Δορυφορικό Συμπόσιο

“Ασθενείς με Καρδιακή Ανεπάρκεια με μειωμένο κλάσμα εξώθησης Προβληματισμοί και Λύσεις στην Κλινική Πρακτική”

Οι ARNIs ως νέα προοπτική στην αντιμετώπιση της Καρδιακής Ανεπάρκειας με μειωμένο κλάσμα εξώθησης Ανάλυση περιστατικών

Ξυδώνας Σωτήριος, MD, PhD, FESC
Β’ Καρδιολογικό Τμήμα, Γ.Ν.Α. «Ο Ευαγγελισμός»
Conflict of Interest

Bayer, Boehringer-Ingelheim, Boston Scientific, Elpen, Medtronic, Merck, Novartis, Pfizer, Servier

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- This presentation represents exclusively the views of the speaker.
- This presentation is accurate at the time of presentation.
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Prevalence of heart failure by sex and age

Acute events and progression of HF

- The increasing rate of acute events leads to high rates of hospitalization and high mortality risk.

Hospitalizations: 70-80% of total HF management
HF-rEF: The building blocks of therapy

<table>
<thead>
<tr>
<th>Rx</th>
<th>VAD</th>
<th>CRT</th>
<th>ICD</th>
<th>Beta-blocker</th>
<th>ACEI/ARB</th>
<th>MRA</th>
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<tbody>
<tr>
<td>Digoxin</td>
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</table>

Mortality reduction

CIBIS ↓34%
CHARM ↓17%
SOLVD ↓16%
RALES ↓30%

Drugs that inhibit the RAS have modest effects on survival.

Overactivation of the RAAS and SNS

**Natriuretic peptide system**

- NPRs ↔ NPs
- **Vasodilation**
  - ↓ Blood pressure
  - ↓ Sympathetic tone
  - ↑ Natriuresis/diuresis
  - ↓ Vasopressin
  - ↓ Aldosterone
  - ↓ Fibrosis
  - ↓ Hypertrophy

**RAAS inhibitors (ACEI, ARB, MRA)**

- Sacubitril
- Valsartan

**RAAS**

- Ang II
- AT₁, R

**SNS**

- Epinephrine
- Norepinephrine
- α₁, β₁, β₂ receptors

**Vasoconstriction**

- RAAS activity ↑
- Vasopressin ↑
- Heart rate ↑
- Contractility ↑

- β-blockers

- 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

Natriuretic Peptide System (NPS)

NP signaling and effects

- ANP
- BNP
- CNP

Sacubitril

- ANP
- BNP
- CNP

Valsartan

- Ang II
- AT₁ receptor

- Endocytosis
- Receptor recycling
- Inactivation of NPs

- Neurohormonal activation
- Vasodilation
- Cardiac fibrosis/hypertrophy
- Natriuresis/diuresis

- Vasoconstriction
- Cardiac fibrosis/hypertrophy
- Sodium/water retention

PARADIGM-HF: study design

Randomization
(N=8,442 patients with chronic HF [NYHA Class II–IV with LVEF ≤40%*]
and elevated NT-proBNP or BNP)

Double-blind randomized treatment period

LCZ696 200 mg BID‡

Enalapril 10 mg BID§

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

Testing tolerability to target doses of
enalapril and LCZ696

Enalapril 10 mg BID**
LCZ696 100 mg BID†
LCZ696 200 mg BID‡

Single-blind run-in period

Primary outcome: CV death or HF hospitalization
(event driven: 2,410 patients with primary events)

Duration: 4.3yrs
Median follow-up: 27 months

*The ejection fraction entry criteria was lowered from ≤40% to ≤35% in a protocol amendment on Dec 15, 2010 (12 months); **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; †200 mg TDD; ‡400 mg TDD; §20 mg TDD. There were 2 short washout periods during the run-in periods to minimize the potential risk of angioedema due to overlapping ACE inhibition and NEP inhibition at Visit 3 and Visit 5: (i) enalapril was stopped a day prior to starting LCZ696 at Visit 3 and (ii) LCZ696 was stopped a day prior to starting randomized study drug at Visit 5.

PARADIGM-HF: Key inclusion criteria

- Chronic HF NYHA 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 EF entry criteria was lowered to ≤35% in a protocol amendment
PARADIGM-HF: Key exclusion criteria

- History of angioedema
- eGFR <30 mL/min/1.73 m$^2$ 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
## Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>LCZ696 (n=4187)</th>
<th>Enalapril (n=4212)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years</strong></td>
<td>63.8 ± 11.5</td>
<td>63.8 ± 11.3</td>
</tr>
<tr>
<td><strong>Women, n (%)</strong></td>
<td>879 (21.0)</td>
<td>953 (22.6)</td>
</tr>
<tr>
<td><strong>Ischemic cardiomyopathy, n (%)</strong></td>
<td>2506 (59.9)</td>
<td>2530 (60.1)</td>
</tr>
<tr>
<td><strong>LV ejection fraction, %</strong></td>
<td>29.6 ± 6.1</td>
<td>29.4 ± 6.3</td>
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<tr>
<td><strong>NYHA functional class, n (%)</strong></td>
<td></td>
<td></td>
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<tr>
<td>II</td>
<td>2998 (71.6)</td>
<td>2921 (69.3)</td>
</tr>
<tr>
<td>III</td>
<td>969 (23.1)</td>
<td>1049 (24.9)</td>
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<td><strong>SBP, mmHg</strong></td>
<td>122 ± 15</td>
<td>121 ± 15</td>
</tr>
<tr>
<td><strong>Heart rate, beats/min</strong></td>
<td>72 ± 12</td>
<td>73 ± 12</td>
</tr>
<tr>
<td><strong>NT pro-BNP, pg/mL (IQR)</strong></td>
<td>1631 (885–3154)</td>
<td>1594 (886–3305)</td>
</tr>
<tr>
<td><strong>BNP, pg/mL (IQR)</strong></td>
<td>255 (155–474)</td>
<td>251 (153–465)</td>
</tr>
<tr>
<td><strong>History of diabetes, n (%)</strong></td>
<td>1451 (34.7)</td>
<td>1456 (34.6)</td>
</tr>
<tr>
<td><strong>Treatments at randomization, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diuretics</td>
<td>3363 (80.3)</td>
<td>3375 (80.1)</td>
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<tr>
<td>Digitalis</td>
<td>1223 (29.2)</td>
<td>1316 (31.2)</td>
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<td>β-blockers</td>
<td>3899 (93.1)</td>
<td>3912 (92.9)</td>
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<tr>
<td>Mineralocorticoid antagonists</td>
<td>2271 (54.2)</td>
<td>2400 (57.0)</td>
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<tr>
<td>ICD</td>
<td>623 (14.9)</td>
<td>620 (14.7)</td>
</tr>
<tr>
<td>CRT</td>
<td>292 (7.0)</td>
<td>282 (6.7)</td>
</tr>
</tbody>
</table>
PARADIGM-HF: Outcomes

Death from CV causes or first hospitalization for HF

Hazard ratio = 0.80 (95% CI: 0.73–0.87)
p<0.0000004

Days since randomization

Cumulative probability

No at risk

<table>
<thead>
<tr>
<th>Days since randomization</th>
<th>LCZ696</th>
<th>4187</th>
<th>3922</th>
<th>3663</th>
<th>3018</th>
<th>2257</th>
<th>1544</th>
<th>896</th>
<th>249</th>
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</thead>
<tbody>
<tr>
<td></td>
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<td>4212</td>
<td>3883</td>
<td>3579</td>
<td>2922</td>
<td>2123</td>
<td>1488</td>
<td>853</td>
<td>236</td>
</tr>
</tbody>
</table>

**PARADIGM-HF: Outcomes**

Death from CV causes

Hazard ratio = 0.80 (95% CI: 0.71–0.89)  
*p<0.001*

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**Cumulative probability**

- Enalapril
- LCZ696

**Days since randomization**

0 180 360 540 720 900 1080 1260

**No at risk**

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>180</th>
<th>360</th>
<th>540</th>
<th>720</th>
<th>900</th>
<th>1080</th>
<th>1260</th>
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</thead>
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<td>3282</td>
<td>2478</td>
<td>1716</td>
<td>1005</td>
<td>280</td>
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<tr>
<td>Enalapril</td>
<td>4212</td>
<td>4051</td>
<td>3860</td>
<td>3231</td>
<td>2410</td>
<td>1726</td>
<td>994</td>
<td>279</td>
</tr>
</tbody>
</table>
PARADIGM-HF: Outcomes

First hospitalization for HF

Hazard ratio = 0.79 (95% CI: 0.71–0.89) p<0.001

Cumulative probability

Days since randomization

No at risk

<table>
<thead>
<tr>
<th></th>
<th>LCZ696</th>
<th>Enalapril</th>
</tr>
</thead>
<tbody>
<tr>
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<td>4187</td>
<td>4212</td>
</tr>
<tr>
<td>180</td>
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<td>3883</td>
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<tr>
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<td>2922</td>
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<td>896</td>
<td>853</td>
</tr>
<tr>
<td>1260</td>
<td>249</td>
<td>236</td>
</tr>
</tbody>
</table>

Reduction in HF hospitalization in the first 30 days

HR 0.60 (95% CI: 0.38–0.94)  
p=0.027

Kaplan-Meier estimate of cumulative rate

Days after randomization

Number of patients at risk
LCZ696  4,187  4,174  4,153  4,140
Enalapril  4,212  4,192  4,166  4,143

PARADIGM-HF: Outcomes

HF hospitalizations

Reduction in HF hospitalization regardless of previous HF admissions

- Sacubitril/Valsartan (N=4,187)
- Enalapril (N=4,212)

29% hospitalized more than once for HF
(n=170 vs. n=240, p=0.001)

HR 0.79 (95% CI: 0.71-0.89) p<0.001

Patients (%)

Number of patients hospitalized for ADHF

HF Rehospitalizations

- 1:
  - Sacubitril/Valsartan: 12.8%, p<0.001
  - Enalapril: 8.8%, p<0.001
- 2:
  - Sacubitril/Valsartan: 9.9%
  - Enalapril: 2.6%
- 3:
  - Sacubitril/Valsartan: 3.4%
  - Enalapril: 0.8%
- ≥4:
  - Sacubitril/Valsartan: 1.3%
  - Enalapril: 0.6%
Clinical benefits of LCZ696 over enalapril

Key clinical outcomes in PARADIGM-HF

<table>
<thead>
<tr>
<th>Primary outcome</th>
<th>HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death or HFH</td>
<td>0.80 (0.73, 0.87)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CV death</td>
<td>0.80 (0.71, 0.89)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HFH</td>
<td>0.79 (0.71, 0.89)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Secondary outcome</th>
<th>HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause death</td>
<td>0.84 (0.76, 0.93)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other outcomes</th>
<th>HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment for outpatient worsening</td>
<td>0.84 (0.74, 0.94)</td>
<td>0.003</td>
</tr>
<tr>
<td>ED visit for HF</td>
<td>0.66 (0.52, 0.85)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CV hospitalization</td>
<td>0.88 (0.81, 0.95)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>All-cause hospitalization</td>
<td>0.88 (0.82, 0.94)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ICU admission</td>
<td>0.87 (0.78, 0.98)</td>
<td>0.019</td>
</tr>
</tbody>
</table>

Cause of death

![Bar graph showing cause of death by NYHA class]

- **SCD**
- **CHF**
- **Other**

**Deaths (%)**

- **NYHA II**
- **NYHA III**
- **NYHA IV**

**MERIT-HF Lancet 1999;353: 2001-07.**
CV deaths account for 80% of all deaths in PARADIGM

Mortality benefit is related to decrease of HF death and Sudden death

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>Sacubitril/Valsartan (N=4,187)</th>
<th>Enalapril (N=4,212)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cause death</td>
<td>711</td>
<td>835</td>
</tr>
<tr>
<td>HF death</td>
<td>558</td>
<td>693</td>
</tr>
<tr>
<td>Sudden death</td>
<td>250</td>
<td>311</td>
</tr>
<tr>
<td>HF deterioration</td>
<td>147</td>
<td>184</td>
</tr>
</tbody>
</table>

HR=0.84 (95% CI: 0.76–0.93) p=0.001

HR*=0.80 (95% CI: 0.71–0.89) p<0.001

HR=0.80 (95% CI: 0.68–0.94) p=0.008

HR=0.79 (95% CI: 0.64–0.98) p=0.034

Mortality benefit

Stable mortality reduction

**Sudden death**

- **Enalapril**
- **Sacubitril/valsartan**

$HR = 0.80 \ (0.68, 0.94)$

$P = .008$

**Death due to worsening HF**

- **Enalapril**
- **Sacubitril/valsartan**

$HR = 0.79 \ (0.64, 0.98)$

$P = .034$
Mortality benefit

Stable mortality reduction

Shocks

VT / NSVT

### Pre-specified subgroup analysis for the primary endpoint

<table>
<thead>
<tr>
<th>Subgroup, n patients</th>
<th>LCZ696</th>
<th>Enalapril</th>
<th>Hazard Ratio* (95%CI)</th>
<th>P value for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>4187</td>
<td>4212</td>
<td></td>
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</tr>
<tr>
<td>Age</td>
<td></td>
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<tr>
<td>&lt;65 years</td>
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<td>≥65 years</td>
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<td>Age</td>
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<td>&lt;75 years</td>
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<td>≥75 years</td>
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Pre-specified subgroup analysis for the primary endpoint

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>LCZ696</th>
<th>Enalapril</th>
<th>Hazard Ratio* (95%CI)</th>
<th>P value for interaction</th>
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<tbody>
<tr>
<td>All patients</td>
<td>4187</td>
<td>4212</td>
<td></td>
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<tr>
<td>NT-proBNP</td>
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<tr>
<td>≤Median</td>
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<td>&gt;Median</td>
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<td>Yes</td>
<td>2607</td>
<td>2667</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time since diagnosis of HF</td>
<td></td>
<td></td>
<td></td>
<td>0.27</td>
</tr>
<tr>
<td>&lt;1 year</td>
<td>1275</td>
<td>1248</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;1 to 5 years</td>
<td>1621</td>
<td>1611</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;5 years</td>
<td>1291</td>
<td>1353</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Figure 3. Treatment effect of sacubitril/valsartan by tertile of left ventricular ejection fraction for all outcomes (upper left, primary endpoint; upper right, cardiovascular death; lower left, HF hospitalization; lower right, all-cause death). CV indicates cardiovascular; and HF, heart failure.
## Treatment effect by Dosing

### Dose reached

Sacubitril/Valsartan vs. Enalapril

<table>
<thead>
<tr>
<th>Dose reached</th>
<th>Events (n)</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>200 mg bd vs 10 mg bd</td>
<td>1262</td>
<td>0.79 (0.71–0.88); P&lt;0.001</td>
</tr>
<tr>
<td>100–200 mg bd vs 5–10 mg bd</td>
<td>541</td>
<td>0.80 (0.67–0.94); P=0.008</td>
</tr>
<tr>
<td>&lt;100 mg bd vs &lt;5 mg bd</td>
<td>225</td>
<td>0.76 (0.58–0.99); P=0.043</td>
</tr>
</tbody>
</table>

## 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 **LCZ696 group** than in **enalapril group** stopped their medication because of **AE** (10.7 vs 12.3%, p=0.03)
• 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 – efficacy

• **Primary outcome**
  • 20% reduction in **CV death or HF hospitalization**
  • 20% reduction in **CV mortality**
  • 21% reduction in **HF hospitalization**

• **Secondary outcomes**
  • 16% reduction in **all-cause mortality**
  • **LCZ696** superior to enalapril in reducing symptoms and physical limitations of HF (indicated by **KCCQ score**)
  • No significant difference in incidence of new onset **AF**
  • No significant difference in protocol-defined **decline in renal function**
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, hyperkalaemia 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

Effect on CV death

- ARB\textsuperscript{[a]}
- ACE Inhibitor\textsuperscript{[b]}
- Angiotensin Neprilysin Inhibition\textsuperscript{[c]}

% Decrease in Mortality

- 15%
- 18%
- 20%
NNT to Reduce Any-Cause Mortality

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

Able to tolerate ACEI (or ARB)\textsuperscript{f,g}

\textbf{ARNI to replace ACE-I}

Sinus rhythm, QRS duration \(\geq 130 \text{ msec}\)

\textbf{Evaluate need for CRT}\textsuperscript{i,j}

Sinus rhythm,\textsuperscript{h} HR \(\geq 70 \text{ bpm}\)

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
2016 ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure: An Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure

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.

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

Treatment with beta-blocker, MRA and sacubitril/valsartan reduces the risk of sudden death and is recommended for patients with HFrEF and ventricular arrhythmias (as for other patients) (see Section 7).
Κλινικό περιστατικό
Άνδρας, 46 ετών

- Καρδιακή ανεπάρκεια V
  LVEF=30%, με διάταση LV 62mm, MR 1+/4+

- Ισχαιμική μυοκαρδιοπάθεια
  πρόσθιο εκτεταμένο έμφραγμα μυοκαρδίου (2016), πρωτογενής PCI στον LAD, χωρίς υπολειπόμενες βλάβες

- Νοσηλεία για απορρύθμιση KA (5/2017)
  Σταθερή NYHA II έκτοτε V

- Φαρμακευτική αγωγή χωρίς αλλαγές από 8/2017 V
  Ramipril 5mg od, Bisoprolol 5mg od, Spironolactone 50mg od, Frusemide 40mg bd,
  Aspirin 100mg od, Ticagrelor 90mg bd

- 122/58mmHg, 68bpm V
- NT-proBNP 1688pg/ml V
- e-GFR 82ml/min/1,73m² V

Μπορούμε να κάνουμε κάτι ακόμα, γιατρέ;
Stable patient

Enalapril group in PARADIGM-HF: ACE inhibitor 100%, beta-blocker 93%, MRA 57%, digitalis 31%

Primary composite endpoint: CV death or HF hospitalization

Expanded composite: CV death, HF hospitalization, emergency dept. visit or increased therapy

Stable patient

Percent of pts with at least 5 points deterioration in KCCQ Clinical Summary Score

Enalapril group in PARADIGM-HF: ACE inhibitor 100%, beta-blocker 93%, MRA 57%, digitalis 31%

Circulation 2015;131:54-61.
Stable patient

Percent of pts with at least 5 points deterioration in KCCQ Clinical Summary Score

Enalapril group in PARADIGM-HF: ACE inhibitor 100%, beta-blocker 93%, MRA 57%, digitalis 31%

- A 5-point change in KCCQ overall score corresponds to:
  - 112 meter change in 6-minute walking distance
  - 2.50 ml/kg/min change in peak VO2 in HFrEF patients

- A 5-point decrease in KCCQ overall score corresponds to a deterioration in the patient’s condition

Am Heart J 20112;163:88-94.
The risk of primary outcome was higher in patients with more recent hospitalization than in those with no prior hospitalization in adjusted models regardless of treatment.
Consistent effect of sacubitril/valsartan over all groups

- Clinically stable patients (without prior HF hospitalization or with remote HF hospitalization) benefited at least as much from sacubitril/valsartan as did less stable patients (recent clinical decompensation).

clinical decompensation. These findings do not support recommendations to wait for evidence of clinical decompensation or instability as a rational strategy for switching patients from a conventional inhibitor of the renin-angiotensin system to sacubitril/valsartan.
Moving away from symptoms-based heart failure treatment: misperceptions and real risks for patients with heart failure

New York Heart Association
Class II symptoms

Perceived stable disease
Perceived low risk
Patients and provider inertia to optimize therapy
Concerns about side effects and multiple healthcare encounters
Change therapy if and when condition worsens

New York Heart Association
Class III-IV symptoms

Unstable
Perceived advanced end stage disease
Focus on advanced therapies and palliative care

Reality
Annual mortality 6-20%
Over a million hospitalizations each year in US and in Europe
Post-discharge 25-30% mortality risk within 1 year
Stable class II – 40+% die of sudden death
Sudden death can occur without worsening symptoms

Patients have at-risk viable vulnerable myocardium
Viable myocardium is amenable to improvement with proven and novel therapies

Risk of sudden death and worsening symptoms reduced by optimizing therapy irrespective of symptoms

Stability of symptoms does not mean lack of risk (especially sudden death)
Worsening symptoms does not mean end stage disease
Either stability or instability of symptoms should not deter from optimizing therapy
Sacubitril/valsartan should be started **36 hours** after the last dose of ACEi.

Sacubitril/valsartan should not be given along with ACEi/ARBs.

**Dosing and Uptitration**

<table>
<thead>
<tr>
<th>LCZ 696</th>
<th>Sacubitril</th>
<th>Valsartan</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 mg</td>
<td>24 mg</td>
<td>26 mg</td>
</tr>
<tr>
<td>100 mg</td>
<td>49 mg</td>
<td>51 mg</td>
</tr>
<tr>
<td>200 mg</td>
<td>97 mg</td>
<td>103 mg</td>
</tr>
</tbody>
</table>

**Up-titration**

- **ACEi/ARBs naïve pts**
- **Low ACEi/ARBs doses**
- **SBP: 100-110mmHg**
- **eGFR: 30-60 ml/min/1,73m²**

Initial dose 49 mg/51 mg bd for 2-4 weeks

Target dose 97 mg/103 mg bd

Initial dose 24 mg/26 mg bd for 3-4 weeks

49 mg/51 mg bd for 3-4 weeks

Target dose 97 mg/103 mg bd

1,5 ημέρες
Sacubitril / Valsartan is indicated for patients with symptomatic Chronic Heart Failure and reduced EF

- NYHA II-IV
- LVEF ≤ 40%
- SBP ≥ 100mmHg
- Stable doses of RAASi + b blockers ± MRAs for ≥ 4 weeks
- $K^+ \leq 5,4\text{mEq/L}$
- eGFR ≥ 30/min/1,73m²
Γ.Ν.Α. «Ο Ευαγγελισμός»