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# The Path to an Angiotensin Receptor Antagonist-Neprilysin Inhibitor in the Treatment of Heart Failure: A Triumph of Academic-Industry Collaboration

Eugene Braunwald, MD

Paul Dudley White Lecture  
New York Cardiovascular Symposium  
December 13, 2015





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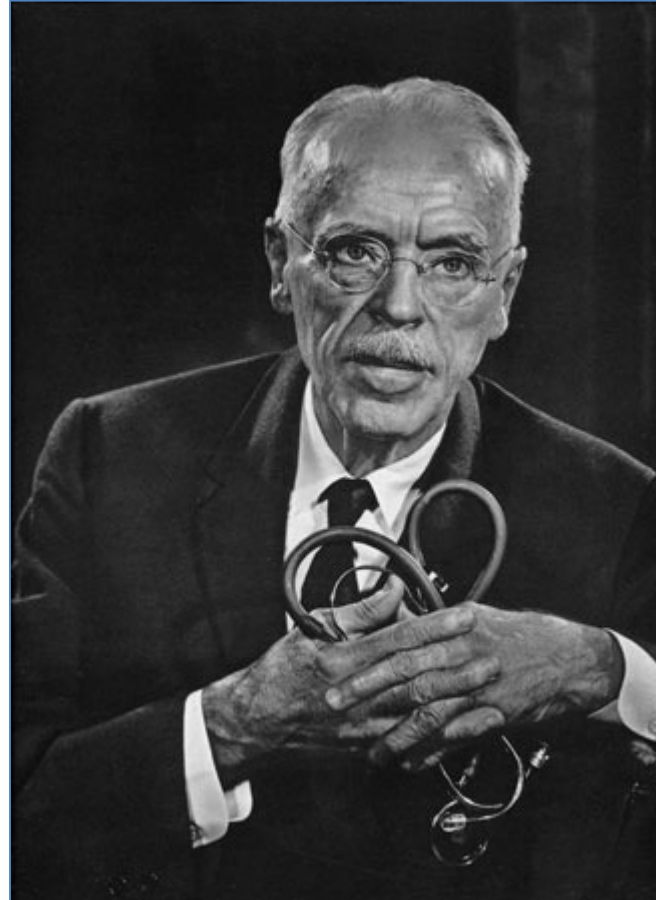
# Relevant disclosures

- Research grants (through the Brigham and Women's Hospital) from AstraZeneca, Daiichi-Sankyo, Merck, and Glaxo Smith Kline
- Personal fees for consultancies/lectures from Genzyme, Medicines Co, Theravance, and Sanofi-Aventis



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## Paul Dudley White (1886-1973)





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**I wish we could do  
something useful with  
tobacco - like making  
fertilizer out of it.**



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# Dual Goals

- To present the history of the physiologic and clinical advances that led to the development of the first angiotensin-receptor blocker-neprilysin inhibitor (ARNi)
- To use this achievement as a “case study” that demonstrates the necessity of devoting efforts of both academia and industry to advance science and improve medical care.



## ORIGINAL ARTICLE

# 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\*

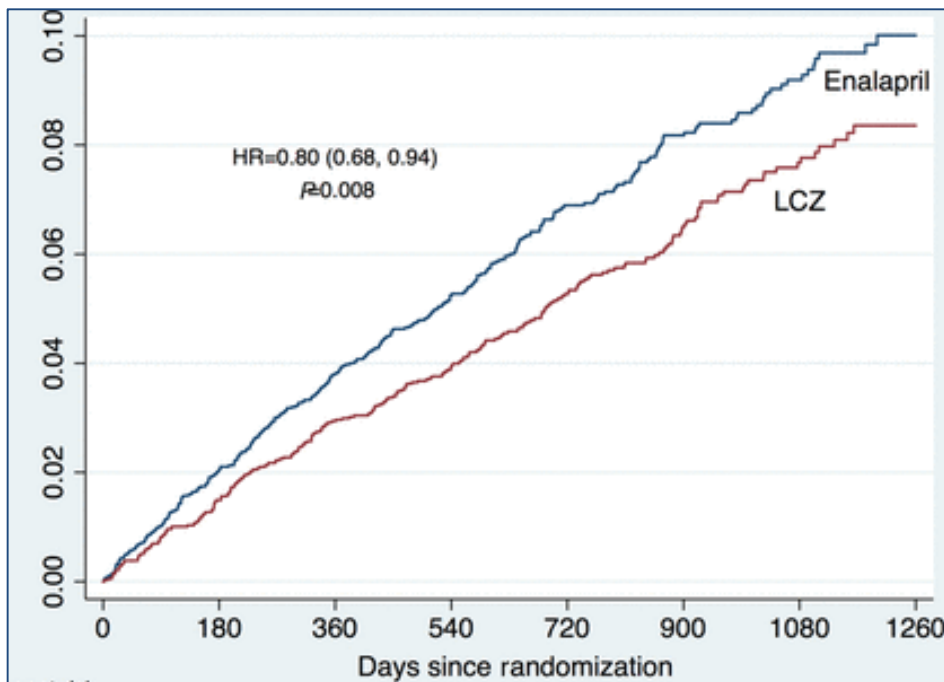


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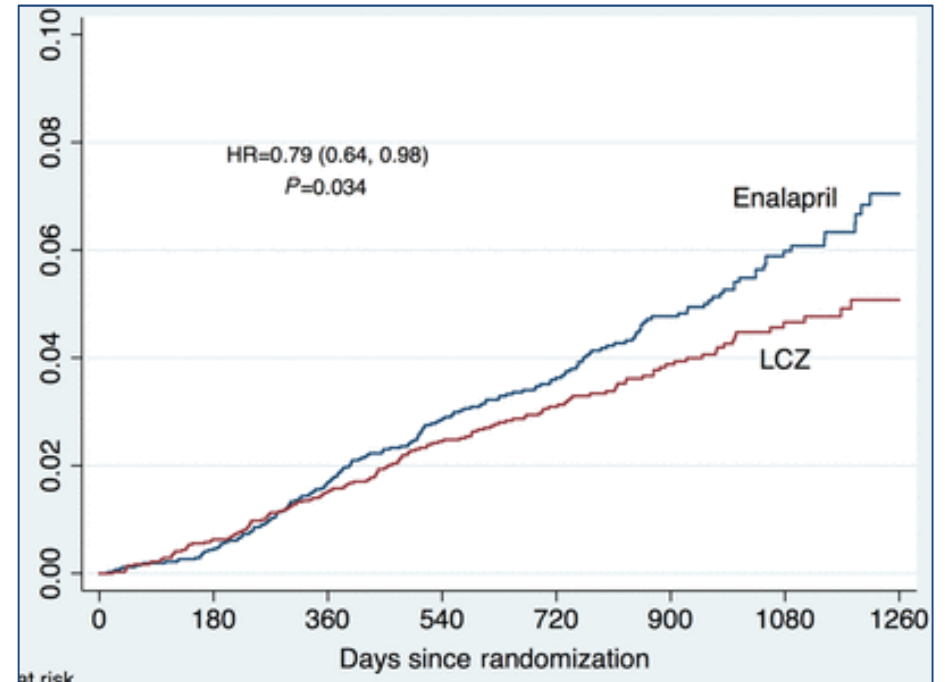
AI

# Cardiovascular Deaths in PARADIGM-HF

## Sudden Death



## Pump Failure



Desai AS, et al.  
*Eur Heart J* 2015;36:1990



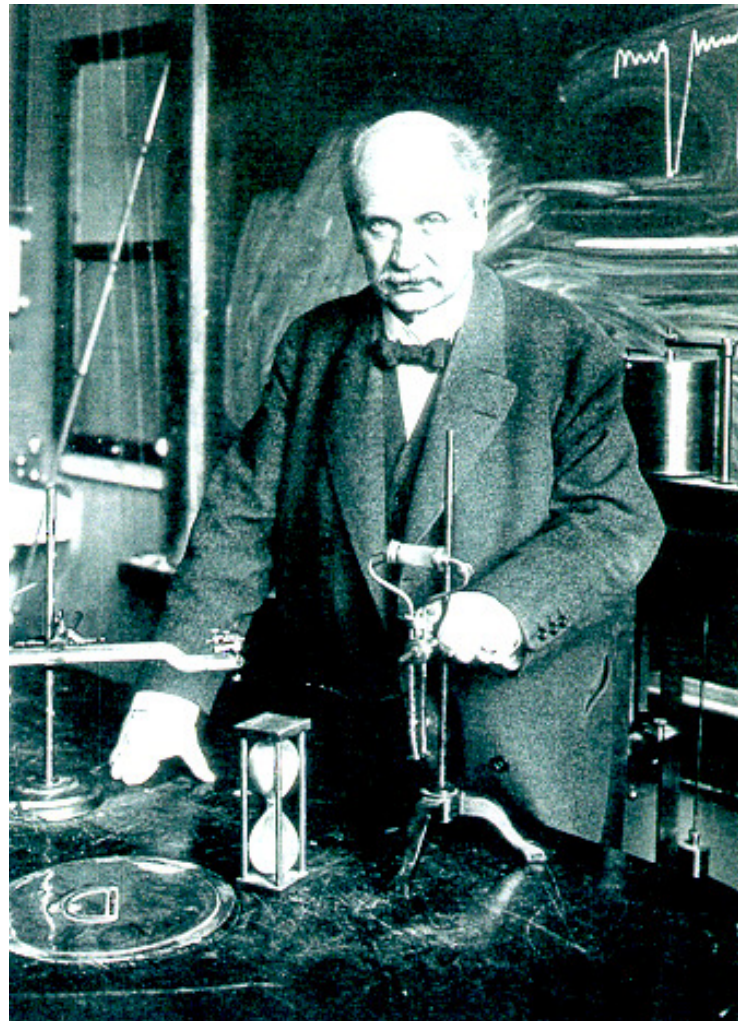


## The consistent benefits of LCZ696 on all outcomes in HF

Compared with enalapril, pts on LCZ696 are **LESS LIKELY TO:**

- die of a cardiovascular cause or any cause
- die suddenly
- be hospitalized for HF or for any reason
- visit the ER
- be admitted to the ICU
- need iv inotropic therapy
- require devices/surgery for worsening/end-stage HF
- show deterioration in renal function
- show biomarker evidence of continuing myocyte injury

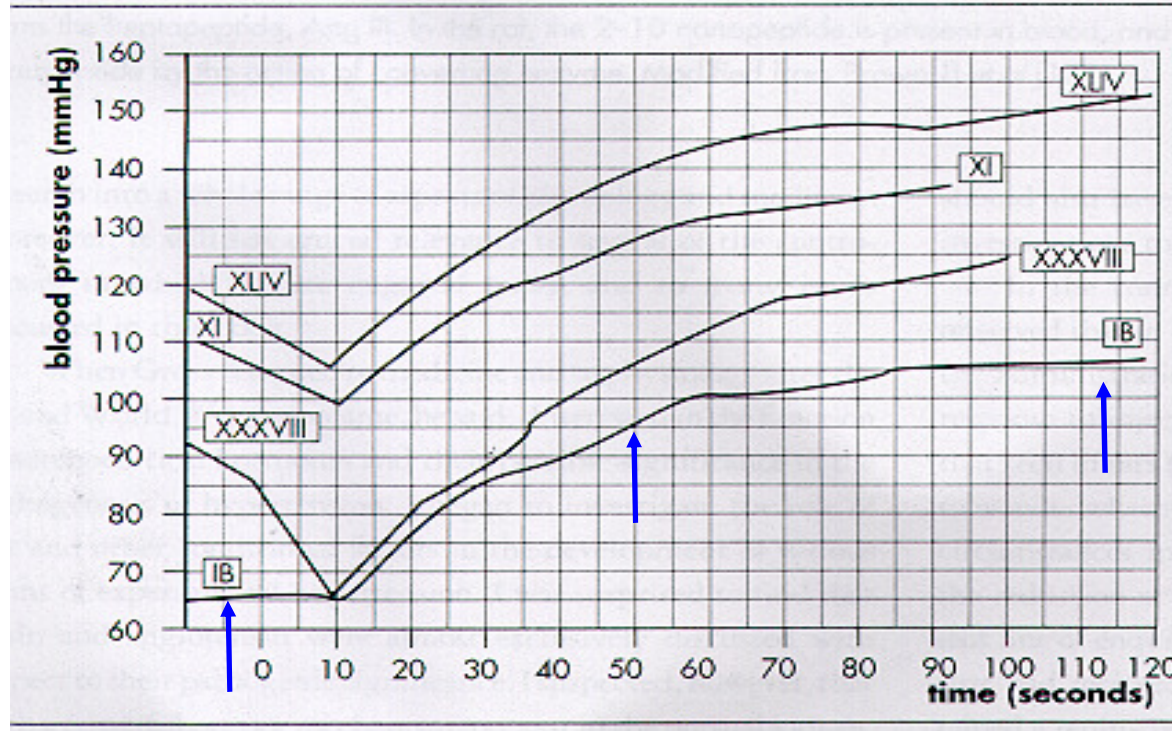
# Robert Adolf Armand Tigerstedt (ca 1910)





## Experiment 1B, November 8, 1896

“A [rabbit] kidney was pulverized with 21 ml of water. Injection into jugular vein. Within 80 s, there is a rise in mean arterial pressure from 62-67 mmHg to 100 mmHg, i.e. an increase by ca. 50%.”



Tigerstedt and Bergman, *Niere und Kreislauf*  
Skand. Arch. Physiol. 8: 223-271, 1898



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# Harry Goldblatt (1891 - 1977)





## STUDIES ON EXPERIMENTAL HYPERTENSION

### I. THE PRODUCTION OF PERSISTENT ELEVATION OF SYSTOLIC BLOOD PRESSURE BY MEANS OF RENAL ISCHEMIA\*†

BY HARRY GOLDBLATT, M.D., JAMES LYNCH, M.D., RAMON F. HANZAL, PH.D., AND WARD W. SUMMERVILLE, M.D.

*(From the Institute of Pathology, Western Reserve University, Cleveland)*



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**A BRADYKININ-POTENTIATING FACTOR (BPF) PRESENT  
IN THE VENOM OF *BOTHROPS JARARACA***

BY

S. H. FERREIRA

*From the Department of Pharmacology, Faculty of Medicine, U.S.P. Ribeirão Preto, E.S. Paulo, Brasil*

*Br J Pharmacol 1965;24:163*





## Activity of Various Fractions of Bradykinin Potentiating Factor against Angiotensin I Converting Enzyme

SH Ferreira, LJ Greene, VA Alabaster, YS Bakhle, JR Vane

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*Nature* 1970;225:379

Bradykinin potentiating factor, the crude extract of peptides from snake venom, also inhibits the peptidase which converts angiotensin I to angiotensin II, both in vitro and in vivo.



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# **Design of Specific Inhibitors of Angiotensin-Converting Enzyme: New Class of Orally Active Antihypertensive Agents**

MIGUEL A. ONDETTI  
BERNARD RUBIN, DAVID W. CUSHMAN

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*Science* 1977;196:441





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# The New England Journal of Medicine

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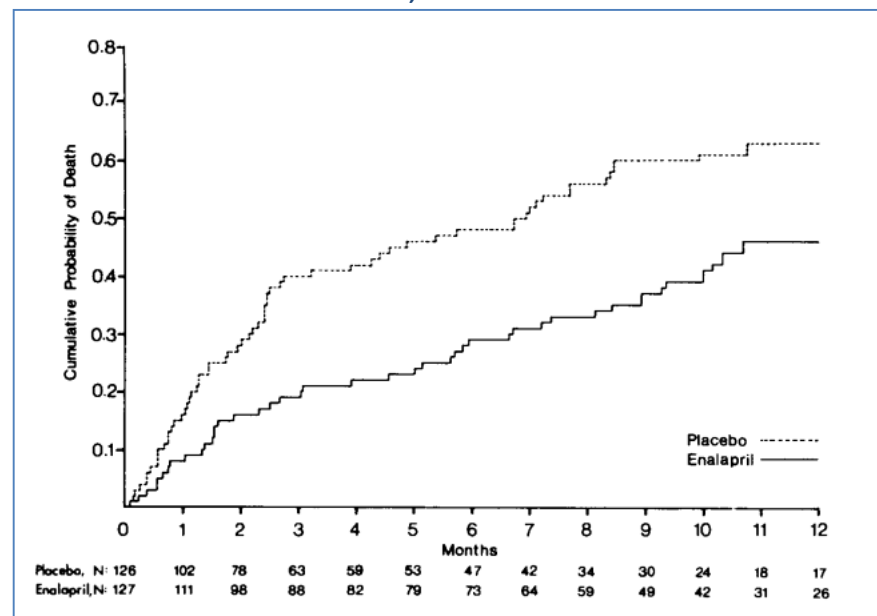
Number 23

## EFFECTS OF ENALAPRIL ON MORTALITY IN SEVERE CONGESTIVE HEART FAILURE

### Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS)

THE CONSENSUS TRIAL STUDY GROUP\*

1987;316:1429



# Adolfo J. De Bold





**ATRIAL SPECIFIC GRANULES OF THE RAT HEART  
LIGHT MICROSCOPIC STAINING AND HISTOCHEMICAL REACTIONS<sup>1</sup>**

**A.J. DE BOLD, J.J. RAYMOND AND S.A. BENCOSME**

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*J Histochem Cytochem* 1978;26:1094

**Heart Atria Granularity Effects of Changes in Water-Electrolyte Balance**

A.J DeBold

---

*Exper Biol Med* 1979;161:508

**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

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*Life Sci* 1981;28:89



**The Purification and Specificity of a Neutral Endopeptidase  
from Rabbit Kidney Brush Border**

By M. A. KERR and A. J. KENNY

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*Biochem J* 1974;137:477

**The hydrolysis of  $\alpha$ -human atrial natriuretic peptide by pig kidney  
microvillar membranes is initiated by endopeptidase-24.11**

Sally L. STEPHENSON and A. John KENNY

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*Biochem J* 1987;243:183



# The First Neprilysin Inhibitor

**The enkephalinase inhibitor thiorphan shows antinociceptive activity in mice**

**B. P. Roques<sup>\*</sup>, M. C. Fournié-Zaluski<sup>\*</sup>, E. Soroca<sup>\*</sup>,  
J. M. Lecomte<sup>†</sup>, B. Malfroy<sup>‡</sup>, C. Llorens<sup>‡</sup>  
& J.-C. Schwartz<sup>‡</sup>**

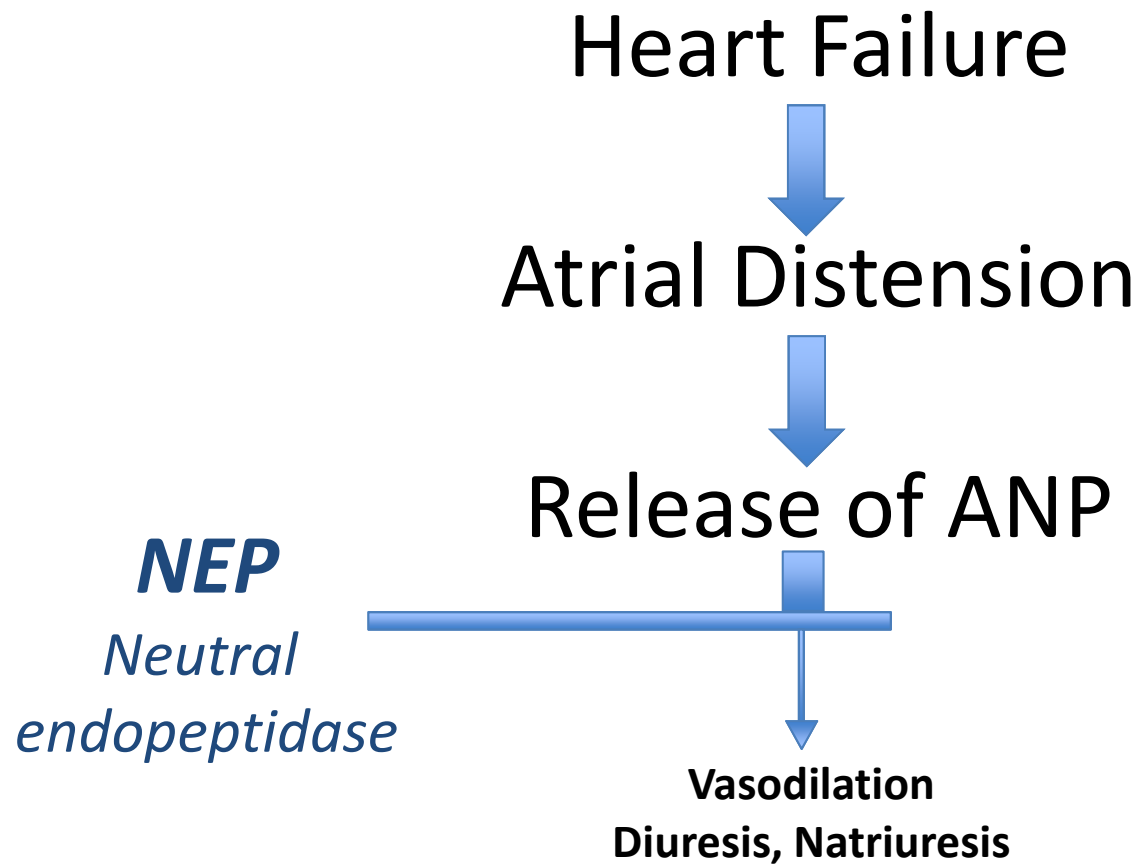
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*Nature* 1980;288:286



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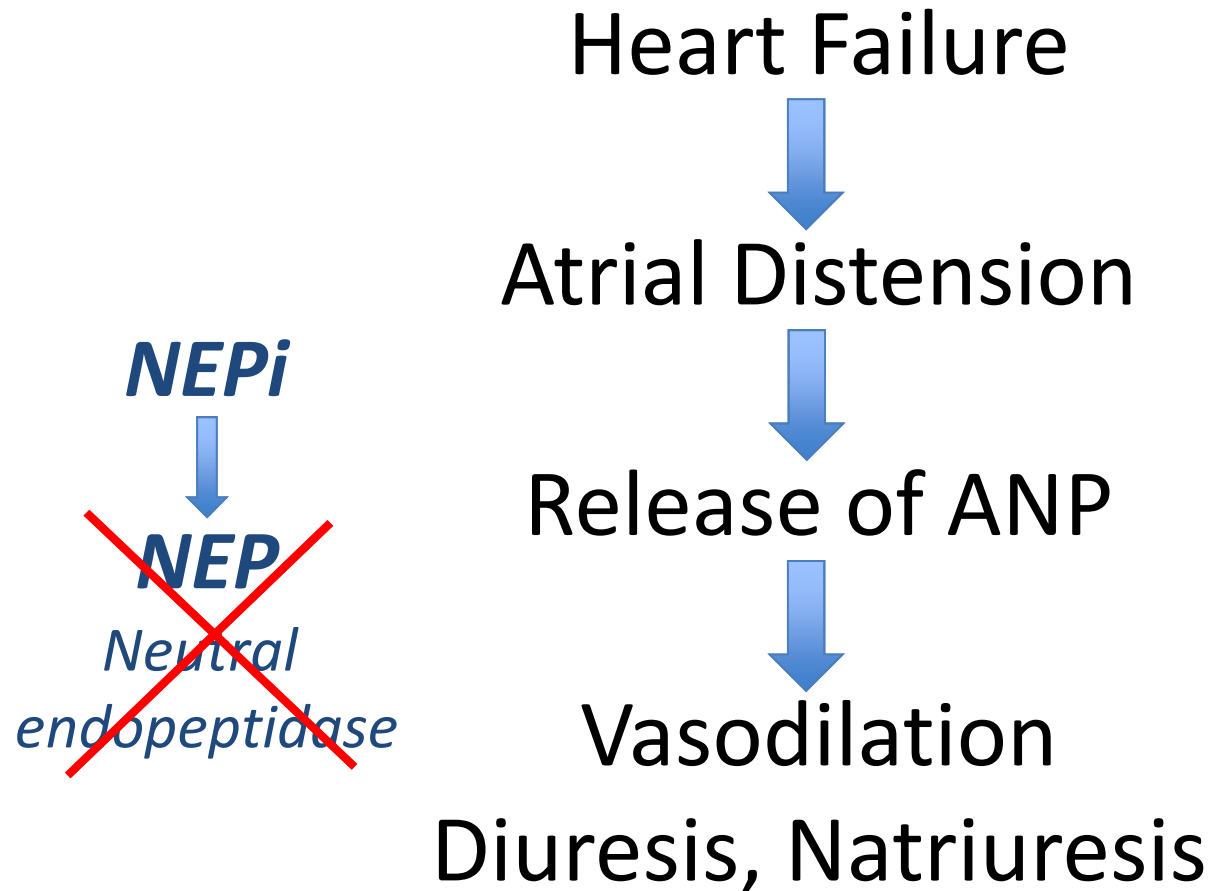
# Natriuretic Peptide System





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# Natriuretic Peptide System





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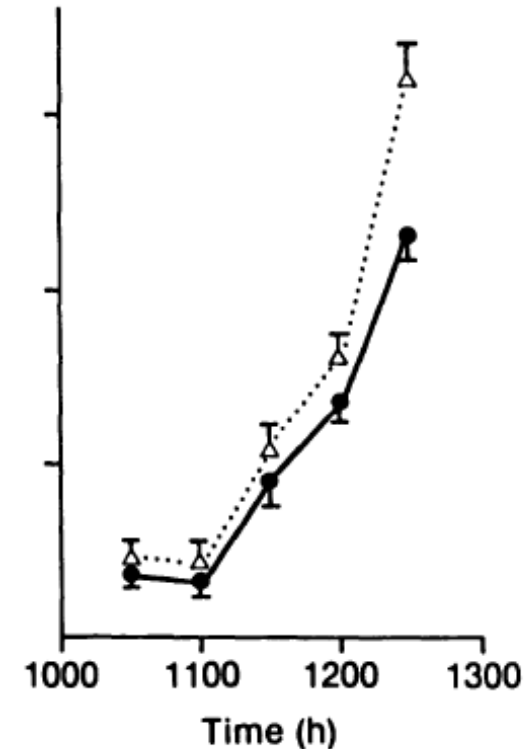
## Neprilysin Inhibition Increases Ang II Levels

### Effect of Inhibition of Endopeptidase 24.11 on Responses to Angiotensin II in Human Volunteers

A. Mark Richards, Gary A. Wittert, Eric A. Espiner, Timothy G. Yandle, Hamid Ikram, and Chris Frampton

Circ Res 1992;71:1501

Plasma  
Ang II  
(pmol/L)



**“It may be necessary to coadminister converting enzyme inhibitors or Ang II antagonists to gain optimum benefit from the use of endopeptidase inhibition in heart failure and hypertension.”**





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## **Dual Metalloprotease Inhibitors: Mercaptoacetyl-Based Fused Heterocyclic Dipeptide Mimetics as Inhibitors of Angiotensin-Converting Enzyme and Neutral Endopeptidase**

Jeffrey A. Robl,\* Chong-Qing Sun, Jay Stevenson, Denis E. Ryono, Ligaya M. Simpkins, Maria P. Cimarusti, Tamara Dejneka, William A. Slusarchyk, Sam Chao, Leslie Stratton, Raj N. Misra, Mark S. Bednarz, Magdi M. Asaad, Hong Son Cheung, Benoni E. Abboa-Offei, Patricia L. Smith, Parker D. Mathers, Maxine Fox, Thomas R. Schaeffer, Andrea A. Seymour, and Nick C. Trippodo

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*J Med Chem* 1997;40:1570



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# Omapatrilat

- A combined inhibitor of ACE and NEP
- Extremely effective at lowering blood pressure
- Developed mainly as an anti-hypertensive



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# Omapatrilat: angioedema





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International Bureau



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24 July 2003 (24.07.2003)

PCT

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WO 03/059345 A1

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(74) Agent: **GROS, Florent**; Novartis AG, Corporate Intellectual Property, Patent & Trademark Department, CH-4002 Basel (CH).

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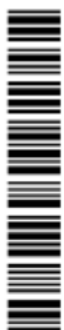
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(71) Applicant (*for all designated States except AT, US*): **NOVARTIS AG** [CH/CH]; Lichtstrasse 35, CH-4056 Basel (CH).

**Published:**

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments



(71) Applicant (*for AT only*): **NOVARTIS PHARMA GMBH** [AT/AT]; Brunner Strasse 59, A-1230 Vienna (AT).

(72) Inventors; and

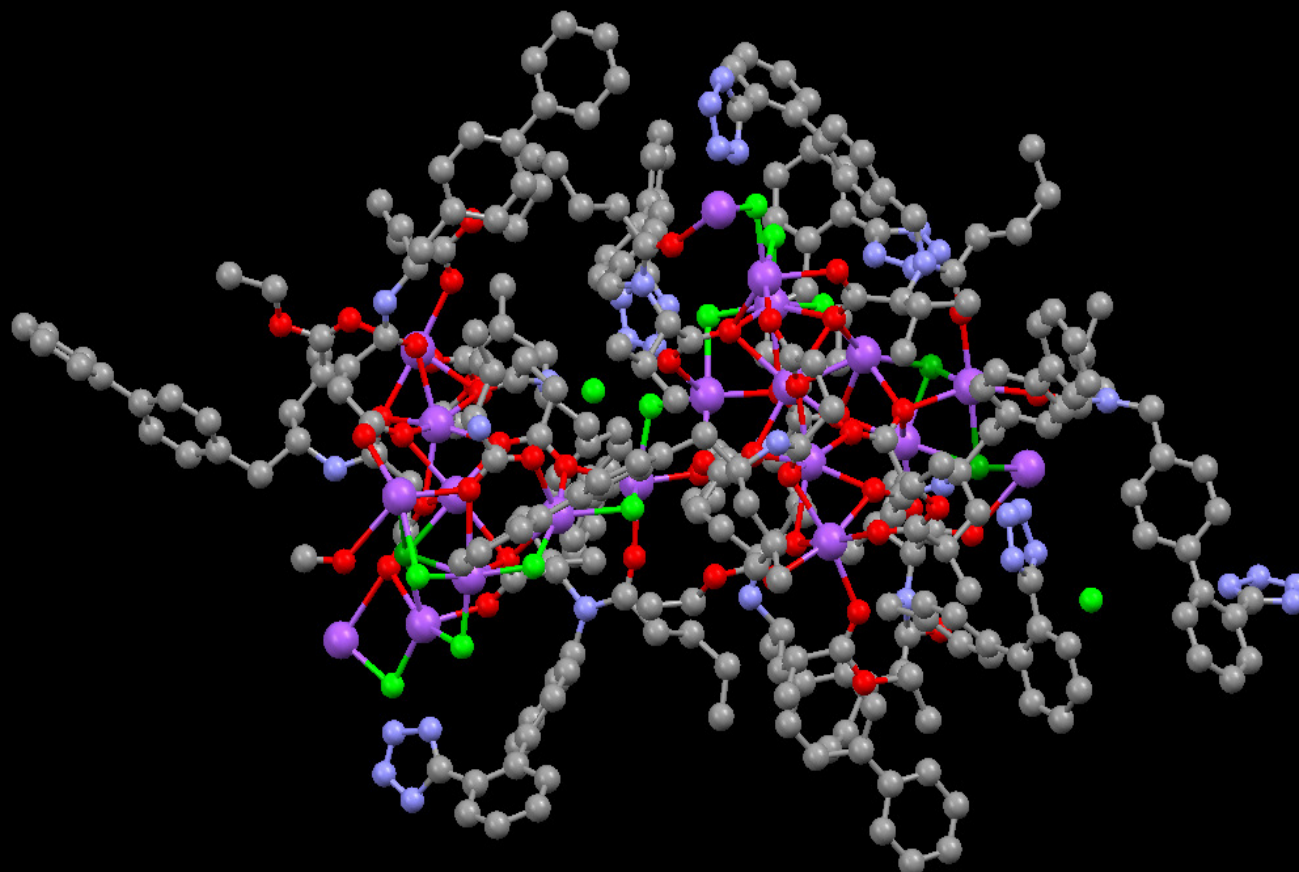
(75) Inventors/Applicants (*for US only*): **WEBB, Randy, Lee** [US/US]; 17 Honeyman Drive, Flemington, NJ 08822 (US). **KSANDER, Gary, Michael** [US/US]; 342 Woolf Road, Milford, NJ 08848 (US).

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.



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## LCZ696 – X-ray: Sodium, Oxygen, and Water Coordination



grey =  
carbon  
atom;

blue =  
nitrogen  
atom;

red =  
oxygen  
atom of  
active  
moieties;

green =  
oxygen  
atom of  
water;

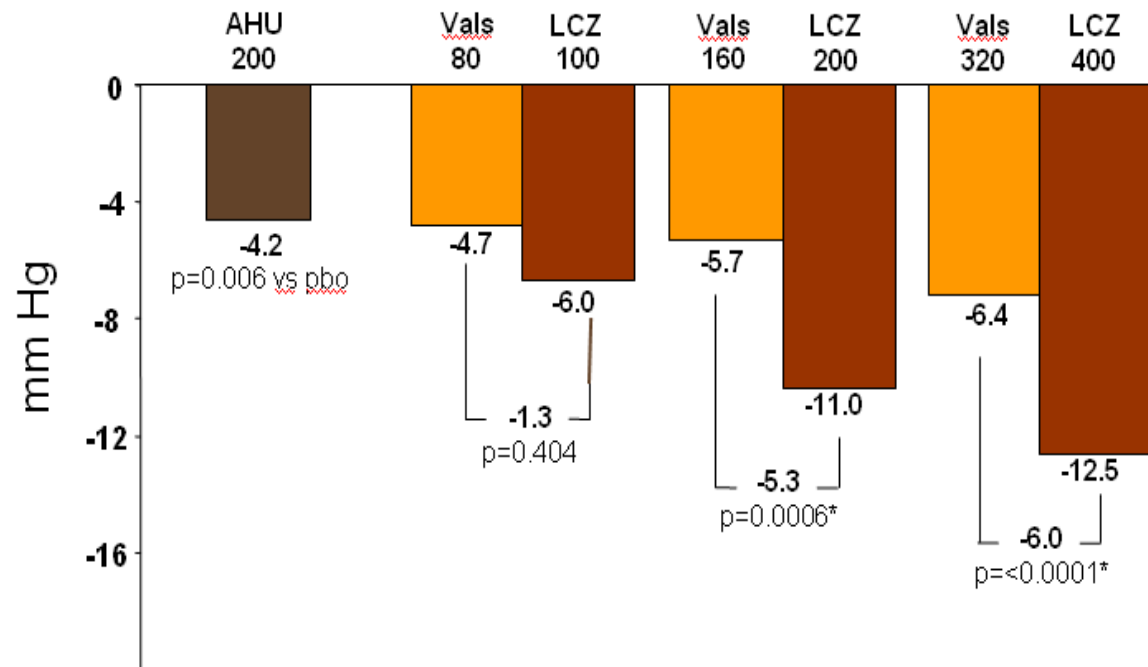
violet =  
sodium  
atom

LCZ696 is a novel crystalline complex consisting of the molecular moieties of valsartan and sacubitril in an equimolar ratio



## Complementary Blood Pressure Lowering with NEP inhibition and ARB

Mean Sitting **Systolic** BP Reduction:



- Valsartan
- LCZ 696
- AHU 200



## Hypothesis-Generating Rationale for Outcomes Trial

### The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial

*Scott D Solomon, Michael Zile, Burkert Pieske, Adriaan Voors, Amil Shah, Elisabeth Kraigher-Krainer, Victor Shi, Toni Bransford, Madoka Takeuchi, Jianjian Gong, Martin Lefkowitz, Milton Packer, John J V McMurray, for the Prospective comparison of ARNI with ARB on Management Of heart failUre with preserved ejection fraction (PARAMOUNT) Investigators\**

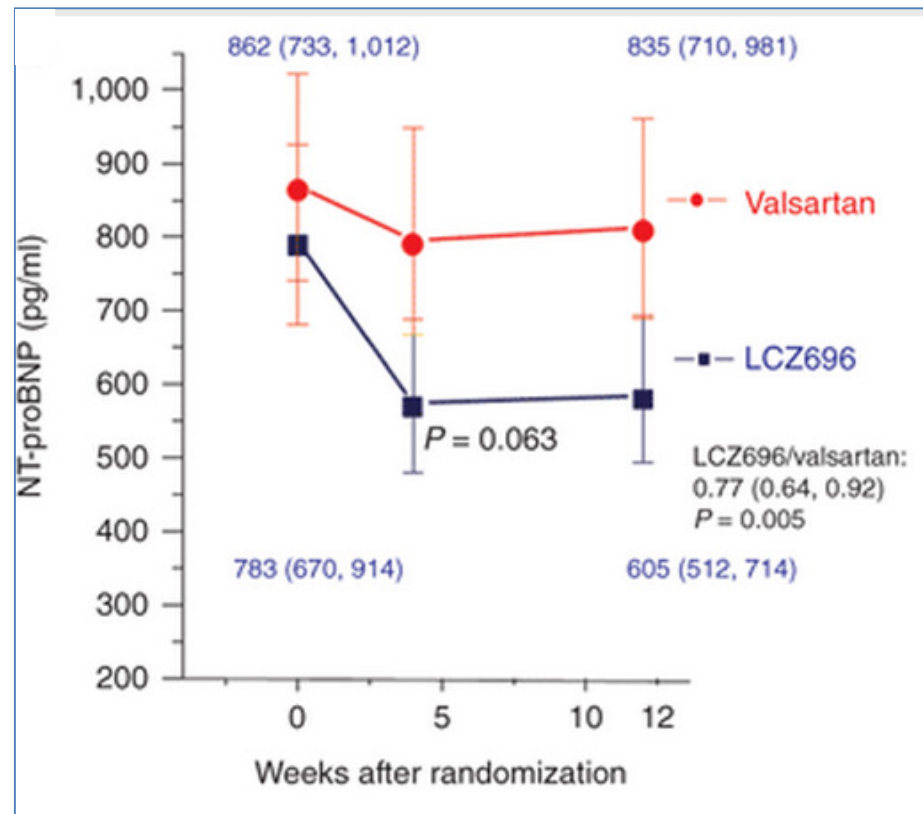
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*Solomon SD et al.  
Lancet 2012;380:1387*



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## *HFpEF - LCZ 696 vs. Valsartan*

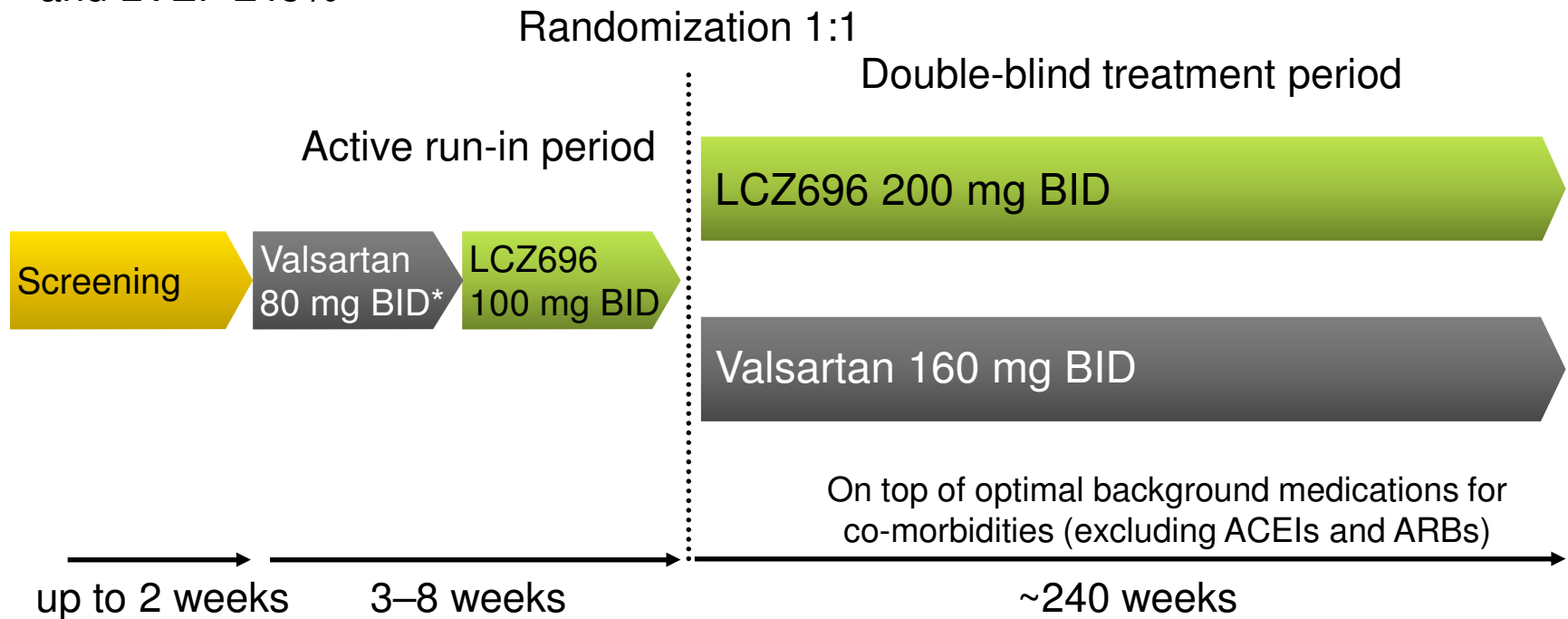


Solomon SD et al.  
*Lancet* 2012;380:1387





Target patient population: ~4,300 patients with symptomatic HF (NYHA Class II–IV) and LVEF  $\geq$ 45%



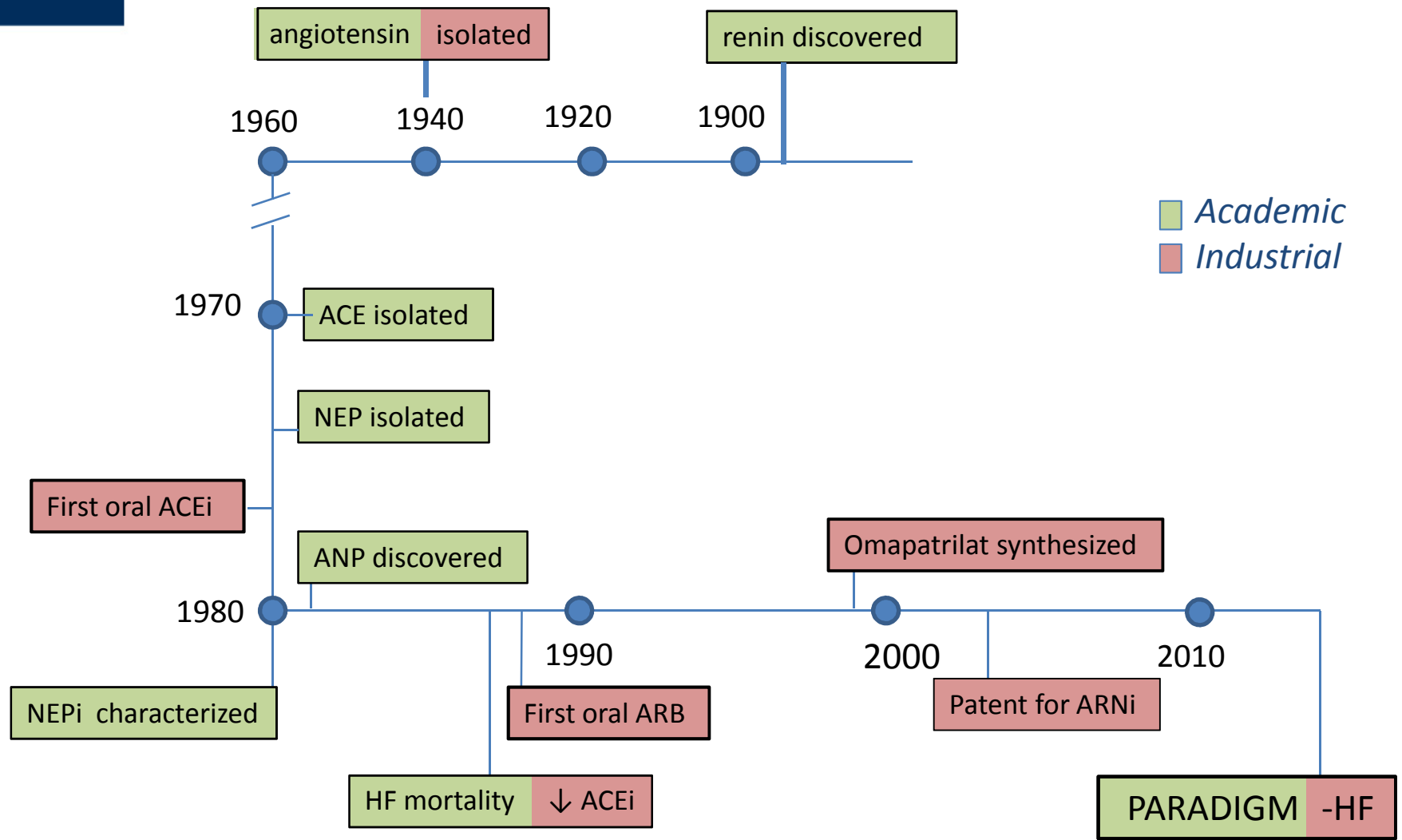
Primary outcome: CV death and total (first and recurrent) HF hospitalizations (anticipated ~1,721 primary events)

**Steering Cmt:** S. Solomon, co-Chair, J. McMurray, Co-Chair, I. Anand, F. Zannad, A. Maggioni, M. Packer, M. Zile, B. Pieske, J. Rouleau, M. Redfield, C. Lam, D. Van Veldhuisen, F. Martinez, J. Ge, H. Krum, M. Pfeffer



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# Path to PARADIGM HF





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# Academic-Industry Contributions to ARNi

## ACADEMIC

Creativity and experimental excellence leading to the discovery of two important physiologic systems and elucidation of their function in health and disease

## INDUSTRY

Ingenuity and resources for the development and application of the most advanced technology to develop safe drugs for altering their function

- ❖ Both components required for the development of Entresto
- ❖ The whole is much greater than the sum of its parts