

Cardio-Metabolic
Franchise



Entresto[®] – Development of sacubitril/valsartan (LCZ696) for the treatment of heart failure with reduced ejection fraction

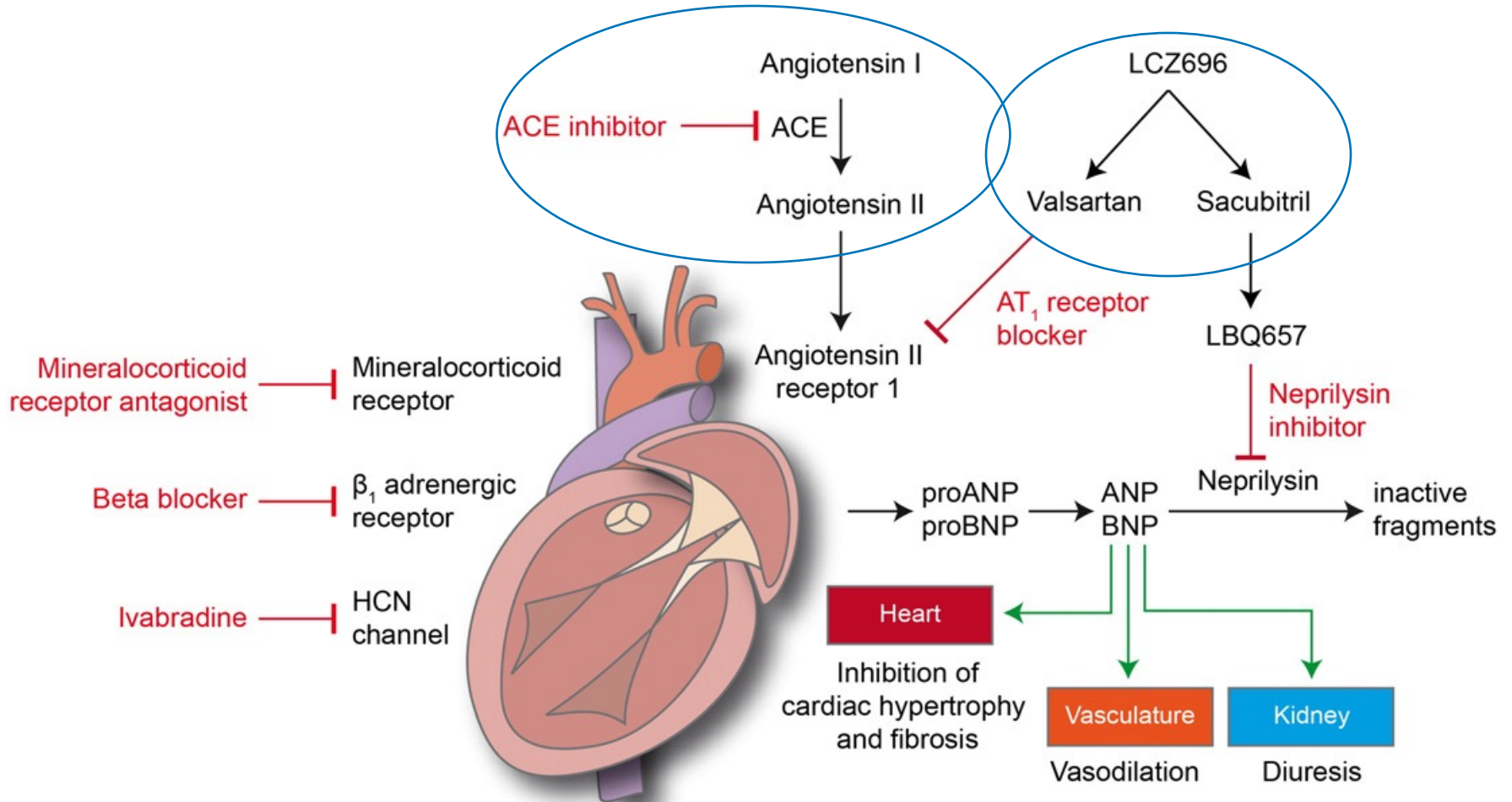
Randy L Webb, PhD
Rutgers Workshop
October 21, 2016

Heart failure

- Prevalence of HF in US and EU up to 10-12% in patients ≥ 70 years old¹
- 5 year mortality of heart failure similar to that of many cancers¹
- NYHA Class I, II, III, and IV⁴
- Heart failure with reduced ejection fraction (HFrEF) and preserved ejection fraction (HFpEF)
- Entresto[®] only approved for HFrEF

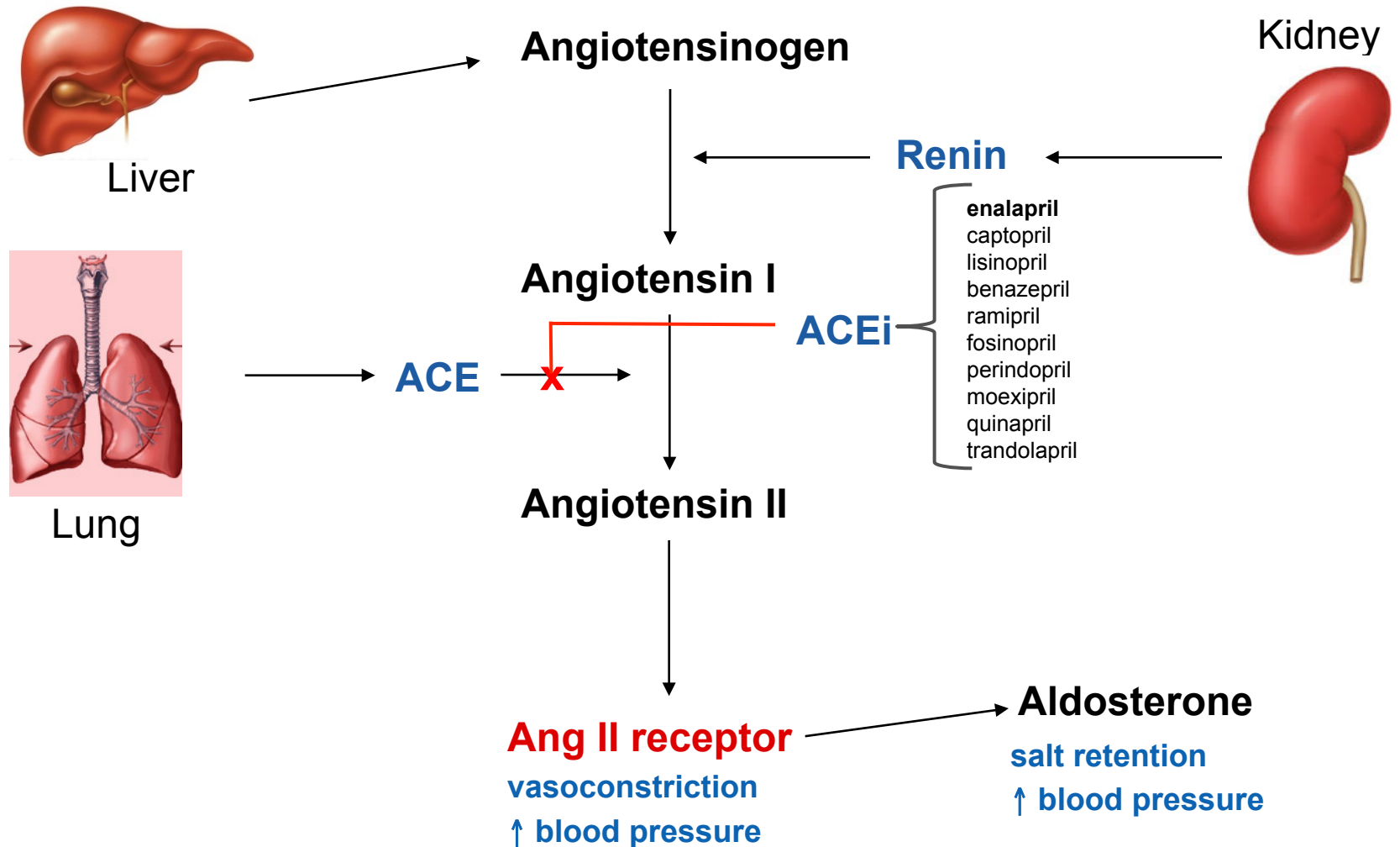
1. Roger VL, *Circ Res*; 113:646-659, 2013
2. Lothar and Hein, *Pharmacol Ther*;166:136-149, 2016
3. McMurray JJV, *N Engl J Med*; 362:228-238, 2010
4. Hunt SA et al, *Circulation*; 119:e391-e479, 2009

Current heart failure therapy

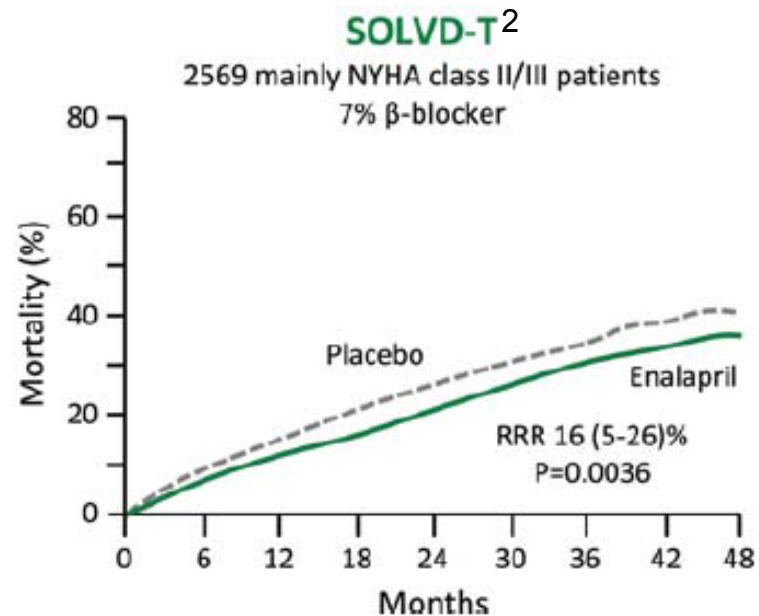
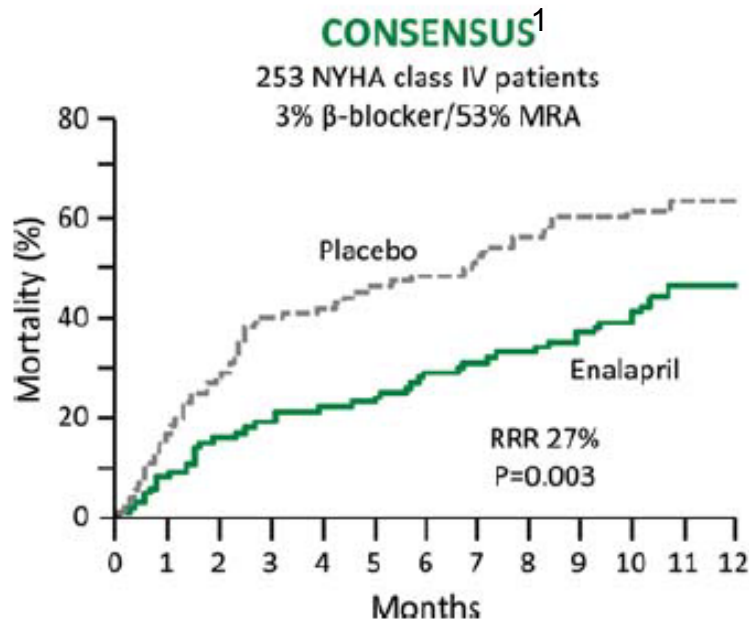


1. Lotter and Hein, *Pharmacol Ther*; 166:136-149, 2016

Renin angiotensin aldosterone system



Effects of an ACE inhibitor in patients with systolic heart failure (enalapril)



1. The CONSENSUS Trial Study Group, *N Engl J Med*; 316:1429-1435, 1987.
2. The SOLVD Investigators, *N Engl J Med*; 325:293-302, 1991.

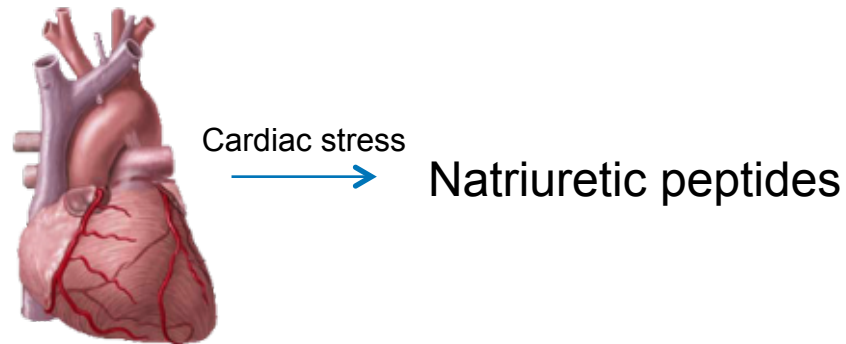
Alternative vasodilator/cardioprotective mechanisms

A RAPID AND POTENT NATRIURETIC RESPONSE TO INTRAVENOUS INJECTION OF
ATRIAL MYOCARDIAL EXTRACT IN RATS

A. J. de Bold, H. B. Borenstein, A. T. Veress, H. Sonnenberg

Dept. of Pathology, Queen's University, Kingston, Ont. and
Dept. of Physiology, University of Toronto, Toronto, Ont.

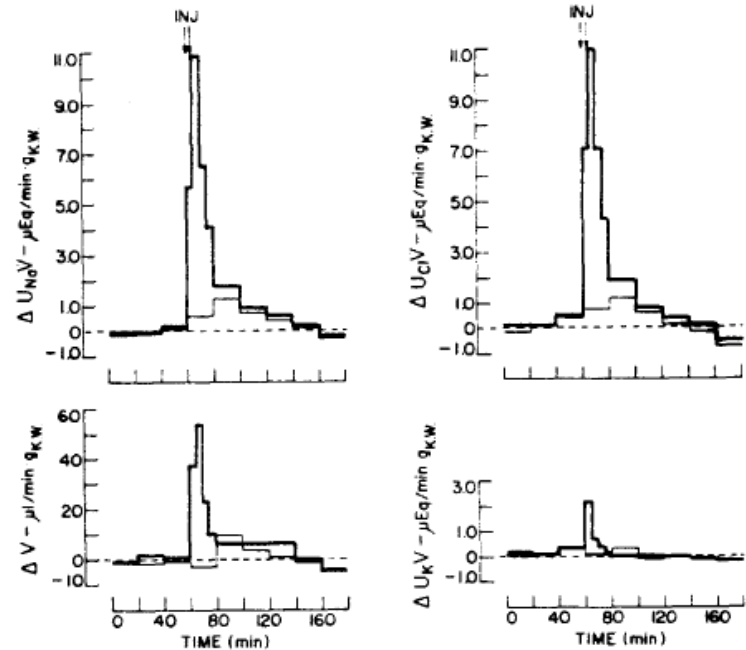
(Received in final form October 21, 1980)



1. de Bold et al, *Life Sciences* 28:78-94, 1981

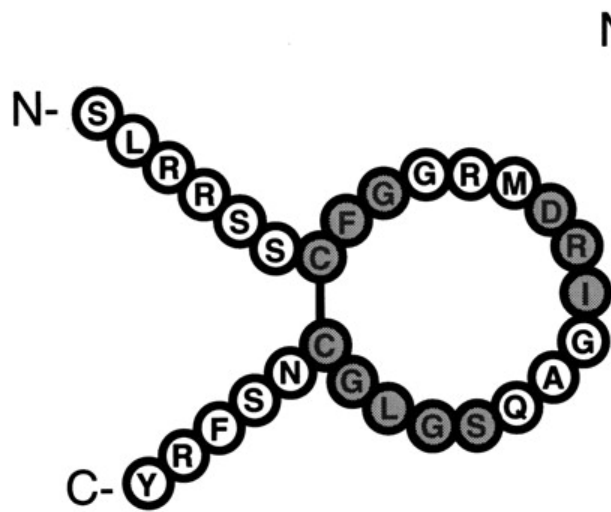
Response to i.v. injection of rat atrial myocardial extracts

- Rapid fall in blood pressure
- Increase in sodium excretion
- Increase in urine volume

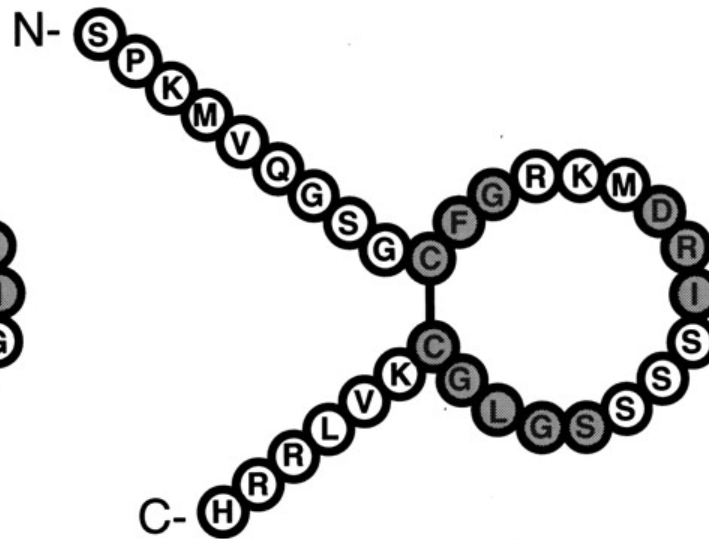


1. de Bold et al, *Life Sciences* 28:78-94, 1981

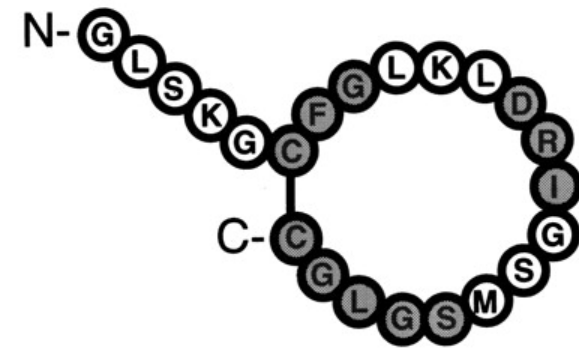
Natriuretic peptides



ANP

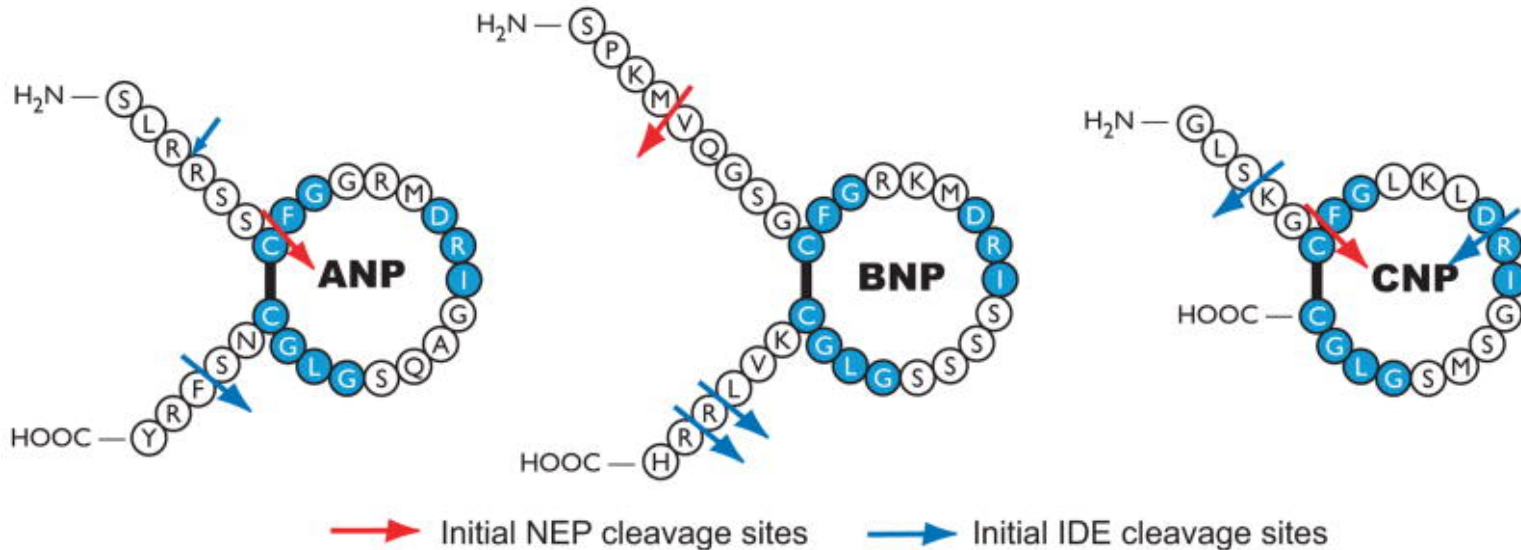


BNP



CNP

Natriuretic peptide degradation by neprilysin (NEP)

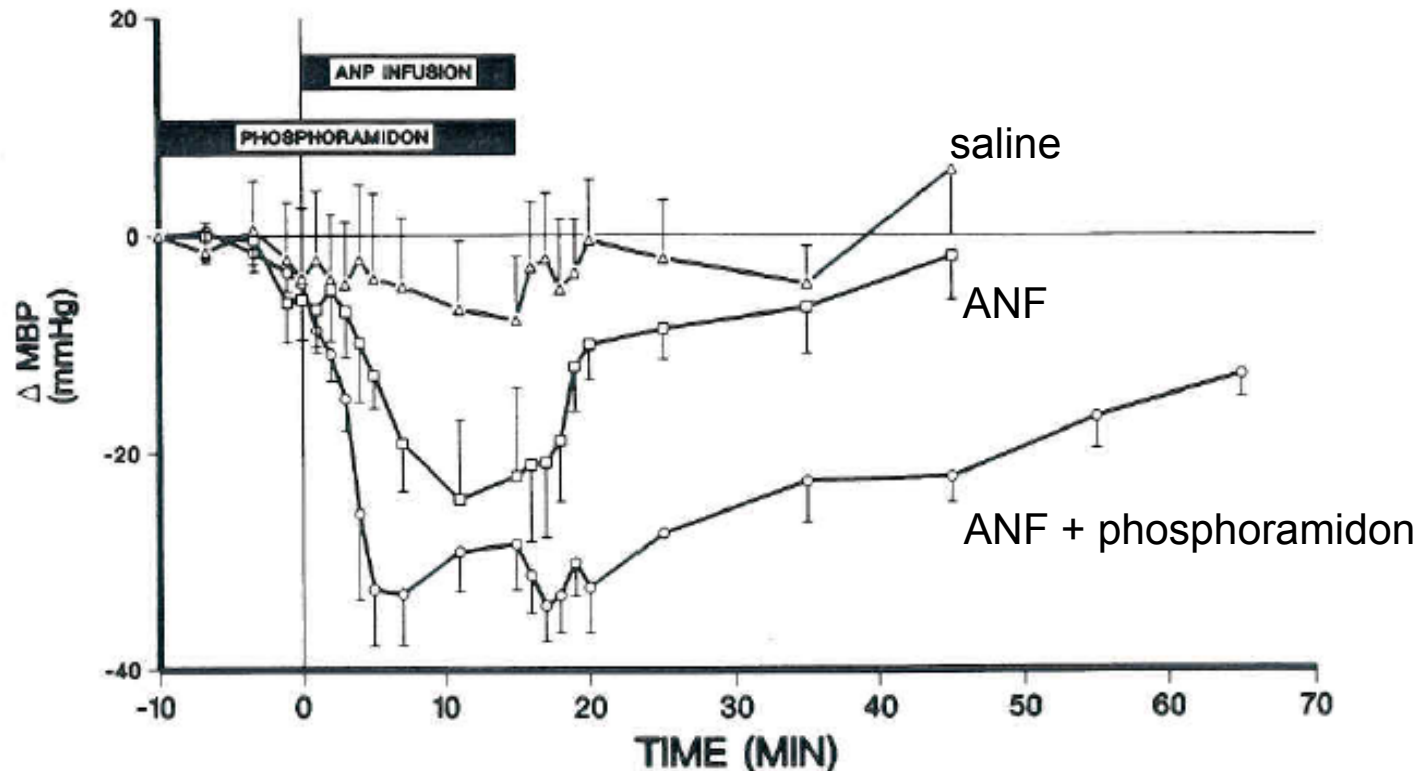


Initial NEP cleavage inactivates ANP

1. Potter LR, *FEBS J*; 278:1808-1817, 2011

NEP inhibitor potentiates ANF

Conscious Spontaneously Hypertensive Rat



1. Webb et al *J Cardiovasc Pharmacol* 14:285-293, 1989

Early Nephrylsin inhibitors

- Racecodotil (oral)¹ and candoxatrilat (iv)²
 - Natriuresis
 - Increased urinary excretion of ANP
- Candoxatril³
 - Oral prodrug
 - Initial reduction in blood pressure was not sustained

1. Gros C et al, *Proc Natl Acad Sci USA* 86:7580-4, 1989

2. Northridge DB et al, *Lancet* 334:591-3, 1989

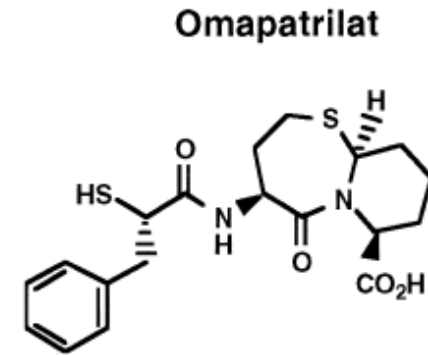
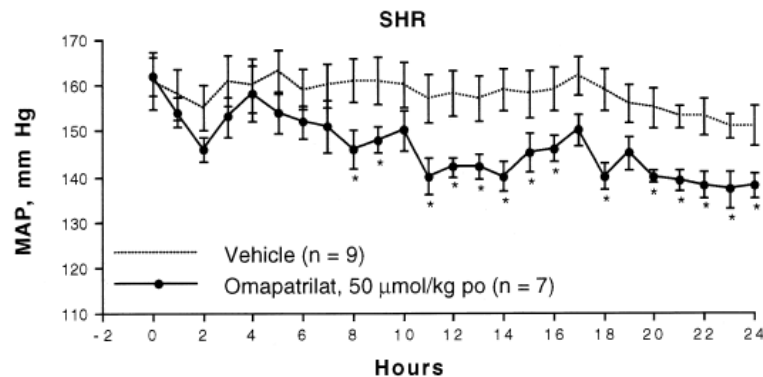
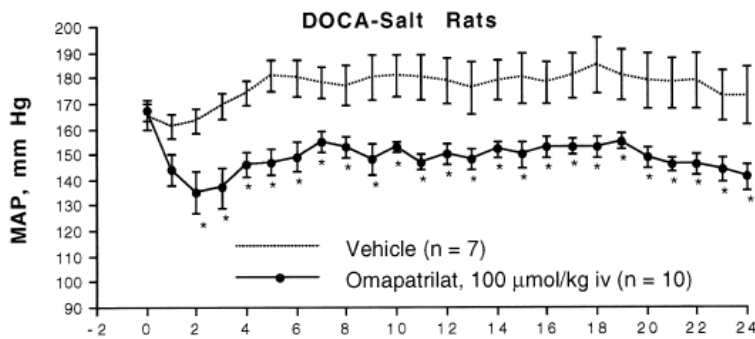
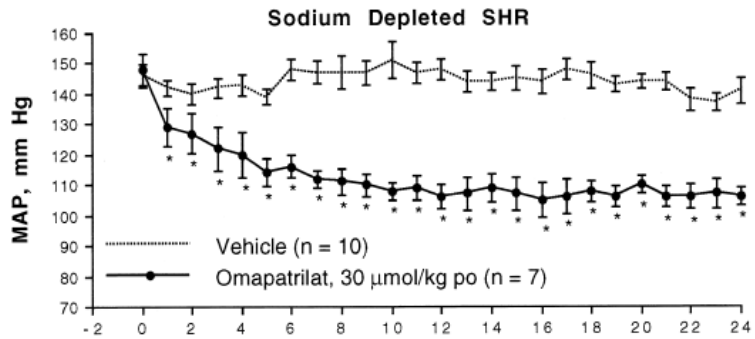
3. Bévan EG et al, *J Hypertens* 10:607-13, 1992

Diminishing effects with chronic NEP inhibition in hypertensive patients

- Acute candoxatril administration
 - Increased sodium excretion
 - Increased ANF in plasma
 - Increased urinary ANF and cGMP
- Chronic candoxatril
 - Diminished increase in plasma ANF
 - Increased plasma angiotensin II and aldosterone
 - Only a slight reduction in mean arterial pressure

1. Richards et al, *J Hypertens*; 11:407-416, 1993
2. Bevan et al, *J Hypertens*; 10:607-613, 1992

Effects of a dual ACE-NEPi on blood pressure

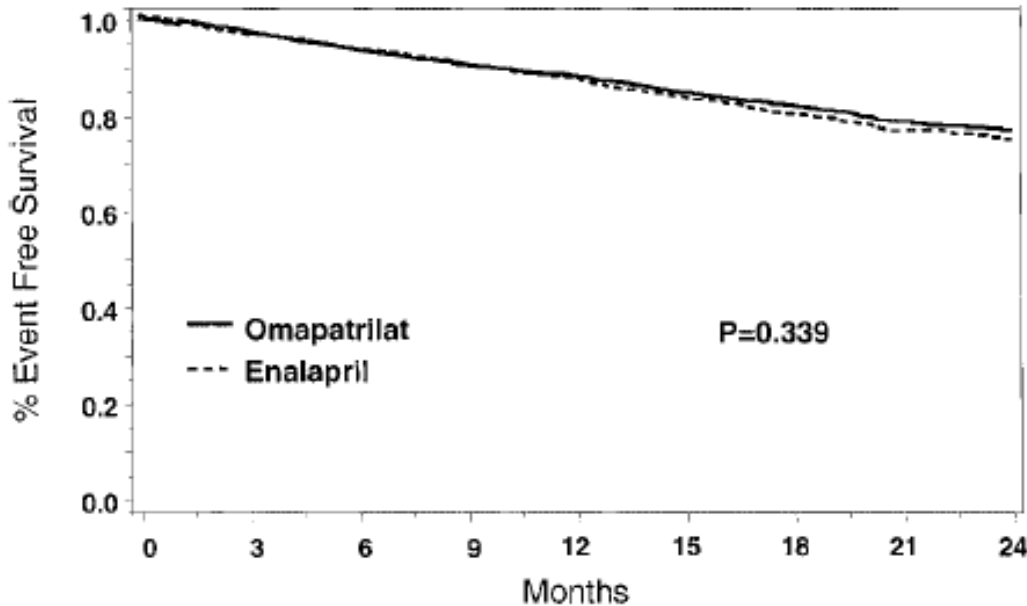


ACE K_i = 6 nmol/L
NEP K_i = 9 nmol/L

Limitations of a dual-acting inhibitor

1. Trippodo et al, *Am J Hypertens*; 11:363-372,1998

Effects of omapatrilat in patients with HF *OVERTURE* Trial



5770 patients with NYHA class II-IV heart failure

Enalapril 10 mg BID

Omapatrilat 40 mg QD

Omapatrilat reduced the risk of death and hospitalization in CHF but was not more effective than enalapril alone

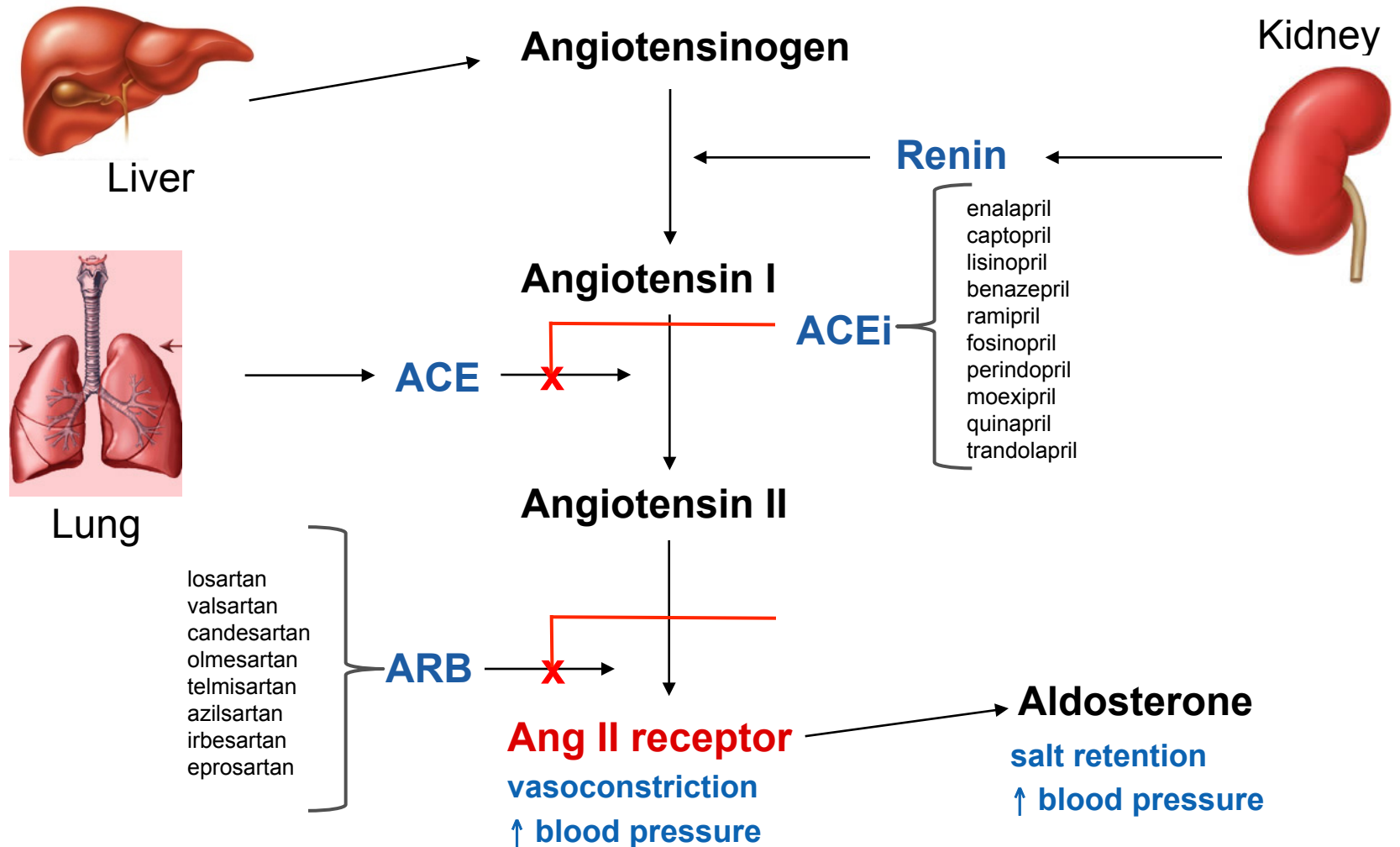
1. Packer et al, *Circulation*; 106:920-926, 2002

Omapatrilat – benefit/risk *angioedema*

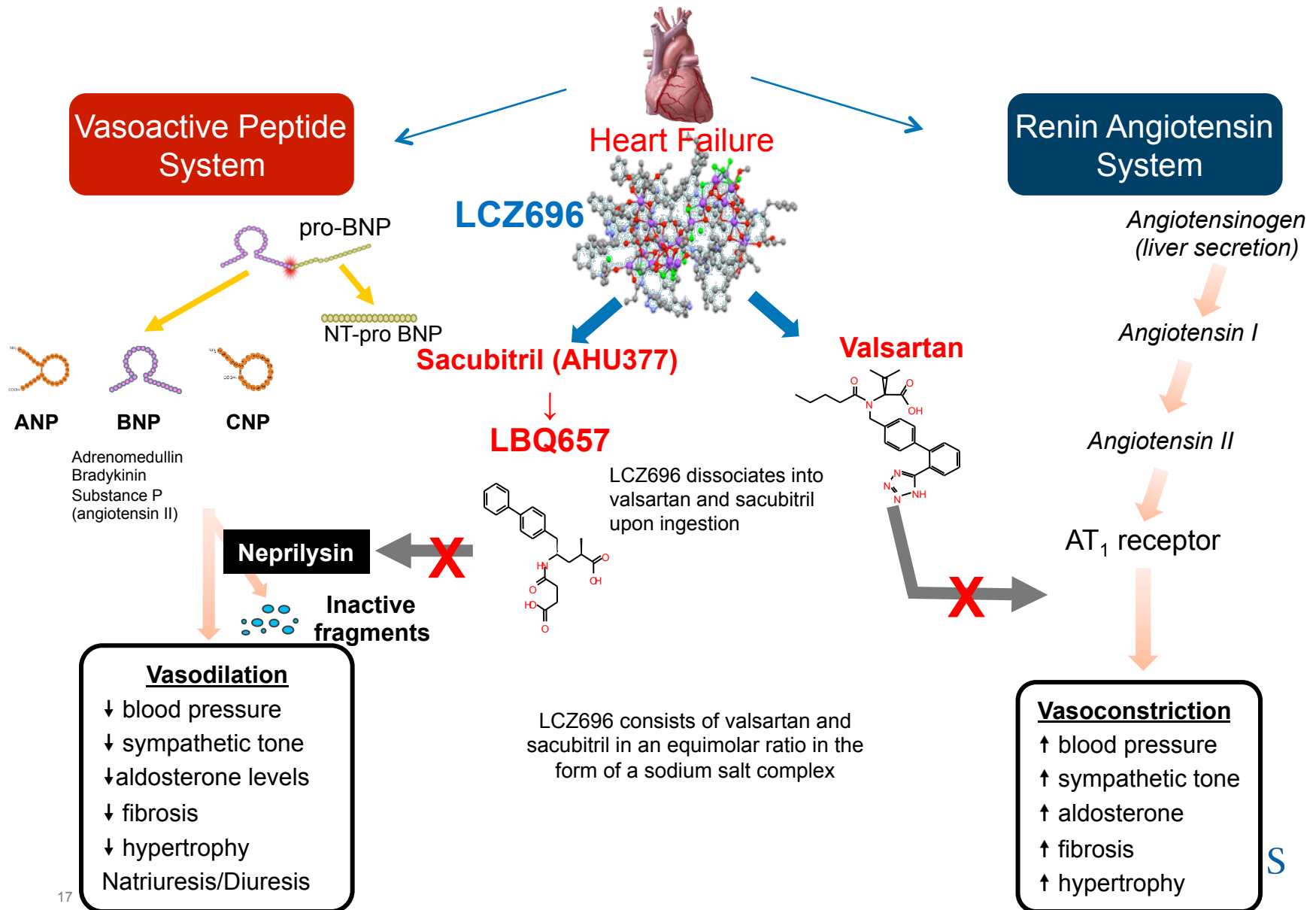
- OVERTURE omapatrilat not superior to enalapril in HF patients
- OCTAVE – 25,267 hypertensive patients
 - Significantly greater reduction in BP with omapatrilat vs enalapril
 - All adverse events, except angioedema similar between drugs
 - Angioedema cases:
 - Overall: 274 (2.17%) with omapatrilat vs 86 (0.68%) with enalapril
 - Blacks: 5.54% vs 1.62%
 - Smokers: 3.93% vs 0.81%

1. Coats, *AJS Int J Cardiol*; 86:1-4, 2002

Renin angiotensin aldosterone system



LCZ696 – A first-in-class Angiotensin Receptor Neprilysin Inhibitor – Simultaneously Inhibits NEP and the RAS



Entresto (LCZ696)

The NEW ENGLAND
JOURNAL *of* MEDICINE

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Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure

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Martin P. Lefkowitz, M.D., Adel R. Rizkala, Pharm.D., Jean L. Rouleau, M.D., Victor C. Shi, M.D.,
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for the PARADIGM-HF Investigators and Committees*

PARADIGM-HF

- 8442 patients with class II, III, and IV heart failure with EF \leq 40%
- LCZ696 200 mg BID, enalapril 10 mg BID
- Primary outcome – composite of death from CV causes or hospitalization for heart failure
- Trial was stopped early after median follow-up of 27 months
- LCZ696 was superior to enalapril in reducing the time to the first occurrence of CV death or HF hospitalization

1. McMurray et al, *N Engl J Med*; 371:993-1004, 2014

PARADIGM-HF

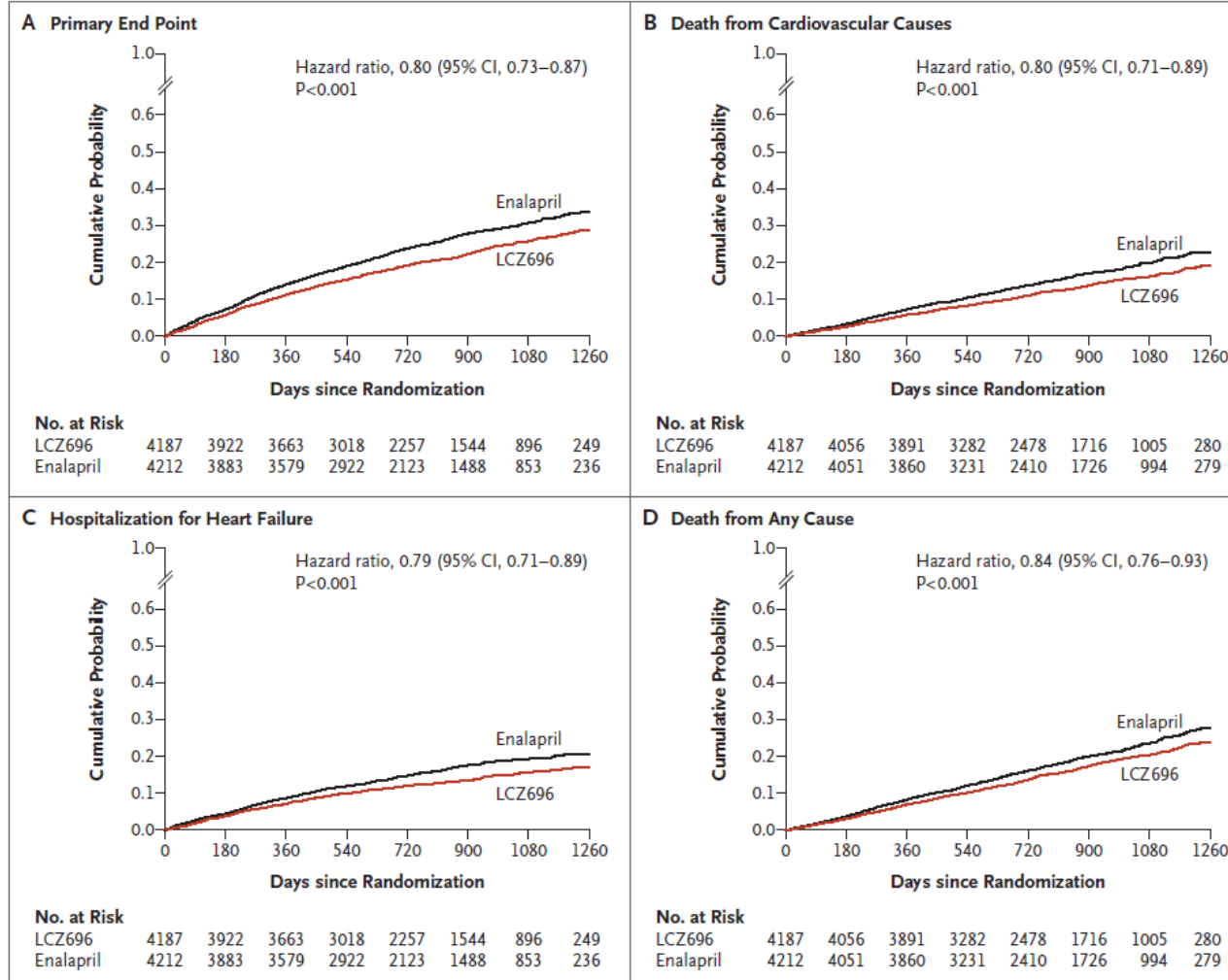


Figure 2. Kaplan–Meier Curves for Key Study Outcomes, According to Study Group.

Shown are estimates of the probability of the primary composite end point (death from cardiovascular causes or first hospitalization for heart failure) (Panel A), death from cardiovascular causes (Panel B), first hospitalization for heart failure (Panel C), and death from any cause (Panel D).

Thank you

Renin angiotensin aldosterone system

