New Anti-hypertensive Drugs

Mohamed Oraby, MD
Professor and Head of Cardiology
Suez Canal University
CardioMilitary 2017

Why New Drugs??

1. We have 69 anti-hypertensive drugs in 15 different classes
2. Optimal control of BP is achieved in less than 8% in developing countries
3. Still hypertension morbidity and mortality unacceptably high
4. Current treatment of hypertension is empirical, choice of therapy is by trial and error
5. Non-compliance on drug treatment remains a major issue (culture- costs- adverse effects)

Unmet Needs

1. Improving efficacy and favorable safety profile
2. Correction of residual damage and interrupting the progression of end-organ damage
3. Addressing associated risk factors and comorbidities
4. Achieving a more rational therapies targeting the underlying pathophysiologic mechanisms

Classic Pressor Targets

- Sympathetic nervous system (alpha and beta blockers)
- RAAS (ACEIs and ARBs)
- Na+ (natruretics)
- Arterial Vasomtion (vasodilators)

New Pressor Targets

- Natruretic peptides
- Aldosterone
- Endothelines
- New RAAS targets

New Therapeutic Agents

- Natriuretic peptides
  - Neutral endopeptidase (NEP) inhibtors
  - Natriuretic peptide receptor agonists
- Aldosterone
  - Mineralocorticoid Receptors Antagonists (MRA)
  - Aldosterone synthase inhibitors
- Endothelines
  - Endothelin-receptor blockers
- New RAAS targets
  - Angiotension receptor AT2 receptor agonist

New Antihypertensive Drugs

1- New Classes

2- New drugs in old classes

3- New combinations of drugs

(1) New Classes

- Neutral endopeptidase (NE) inhibitors
- Renin inhibitors
- Endothelin receptor antagonists
- Angiotensin-targeting vaccines
- Aldosterone-synthase inhibitors
- Phosphdisterase inhibitors
- Nicotine-channel blocker
- Allopurinol

(2) New Drugs in Old Classes

Clevidipine

- **Fourth-generation dihydropyridin CCB**
- **Purely vascular selective**
- **Ultrashort-acting**
- **IV infusion**
- **hypertensive emergencies**

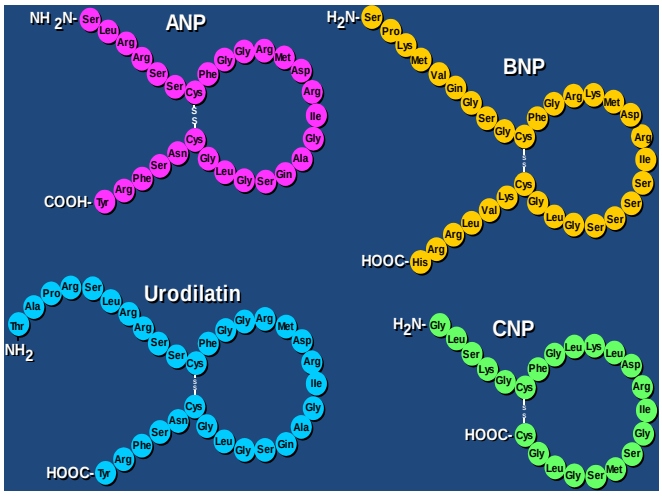
(3) New Combinations

- Dual-acting angiotensin-plus endothelin-receptor antagonist
- Dual-acting angiotensin receptors - NEP inhibitors
- Dual-acting NEP and endothelins inhibitors

The Great HOPE

Natruretic Peptide Pathway

Natriuretic Peptide System



All have a 17-amino acid (AA) ring structure with 11 identical AA's

Natriuretic Peptide System

ANP

- present in cardiac atria (but also other tissues)
- secretion from ↑atrial pressure
- removal via endopeptidase or clearance receptors, (~8 min)

BNP

- mainly present in cardiac ventricles, brain
- removal via endopeptidase, clearance receptors, (~20 min)

CNP

- mainly in vascular issue
- vasodilatory, not natriuretic
- autocrine function

Urodilatin

- produced in kidney
- excreted in urine
- exact function unclear

p

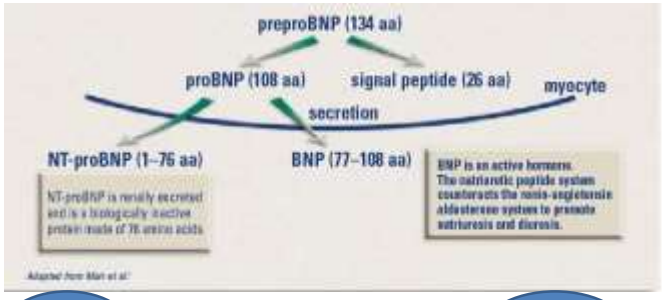
Natriuretic Peptide : Function

- **Major natural RAAS counteracting system**
  - Vasodilatory
  - Diuretic and natriuretic
  - Anti-proliferative
  - Anti-apoptotic

All Favourable Biological Actions

p

Natriuretic Peptides: Biology



2 hours

20 minutes

BNP is cleared by:

(1) Binding to NPRC

(2) Enzymatic degradation (NEP: Nebrilysin)

Pharmacologic approaches to enhance NP effects

- Exogenous natriuretic peptides /analogues
- Neprilysin Inhibitors
- Neprilysin inhibitors associated with an angiotensin-converting enzyme inhibitor.
- Angiotensin receptor neprilysin inhibitor (ARNI).

Pharmacologic approaches to enhance NP effects

- Exogenous natriuretic peptides /analogues.
- Neprilysin Inhibitors.
- Neprilysin inhibitors associated with an angiotensin-converting enzyme inhibitor.
- Angiotensin receptor neprilysin inhibitor (ARNI). LCZ696 (sacubitril/valsartan) compound.

Human recombinant BNP

- Nesiritide
  - Synthetic recombinant form of BNP.
  - Decreases PCWP and improves global clinical status of HF patients.
  - ***Approved in acute decompensated HF.***
  - ***Meta-analysis of randomized trials reported increased mortality and worsening renal function compared with control therapy.***

Pharmacologic approaches to enhance NP effects

- Exogenous natriuretic peptides /analogues.
- Neprilysin (NEP) Inhibitors.
- Neprilysin inhibitors associated with an angiotensin-converting enzyme inhibitor.
- Angiotensin receptor neprilysin inhibitors (ARNI). LCZ696 (sacubitril/valsartan) compound.

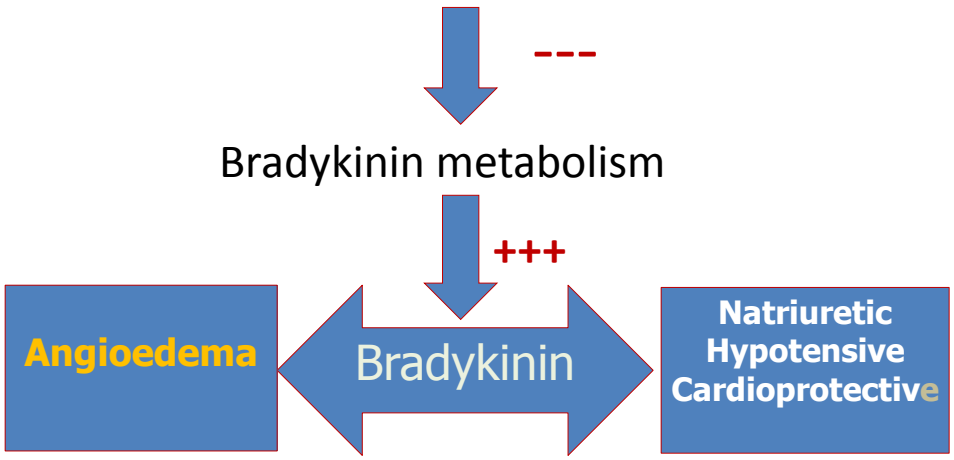
Neprilysin Inhibitors

- **Neprilysin (NEP) has many substrates**
  - **Ang-I**
  - **Ang-II**
  - Kinin peptides
  - Substance P
  - Adrenomedullin
  - **Endothelin**
  - Chemotactic peptide
  - Enkephalins
  - Amyloid-ß (A ß) peptide

Pharmacologic approaches to enhance NP effects

- Exogenous natriuretic peptides /analogues.
- Neprilysin Inhibitors.
- Neprilysin inhibitors associated with an angiotensin-converting enzyme inhibitor.
- Angiotensin receptor neprilysin inhibitors (ARNI). LCZ696 (sacubitril/valsartan) compound.

Neprilysin inhibition + ACEI



Neprilysin inhibitor + ACEI

- The most extensively investigated was **OMAPATRILAT.**
- **OCTAVE and OVERTRUE trials showed increased risk of angiodema**

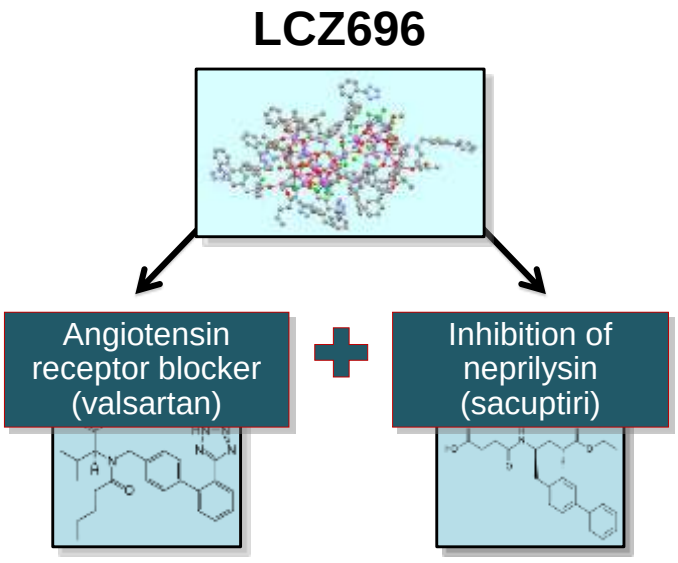
Pharmacologic approaches to enhance NP effects

- Exogenous natriuretic peptides /analogues.
- Neprilysin Inhibitors.
- Neprilysin inhibitors associated with an angiotensin-converting enzyme inhibitor.
- Angiotensin receptor neprilysin inhibitors (ARNI).

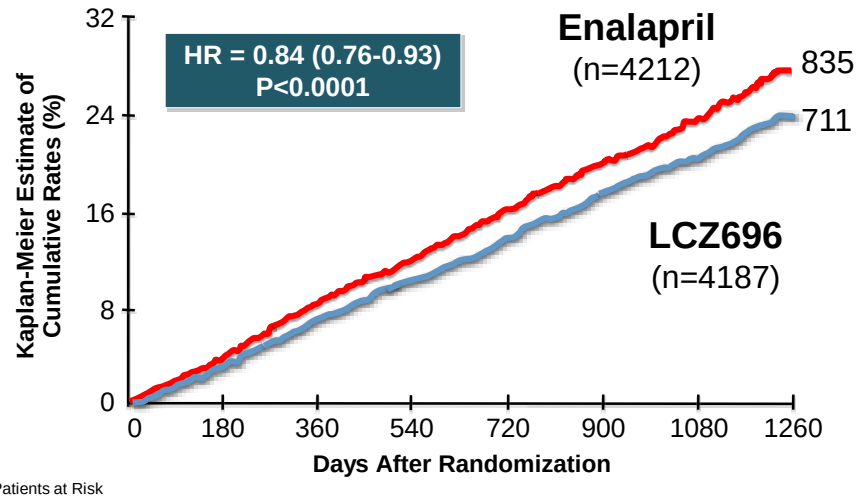
Rationale of ARNI

To target NP enhancement and RAAS blockade without increasing side effects

LCZ696: Angiotensin Receptor Neprilysin Inhibition



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

European Heart Journal – Cardiovascular Pharmacotherapy (2015) 1, 240–244
doi:10.1093/ehjcvp/pvv031

REVIEW

Hypertension

Angiotensin receptor neprilysin inhibitor LCZ696: a novel targeted therapy for arterial hypertension?

Vasiliki Katsi[1], Georgios Skalis[2], Antonis N. Pavlidis[3]*, Thomas Makris[2], Petros Nihoyannopoulos[4], Dimitris Tousoulis[4], and Ioannis Kallikazaros[1]

Blood-pressure reduction with LCZ696, a novel dual-acting inhibitor of the angiotensin II receptor and neprilysin: a randomised, double-blind, placebo-controlled, active comparator study

Prof Luis Miguel Ruilope, MD, Prof Andrej Dukat, MD, Prof Michael Böhm, MD, Yves Lacourcière, MD, Jianjian Gong, PhD, Martin P Lefkowitz, MD

Published: 16 March 2010

Interpretation

Compared with valsartan, dual-acting LCZ696 provides complementary and fully additive reduction of blood pressure, which suggests that the drug holds promise for treatment of hypertension and cardiovascular disease.

THE LANCET

Principal results of the **P**rospective comparison of **A**ngiotensin **R**eceptor neprilysin inhibitor with **A**ngiotensin Receptor blocker **ME**asuring arterial s**T**iffness in the eld**ER**ly (***PARAMETER***) Study

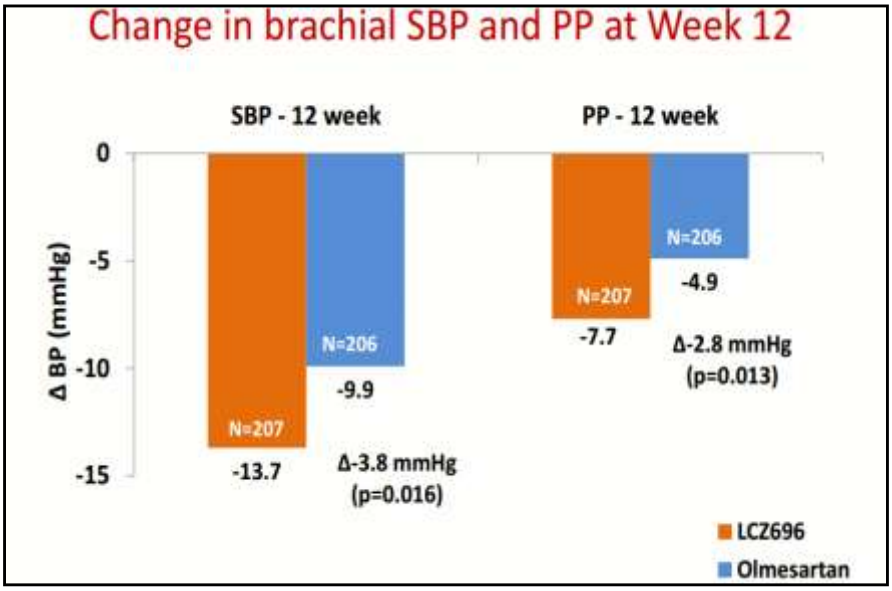
Hypothesis:

In older hypertensive patients with stiff arteries and an increased pulse pressure, LCZ696 will reduce central aortic systolic and pulse pressure more effectively than angiotensin receptor blockade

Primary End-Point:

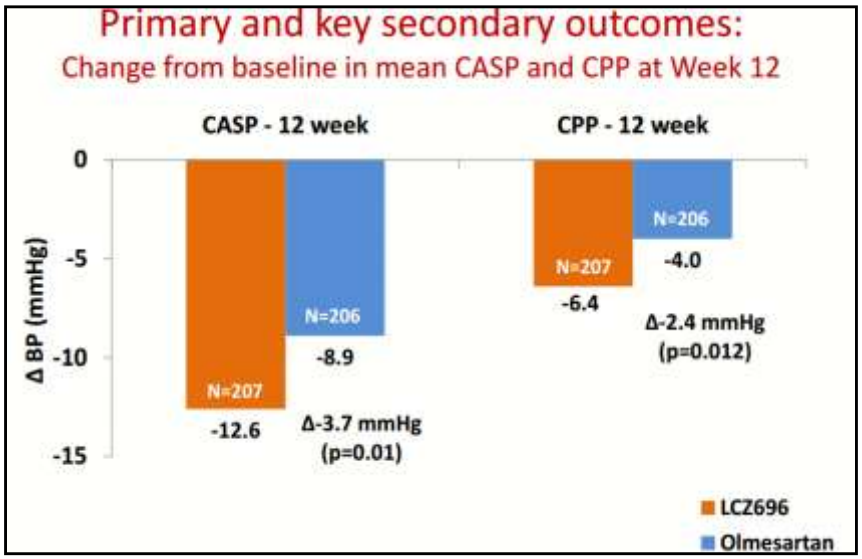
To demonstrate the superiority of LCZ696 400 mg daily, compared with olmesartan 40 mg daily, in reducing central aortic systolic pressure (CASP) after 12 weeks of treatment

Change in brachial SBP and PP at Week 12



Primary and key secondary outcomes:

Change from baseline in mean CASP and CPP at Week 12



Take-Home Messages

- Despite plethora of current anti-HTN drugs we do not have the ideal one yet
- Majority of new classes of anti-HTN drugs failed to show morbidity and mortality benefits while investigated
- Natreutritic peptide pathway represent a promising pressor target for ARNI
- Non-drug interventions for HTN control should be considered and further investigated in parallel.

Thank You