

Results of PARADIGM-HF:

Biomarkers and renal function

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Declaration of interest

Consulting: Novartis

Overview

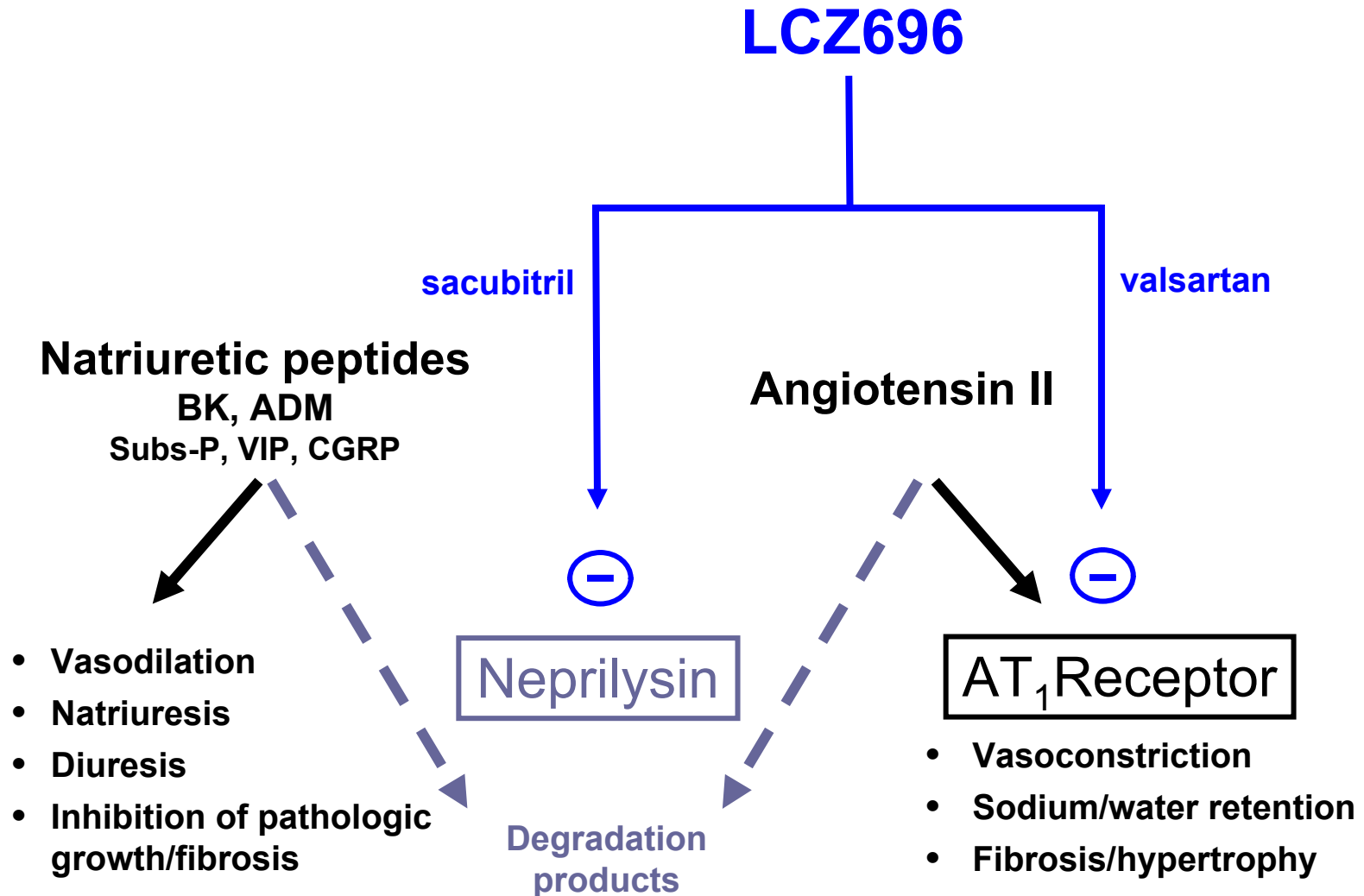
- **Biomarkers**

- natriuretic peptides
- aldosterone
- hsTnT
- galectin-3

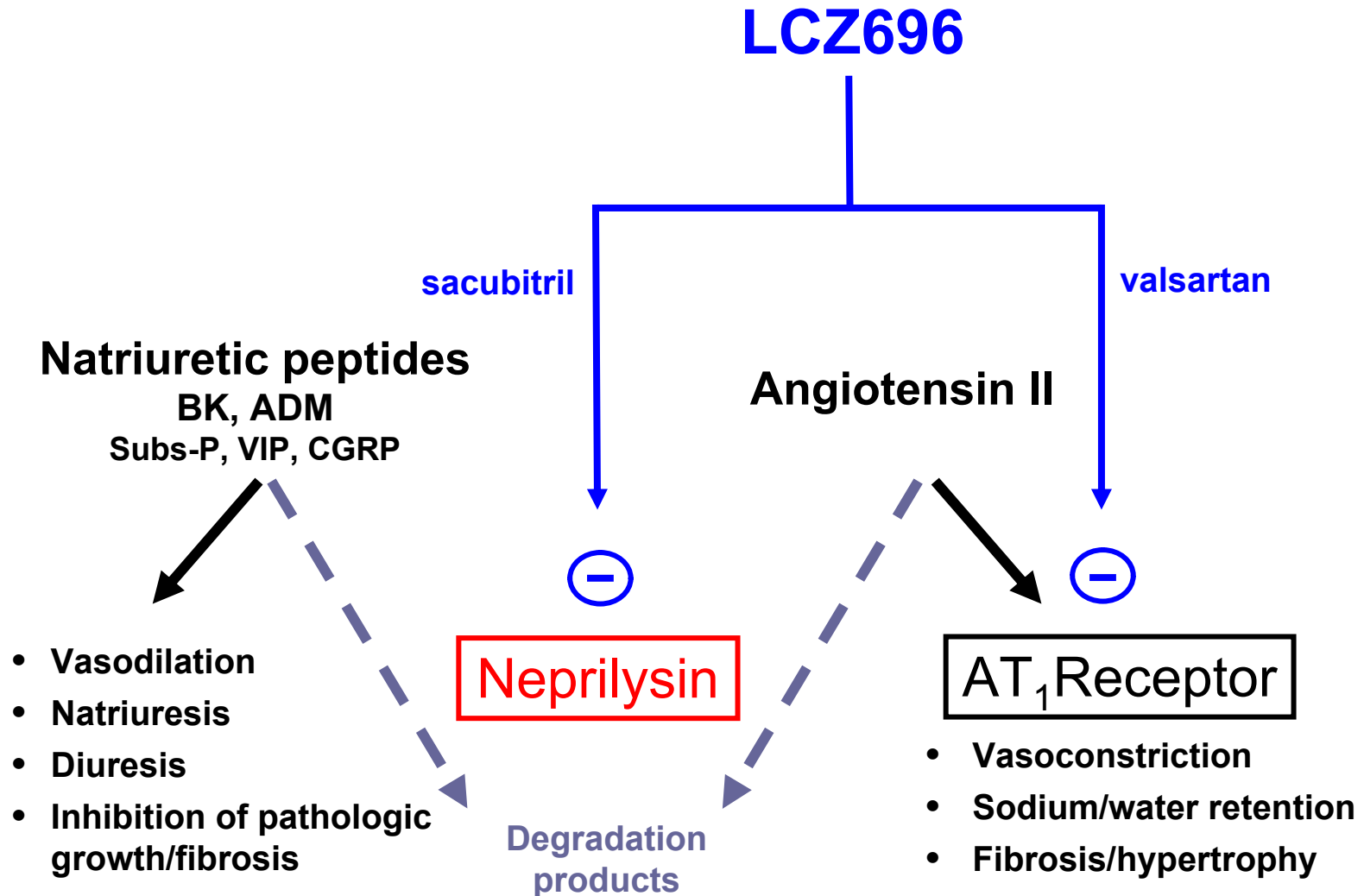
- **Renal**

- cystatin C
- Renal outcomes
- Renal safety

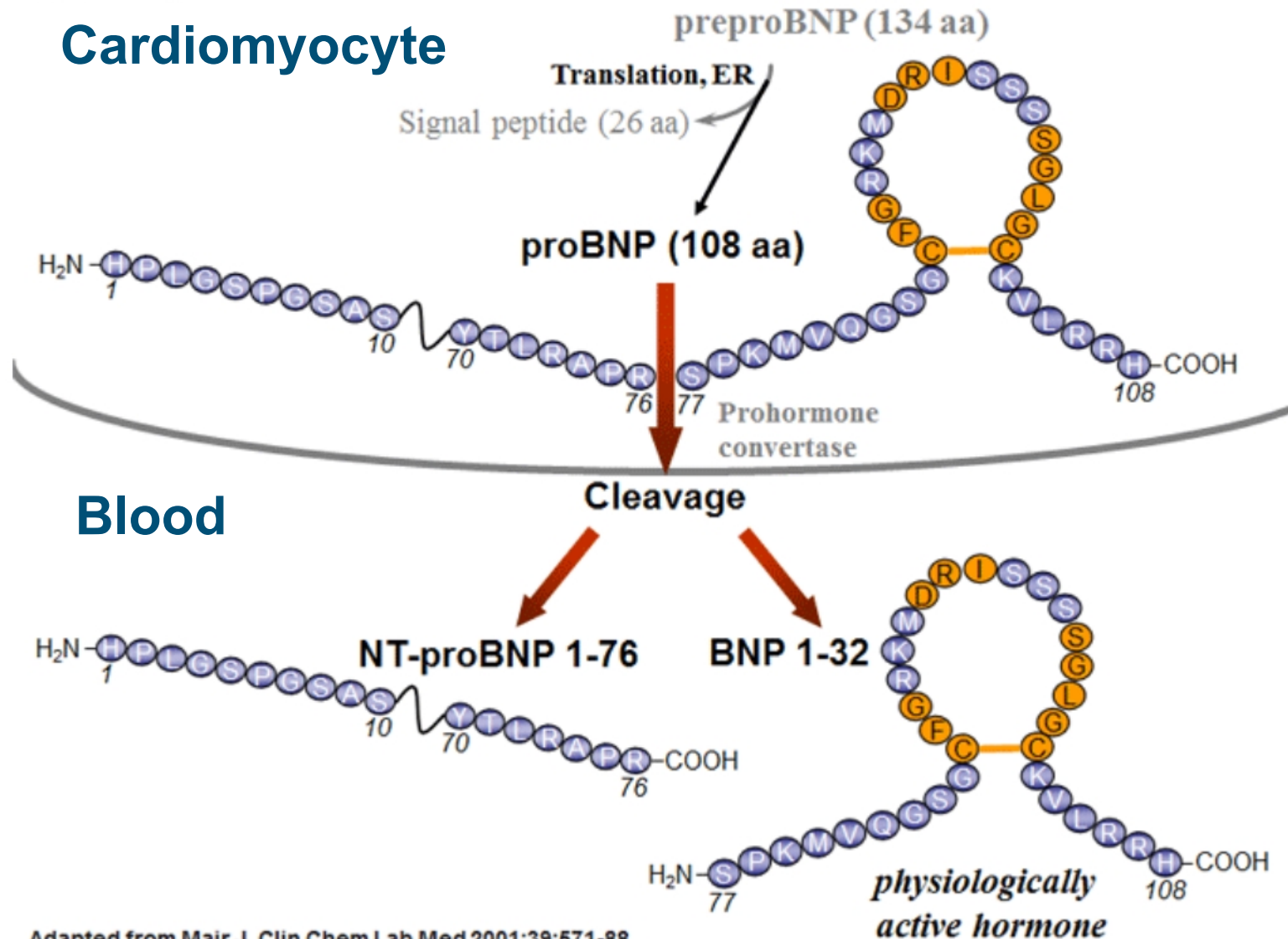
Angiotensin Receptor Neprilysin Inhibition (ARNI): LCZ696



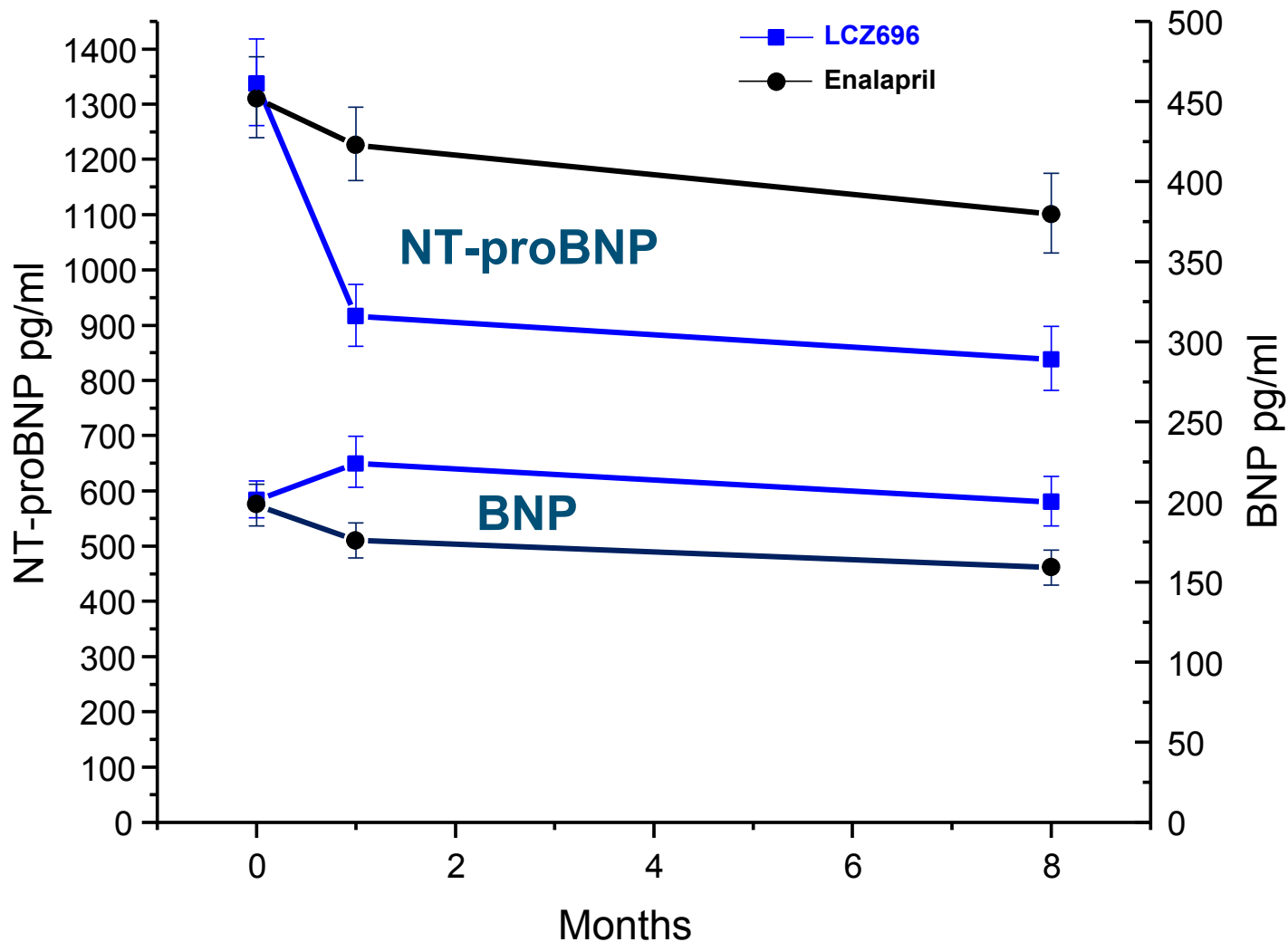
Angiotensin Receptor Neprilysin Inhibition (ARNI): LCZ696



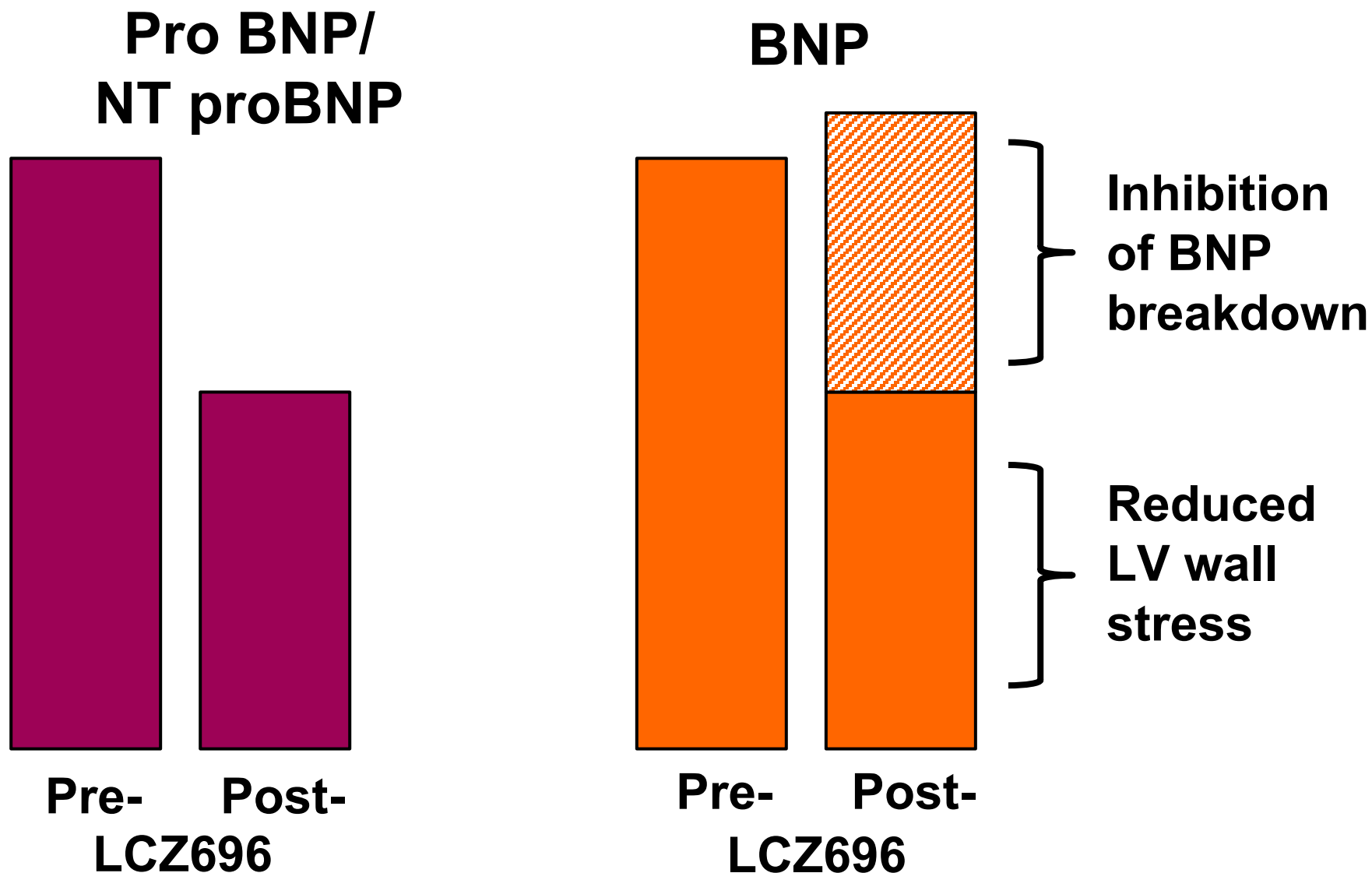
NT pro BNP and BNP



PARADIGM-HF: NT-proBNP and BNP

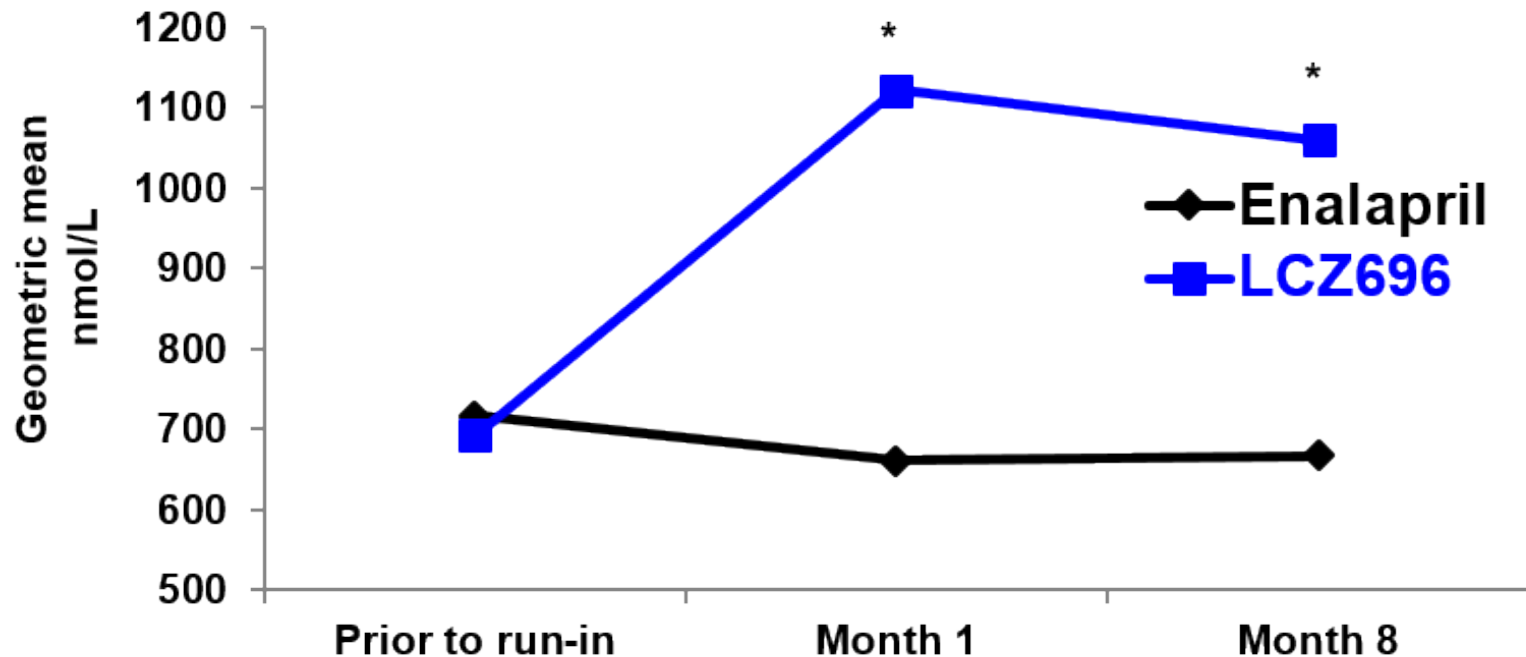


Explaining the NT pro BNP and BNP changes with LCZ696 (*schematic*)

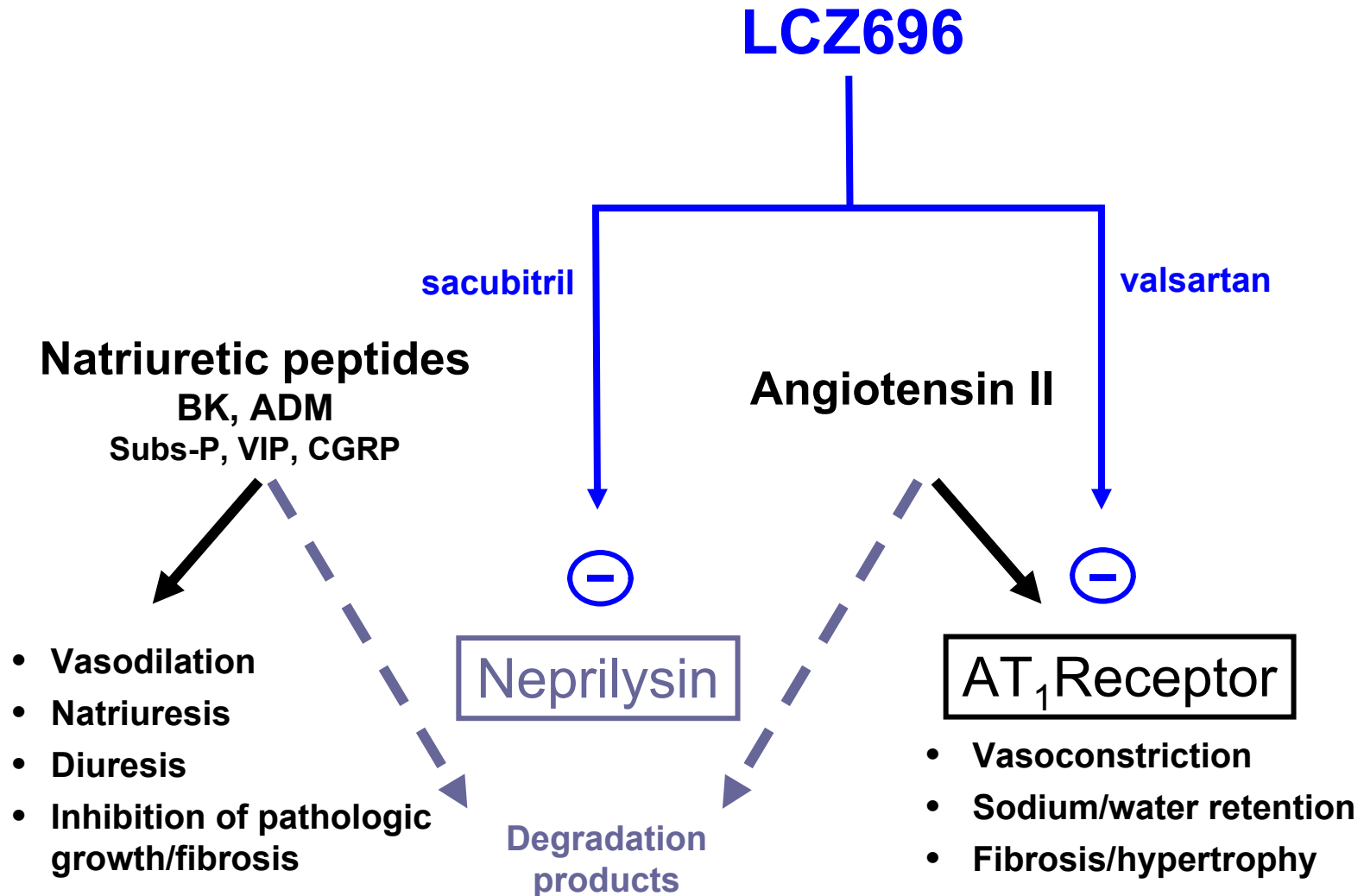


PARADIGM-HF: Geometric mean urinary cyclic GMP concentration by visit

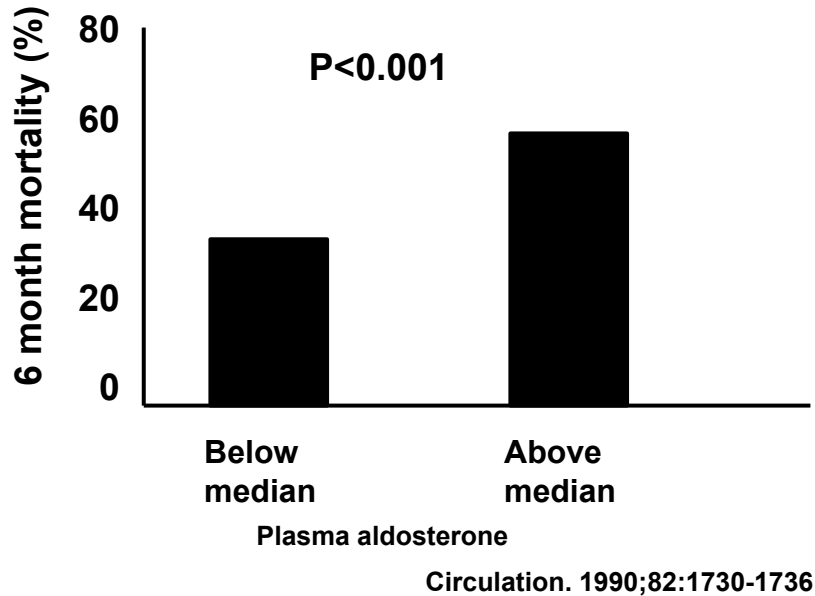
Cyclic GMP is the intracellular second messenger stimulated by natriuretic peptides and other vasoactive substances including nitric oxide



Angiotensin Receptor Neprilysin Inhibition (ARNI): LCZ696

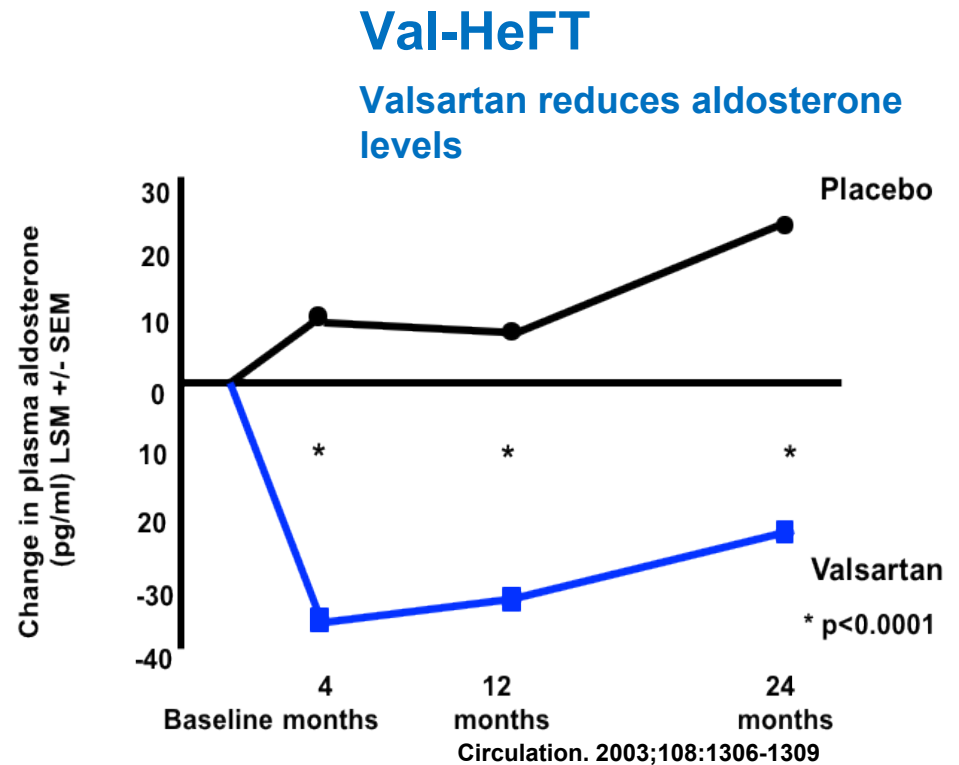


Aldosterone

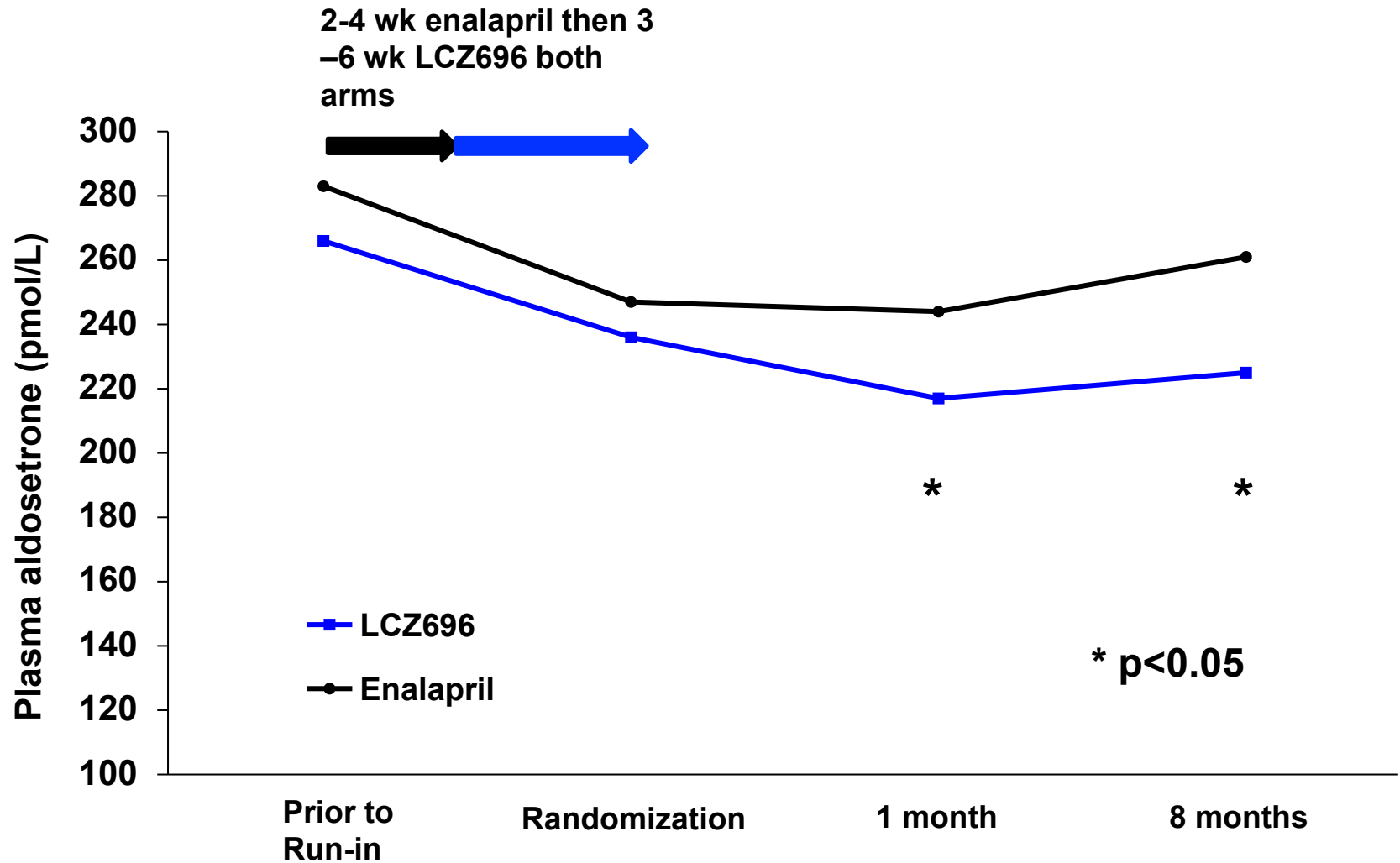


CONSENSUS

Raised plasma aldosterone is associated with higher mortality



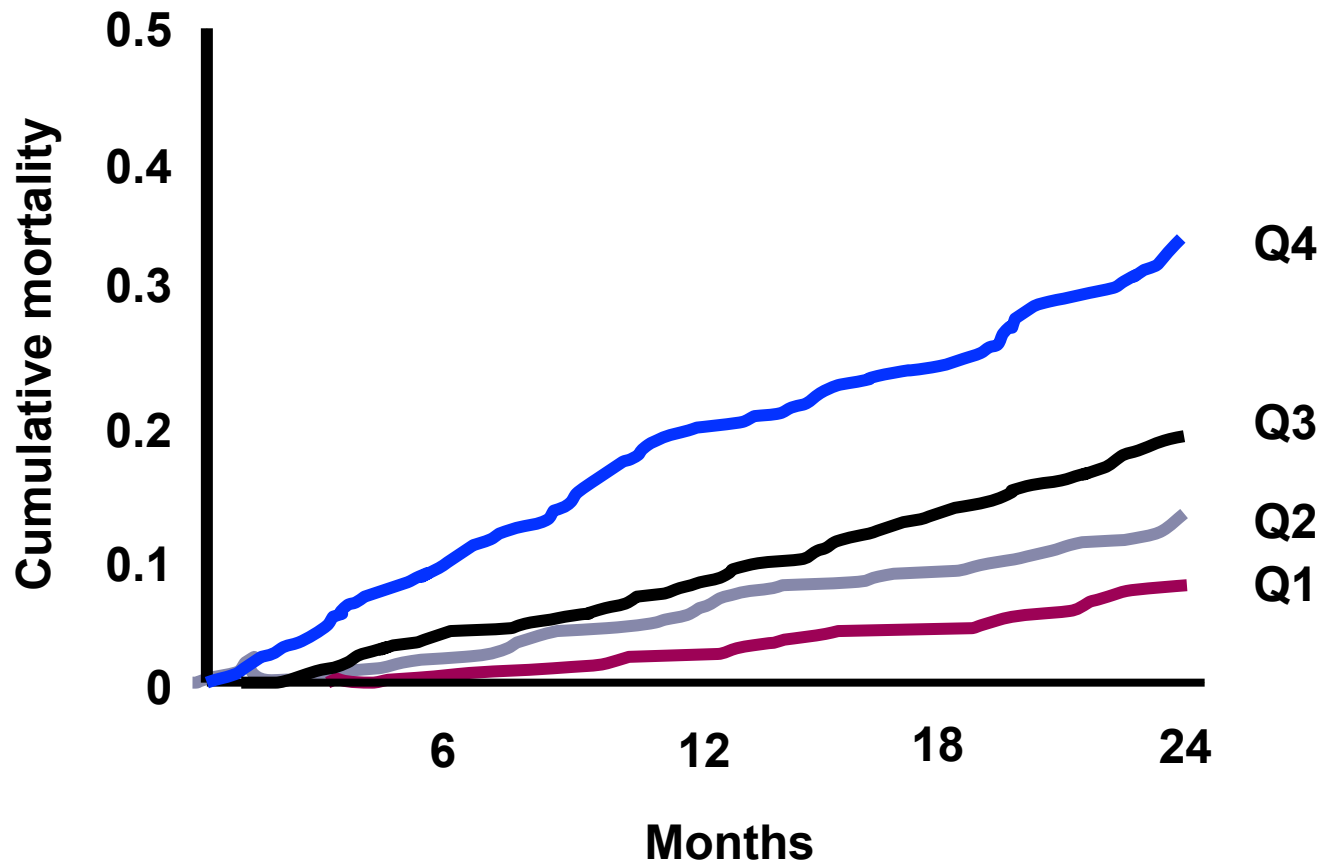
PARADIGM-HF: Aldosterone



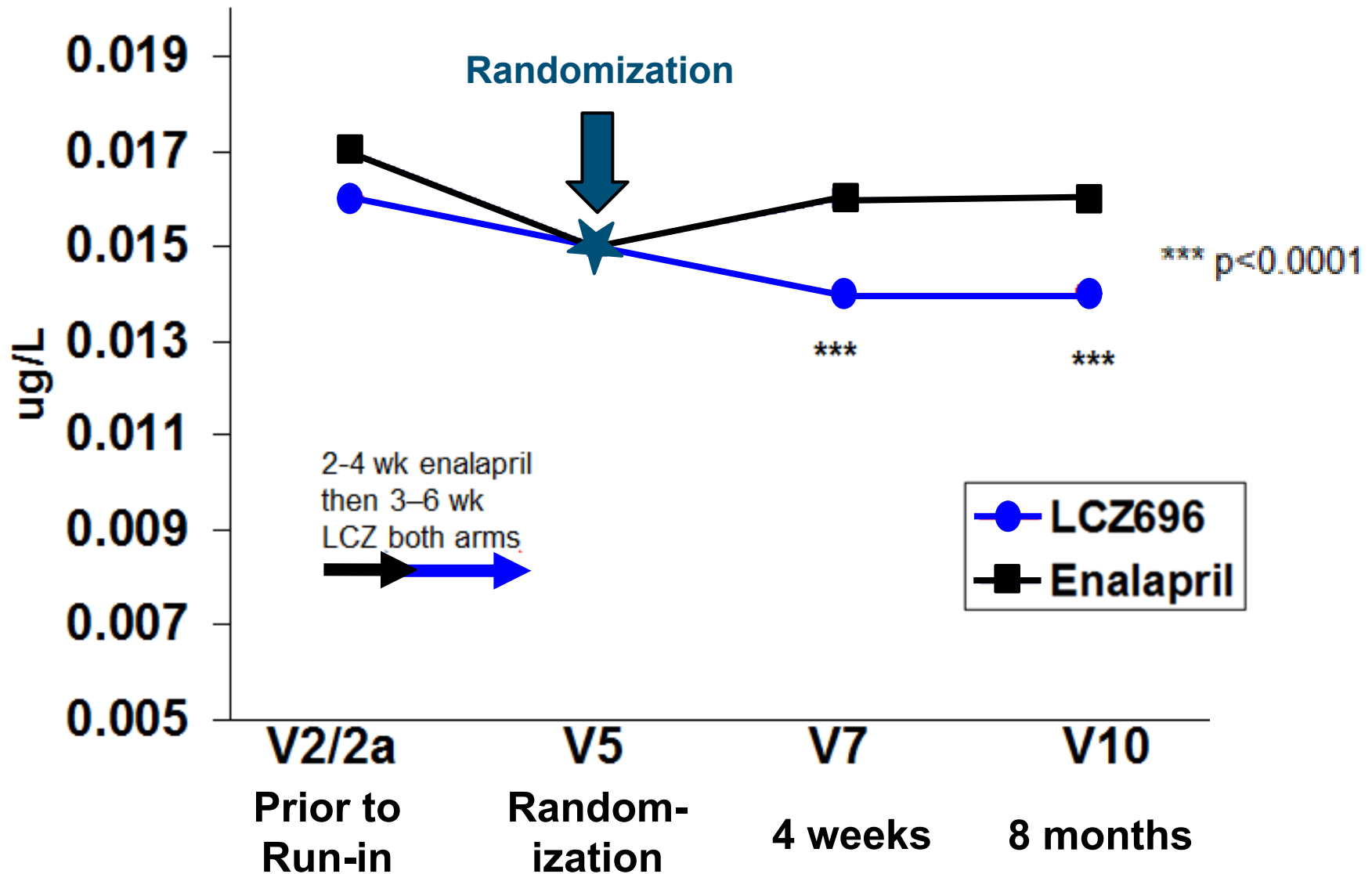
Troponin and prognosis in HFREF

Val-HeFT

HR per 0.05ng/mL increase 1.20 (95% CI 1.10-1.30)



PARADIGM-HF: median hs-TnT ($\mu\text{g/l}$) concentration by visit



PARADIGM-HF: hs-TnT ($\mu\text{g/l}$) by visit

hs-TnT: % of patients $>99^{\text{th}}$ centile ($>0.014 \mu\text{g/l}$)

Treatment	Baseline (prior to run -in)*	Random- ization	4 weeks	8 months
Enalapril	58.2%	52.9%	58.0%	56.9%
LCZ696	56.0%	50.8%	48.4%	48.1%

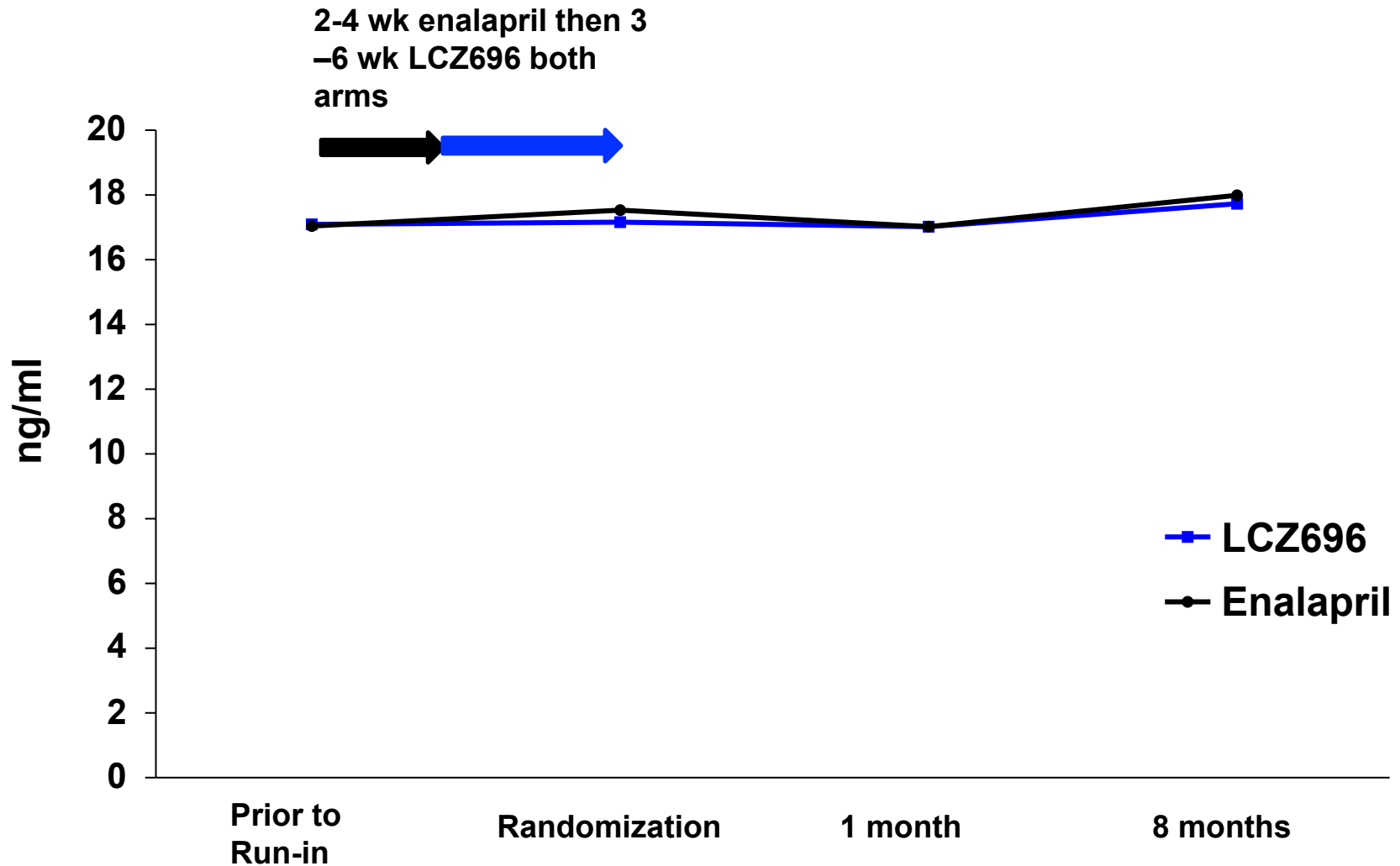
LOD = $0.005 \mu\text{g/l}$ (5 pg/ml)

LOQ = $0.013 \mu\text{g/l}$ (13 pg/ml)

99^{th} centile = $0.0142 \mu\text{g/l}$ (14.2 pg/ml)

**3.9% had values $<LOD$ at baseline*

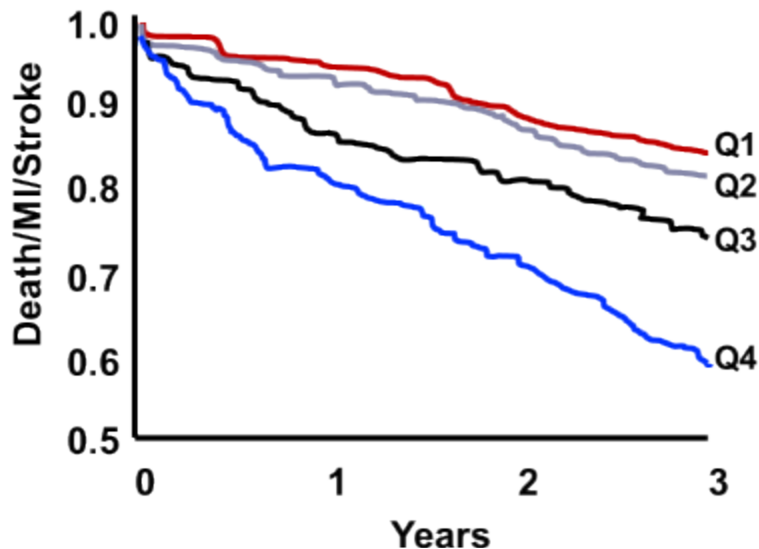
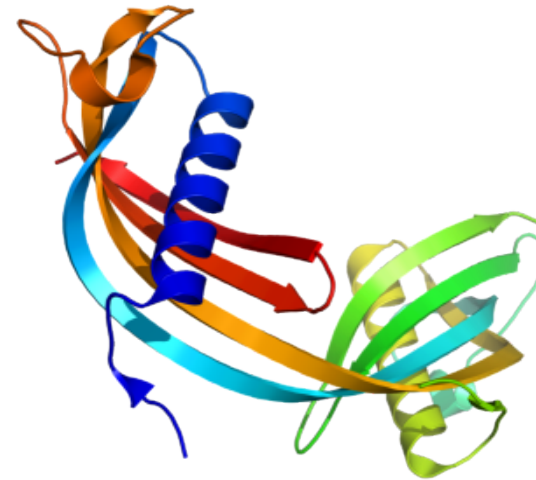
PARADIGM-HF: Galectin-3 by visit



Renal biomarkers and outcomes

Cystatin C

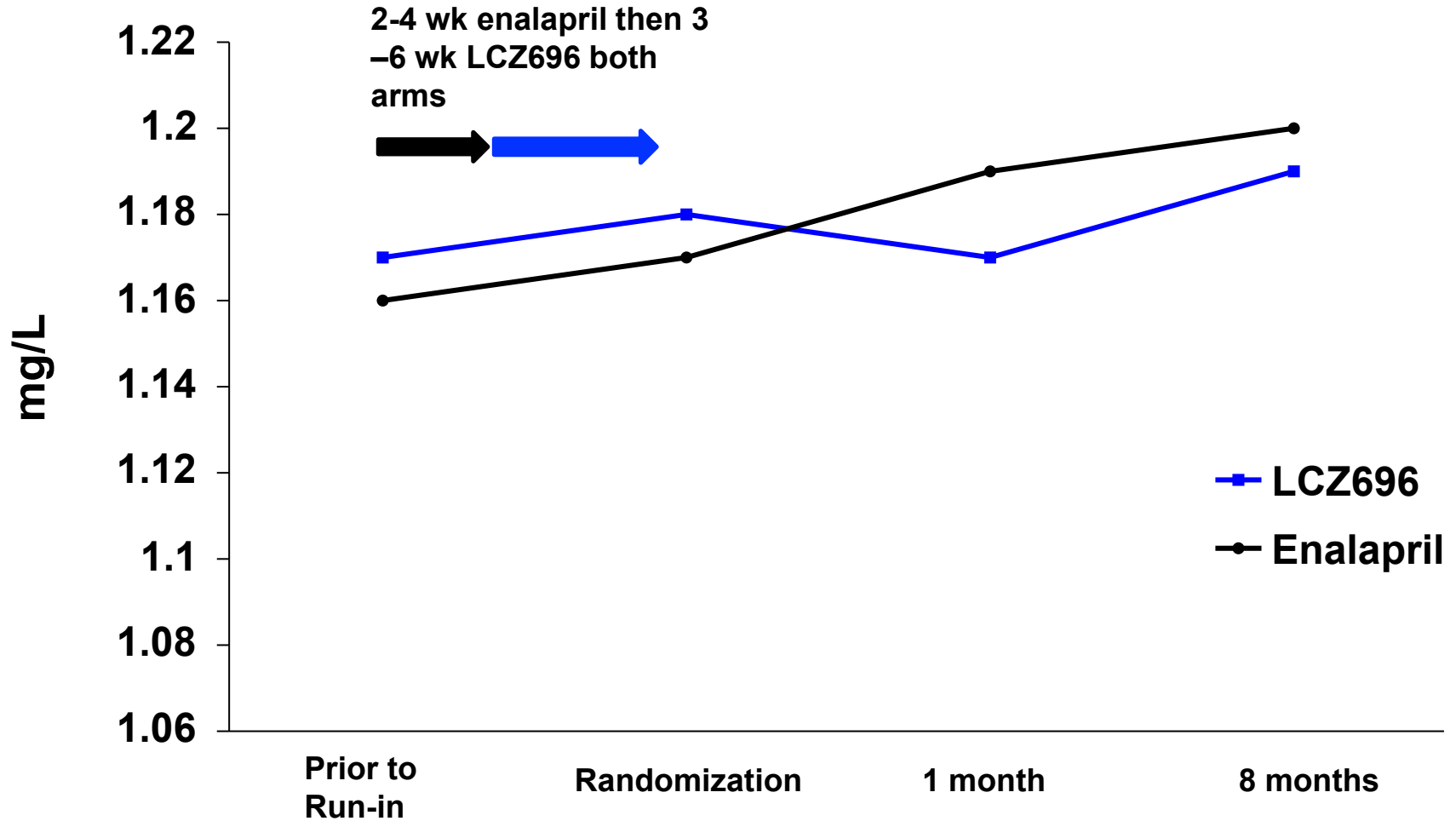
- Cysteine protease inhibitor
- Less influenced by age, sex, or race
- Low molecular weight
- Freely filtered and neither secreted nor reabsorbed



Circulation: Heart Failure. 2012; 5: 602-609

- Sensitive measure of glomerular filtration
- Higher levels associated with poorer prognosis

PARADIGM-HF: Cystatin C



Renal Outcomes

Renal progression: Protocol-defined endpoint

Endpoint	LCZ696 n/N (%)	Enalapril n/N (%)	Hazard Ratio (95% CI)	P- value 1-sided
Composite	94/4187 (2.2)	108/4212 (2.6)	0.86 (0.65, 1.13)	0.1424
(i) 50% decline in eGFR	32/4187 (0.8)	42/4212 (1.0)	0.75 (0.47, 1.19)	0.1118
(ii) >30 ml/min/1.73m ² decline in eGFR to <60 ml/min/1.73m ²	77/4187 (1.8)	69/4212 (1.6)	1.11 (0.80, 1.53)	0.7283
(iii) Reaching ESRD	8/4187 (0.2)	16/4212 (0.4)	0.50 (0.21, 1.16)	0.0529

Renal progression: Conventional renal endpoint (*post-hoc analysis*)

Post-hoc analysis – based on conventional endpoint for renal disease progression (50% decline in eGFR or reaching ESRD)

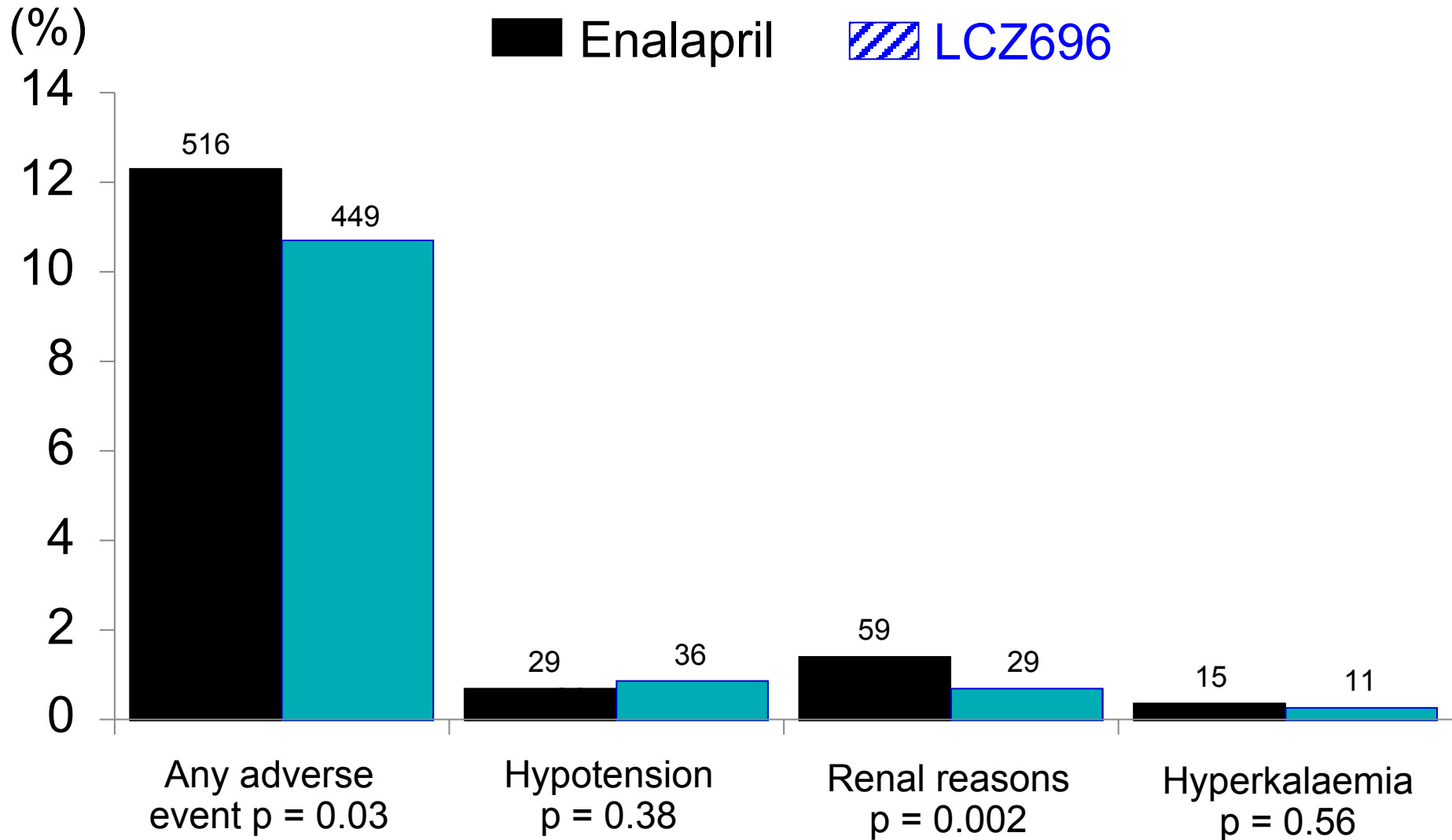
Endpoint	LCZ696 n/N (%)	Enalapril n/N (%)	Hazard Ratio (95% CI)	P Value 2-sided
Composite	37/4187 (0.9)	58/4212 (1.4)	0.63 (0.42, 0.95)	0.0276
(i) 50% decline in eGFR	32/4187 (0.8)	42/4212 (1.0)	0.75 (0.47, 1.19)	0.2236
(iii) Reaching ESRD	8/4187 (0.2)	16/4212 (0.4)	0.50 (0.21, 1.16)	0.1057

Safety

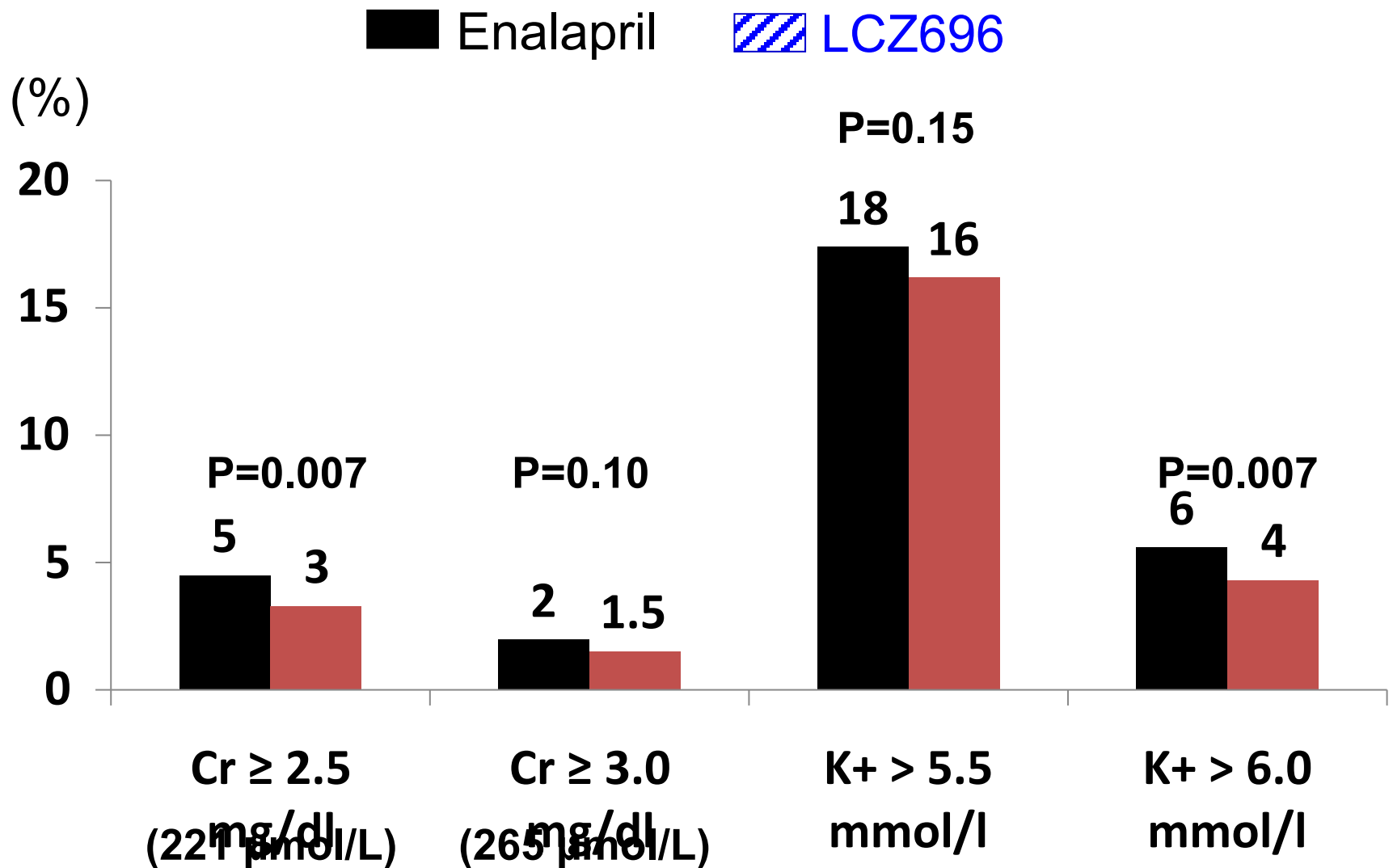
“With regard to healing the sick, I will take care that they suffer no hurt or damage”

Hippocratic Oath

PARADIGM-HF: Adverse events leading to permanent study drug discontinuation



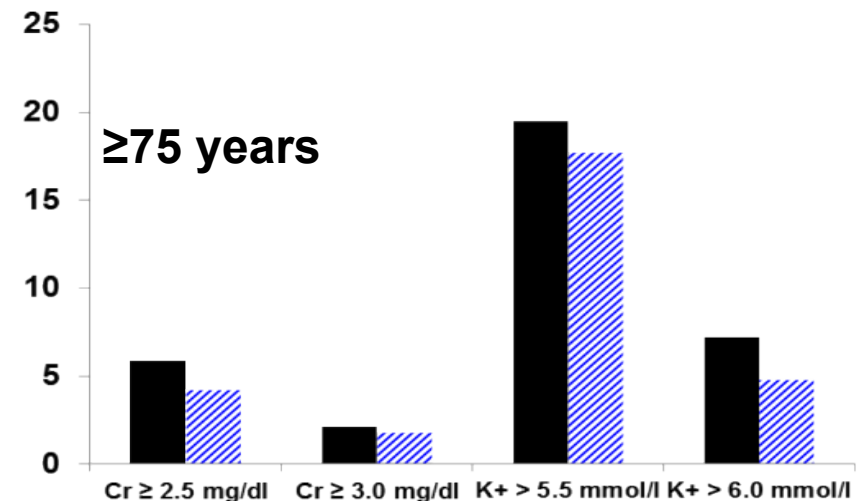
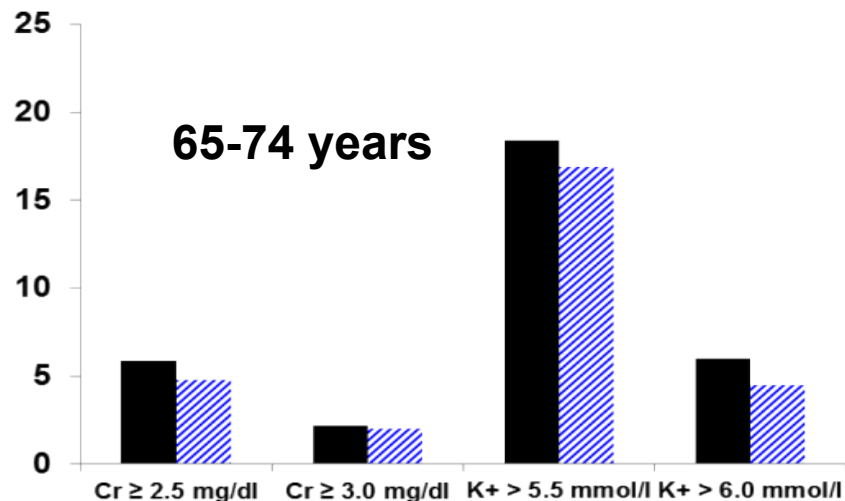
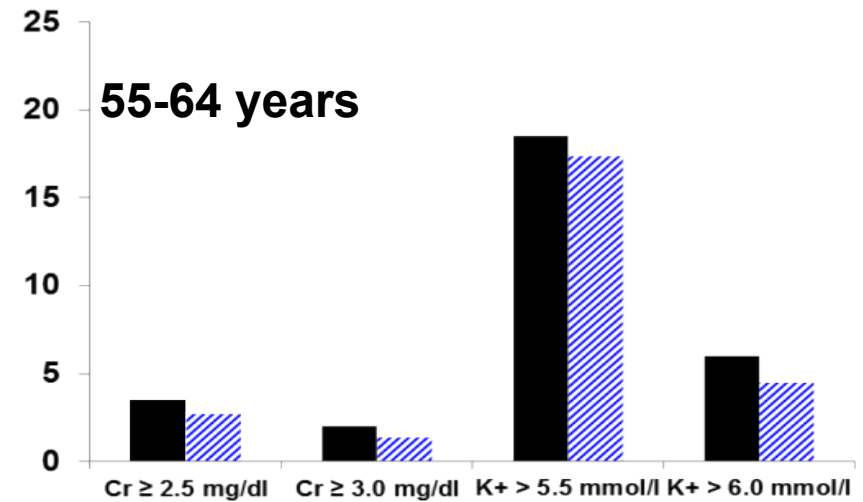
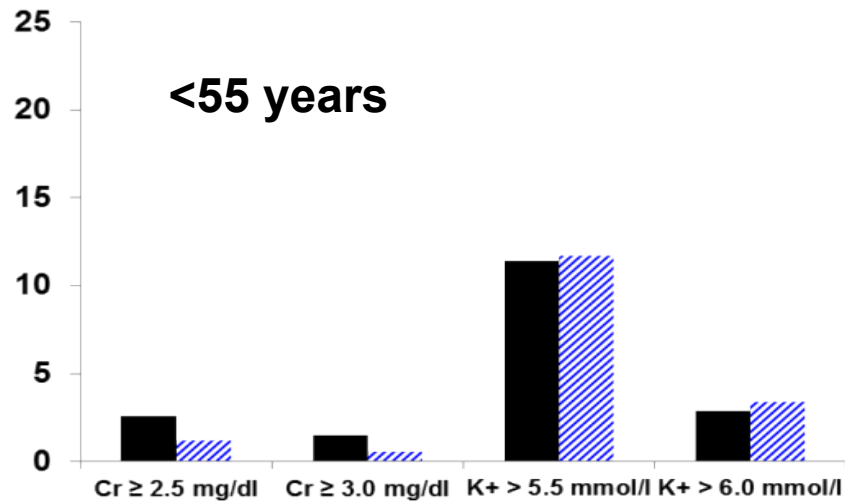
PARADIGM-HF: Renal safety



PARADIGM-HF: Renal safety by age

P for interaction >0.05 for all events

Enalapril LCZ696



Summary

Treatment with LCZ696 led to:

- **Lower NT-proBNP and higher BNP levels**
- **Lower troponin**
- **No change in galectin-3 and cystatin C**
- **No difference in rates of the composite renal outcome though reduction in 50% decline eGFR/ESRD**
- **Less renal adverse events, even in the elderly**

Thank you