RAS and Neutral Endopeptidase

- RAS and its companion-

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Content

1. Novel RAS and Neutral Endopetidase (NEP)

   - Complex network of RAS

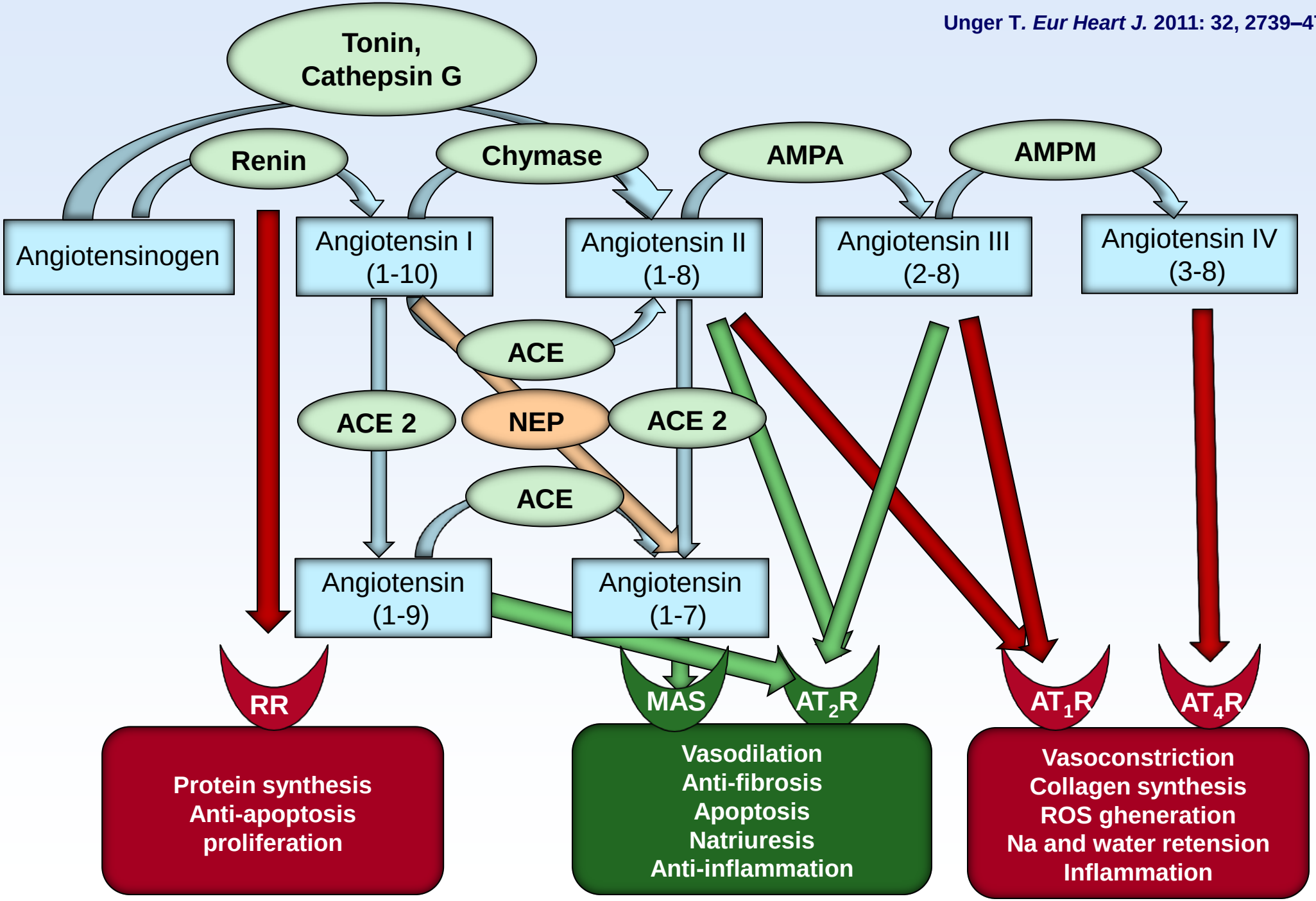
   - NEP and vasoactive peptide

2. Novel strategy to inhibit the RAS and NEP

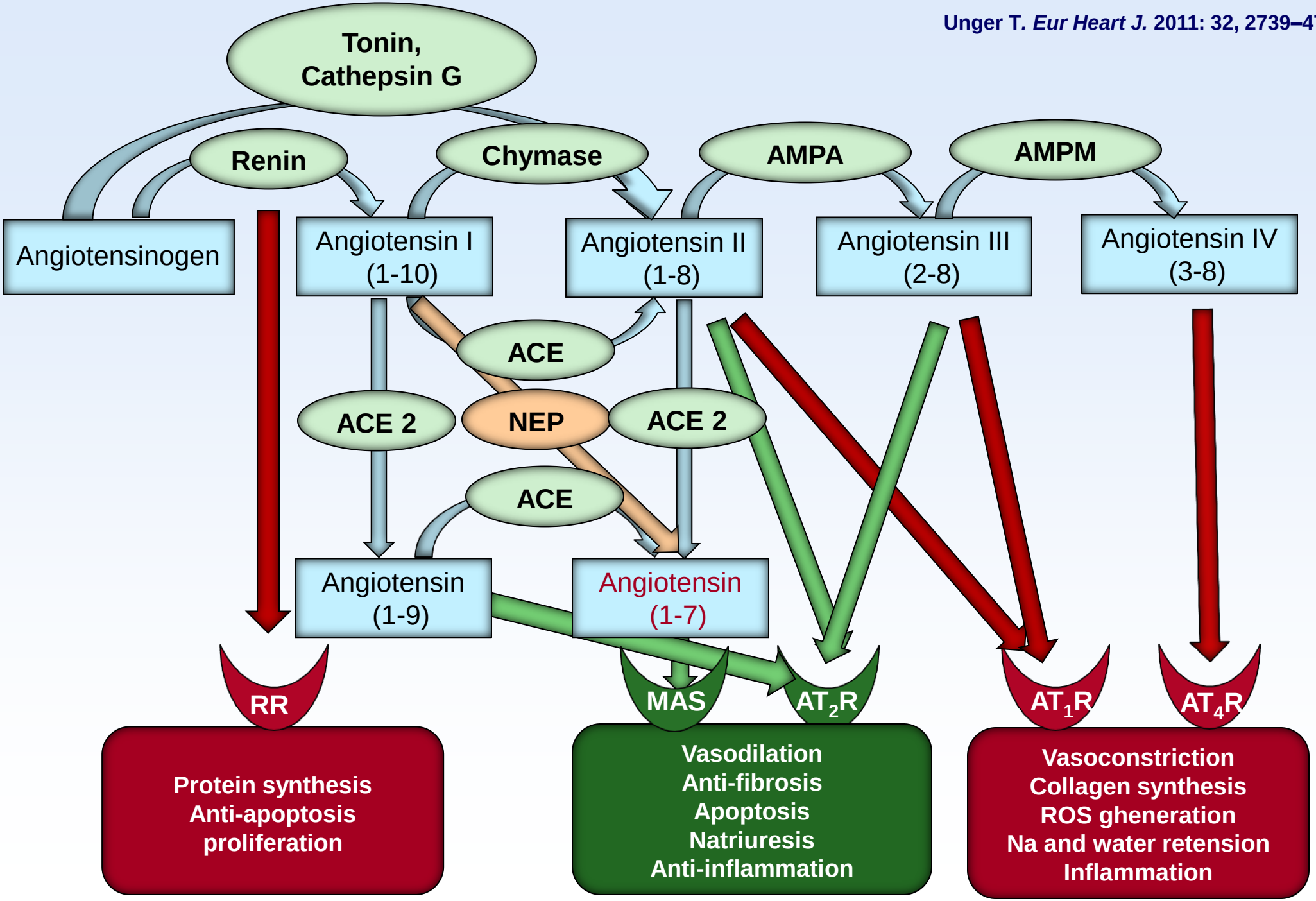
   - First-in class dual ACE and NEP antagonist, Omapatrilat

   - First-in-class dual AT1R and NEP antagonist, LCZ 696

Unger T. *Eur Heart J.* 2011: 32, 2739–47



Unger T. *Eur Heart J.* 2011: 32, 2739–47



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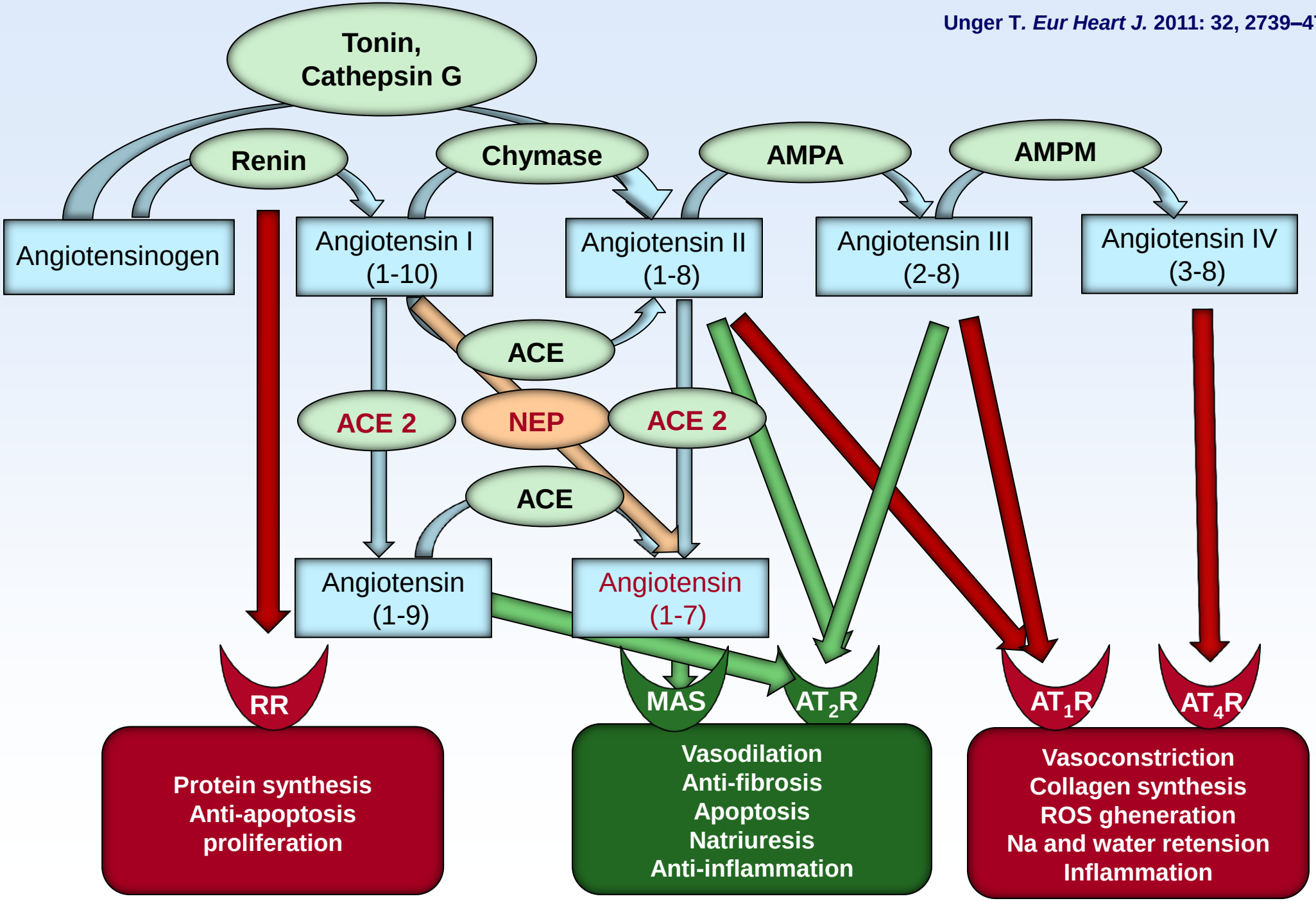
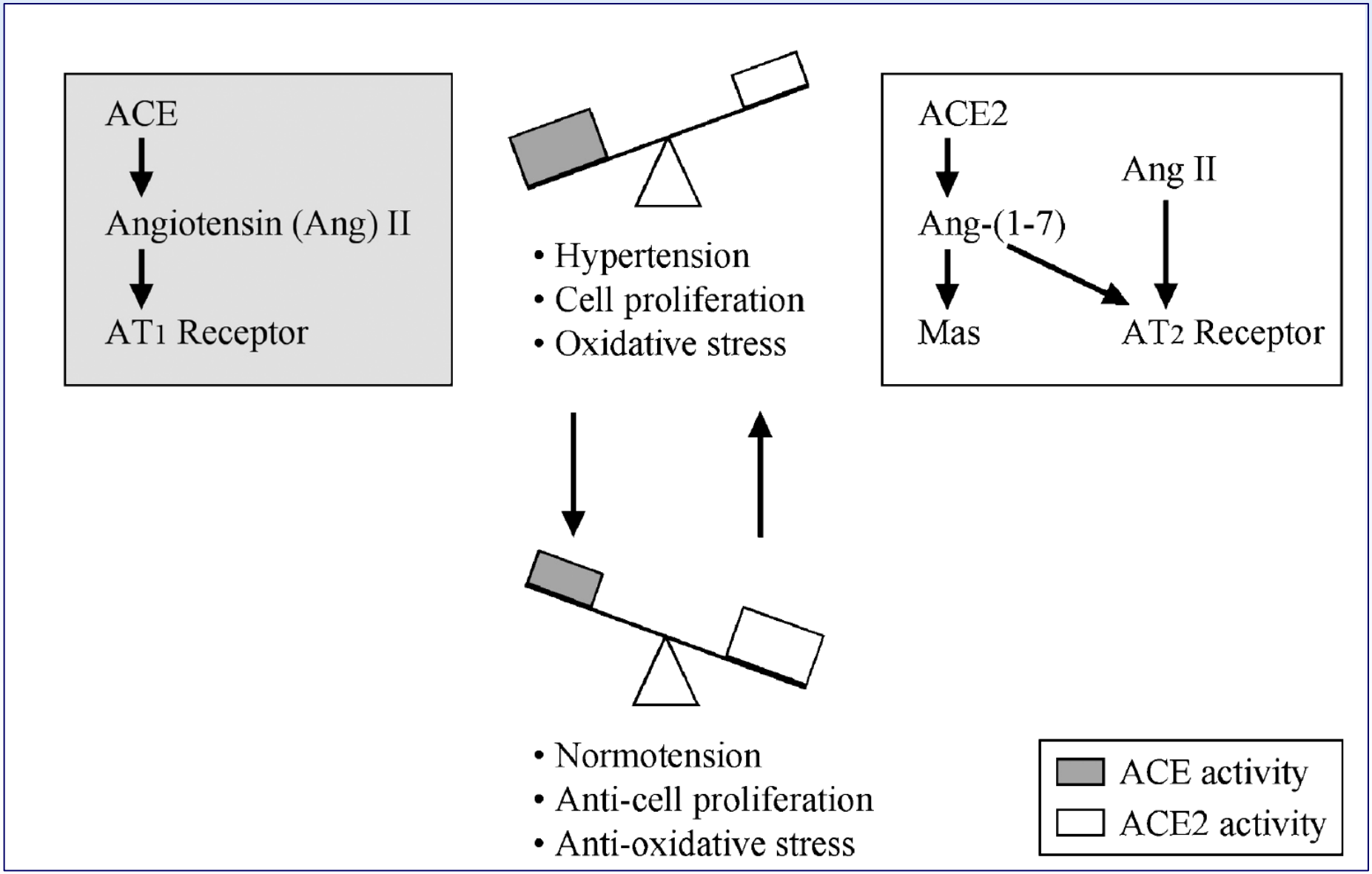




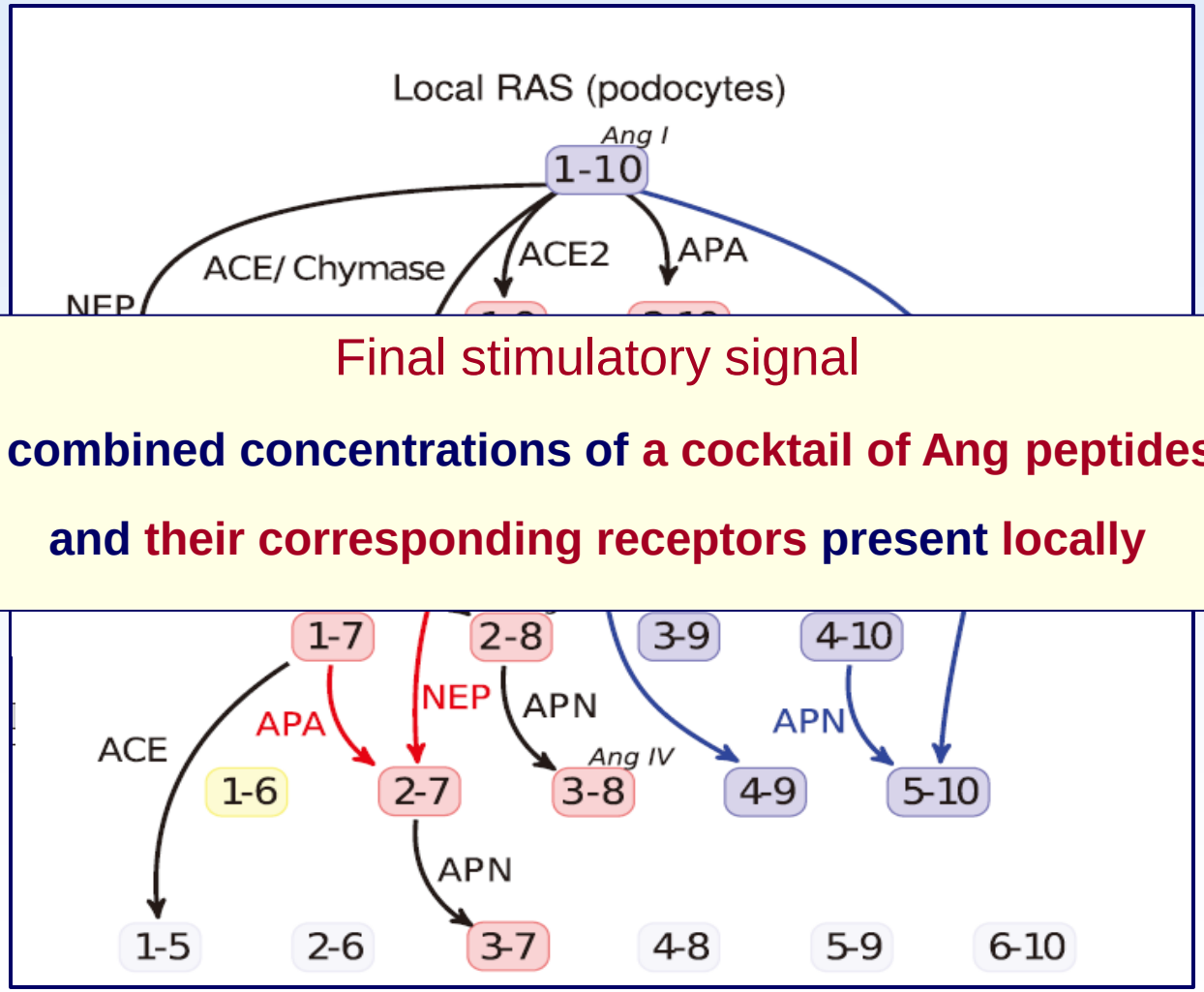
Iwai M. *Hypertension Res.* 2009: 32, 533–536

Complex Network of the Renin-Angiotensin-Aldosterone System

- **Angiotensin I (1-10)**
  → Angiotensin 1–7 by neutral endopeptidase
  → Angiotensin 1–9 (intermmediate product) → angiotensin 1–7 by ACE and ACE2
- **Angiotensin 1–7**
  → Angiotensin 1–5 by ACE
- **Angiotensin II (1-8)**: to **angiotensin III (2-8) and IV (3-8)** by aminopeptidase A and M.
- **Angiotensin II type 1 receptor**: by angiotensin II and III
- **Angiotensin type 4 receptor**: stimulation by angiotensin IV
- **Angiotensin II type 2 receptor** : by angiotensin II, angiotensin 1–9, and angiotensin III
- **Mas receptor**: by angiotensin 1–7

Unger T. *Eur Heart J.* 2011: 32, 2739–47

Proposed Network Modeling: Angiotensin Peptide Processing



Final stimulatory signal

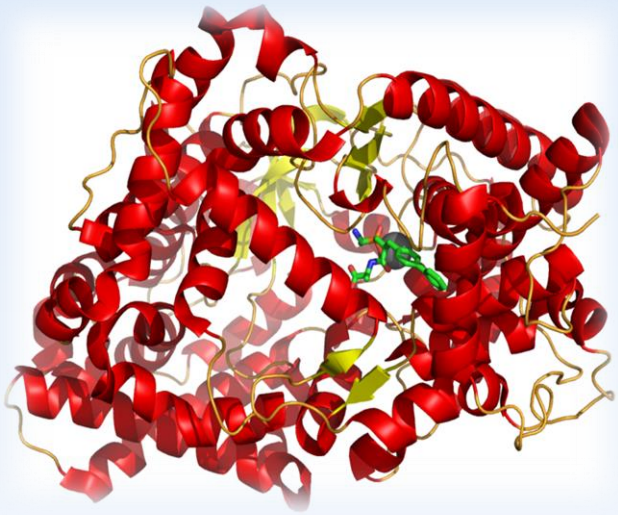
: combined concentrations of a cocktail of Ang peptides

and their corresponding receptors present locally

bioactive peptides (red), undetected peptides (yellow), all other peptides (blue)
black line: supported in literature

Schwacke JH. *Hypertension.* 2013: 61, 690–700

Neutral Endopeptidase (NEP)



- Also known as
  neprilysin,
  membrane metallo-endopeptidase (MME),
  cluster of differentiation 10 (CD10),
  common acute lymphoblastic leukemia antigen (CALLA)
- Enzyme encoded by the MME gene (human)

- NEP: zinc-dependent, membrane bound endopeptidase
  - hydrolyses peptides on the amino side of hydrophobic residues
- Expression: widely expressed in mammals
  - kidney, lung, endothelial cells, vascular smooth muscle cells, cardiac myocytes, fibroblasts, neutrophils, adipocytes, testes, brain

Neutral Endopeptidase (NEP)

- Critical for the processing and catabolism

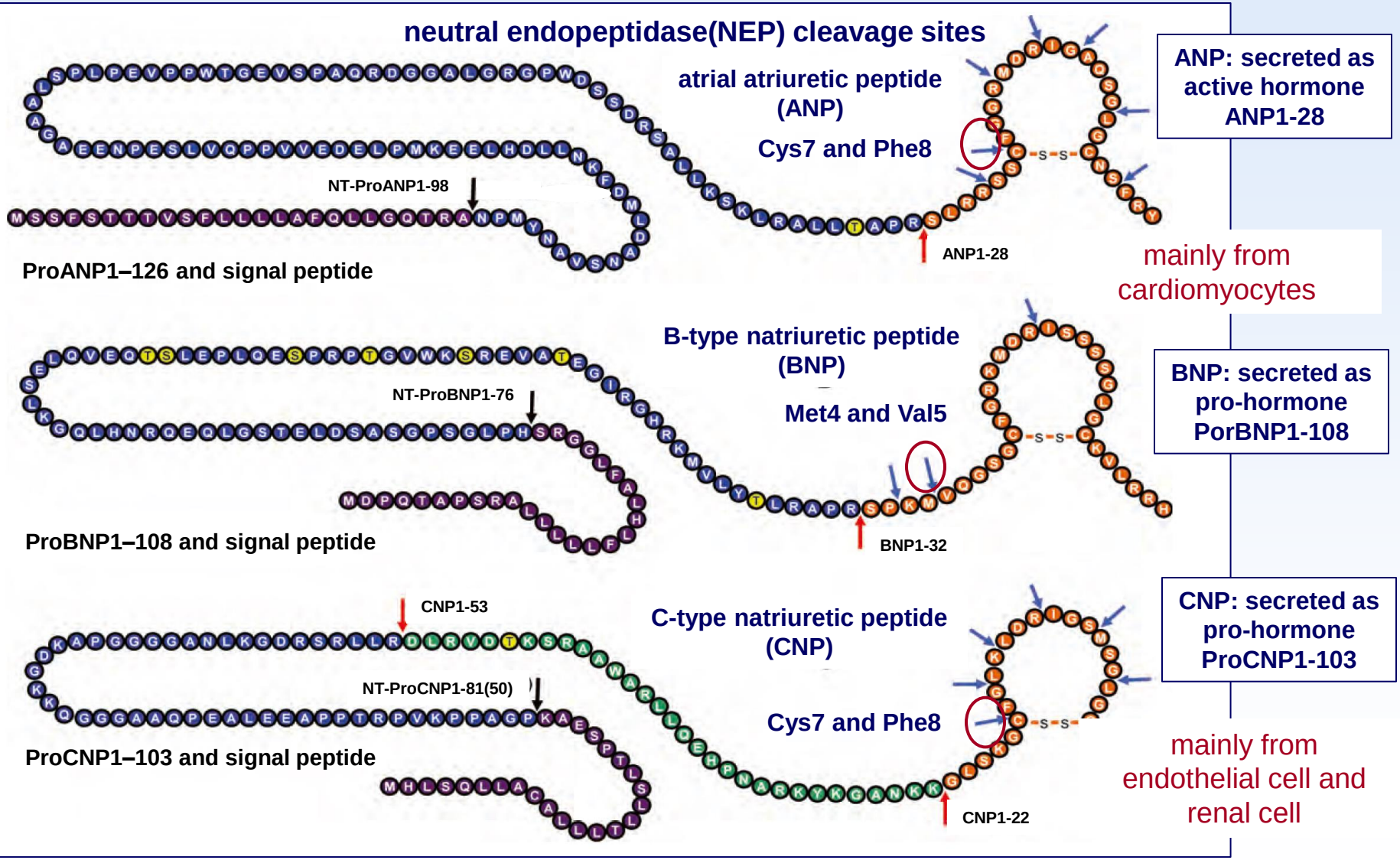
  ① vasoactive peptides and peptides involved in diuresis, natriuresis

  : natriuretic peptides (NPs), angiotensin I, bradykinin, endothelin-1

  ② other substrates

  opioid peptides
  substance P
  peptides involved in regulation of inflammation
  amyloid β-protein
  gastrin

Three major human endogenous natriuretic peptides (NP)



Mangiafico S. *Eur Heart J.* 2013: 34, 2886–93

Natriuretic Peptide(NP) System

- ANP: mainly from cardiomyocytes in reponse to cardiac stretch
  - secreted as the active hormone ANP1–28

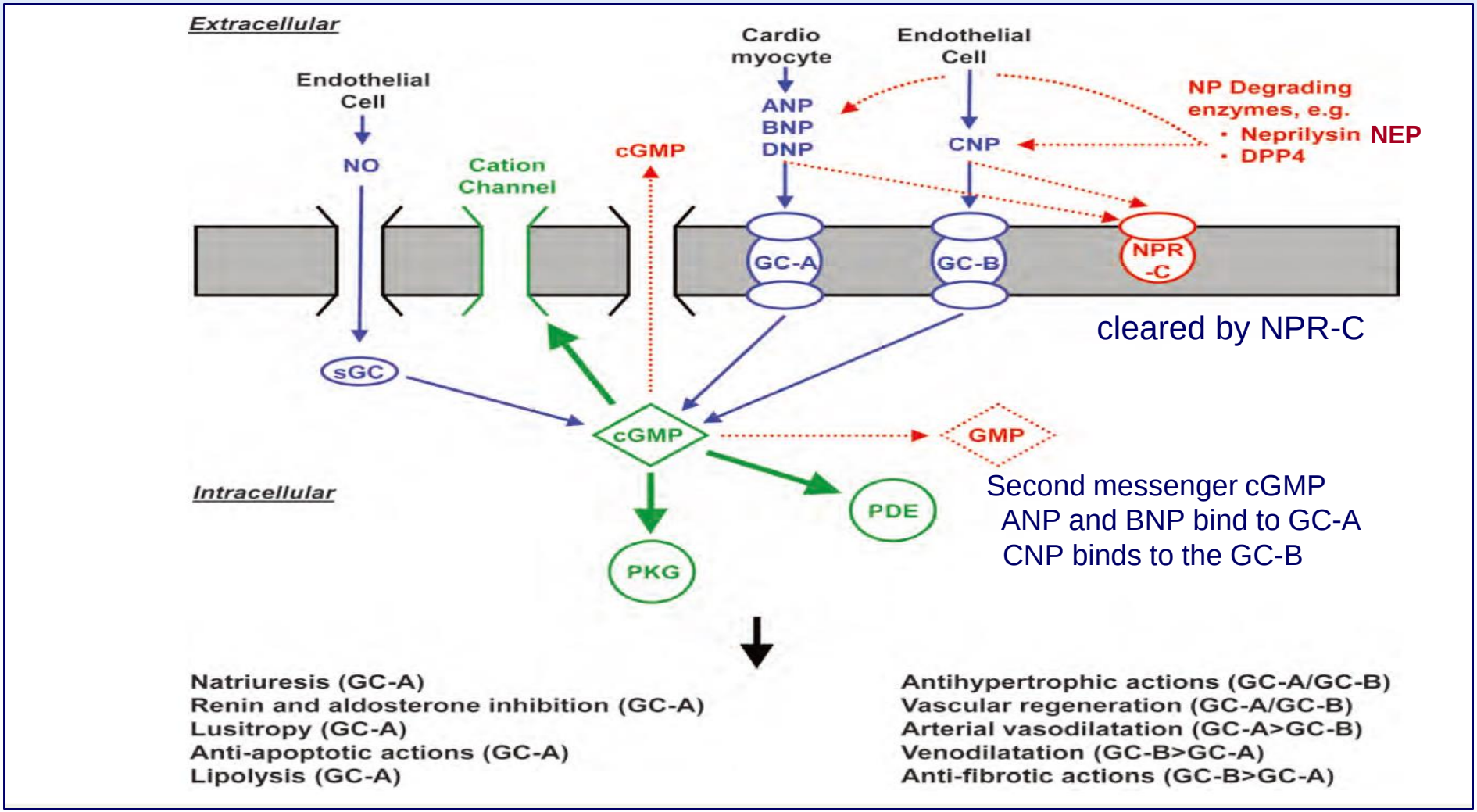
- BNP: mainly from cardiomyocytes in reponse to cardiac stretch
  - secreted as 108 amino acid prohormone (proBNP1–108) in a glycosylated form biologically active BNP1-32, inactive N-terminal (NT)-proBNP1-76

- CNP : mostly from endothelial cells in response to cytokines and endothelium dependent agonists such as Acetylcholine
  - secreted as prohormone (pro-CNP1-103) biologically active CNP1-22 and CNP 1-53

- CNP : potent systemic cardiovascular actions
  - vasorelaxation, $\downarrow$ in venous return $\rightarrow$ $\downarrow$ cardiac filling pressures
  - the most anti-fibrotic of the three NPs

Mangiafico S. *Eur Heart J.* 2013: 34, 2886–93

Actions of the NPs through GC-A and GC-B activation



Mangiafico S. *Eur Heart J.* 2013: 34, 2886–93

Actions of the NPs

- Biological properties
  - natriuresis
  - vasodilatation
  - inhibition of the RAS
  - positive lusitropism
  - inhibition of fibrosis

- Modulation of NP for target-organ protection,
  BP control,
  optimal volume homeostasis,
  inhibition or reversal of myocardial and renal remodeling

  $\rightarrow$ novel therapeutic opportunity

Content

Novel RAS and Neutral Endopetidase (NEP)

- **Complex network of RAS**
- **NEP and vasoactive peptide**

Novel strategy to inhibit the RAS and NEP

- **First-in class dual ACE and NEP antagonist, Omapatrilat**
- **First-in-class dual AT1R and NEP antagonist, LCZ 696**

Selective Neutral Endopeptidase (NEP) Inhibition

- Degradation of NPs by NEP
- Many substrates for NEP : peptides with vasoactive and diuretic/natriuretic actions
- NEP also degrades other vasoactive peptides with opposing physiological actions

  - desirable vs undesirable effects

- NEP : ① hydrolyses Ang I to angiotensin 1–7 (counteraction of vasoconstrictor Ang II)
  ② catabolizes the potent vasoconstrictor ET-1
  → produces a potentially beneficial BP-lowering effect.

- NEP: ① hydrolyses NPs
  ② hydrolyses BK to the inactivated BK 1–7

Candoxatril : one of the first NEP inhibitor

- In humans,
  - dose-dependent increase in plasma ANP, natriuresis, cGMP
    also increased Ang II level

- Candoxatril's effects on BP in hypertensive patients were not consistently impressive
  - candoxatril 200 mg, twice/day for 28 days, compared with placebo in essential HT
    → no relevant BP decrease occurred despite significantly increased ANP levels

NEP inhibition in HT
- produces the competing effects of increased pressors and increased vasodilators
- an insignificant BP-lowering

- In human HF
  - increased ANP and BNP, diuresis and natriuresis, and decreased ANP clearance
  - systemic and pulmonary vascular resistances were not affected

- In small studies of chronic HF patients
  - increased levels of the vasoconstrictor ET-1 as well as ANP levels
  - dose-dependent increase in systemic vascular resistance, decrease in cardiac index

Lesson from inhibition of NEP only

NEP inhibition alone
- increase in circulating levels of both vasodilators as well as vasoconstrictors

New strategy

- NEP inhibition: increases endogenous NP levels
- ACE inhibition attenuates the Ang II increases seen with NEP inhition alone

Inhibition both NEP and ACE, and vasopeptidase inhibitors

- In preclinical studies, these compounds showed promise for HT, HF, and renal disease however, their side effect profile in clinical trials stunted development
- Of particular concern was the high incidence of angioedema

Dual inhibition of NEP and ACE: Omapatrilat

- Omapatrilat : VPI in the most advanced stage of development

- IMPRESS trial: N= 573 (289 vs 284) for 24 wks, compared with lisinopril in HF patients
  - positive in composite of death, admission, or study treatment discontinuation for worsening HF, improvement of NYHA class (p=0·035; 0·52 [0·28–0·96])

Rouleau JL. *Lancet.* 2000: 356, 615–20

- OVERTURE trial: N=5770, for 14.5 months
  Omapatrilat (n:2886) vs enalapril (n:2884) in chronic HF patients
  - no superiority of omapatrilat over enalapril with respect to the primary endpoint (combined risk of death or hospitalization for HF requiring intravenous treatment)

McMurray JJ. *Circulation*. 2002;106:920-926

- Safety database: relatively high occurrence of severe angioedema in African-Americans

Dual inhibition of NEP and ACE: Omapatrilat

- OCTAVE trial, large (n= 25,302), randomized, active controlled, multicenter trial
  - omapatrilat vs enalapril for 6 months in HT patients
  - omapatrilat : started at a low dose and titrated up
  - by 8 wks, reduced systolic BP 3.6 mmHg more than enalapril
    by 24 wks, less adjunctive anti-HT therapy than enalapril

Kostis JB. *Am J Hypertens* 2004;17:103–111

- Higher incidence of angioedema (2.17% for omapatrilat vs. 0.68% for enalapril)
  - occurred early in the course of therapy
- Angioedema development with VPIs remains a persistent concern
- Inhibition of aminopeptidase P (APP), which was also potently inhibited by omapatrilat, is an important consideration.
- Aminopeptidase P has a role both in BK degradation when ACE is inhibited and in the inactivation of the pro-inflammatory BK metabolite, des-Arg9-BK

Lesson form dual inhibition of NEP and ACE

- NEP inhibition: increases endogenous NP levels
- ACE inhibition attenuates the Ang II increases seen with NEP inhibition alone

“ angioedema” - mainly bradykinin

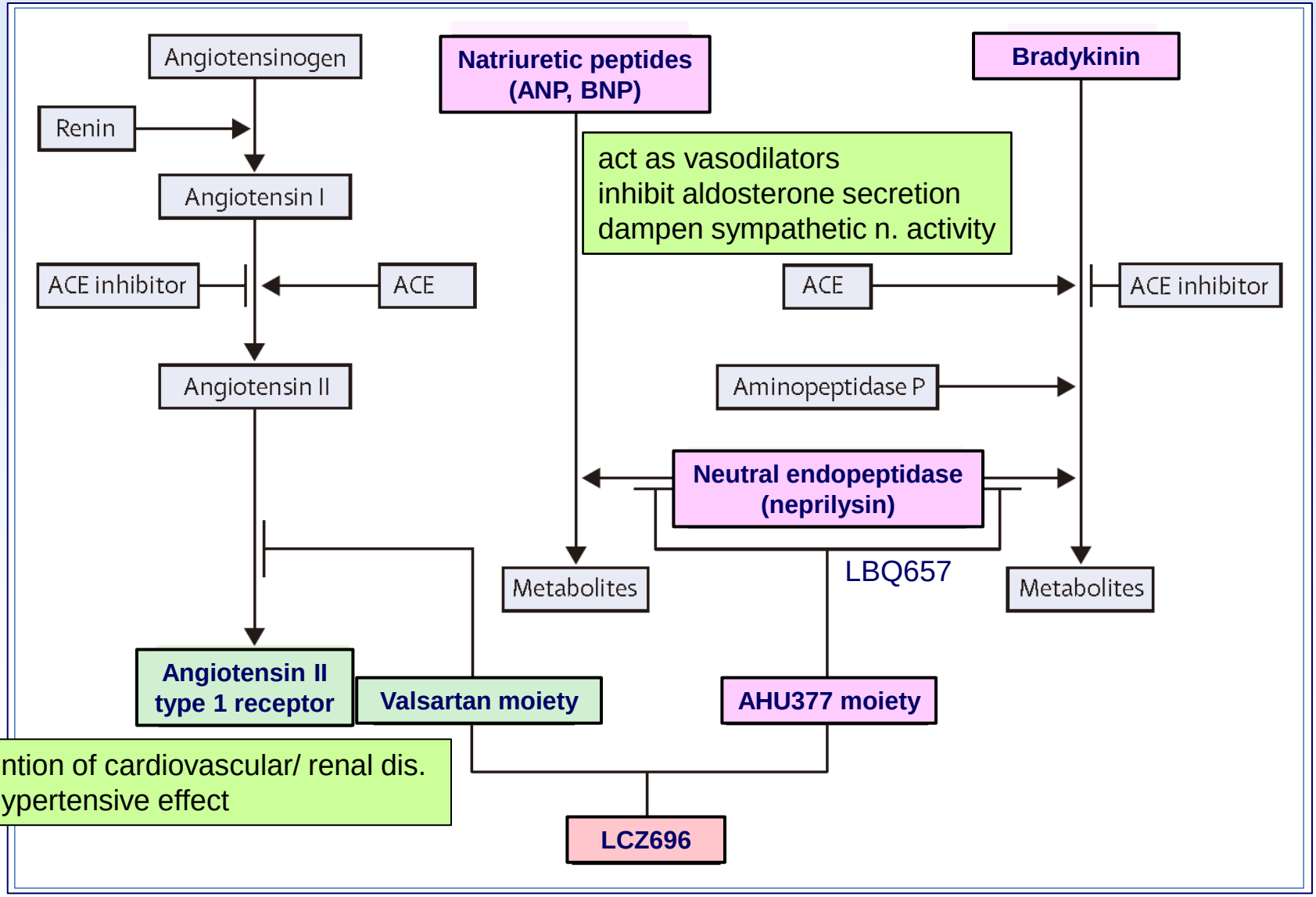
- NEP inhibition: increases endogenous NP levels
- ARB inhibition attenuates the Ang II increases seen with NEP inhibition alone

ARB: do not disrupt BK metabolism as much as ACE-inhibitors

Dual inhibition of NEP and ARB: LCZ696

- ARB : not disrupt BK metabolism as much as ACE-inhibitors
- Novel class of drug: ARB and neutral endopeptidase inhibition (ARNi).
- LCZ696 (sucabitril valsartan sodium hydrate)
  - 1:1 ratio blockade of AT1R (valsartan moiety) and NEP inh (AHU377 prodrug moiety)
    AHU377 prodrug : LBQ657 active moiety

Mechanism of LCZ696 on RAS and natriuretic peptides



Waeber B, Lancet 2010 375: 1228-9

Dual inhibition of NEP and ARB: LCZ696 in HT

- In an 8-week, randomized, double-blind, Phase II trial in HT patients
  - various doses of LCZ696 vs comparable doses of valsartan.

- Result
  - greater reductions in sitting SBP and DBP than valsartan-treated subjects.
  - 200 mg LCZ696, (mid range dose) vs. 160 mg valsartan
    400 mg LCZ696 (highest dose) vs. 320 mg valsartan
  - in a separate group treated with AHU377 alone

- Angioedema did not occurs with 8% of the ARNi-treated subjects being black

Dual inhibition of NEP and ARB: LCZ696 in HF

- Ongoing trial: LCZ696 in chronic HF and in chronic HF with preserved EF

- PARADIGM-HF trial
  - Phase III study in symptomatic HF
    LCZ696 vs enalapril : first occurrence of HF hospitalization or CV mortality

- Paramount HF trial
  - Phase II, HF with preserved EF
  - NYHA class II–III HF, LV EF 45% or higher, NT-proBNP greater than 400 pg/mL
  - LCZ696 vs valsartan: actions on neurohormones and on EchoCG findings

Angiotensin II receptor and neprilysin inhibitor LCZ696 in HT

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.

Ruilope LM, *Lancet* 2010, 375: 1255-66

- N = 1328, aged 18-75 years, ucomplicated mild-to moderate essential HT
  mean sitting DBP 90-109 mm Hg after antihypertensive washout
  or 95-109 mm Hg for untreated pts

- 8 weeks' treatment
  8 groups: LCZ 696 - 100 mg (n=156), 200 mg (n=169), or 400 mg (n=172)
  Valsartan - 80 mg (n=163), 160 mg (n=166), or 320 mg (n=164)
  AHU377 - 200 mg (n=165)
  placebo (n=173)

- primary endpoint :
  mean sitting DBP difference across: three single-dose pair LCZ696 vs valsartan
  (100 *vs* 80 mg, 200 *s* 160 mg, and 400 *s* 320 mg)

Results

- N= 1328 $\rightarrow$ 1215 pts completed 8-week treatment.
  - average reduction in mean sitting DBP in LCZ696 vs comparator dose of valsartan
    : significantly greater reductions (mean reduction: -2.17 mmHg, p<0·0001).
    200 mg LCZ696 vs 160 mg valsartan (-2.97 mmHg, p=0·0023)
    400 mg LCZ696 vs 320 mg valsartan (-2.70 mmHg, p=0·0055)

  - LCZ696 was well tolerated and no cases of angio-oedema were reported

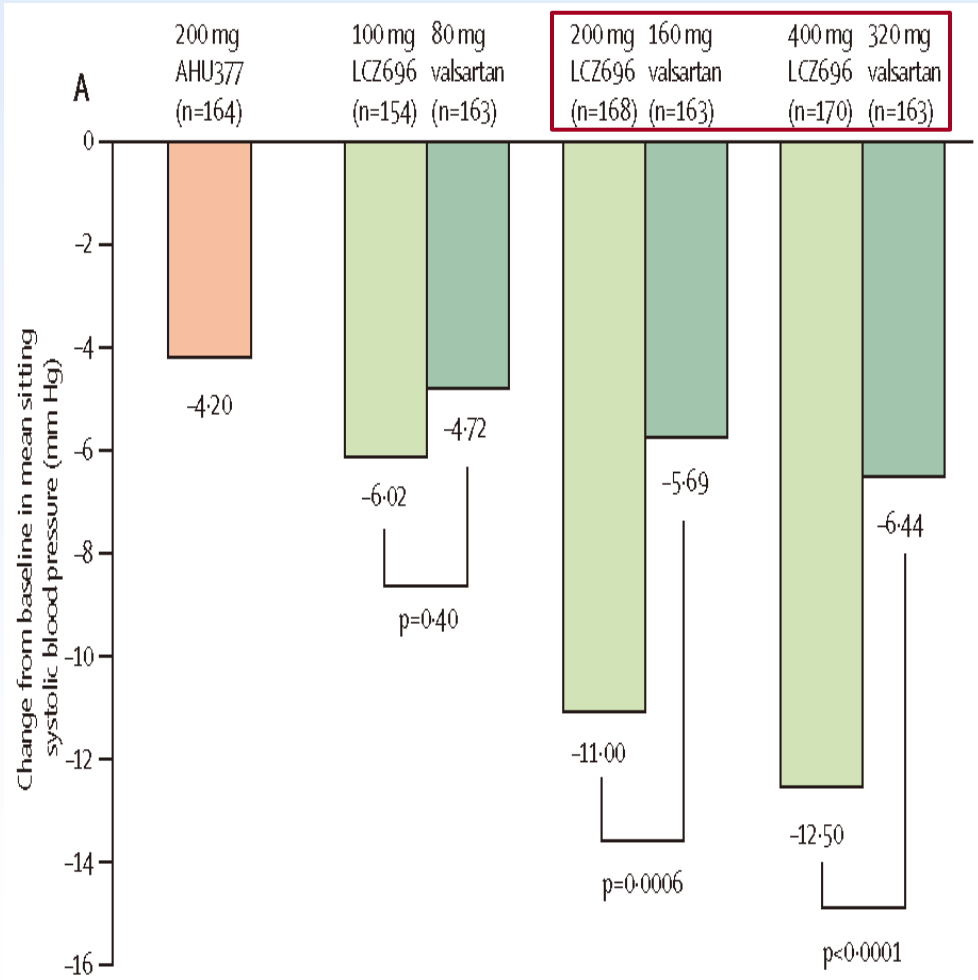
	Placebo (n=173)	200 mg AHU377 (n=165)	100 mg LCZ696 (n=156)	200 mg LCZ696 (n=169)	400 mg LCZ696 (n=172)	80 mg valsartan (n=163)	160 mg valsartan (n=166)	320 mg valsartan (n=164)
Age (years)	54 (10·6)	53 (10·7)	53 (10·4)	54 (9·7)	52 (10·9)	53 (9·6)	53 (9·7)	53 (10·1)
<65 years	145 (84%)	139 (84%)	129 (83%)	145 (86%)	152 (88%)	142 (87%)	146 (88%)	143 (87%)
≥65 years	28 (16%)	26 (16%)	27 (17%)	24 (14%)	20 (12%)	21 (13%)	20 (12%)	21 (13%)
Sex								
Female	79 (46%)	75 (45%)	61 (39%)	77 (46%)	75 (44%)	68 (42%)	68 (41%)	65 (40%)
Male	94 (54%)	90 (55%)	95 (61%)	92 (54%)	97 (56%)	95 (58%)	98 (59%)	99 (60%)
Race								
White	155 (90%)	140 (85%)	139 (89%)	148 (88%)	150 (87%)	144 (88%)	139 (84%)	145 (88%)
Black	10 (6%)	17 (10%)	10 (6%)	13 (8%)	15 (9%)	9 (6%)	19 (11%)	12 (7%)
Asian	4 (2%)	5 (3%)	4 (3%)	4 (2%)	2 (1%)	7 (4%)	5 (3%)	5 (3%)
Other	4 (2%)	3 (2%)	3 (2%)	4 (2%)	5 (3%)	3 (2%)	3 (2%)	2 (1%)
Ethnic origin								
Hispanic or Latino	30 (17%)	34 (21%)	26 (17%)	26 (15%)	34 (20%)	27 (17%)	31 (19%)	27 (16%)
Mixed	7 (4%)	5 (3%)	5 (3%)	6 (4%)	3 (2%)	6 (4%)	8 (5%)	3 (2%)
Chinese	3 (2%)	6 (4%)	3 (2%)	3 (2%)	2 (1%)	3 (2%)	3 (2%)	2 (1%)
Filipino	1 (1%)	1 (1%)	0	3 (2%)	1 (1%)	2 (1%)	2 (1%)	1 (1%)
Indian (Indian subcontinent)	0	0	2 (1%)	0	0	0	0	1 (1%)
Other	132 (76%)	119 (72%)	120 (77%)	131 (78%)	132 (77%)	125 (77%)	122 (73%)	130 (79%)
Duration of hypertension (years)*	6·8 (7·3)	6·7 (7·8)	6·9 (7·2)	7·2 (6·7)	6·5 (7·5)	6·6 (6·7)	7·1 (7·4)	6·5 (6·7)
Blood pressure (mm Hg)								
Diastolic	99·0 (3·82)	99·9 (4·46)	99·9 (3·62)	99·9 (4·06)	100·4 (4·06)	99·5 (4·10)	99·8 (4·41)	99·5 (3·63)
Systolic	155·1 (11·26)	156·4 (13·22)	154·9 (11·89)	156·8 (11·98)	156·3 (12·32)	154·8 (10·53)	155·3 (10·79)	156·0 (11·48)

Data are mean (SD) or number of patients (%). *Data supplied for 170 patients on placebo, 164 on 200 mg AHU377, 154 on 100 mg LCZ696, 168 on 200 mg LCZ696, 172 on 400 mg LCZ696, 162 on 80 mg valsartan, 166 on 160 mg valsartan, and 162 on 320 mg valsartan; data were missing for remaining patients. †Data were recorded at study entry (week 0) apart from blood pressure measurements, which were recorded at baseline (week 4) just before patients were given the first dose of study drug.

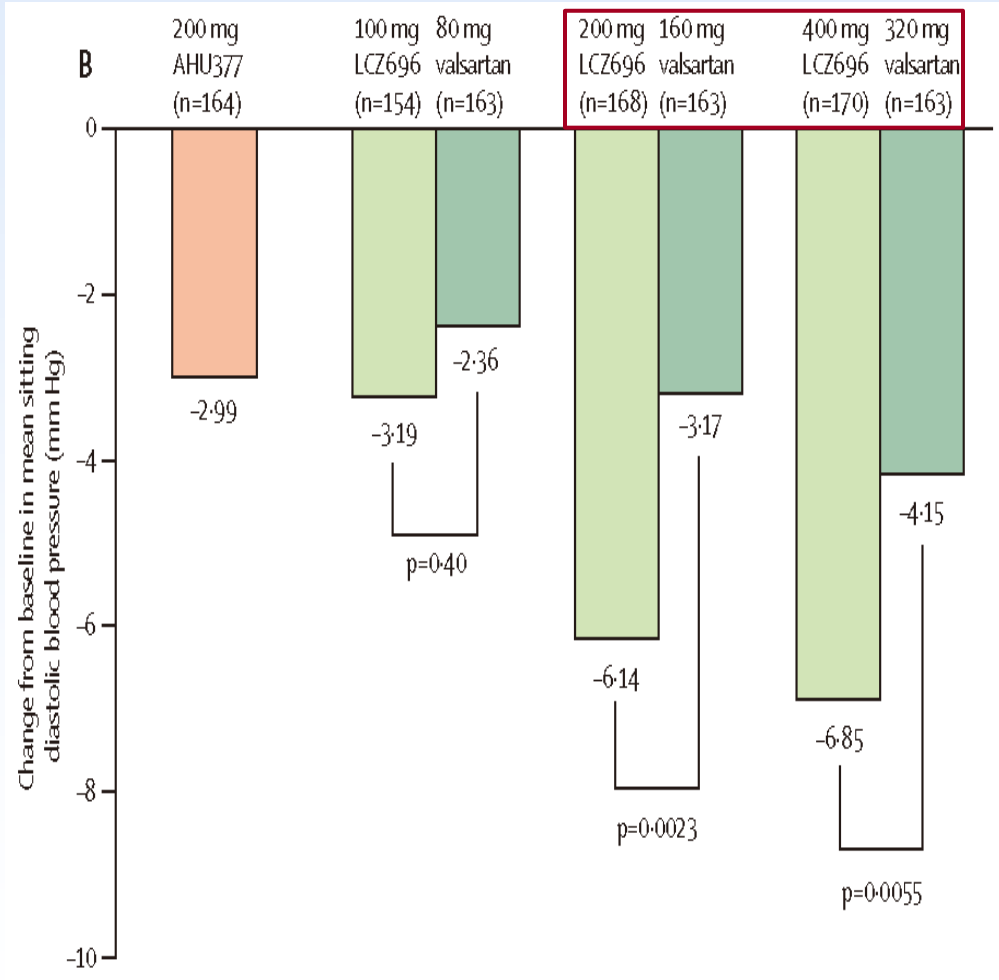
Ruilope LM, *Lancet* 2010, 375: 1255-66

Change in placebo-subtracted mean sitting SBP and DBP - during the 8-week treatment period

Mean sitting systolic blood pressure

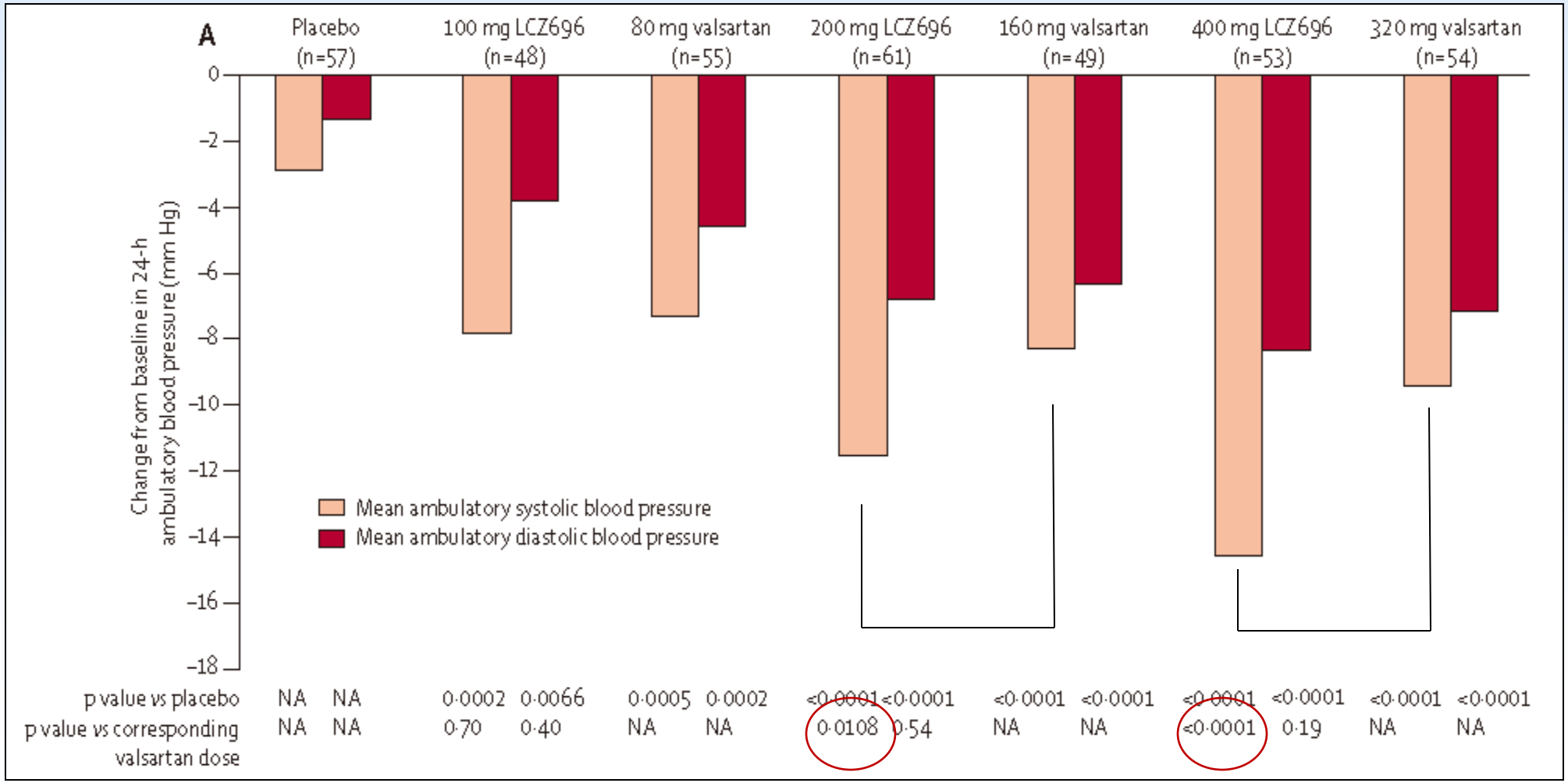


Mean sitting diastolic blood pressure

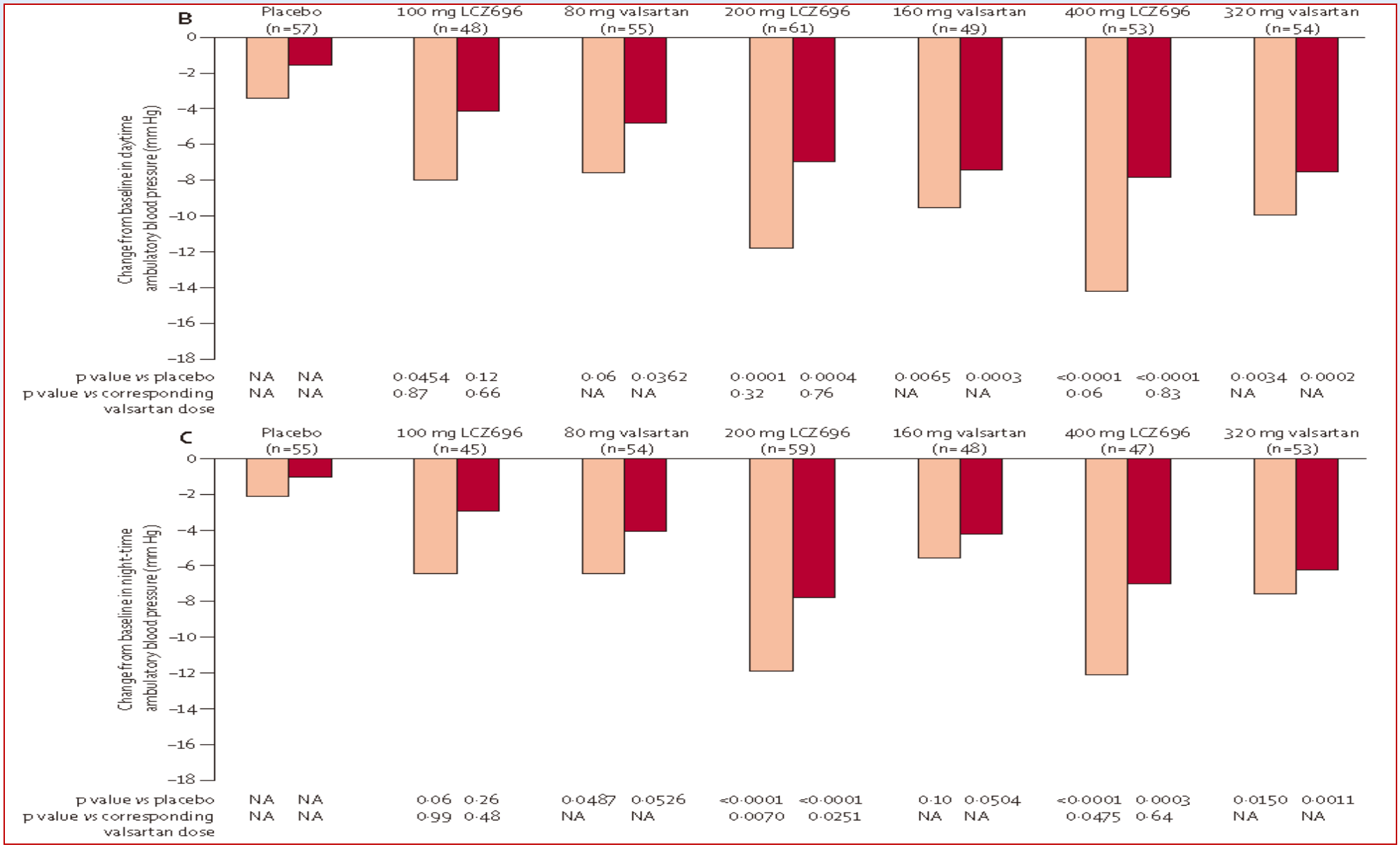


Ruilope LM, *Lancet* 2010, 375: 1255-66

Change in 24-h Ambulatory Blood Pressure

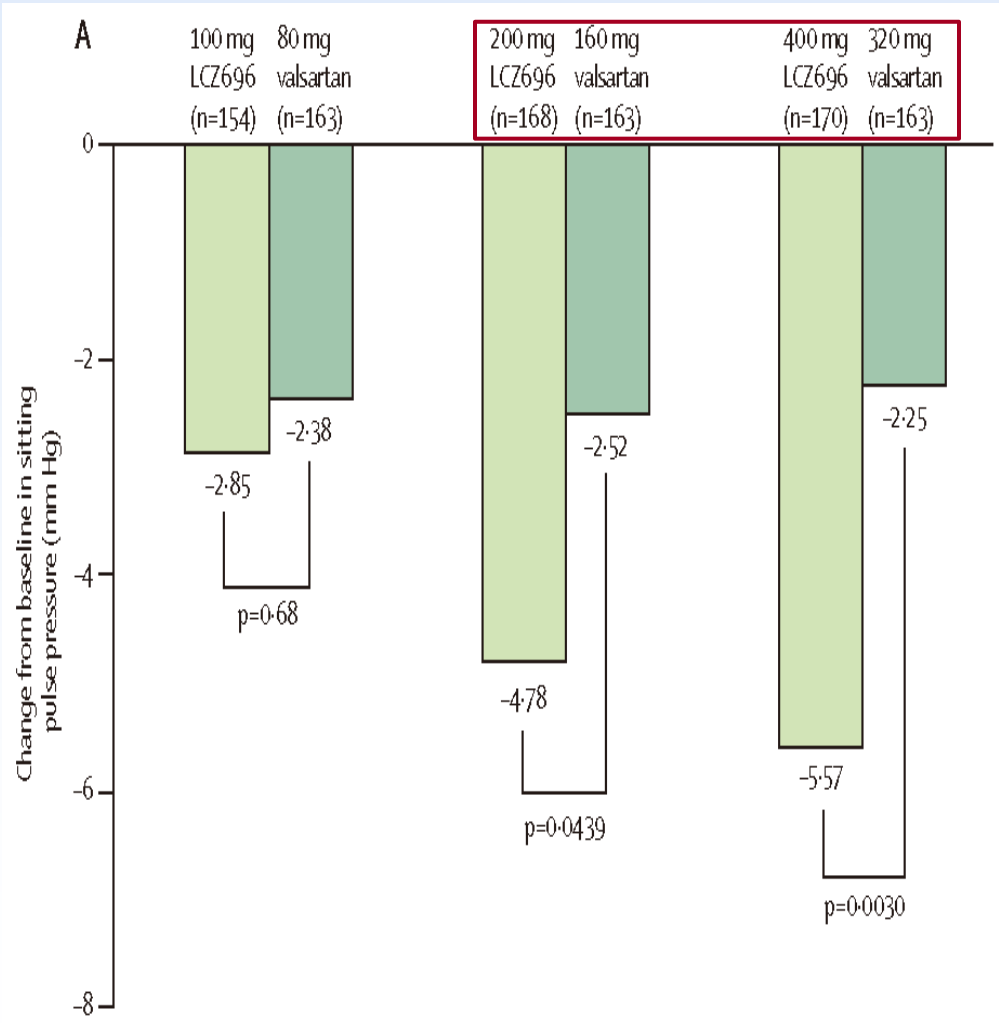


Change in daytime and night-time Ambulatory Blood Pressure

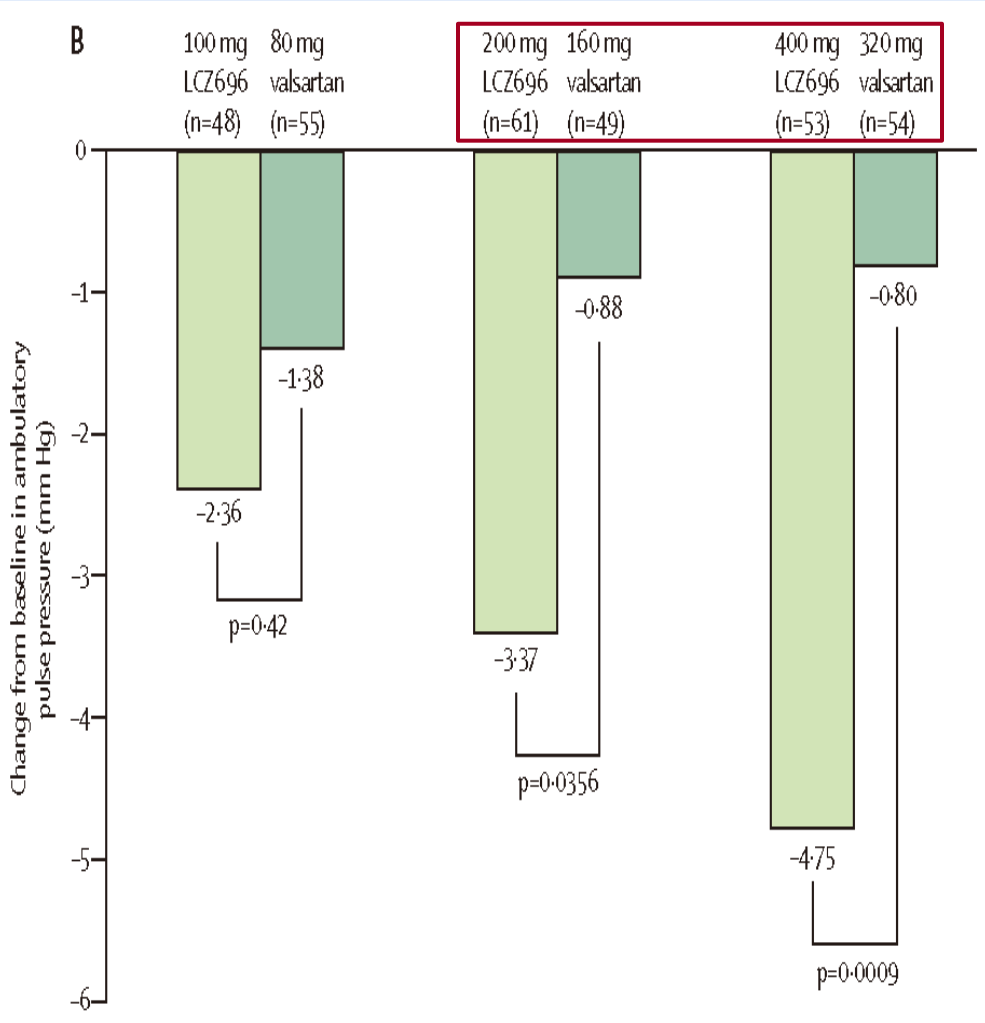


Change in placebo-subtracted sitting, ambulatory pulse pressure - during the 8-week treatment period

Mean sitting pulse pressure



Mean ambulatory pulse pressure



Ruilope LM, *Lancet* 2010, 375: 1255-66

Neurohormonal and Biomarker measurements for the 8-week

	Placebo	200 mg AHU377	p value*	100 mg LCZ696	80 mg valsartan	p value†	200 mg LCZ696	160 mg valsartan	p value†	400 mg LCZ696	320 mg valsartan	p value†
Plasma atrial natriuretic peptide (pg/mL)			**ANP**									
Number of patients	57	64	..	59	62	..	72	61	..	76	62	..
Baseline	46·8 (41·4 to 52·8)	40·7 (36·4 to 45·5)	..	39·1 (35·6 to 43·0)	43·2 (39·0 to 47·8)	..	42·7 (38·8 to 46·9)	43·3 (38·6 to 48·5)	..	41·7 (37·6 to 46·1)	42·9 (38·9 to 47·2)	..
Change from baseline	0% (−9 to 10)	32% (21 to 44)¶	<0·0001	13% (2 to 24)	−9% (−17 to 0)	0·0008	18% (8 to 28)‡	−11% (−19 to −3)	<0·0001	15% (5 to 24)‡	−3% (−16 to 6)	0·0042
Cyclic guanosine monophosphate (nmol/L)			**cGMP**									
Number of patients	61	66	..	61	65	..	75	63	..	77	69	..
Baseline	6·7 (6·1 to 7·2)	6·2 (5·7 to 6·8)	..	5·7 (5·2 to 6·2)	5·7 (5·2 to 6·2)	..	5·9 (5·5 to 6·4)	6·1 (5·5 to 6·6)	..	6·2 (5·9 to 6·6)	6·3 (5·9 to 6·7)	..
Change from baseline	−3% (−10 to 5)	21% (13 to 30)¶	<0·0001	10% (2 to 19)‡	−7% (−14 to 0)	0·0006	10% (3 to 18)‡	−8% (−15 to −1)	0·0002	9% (2 to 17)‡	−9% (−16 to −3)	<0·0001
Plasma renin (mU/L)			**Renin**									
Number of patients	34	42	..	31	51	..	46	43	..	56	51	..
Baseline	11·8 (9·1 to 15·2)	10·7 (9·4 to 12·1)	..	11·0 (9·1 to 13·2)	9·6 (8·4 to 11·0)	..	10·2 (8·9 to 11·6)	10·6 (9·0 to 12·5)	..	11·3 (9·6 to 13·3)	13·1 (10·5 to 16·4)	..
Change from baseline	13% (−13 to 47)	12% (−11 to 42)	<0·0001	72% (31 to 126)‡	79% (44 to 123)‡	0·82	94% (55 to 143)§	77% (41 to 124)‡	0·56	157% (108 to 216)¶	162% (111 to 226)¶	0·89

Neurohormonal and Biomarker measurements for the 8-week

	Placebo	200 mg AHU377	p value*	100 mg LCZ696	80 mg valsartan	p value†	200 mg LCZ696	160 mg valsartan	p value†	400 mg LCZ696	320 mg valsartan	p value†
Plasma aldosterone (pmol/L)												
Number of patients	50	54	..	43	54	..	58	48	..	67	52	..
Baseline	217·7 (192·5 to 246·2)	233·0 (206·2 to 263·2)	..	237·8 (206·3 to 274·0)	200·8 (179·8 to 224·3)	..	231·1 (206·9 to 258·2)	245·7 (212·4 to 284·3)	..	224·6 (202·1 to 249·7)	263·4 (234·4 to 296·0)	..
Change from baseline	8% (–6 to 23)	4% (–9 to 19)	0·85	14% (–1 to 32)	10% (–4 to 25)	0·64	4% (–8 to 17)	–8% (–20 to 5)	0·15	8% (–4 to 22)	2% (–11 to 16)	0·46
High-sensitivity C-reactive protein (mg/L)												
Number of patients	61	69	..	60	65	..	73	60	..	82	69	..
Baseline	2·1 (1·6 to 2·7)	2·1 (1·6 to 2·7)	..	2·5 (2·0 to 3·3)	2·6 (2·1 to 3·2)	..	1·9 (1·5 to 2·5)	2·1 (1·7 to 2·7)	..	1·9 (1·5 to 2·4)	2·1 (1·7 to 2·6)	..
Change from baseline	17% (–6 to 45)	6% (–14 to 31)	0·60	–2% (–22 to 23)	23% (–1 to 53)	0·14	14% (–7 to 39)	–3% (–23 to 22)	0·28	–8% (–24 to 11)	18% (–5 to 45)	0·07
Urinary albumin-to-creatinine ratio (mg/mmol)												
Number of patients	49	62	..	54	60	..	59	49	..	68	58	..
Baseline	1·2 (0·9 to 1·6)	1·5 (1·2 to 2·0)	..	1·2 (0·9 to 1·6)	1·5 (1·1 to 2·1)	..	1·3 (1·0 to 1·6)	1·5 (1·1 to 2·2)	..	1·2 (0·9 to 1·4)	1·1 (0·9 to 1·3)	..
Change from baseline	24% (2 to 49)	–2% (–18 to 16)	0·28	–10% (–25 to 9)‡	–16% (–30 to 0)‡	0·55	–4% (–20 to 14)‡	–12% (–27 to 6)‡	0·49	–12% (–25 to 4)‡	–10% (–24 to 8)‡	0·86

Adverse Events

	Placebo (n=173)	200 mg AHU377 (n=165)	100 mg LCZ696 (n=156)	200 mg LCZ696 (n=169)	400 mg LCZ696 (n=172)	80 mg valsartan (n=163)	160 mg valsartan (n=166)	320 mg valsartan (n=164)
Any adverse event	49 (28%)	45 (27%)	36 (23%)	40 (24%)	50 (29%)	36 (22%)	34 (20%)	38 (23%)
Adverse events reported in ≥2% of patients in any treatment group								
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%)
Pharyngolaryngeal pain	0	4 (2%)	0	0	1 (1%)	0	0	0
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%)
Upper-respiratory-tract infection	0	2 (1%)	2 (1%)	0	1 (1%)	2 (1%)	3 (2%)	2 (1%)
Vomiting	0	1 (1%)	0	1 (1%)	3 (2%)	1 (1%)	1 (1%)	1 (1%)
Discontinuations due to adverse events	4 (2%)	5 (3%)	1 (1%)	3 (2%)	1 (1%)	2 (1%)	1 (1%)	0

Data are number of patients (%).

Angiotensin receptor neprilysin inhibitor LCZ696 in HFpEF

Efficacy and Safety of LCZ696, a First-in-Class Angiotensin Receptor Neprilysin Inhibitor, in Asian Patients With Hypertension

A Randomized, Double-Blind, Placebo-Controlled Study

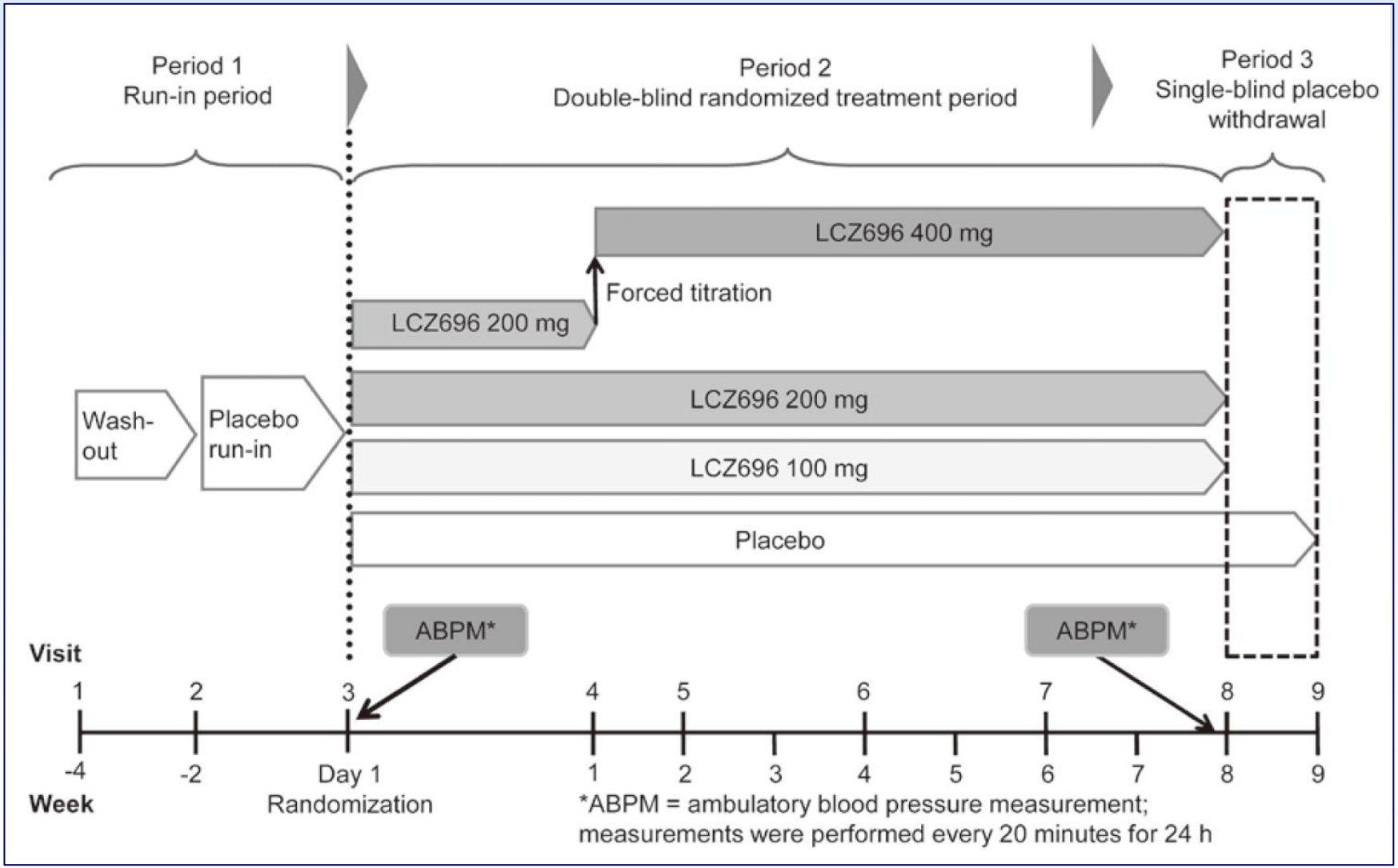
Kazuomi Kario, Ningling Sun, Fu-Tien Chiang, Ouppatham Supasyndh, Sang Hong Baek, Akiko Inubushi-Molessa, Ying Zhang, Hiromi Gotou, Martin Lefkowitz, Jack Zhang

Abstract—LCZ696 (Japanese adopted name: sucabitril valsartan sodium hydrate), a first-in-class angiotensin receptor neprilysin inhibitor, concomitantly inhibits neprilysin and blocks angiotensin type 1 receptor. This randomized, double-blind, placebo-controlled study, the first in Asia for this drug, evaluated the dose-related efficacy and safety of LCZ696 in patients with hypertension using 24-hour ambulatory blood pressure (BP) monitoring. Asian patients aged ≥18 years (n=389) with hypertension were randomized to receive LCZ696 100 mg (n=100), 200 mg (n=101), 400 mg (n=96), or placebo (n=92) for 8 weeks. The primary end point was mean difference across the 3 single-dose pairwise comparisons of LCZ696 versus placebo in clinic diastolic BP after 8-week treatment. Key secondary efficacy variables included changes in clinic systolic BP and pulse pressure and changes in 24-hour, daytime, and nighttime ambulatory BPs and pulse pressure. Safety assessments included recording all adverse events and serious adverse events. A total of 362 patients completed the study. Reductions in clinic systolic BP, diastolic BP ($P<0.0001$), and pulse pressure ($P<0.001$) were significantly greater with all doses of LCZ696 than with placebo. There were also significant reductions in 24-hour, daytime, and nighttime ambulatory systolic BP, diastolic BP, and pulse pressure for all doses of LCZ696 compared with placebo ($P<0.0001$). LCZ696 was well tolerated, and no cases of angioedema were reported. In conclusion, LCZ696 is effective for the treatment of hypertension in Asian population and, in general, is safe and well tolerated.

Clinical Trial Information—URL: http://www.clinicaltrials.gov. Unique identifier: NCT01193101.

(***Hypertension.*** **2014;63:00-00.)** • **Online Data Supplement**

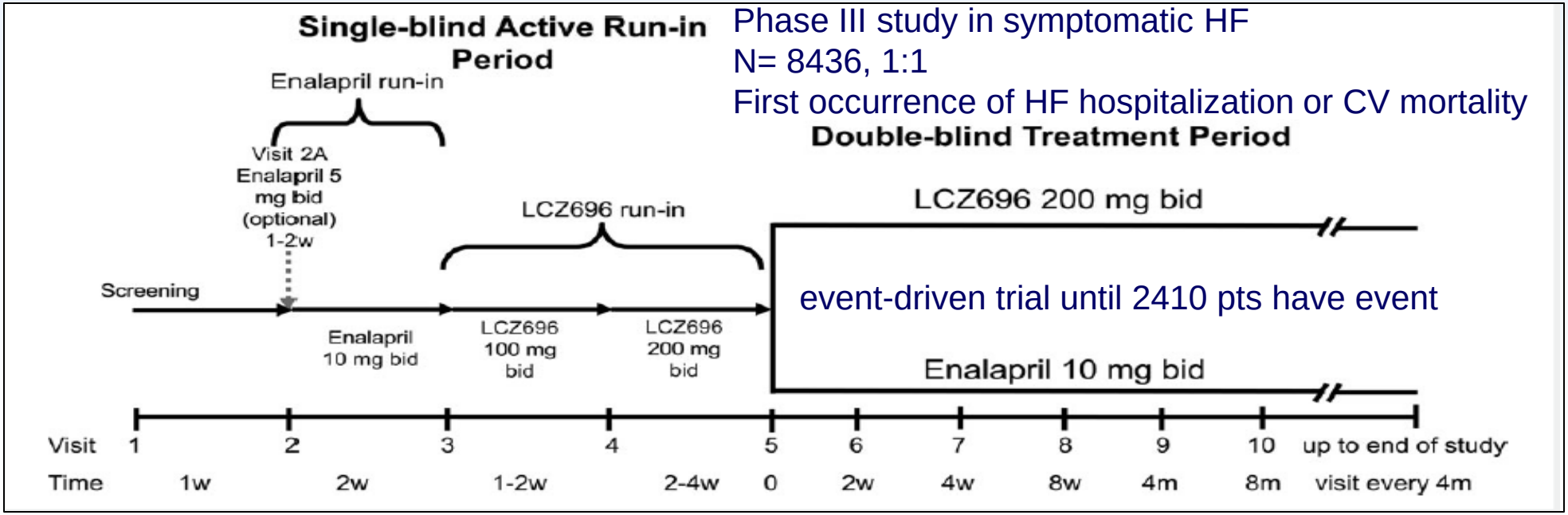
Kario K, Hypertension 2014:63:00–00


Period 1
Run-in period
Period 2
Double-blind randomized treatment period
Period 3
Single-blind placebo withdrawal
LCZ696 400 mg
Forced titration
LCZ696 200 mg
Wash-out
Placebo run-in
LCZ696 200 mg
LCZ696 100 mg
Placebo
ABPM*
ABPM*
Visit
1 2 3 4 5 6 7 8 9
-4 -2 Day 1 1 2 3 4 5 6 7 8 9
Week
Randomization
*ABPM = ambulatory blood pressure measurement;
measurements were performed every 20 minutes for 24 h

STUDY DESIGN PAPER

Dual angiotensin receptor and neprilysin inhibition as an alternative to angiotensin-converting enzyme inhibition in patients with chronic systolic heart failure: rationale for and design of the Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF)

John J. V. McMurray[1]*, Milton Packer[2], Akshay S. Desai[3], Jim Gong[4], Martin P. Lefkowitz[4], Adel R. Rizkala[4], Jean Rouleau[5], Victor C. Shi[4], Scott D. Solomon[3], Karl Swedberg[6], and Michael R. Zile[7], on behalf of the PARADIGM-HF Committees and Investigators†



Phase III study in symptomatic HF
N= 8436, 1:1
First occurrence of HF hospitalization or CV mortality

McMurray J, *Eur J Heart Fail* 2013, 15: 1066-73

PARAMOUNT: RCT, Phase 2 trial

- Phase 2, randomised, parallel-group, double-blind multicenter trial
- Patients with NYHA class II–III HF, LV EF 45% or higher, NT-proBNP greater than 400 pg/mL.
- Randomly assigned (1:1) by central interactive voice response system
  LCZ696 titrated to 200 mg twice daily
  or valsartan titrated to 160 mg twice daily, and treated for 36 weeks.
- Primary endpoint was change in NTproBNP, a marker of left ventricular wall stress, from baseline to 12 weeks;

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

*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**

Summary

Background Heart failure with preserved ejection fraction is associated with substantial morbidity and mortality, but effective treatments are lacking. We assessed the efficacy and safety of LCZ696, a first-in-class angiotensin receptor neprilysin inhibitor (ARNI), in patients with this disorder.

Methods PARAMOUNT was a phase 2, randomised, parallel-group, double-blind multicentre trial in patients with New York Heart Association (NYHA) class II–III heart failure, left ventricular ejection fraction 45% or higher, and NT-proBNP greater than 400 pg/mL. Participants were randomly assigned (1:1) by central interactive voice response system to LCZ696 titrated to 200 mg twice daily or valsartan titrated to 160 mg twice daily, and treated for 36 weeks. Investigators and participants were masked to treatment assignment. The primary endpoint was change in NT-proBNP, a marker of left ventricular wall stress, from baseline to 12 weeks; analysis included all patients randomly assigned to treatment groups who had a baseline and at least one postbaseline assessment. This trial is registered at Clinicaltrials.gov, number NCT00887588.

Findings 149 patients were randomly assigned to LCZ696 and 152 to valsartan; 134 in the LCZ696 group and 132 in the valsartan group were included in analysis of the primary endpoint. NT-proBNP was significantly reduced at 12 weeks in the LCZ696 group compared with the valsartan group (LCZ696: baseline, 783 pg/mL [95% CI 670–914], 12 weeks, 605 pg/mL [512–714]; valsartan: baseline, 862 pg/mL [733–1012], 12 weeks, 835 [710–981]; ratio LCZ696/valsartan, 0·77, 95% CI 0·64–0·92, p=0·005). LCZ696 was well tolerated with adverse effects similar to those of valsartan; 22 patients (15%) on LCZ696 and 30 (20%) on valsartan had one or more serious adverse event.

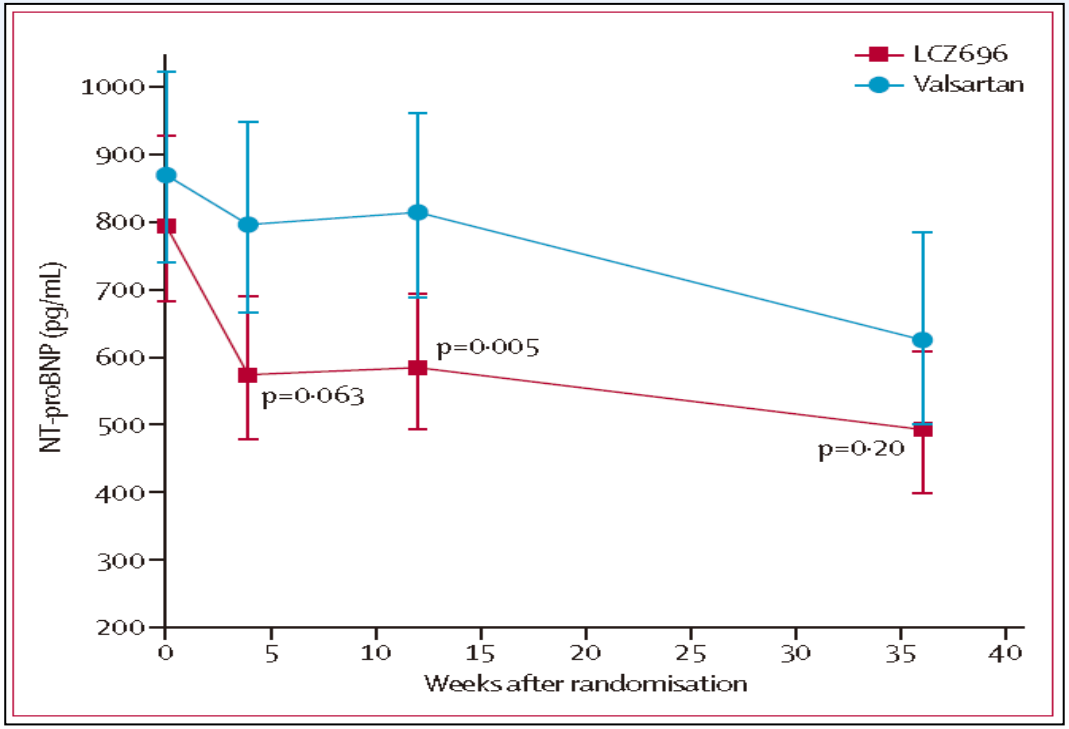
Interpretation In patients with heart failure with preserved ejection fraction, LCZ696 reduced NT-proBNP to a greater extent than did valsartan at 12 weeks and was well tolerated. Whether these effects would translate into improved outcomes needs to be tested prospectively.

Solomon SD, Lancet 2012 380: 1387–95

NT-proBNP at baseline, 12 weeks, and 36 weeks

	NT-proBNP (pg/mL) at 12 weeks			NT-proBNP (pg/mL) at 36 weeks		
	n	Baseline	12 weeks	n	Baseline	36 weeks
LCZ696	134	783 (670–914)	605 (512–714)	115	763 (646–901)	496 (401–613)
Valsartan	132	862 (733–1012)	835 (710–981)	116	822 (688–983)	607 (484–760)
Ratio of change (LCZ696/valsartan)	..	..	0·77 (95% CI 0·64–0·92), p=0·005	..	..	0·85 (95% CI 0·65–1·09), p=0·20

Data for NT-proBNP are geometric mean (95% CI).



Solomon SD, Lancet 2012380: 1387–95

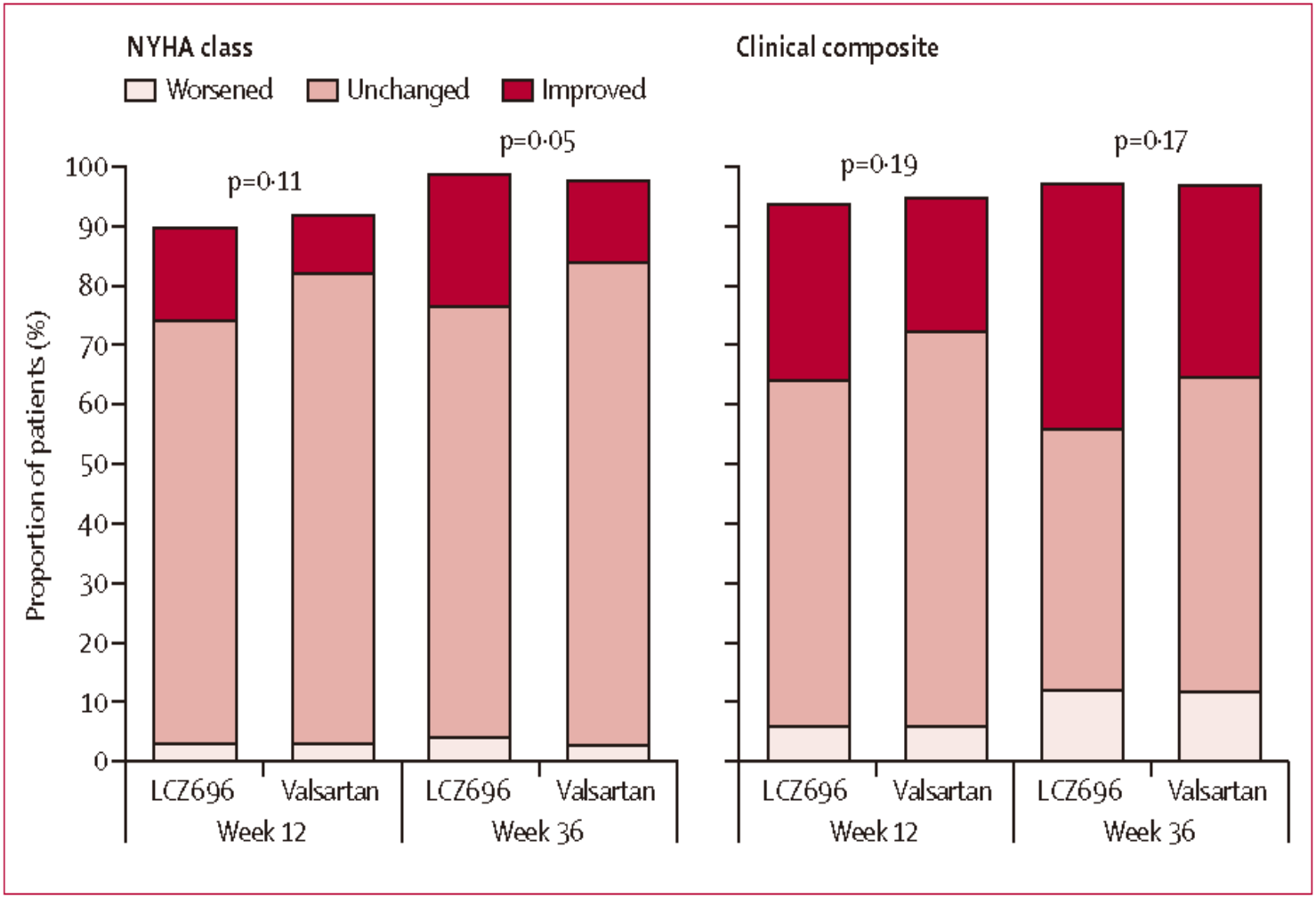
Changes in EchoCG parameters at 12 and 36 weeks

	12 weeks							36 weeks						
	LCZ696			Valsartan			p value	LCZ696			Valsartan			p value
	n	Baseline	Δ from baseline	n	Baseline	Δ from baseline		n	Baseline	Δ from baseline	n	Baseline	Δ from baseline	
Ejection fraction	114	58·2% (7·6)	1·06% (5·0)	118	58·0% (8·0)	1·04% (4·9)	0·85	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)	97	7·7 (2·7)	0·57 (1·7)	106	7·2 (2·9)	0·55 (1·5)	0·56	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′)	96	12·6 (8·4)	−1·3 (3·4)	106	13·0 (7·3)	−1·3 (4·3)	0·71	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)	72	1·1 (0·56)	−0·09 (0·36)	78	1·1 (0·66)	−0·08 (0·67)	0·90	60	1·1 (0·51)	−0·05 (0·39)	68	1·1 (0·65)	−0·03 (0·61)	0·43
Left atrial width (cm)	116	3·7 (0·42)	−0·07 (0·25)	114	3·7 (0·53)	−0·02 (0·22)	0·07	99	3·7 (0·43)	−0·15 (0·31)	108	3·7 (0·53)	−0·08 (0·30)	0·03
Left atrial volume (mL)	113	67·0 (23·2)	−3·2 (12·2)	119	68·1 (28·1)	−1·3 (12·5)	0·18	96	65·3 (22·5)	−4·6 (13·7)	112	68·3 (29·3)	0·37 (15·9)	0·003
Left atrial volume index (mL/m²)	110	35·9 (12·5)	−0·98 (7·6)	118	36·5 (14·4)	−0·41 (6·8)	0·45	90	35·0 (11·7)	−2·6 (7·3)	106	36·8 (14·8)	0·31 (9·3)	0·007
Left ventricular end-diastolic volume (mL)	114	110·3 (26·4)	−2·90 (10·5)	118	113·1 (31·3)	−3·27 (12·3)	0·99	94	111·8 (26·3)	−10·4 (14·4)	111	114·3 (31·5)	−12·7 (17·3)	0·39
Left ventricular end-systolic volume (mL)	114	46·5 (15·7)	−3·3 (6·5)	118	48·5 (20·9)	−2·7 (8·9)	0·97	95	46·9 (15·8)	−6·9 (9·1)	111	48·8 (20·6)	−8·70 (11·0)	0·31
Left ventricular mass index (kg/m²)	112	77·4 (20·7)	−1·2 (13·0)	112	78·8 (21·5)	−4·2 (11·8)	0·10	91	76·6 (19·8)	−2·8 (14·0)	100	79·5 (22·7)	−1·9 (19·2)	0·35
Relative wall thickness	116	0·38% (0·09)	−0·002% (0·045)	114	0·37% (0·07)	0·001% (0·033)	0·76	98	0·37% (0·07)	0·01% (0·06)	107	0·37% (0·07)	0·01% (0·06)	0·96
Tricuspid regurgitant velocity (m/s)	45	2·5 (0·36)	0·008 (0·25)	42	2·5 (0·33)	0·09 (0·33)	0·19	35	2·6 (0·44)	−0·01 (0·24)	42	2·52 (0·34)	0·06 (0·35)	0·38

Data are mean (SD). Baseline data are presented for follow-up values.

Table 3: **Changes in echocardiographic measures at 12 weeks and 36 weeks**

Changes in NYHA and Clinical Composite Assessment



Solomon SD, Lancet 2012380: 1387–95

Independence of the blood pressure lowering effect and efficacy of the angiotensin receptor neprilysin inhibitor, LCZ696, in patients with heart failure with preserved ejection fraction: an analysis of the PARAMOUNT trial

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Aims The first in class angiotensin receptor neprilysin inhibitor, LCZ696 has been shown to reduce levels of *N*-terminal pro-brain natriuretic peptide (NT-proBNP), reduce left atrial size and improve New York Heart Association (NYHA) class in patients with heart failure with preserved ejection fraction (HFpEF). We examined whether the effects of LCZ696 were independent of systolic blood pressure (SBP) lowering.

Methods and results In the Prospective comparison of ARNi (angiotensin receptor neprilysin inhibitor) with ARB (angiotensin receptor blocker) on Management Of heart failUre with preserved ejectioN fracTion (PARAMOUNT) trial 301 patients were randomly assigned to LCZ696 or valsartan. We examined the relationship between SBP lowering and LCZ696 on NT-proBNP level, left atrial size, NYHA class and estimated glomerular filtration rate (eGFR). By 12 weeks blood pressure was reduced by 9 mmHg (SD 15)/5 mmHg (SD 11) in patients receiving LCZ696 in comparison with 3 mmHg (SD 17)/2 mmHg (SD 12) in those receiving valsartan. The change in NT-proBNP was poorly correlated with change in SBP (LCZ696, $r = 0.17$, $P = 0.06$; valsartan, $r = 0.05$, $P = 0.58$) After adjustment for change in SBP, the ratio of change in NT-proBNP at 12 weeks for LCZ696 vs. valsartan was 0.76 (95% CI 0.63–0.93, $P = 0.008$), and similar to the ratio not adjusting for SBP (0.76, 95% CI 0.63–0.92, $P = 0.006$); P for interaction was 0.38). Similarly, reduction in left atrial volume index at 36 weeks, improvement in NYHA class and eGFR were all independent of the change in SBP.

Conclusion In patients with HFpEF, the effect of the angiotensin receptor neprilysin inhibitor LCZ696 on NT-proBNP, left atrial volume, functional class, and eGFR was independent of reduction in SBP.

Keywords Blood pressure • Heart failure • Neprilysin inhibitor • NT-proBNP • Preserved ejection fraction

PARAMOUNT: RCT, Phase 2 trial

- N=301, Phase 2, randomised, parallel-group, double-blind multicenter trial
- Patients with NYHA class II–III HF, LV EF 45% or higher, NT-proBNP greater than 400 pg/mL.
- Randomly assigned (1:1) by central interactive voice response system
  LCZ696 titrated to 200 mg twice daily
  or valsartan titrated to 160 mg twice daily, and treated for 36 weeks.
- Primary endpoint: change in NTproBNP, a marker of LV wall stress, from baseline to 12 wks
- Relationship b/t SBP lowering and LCZ696 on NT-proBNP, LA size, NYHA and eGFR

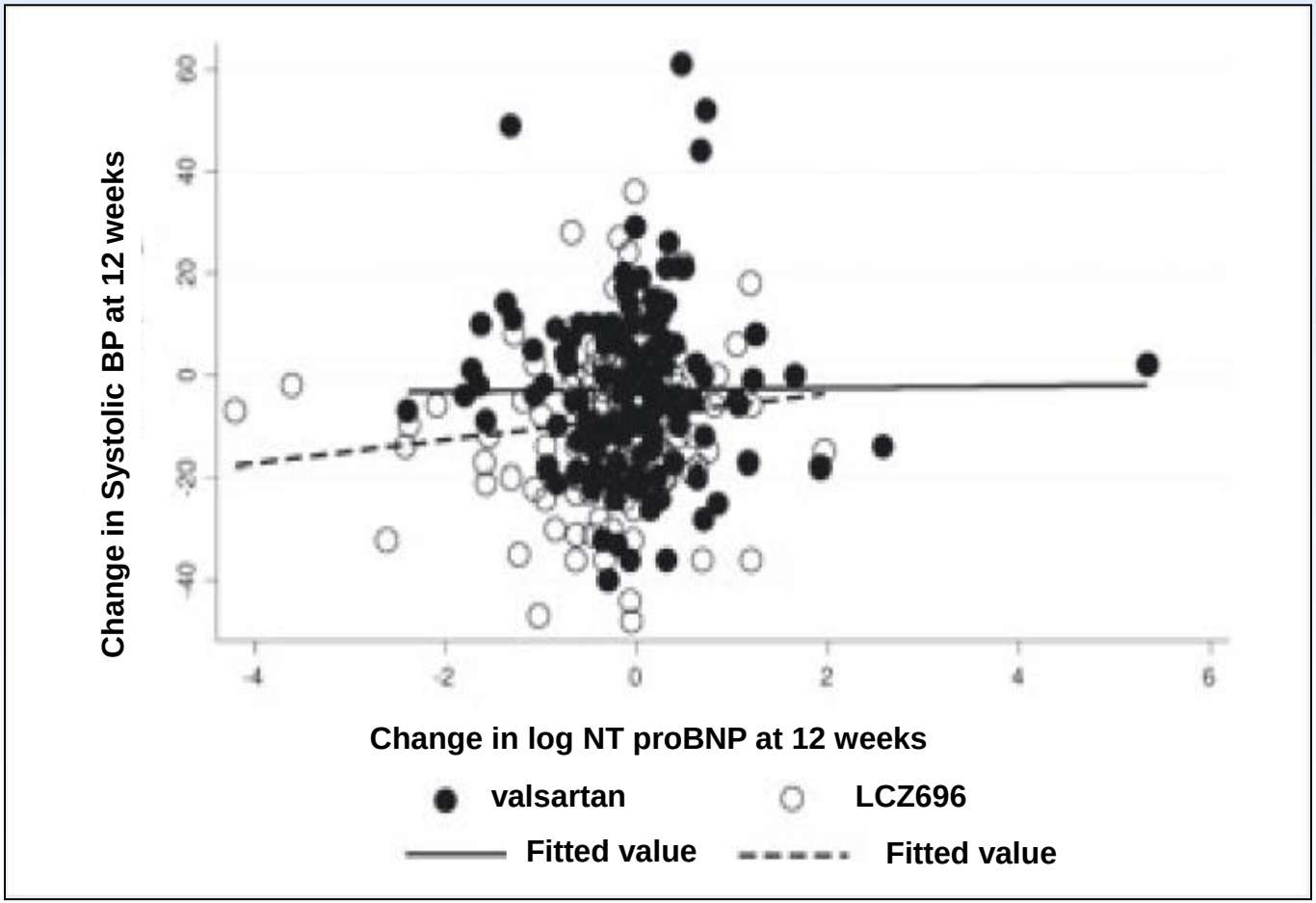
  ① BP-lowering at 12 wks - 9 /5 mmHg in LCZ696 vs 3/2mmHg in valsartan

  ② change in NT-proBNP at 12 wks: poorly correlated with change in SBP
  - after adjustment for change in SBP
  the ratio of change in NT-proBNP at 12wks for LCZ696 vs. valsartan
  : 0.76 (95% CI 0.63–0.93, *P* =0.008)

  ③ reduction in LA volume index, improvement in NYHA class and eGFR at 36 wks
  : all independent of the change in SBP

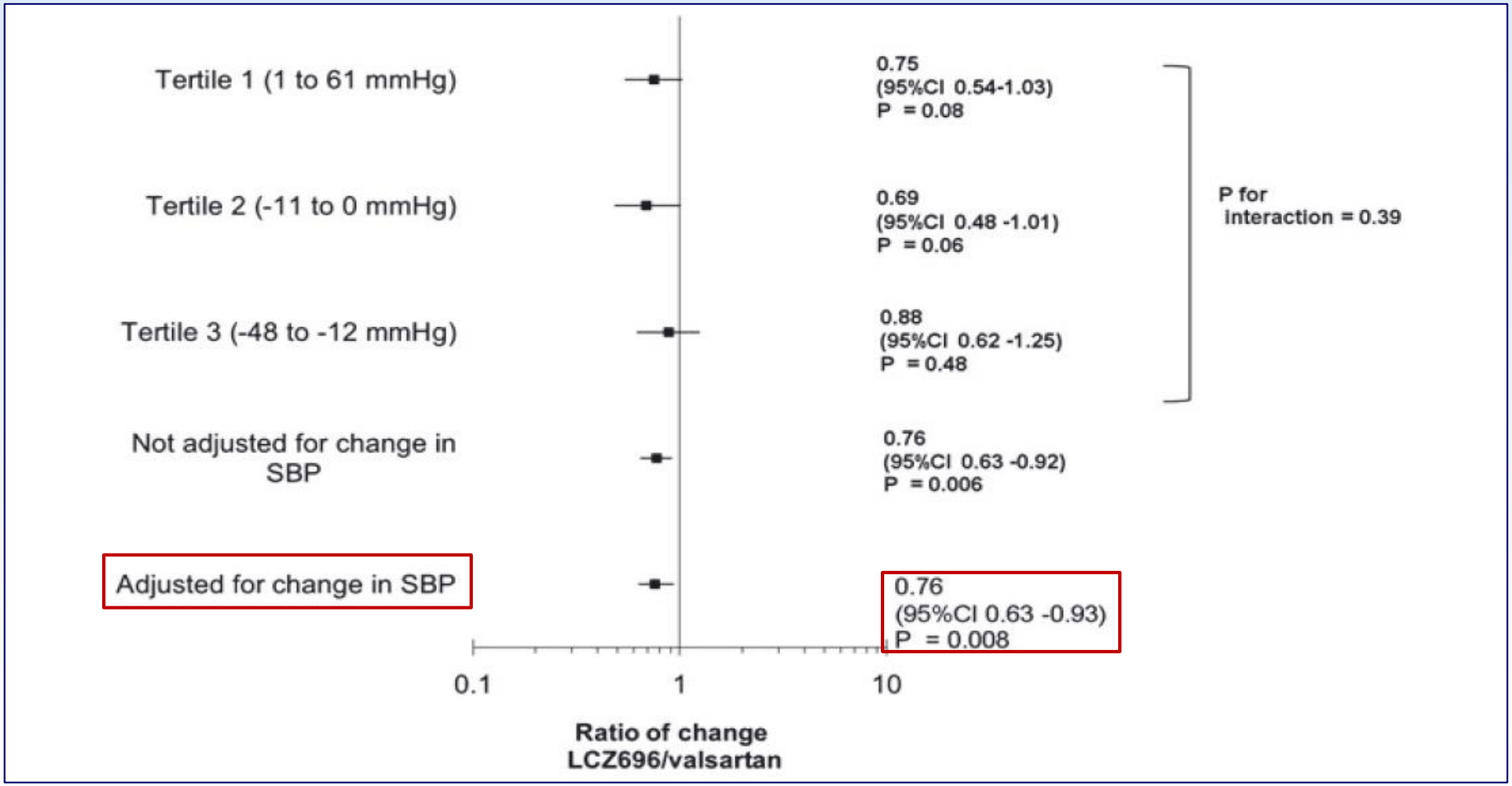
Jhund PS, *Eur J Heart Fail* 2014,

Correlation between change in SBP and NT-proBNP at 12weeks



Jhund PS, Eur Heart Fail 2014

Ratio of Change in NT-proBNP at 12 weeks : LCZ696 vs Vlasartan



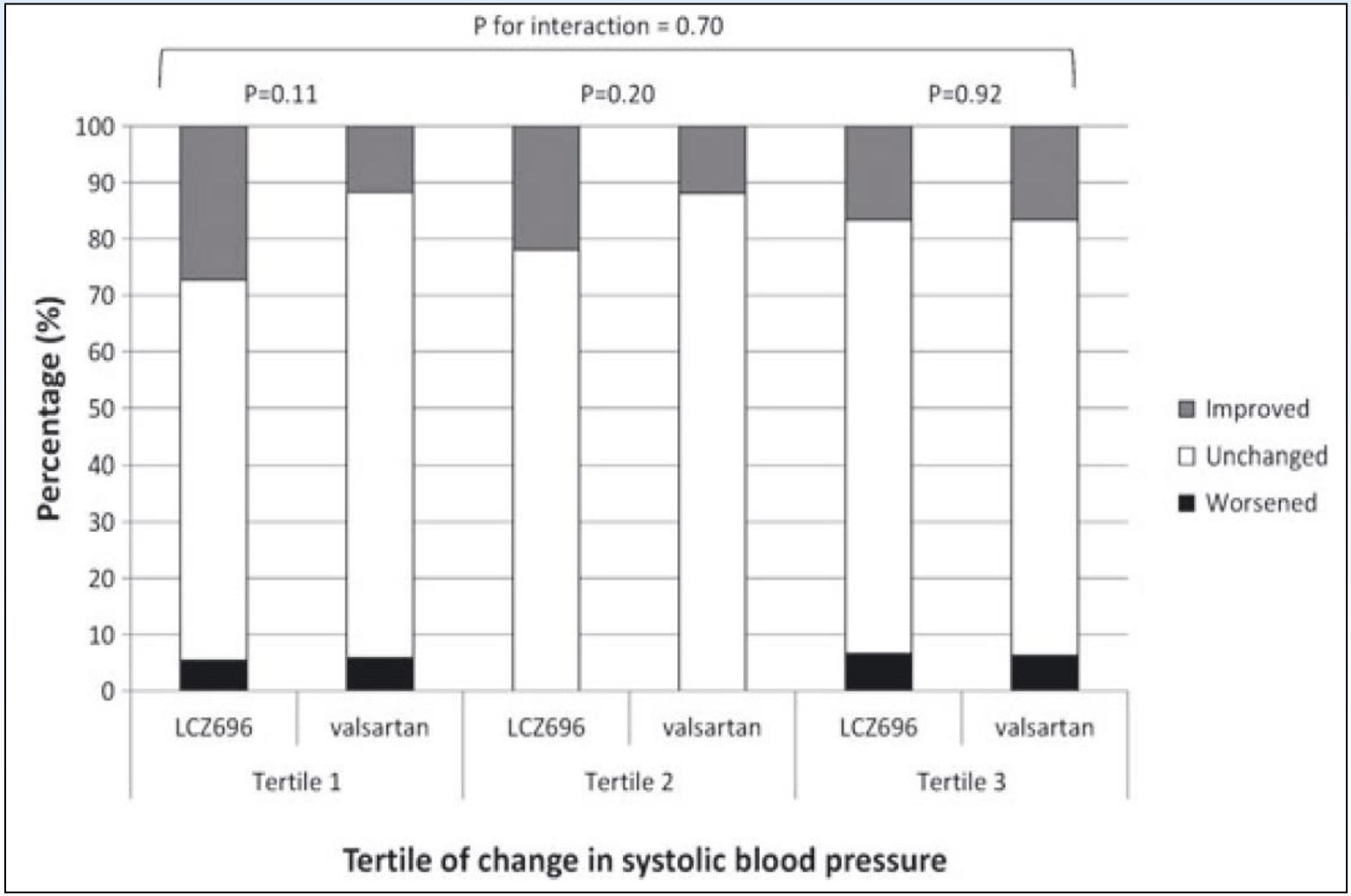
Jhund PS, Eur Heart Fail 2014

Change in LA diameter, LA volume and eGFR at 36 Weeks

	Tertile 1, $n = 89$ (−50 to −12 mmHg) Change (95%CI)	Tertile 2, $n = 83$ (−11 to −2 mmHg) Change (95%CI)	Tertile 3, $n = 78$ (3–62 mmHg) Change (95%CI)	Overall	
				P LCZ696 vs. valsartan (adjusted for change in SBP at 36 weeks)	*P* for interaction
Left atrial diameter					
LCZ696	−0.15(−0.25 to −0.06)	−0.12(−0.23 to −0.01)	−0.19(−0.32 to −0.05)	0.03	0.91
Valsartan	−0.04(−0.14 to −0.06)	−0.07(−0.16 to −0.02)	−0.11(−0.22 to −0.01)		
Left atrial indexed volume					
LCZ696	−2.65 (−4.71 to −0.59)	−1.77 (−4.87 to −1.34)	−3.74 (−7.18 to −0.29)	0.01	0.61
Valsartan	−0.28(−3.54 to −2.98)	0.22 (−2.69 to −3.14)	0.80(−2.53 to 4.13)		
eGFR					
LCZ696	−3.83(−6.99 to −0.67)	−1.28(−6.26 to −3.70)	1.86(−3.02 to −6.74)	0.002	0.69
Valsartan	−9.09(−12.78 to −5.41)	−3.03(−7.16 to −1.11)	−4.28(−7.34 to −1.23)		

Jhund PS, Eur Heart Fail 2014

New York Heart Association (NYHA) class at 36 weeks



Jhund PS, Eur Heart Fail 2014

Summary I

- **Modulation of the RAS**
  - key approach to reduce deleterious properties of over-activated RAS in HT and CVD

- **Novel puzzle RAS: classical simplified RAS has turn to a very complex network**
  - promising drug targets.

- **One of promising targets is neutral endopeptidase (NEP)**
  - processing/ catabolism of vasoactive peptides and the peptides involved in diuresis and natriuresis (natriuretic peptides (NPs), angiotensin I, bradykinin, endothelin-1)

Summary II

- NPs : multiple biologic effects
  - natriuresis, vasodilatation, inhibition of RAS and sympathetic nervous system, inhibition of fibrosis

- Omapatrilat : first dual antagonist of neprilysin (NEP) and ACE
  - significant SBP and pulse pressure-lowering effects than ACE inhibitor alone in HT
  - increased risk of angioedema

- LCZ 696 (sucabitril valsartan sodium hydrate)
  - first-in-class dual AT1R and NEP antagonist
  - significant BP reduction than comparable to valsartan

    in a phase II randomized double-blind trial in mild-to-moderate HT pts.

    : After 8 wks, LCZ 696 (200, 400 mg) vs comparable doses of valsartan (160, 320 mg)

    larger reduction in sitting SBP and DBP with no cases of angioedema

    well tolerated in patients with HT

Conclusion

- **Although clinical experience with LCZ696 is restricted in relative small number of HT, dual AT1R and NEP antagonism, LCZ696, suggests a promising strategy for HT control**

- **More convincing data in large clinical trials including a sufficient proportion of black and elderly patients are need**