Radboud UMC, Nijmegen
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Primary Aldosteronism: screening, diagnosis and therapy

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Issues to be addressed

- what is the prevalence of primary aldosteronism (PA)?
- why is it useful to detect patients with PA?
- which patients should be screened for PA?
- what is the biochemical testing strategy?
- specific pre-analytical test conditions required?
- how to establish a definite diagnosis of PA?
- how to do subtyping: uni- versus lateral PA?
- how to treat unilateral and bilateral PA?

Mineralocorticoid hypertension

Diagnosis	plasma renin	plasma aldosterone	Primary defect
Primary aldosteronism	decreased	increased	↑ secretion aldosteron
Pseudo-aldosteronism	decreased	decreased	↑secretion other mineralocorticoid or Δ ENaC function or Δ MC receptor
Pseudo-hypoaldosteronism II (Gordon's syndrome)	decreased	variable	overactive NaCl cotransporter
Secondary aldosteronism	increased	increased	↑ secretion renin

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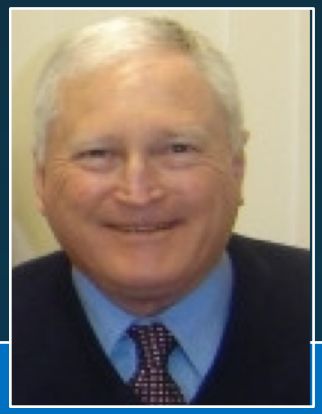
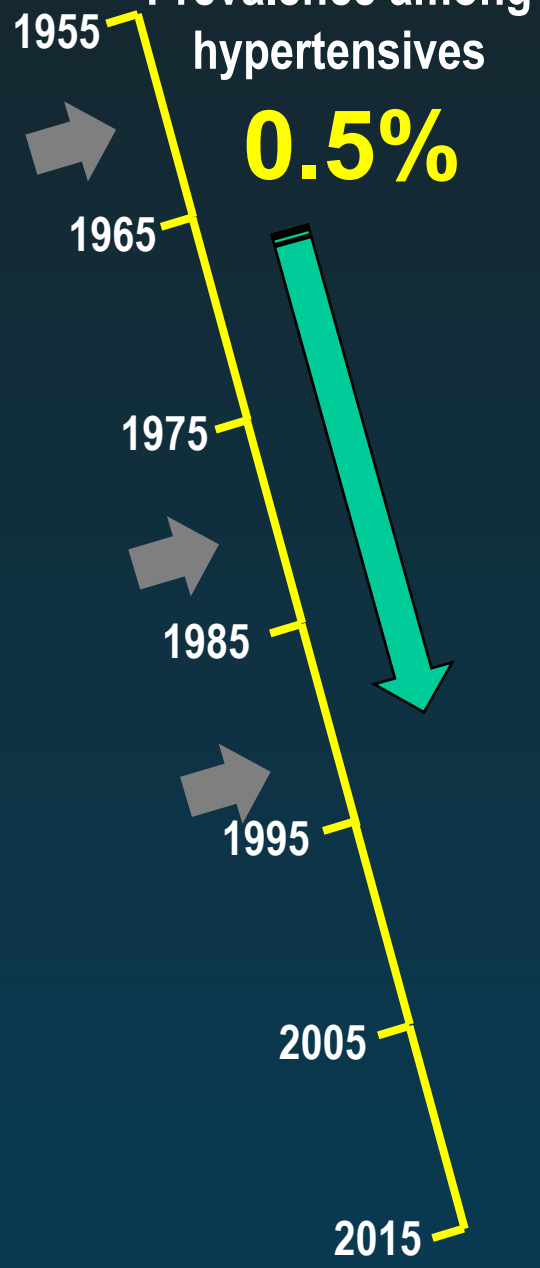
Hiramatsu K et al.
Arch Int Med 1981
Aldo/Renin ratio



Richard Gordon
Adr. ven. sampling



ORIGINAL ARTICLE *2016;101:2826*

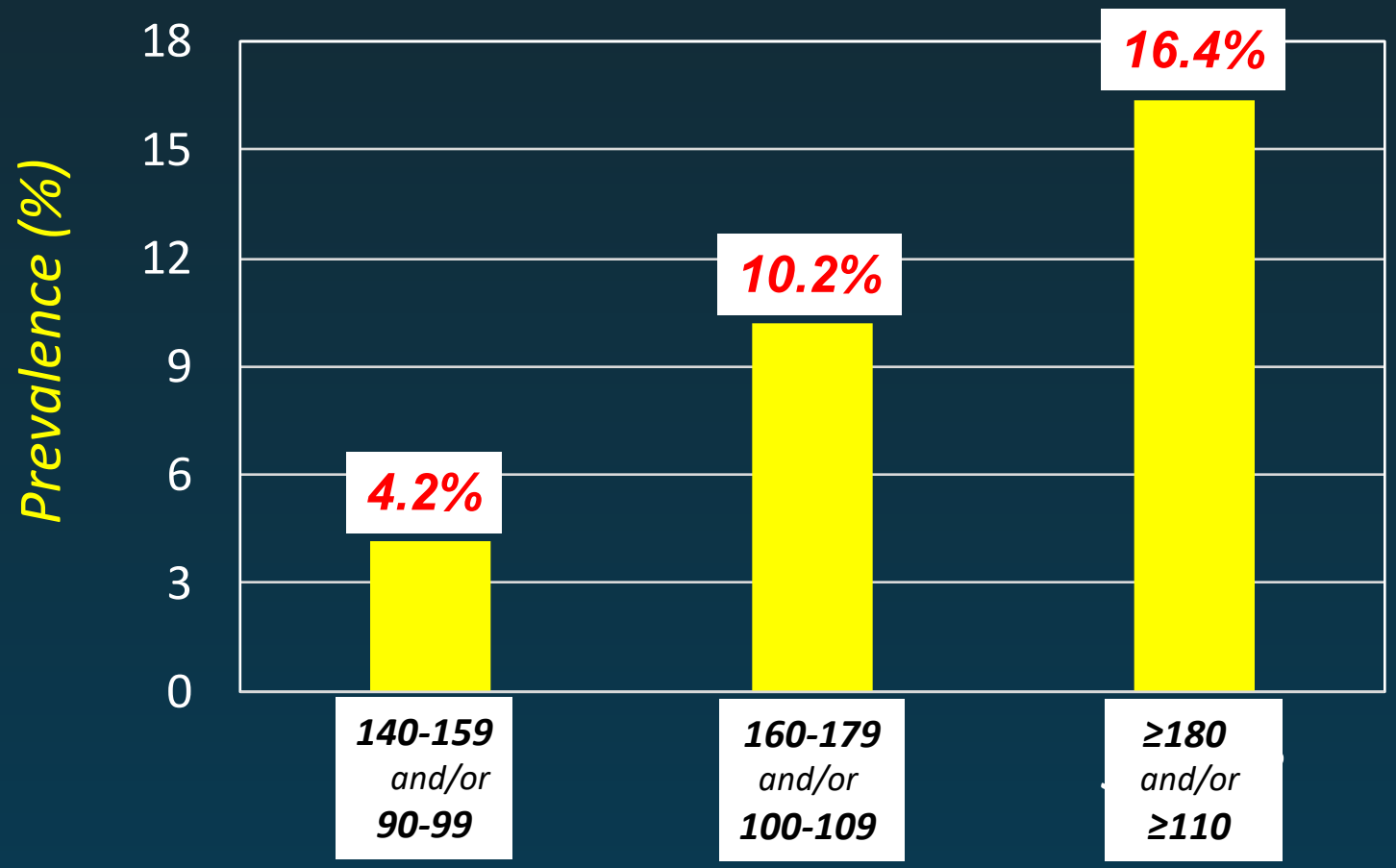
Study Heterogeneity and Estimation of Prevalence of Primary Aldosteronism: A Systematic Review and Meta-Regression Analysis

Sabine C. Käyser,* Tanja Dekkers,* Hans J. Groenewoud, Gert Jan van der Wilt, J. Carel Bakx,† Mark C. van der Wel, Ad R. Hermus, Jacques W. Lenders, and Jaap Deinum

*Primary care (9 studies); prevalence **3.2 - 12.7%***

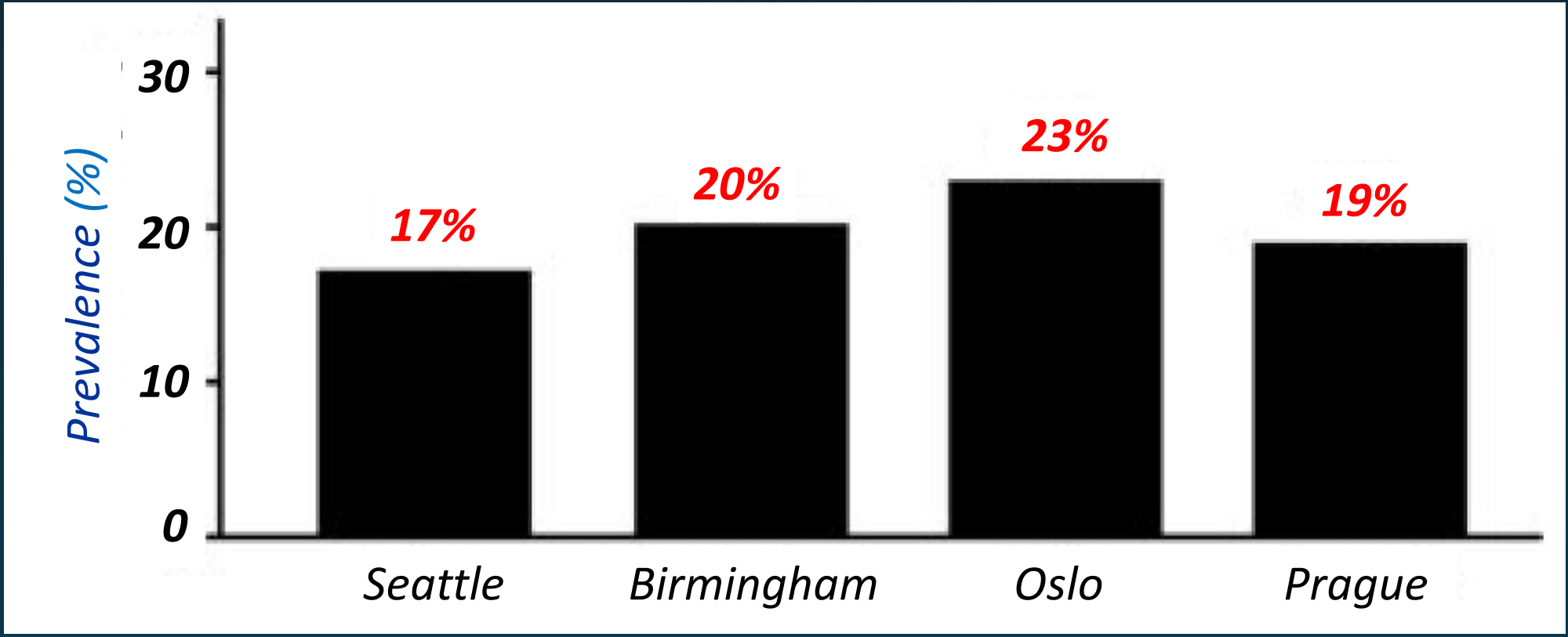
*Referral centers (30 studies; prevalence **1.0 – 29.8%***

Prevalence of primary aldosteronism according to severity of hypertension



Kayser et al. JCEM 2016;101-2826

Prevalence of primary aldosteronism in patients with resistant hypertension



Calhoun. Clin J Am Nephrol 2006;1:1039

Primary aldosteronism

- Unilateral source (adenoma = Conn) ±45% Rx: Adrenalectomy
- Bilateral source (bilateral hyperplasia) ± 55% Rx: Medication
- Glucocorticoid Remediable Aldosteronism (GRA) < 1%
  (= familial hyperaldosteronism type I)
- Adrenal carcinoma < 0.1%

Why is it useful to detect patients with primary aldosteronism? (1)

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

3838 patients with primary aldosteronism

9284 patients with primary hypertension

(similar blood pressure levels)

Odds ratios

- Stroke 2.58 (1.93-3.45)
- CAD: 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)

Monticone et al. 2018;6:41
THE LANCET Diabetes & Endocrinology

Why is it useful to detect patients with primary aldosteronism? (2)

Very effective specific treatment available

- Adrenalectomy for unilateral aldosterone excess (adrenal adenoma)
  - normalizes aldosterone secretion
  - improves blood pressure regulation
  - improves quality of life
- Medication (MRA) for bilateral aldosterone excess (hyperplasia)

Outcomes after adrenalectomy for unilateral primary aldosteronism: an international consensus on outcome measures and analysis of remission rates in an international cohort

2017;5:689

Tracy A Williams, Jacques W M Lenders, Paolo Mulatero, Jacopo Burrello, Marietta Rottenkolber, Christian Adolf, Fumitoshi Satoh, Laurence Amar, Marcus Quinkler, Jaap Deinum, Felix Beuschlein, Kanako K Kitamoto, Uyen Pham, Ryo Morimoto, Hironobu Umak
Tomaz Kocjan, Mitsuhide Naruse, Michael Stowasser, Tetsuo Nishikawa, William F Young Jr, Celso E Gomez-Sanch
Martin Reincke, for the Primary Aldosteronism Surgery Outcome (PASO) investigators*

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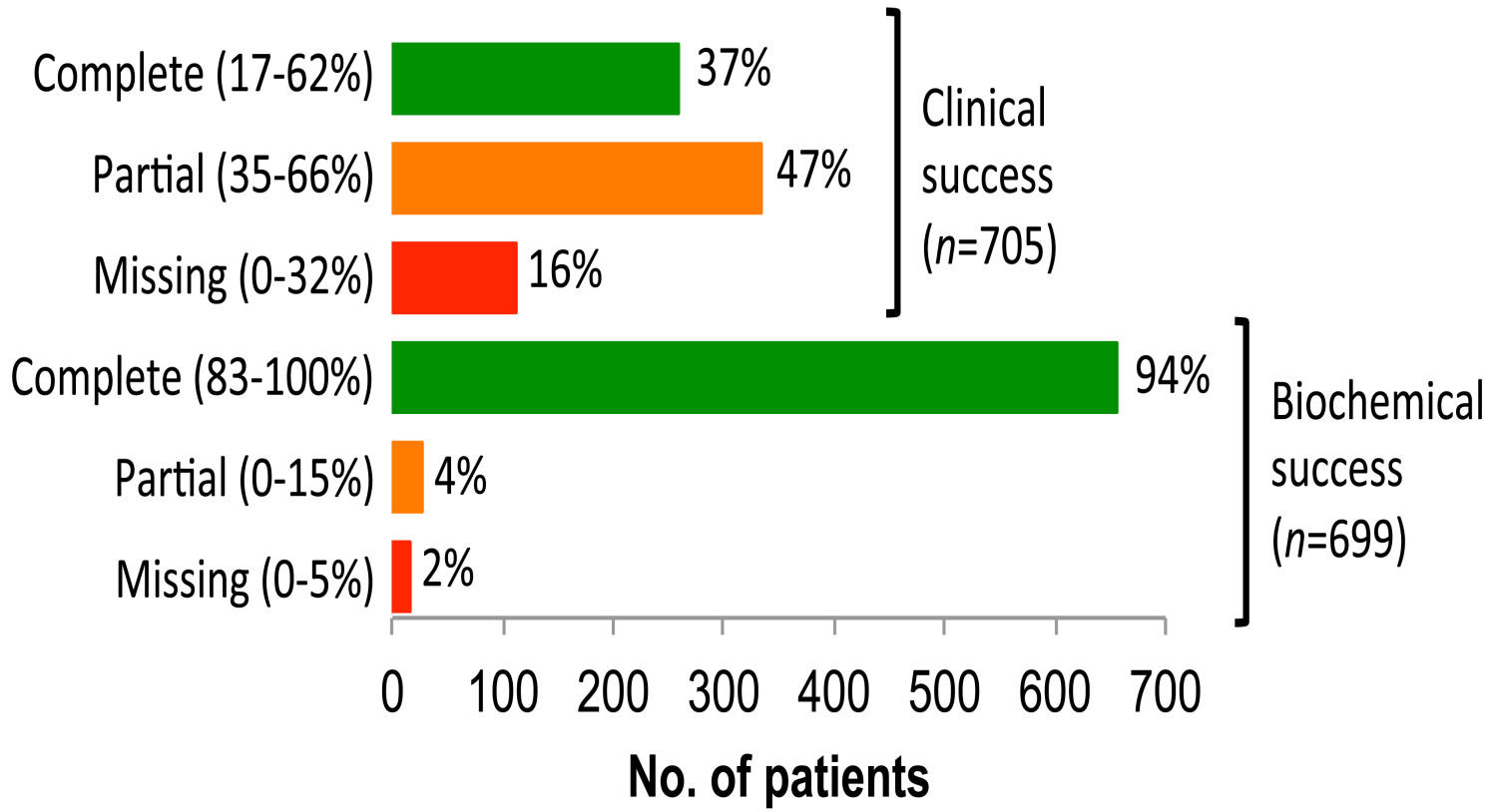


Which patients to be tested for mineralocorticoid hypertension?

- blood pressure > 150/100 mm Hg
- therapy-resistant hypertension
- hypokalemia (K < 3.5 mmol/L) or during diuretic therapy (K < 3.0 mmol/L)
- hypertension + incidentaloma
- hypertension + early onset familial hypertension or hemorrhagic stroke < 40 yrs
- 1^{e} relatives of patients with primary aldosteronism
- hypertension + OSAS

JCEM THE JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM

Funder et al.2016;101:1889

IAL FEATURE

Clinical Practice Guideline

The Management of Primary Aldosteronism: Case Detection, Diagnosis, and Treatment: An Endocrine Society Clinical Practice Guideline

What is the biochemical test strategy?

- Case finding ('screening'): plasma aldosterone and renin
- Confirming the diagnosis: unsuppressable aldosterone secretion
- Subtyping: locate the source aldosterone secretion: uni- or bilateral

Case finding ('screening ')

- plasma aldosterone ↑
- plasma renin ↓

→ Aldosterone/Renin Ratio (ARR) ↑

- mid-morning in the sitting position (5-15 min)
- renin: as activity (PRA) or concentration (PRC)
- 2 x measurement

- plasma sodium, potassium and bicarbonate: may support the diagnosis

Cut-off levels for the Aldosterone/Renin Ratio (ARR)

CAVE MEASUREMENT UNITS!!!!

aldosterone	renin	ARR
ng/dl	ng/ml/hr	< 27
ng/dl	mU/L	< 3.3
pmol/L	ng/ml/hr	< 750
pmol/L	mU/L	< 91

What about hypokalemia?

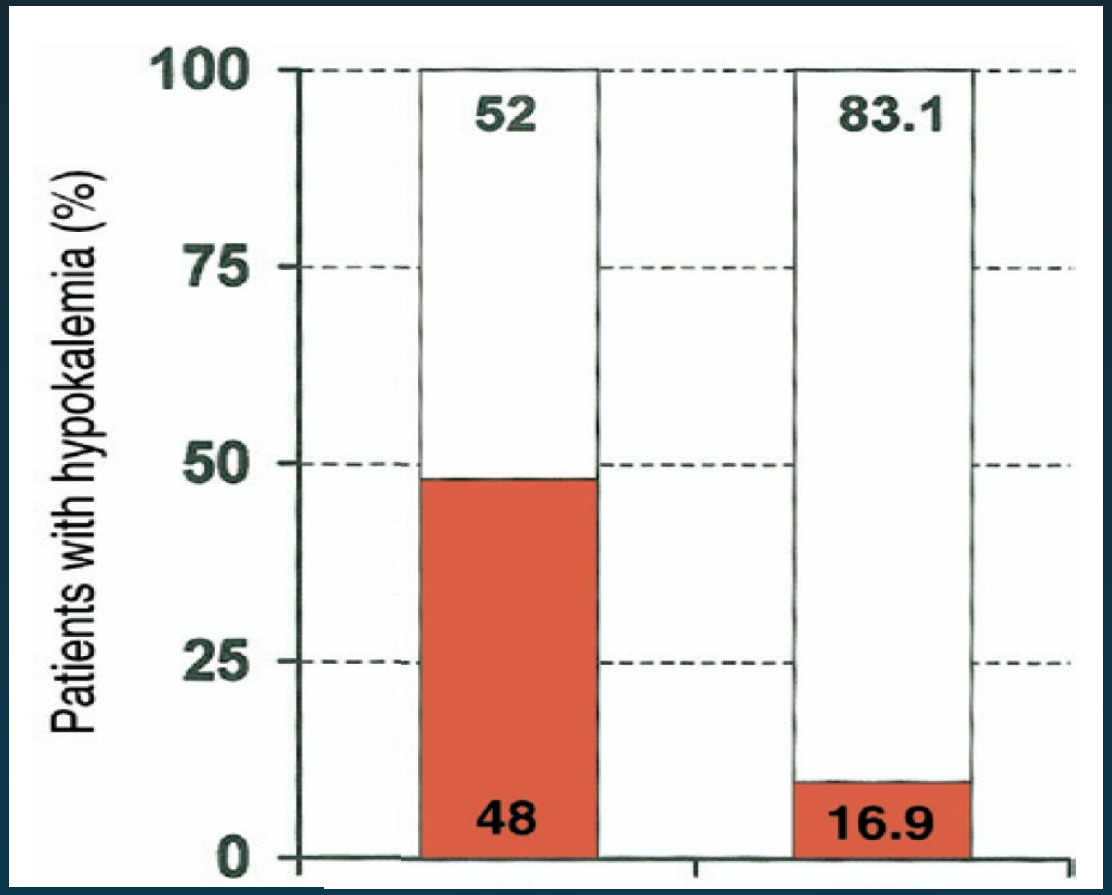
Of all patients with prim. aldo

↓

33% K: < 3.5 mmol/L

Hypokalemia can be masked by:

- *Low salt diet*
- *ACE inhibitors*
- *AII-blockers*
- *β-blockers*



Adenoma *Hyperplasia*

Rossi et al. JACC 2006;48:2293

Which pre-analytical test conditions?

- *blood sample mid-morning after 5-15 minutes rest (sitting position)*
- *liberal sodium intake, no salt restriction!*
- *if hypokalemia: should be corrected*
- *consider adjustment of medication*

	Aldosterone	Renin	ARR
diuretics	↑	↑↑	FN
ace inhibitors / ARB's	↓	↑↑	FN
renin inhibitors	↓	↑ PRC	FN
dihydropyridines	-↓	↑	FN
renin inhibitors	↓	↓↓PRA	FP
β-blockers	↓	↓↓	FP
NSAIDs	↓	↓↓	FP

no significant effects: verapamil; α–blockers; hydralazine

	Aldosterone	Renin	ARR
hypokalemia	↓	-	FN
salt restriction	↑	↑↑	FN
impaired renal function	↓	↓↓	FP
high age	↓	↓↓	FP

What to do when the patient is on medication?

- *try to stop or adjust all drugs if possible*
- *alternatives: α-adrenoceptor blockers, verapamil, hydralazine;*

	> 2 weeks	> 4 weeks
betablockers	X	
ACE-inhibitors	X	
ARBs	X	
dihydropyridines	X	
diuretics (including amiloride)		X
spironolactone / eplerenone		X
renin inhibitors		X

Confirmatory test: salt infusion testing

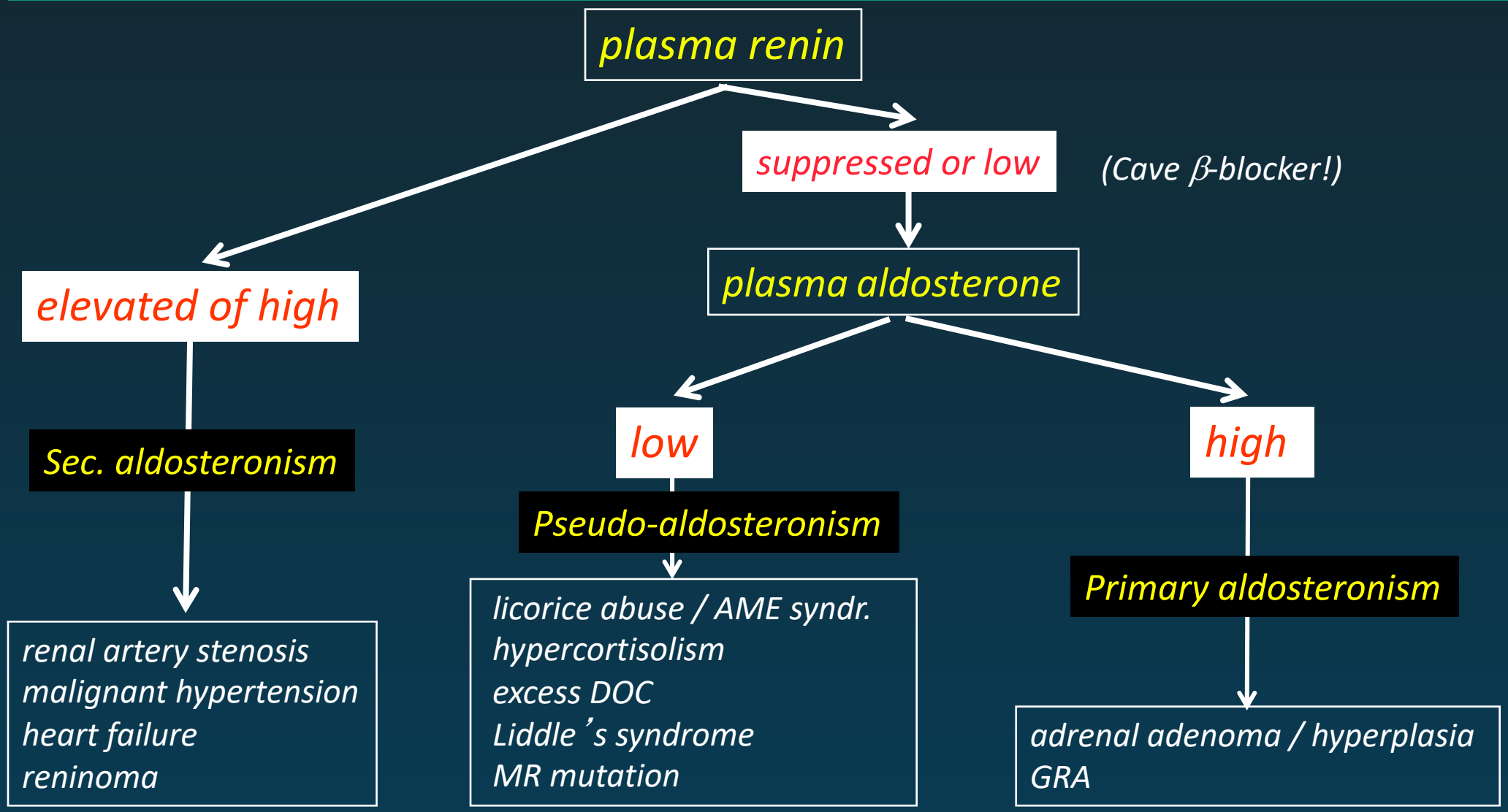
i.v. infusion 2 liter NaCl 0,9% in 4 hours.

After infusion: plasma aldosterone:

Plasma aldosterone ≤ 0.17 nmol/L : no primary aldosteronism

Plasma aldosterone > 0.17 nmol/L : confirmed primary aldosteronism

Suspicion of mineralocorticoid-type hypertension



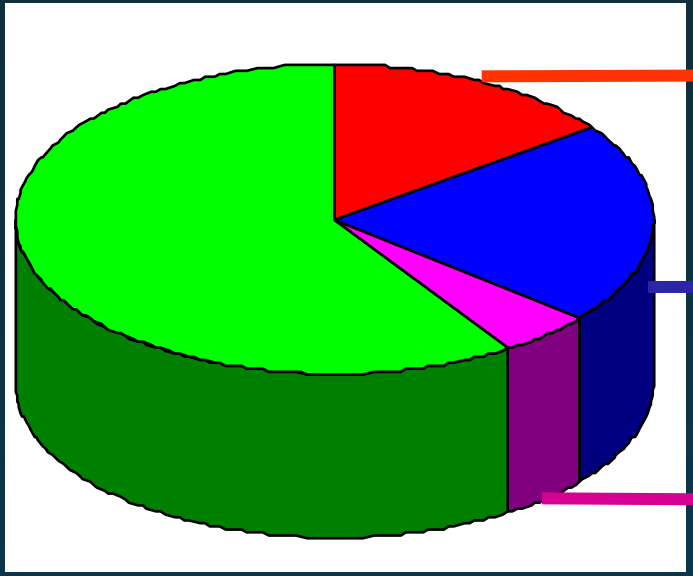
How to do subtyping (locating): uni- versus lateral PA?

- *CT scan*
- *Adrenal venous sampling (AVS)*

Meta-analysis: CT/MRI compared to AVS (Gold standard)

950 patients

Based on CT:



14.6 % unjustified adrenalectomy

19.1 % unjustified no adrenalectomy

3.9 % adrenalectomy on wrong side

If only CT/MRI was used: 37.8% incorrect therapeutic decision

Kempers et al. Ann Int Med 2009;151:329-37

Advatages and disadvantages

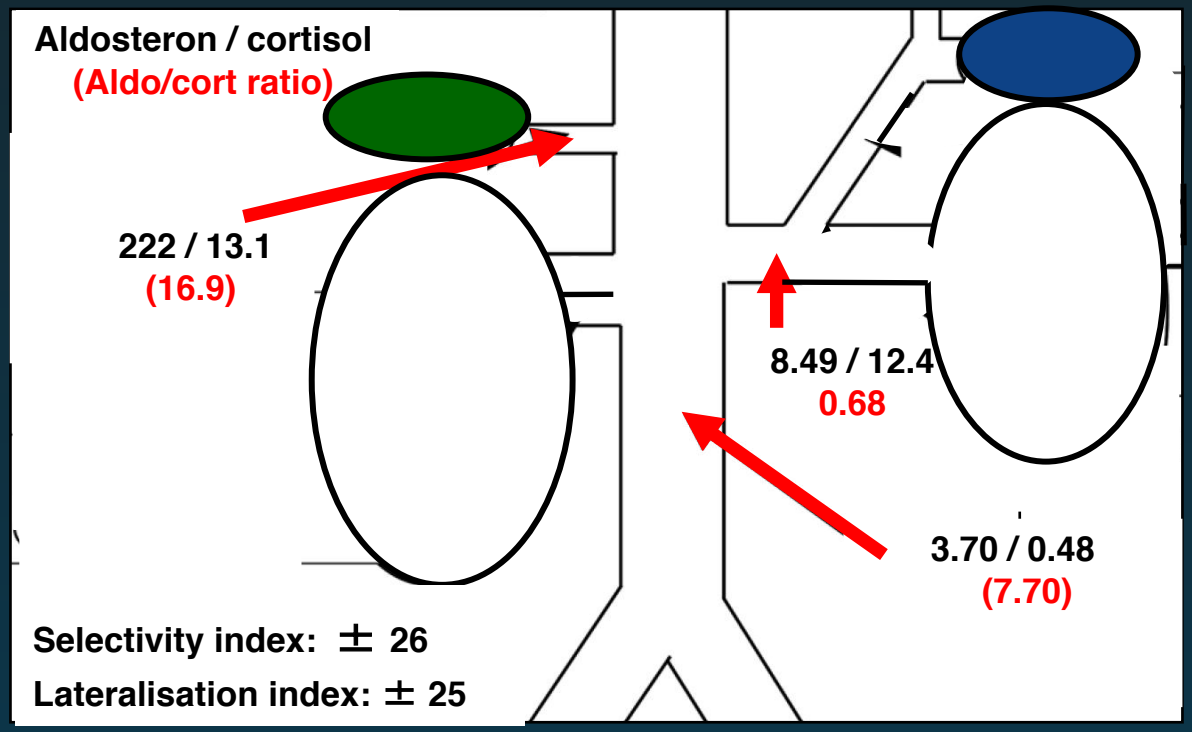
CT scan

+ Widely available
+ Non-invasive and cheap
+ Patient-friendly
- Can not distinguish functional from non-functional adenoma
- May miss small adenoma (sensitivity: 25% if < 1cm)
- Few prospective studies that assessed diagnostic accuracy

AVS: adrenal venous sampling

+ Determines source of aldosterone
+ Few complications (< 0.6%)
- Invasive and expensive
- Only in specialised centers
- Patient unfriendly
- Lack of procedural standardisation
- Uncertain diagnostic accuracy from prospective studies using gold standard

Adrenal venous sampling (AVS)



1. *to distinguish:*

   - *unilateral from bilateral aldosterone-producing source*

   - *hormonally active adenoma from incidentaloma*

2. *to diagnose microadenomas*

Clinical Practice Guideline Endocrine Society 2016

SPECIAL FEATURE

Clinical Practice Guideline

The Management of Primary Aldosteronism: Case Detection, Diagnosis, and Treatment: An Endocrine Society Clinical Practice Guideline

*3.2 **We recommend** that when surgical treatment is feasible and desired by the patient, an experienced radiologist should use adrenal venous sampling (AVS) to make the distinction between unilateral and bilateral adrenal disease **(1 / ⊕⊕⊕O)**.*

We suggest** that in younger patients (< age 35) with spontaneous hypokalemia, marked aldosterone excess, and unilateral cortical adenoma on adrenal CT scan, AVS may not be needed before proceeding to unilateral adrenalectomy. **(2 / ⊕OOO)

A Randomized Trial comparing Adrenal Vein Sampling and Computed Tomography Scan for subtyping primary aldosteronism

	CT (n=92)	AVS (n=92)	p
Defined daily dose	**3.0** (1.0-5.0)	**3.0** (1.1-5.9)	0.52
Number of antihypertensive drugs	**2** (1-3)	**2** (1-3)	0.87
24 h ABPM			
Systolic (mm Hg)	**127** (120-138)	**128** (121-135)	0.93
Diastolic (mm Hg)	**80** (75-86)	**81** (76-85)	0.76
Target BP reached	**43%**	**45%**	1.00
Persistent PA	**20%**	**11%**	0.25

Dekkers et al. Lancet Diabetes & Endocrinology 2016; 4: 739-46

THE LANCET Diabetes & Endocrinology
Volume 4, Issue 9, September 2016, Pages 739-746

How to treat unilateral PA?

Retroperitoneoscopic adrenalectomy

How to treat bilateral PA?

1. MR antagonists
   - Steroid MR antagonists
     - Spironolactone, Eplerenone
   - ~~Non-steroid MR antagonists~~
     - ~~Dihydropyridine-based: BR-4682; Bay-94-8862, etc~~

2. Diuretics: low-dose thiazides, triamterene and amiloride (as add-on)

3. ~~Aldosterone synthase inhibitors: Fadrozole; FAD286; LCI699~~

Summary

Primary aldosteronism: the most prevalent cause of secondary hypertension

- *diagnosing and treating is very beneficial for the patient*
- *screening: plasma aldosterone and renin: sitting / mid-morning, 2x*
- *correct eventual hypokalemia; adjust interfering medication*
- *differentiate prim. aldosteronism from pseudo-aldosteronism*
- *use confirmation testing in patients with positive ARR*
- *locate source of aldosterone by CT and / or adrenal venous sampling*
- *retroperitoneoscopic adrenalectomy is first choice*