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

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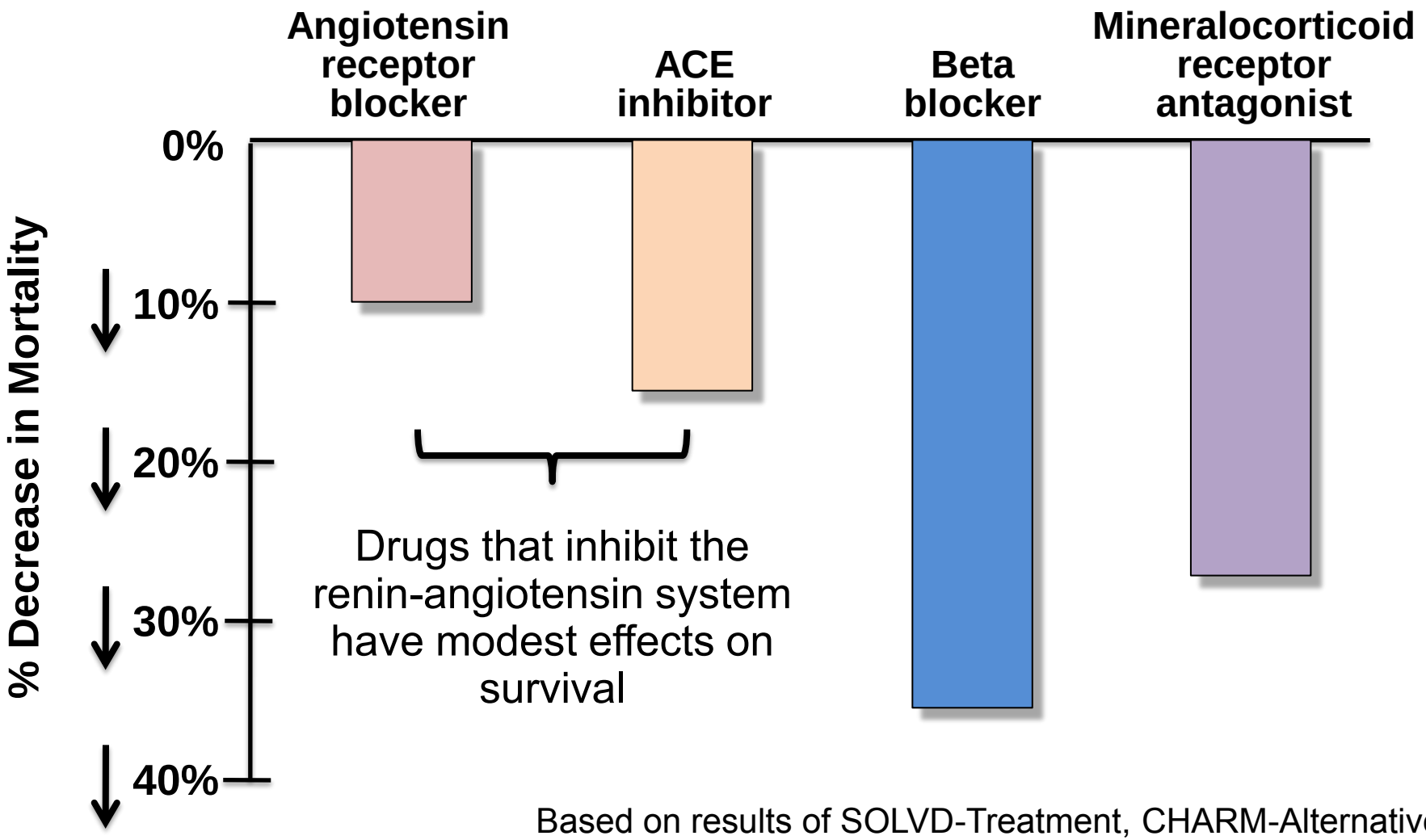
Disclosures for Presenter

Within past 3 years (related to any aspect of heart failure):

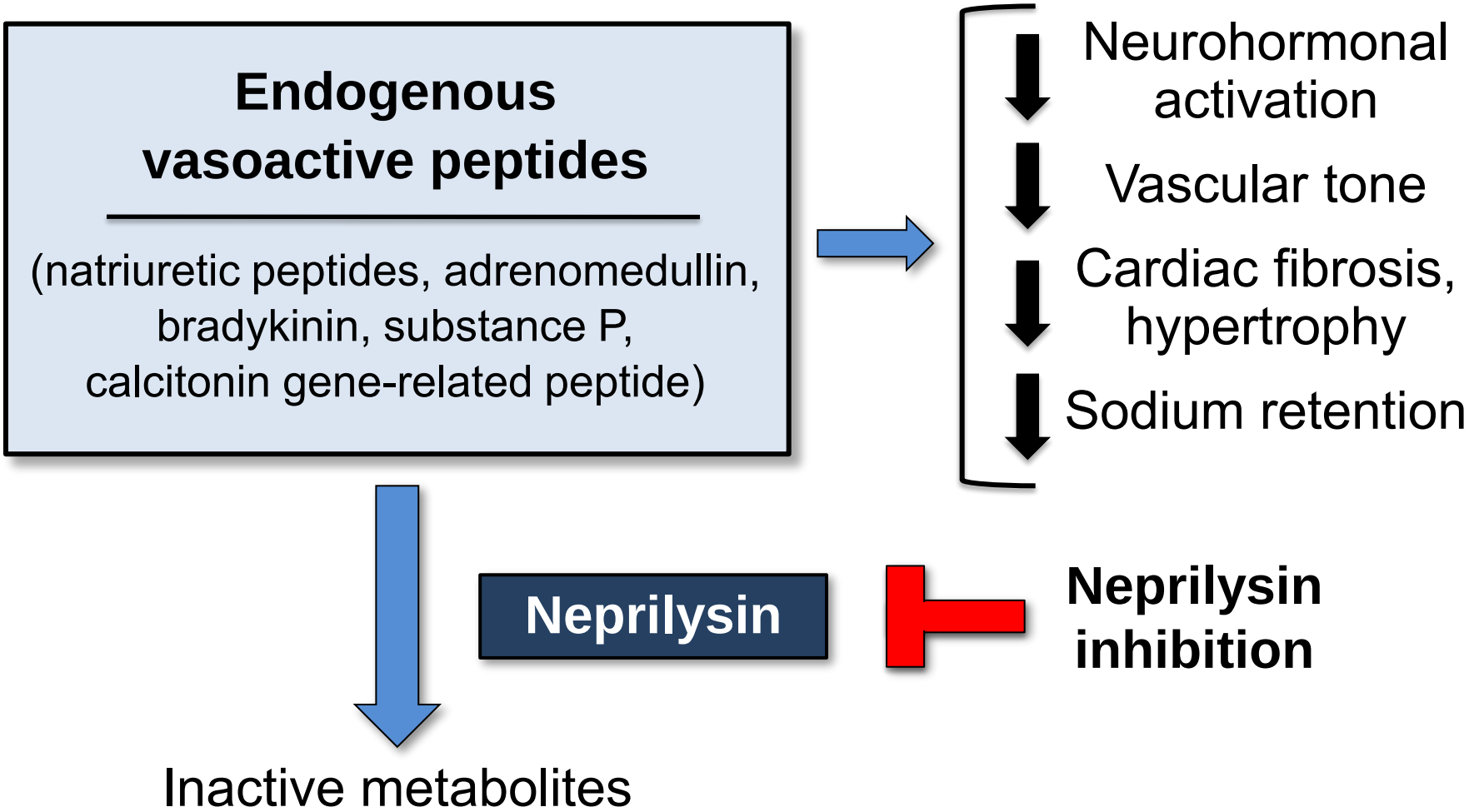
Consultant to: AMAG, Amgen, BioControl, CardioKinetix, CardioMEMS, Cardiorentis, Daiichi, Janssen, Novartis, Sanofi

Drugs That Reduce Mortality in Heart Failure With Reduced Ejection Fraction



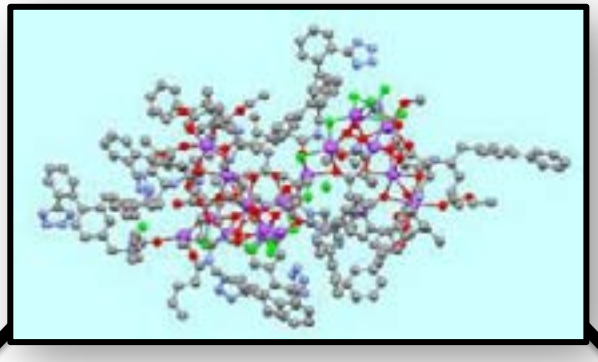
Based on results of SOLVD-Treatment, CHARM-Alternative, COPERNICUS, MERIT-HF, CIBIS II, RALES and EMPHASIS-HF

Neprilysin Inhibition Potentiates Actions of Endogenous Vasoactive Peptides That Counter Maladaptive Mechanisms in Heart Failure

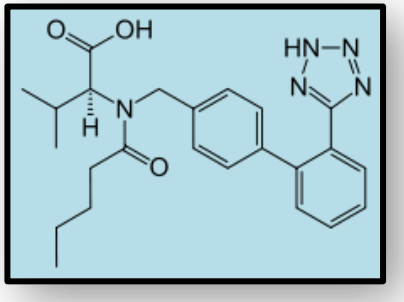


LCZ696: Angiotensin Receptor Neprilysin Inhibition

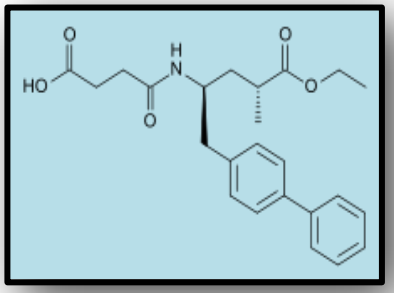
LCZ696



Angiotensin receptor blocker



Inhibitor of neprilysin



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 ≤ 35-40%
- At least mild increases in BNP or N-terminal proBNP
- Any use of ACE inhibitor or ARB, but able to tolerate stable dose equivalent to at least enalapril 10 mg daily for ≥ 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: Primary Objective

Primary endpoint was cardiovascular death or hospitalization for heart failure, but PARADIGM-HF was designed as a cardiovascular mortality trial

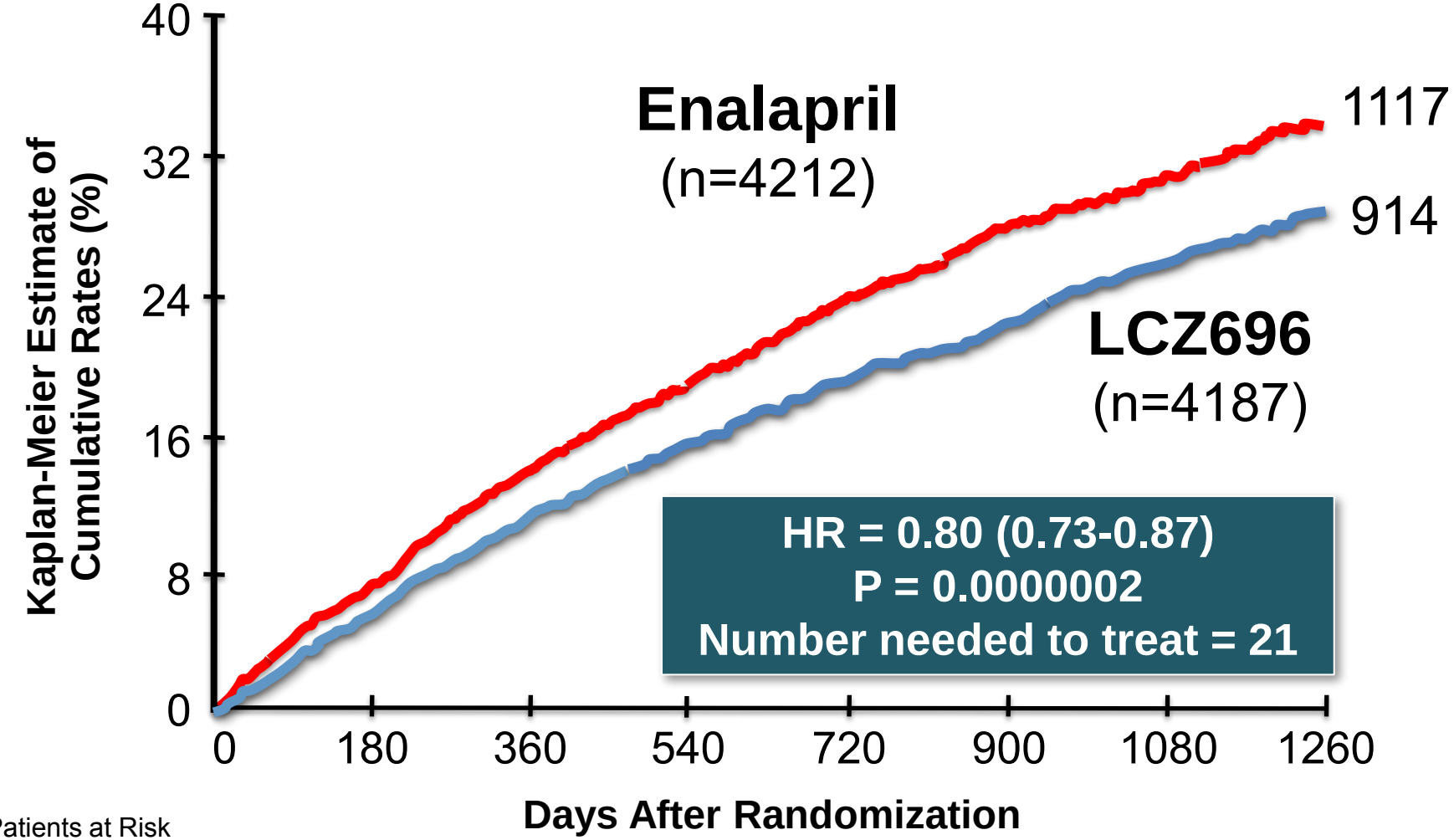
The trial size was determined by effect on **cardiovascular mortality**. The Data Monitoring Committee was allowed to stop the trial only for a compelling effect on **cardiovascular mortality.**

Difference of 15% in cardiovascular mortality between LCZ696 and enalapril was prospectively identified as being clinically important, since it would allow us to detect LCZ696-related **doubling** of the survival benefits of current inhibitors of the renin-angiotensin system.

PARADIGM-HF: Baseline Characteristics of 8399 Randomized Patients in ITT Analysis

	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%

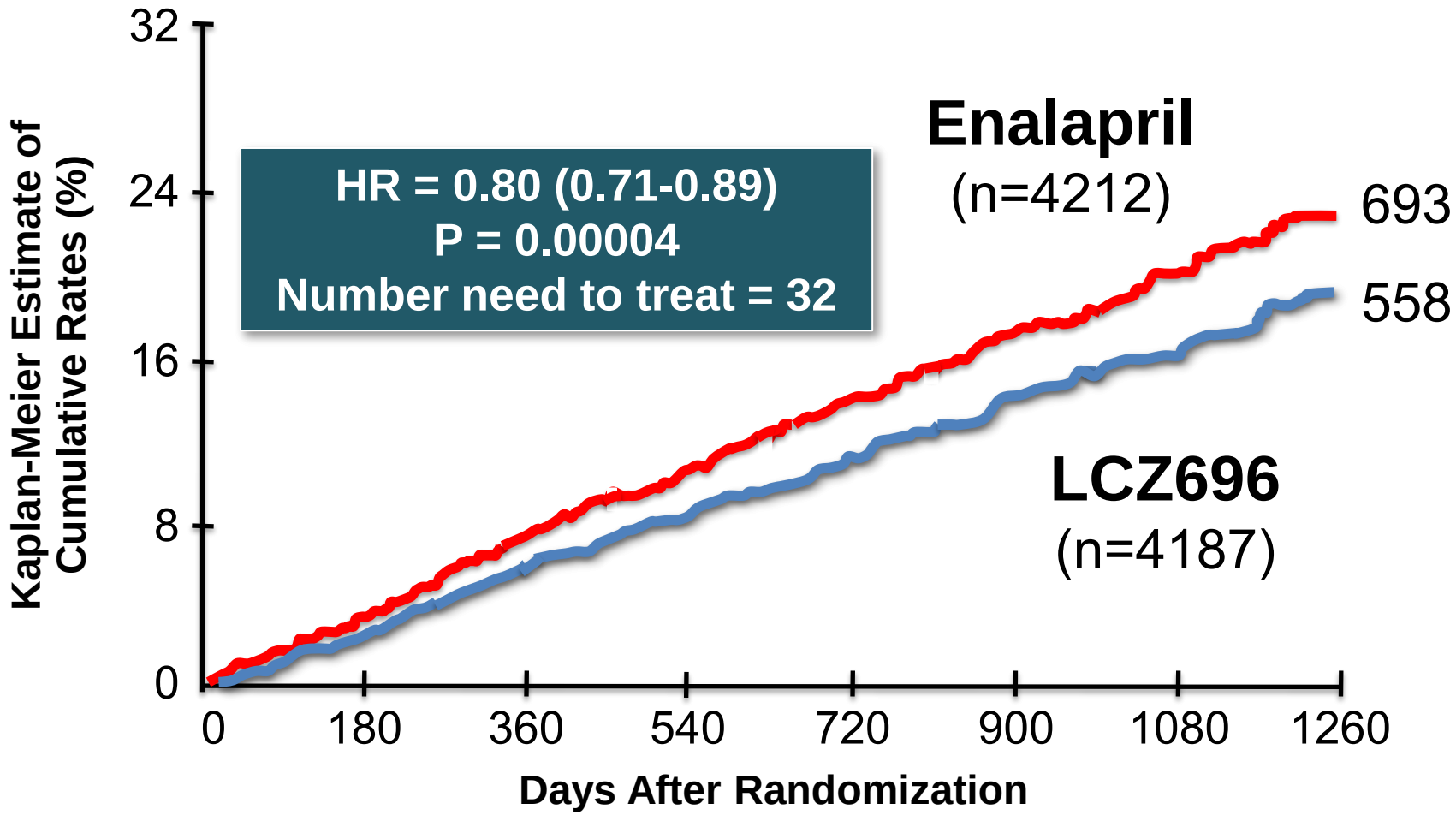
PARADIGM-HF: Cardiovascular Death or Heart Failure Hospitalization (Primary Endpoint)



Patients at Risk

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

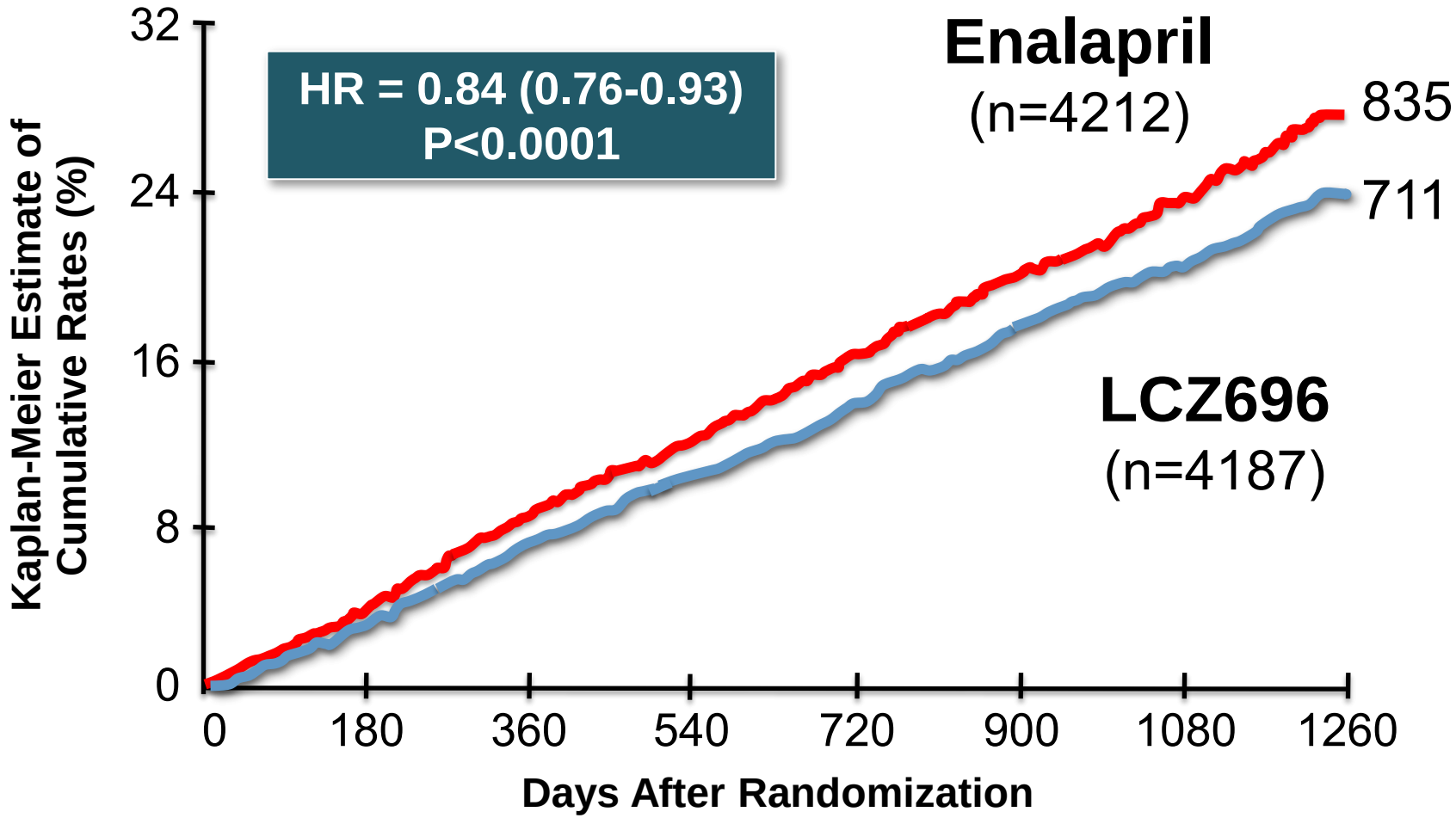
PARADIGM-HF: Cardiovascular Death



Patients at Risk

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

PARADIGM-HF: All-Cause Mortality



Patients at Risk

LCZ696	4187	4056	3891	3282	2478	1716	1005	280
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PARADIGM-HF: Additional Findings

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

- Reducing the risk of a heart failure hospitalization by *incremental* 21%
- *Incrementally* improving symptoms and physical limitations of heart failure

LCZ696 was *better tolerated* than enalapril . . .

- Less likely to cause cough, hyperkalemia or renal impairment or be discontinued for an adverse event
- More hypotension, but no increase in discontinuations
- No increase in risk of serious angioedema

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Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure

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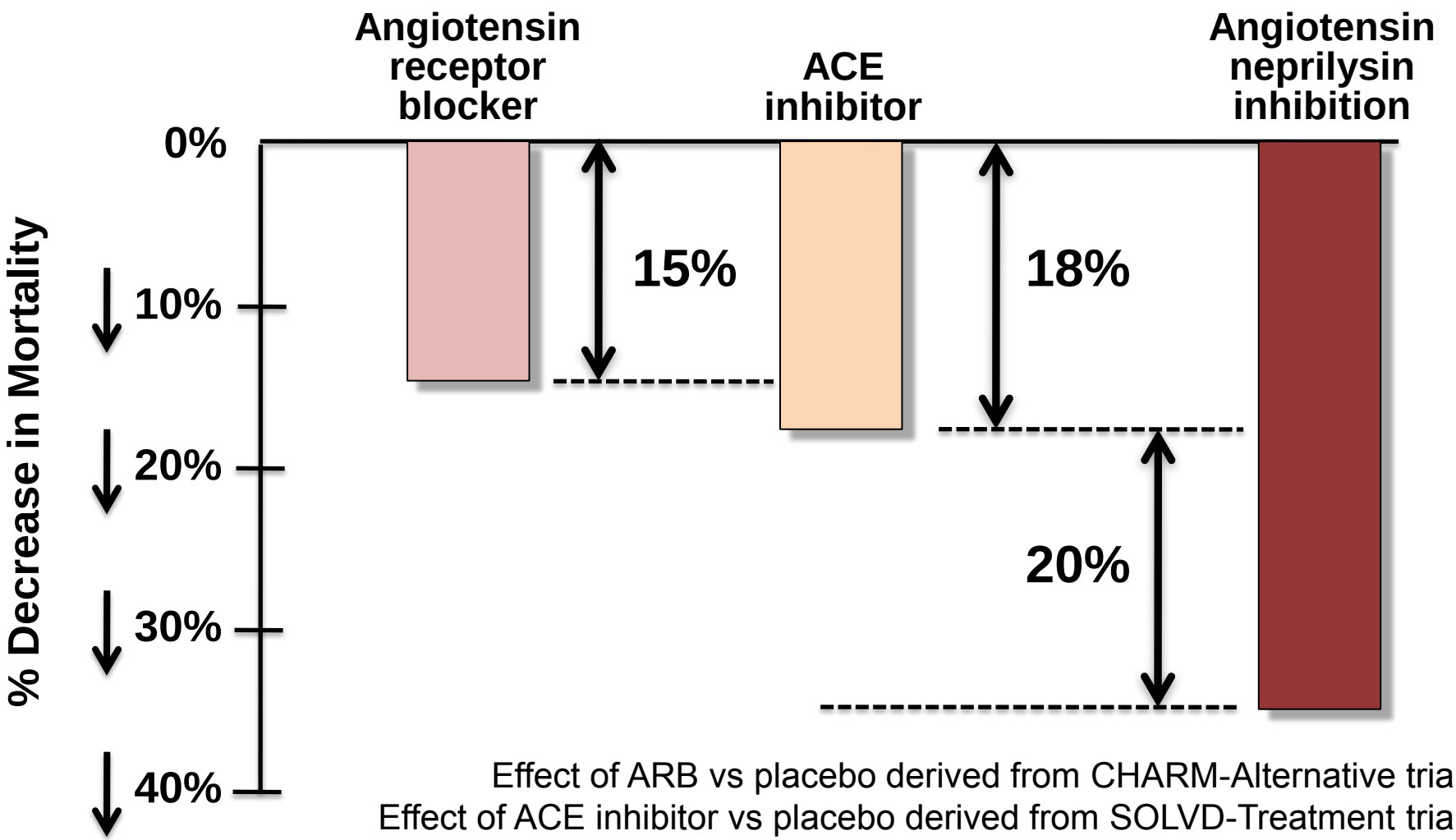
The primary results of the PARADIGM-HF trial are being published online today at nejm.org

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

Clinical Importance of the Findings of the PARADIGM-HF Trial

For the last 25 years, the magnitude of the effect of ACE inhibitors on cardiovascular mortality (18%) has created an ethical mandate for their use in all patients with chronic heart failure who could tolerate treatment with these drugs.

The finding that LCZ696 has an 20% *greater* effect on cardiovascular mortality than ACE inhibitors strongly supports the conclusion that LCZ696 should replace current use of ACE inhibitors and angiotensin receptor blockers in the management of chronic heart failure.