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Hyperaldosteronism: An under-recognized, but prevalent contributor to hypertension

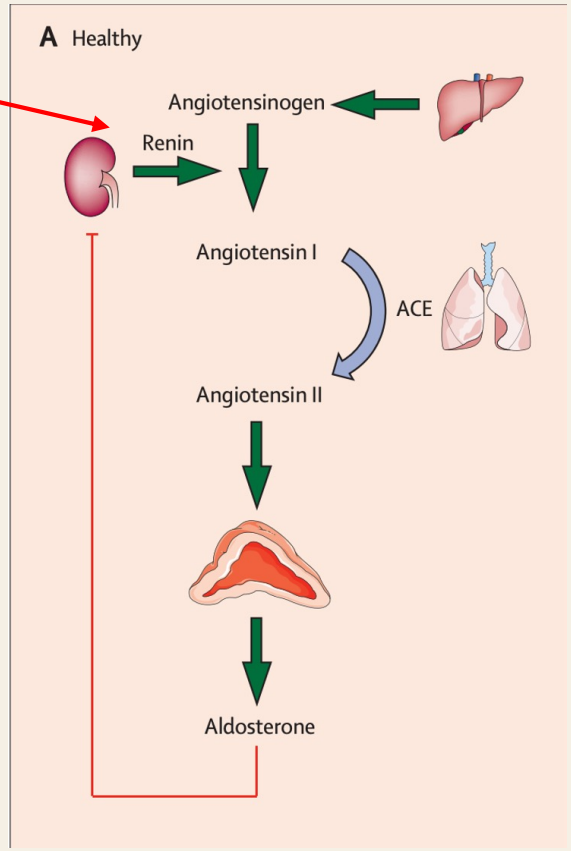
Nandi Shah, MD
Division of Endocrinology
UC San Diego

Learning Objectives

1. Review the regulation and actions of aldosterone
2. Recognize the high prevalence of underdiagnosed aldosteronism
3. Show that hyperaldosteronism contributes to a large portion of “essential” hypertension
4. Re-define primary aldosteronism (PA) from a categorical disease to a syndrome across a continuum of severity
5. Review diagnostics and management of overt, primary hyperaldosteronism

Renin-**dependent** aldosteronism

Volume depletion / hypotension



El-Asmar N. Med Clin North Am 2021

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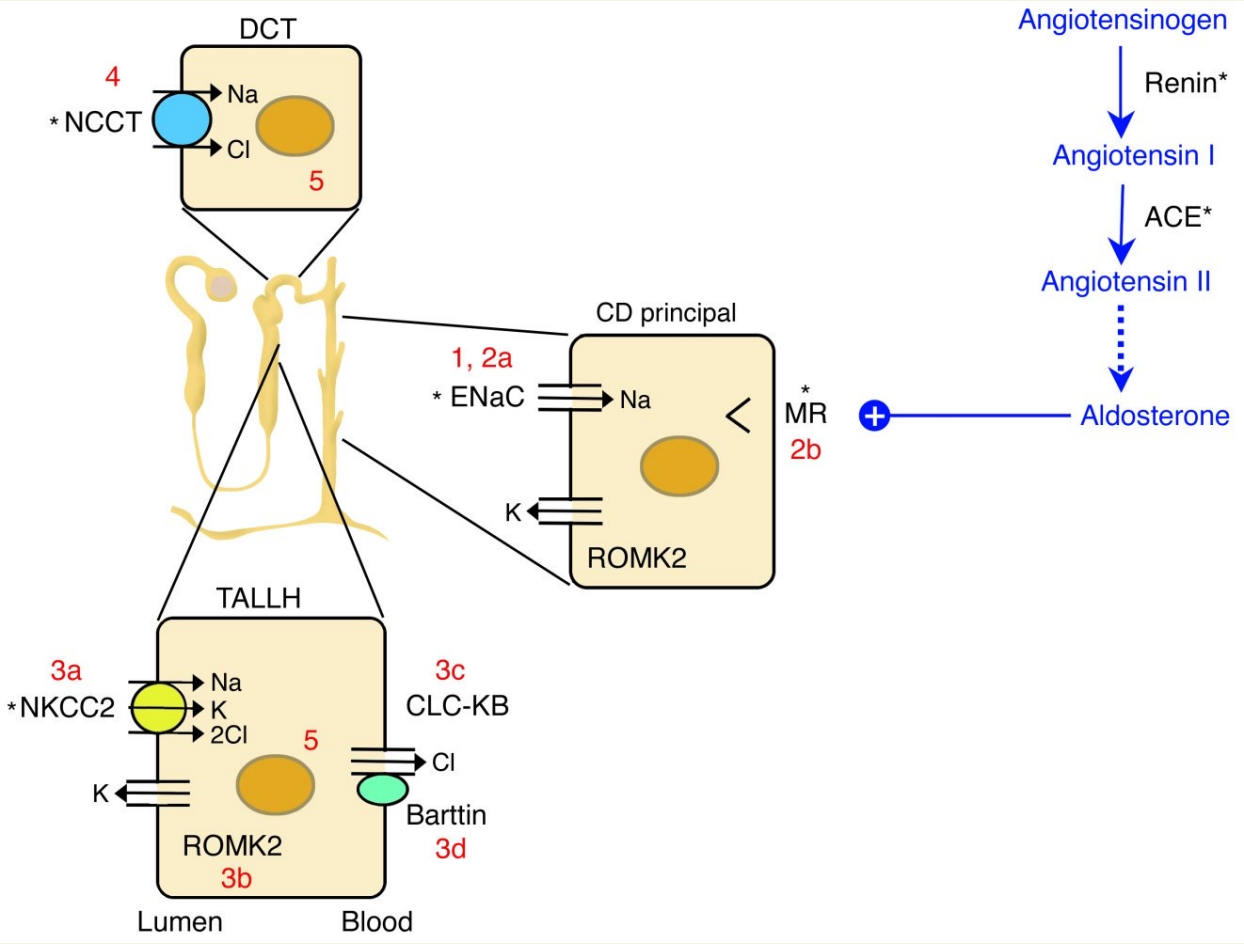
DCT
4
* NCCT
Na
Cl
5
CD principal
1, 2a
* ENaC
Na
K
ROMK2
*
MR
2b
Angiotensinogen
Renin*
Angiotensin I
ACE*
Angiotensin II
Aldosterone
TALLH
3a
*NKCC2
Na
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2Cl
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ROMK2
3b
3c
CLC-KB
Cl
Barttin
3d
Lumen
Blood

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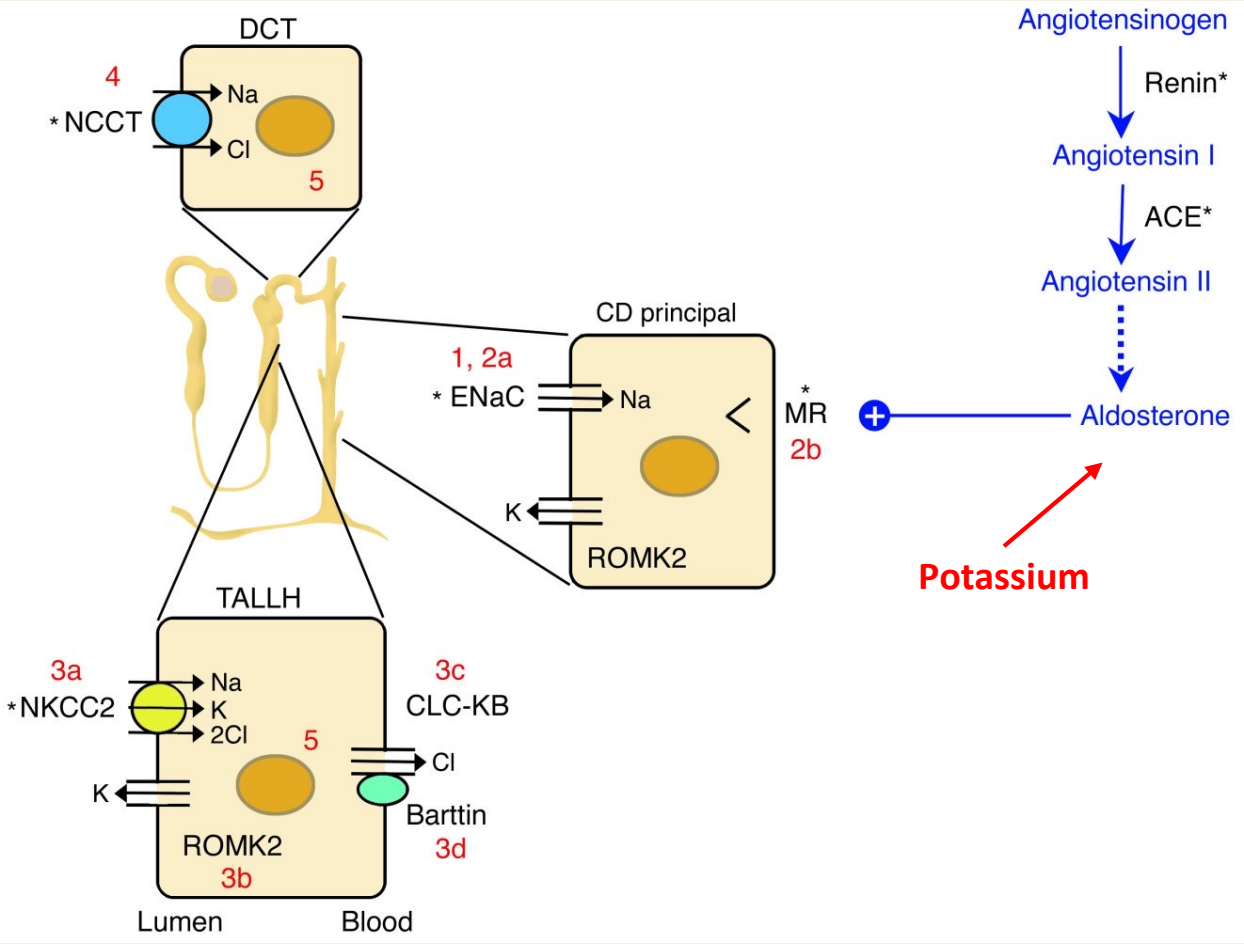
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Renin-**independent** aldosteronism

- Jerome Conn, MD

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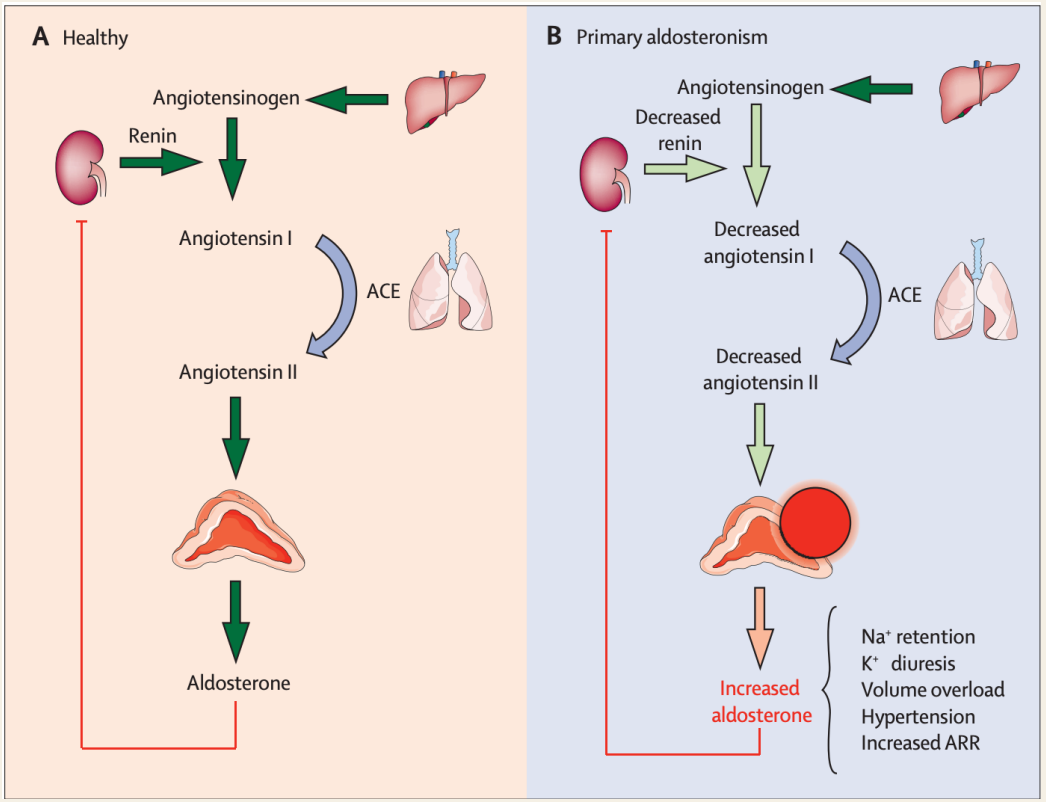
Renin-**independent** aldosteronism



MR is also expressed in myocardium, and vascular endothelium

When already sodium/volume expanded, aldosterone-mediated mineralocorticoid activation is pathological and induces **cardiovascular injury**

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Definition of primary hyperaldosteronism

- Inappropriate, Relatively non-suppressible, Renin independent aldosterone production
  - Results in excessive activation of the renal mineralocorticoid receptor (MR) & vicious cycle of volume expansion

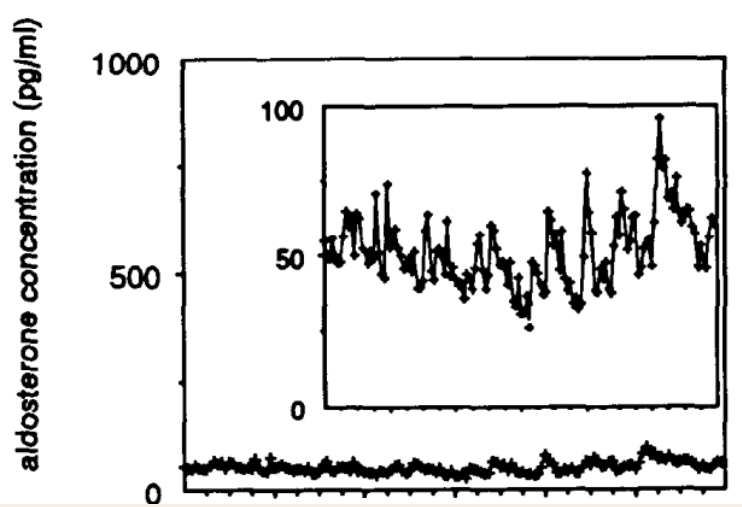
  => can increase BP, increases K+ /H+ excretion, increases risk for CV disease independent of BP (extra-renal MR)
- Hallmark Biochemical Diagnosis:

  Suppression of Renin

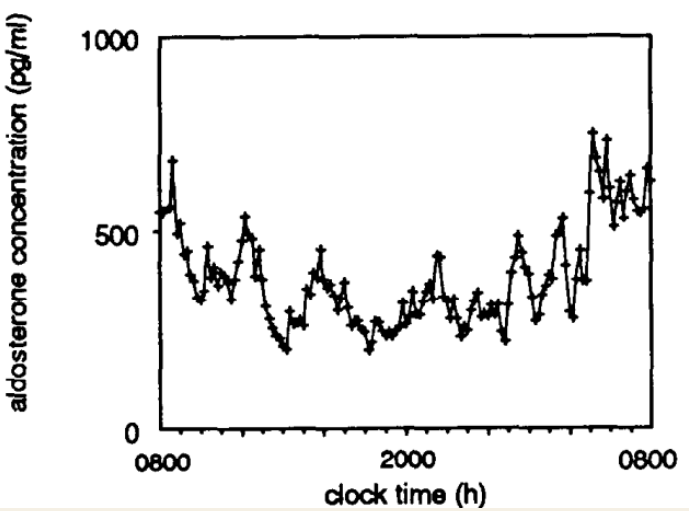
  Inappropriate/Dysregulated Production of Aldosterone

Variability of Aldosterone Production

Aldosterone release in normal subject on high sodium diet



Aldosterone release in primary hyperaldosteronism



Siragy et al. JCEM 1995

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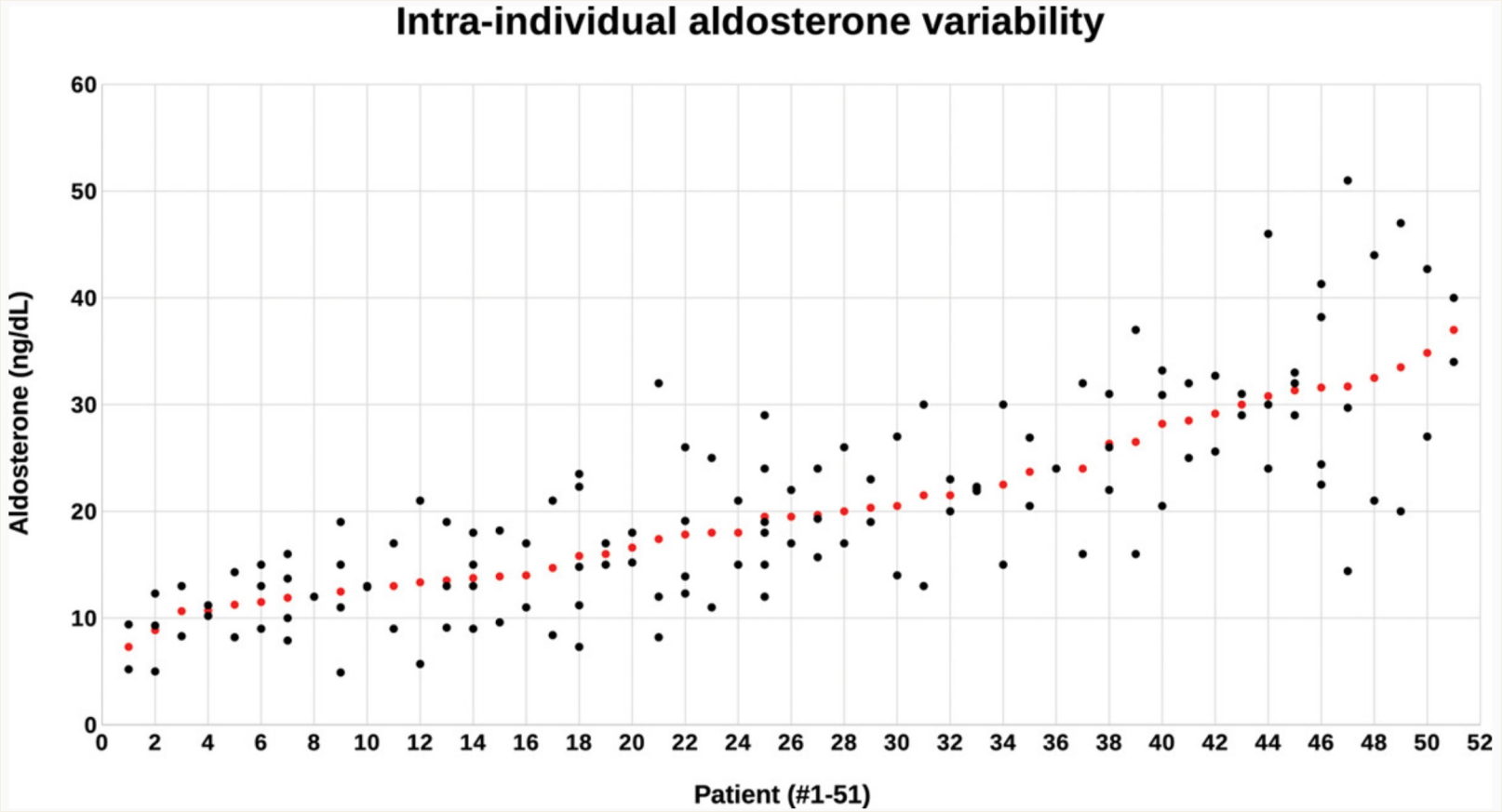
Intra-individual aldosterone variability
Aldosterone (ng/dL)
0
10
20
30
40
50
60
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40 42 44 46 48 50 52
Patient (#1-51)

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LC-MS Aldosterone Assays

- Current threshold values for primary aldosteronism diagnostic testing are based on measuring aldosterone using immunoassays
- Quantification of PAC by LC-MS assays yields lower values
- Median serum $PAC_{LC\text{-}MS/MS}$ was **27.8% lower** ($P < 0.05$) than plasma PAC_{RIA} in 164 pairs of fludrocortisone suppression testing samples

Guo et al. JCEM 2018

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Prevalence of primary aldosteronism

	Prevalence of primary aldosteronism confirmed by suppression testing
Hypertension in a primary care setting	
Buffolo et al (2017)[15]	5·9% (range 3·2–12·7)
Hypertension in people referred to a referral centre	
Buffolo et al (2017)[15]	7·2% (range 0·7–21·9)
Stage 1 hypertension	
Monticone et al (2017)[16]	44/1133 (3·9%)
Rossi et al (2006)[12]	32/484 (6·6%)
Brown et al (2020)[13]	15·7% (95% CI 8·6–27·0)
Stage 2 hypertension	
Monticone et al (2017)[16]	40/413 (9·7%)
Rossi et al (2006)[12]	54/349 (15·5%)
Brown et al (2020)[13]	21·6% (95% CI 16·9–22·9)
Stage 3 hypertension	
Monticone et al (2017)[16]	15/126 (11·9%)
Rossi et al (2006)[12]	29/154 (19·0%)

Stage 1 HTN: 130-139/80-89 → **5%**

Stage 2 HTN: 140-179/90-109 → **10-15%**

Stage 3 HTN: >180/110→ **12-19%**

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Reincke M, et al. Lancet Diabetes Endocrinol. 2021

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Resistant hypertension	
Calhoun et al (2002)[17]	18/88 (20·5%)
Douma et al (2008)[18]	182/1616 (11·3%)
Parasiliti-Caprino et al (2020)[19]	32/110 (29·1%)
Brown et al (2020)[13]	22·0% (95% CI 17·2–26·8)
Hypertension and hypokalaemia	
Burello et al (2020)[20]	226/804 (28·1%)
Adrenal incidentaloma	
Mantero et al (2000)[21]	16/1004 (1·6%)
Li et al (2017)[22]	82/1941 (4·2%)
Hypertension and atrial fibrillation	
Seccia et al (2020)[23]	31/73 (42·5%)
Hypertension and diabetes mellitus	
Murase et al (2013)[24]	14/124 (11·3%)
Hu et al (2020)[25]	49/256

Data are n/N (%), median (range), or median (95% CI).

~20-30%

<3% screened for PA

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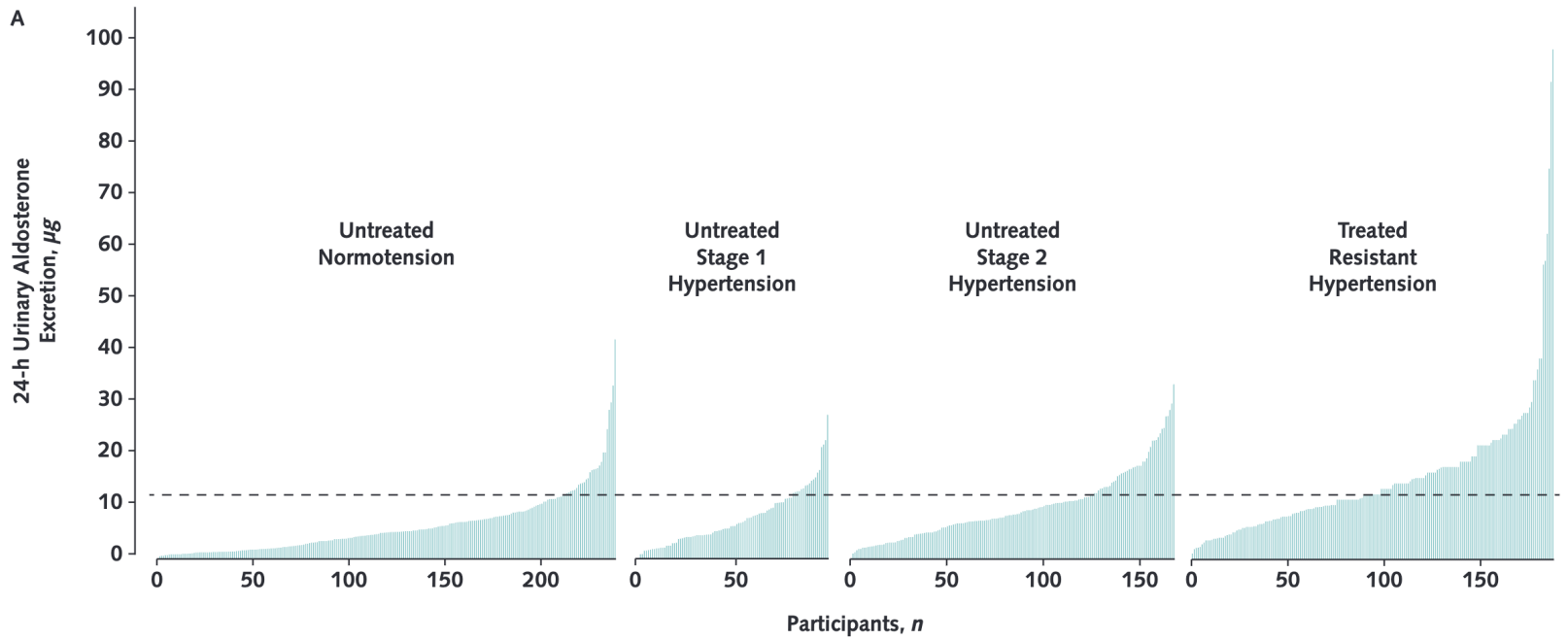
Reincke M, et al. Lancet Diabetes Endocrinol. 2021

Prevalence of Overt Primary Hyperaldosteronism

Figure 2. Distribution of renin-independent aldosterone production, by blood pressure category.



Brown et al. Annals of Int Med 2020

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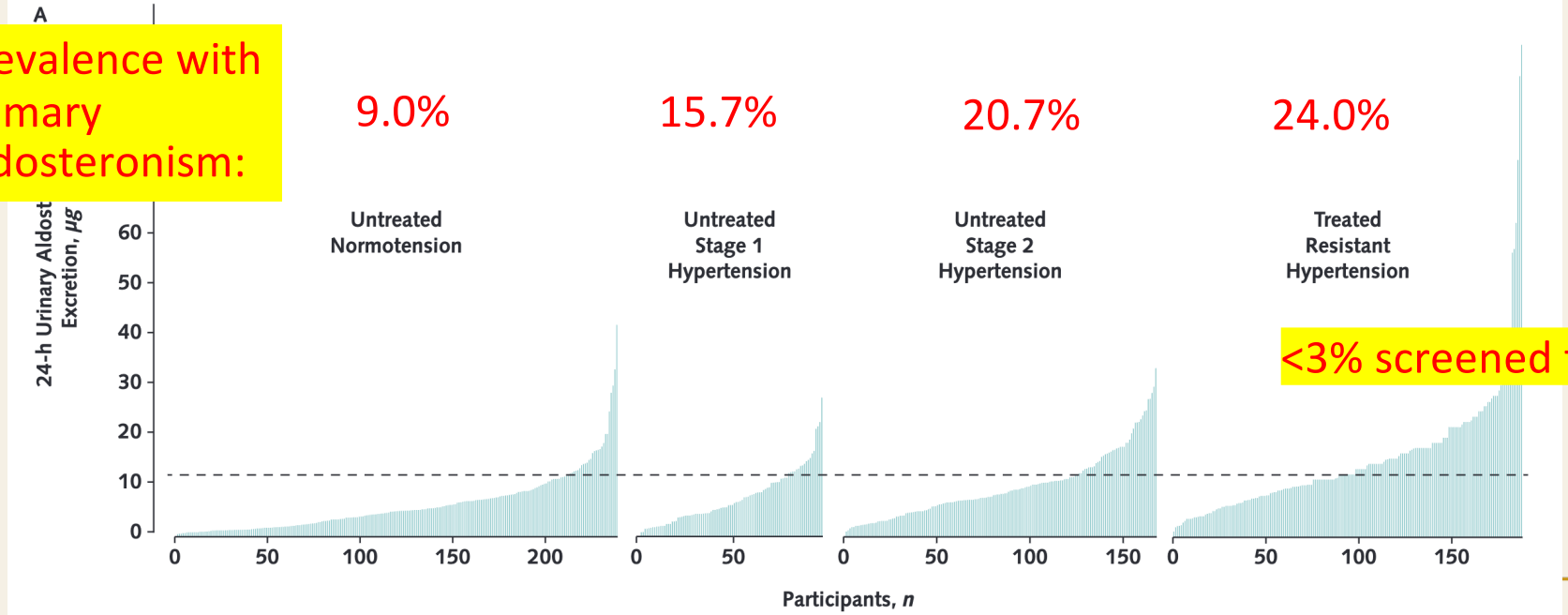
Prevalence of Overt Primary Hyperaldosteronism

Prevalence with Primary Aldosteronism:



<3% screened for PA

Brown et al. Annals of Int Med 2020

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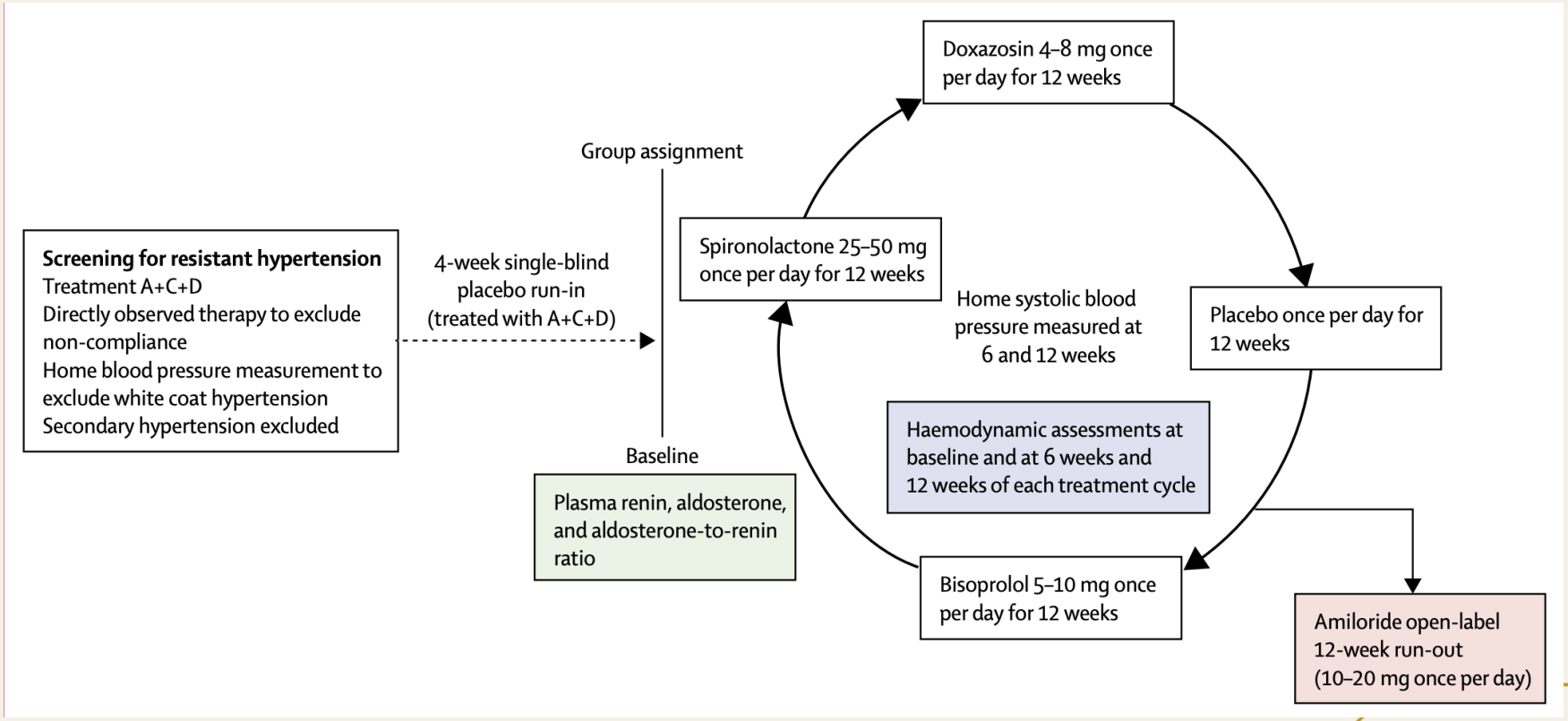
Pathway-2: best 4th agent to add for resistant hypertension



Williams, et al. Lancet 2018

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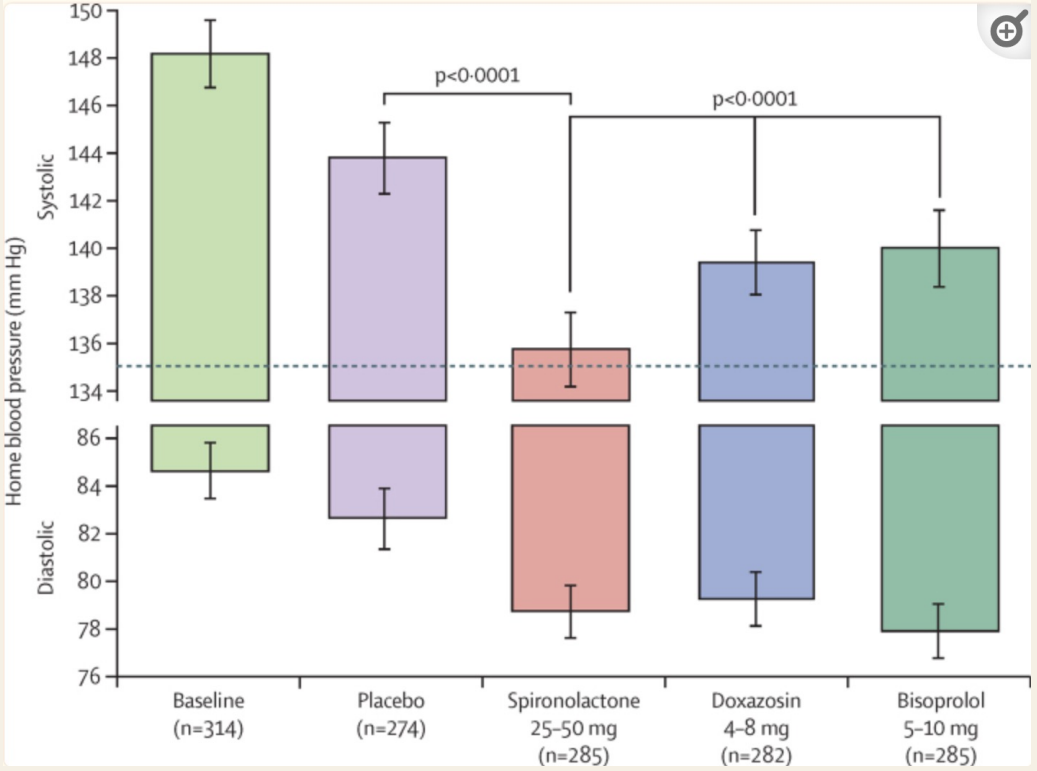
Pathway-2: best 4th drug is spironolactone



Williams, et al. Lancet 2015

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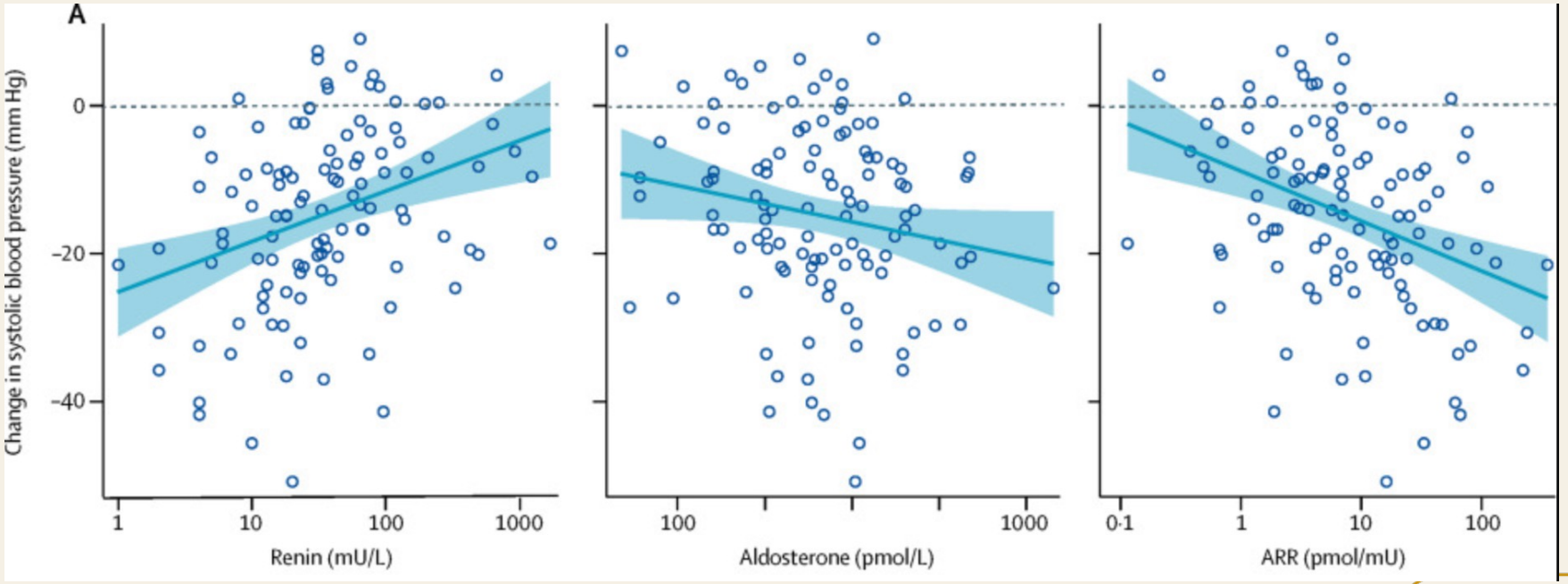
Spironolactone works best with renin-independent aldosteronism



Williams, et al. Lancet 2018

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Prevalence of Hyperaldosteronism

- Overt, “classic” primary hyperaldosteronism has a high and mostly under-diagnosed prevalence

- Even in patients who do not meet “classic” primary hyperaldosteronism diagnostic thresholds:
  - There is a continuum of renin-independent aldosterone production that contributes to HTN, ranging from mild to severe
  - These patients respond preferentially to MRA

Screening Guidelines for Hyperaldosteronism (JCEM, 2016 clinical practice guidelines)

- Sustained blood pressure > 150/100

  +

  - Uncontrolled HTN on 3 antihypertensives, including a diuretic
  - Controlled HTN on 4+ antihypertensives
  - Spontaneous or diuretic induced hypokalemia
  - Adrenal incidentaloma
  - Sleep apnea
  - Family history of early onset HTN or CVA (<40 years)
  - First degree relative with primary aldosteronism

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Funder JW, et al. J Clin Endocrinol Metab. 2016.

Liberalized Indications to Screen for Primary Aldosteronism

Anyone with:

1) **Severe or Resistant Hypertension**

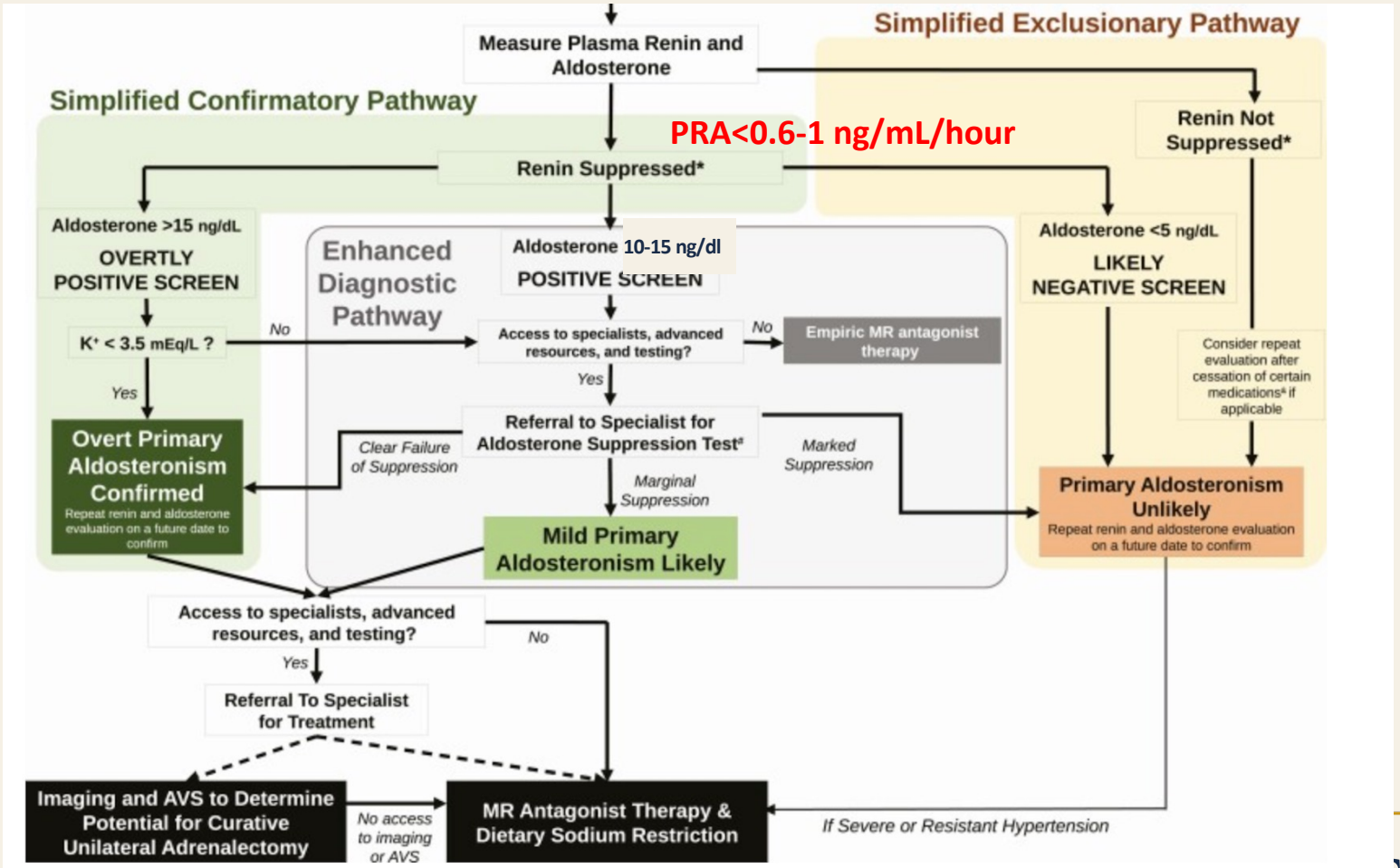
   or

2) **Any spontaneous hypokalemia**

Regardless of BP, HTN + adrenal mass or sleep apnea, or, suggestive family history

Comorbidities in Primary Aldosteronism

- Independent of blood pressure, increased organ damage
  - LVH, cardiac fibrosis, renal hyperfiltration, albuminuria, and glomerulosclerosis
- Higher incidence of stroke, myocardial infarction, HF, Afib, and CKD than in patients with essential hypertension and similar blood pressure
- Associated with worsening of OSA, insulin resistance, hypercalciuria causing secondary hyperparathyroidism, and all cause mortality



Vaidya, et al. J Clin Endocrinol Metab. 2021.

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Drugs & conditions that interfere with ARR

FALSE POSITIVE SCREENING TEST			
Anti-Hypertensive Drugs that Frequently Cause False-positive ARR[c]			
	Renin	**Aldo**	**ARR**
Beta-Blockers	↓↓	↓	↑
Clonidine/Alpha-Methyl Dopa	↓↓	↓	↑
Aliskiren[a]	↓↓	↓	↑
Other Conditions			
Advancing age/reduced renal function	↓↓	↓	↑
FHH	↓↓	↓↔	↑
Women under estrogen contraceptive agents[b]	↓	↑	↑
Anti-inflammatory drugs	↓↓	↓	↑

FALSE NEGATIVE SCREENING TEST			
Anti-Hypertensive Drugs that Frequently Cause False-negative ARR[c]			
	Renin	**Aldo**	**ARR**
MRAs and ENaC blockers	↑↑	↑	↓
Thiazides and Loop Diuretics	↑↑	↑	↓
Anti-Hypertensive Drugs that May Cause False-negative ARR			
ACE-Is, ARBs and Aliskiren[b]	↑	↓	↓
Other Conditions			
Hypokalemia	↔	↓	↓
Concomitant Malignant or RVH	↑↑	↑	↓
Pregnancy	↑↑	↑	↓

Superiority of Surgical > Medical Treatment

Surgery may be more effective at:

- Controlling blood pressure
- Reducing number of hypertensive drugs
- Reversing left ventricular hypertrophy
- Reducing the risk of atrial fibrillation
- Reducing CKD
- Normalizing quality of life
- Lowering long term mortality

Katabami J Hypertens 2019
Rossi Hypertension 2013
Rossi Hypertension 2018
Hundemer Hypertension 2018
Ahmed JCEM 2011
Chen J Endoc Soc 2019

Medical therapy for Hyperaldosteronism

Compound	Mechanism of action	Starting dose per day	Application schedule	Typical side-effects
Spironolactone	Competitive mineralocorticoid receptor antagonist (also a progesterone receptor agonist and an androgen receptor antagonist)	12·5–25 mg	Once a day	In males, gynecomastia and impotency; in females, menstrual irregularities; in both sexes, hyperkalaemia
Eplerenone	Competitive mineralocorticoid receptor antagonist	50 mg	Twice a day	Hyperkalaemia
Amiloride	Epithelial sodium channel blocker	5–20 mg	Twice a day	Hyperkalaemia, nausea, stomach pain, and loss of appetite

Treatment goals:

1. Normalize BP and serum potassium

2. Un-suppress renin

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Reincke, et al. Lancet Diabes Endocrinol 2021

Summary of Key Points

- Primary aldosteronism is highly prevalent and underdiagnosed
- Hyperaldosteronism contributes to a large portion of “essential” hypertension
- Primary aldosteronism (PA) is not a categorical disease, but rather a syndrome across a continuum of severity
- Diagnostics and management of overt, primary hyperaldosteronism including screening, confirmatory testing, imaging, AVS, surgical & medical therapy