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

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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

2. Lother and Hein, Pharmacol Ther;166:136-149, 2016
Current heart failure therapy

Renin angiotensin aldosterone system

Liver → Angiotensinogen → Renin

Renin

Kidney

Angiotensinogen → Angiotensin I → Angiotensin II

Angiotensin II → Ang II receptor

Ang II receptor:
- vasoconstriction
- ↑ blood pressure

Aldosterone:
- salt retention
- ↑ blood pressure

ACE → ACEi

Liver

Lung

ACEi:
- enalapril
- captopril
- lisinopril
- benazepril
- ramipril
- fosinopril
- perindopril
- moexipril
- quinapril
- trandolapril

Blood pressure:
- ↑

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

Alternative vasodilator/cardioprotective mechanisms

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


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(Received in final form October 21, 1980)

Cardiac stress

Natriuretic peptides

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

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

Natriuretic peptides

ANP

BNP

CNP
Natriuretic peptide degradation by neprilysin (NEP)

Initial NEP cleavage inactivates ANP

NEP inhibitor potentiates ANF

Conscious Spontaneously Hypertensive Rat

Early Neprilysin inhibitors

- Racecodotil (oral)\(^1\) and candoxatrilat (iv)\(^2\)
  - Natriuresis
  - Increased urinary excretion of ANP
- Candoxatril\(^3\)
  - Oral prodrug
  - Initial reduction in blood pressure was not sustained

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

Effects of a dual ACE-NEPi on blood pressure


Limitations of a dual-acting inhibitor
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

Liver

Angiotensinogen → Angiotensin I → Angiotensin II

Kidney

Renin

Lung

ACE

Ang II receptor

Aldosterone

Acei

Losartan

Valsartan

Candesartan

Olmesartan

Telmisartan

Azilsartan

Irbesartan

Eprosartan

Enalapril

Captopril

Lisinopril

Benazepril

Ramipril

Fosinopril

Perindopril

Moexipril

Quinapril

Trandolapril

Salt retention

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

Vasoactive Peptide System

Heart Failure

Renin Angiotensin System

Pro-BNP

NT-pro BNP

Adrenomedullin
Bradykinin
Substance P
(angiotensin II)

ANP

BNP

CNP

Sacubitril (AHU377)

Valsartan

LBQ657

Neprilysin

Inactive fragments

Vasodilation

↓ blood pressure
↓ sympathetic tone
↓ aldosterone levels
↓ fibrosis
↓ hypertrophy
Natriuresis/Diuresis

Vasoconstriction

↑ blood pressure
↑ sympathetic tone
↑ aldosterone
↑ fibrosis
↑ hypertrophy

LCZ696 consists of valsartan and sacubitril in an equimolar ratio in the form of a sodium salt complex

LCZ696 dissociates into valsartan and sacubitril upon ingestion.
Entresto (LCZ696)

Angiotensin–Nephrilysin Inhibition versus Enalapril in Heart Failure

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PARADIGM-HF

- 8442 patients with class II, III, and IV heart failure with EF ≤ 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

Thank you
Renin angiotensin aldosterone system

Liver → Angiotensinogen → Angiotensin I → Angiotensin II

- **Renin**
- **ACE**
- **ARB**
- **ACEi**

Kidney → Aldosterone → Salt retention → ↑ blood pressure

- **ANG II receptor**
- **Ang II receptor**

Liver:
- losartan
- valsartan
- candesartan
- olmesartan
- telmisartan
- azilsartan
- irbesartan
- eprosartan

Kidney:
- enalapril
- captopril
- lisinopril
- benazepril
- ramipril
- fosinopril
- perindopril
- moexipril
- quinapril
- trandolapril

Spironolactone
- eplerenone

MRA

**ARB**

**ACEi**

**RI**