Comparison of Low-Dose Versus High-Dose Losartan Treatment on Morbidity and Mortality in Angiotensin-Converting-Enzyme-Inhibitor-Intolerant Patients with Heart Failure and Reduced Left Ventricular Ejection Fraction: Results of the HEAAL* Study

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* Heart failure Endpoint evaluation with the Angiotensin II Antagonist Losartan

*Lancet* 2009; 374: 1840–48
### ARBs in Heart Failure

**HYPOTHESIS:**
Increased ARB dose is associated with improved clinical outcomes in heart failure

**POPULATION:**
Patients with clinical heart failure, low LVEF and ACE-inhibitor intolerance

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*Pfeffer et al. NEJM 2003*

*Pitt B et al: Lancet 2000*
Inclusion Criteria

**Inclusion**
- NYHA II-IV Heart Failure
- LVEF ≤40%
- Intolerance to ACEI

**Exclusion**
- Known intolerance to ARBs
- Systolic BP < 90 mm Hg
- Myocarditis, pericarditis, or stenotic valvular disease
- MI, unstable angina, PTCA, or CABG within prior 12 wks
- CVA or TIA within prior 12 weeks

*Konstam MA et al, Lancet 2009; 374: 1840–48*
Study Design and Sample Size

Losartan 12.5 mg- 25 mg qd

Screen

Open Titration

2 weeks

1 week

1 week

(1 week)

Randomization

150 mg qd

100 mg qd

50 mg qd

150 mg group

50 mg group

50 mg qd + P

50 mg qd + P


- **Primary endpoint**: death or hospitalization for HF

- 1710 patients with primary endpoint events provided 95% power for HR = 0.837 for superiority with 2-sided $\alpha = 0.043$
Disposition of Patients

**3846 Randomized**

1927 Randomized to losartan 150 mg

6 excluded for data quality

N=1921 Analyzed
- 828 experienced primary endpoint
- 41 primary endpoint status unknown; 48 vital status unknown at closing date

1919 Randomized to losartan 50 mg

6 excluded for data quality

N=1913 Analyzed
- 889 experienced primary endpoint
- 54 primary endpoint status unknown; 62 vital status unknown at closing date

## Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Losartan 150 mg (N=1921)</th>
<th>Losartan 50 mg (N=1913)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (years)</td>
<td>64.4</td>
<td>64.1</td>
</tr>
<tr>
<td>Gender (% male)</td>
<td>69.7</td>
<td>70.7</td>
</tr>
<tr>
<td>Atrial fibrillation (%)</td>
<td>27.9</td>
<td>28.0</td>
</tr>
<tr>
<td>Ischemic heart disease (%)</td>
<td>63.6</td>
<td>64.6</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>59.8</td>
<td>59.7</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>31.0</td>
<td>31.6</td>
</tr>
<tr>
<td>NYHA Class (% II/III/IV)</td>
<td>69/30/1</td>
<td>70/30/1</td>
</tr>
<tr>
<td>Ejection fraction, mean (%)</td>
<td>31.6</td>
<td>31.6</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>1.2</td>
<td>1.1</td>
</tr>
<tr>
<td>ARB (at screening) (%)</td>
<td>77.2</td>
<td>76.2</td>
</tr>
<tr>
<td>Beta-blocker (%)</td>
<td>72.3</td>
<td>71.9</td>
</tr>
<tr>
<td>Diuretics (%)</td>
<td>76.9</td>
<td>75.6</td>
</tr>
<tr>
<td>Aldosterone Antagonists (%)</td>
<td>37.9</td>
<td>38.4</td>
</tr>
</tbody>
</table>

*Konstam MA et al, Lancet 2009; 374: 1840–48*
# Patient Follow-up and Dosing

<table>
<thead>
<tr>
<th>Losartan 150 mg</th>
<th>Losartan 50 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median follow-up time (yrs)</strong></td>
<td>4.7</td>
</tr>
<tr>
<td><strong>Discontinuations (%)</strong></td>
<td>28.3</td>
</tr>
<tr>
<td><strong>Discontinuations for AE (%)</strong></td>
<td>7.7</td>
</tr>
<tr>
<td><strong>Mean dose (mg/day)</strong></td>
<td>128.9</td>
</tr>
</tbody>
</table>

*Follow up = time from randomization to study end or primary endpoint
**Including time off drug

Primary Endpoint
Death or Hospitalization for HF

% of Patients with First Event

Number of patients at risk

Losartan 50 mg

Losartan 150 mg

0 1 2 3 4 5

0 10 20 30 40 50

HR 0.90 (0.82, 0.99)
P=0.027

## Primary and Major Secondary Endpoints and Components

<table>
<thead>
<tr>
<th>Event</th>
<th>Losartan 150mg</th>
<th>Losartan 50mg</th>
<th>Hazard Ratio (95%CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death or HF hospitalization</td>
<td>828 11.1</td>
<td>889 12.4</td>
<td>0.90</td>
<td>0.027</td>
</tr>
<tr>
<td>Death or CV hospitalization</td>
<td>1037 15.6</td>
<td>1085 17.0</td>
<td>0.92</td>
<td>0.068</td>
</tr>
<tr>
<td>Death</td>
<td>635 7.6</td>
<td>665 8.2</td>
<td>0.94</td>
<td>0.24</td>
</tr>
<tr>
<td>HF hospitalization</td>
<td>450 6.0</td>
<td>503 7.0</td>
<td>0.87</td>
<td>0.025</td>
</tr>
<tr>
<td>CV hospitalization</td>
<td>762 11.5</td>
<td>826 12.9</td>
<td>0.89</td>
<td>0.023</td>
</tr>
</tbody>
</table>

*Rate per 100 person years

*Konstam MA et al, Lancet 2009; 374: 1840–48*
### Other Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Losartan 150mg</th>
<th>Losartan 50mg</th>
<th>Hazard Ratio (95%CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death or all cause hospitalization</td>
<td>1237 21.6</td>
<td>1269 22.8</td>
<td>0.95</td>
<td>0.24</td>
</tr>
<tr>
<td>CV death</td>
<td>448 5.4</td>
<td>478 5.9</td>
<td>0.92</td>
<td>0.20</td>
</tr>
<tr>
<td>CV death or CV hospitalization</td>
<td>942 14.2</td>
<td>1003 15.7</td>
<td>0.91</td>
<td>0.034</td>
</tr>
<tr>
<td>CV death or HF hospitalization</td>
<td>698 9.3</td>
<td>771 10.7</td>
<td>0.88</td>
<td>0.011</td>
</tr>
</tbody>
</table>

*Rate per 100 person years

*Konstam MA et al, Lancet 2009; 374: 1840–48*
**HEAAL**

**Change in NYHA Class**

Percent of Patients

- **Improved**: 33.7% (Losartan 150 mg, n=1912), 31% (Losartan 50 mg, n=1905)
- **Unchanged**: 57.3% (Losartan 150 mg, n=1912), 58.5% (Losartan 50 mg, n=1905)
- **Worsened**: 9.3% (Losartan 150 mg, n=1912), 10.6% (Losartan 50 mg, n=1905)

**With Imputation for Death**

- **Improved**: 25.1% (Losartan 150 mg, n=1919), 22.2% (Losartan 50 mg, n=1911)
- **Unchanged**: 38.5% (Losartan 150 mg, n=1919), 39.1% (Losartan 50 mg, n=1911)
- **Worsened**: 39.4% (Losartan 150 mg, n=1919), 39.7% (Losartan 50 mg, n=1911)

*From baseline to last available data

HEAAL

Primary Endpoint: Selected Subgroups

Age < 65
Age ≥ 65

Female
Male

Europe/ME/Africa
Asia/Pacific
Latin Amer

NYHA I or II
NYHA III or IV

LVEF < 25%
LVEF 25-34%
LVEF ≥ 35%

Ischemic Disease
No Ischemic Disease

Hypertension
No HTN

Medications
Aldosterone Blocker
No Aldo Blocker

Beta-blocker
No Beta Blocker

Prior ARB
No prior ARB

0.75 1 1.33
0.75 1 1.33

150 mg Better 50 mg Better
150 mg Better 50 mg Better


* p for interaction

p* = 0.01
Selected Adverse Events
Rate / 100 person-years

Hyperkalemia * Hypotension ** Renal Impairment *

Losartan 150 mg (n=1912)
Losartan 50 mg (n=1905)

* p < .001
** p = .002

Summary

- HEAAL represents the first study to investigate the dose-response of an ARB on clinical outcomes in patients with HF.
- Compared with losartan 50 mg daily, losartan 150 mg daily reduced the rate of the combined endpoint of all-cause mortality or HF hospitalization.
- The 150 mg dose was associated with higher rates of hypotension, hyperkalemia, and renal impairment, although the overall rates of clinically relevant adverse events were small.

Conclusions

- In patients with HF, reduced LVEF, and ACE inhibitor intolerance, incremental value is derived from up-titrating ARB doses to levels demonstrated to confer benefit on clinical outcomes.
- Our findings confirm the view that incremental inhibition of the renin-angiotensin system, within the range explored in HF trials to date, achieves a progressively favorable impact on clinical outcomes.