Role of LCZ696 in Contemporary Treatment of HFrEF and HFpEF - Present and Future

Kirkwood F. Adams, Jr. MD
Associate Professor of Medicine and Radiology
On Behalf of the UNC Heart Failure Research Group

Toronto Ottawa Heart Summit
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Disclosures

Novartis Pharmaceutics

- Clinical Research Funding
- Consultation and Ad Boards

Outline of LCZ696 Update

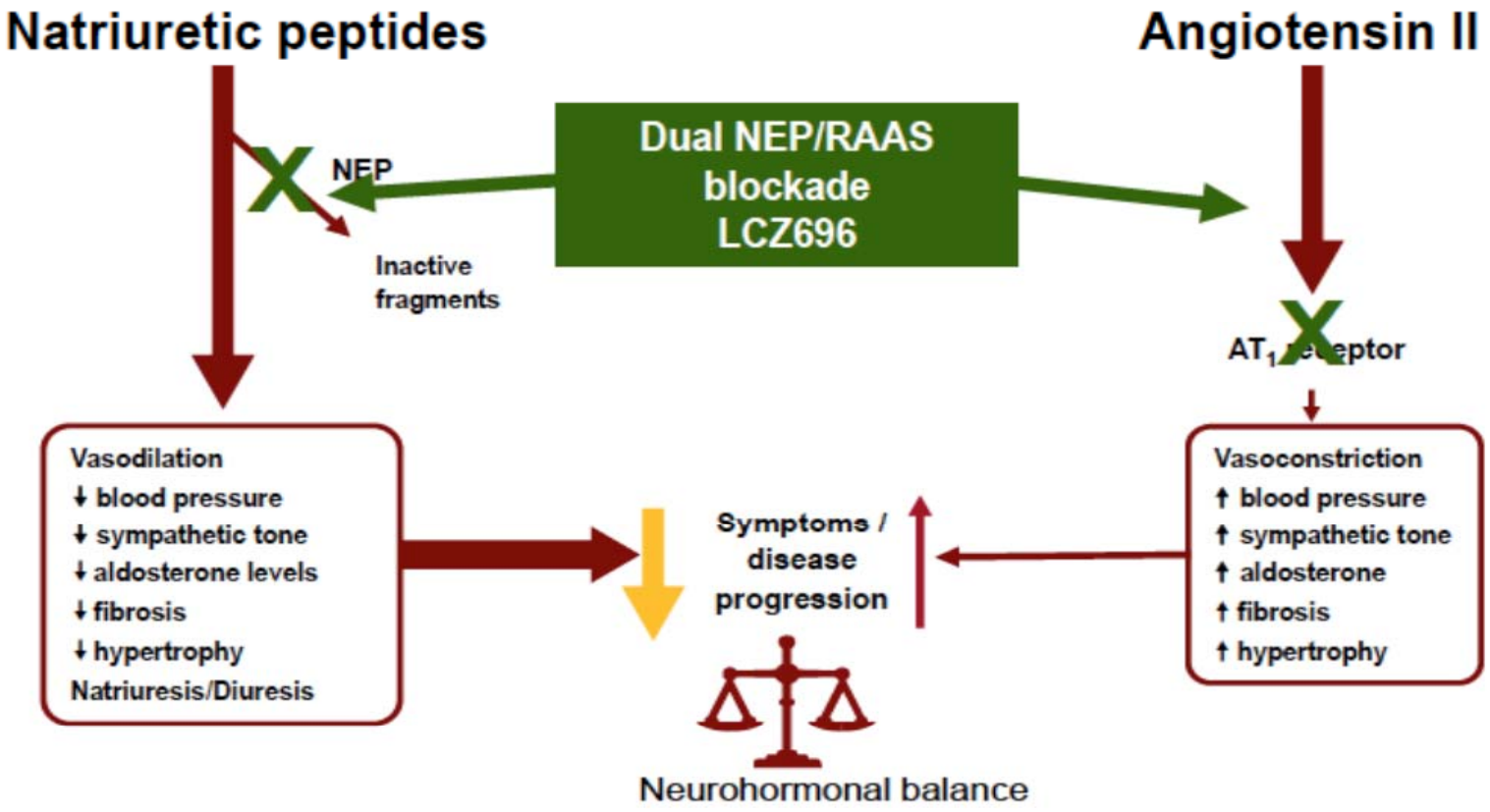
HFrEF Now and HFpEF Future?

- Scientific Rationale for LCZ696 Como
- HFrEF - PARADIGM Primary Trial Results
- PARADIGM - Supportive Analysis
- LCZ Practice Guidelines
- PARAMONT – Pilot LCZ696 in HFpEF
- PARAGON – LCZ696 Outcomes HFpEF

Rationale for LCZ696 – Blockade/Activation

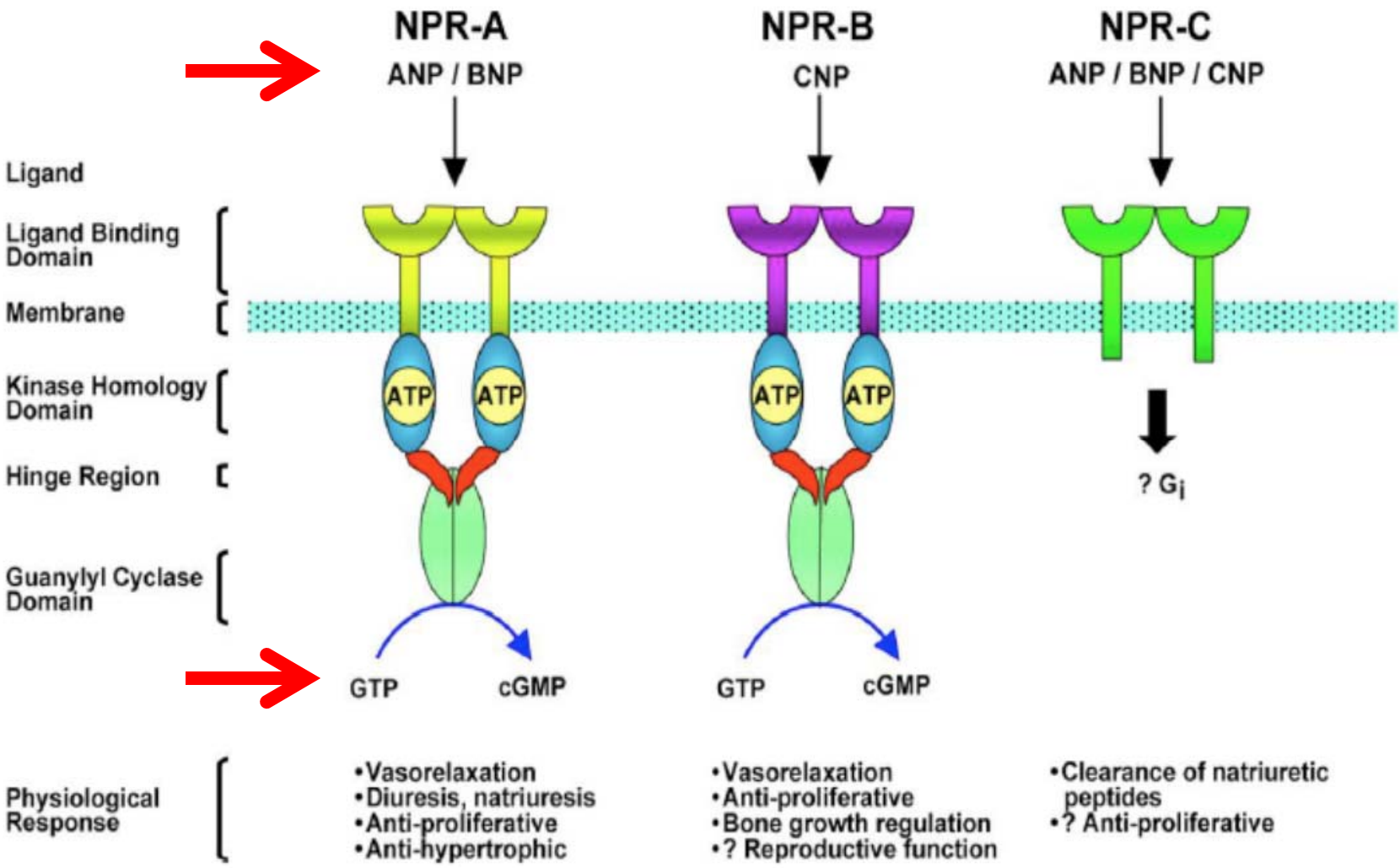
Dual angiotensin receptor blockade and NEP inhibition

Counter-regulatory systems



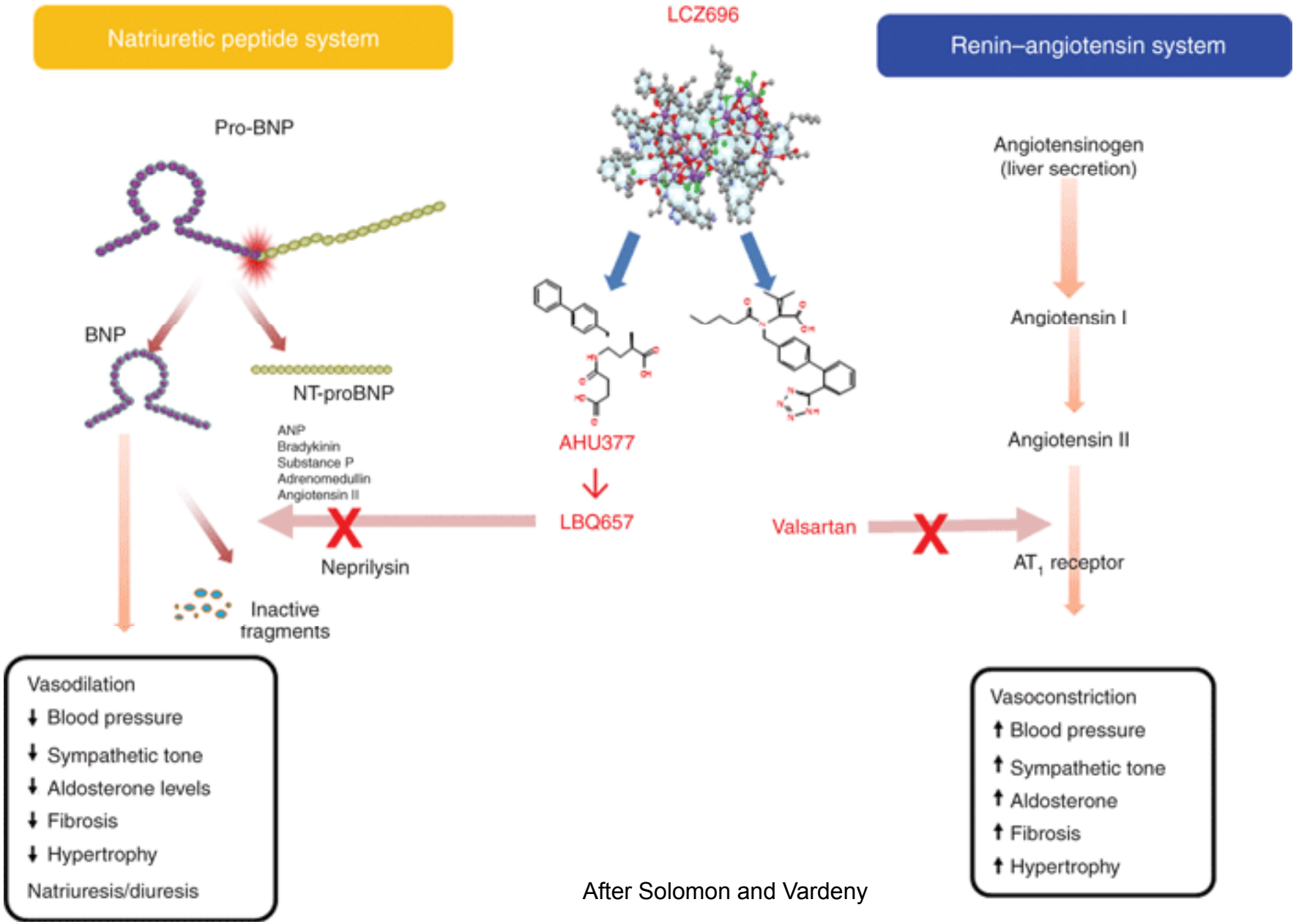
Schrier, et al. N Engl J Med 1999;341:577–85; Levin et al. N Engl J Med 1998;339:321–8;

Structure and Known Functions of the Natriuretic Peptide Receptors (NPRs)



Source: Gardner, D. G. et al. Hypertension 2007;49:419-426

LCZ696 – 2 Drugs = ARB and Neprilysin Inhibition

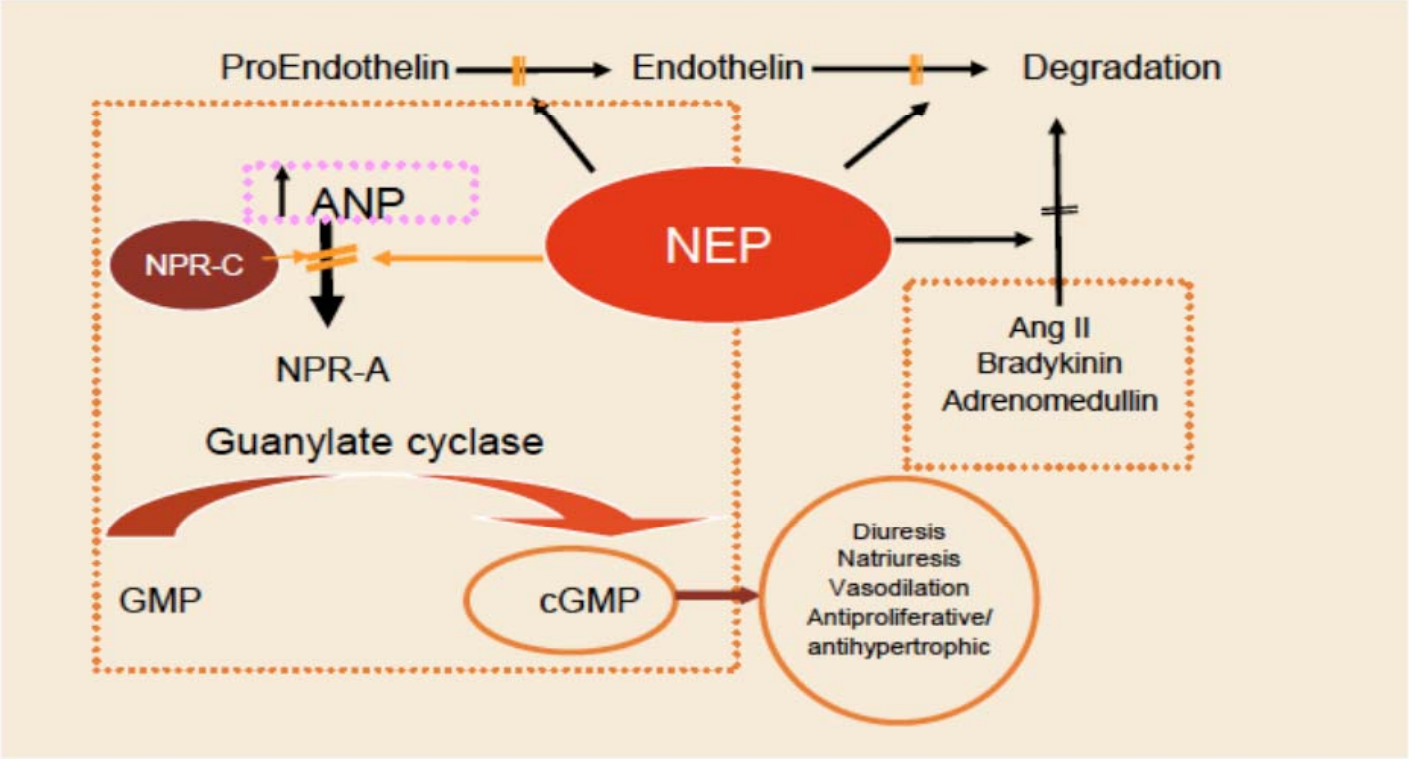


After Solomon and Vardeny

Don’t forget ANP – Also Substrate for NEP

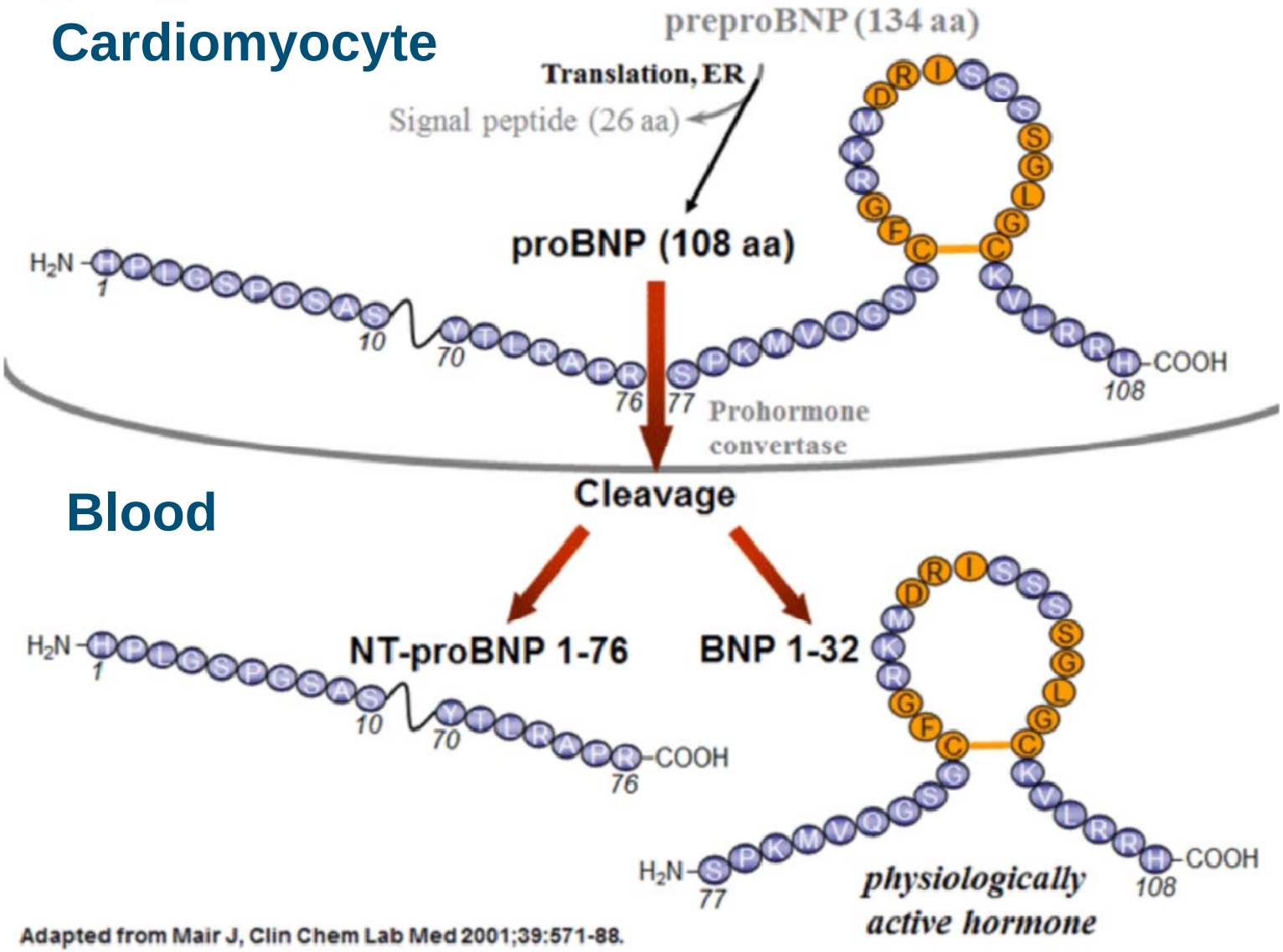
Neprilysin (NEP) is responsible for natriuretic peptide degradation

Metabolism of ANP and other peptide hormones by NEP



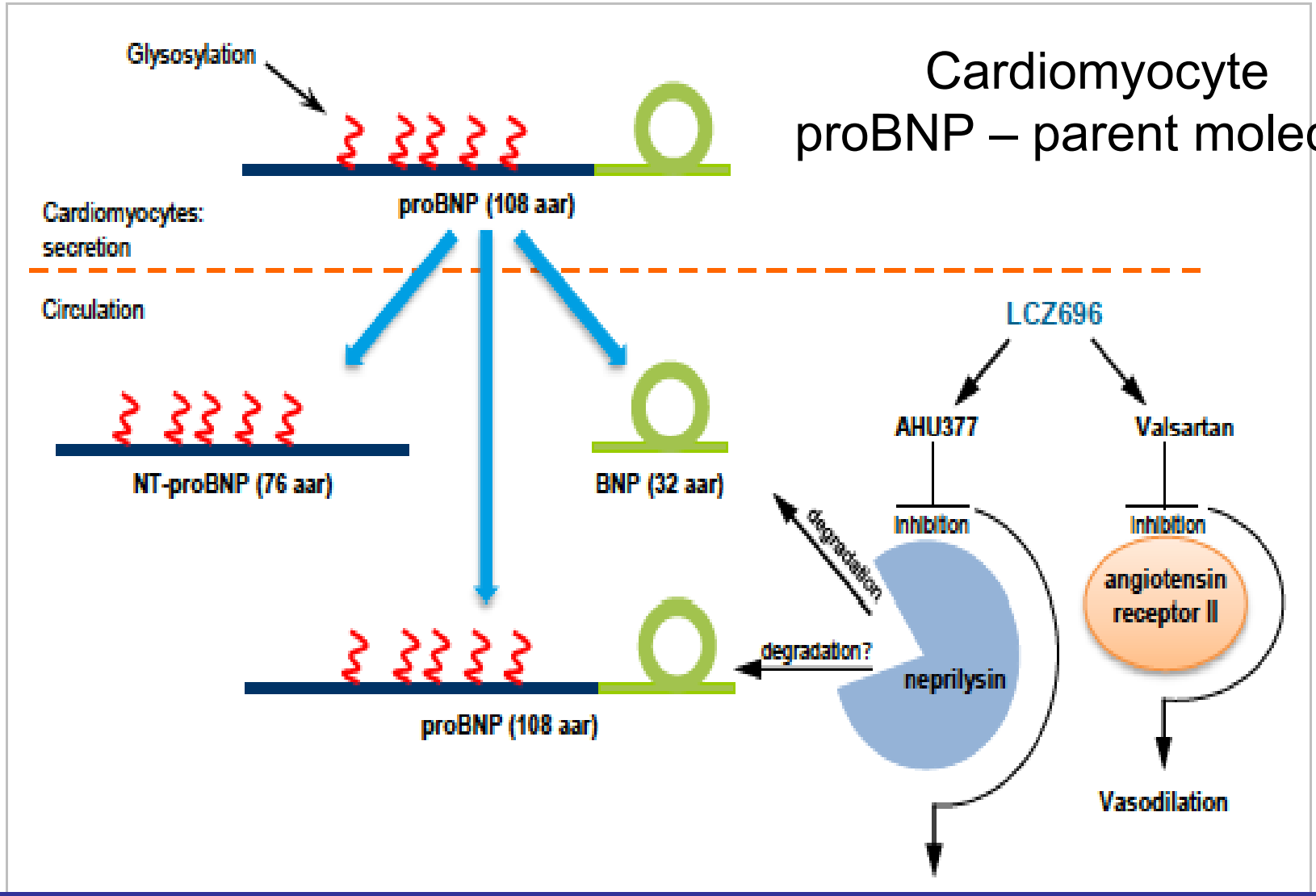
Ferro et al. Circulation 1998;97:2323–30

NT pro BNP and BNP



Adapted from Mair J, Clin Chem Lab Med 2001;39:571-88.

Neprilysin – Enzymatic Action – LCZ Block

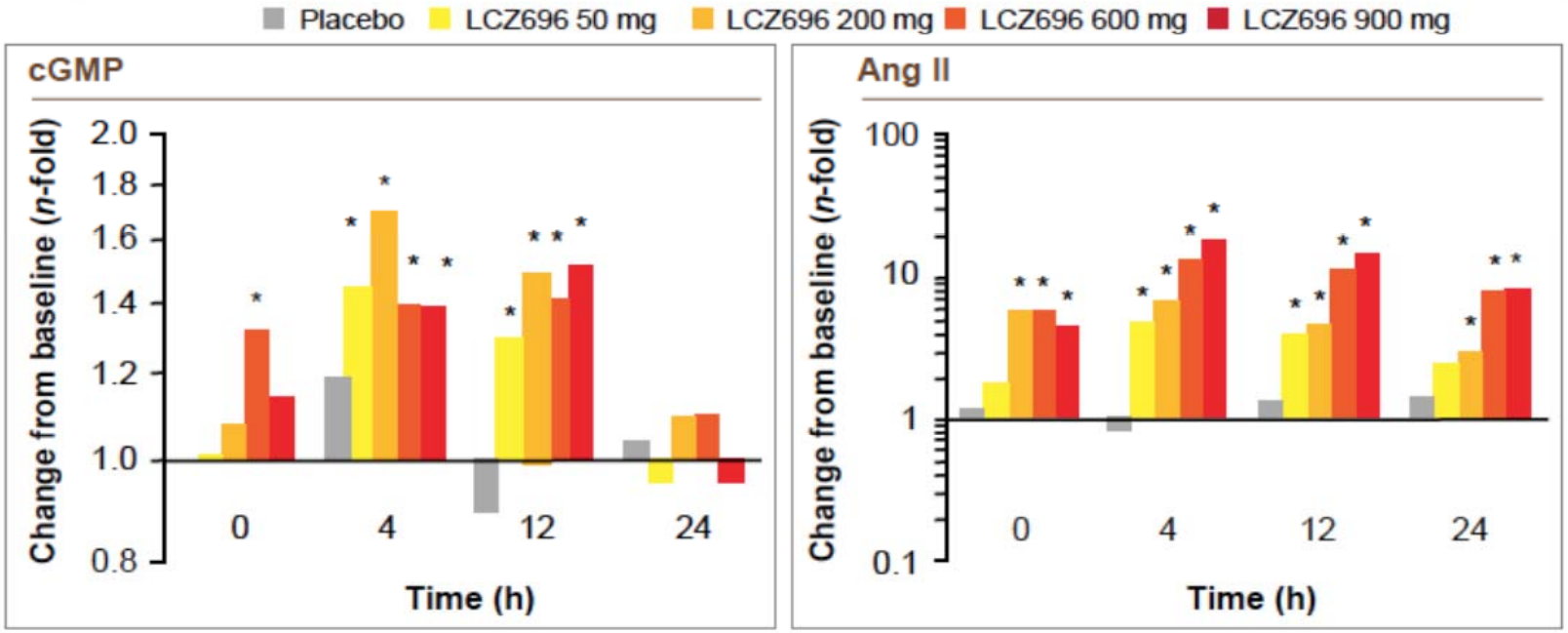


Cardiomyocyte
proBNP – parent molecule

In Vivo Effects of LCZ – Key Biomarkers

Effects of LCZ696 on biomarkers of NEP inhibition and AT1 receptor blockade

- Healthy volunteers received once-daily oral LCZ696 50, 200, 600 or 900 mg or placebo for 14 days
- cGMP measured as a biomarker of NEP inhibition and Ang II as a measure of AT1 receptor blockade



*p < 0.05 vs placebo, n=8/group
Values are n-fold change from baseline (logarithmic scale) at the post-dose time points indicated
Ang, angiotensin; AT1, angiotensin II type 1; cGMP, cyclic guanosine monophosphate; NEP, neprilysin

Gu et al. J Clin Pharmacol 2010;50:401–14

A Comparison of Angiotensin Receptor-Neprilysin Inhibition (ARNI) With ACE Inhibition in the Long-Term Treatment of Chronic Heart Failure With a Reduced Ejection Fraction

Milton Packer, John J.V. McMurray, Akshay S. Desai, Jianjian Gong, Martin P. Lefkowitz, Adel R. Rizkala, Jean L. Rouleau, Victor C. Shi, Scott D. Solomon, Karl Swedberg and Michael R. Zile for the PARADIGM-HF Investigators and Committees

Aim of the PARADIGM-HF Trial

Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF)

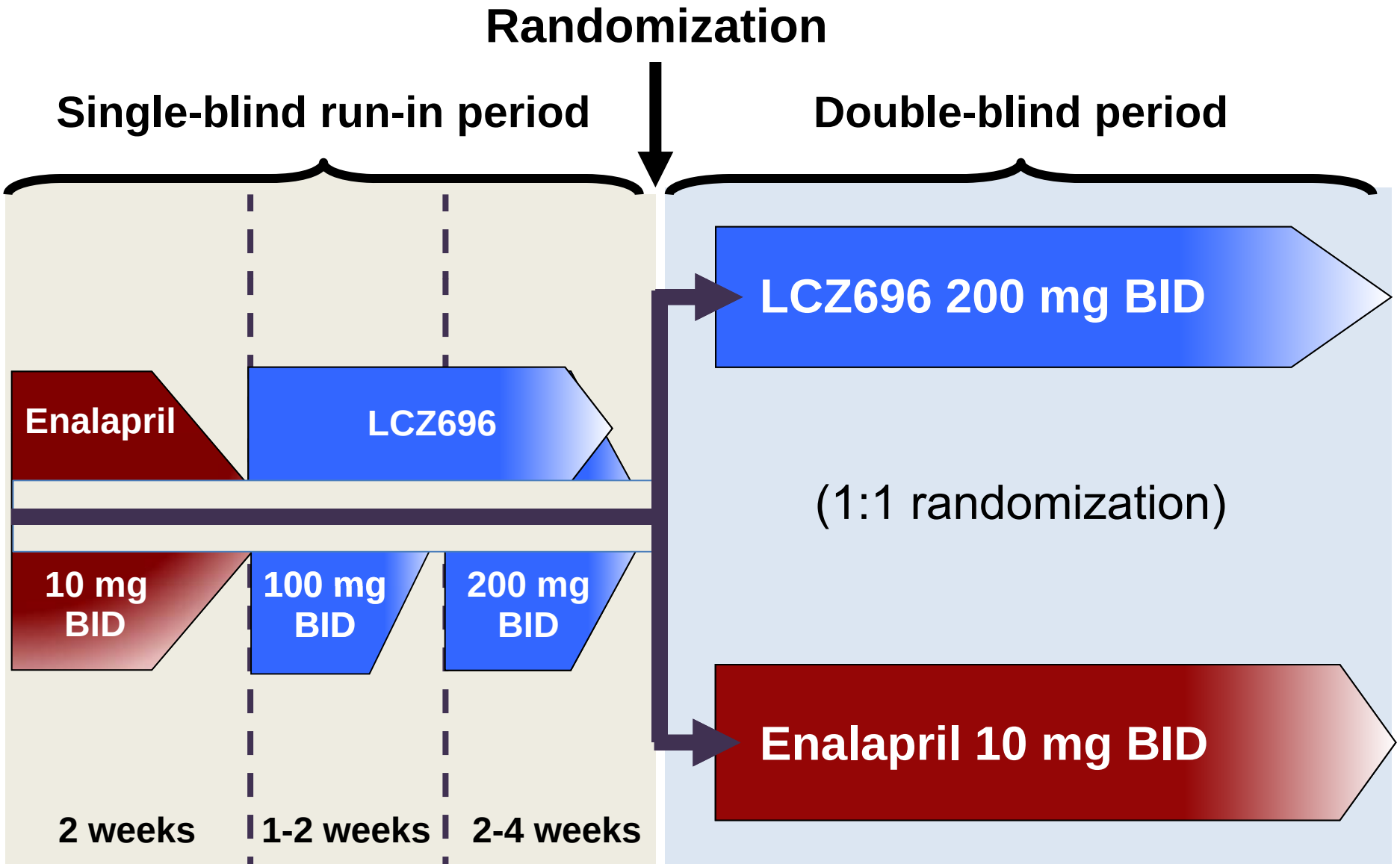
LCZ696 400 mg daily ⟷ **Enalapril 20 mg daily**

SPECIFICALLY DESIGNED TO REPLACE CURRENT USE OF ACE INHIBITORS AND ANGIOTENSIN RECEPTOR BLOCKERS AS THE CORNERSTONE OF THE TREATMENT OF HEART FAILURE

PARADIGM-HF: Entry Criteria

- NYHA class II-IV heart failure
- LV ejection fraction ≤ 40% ➔ 35%
- BNP ≥ 150 (or NT-proBNP ≥ 600), but one-third lower if hospitalized for heart failure within 12 months
- Any use of ACE inhibitor or ARB, but able to tolerate stable dose equivalent to at least enalapril 10 mg daily for at least 4 weeks
- Guideline-recommended use of beta-blockers and mineralocorticoid receptor antagonists
- Systolic BP ≥ 95 mm Hg, eGFR ≥ 30 ml/min/1.73 m^2 and serum K ≤ 5.4 mEq/L at randomization

PARADIGM-HF: Study Design



PARADIGM-HF: Baseline Characteristics

	LCZ696 (n=4187)	Enalapril (n=4212)
Age (years)	63.8 ± 11.5	63.8 ± 11.3
Women (%)	21.0%	22.6%
Ischemic cardiomyopathy (%)	59.9%	60.1%
LV ejection fraction (%)	29.6 ± 6.1	29.4 ± 6.3
NYHA functional class II / III (%)	71.6% / 23.1%	69.4% / 24.9%
Systolic blood pressure (mm Hg)	122 ± 15	121 ± 15
Heart rate (beats/min)	72 ± 12	73 ± 12
N-terminal pro-BNP (pg/ml)	1631 (885-3154)	1594 (886-3305)
B-type natriuretic peptide (pg/ml)	255 (155-474)	251 (153-465)
History of diabetes	35%	35%
Digitalis	29.3%	31.2%
Beta-adrenergic blockers	93.1%	92.9%
Mineralocorticoid antagonists	54.2%	57.0%
ICD and/or CRT	16.5%	16.3%

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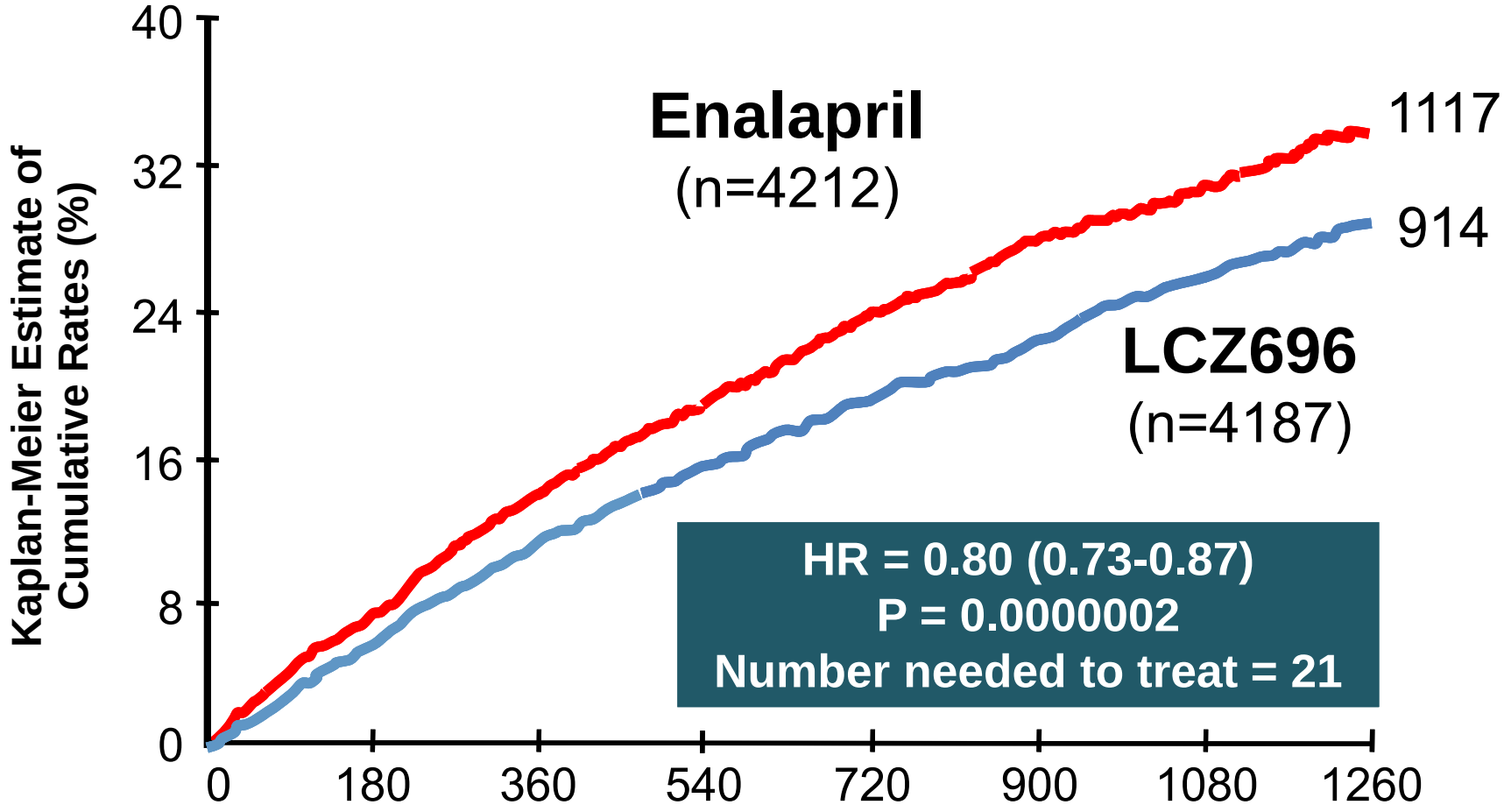
ESTABLISHED IN 1812 SEPTEMBER 11, 2014 VOL. 371 NO. 11

Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure

John J.V. McMurray, M.D., Milton Packer, M.D., Akshay S. Desai, M.D., M.P.H., Jianjian Gong, Ph.D., Martin P. Lefkowitz, M.D., Adel R. Rizkala, Pharm.D., Jean L. Rouleau, M.D., Victor C. Shi, M.D., Scott D. Solomon, M.D., Karl Swedberg, M.D., Ph.D., and Michael R. Zile, M.D., for the PARADIGM-HF Investigators and Committees*

(all comparisons are versus enalapril 20 mg daily, not versus placebo)

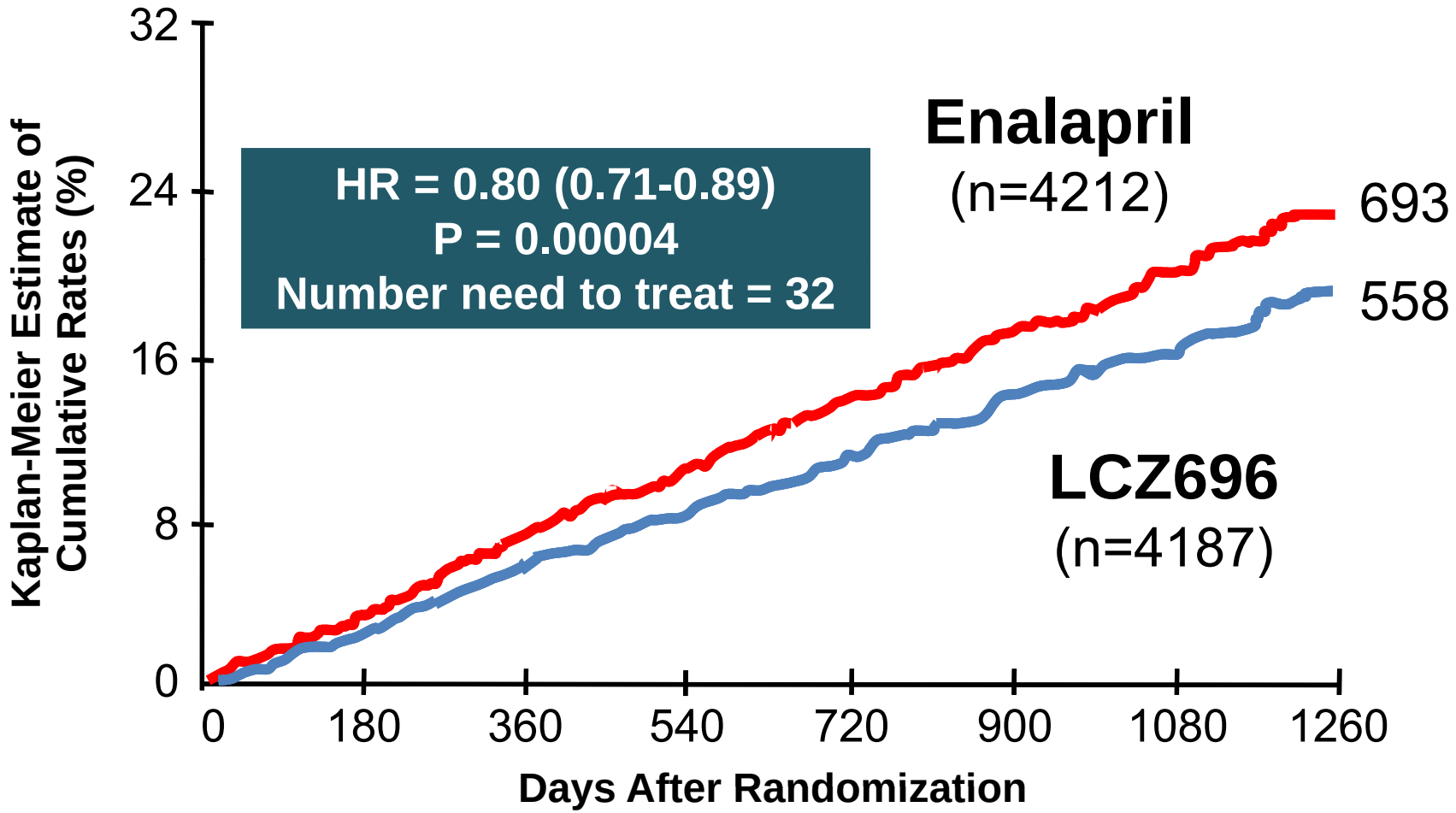
PARADIGM-HF: Cardiovascular Death or Heart Failure Hospitalization (Primary Endpoint)



Patients at Risk

LCZ696	4187	3922	3663	3018	2257	1544	896	249
Enalapril	4212	3883	3579	2922	2123	1488	853	236

PARADIGM-HF: Cardiovascular Death



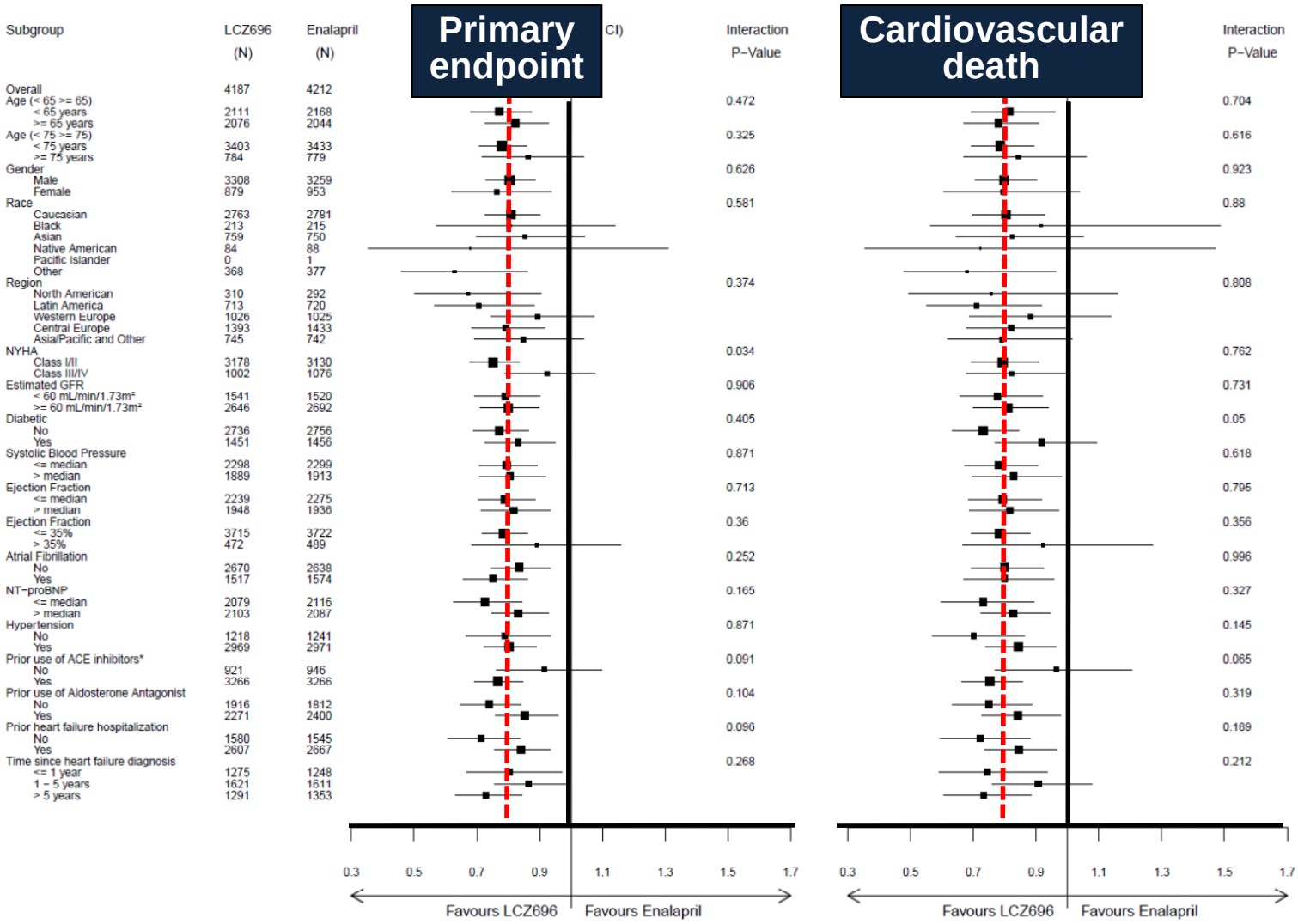
Patients at Risk

LCZ696	4187	4056	3891	3282	2478	1716	1005	280
Enalapril	4212	4051	3860	3231	2410	1726	994	279

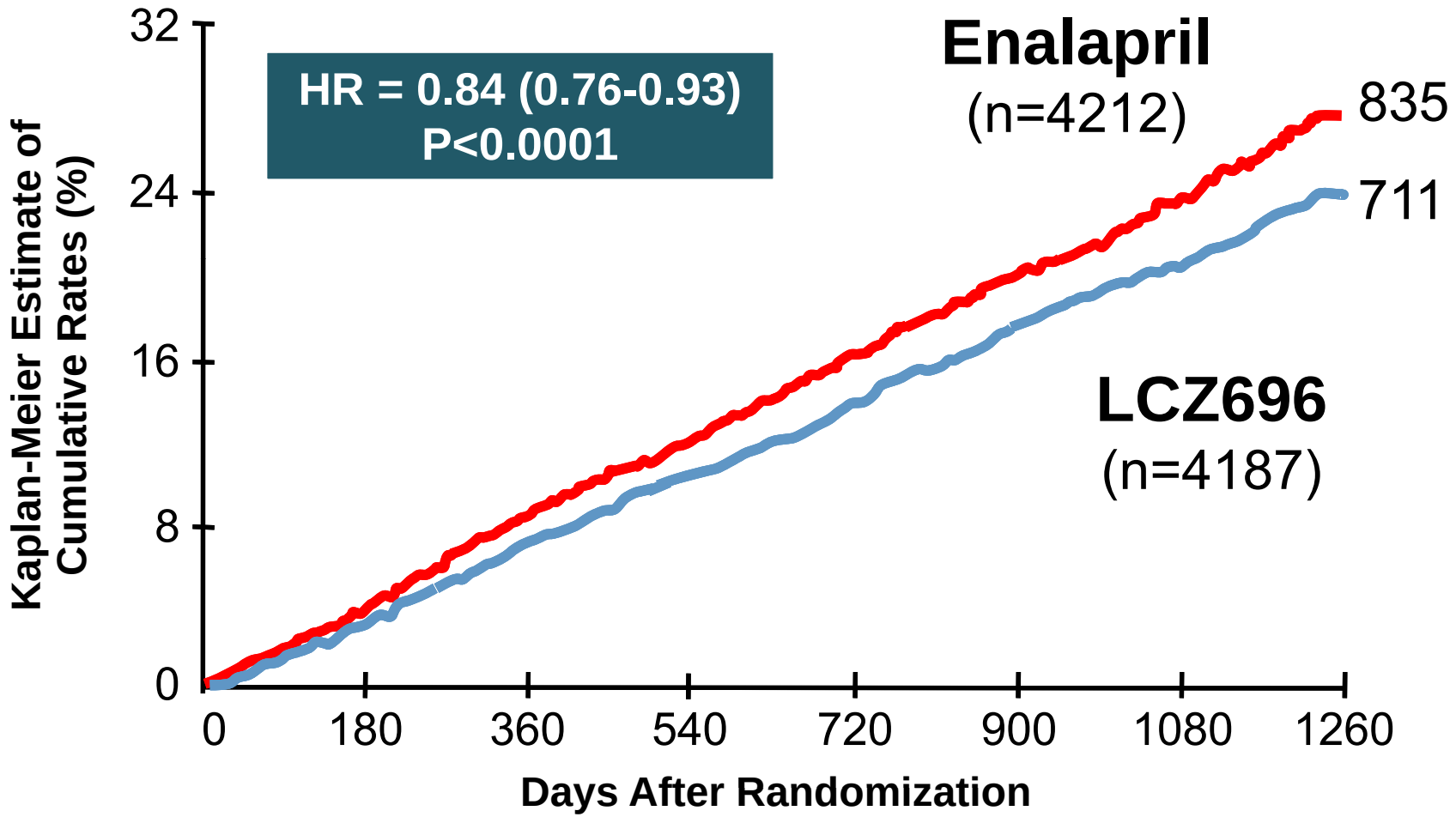
PARADIGM-HF: Effect of LCZ696 vs Enalapril on Primary Endpoint and Its Components

	LCZ696 (n=4187)	Enalapril (n=4212)	Hazard Ratio (95% CI)	P Value
Primary endpoint	914 (21.8%)	1117 (26.5%)	0.80 (0.73-0.87)	0.0000002
Cardiovascular death	558 (13.3%)	693 (16.5%)	0.80 (0.71-0.89)	0.00004
Hospitalization for heart failure	537 (12.8%)	658 (15.6%)	0.79 (0.71- 0.89)	0.00004

LCZ696 vs Enalapril on Primary Endpoint and on Cardiovascular Death, by Subgroups



PARADIGM-HF: All-Cause Mortality



Patients at Risk

LCZ696	4187	4056	3891	3282	2478	1716	1005	280
Enalapril	4212	4051	3860	3231	2410	1726	994	279

PARADIGM-HF: Effect of LCZ696 vs Enalapril on Secondary Endpoints

	LCZ696 (n=4187)	Enalapril (n=4212)	Treatment effect	P Value
KCCQ clinical summary score at 8 months	– 2.99 ± 0.36	– 4.63 ± 0.36	1.64 (0.63, 2.65)	0.001
New onset atrial fibrillation	84/2670 (3.2%)	83/2638 (3.2%)	Hazard ratio 0.97 (0.72,1.31)	0.84
Protocol-defined decline in renal function	94/4187 (2.3%)	108/4212 (2.6%)	Hazard ratio 0.86 (0.65, 1.13)	0.28

PARADIGM-HF: Adverse Events

	LCZ696 (n=4187)	Enalapril (n=4212)	P Value
Prospectively identified adverse events			
Symptomatic hypotension	588	388	< 0.001
Serum potassium > 6.0 mmol/l	181	236	0.007
Serum creatinine ≥ 2.5 mg/dl	139	188	0.007
Cough	474	601	< 0.001
Discontinuation for adverse event	**449**	**516**	**0.02**
Discontinuation for hypotension	36	29	NS
Discontinuation for hyperkalemia	11	15	NS
Discontinuation for renal impairment	29	59	0.001
Angioedema (adjudicated)			
Medications, no hospitalization	16	9	NS
Hospitalized; no airway compromise	3	1	NS
Airway compromise	0	0	----

PARADIGM-HF: Summary of Findings

In heart failure with reduced ejection fraction, when compared with recommended doses of enalapril:

LCZ696 was *more effective* than enalapril in . . .

- Reducing the risk of CV death and HF hospitalization
- Reducing the risk of CV death by *incremental* 20%
- Reducing the risk of HF hospitalization by *incremental* 21%
- Reducing all-cause mortality by *incremental* 16%
- *Incrementally* improving symptoms and physical limitations

LCZ696 was *better tolerated* than enalapril . . .

- Less likely to cause cough, hyperkalemia or renal impairment
- Less likely to be discontinued due to an adverse event
- More hypotension, but no increase in discontinuations
- Not more likely to cause serious angioedema

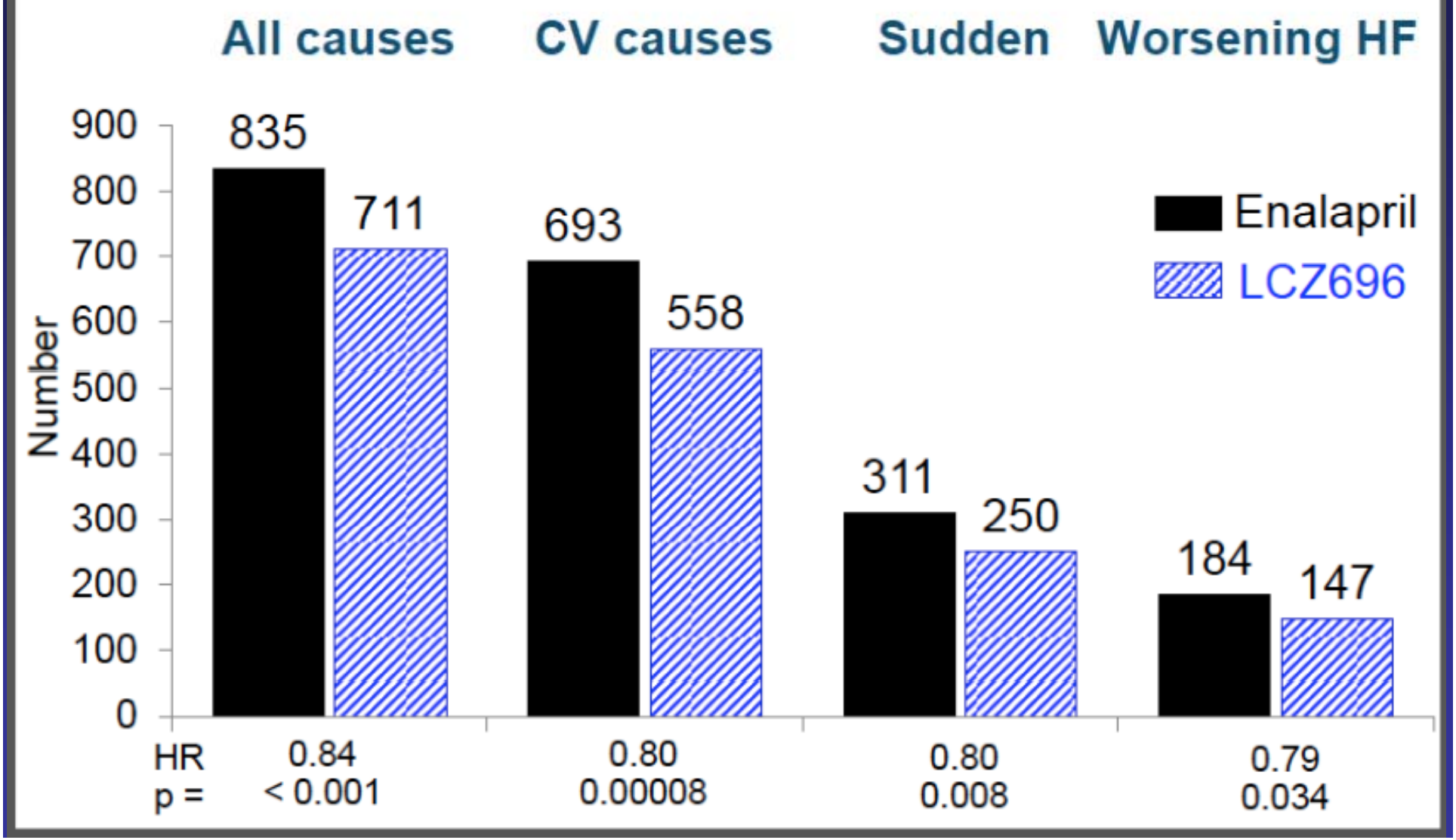
Key Ancillary Evidence on LCZ696 in HFrEF

A View At Totality of Evidence

Supportive Endpoints

Key Biomarker Findings

PARADIGM-HF: cause/ mode of death

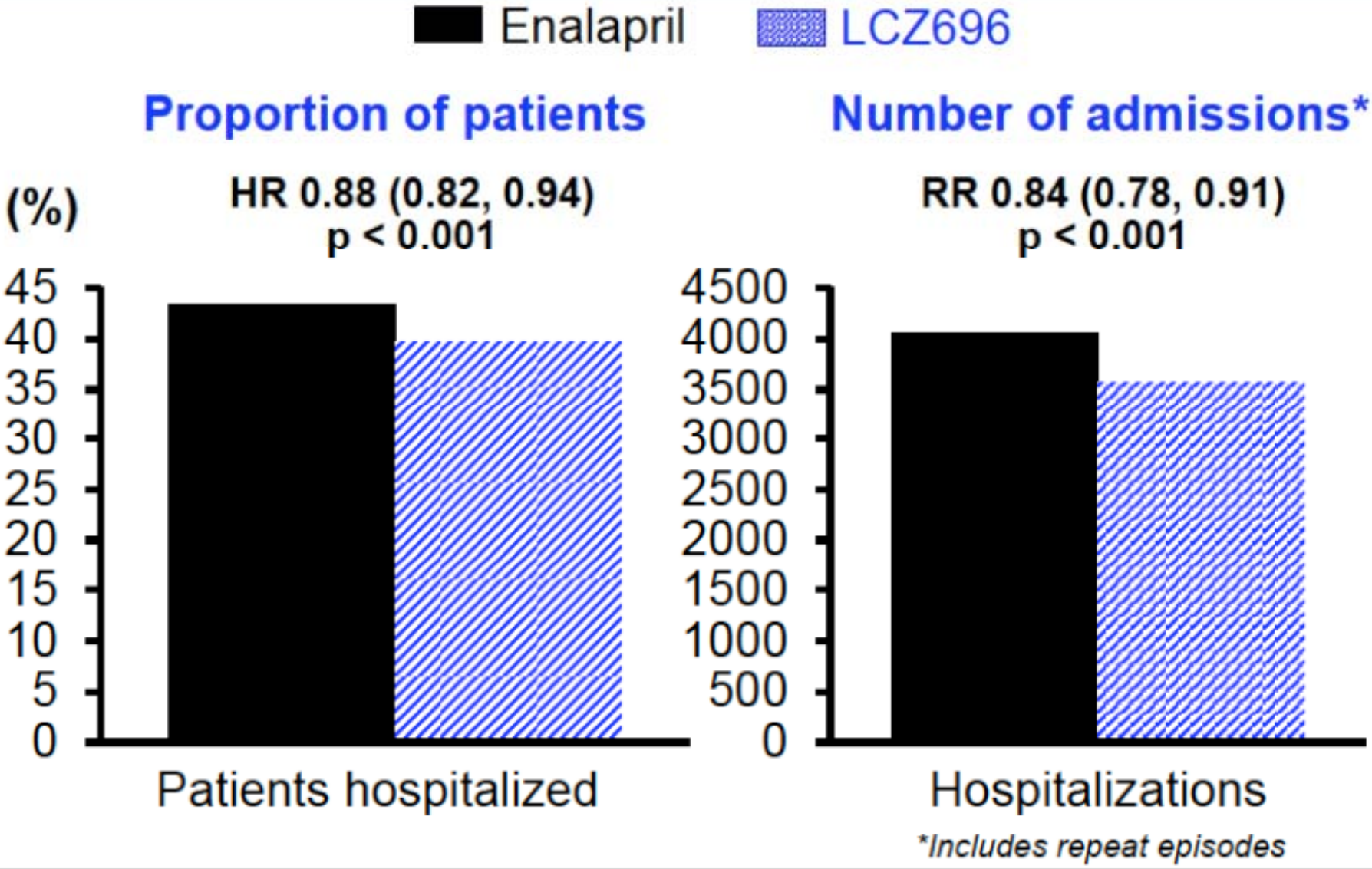


PARADIGM-HF: Intensive care management

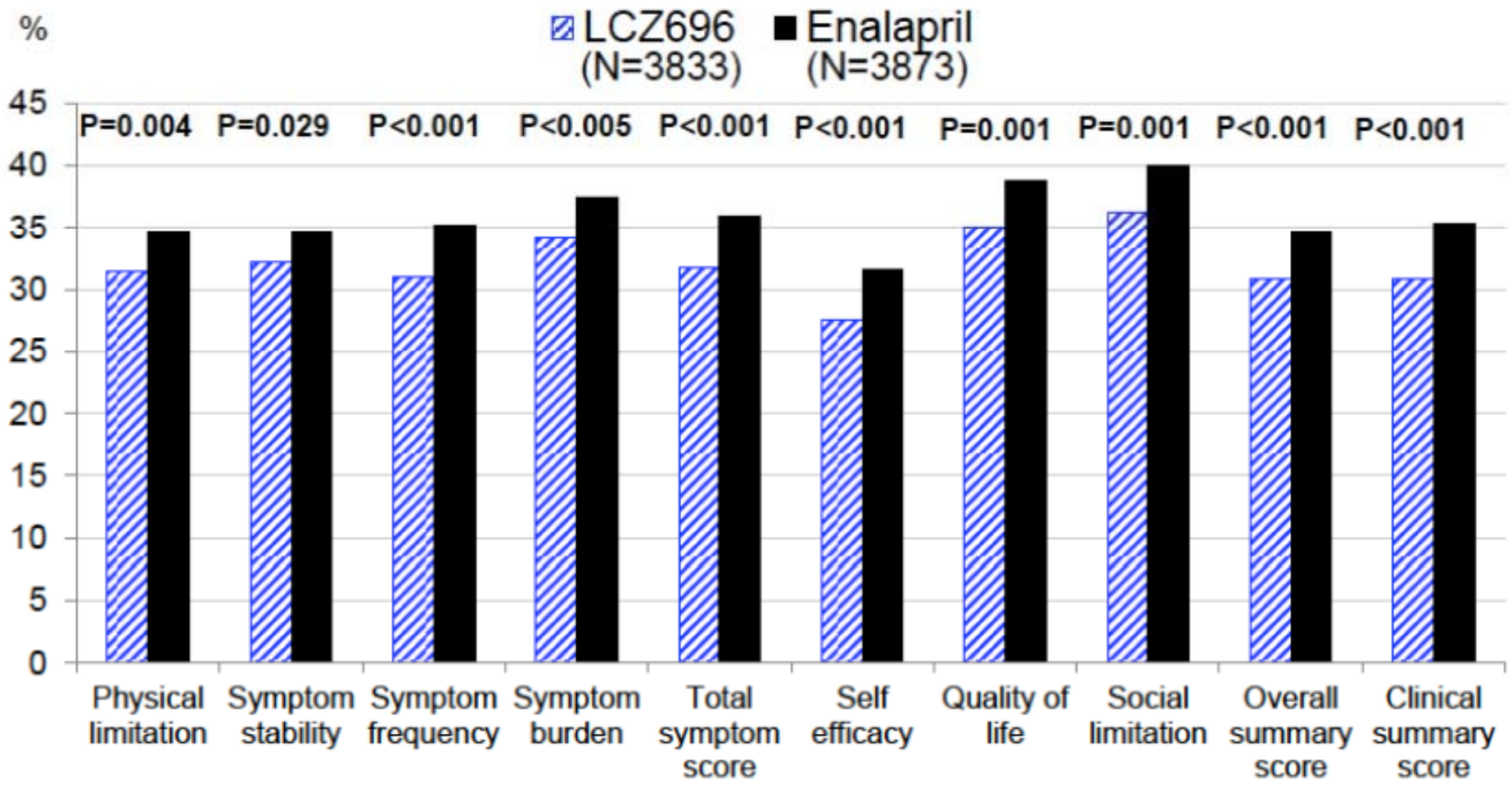
Intensive management in hospital

	LCZ696 N=4187 n (%)	Enalapril N=4212 n (%)	P-value
Number of patients requiring intensive care	549 (13.1)	623 (14.8)	0.87 (0.78, 0.98) P=0.019
Total number of stays in intensive care	768	879	0.82 (0.72, 0.94) P=0.005
Patients receiving IV positive inotropic drugs	161 (3.8%)	229 (5.4%)	0.69 (0.57, 0.85) P < 0.001

PARADIGM-HF: Hospitalization for any cause

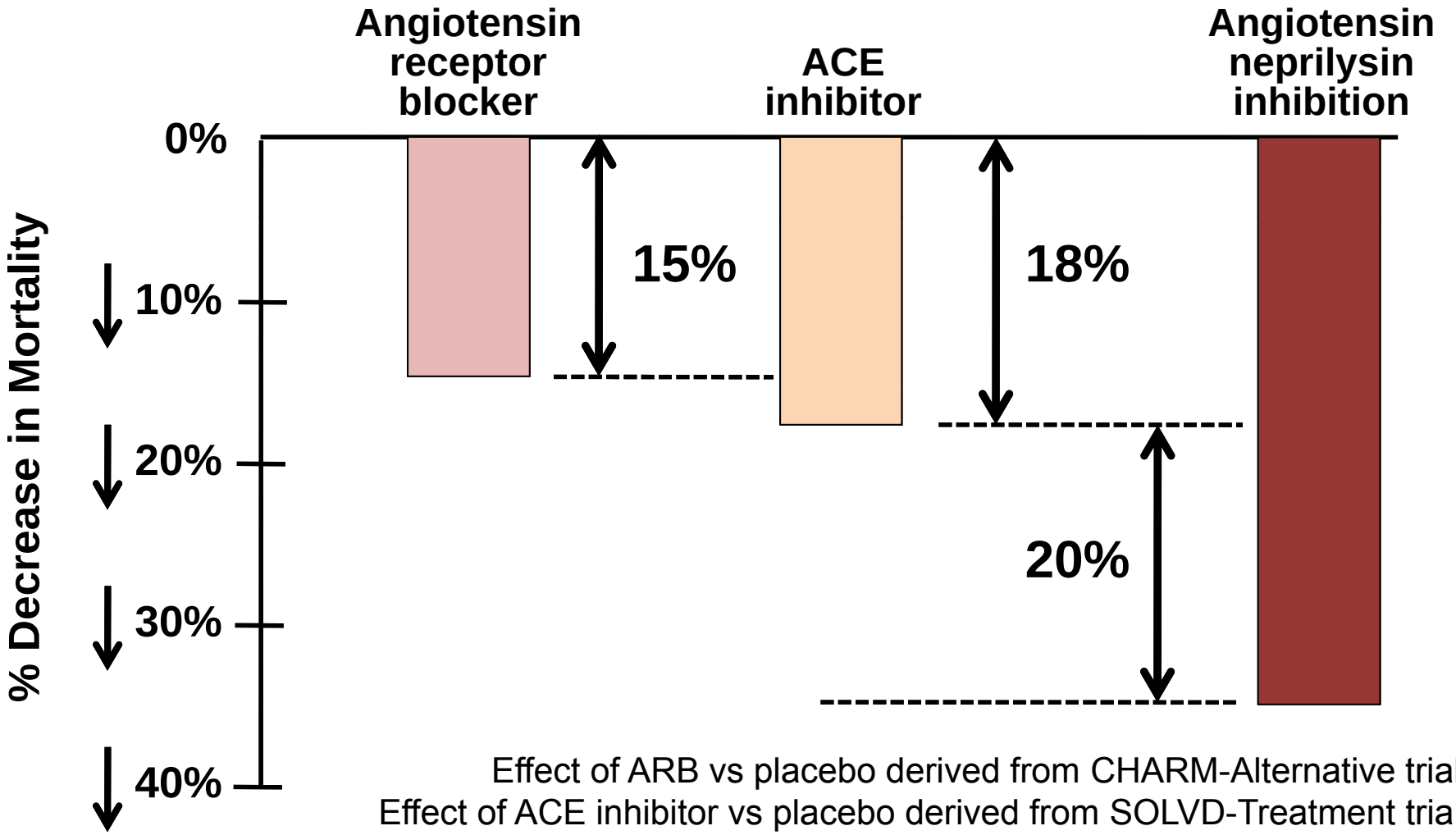


PARADIGM-HF: Percentage of patients with *at least 5 points deterioration* in KCCQ scores at month 8



Clinical summary score based on the physical limitation and total symptom score domains. Death imputed as zero. The analysis included all patients with at least one KCCQ data point

Angiotensin Neprilysin Inhibition With LCZ696 Doubles Effect on Cardiovascular Death of Current Inhibitors of the Renin-Angiotensin System



Effect of ARB vs placebo derived from CHARM-Alternative trial
Effect of ACE inhibitor vs placebo derived from SOLVD-Treatment trial
Effect of LCZ696 vs ACE inhibitor derived from PARADIGM-HF trial

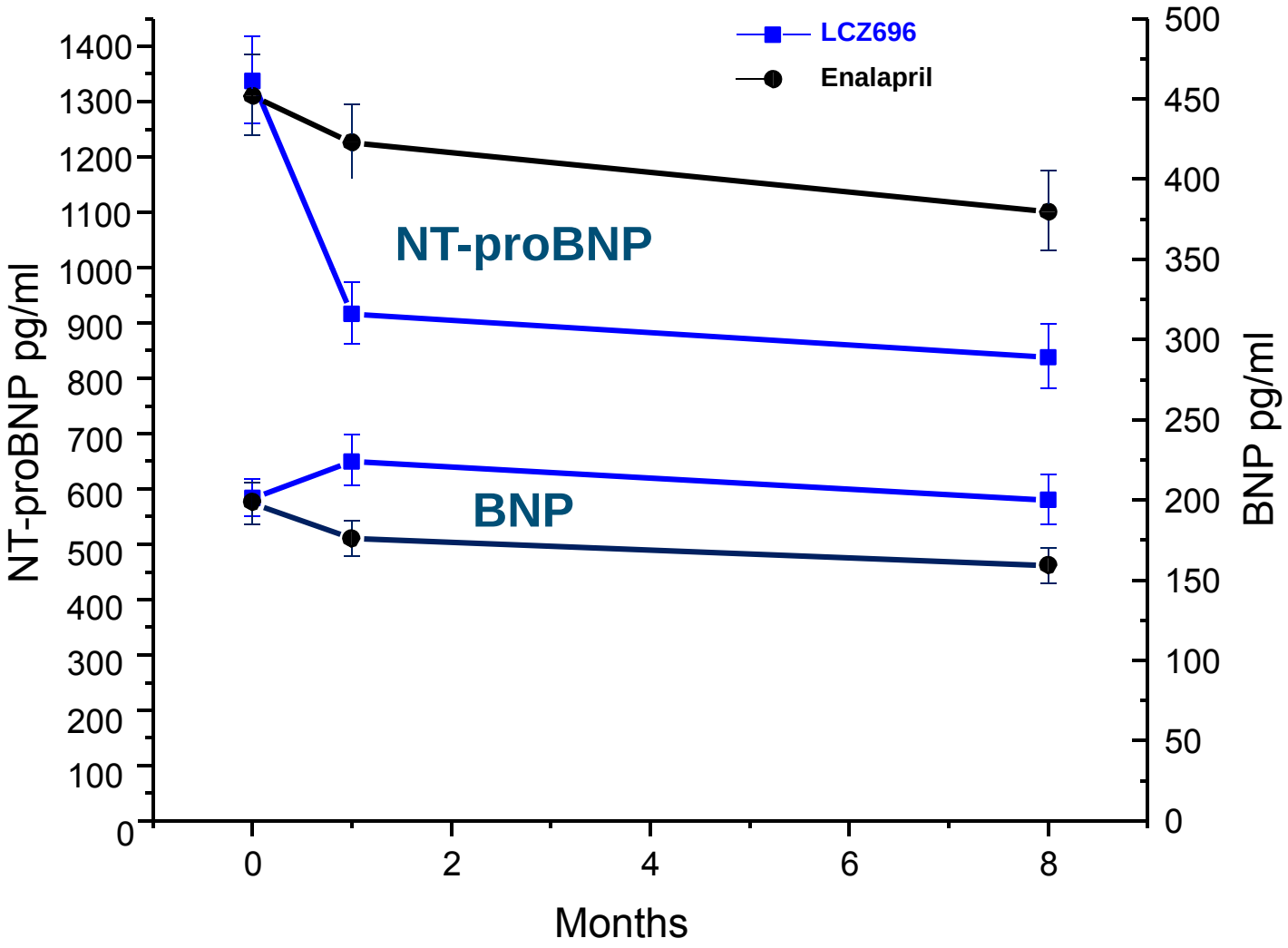
Is 1 trial enough?

Do we need to do another trial to obtain regulatory approval/change clinical practice?			
Number of trials with P < 0.05 showing efficacy	**P value required in a single trial to provide same strength of evidence**	**PARADIGM-HF: Effect on primary endpoint**	**PARADIGM-HF: Effect on cardiovascular death**
1	0.05		
2	0.00125		
3	0.00003125		0.00004
4	0.00000078	0.0000004	
5	0.0000000195		

Based on formula $(0.025)^n$ x2 (personal communication Stuart Pocock)

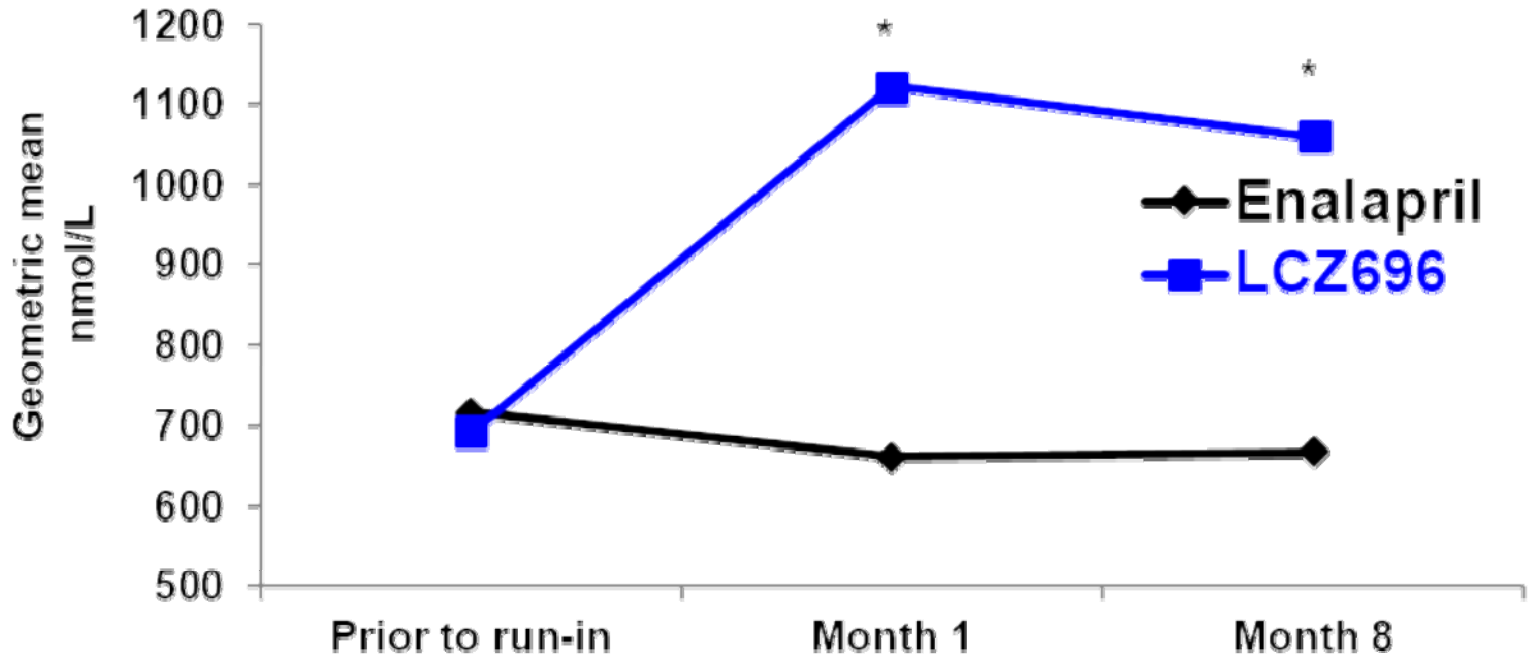
Slide courtesy of J McMurray

PARADIGM-HF: NT-proBNP and BNP

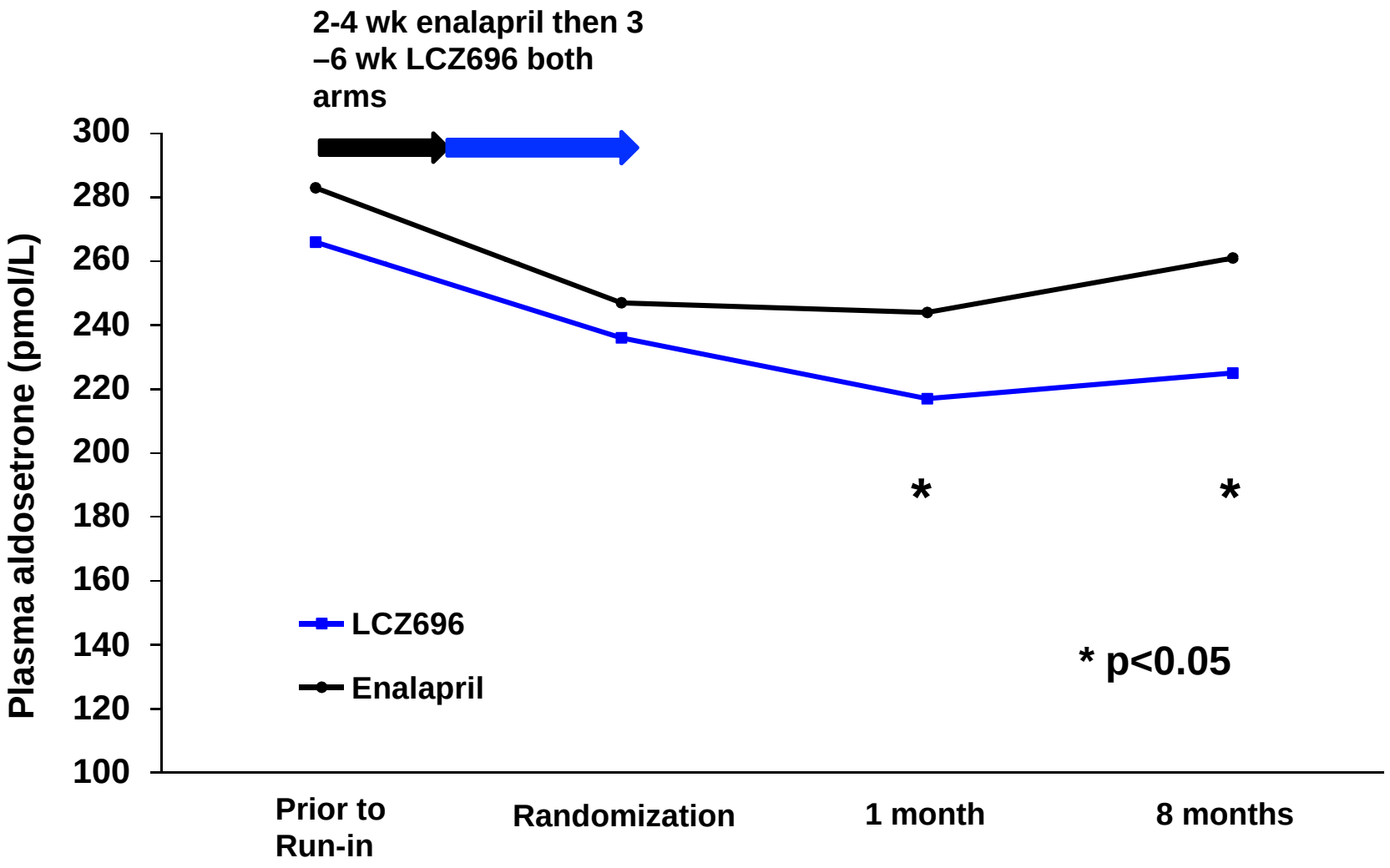


PARADIGM-HF: Geometric mean urinary cyclic GMP concentration by visit

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



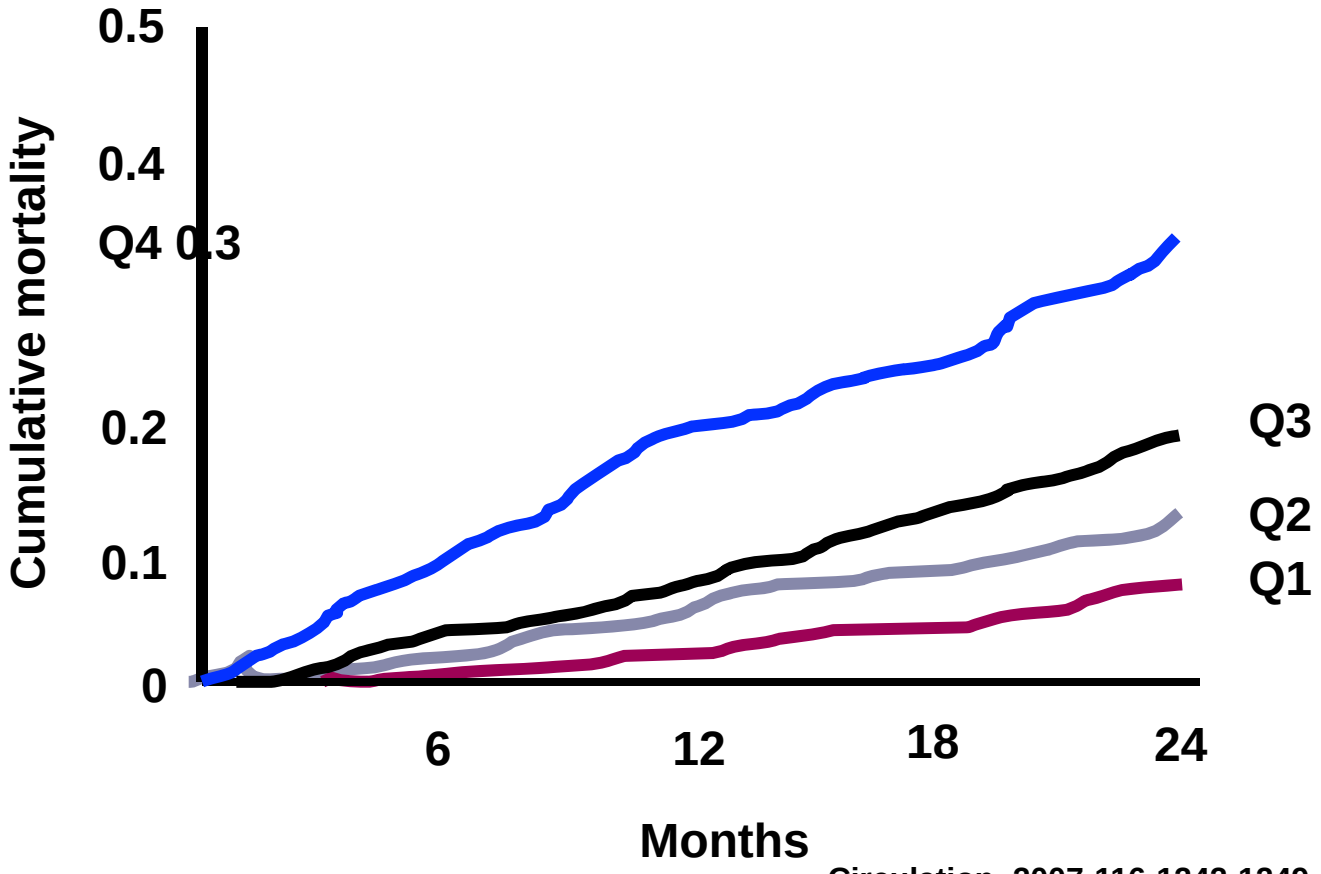
PARADIGM-HF: Aldosterone



Troponin and prognosis in HFREF

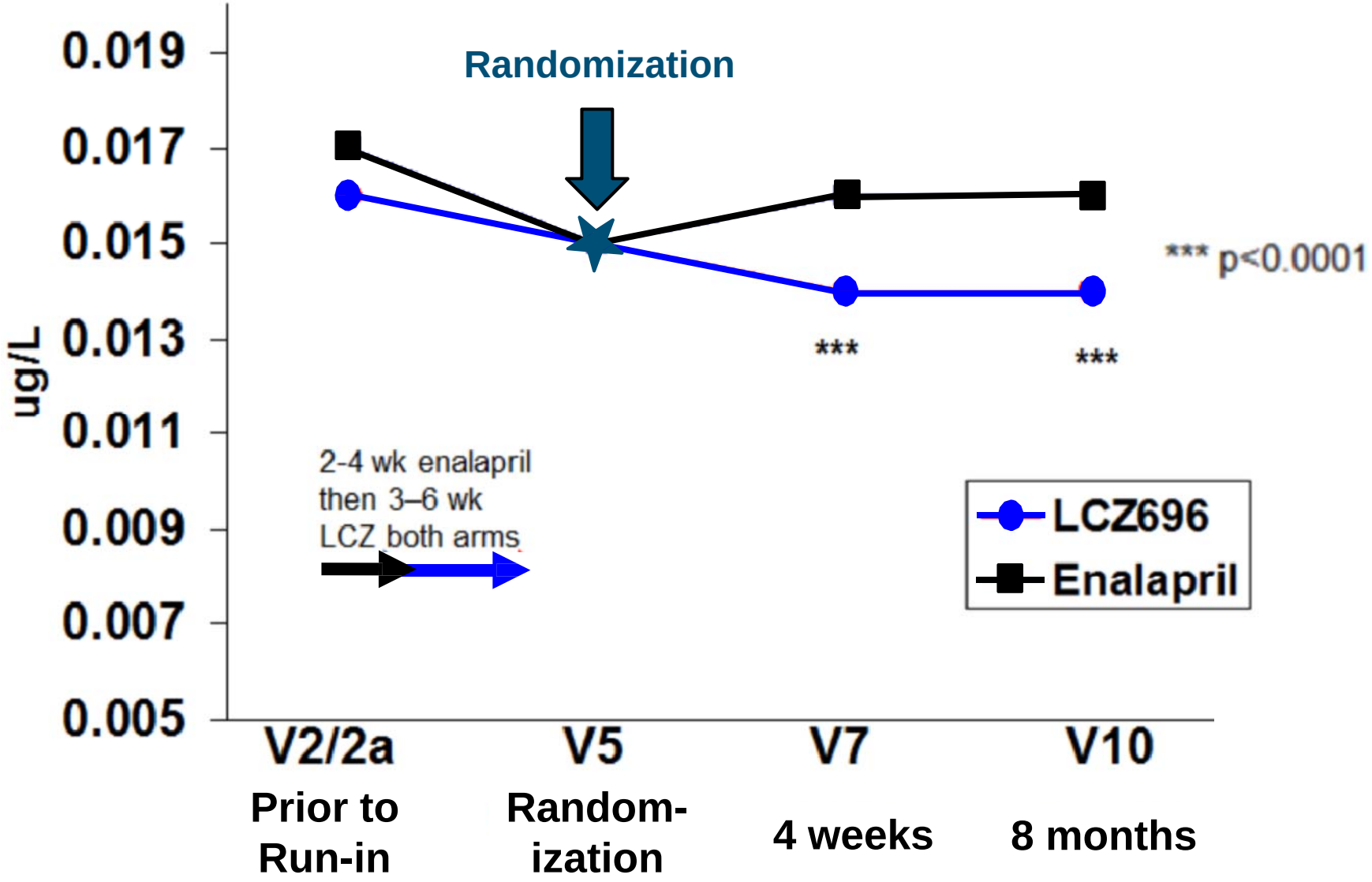
Val-HeFT

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



Circulation. 2007;116:1242-1249

PARADIGM-HF: median hs-TnT (µg/l) concentration by visit

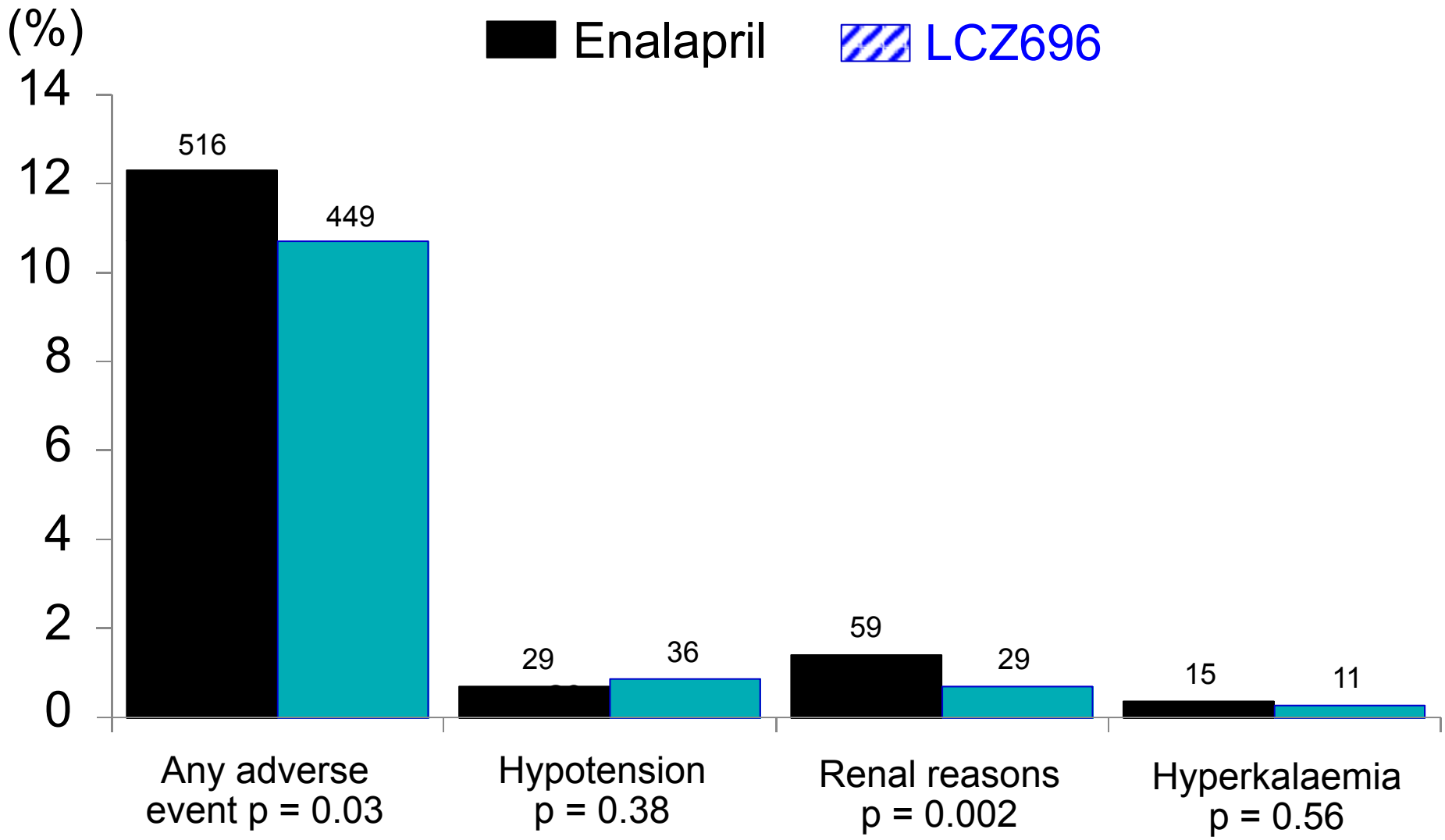


Safety

“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



The Angiotensin Receptor Neprilysin Inhibitor LCZ696 in Heart Failure with Preserved Ejection Fraction

The Prospective comparison of ARNI with ARB on Management Of heart failUre with preserved ejectioN fraction (PARAMOUNT) Trial

Scott D. Solomon, MD,

Professor of Medicine, Harvard Medical School Director,

Noninvasive Cardiology Brigham and Women's Hospital

On behalf of the PARAMOUNT Investigators

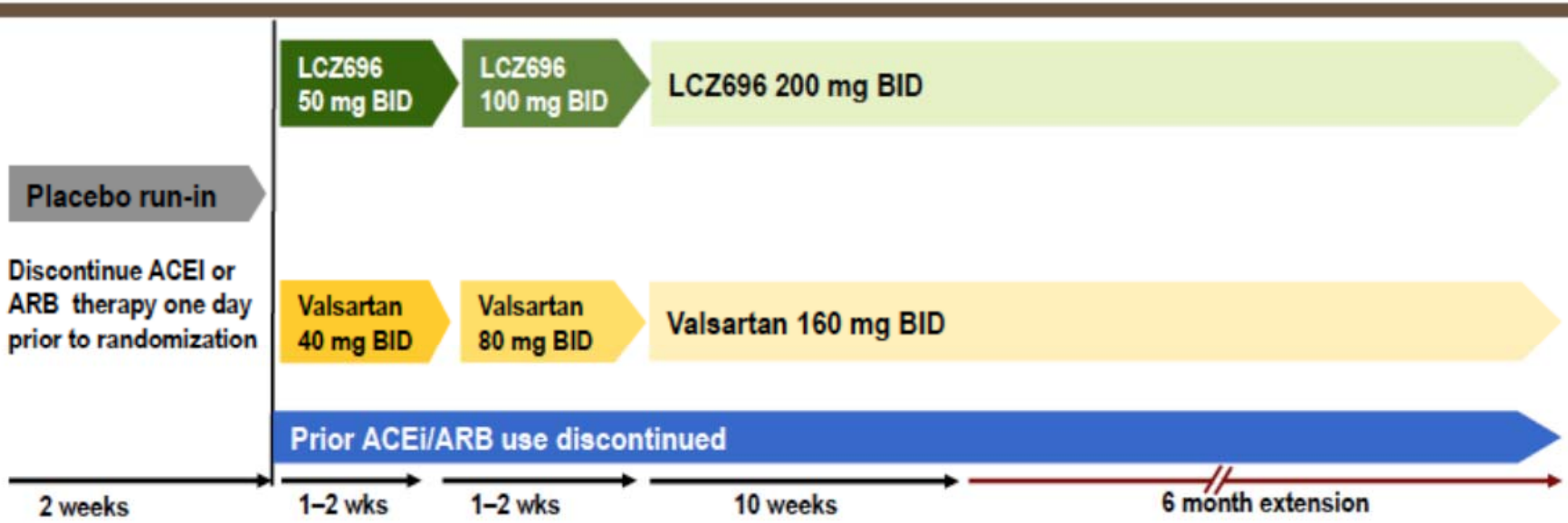
Disclosures: Dr. Solomon has received research support and has consulted for Novartis

Background

- Heart failure with preserved ejection fraction (HFpEF) accounts for up to half of heart failure cases, and is associated with substantial morbidity and mortality, yet no therapies have been shown to improve clinical outcomes in this condition.
- LCZ696 is a first-in-class angiotensin receptor neprilysin inhibitor that comprises the molecular moieties of a neprilysin inhibitor and the angiotensin receptor blocker (ARB) valsartan as a single compound.
- As such, this compound simultaneously inhibits the renin-angiotensin-aldosterone system and augments the endogenous natriuretic peptide system, both of which may offer benefits in patients with heart failure. This drug is currently being tested in an 8000 patient reduced ejection fraction heart failure trial.
- The PARAMOUNT trial was designed to test the safety and efficacy of LCZ696 in patients with HFpEF.

PARAMOUNT: Phase 2 study in HF-PEF

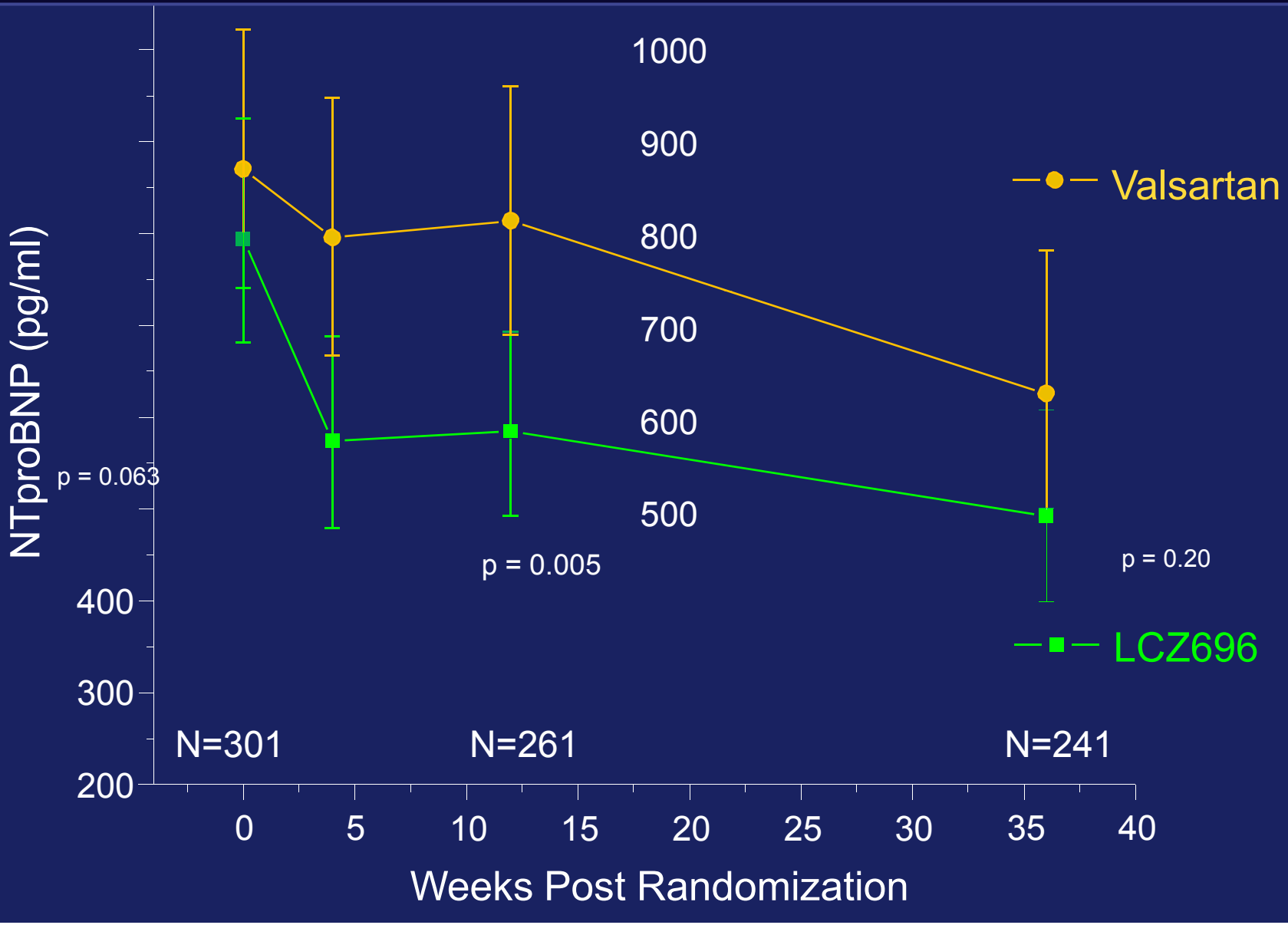
Prospective comparison of ARNI with ARB on exaMination Of heart failUre with preserved ejectioN fracTion



Primary endpoint	Reduction in **NT-proBNP**
Secondary endpoints	• Echocardiographic parameters of diastolic function, cardiac filling pressures and structure • QoL – KCCQ • Patient global symptom assessment/NYHA class • Biomarkers (BNP, ANP, cGMP, aldosterone, collagen/fibrosis biomarkers) • Renal function • Arterial stiffness (substudy)
Population	Approximately 300 patients with CHF (NYHA II-IV), LVEF ≥45%, baseline NT-proBNP >400 pg/mL, symptoms of HF, diuretic therapy required

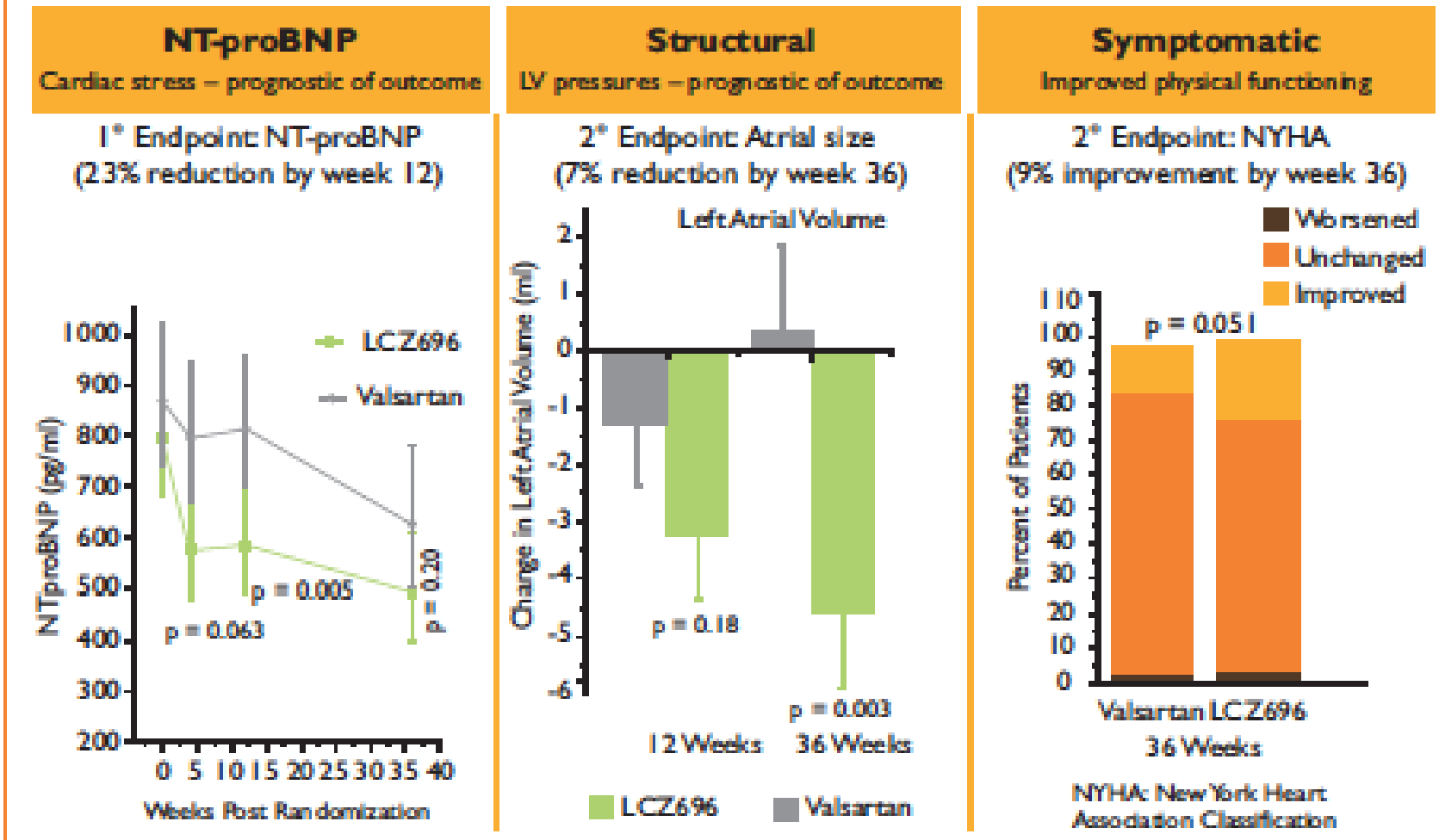
Clinicaltrials.gov; http://clinicaltrials.gov/ct2/show/NCT00887588

Change in NT-proBNP at 12 and 36 weeks



Key Positive Signals PARAMOUNT Trial

Figure 2. Summary of results of the PARAMOUNT trial



Conclusions From PARAMOUNT Investigators

- The angiotensin receptor neprilysin inhibitor LCZ696 reduced NT- proBNP to a greater extent than valsartan after 12 weeks of therapy, in association with reduction in left atrial size and improvement in NYHA class. These are all measures that have been associated with worse prognosis in patients with HFpEF.
- Overall LCZ696 was well tolerated with fewer serious and overall adverse events than the comparator valsartan.
- We consider these findings hypothesis generating, but they suggest that LCZ696 may have beneficial effects in patients with HFpEF and that further testing of this compound may be warranted in patients with this condition.

TOPCAT: Enrollment strata

- **BNP/NT-proBNP: 28.5%**
- **Prior HF hosp: 71.5%**

Enrolled by:	Spiro event rate	Placebo event rate	Hazard Ratio (95% CI)	P-value
Natriuretic peptide	15.9%	23.6%	**0.65** (0.49-0.87)	**0.003**
Heart Failure Hosp	19.6%	19.1%	**1.01** (0.84-1.21)	**0.923**

*P=0.013 for interaction

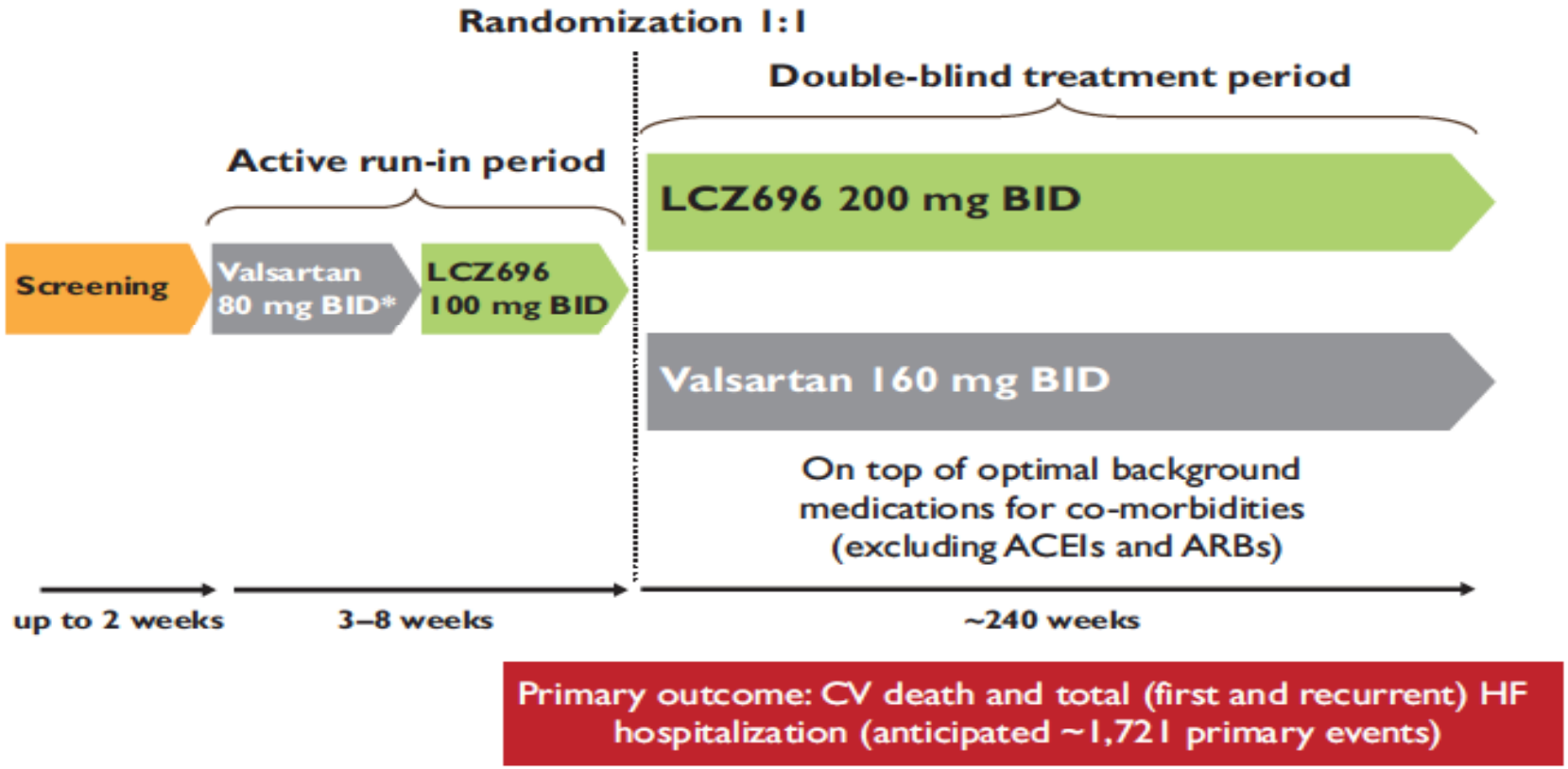
Moe GW, Ezekowitz JA et al., *Can J Cardiol*

Pfeffer, TOPCAT *NEJM* 2013

Design of the PARAGON-HF Trial

- PARAGON-HF will assess the effect of LCZ696 on outcomes (cardiovascular [CV] death and total – first and recurrent – HF hospitalizations) in patients with HFpEF.

Figure 3. Trial design



*Valsartan 40 mg BID (up to 2 weeks) followed by valsartan 80 mg BID as an optional starting run-in dose for those patients being treated with less than the minimum dose of ACEI or ARB at Visit 1.

Key Inclusion Criteria PARAGON-HF Trial

Figure 4. Key inclusion criteria

1. ≥55 years of age and LVEF ≥45%
2. Symptom(s) of HF requiring treatment with diuretic(s) for HF for ≥30 days prior to Visit 1
3. Current symptomatic HF (NYHA class II-IV)
4. Structural heart disease (LAE or LVH)

AND at least one of the following:

A HF hospitalization within 9 months prior to Visit 1	Elevated NT-proBNP (>300 pg/ml for patients not in AF **OR** >900 pg/ml for patients in AF at baseline)

LAE = left atrial enlargement, LVH = left ventricular hypertrophy, AF = atrial fibrillation

Canadian Cardiovascular Society
Leadership. Knowledge. Community.

Société canadienne de cardiologie
Communauté. Connaissances. Leadership.

CCS Heart Failure Guidelines: 2014 Update On New Therapies, Biomarkers, Anemia Management, And Complex Cases

May 2015

HF – Reduced Ejection Fraction

Recommendation

We recommend that in patients with mild to moderate HF, an EF < 40%, an elevated NP level or hospitalization for HF in the past 12 months, a serum potassium < 5.2 mmol/L and an eGFR ≥ 30 mL/min and treated with appropriate doses of guideline-directed medical therapy should be treated with LCZ696 in place of an ACE inhibitor or an angiotensin receptor blocker, with close surveillance of serum potassium and creatinine (***Conditional*** Recommendation, High-Quality Evidence).

Values and Preferences:
This recommendation places high value on medications proven in large trials to reduce mortality, HF rehospitalization, and symptoms. It also considers the health economic implications of new medications. The recommendation is conditional because the drug is not yet approved for clinical use in Canada and the price is still not known.

CCS HF Guidelines, Moe, Ezekowitz, et al CJC 2014

The Anatomy of a Recommendation

NPs mostly not available in Canada as outpt; no interaction of either of these on outcome so anticipate this may be changed in future

EF < 40% until amendment to <35%; no difference on primary endpoint

NYHA 2-3

Recommendation

We recommend that in patients with mild to moderate HF, an EF < 40%, an elevated NP level or hospitalization for HF in the past 12 months, a serum potassium < 5.2 mmol/L and an eGFR ≥ 30 mL/min and treated with appropriate doses of guideline-directed medical therapy should be treated with LCZ696 in place of an ACE inhibitor or an angiotensin receptor blocker, with close surveillance of serum potassium and creatinine (***Conditional*** Recommendation, High-Quality Evidence)

HQ RCT Adeq powered

GDMT at a reasonable dose is first step; don't forget the basics

Pending HC approval

After Ezekowitz

Safety vs Events

Striking the Risk Benefit Balance in HFrEF

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

Hippocratic Oath

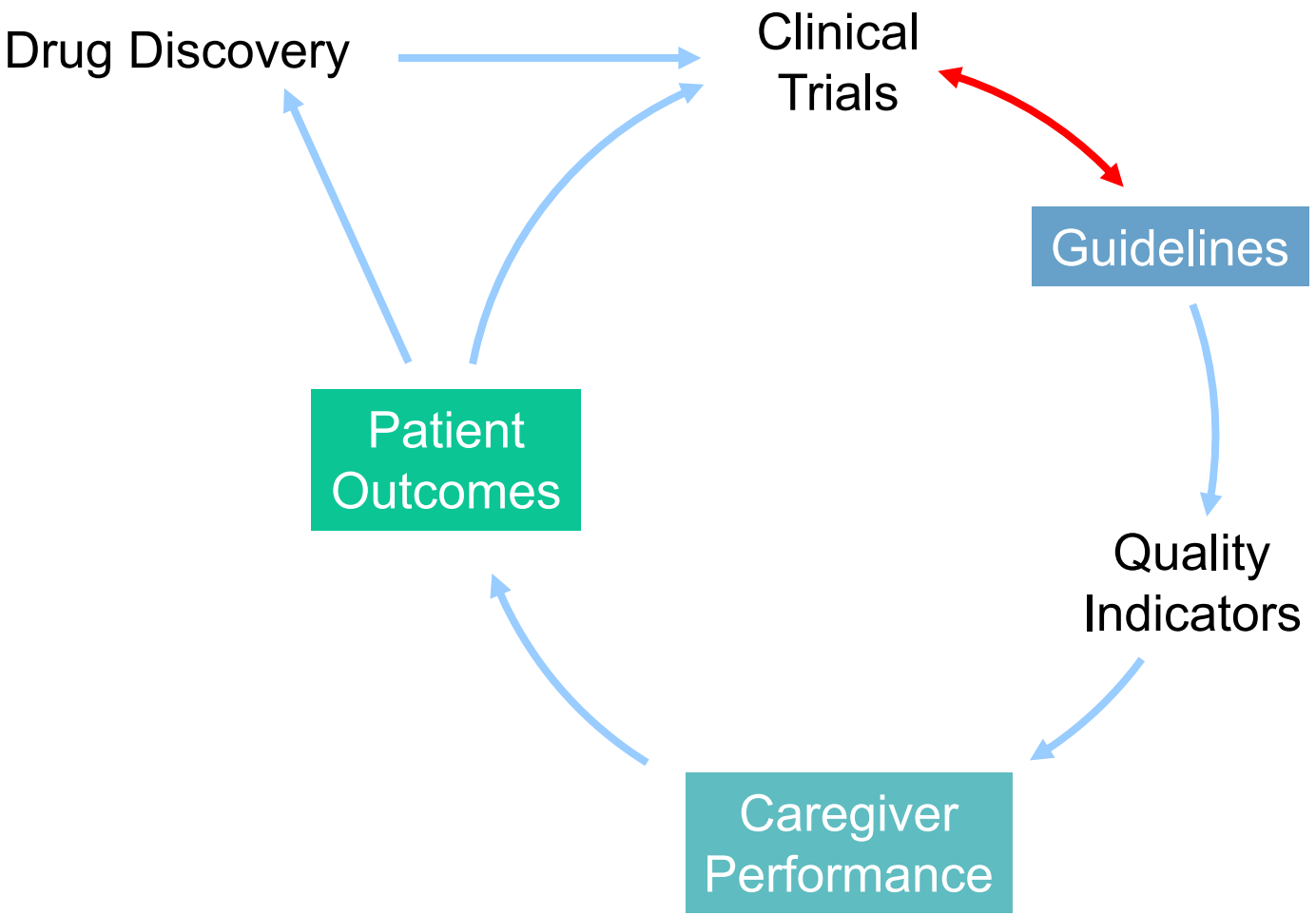
LCZ696 and FDA - Indication

INDICATIONS AND USAGE

ENTRESTO is a combination of sacubitril, a neprilysin inhibitor, and valsartan, an angiotensin II receptor blocker, indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure (NYHA Class II-IV) and reduced ejection fraction. (1.1)

ENTRESTO is usually administered in conjunction with other heart failure therapies, in place of an ACE inhibitor or other ARB. (1.1)

Randomized controlled trials play a critical role in advancing patient care through guidelines



Moe GW, Ezekowitz JA et al., *Can J Cardiol*

Califf, R et al *JACC* 2002;40(11):1895-1901

Initiating sacubitril/valsartan (LCZ696) in heart failure: results of TITRATION, a double-blind, randomized comparison of two uptitration regimens

Michele Senni[1]*, John J.V. McMurray[2], Rolf Wachter[3], Hugh F. McIntyre[4], Antonio Reyes[5], Ivan Majercak[6], Peter Andreka[7], Nina Shehova-Yankova[8], Inder Anand[9], Mehmet B. Yilmaz[10], Harinder Gogia[11], Manuel Martinez-Selles[12], Steffen Fischer[13], Zsolt Zilahi[14], Franco Cosmi[15], Valeri Gelev[16], Enrique Galve[17], Juanjo J. Gómez-Doblas[18], Jan Nociar[19], Maria Radomska[20], Beata Sokolova[21], Maurizio Volterrani[22], Arnab Sarkar[23], Bernard Reimund[24], Fabian Chen[25], and Alan Charney[25]

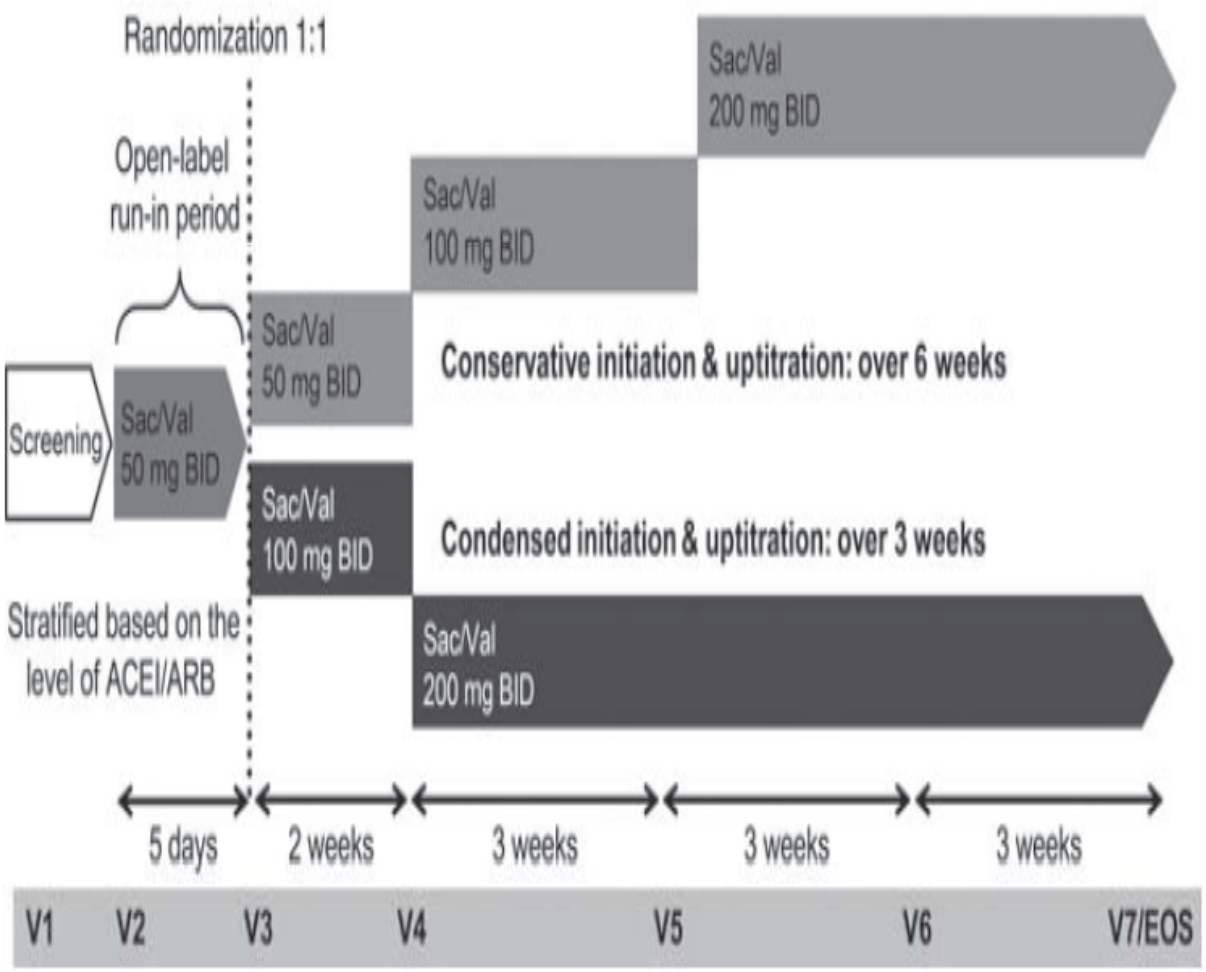
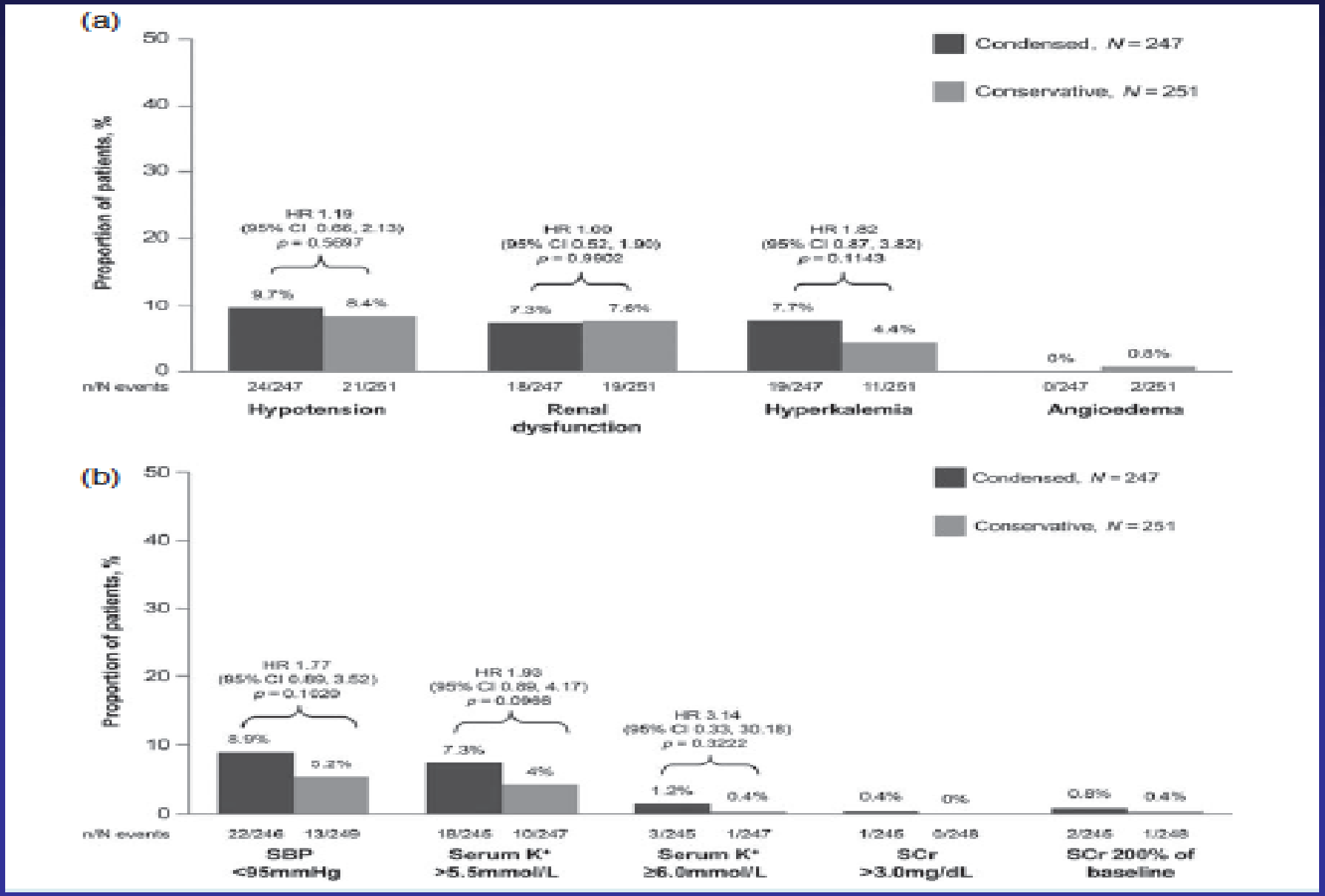


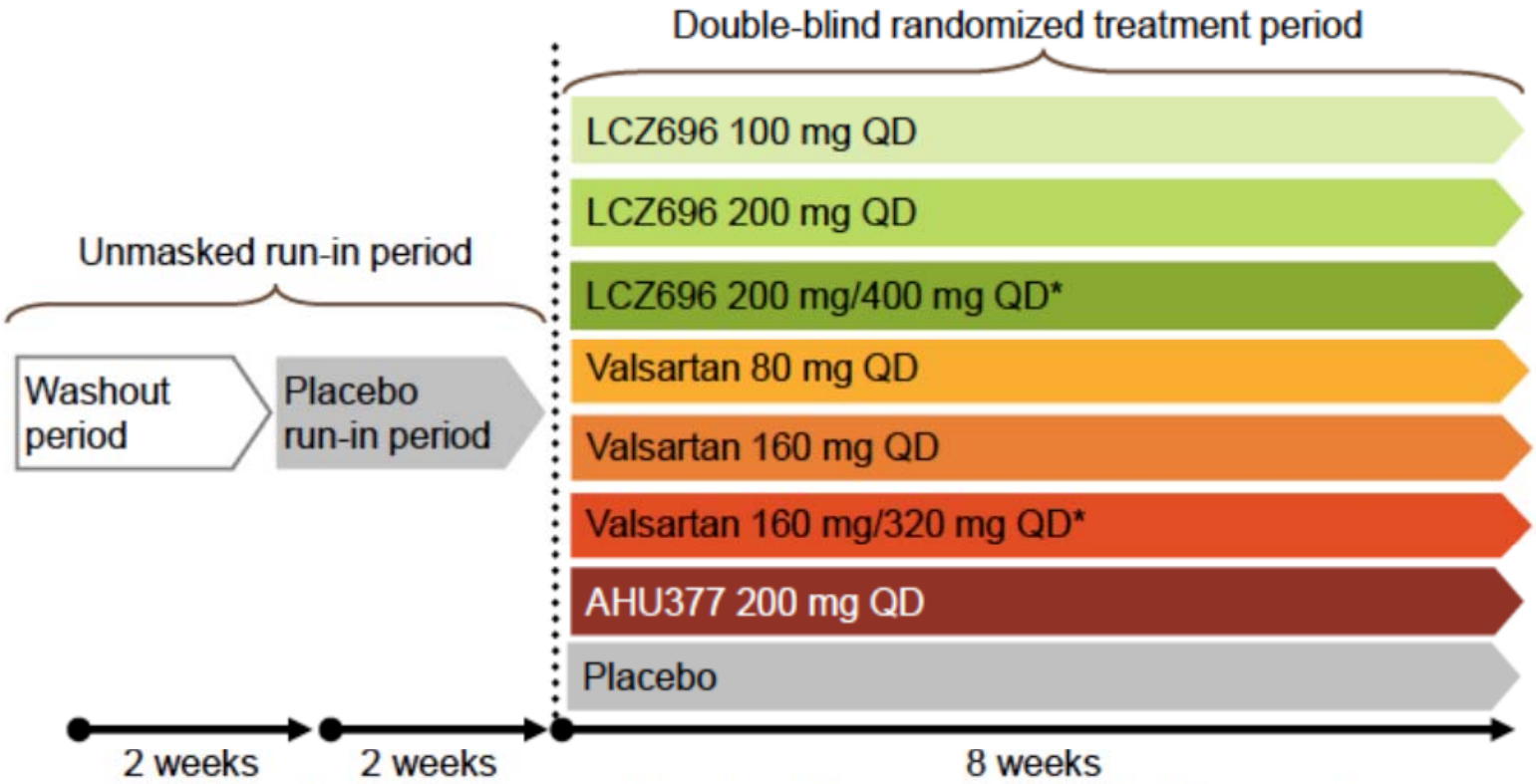
Figure 1 Study design. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BID, twice daily; EOS, end of study; Sac/Val, sacubitril/valsartan; V, visit.

TITRATION Study – Risk of AE



LCZ696 in mild-to-moderate hypertension

- A randomized, double-blind, placebo-controlled, active-comparator study in 1,328 patients with mild-to-moderate hypertension



*1 week on lower dose followed by 7 weeks on higher dose; †Mean sitting DBP of 90–109 mmHg after antihypertensive washout, or 95–109 mmHg for untreated patients

Ruilope et al. Lancet 2010;375:1255–66