

Uitdagingen bij de Diagnose Endocriene Hypertensie

Anton H. van den Meiracker
EMC, Rotterdam



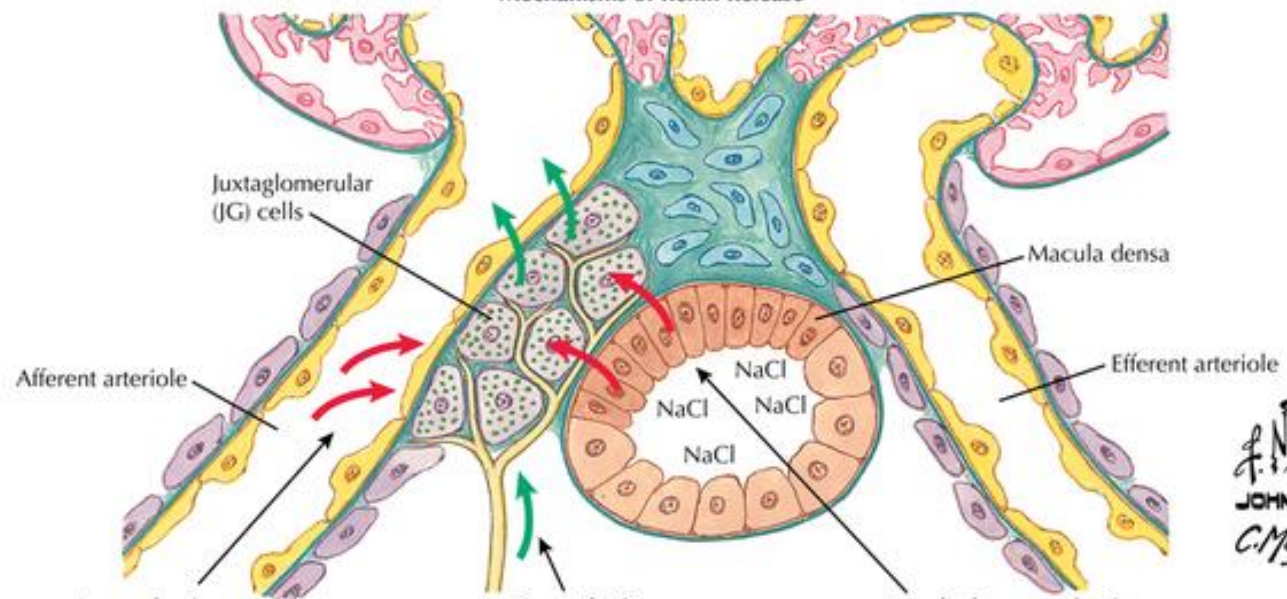
Inhoud

- **Fysiologie van RAAS**
- **Primair hyperaldosteronisme**
- **Diagnostiek van primair hyperaldosteronisme**
- **Uitdagingen**

Evolutie en het RAAS



Mechanisms of Renin Release



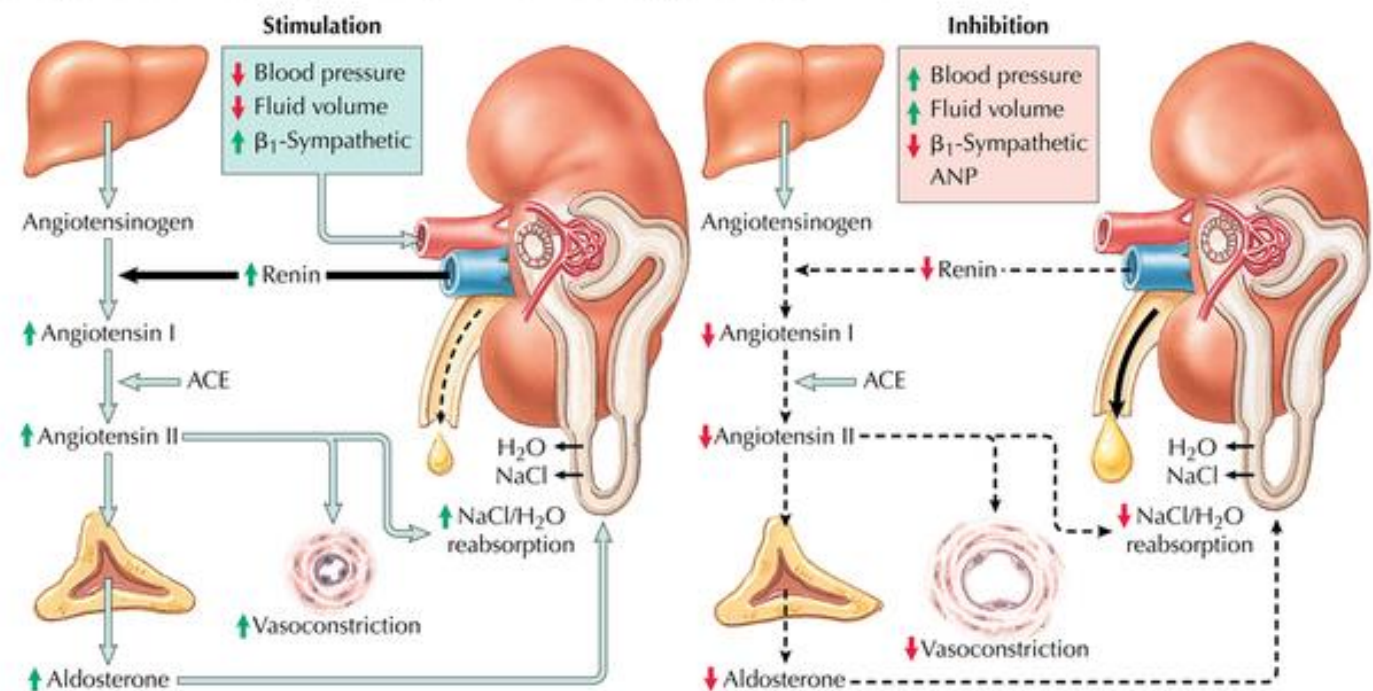
J. Netter M.D.
JOHN A. CRAIG M.D.
C. Machado M.D.

Baroreceptor mechanism:
 Increased pressure in afferent arteriole inhibits renin release from JG cells (red arrows); decreased pressure promotes renin release (green arrows)

Sympathetic nerve mechanism:
 β_1 -Adrenergic nerves stimulate renin release (green arrows)

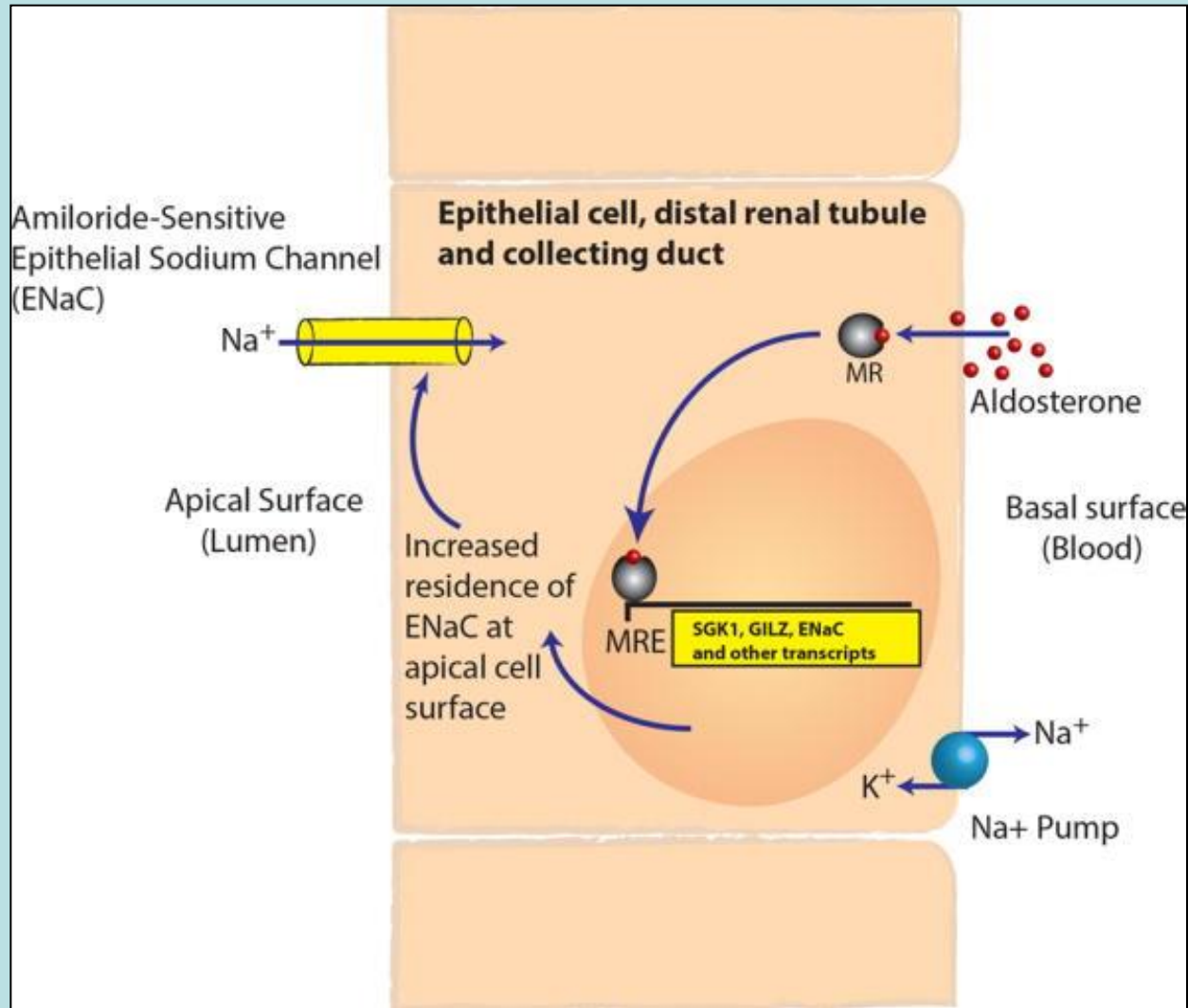
Macula densa mechanism:
 Increased NaCl in distal nephron inhibits renin release (red arrows); decreased load promotes renin release

A



B

Aldosterone => toename epitheliale natriumkanalen in distale nefron



Yanomami Indians



**Natrium excretie 1 meq/dag,
Extreem hoog renine (30-voudig)**

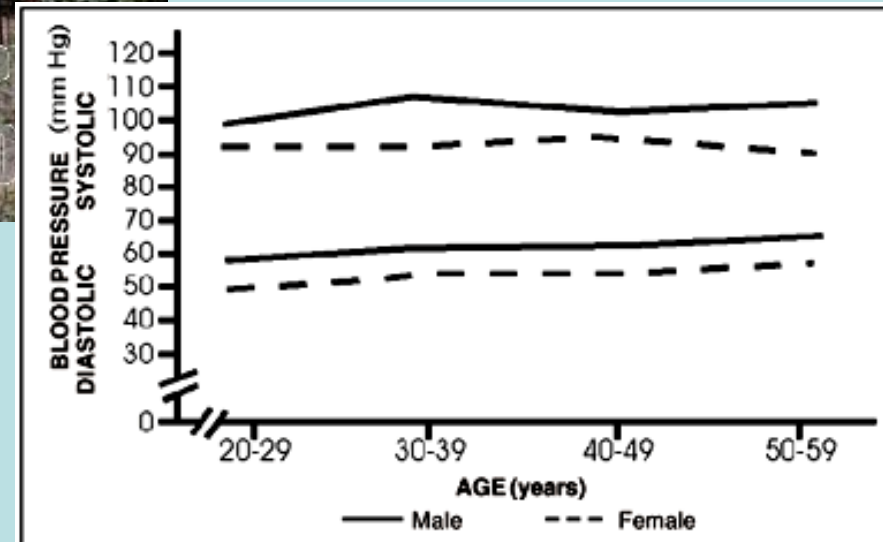
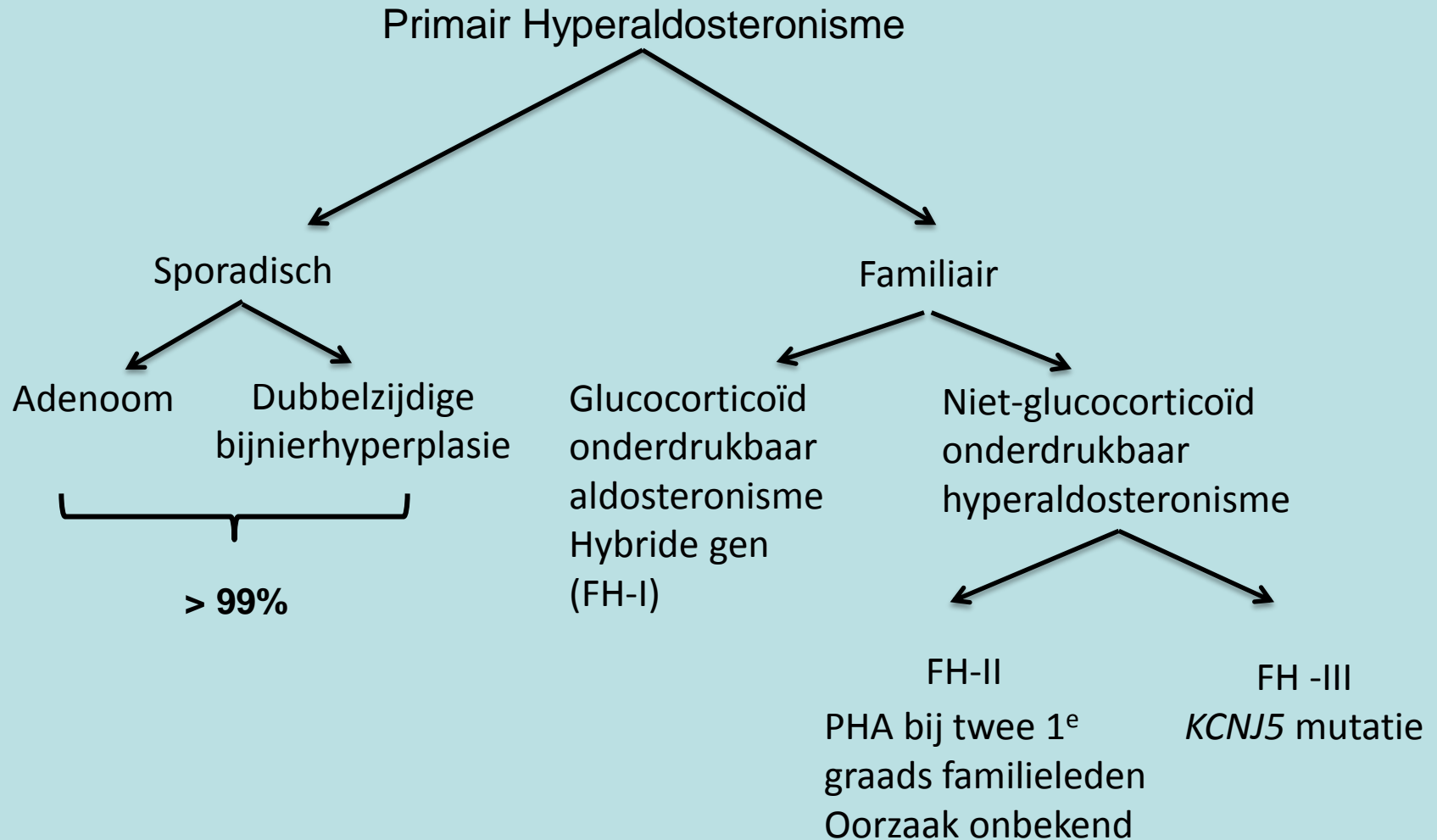


Fig. 3 - Blood pressure and age (Yanomami Indians).

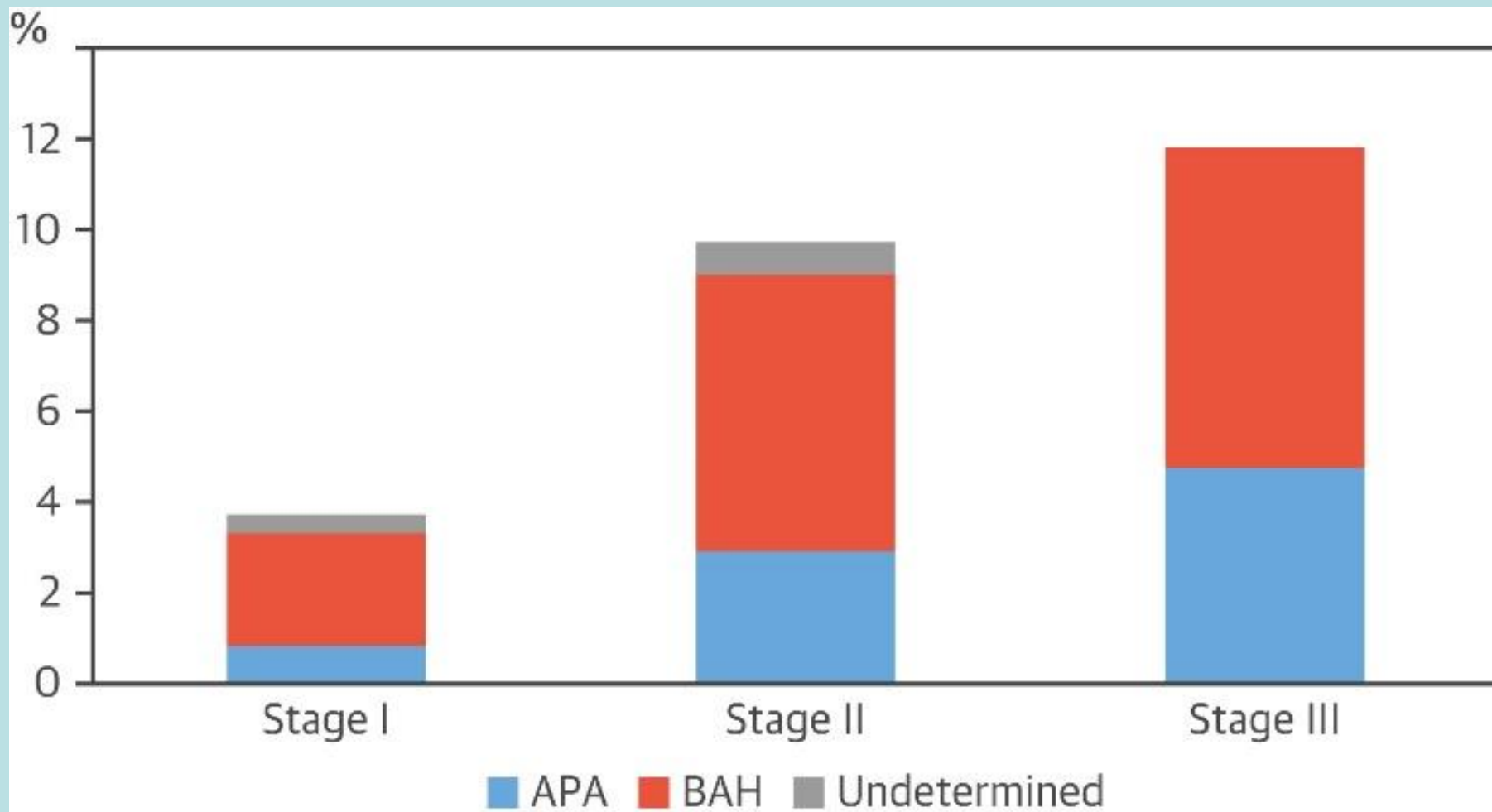
Primair hyperaldosteronisme

**Overmatige “autonome” aldosteronproductie
bij een onderdrukt renine**

Primair hyperaldosteronisme: Classificatie



Prevalence of subtypes of PA in relation to severity of hypertension



PA and risk of complications compared to EH*

	ODDs ratio	95% CI
Stroke	2.58	1.93-3.45
Coronary heart disease	1.77	1.10-2.83
Atrial fibrillation	3.52	2.06-5.99
Heart failure	2.05	1.11-3.78
LVH	2.29	1.65-3.17
DM	1.33	1.01-1.74
Metabolic syndrome	1.53	1.22-1.91

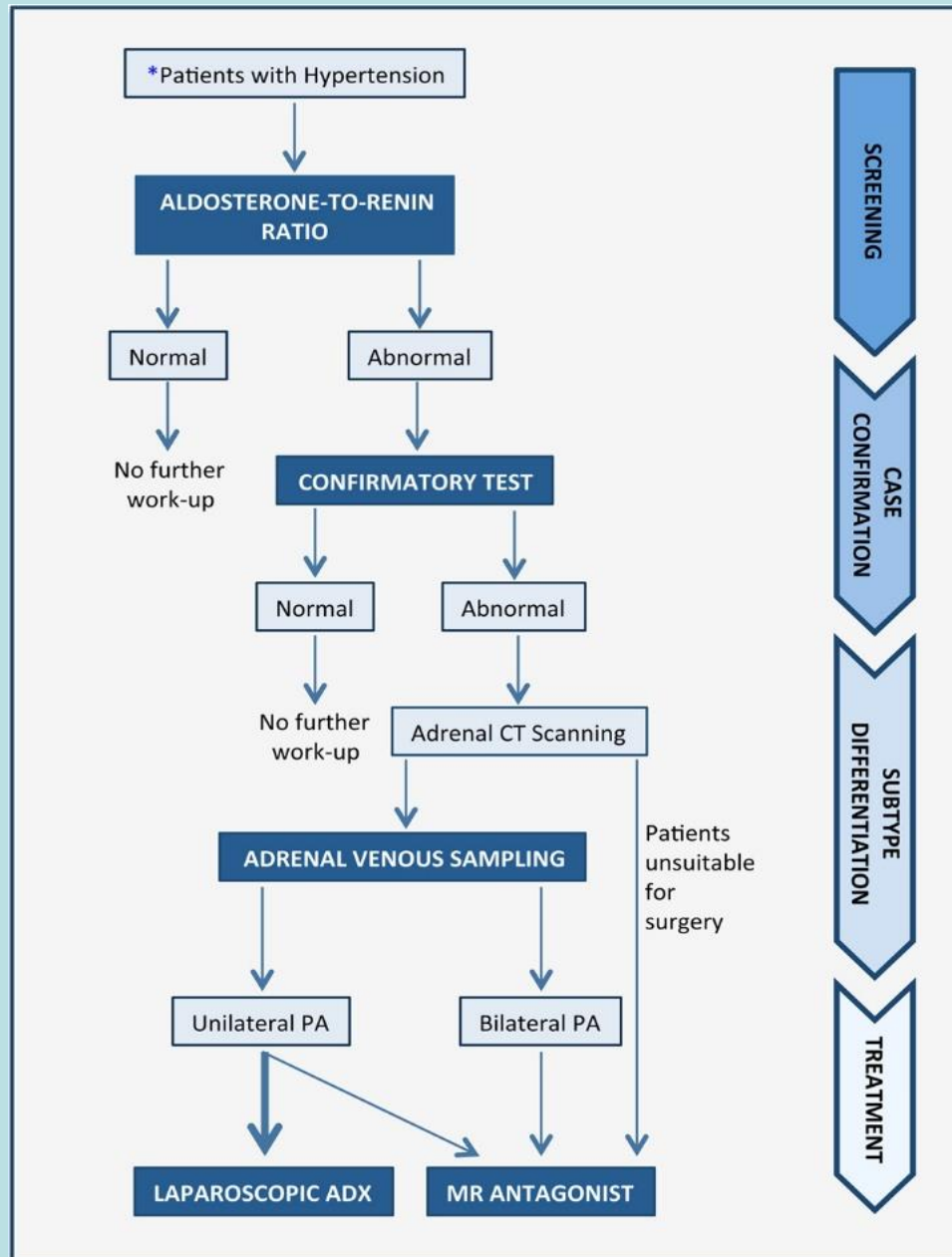
Monticone et al: Lancet Diabetes/Endocrinol 2018

Pts with PA n= 3838

Pts with EH n=9284

Median FU 8.8 yrs

Diagnostisch algoritme bij verdenking op primair hyperaldosteronisme



The Management of PA: Case detection, Diagnosis and Treatment: An Endocrine Society Clinical Practice Guideline *JCEM 2016;101:1889-1916*

Wie Screenen op PHA?

- **BD bij herhaling > 150/100 mmHg (HT graad 2)**
- **Resistente HT (RR > 140/90 (>130/80) ondanks 3 middelen)**
- **Gecontroleerde HT onder 4 middelen**
- **HT en spontane of diuretica-geïnduceerde hypokaliëmie**
- **HT en bijnierincidentaloom**
- **HT en OSAS**
- **HT + familieanamnese van hypertensie en/of CVA op jonge leeftijd (< 40 jaar)**
- **Hypertensieve eerstegraadsfamilieleden van indexpatiënt met PHA**

The Management of PA: Case detection, Diagnosis and Treatment: An Endocrine Society Clinical Practice Guideline *JCEM 2016;101:1889-1916*

We recommend using the plasma aldosterone/renin ratio (ARR) to detect possible case of PA in these patient groups.

Importantly, laboratories need to report individual values for PAC and renin. Like all biochemical case detection tests, the ARR is not without false positives and false negatives. The ARR should therefore be regarded as a detection test only.

- **Bloedafname 's ochtends**
- **Normokaliëmie**
- **MRA's > 4 weken stoppen**
- **In many cases the ARR can be confidently interpreted despite the effect of continued medications or other suboptimal conditions of testing**

ARR waarde sterk afhankelijk van renine, dus ARR kan verhoogd zijn ondanks een relatief lage aldosteronwaarde (vals positieven).

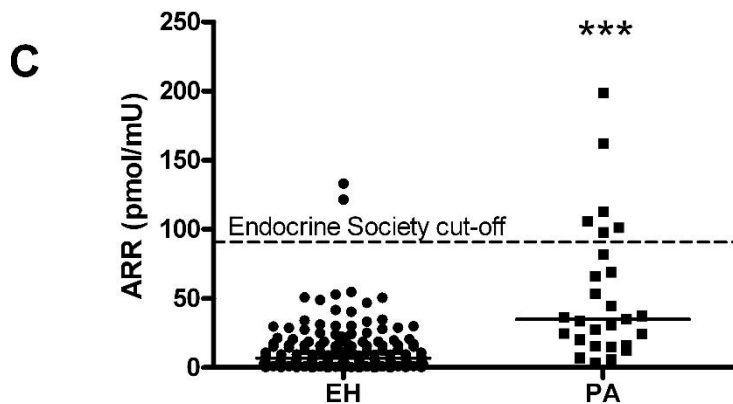
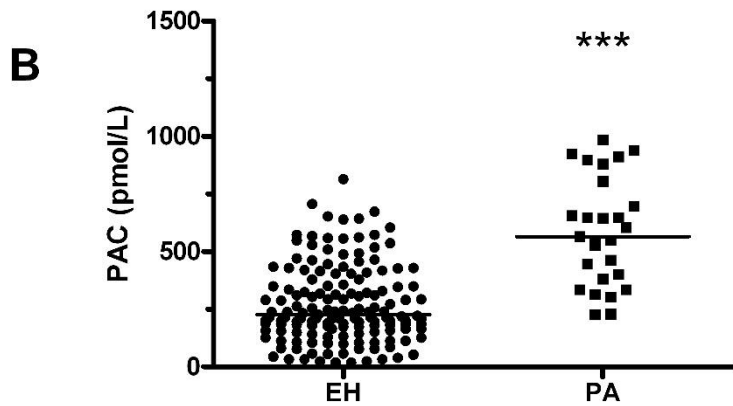
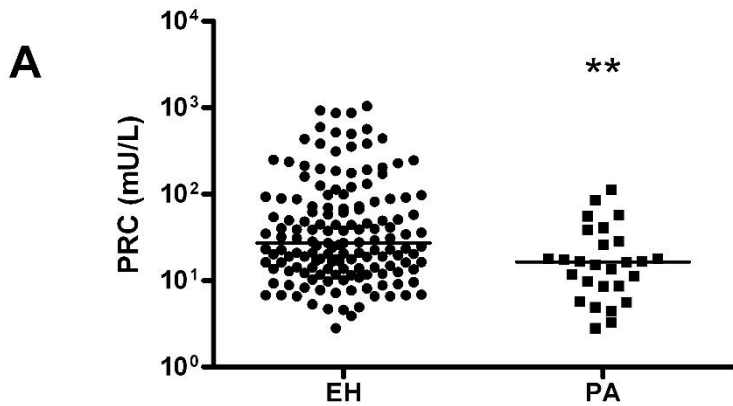
Minimale aldosteronwaarde waarbij PHA is uitgesloten?

In een studie van 125 ptn met een APA verwijderd: 20 een ochtend aldo < 400, 5 < 280 pmol/l!

ARR cut-off values

	PRA ng.mL/h	PRA pmol/L/min	Renin concentration (mU/L)	Renin Concentration (ng/mL)
PAC (pg/mL)	300	25	37	57
PAC (ng/dL)	30 (20-40)	2.5 (1.6-3.1)	3.7 (2.4-4.9)	5.7 (3.8-5.7)
PAC (pmol/L)	750 (1000)	60 (80)	91 (122)	144 (192)

Aldosteron: 1 pg/mL = 2.8 pmol/L

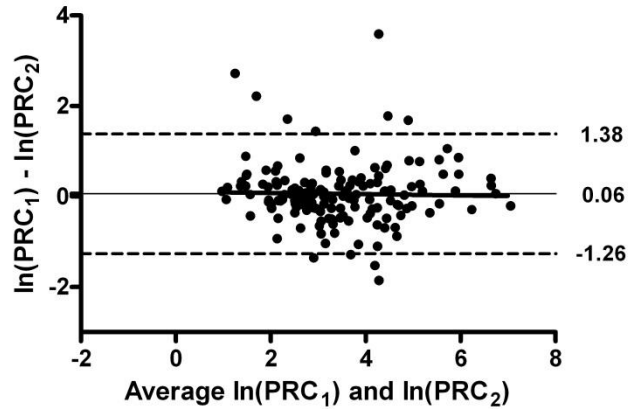
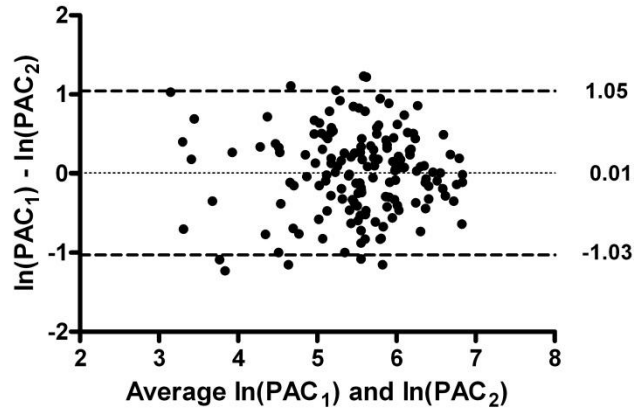
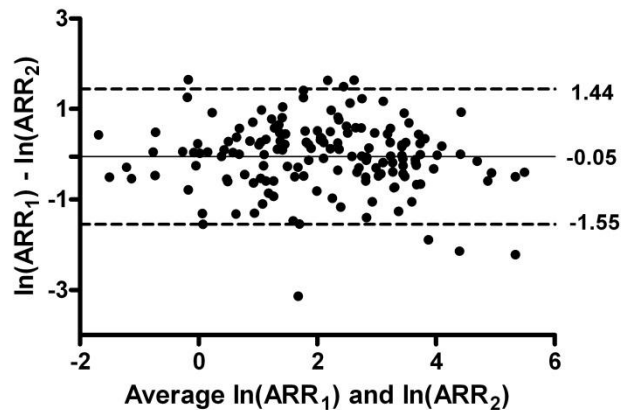


Renin, aldosterone & **ARR** in patients with essential hypertension (EH) versus primary aldosteronism (PA): low specificity

Large Overlap

Jansen et al.,
J Hypertens 2014

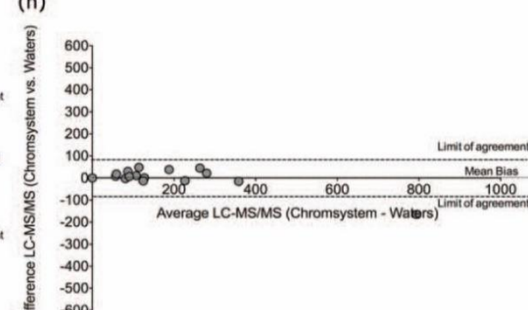
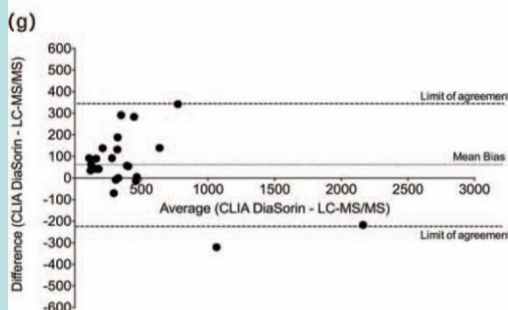
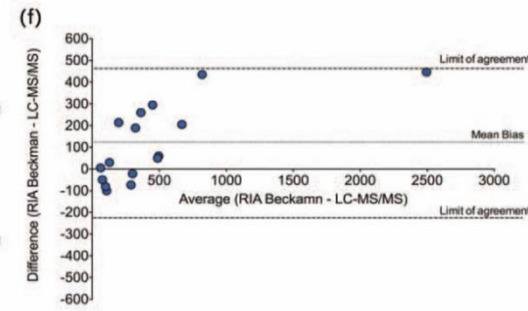
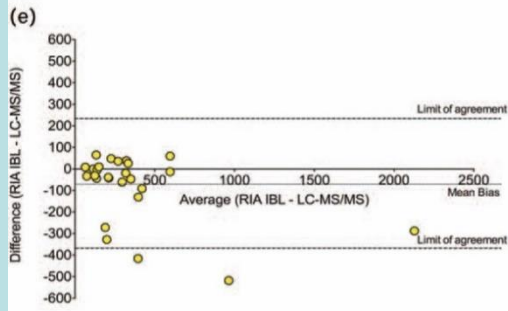
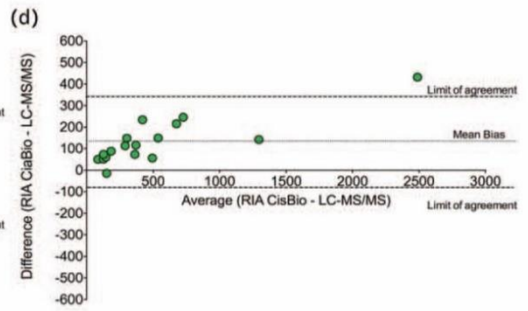
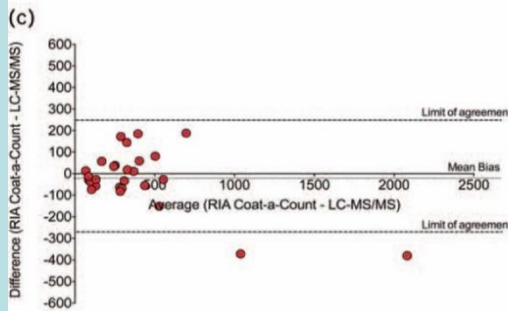
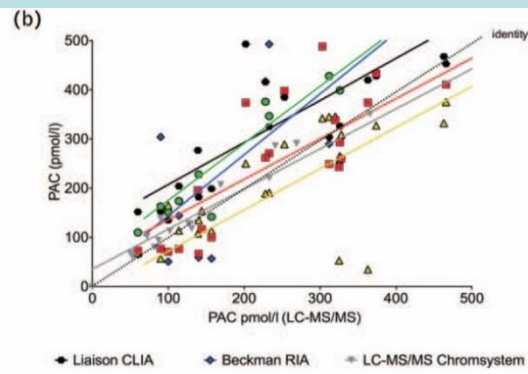
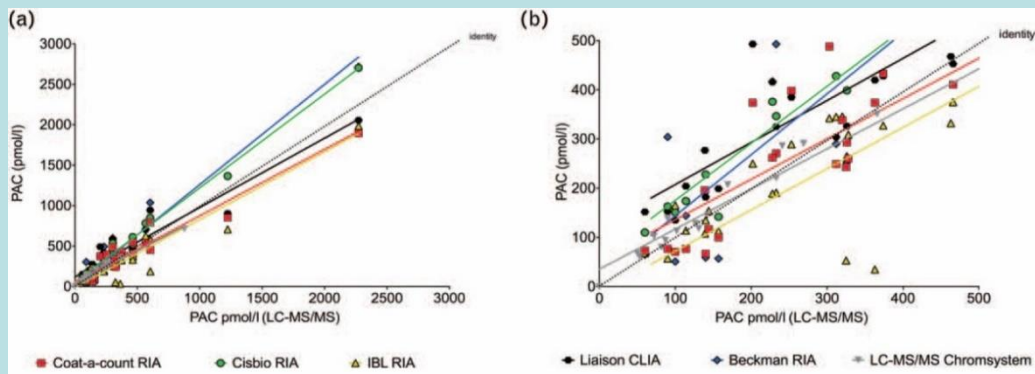
PA definition: PAC >235 pmol/L after salt-loading test

A**B****C**

Variation in
duplicate
measurements:

$\text{ARR} \geq \text{renin} >$
aldosterone

Jansen et al.,
J Hypertens 2014



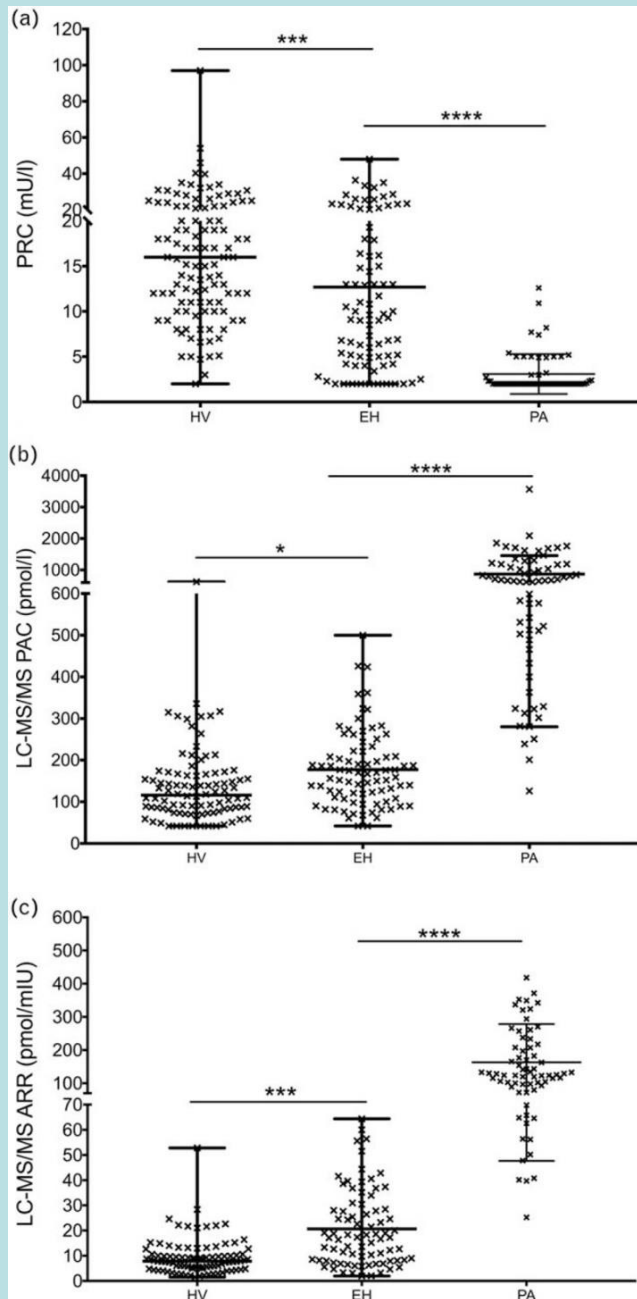
**Aldosterone:
HPLC tandem mass spectrometry
versus RIA or Chemiluminescent
immune assay**

**Aldosterone met LC-MS/MS
lager**

**2 verschillende LC-MS/MS
assays goede overeenkomst**

Baron et al. J Hypertens 2018

Plasma renin, plasma aldosteron en ARR in gezonde vrijwilligers en patienten met EHT en PHA



Baron et al. J Hypertens 2018

ROC curve:

ARR afkapwaarde van 46 pmol/mU
sensitiviteit van 94.4%
specificiteit van 93.3%

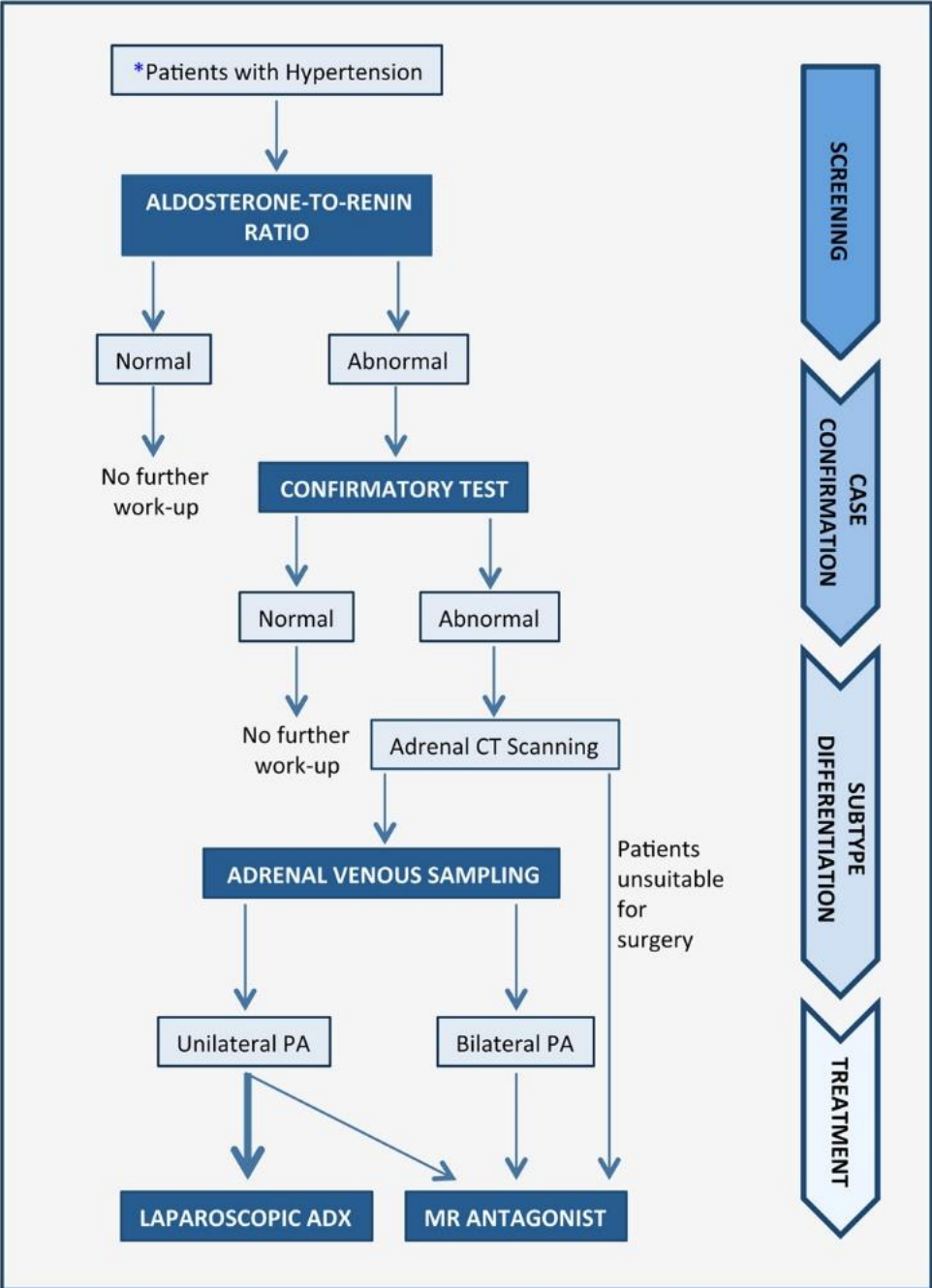
ARR afkapwaarde van 64.5 pmol/mU
sensitiviteit van 100%
specificiteit van 87.3%.

95 ste percentile aldosterone in EH is 360 pmol/l (130 pg/ml) kan gebruikt worden als afkapwaarde om onderscheid te maken tussen PA en EHT

Endocrine Society:

PAC > 550 pmol/l (200 pg/ml) en PCR <2 mU/l geen confirmatie test meer nodig.

Diagnostisch algoritme bij verdenking op primair hyperaldosteronisme



Zoutbelastingtest

- Principe
- Uitvoering
- Afkapwaarde

PAC <140 pmol/l PHA onwrschl

PAC >280 pmol/l PHA wrschl

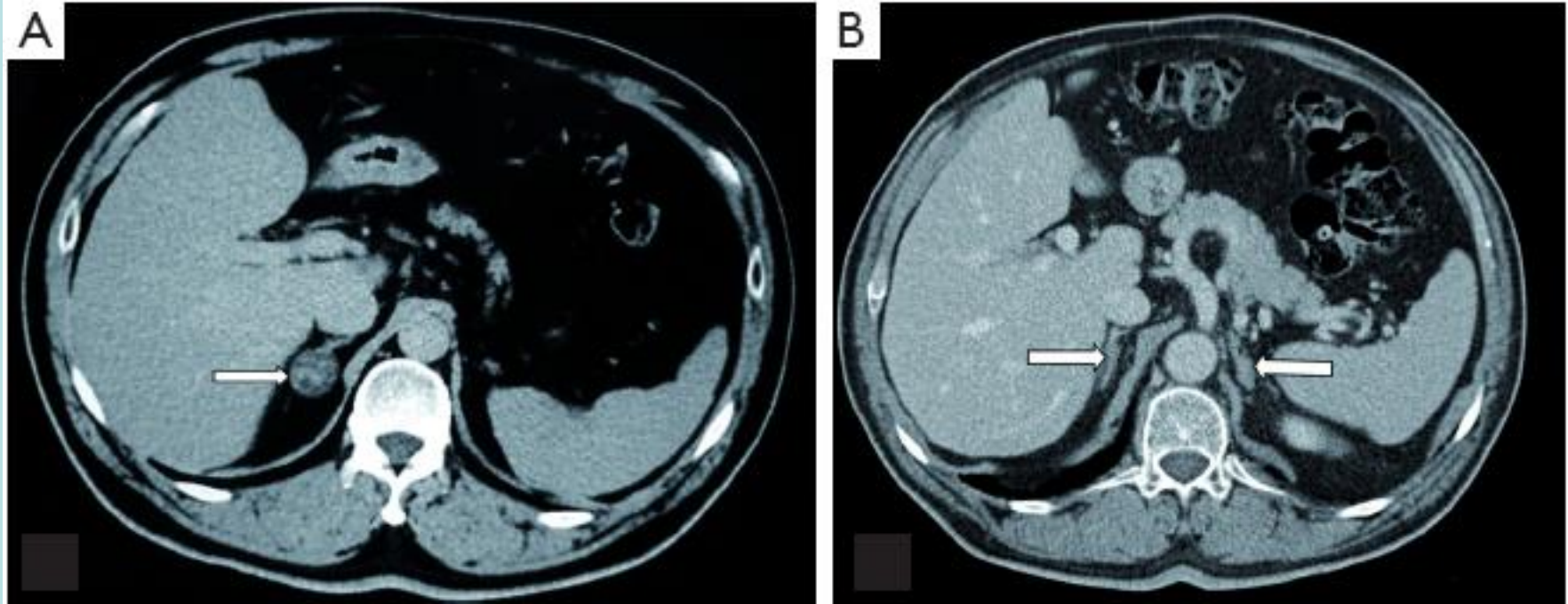
Indien test zittend wordt uitgevoerd

PAC > 170 pmol/l bevestigt diagnose

Reproduceerbaarheid matig (60-80%)

Volgens recente richtlijn ZBT niet nodig indien spontane hypokaliëmie, renine onder detectiewaarde en PAC > 550 pmol/l

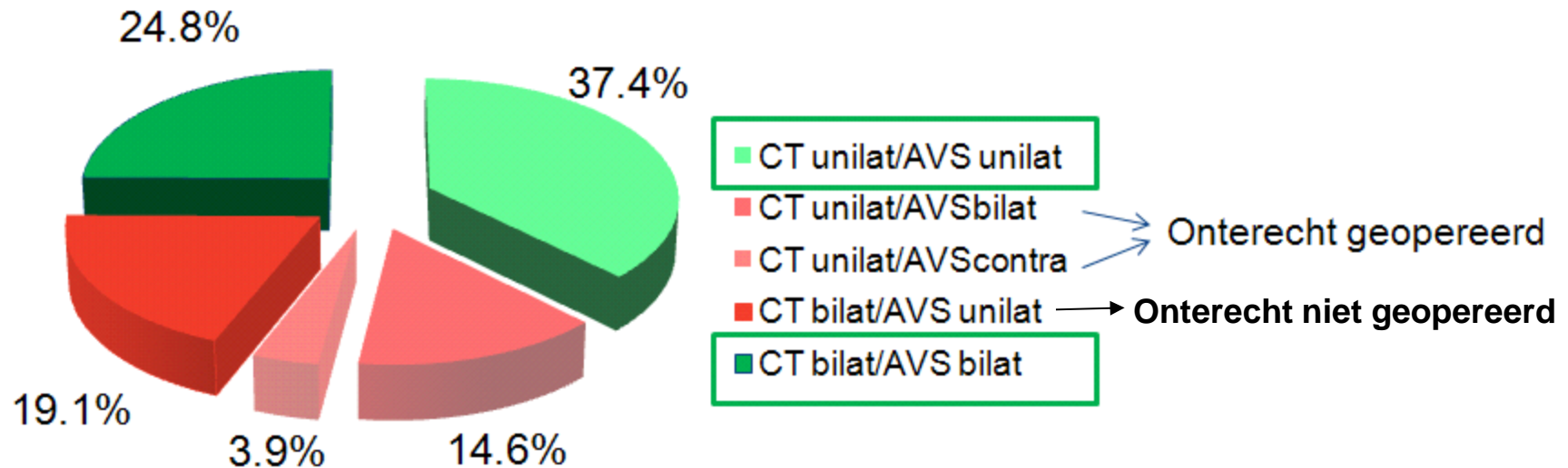
Klinische vormen van hyperaldosteronisme



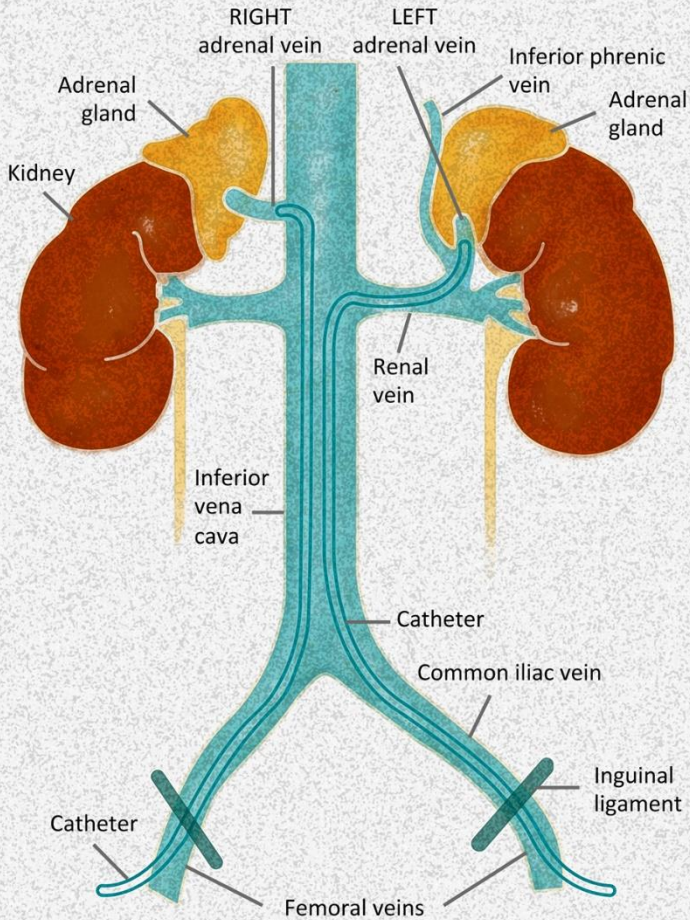
**Zeldzaam: familiale vormen door bekende of nog onbekende genetische defecten:
Voorbeelden: FH-1: glucocorticoid remediable aldosteronism
FH-3: Mutatie in KCNJ5 gen coderend voor kaliumkanaal in ZG cel**

Discrepancies between CT-scan and inferior vena cava sampling: meta-analysis

Resultaten systematische review (n=950)

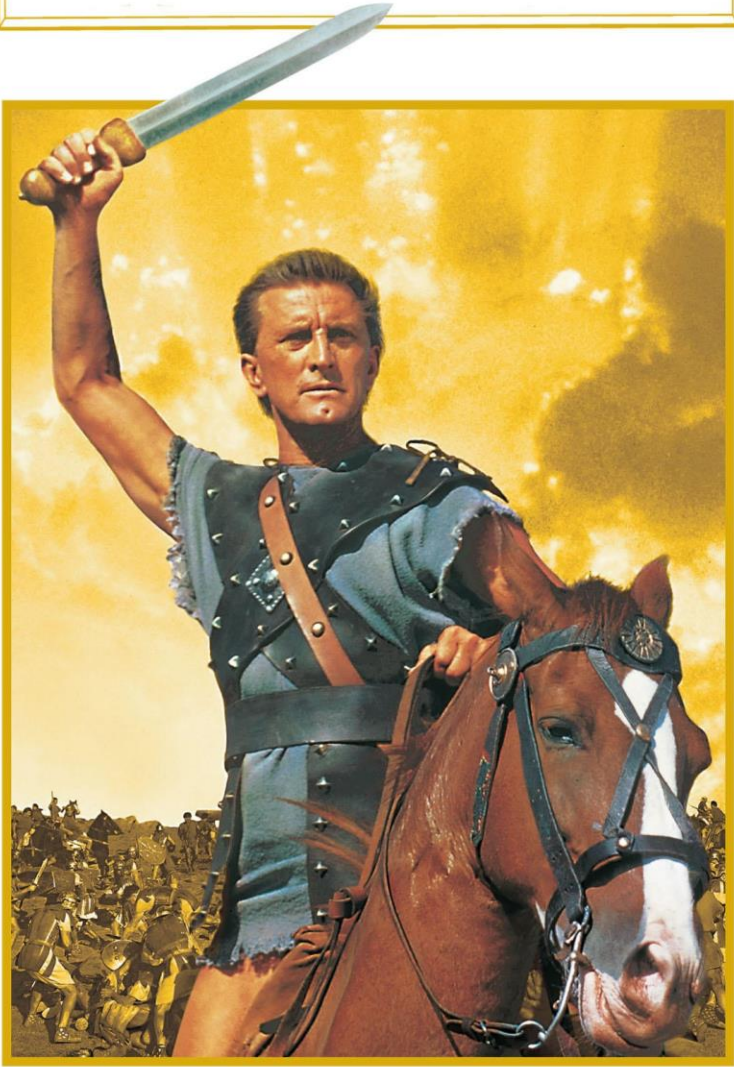


Bijniervene sampling op aldosteron



Referral center	Unstimulated or ACTH infusion	Successful AVS	Diagnosis of unilateral PA
Munich, Paris	Unstimulated	SI \geq 2	LI \geq 4
Torino	Unstimulated + continuous ACTH infusion	SI \geq 3	LI \geq 4 or LI \geq 3 and CLR \leq 1
Brisbane	Unstimulated	SI \geq 3	LI \geq 2.5 and CLR \leq 1
Rochester	Continuous ACTH infusion	SI \geq 5	LI \geq 4
Sendai	Bolus ACTH infusion	SI \geq 5	LI \geq 2.6
Yokohama City	Bolus + continuous ACTH infusion	(Cortisol) _{AV} $>$ 200 μ g/dL*	(PAC) _{ipsilateral/AV} $>$ 1400 ng/dL*

SPARTACUS



Adrenal vein sampling versus CT scan to determine treatment in primary aldosteronism: an outcome-based randomized diagnostic trial (SPARTACUS)
Lancet Diabetes Endocrinol 2016

Vergelijking van AVS-gebaseerde versus CT-scan gebaseerde adrenalectomie op uitkomst

Primaire uitkomst:

- **Hoeveelheid antihypertensiva om streefbloeddrukwaarde te bereiken na 1 jaar follow-up**

Secundaire uitkomst:

- **Normalisatie van renine en aldosteron**
- **Kosteneffectiviteit**
- **Bijwerkingen**

SPARTACUS

Inclusie criteria:

- >18 jaar
- Tenminste 3 antihypertensiva
- Of spontane of diuretica-geïnduceerde hypokaliëmie
- Positieve zoutbelastingtest

99 allocated to CT



47 treated with ARA
49 treated with adrenalectomy



92 analysed
46 CT based adrenalectomy
46 CT-based ARA therapy

97 allocated to AVS



46 treated with ARA
50 treated with adrenalectomy



92 analysed
46 AVS-based adrenalectomy
46 AVS based ARA therapy

SPARTACUS

	CT (n=92)	AVS (n=92)
V/M, %/%	25/75	18/82
Lft, jaren	53	53
Hypokaliëmie of kaliumsuppletie, %	68	68
Ongecontroleerde HT, %	72	80
Systolische ABPM Dag, mmHg	147/95	153/92

Aldosteron, pmol/l	645	685
Plasma renine, mU/l	3.5	4.2
Post ZBT aldosteron, pmol/l	418	406

SPARTACUS

	Adrenalectomie		Aldosteronblokker	
	CT (n=46)	AVS (n=46)	CT (n=46)	AVS (n=46)
DDD	1.2 (0-3.0)	1.2(0-3.0)	4.0 (2.3-6.7)	5.7 (3.4-8.7)
Number of antihypertensive drugs	1(0-2)	1 (0-2)	2 (2-3)	3 (2-4)
Dag ABPM, mmHg	133/83	132/84	128/84	130/84
ABPM < 135/85 mmHg, %	40	43	46	46
Kalium, mmol/l	4.3 (3.9-4.6)	4.2 (4.0-4.4)	4.3 (4.0-4.6)	4.4 (4.1-4.6)
Costs, euro's	6299	9042*	2219	4526*

SPARTACUS

Conclusie

- **Geen voordeel AVS mbt primaire uitkomstmaat**
- **Geen verschil in bloeddruk medicamenteus of operatief**
- **Na adrenalectomie minder antihypertensiva**
- **Is AVS wel de goudstandaard?**
- **Consequenties voor de praktijk?**

Hypertension outcomes of adrenalectomy in pts with PA: a systematic review and meta-analysis

Zhou et al. BMC Endocrine disorders 2017;17:61

Category	Subgroup	n	Cure rate, % (95%CI)
Country	China	1849	61 (49-73)
	Other	1972	44 (38-49)
FU time	>6 months	3081	50 (41-58)
	<6 months	695	53 (36-71)
Age	>50 years	3285	47 (37-56)
	<50 years	491	56 (47-72)
Publication year	2001-2010	1396	51 (41-61)
	2011-2016	2380	50 (39-65)
Pathology	APA only	1381	51 (44-58)
	other	2395	50 (40-61)

Genezingspercentage niet gestegen na invoering bijniervenecsamplng

Uitdagingen

- **Versnellen van diagnostisch en therapeutisch proces**
- **Bij wie *geen* bijniervenesisampling**
- **Definiëren van cut-off waarden met nieuwe bepalingen**
- **Streven naar uniforme meetmethoden, afkapwaarden en protocollen in Nederland**

THANK YOU

