New Antihypertensive Agents

2013.04.20.

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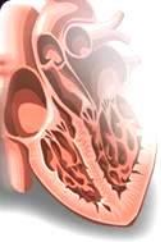

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- RAAS blockers
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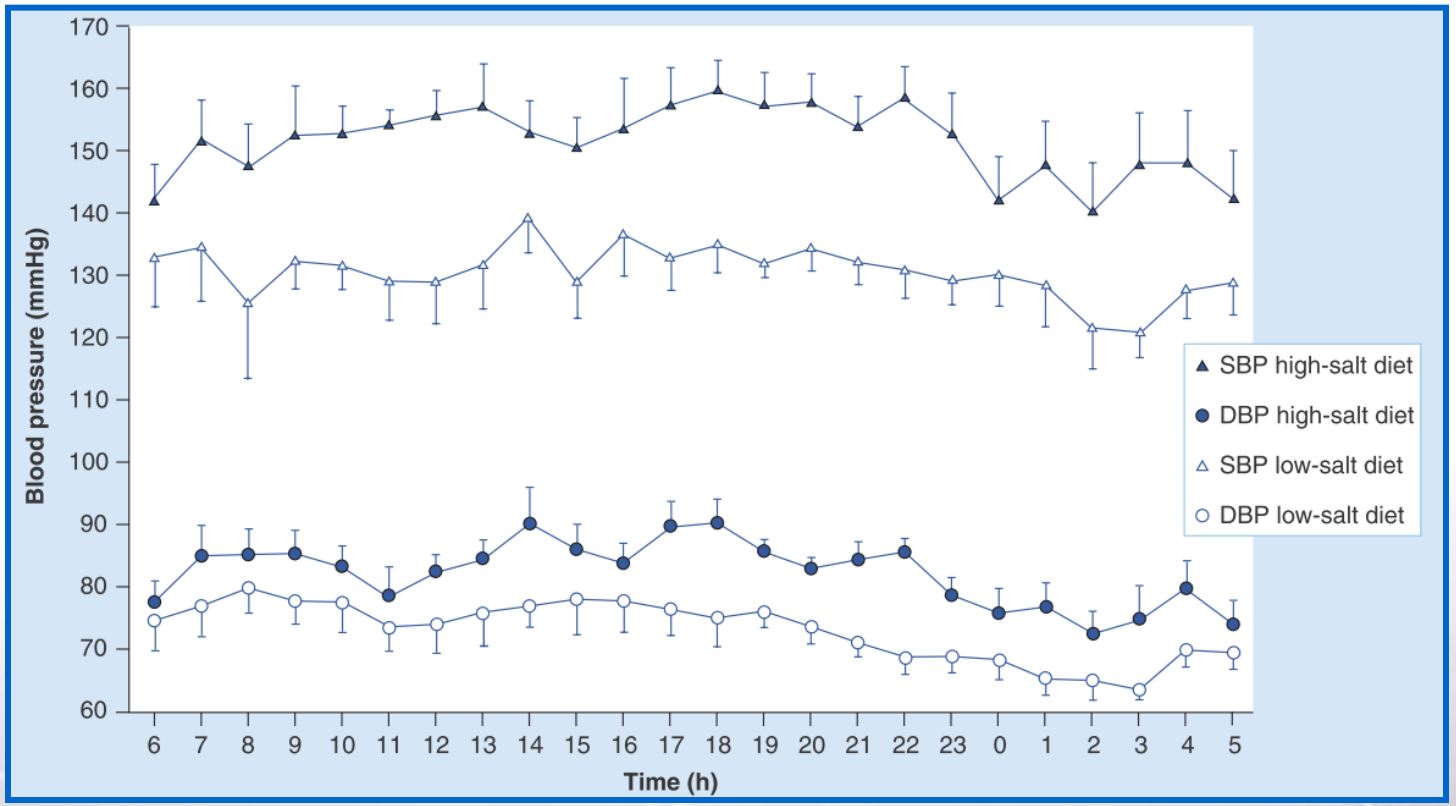
Introduction

- Several classes of anti-HTN drug → Successful Tx. of HTN is difficult
- Resistant HTN : 5-30% of the overall hypertensive population.

  → only about 10% of patients have true RH.
- Novel approaches, novel devices and novel drugs including either novel pharmacological classes or novel molecules

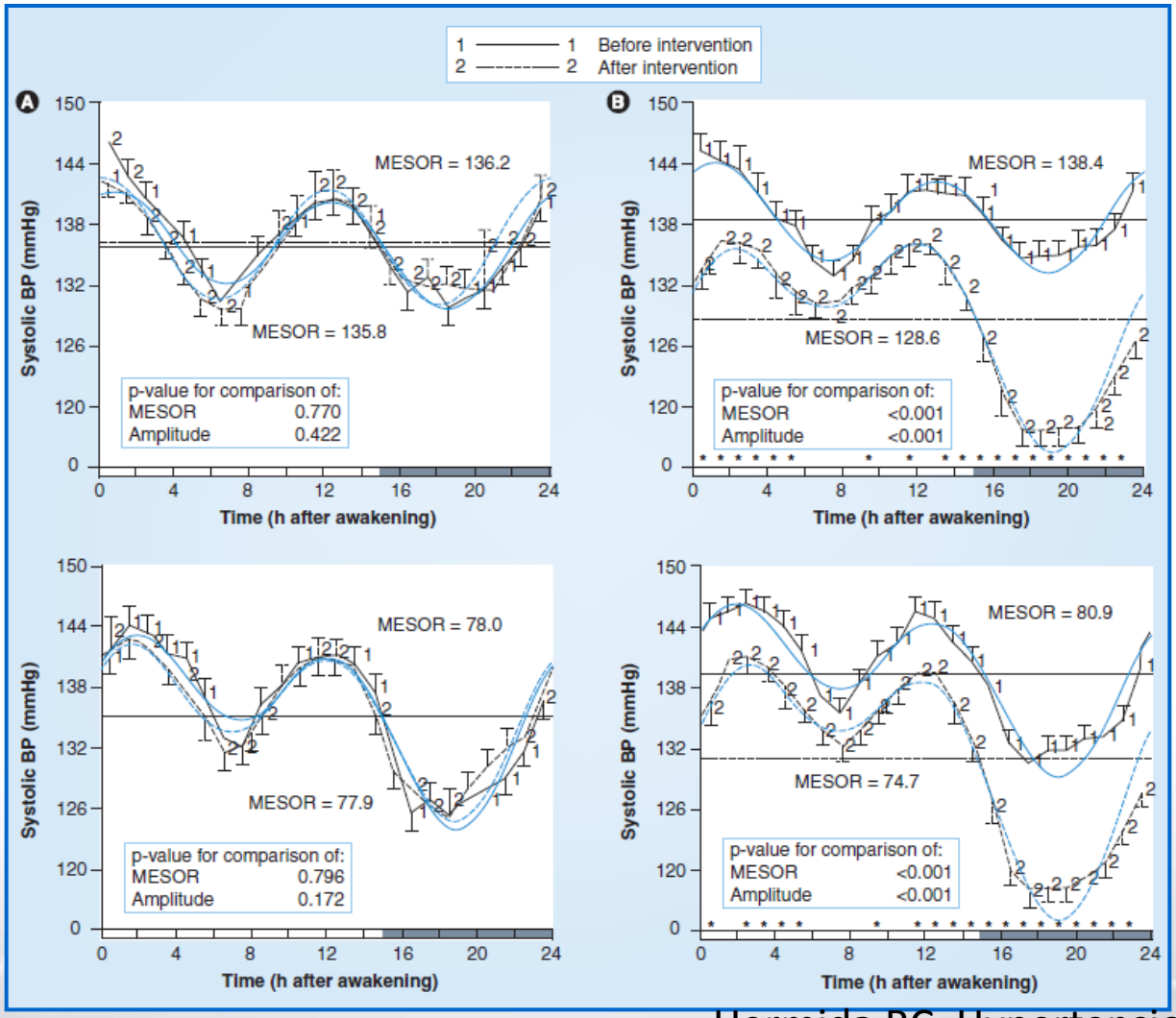
New approaches (1)

- Low salt diet in patients with resistant hypertension.



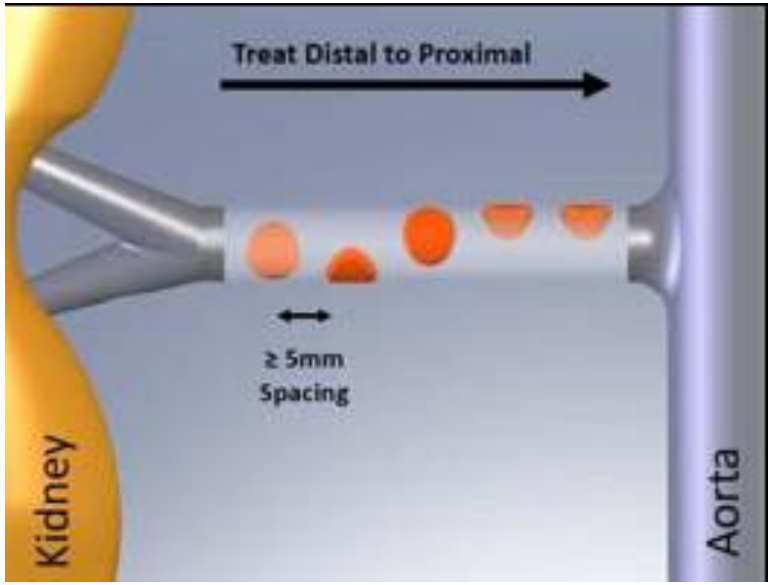
Pimenta E. Hypertension 2009;54: 475–481.

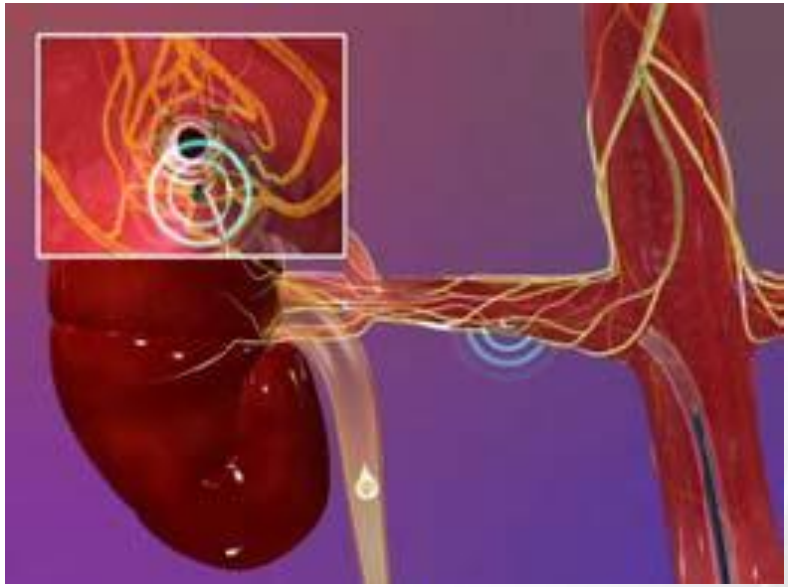
New approaches (2) : chronotherapy



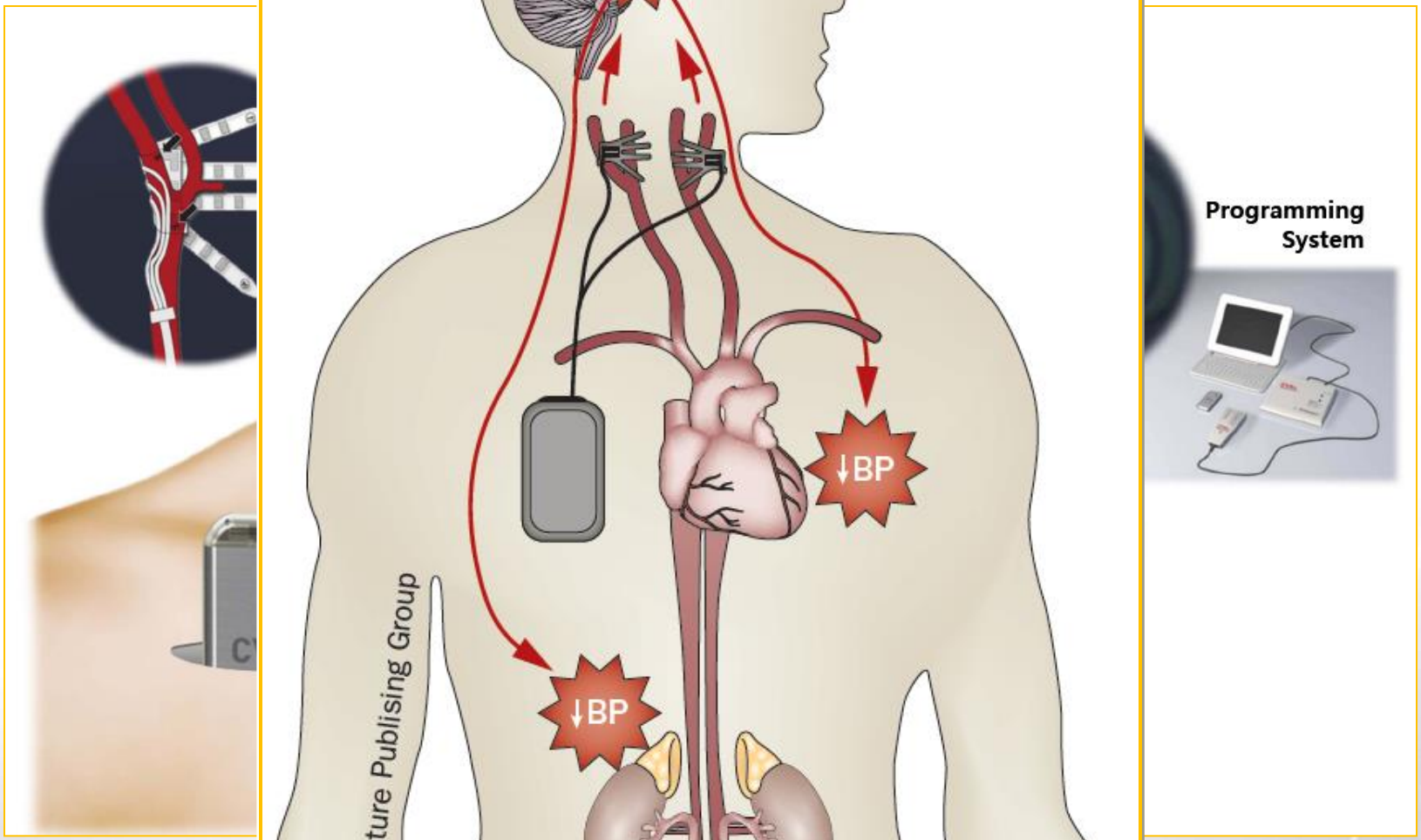
Hermida RC. Hypertension 2008;51:69–76.

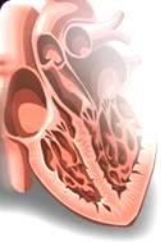
New approaches (3)
: Renal Nerve Denervation





: Barc herapy



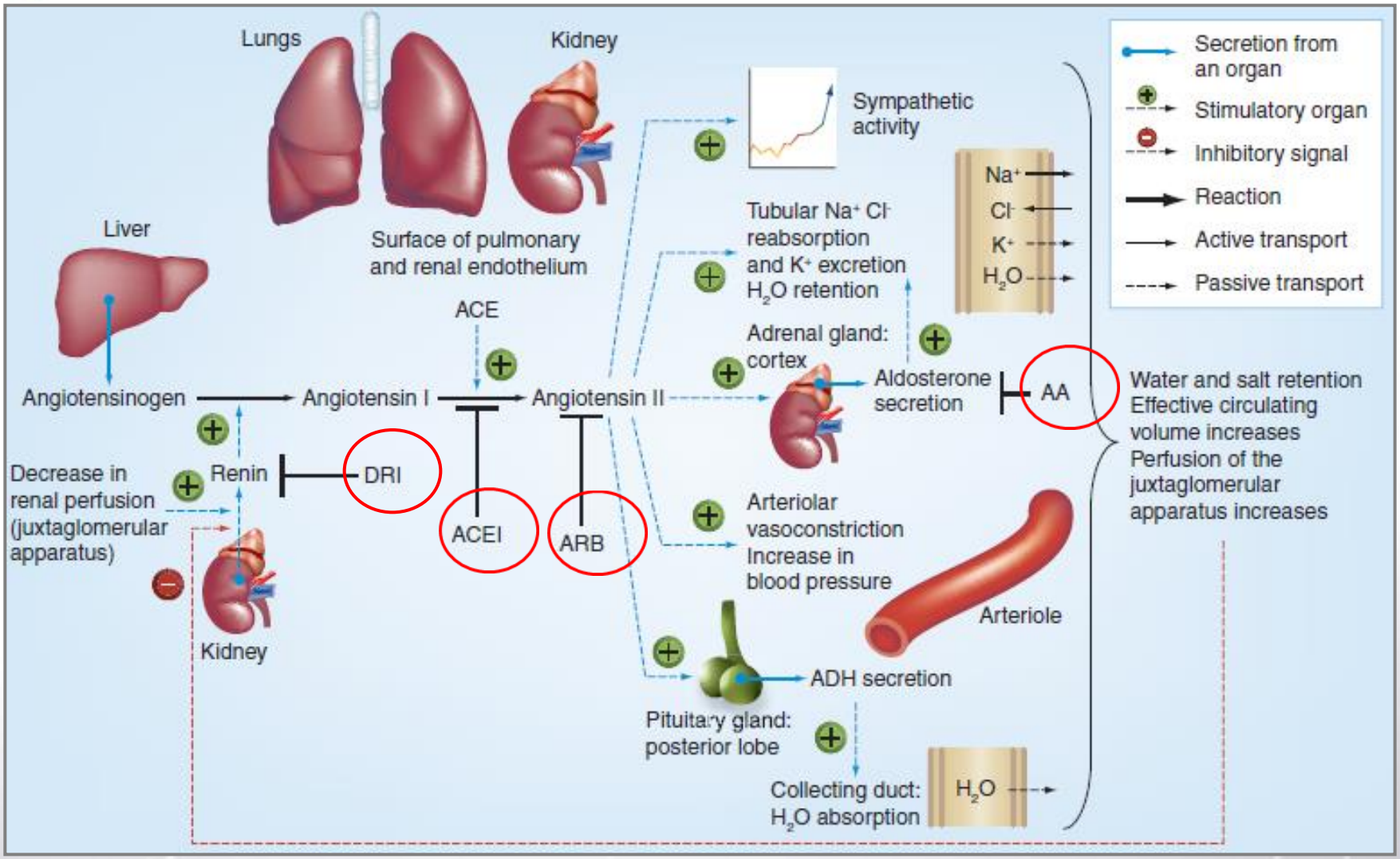


The Goals for anti-HTN drugs

- Improvement of BP
- Treatment of resistant hypertension
- Possibly also reduction of cardiovascular risk factors other than BP

  : myocardial hypertrophy, fibrosis, or increased arterial stiffness

RAAS blockers



Hering D. Expert Rev. Cardiovasc. Ther. 2011;9:729–744.

AT1R blockers & AT2R agonist

- **New ARB**

: **Azilsartan medoxomil** (2011, FDA & EMA)

→ AT1R blocker with PPAR-γ activity

→ Edarbi (20, 40, 80 mg (Valsartan : 320mg, Olmesartan medoxomil : 40 mg))

- **AT2R agonist**

: vasodilatory, antiproliferative, and anti-inflammatory effects

→Nonpeptide AT2R agonist **compound 21**

→Animal studies (+ ARB)

Aldosterone synthase inhibitors

- **Aldosterone antagonist (Mineralocorticoid receptor-blockers) → growing awareness**

  : spironolactone and eplerenone

  : primary aldosteronism, resistant hypertension and **CHF**

  : the poor selectivity of spironolactone

  --> progesterone or testosterone-dependent adverse effects

  : Eplerenone → more selective inhibitor

  cf.) both : hyperkalemia (particularly in CKD)

- **LCI 699 (1st in-class aldosterone synthase inhibitor)**

Effects of a Novel Aldosterone Synthase Inhibitor for Treatment of Primary Hypertension

Results of a Randomized, Double-Blind, Placebo- and Active-Controlled Phase 2 Trial

David A. Calhoun, MD; William B. White, MD; Henry Krum, MB, PhD; Weinong Guo, MD, PhD; Georgina Bermann, PhD; Angelo Trapani, PhD; Martin P. Lefkowitz, MD; Joël Ménard, MD

Background—LCI699, a novel inhibitor of aldosterone synthase, reduces serum aldosterone, and may have benefit in the treatment of hypertension.

Methods and Results—We performed the first double-blind, randomized trial with LCI699 in patients with primary hypertension. We randomized 524 patients to LCI699 0.25 mg once daily (n=92), 0.5 mg once daily (n=88), 1.0 mg once daily (n=86), and 0.5 mg twice daily (n=97); eplerenone 50 mg twice daily (n=84); or placebo (n=77) for 8 weeks. Adrenocorticotropic hormone (250 μg IV) stimulation testing was performed in a subset of patients to quantify the selectivity of LCI699 for aldosterone synthase compared with 11-β-hydroxylase. Reductions in clinic diastolic blood pressure were significant for LCI699 1.0 mg (−7.1 mm Hg; P=0.0012) and eplerenone 50 mg twice daily (−7.9 mm Hg; P<0.0001) compared with placebo (−2.6 mm Hg) but not other doses of LCI699. Significant reductions in clinic systolic blood pressure were observed with all doses of LCI699 (P<0.005 or better) and eplerenone (P<0.0001). All doses of LCI699 significantly reduced 24-hour ambulatory blood pressure compared with placebo (P<0.01). Adrenocorticotropic hormone stimulation of cortisol was suppressed in ≈20% of subjects receiving LCI699 at a total daily dose of 1.0 mg. Safety and tolerability were similar among LCI699, placebo, and eplerenone.

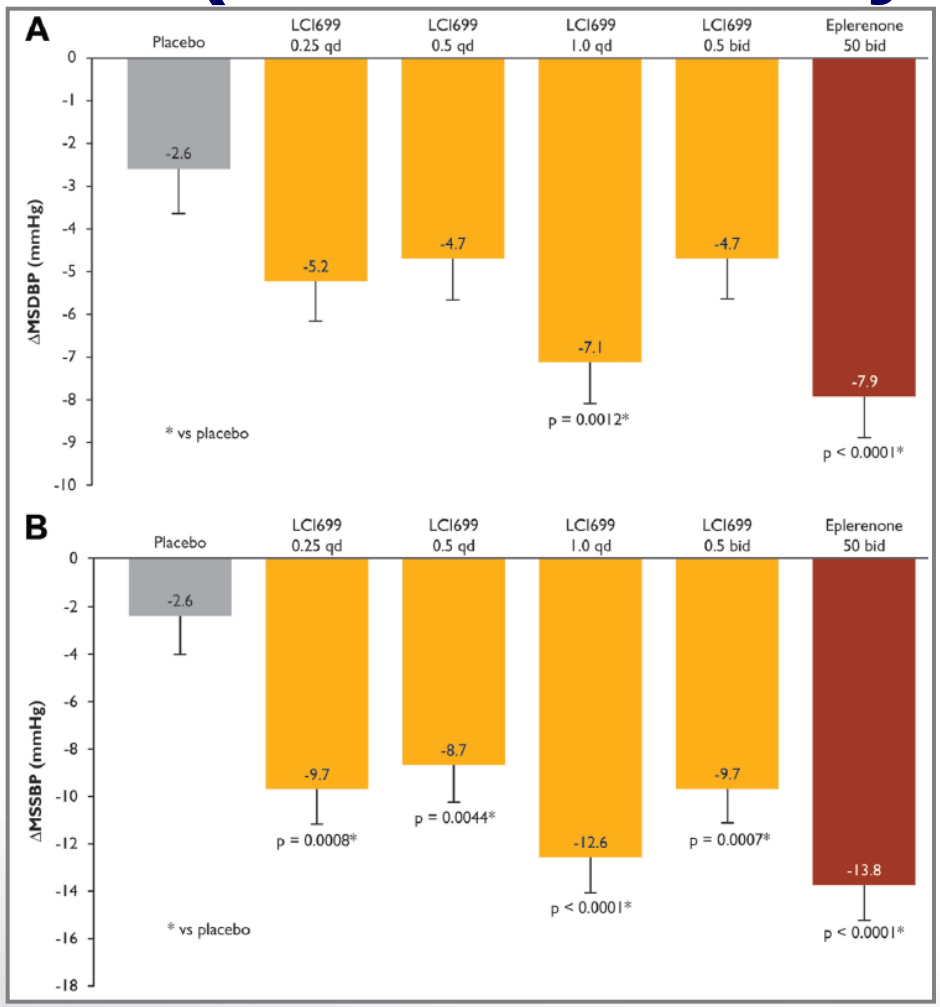
Conclusions—Aldosterone synthase inhibition with LCI699 significantly lowered clinic and ambulatory blood pressure. A minority of subjects developed blunted adrenocorticotropic hormone–stimulated release of cortisol. These results support additional research to evaluate use of aldosterone synthase inhibition in primary hypertension and/or patients characterized by aldosterone excess.

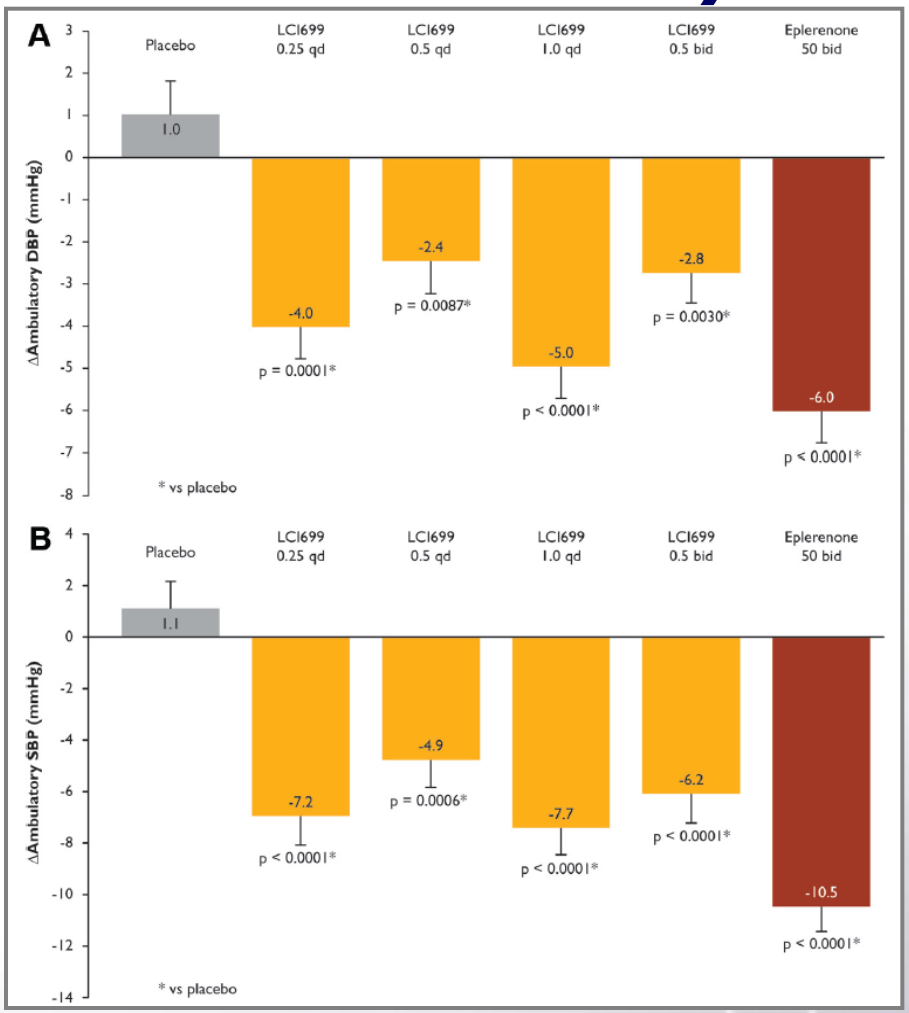
Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00758524.

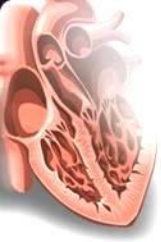
(*Circulation*. 2011;124:1945-1955.)

Key Words: blood pressure ■ hypertension ■ inhibitors ■ trials

LCI 699
(Aldosterone synthase inhibitor)



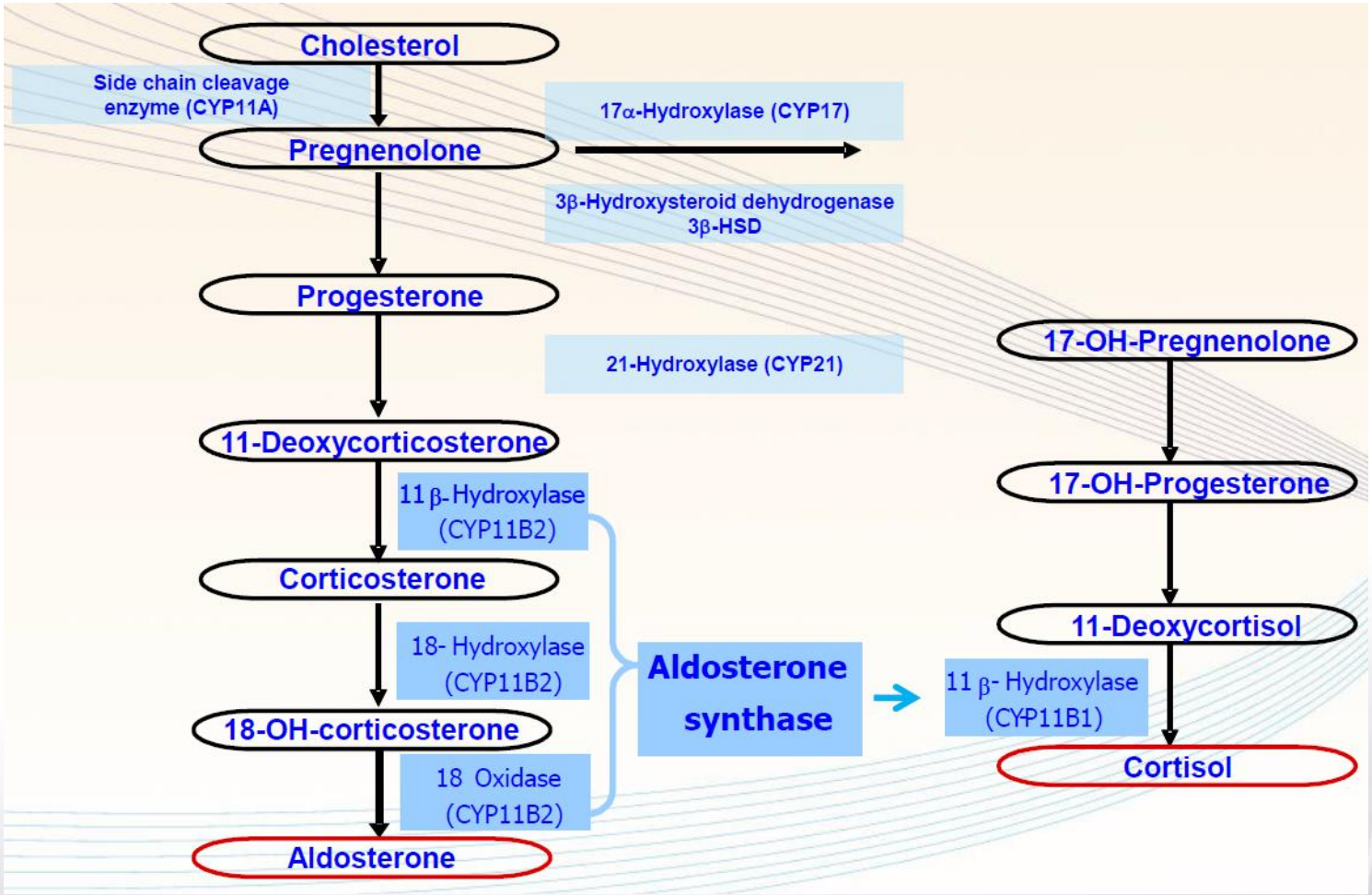


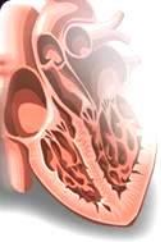


LCI 699
(Aldosterone synthase inhibitor)

- Effectively lowered clinic and 24-hour BP
- Generally well tolerated.
- **Suppressed ACTH-stimulated release of cortisol in ~20% of patients.**
- the development of more selective compounds to determine whether inhibition of aldosterone synthesis provides advantages over other classes of antihypertensive agents in terms of tolerability and clinical benefit.
- aldosterone excess such as resistant hypertension, congestive heart failure, post–myocardial infarction, and chronic renal failure.

Biosynthetic Pathway of Aldosterone





Dual Vasopeptidase inhibitors

- Pharmachological targets for HTN

1) ACE or AT1R

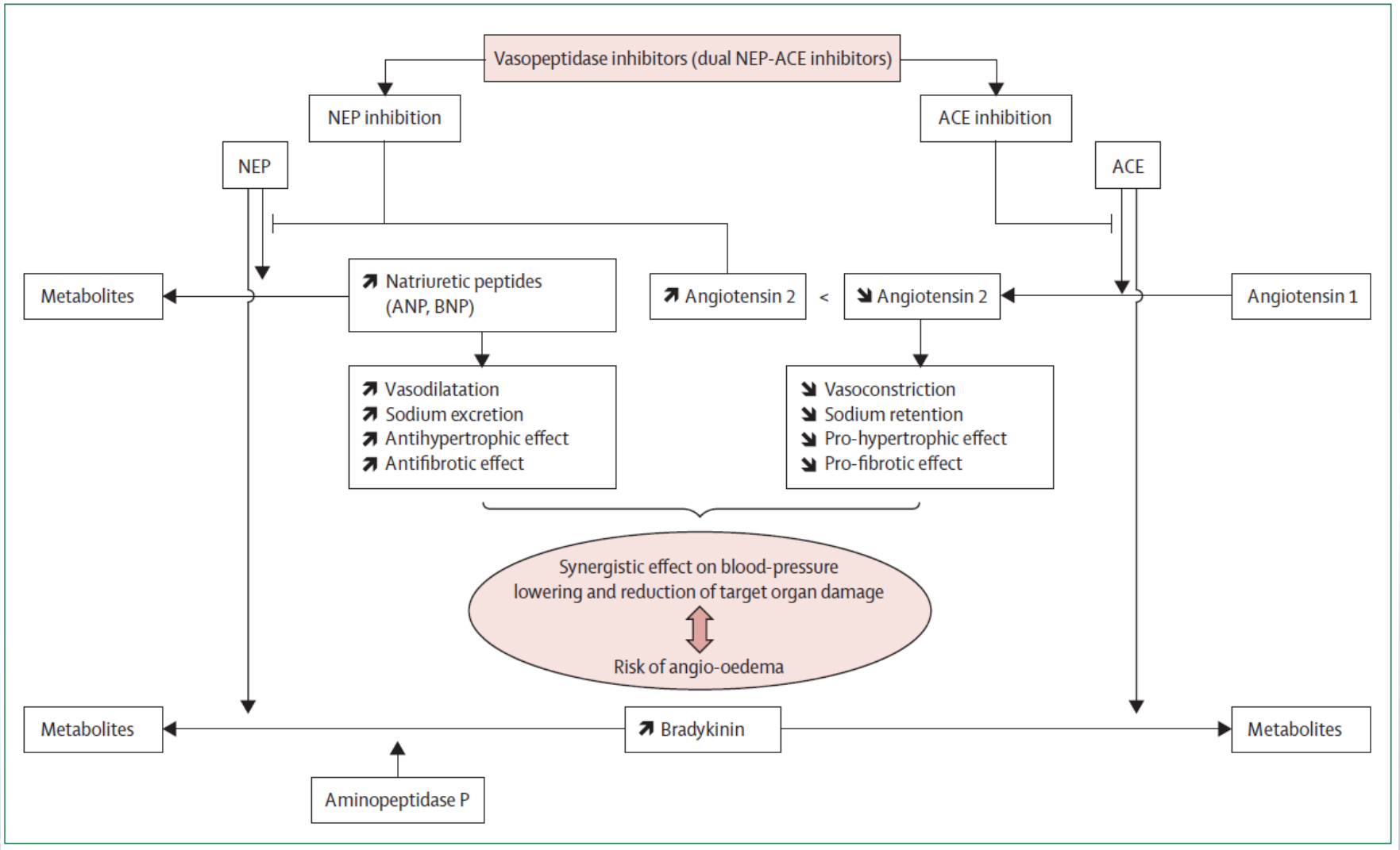
2) Two other zinc metalloproteinase

- **Nephrilysin** (neural endopeptidase (NEP))
- **Endothelin-converting enzyme (ECE)**

➔**Dual Vasopeptidase inhibitors**

➔Anti-proliferative, anti-fibrotic and anti-inflammatory effects

Dual NEP-ACE inhibitors



Lancet 2012; 380: 591–600

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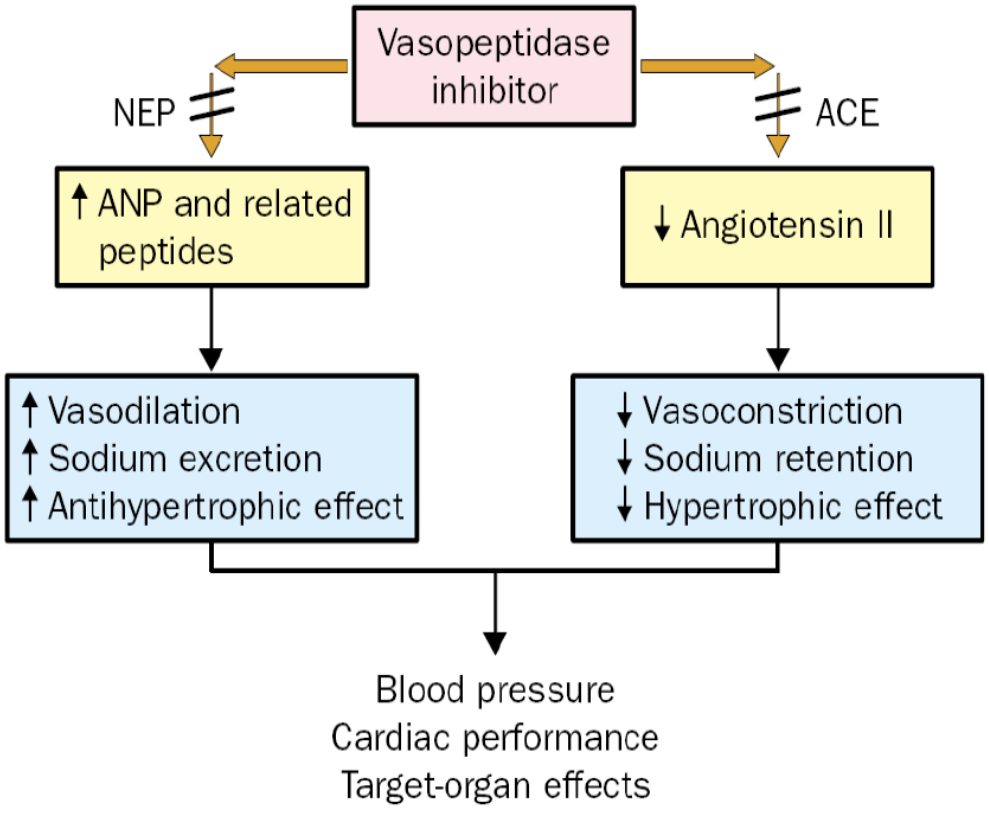
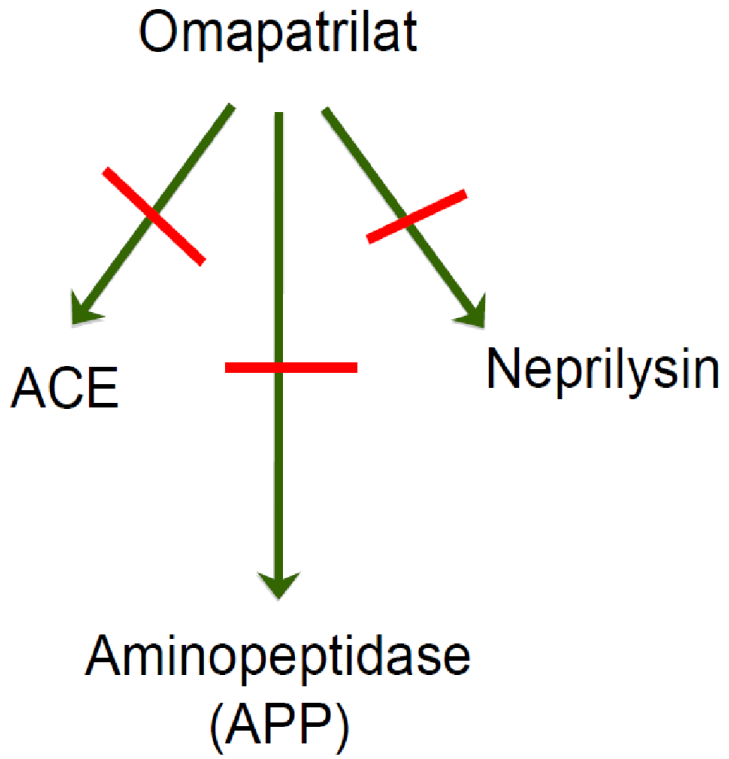
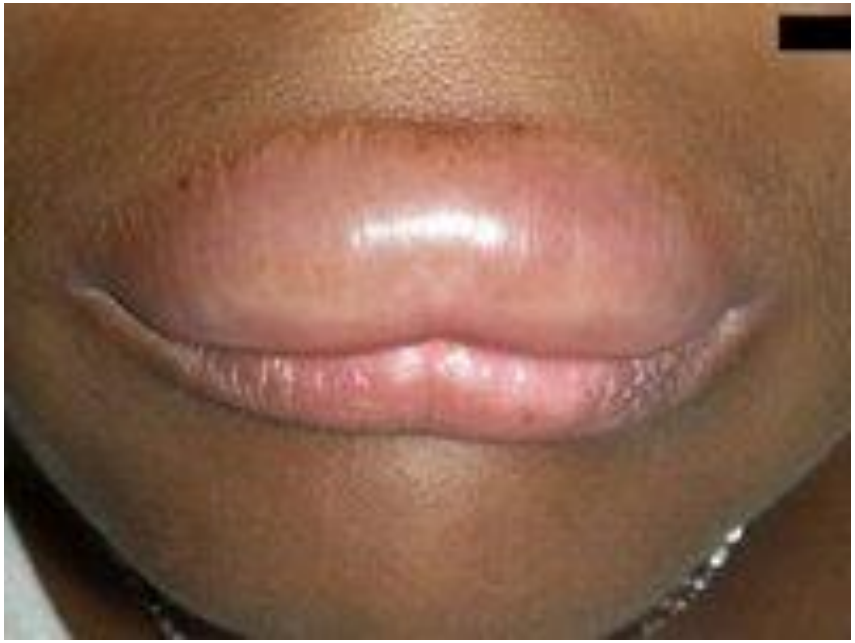
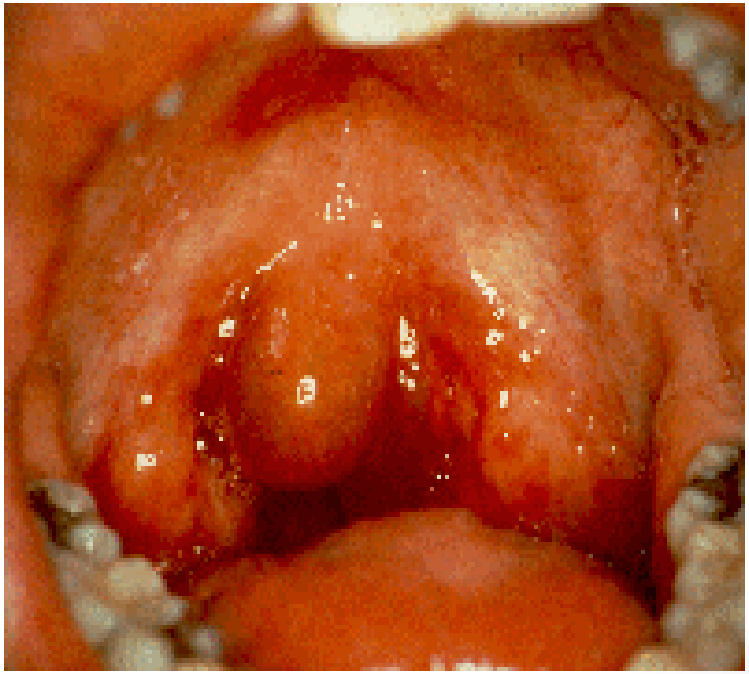




Angioedema

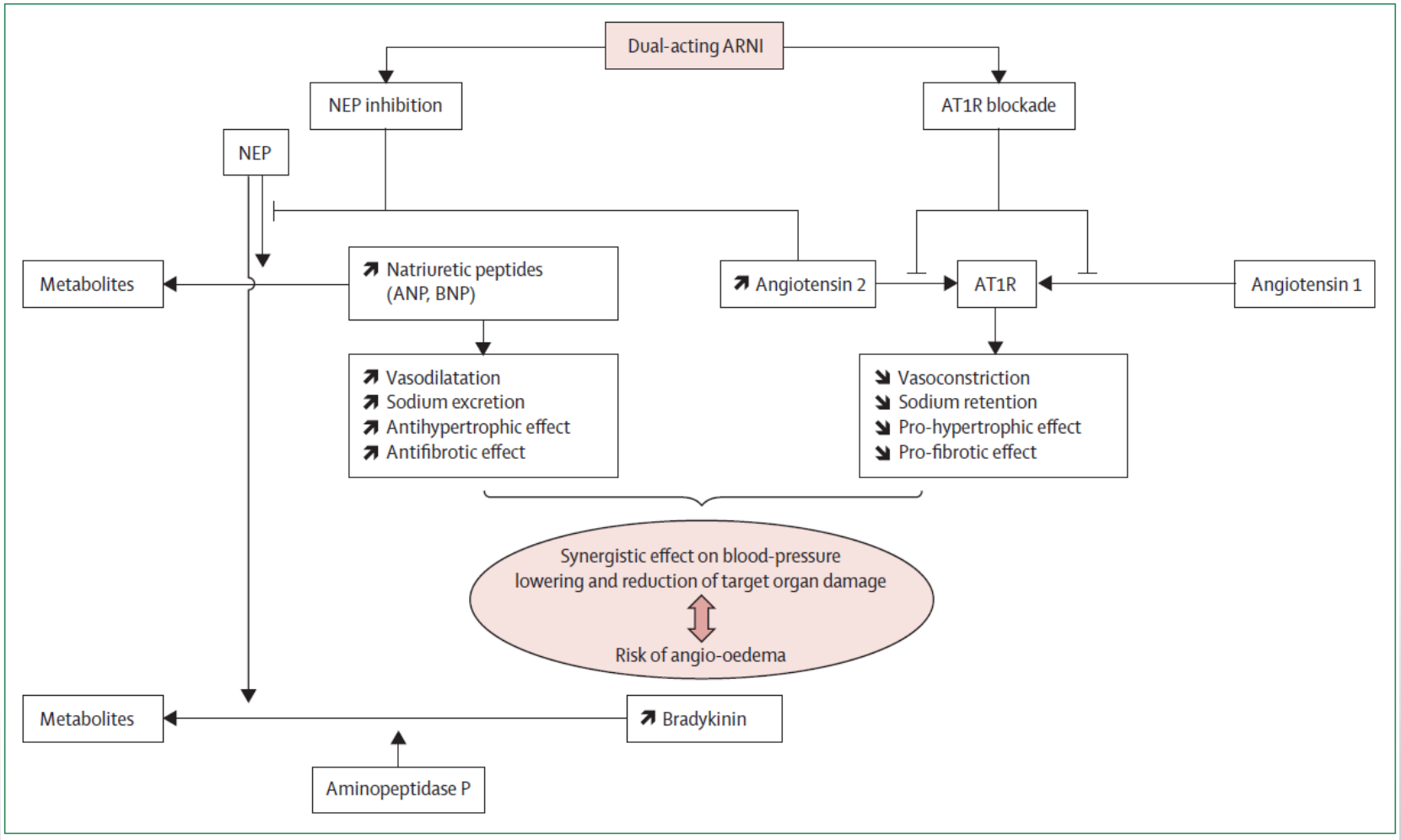




- **Ilepatril (Sanofi-Aventis)**

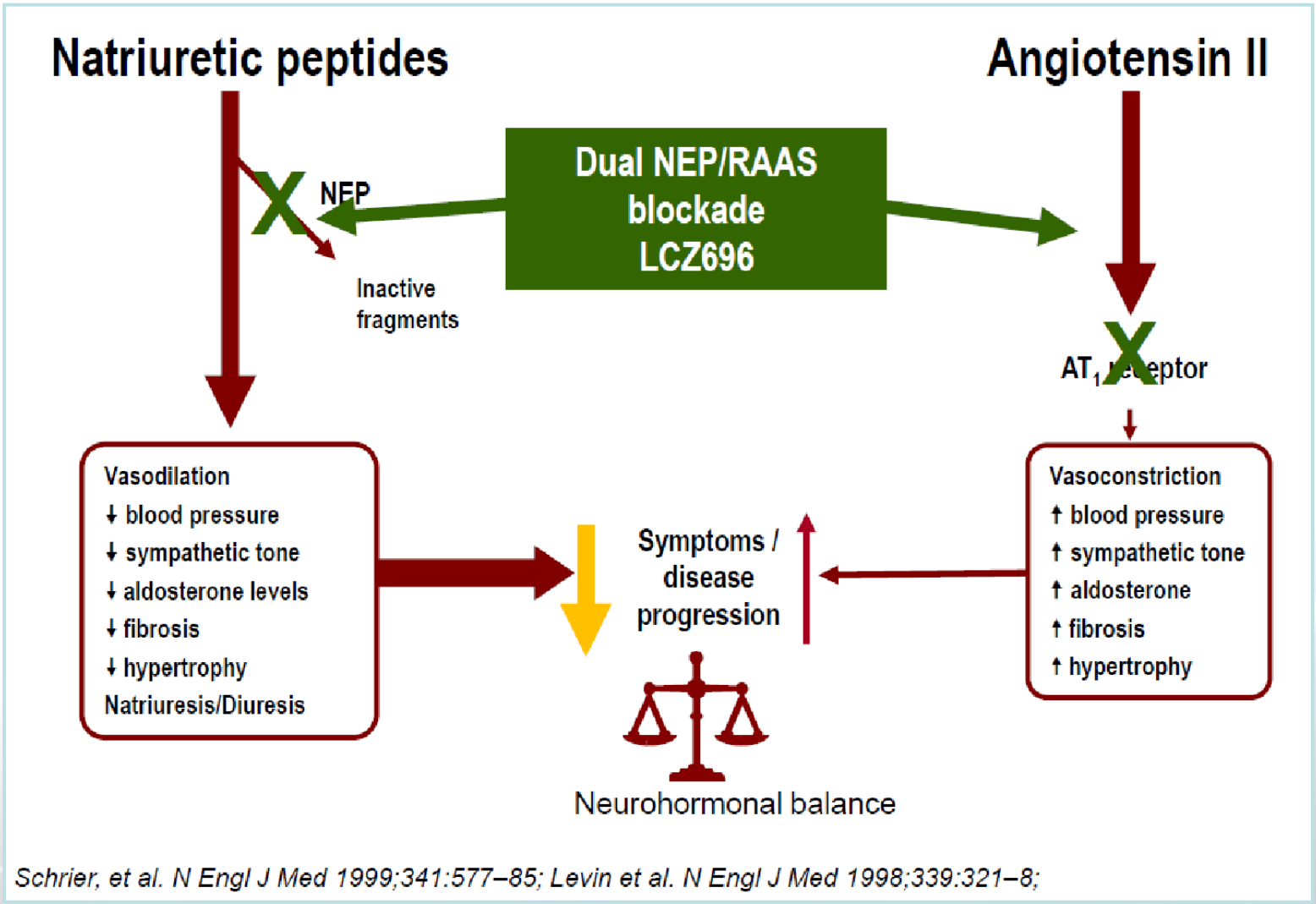
  : Phase III

Angiotensin Receptor-Neprilysin Inhibitor (ARNI)



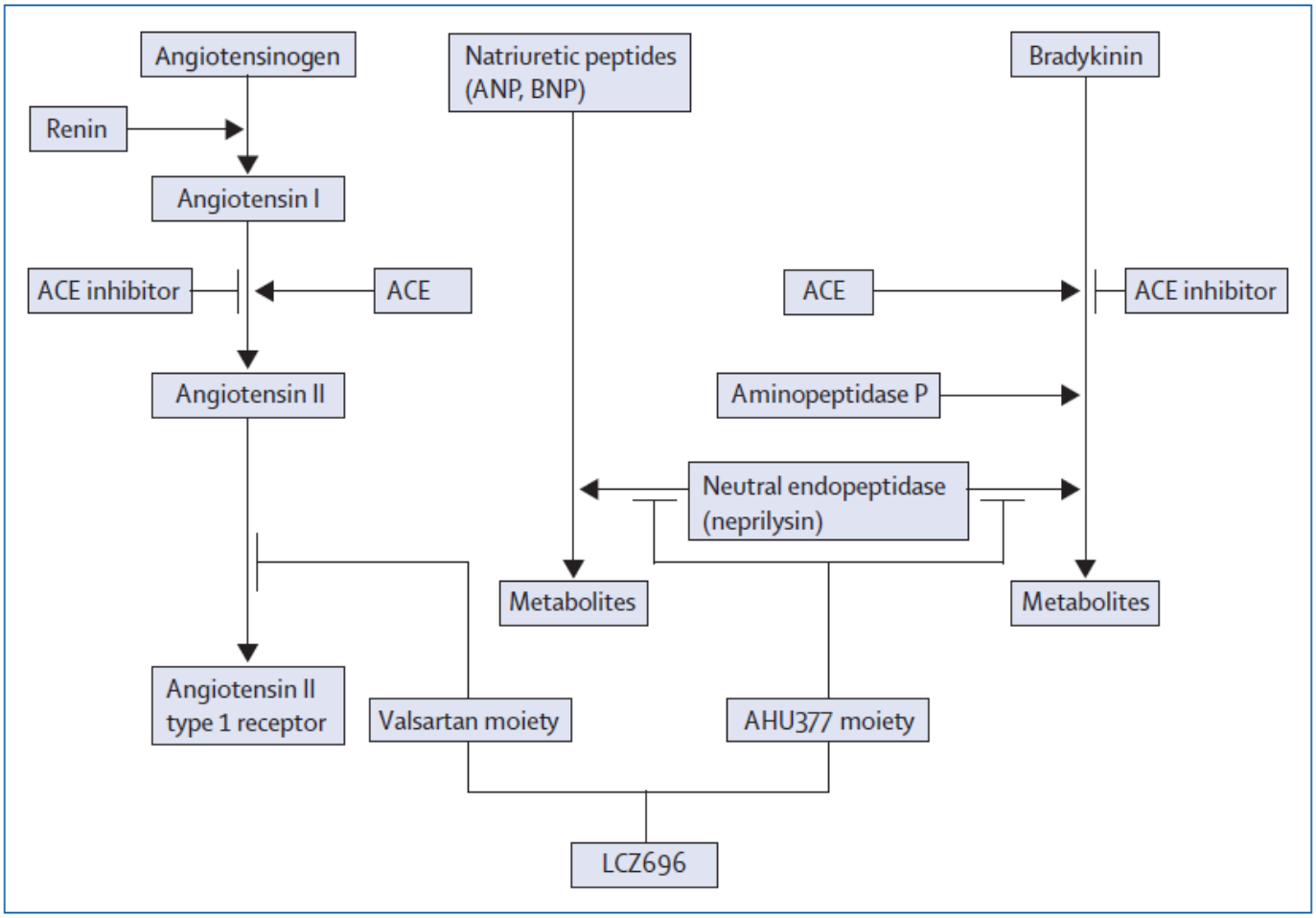
Lancet 2012; 380: 591–600

LCZ696 : a first-in class inhibitor of dual-acting ARNI



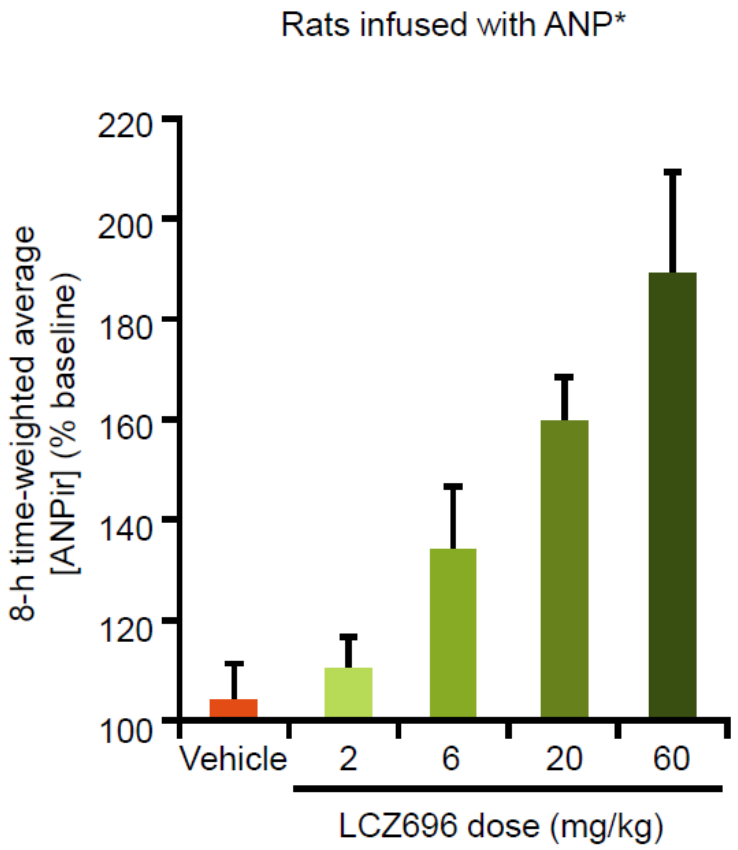
Schrier, et al. N Engl J Med 1999;341:577–85; Levin et al. N Engl J Med 1998;339:321–8;

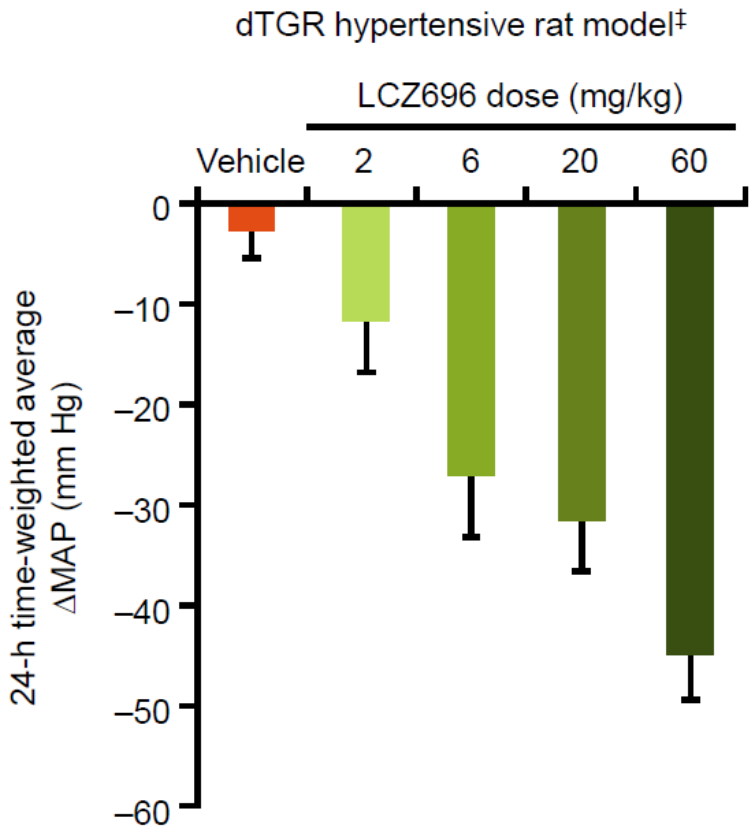
LCZ696 : Valsartan + AHU77



Lancet 2010;375:1228-1229.

LCZ696 dose-dependently enhances ANP levels and reduces BP



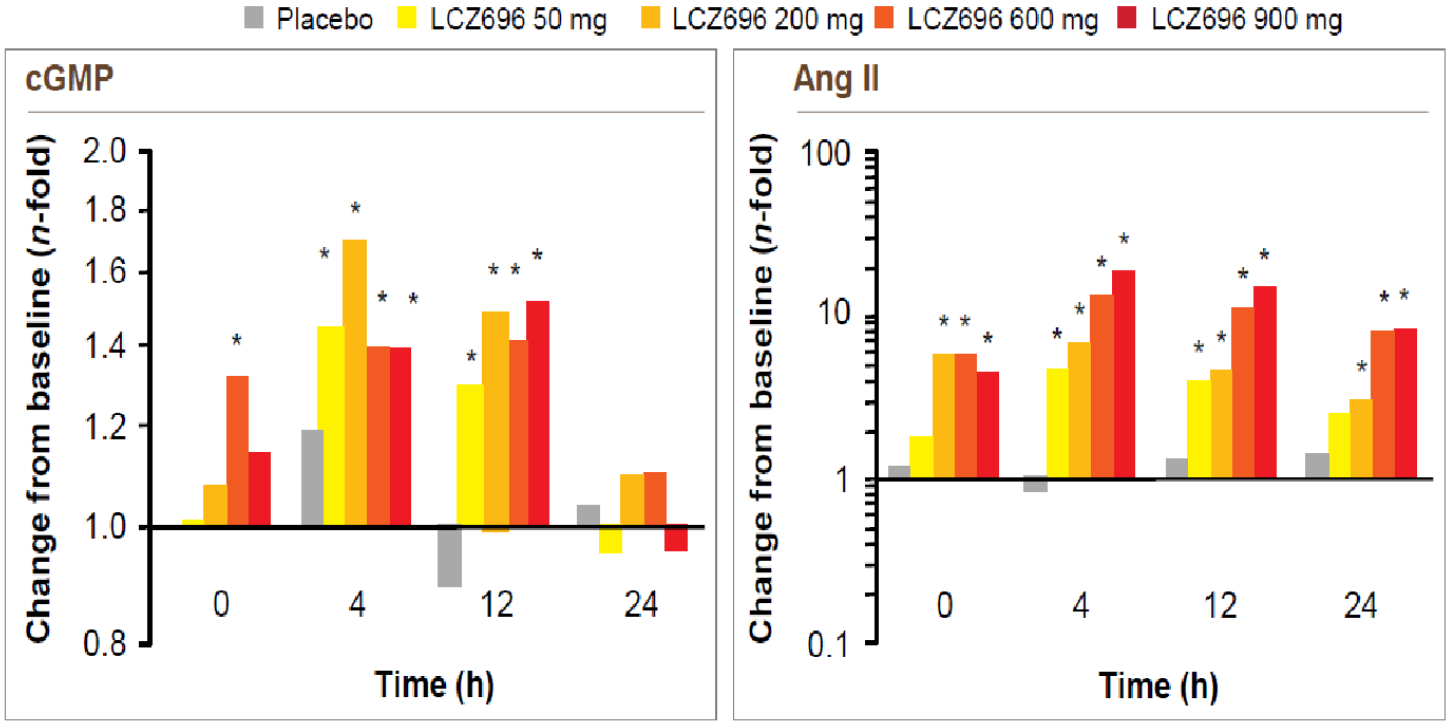


*Conscious Sprague-Dawley rats infused with ANP (450 ng/kg/min; n=4 per treatment group)
‡dTGR = double transgenic rats over-expressing renin and angiotensinogen (n=6 per treatment group)

Gu et al. J Clin Pharmacol 2010;50:401–14

Effects of LCZ696 on biomarkers of NEP inhibition and AT1R blockade

- Healthy volunteers received once-daily oral LCZ696 50, 200, 600 or 900 mg or placebo for 14 days
- cGMP measured as a biomarker of NEP inhibition and Ang II as a measure of AT1 receptor blockade



*p < 0.05 vs placebo, n=8/group
Values are n-fold change from baseline (logarithmic scale) at the post-dose time points indicated
Ang, angiotensin; AT1, angiotensin II type 1; cGMP, cyclic guanosine monophosphate; NEP, neprilysin

Gu et al. J Clin Pharmacol 2010;50:401–14

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

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

Summary

Background LCZ696 is a first-in-class inhibitor of the angiotensin II receptor and neprilysin. We aimed to establish whether the dual actions of LCZ696 lead to further lowering of blood pressure, compared with the angiotensin-receptor blocker valsartan.

Methods 1328 patients aged 18–75 years with mild-to-moderate hypertension were randomly assigned (double-blind) to 8 weeks' treatment in one of eight groups: 100 mg (n=156 patients), 200 mg (n=169), or 400 mg (n=172) LCZ696; 80 mg (n=163), 160 mg (n=166), or 320 mg (n=164) valsartan; 200 mg AHU377 (n=165); or placebo (n=173). The primary endpoint was the mean difference across the three single-dose pairwise comparisons of LCZ696 versus valsartan (100 mg *vs* 80 mg, 200 mg *vs* 160 mg, and 400 mg *vs* 320 mg) in mean sitting diastolic blood pressure during the 8-week treatment period. Analysis was by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT00549770.

Findings 1215 patients completed the 8-week treatment period. The average reduction in mean sitting diastolic blood pressure across the doses of LCZ696 versus the appropriate comparator dose of valsartan showed significantly greater reductions with LCZ696 (mean reduction: –2·17 mm Hg, 95% CI –3·28 to –1·06; p<0·0001). The reduction in mean sitting diastolic blood pressure was significantly different for 200 mg LCZ696 versus 160 mg valsartan (–2·97 mm Hg, 95% CI –4·88 to –1·07, p=0·0023) and for 400 mg LCZ696 versus 320 mg valsartan (–2·70 mm Hg, –4·61 to –0·80, p=0·0055). LCZ696 was well tolerated and no cases of angio-oedema were reported; only three serious adverse events occurred during the 8-week treatment period, of which none was judged to be related to the study drug, and no patients died.

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.

Funding Novartis.

Lancet 2010; 375: 1255–66

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See Comment page 1228

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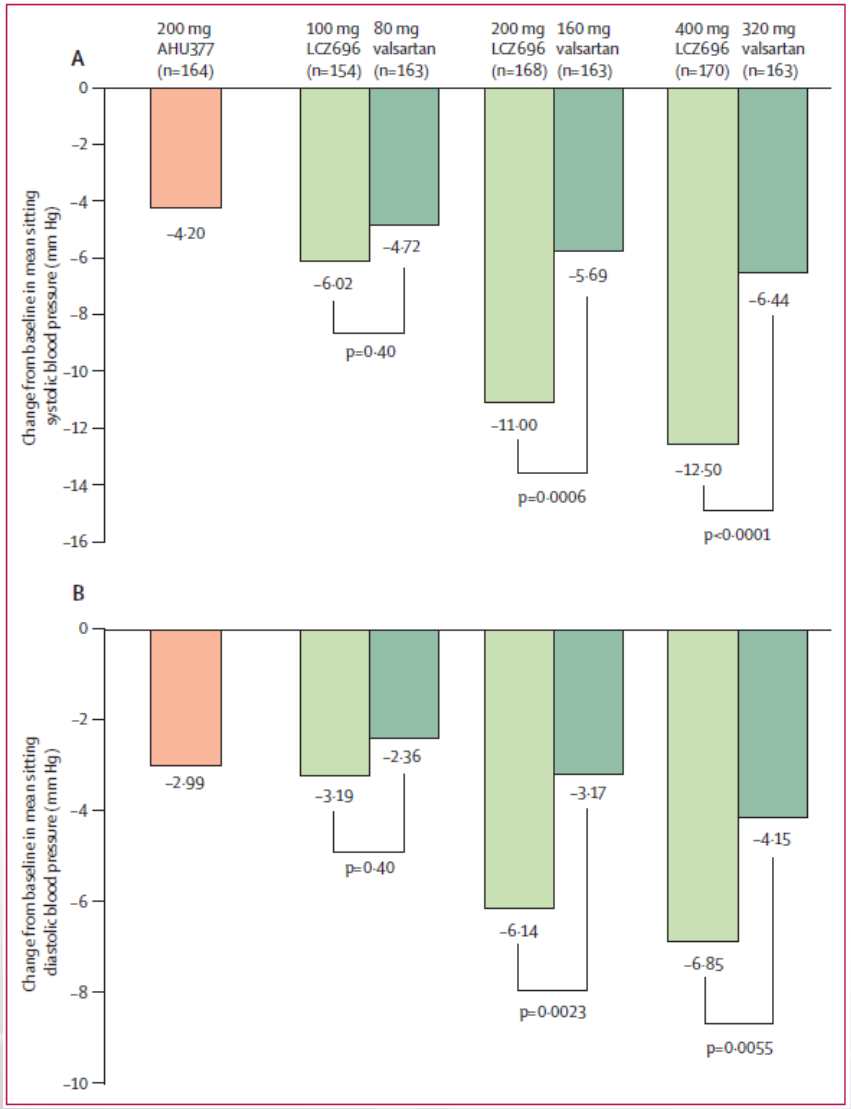
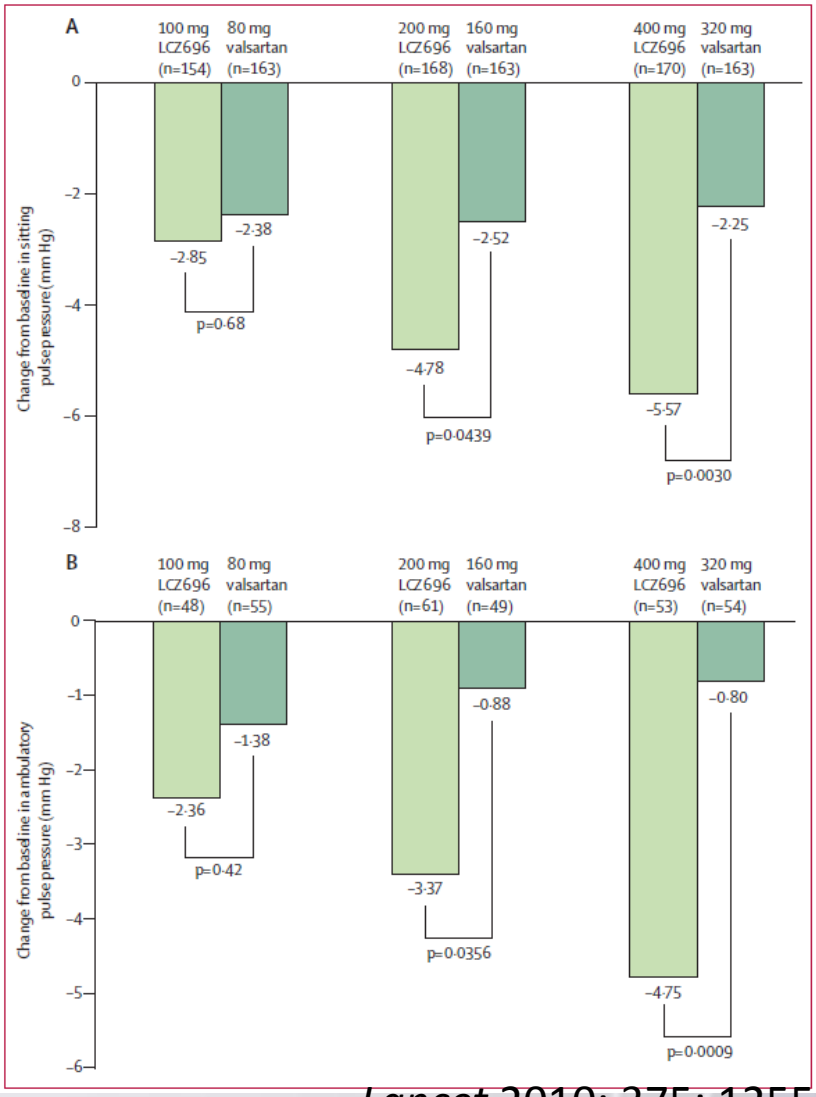
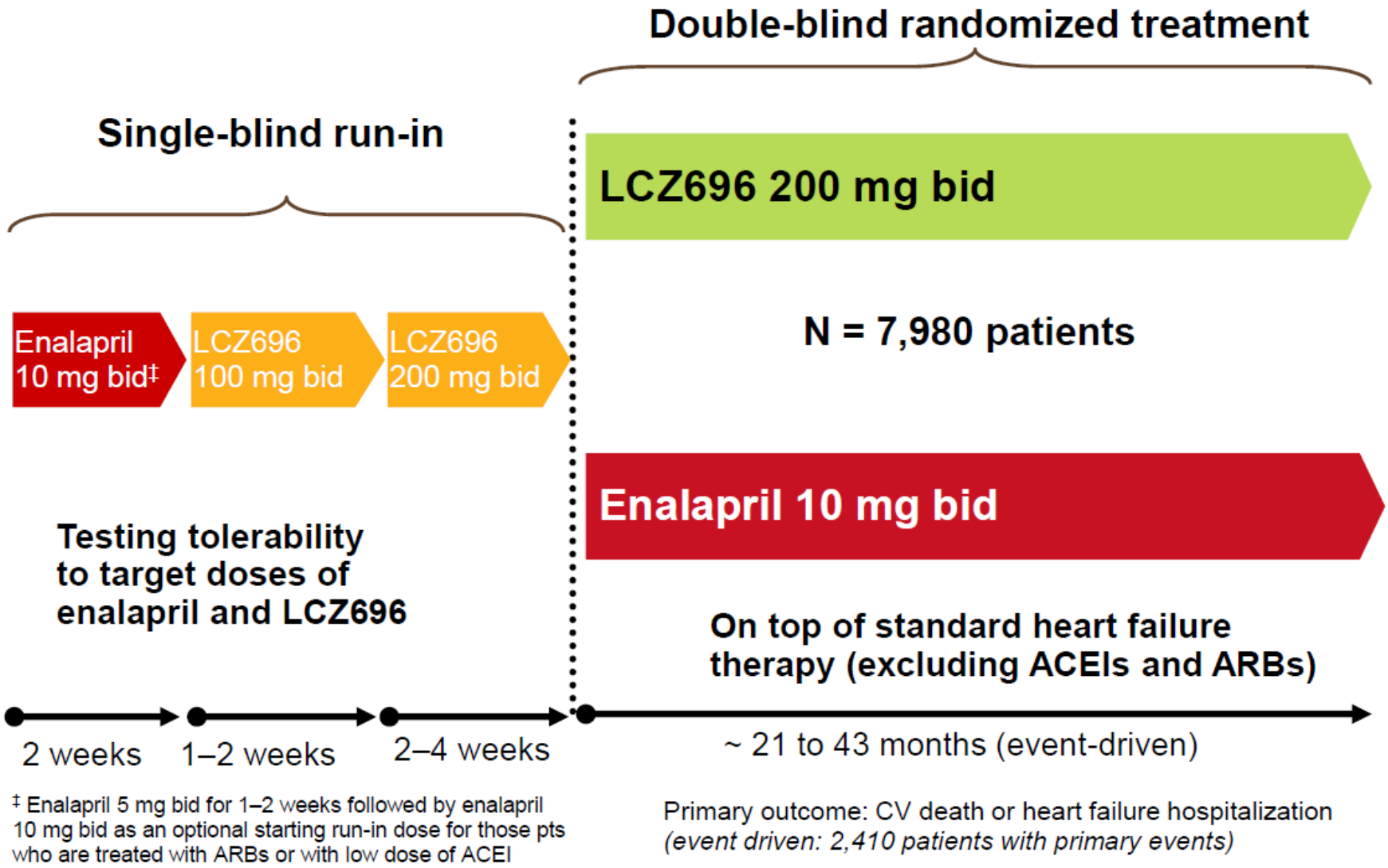
LCZ696 : mild to moderate HTN





Lancet 2010; 375: 1255–66

PARADIGM-HF: Study Design



‡ Enalapril 5 mg bid for 1–2 weeks followed by enalapril 10 mg bid as an optional starting run-in dose for those pts who are treated with ARBs or with low dose of ACEI

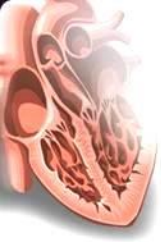
Primary outcome: CV death or heart failure hospitalization
(event driven: 2,410 patients with primary events)

Clinicaltrials.gov; http://clinicaltrials.gov/ct2/show/NCT01035255: Accessed July 2010

PARADIGM-HF: key efficacy outcomes

- **Primary outcome measure**:
  - Time to first occurrence of either CV mortality or HF hospitalization
- **Secondary outcomes measures**:
  - HF symptoms and physical limitations measured by the clinical summary score of the Kansas City Cardiomyopathy Questionnaire (KCCQ)
  - All-cause mortality
  - Renal progression assessed by first occurrence of 50% decline in eGFR, >30 mL/min/1.73m^2, or reaching end-stage renal disease

Clinicaltrials.gov; http://clinicaltrials.gov/ct2/show/NCT01035255



Endothelin Receptor Antagonist

- **Endothelin-1** : a powerful vasoconstrictor
- **Endothelin A and B receptor antagonists**

  : an additional therapeutic target to conventional antihypertensive treatment strategies
- **Darusentan (selective ETA receptor antagonist**)

  : Resistant hypertension (Phase III)

  : 100 mg → lowered BP by 11.3/8.3 mmHg without reflex alteration in heart rate

  : Salt & water retention → peripheral edema

Dual NEP-ECE inhibitor

- **Endothelin-converting enzyme (ECE)**

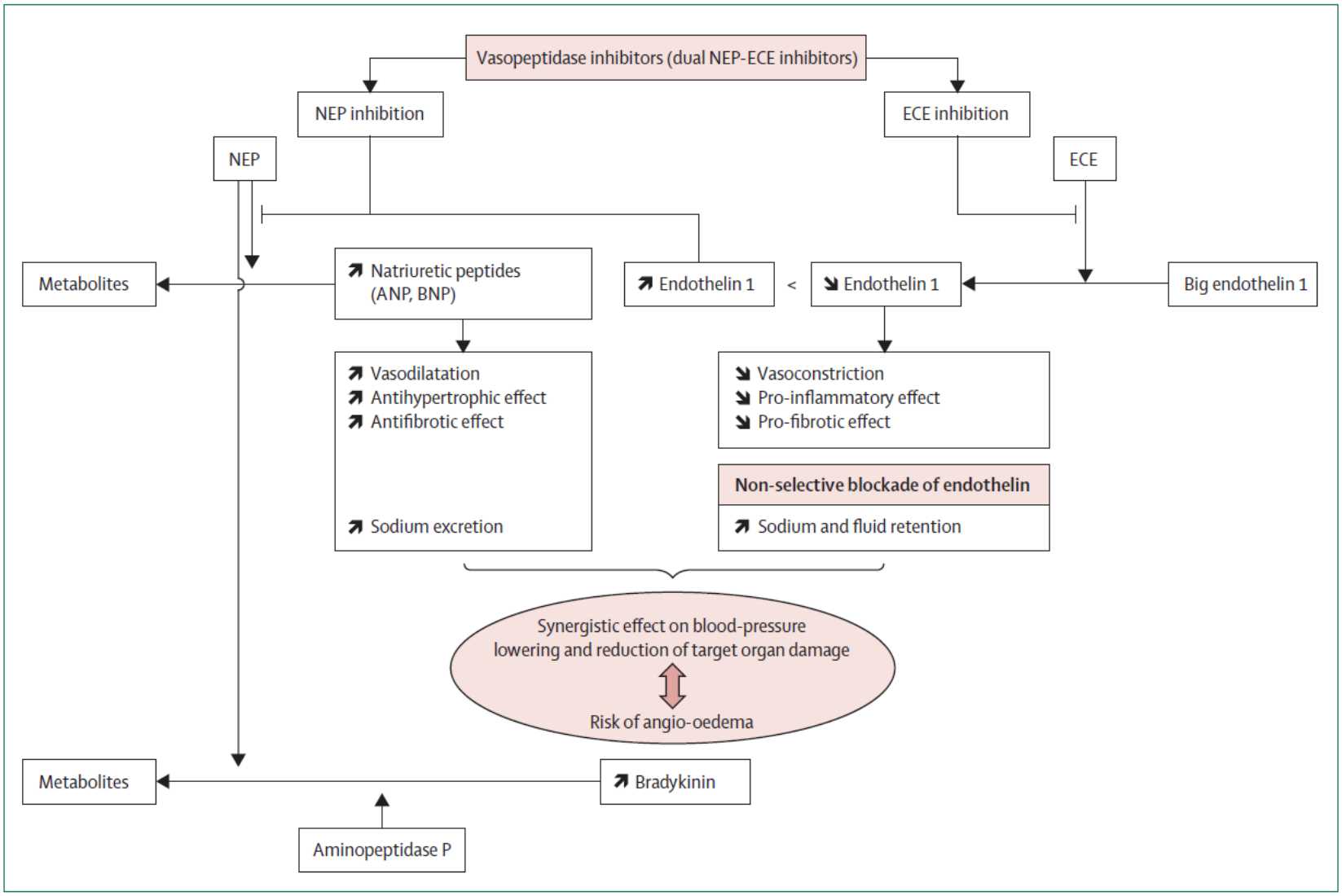
  : a key peptidase in the endothelin system

  : This enzyme cleaves inactive big endothelin-1 to active endothelin-1

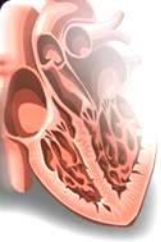
  → binds to endothelin type-A receptors

  → exerts its vasoconstrictor effect

Dual NEP-ECE inhibitor



Lancet 2012; 380: 591–600



Dual NEP-ECE inhibitor

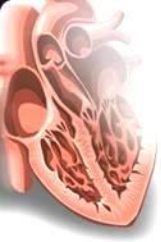
- Block the pro-inflammatory and pro-fibrotic effects of endothelin-1
- Enhance the plasma concentrations of natriuretic peptides
- Overcome some vasoconstriction because neprilysin degrades endothelin-1.
- The natriuretic action of neprilysin can oppose the salt and fluid retention caused by non-selective blockade of endothelin receptor.

Dual NEP-ECE inhibitor

- **Daglutril** (Solvay Pharmaceuticals)

  : a potent inhibitor of combined neprilysin and endothelin converting enzyme.

  : in phase 2 clinical development in patients with hypertension.



AT1R and Endothelin A Receptor Antagonist

- **PS 433540**

: dual-specificity AT1R and endothelin A receptor antagonists

: more effective and better tolerated

: Phase IIb (200 mg, 400 mg, and 800 mg)

- reduction of SBP & DBP more effectively than placebo

- the highest dose achieving a greater reduction than the AT1R blocker irbesartan

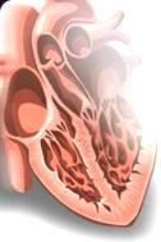
New molecules or compounds

Agent	Mechanism of action	Status
Azilsartan medoxomil	AT_1R blocker with peroxisome proliferator-activated receptor γ activity	Approved in 2011 by EMA and FDA
LCI 699	Aldosterone synthase inhibitor	Phase II
LCZ 696	Dual AT_1R blocker and neutral endopeptidase inhibitor	Phase II (phase III for heart failure)
PS 433540	Dual AT_1R and endothelin A receptor blocker	Phase II
Daglutril	Dual endothelin-converting enzyme and neutral endopeptidase inhibitor	Phase III
PL 3994	Natriuretic peptide receptor agonist	Phase II (also phase II for congestive heart failure)
AR 9281	Soluble epoxide hydrolase inhibitor	Phase II (also phase II for diabetes mellitus type 2)
Lercandipine, modified release	Calcium-channel antagonist	Phase II
Clonidine, controlled release	Centrally acting α_2-adrenergic agonist	Phase III

*Only compounds approved by the FDA in 2010–2011[3,4] or listed as clinically investigated by the Pharmaceutical Research and Manufacturers of America website[5] on 1 December 2011 are included. Abbreviation: AT_1R, angiotensin II type 1 receptor; EMA, European Medicines Agency.

- AT2R agonist & ACE2 activator
- Renin-prorenin blocker
- Amnopeptidase-A inhibitors, Nitric Oxide donors

Paulis, L. *et al. Nat. Rev. Cardiol. 2012;9: 276–285.*



New targeting (1)

- **Two angiotensin-based vaccines** (In a phase 2a study)

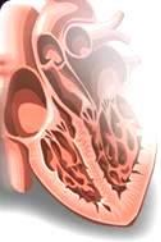
  1) **CYT006-AngQb**

  - an angiotensin-2 vaccine (Cytos Biotechnology AG), significantly reduced BP in HTN Pts.

  2) **PMD3117**

  - an angiotensin-1 vaccine (Protherics Inc)
  - lowered blood pressure in rats, but not in a subsequent placebo-controlled clinical study.

➔ Further studies with modified immunogen or adjuvant are needed to boost antibody titres.



New targeting (2)

- **Advanced glycation end-products (AGE)**

  : targeting vascular ageing and isolated systolic HTN

  : AGE inhibitior (Aminoguanidine & pyridoxamine)

  ➔ prevent the formation of AGE crosslinks

  : AGE breakers (alagebrium & pyridinium analogues TRC4186 and TRC4149)

  ➔ catalytically break these crosslinks

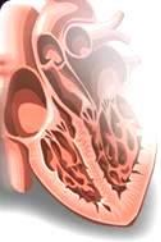
  ➔ a promising molecule to reduce aortic stiffness independently of BP in patients with isolated systolic hypertension. (not show benefit in patients)

Combinations newly approved or in clinical trials for the treatment of hypertension

Combination	Mechanism of action	Status
Olmesartan, amlodipine, and hydrochlorothiazide	AT_1R antagonist, calcium-channel blocker, and diuretic	FDA and German‡ approval in 2010
Aliskiren, amlodipine, and hydrochlorothiazide	Renin inhibitor, calcium-channel blocker, and diuretic	FDA approved in 2010, EMA approved in 2011
Aliskiren and amlodipine	Renin inhibitor and calcium-channel blocker	FDA approved in 2010, EMA approved in 2011
Azilsartan medoxomil and chlortalidone	AT_1R antagonist and diuretic	Preregistration
Candesartan cilexetil and nifedipine	AT_1R antagonist and calcium-channel blocker	Phase II

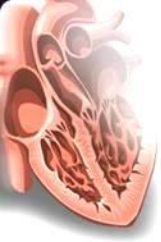
*Only combinations approved by the FDA in 2010–2011[3,4] or listed as clinically investigated by the Pharmaceutical Research and Manufacturers of America[5] on 1 December 2011 are included. ‡Approval via the European decentralized procedure. Abbreviation: AT_1R, angiotensin II type 1 receptor; EMA, European Medicines Agency.

Paulis, L. *et al. Nat. Rev. Cardiol. 2012;9: 276–285.*



Conclusion (1)

- One novel antihypertensive—**azilsartan**—as well as several novel fixed-dose combinations of existing antihypertensive agents, including **aliskiren** double and triple combinations and an *olmesartan* triple combination were approved.
- An angiotensin II type 2 receptor agonist—**compound 21**—is in preclinical development.
- Novel antihypertensive compounds in clinical development include an **aldosterone synthase inhibitor**, a **natriuretic peptide agonist**, and a **soluble epoxide hydrolase inhibitor**.



Conclusion (2)

- Novel antihypertensives with dual activity, including an **ARB & neutral endopeptidase inhibitor**, an **ARB & endothelin receptor A blocker**, and an **endothelin-converting enzyme & neutral endopeptidase inhibitor**, are in clinical development.
- Upcoming fixed-dose combinations of antihypertensives are expected to include **CCBs** other than amlodipine, and **diuretics** other than hydrochlorothiazide (which are included in the current combinations).

	Drug	Preclinical stage	Phase 1–3	Pharmaceutical industry
Dual vasopeptidase inhibitor				
Dual neprilysin-ACE inhibitor	Ilepatril (AVE7688)	..	Phase 3	Sanofi-Aventis
Dual neprilysin-ECE inhibitor	Daglutril (SLV306)	..	Phase 2	Solvay Pharmaceuticals
Dual ARNI	LCZ696	..	Phase 3	Novartis Pharmaceuticals
Aldosterone-synthase inhibitor	LCI699	..	Phase 2*	Novartis Pharmaceuticals
Endothelin antagonist	Bosentan	..	Phase 2	Actelion Pharmaceuticals
	Darusentan		Phase 3*	Gilead Sciences
Nitric oxide donor				
Nitric oxide-releasing drugs	Nitrosyl-cobinamide	Yes	..	..
Nitrix oxide-releasing hybrids	Nitric oxide-losartan	Yes	..	Cayman Chemicals
	Nitric oxide-telmisartan	Yes	..	Cayman Chemicals
CINOD	Naproxcinod	..	Phase 3	NicOx
Renin-prorenin blocker	..	Yes	..	..
ACE-2 activator	..	Yes	..	..
Aminopeptidase-A inhibitor	QGC001	Yes	..	Quantum Genomics Corp
Vaccine				
Angiotensin 1 vaccine	PMD3117	..	Phase 2	Protherics Inc
Angiotensin 2 vaccine	Cyt006-AngQb	..	Phase 2	Cytos Biotechnology AG
Dual AT1R/ETA antagonist	PS-433540	..	Phase 2	Ligand Pharmaceuticals
Novel dual ARB and partial PPAR-γ agonist	..	Yes	..	..
AGE breaker	Alagebrium (ALT-711)	..	Phase 2*	Synvista Therapeutics

We have only listed molecules described in the text. ACE=angiotensin-I converting enzyme. ARNI=dual-acting angiotensin receptor-neprilysin inhibitor. CINOD=cyclo-oxygenase-inhibiting nitric-oxide donator. ARB=angiotensin-receptor blocker. PPAR-γ=peroxisome proliferator-activated receptor-γ. AGE=advanced glycation end-product. *Development stopped.

Table: **New drugs for hypertension**

Lancet 2012; 380: 591–600

Thank you very much for your attention