



Natriuretische peptiden als nieuwe behandelingstarget voor hypertensie

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Disclosures

Voor presentatie mogelijk relevante relaties	
Sponsoring of onderzoeksgeld:	NVT
Honorarium of andere (financiële) vergoeding:	NVT
Aandeelhouder:	NVT
Andere relatie, namelijk ...	NVT

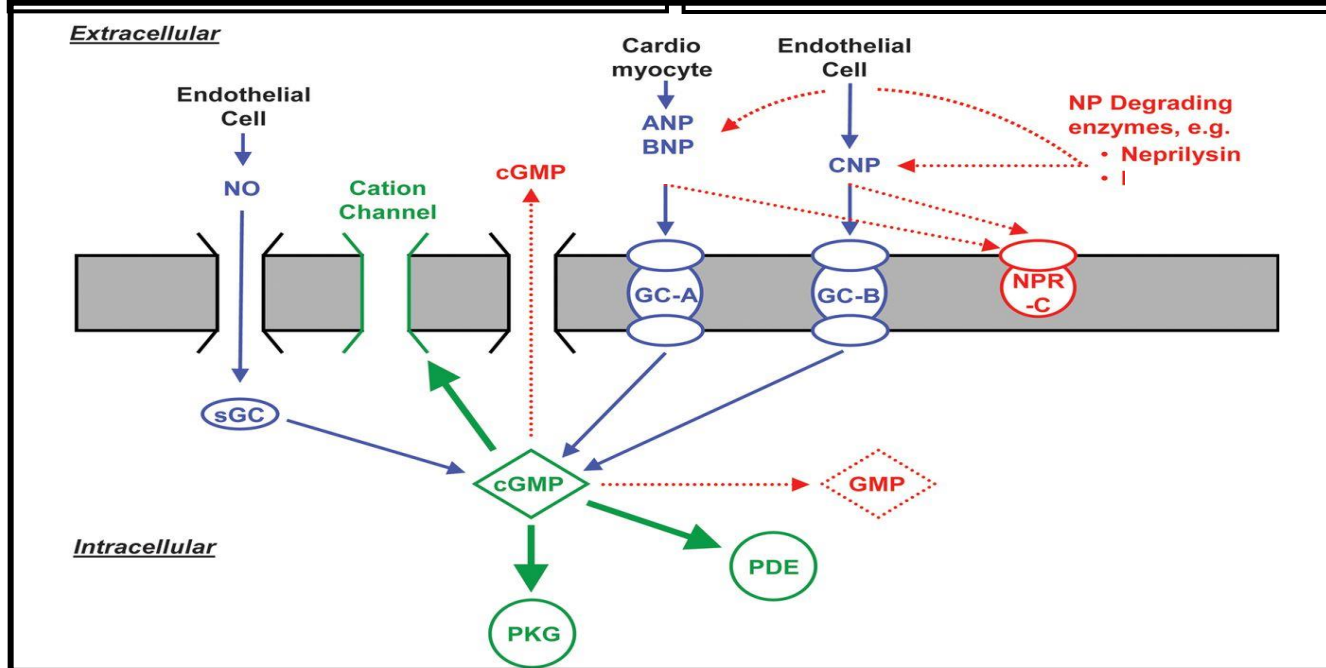
Natriuretic peptide system

Natriuretic peptides

- ANP – atrial natriuretic peptide
- BNP – B-type natriuretic peptide
- CNP – C-type natriuretic peptide

Biological effects

- vasodilation
- natriuresis and diuresis
- inhibition of the RAAS, endothelin and lipid mobilization



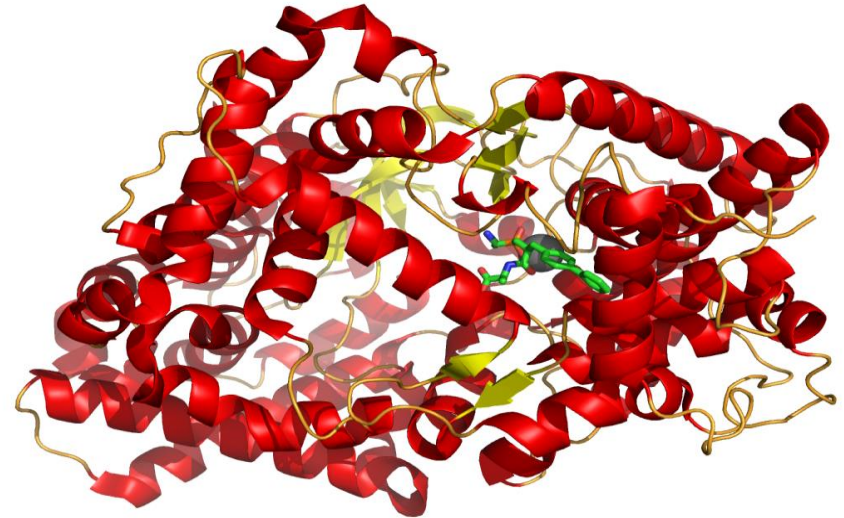
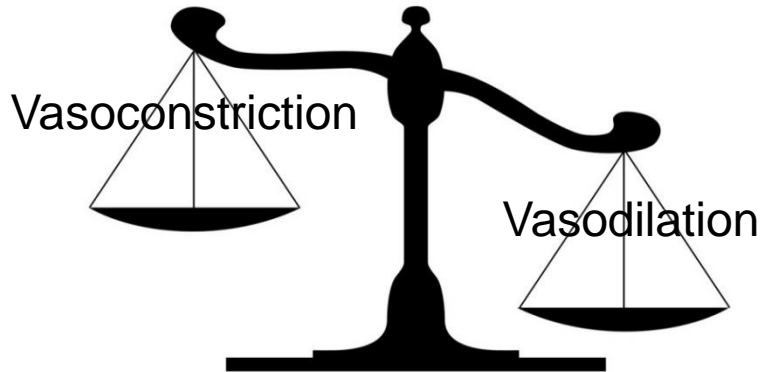
Natriuretic peptide system

Clearance of NPs by neutral endopeptidase (NEP; neprilysin)

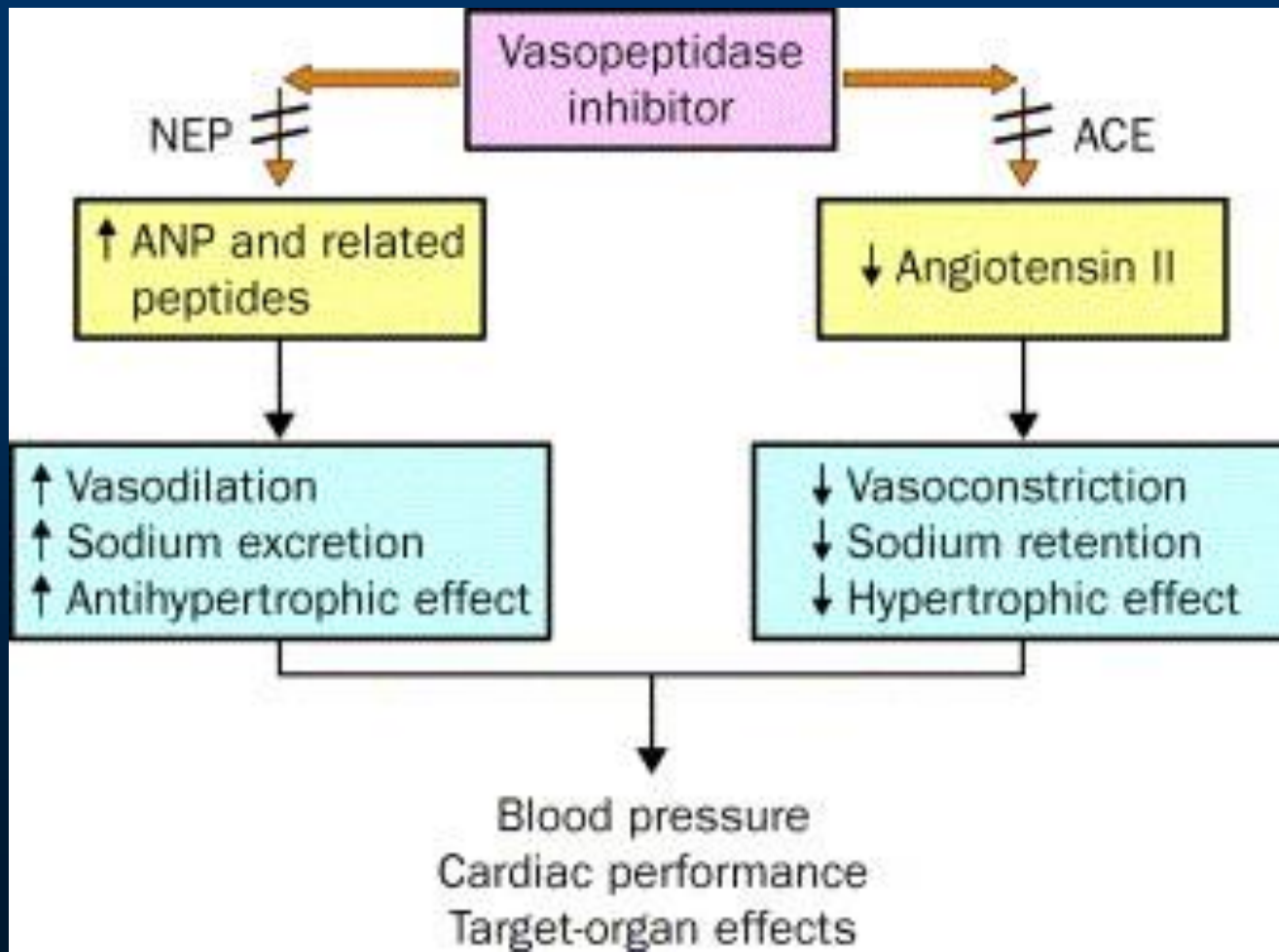
NEP

- membrane-bound endopeptidase
- ubiquitously expressed
- essential for processing and catabolism of vasoactive peptides (NPs, Ang II, bradykinin & endothelin-1)

⇒ opposing physiological actions

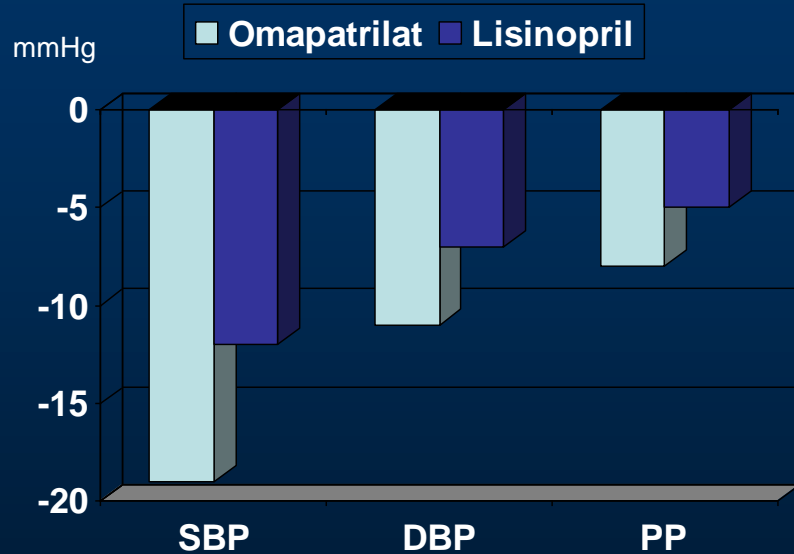


Effect of vasopeptidase inhibitor

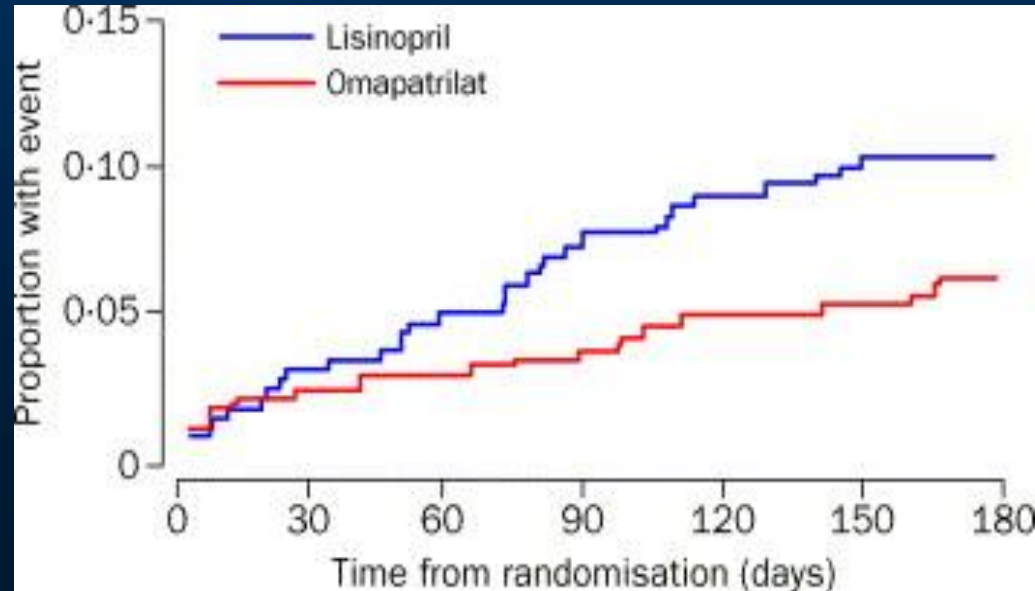


Omapatrilat vs lisinopril

Hypertension



Heartfailure



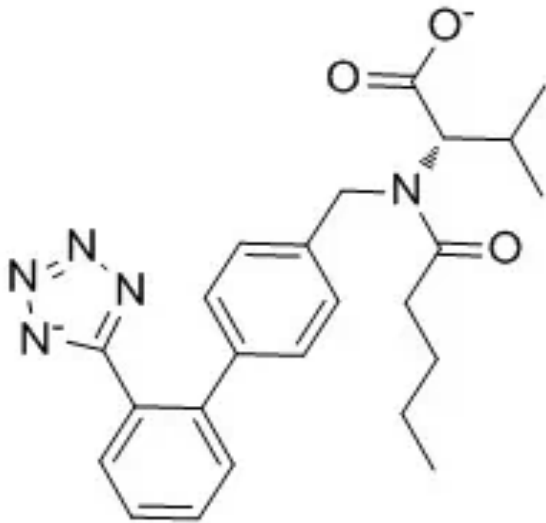
Angio-oedema



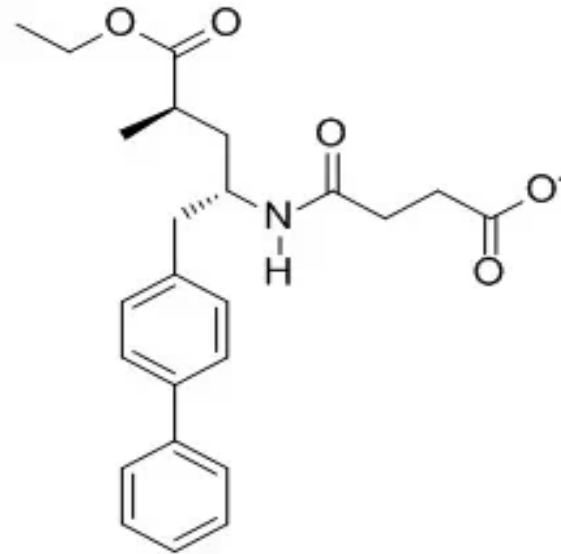
Solution: combine NEP inhibitor with AT_1 receptor blocker (ARNI)!

ARB

Valsartan



NEP Inhibitor



Sacubitril

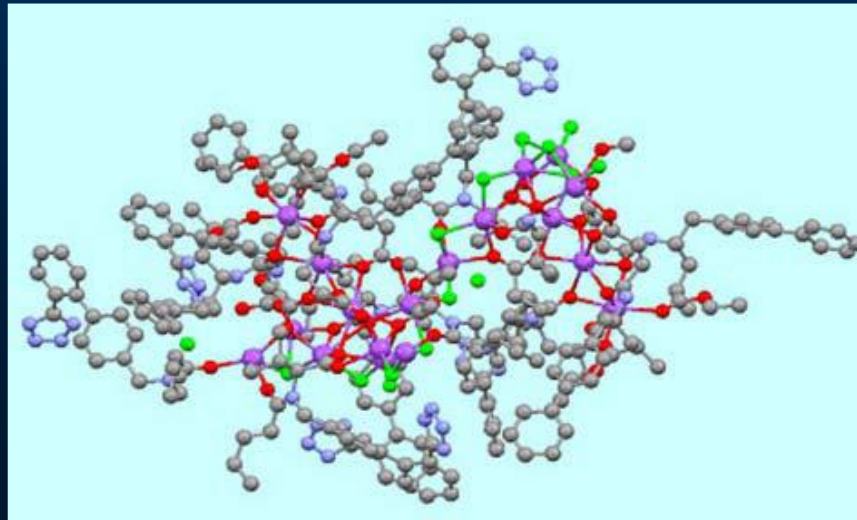
Erasmus MC



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

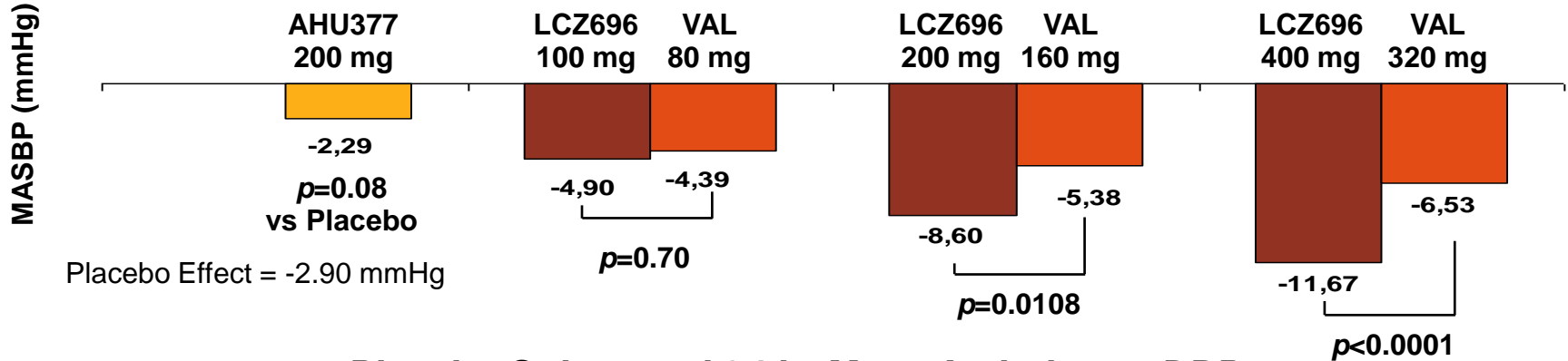
The Lancet 2010



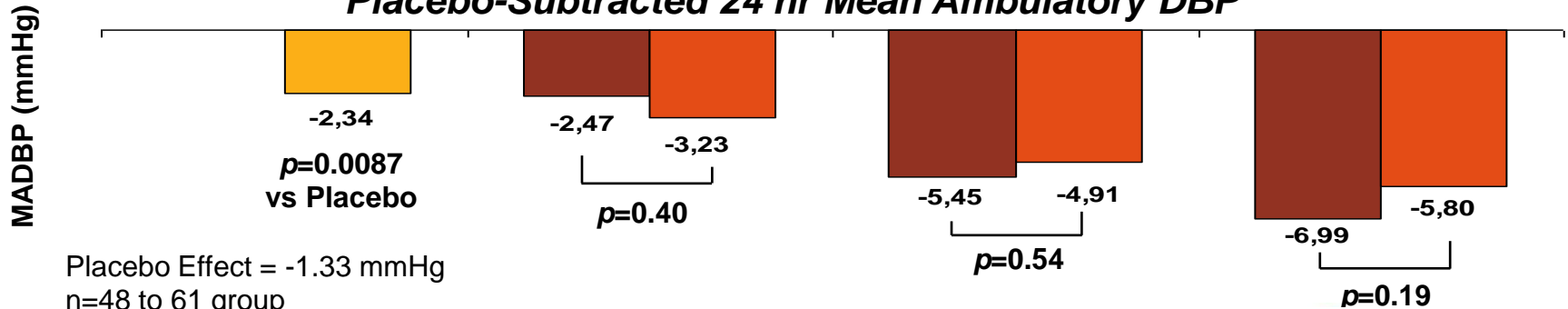
LCZ696 Hypertension Study

Results: Ambulatory Blood Pressure at Week 8 Endpoint

Placebo-Subtracted 24 hr Mean Ambulatory SBP

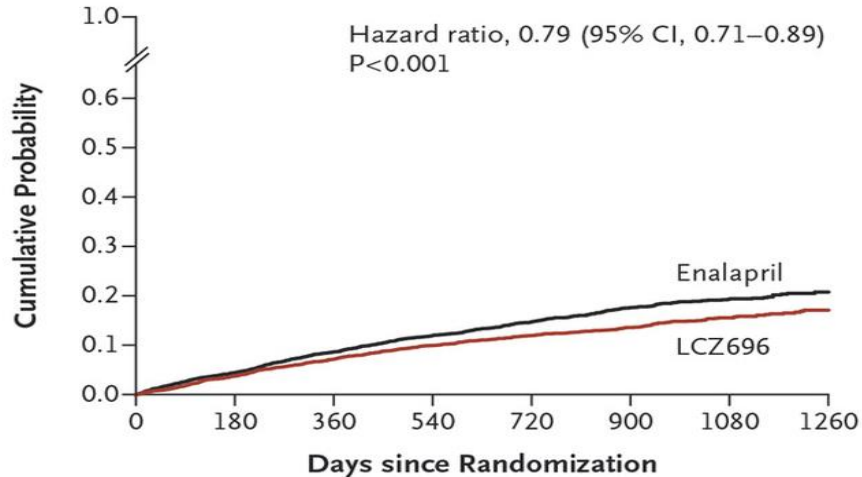


Placebo-Subtracted 24 hr Mean Ambulatory DBP

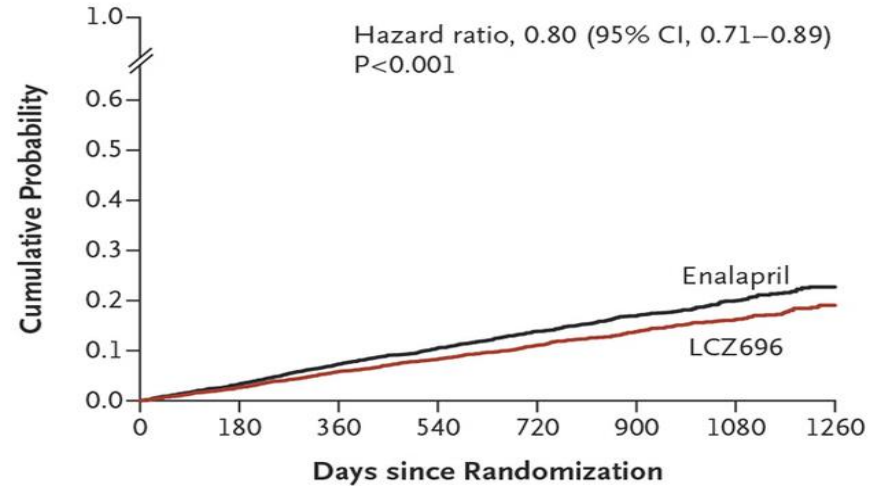


ARNI in heart failure and kidney disease

Hospitalization for Heart Failure



Death from Cardiovascular Causes

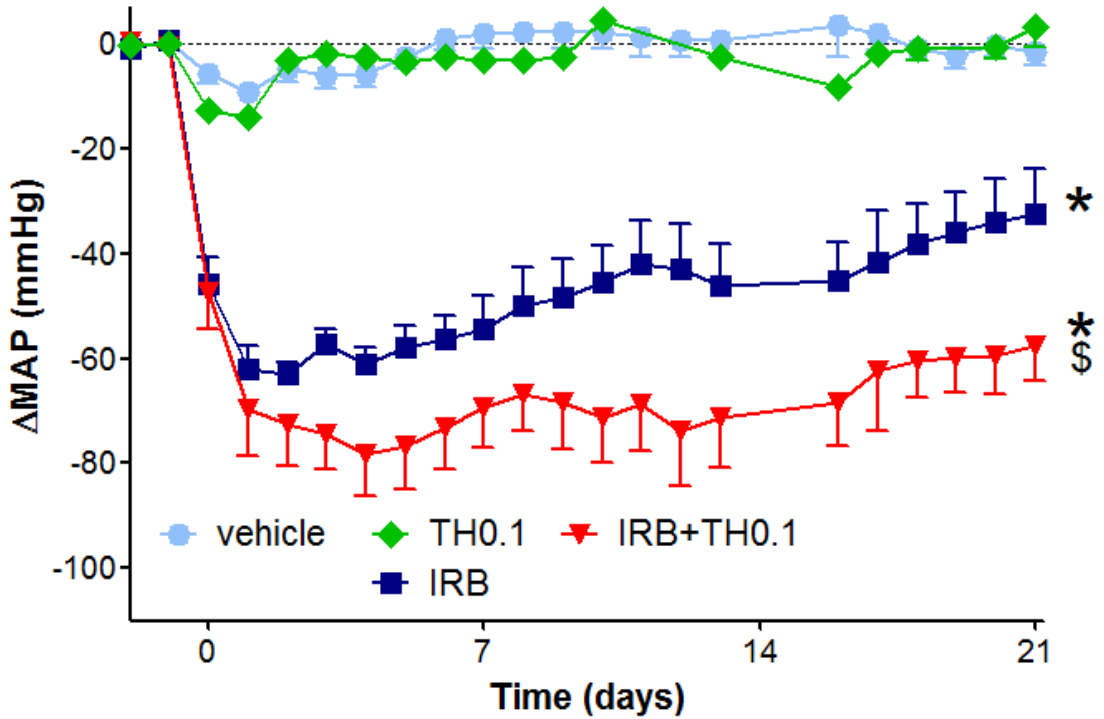


8442 patients with **heart failure** NYHA II-IV and EF <40%, 27 months follow-up (McMurray et al., *NEJM* 2014)

PARADIGM-HF: slower rate of decrease of eGFR, particularly in patients with **diabetes**; modest increase in UACR (Packer et al., *Lancet Diabetes Endocrinol* 2018)

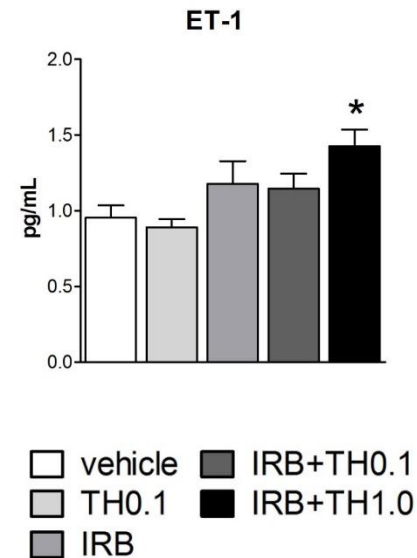
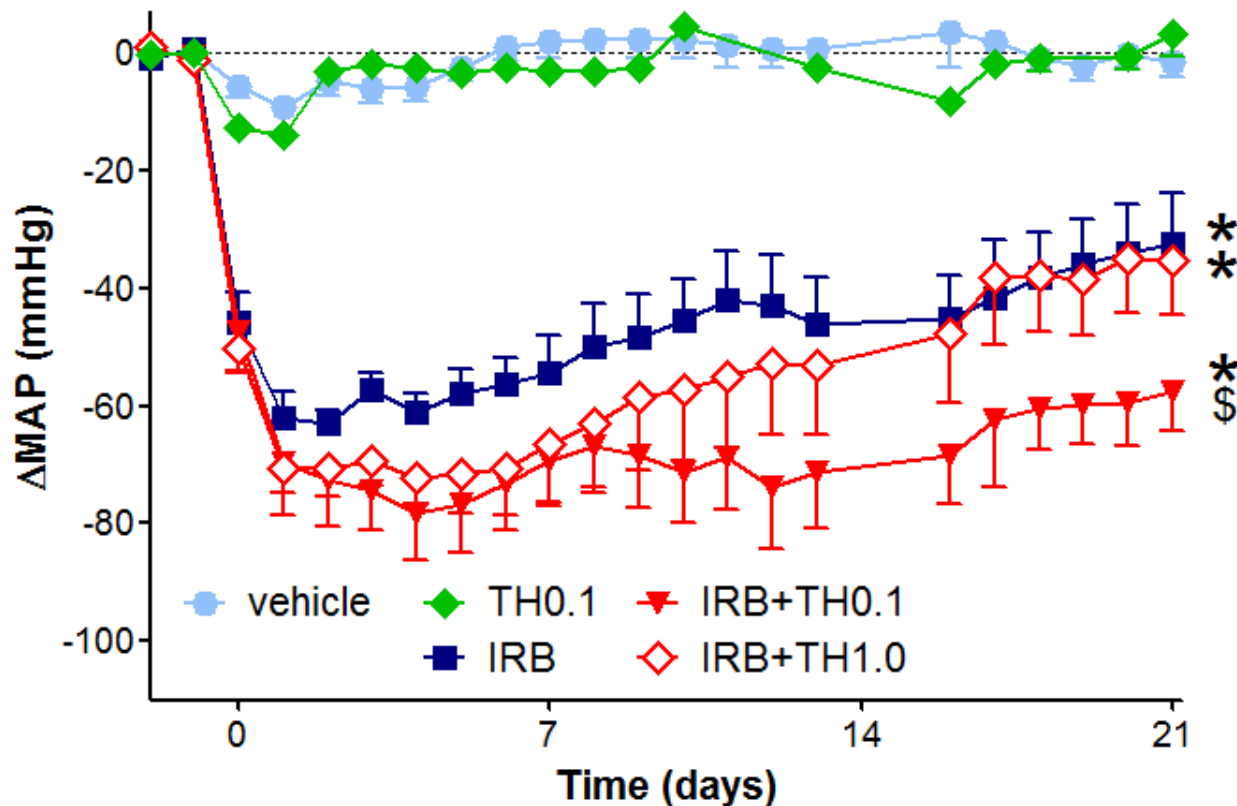
UK-HARP-III Collaborative Group: superior effects vs. irbesartan in **chronic kidney disease** (*Circulation* 2018)

Enhanced blood pressure-lowering in Ren2 rats by ARNI



IRB, irbesartan (ARB)
TH, thiorphan (NEP inhibitor)

Too much NEP inhibition may increase endothelin-1



Roksnoer et al., *Kidn Int* 2015

Greater effect on cardiac hypertrophy by ARNI

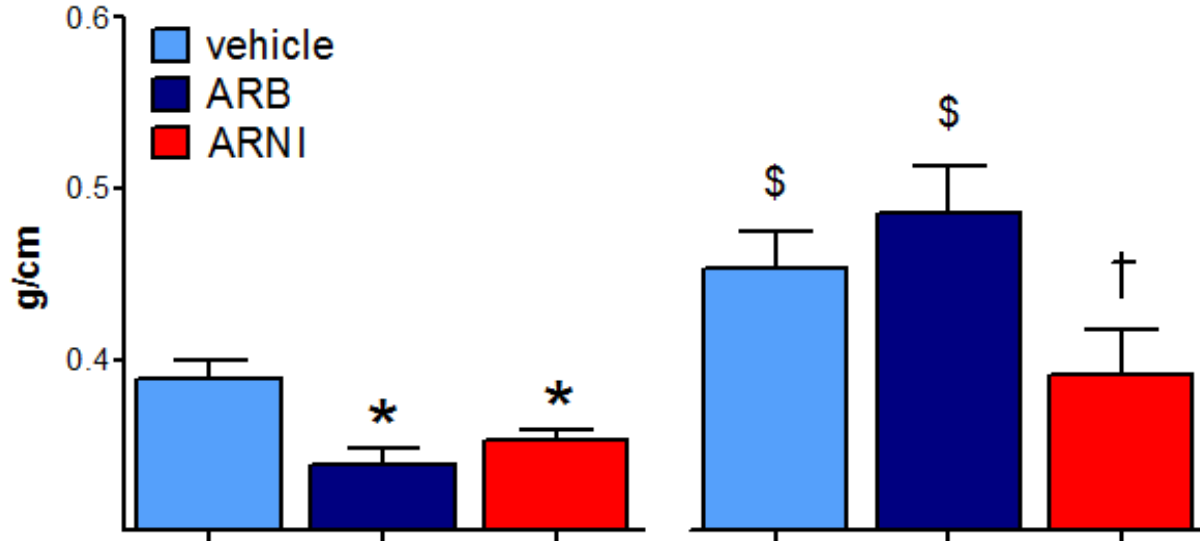
5 weeks DM

12 weeks DM

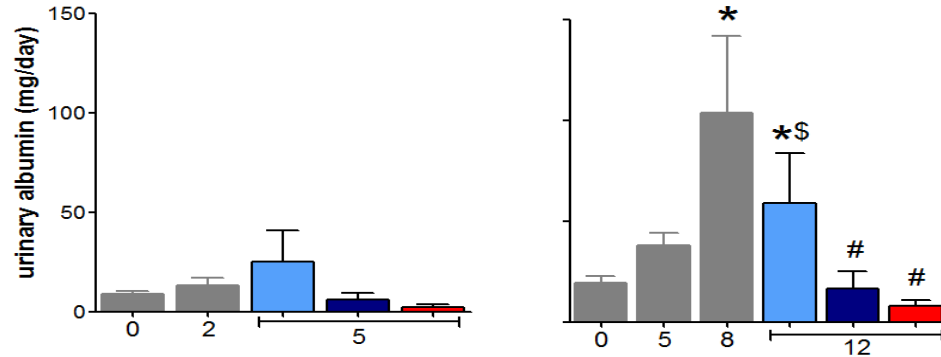
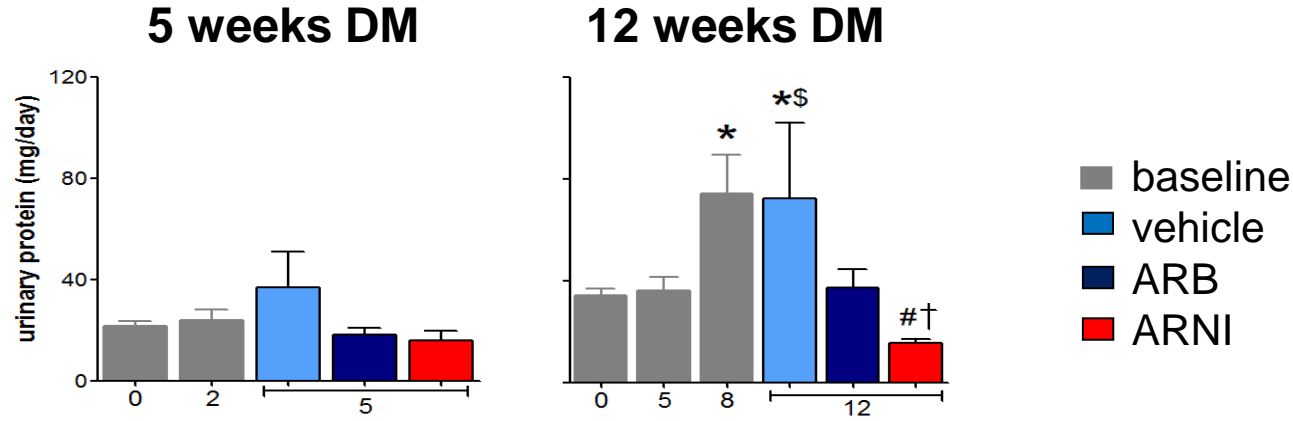
DM=Diabetes Mellitus

ARB=irbesartan

ARNI=irbesartan+thiorphan



Greater reduction in proteinuria & albuminuria by ARNI



N=7-12 per group
*P<0.05 versus baseline (0 weeks)
\$P<0.05 versus 5 weeks DM
#P<0.05 versus vehicle treatment
† versus ARB treatment

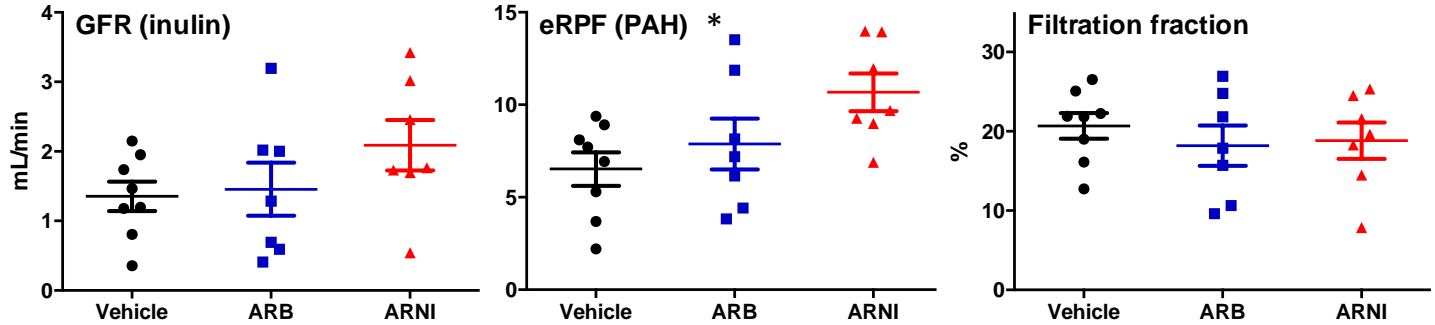
time after diabetes induction (weeks)

Roksnoer et al., *Clin Sci* 2016

Renal hemodynamic effects of ARNI

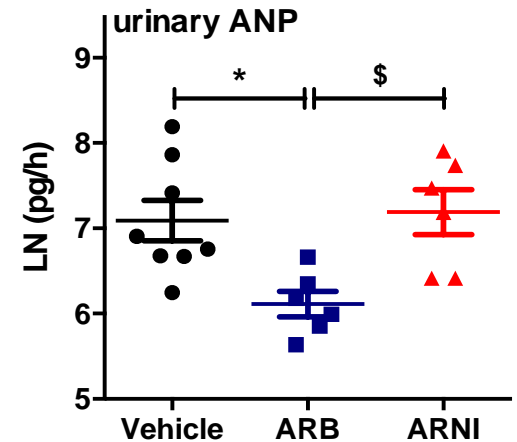
ARB=valsartan

ARNI=valsartan+
sacubitril



	control	ARB	ARNI	
GFR (mL/min)	1.36 ± 0.21	1.46 ± 0.38	2.09 ± 0.36	↑ 44%
eRPF (mL/min)	6.53 ± 0.91	7.88 ± 1.38	10.68 ± 1.02*	↑ 36%
Filtration fraction (%)	21 ± 2	18 ± 3	19 ± 2	
Fractional sodium excretion (%)	0.02 ± 0.01	0.04 ± 0.01	0.03 ± 0.01	
Fractional potassium excretion (%)	21.5 ± 2.6	33.9 ± 5.4*	23.7 ± 0.8	

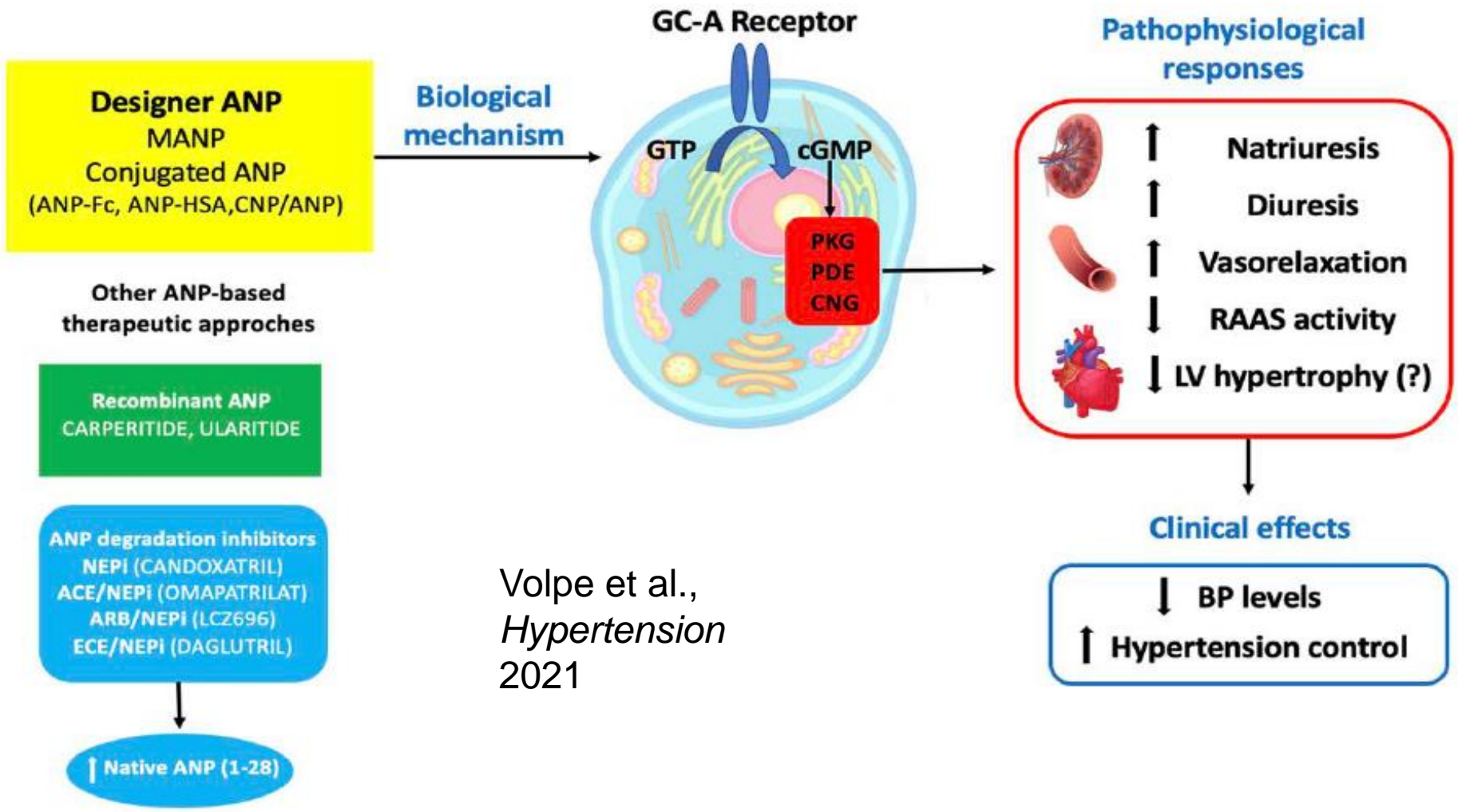
Mean ± SEM; * p<0.05 vs control



Uijl et al.,
J Hypertens
2020

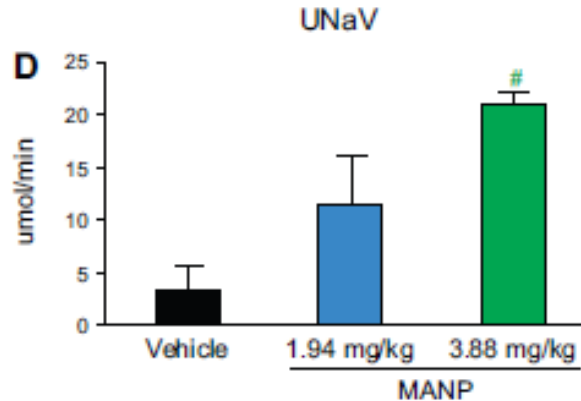
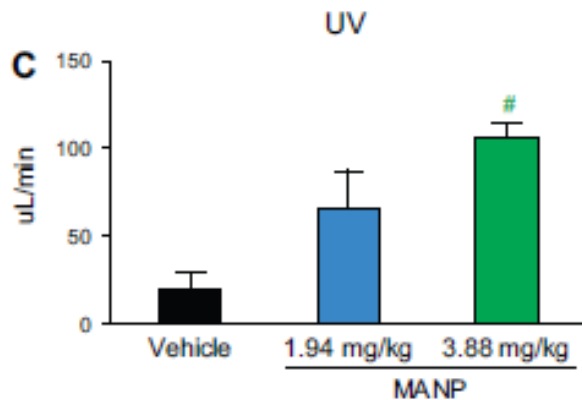
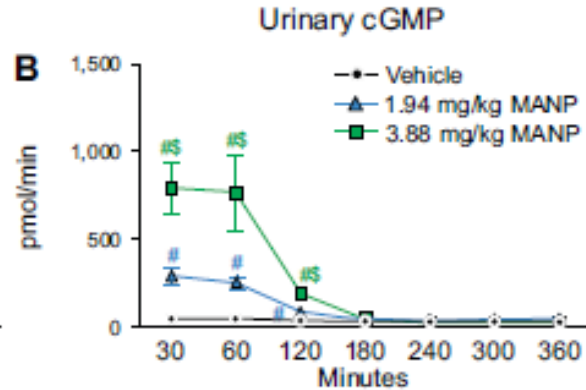
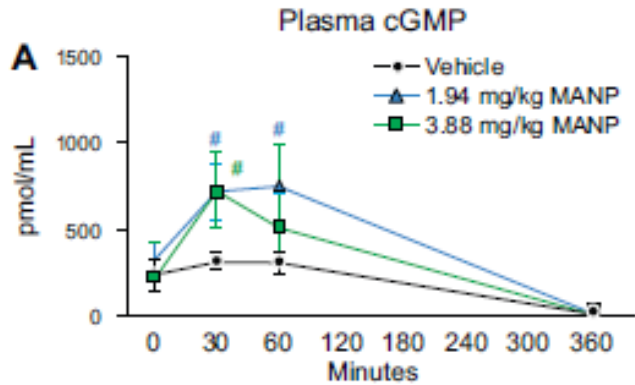
ARNI vs. ANP receptor agonist

- ❖ ARNI verlaagt de bloeddruk, is gunstig bij hartfalen, en kan ook de nierfunctie verbeteren – dit hangt allemaal samen met verhoogde concentraties van natriuretische peptiden.
- ❖ Waarom werken we eigenlijk niet met ANP zelf? Of een ANP receptor agonist? Dan heb je geen last van andere peptiden die door NEP remming beïnvloed worden.



ANP analogue MANP: rat studies

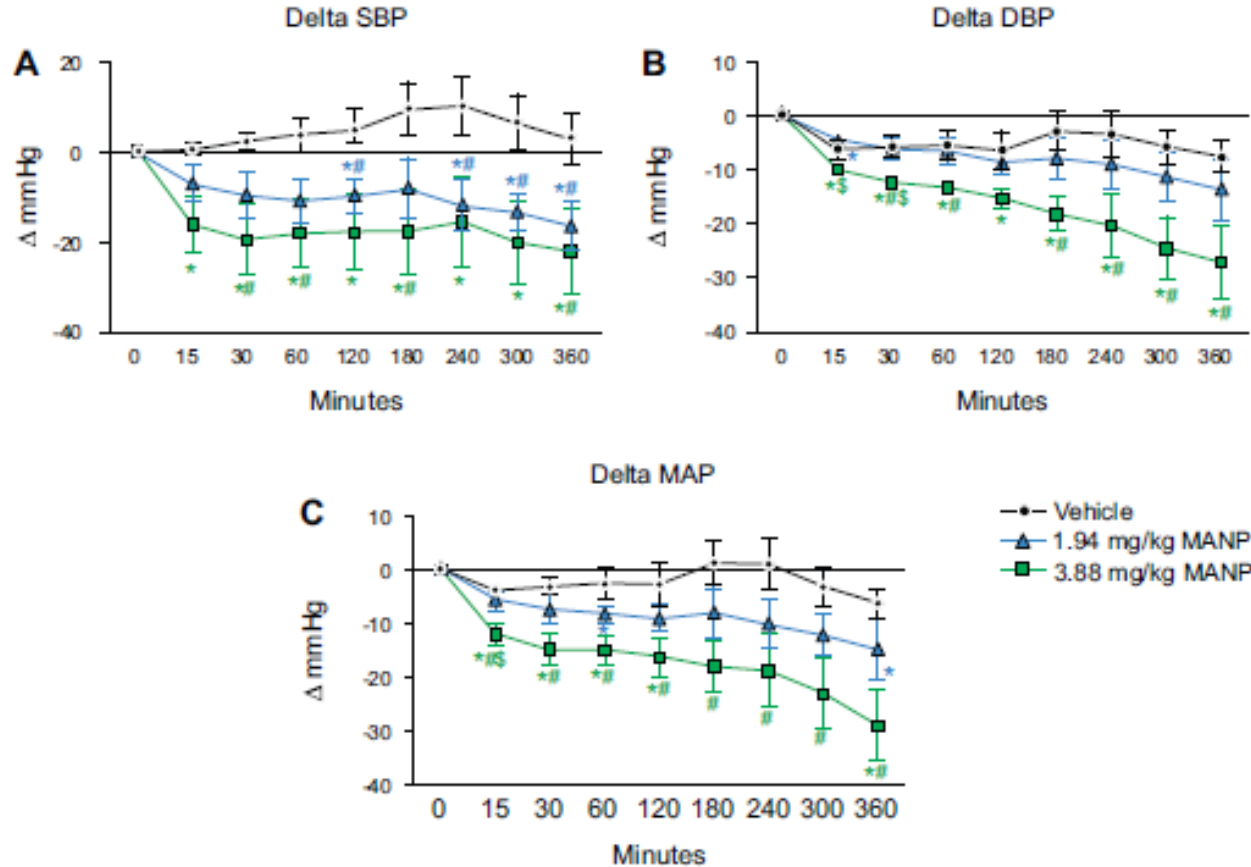
ACUTE STUDY



Chen et al.,
Am J Physiol Regul Integr Comp Physiol 2020

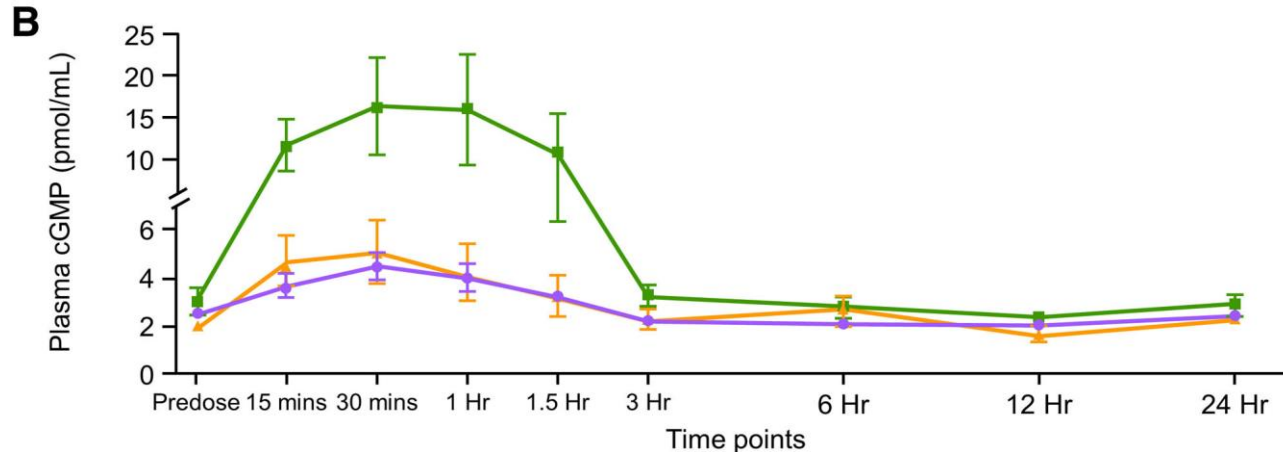
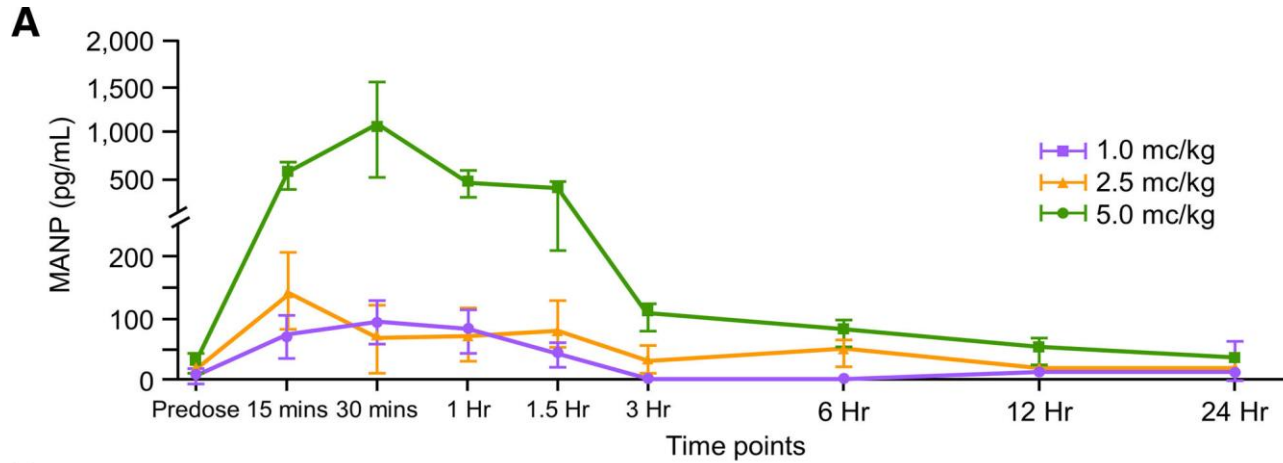
ANP analogue MANP: rat studies

ACUTE STUDY



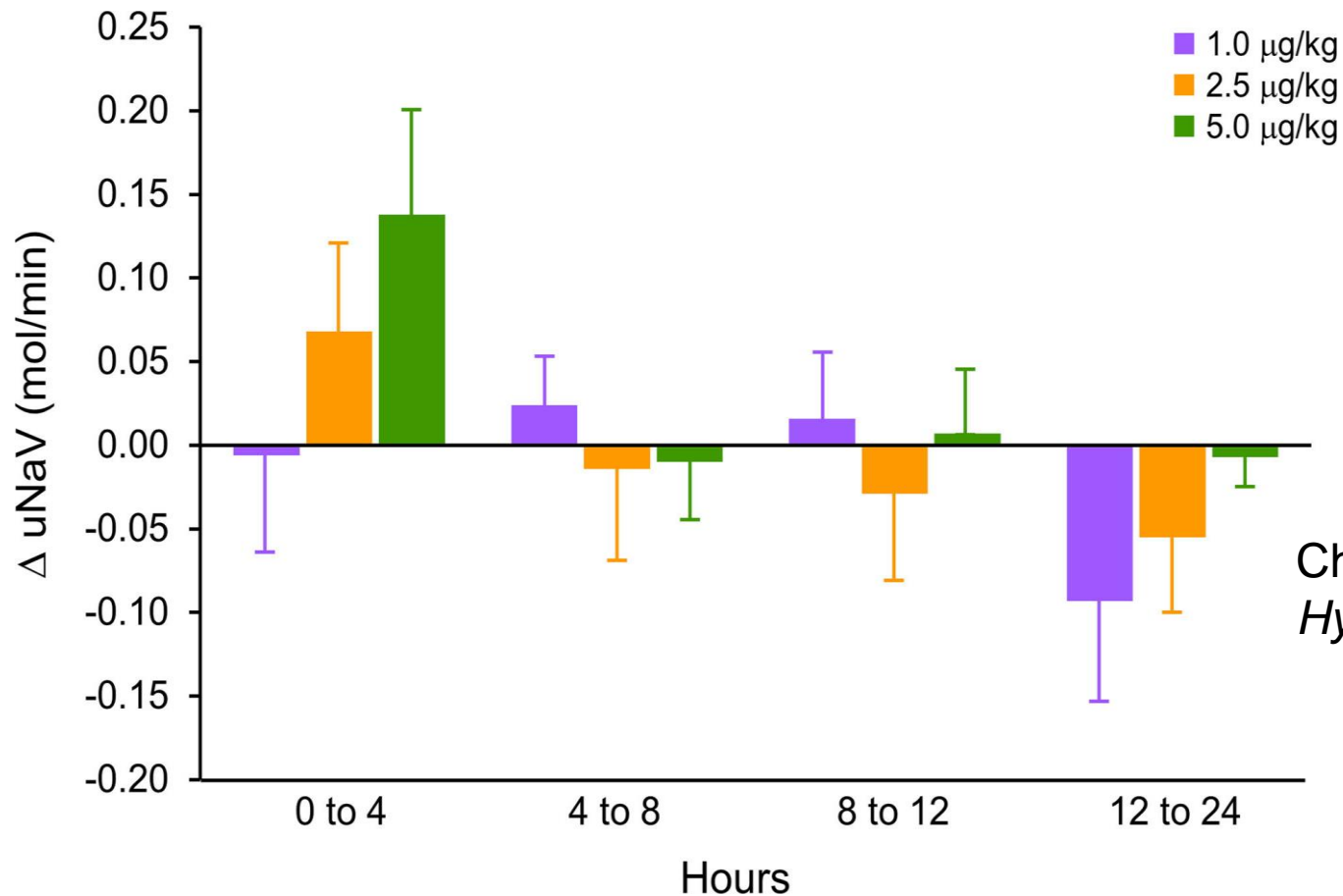
Chen et al.,
Am J Physiol
Regul Integr Comp
Physiol 2020

ANP analogue MANP: first human data



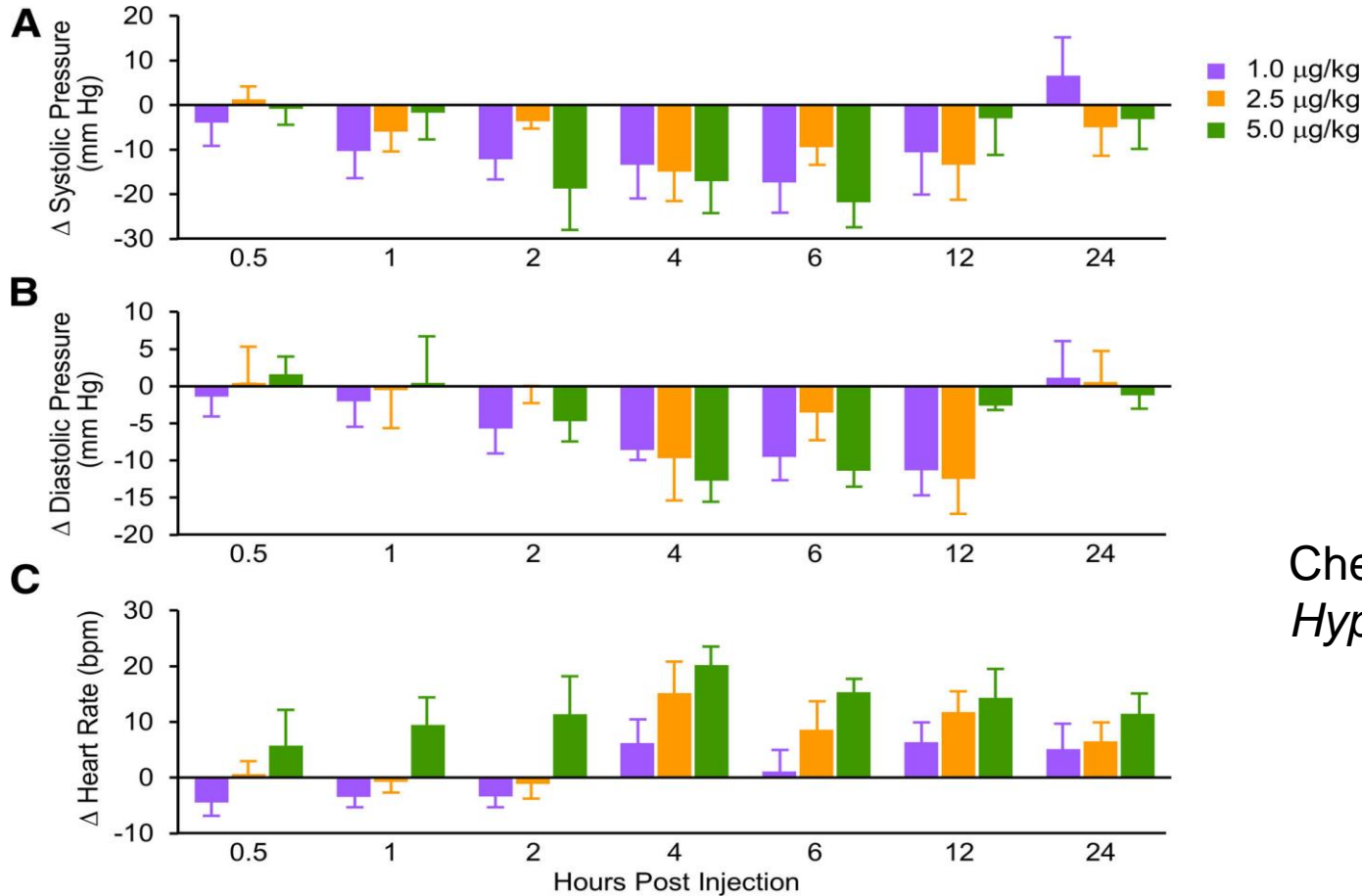
Chen et al.,
Hypertension 2021

ANP analogue MANP: first human data



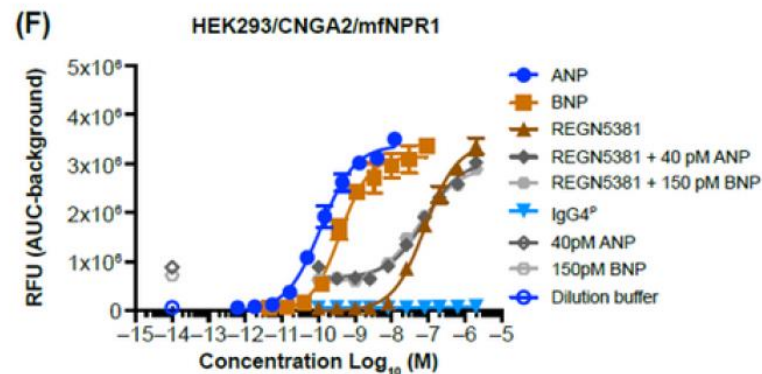
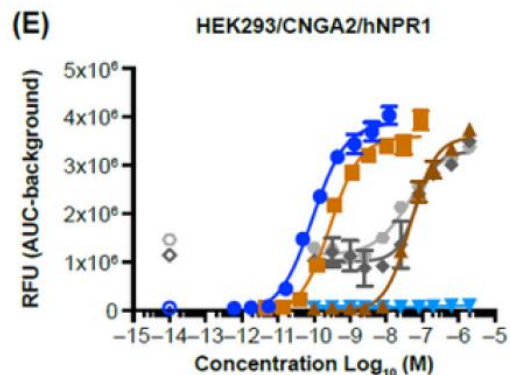
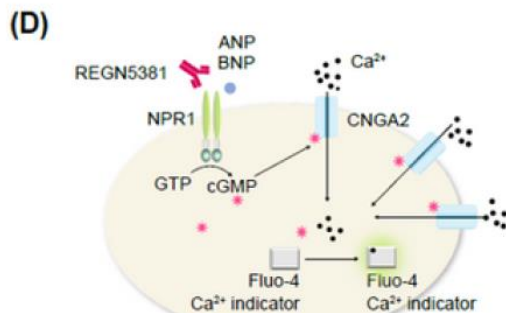
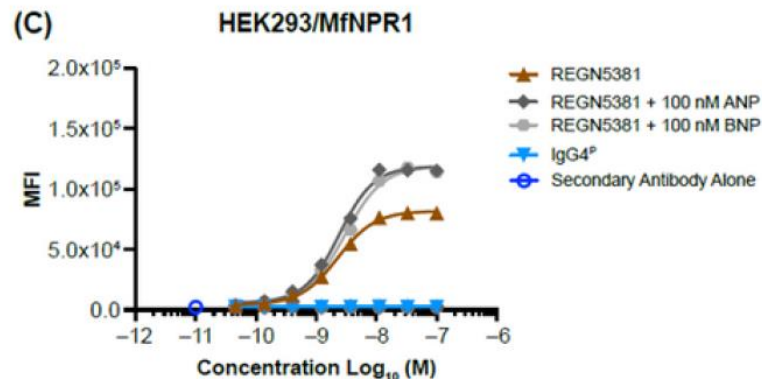
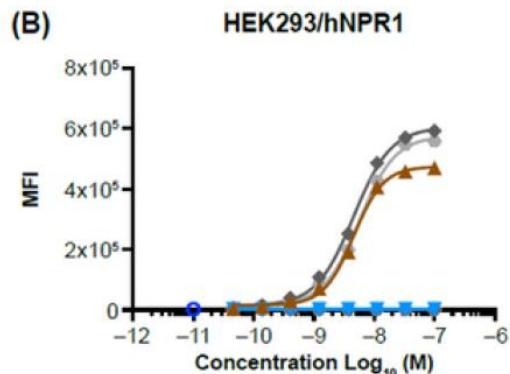
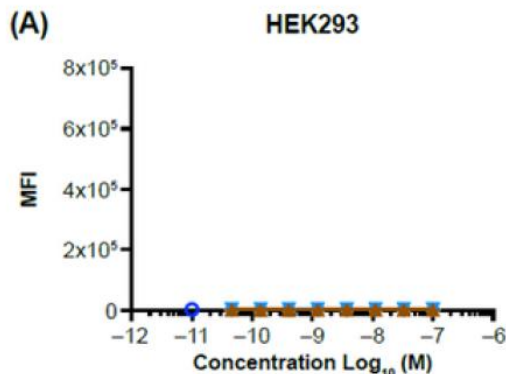
Chen et al.,
Hypertension 2021

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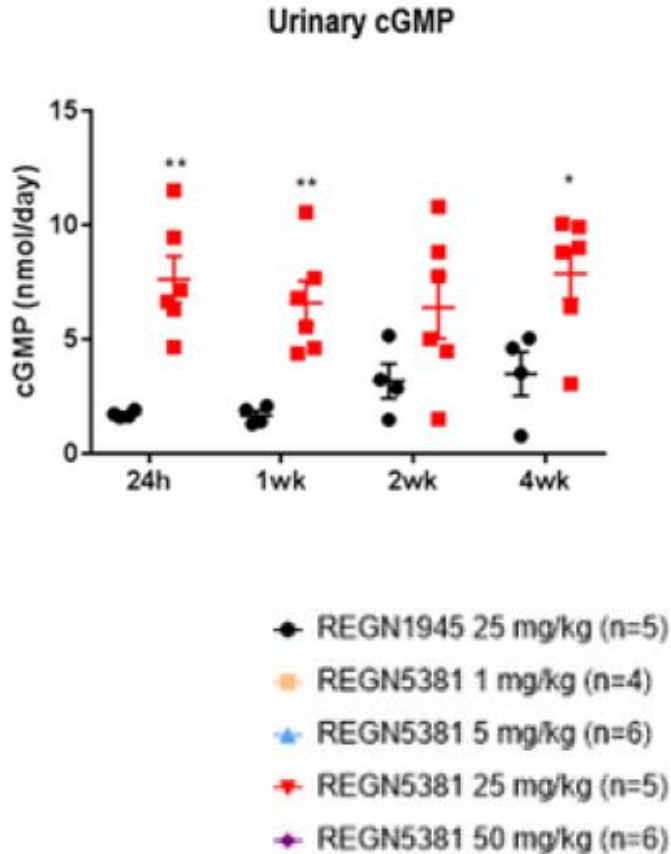


Chen et al.,
Hypertension 2021

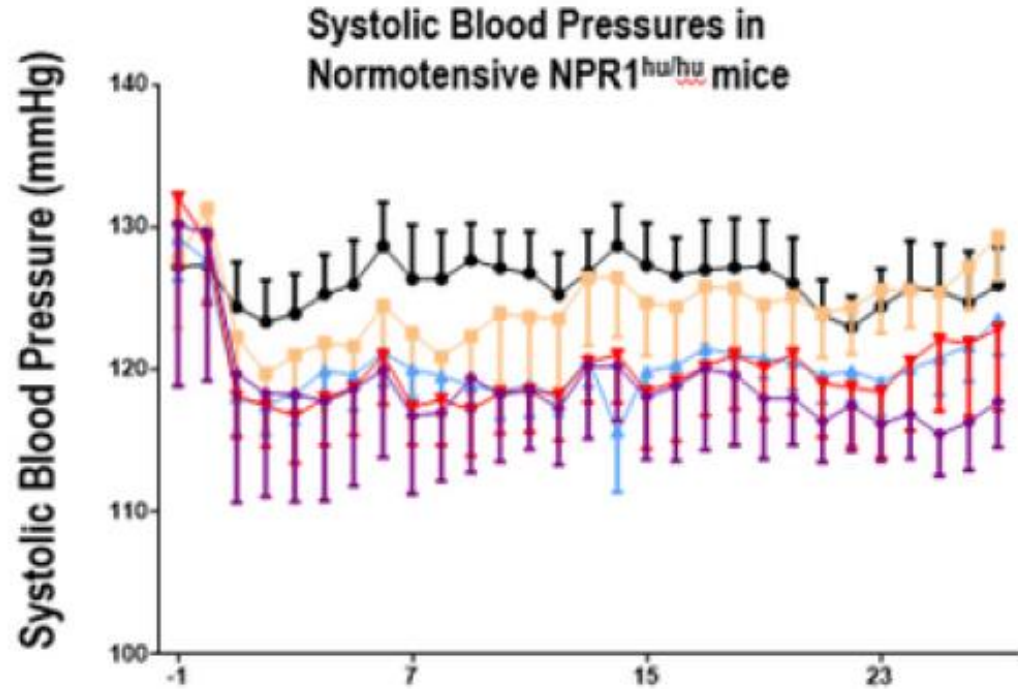
Next phase: long-acting NPR1 agonist antibody



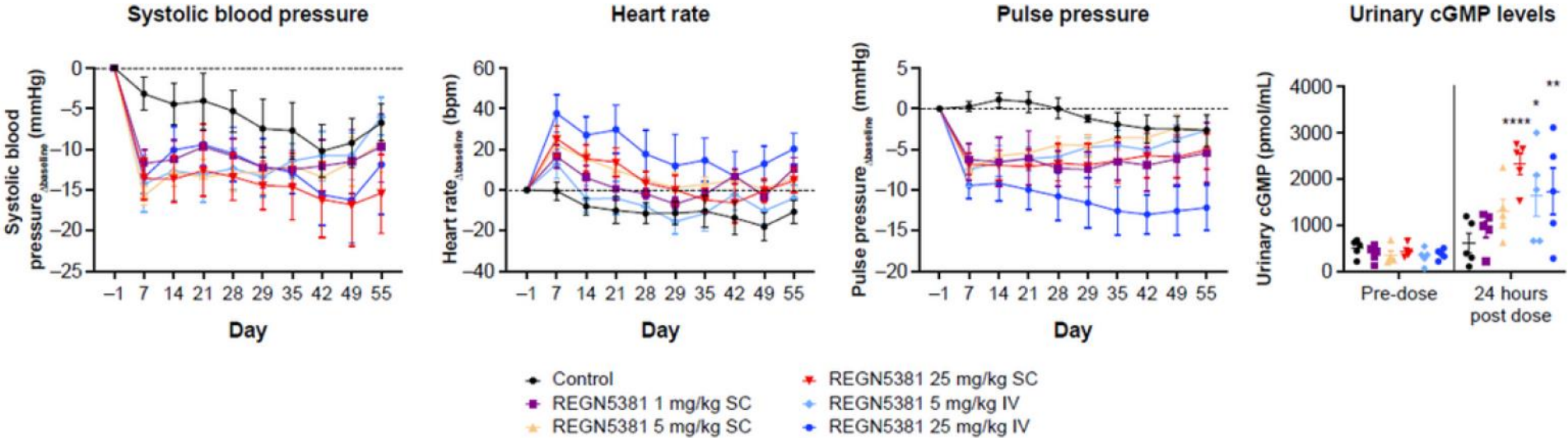
Next phase: long-acting NPR1 agonist antibody



effect of 1 s.c. injection lasts 28 days!



Next phase: long-acting NPR1 agonist antibody

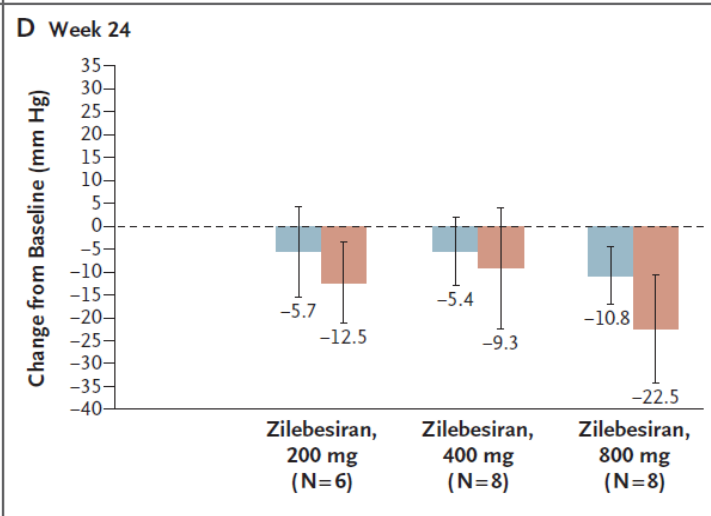
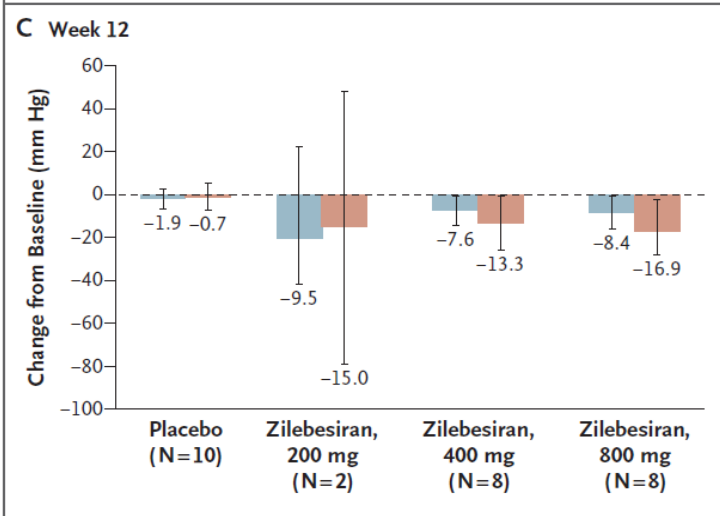
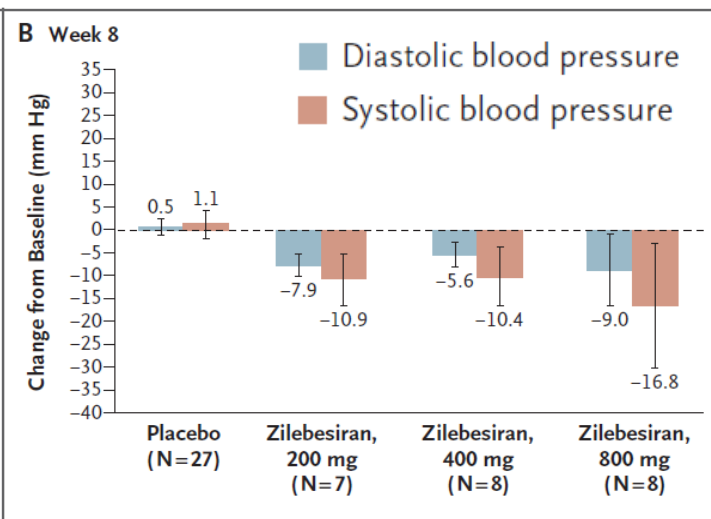
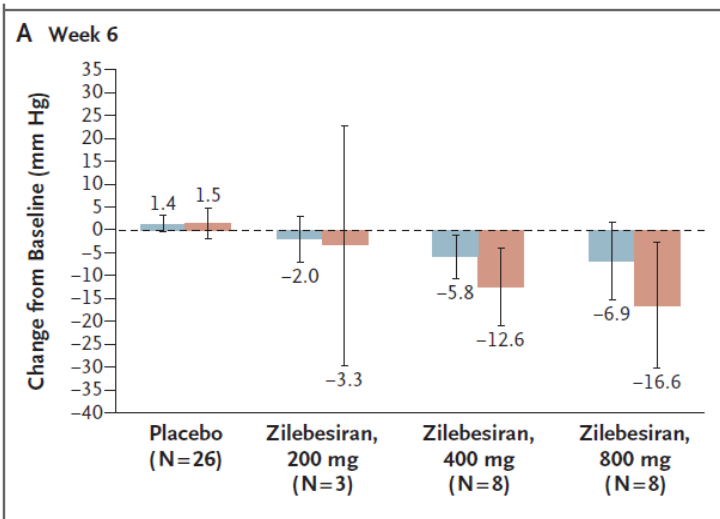


cynomolgous monkeys: blood pressure measurement by radiotelemetry

Dunn et al., unpublished data Regeneron (Preprint 2023)

Clinical trials: Regeneron en Novartis

- ❖ **NCT04506645 Phase 1 Trial:** A Randomized, Double-Blind, Placebo-Controlled, Two-Part Single Ascending Dose Study to Assess the Safety, Tolerability, and Pharmacokinetics of REGN5381 in Humans (n=24)
- ❖ presented at AHA meeting in Philadelphia (nov. 2023): single i.v. dose is well-tolerated in healthy humans (orthostatic hypotension & headache comparable to placebo) and induced a 7-11 mm Hg reduction in SBP that lasted 72 hours
- ❖ **NCT05562934 Phase 2 trial:** An Efficacy, Safety, Tolerability and Dose Finding Study of XXB750 in Resistant Hypertension Patients (n=170)
- ❖ 4 s.c. injections of XXB750 over 20 weeks to be given on top of maximally tolerated background antihypertensive therapy (diuretic/RASi/CCB) - recruitment is ongoing (multicenter, including Amsterdam UMC)

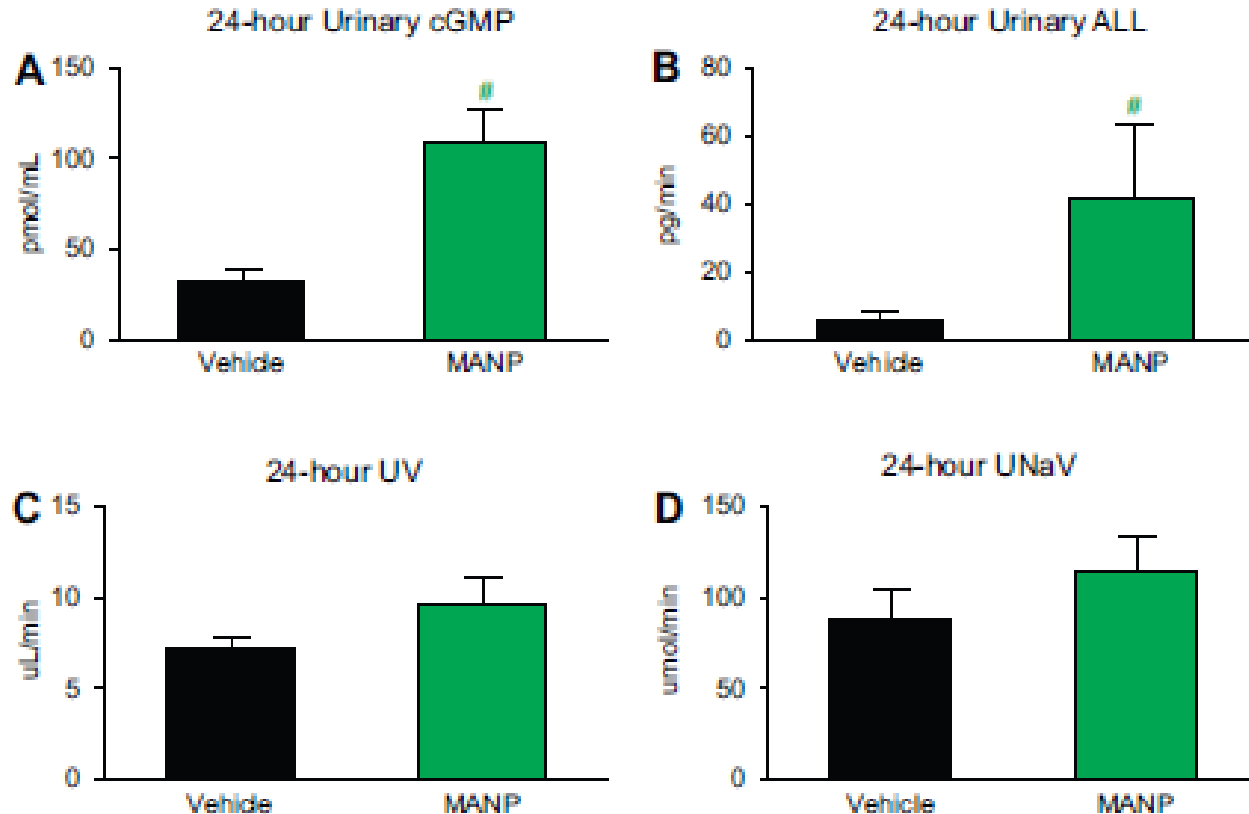


BUT:
 the blood pressure decreases after 1 s.c. injection of angiotensinogen siRNA (zilebesiran) last 6 months!

Desai et al.,
NEJM 2023

ANP analogue MANP: rat studies

CHRONIC STUDY

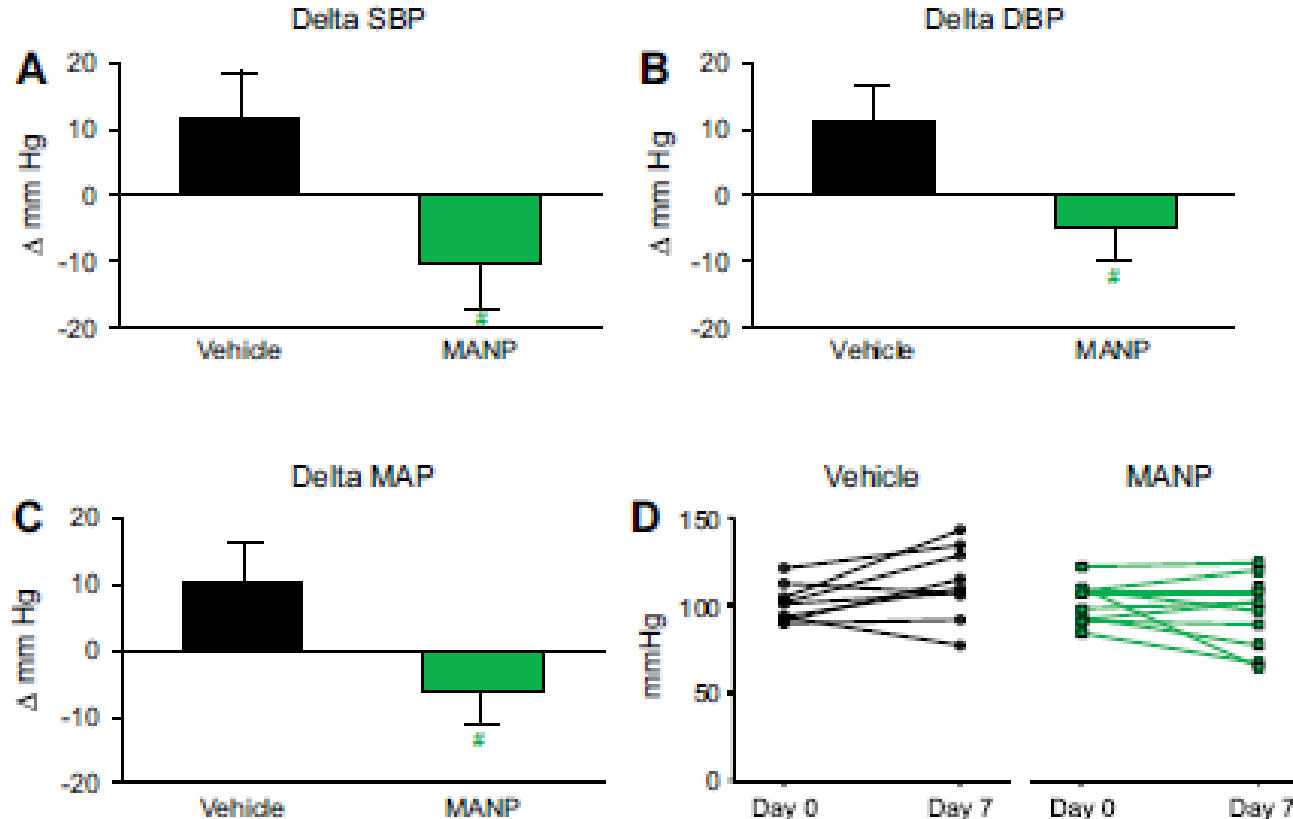


data on day 7 after
7 daily s.c. injections

Chen et al.,
*Am J Physiol
Regul Integr Comp
Physiol* 2020

ANP analogue MANP: rat studies

CHRONIC STUDY



data on day 7 after
7 daily s.c. injections

Chen et al.,
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ANP analogue MANP: first human data

Graphic Abstract

