

## **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

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- The full title of the study is "A Multi-center, Double-Blind, Randomized, Paralleled Group Study to Evaluate the Effects of Two Different Doses of Losartan on Morbidity and Mortality in patients with Symptomatic Heart Failure Intolerant to ACE Inhibitor Treatment". [PN 948-05 Protocol p10A]

## Dedication



## Disclosure Information

- Marvin A. Konstam Grants/contracts, consultant (moderate)
- Philip A. Poole-Wilson Grants/contracts, consultant (moderate)
- Kenneth Dickstein Grants/Contracts, consultant (moderate)
- Helmut Drexler Grants/Contracts, consultant (moderate)
- Michel Komajda Grants/Contracts, consultant (moderate)
- Felipe A. Martinez Grants/Contracts, consultant (moderate)
- James D. Neaton Grants/Contracts, consultant (moderate)
- Gunter A.J. Riegger Grants/Contracts, consultant, (moderate)
- Soneil Guptha Former Merck employee, consultant (moderate)
- William Malbecq Merck employee

HEAAL was funded by Merck & Co., Inc.

All analyses were performed or replicated independently at the University of Minnesota School of Public Health.

Losartan is approved for treating heart failure in 36 countries, but not in the US.

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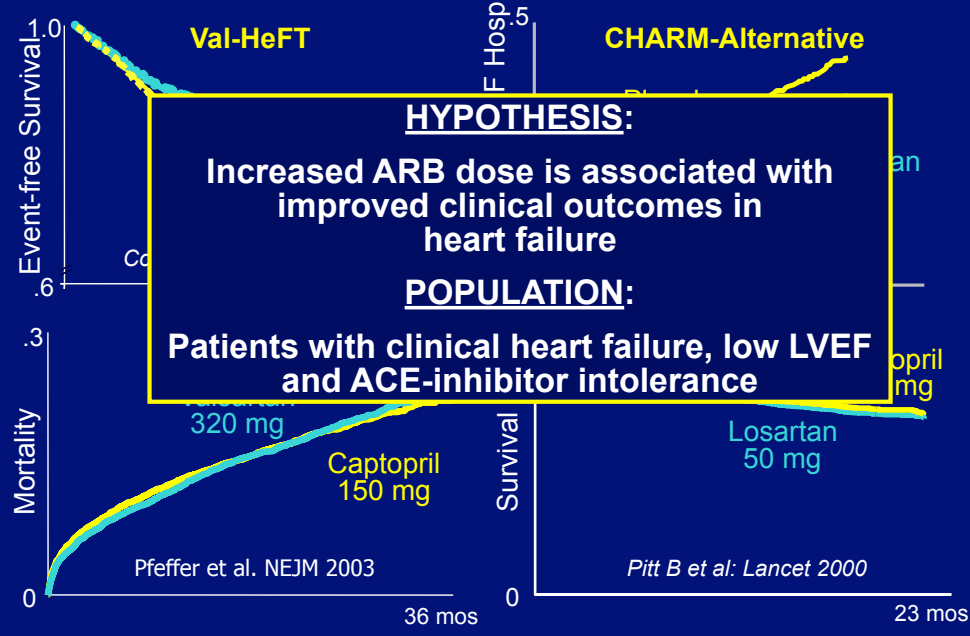
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- EU member states as of Jan 1, 2007

# ARBs in Heart Failure



## **Inclusion Criteria**

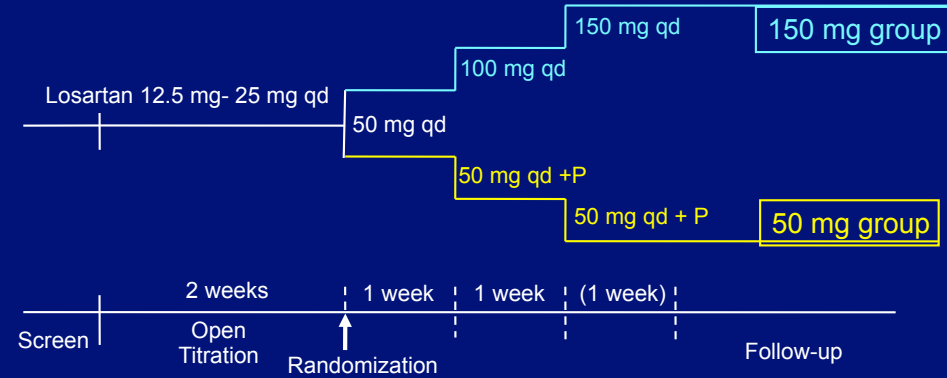
- **Inclusion**

- NYHA II-IV Heart Failure
- LVEF  $\leq$ 40%
- Intolerance to ACEI

- **Exclusion**

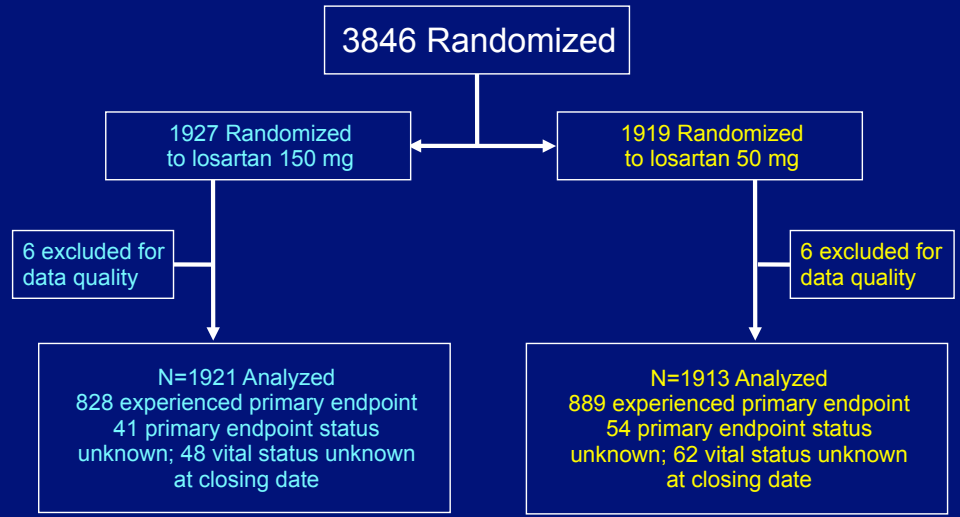
- Known intolerance to ARBs
- Systolic BP < 90 mm Hg
- Myocarditis, pericarditis, or stenotic valvular disease
- MI, unstable angina, PTCA, or CABG within prior 12 wks
- CVA or TIA within prior 12 weeks

## Study Design and Sample Size



- 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



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

- Chuck please add data from Appendix 2 page 23

**HEAAL****Baseline Characteristics**

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

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

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- do not have the data yet - hopefully will know when soon

**Patient Follow-up and Dosing**

	<b>Losartan 150 mg</b>	<b>Losartan 50 mg</b>
<b>Median follow-up time (yrs)*</b>	<b>4.7</b>	<b>4.7</b>
<b>Discontinuations (%)</b>	<b>28.3</b>	<b>27.3</b>
<b>Discontinuations for AE (%)</b>	<b>7.7</b>	<b>7.0</b>
<b>Mean dose (mg/day)**</b>	<b>128.9</b>	<b>45.6</b>

\*Follow up = time from randomization to study end or primary endpoint

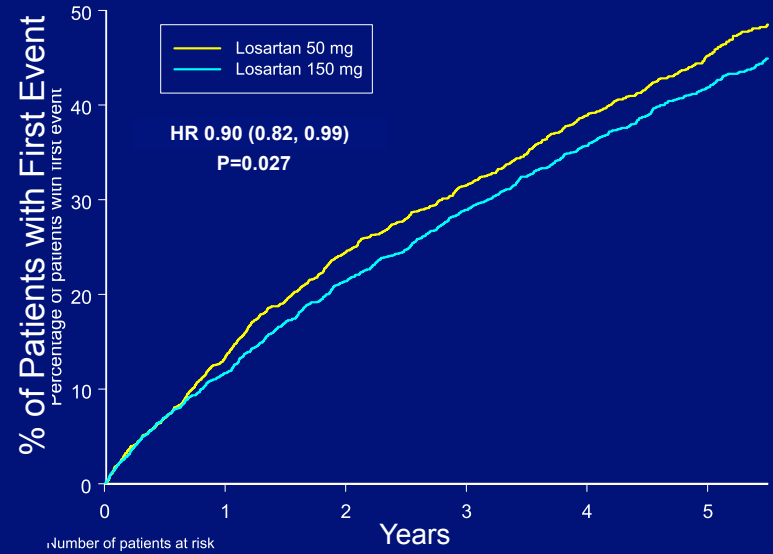
\*\*Including time off drug

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

- do not have the data yet - hopefully will know when soon

HEAAL

### Primary Endpoint Death or Hospitalization for HF



Number of patients at risk

	0	1	2	3	4	5
Losartan 50 mg	1646	1422	1277	1126	644	
Losartan 150 mg	1684	1493	1344	1205	711	

Konstam MA et al, *Lancet* 2009; **374**: 1840-48 12

- Chuck please add fig 3 of ERM

# HEAAL

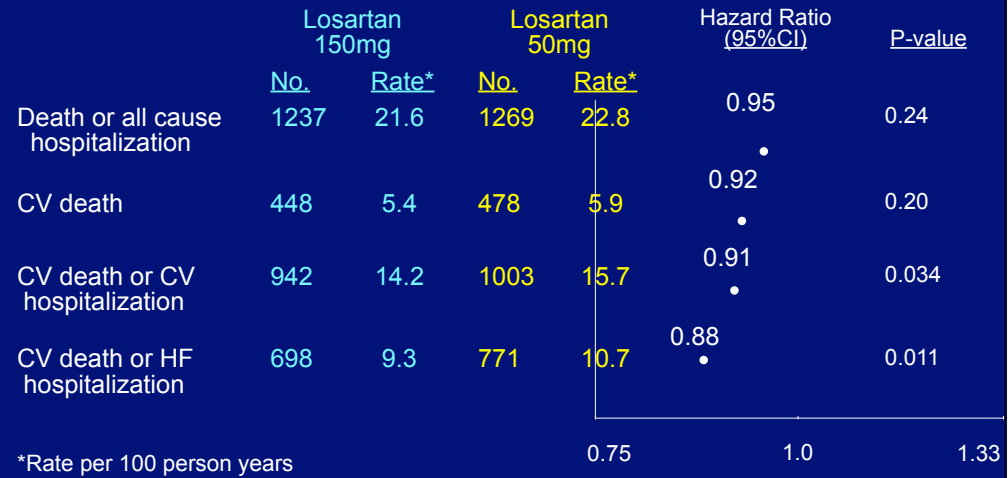
## Primary and Major Secondary Endpoints and Components

	Losartan 150mg		Losartan 50mg		Hazard Ratio (95%CI)	P-value
	No.	Rate*	No.	Rate*		
Death or HF hospitalization	828	11.1	889	12.4	0.90	0.027
Death or CV hospitalization	1037	15.6	1085	17.0	0.92	0.068
Death	635	7.6	665	8.2	0.94	0.24
HF hospitalization	450	6.0	503	7.0	0.87	0.025
CV hospitalization	762	11.5	826	12.9	0.89	0.023

\*Rate per 100 person years

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

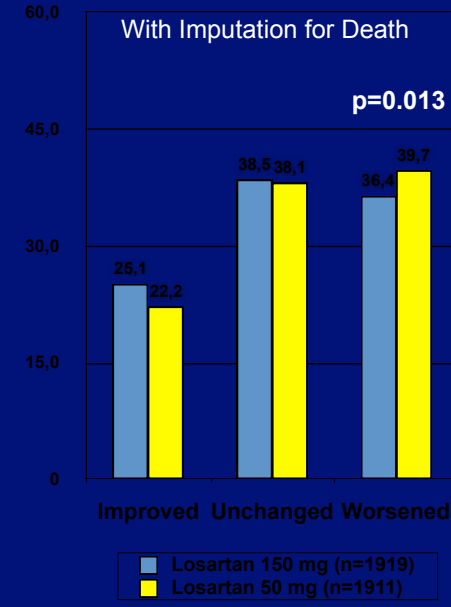
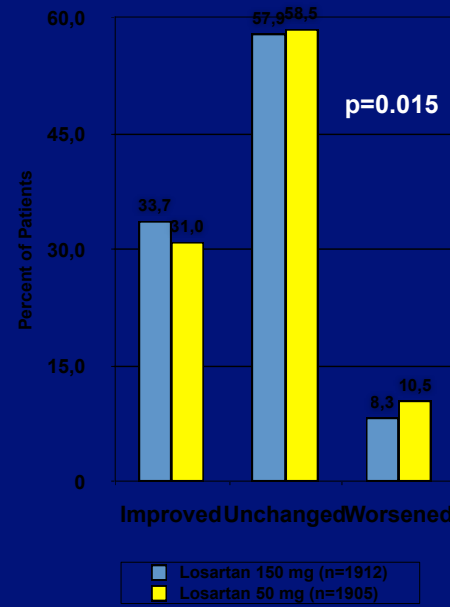
**Other Outcomes**



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

**HEAAL**

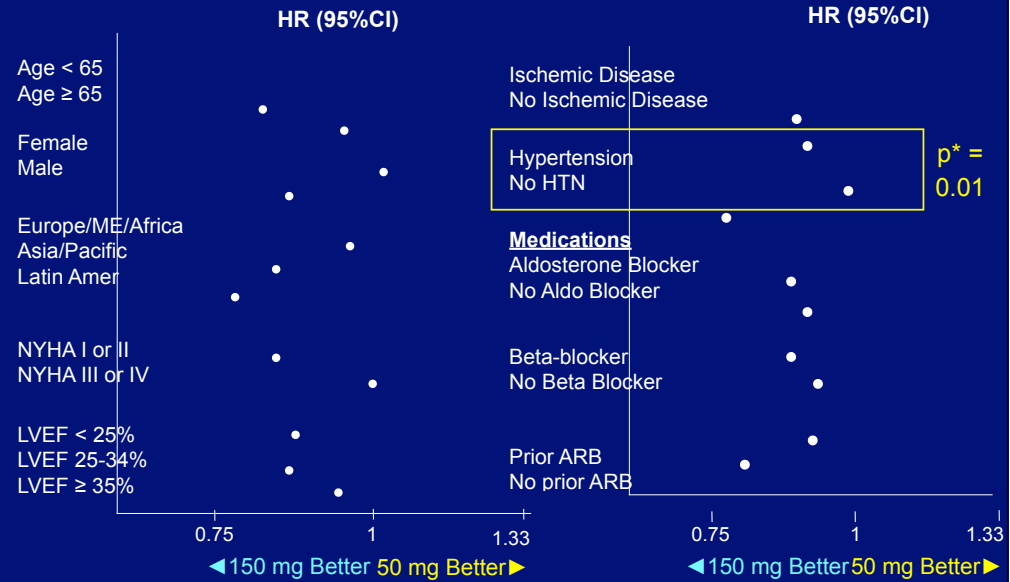
### Change in NYHA Class\* Percent of Patients



\*From baseline to last available data *Konstan MA et al. Lancet 2009; 374: 1840-48*

# HEAAL

## Primary Endpoint: Selected Subgroups

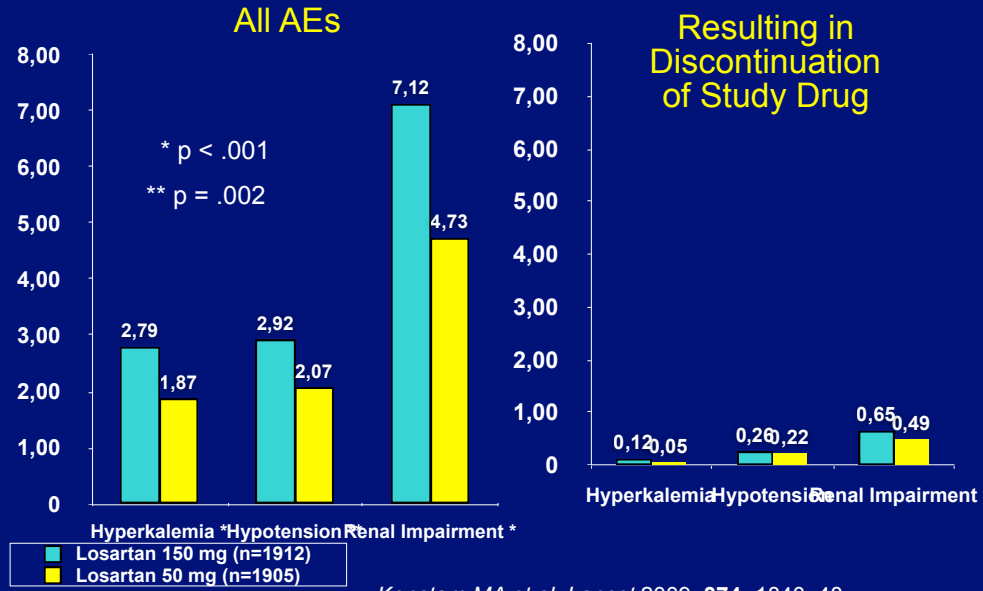


Konstam MA et al, Lancet 2009; 374: 1840-48

\* p for interaction

### Selected Adverse Events

Rate / 100 person-years



Konstam MA et al, Lancet 2009; 374: 1840-48

## HEAAL

### 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.

- have to await text