Aldosteron: remmen van de vorming of blokkeren van de werking?

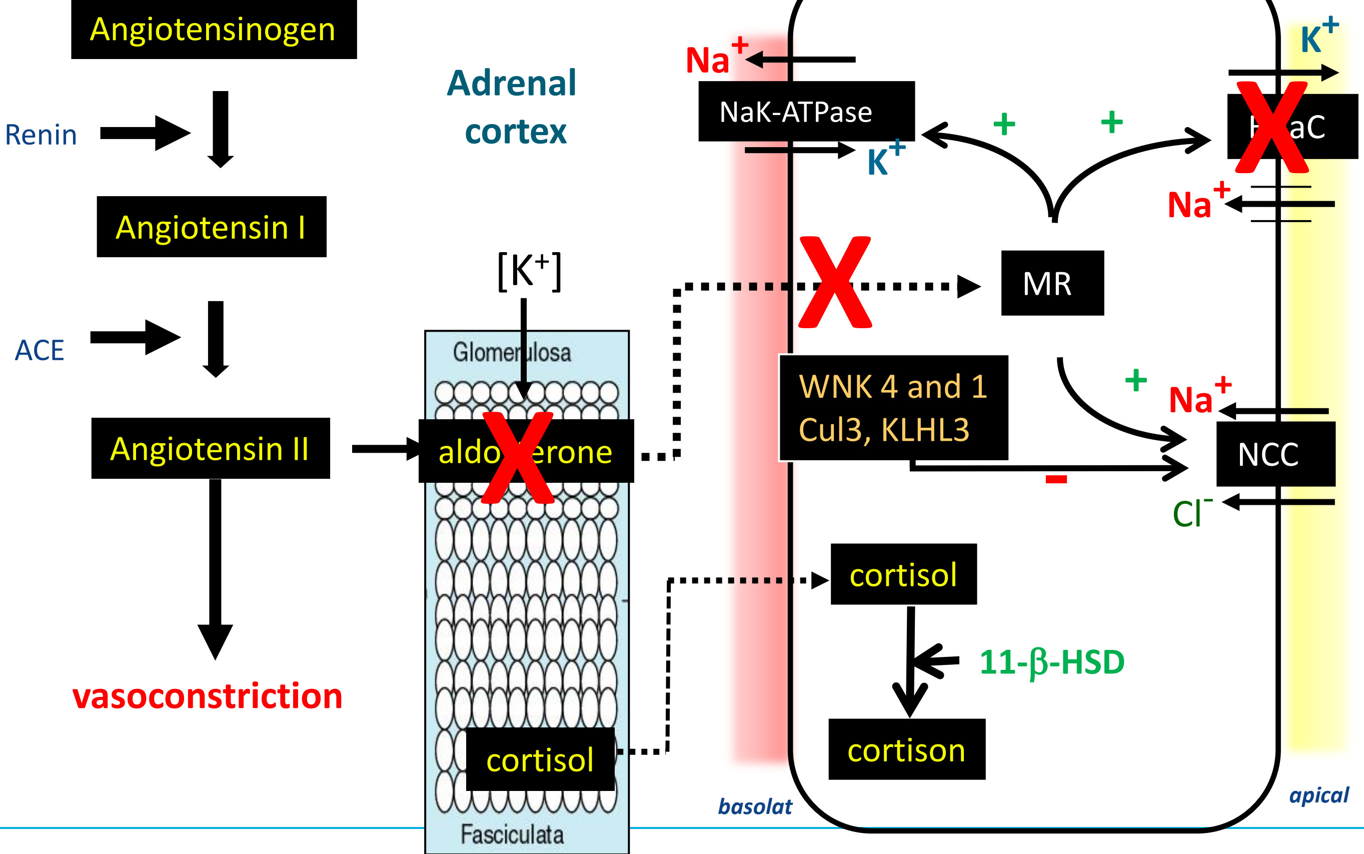
Dr. Jaap Deinum
Internist-vasculair geneeskundige, Radboudumc, Nijmegen

nhv

C V G K

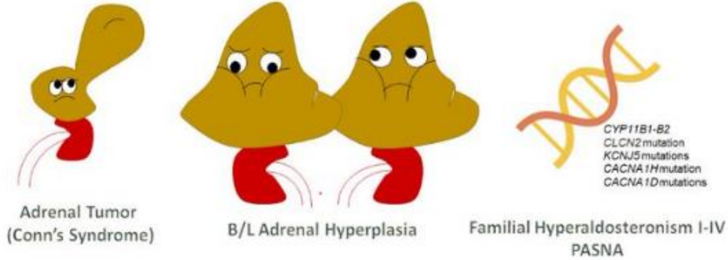
Disclosure sheet presentator: Jaap Deinum	
Nationaal Hypertensiecongres– January 26th, 2024	
(possible) Conflict of interest	
For topic relevant relations with companies	Astra-Zeneca Mineralys
• Sponsoring or research funds	Pentixapharm ZONMW, EU
• Fee or other (financial) reimbursement	None
• Shareholder	None
• Other relationship, such as:	None

DCT / CD cell

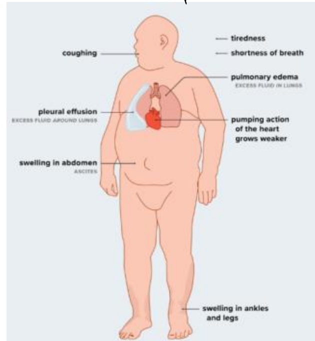


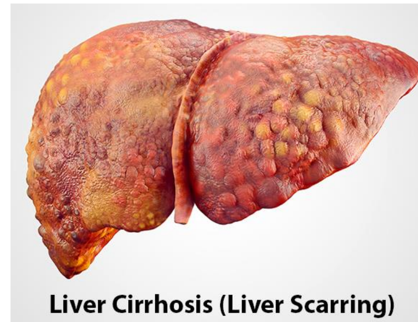
Aldosterone, the driver of misery

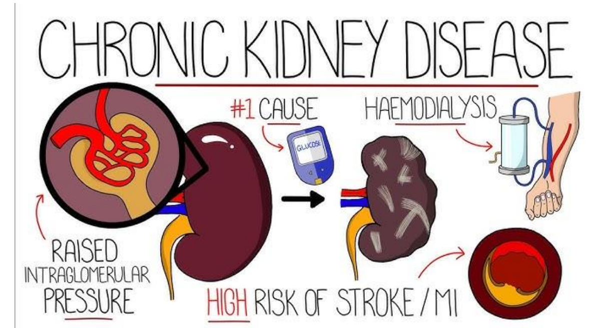
Therapy-resistant hypertension



Heart failure







Aldosteron in primair hyperaldosteronisme

Cardiovascular events and target organ damage in primary aldosteronism compared with essential hypertension: a systematic review and meta-analysis

Silvia Monticone, Fabrizio D'Ascenzo*, Claudio Moretti, Tracy Ann Williams, Franco Veglio, Fiorenzo Gaita, Paolo Mulatero*

3838 patiënten met primair hyperaldosteronisme

9284 patiënten met primaire hypertensie

(vergelijkbare bloeddrukken)

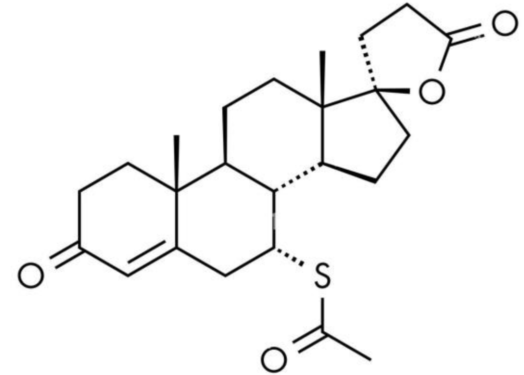
Odds ratios

- Stroke 2.58 (1.93-3.45)
- CAD: 1.77 (1.10-2.83)
- atriumfibrilleren 3.52 (2.06-5.99)
- hartfalen: 2.05 (1.11-3.78)
- LVH: 2.29 (1.65-3.17)

Lancet Diab Endocrinol 2018;6:41

Het werkpaard: spironolacton, een blokkeerder

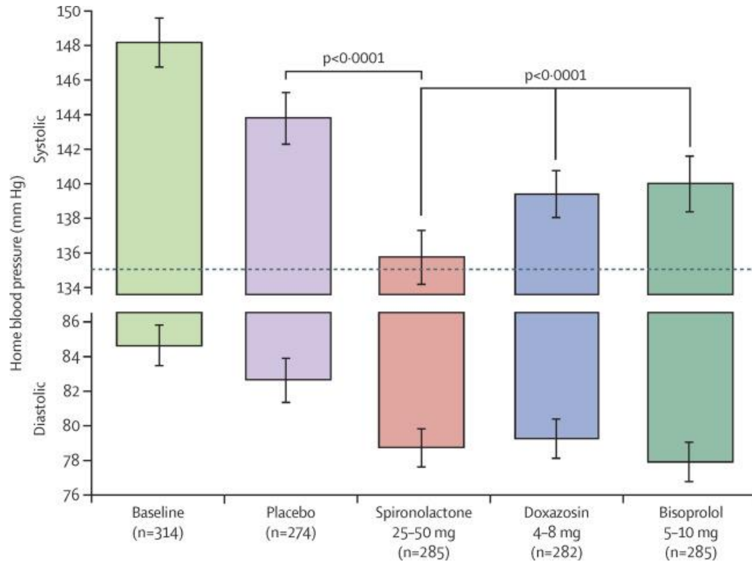
- 1957
- Prodrug, korte halfwaardetijd, actieve metabolieten lange halfwaardetijd (canrenoaat, 7α-thiomethylspironolactone), hogere spiegels bij inname tijdens de maaltijd
- Steroïd (afgeleide van progesteron)
- Ook anti-androgeen, werkt bij acne en PCOS
- Moeilijk middel: erectiele dysfunctie, gynaecomastie, pijnlijke tepels, libidoverlies, menstruatiestoornissen, gedeeltelijk dosisafhankelijk (vanaf 50-75 mg), hyperkaliëmie, hyponatriëmie
- ***Wordt beschouwd als een zwak antihypertensivum***
- Evidence voor werkzaamheid in hartfalen (RALES), verder onder andere in cirrose, als kaliumspaarder en in primair hyperaldosteronisme, recalcitrante hypertensie

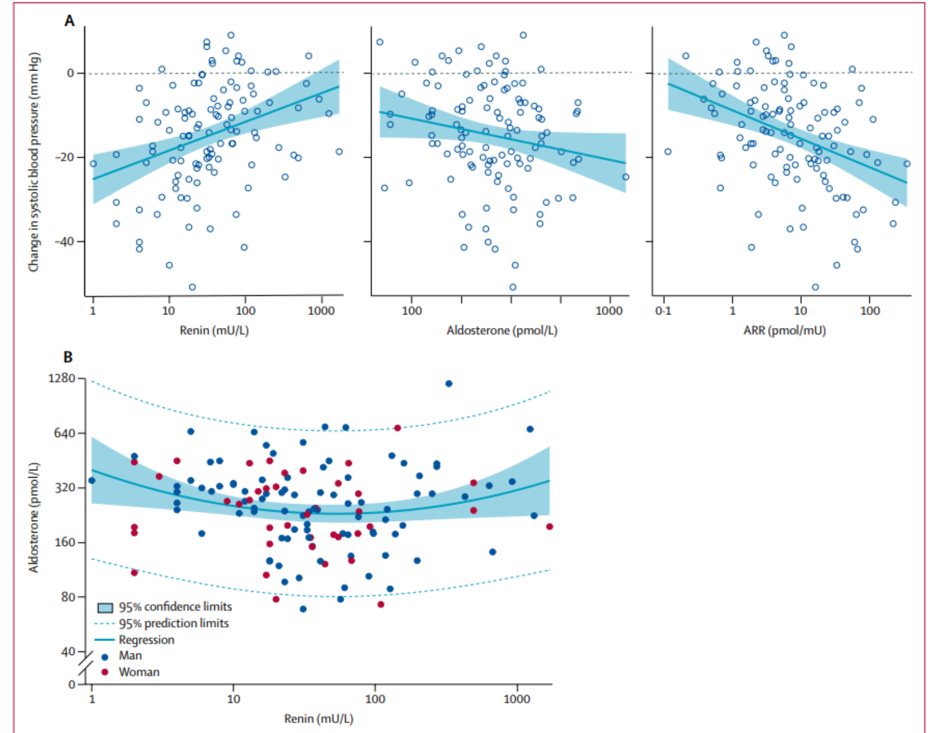


- Gemiddelde prijs per dag: € 0,20

PATHWAY2

- hypertensie op drie middelen, n=230
- multiple cross-over trial





Lancet 2015 386: 2059

Lancet Diabetes Endocrinol 2018 6: 464

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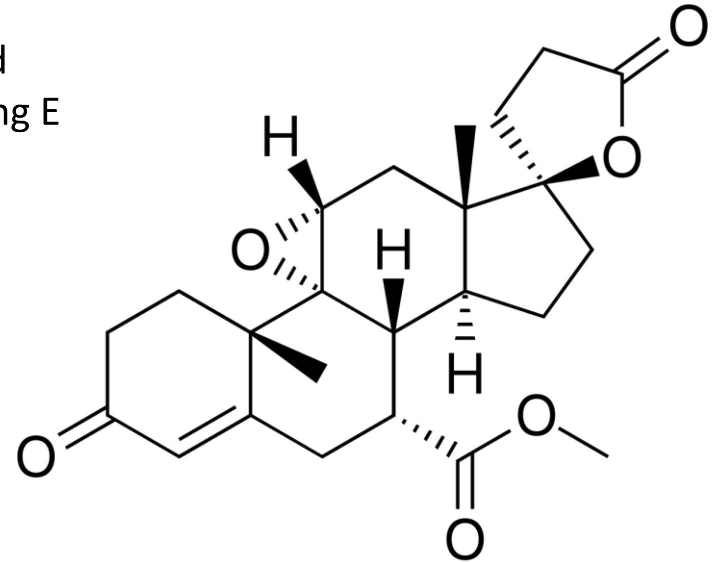
Eplerenone

- 1983
- Sspecifieke aldosteron receptor antagonist (SARA)
- Korte halfwaardetijd, inactieve metabolieten
- 2x daags doseren, maar is daarvoor niet geregistreerd
- Half zo actief als spironolacton, dus 25 mg S = 2x 25 mg E
- Geregistreerd voor hartfalen (EPHESUS)

- Gemiddelde prijs per dag: € 0,51

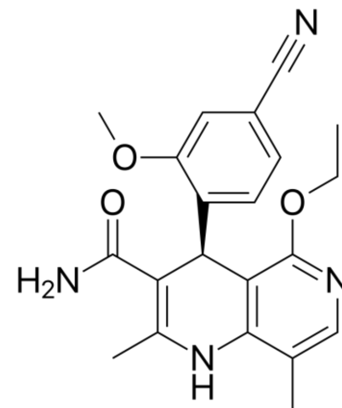


Niet-steroide MRA: finerenon

- 2022
- Afgeleid van dihydropyridines
- Geregistreerd voor chronische nierschade (albuminurie) in DM2
- ’Blood pressure’ komt maar twee keer voor in de sleutelpublicaties:

Finerenone had modest effects on blood pressure: the changes in mean systolic blood pressure from baseline to month 1 and to month 12 were −3.0 and −2.1 mm Hg, respectively, with finerenone and −0.1 and 0.9 mm Hg, respectively, with placebo (Fig. S7).

Finerenone treatment had modest effects on blood pressure; the mean difference between finerenone and placebo in the change from baseline in the systolic blood pressure was −3.5 mm Hg at month 4 and −2.6 mm Hg at month 24 (Fig. S9).



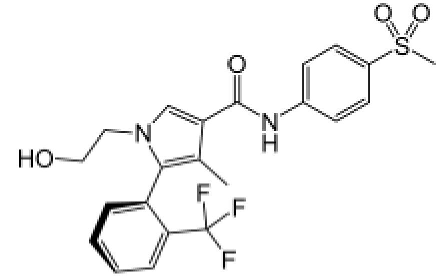
- Vooral effect op hartfalen, wél hyperkaliemie
- Gemiddelde prijs per dag € 2,19, artsenverklaring nodig

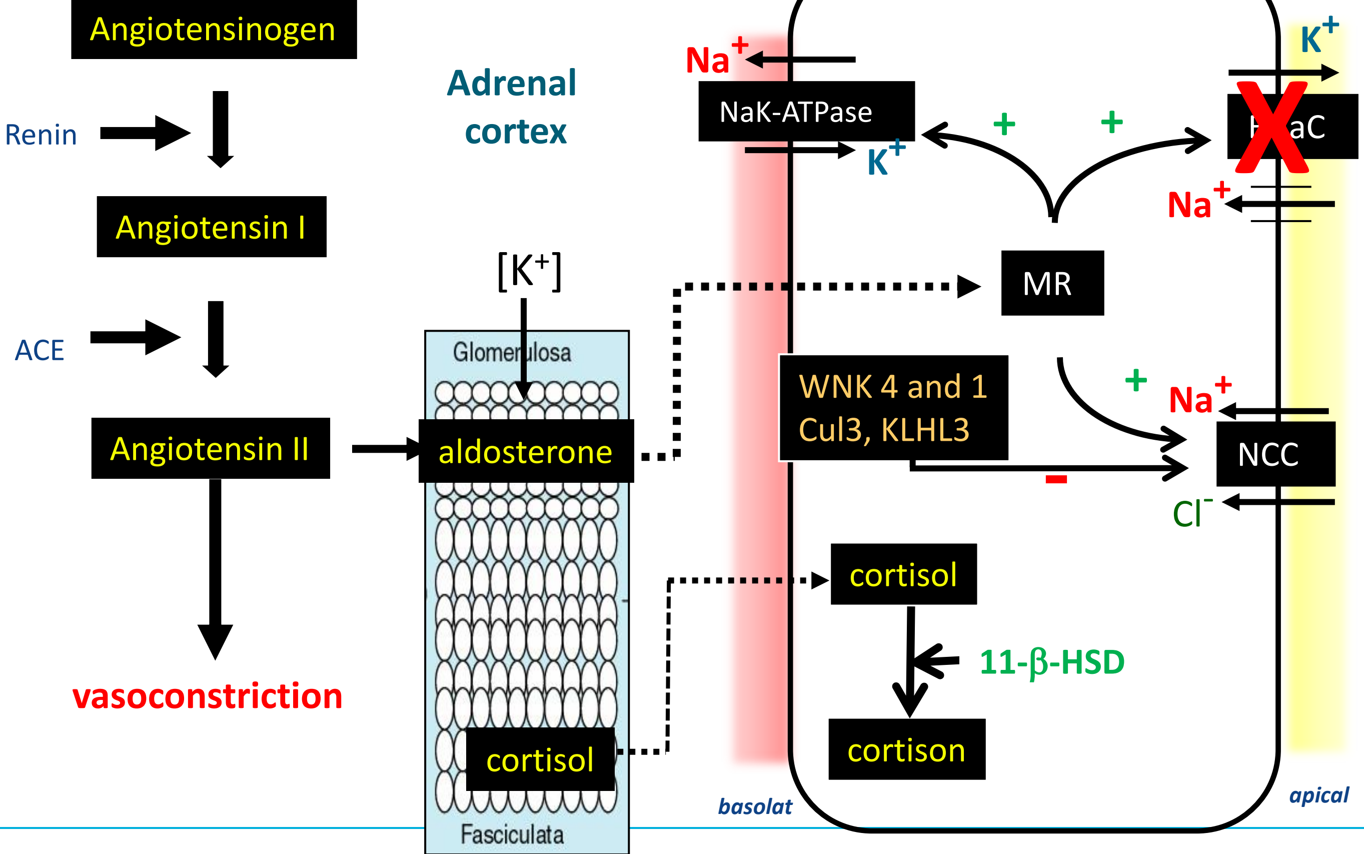
	Spironolactone	Eplerenone	Finerenone
Mineralocorticoid receptor	24	990	18
Glucocorticoid receptor	2400	22,000	>10,000
Androgen receptor	77	21,200	>10,000
Progesterone receptor	740	31,200	>10,000

NEJM 2020 383:2219
NEJM 2021 385:2252

Niet-steroïde MRA: esaxerenon(e)

- 2021
- Geregistreerd in Japan voor hypertensie
- In ontwikkeling voor diabetische nefropathie

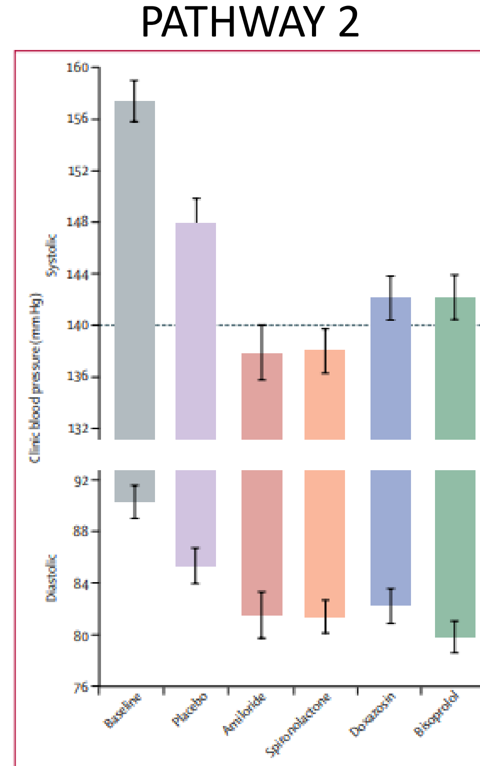


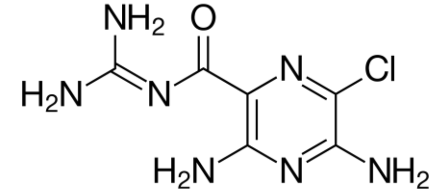

DCT / CD cell
Angiotensinogen
Renin
Angiotensin I
ACE
Angiotensin II
vasoconstriction
Adrenal
cortex
[K+]
Glomerulosa
aldosterone
cortisol
Fasciculata
Na+
NaK-ATPase
K+
K+
aC
Na+
MR
WNK 4 and 1
Cul3, KLHL3
Na+
NCC
Cl-
cortisol
11-β-HSD
cortison
basolat
apical

Amiloride (triamtereen niet meer verkrijgbaar?)

- 1967
- Kosten?
- In FTK alleen in combinatie met HCTZ
- Wordt beschouwd als zwak antihypertensivum

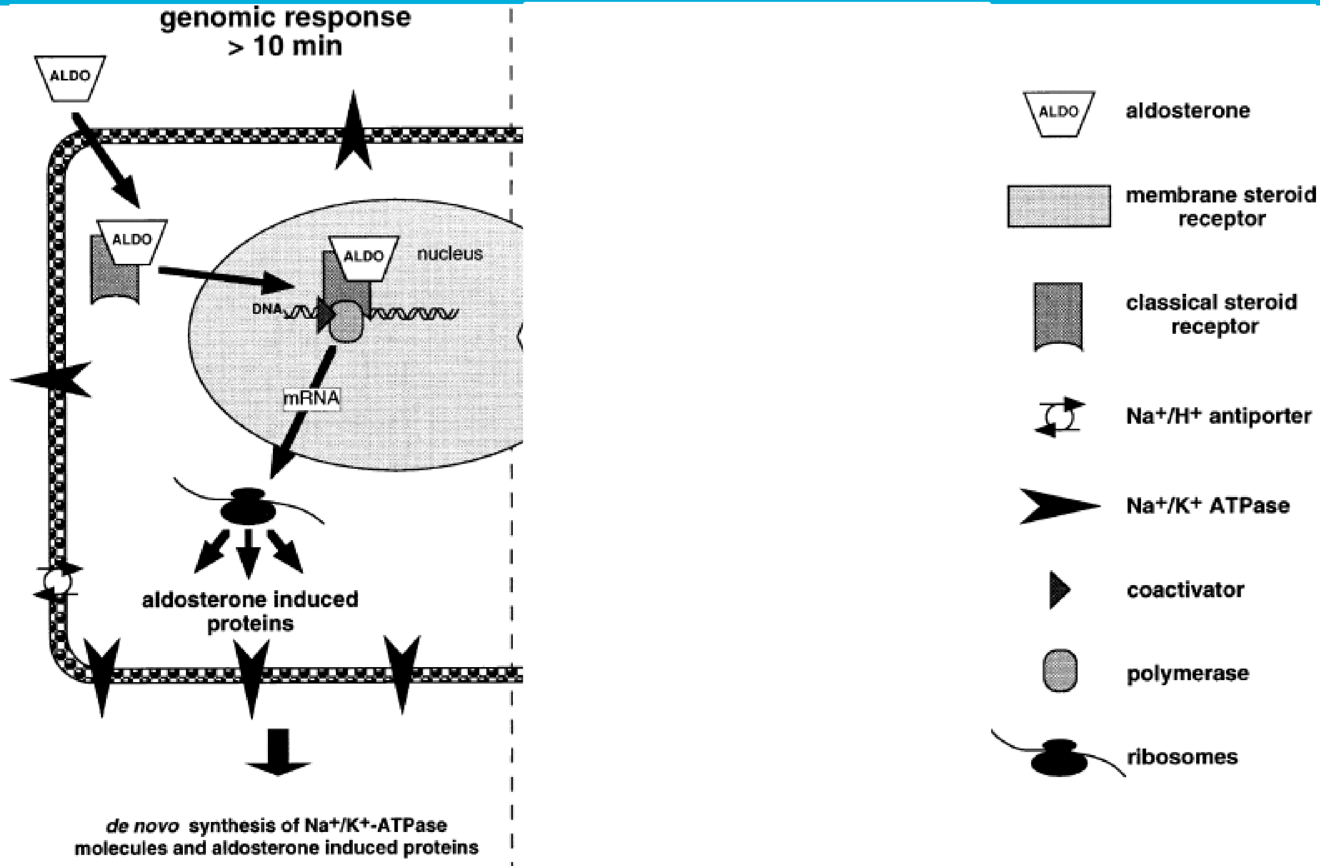
PATHWAY 2





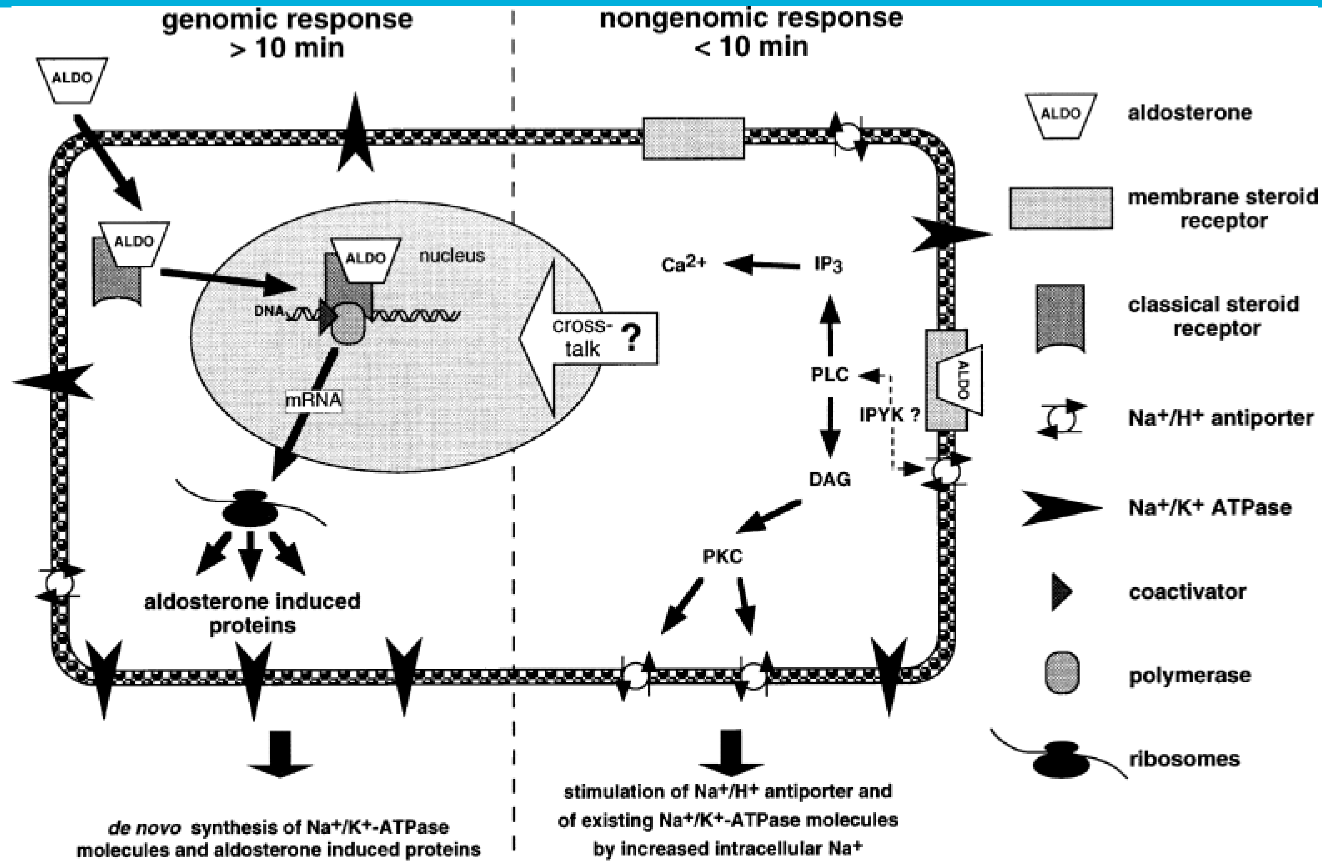
Lancet Diabetes Endocrinol 2018 6: 464

Waarom zou je liever de vorming van aldosteron remmen?



Kidney International 2000 57:1390

Waarom zou je liever de vorming van aldosteron remmen?



Kidney International 2000 57:1390

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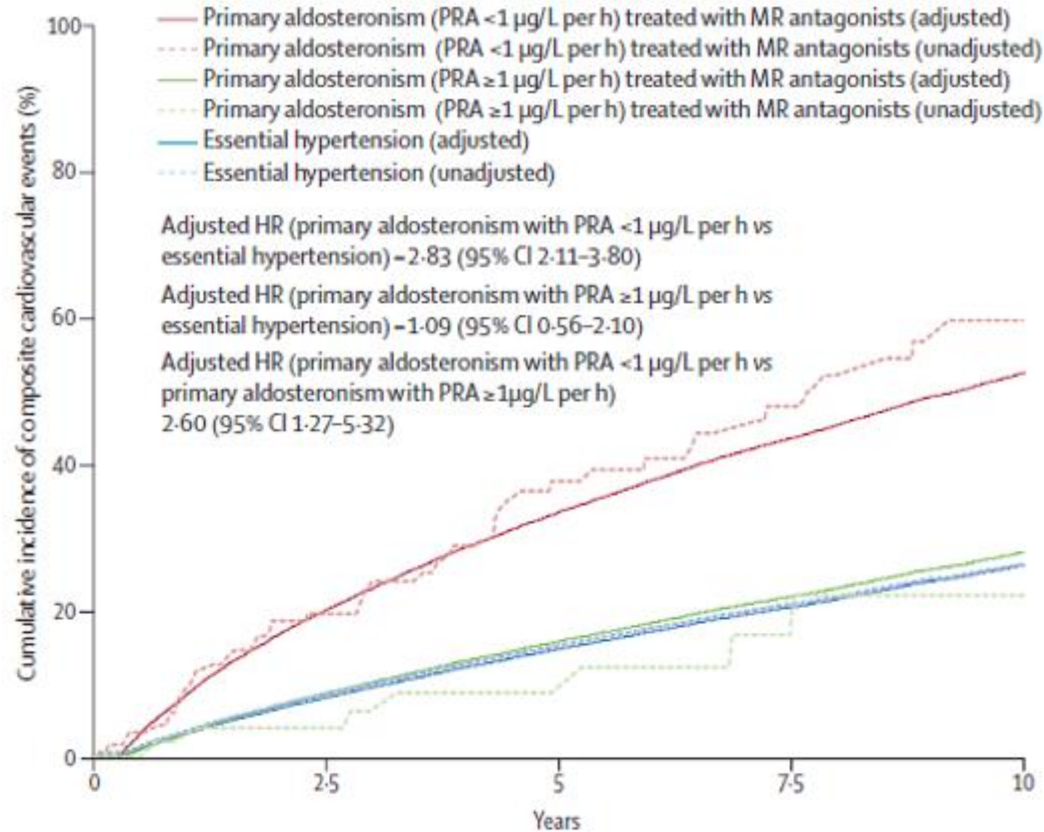
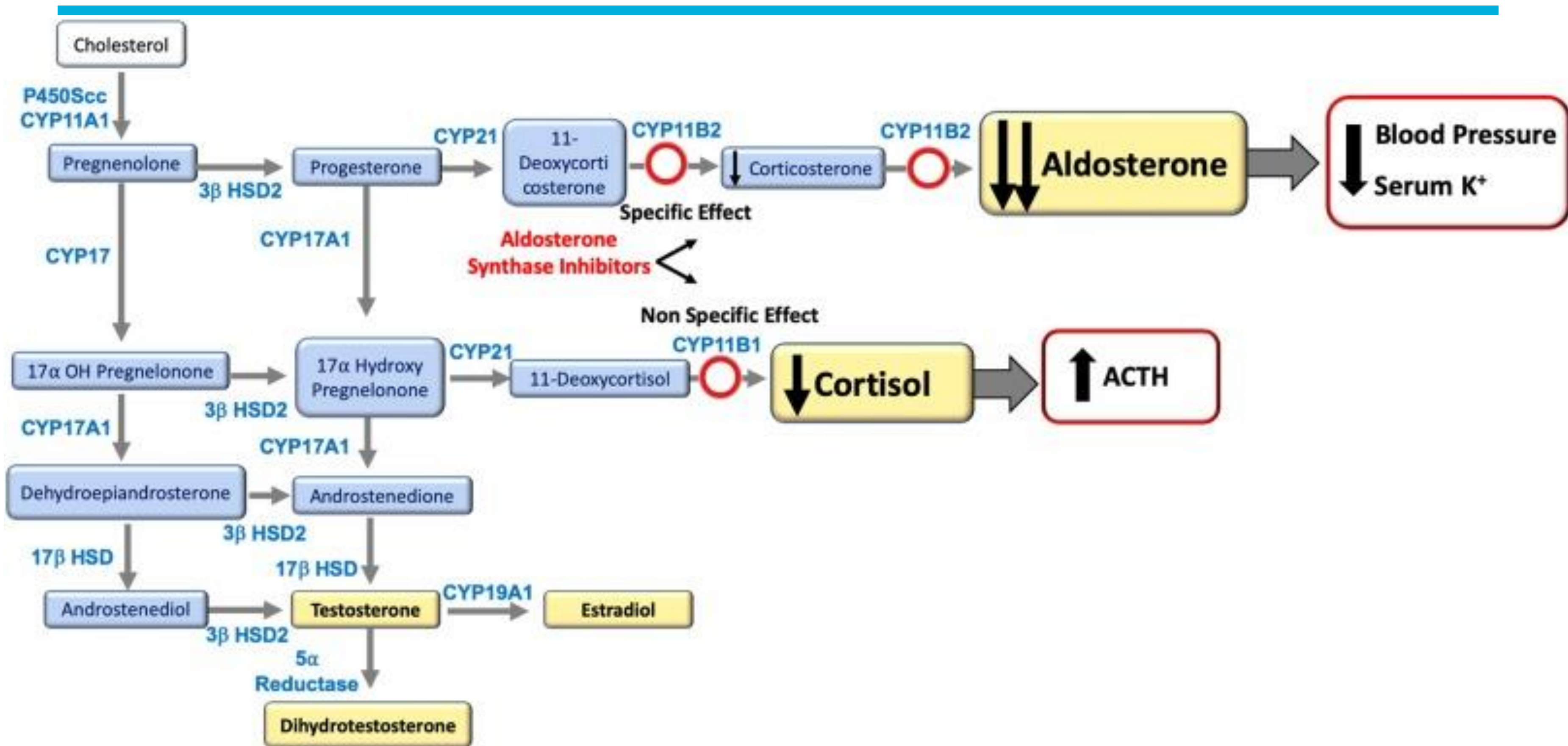
Een verhoging van aldosteron onder MRA belemmert gunstig effect MRA niet?



Radboudumc

Hundemer et al Lancet Diabetes Endocrinology 2018



Pharmacological Research 163 (2021) 105332

Radboudumc

Baxdrostat

Hypothesis: ‘Aldosterone is the driver of resistant hypertension’

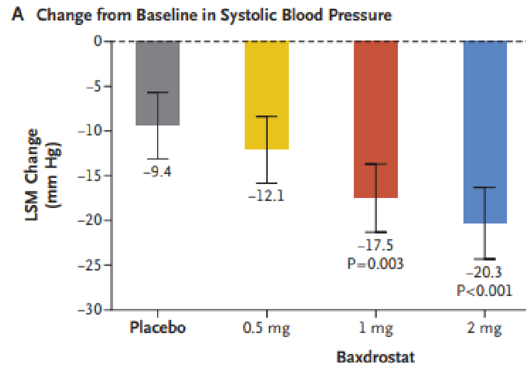
Phase 2 trial of Baxdrostat for treatment-resistant hypertension

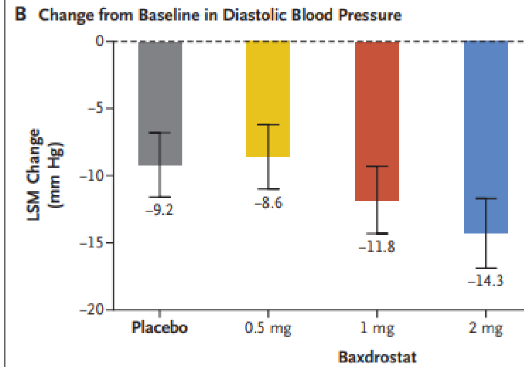
- N=248
- 3 doses vs placebo
- Background $\geq$ 3 aHT, incl diureticum
- Uitkomst: verschil in systolische bloeddruk 0-12 weken (zittend, automatische meter)

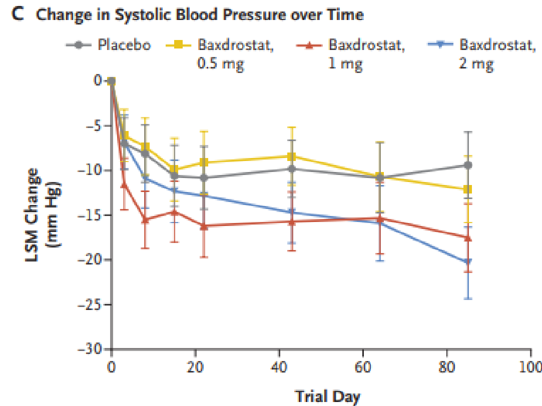
NEJM 2023 388: 395

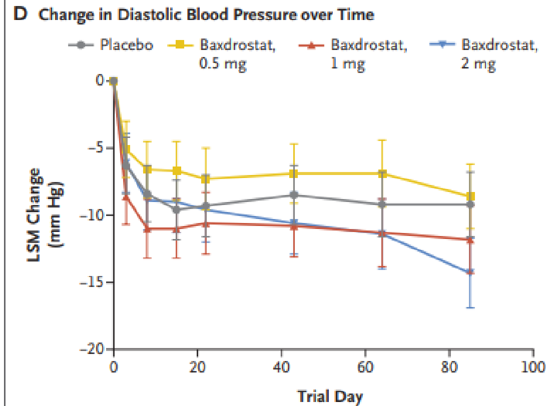
Radboudumc

Resultaten: trial stopped early for overwhelming efficacy

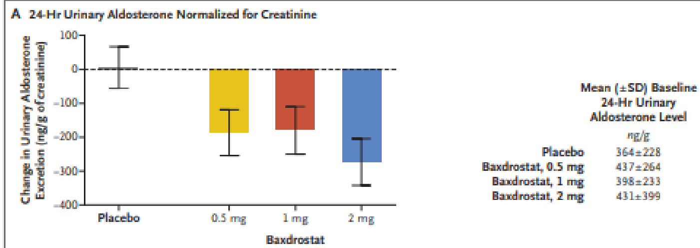


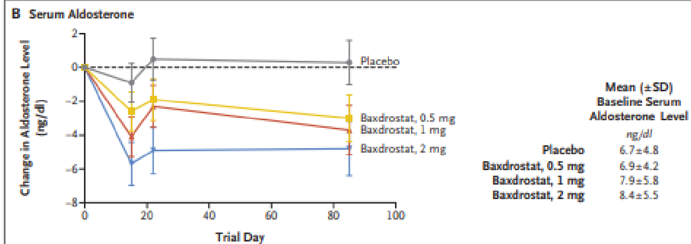


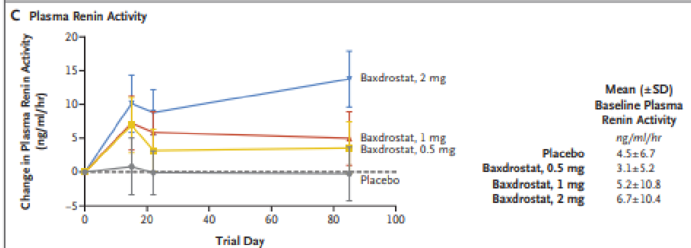




NEJM 2023 388: 395







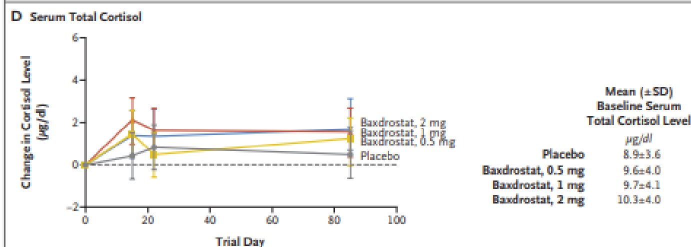


Table 2. Adverse Events That Occurred during the Treatment Period.

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

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ASI #2: Lorundrostat

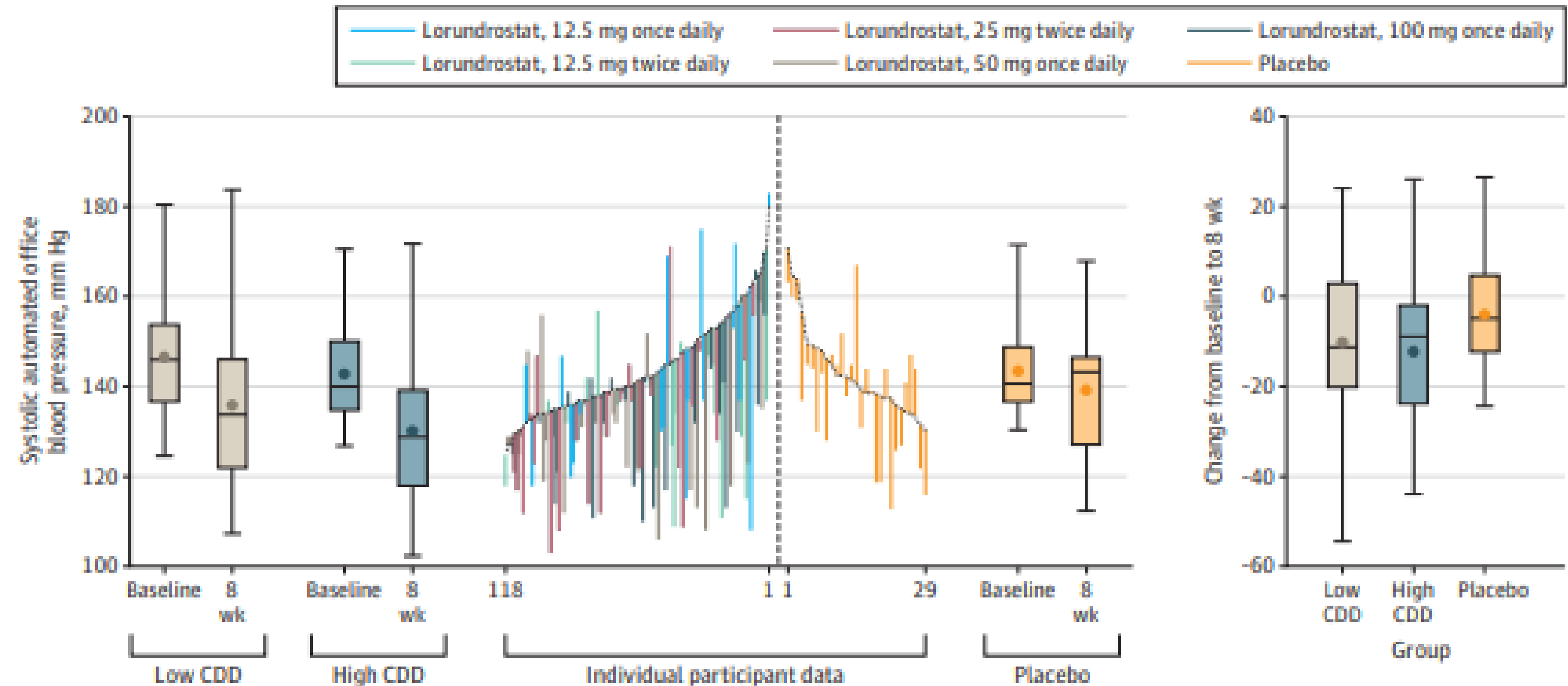
- Inclusie BP>130 mm Hg, ≥ 2 aHT, max gedoseerd

  - cohort 1: suppressed renin, PRA < 1 ng/mL/H, n=150, various dosages
  - cohort 2: PRA > 1 ng/mL/h. n=37, 100 mg vs placebo (31 vs 6)

- End point: change in systolic AOBP, seated

JAMA 2023;330:1140

Cohort 1 (suppressed renin)



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Cohort 2, non-suppressed renin

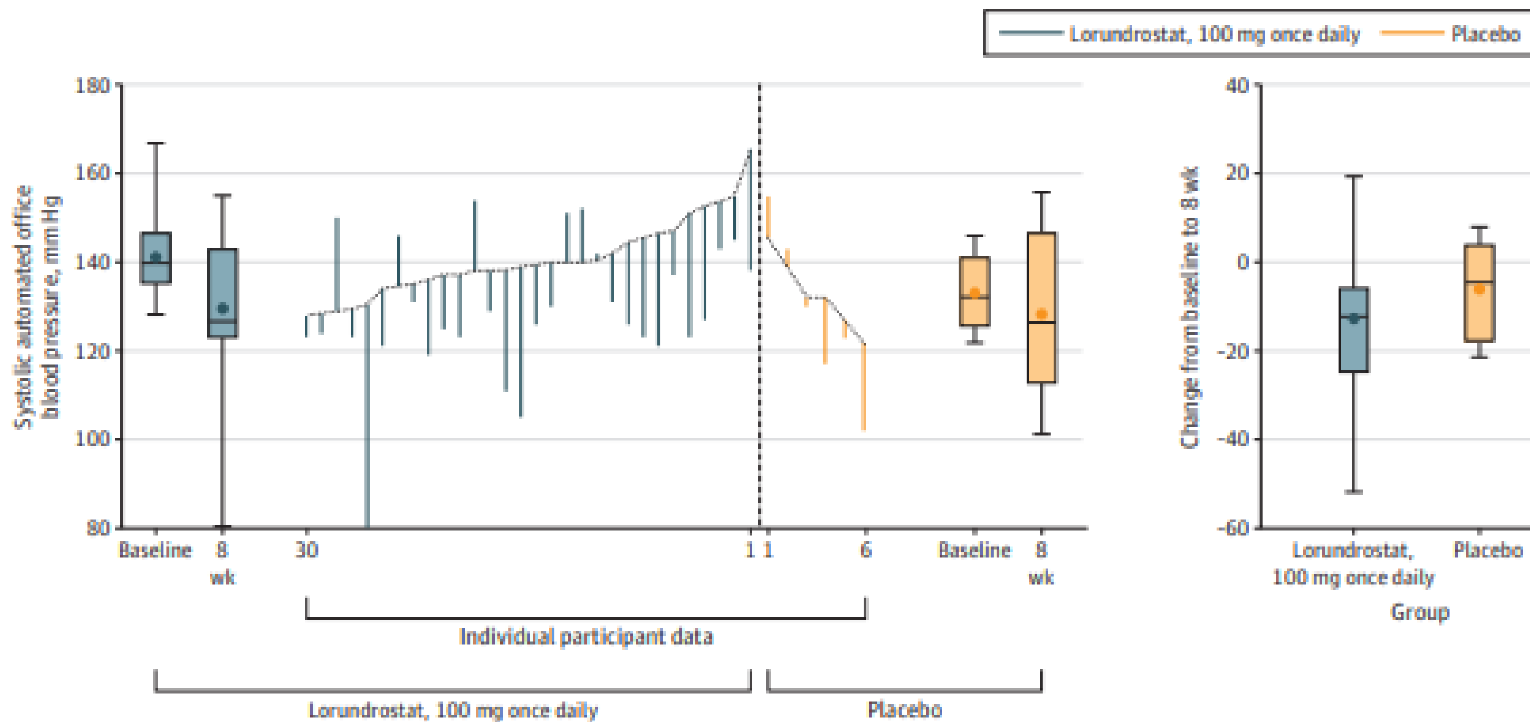


Table 3. Adverse Events and Serum Potassium Changes

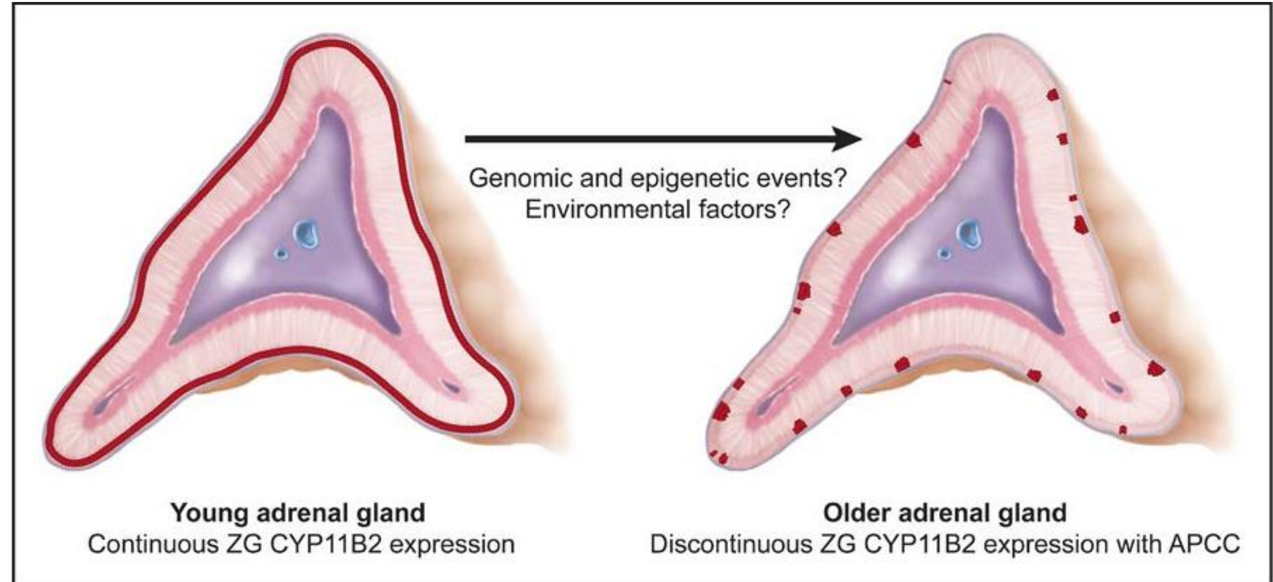
Measures	Cohort 1 (PRA ≤1.0 ng/mL/h)					
	Lorundrostat					
	100 mg once daily (n = 30)	50 mg once daily (n = 28)	25 mg twice daily (n = 30)	12.5 mg twice daily (n = 22)	12.5 mg once daily (n = 23)	Placebo (n = 30)
Participants with any serious adverse event, No. (%)	0	0	0	0	2 (9)[a]	0
Participants with any adverse event, No. (%)[c]	17 (57)	12 (43)	20 (67)	13 (59)	16 (70)	12 (40)
Participants with hypotension, No. (%)	1 (3)	0	0	1 (5)	0	0
Potassium-related events[d]						
Change from baseline in serum potassium level, mean (SD), mmol/L	0.29 (0.59)	0.25 (0.36)	0.34 (0.46)	0.32 (0.53)	0.31 (0.44)	0.03 (0.37)
Participants with serum potassium level 5.6-6.0 mmol/L, No. (%)	5 (16)	1 (4)	2 (7)	2 (9)	3 (13)	0
Participants with serum potassium level 6.1-6.5 mmol/L, No. (%)	0	0	1 (3)	1 (5)	1 (4)	0
Participants with serum potassium level >6.5 mmol/L, No. (%)	1 (3)	1 (4)	0	0	0	0

-doses van 50 en 100 mg effectief
-lorundrostat even effectief bij onderdrukt renine als bij (niet-onderdrukt) renine

	Body mass index (kg/m^2)		Use of thiazide-type diuretic		Race	
	25-30	>30	No	Yes	Black or African American	Other
50 mg daily dose						
LSM difference with placebo in systolic AOBP change, mmHg (90%CI)	2.2 (-7.4 to 11.8) P=0.7 *(n=11)*	-16.7 (-25.5 to -7.9) P<0.01 *(n=15)*	-4.4 (-14.0 to 5.1) P=0.44 *(n=12)*	-12.9 (-21.2 to -4.7) P=0.01 *(n=16)*	-6.9 (-16.9 to 3.2) P=0.26 *(n=8)*	-12.0 (-20.4 to -3.7) P=0.02 *(n=20)*
100 mg daily dose						
LSM difference with placebo in systolic AOBP change, mmHg (90%CI)	-4.5 (-14.5 to 5.5) P=0.46 *(n=10)*	-12.3 (-21.6 to -3.1) P=0.03 *(n=14)*	-5.3 (-15.1 to -4.4) P=0.36 *(n=13)*	-10.0 (-18.4 to -1.6) P=0.05 *(n=17)*	-7.1 (-15.8 to 1.5) P=0.17 *(n=15)*	-9.4 (-18.6 to -0.3) P=0.09 *(n=15)*

Maar waarom alleen maar in therapieresistente hypertensie?

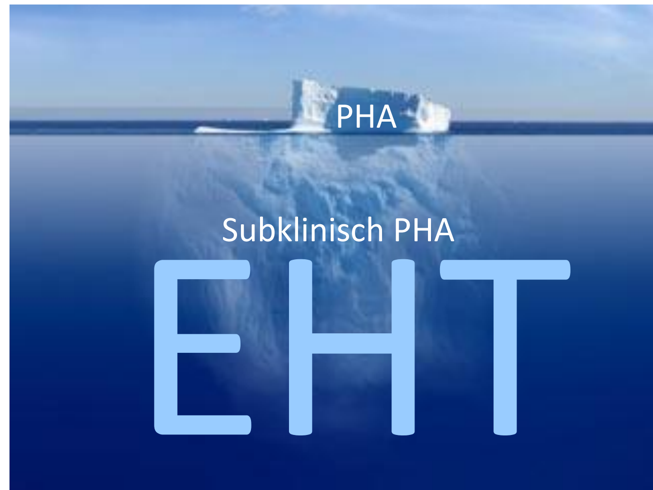
Somatic mutations implicated:
KCNJ5
ATP1A1
ATP2A3
CACNA1D
CACNA1H
CLCN2
CTNNB1
GNA11
GNAQ
GNAS



The Spectrum of Subclinical Primary Aldosteronism and Incident Hypertension

A Cohort Study

Jenifer M. Brown, MD; Cassianne Robinson-Cohen, PhD; Miguel Angel Luque-Fernandez, MSc, MPH, PhD;
Matthew A. Allison, MD, MPH; Rene Baudrand, MD; Joachim H. Ix, MD, MS; Bryan Kestenbaum, MD, MS; Ian H. de Boer, MD, MS;
and Anand Vaidya, MD, MMSc



- Is primair hyperaldosteronisme de top van de ijsberg?
- Primair hyperaldosteronisme:
  laag renine, hoog aldosteron, veel CV schade

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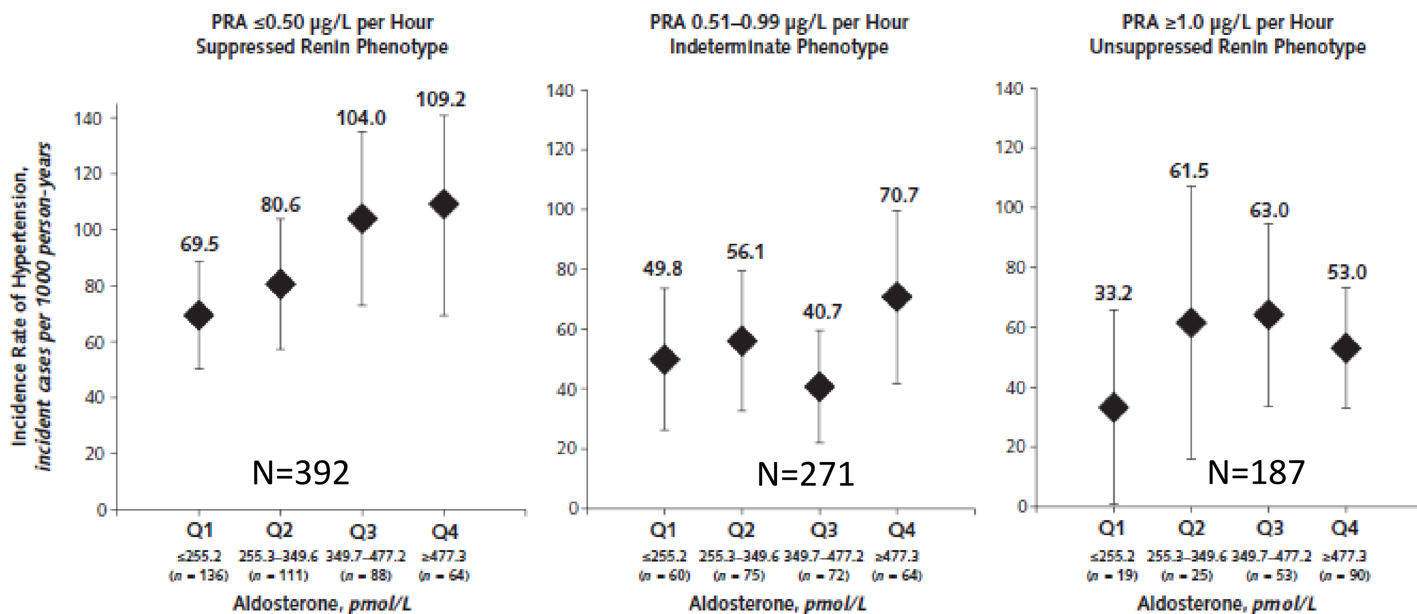
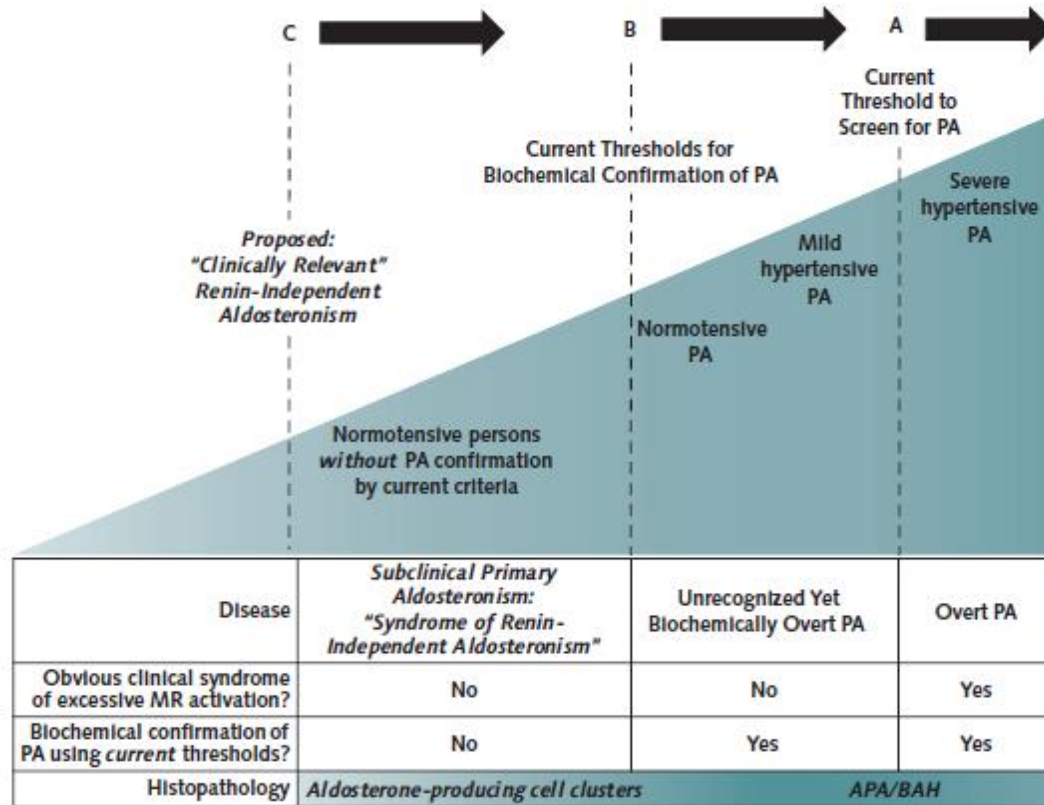
Figure 1. Renin-independent aldosteronism and the incidence rate of hypertension.



Unadjusted incidence rate of hypertension (number of incident cases per 1000 person-years at risk) by phenotypes of renin and quartiles of aldosterone. To convert PRA from SI to conventional units: 1 µg/L/h = 1 ng/mL/h. To convert aldosterone from SI to conventional units: 1 pmol/L = 0.036 ng/dL. Quartiles of aldosterone in conventional units are <9.23 ng/dL (Q1), 9.23-12.73 ng/dL (Q2), 12.74-17.32 ng/dL (Q3), and ≥17.32 ng/dL (Q4). PRA = plasma renin activity; Q = quartile.

Ann Intern Med 2017 167:630

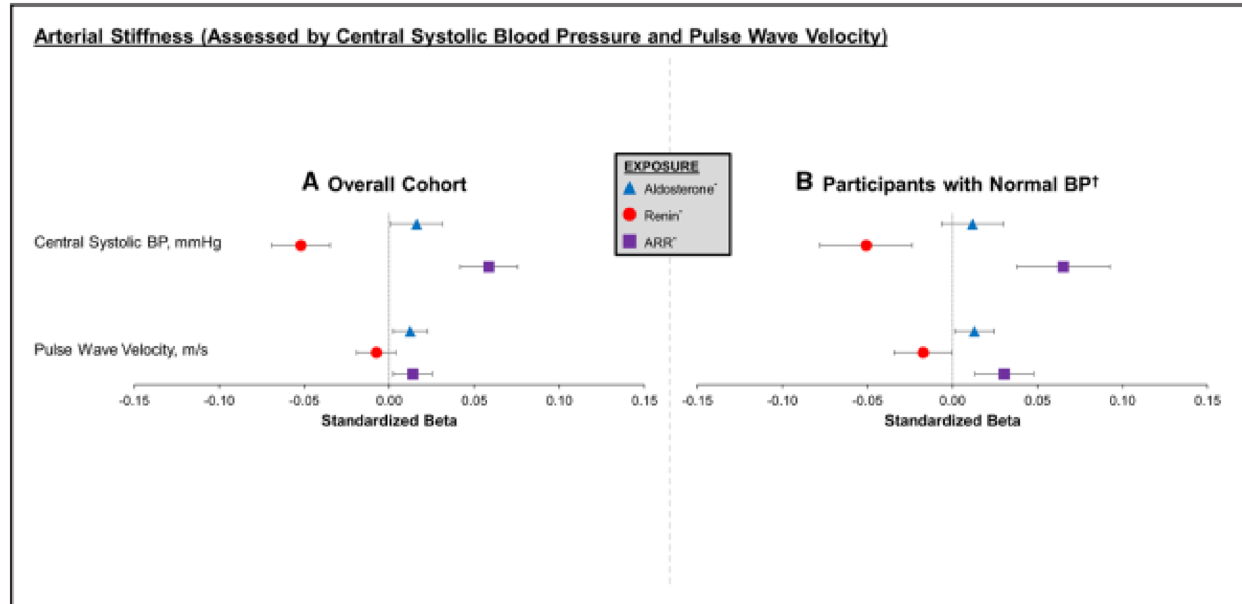


Ann Intern Med 2017 167:630

ORIGINAL RESEARCH ARTICLE

Subclinical Primary Aldosteronism and Cardiovascular Health: A Population-Based Cohort Study

Gregory L. Hundemer, MD, MPH; Mohsen Agharazii, MD; François Madore, MD, MSc; Anand Vaidya, MD, MMSc; Jenifer M. Brown, MD; Alexander A. Leung, MD, MPH; Gregory A. Kline, MD; Eric Larose, DVM, MD; Marie-Eve Piché, MD, PhD; Andrew M. Crean, MRCP, MPH; Julie L.V. Shaw, PhD; Tim Ramsay, PhD; Bernhard Hametner, DrSci; Siegfried Wassertheurer, DrSci; Manish M. Sood, MD, MSc; Swapnil Hiremath, MD, MPH; Marcel Ruzicka, MD, PhD; Rémi Goupil, MD, MSc



Circulation 2024 149:124

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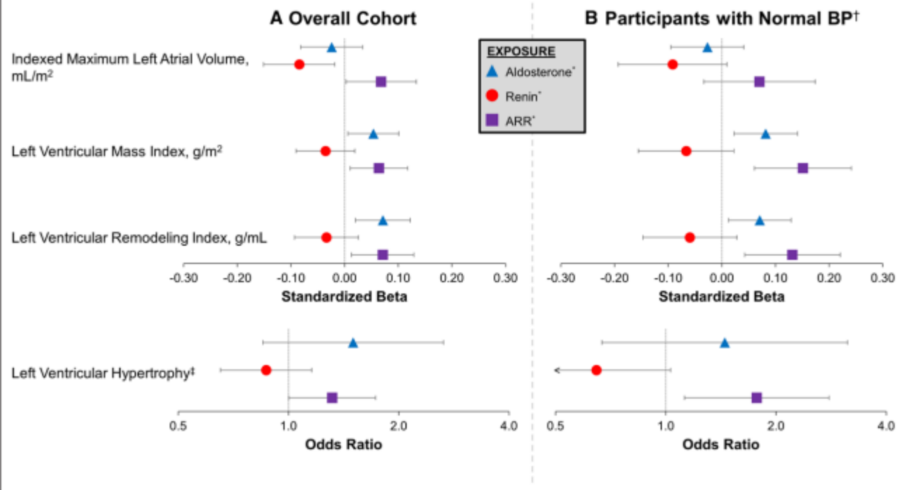
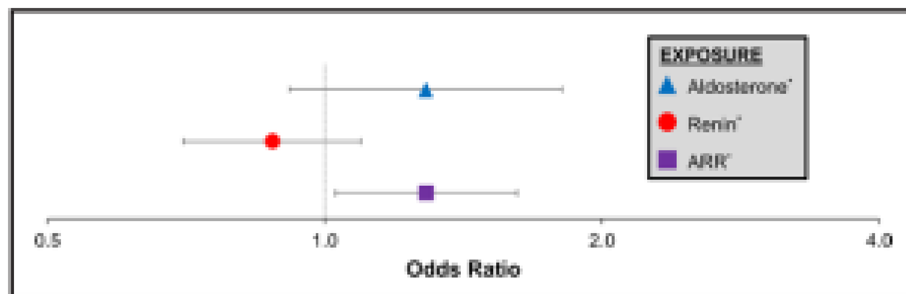

Cardiac Remodeling (Assessed via Cardiac MRI)
A Overall Cohort
B Participants with Normal BP†
EXPOSURE
Aldosterone*
Renin*
ARR*
Indexed Maximum Left Atrial Volume, mL/m²
Left Ventricular Mass Index, g/m²
Left Ventricular Remodeling Index, g/mL
-0.30 -0.20 -0.10 0.00 0.10 0.20 0.30
Standardized Beta
Left Ventricular Hypertrophy‡
0.5 1.0 2.0 4.0
Odds Ratio


EXPOSURE
Aldosterone*
Renin*
ARR*
0.5 1.0 2.0 4.0
Odds Ratio

Samenvatting

- Het maakt waarschijnlijk niet uit of je vorming remt of werking blokkeert
- Aldosteronsythaseremmers lijken verder ontwikkeld te worden
- Indicatiegebied voor anti-aldosteron therapie is misschien wel veel groter:
- Eplerenon of baxdrostat als initiële behandeling van hypertensie?