Nouvelles molécules anti-hypertensives

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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
MENARINI
MSD
NEGMA
NOVARTIS
PFIZER
RECORDATI
SERVIER

Manufacturers

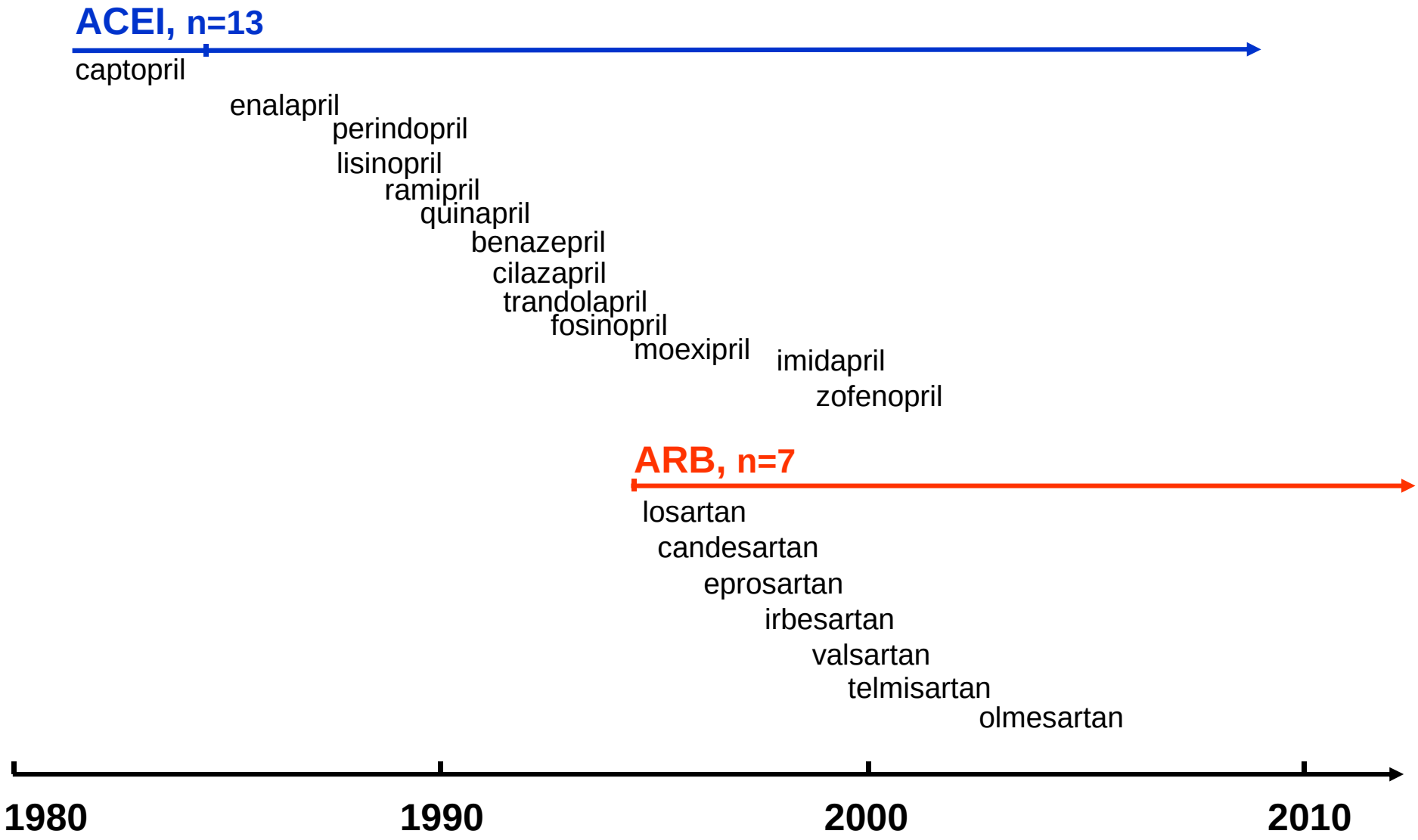
ALAM MEDICAL
ATCOR
AXELIFE
ESAOTE-PIE MEDICAL
FUKUDA-DENSHI
HEMO SAPIENS
OMRON
TENSIOMED

Rate of discovery of antihypertensive agents … a peak during the 1970's

Kotchen T. Hypertension 2011

Year(s)	Antihypertensive Agent(s)	
1900	Sodium thiocyanate	
1931	Reserpine	
1947–1950	Ganglion blocking drugs	
1958	Thiazide-type diuretics	
1950s	Hydralazine	
1950s	Guanethidine	
1957	Spironolactone	
1960	Methyldopa	
1973	β-Receptor blockers (eg, propranolol)	BB
1970s	Central α_2 agonists (eg, clonidine)	Centrally acting
1975	Peripheral α_1 receptor blockers (eg, prazosin)	$\alpha 1$ blockers
1977	ACE inhibitors (eg, captopril)	ACEI
1977	Calcium channel blockers (eg, verapamil, nifedipine)	CCB
1993	Angiotensin II receptor blockers (eg, losartan)	
2000	Renin inhibitors (eg, aliskiren)	

The 1980's and 1990's: two decades of novel ACEIs and ARBs



Date of market authorization in Europe

No novel anti-HT drug during the last 15 years…

…except aliskiren, a renin-inhibitor

Still using « old » antihypertensive agents

Kotchen T. Hypertension 2011

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1931	Reserpine	
1947–1950	Ganglion blocking drugs	
1958	Thiazide-type diuretics	Thiazides
1950s	Hydralazine	
1950s	Guanethidine	
1957	Spironolactone	Spironolactine
1960	Methyldopa	
1973	β-Receptor blockers (eg, propranolol)	BB
1970s	Central α_2 agonists (eg, clonidine)	
1975	Peripheral α_1 receptor blockers (eg, prazosin)	
1977	ACE inhibitors (eg, captopril)	
1977	Calcium channel blockers (eg, verapamil, nifedipine)	
1993	Angiotensin II receptor blockers (eg, losartan)	
2000	Renin inhibitors (eg, aliskiren)	

New vasodilators: the pipeline

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

New drugs for hypertension: most of them target the RAAS (I)

Laurent S et al. Lancet 2012

Pharmacological class		Drug	Pre-clinical stage	Phase I-III	Pharmaceutical industry
RERB (renin/prorenin blocker)			❒		
ACE2 activator			❒		
AT2-receptor agonist, non peptide		C21	❒	No anti-HT effect Tissue protection	Vicore Pharma
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 * Development stopped		Alagebrium (ALT-711)		Phase II*	Synvista Therapeutics

New drugs for hypertension: most of them target the RAAS (II)

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		Ilepatril – AVE7688		Phase III	Sanofi-Aventis
2. Dual NEP/ECE inhibitor		Daglutril- SLV306		Phase II*	Solvay Pharmaceuticals
Dual ARNI (Dual NEPI/ARB)		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

New drugs for hypertension (II)

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		Ilepatril – AVE7688		Phase III	Sanofi-Aventis
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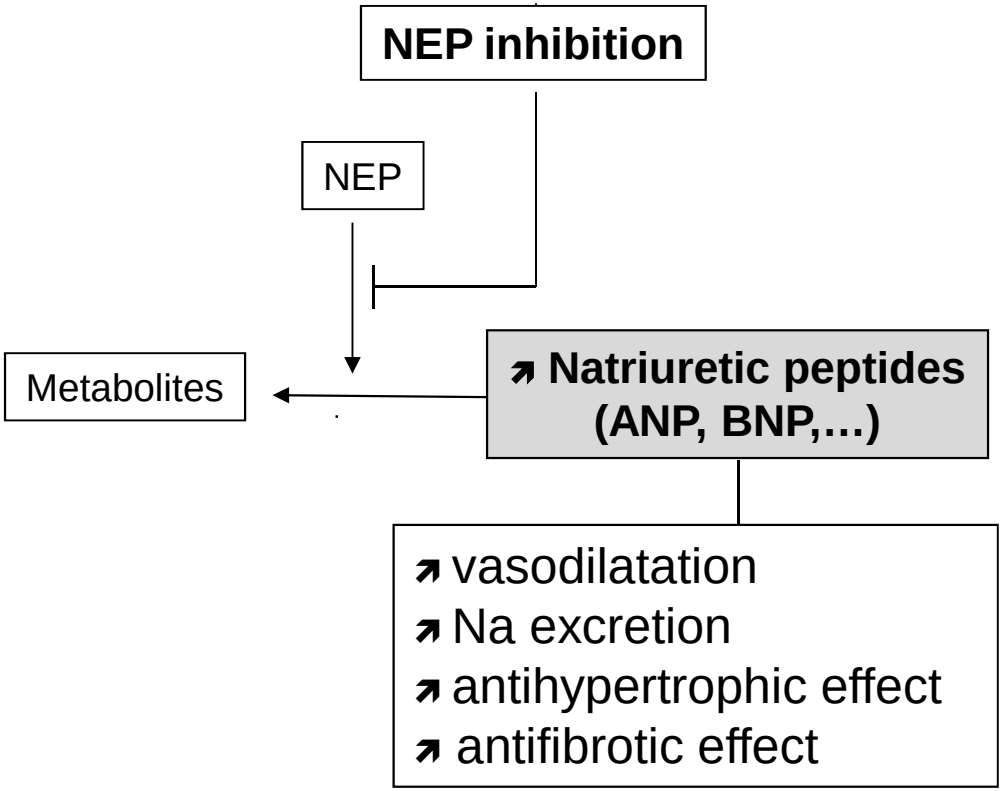
Endothelin antagonist		Bosentan		Phase II	Actelion Pharmaceuticals
		Darusentan		Phase III *	Gilead Sciences
NO donor	NO-releasing drugs	Nitrosyl-cobinamide	❒		
	NO-releasing hybrids	NO-losartan NO-telmisartan	❒ ❒		Cayman Chemicals
	CINOD	Naproxcinod		Phase III	NicOx

* Development stopped

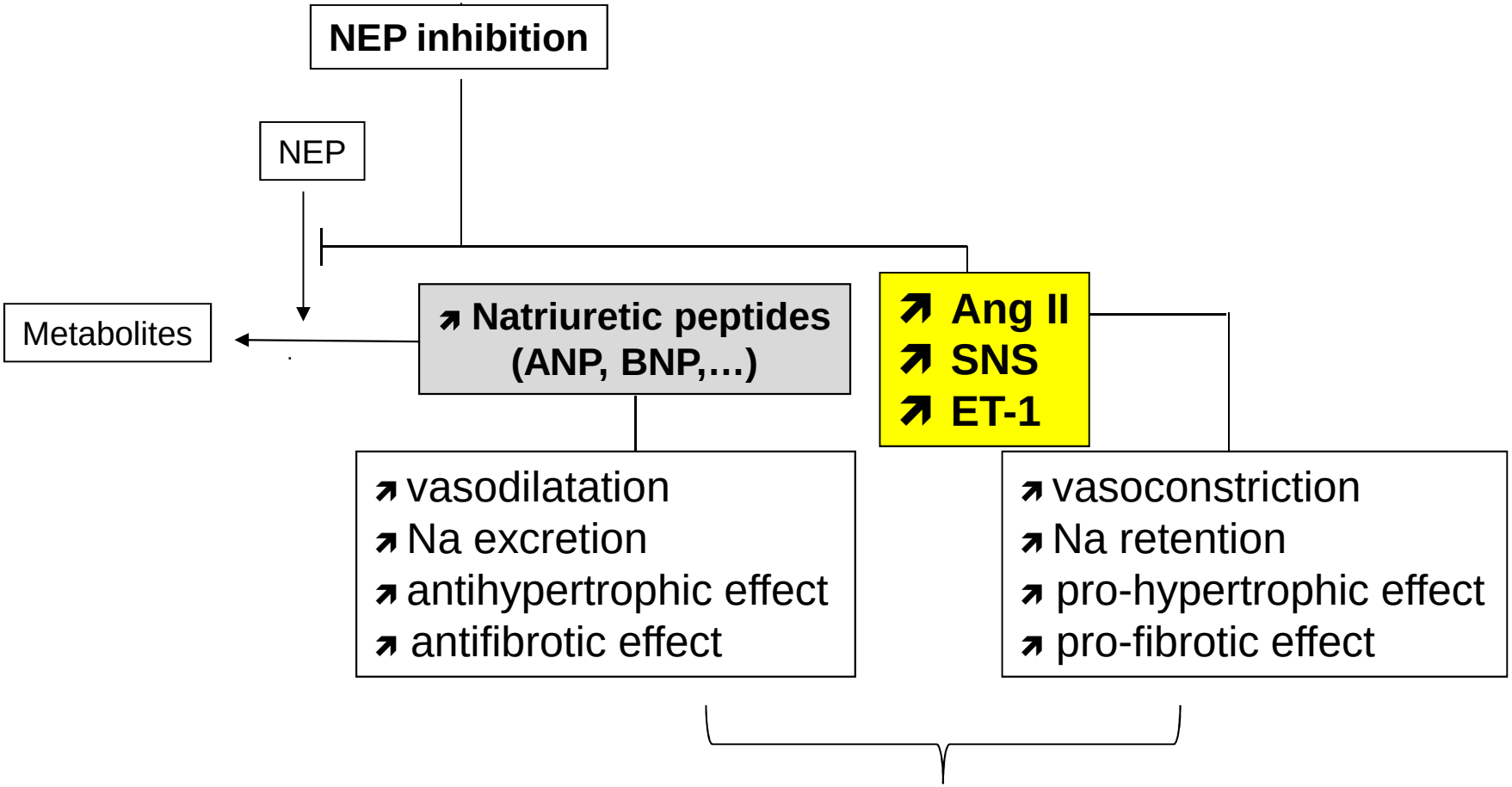
Pure and dual NEP inhibitors

Pure NEP inhibitors	
candoxatril	Pfizer
ecadotril	Bioprojet
thiorphan	Bioprojet

Counter-regulation with pure NEP inhibitors

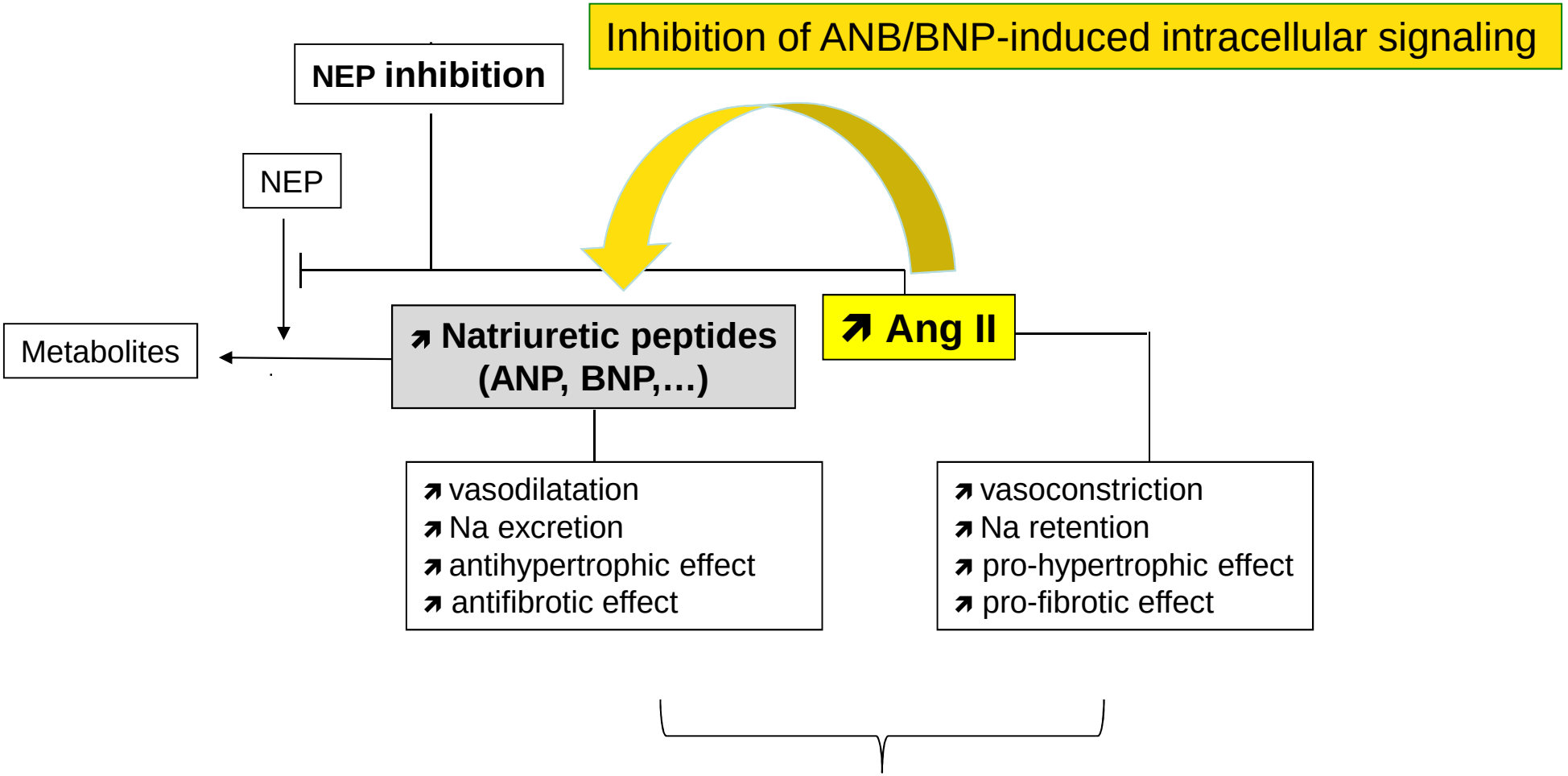


Counter-regulation with pure NEP inhibitors



Weak antihypertensive effect and protection of target organs

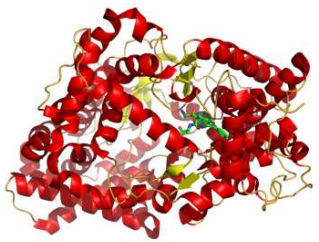
Counter-regulation with pure NEP inhibitors



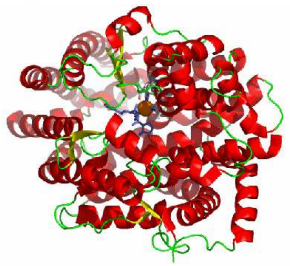
Weak antihypertensive effect and protection of target organs

Pure and dual NEP inhibitors

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

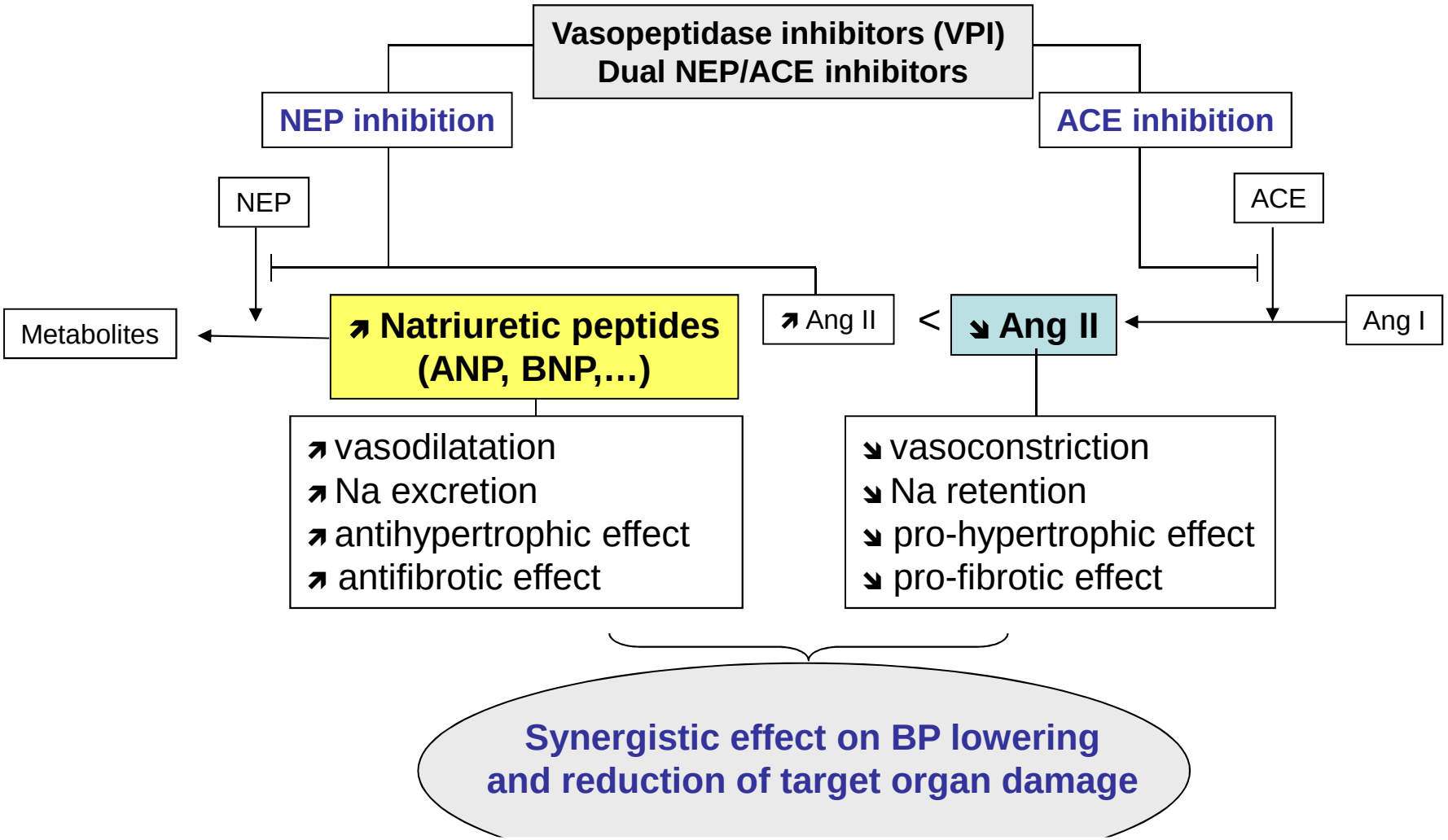


Neprilysin



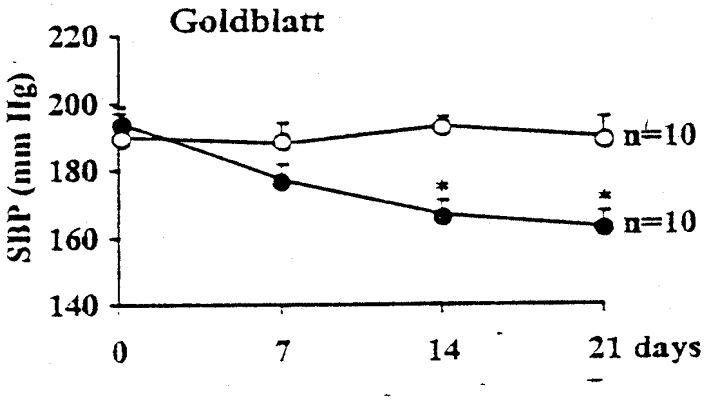
ACE

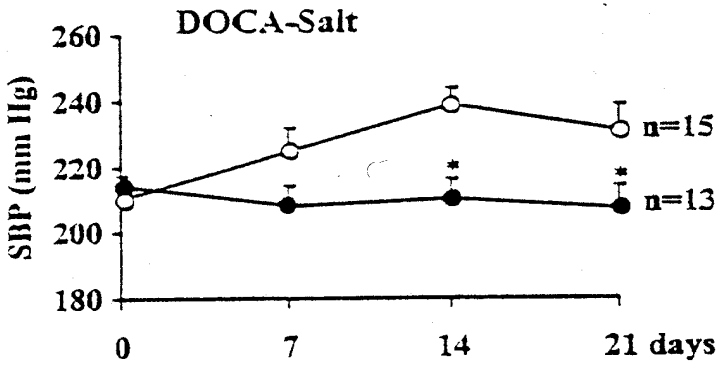
Dual NEP/ACE inhibitors



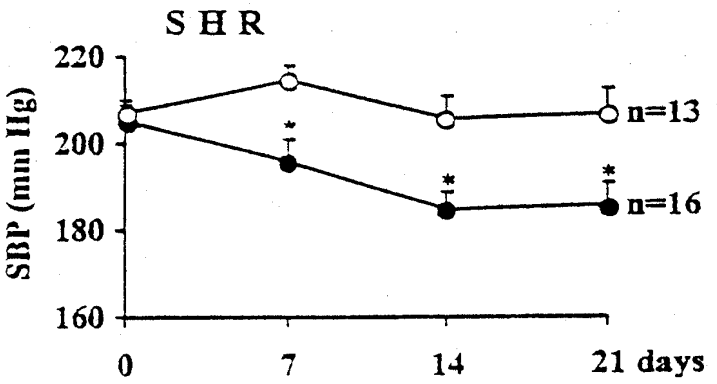
Antihypertensive effects of fasidotril in low- and high-renin hypertension in rat

Laurent S et al. Hypertension 2000



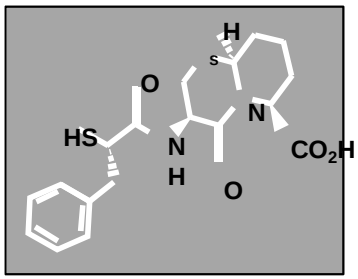


Model	*Hypertension*
Goldblatt 2K-1Clip	*renin-dependent*
DOCA-sel	*volume-dependent*
SHR	*renin > volume*



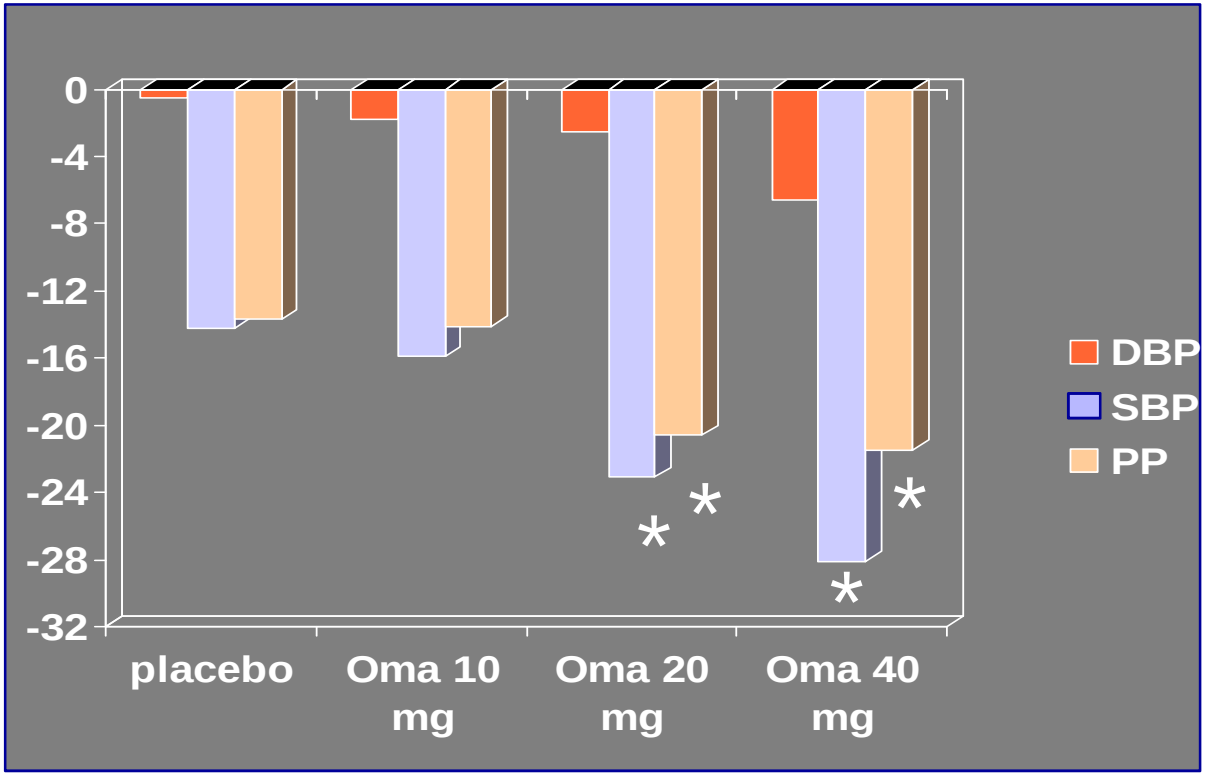
Omapatrilat

- Dual NEP/ACE inhibitor
  ACE K_i = 6 nM
  NEP K_i = 9 nM
- Orally active



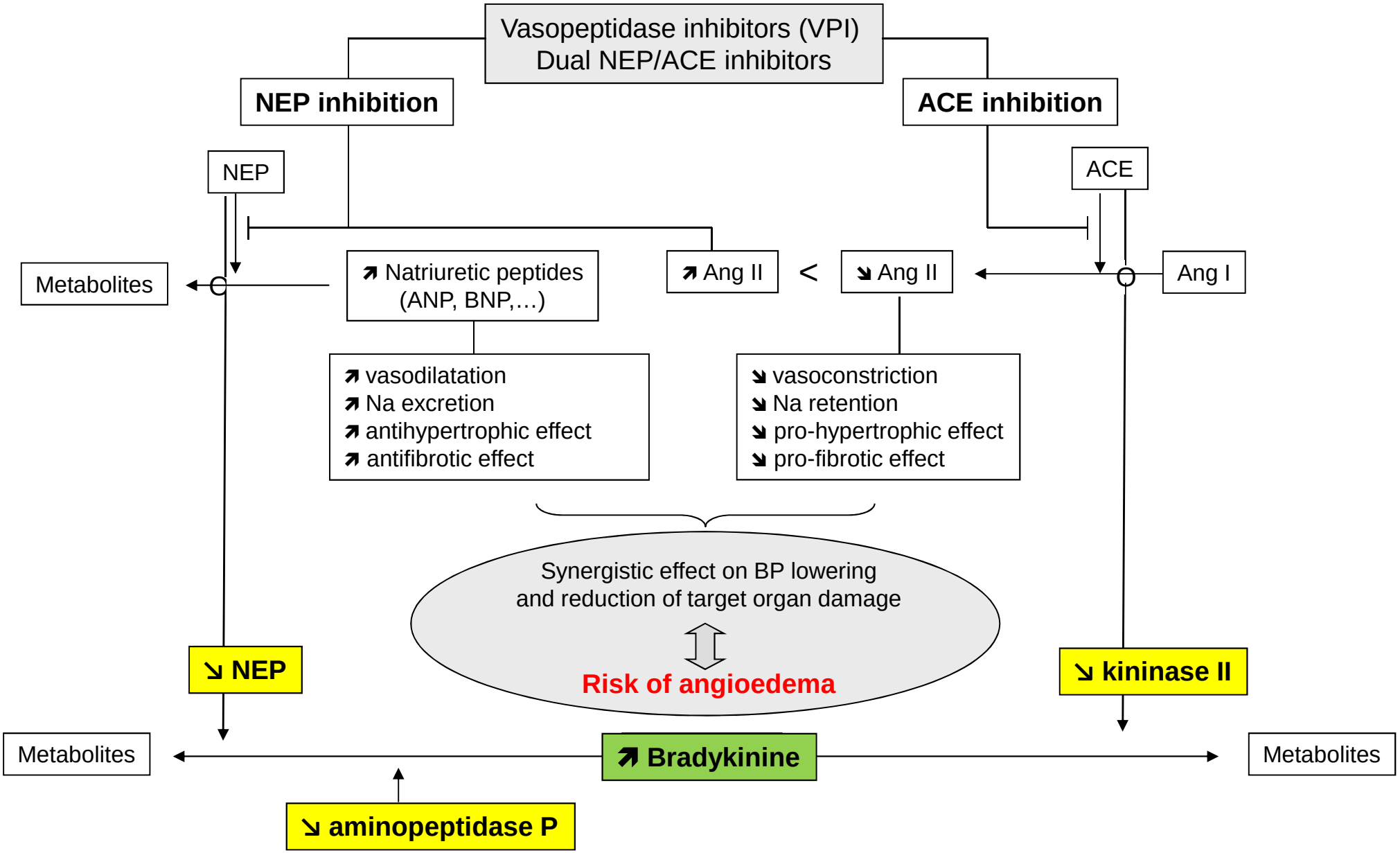
- Antagonises the BP response to Ang I in rats
- Enhances the natriuretic effect of ANP in rats
- Lowers BP in different animal models of hypertension independently of the renin status
- Increases urine ANP concentrations in humans dose-dependently

Larochelle et al. Am J Hypertens. 2003



Changes in trough BP at week 9 (mmHg)

Dual NEP/ACE inhibitors



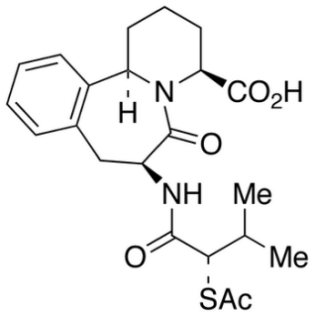
OCTAVE: Severity of angioedema

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**	_

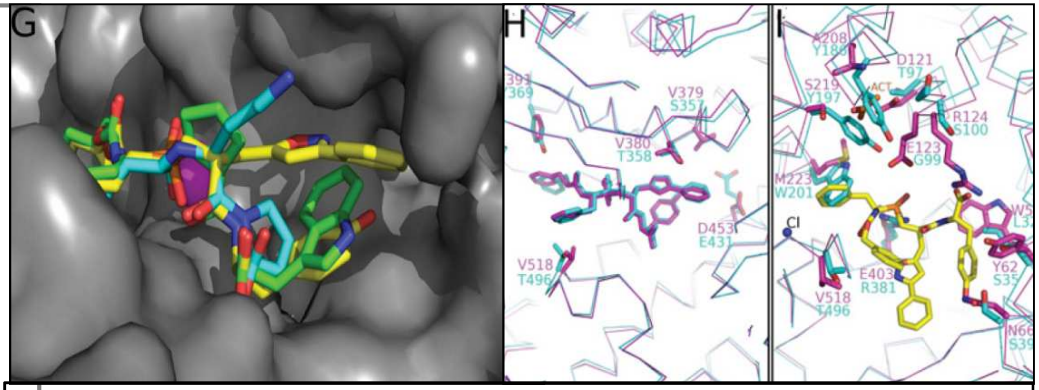
Double-blind, randomized, multicenter, parallel groups, 6 months

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



Ilepatril, AVE 7688

AVE 7688	**IC50 ACE**	**0.052 nM**
(Ilapatril)	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

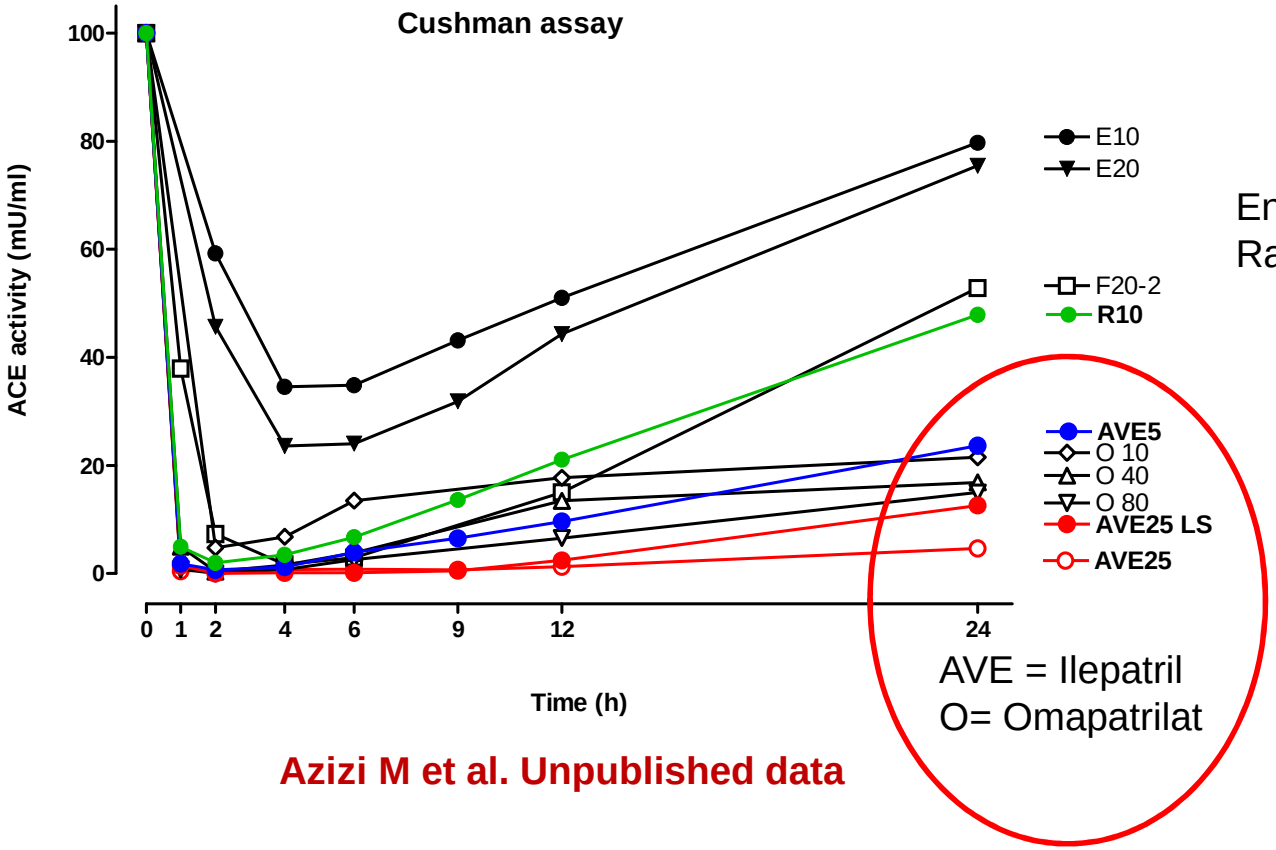


IC50
human aminopeptidase P (APP)

AVE 7688 (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

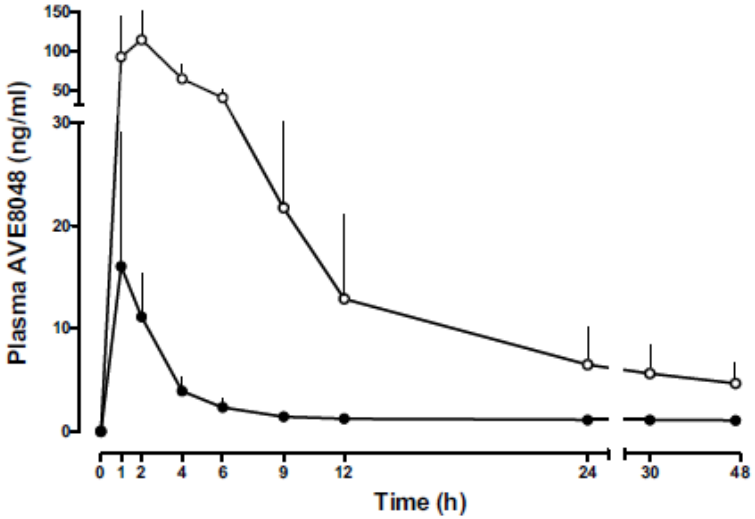
Ilepatril: intensity and duration of ACE inhibition by comparison to other ACEIs or VPI



AVE = Ilepatril
O= Omapatrilat

Azizi M et al. Unpublished data

Enalapril
Ramipril



Azizi M et al. Clin Pharm Ther 2006

Ilepatril: intensity and duration of ACE inhibiti n by comparison to other AC

www.clinical trial.gov

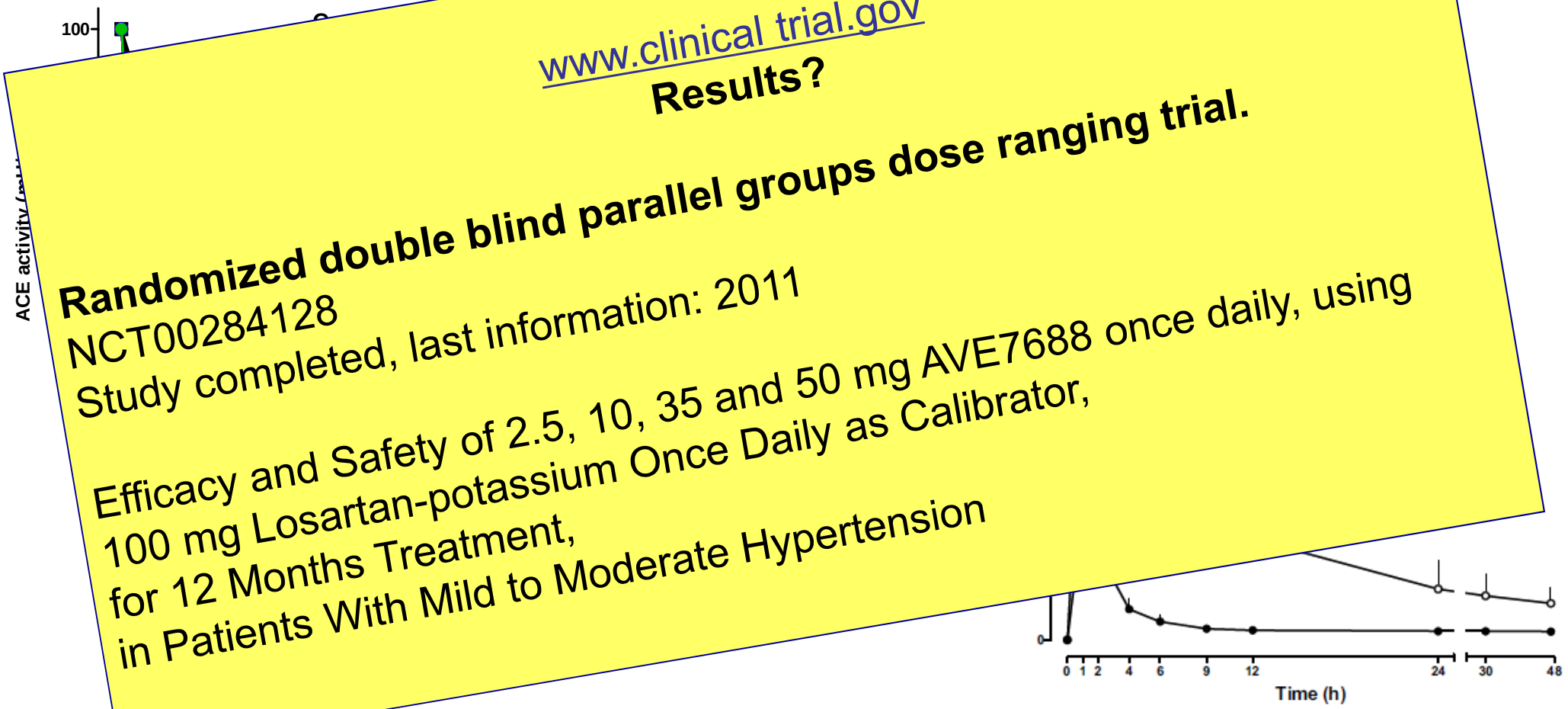
Results?

Randomized double blind parallel groups dose ranging trial.

NCT00284128

Study completed, last information: 2011

Efficacy and Safety of 2.5, 10, 35 and 50 mg AVE7688 once daily, using 100 mg Losartan-potassium Once Daily as Calibrator, for 12 Months Treatment, in Patients With Mild to Moderate Hypertension



Azizi M et al. Clin Pharm Ther 2006

3 pharmacological classes around NEP inhibition

Laurent S et al. Lancet 2012

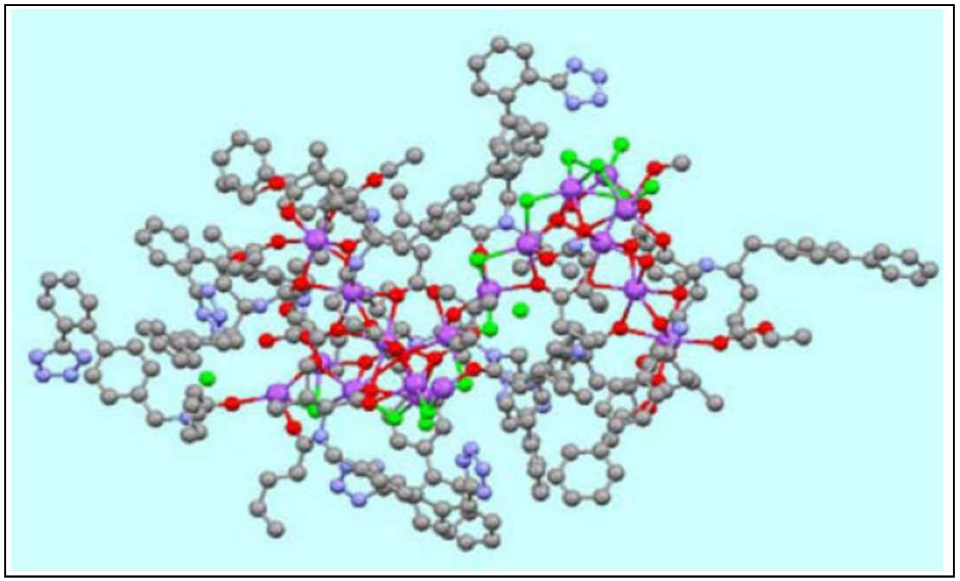
Pharmacological class		Drug	Pre-clinical stage	Phase I-III	Pharmaceutical industry
Pure NEP inhibitor					
Dual vasopeptidase inhibitor					
1. Dual NEP/ACE inhibitor		Ilepatril – AVE7688		Phase III*	Sanofi-Aventis
2. Dual NEP/ECE inhibitor		Daglutril- SLV306		Phase II*	Solvay Pharmaceuticals
Dual ARNI (Dual NEPI/ARB)		**LCZ696**		**Phase IV**	**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

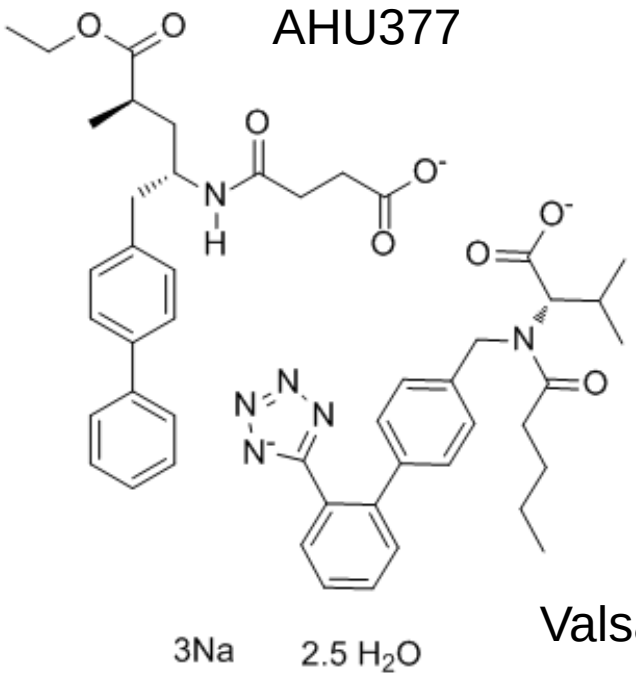
LCZ696: a dual-acting inhibitor of the angiotensin II receptor and neprilysin (dual ARNi)

Gu J et al. J Clin Pharmacol, 2010

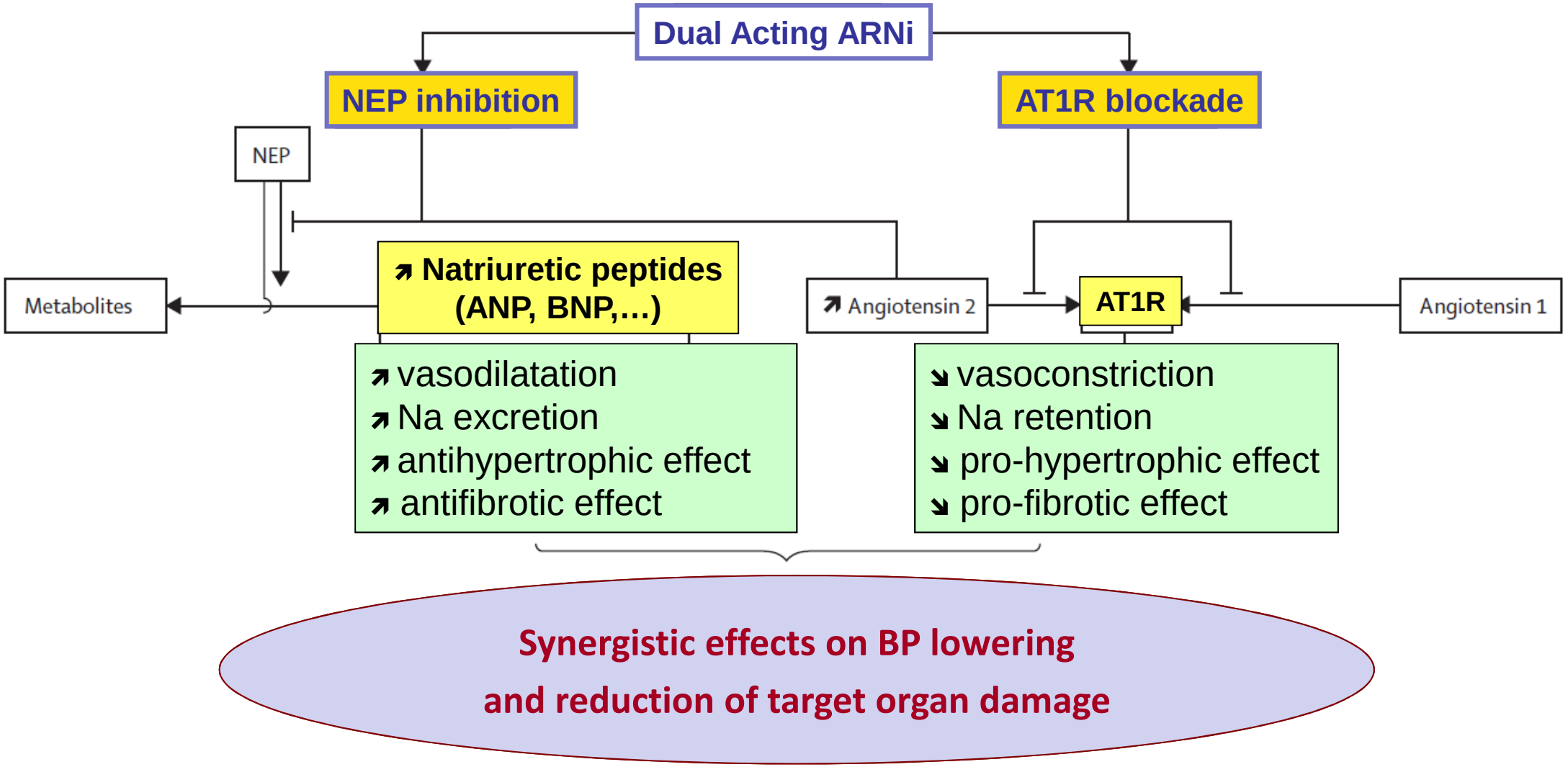
Single molecule in which the molecular moieties of valsartan and the molecular moieties of the NEP inhibitor prodrug AHU377 are present in a 1:1 molar ratio.



Valsartan + Sacubitril (AHU377, prodrug of LBQ657)



LCZ696: a dual-acting inhibitor of the Angiotensin II Receptor and Neprilysin (dual ARNi)



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

Ruilope LM et al. Lancet 2010

Phase III, randomised, parallel-group, double-blind multicenter trial

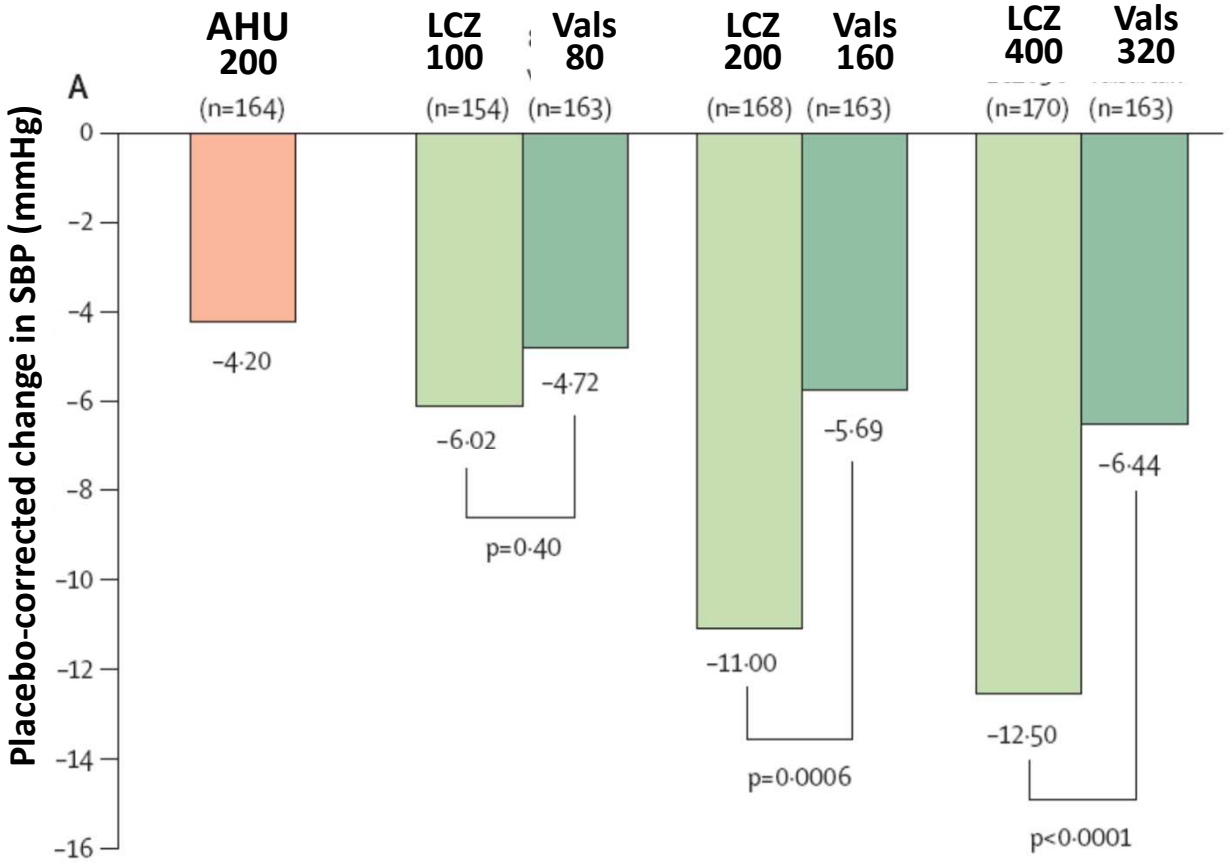
Grade I-II hypertension
n=1328
Age 18-75

Office BP

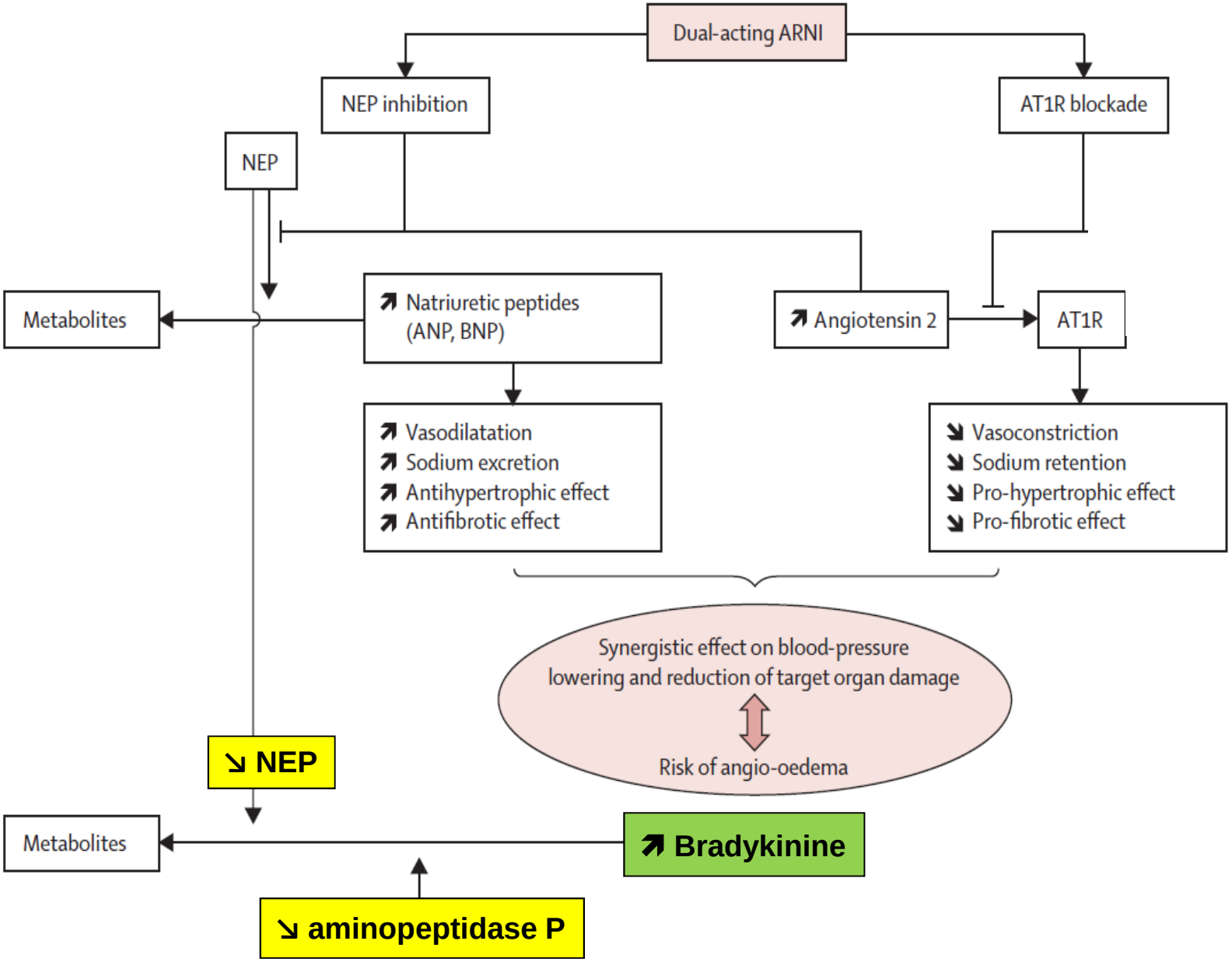
Equipotent ARB doses

AHU 200 mg # LCZ 400 mg for NEPI

Duration 8 weeks

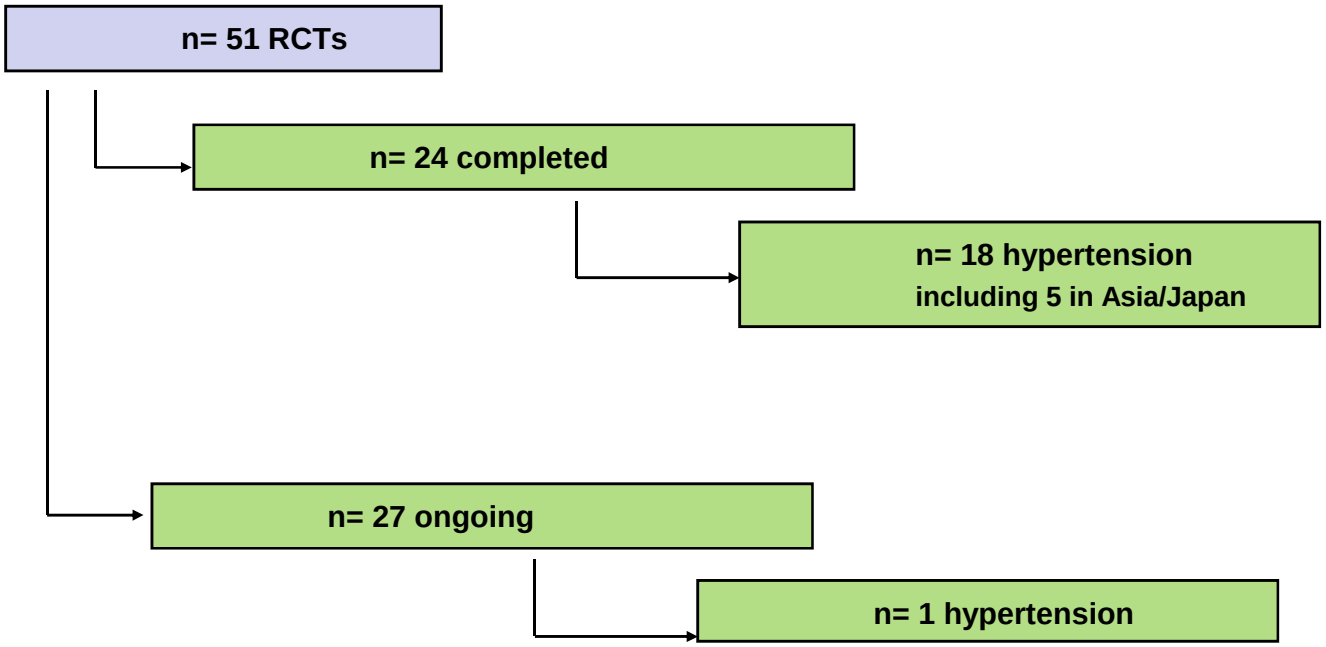


Dual ARNi vs dual NEP/ACE inhibitors
Less increase in BK → less risk of angioedema



LCZ696: RCTs (March 2017)

www.clinicaltrials.org



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 …but n=3 expected at a rate of 0.5%

Antihypertensive efficacy of LCZ696 in 389 mild to moderate Asian hypertensive patients

Kario K et al. Hypertension 2014

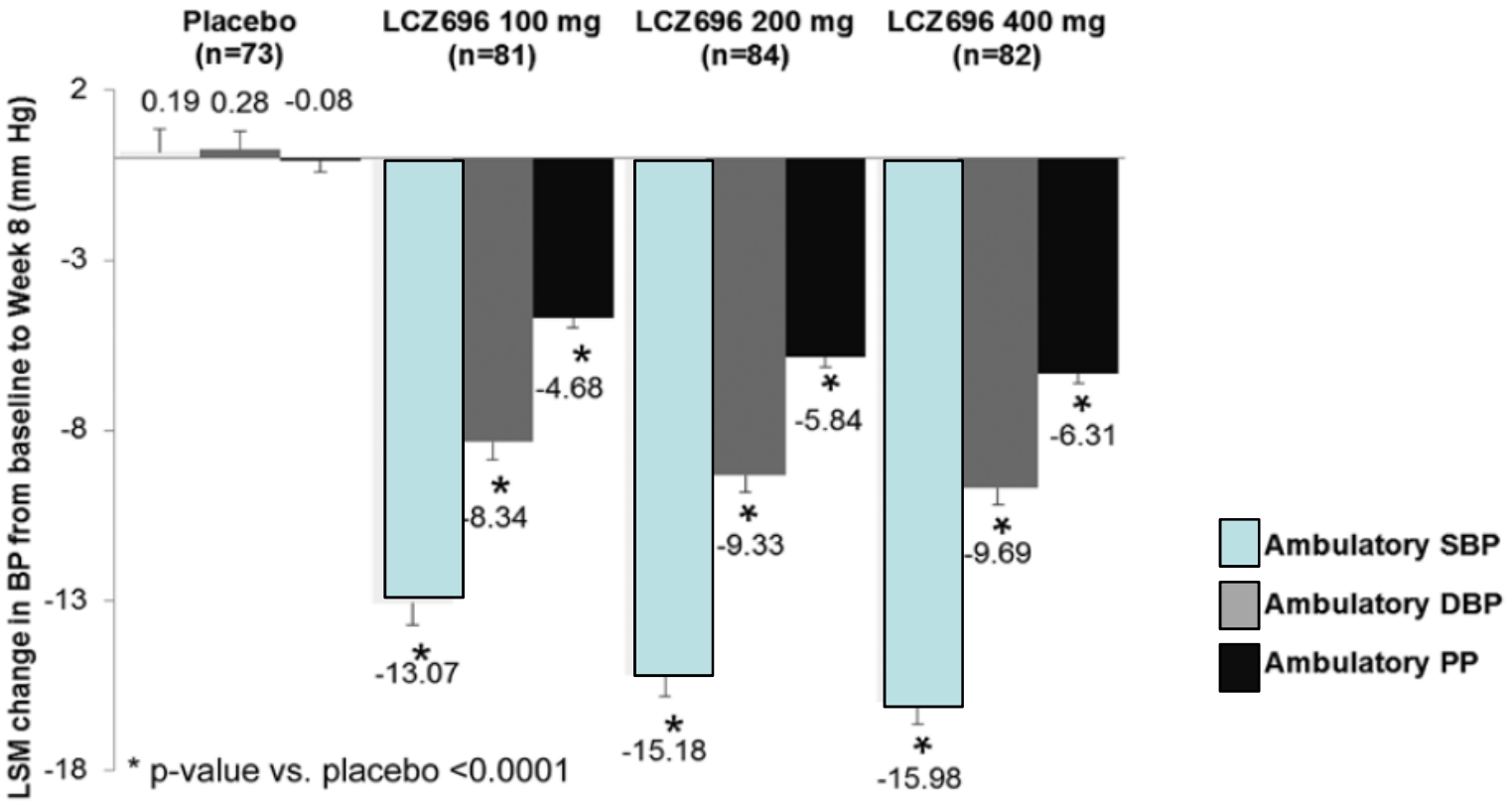
Phase III, randomised, parallel-group, double-blind multicenter trial

Grade I-II hypertension
n=389
Age 18-75

ABPM

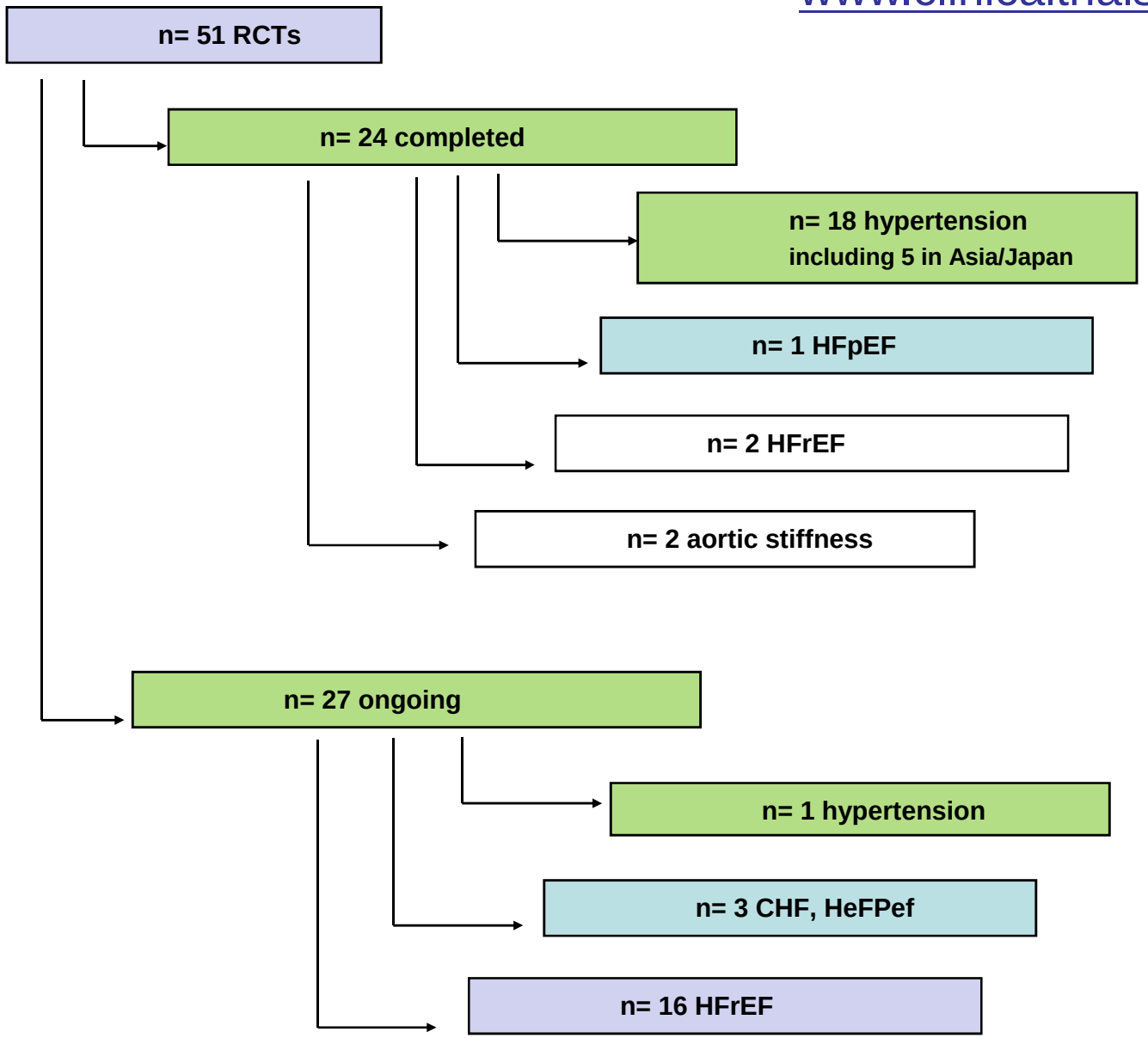
Asian population
Japan, China, Korea, Taiwan, Thailand

Duration 8 weeks



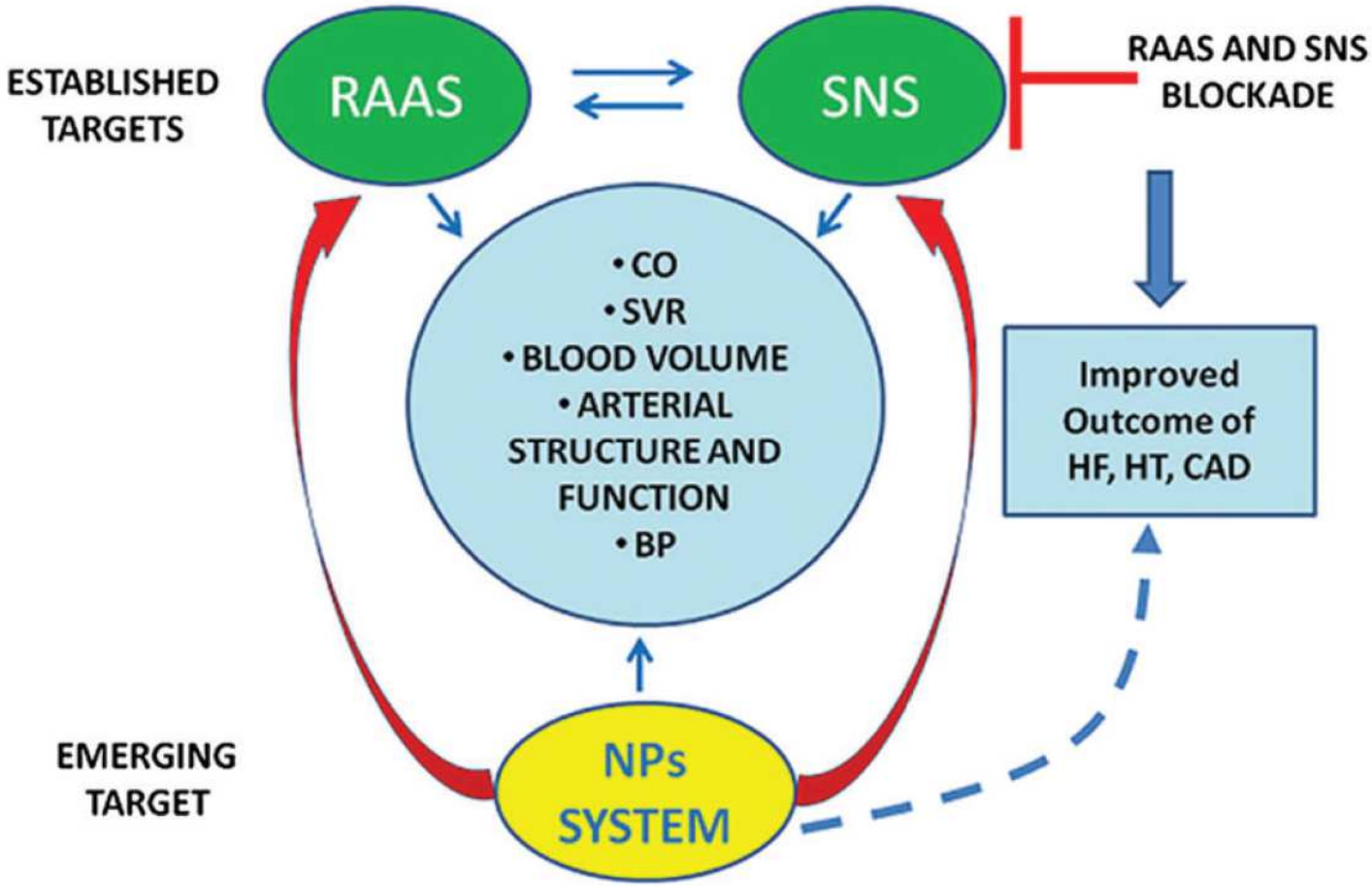
LCZ696: RCTs (March 2017)

www.clinicaltrials.org



The system of natriuretic peptides as an emerging target for the treatment of heart failure and hypertension

Volpe et al. Eur Heart J 2014



PARAMOUNT

The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial

Lancet 2012

*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 J V McMurray, for the Prospective comparison of ARNI with ARB on Management Of heart failUre with preserved ejectioN fracTion (PARAMOUNT) Investigators**

Phase II, randomised, parallel-group, double-blind multicenter trial

Proof of concept in HFpEF

NYHA class II-III heart failure
+ LVEF > 45%
+ NT-proBNP > 400 pg/ml

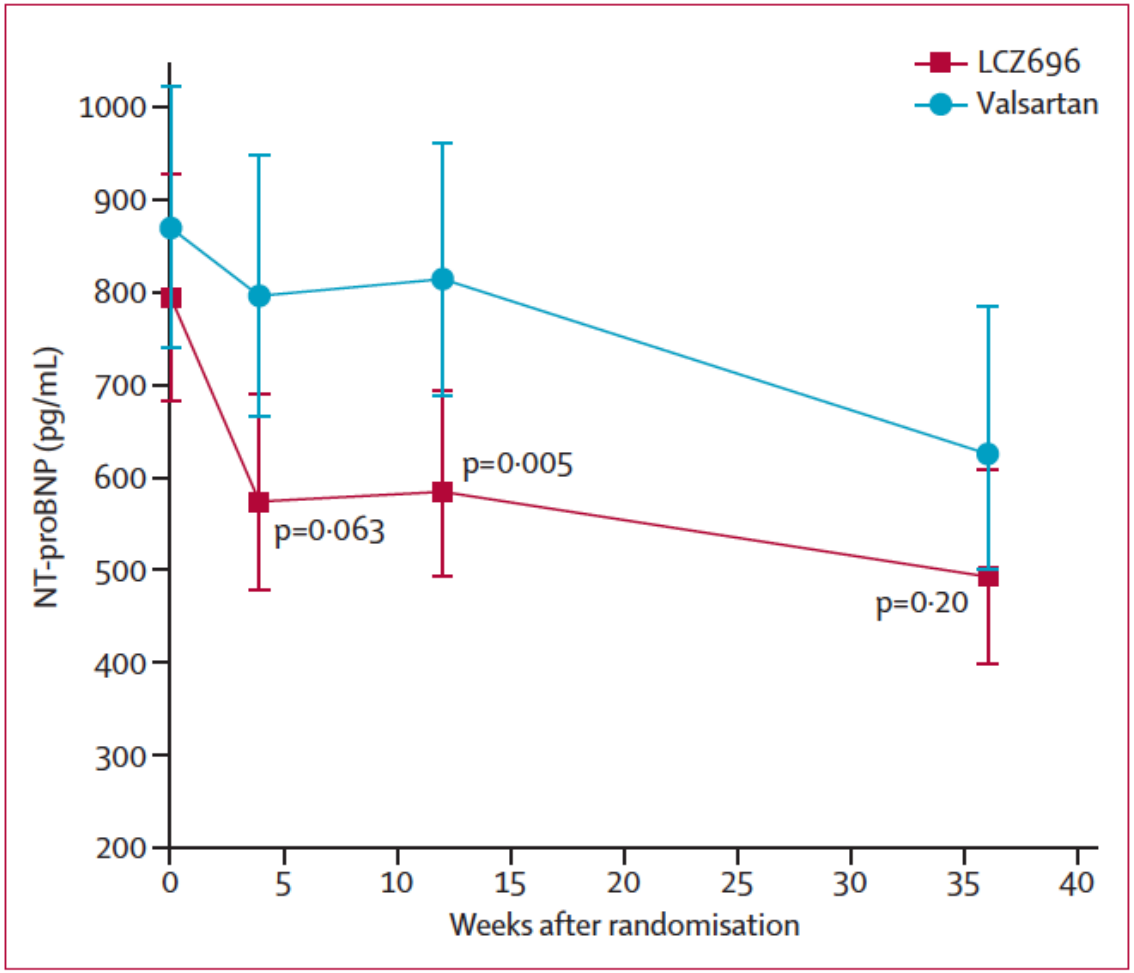
n= 149, LCZ696 up to 200 mg bid

n=152, valsartan up to 160 mg bid

Equipotent ARB doses

Duration 36 weeks (9M)

NT-proBNP, surrogate for HF



PARAMOUNT

The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial

Lancet 2012

*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 J V McMurray, for the Prospective comparison of ARNI with ARB on Management Of heart failUre with preserved ejectioN fracTion (PARAMOUNT) Investigators**

	36 weeks						
	LCZ696			Valsartan			p value
	n	Baseline	Δ from baseline	n	Baseline	Δ from baseline	
Ejection fraction	94	58·3% (7·7)	2·7% (6·5)	111	58·1% (8·0)	3·07% (5·9)	0·69
Lateral mitral annular relaxation velocity (e'; cm/s)	84	7·6 (2·7)	0·55 (2·3)	96	7·3 (2·8)	0·92 (2·0)	0·40
Mitral inflow velocity to mitral annular relaxation velocity ratio (E/e')	83	12·3 (5·5)	−1·3 (3·1)	95	12·7 (6·2)	−1·0 (4·7)	0·42
Early to late mitral inflow velocity ratio (E/A)	60	1·1 (0·51)	−0·05 (0·39)	68	1·1 (0·65)	−0·03 (0·61)	0·43
Left atrial width (cm)	99	3·7 (0·43)	−0·15 (0·31)	108	3·7 (0·53)	−0·08 (0·30)	0·03
Left atrial volume (mL)	96	65·3 (22·5)	−4·6 (13·7)	112	68·3 (29·3)	0·37 (15·9)	0·003

PARAGON-HF Experimental design (clinicaltrials.gov)

Phase III, randomised, parallel-group, double-blind multicenter trial

End point study in HFpEF

Age > 55 yrs
NYHA class II-IV heart failure with Preserved Ejection Fraction (LVEF ≥ 45%)

Total number of patients 4300

LCZ696 100 mg bid
Valsartan 80 mg bid

FU up to 57 months

Primary end-point
CV death + hosp. for CHF

Expected primary completion: May 2019

PARADIGM-HF 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*

McMurray JJV et al. NEJM 2014

Phase III, randomised, parallel-group, double-blind multicenter trial

End point study in HFrEF

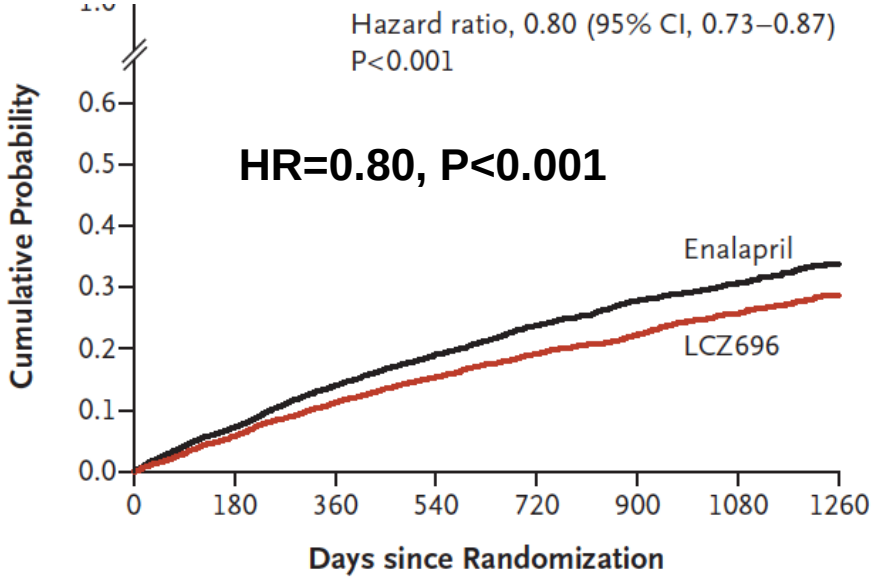
NYHA class II-IV heart failure
LVEF < 40% and then < 35%
NT-proNBP > 600 pg/ml

n = 4187 LCZ696 200 mg bid
n = 4212 Enalapril 10 mg bid

Median FU 27 months

Primary end-point
CV death + hosp. for CHF

Primary end-point



No. at Risk								
LCZ696	4187	3922	3663	3018	2257	1544	896	249
Enalapril	4212	3883	3579	2922	2123	1488	853	236

PARADIGM-HF

Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure

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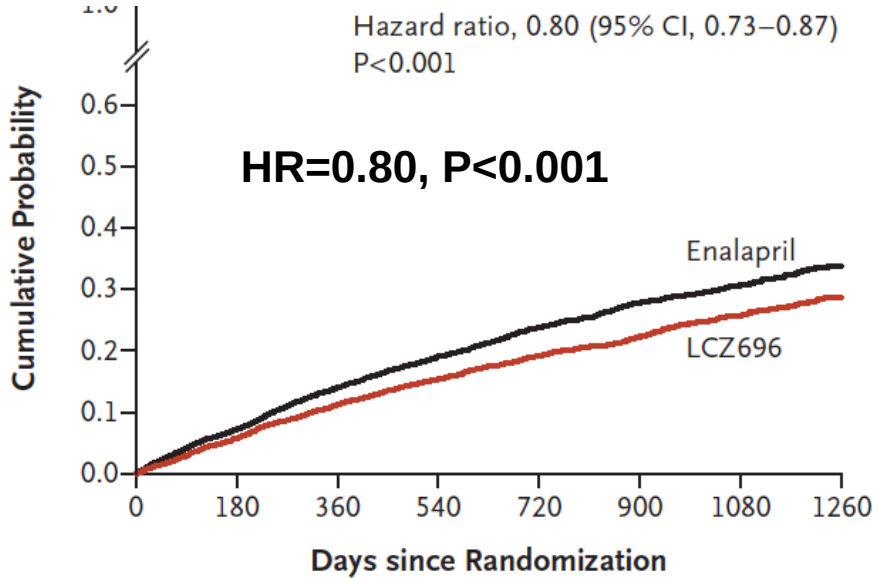
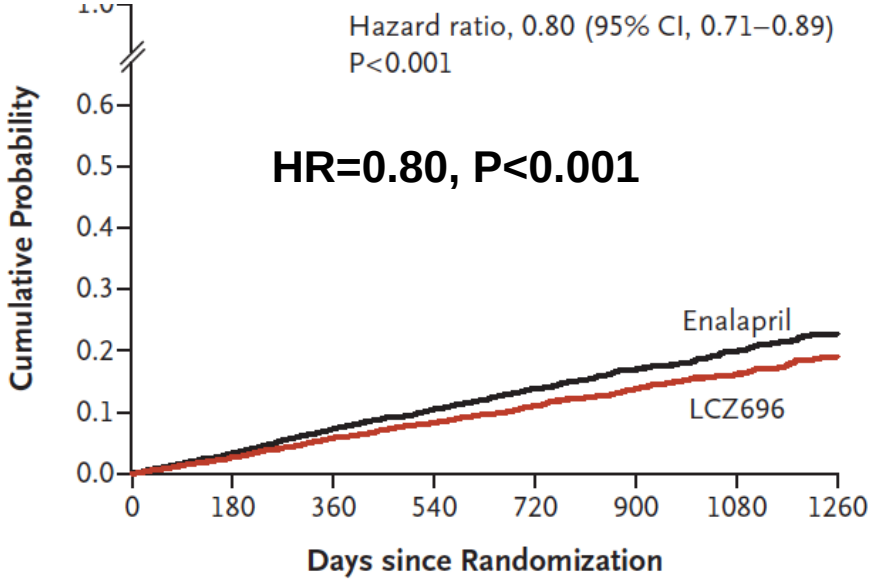
McMurray JJV et al. NEJM 2014

Primary end-point



No. at Risk								
LCZ696	4187	3922	3663	3018	2257	1544	896	249
Enalapril	4212	3883	3579	2922	2123	1488	853	236

Death from CV cause



No. at Risk								
LCZ696	4187	4056	3891	3282	2478	1716	1005	280
Enalapril	4212	4051	3860	3231	2410	1726	994	279

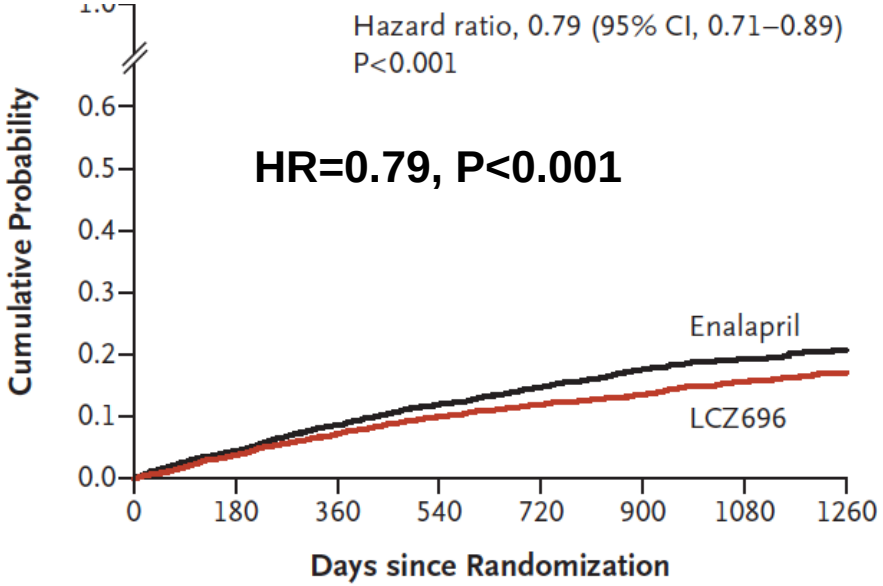
PARADIGM-HF

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*

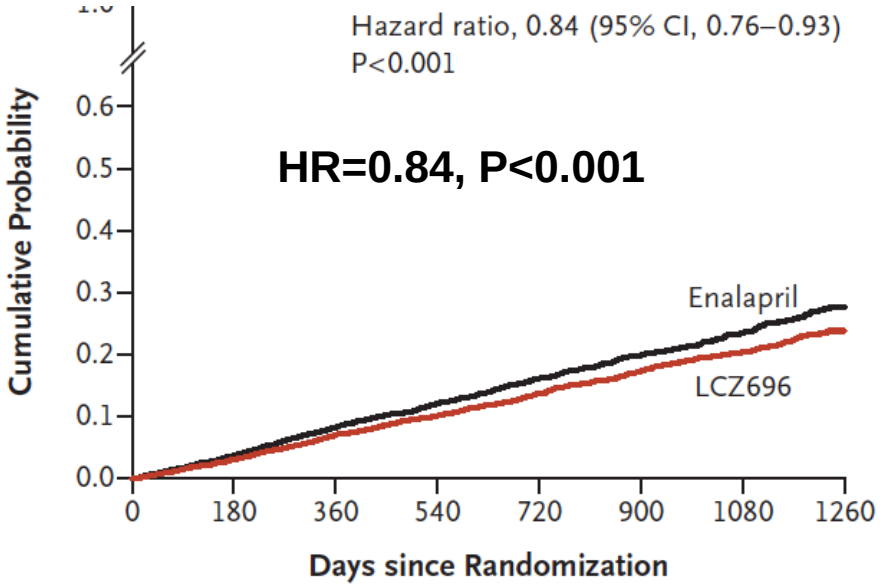
McMurray JJV et al. NEJM 2014

Hospitalization for heart failure



No. at Risk								
LCZ696	4187	3922	3663	3018	2257	1544	896	249
Enalapril	4212	3883	3579	2922	2123	1488	853	236

Death from any cause



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LCZ696	4187	4056	3891	3282	2478	1716	1005	280
Enalapril	4212	4051	3860	3231	2410	1726	994	279

PARADIGM-HF

Adverse effects

Event	LCZ696 (N=4187)		Enalapril (N=4212)	P Value
	no. (%)			
Hypotension				
Symptomatic	588 (14.0)	>	388 (9.2)	<0.001
Symptomatic with systolic blood pressure <90 mm Hg	112 (2.7)	>	59 (1.4)	<0.001
Elevated serum creatinine				
≥2.5 mg/dl	139 (3.3)	<	188 (4.5)	0.007
≥3.0 mg/dl	63 (1.5)		83 (2.0)	0.10
Elevated serum potassium				
>5.5 mmol/liter	674 (16.1)		727 (17.3)	0.15
>6.0 mmol/liter	181 (4.3)	<	236 (5.6)	0.007
Cough	474 (11.3)	<	601 (14.3)	<0.001

PARADIGM-HF

Adverse effects and angioedema: no significant difference

Table 3. Adverse Events during Randomized Treatment.*

Event	LCZ696 (N = 4187)	Enalapril (N = 4212)	P Value
	no. (%)		
Angioedema†	n=19	n=10	
No treatment or use of antihistamines only	10 (0.2)	5 (0.1)	0.19
Use of catecholamines or glucocorticoids without hospitalization	6 (0.1)	4 (0.1)	0.52
Hospitalization without airway compromise	3 (0.1)	1 (<0.1)	0.31
Airway compromise	0	0	—

Angioedema Adjudication Committee: Allen P. Kaplan (Chair), Nancy Brown, Bruce Zuraw.

PARADIGM-HF

Adverse effects and angioedema: no significant difference

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Airway compromise	0	0	—

The benefit / risk ratio is very much in favor of the benefit in very high risk patients

NEP inhibitors

- 30 years of research and development until the PARADIGM study …

- Effective when combined with an angiotensin II AT1-R antagonist

- A promising novel pharmacological class for heart failure

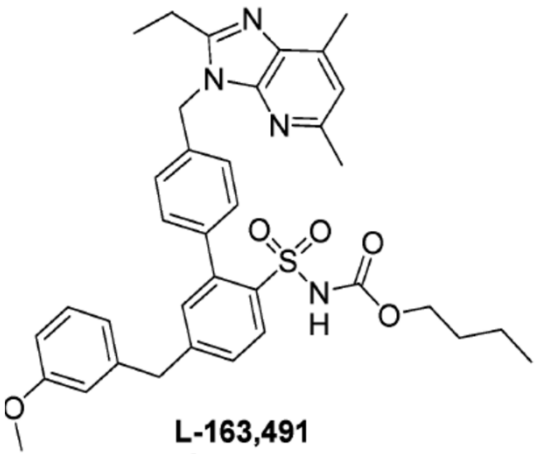
- Angioedema remain a matter of concern and require a close follow-up in hypertensive patients

Additional novel drugs for hypertension (II)

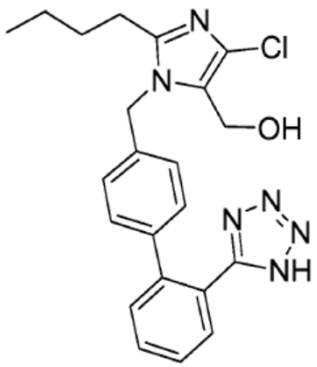
Pharmacological class		Drug	Pre-clinical stage	Phase I-III	Pharmaceutical industry
RERB (renin/prorenin blocker)			❒		
ACE2 activator			❒		
AT2-receptor agonist, non peptide		C21	❒	No anti-HT effect Tissue protection	Vicore Pharma
Aminopeptidase A (APA) inhibitor		QGC001	❒		Quantum Genomics Corp.
Vaccine	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 * Development stopped		Alagebrium (ALT-711)		Phase II*	Synvista Therapeutics

Non peptide agonists and antagonists of the angiotensin II AT1 and AT2 receptors

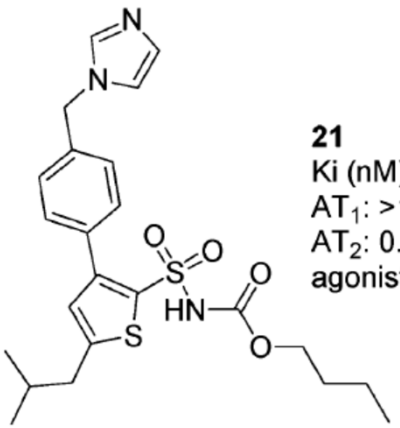
Wan et al. J Med Chem 2004



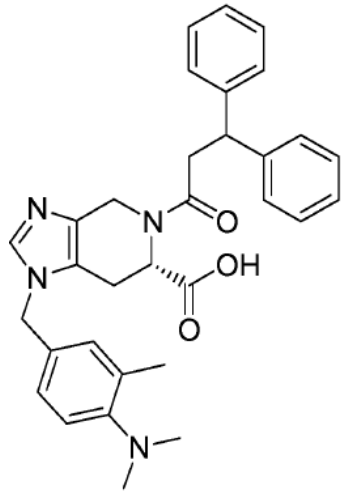
L-163,491
IC_{50} (nM)
AT_1: 1.4
AT_2: 101
agonist (AT_1)



Losartan
IC_{50} (nM)
AT_1: 12.1
AT_2: >10000
antagonist (AT_1)



21
Ki (nM)
AT_1: >10000
AT_2: 0.4
agonist (AT_2)



PD 123,319
IC_{50} (nM)
AT_1: >10000
AT_2: 34
antagonist (AT_2)

L-163,491	**Losartan**	**Compound 21**	**PD 123,319**
AT1-R agonist	AT1-R antagonist	AT2-R agonist	AT2-R antagonist

AT1-R	AT1-R	AT2-R	AT2-R
+		+	
	-		-

Compound 21, a selective agonist of angiotensin AT2 receptors

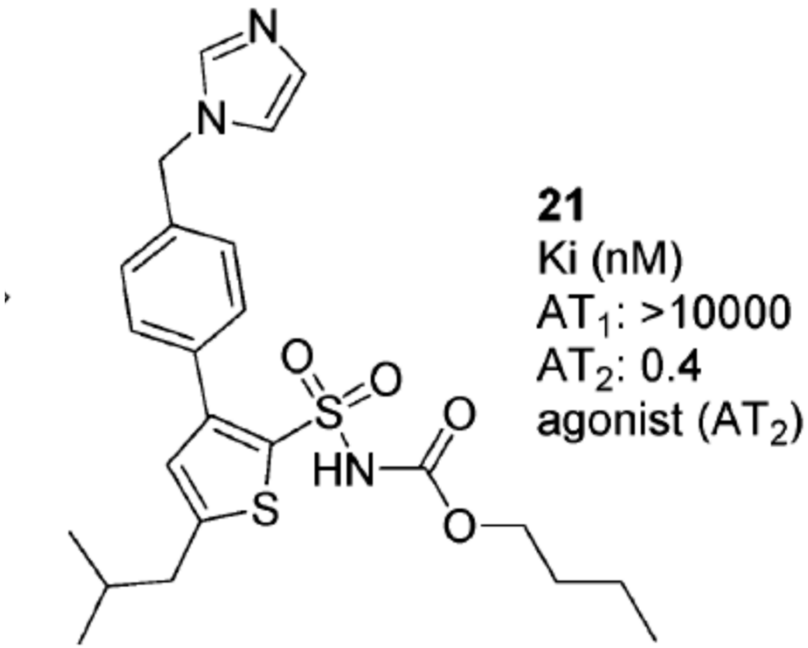
Compound 21 = first non peptide selective angiotensin II AT2 receptor agonist

*K*i value = 0.4 nM for the AT2 receptor

*K*i >10 μM for the AT1 receptor

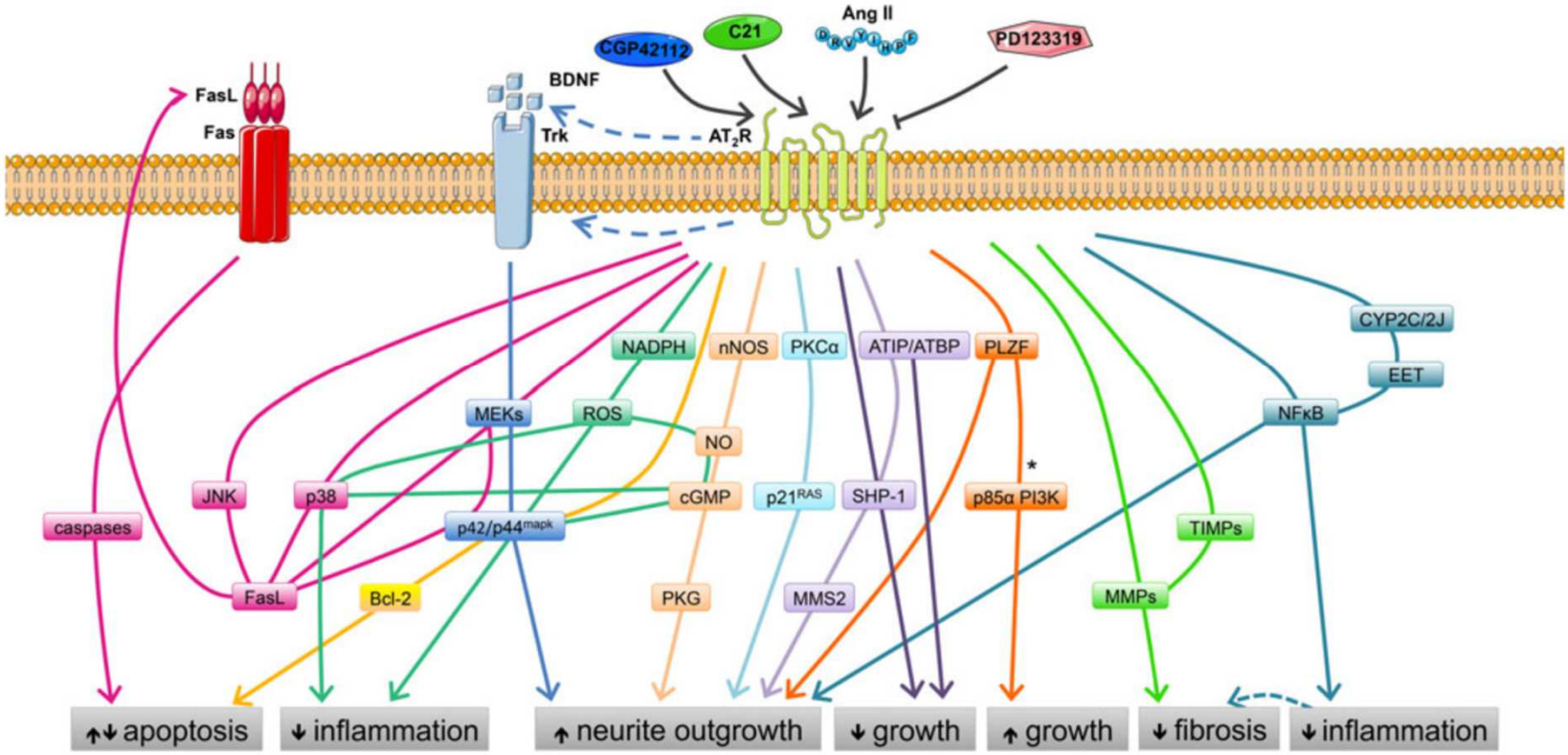
Oral bioavailability = 20-30%

Half-life # 4 h in rat



AT2-R mediated molecular pathways involved in tissue injury

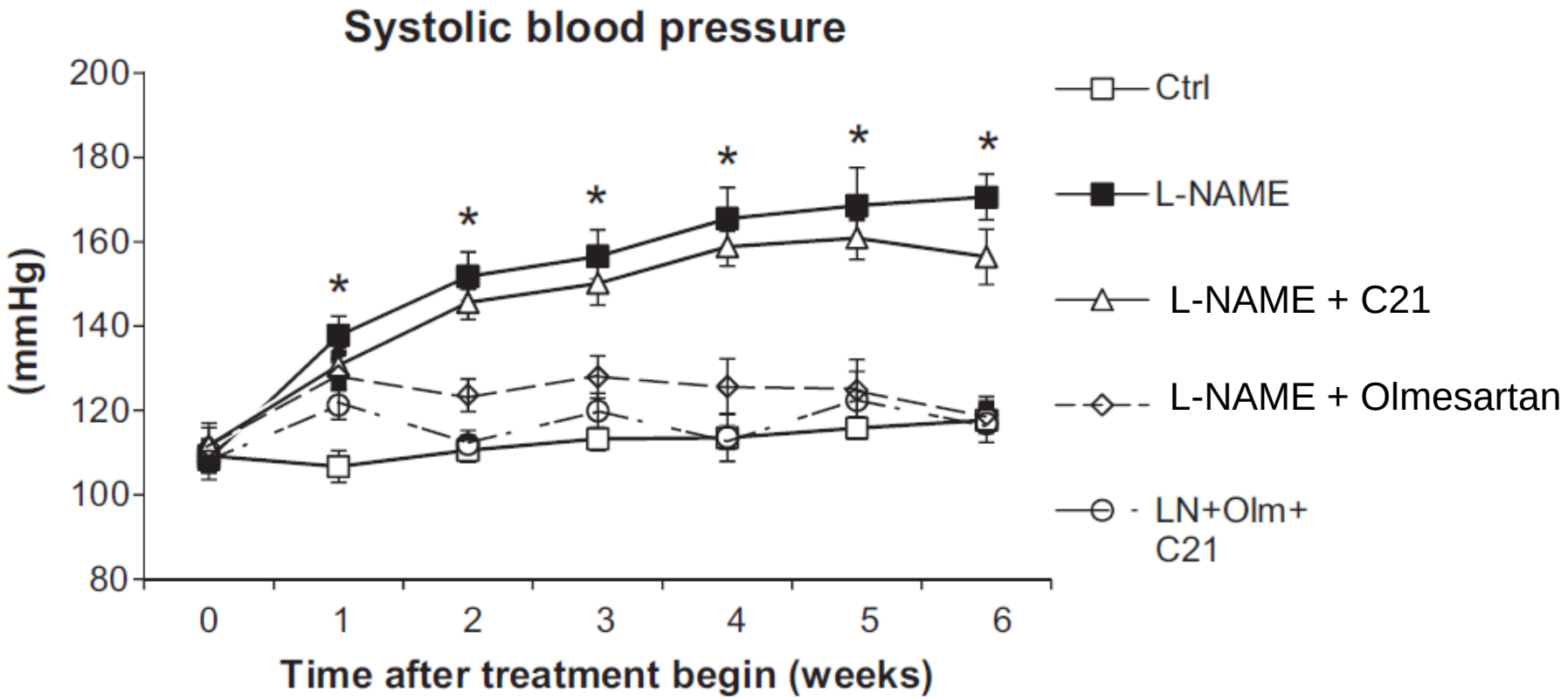
Steckeling UM et al. Curr Hypertens Rep 2014



AT2-receptor stimulation
- prevents hypertensive end-organ damage
- improves neurological outcome after stroke
- prevents pulmonary hypertension in a pulmonary fibrosis model

C21, an AT2-R agonist, is not a BP lowering drug

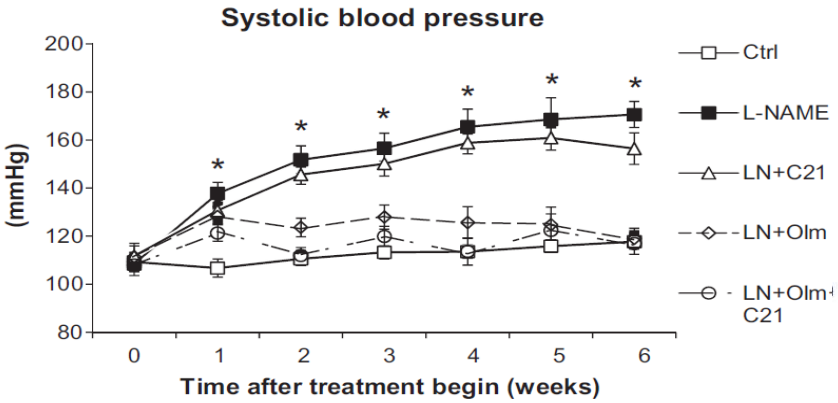
Paulis L, … Steckeling UM. Hypertension 2012

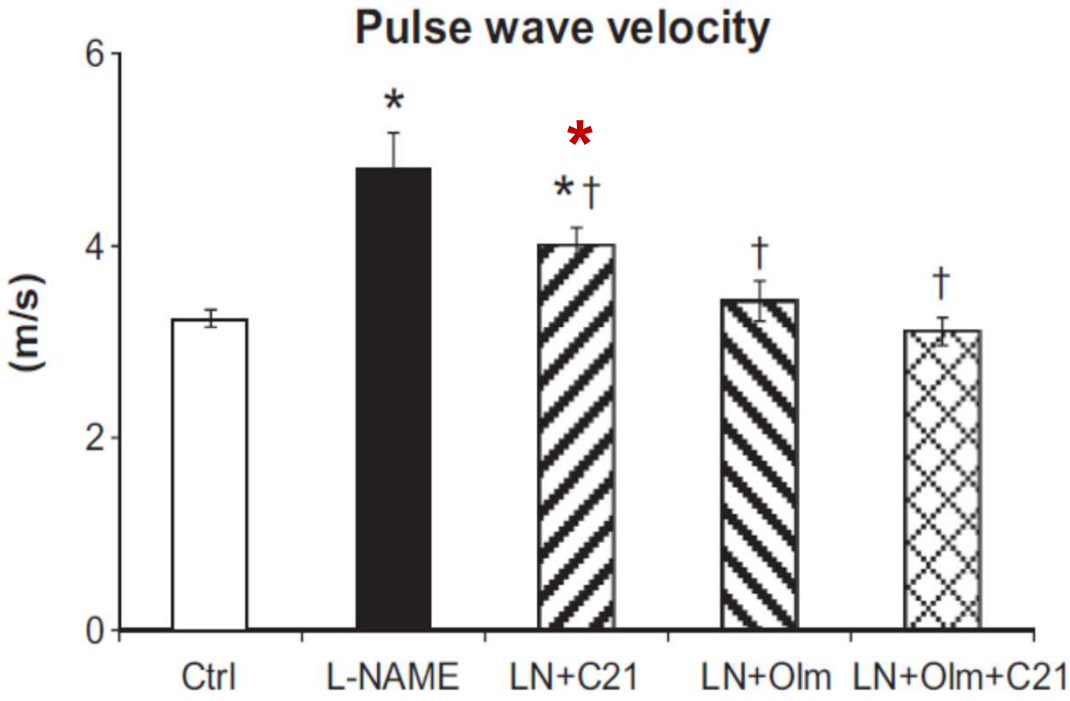


L-NAME = inhibitor of constitutive NO synthase (NOS)

Effects of AT2-R stimulation on the rat aorta

Paulis L, … Steckeling UM, Hypertension 2012





*** Disproprotionate to the reduction in MBP**

Effects of AT2-R stimulation on the rat aorta

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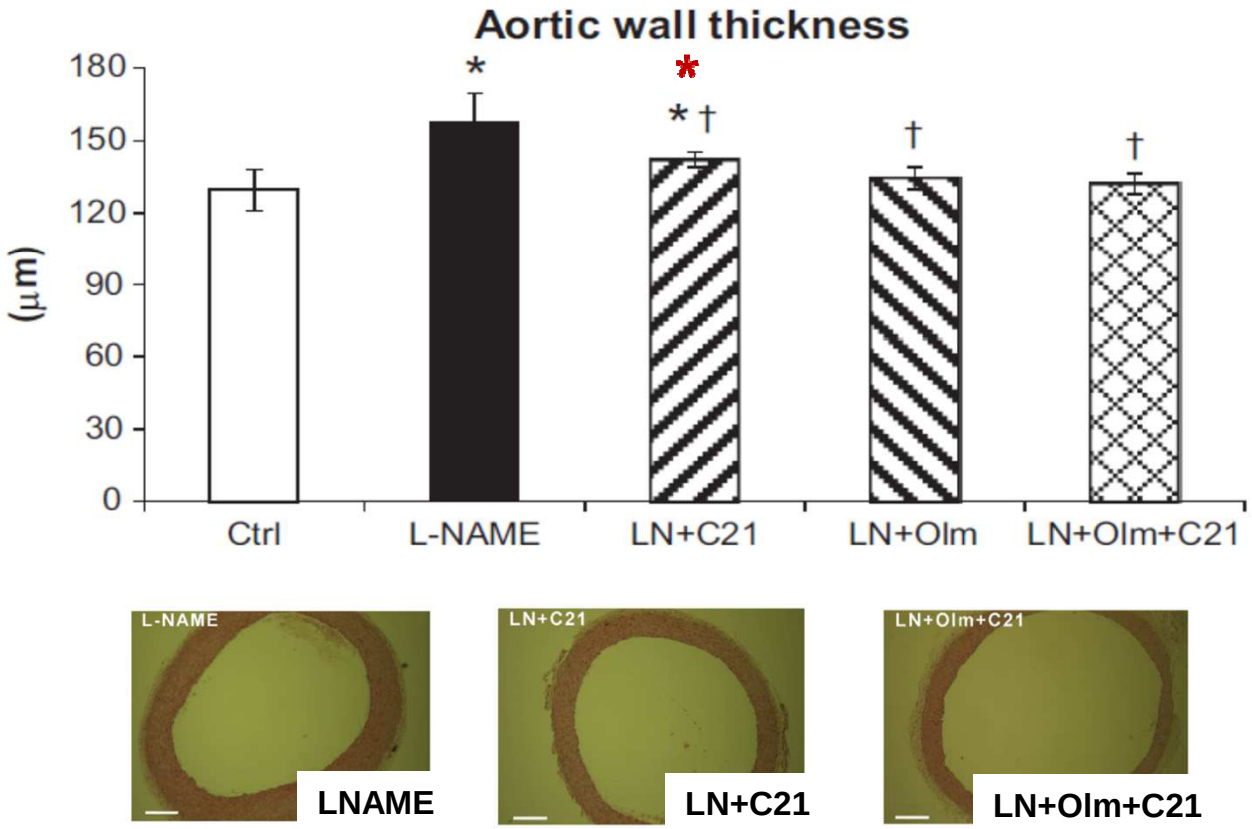
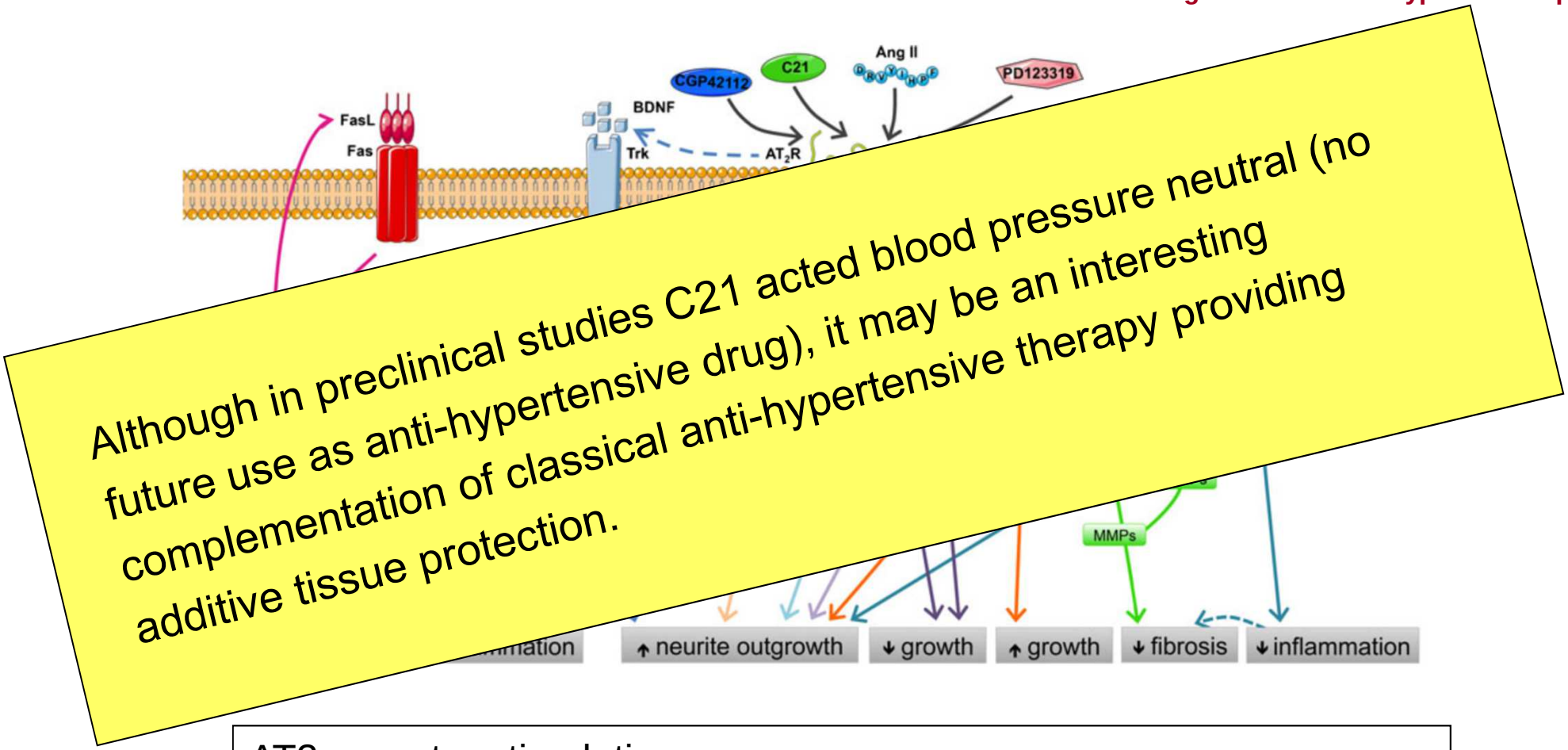


* Disproprotionate to the reduction in MBP

AT2-R mediated molecular pathways involved in tissue injury

Steckeling UM et al. Curr Hypertens Rep 2014



Although in preclinical studies C21 acted blood pressure neutral (no future use as anti-hypertensive drug), it may be an interesting complementation of classical anti-hypertensive therapy providing additive tissue protection.

AT2-receptor stimulation
- prevents hypertensive end-organ damage
- improves neurological outcome after stroke
- prevents pulmonary hypertension in a pulmonary fibrosis model

Additional novel drugs for hypertension (II)

Pharmacological class		Drug	Pre-clinical stage	Phase I-III	Pharmaceutical industry
RERB (renin/prorenin blocker)			❒		
ACE2 activator			❒		
AT2-receptor agonist, non peptide		C21	❒	No anti-HT effect Tissue protection	Vicore Pharma
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

A new strategy for treating hypertension by blocking the activity of the brain renin–angiotensin system with aminopeptidase A inhibitors

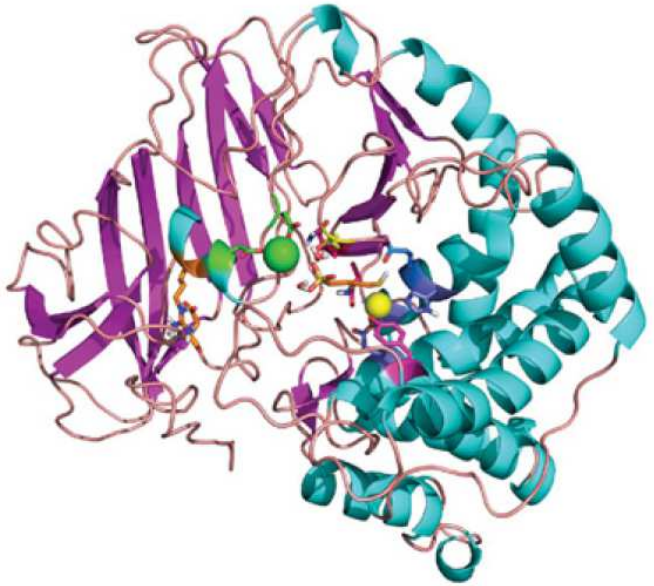
Ji GAO*, Yannick MARC*†, Xavier ITURRIOZ*, Vincent LEROUX*, Fabrice BALAVOINE† and Catherine LLORENS-CORTES*

*Laboratory of Central Neuropeptides in the Regulation of Body Fluid Homeostasis and Cardiovascular Functions, CIRB, Collège de France, INSERM U1050, Paris, F-75231, France
†Quantum Genomics, Massy, F-91300, France

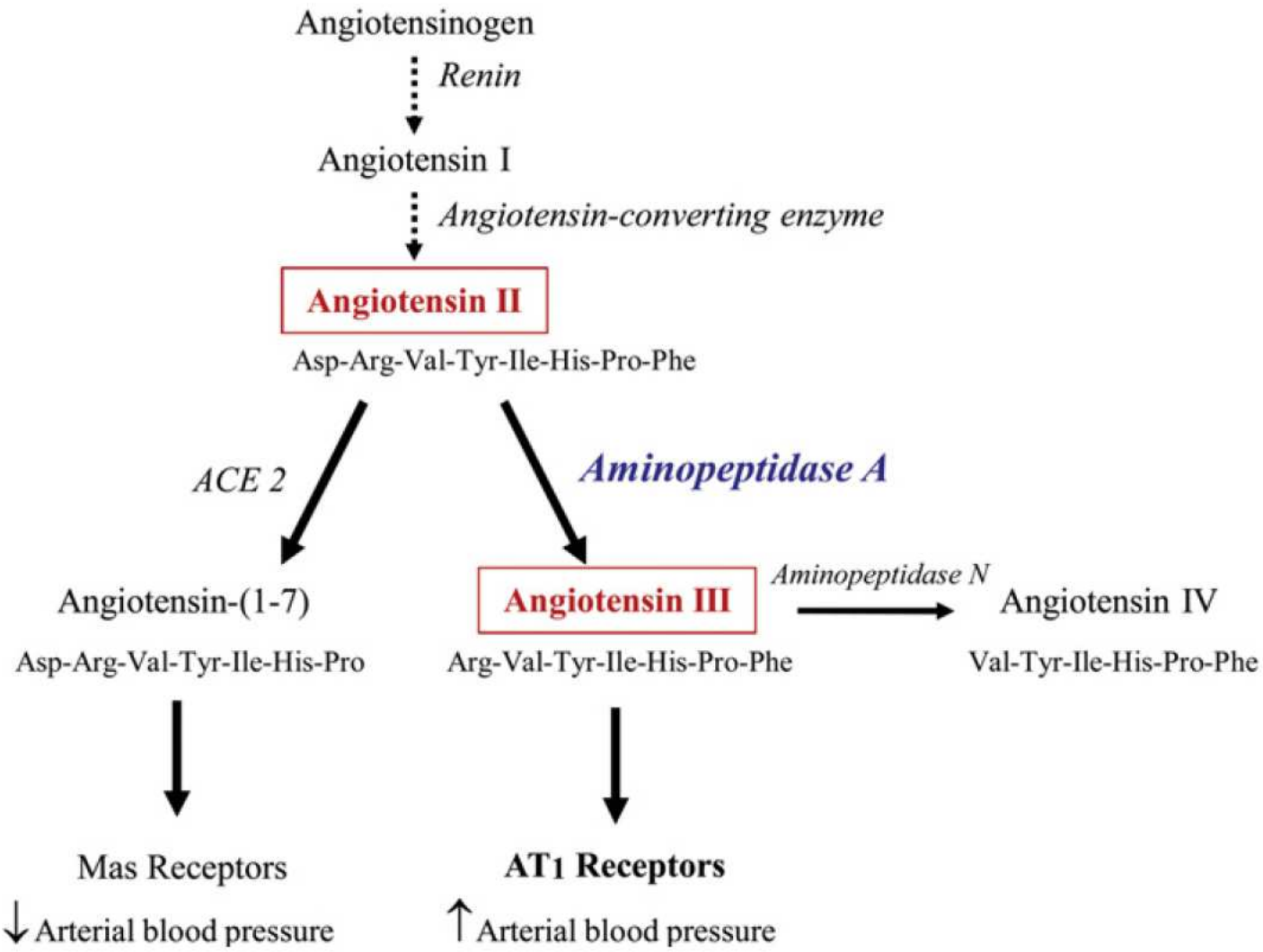
Gao J et al, Clinical Science 2014

Aminopeptidase A (APA)

- membrane bound zinc metalloprotease
- involved in the metabolism of Ang II ad Ang III
- can be blocked *in vivo* (PNAS 1999)



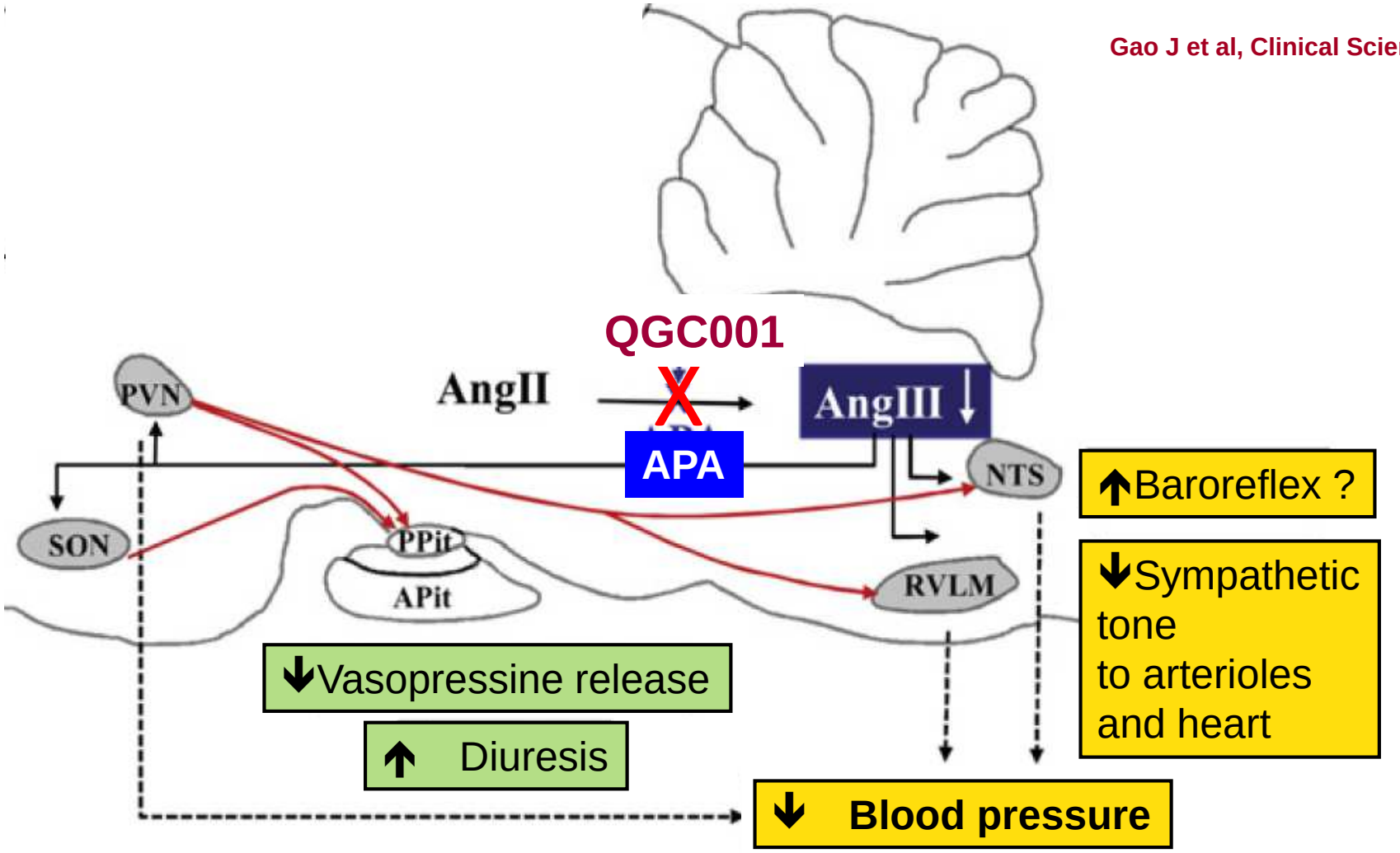
Brain Renin-Angiotensin System



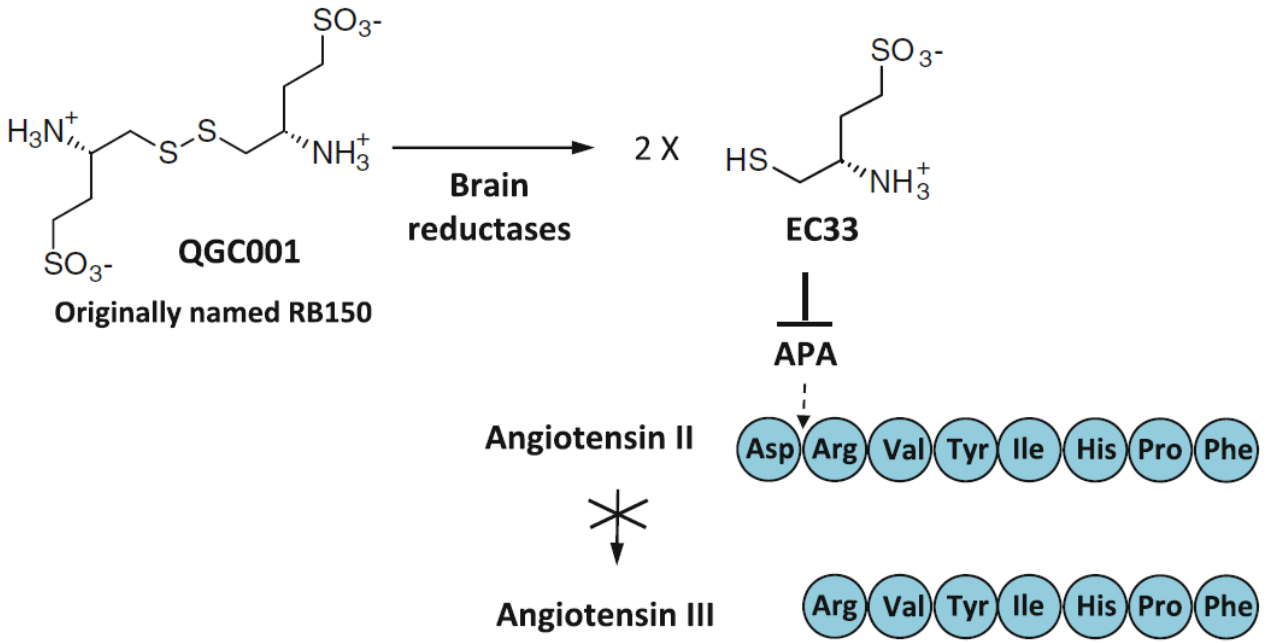
Gao J et al, Clinical Science 2014

QGC001, an orally active APA inhibitor (BAPAi), is a centrally acting antiHT

Gao J et al, Clinical Science 2014

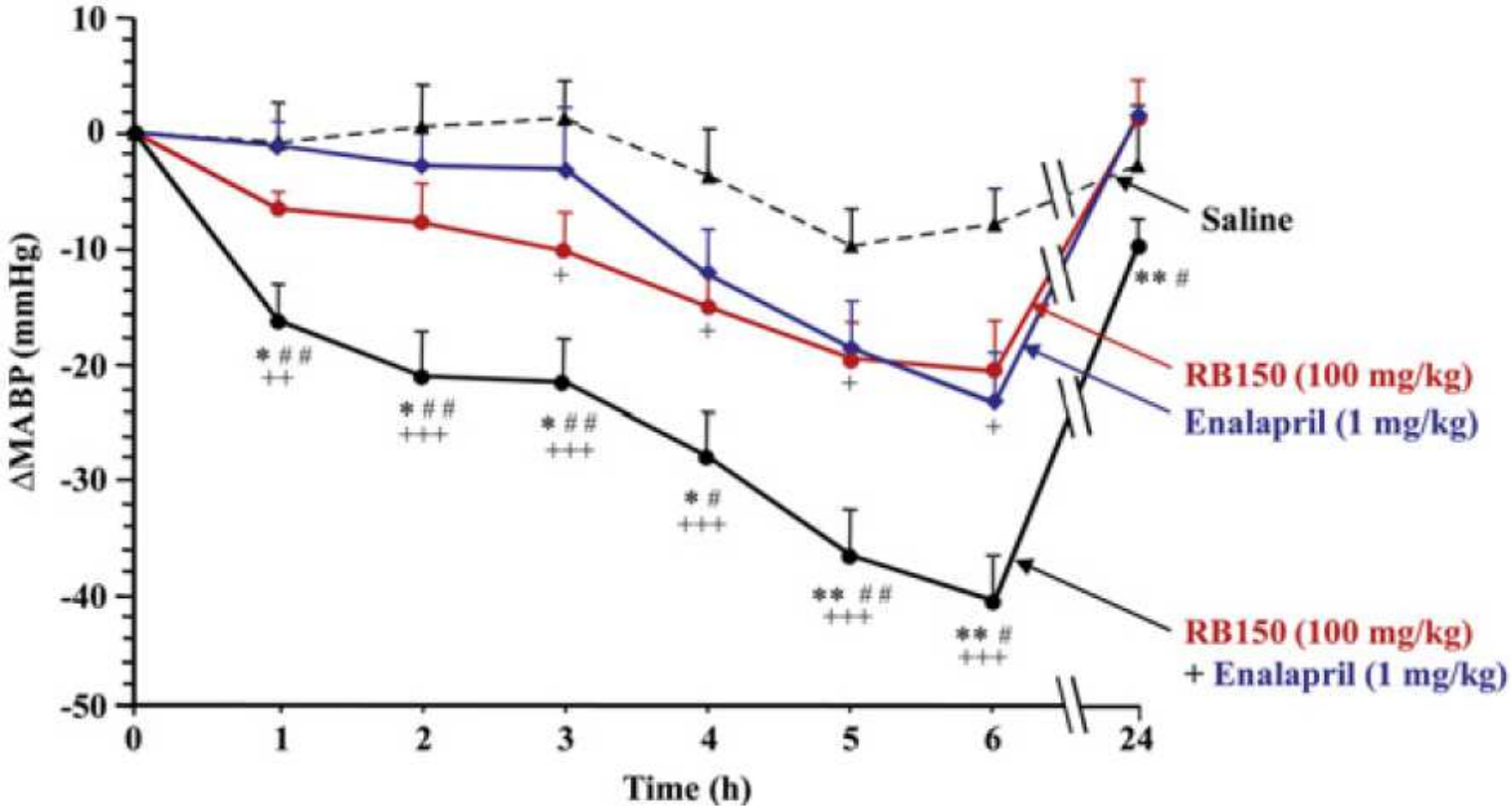


Orally active QGC001 is a pro-drug, generating 2 active molecules of APA inhibitor (EC33)



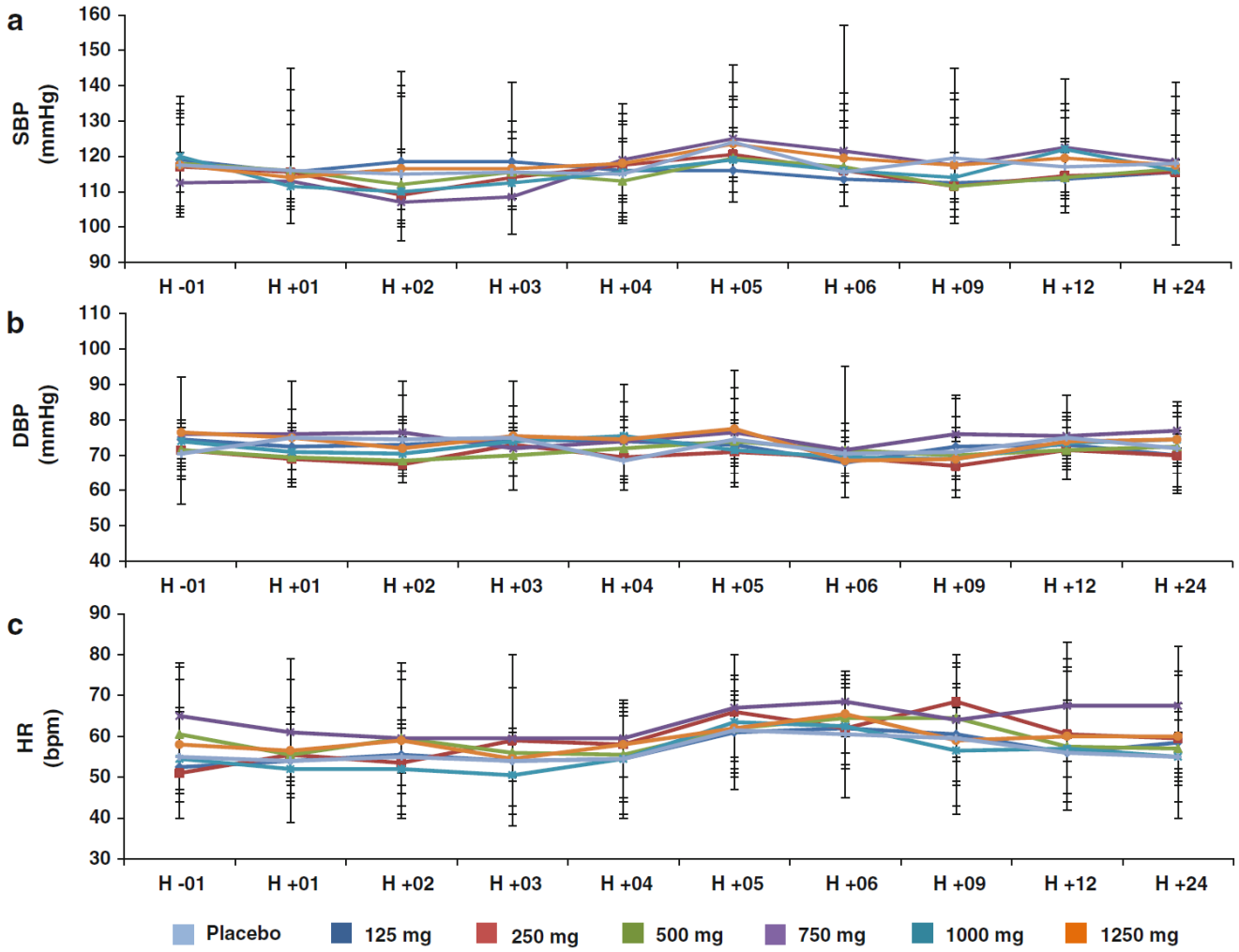
Change in BP in conscious SHR after oral RB150 or enalapril

Marc Y et al, Hypertension 2012



- RB150 (= QGC001) does not modify the systemic RAS activity
- RB150 (= QGC001) might be used in combination with classic RAS blockers to improve BP control

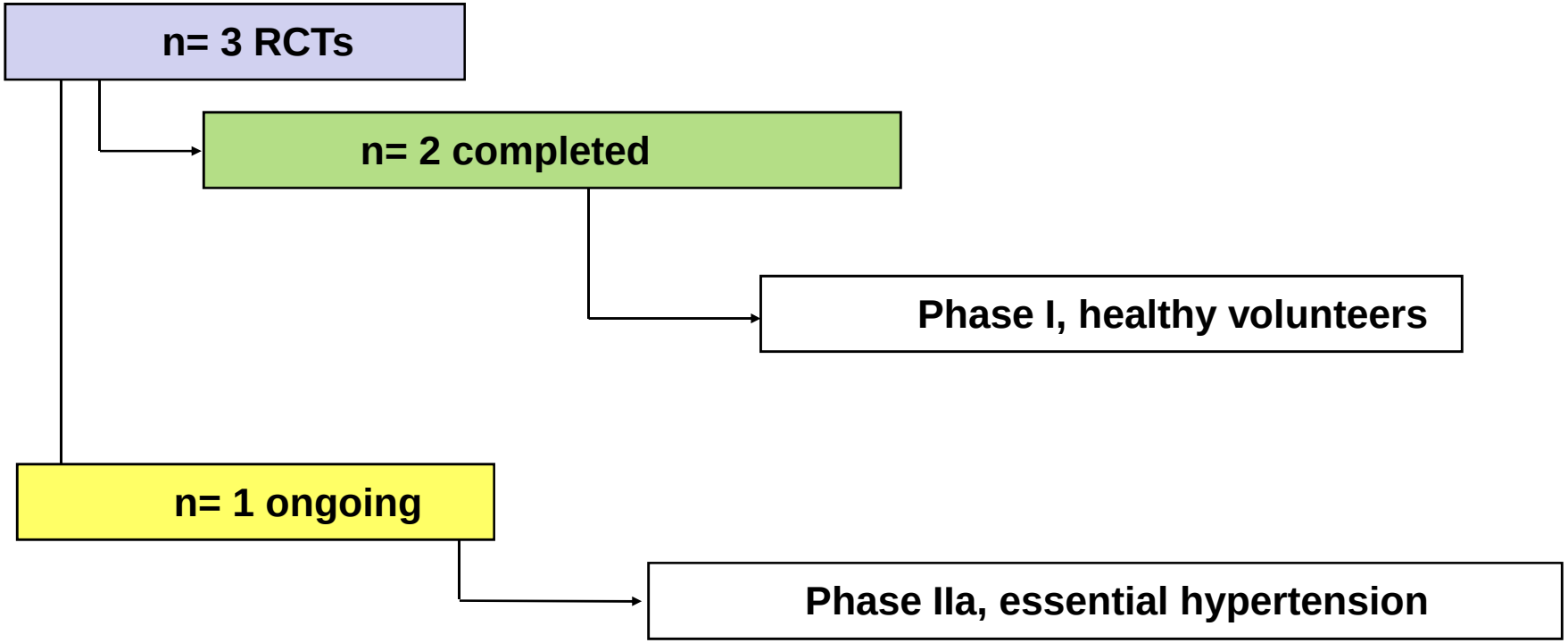
Phase I study: Single oral administration of QGC001 on supine BP



Balavoine F et al, Clin Pharmacokinet 2014

QGC001, APA inhibitor: ongoing RCTs (March 2016)

www.clinicaltrials.org



New drugs for hypertension: conclusion

- The pipeline is not dry….
- Several novel pharmacological classes are in development, with first-in-class molecules reaching phase II and III
- …but the development of some promising novel drugs has been stopped

- A gap of few years is expected before leading compounds of novel pharmacological classes are marketed

New drugs for hypertension: conclusion

- The pipeline is not dry….
- Several novel pharmacological classes are in development, with first-in-class molecules reaching phase II and III
- …but the development of some promising novel drugs has been stopped

- A gap of few years is expected before leading compounds of novel pharmacological classes are marketed
- Huge efforts have been made to synthesize novel molecules either combining the beneficial effects of known pharmacological classes or addressing an entirely novel mechanism of action
- These efforts may not only benefit to hypertensive patients …
- …but also to patients suffering from other disease (Pulmonary Hypertension, CHF, Cushing syndrome)

Merci !