The Path to an Angiotensin Receptor Antagonist-Nephrilysin 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
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
Paul Dudley White (1886-1973)
I wish we could do something useful with tobacco - like making fertilizer out of it.
Dual Goals

- To present the history of the physiologic and clinical advances that led to the development of the first angiotensin-receptor blocker-nephrilysin 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.
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*
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
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)

J Exp Med 1934;59:347
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 Prêto, E.S. Paulo, Brasil

Br J Pharmacol 1965;24:163
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.
Design of Specific Inhibitors of Angiotensin-Converting Enzyme: New Class of Orally Active Antihypertensive Agents

Miguel A. Ondetti
Bernard Rubin, David W. Cushman

Science 1977;196:441
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
ATRIAL SPECIFIC GRANULES OF THE RAT HEART
LIGHT MICROSCOPIC STAINING AND HISTOCHEMICAL REACTIONS

A.J. de BOLD, J.J. RAYMOND AND S.A. BENCOSME

Heart Atria Granularity Effects of Changes in Water-Electrolyte Balance

A.J DeBold

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


J Histochem Cytochem 1978;26:1094

Exper Biol Med 1979;161:508

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

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

Biochem J 1974;137:477

Biochem J 1987;243:183
The First Neprilysin Inhibitor

The enkephalinase inhibitor thiorphan shows antinociceptive activity in mice

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

*Correspondence to B. P. Roques or M. C. Fournié-Zaluski

Nature 1980;288:286
Natriuretic Peptide System

Heart Failure

Atrial Distension

Release of ANP

NEP
Neutral endopeptidase

Vasodilation
Diuresis, Natriuresis
Natriuretic Peptide System

Heart Failure

Atrial Distension

Release of ANP

Vasodilation

Diuresis, Natriuresis
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


“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.”
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

J Med Chem 1997;40:1570
Omapatrilat

- A combined inhibitor of ACE and NEP

- Extremely effective at lowering blood pressure

- Developed mainly as an anti-hypertensive
Omapatrilat: angioedema
(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date

(10) International Publication Number
WO 03/059345 A1


(21) International Application Number: PCT/EP03/00415

(22) International Filing Date: 16 January 2003 (16.01.2003)

(25) Filing Language: English

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(30) Priority Data:
60/349,660 17 January 2002 (17.01.2002) US

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

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

(72) Inventors: and
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:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>80</th>
<th>100</th>
<th>160</th>
<th>200</th>
<th>320</th>
<th>400</th>
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<tbody>
<tr>
<td>AHU 200</td>
<td>-4.2</td>
<td>-4.7</td>
<td>-6.0</td>
<td>-5.7</td>
<td>-6.4</td>
<td>-12.5</td>
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<tr>
<td>Vals 80</td>
<td>-1.3</td>
<td>-6.0</td>
<td>-5.3</td>
<td>-11.0</td>
<td>-6.0</td>
<td>-12.5</td>
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<td>LCZ 100</td>
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<td>Vals 160</td>
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<td>LCZ 200</td>
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<td>Vals 320</td>
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<td>LCZ 400</td>
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Placebo effect = -7.72 mmHg
n = 154 to 172 /group

Ruillope LM et al
*Lancet* 2010;375:1255
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 JV McMurray, for the Prospective comparison of ARNI with ARB on Management Of heart failUre with preserved ejectionN fraction (PARAMOUNT) Investigators*

Solomon SD et al.
Lancet 2012;380:1387
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 ≥45%

Randomization 1:1

Active run-in period

- Screening
- Valsartan 80 mg BID*
- LCZ696 100 mg BID

up to 2 weeks

3–8 weeks

Double-blind treatment period

- LCZ696 200 mg BID
- Valsartan 160 mg BID

~240 weeks

On top of optimal background medications for co-morbidities (excluding ACEIs and ARBs)

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
<table>
<thead>
<tr>
<th>ACADEMIC</th>
<th>INDUSTRY</th>
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<tr>
<td>Creativity and experimental</td>
<td>Ingenuity and resources for the development</td>
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<td>excellence leading to the</td>
<td>and application of the most advanced technology</td>
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<td>to develop safe drugs for altering their</td>
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- Both components required for the development of Entresto
- The whole is much greater than the sum of its parts