>93.1%</td>
<td>92.9%</td>
</tr>
<tr>
<td>Mineralocorticoid antagonists</td>
<td>54.2%</td>
<td>57.0%</td>
</tr>
<tr>
<td>ICD and/or CRT</td>
<td>16.5%</td>
<td>16.3%</td>
</tr>
</tbody>
</table>
PARADIGM-HF: Baseline NT-proBNP levels were higher compared with some recent HFrEF trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Median NT-proBNP (pg/mL)</th>
</tr>
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<tbody>
<tr>
<td>PARADIGM-HF</td>
<td>1608</td>
</tr>
<tr>
<td>Val-HeFT</td>
<td>861</td>
</tr>
<tr>
<td>COPERNICUS</td>
<td>1767</td>
</tr>
<tr>
<td>CORONA</td>
<td>1497</td>
</tr>
<tr>
<td>COMET</td>
<td>1242</td>
</tr>
<tr>
<td>CARE-HF</td>
<td>1814</td>
</tr>
</tbody>
</table>

- **NT-proBNP levels at baseline were:**
  - Higher compared with several recent HF trials
  - Lower than in trials with severely symptomatic patients with low LVEF (CARE-HF and COPERNICUS)

- **May reflect:**
  - Enrollment criteria
  - High proportion (24%) of patients with atrial fibrillation detected by ECG at baseline

- High NT-proBNP levels will help ensure anticipated rates of CV mortality and HF hospitalization occur
PARADIGM-HF: Cardiovascular Death or Heart Failure Hospitalization (Primary Endpoint)

Kaplan-Meier Estimate of Cumulative Rates (%)

Days After Randomization

Enalapril (n=4212)

LCZ696 (n=4187)

HR = 0.80 (0.73-0.87)

P = 0.0000002

Number needed to treat = 21

Patients at Risk

<table>
<thead>
<tr>
<th></th>
<th>LCZ696</th>
<th>Enalapril</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>4187</td>
<td>4212</td>
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<tr>
<td>180</td>
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<td>853</td>
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<td>1260</td>
<td>249</td>
<td>236</td>
</tr>
</tbody>
</table>
PARADIGM-HF: All-Cause Mortality

HR = 0.84 (0.76-0.93)  
P<0.0001

Kaplan-Meier Estimate of Cumulative Rates (%)

Patients at Risk

<table>
<thead>
<tr>
<th></th>
<th>LCZ696</th>
<th>Enalapril</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients at Risk</td>
<td>4187</td>
<td>4212</td>
</tr>
<tr>
<td>Days After Randomization</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>180</td>
<td>180</td>
</tr>
<tr>
<td></td>
<td>360</td>
<td>360</td>
</tr>
<tr>
<td></td>
<td>540</td>
<td>540</td>
</tr>
<tr>
<td></td>
<td>720</td>
<td>720</td>
</tr>
<tr>
<td></td>
<td>900</td>
<td>900</td>
</tr>
<tr>
<td></td>
<td>1080</td>
<td>1080</td>
</tr>
<tr>
<td></td>
<td>1260</td>
<td>1260</td>
</tr>
<tr>
<td>Days After Randomization</td>
<td>0</td>
<td>180</td>
</tr>
<tr>
<td></td>
<td>360</td>
<td>360</td>
</tr>
<tr>
<td></td>
<td>540</td>
<td>540</td>
</tr>
<tr>
<td></td>
<td>720</td>
<td>720</td>
</tr>
<tr>
<td></td>
<td>900</td>
<td>900</td>
</tr>
<tr>
<td></td>
<td>1080</td>
<td>1080</td>
</tr>
<tr>
<td></td>
<td>1260</td>
<td>1260</td>
</tr>
</tbody>
</table>

Enalapril  
(n=4212)  

LCZ696  
(n=4187)
Enalapril \((n=4212)\)

LCZ696 \((n=4187)\)

HR = 0.80 (0.71-0.89)  
\(P = 0.00004\)  
Number need to treat = 32
PARADIGM-HF: Cause/Mode of death

<table>
<thead>
<tr>
<th>Category</th>
<th>All causes</th>
<th>CV causes</th>
<th>Sudden</th>
<th>Worsening HF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events (Number)</td>
<td>835</td>
<td>711</td>
<td>693</td>
<td>311</td>
</tr>
<tr>
<td>HR</td>
<td>0.84</td>
<td>0.80</td>
<td>0.80</td>
<td>0.79</td>
</tr>
<tr>
<td>p</td>
<td>&lt; 0.001</td>
<td>0.00008</td>
<td>0.008</td>
<td>0.034</td>
</tr>
</tbody>
</table>

Legend:
- Black: Enalapril
- Blue: LCZ696
PARADIGM-HF: First HF and total repeat HF hospitalization

Proportion of patients:
- Enalapril: HR 0.79 (0.71, 0.89), p < 0.0001
- Sacubitril/valsartan: 658

Number of admissions including repeat episodes:
- Enalapril: RR 0.77 (0.67, 0.89), p = 0.0004
- Sacubitril/valsartan: 537
SUMMARY OF PRIMARY OUTCOME

- 20% reduction in CV death or HF hospitalization
- 21% reduction in HF hospitalization
- 20% reduction in CV mortality
NNT: Number Needed to Treat to Prevent

1 Primary Event

21

1 death from CV causes

32

Over the duration of 27 months over Enalapril
Prospectively defined safety events

<table>
<thead>
<tr>
<th>Event, n (%)</th>
<th>LCZ696 (n=4187)</th>
<th>Enalapril (n=4212)</th>
<th>p-value‡</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hypotension</strong></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><strong>Elevated serum creatinine</strong></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><strong>Elevated serum potassium</strong></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><strong>Cough</strong></td>
<td>474 (11.3)</td>
<td>601 (14.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Angioedema</strong> (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)
Angiotensin Receptor Neprilysin Inhibition With LCZ696 Doubles Effect on Cardiovascular Death of Current Inhibitors of the Renin-Angiotensin System

Effect of ARB vs placebo derived from CHARM-Alternative trial
Effect of ACE inhibitor vs placebo derived from SOLVD-Treatment trial
Effect of LCZ696 vs ACE inhibitor derived from PARADIGM-HF trial
For every 1000 patients switched from enalapril to sacubitril/valsartan, over a median of 27 months, there would be:

- 47 less primary end points (CV death or HF hospitalisations),
- 33 less CV deaths,
- 28 less first hospitalisations for HF,
- 53 less total hospitalisations for HF, and
- 32 less deaths from any cause.
WHO SHOULD BE PRESCRIBED ARNI?

- HFrEF in NYHA class II-IV, already optimized with Beta Blocker and MRA
- Systolic BP ≥100 mmHg
- eGFR ≥30 mL/min/1.73 m²
- Serum potassium ≤5.2 mmol/L

Avoid in pregnancy, severe kidney or hepatic dysfunction, known hypersensitivity or angioedema
Patient with symptomatic HFpEF

- Therapy with ACE-I and beta-blocker (up-titrate to maximum tolerated evidence-based doses)
  - Still symptomatic and LVEF ≤35%
    - Yes
    - Add MR antagonist (up-titrate to maximum tolerated evidence-based dose)
      - Yes
      - Still symptomatic and LVEF ≤35%
        - Able to tolerate ACEI (or ARB)
          - Sinus rhythm, QRS duration ≥130 msec
          - Sinus rhythm, HR ≥70 bpm
        - ARNI to replace ACE-I
        - Evaluate need for CRT
          - These above treatments may be combined if indicated
            - Yes
            - Consider digoxin or H-ISDN or LVAD, or heart transplantation
            - No
            - No further action required
  - No

Diuretics to relieve symptoms and signs of congestion

If LVEF ≤35% despite OMT or a history of symptomatic VT/VF, implant ICD
HOW SHOULD ARNI BE PRESCRIBED?

• Do not give in conjunction with another ARB/ACEI/Renin inhibitor
• Discontinuation period for at least 36 hours
• Start at 50/100 mg BID → 200 mg BID as tolerated
Perhaps it is more important to know what kind of patient has the disease, than what kind of disease has the patient ...

SIR WILLIAM OSLER
Eras of Heart Failure Therapy

Cardiorenal Hemodynamic | Neurohormonal | Biomechanical Neurohormonal

Interventions
- Diuretics
- Vasodilators
- Digitalis
- Inotropes
- ACE-I
- β-Blockers
- ARBs
- Aldosterone Antagonists
- HDZ/Isosorbide
- ICDs
- CRT
- CSD
- LVAD
- Repair and Regeneration
- Metabolism
- ARNI
- Ivabradine

And the plot thickens...
Remember This: Heart Failure Management More Than Just Drugs Or Clinical Trials

It’s About The Patient & His/Her Family