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

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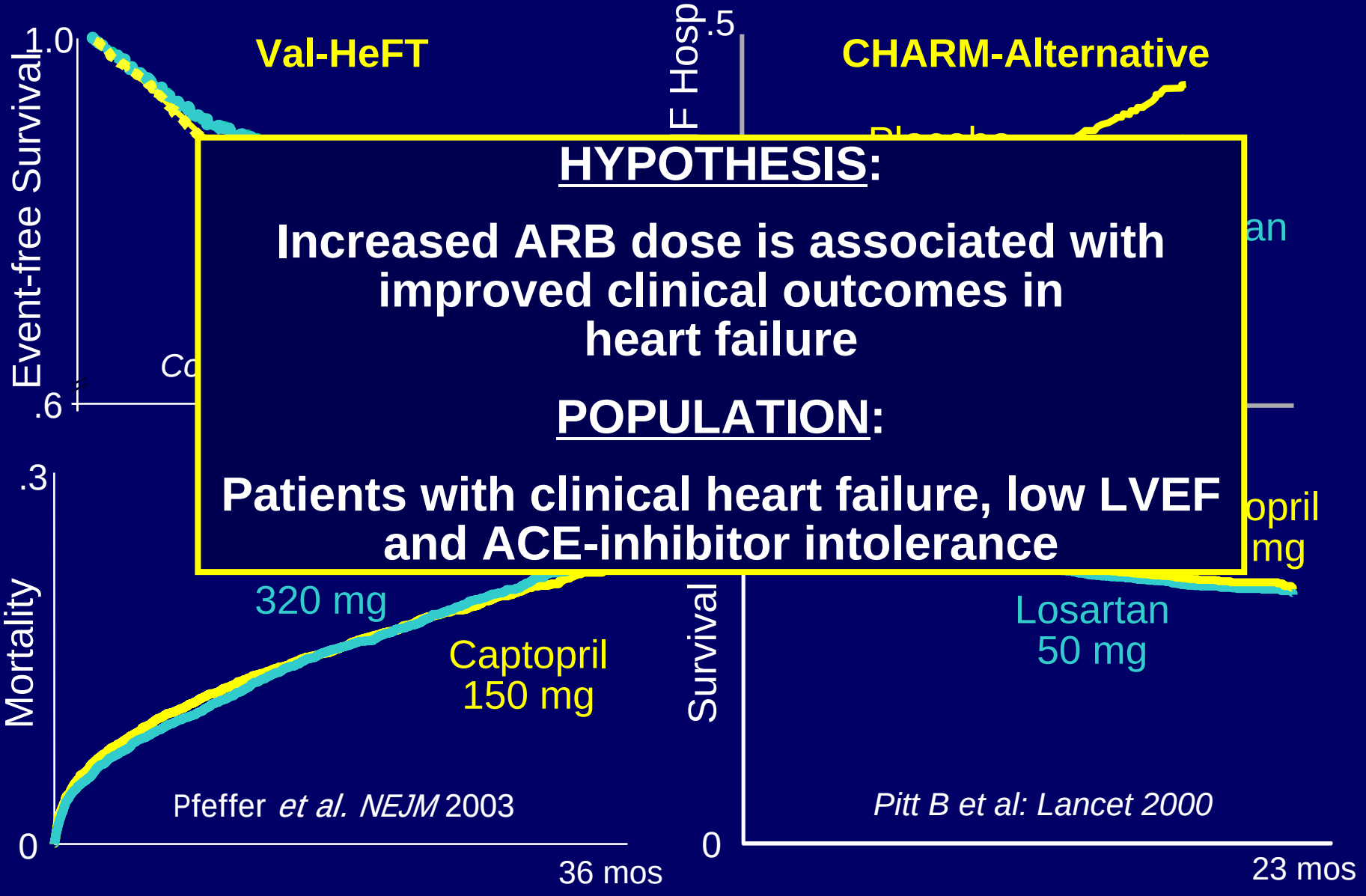
ARBs in Heart Failure



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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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

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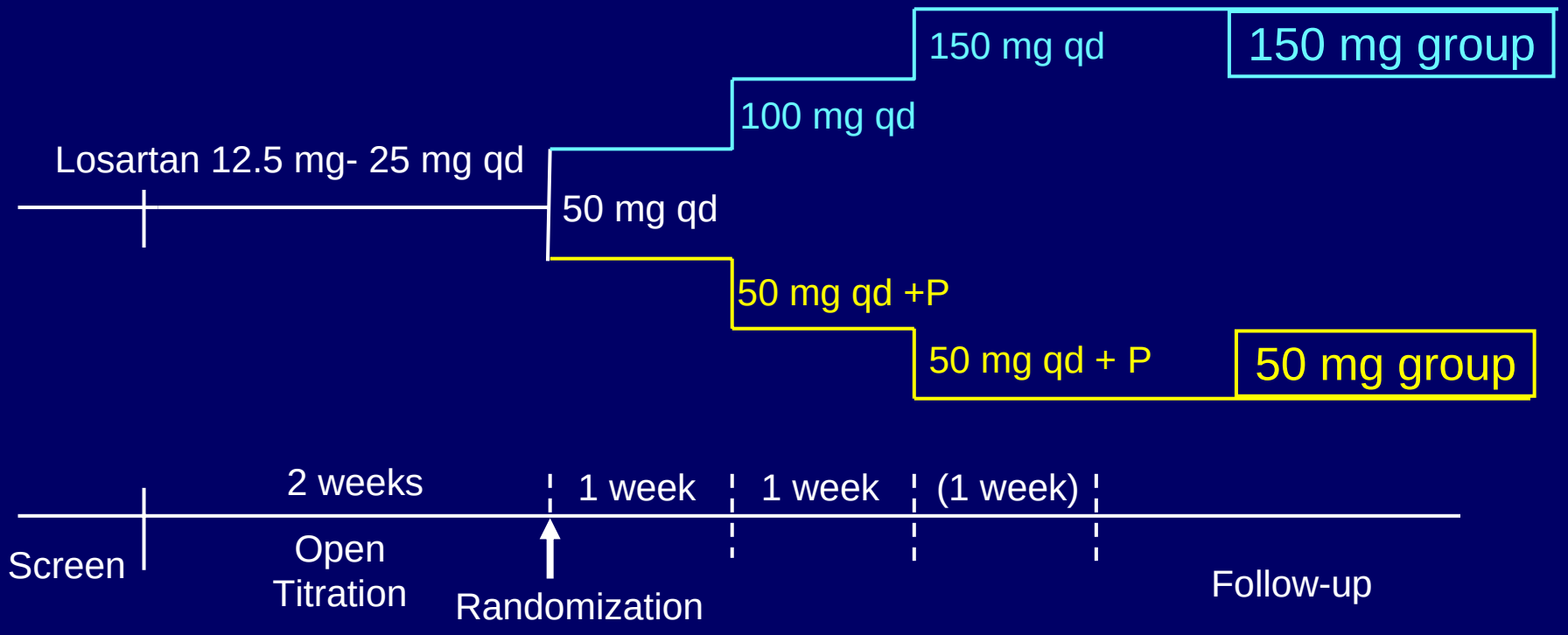
Study Design and Sample Size



- 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 α = 0.043

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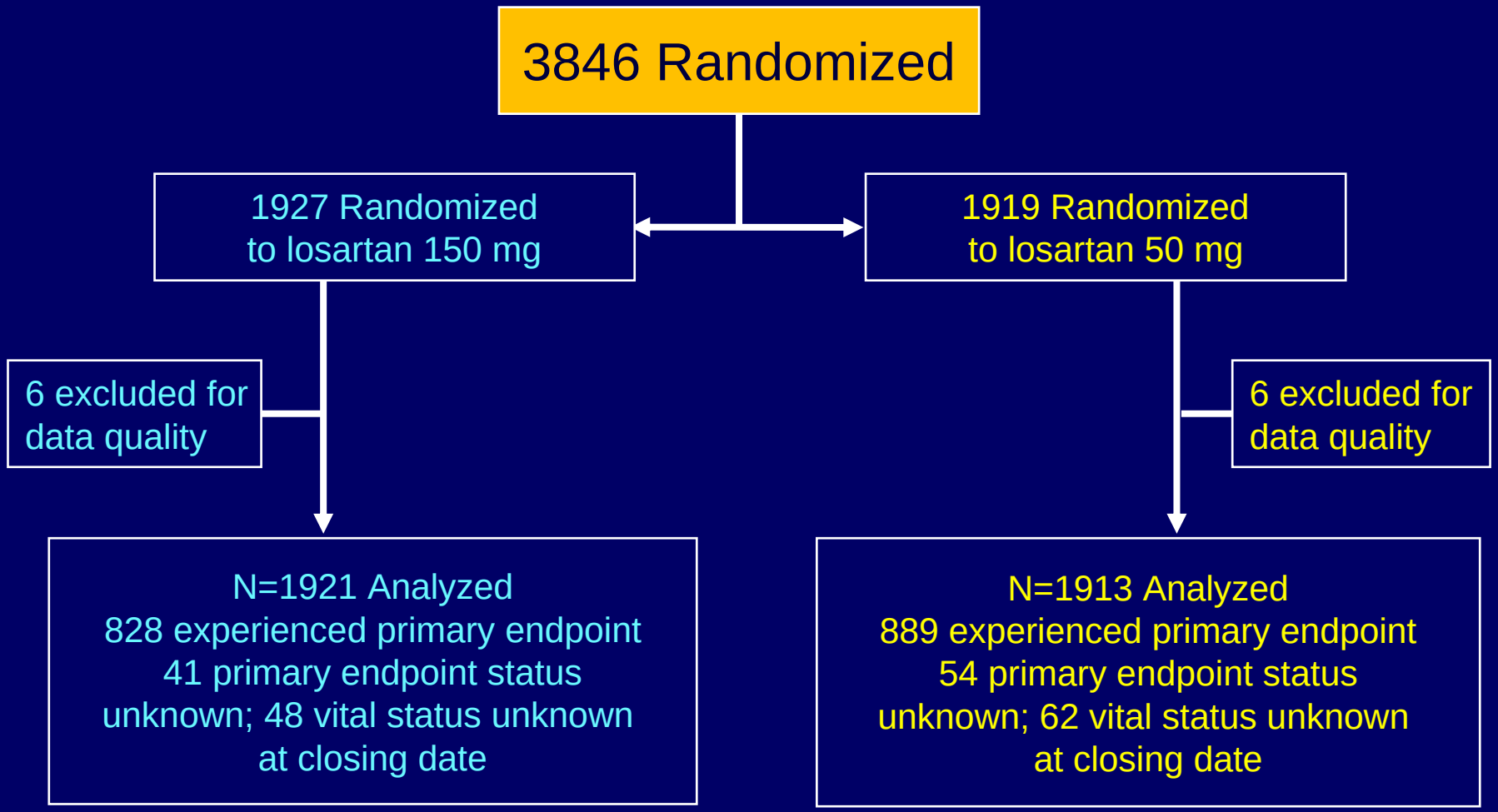
Disposition of Patients



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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

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Patient Follow-up and Dosing

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

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

**Including time off drug

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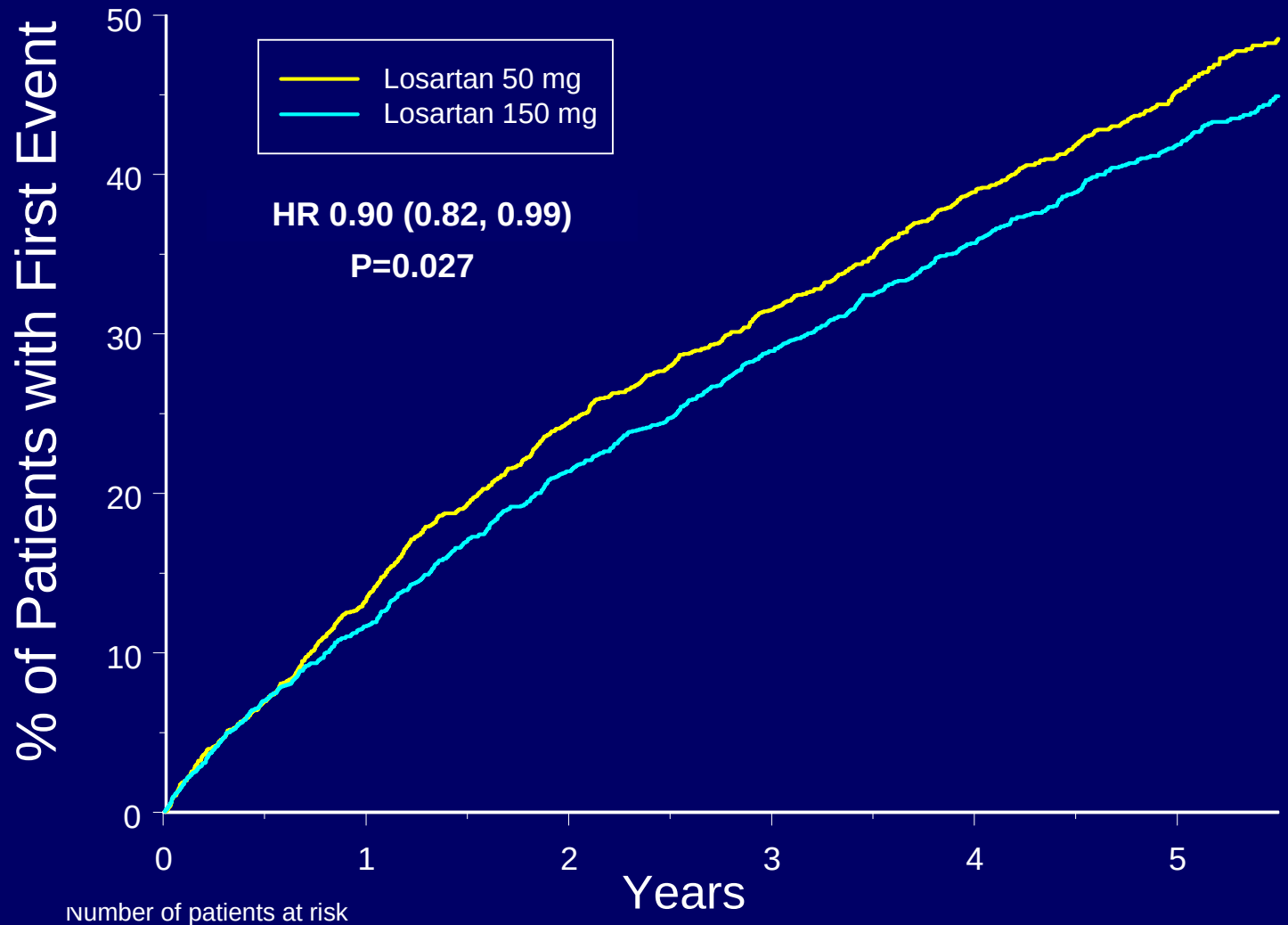
Primary Endpoint
Death or Hospitalization for HF



Number of patients at risk					
Losartan 50 mg	1646	1422	1277	1126	644
Losartan 150 mg	1684	1493	1344	1205	711

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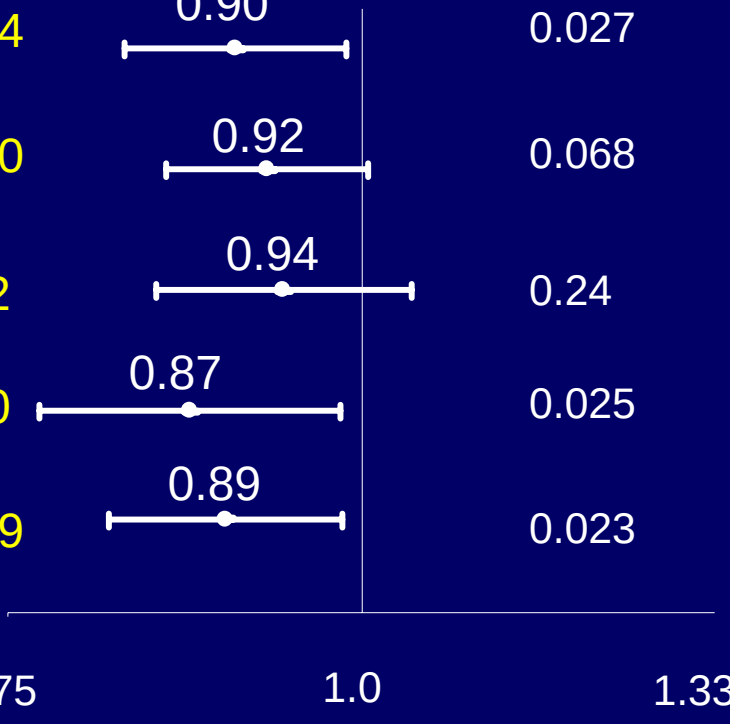
Primary and Major Secondary Endpoints and Components

	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

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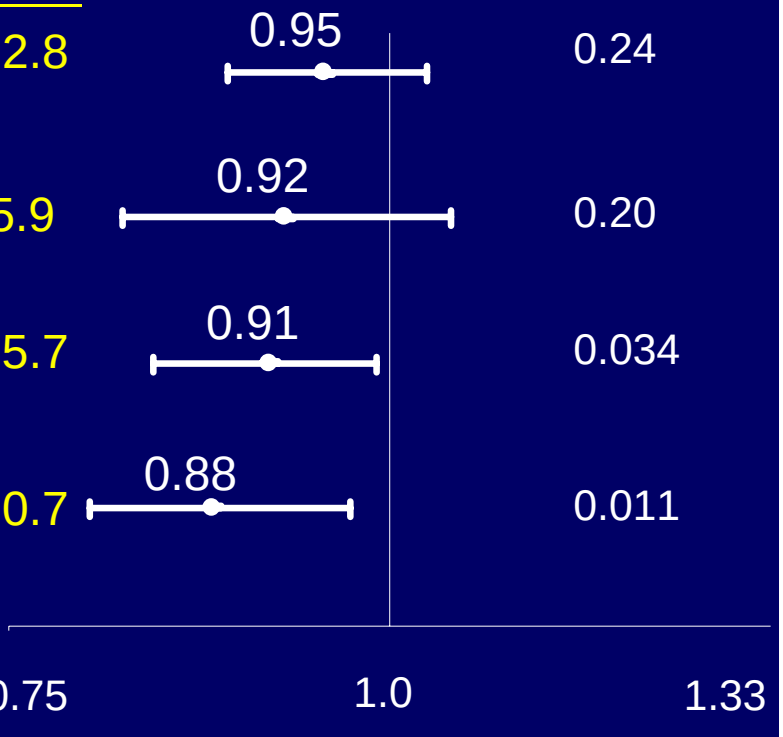
Other Outcomes

	Losartan 150mg		Losartan 50mg		Hazard Ratio (95%CI)	P-value
	No.	Rate*	No.	Rate*		
Death or all cause hospitalization	1237	21.6	1269	22.8	0.95	0.24
CV death	448	5.4	478	5.9	0.92	0.20
CV death or CV hospitalization	942	14.2	1003	15.7	0.91	0.034
CV death or HF hospitalization	698	9.3	771	10.7	0.88	0.011



*Rate per 100 person years

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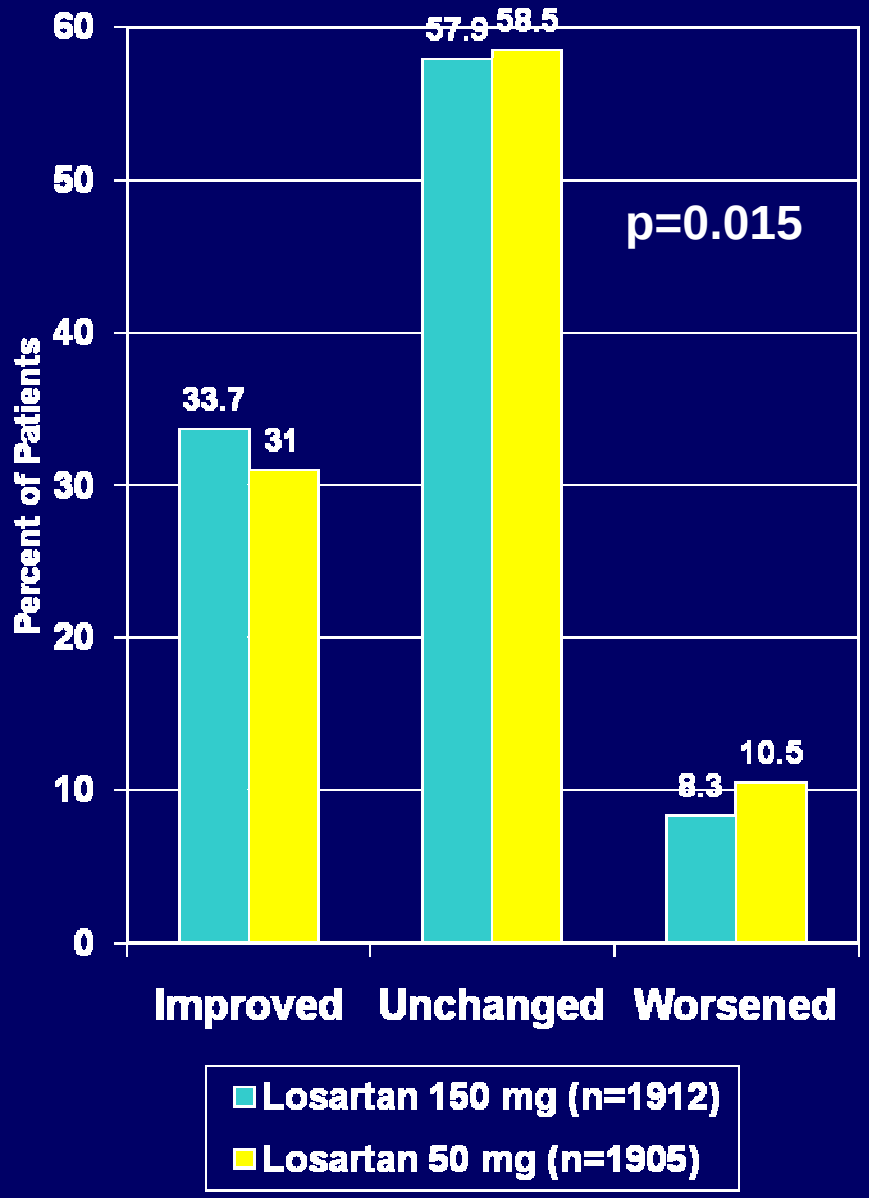
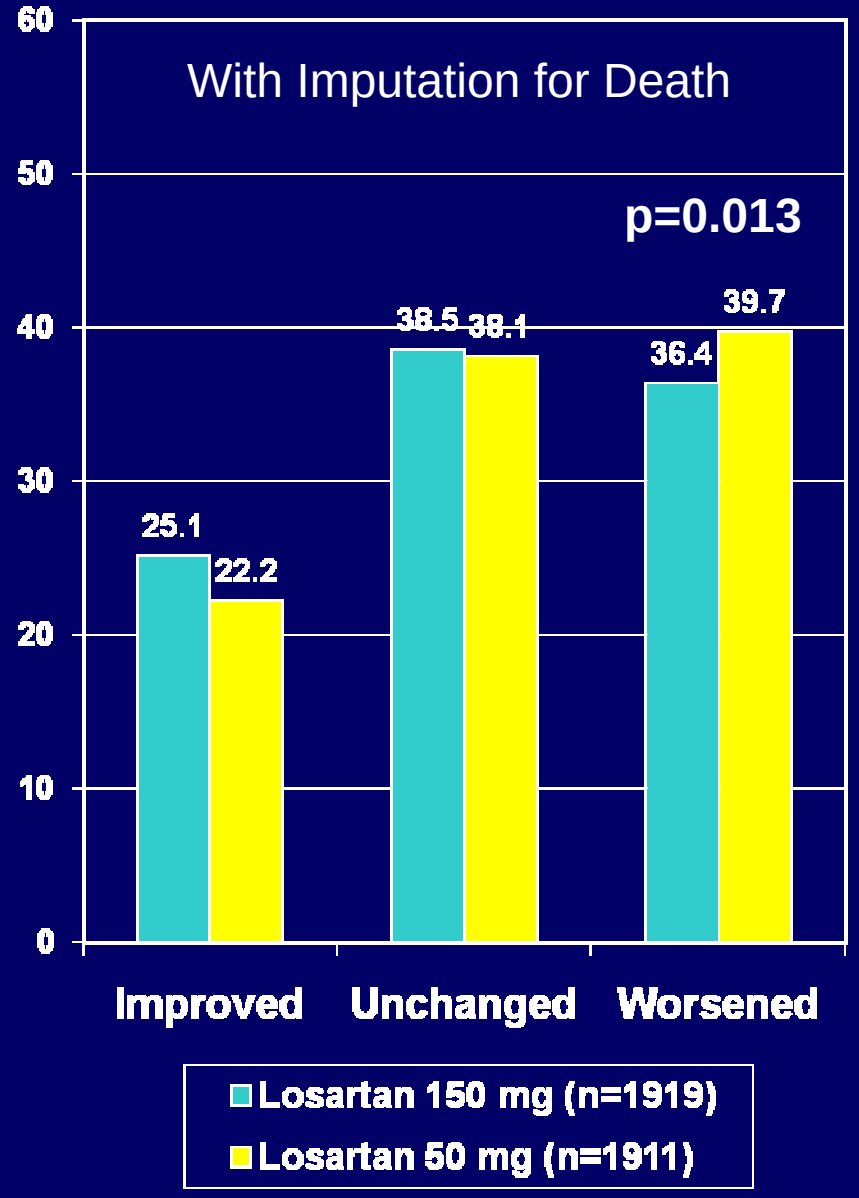
Change in NYHA Class*

Percent of Patients





*From baseline to last available data

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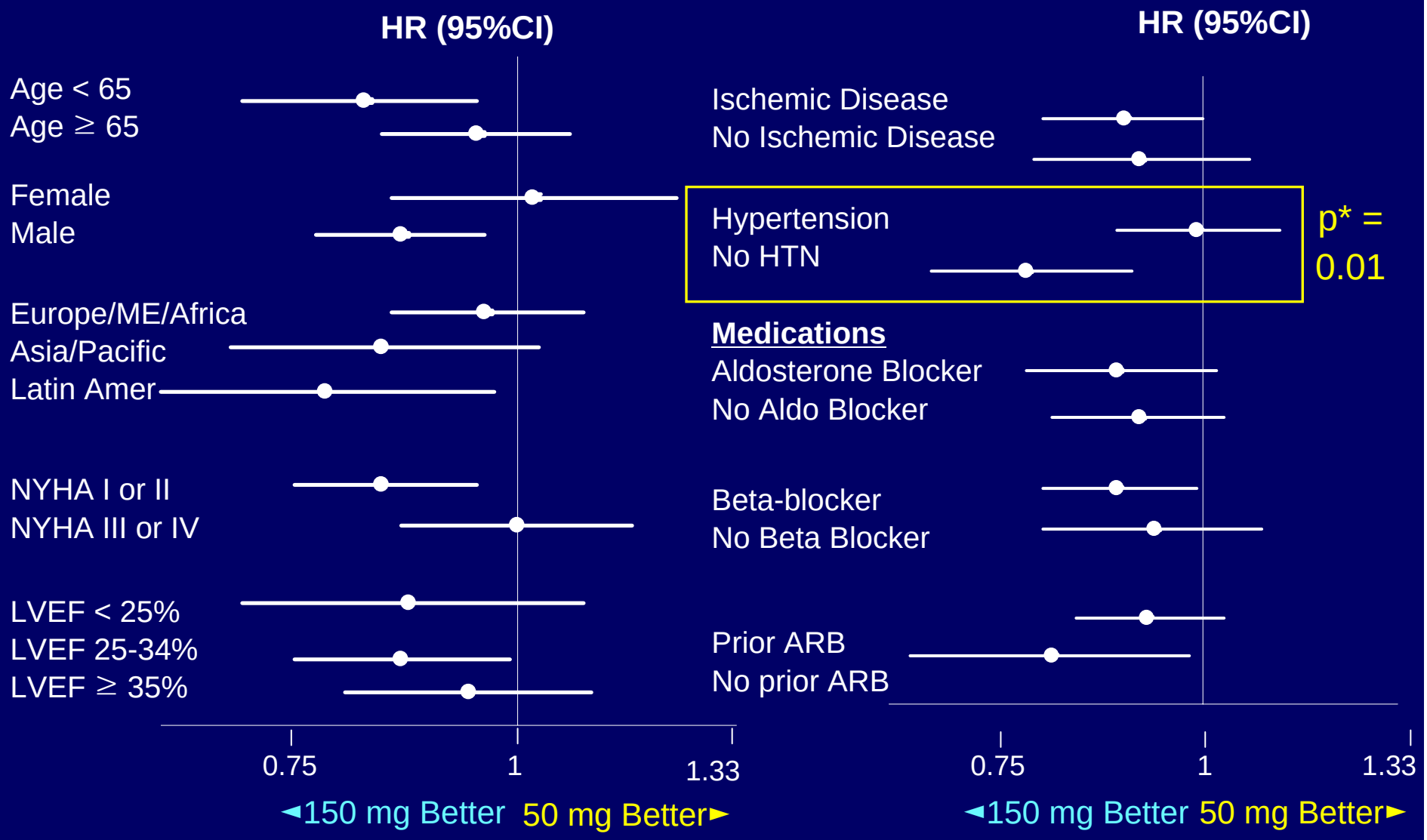
Primary Endpoint: Selected Subgroups



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* p for interaction

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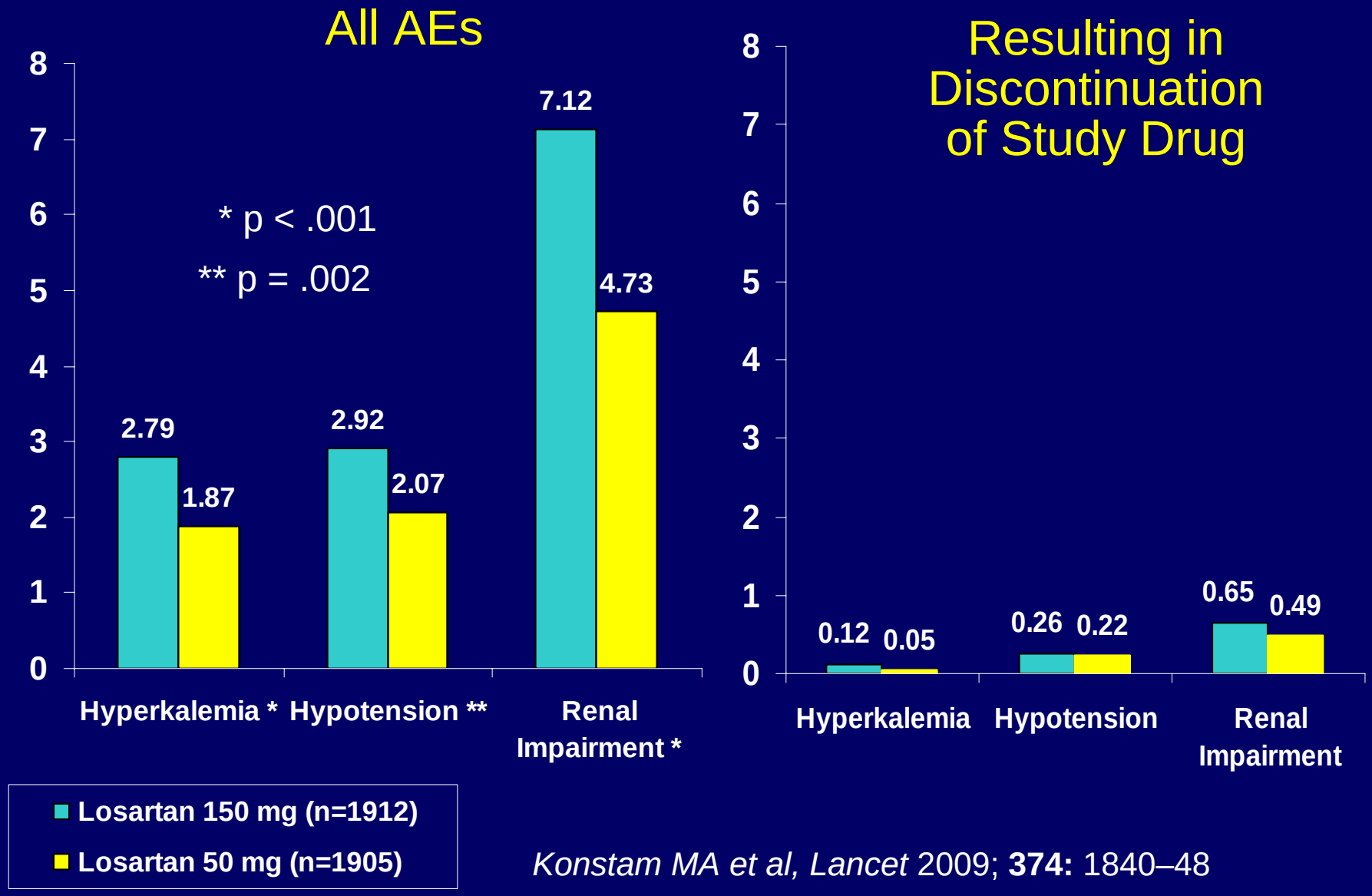
Selected Adverse Events

Rate / 100 person-years



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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.