Novel drugs in development for hypertension

Stéphane LAURENT, MD, PhD, FESC
Pharmacology Department, Hôpital Européen Georges Pompidou,
Paris Cardiovascular Research Center (P.A.R.C.C.), INSERM U970
Université Paris Descartes, Assistance Publique-Hôpitaux de Paris

Inserm
Institut national
de la santé et de la recherche médicale

PARIS
DESCARTES

DISCLOSURE

Stéphane LAURENT, MD, PhD

Potential conflict of interest:
Research grant, advisory board, honorarium as speaker or chairman

Drug companies

ASTRA-ZENECA
BAYER-SCHERING
BOEHRINGER-INGELHEIM
CHIESI
DAICHII-SANKYO
ESTEVE
GILEAD
MENARINI
MSD
NEGMA
NOVARTIS
PFIZER
RECORDATI
SANOFI-AVENTIS
SERVIER
TAKEDA

Manufacturers

ATCOR
ESAOTE-PIE MEDICAL
HEMO SAPIENS
OMRON
TENSIOMED

Novel drugs for the management of hypertension

Various indications

- Novel monotherapies, first line…
- Special conditions: resistant hypertension, 4th or 5th line…
- New combinations, novel strategies…

Causes of resistant hypertension

- Poor compliance to therapeutic plan
- Unsuspected secondary cause
- Failure to modify lifestyle including
  - weight gain
  - heavy alcohol intake
- Continued intake of drugs that raise BP
  - liquorice, cocaine, glucocorticoids, NSAID
- Obstructive sleep apnea
- Irreversible or scarcely reversible organ damage
- Volume overload due to
  - Inadequate diuretic therapy
  - Progressive renal insufficiency
  - High sodium intake
  - Hyperaldosteronism
- Metabolic syndrome and diabetes
- Chronic kidney disease
- Old age

Adapted from 2007 ESH Guidelines for the Management of Hypertension.
Mancia G et al. J Hypertens 2007, 25:1105-1187

Hypertension 1

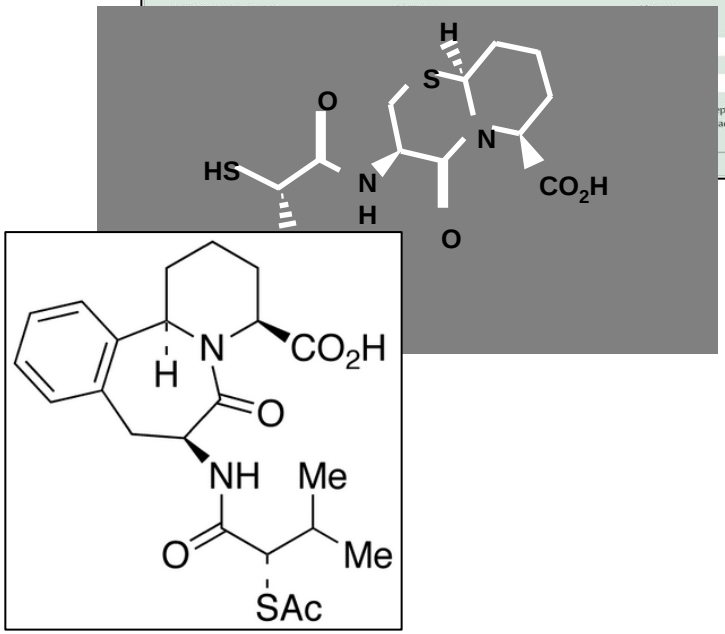
New drugs, procedures, and devices for hypertension

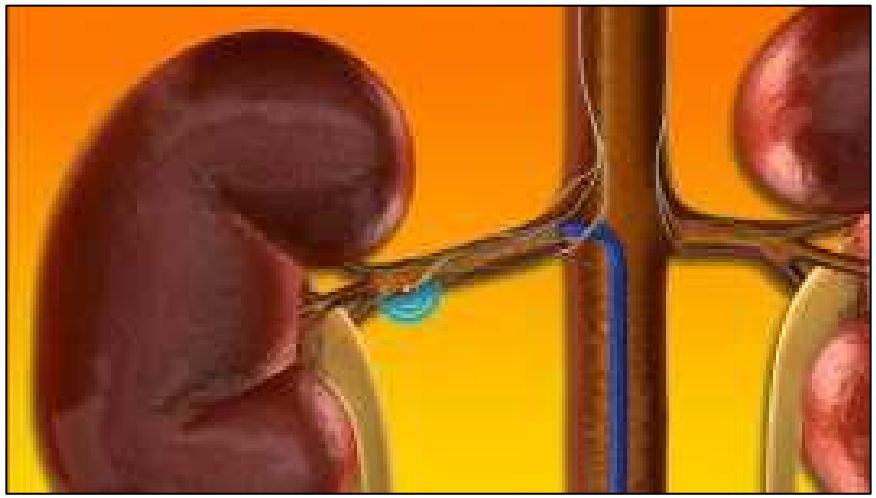
Stéphane Laurent, Markus Schlaich, Murray Esler

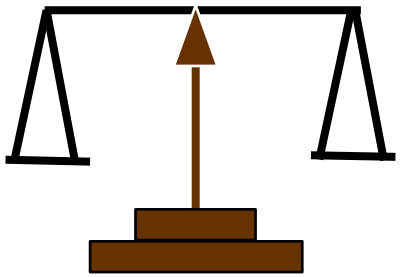
Laurent S et al. Lancet 2012

	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 Darusentan	..	Phase 2 Phase 3*	Actelion Pharmaceuticals Gilead Sciences
Nitric oxide donor				
Nitric oxide-releasing drugs	Nitrosyl-cobinamide	Yes	..	..
Nitrix oxide-releasing hybrids	Nitric oxide-losartan Nitric oxide-telmisartan	Yes Yes	.. ..	Cayman Chemicals Cayman Chemicals
CINOD	Naproxcinod	..	Phase 3	NicOx
Renin-prorenin blocker	..	Yes	..	..
ACE-2 activator	..	Yes	..	..
Aminopeptidase-A inhibitor	QGC001	Yes	..	Quantum Genomics Corp
Vaccine				
				Protherics Inc
				Cytos Biotechnology AG
				Ligand Pharmaceuticals
				..
				Synvista Therapeutics

ptor-neprilysin inhibitor.
activated receptor-γ. AGE=advanced glycation







New drugs or new procedures?

Research Correspondence

Eligibility for Renal Denervation in Patients With Resistant Hypertension

When Enthusiasm Meets Reality in Real-Life Patients

Savard, Frank, Bobrie, Plouin, Sapoval, Azizi. JACC 2012

Our findings demonstrate that percutaneous RDN, whether for clinical trials or specific patients, is limited to a highly selected fraction of patients with RH—even in a specialist hypertension unit—and that a thorough diagnostic work-up is essential for appropriate patient selection.

Only 15 patients

…among 200 with true resistant hypertension

…among 87 without secondary hypertension

…among 31 with severe hypertension

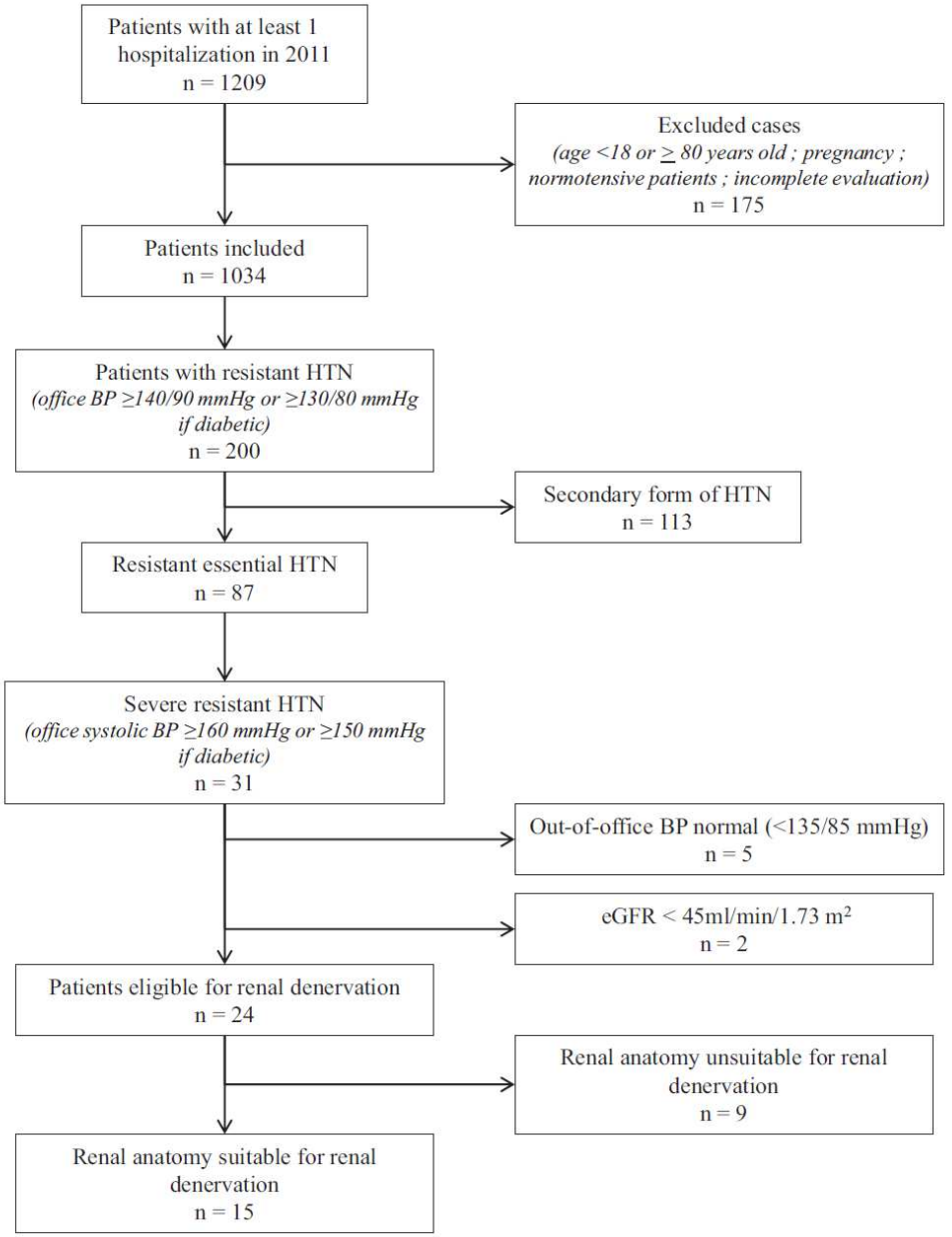


Figure 1 Patient Screening and Selection

New drugs for hypertension: the pipeline is not dry

Laurent S et al. Lancet 2012

Pharmacological class		Drug	Pre-clinical stage	Phase I-III	Pharmaceutical industry
Dual vasopeptidase inhibitor					
1. Dual NEP/ACE inhibitor					
2. Dual NEP/ECE inhibitor					
Dual ARNI					
Aldosterone synthase inhibitor					
Endothelin antagonist					
NO donor	NO-releasing drugs				
	NO-releasing hybrids				
	CINOD				

New vasodilators: not only hypertension

- Systemic hypertension
- Pulmonary hypertension
- Heart failure
- Chronic kidney disease
- Migraine
- Spasm of cerebral artery after subarachnoid hemorrage
- Raynaud phenomenon
- ...

New drugs for hypertension

Pharmacological class		Drug	Pre-clinical stage	Phase I-III	Pharmaceutical industry
Dual vasopeptidase inhibitor					
1. Dual NEP/ACE inhibitor		Ilepatril – AVE7688		Phase III	Sanofi-Aventis
2. Dual NEP/ECE inhibitor		Daglutril- SLV306		Phase II	Solvay Pharmaceuticals
Dual ARNI		LCZ696		Phase III	Novartis Pharmaceuticals
Aldosterone synthase inhibitor		LCI699		Phase II *	Novartis Pharmaceuticals
Endothelin antagonist		Bosentan		Phase II	Actelion Pharmaceuticals
		Darusentan		Phase III *	Gilead Sciences
NO donor	NO-releasing drugs	Nitrosyl-cobinamide	❐		
	NO-releasing hybrids	NO-losartan NO-telmisartan	❐ ❐		Cayman Chemicals
	CINOD	Naproxcinod		Phase III	NicOx

* Development stopped

Laurent S et al. Lancet 2012

Neutral endopeptidase - NEP
EC 3.4.24.11 ou 24.11

- neutral endopeptidase = neprilysin = atriopeptidase = enkephalinase
- Zinc metalloprotease
- Ecto-enzyme present in the kidney

  also : lung, gut, adrenals, brain, heart, and vessels

- Substrates

  ANP, BNP, CNP

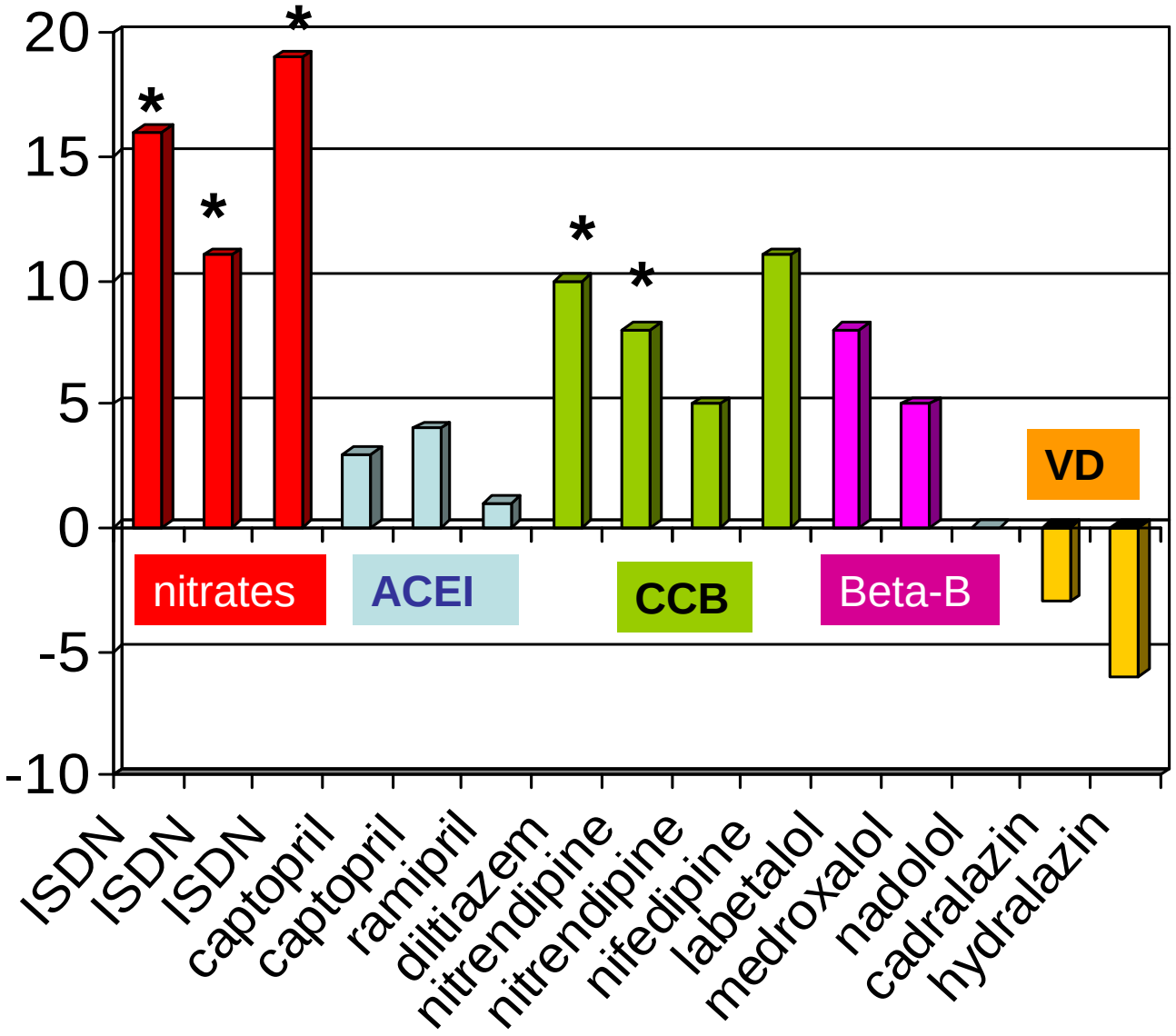
  also : bradykinine, kallidine, **angiotensin II, endothelin**
  adrenomedullin

- **Effects**: vasodilation of small and large arteries (« nitrate like effect »)

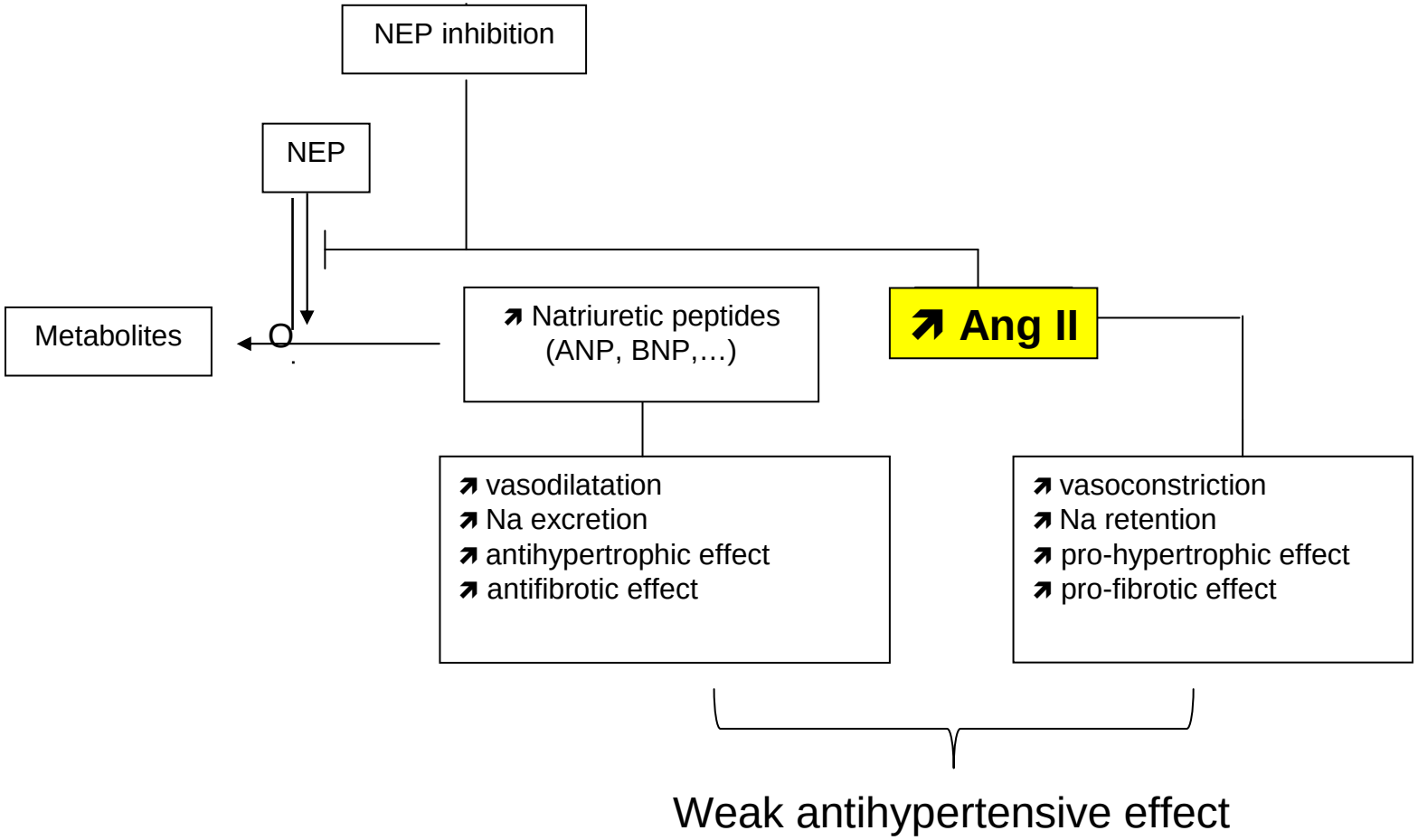
Na excretion (« diuretic like effect ») , antihypertrophic effect, antifibrotic effect

Acute changes (%) in brachial artery diameter in response to vasodilatory agents

Laurent S et al. Unpublished data



Counter-regulation with pure NEP inhibitors

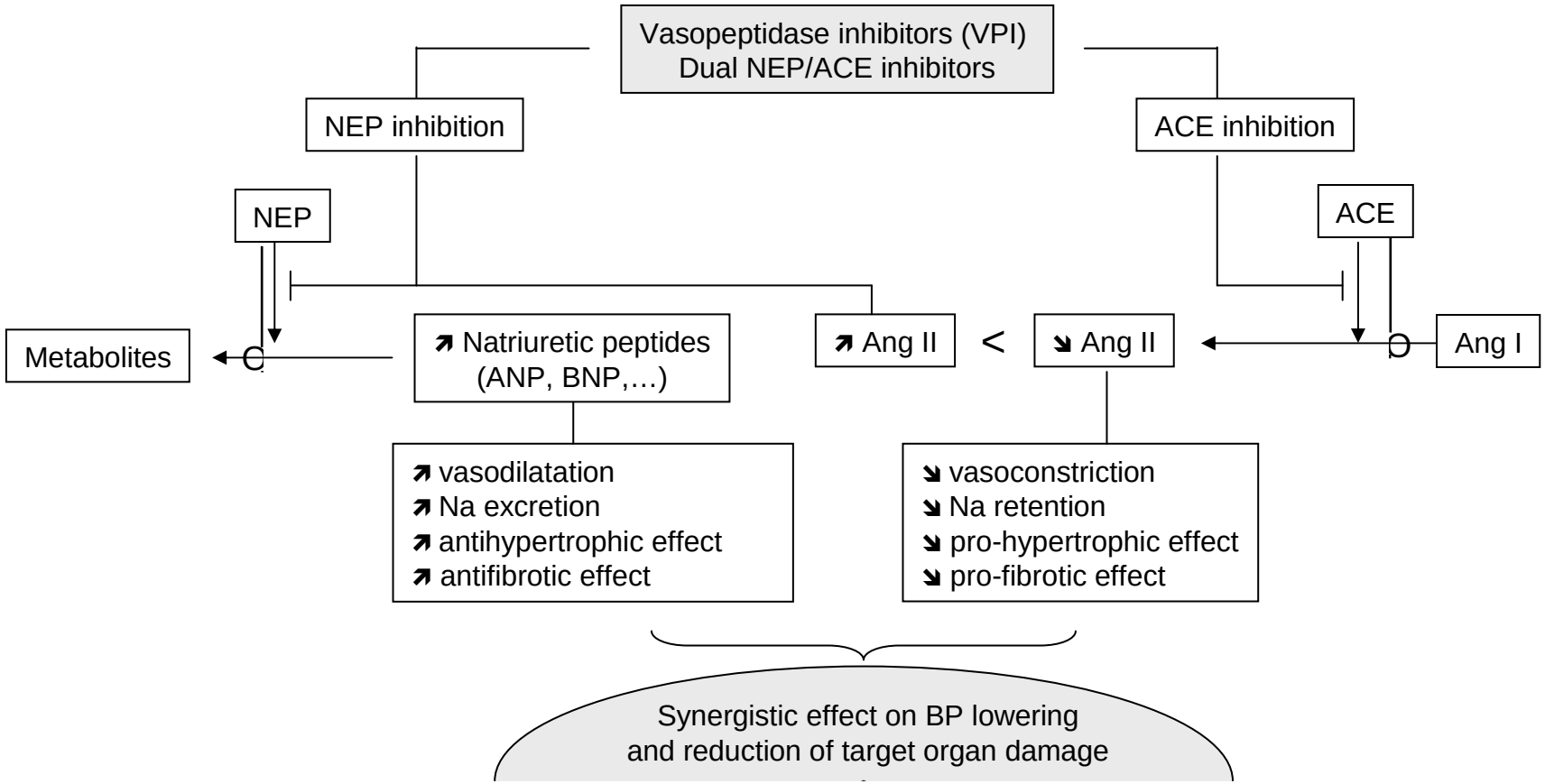


NEP inhibitors

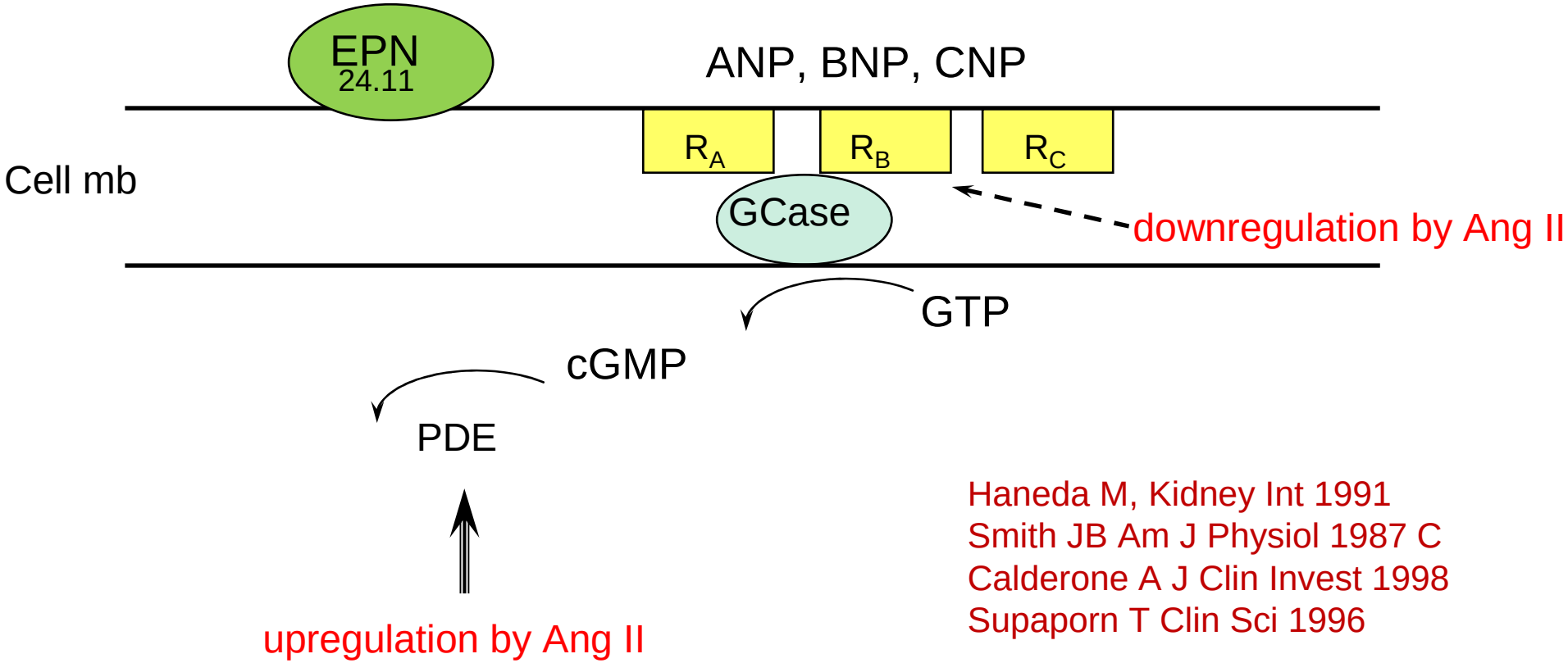
Pure NEP inhibitors		Dual NEP/ACE inhibitors	
candoxatril	Pfizer	fasidotril, alatriopril	Bioprojet
ecadotril	Bioprojet	*Ki NEP 5.1 nM , Ki ECA 9.8 nM*	
thiorphan	Bioprojet	omapatrilat	BMS
		Ki NEP 8.9 nM , Ki ECA 6.0 nM	
		sampatrilat	Pfizer
		MDL 100-240	Merrell Dow
		Also: BMS-Sanofi, Novartis, Schering, Zambon	

Dual NEP/ACE inhibitors:

Increased circulating natriuretic peptides can mimic the effects of nitrates and diuretics on large arteries and be synergistic of the reduction in Ang II

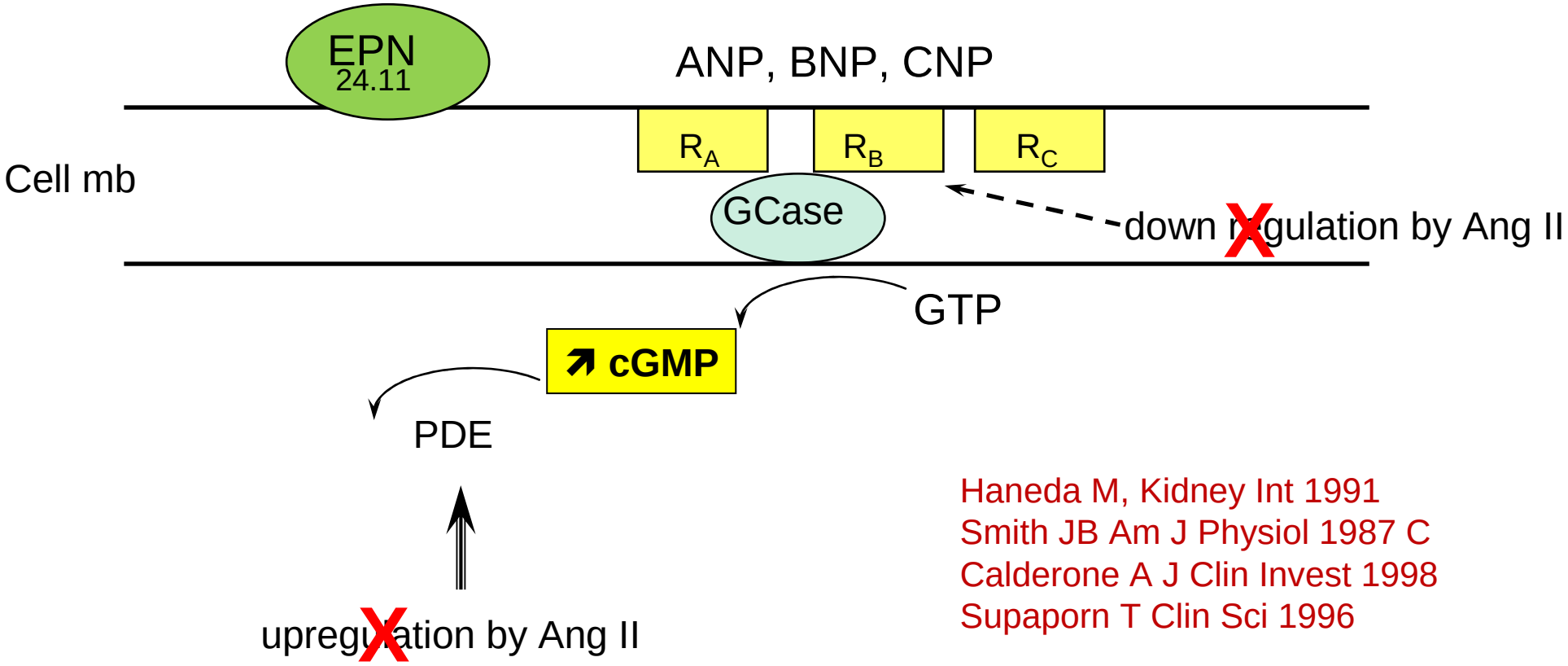


Counter-regulation after NEP inhibition



Haneda M, Kidney Int 1991
Smith JB Am J Physiol 1987 C
Calderone A J Clin Invest 1998
Supaporn T Clin Sci 1996

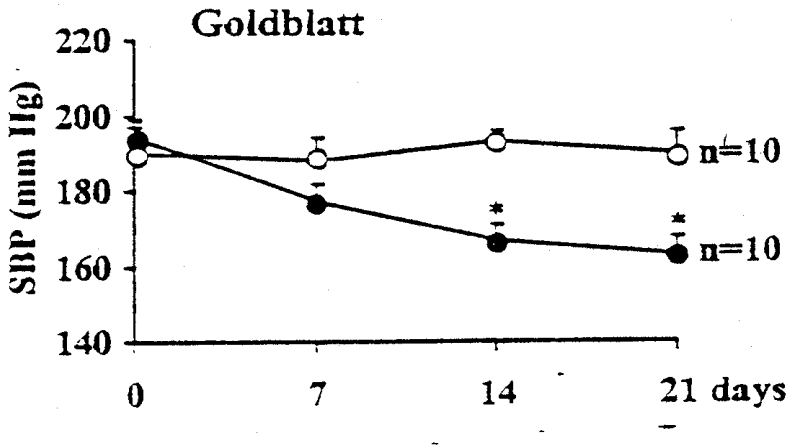
Synergistic effect of dual NEP/ACE inhibition

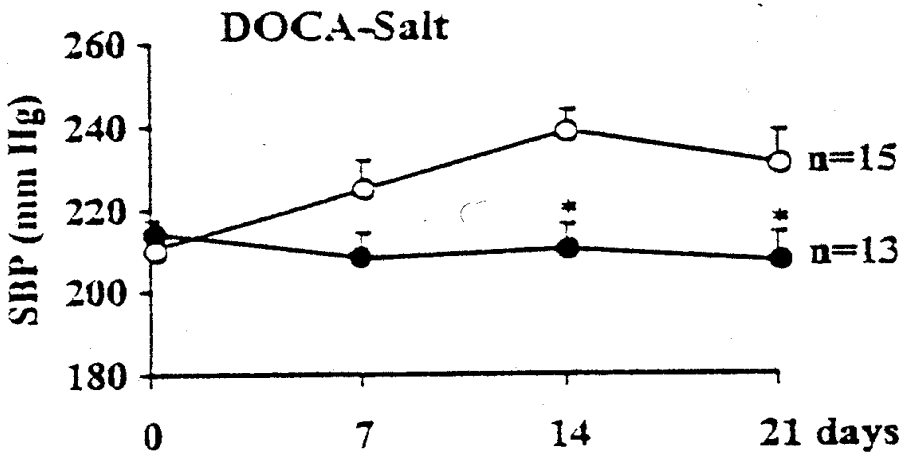


Haneda M, Kidney Int 1991
Smith JB Am J Physiol 1987 C
Calderone A J Clin Invest 1998
Supaporn T Clin Sci 1996

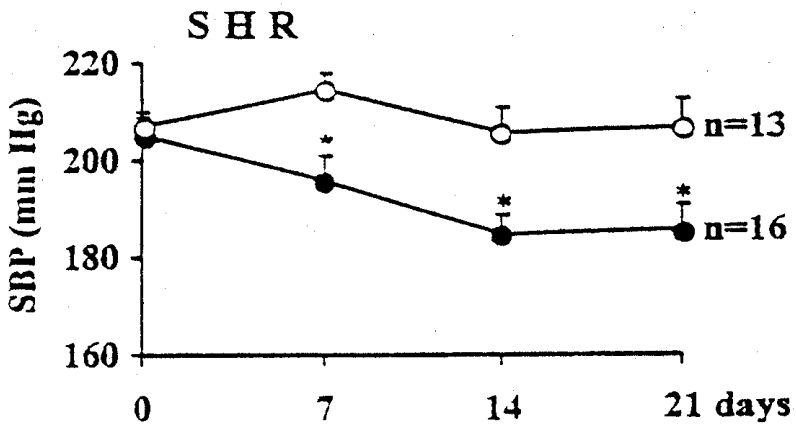
Antihypertensive effects of fasidotril in low- and high-renin hypertension in rat

Laurent S et al. Hypertension 2000



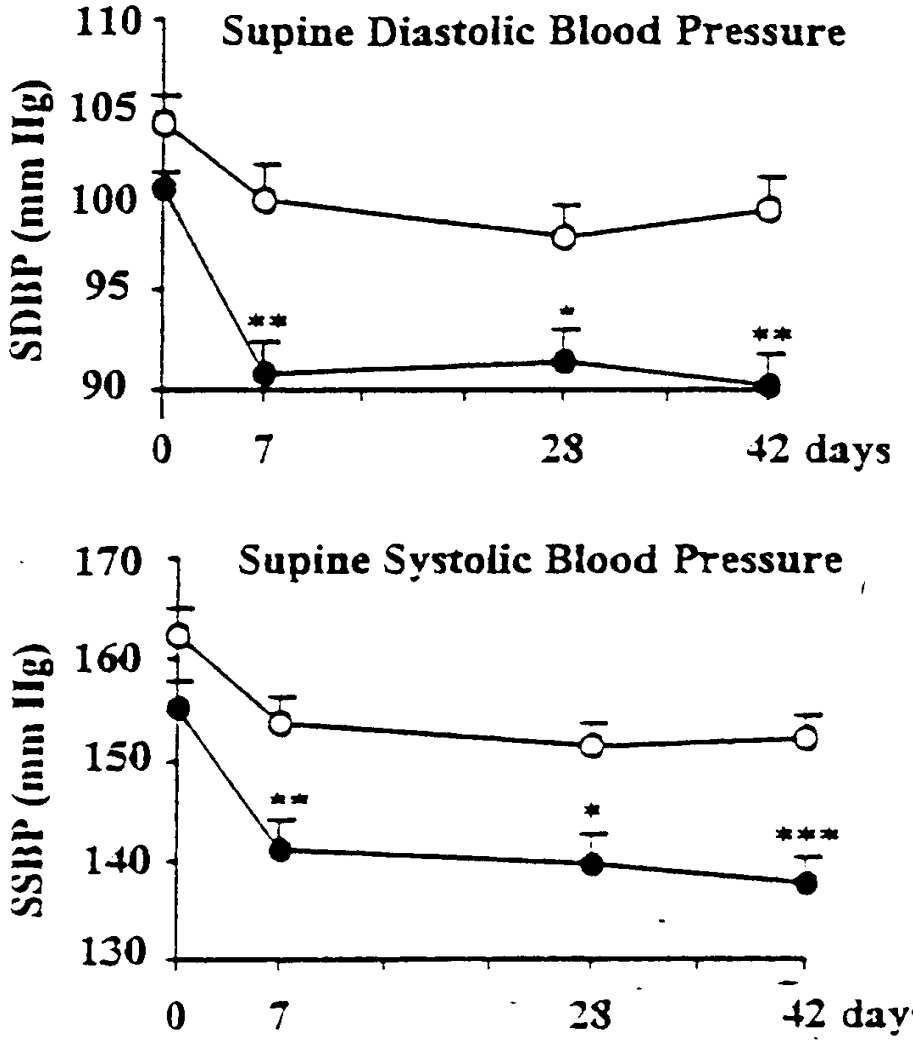


Model	*HTA*
Goldblatt 2K-1Clip	*renine-dependent*
DOCA-sel	*volume-dependent*
SHR	*renin> volume*



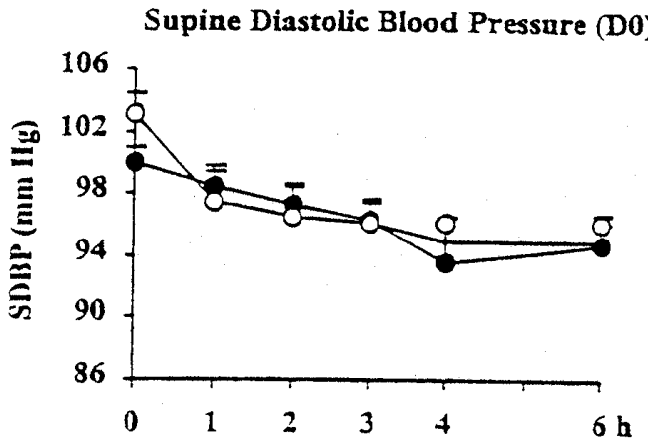
Antihypertensive effects of fasidotril 200 mg b.i.d. in humans

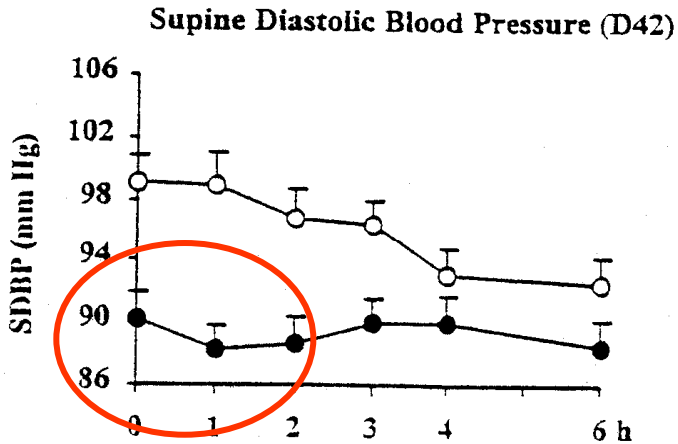
Laurent S et al. Hypertension 2000



Antihypertensive effects of fasidotril 200 mg b.i.d. in humans

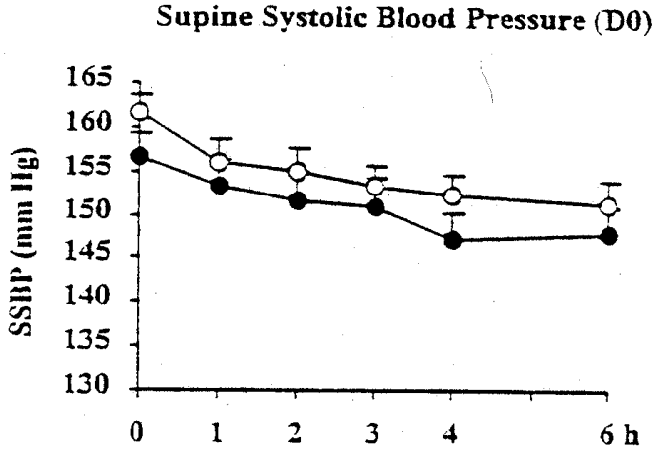
Laurent S et al. Hypertension 2000

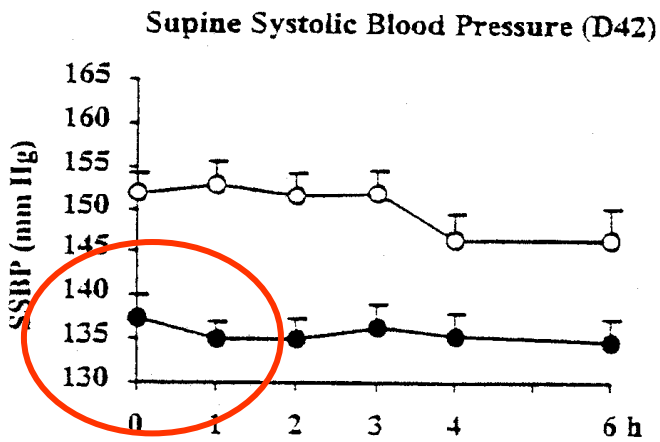




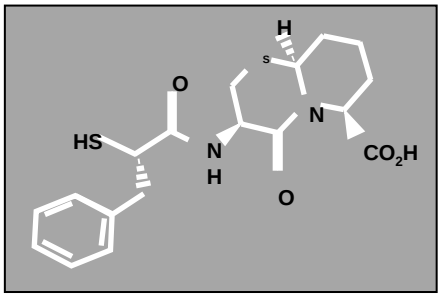
Day 0

Day 42

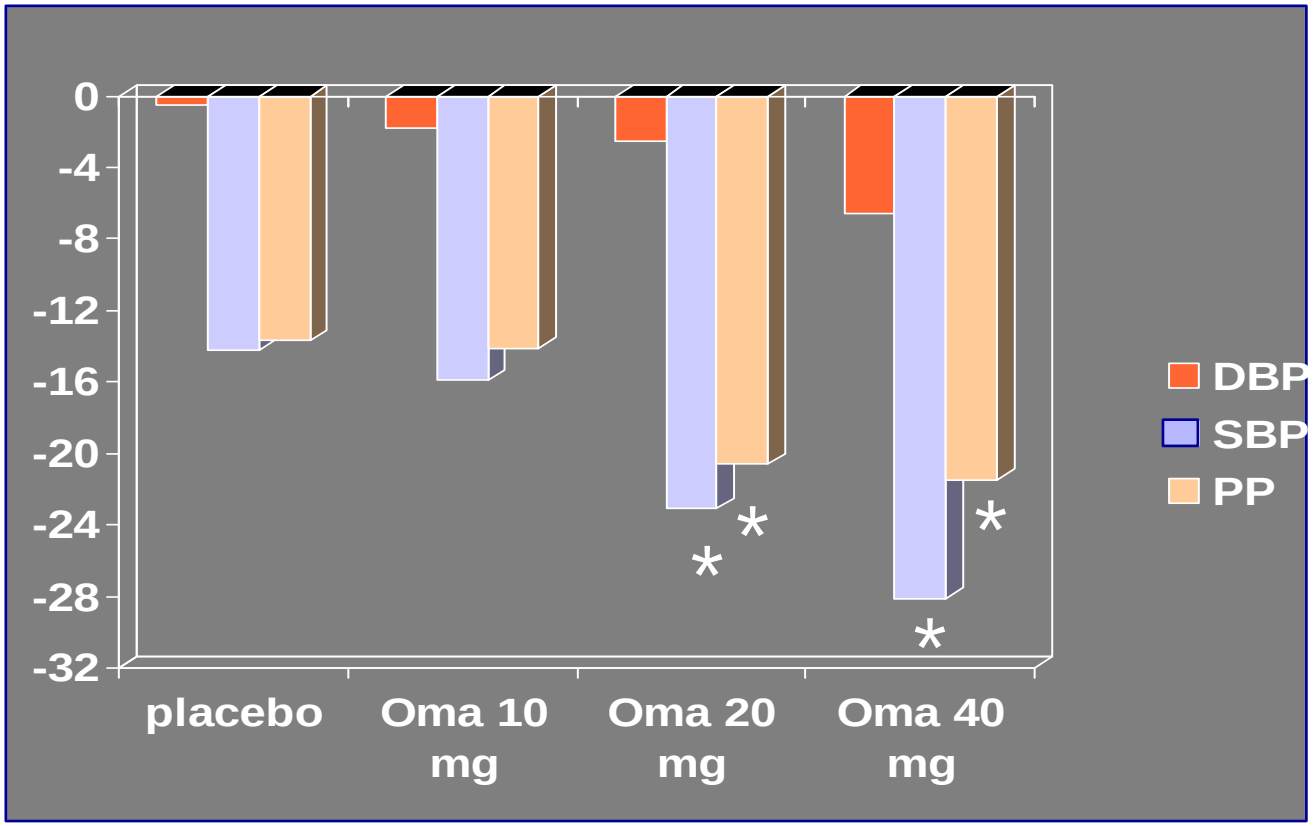




Omapatrilat



- **Dual NEP/ACE inhibitor**
  ACE K_i = 6 nM
  NEP K_i = 9 nM
- **Orally active**
- **Antagonises the BP response**
  to Ang I in rats
- **Enhances the natriuretic effect of ANP in rats**
- **Lowers BP**
  in different animal models of hypertension independently of the renin status
- **Increases urine ANP concentrations in humans dose-dependently**



Changes in trough BP at week 9 (mmHg)

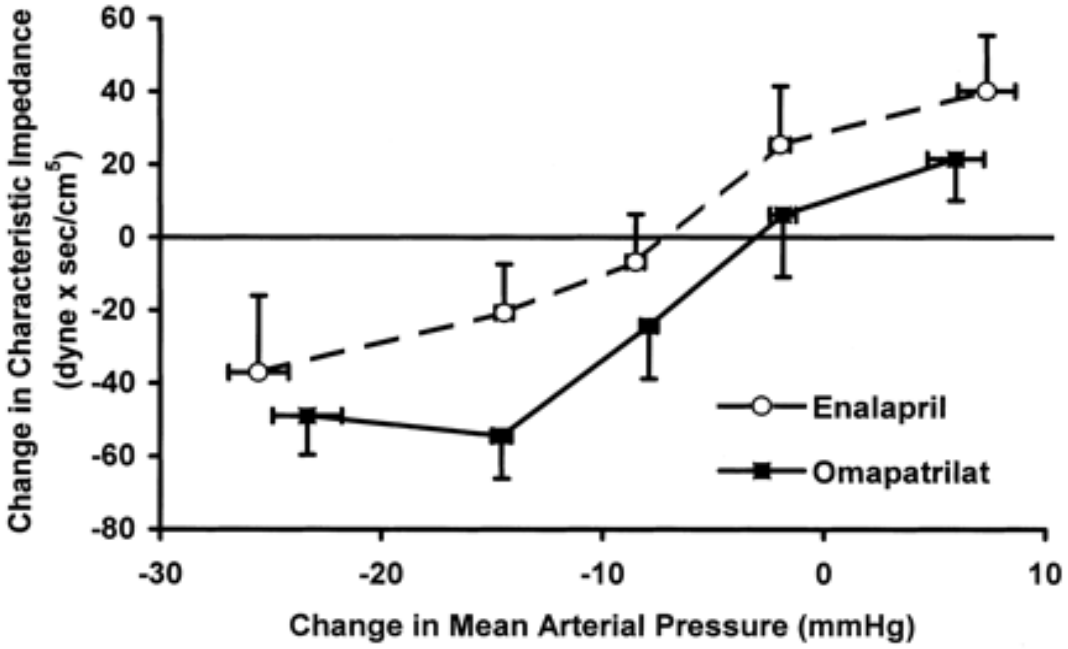
Larochelle et al. Am J Hypertens. 2003

Omapatrilat (dual NEP/ACE inhibitor) reduces central PP and proximal aortic stiffness in patients with ISH

Mitchell G et al. Circulation 2002

- **study design : 12 W, randomized, double- blind,**
- **parallel groups : enalapril 40 mg (n=87) or omapatrilat 80 mg (n=80)***
- **characteristic impedance :**

Δ carotid pressure / Δ aortic flow in early systole



Enalapril	11	16	18	20	22
Omapatrilat	24	18	19	11	8
Total	35	34	37	31	30

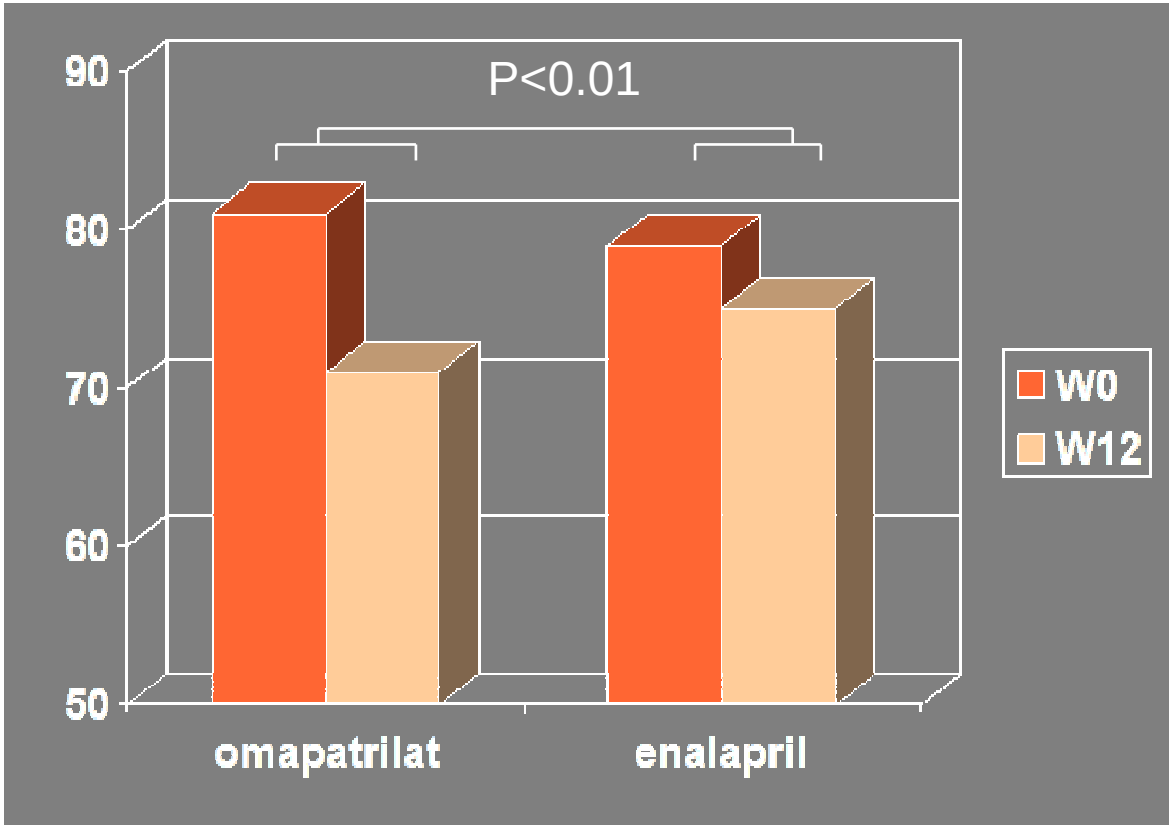
Omapatrilat (dual NEP/ACE inhibitor) reduces central PP and proximal aortic stiffness in patients with ISH

Mitchell G et al. Circulation 2002

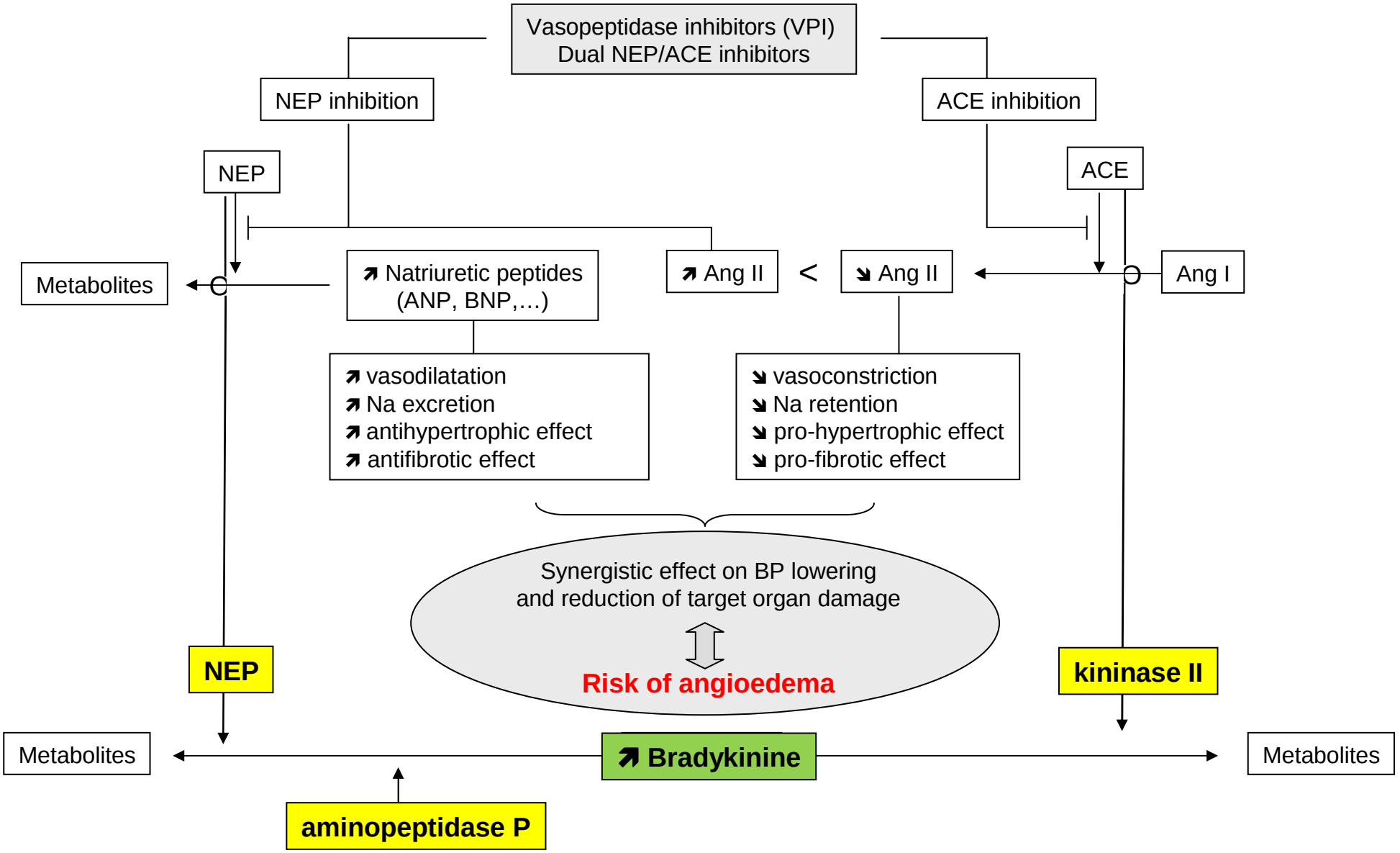
- **study design : 12 W, randomized, double- blind,**
- **parallel groups : enalapril 40 mg (n=87) or omapatrilat 80 mg (n=80)***
- **characteristic impedance :**

Δ carotid pressure / Δ aortic flow in early systole

Central pulse pressure (mmHg)



Dual NEP/ACE inhibitors



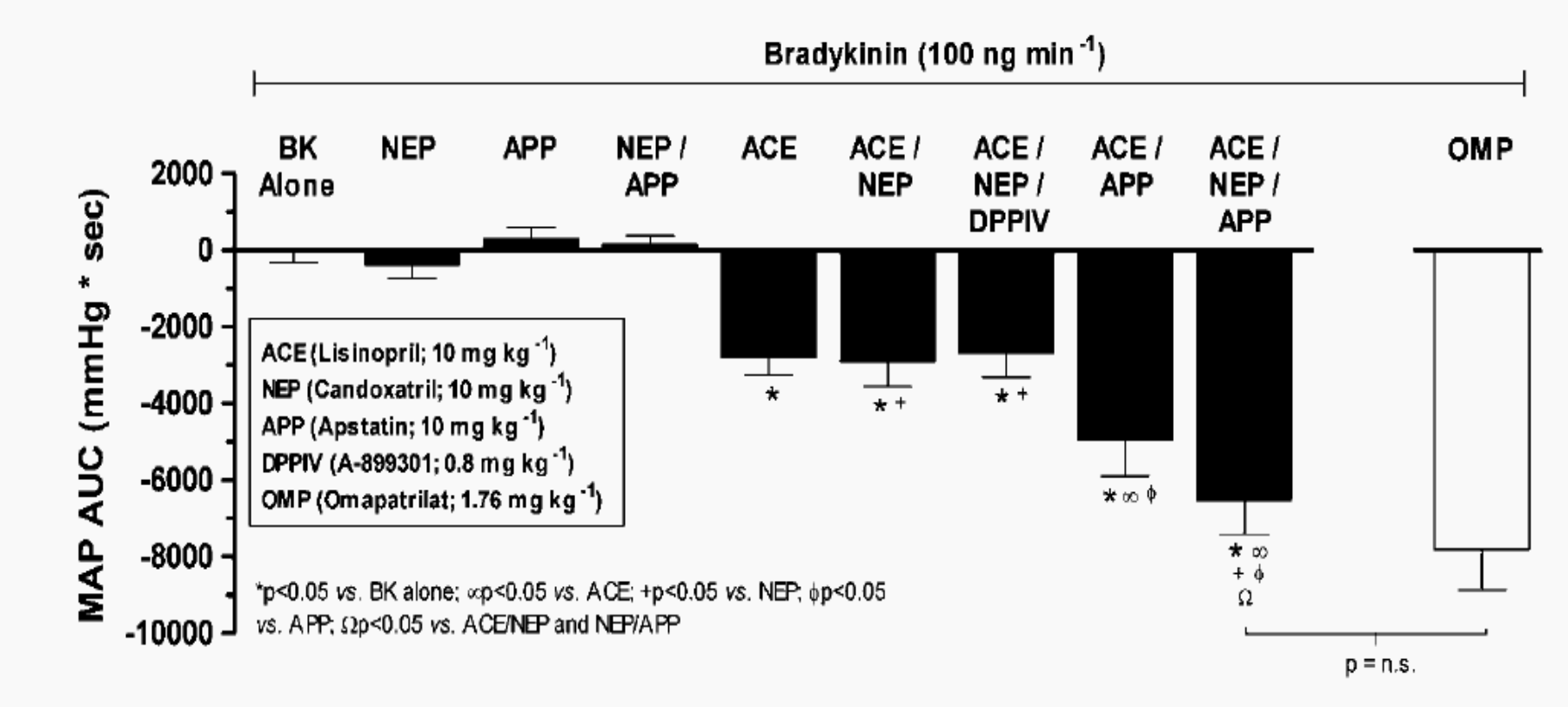
OCTAVE: Severity of angioedema

Kostis JB et al. . Am J Hypertens. 2004

	Omapatrilat (n=12,609)	Enalapril (n=12,557)	Absolute difference
No treatment, or treated with antihistamines only	162 (1.28%)	65 (0.52%)	0.76%
Treated with epinephrine or steroids; no airway compromise	110 (0.87%)	21 (0.17%)	0.71%
Airway compromise	2	0	_
TOTAL	274	86	_

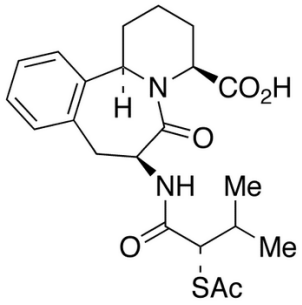
The effects of omapatrilat on BP are mediated by inhibition of three bradykinin metabolizing enzymes, ACE/APP/NEP, in rats

Fryer RM. BJP 2008; 153: 947



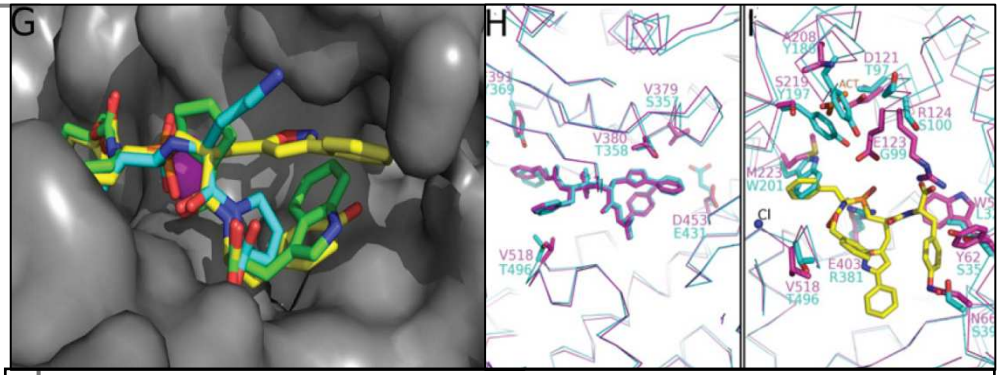
Inhibitors were infused for 35 min and BK was infused during the last 5 min to elicit hypotension
MAP AUC was recorded during the last 5 min of the BK infusion

In vitro inhibitory effects of AVE 7688 (Ilepatril) and omapatrilat on ACE and NEP



Ilepatril, AVE 7688

AVE 7688	**IC50 ACE**	**0.052 nM**
	IC 50 NEP	5 nM
	ratio ACE/NEP	**0.01**
Omapatrilat	Ki ACE	6 nM
	Ki NEP	8.9 nM
	ratio ACE/NEP	0.67



IC50
human aminopeptidase P (APP)

AVE7688 (AVE8048)	**6 100 000 nM**
Omapatrilat	**66 nM**
M100240 (MDL100,173)	**18 000 nM**
Apstatin (a specific APP inhibitor)	**2 300 nM**

Adam et al., 2004

New drugs for hypertension (I)

Pharmacological class		Drug	Pre-clinical stage	Phase I-III	Pharmaceutical industry
Dual vasopeptidase inhibitor					
1. Dual NEP/ACE inhibitor		Ilepatril – AVE7688		Phase III	Sanofi-Aventis
2. Dual NEP/ECE inhibitor		Daglutril- SLV306		Phase II	Solvay Pharmaceuticals
Dual ARNI		LCZ696		Phase III	Novartis Pharmaceuticals
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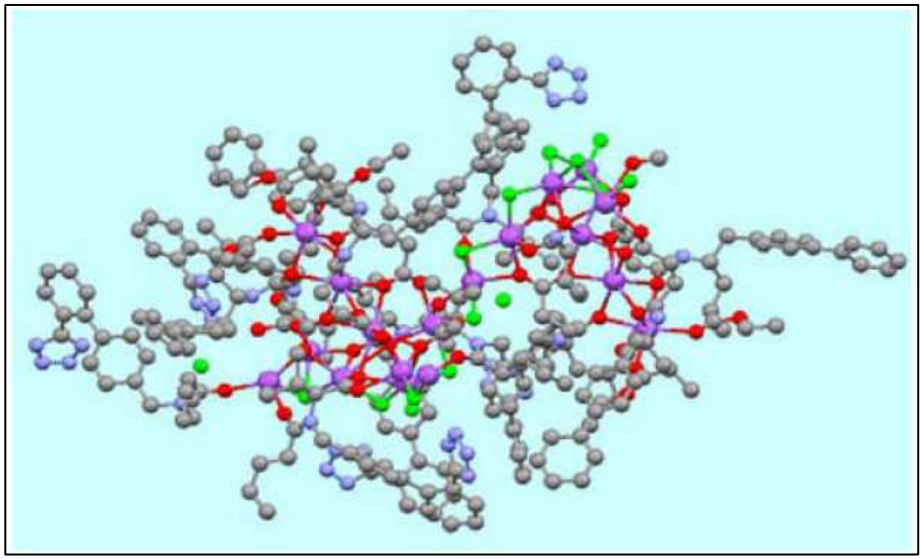
		Darusentan		Phase III *	Gilead Sciences
NO donor	NO-releasing drugs	Nitrosyl-cobinamide	❐		
	NO-relasing hybrids	NO-losartan NO-telmisartan	❐ ❐		Cayman Chemicals
	CINOD	Naproxcinod		Phase III	NicOx

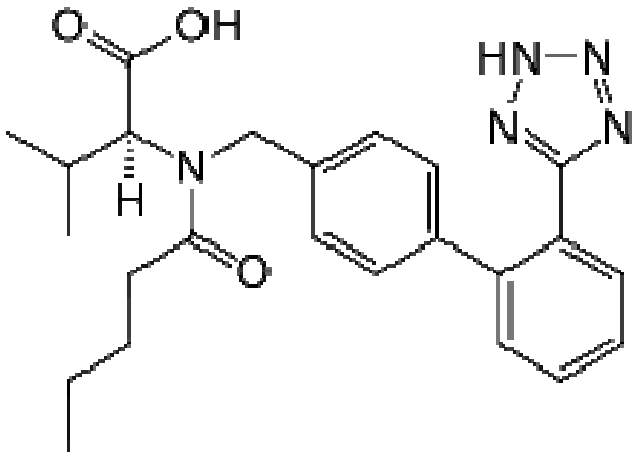
* Development stopped

LCZ696: a dual-acting inhibitor of the angiotensin II receptor and neprilysin (dual ARNi)

Gu J et al. J Clin Pharmacol, 2010

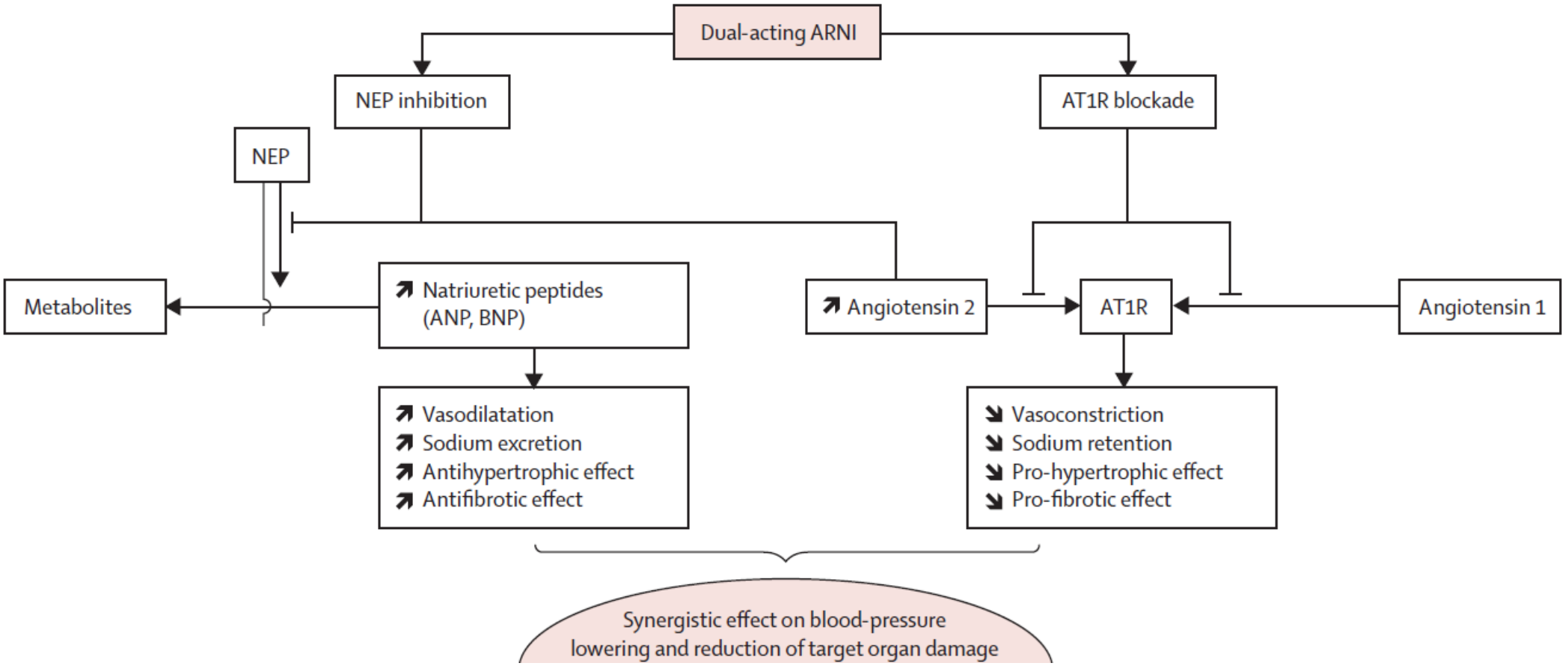
Single molecule in which the molecular moieties of valsartan and the molecular moieties of the NEP inhibitor prodrug AHU377 are present in a 1:1 molar ratio.





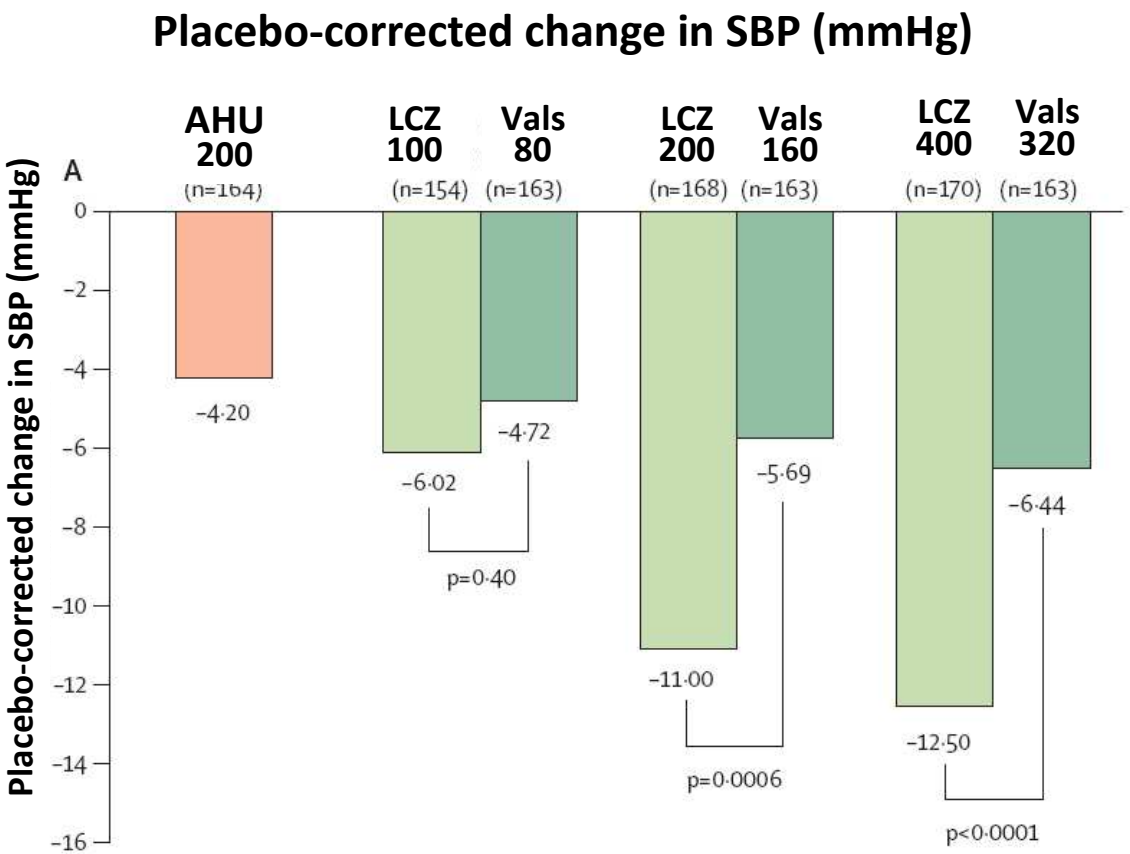
Valsartan + AHU377

Dual ARNi: the increase in circulating natriuretic peptides can mimic the effects of nitrates and diuretics on large arteries



Effects of AHU377 and LCZ696 on SBP in 1085 mild to moderate hypertensive patients

Ruilope LM et al. Lancet 2010



Dual ARNi vs dual NEP/ACE inhibitors
Less increase in BK → less risk of angioedema

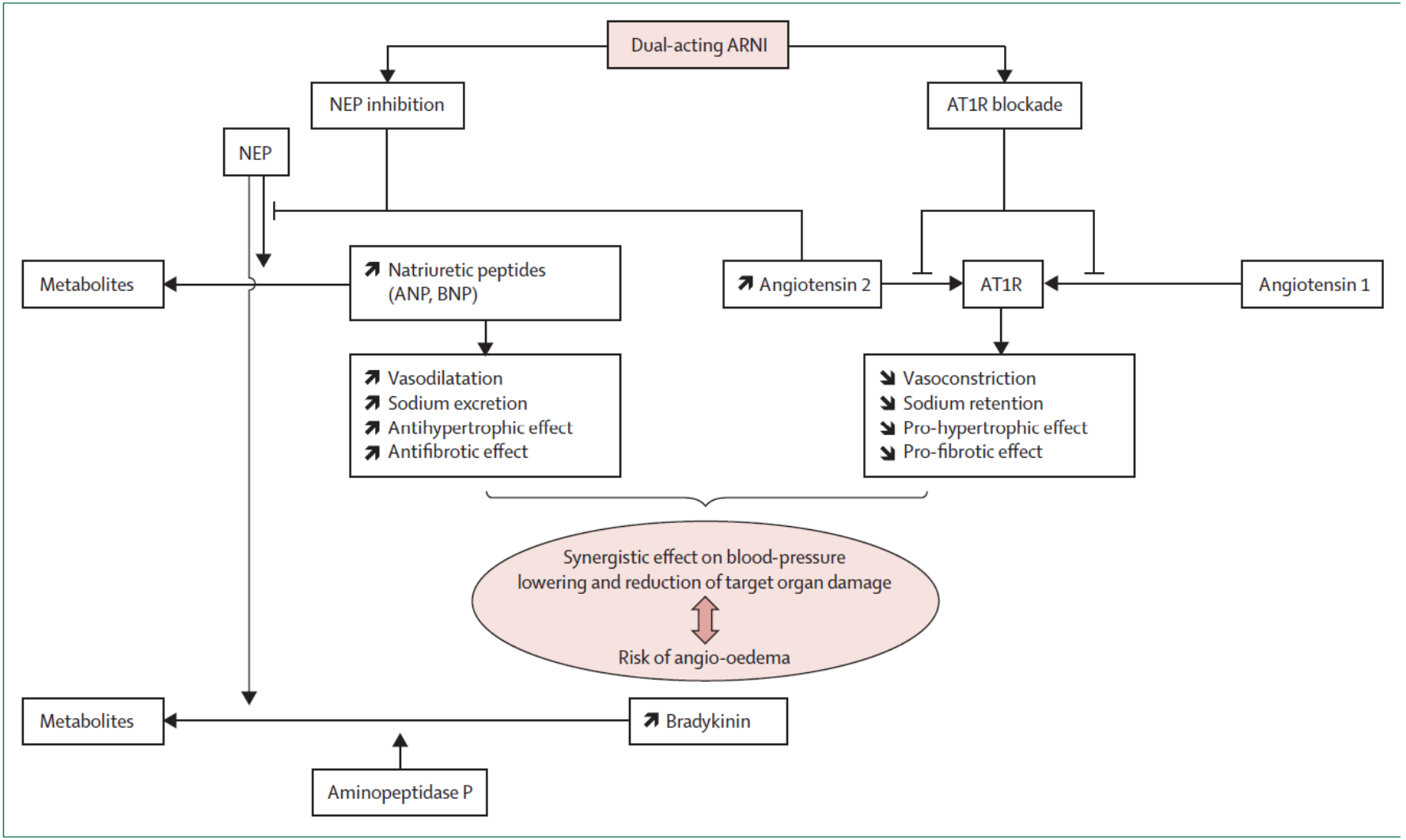


Figure 3: Dual-acting ARNI

Safety of AHU377 and LCZ696 in 1085 mild to moderate hypertensive patients

Ruilope LM et al. Lancet 2010

	Pbo	AHU377	LCZ696 100 mg	LCZ696 200 mg	LCZ696 400 mg	Vals. 80 mg	Vals. 160 mg	Vals. 320 mg
Any AE	**49 (28%)**	**45 (27%)**	**36 (23%)**	**40 (24%)**	**50 (29%)**	**36 (22%)**	**34 (20%)**	**38 (23%)**
Diarrhoea	3 (2%)	3 (2%)	2 (1%)	0	5 (3%)	1 (1%)	1 (1%)	3 (2%)
Back pain	2 (1%)	3 (2%)	1 (1%)	1 (1%)	4 (2%)	3 (2%)	1 (1%)	1 (1%)
Bronchitis	4 (2%)	2 (1%)	1 (1%)	0	4 (2%)	3 (2%)	4 (2%)	1 (1%)
Cough	2 (1%)	2 (1%)	1 (1%)	2 (1%)	4 (2%)	2 (1%)	0	1 (1%)
Dizziness	2 (1%)	0	1 (1%)	1 (1%)	1 (1%)	0	1 (1%)	3 (2%)
Dyspepsia	0	0	1 (1%)	0	3 (2%)	1 (1%)	0	0
Headache	13 (8%)	5 (3%)	4 (3%)	4 (2%)	4 (2%)	5 (3%)	4 (2%)	3 (2%)
Influenza	3 (2%)	1 (1%)	3 (2%)	2 (1%)	3 (2%)	2 (1%)	1 (1%)	4 (2%)
Nasopharyngitis	3 (2%)	3 (2%)	5 (3%)	2 (1%)	2 (1%)	3 (2%)	2 (1%)	2 (1%)
Pruritus	0	2 (1%)	0	4 (2%)	1 (1%)	2 (1%)	0	0
Pharyngitis	4 (2%)	1 (1%)	2 (1%)	1 (1%)	0	0	0	1 (1%)
Sinusitis	2 (1%)	2 (1%)	3 (2%)	0	1 (1%)	2 (1%)	1 (1%)	2 (1%)
URTI	0	2 (1%)	2 (1%)	0	1 (1%)	2 (1%)	3 (2%)	2 (1%)
GI	0	1 (1%)	0	1 (1%)	3 (2%)	1 (1%)	1 (1%)	1 (1%)

No episode of angioedema

New drugs for hypertension (I)

Pharmacological class		Drug	Pre-clinical stage	Phase I-III	Pharmaceutical industry
Dual vasopeptidase inhibitor					
1. Dual NEP/ACE inhibitor		Ilepatril – AVE7688		Phase III	Sanofi-Aventis
2. Dual NEP/ECE inhibitor		Daglutril- SLV306		Phase II	Solvay Pharmaceuticals
Dual ARNI		LCZ696		Phase III	Novartis Pharmaceuticals
Aldosterone synthase inhibitor		LCI699		Phase II *	Novartis Pharmaceuticals
Endothelin antagonist		Bosentan		Phase II*	Actelion Pharmaceuticals
		Darusentan		Phase III *	Gilead Sciences
NO donor	NO-releasing drugs	Nitrosyl-cobinamide	❒		
	NO-relasing hybrids	NO-losartan NO-telmisartan	❒ ❒		Cayman Chemicals
	CINOD	Naproxcinod		Phase III	NicOx

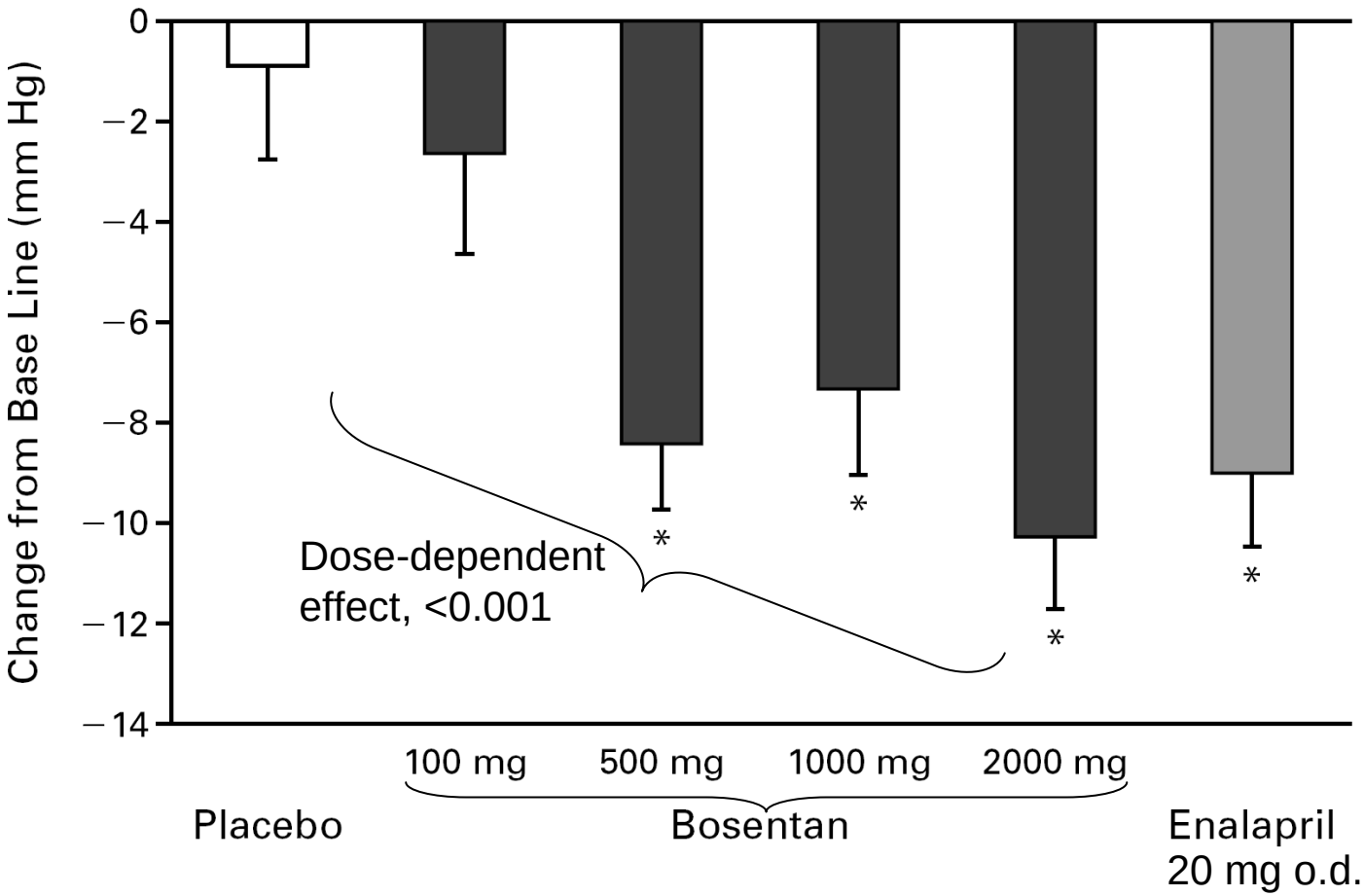
* Development stopped

Endothelin antagonists

Dual ET_A-ET_B antagonists	**Clinical trials (pulmonary HT, systemic HT, CHF)**
Avosentan	
Bosentan	BREATH-1,4, ENABLE, REACH-1,2, RAPIDS-1, ASSET-1,2, BENEFIT, BUILD, COMBI, COMPASS, EARLY
Enrasantan	ENCOR
Tezosentan	RITZ-1,5, VERITAS-1,2
Selective ET_A antagonists	
Ambrisentan	ARIES-2
Atrasentan	
Darusentan	EARTH, HEAT-CHF, HEAT-HTN, DAR-201, SHORT 311
Edonentan	
Sitaxsentan	STRIDE-1,6 and IX,IXC

Randomized double-blind 4W study: effects of Bosentan on SBP in 293 patients with essential hypertension

Krum H et al. NEJM 1998



Endothelin antagonists : indication

- Only one current indication : pulmonary hypertension
- Stopped: CHF, systemic HT
- Under development: diabetic nephropathy?

Endothelin antagonists : side effects

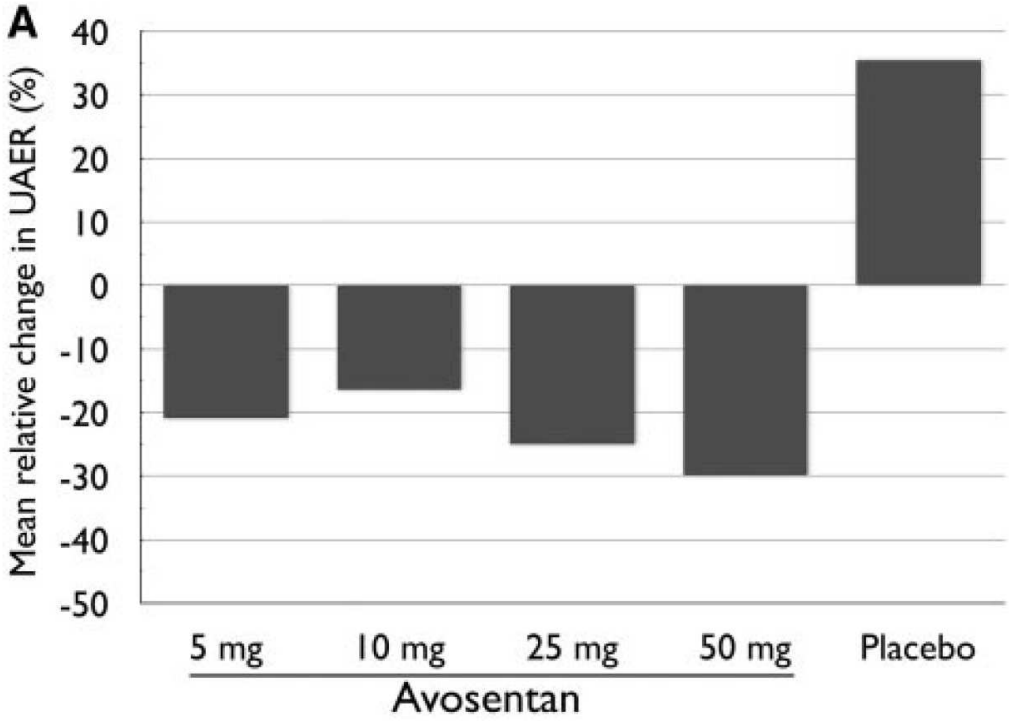
- Liver toxicity

  Discontinuation if transaminases x 3 upper level
- Fluid retention
- Anaemia
- Teratogenicity
- Male sexual dysfunction

Avosentan, a dual ET_A/ET_B antagonist, reduces albumin excretion in diabetics with macroalbuminuria

Wenzel RR et al. JASN 2009

n= 286
12 weeks



- ET-1 exaggerates proteinuria, and contributes to glomerular capillary hypertension and excessive protein filtration

- Renal inflammation and TGF-β production are ET_A- R mediated

- Experimental data for nephroprotection by ET_A antagonists

Despite no significant change in SBP

New drugs for hypertension (I)

Pharmacological class		Drug	Pre-clinical stage	Phase I-III	Pharmaceutical industry
Dual vasopeptidase inhibitor					
1. Dual NEP/ACE inhibitor		Ilepatril – AVE7688		Phase III	Sanofi-Aventis
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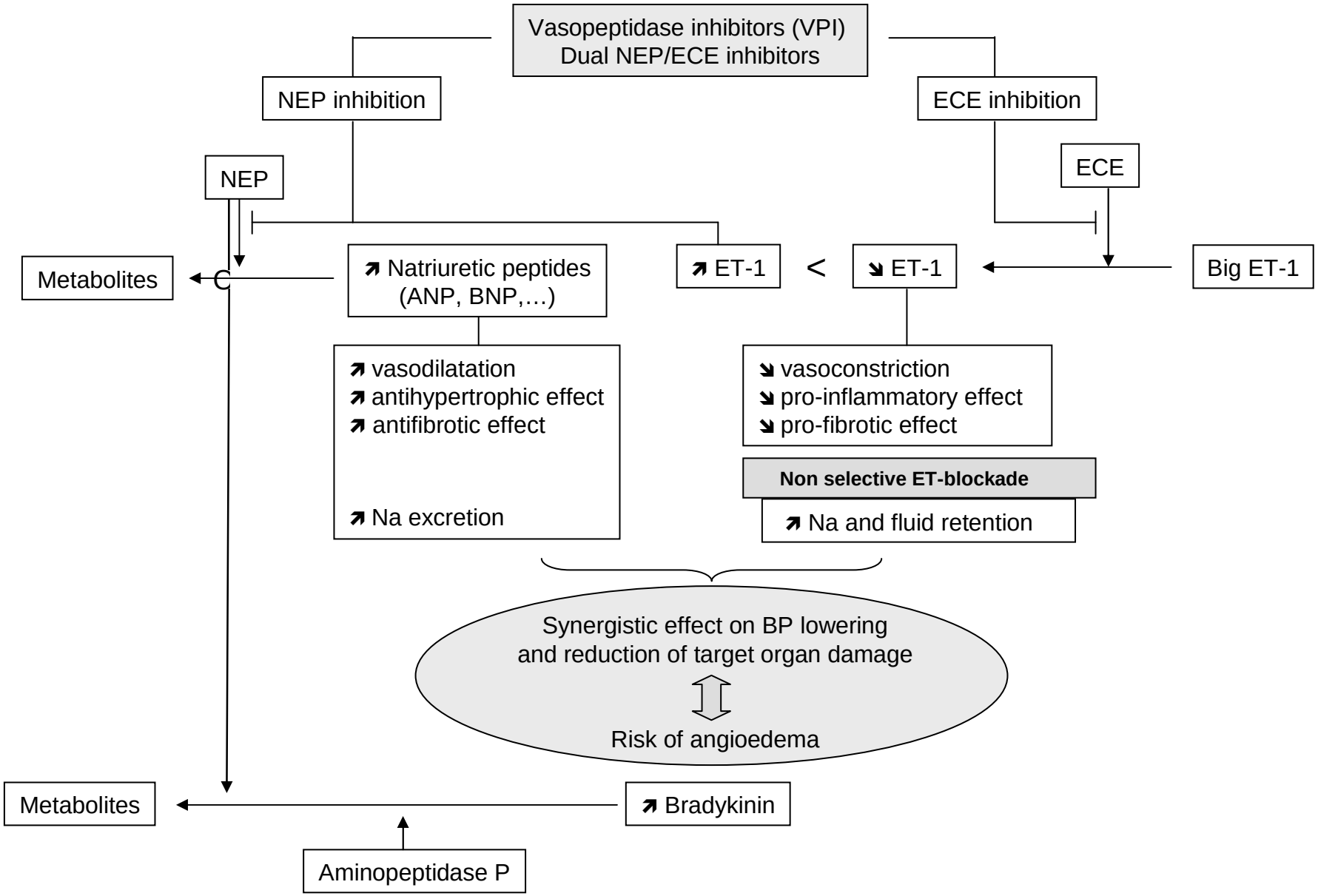
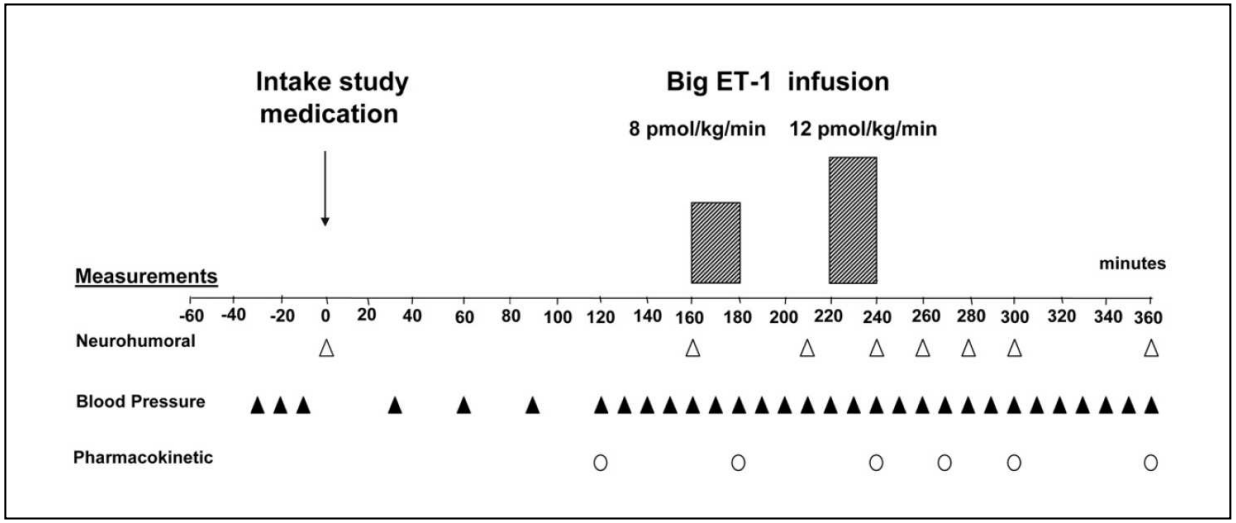
		Darusentan		Phase III *	Gilead Sciences
NO donor	NO-releasing drugs	Nitrosyl-cobinamide	❐		
	NO-relasing hybrids	NO-losartan NO-telmisartan	❐ ❐		Cayman Chemicals
	CINOD	Naproxcinod		Phase III	NicOx

* Development stopped

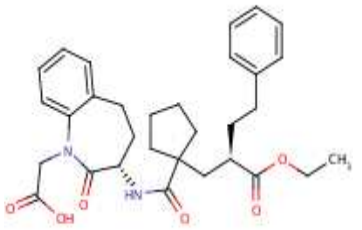
Dual NEP / ECE inhibitors



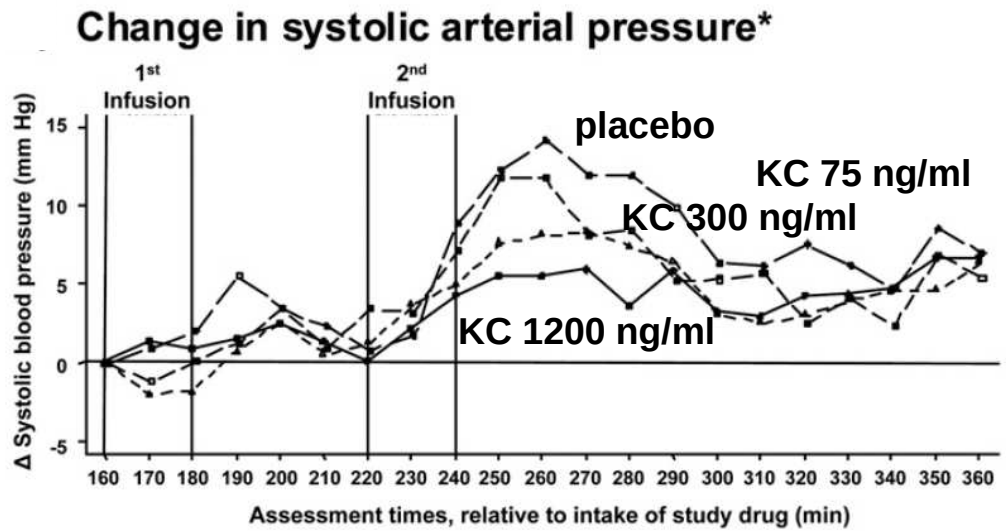
SLV-306 (daglutril), a dual NEP/ECE inhibitor, inhibits systemic conversion of big endothelin-1 in humans

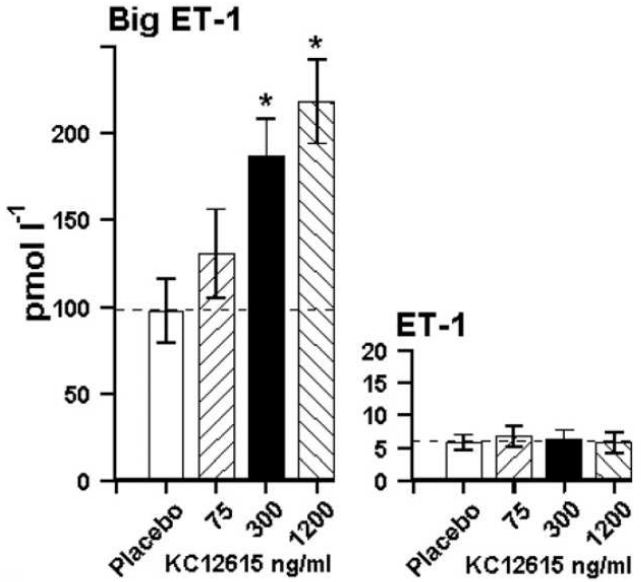


Seeds A et al. Life Sci 2013



Daglutril, SLV 306





Treatment: KC-1200ng/ml KC-300ng/ml KC-75ng/ml placebo

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ds A et al. Life Sci 2013

www.clinical trial.gov

Effects of daglutril on albuminuria in T2D.
Results?

Randomized double blind cross-over trial

Background
- No superiority of dual ACEI/ARB
- Additional value of NEP/ACE inhibitor on top of ARB?

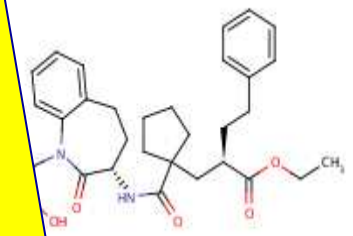
Intake study medication

Measuren

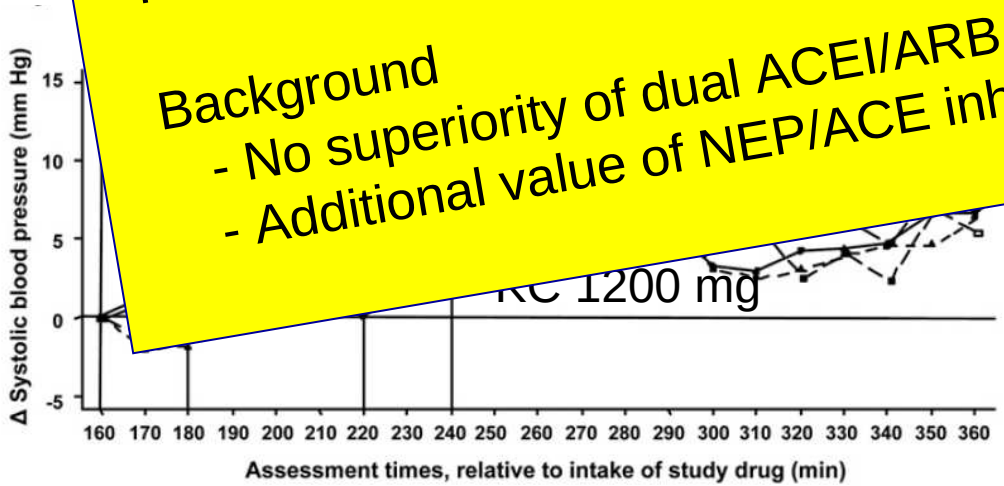
Neurohumor

Blood Pressu

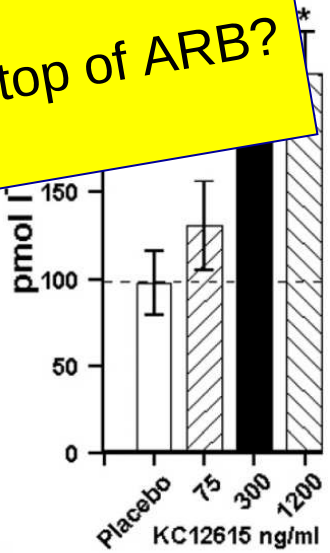
Pharmacokinet

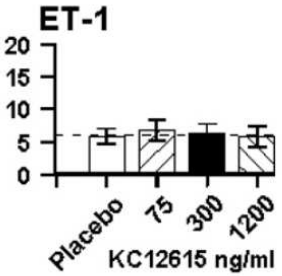


lutril, SLV 306



KC 1200 mg





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* Development stopped

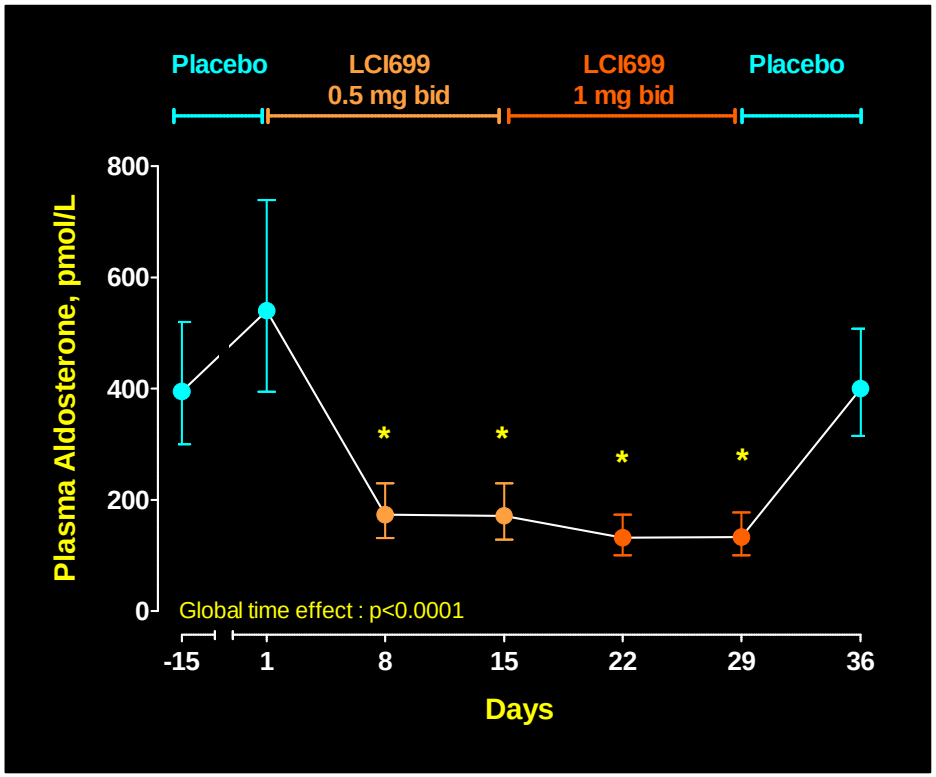
Aldosterone antagonists
i.e. mineralocorticoid receptor-blocking drugs

Spironolactone and eplerenone

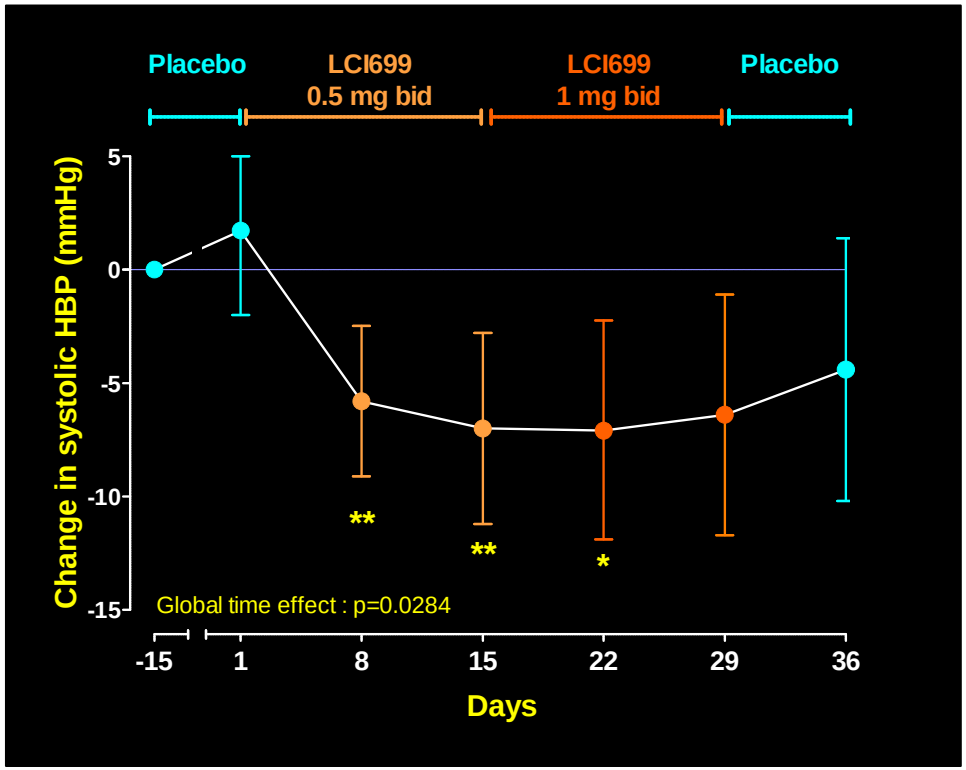
- Effective in patients with resistant hypertension
- 3 major side effects
  - Poor selectivity for MR (E>S) → side effects: gynecomastia (progesterone- and testosterone-dependent)
  - Reactive increase in plasma aldosterone, which could act through non genomic effect
  - Hyperkalemia (E<S)
- Alternative : inhibition of aldosterone synthase

The aldosterone synthase inhibitor LCI699 dose-dependently decreases plasma and aldosterone and home SBP in patients with primary aldosteronism

Amar L et al. Hypertension 2010



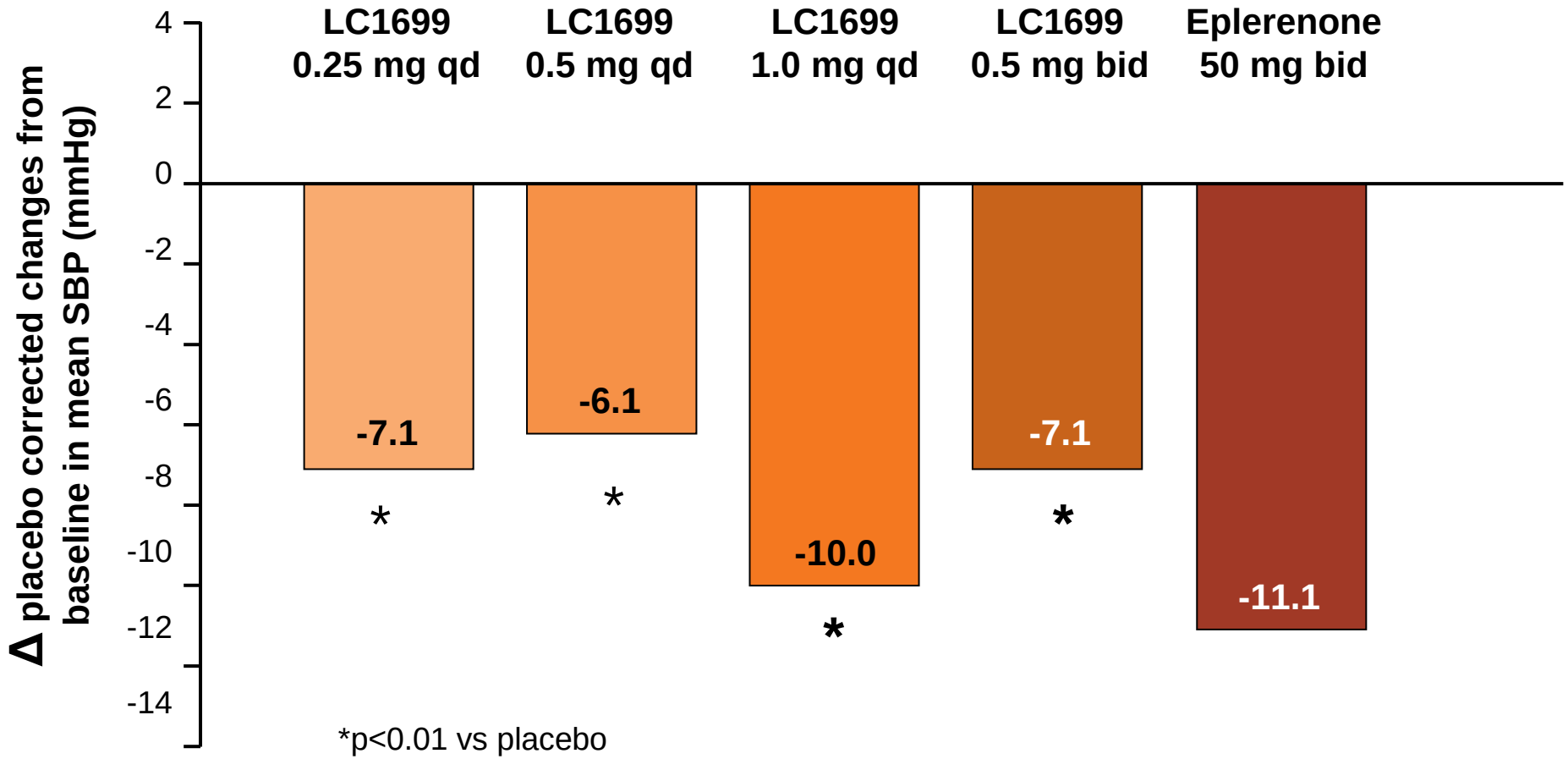
* adjusted P<0.0001 vs Day 1



** adjusted P<0.01 and * adjusted P<0.05 vs Day 1
Teletransmitted home BP

The aldosterone synthase inhibitor LCI699 reduces 24-hour mean ambulatory SBP at week 8, in patients with essential HT

Calhoun D et al. Circulation 2012

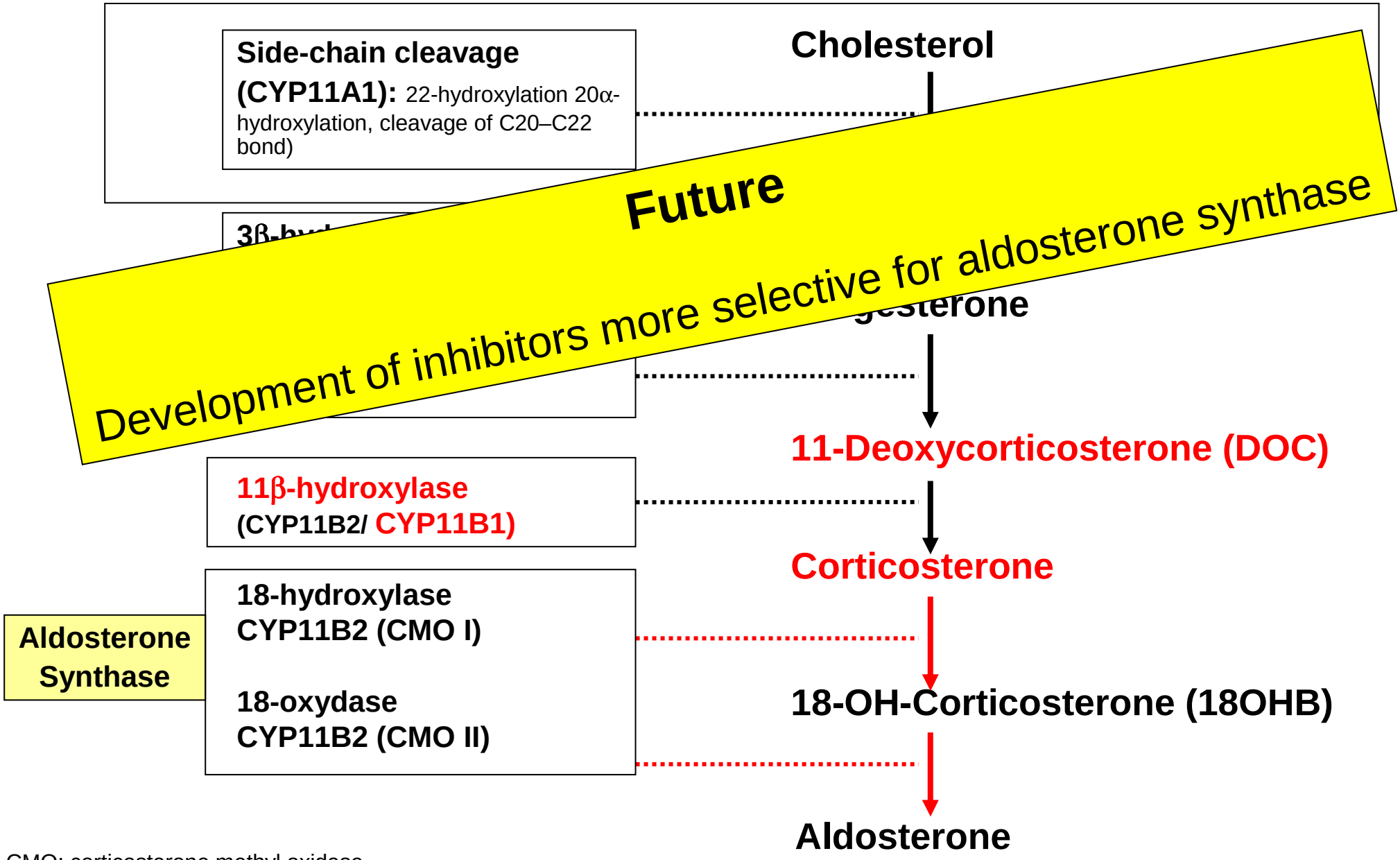


The aldosterone synthase inhibitor LCI699 reduces 24-hour mean ambulatory SBP at week 8, in patients with essential HT

Calhoun D et al. Circulation 2012

Phase 1 studies with LCI699 also showed no effect on baseline morning cortisol levels. Similar results were obtained in the present study. However, with the highest dose of LCI699 (1.0 mg either as a single dose or in divided doses), ≈20% of subjects had suppression of ACTH-induced cortisol release. This effect is likely attributable to partial inhibition of 11-β-hydroxylase (CYP11B1), the enzyme responsible for the final step in cortisol biosynthesis. The significance of the observed impaired ACTH-stress response is unknown.

Biosynthetic pathway to aldosterone (adrenal cortex)



CMO: corticosterone methyl oxidase

Additional novel drugs for hypertension

Pharmacological class		Drug	Pre-clinical stage	Phase I-III	Pharmaceutical industry
RERB (renin/prorenin blocker)			❒		
ACE2 activator			❒		
Aminopeptidase A (APA) inhibitor		QGC001	❒		Quantum Genomics Corp.
Vaccine	Ang I vaccine	PMD3117		Phase II	Protherics Inc.
	Ang II vaccine	Cyt006-AngQb		Phase II	Cytos Biotechnology AG
Dual AT1R/ETA antagonist (DARAs)		PS-433540		Phase II	Ligand Pharmaceuticals
Novel dual ARB/partial PPARγ agonist			❒		
AGE breaker		Alagebrium (ALT-711)		Phase II*	Synvista Therapeutics

* Development stopped

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Novel dual ARB/partial PPARγ agonist			❒		
AGE breaker		Alagebrium (ALT-711)		Phase II*	Synvista Therapeutics

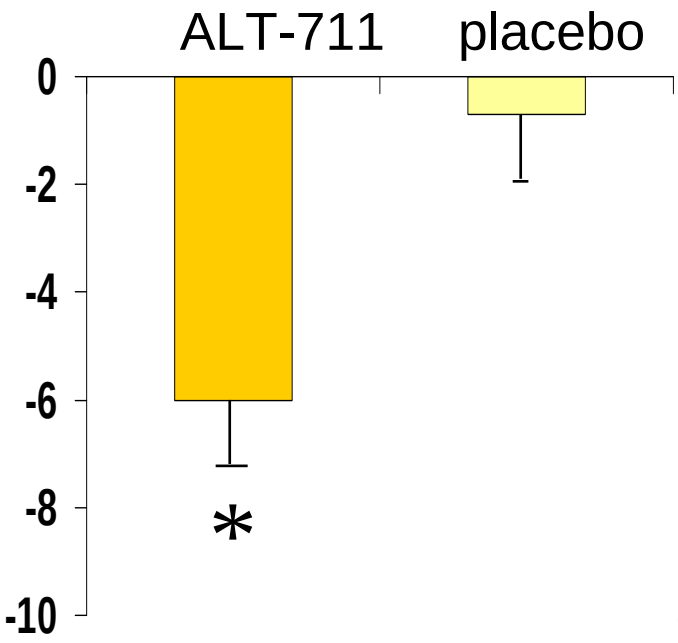
* Development stopped

Reduction of aortic stiffness by ALT-711 (alagebrium), an AGE cross-link breaker

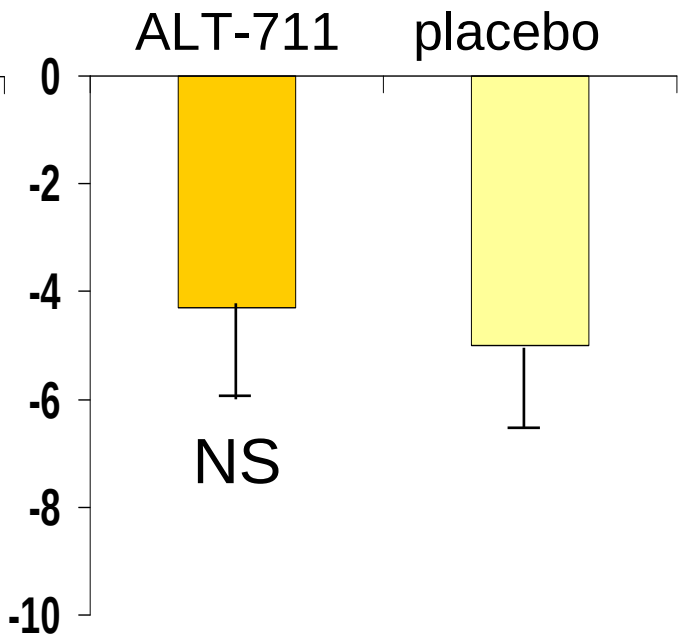
Kass DA et al., Circulation 2001

Borderline ISH : SBP > 140 mm Hg and PP > 60 mm Hg; 2 months TT
double-blind parallel groups, ALT-711 (n=62) vs placebo (n=31)

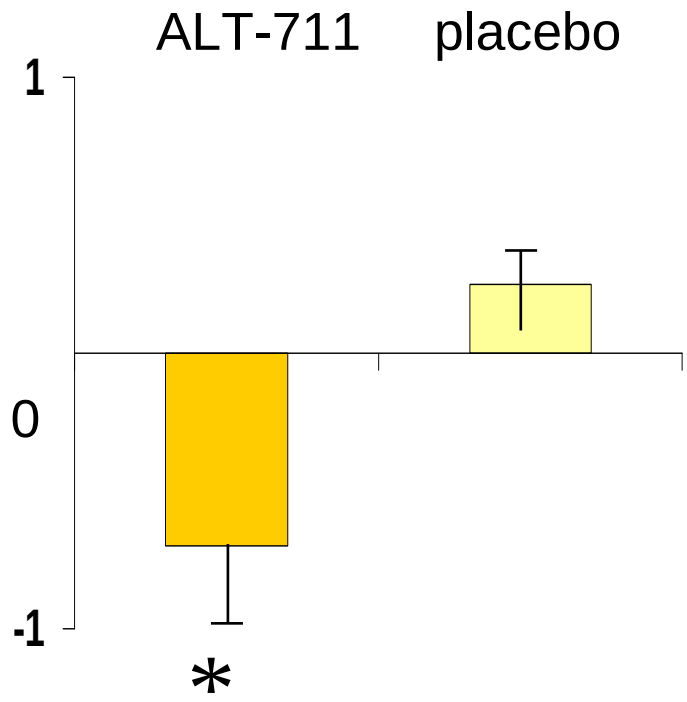
Change in PP (mmHg)



Change in MBP (mmHg)



Change in PWV (m/s)



AGE breakers and inhibitors under development

- **ALT-711 alagebrium, stopped in hypertension**

- **TRC 4186 (AGE breaker)**

  - Phase I, 250 - 1000 mg, 4 RCTs, 6 days

    -Chandra, Clin Drug Invest 2009

- **Aminoguanidine (pimagedine)**

  - **ACTION I**: RCT, n=690 vs placebo, T1D, 36 months.

    End-point: time to 2 x creatinine: **Not significant**

    eGFR p=0.05. Bolton, Am J Nephrol 2004

  - **ACTION II**: RCT, n=599 T2D. End-point: time x 2 creatinine. **Stopped**

    Freedman, Control Clin Trials 1999

- **Pyridoxamine**

  -Phase II, T1D+T2D, overt nephropathy, 24 weeks.

  End-point: significantly less increase in serum creatinin

  Williams, Am J Nephrol 2007

New drugs for hypertension: conclusion

- The pipeline is not dry….
- …but the development of promising novel drugs had been stopped
- Huge efforts have been made to synthesize novel molecules combining the beneficial effects of know pharmacological classes
- These efforts may not benefit to hypertensive patients …
- …but to patients suffering from other disease

Thank you !