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

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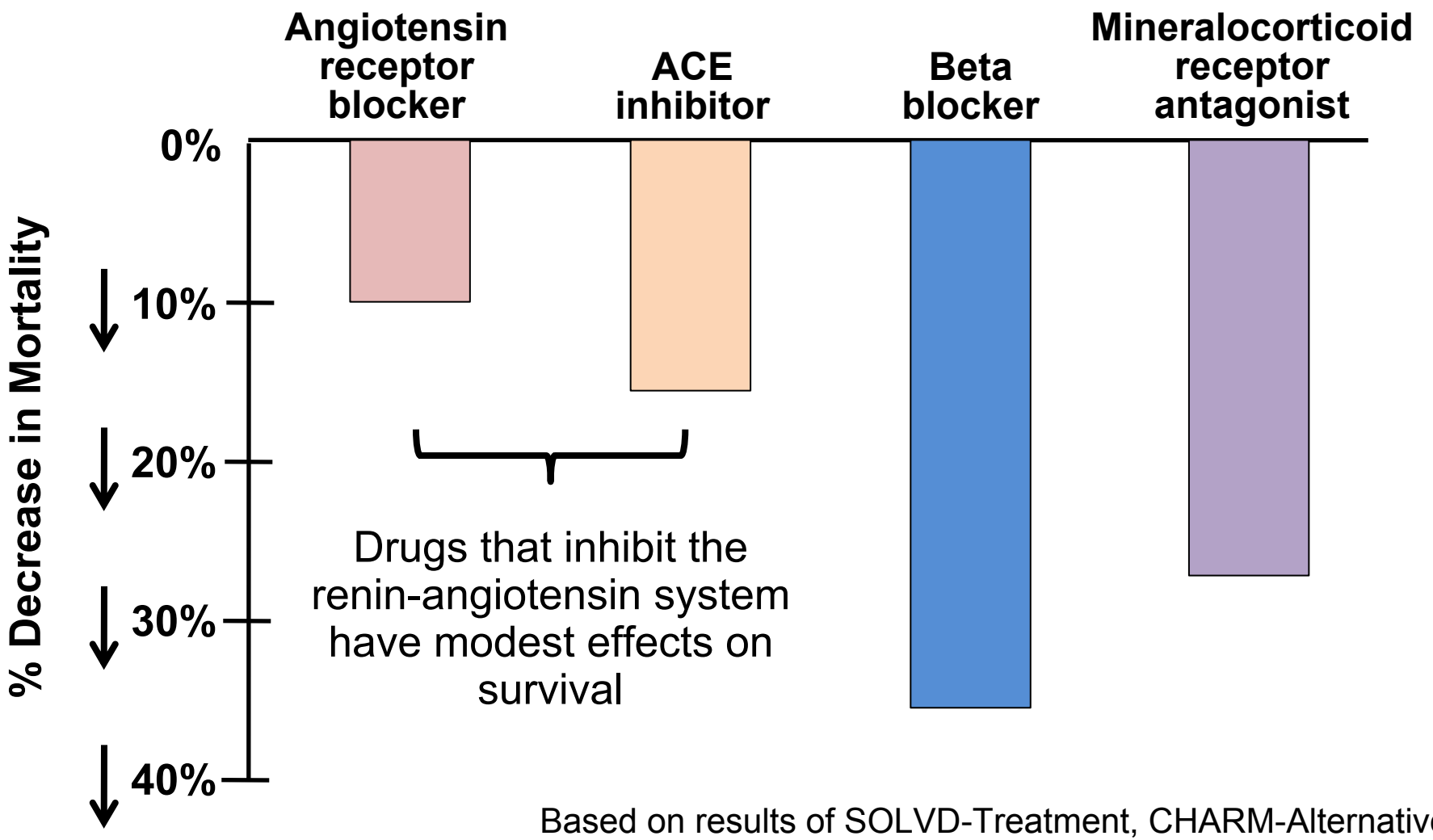
Disclosures for Presenter

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

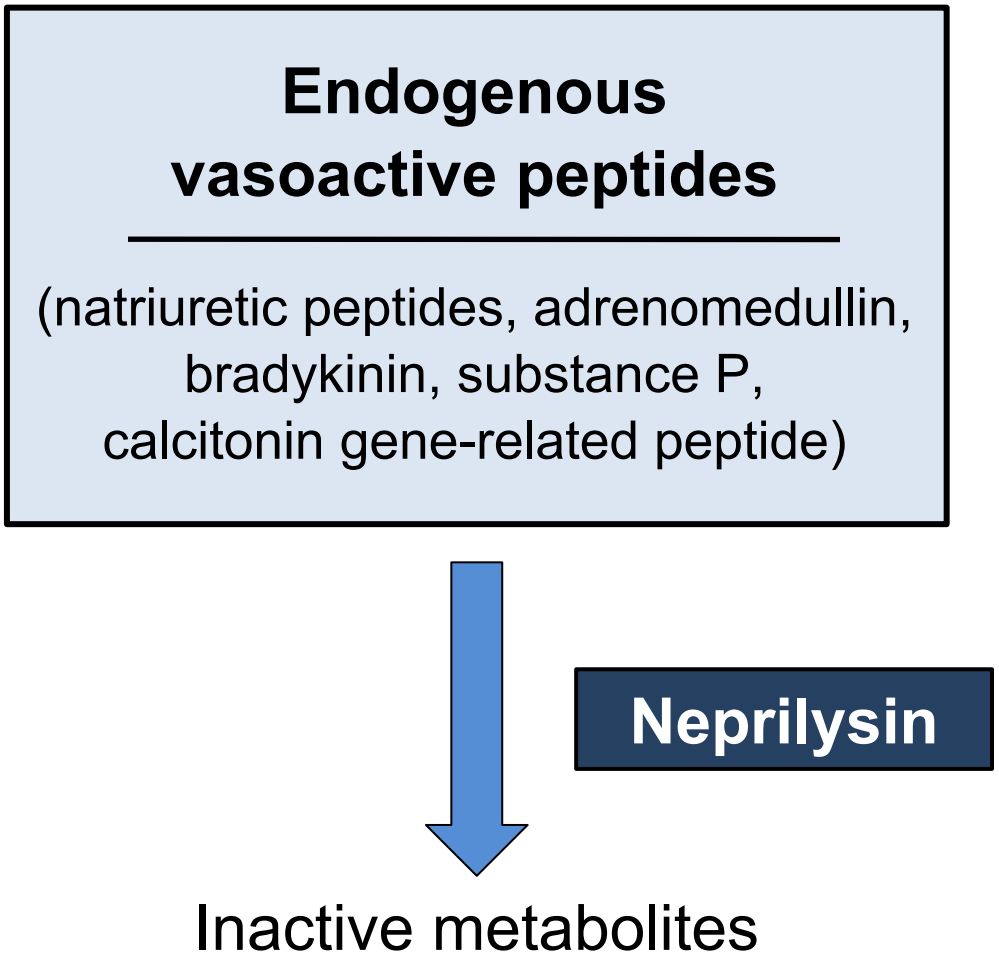
Consultant to: AMAG, Amgen, BioControl, CardioKinetix, CardioMEMS, Cardiorentis, Daiichi, Janssen, Novartis, Sanofi

Drugs That Reduce Mortality in Heart Failure With Reduced Ejection Fraction

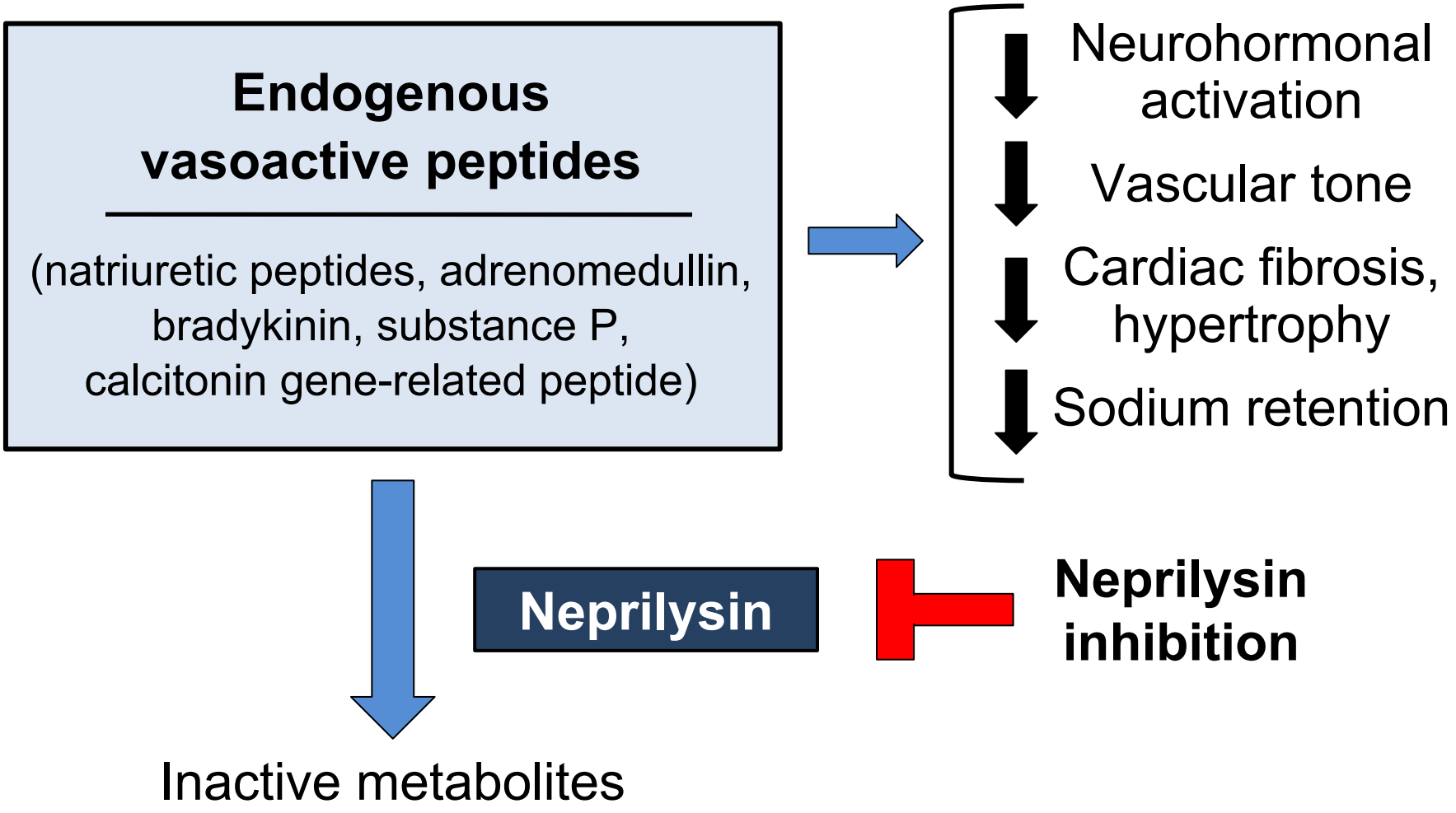


Based on results of SOLVD-Treatment, CHARM-Alternative, COPERNICUS, MERIT-HF, CIBIS II, RALES and EMPHASIS-HF

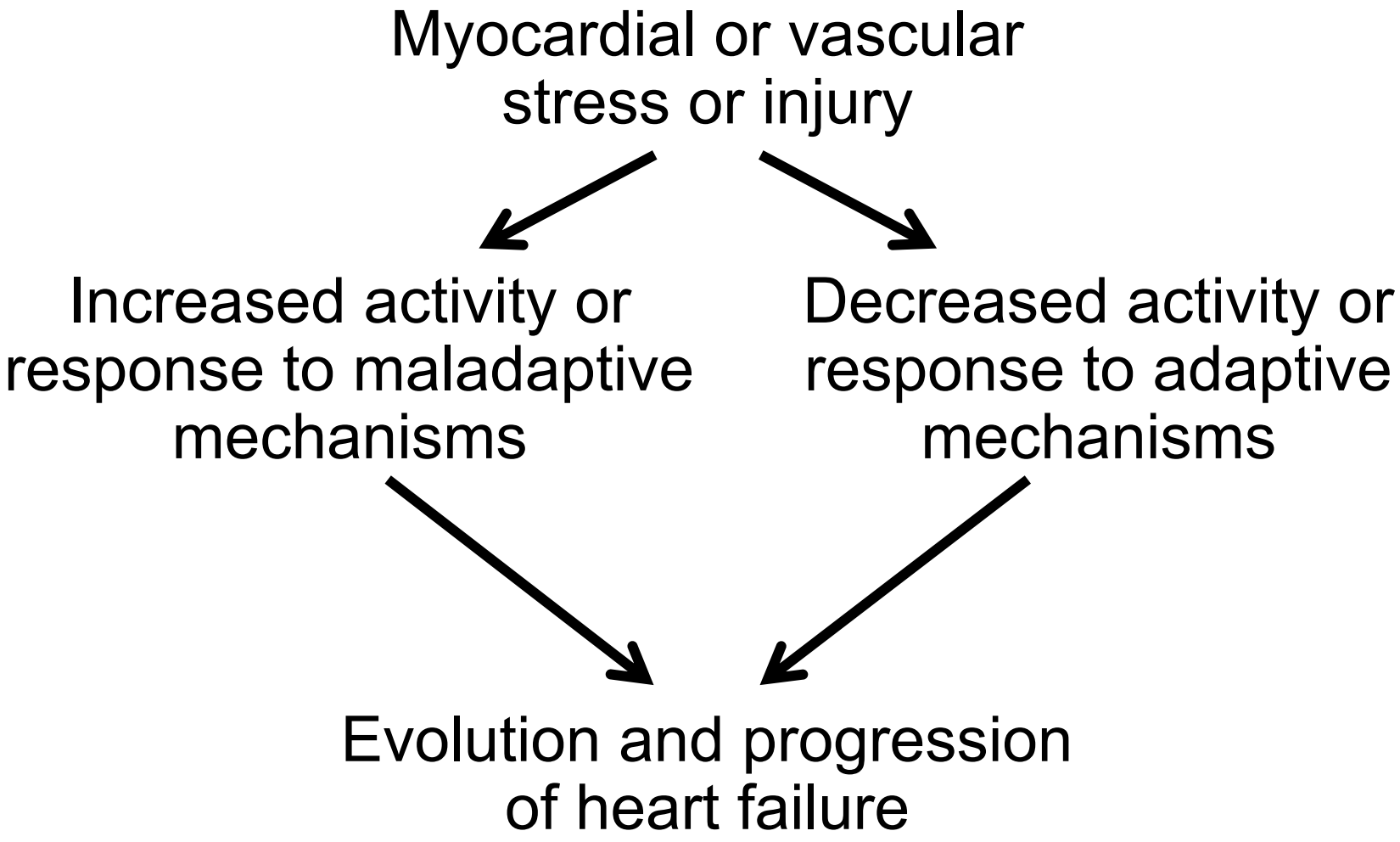
One Enzyme — Neprilysin — Degrades Many Endogenous Vasoactive Peptides



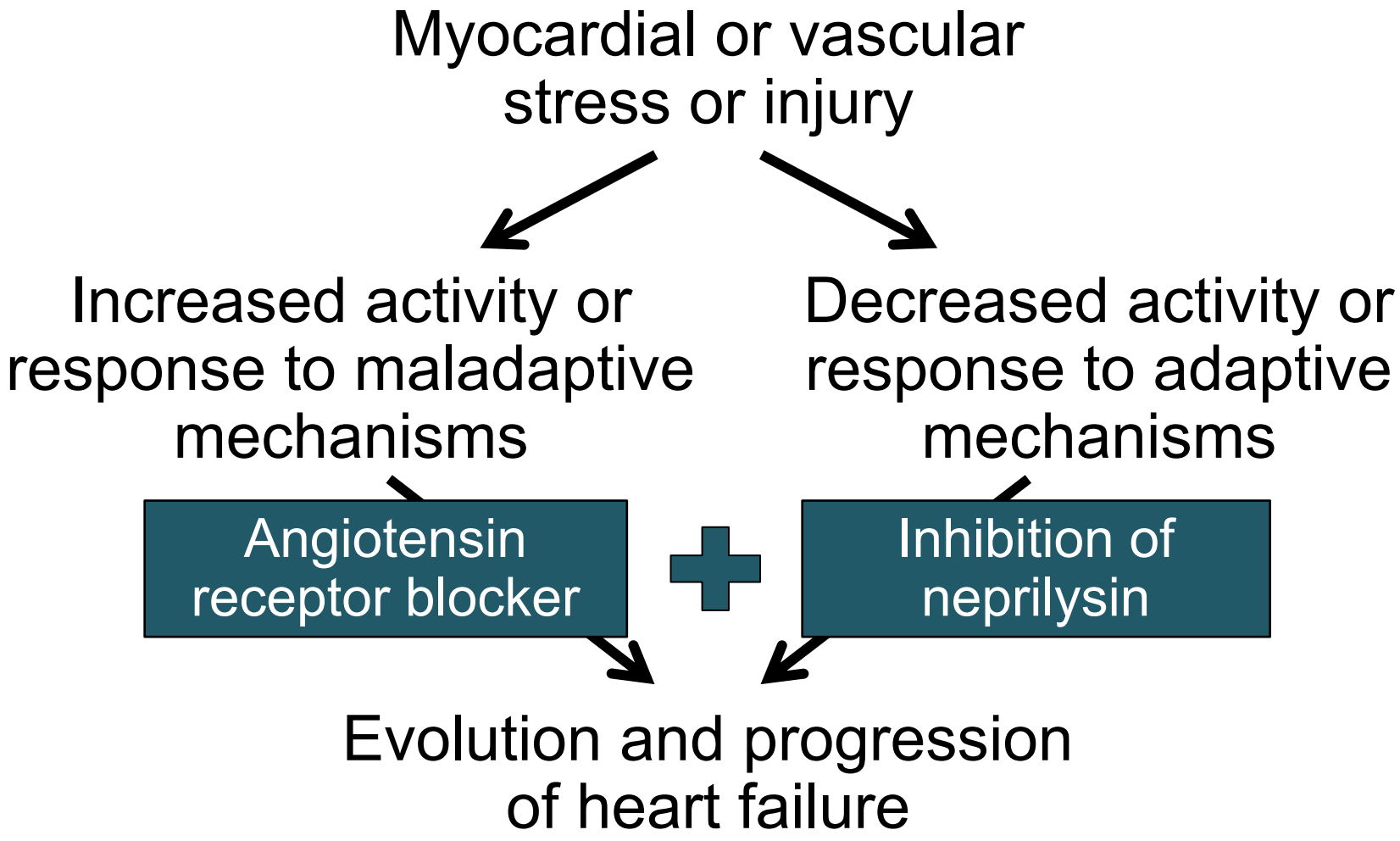
Neprilysin Inhibition Potentiates Actions of Endogenous Vasoactive Peptides That Counter Maladaptive Mechanisms in Heart Failure



Mechanisms of Progression in Heart Failure

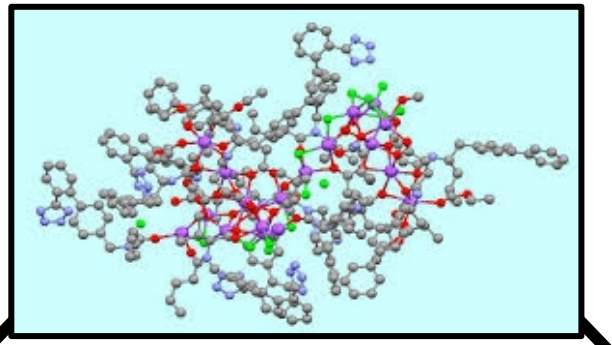


Mechanisms of Progression in Heart Failure



LCZ696: Angiotensin Receptor Neprilysin Inhibition

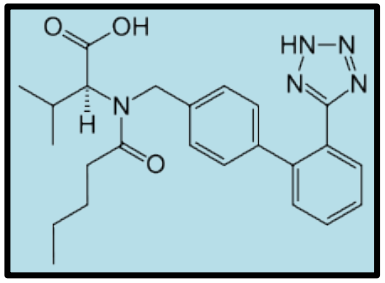
LCZ696

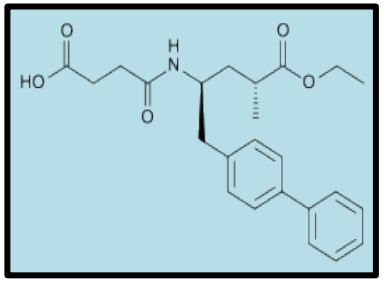


Angiotensin receptor blocker

+

Inhibition 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)

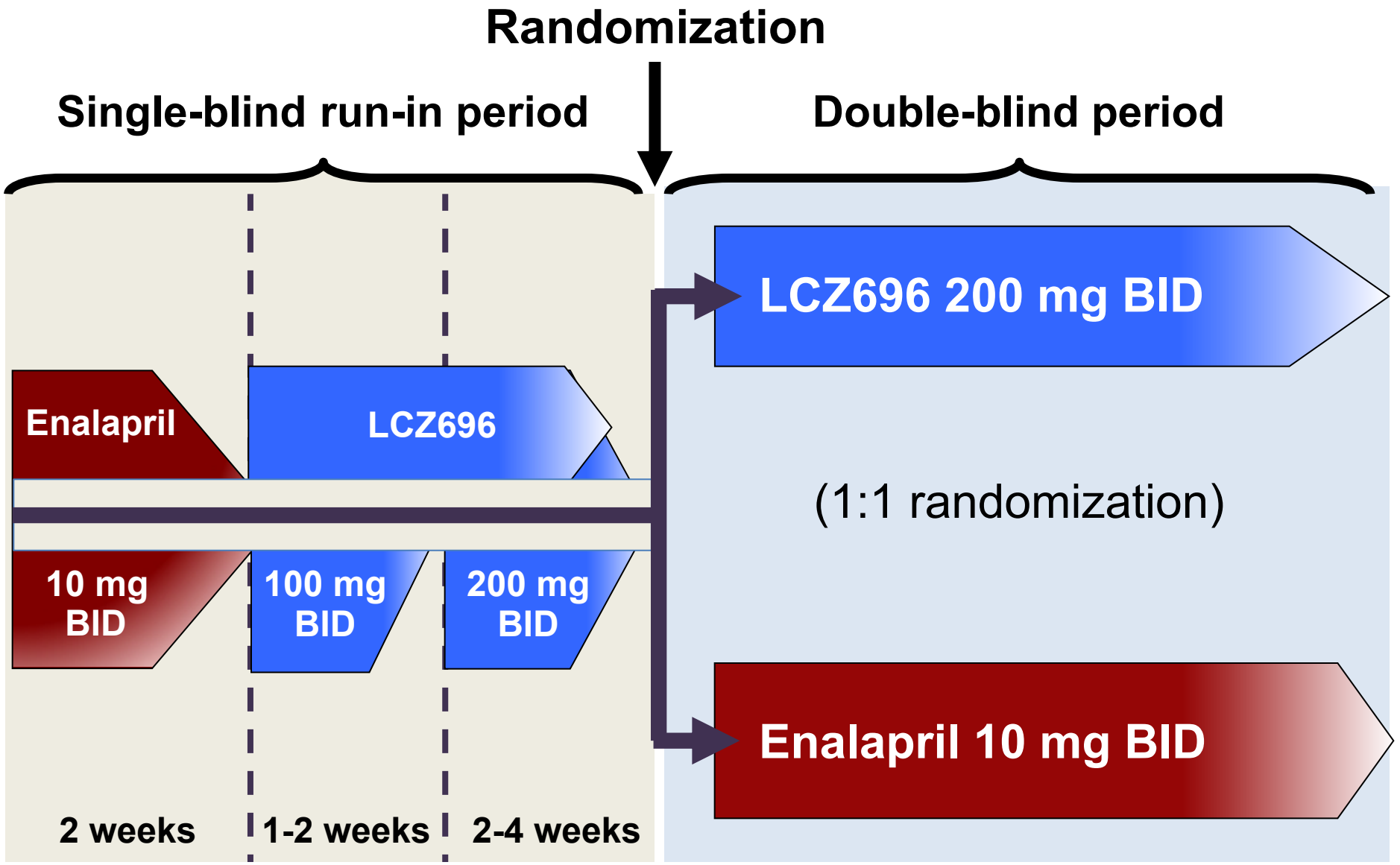
LCZ696 400 mg daily ⟺ **Enalapril 20 mg daily**

SPECIFICALLY DESIGNED TO REPLACE CURRENT USE OF ACE INHIBITORS AND ANGIOTENSIN II 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 Was Designed to Show Incremental Effect on Cardiovascular Death

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

The sample size of the trial was determined by effect on **cardiovascular mortality**, not the primary endpoint

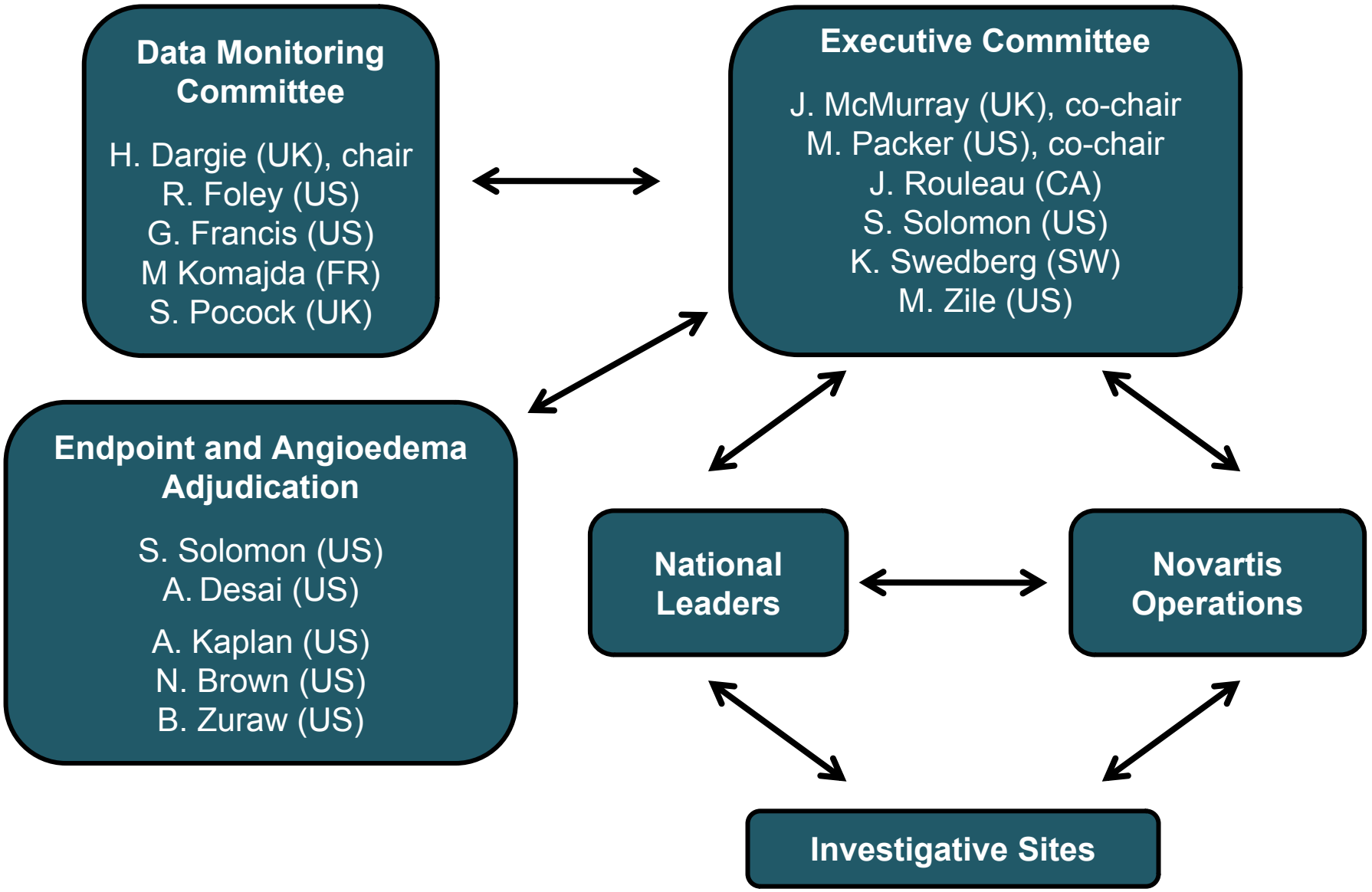
The Data Monitoring Committee was allowed to stop the trial only for a compelling effect on **cardiovascular mortality** (in addition to the primary endpoint)

Difference in cardiovascular mortality of 15% between LCZ696 and enalapril was prospectively identified as being clinically important (n=8000 yielded 80% power)

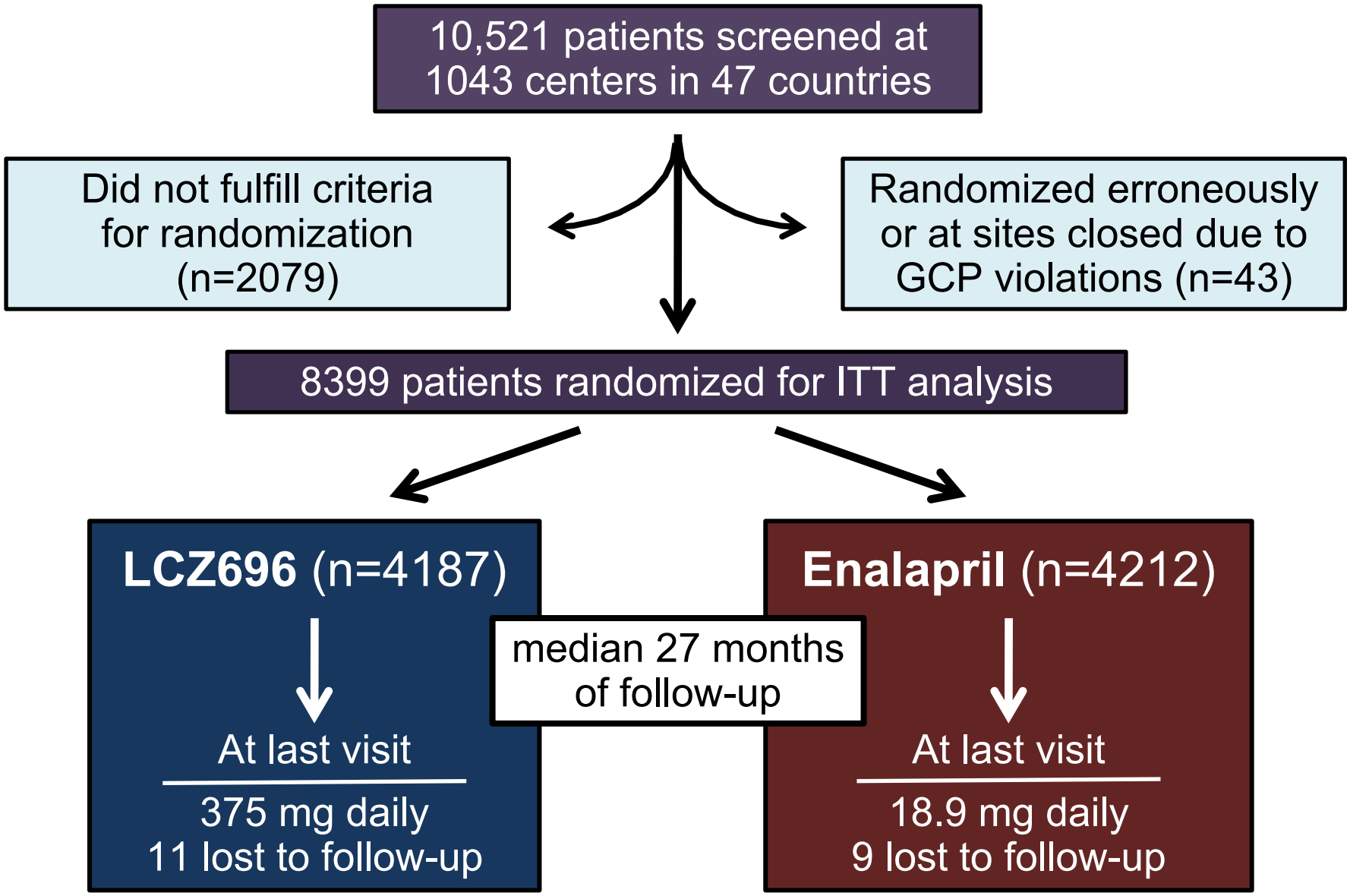
PARADIGM-HF: Secondary Endpoints

- All-cause mortality
- Change from baseline in the clinical summary score of the Kansas City Cardiomyopathy Questionnaire at 8 months
- Time to new onset of atrial fibrillation
- Time to first occurrence of a protocol-defined decline in renal function

PARADIGM-HF: Study Organization



PARADIGM-HF: Patient Disposition

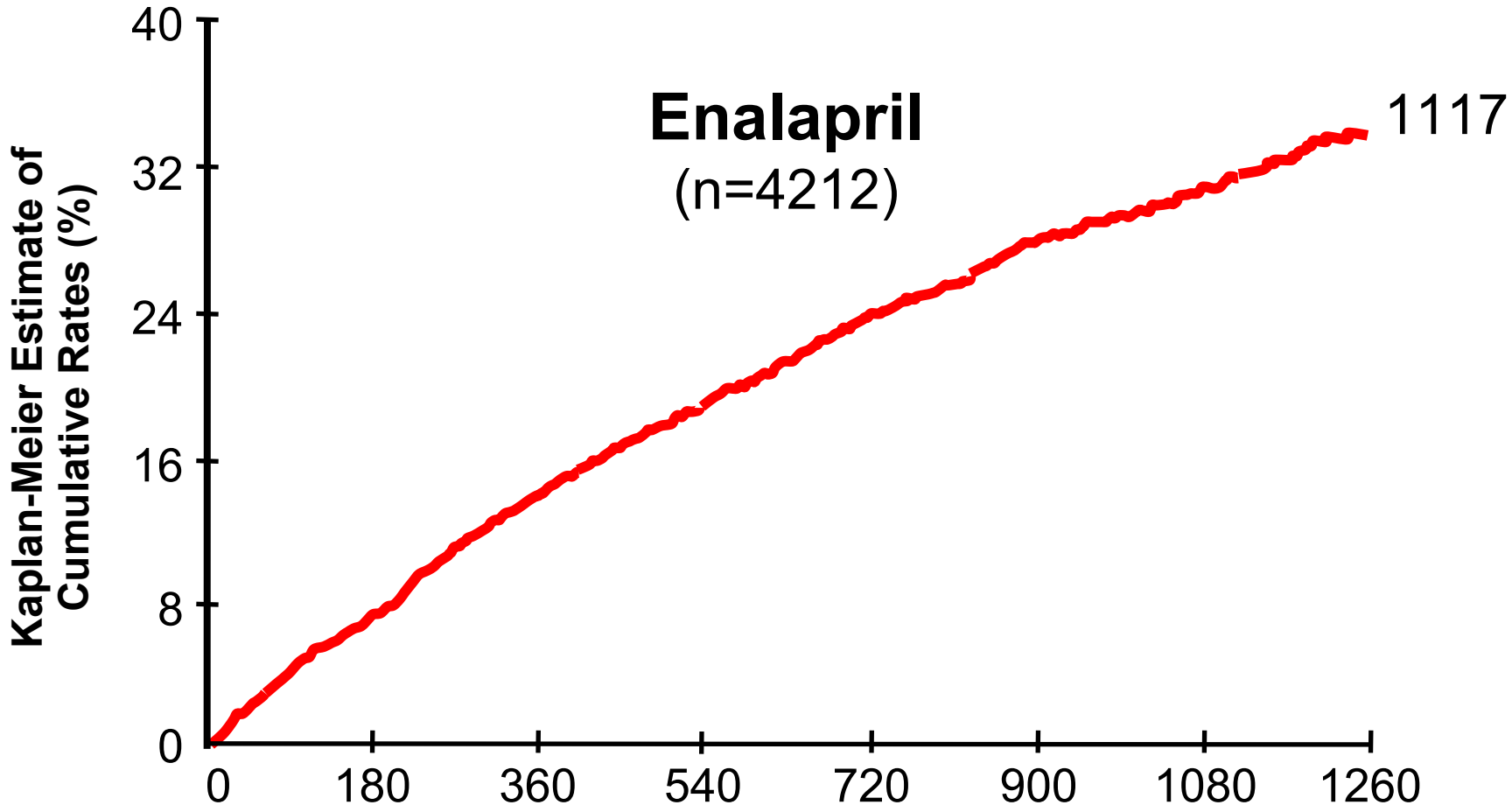


PARADIGM-HF: Baseline Characteristics

	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%

(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

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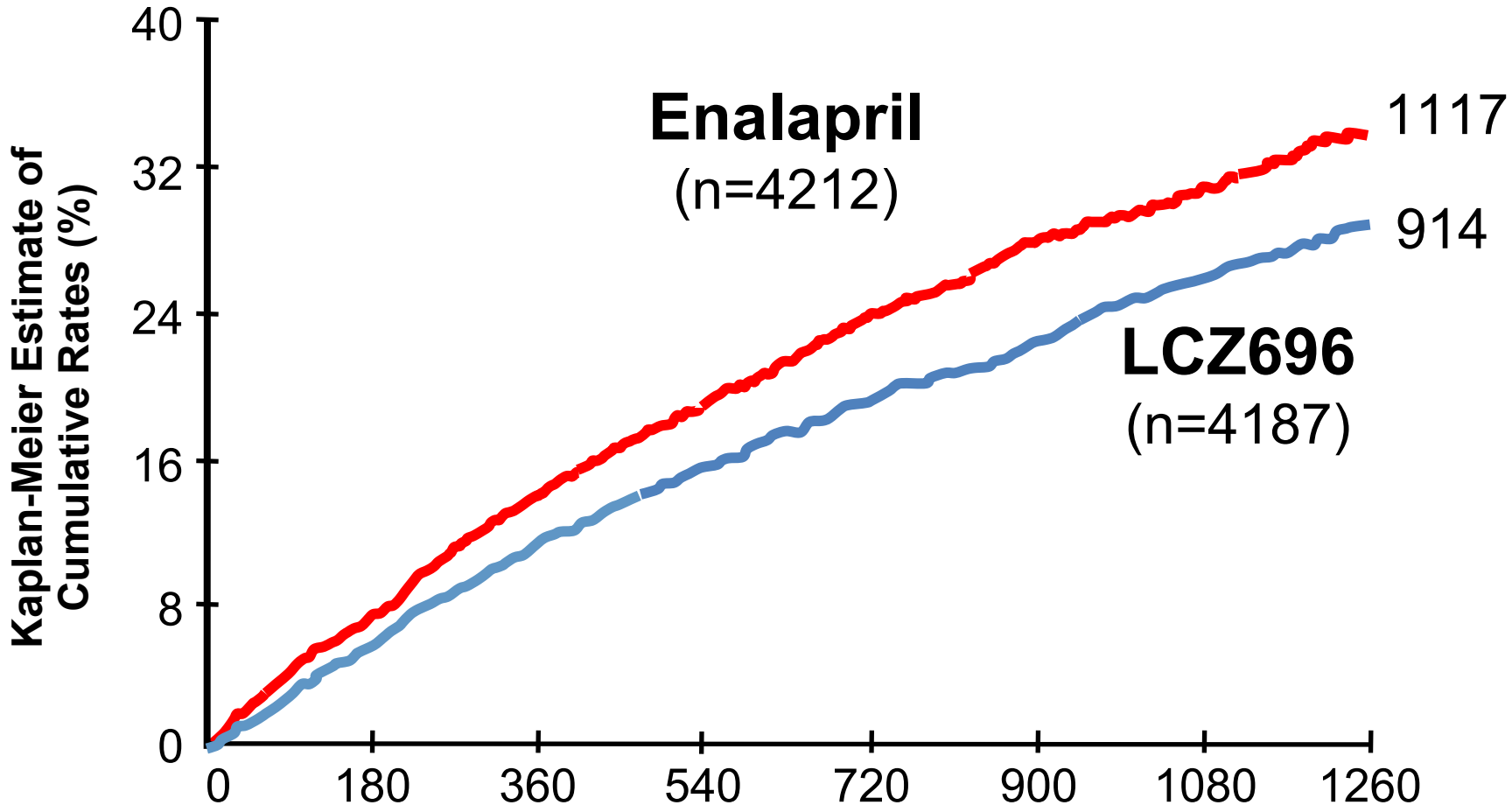

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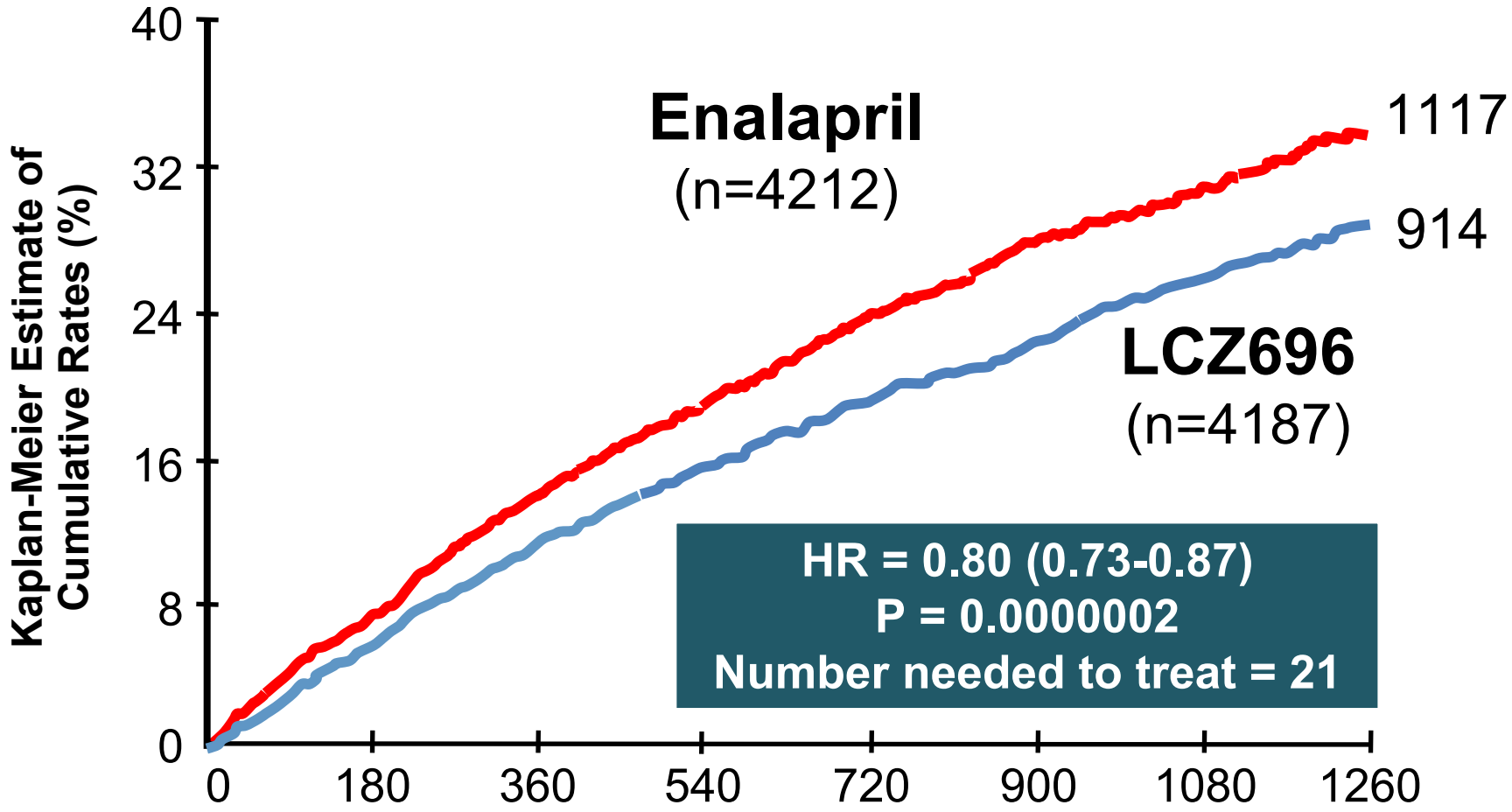

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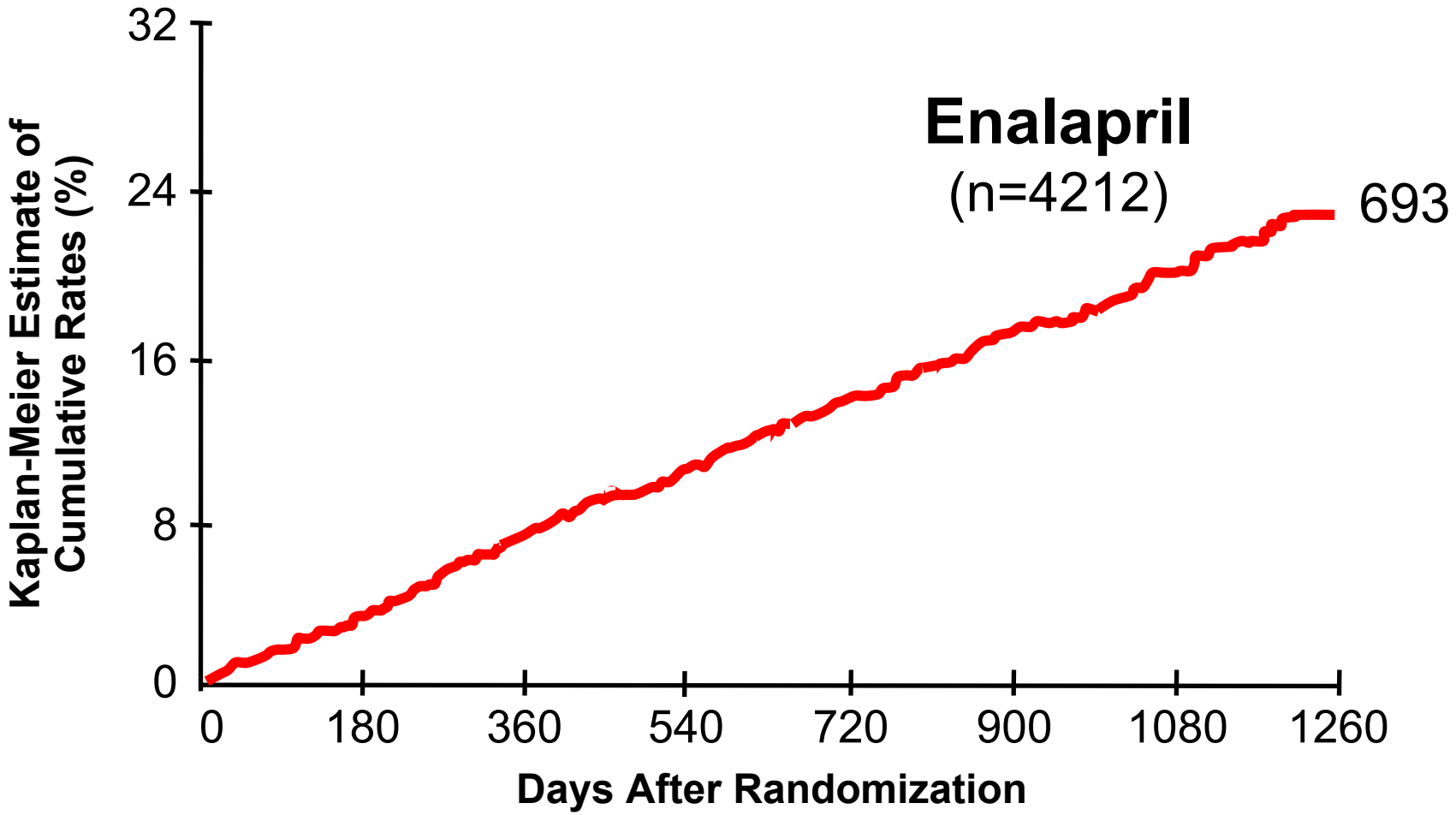
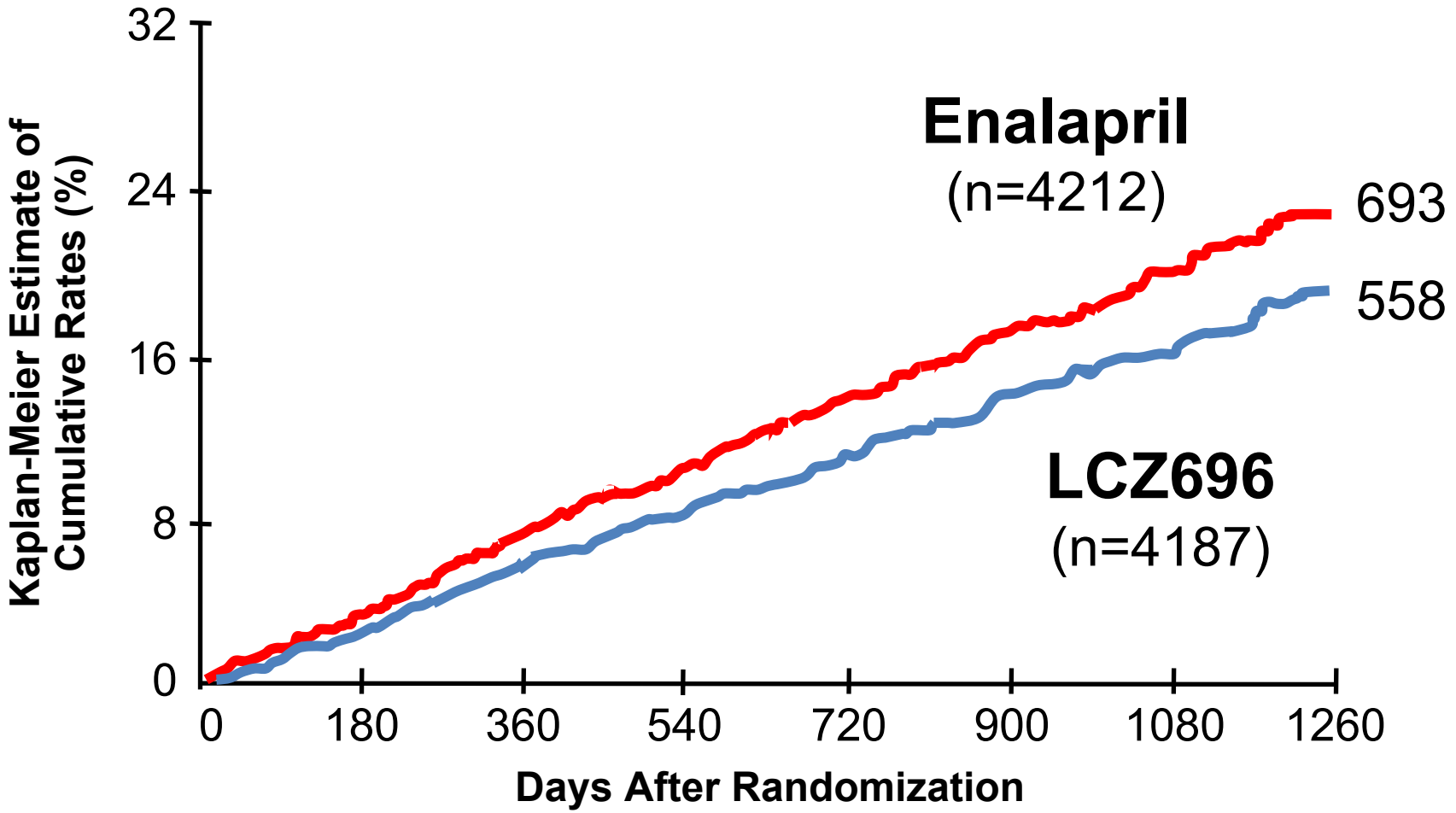
PARADIGM-HF: Cardiovascular Death



Patients at Risk

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

PARADIGM-HF: Cardiovascular Death



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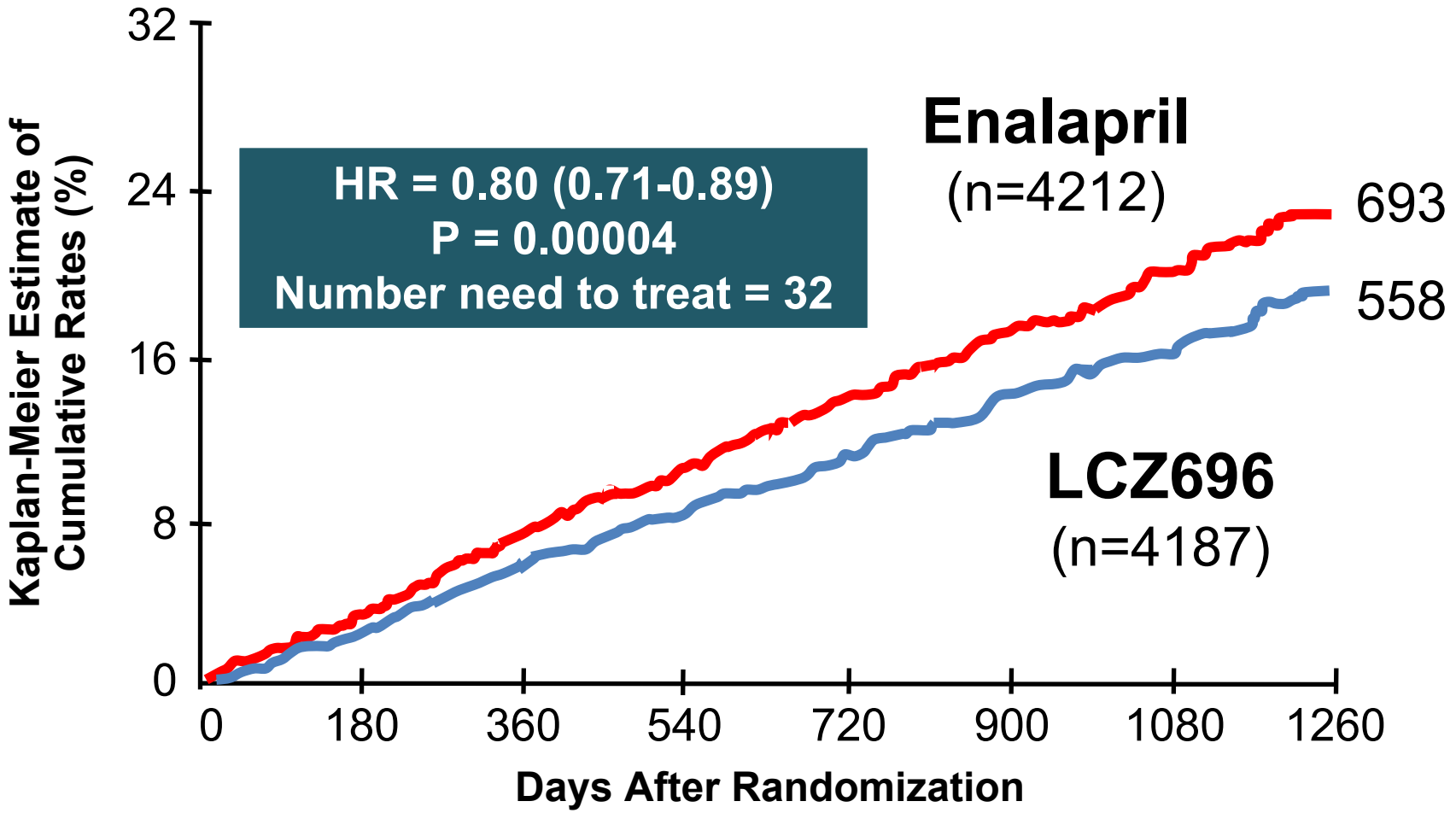
PARADIGM-HF: Cardiovascular Death



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LCZ696	4187	4056	3891	3282	2478	1716	1005	280
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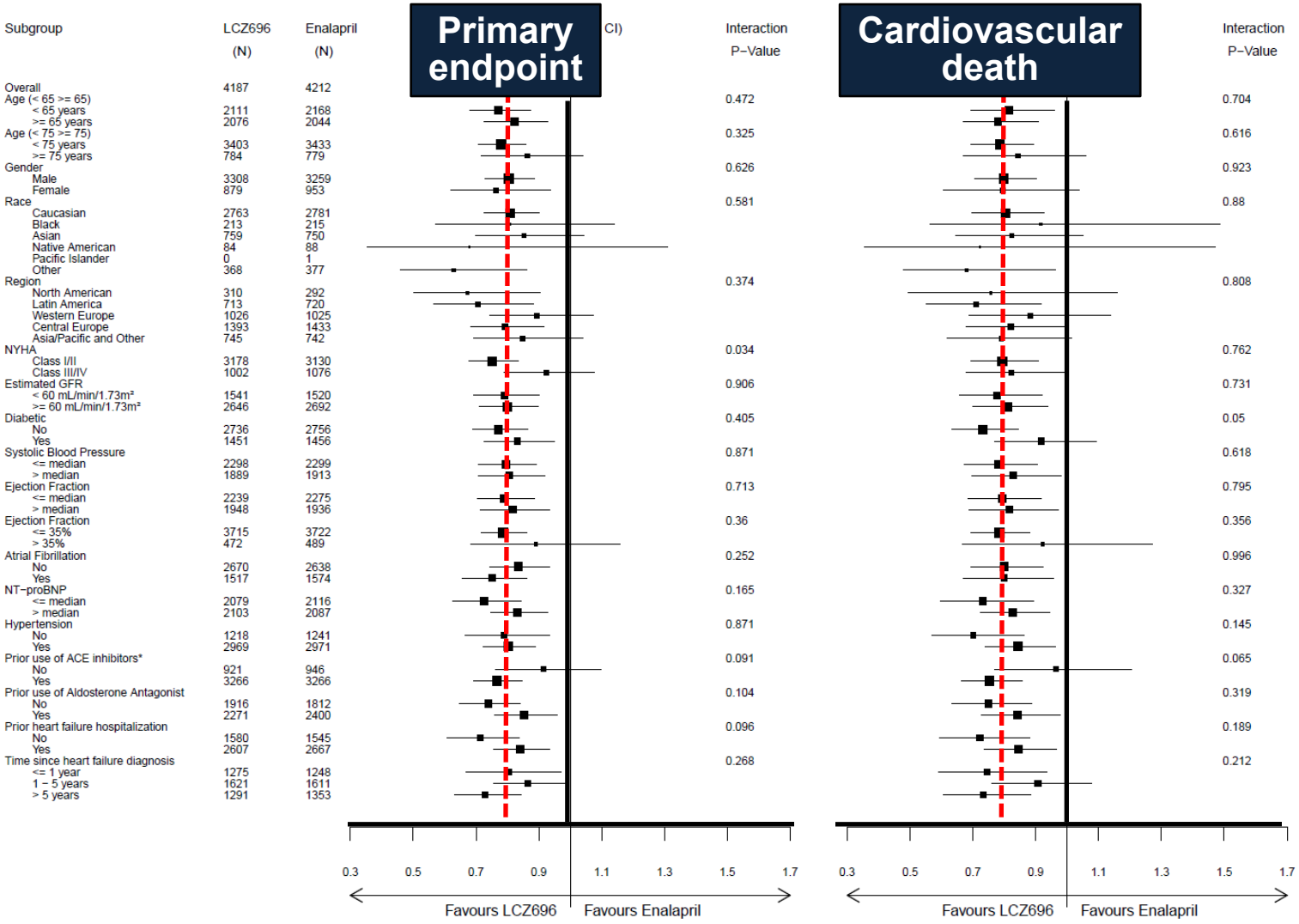
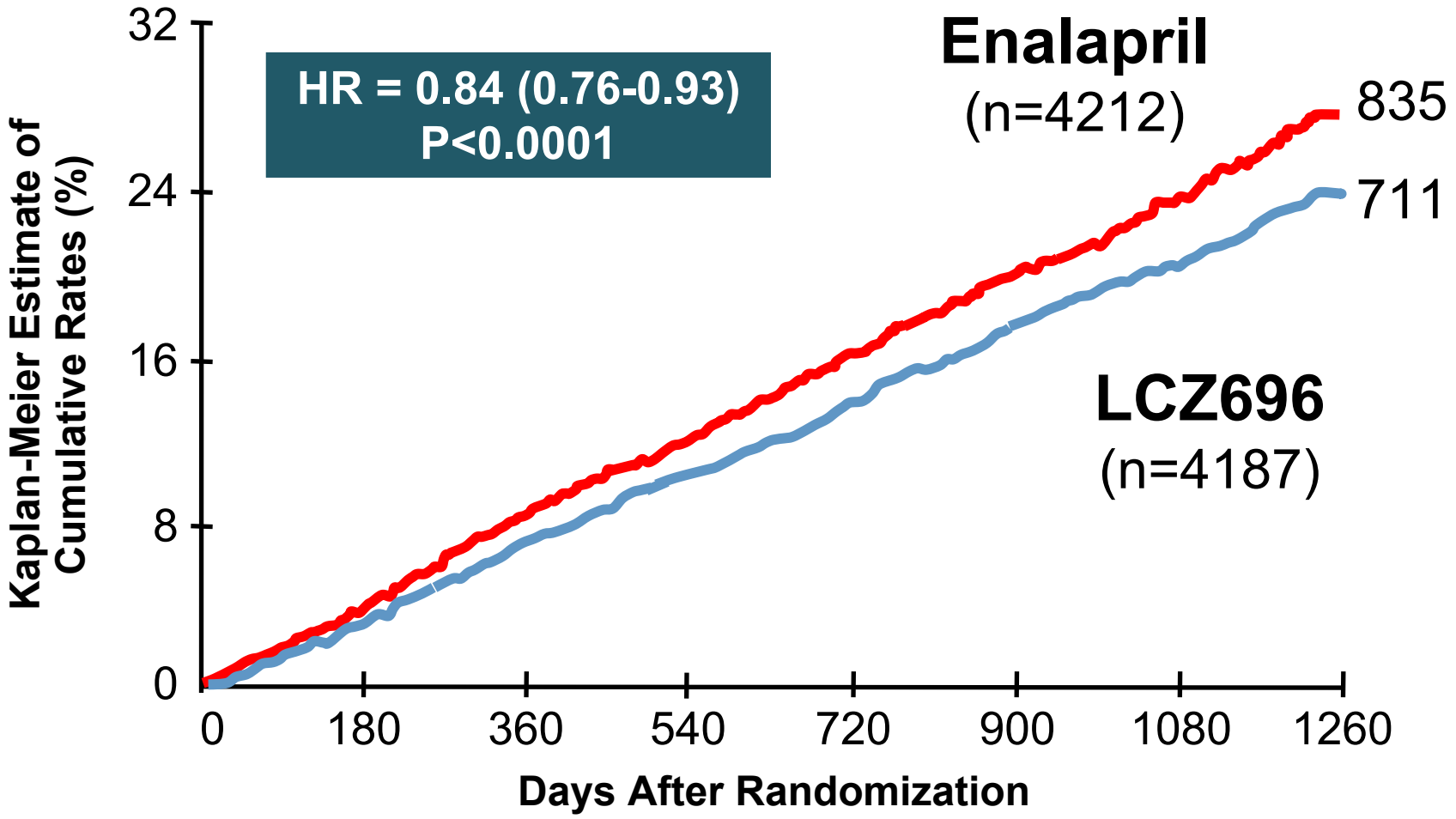
PARADIGM-HF: Effect of LCZ696 vs Enalapril on Primary Endpoint and Its Components

	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			
Discontinuation for adverse event			
Discontinuation for hypotension	36	29	NS

PARADIGM-HF: Adverse Events

	LCZ696 (n=4187)	Enalapril (n=4212)	P Value
Prospectively identified adverse events			
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 hyperkalemia	11	15	NS
Discontinuation for renal impairment	29	59	0.001

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:

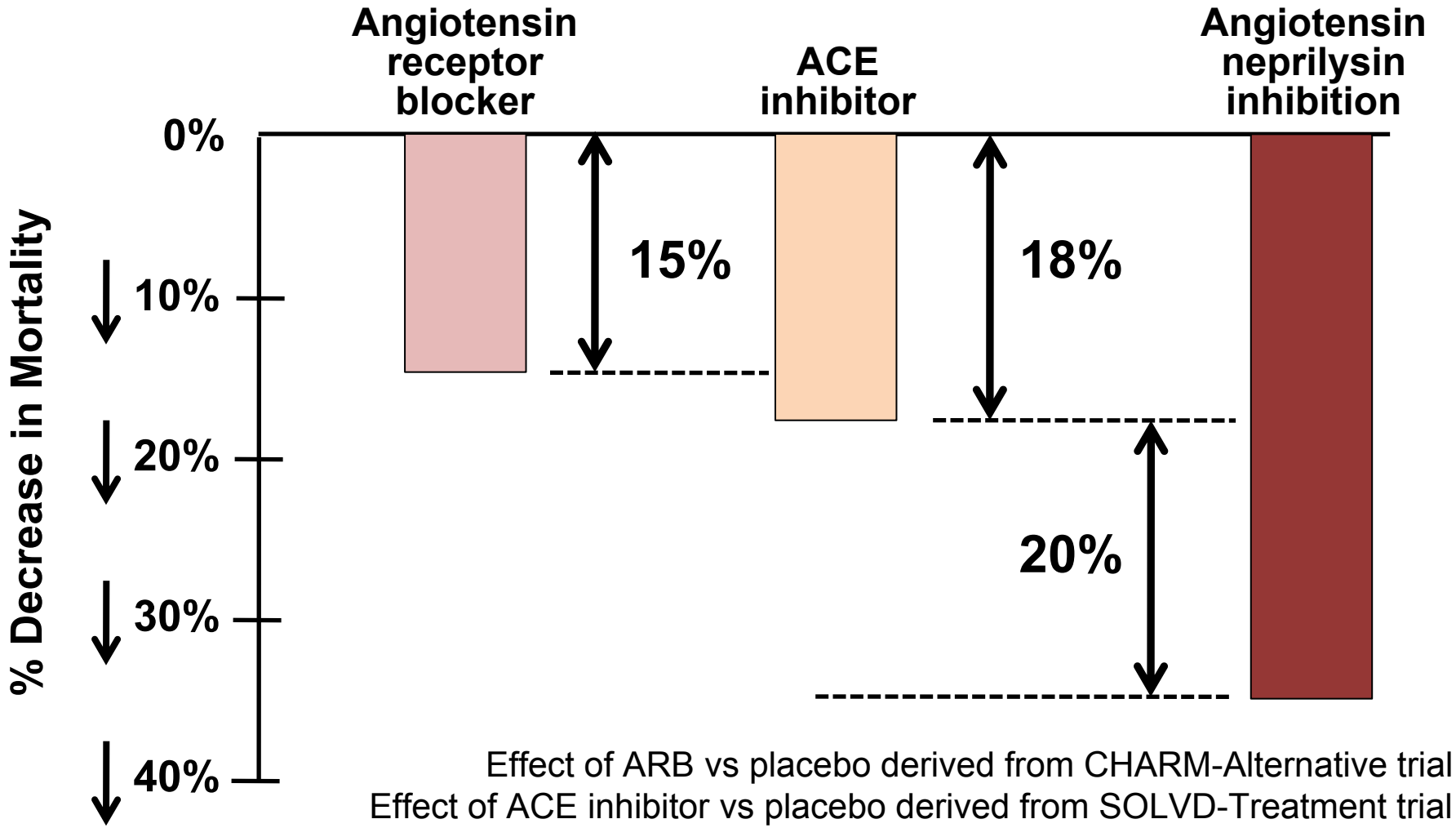
LCZ696 was *more effective* than enalapril in . . .

- 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

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