HartVaatHAG Kaderdag

Roermond, 7 juni 2024

Nieuwe middelen bij hypertensie

A.H. Jan Danser

Interne Geneeskunde, Erasmus MC, **Rotterdam**

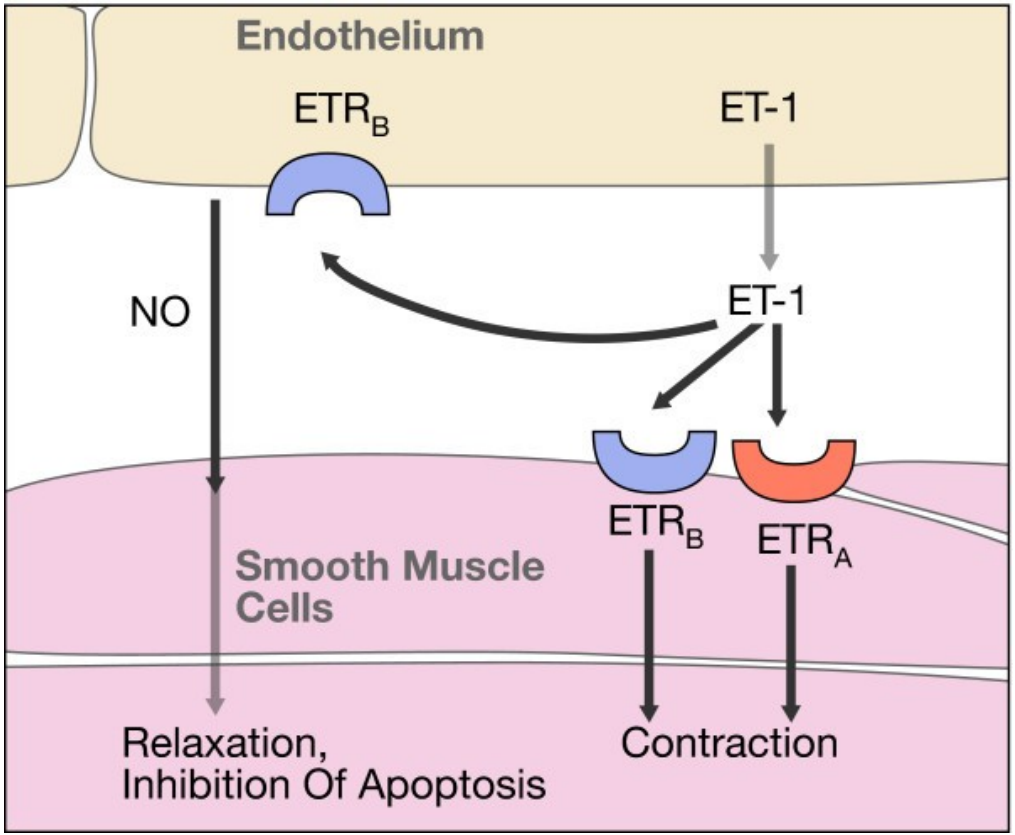
A ACEi, ARBs
(B beta-blockers)
C calcium antagonists
D diuretics

No new drugs over the last 2 decades!

11. ANTIHYPERTENSIVE DRUGS AND TREATMENT
- 11.1 Blockers of the renin–angiotensin system (RAS)
  - 11.1.1 Angiotensin-converting-enzyme inhibitors
  - 11.1.2 Angiotensin receptor blockers
  - 11.1.3 Renin inhibitors
  - 11.1.4 Combination of RAS inhibitors
- 11.2 Calcium channel blockers
  - 11.2.1 Dihydropyridine CCBs
  - 11.2.2 Nondihydropyridine CCBs
- 11.3 Diuretics
  - 11.3.1 Thiazide/Thiazide-like
  - 11.3.2 Loop diuretics
  - 11.3.3 Potassium-sparing diuretics
- 11.4 Mineralocorticoid receptor antagonists
- 11.5 Beta-blockers
- 11.6 Alpha-1 blockers
- 11.7 Centrally acting drugs
- 11.8 Vasodilators
- 11.9 Angiotensin receptor-neprilysin inhibitor (ARNI)

Large Hypertension Trials

- PRECISION: aprocitentan (endothelin receptor antagonist)
- BrigHTN: baxdrostat (aldosterone synthase inhibitor)
- Zilebesiran: angiotensinogen siRNA
- ANP-A receptor activating antibodies (ongoing)



ENDOTHELIN-1

potent vasoconstrictor

ambrisentan (ETR$_A$-selective)

and bosentan/macitentan (dual ETR antagonist) used in pulmonary hypertension

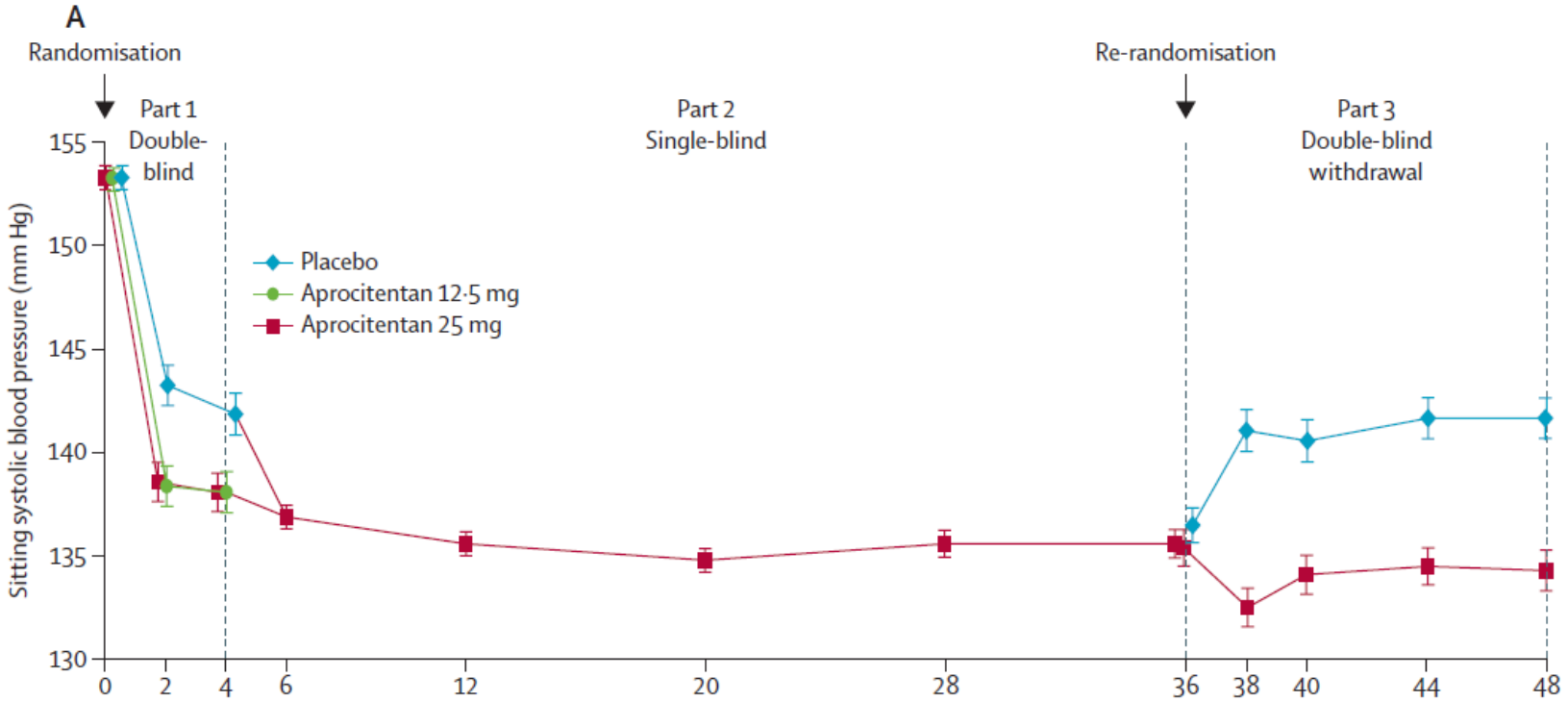
atrasentan (ETR$_A$-selective)

lowered albuminuria and BP in type 2 diabetes mellitus

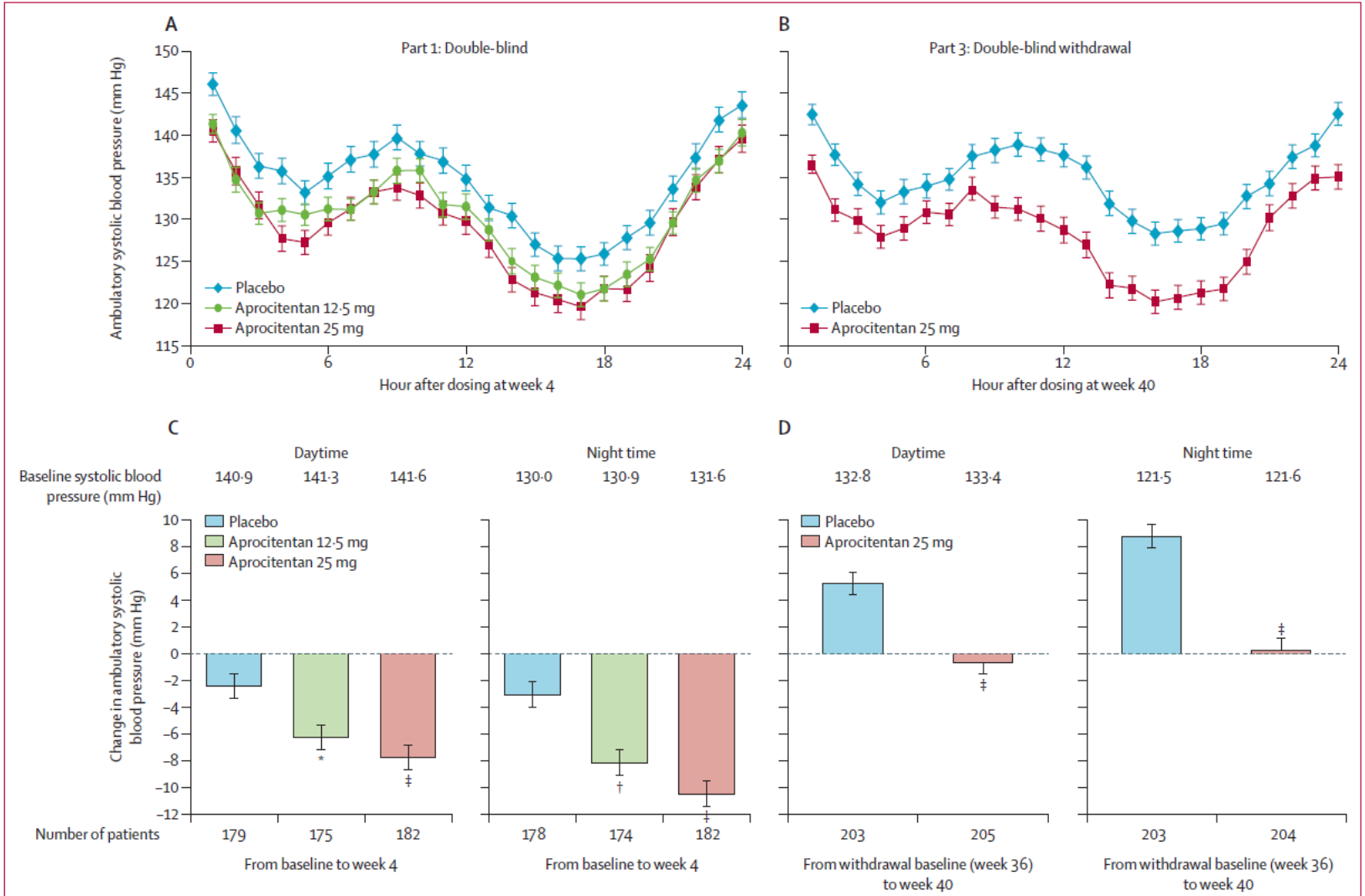
APROCITENTAN: dual ETR antagonist

- Parallel-Group, Phase 3 Study with Aprocitentan in Subjects with Resistant Hypertension (PRECISION): multicenter, 84% white patients, sitting systolic BP $\geq$ 140 mm Hg despite taking 3 antihypertensive drugs including a diuretic , 12.5 or 25 mg versus placebo (on top of amlodipine + valsartan + HCTZ)
- primary endpoint is unattended systolic BP, secondary 24-h ambulatory BP changes

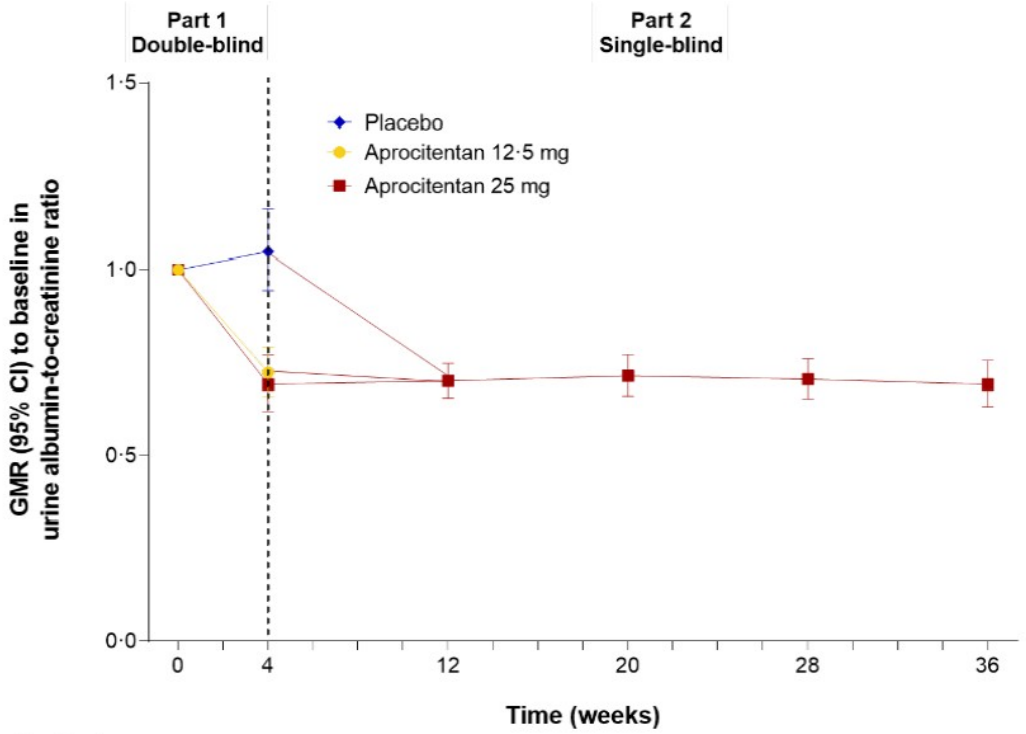
Sitting systolic BP (measured as unattended automated office BP)



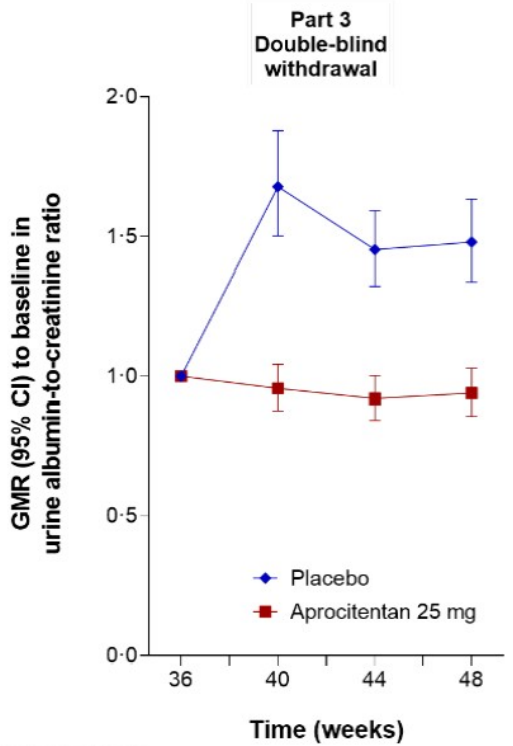
Schlaich et al., *The Lancet* 2022


A
Part 1: Double-blind
Ambulatory systolic blood pressure (mm Hg)
150
145
140
135
130
125
120
115
0
6
12
18
24
Hour after dosing at week 4
Placebo
Aprocitentan 12·5 mg
Aprocitentan 25 mg
B
Part 3: Double-blind withdrawal
Hour after dosing at week 40
Placebo
Aprocitentan 25 mg
C
Daytime
Night time
Baseline systolic blood pressure (mm Hg)
140·9
141·3
141·6
130·0
130·9
131·6
Change in ambulatory systolic blood pressure (mm Hg)
10
8
6
4
2
0
−2
−4
−6
−8
−10
−12
Placebo
Aprocitentan 12·5 mg
Aprocitentan 25 mg
*
†
‡
Number of patients
179
175
182
178
174
182
From baseline to week 4
From baseline to week 4
D
Daytime
Night time
132·8
133·4
121·5
121·6
Placebo
Aprocitentan 25 mg
‡
203
205
203
204
From withdrawal baseline (week 36) to week 40
From withdrawal baseline (week 36) to week 40

Change in urine albumin-creatinine ratio



Number of patients						
Placebo	238	221				
Aprocitentan 12·5 mg	241	221				
Aprocitentan 25 mg	238	227	648	633	609	428



Number of patients			
Placebo	257	282	272
Aprocitentan 25 mg	249	287	267

	Aprocitentan 12·5 mg	Aprocitentan 25 mg	Placebo
Part 1: Double-blind	243	245	242
Patients with at least one event	30 (12·3%)	47 (19·2%)	7 (2·9%)
Oedema or fluid retention	22 (9·1%)	45 (18·4%)	5 (2·1%)
Anaemia or haemodilution	9 (3·7%)	3 (1·2%)	0
Hepatic disorder	0	1 (0·4%)	2 (0·8%)
Part 2: Single-blind	..	704	..
Patients with at least one event	..	185 (26·3%)	..
Oedema or fluid retention	..	128 (18·2%)	..
Anaemia or haemodilution	..	63 (8·9%)	..
Hepatic disorder	..	16 (2·3%)	..
Part 3: Double-blind withdrawal	..	310	303
Patients with at least one event	..	18 (5·8%)	15 (5·0%)
Oedema or fluid retention	..	8 (2·6%)	4 (1·3%)
Anaemia or haemodilution	..	6 (1·9%)	4 (1·3%)
Hepatic disorder	..	4 (1·3%)	7 (2·3%)

side effect:

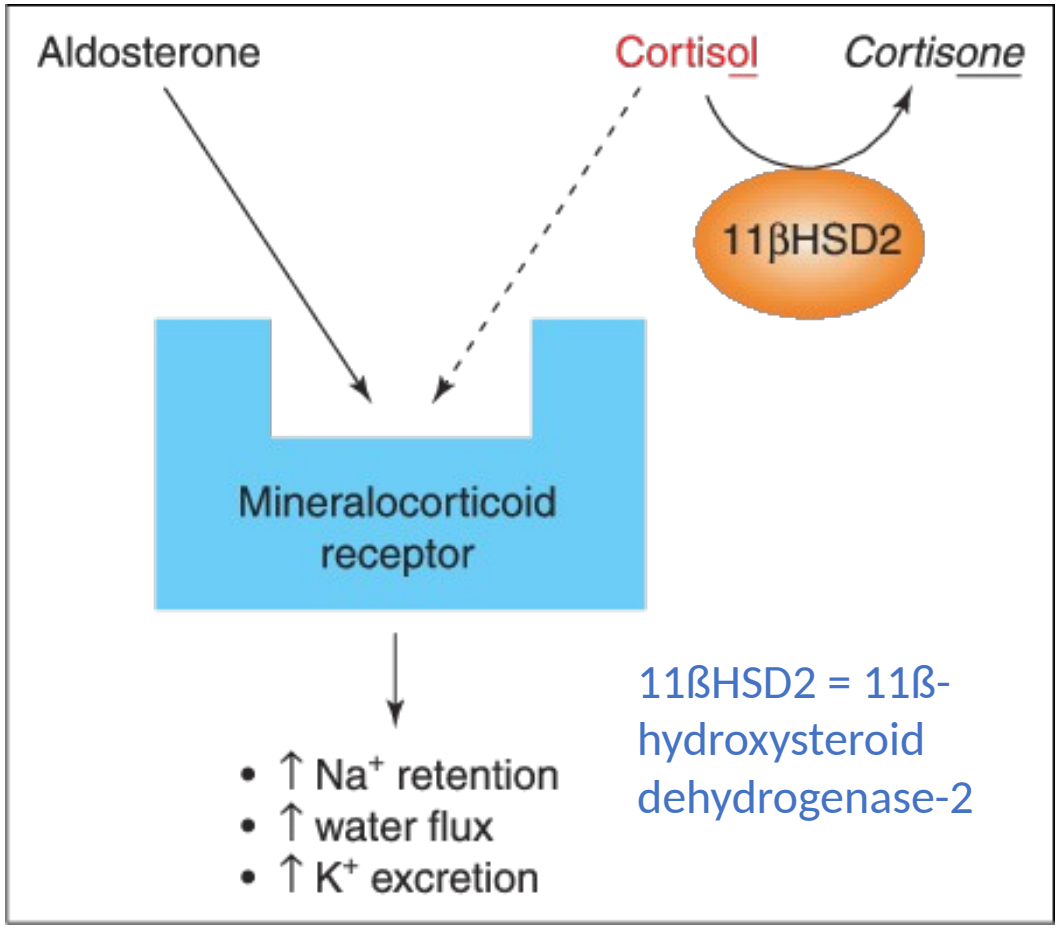
oedema or fluid retention, dose-related but manageable with addition or uptitration of diuretic therapy

March 20th, 2024:

FDA Approves Aprocitentan for Inadequately Controlled Hypertension

…known as Tryvio, the endothelin receptor antagonist is indicated for use with other antihypertensive drugs…

Erasmus MC



11ßHSD2 = 11ß-hydroxysteroid dehydrogenase-2

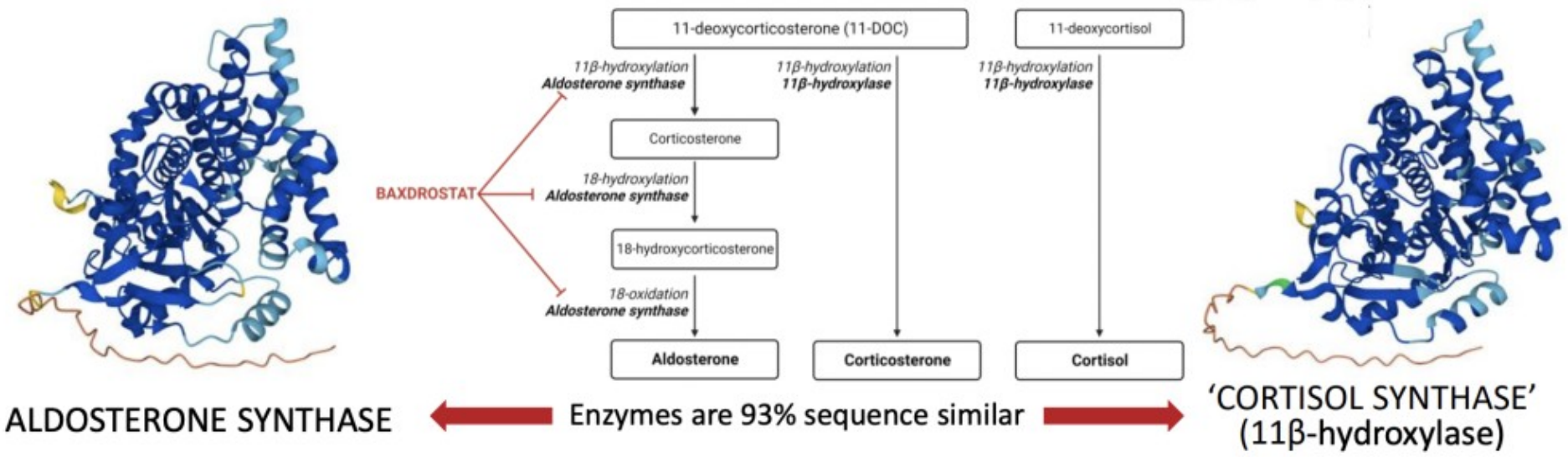
MR antagonists

spironolactone, eplerenone and finerenone:
hypertension, heart failure and (diabetic) kidney disease

side effect: hyperkalemia

blockade of aldosterone-mediated effects via other receptors (GPR30)?

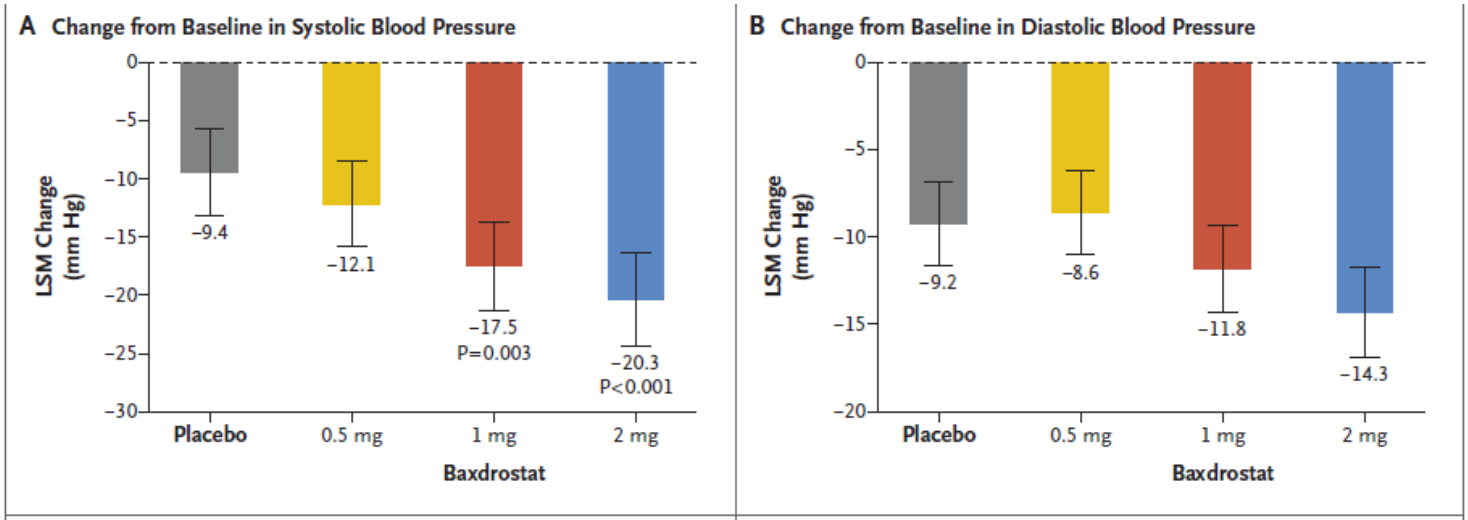
BAXDROSTAT: first selective aldosterone synthase inhibitor

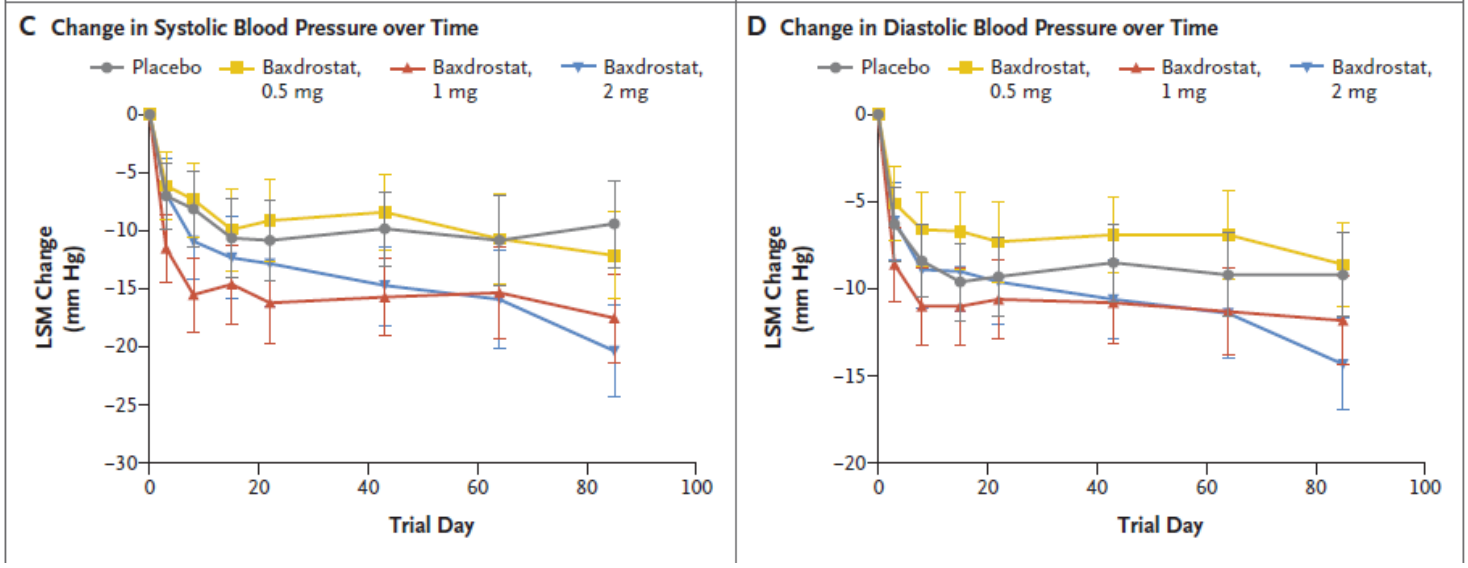


Concept: treatment-resistant hypertension is associated with autonomous aldosterone production (based on the superior effects of spironolactone in the PATHWAY-2 trial)

BrigHTN

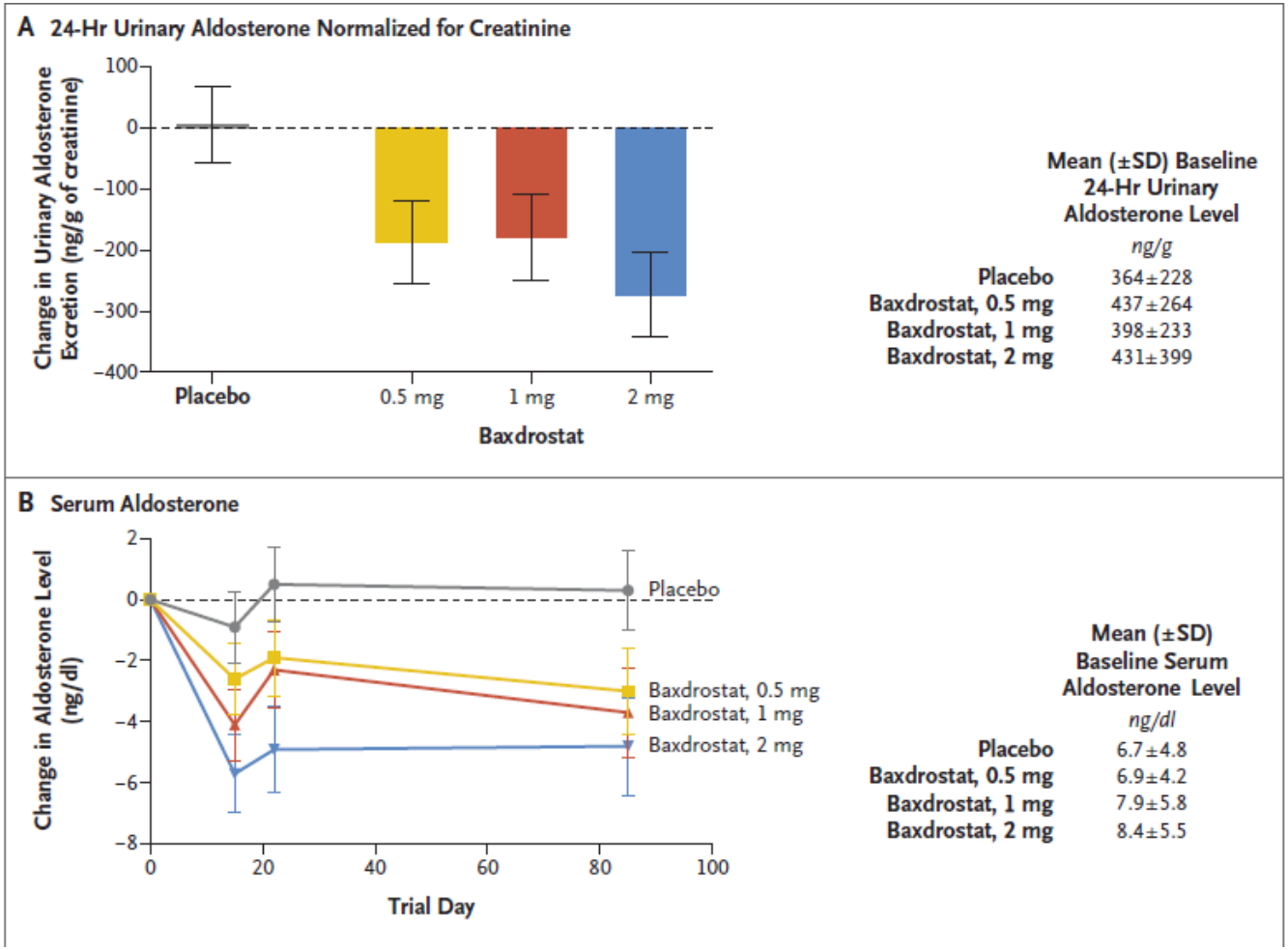
- multicenter, randomized, placebo-controlled parallel-group trial in 248 subjects receiving ≥ 3 antihypertensive drugs incl. a diuretic, sitting BP ≥ 130/80 mm Hg, eGFR > 45 mL/min per 1.73 m^2; 0.5-1-2 mg baxdrostat vs. placebo during 12 weeks
- primary endpoint is change in seated systolic BP, secondary change in seated diastolic BP, and % of patients with BP < 130/80 mm Hg



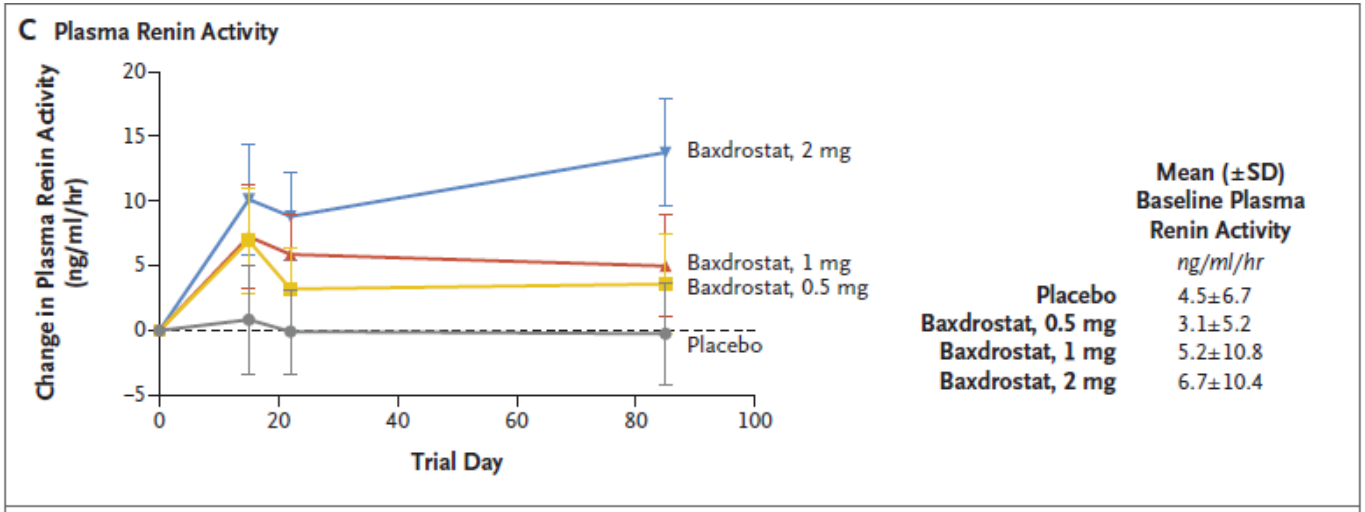


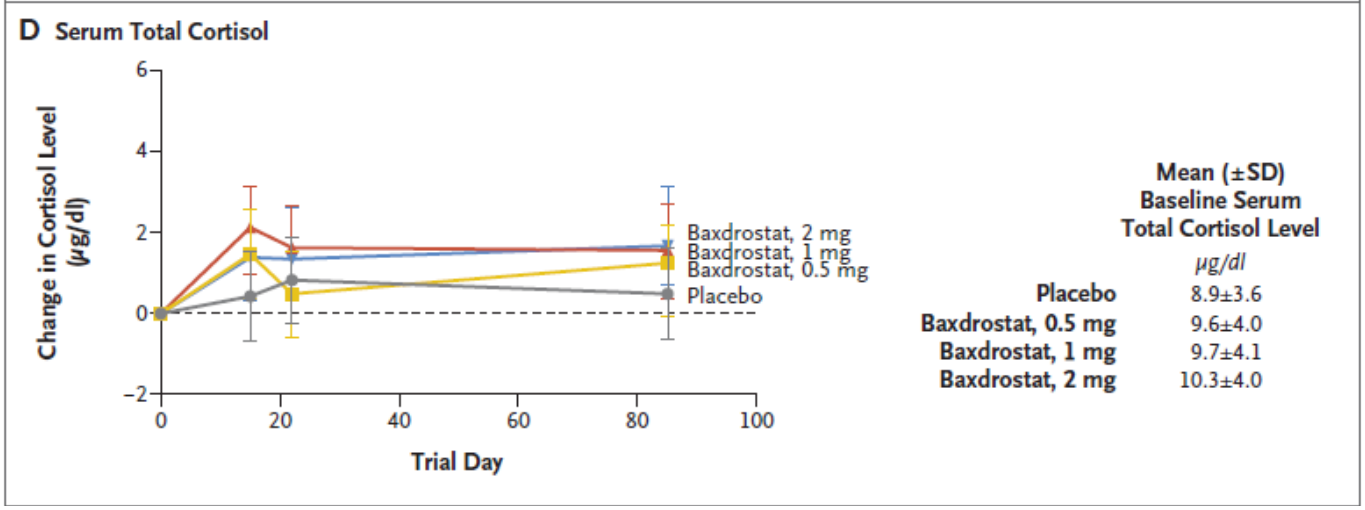
Freeman et al., *NEJM* 2022

P<0.001



changes in aldosterone in urine and plasma





rise in renin, but no change in cortisol

Adverse effects

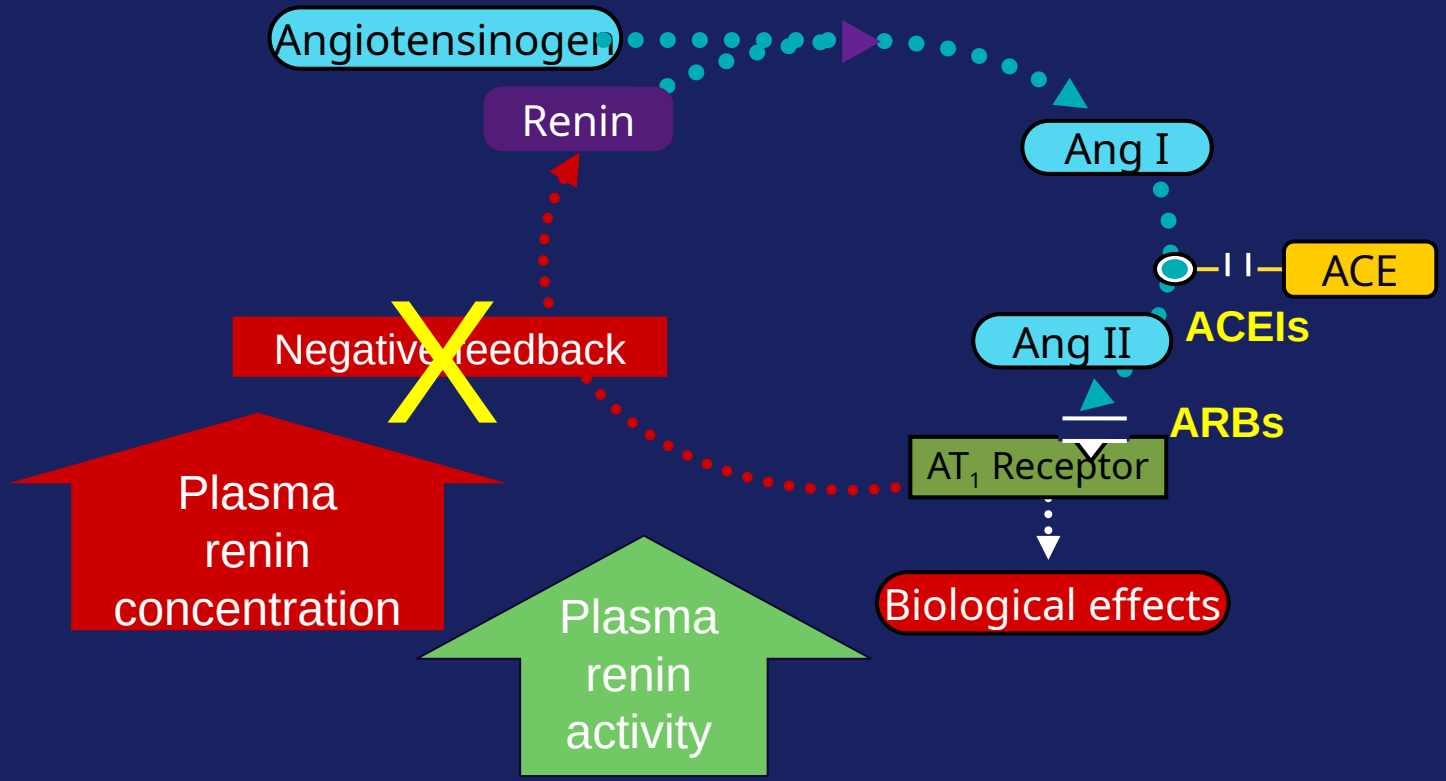
Event	Placebo (N=69)		Baxdrostat, 0.5 mg (N=69)		Baxdrostat, 1 mg (N=69)		Baxdrostat, 2 mg (N=67)	
	No. of Patients with Event (%)	No. of Events	No. of Patients with Event (%)	No. of Events	No. of Patients with Event (%)	No. of Events	No. of Patients with Event (%)	No. of Events
Any serious adverse event*	2 (3)	3	0	0	2 (3)	3	6 (9)	12
Any adverse event	28 (41)	50	24 (35)	38	36 (52)	77	32 (48)	67
Adverse event of special interest†	0	0	1 (1)	1	5 (7)	6	2 (3)	3
Hyponatremia	0	0	0	0	2 (3)	2	1 (2)	1
Hypotension	0	0	0	0	1 (1)	1	0	0
Potassium level ≥6.0 mmol/liter	0	0	0	0	2 (3)	2	1 (2)	1
Potassium level between 5.5 and 5.9 mmol/liter on at least two consecutive occasions‡	0	0	1 (1)	1	2 (3)	2	1 (2)	1

Other aldosterone synthase inhibitors

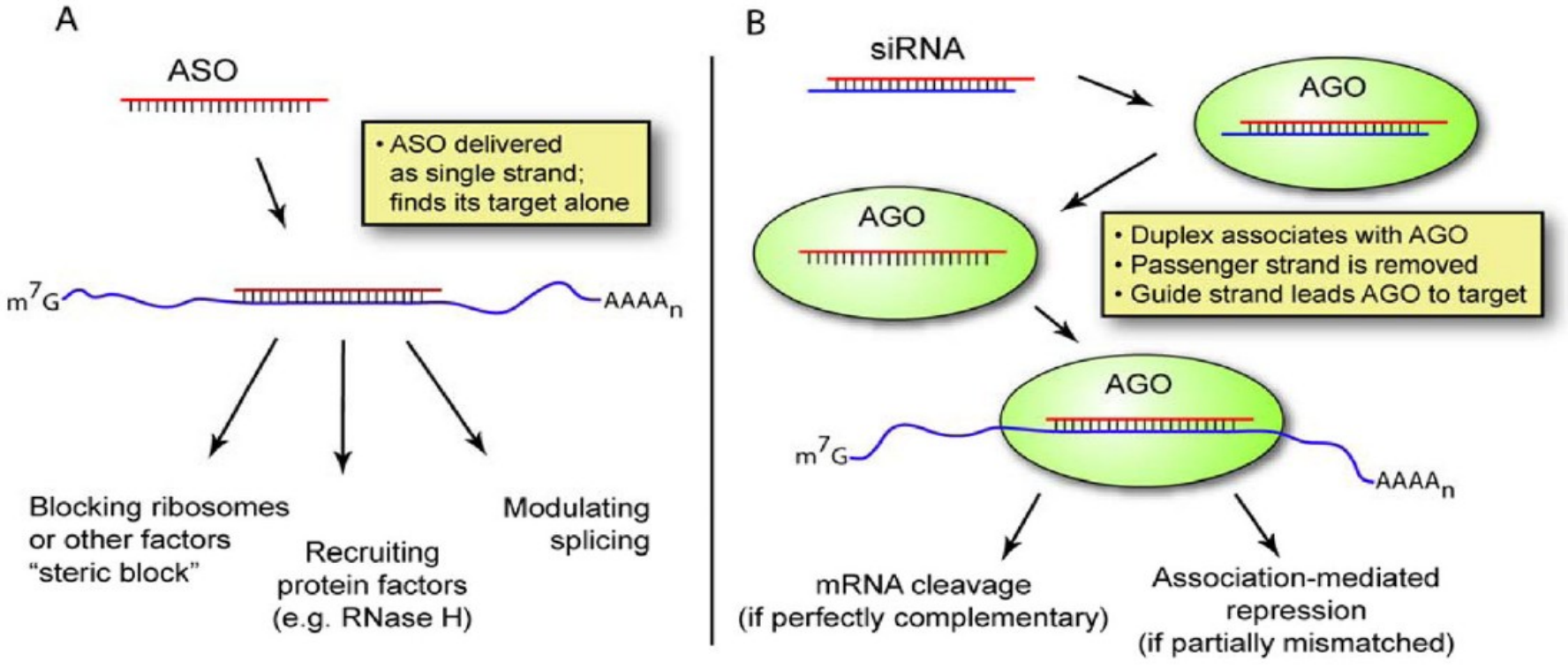
- baxdrostat (Freeman et al., *NEJM* 2023)
- lorundostat (Laffin et al. *JAMA* 2023)
  dexfadrostat (Mulatero et al., *Br J Clin Pharmacol*

  2023)
  BI690517 (Tuttle et al., *Lancet* 2024: +/- SGLT2
  inhibitor)

Renin-angiotensin system (RAS) blockers and the negative feedback loop



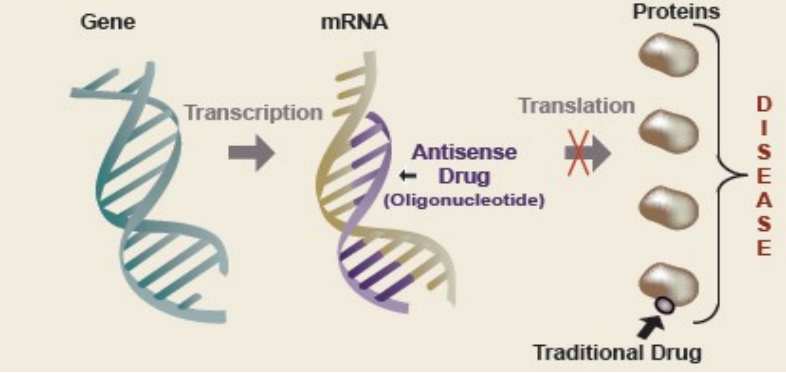
Angiotensinogen: antisense oligonucleotide (ASO) vs. siRNA



Watts & Corey, *J Pathol* 2012

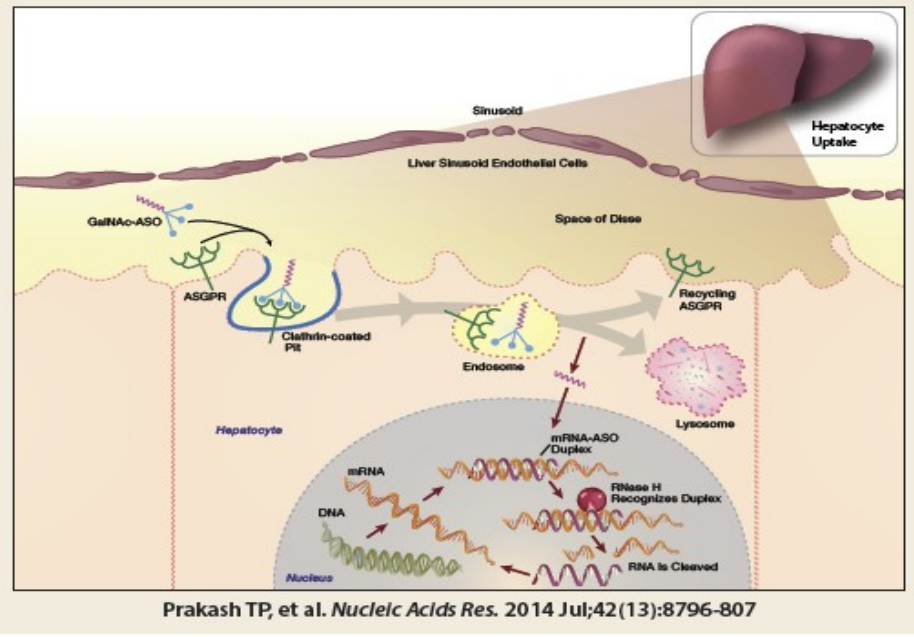
AGO, Argonaute

Erasmus MC



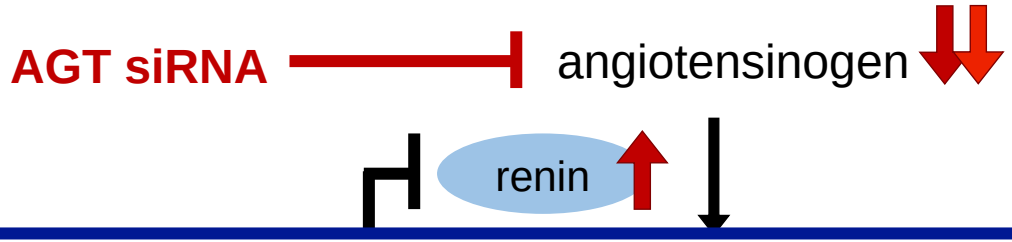
angiotensinogen is exclusively (?) generated in the liver: how to target ASO/siRNA to this organ?

- asialoglycoprotein receptor is a C-type lectin which is abundantly expressed by hepatocytes (> 0.5 million receptors/cell)
- high specificity for N-acetyl-galactosamine (GalNAc)-terminated oligosaccharides
- one receptor can internalize 250 GalNac-conjugated molecules during its lifetime: ideal way to transport oligonucleotide into hepatocytes!



Prakash TP, et al. *Nucleic Acids Res.* 2014 Jul;42(13):8796-807

RNA interference targeting angiotensinogen: AGT siRNA



AGT depletion may prevent RAS escape

Effects of siRNA appear to be long-lasting

Experimental application of PCSK9 siRNA in patients demonstrates >6 months of stable target suppression

Liver specific AGT siRNA knocks plasma AGT down by 97.9 - 99.8%

Spontaneously Hypertensive Rats (SHR)



male (n=8 / group)

97.9%

99.8%



Vehicle

Valsartan+AGT siRNA



ARB: valsartan

oral

31 mg/kg/day



AGT siRNA

liver specific

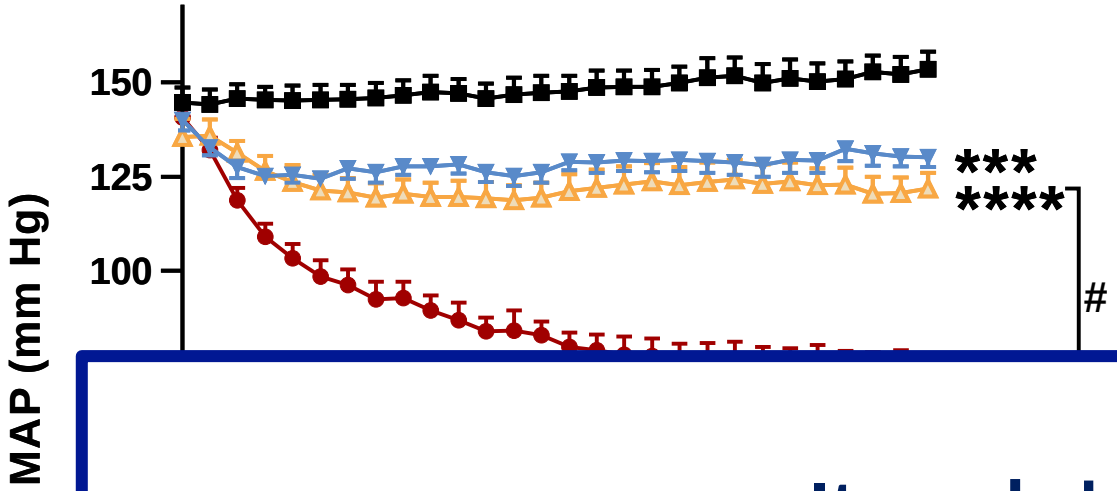
s.c.

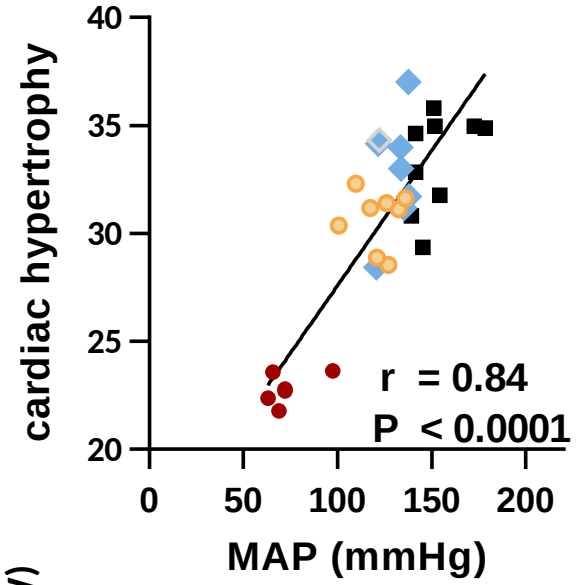
10 mg/kg per 2 weeks

Treatment

Continuous BP measurement

AGT siRNA provides strong and sustained BP lowering





It works!

Uijl et al., Hypertension 2019

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Zilebesiran, an RNA Interference Therapeutic Agent for Hypertension

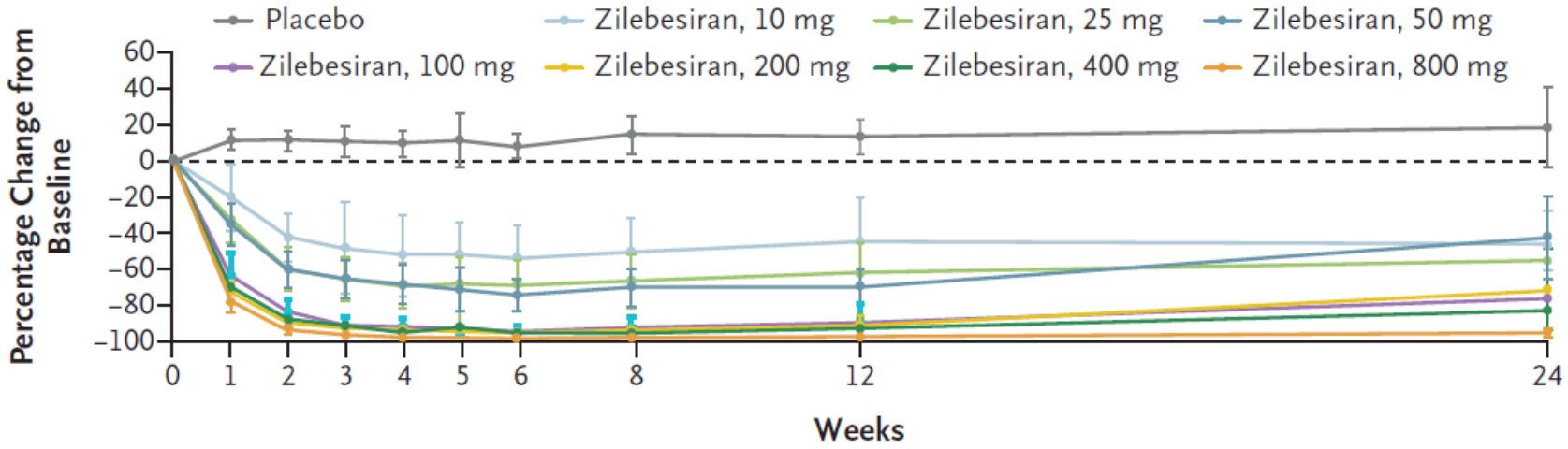
Akshay S. Desai, M.D., M.P.H., David J. Webb, M.D., D.Sc., Jorg Taubel, M.D., Sarah Casey, M.B., Ch.B., Yansong Cheng, Ph.D., Gabriel J. Robbie, Ph.D., Don Foster, M.S., Stephen A. Huang, M.D., Sean Rhyee, M.D., M.P.H., Marianne T. Sweetser, M.D., Ph.D., and George L. Bakris, M.D.

107 patients, mean age 54 years (target range 18-65), 62% men, 25% black, SBP 140±9 mm Hg (target >130 mm Hg)

Single ascending doses of zilebesiran (10-800 mg)

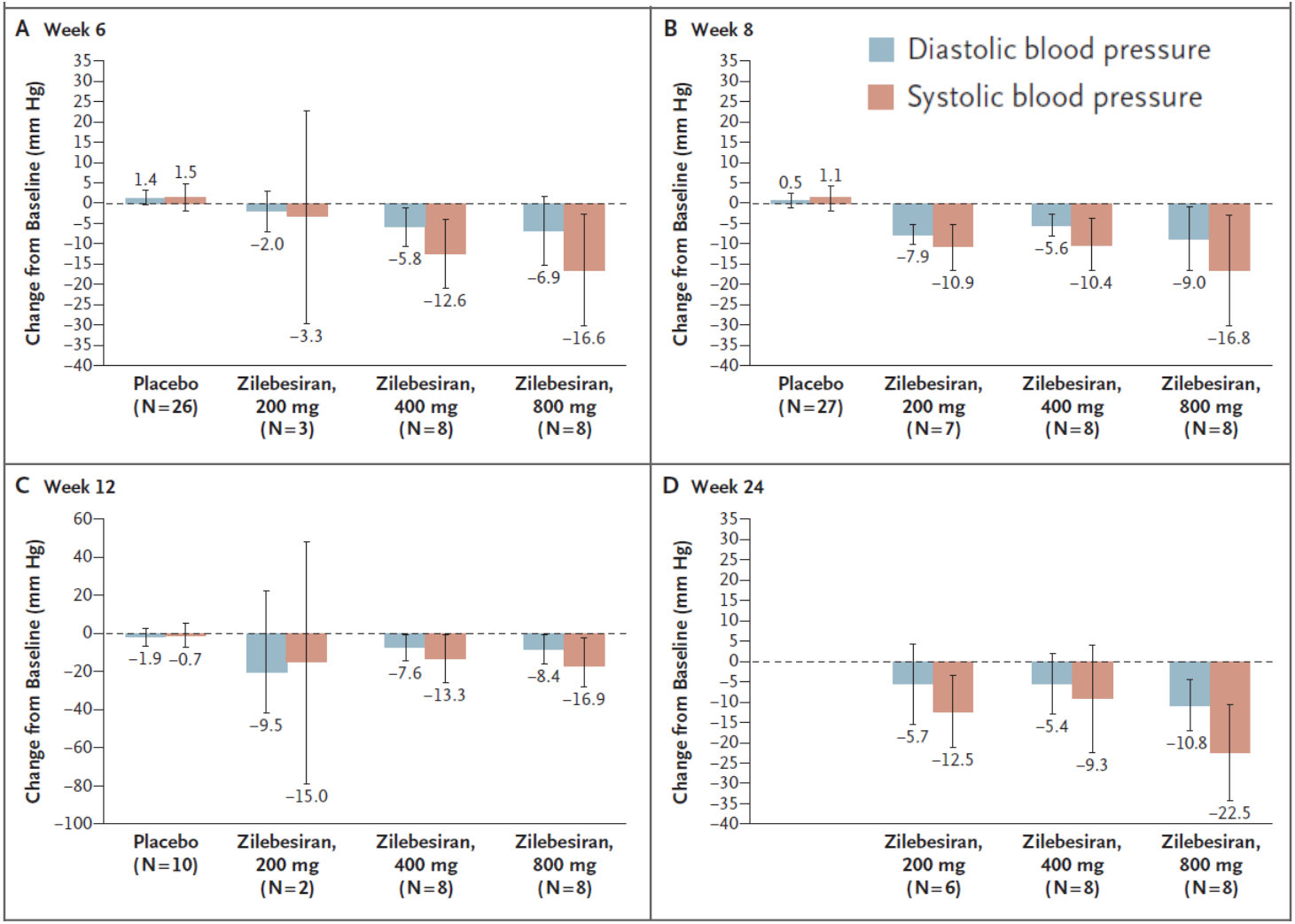
N Engl J Med 2023;389:228-38.
DOI: 10.1056/NEJMoa2208391

A Part A

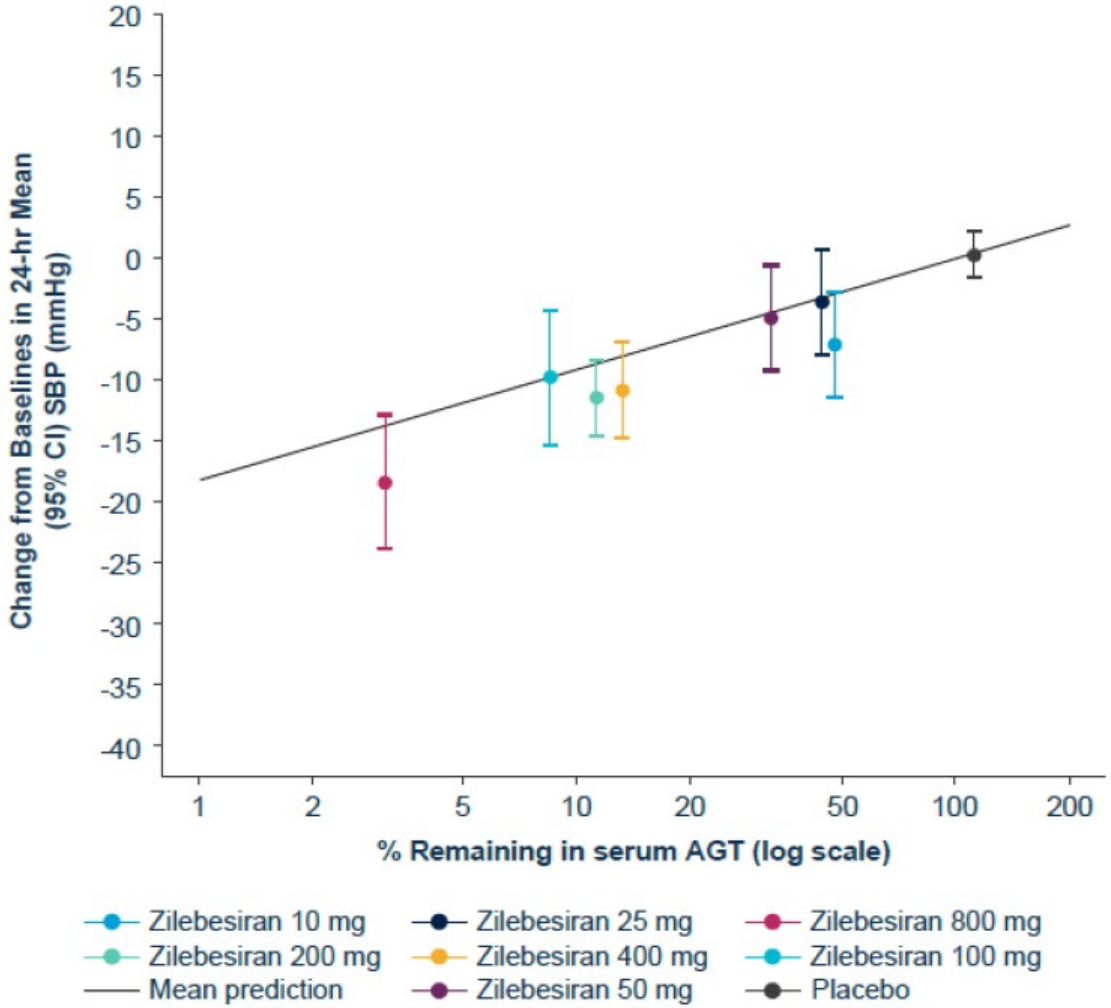


No. of Patients

Placebo	28	28	28	28	27	17	26	27	28	12
Zilebesiran, 10 mg	8	8	8	8	8	8	8	8	8	5
Zilebesiran, 25 mg	8	8	8	8	8	8	8	8	8	8
Zilebesiran, 50 mg	8	8	8	8	8	8	8	7	7	7
Zilebesiran, 100 mg	8	7	8	8	8	8	8	8	7	7
Zilebesiran, 200 mg	8	8	8	7	6	2	3	7	8	8
Zilebesiran, 400 mg	8	8	8	8	8	0	8	8	8	8
Zilebesiran, 800 mg	8	8	8	8	8	0	8	8	8	8



the blood pressure decreases after 1 injection last 6 months!



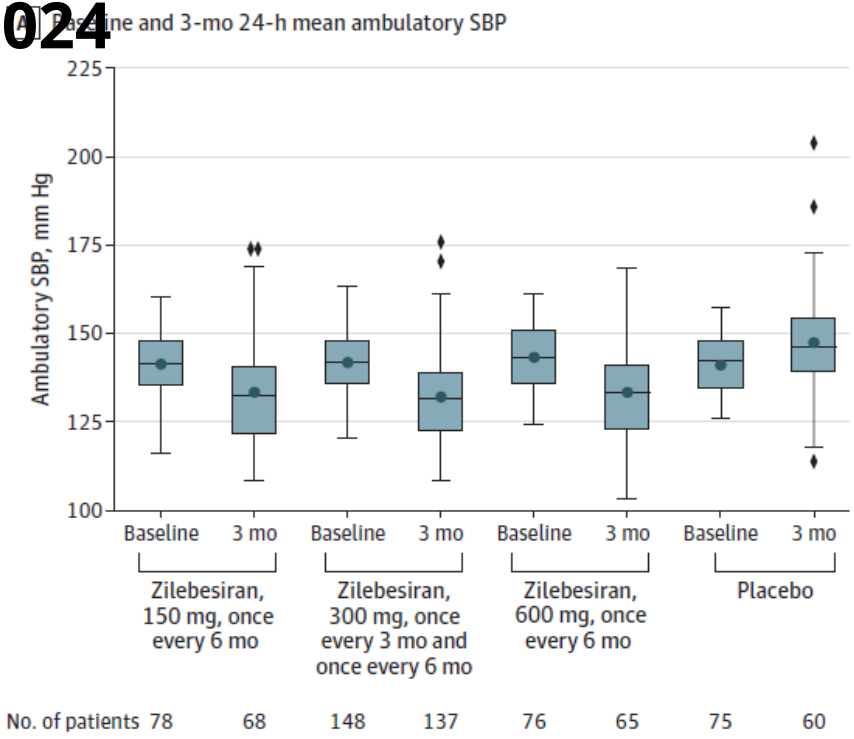
the larger the drop in AGT, the larger the drop in blood pressure

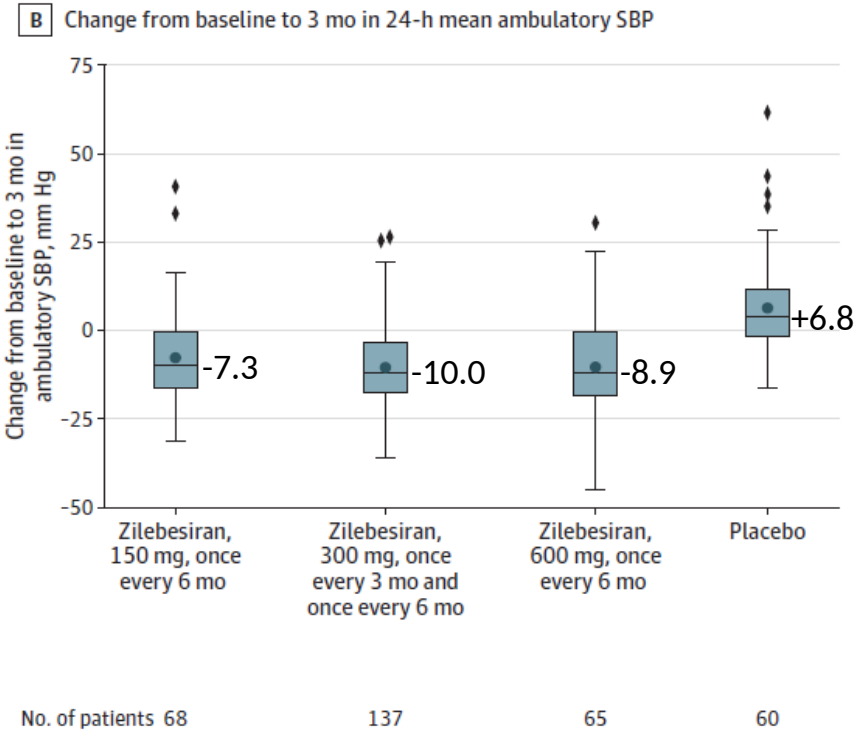
Ongoing Phase-2 Trials

KARDIA-1: randomized, double-blind dose-ranging study (150-600 mg) evaluating the efficacy and safety of zilebesiran in patients with mild-to-moderate hypertension, inclusion: daytime mean SBP≥135 mmHg and ≤160 mmHg by ABPM without antihypertensive medication, n=394, completion 31/12/24

KARDIA-2: efficacy and safety of zilebesiran on top of 3 different classes of antihypertensives (olmesartan, amlodipine & andapamide), inclusion: office SBP≥145 mmHg and ≤180 mmHg, primary outcome delta vs. baseline at month 3 in 24-hour mean SBP by ABPM, n=672, completion 31/12/25

24-hour Ambulatory SBP at 3 and 6 months: Bakris et al., *JAMA* 2024





6 months data (change from baseline in mm Hg)

150 mg once	300 mg once	300 mg twice	600 mg once	placebo
-6.5 (-9.7 to -3.3)	-9.9 (-13.0 to -6.8)	-9.5 (-12.8 to -6.3)	-9.6 (-12.8 to -6.4)	4.6 (1.2 to 8.0

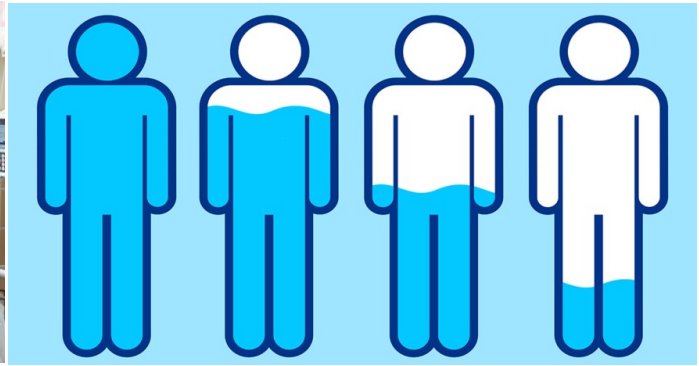
Adverse event	Patients, No. (%)					
	Zilebesiran					
	150 mg every 6 mo (n = 78)	300 mg every 6 mo (n = 73)	300 mg every 3 mo (n = 75)	600 mg every 6 mo (n = 76)	Zilebesiran total (n = 302)	Placebo (n = 75)
At least 1 AE	45 (58)	44 (60)	46 (61)	49 (64)	184 (61)	38 (51)
Related to study drug[b]	12 (15)	12 (16)	14 (19)	13 (17)	51 (17)	6 (8)
At least 1 SAE[c]	0	1 (1)	4 (5)	6 (8)	11 (4)	5 (7)
Related to study drug[b]	0	0	0	0	0	0
At least 1 study drug-related AE leading to study drug interruption[b,d]	1 (1)	0	1 (1)	1 (1)	3 (1)	0
At least 1 study drug-related AE leading to study drug discontinuation[b,e]	1 (1)	1 (1)	1 (1)	1 (1)	4 (1)	0
Death	0	0	1 (1)	0	1 (0)	0
Study drug-related AEs occurring in at least 5% of patients[b]						
Hyperkalemia	4 (5)	3 (4)	4 (5)	5 (7)	16 (5)	1 (1)
Injection site reaction	3 (4)	4 (5)	8 (11)	4 (5)	19 (6)	0
Additional treatment-emergent AE of clinical interest (any relatedness)						
Potential hypotension[f]	6 (8)	6 (8)	5 (7)	7 (9)	24 (8)	5 (7)
Hyperkalemia[g]	5 (6)	4 (5)	5 (7)	5 (7)	19 (6)	2 (3)
Hypotension[h]	3 (4)	3 (4)	3 (4)	4 (5)	13 (4)	1 (1)
Hepatic AE[i]	2 (3)	2 (3)	4 (5)	1 (1)	9 (3)	1 (1)
Acute kidney failure[j]	1 (1)	1 (1)	1 (1)	1 (1)	4 (1)	0

Strong and long-term antihypertensive effect, lasting weeks to months…

What to do in case of emergency?





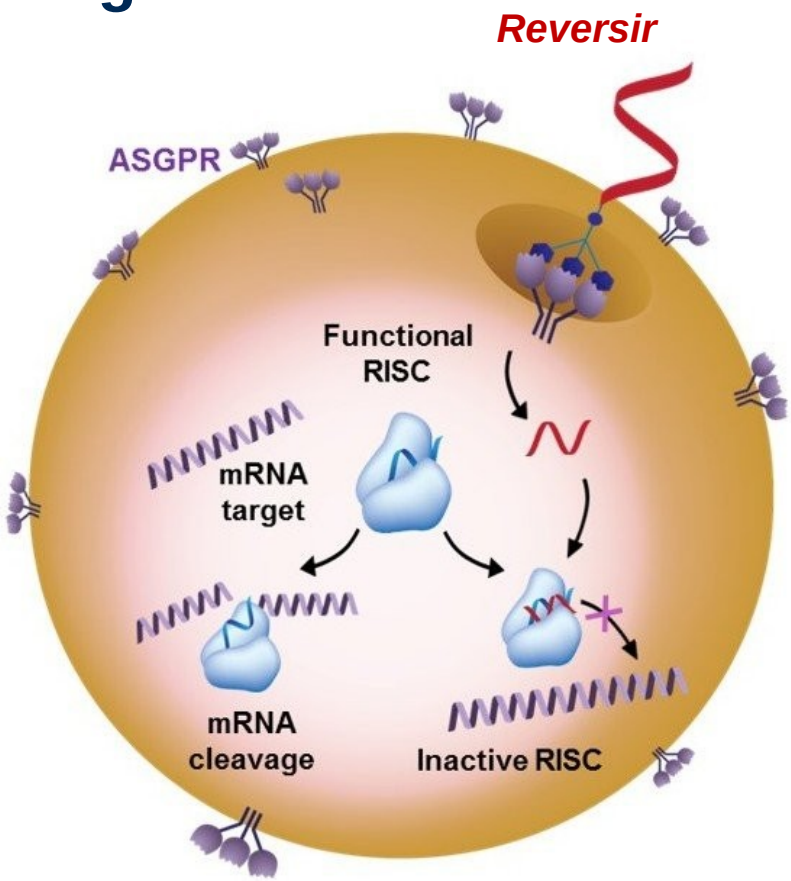


REVERSIR: Reverse siRNA silencing

1. internalization of REVERSIR by asialoglycoprotein receptor (ASGPR)

2. irreversible binding of REVERSIR as a “synthetic target” to guide strand in functional RISC

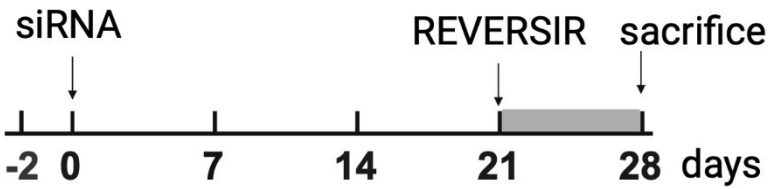
3. abolition of mRNA target recognition and cleavage

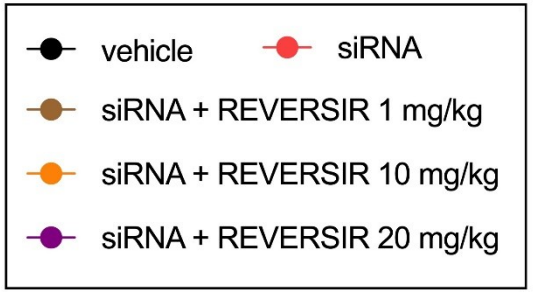


Cruz-López et al., *Hypertension* 2022

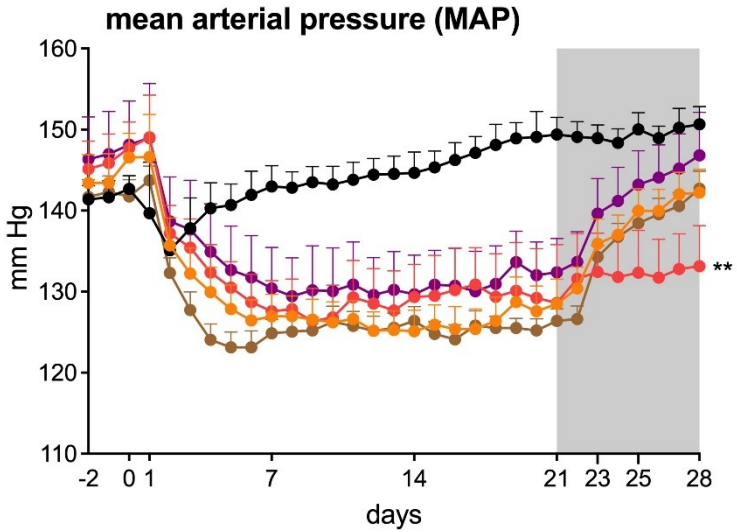
Effects on Blood Pressure

A





B



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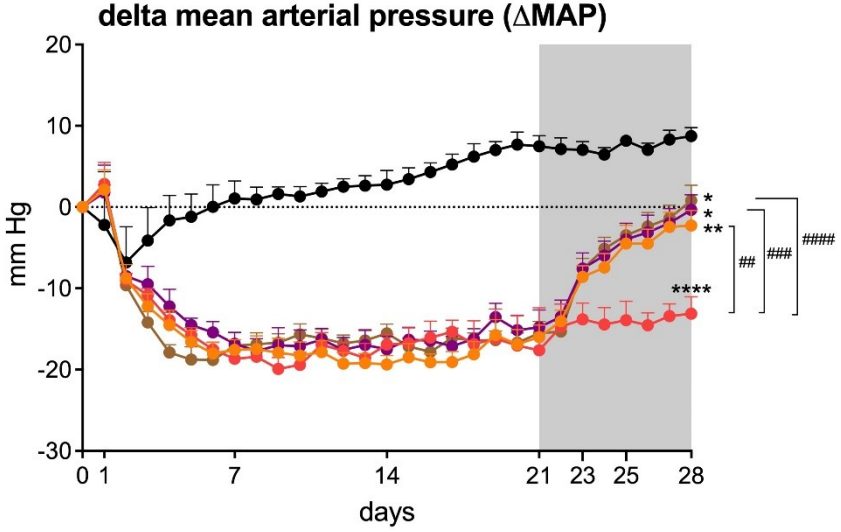
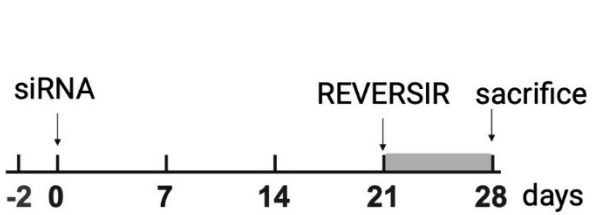
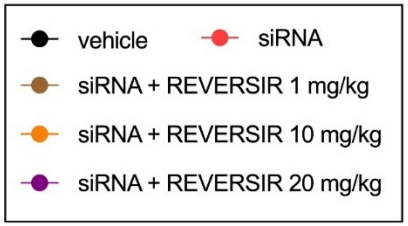
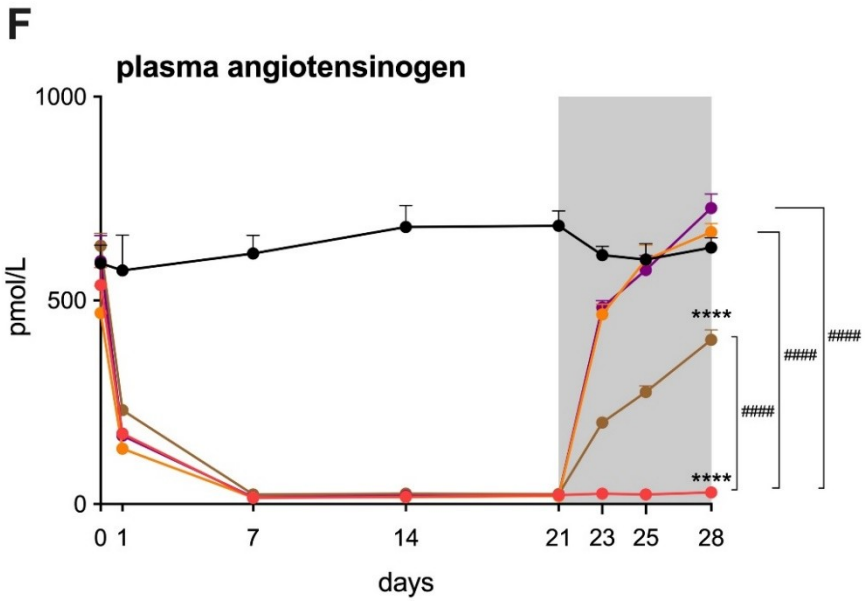


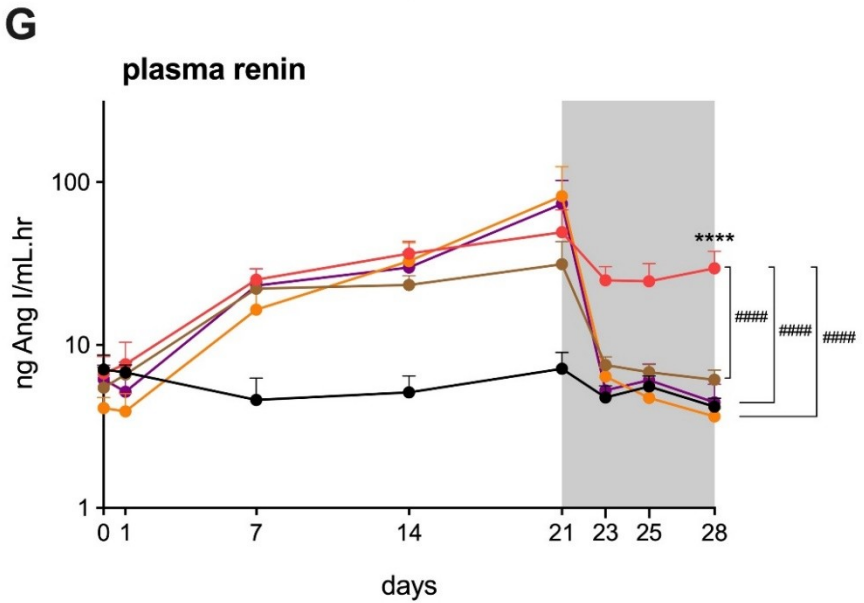
Effects on angiotensinogen and renin





Ye et al., *Hypertension* 2024

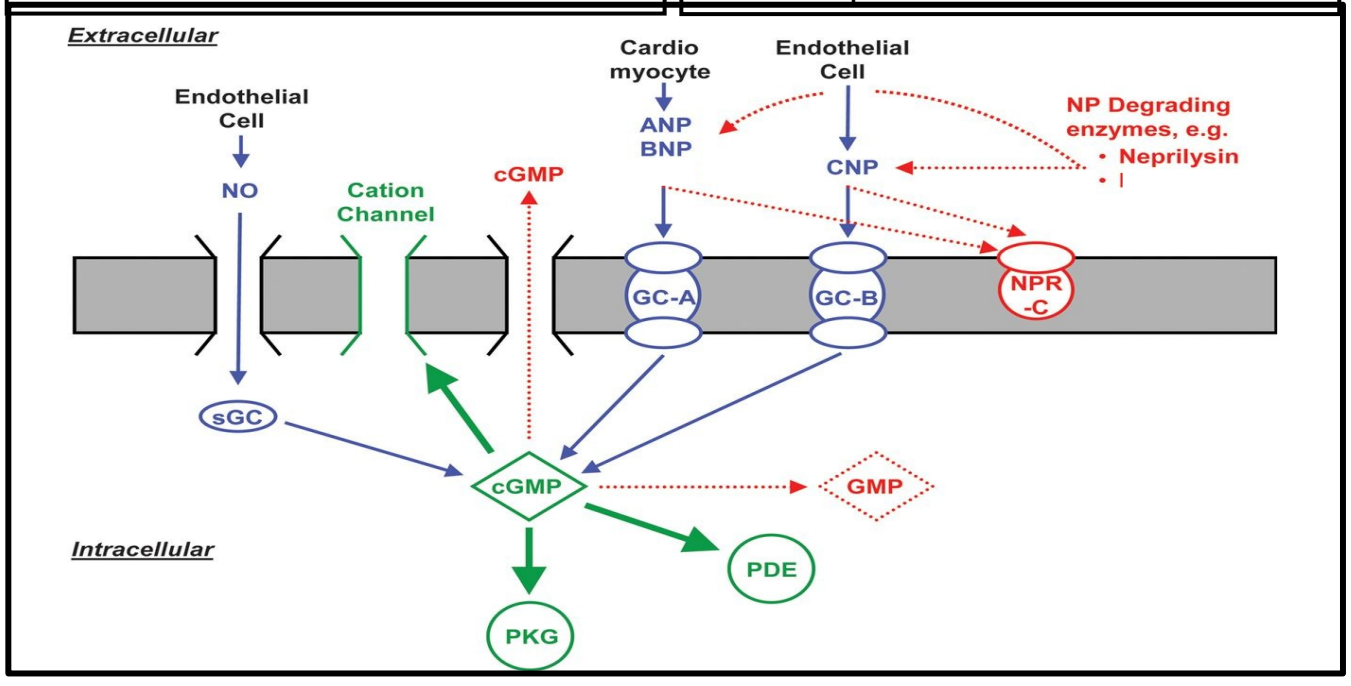




Natriuretic peptide system

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



Magniafico et al., *Eur Heart J* 2012

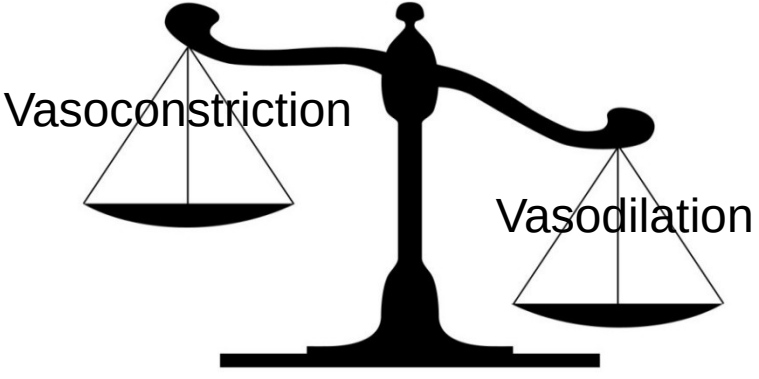
Natriuretic peptide system

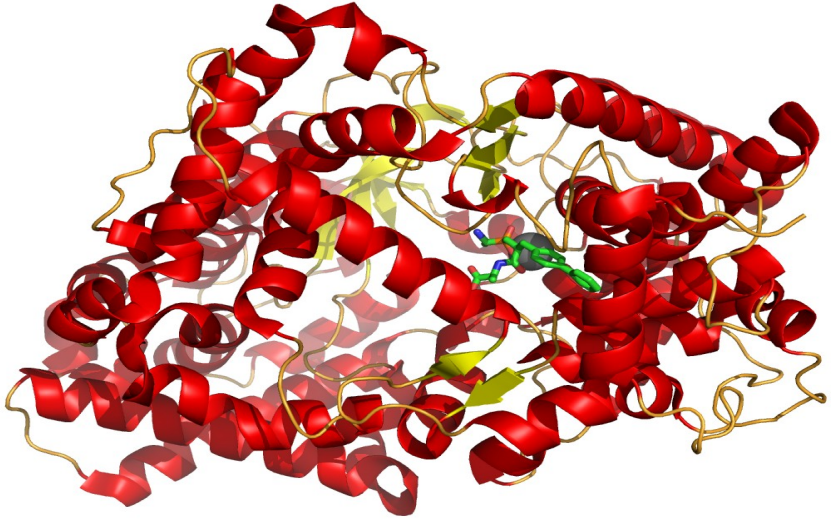
Clearance of NPs by neutral endopeptidase (NEP; neprilysin)

NEP

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

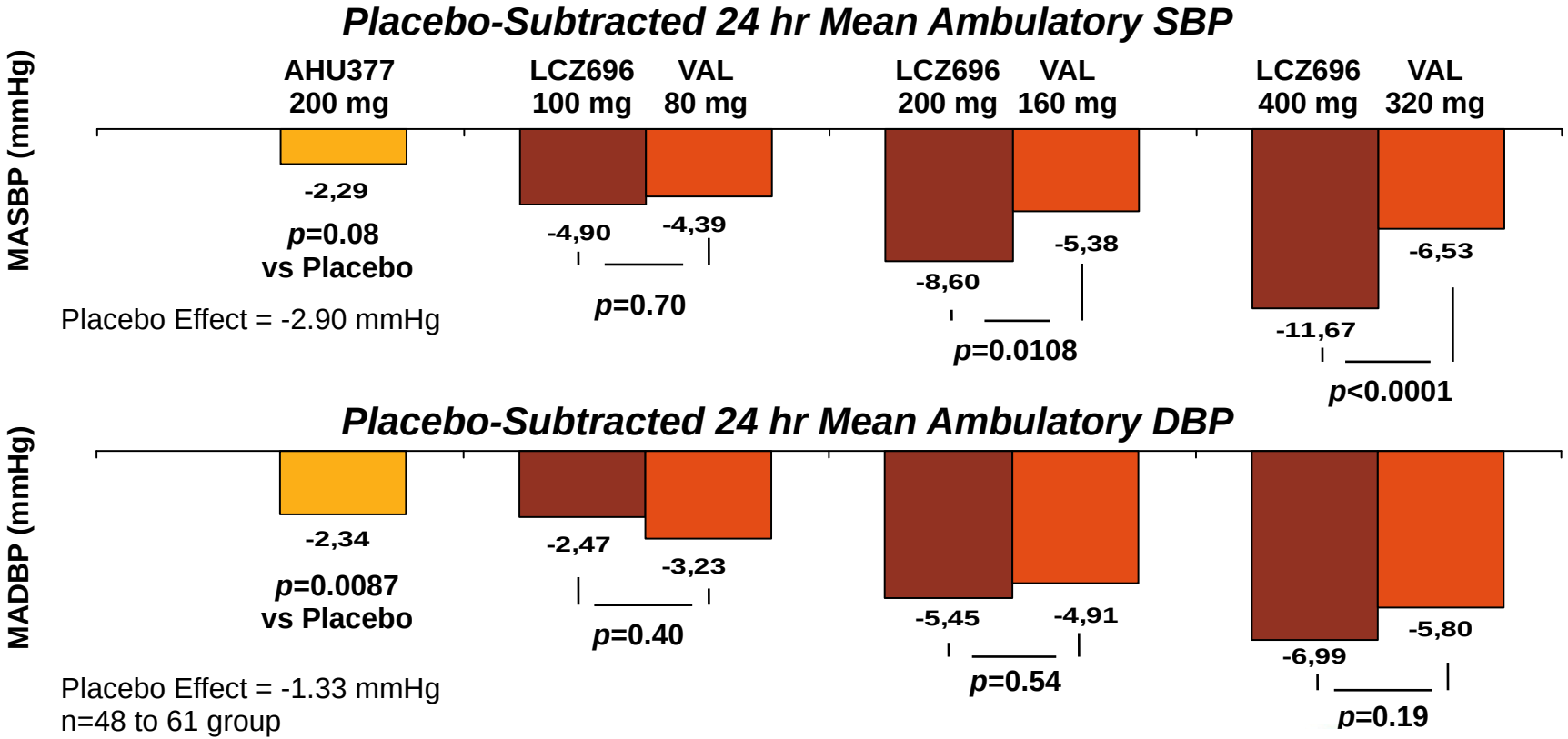
opposing physiological actions





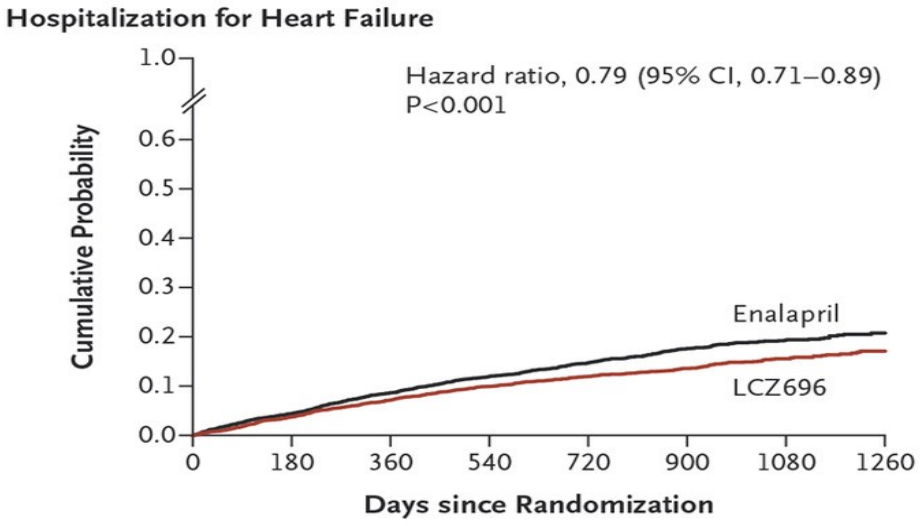
LCZ696 Hypertension Study

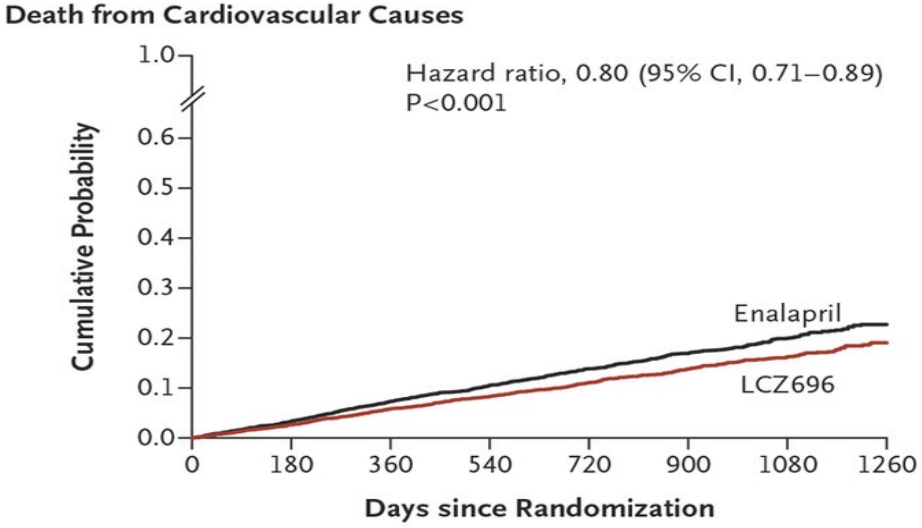
Results: Ambulatory Blood Pressure at Week 8 Endpoint



Ruilope et al., *The Lancet* 2010

ARNI in heart failure and kidney disease





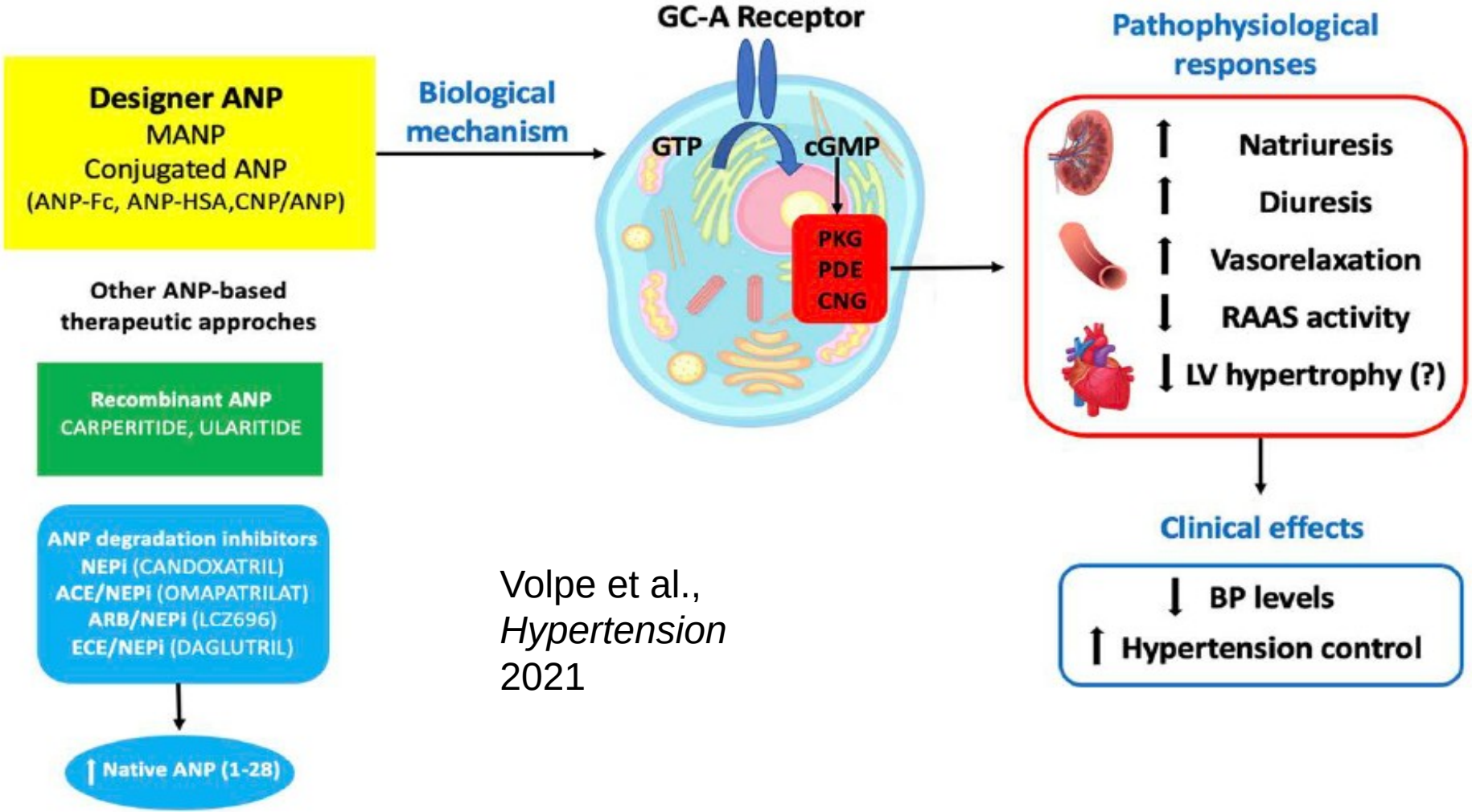
8442 patients with heart failure NYHA II-IV and EF <40%, 27 months follow-up (McMurray et al., *NEJM* 2014)

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)

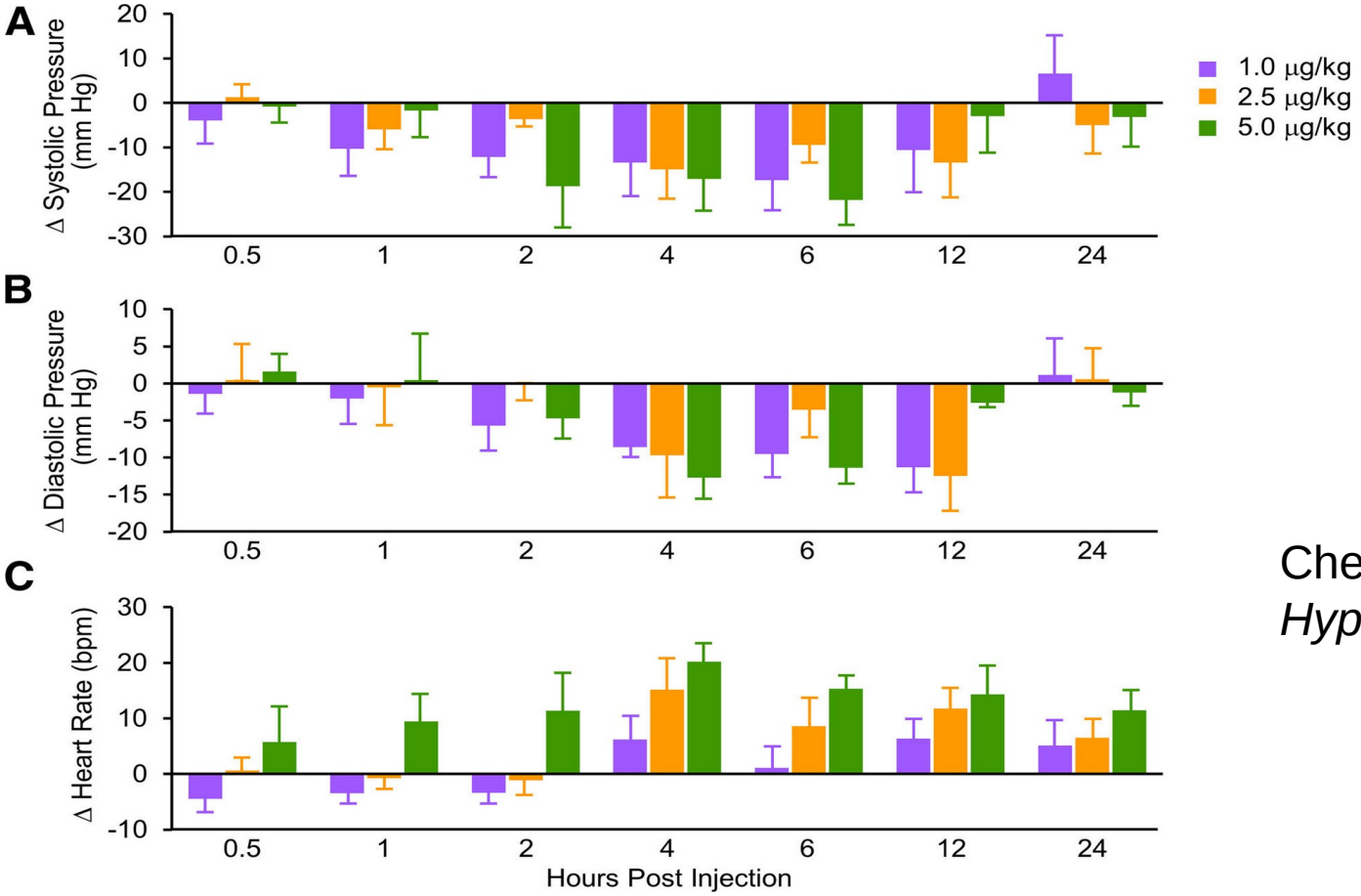
ARNI vs. ANP receptor agonist

- 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.



Volpe et al.,
Hypertension
2021

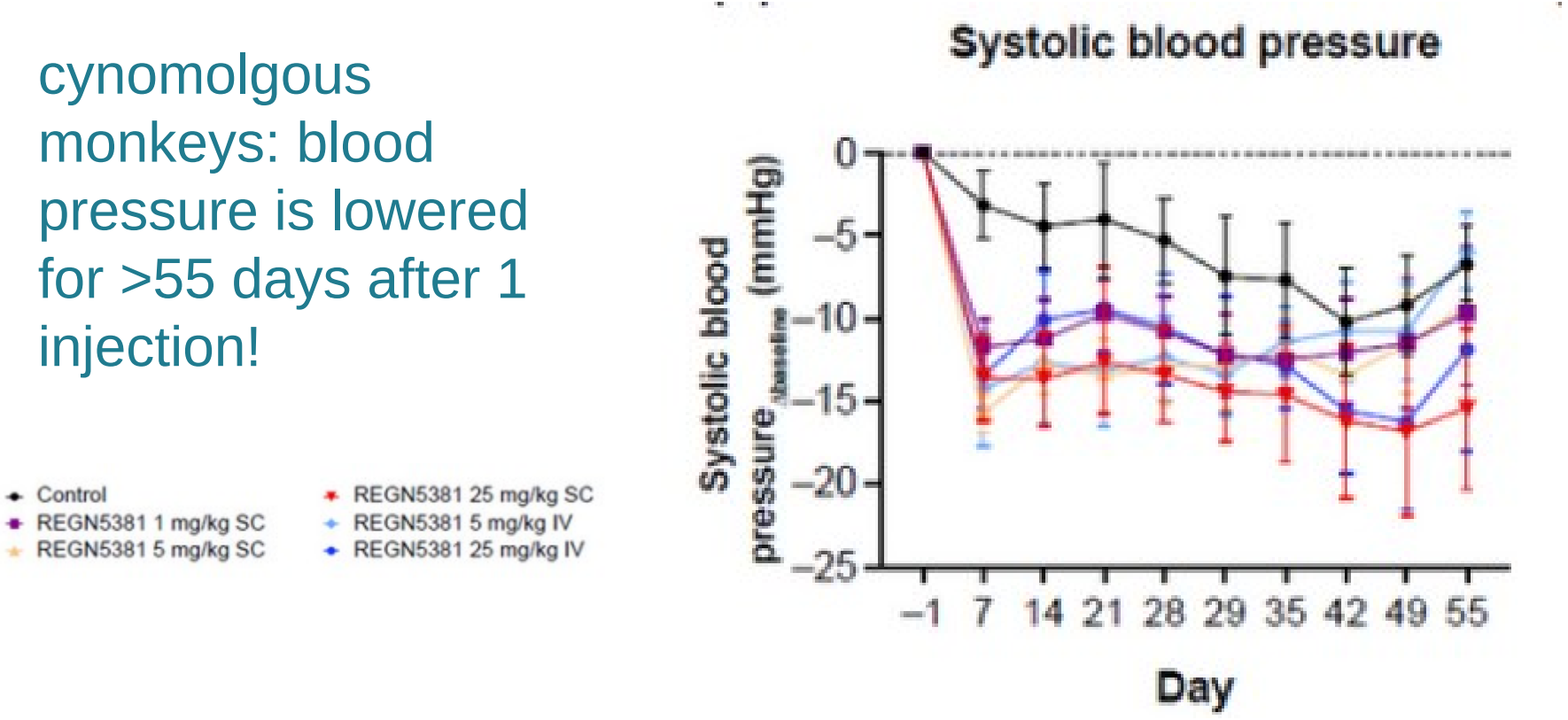
ANP analogue MANP: first human data



Chen et al.,
Hypertension 2021

Next phase: ANP-A receptor activating antibody

cynomolgous monkeys: blood pressure is lowered for >55 days after 1 injection!



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)

Conclusions: the future is here!

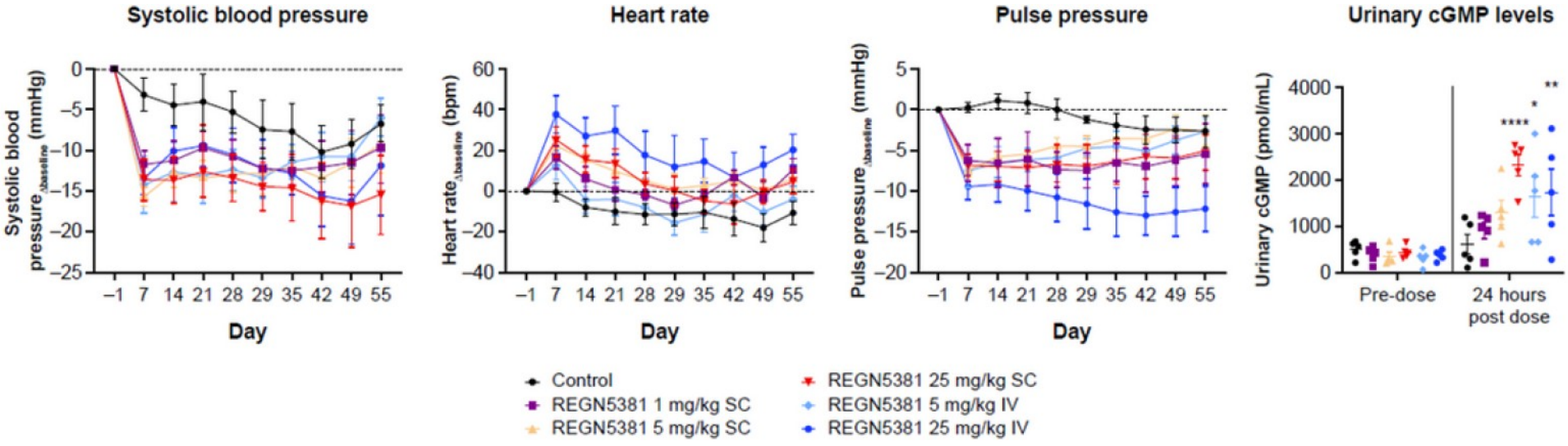
- new drug classes are entering the market: opportunities for resistant hypertension?
- some of these have an exceptional long duration of action (AGT siRNA and ANP-A receptor activating antibodies)
- will this solve the problem of non-adherence (the major reason for therapy resistance)
- what about safety?

Lowering of both plasma and renal Ang II requires AGT depletion



siRNA is particularly effective at the tissue level

Next phase: long-acting NPR1 agonist antibody



cynomolgous monkeys: blood pressure measurement by radiotelemetry

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