Primary Hyperaldosteronism

a horse in zebra's clothing

Grand Rounds 02-10-2025

Stuti Fernandes, MD (endocrinologist)

Disclosures

🚨 🚨 🚨

THERE WILL BE
A TEST AT THE END

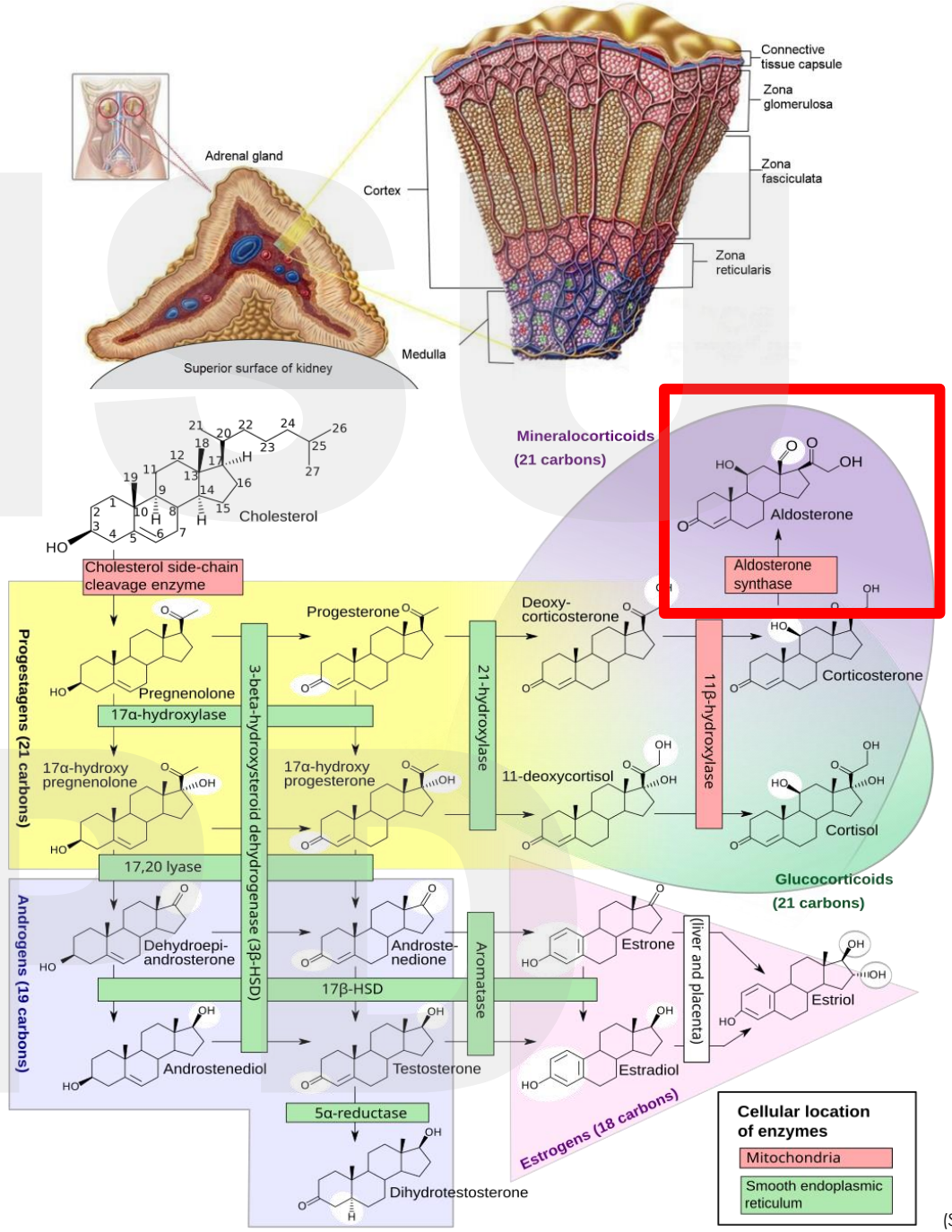
🚨 🚨 🚨

Objectives

- Define primary hyperaldosteronism (PA) and differentiate it from essential HTN
- Screen for PA
  - Convince you to screen at least 1 patient this month
- Diagnose PA
  - Role adrenal vein sampling (AVS)
- Treat PA

What is Aldosterone

- Mineralocorticoid
- Synthesized from cholesterol
- important in salt, potassium and blood pressure regulation



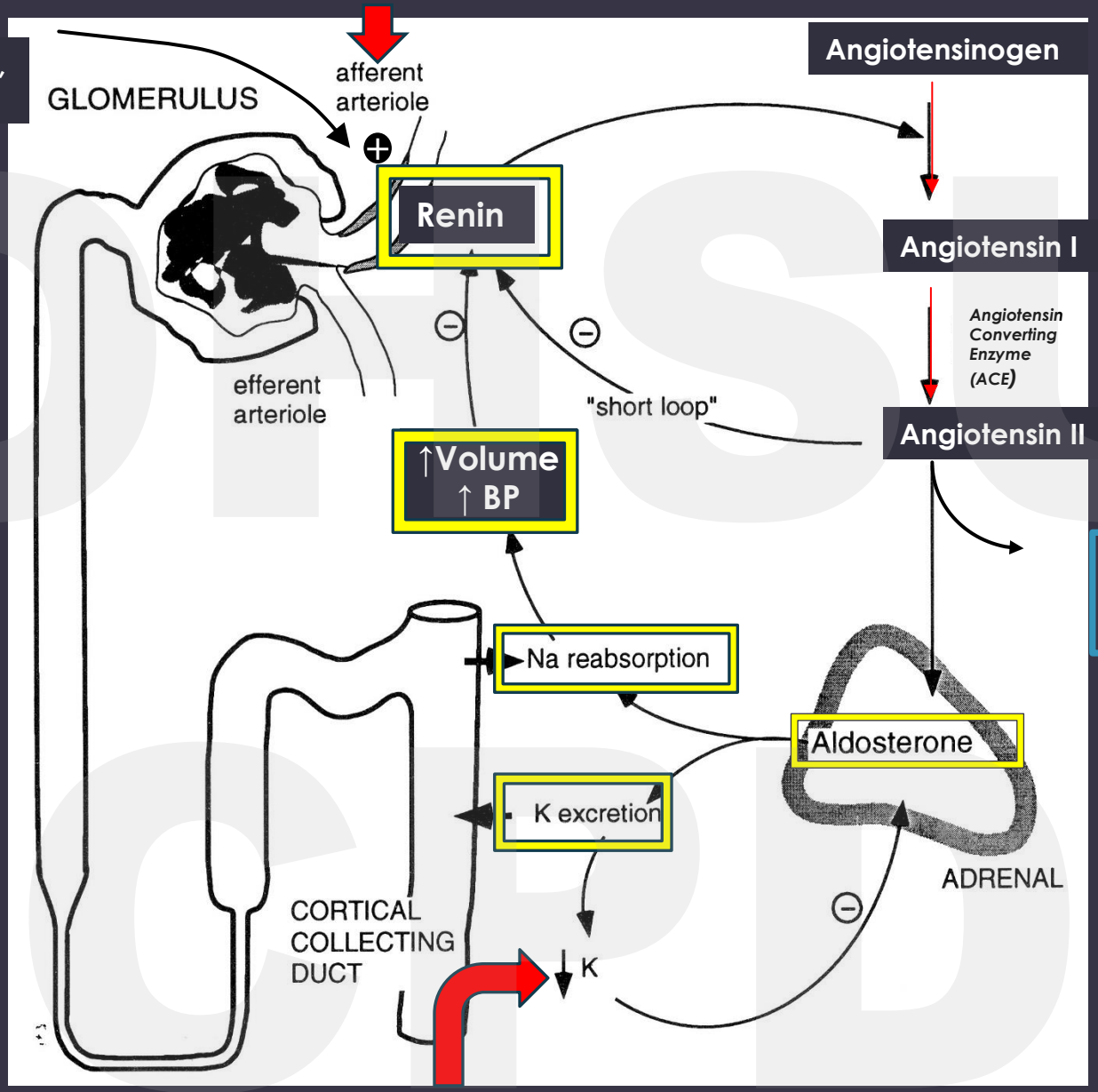
(Aldosterone, 2024)
(Steroidogenic enzyme, 2024)

Hypovolemia, Hypotension

CHEAT SHEET:

↑ Aldosterone

- ↓ K+
- ↑ Na +
- ↑ blood pressure



- Increase thirst
- Release ADH/VP

Renin- Angiotensin-Aldosterone System

Primary Hyperaldosteronism

- Also known as Conn's syndrome (first described in 1955)
  - Specifically from an adrenal adenoma
- Adrenal gland(s) produce too much aldosterone autonomously

(Liu et al., 2020) (Li, Kong, Yang, & Wang, 2004)

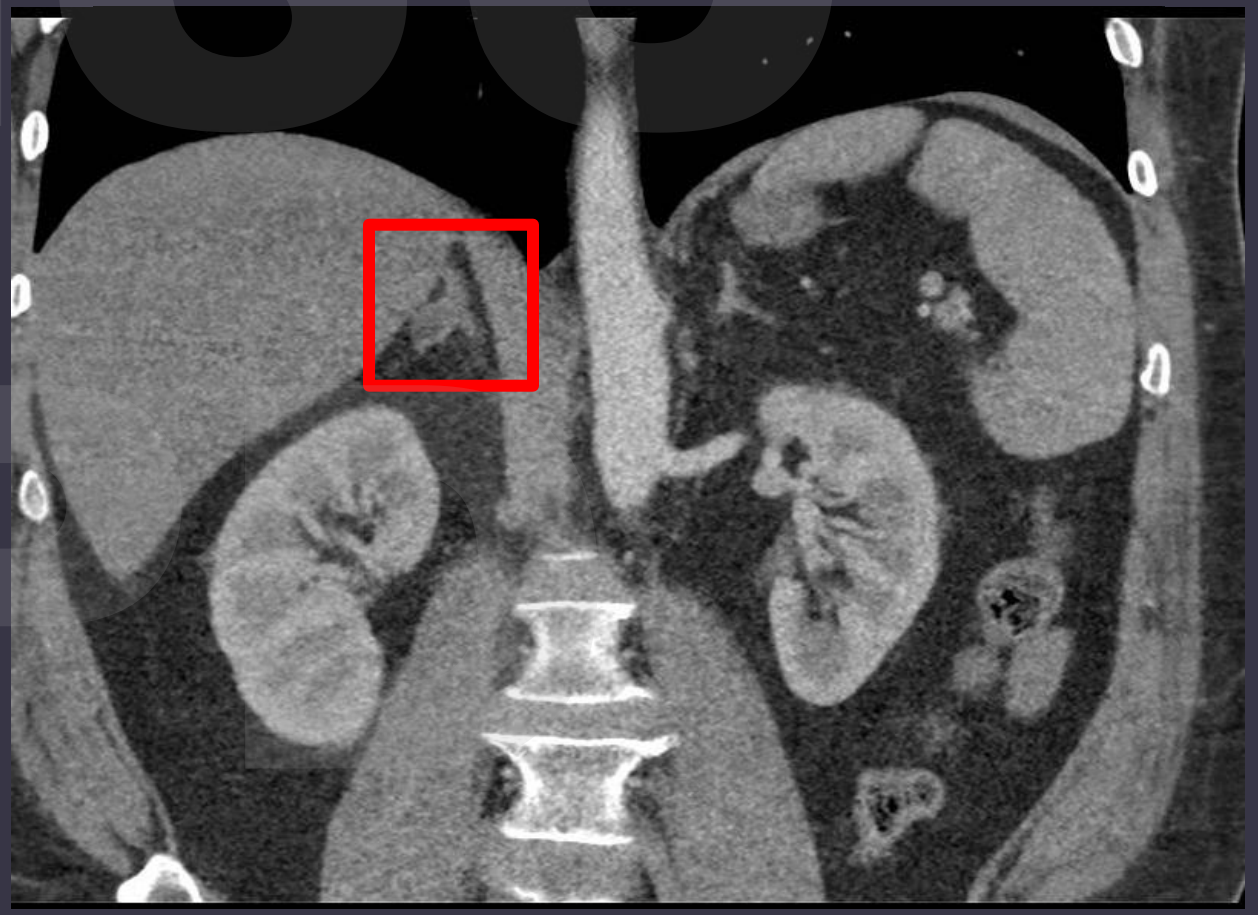
Dr Bill Young

(Young, 2003) (Young, 2007)

Mr BP: Presentation

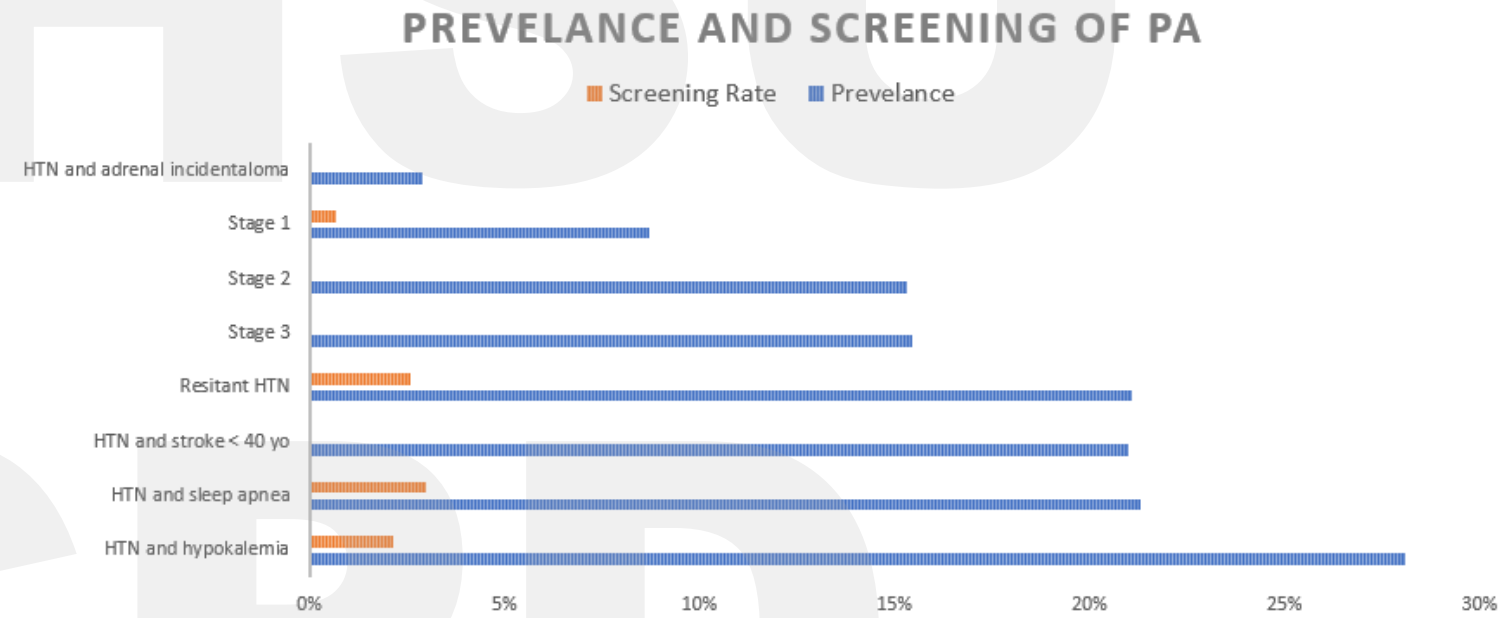
Mr BP is a 50 year old male

- **Adrenal nodule (1.5 x 0.9 cm)**
- **High blood pressure for 10 years**
- **Intermittent hypokalemia**
- Meds:
  - Potassium supplementation (current)
  - Spironolactone stopped due to breast pain
  - Tolerated eplerenone in the past
- Blood pressure was initially 160-180/100s
- Now blood pressure 140/80s on lisinopril and amlodipine



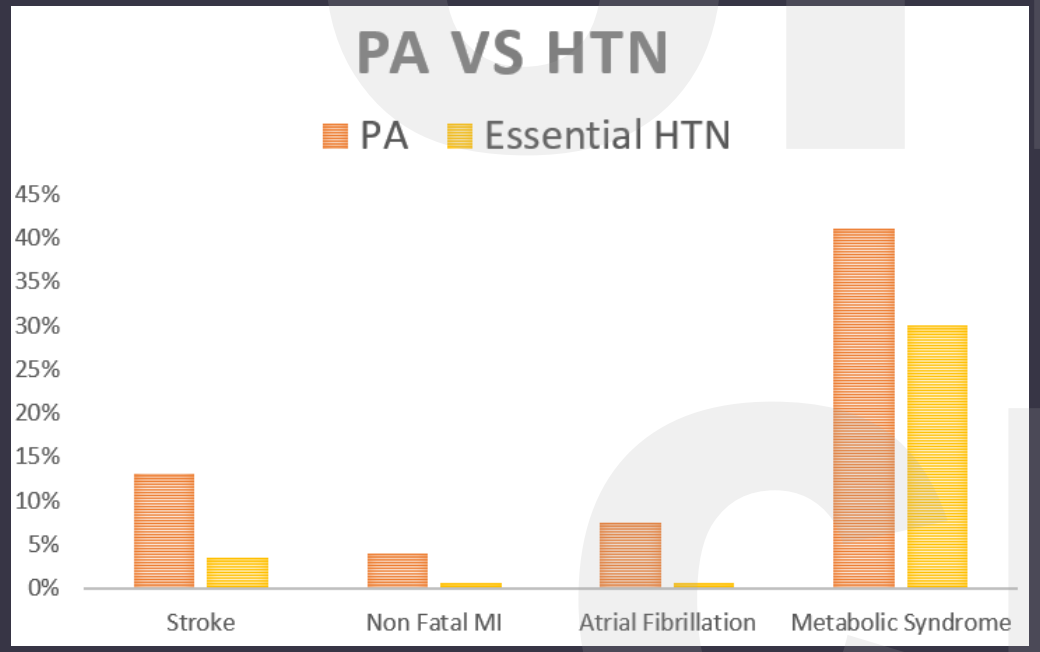
Underrecognized and Underdiagnosed

- Most common curable form of secondary hypertension
- "**woefully** underdiagnosed as a cause of hypertension and end-organ damage"
- Initially thought to be rare with a prevalence of 0.5%
- Estimated prevalence of PA 0.7%-8.5% in primary care and 4.7-24% in HTN referral centers

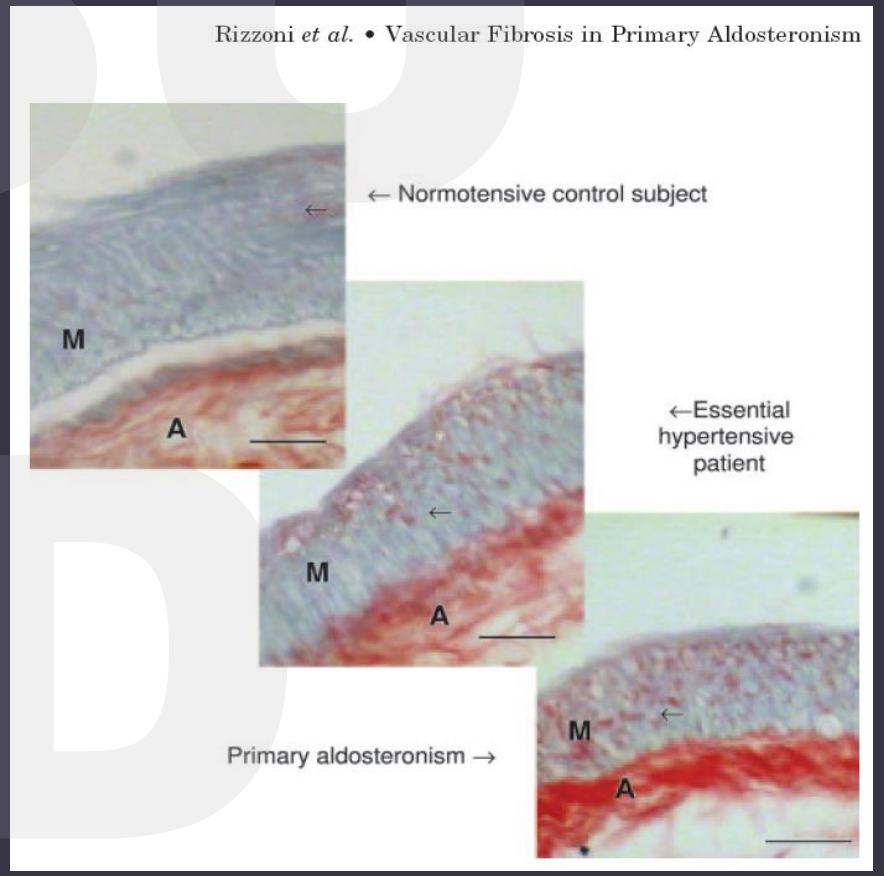


(Funes Hernandez & Bhalla, 2023) (Young, 2007) (Liu et al., 2024)

Different Than Essential HTN



- Higher rates of
  - Microalbuminuria -(Rossi et al., 2006)
  - Arterial wall stiffness - (Strauch et al., 2006)



J Clin Endocrinol Metab, July 2006, 91(7):2638–2642

(Milliez et al., 2005) (Fallo et al., 2005)

Why Are We Missing The Mark?

- Complicated testing algorithms
- Interference of medications with testing
- Not all patients present classically
  - ***** Hypokalemia only present in 9-37% of patient with PA *****
  - Hard to distinguish from essential HTN
- Changes in care providers
- Not clear on who we should screen
- Debate about cut off values for screening

(Gruber & Beuschlein, 2020)

Who To Screen?: Endo Society 2016

- Sustained BP > 150/100 mm/Hg
- HTN resistant to ≥ 3 antihypertensive drugs (including a diuretic)
- HTN +
  - hypokalemia
  - adrenal incidentaloma
  - OSA
  - family history early onset HTN
- First degree relatives of patients with PA who have HTN

(Funder et al., 2016) (Ha et al., 2023) (Faconti et al., 2024)

Testing Correctly

- Collected in the morning after patients have been out of bed for at least 2 hours
- Seated for 5-15 minutes
- Unrestricted dietary salt intake prior to testing
- **Potassium replete (goal 4.0 mmol/L) *****
- Maintain sample at room temperature (not on ice as this will inactivate renin)

(Funder et al., 2016) (Han, 2021)

How To Screen?

- Cut offs not agreed upon
- Endocrine Society 2016:
  - plasma aldosterone/renin ratio (ARR) > 20 - 30
  - plasma aldosterone > 15 ng/dL or 6 ng/dL?
- British and Irish HTN Society 2023: ARR > 30 and consideration of aldosterone level
- Dr Fernandes: consult if concerned about PA and **aldosterone > 10 ng/dL with low/suppressed renin**, ARR > 20 or if otherwise high suspicion of PA

(Funder et al., 2016) (Han, 2021)

Interfering Medications

Medication			Impact on diagnosis
Beta Blockers		Increa	False positive
ACE Inhibitor		Decreases	negative
Angiotensin R Blockers (AR	↓Ald ↑Renin	Decreases	egative
Calcium Ch Blockers	No significa change*	ange*	egative (rare)
Diuretics	↑Aldo ↑Renin	ondar	e false ive
Alpha-Blockers	o significant nge	No	e
Spironolactone and **Eplerenone**		May	alse negative

*Calcium channel blockers *acutely* decrease
Stop MR antagonists **6 weeks** before testing, others

(Burrello, 2020) (Young, 2003) (Young, 2007)

Non Interfering Medications on Aldosterone

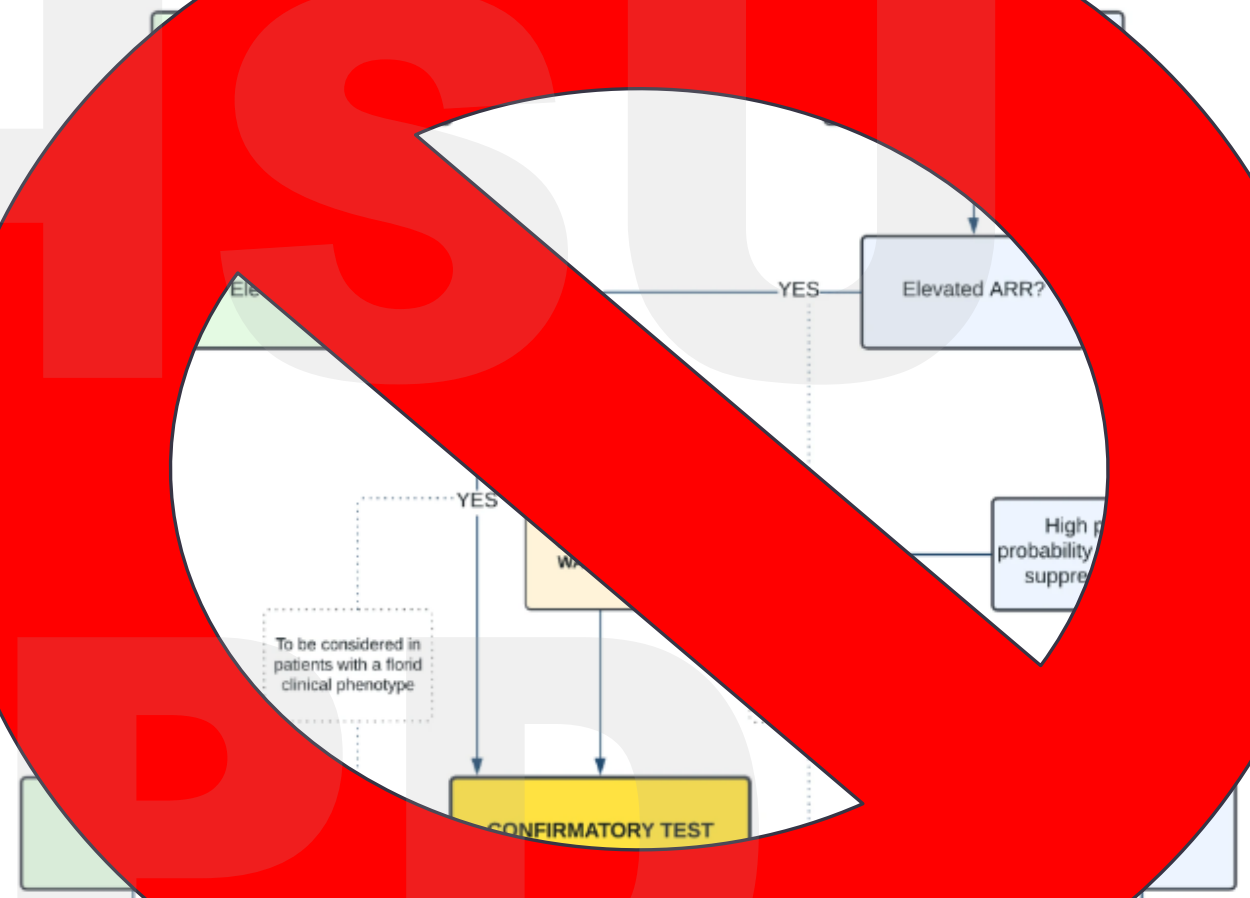
- Verapamil
- Hydralazine
- Prazosin
- Doxazosin
- Terazosin

(Funder et al., 2016)

Simplified?

Fig. 2: Simplified BIHS algorithm for the diagnostic workup of suspected primary hyperaldosteronism (PA) in ...ion.

From: Diagnosis and management ...d by the British and Irish Hypertension Society

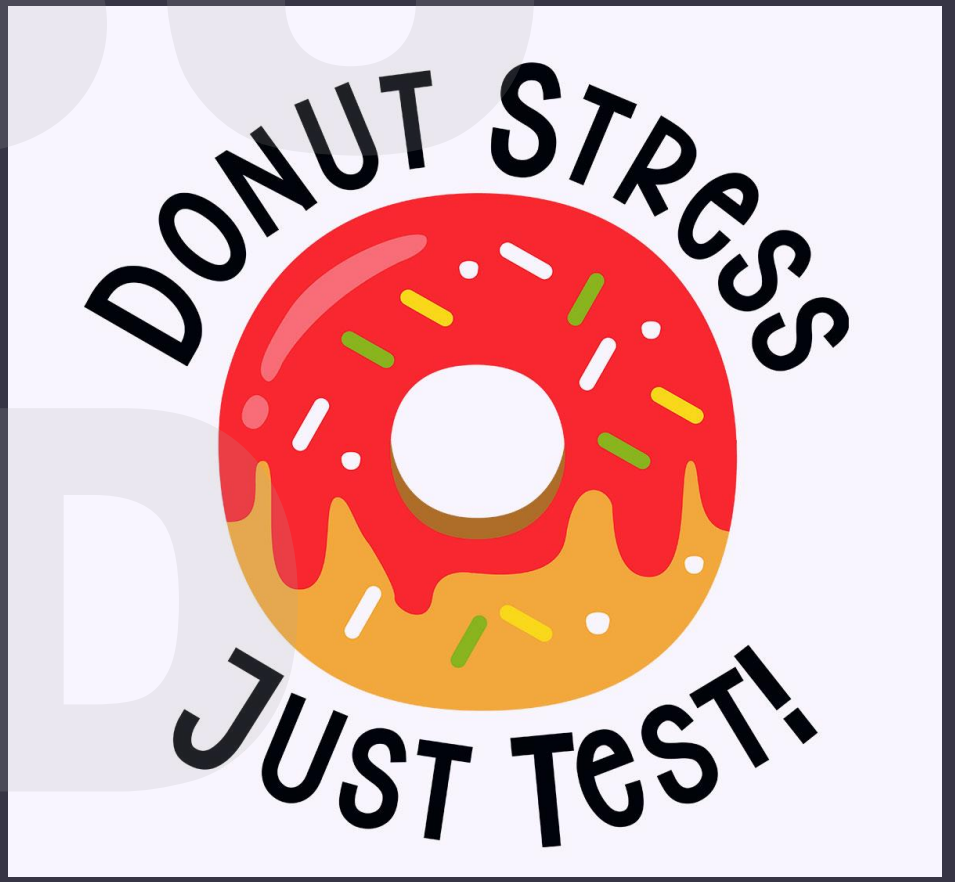


- If patients ..., consider the individual comp...

(Faconti et al., 2024)

Just Test !!!

- Discontinue for 6 weeks
  - Mineralocorticoid receptor antagonists
    - Spironolactone
    - Eplerenone
  - Amiloride



(Young, 2003) (Young, 2007)

Mr BP: Screening Tests

- On lisinopril and amlodipine
- On potassium supplement

Lab Test			Reference Range
Aldosterone			0.00 - 30 ng/dL
Renin			0.167-5.380 ng/mL/hr
ARR			< 20 ?
Potassium			3.5-5.1 mmol/L

Confirmatory Testing

- **Give a stimulus in which non affected patients should suppress their aldosterone production**
- Correct hypokalemia to avoid a false-negative
- Cut offs debated
- Some say can skip if screening testing very positive and classic presentation

Table 2 Confirmatory testing for primary aldosteronism.

Confirmatory test	Diagnostic cut-off values
Saline infusion test (SIT)	PAC > 5–10 ng/dL (140–280 pmol/L)
Oral salt loading test (SLT)	uAldo > 12 µg/24 h (33 nmol/day)* or > 14 µg/24 h (39 nmol/24 h)†
Fludrocortisone suppression test (FST)	Upright PAC > 6 ng/dL (170 pmol/L) on day 4 at 10:00 h with PRA < 1 ng/mL/h and plasma cortisol less than the value at 07:00 h‡
Captopril challenge test (CCT)	Decrease in PAC ≤ 30% (or ARR > 200 pg/mL/ng/mL/h)**

Protocols describing confirmatory testing in detail are described in Stowasser and Gordon (20). Includes data from Funder *et al*. (3).
*At the Mayo clinic; †At the Cleveland clinic; ‡To exclude any confounding effect of ACTH; **Decrease in PAC ≤ 30% as defined by the ES Guideline (3) and ARR > 200 pg/mL/ng/mL/h by the Japan ES Guidelines (23).
PAC, plasma aldosterone concentration; PRA, plasma renin activity; uAldo, urinary aldosterone.

(Funder et al., 2016) (Fernandez et al., 2024) (Williams & Reincke, 2018)

Mr BP: Confirmatory Testing

- Oral salt loading test

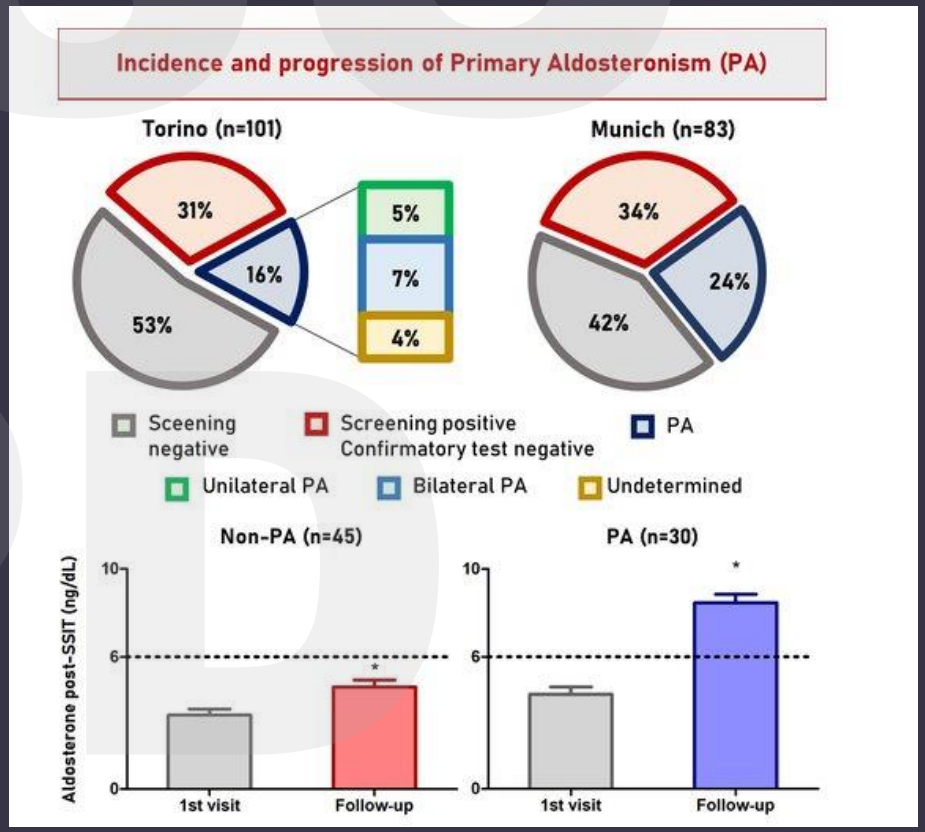
- Had to stop amiloride and increase potassium supplement for this
- Was on lisinopril and amlodipine for testing

- Aldosterone 34.66 (0.00-19.00) mcg/24 hour
- Sodium 452 (40-220) mmol/day
- Creatinine 2.8 (0.7 - 2.3) g/24 hour
- Total volume 4.3 L
- K 3.2 (3.5-5.1) mmol/L

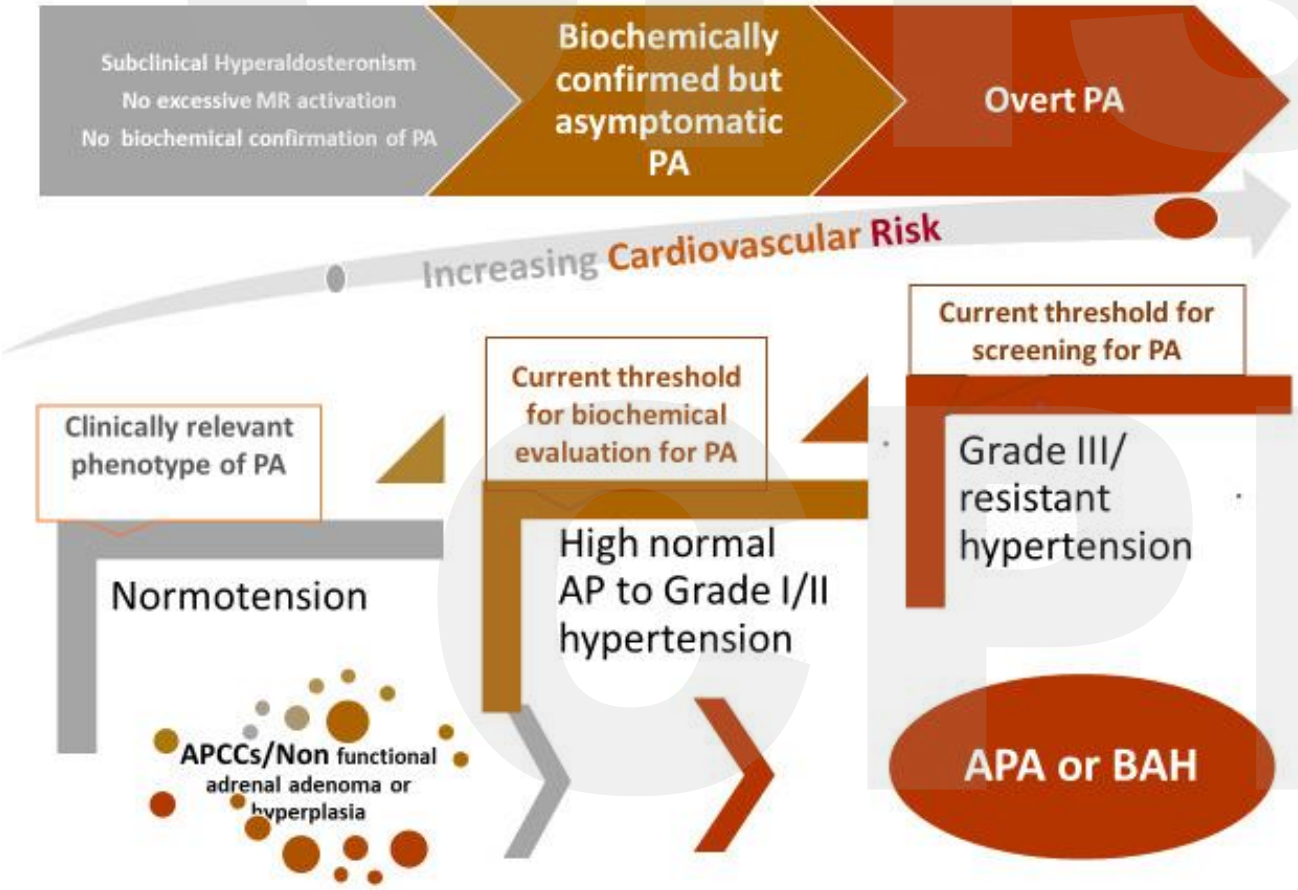
Not One and Done?!

Hypertension. 2024 Feb;81(2):340-347. doi: 10.1161/HYPERTENSIONAHA.123.21983. Epub 2023 Dec 12.

Long-Term Follow-Up of Patients With Elevated Aldosterone-to-Renin Ratio but Negative Confirmatory Test: The Progression of Primary Aldosteronism Phenotypes

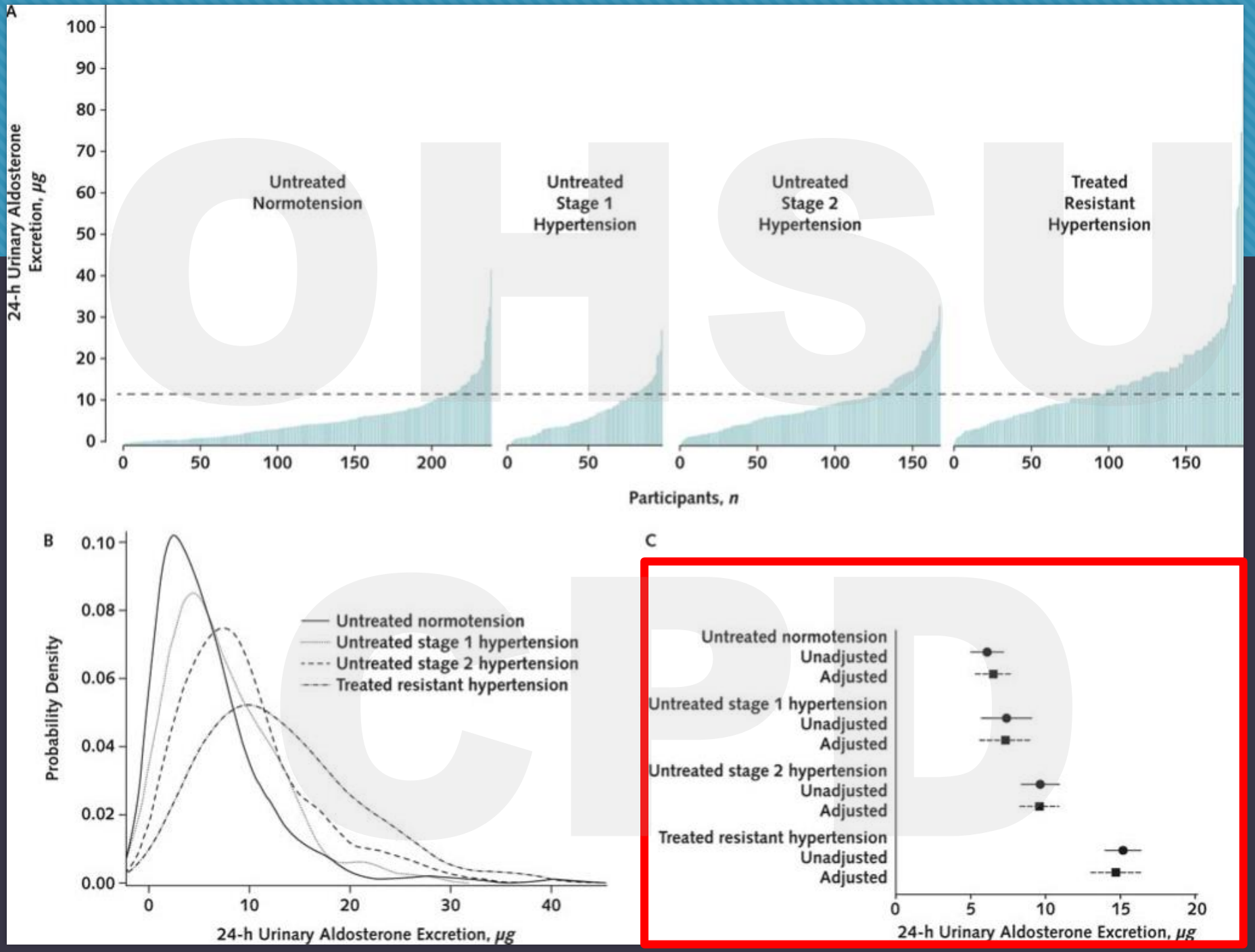


Aldosterone On A Spectrum



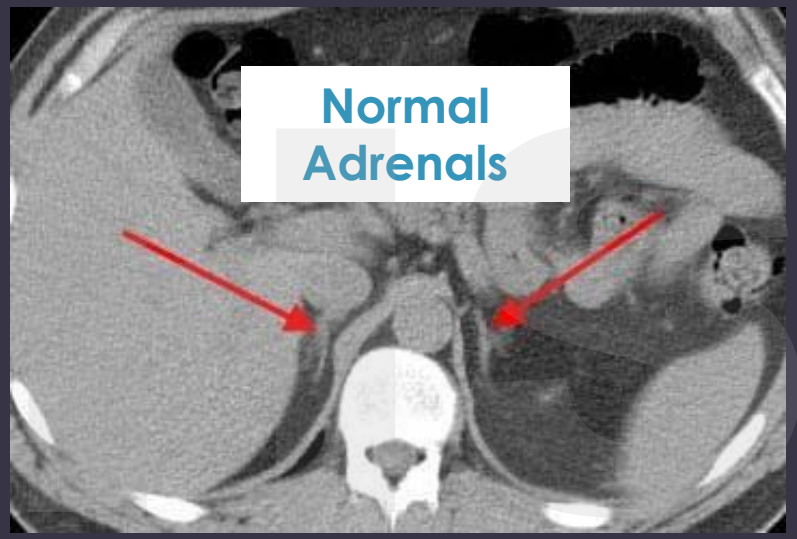
- "Formerly seen as a rare syndrome of resistant hypertension and hypokalemia, primary aldosteronism should now be viewed as a **spectrum of autonomous renin-independent aldosterone production that is prevalent across the continuum of blood pressure severity**."
- "Current screening and diagnostic guidelines capture only a fraction of the more severe forms of primary aldosteronism"

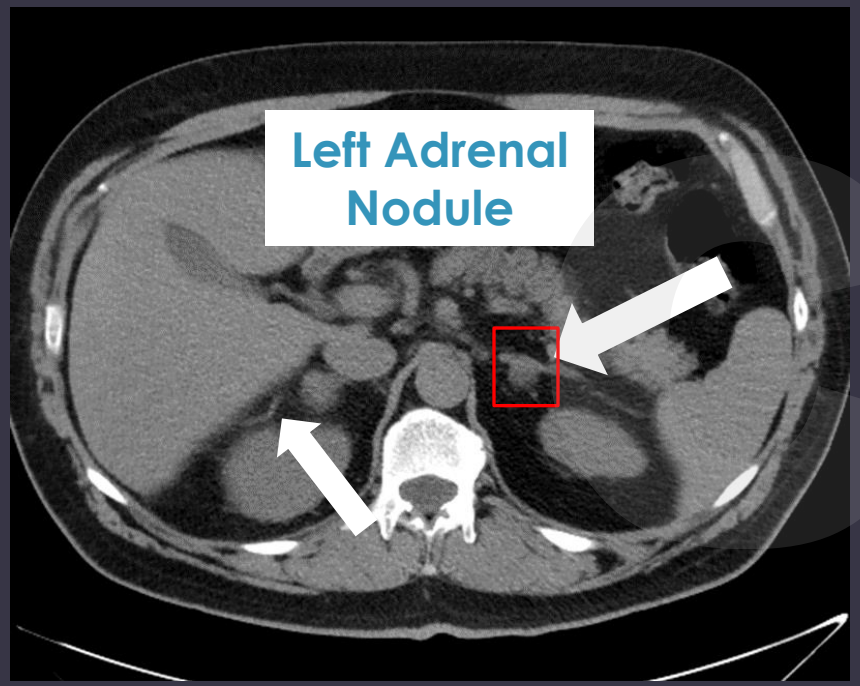
(Papadopoulou-Marketou et al., 2024)
(Mehdi, Rao, & Thomas, 2021)

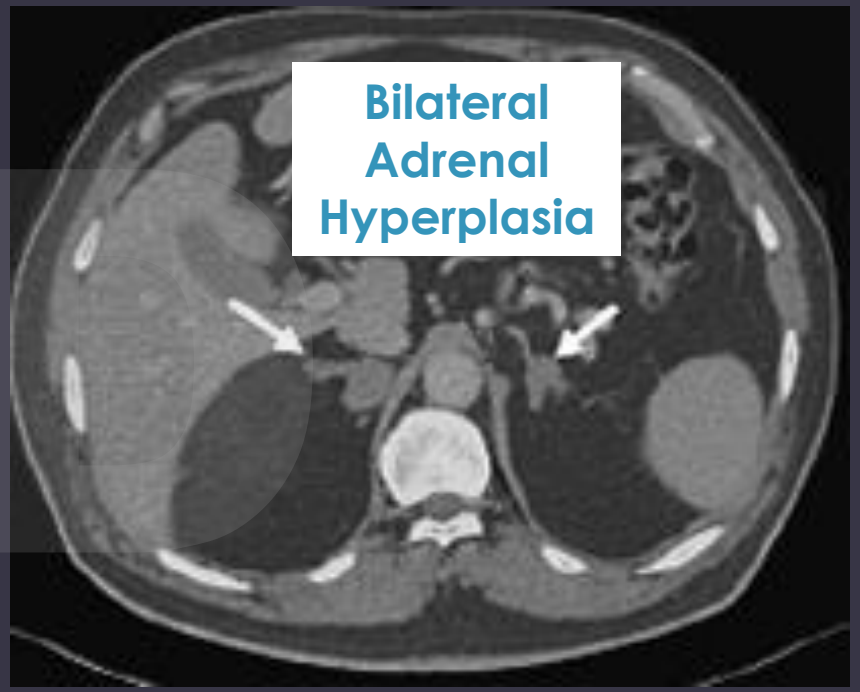


(Brown et al., 2024)

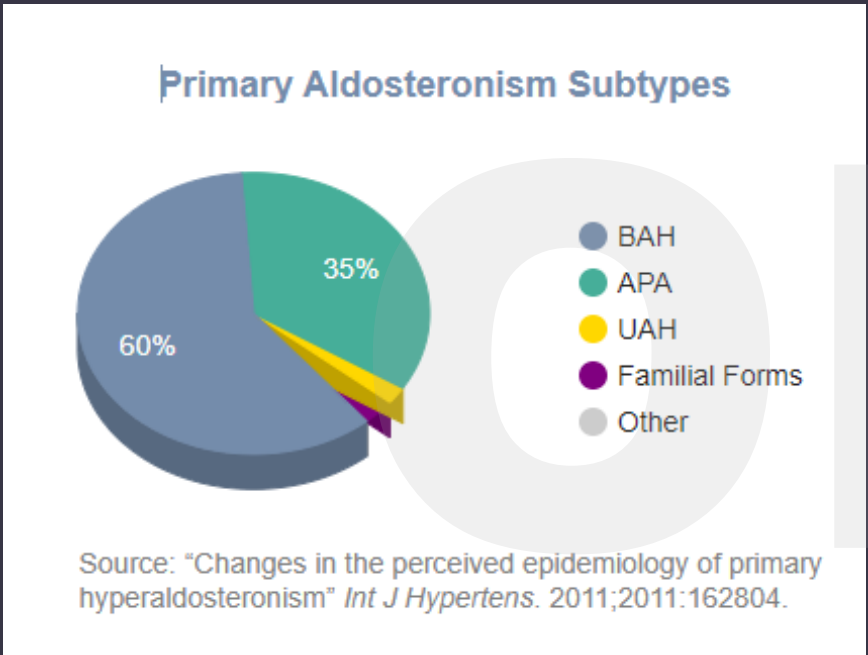
CT Imaging



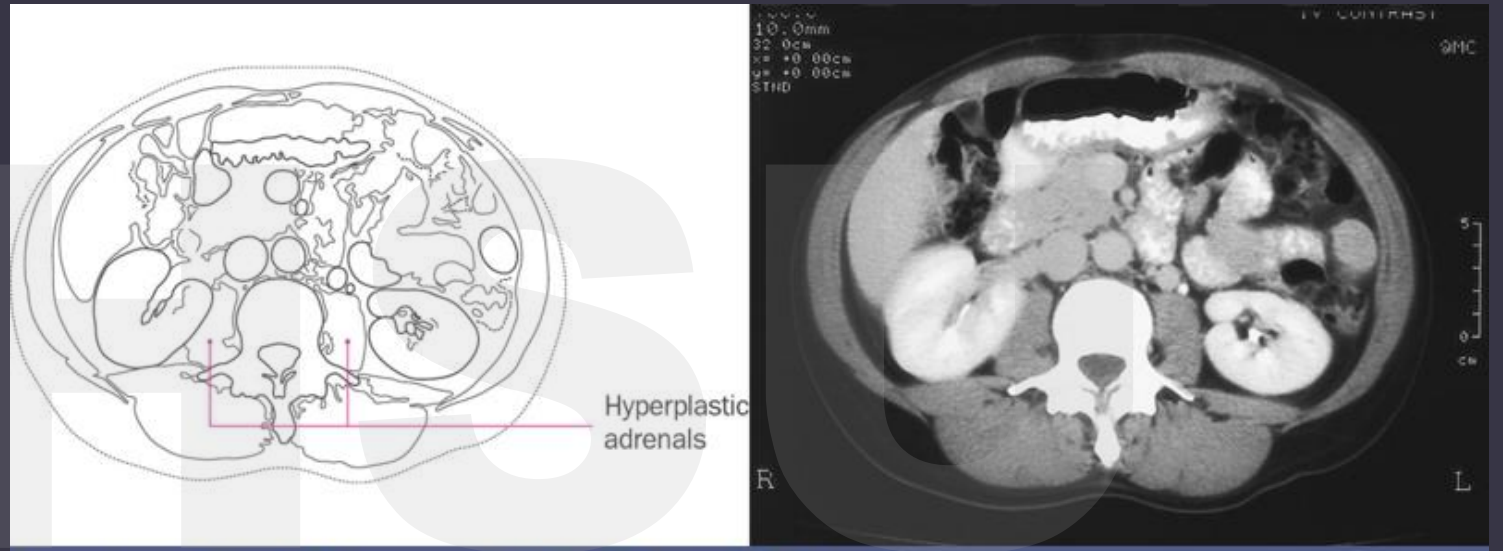




(Vitellius et al., 2018) (Funder 2016) (Gu, 2024.)



Source: "Changes in the perceived epidemiology of primary hyperaldosteronism" *Int J Hypertens*. 2011;2011:162804.



Comprehensive Clinical Endocrinology 3e: edited by Besser & Thorner
Elsevier Science Ltd

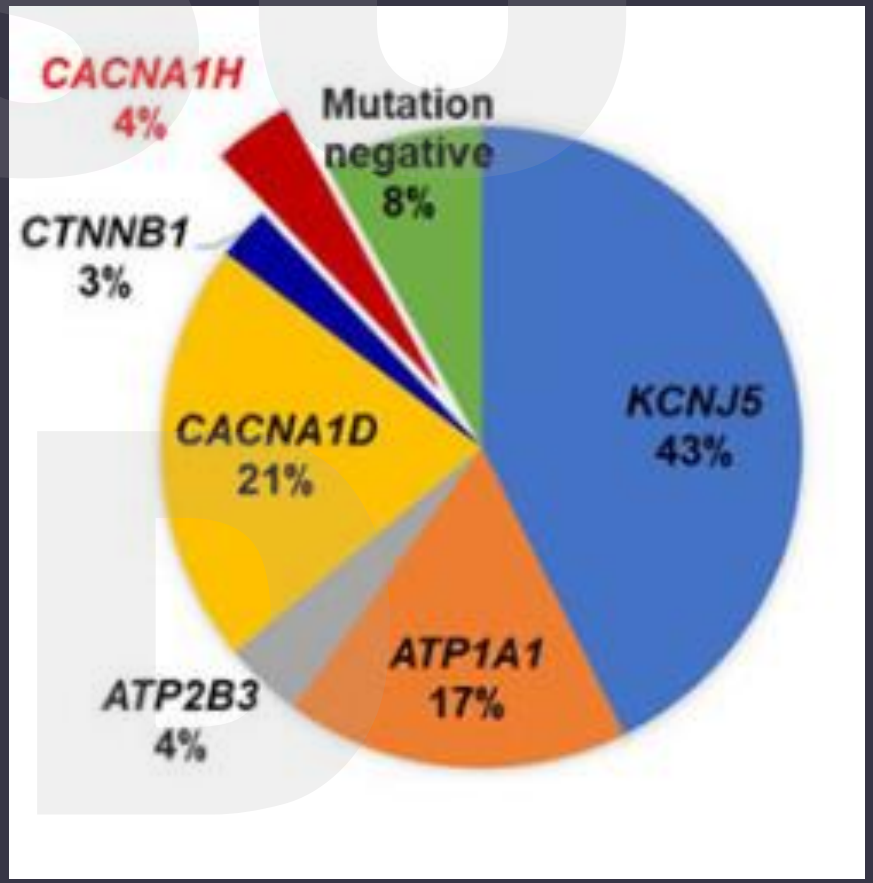
Subtypes of Primary Hyperaldosteronism

- **Bilateral Adrenal Hyperplasia (BAH)**
- **Aldosterone-Producing Adenoma (APA)**
  - More accelerated HTN
  - More profound hypokalemia
  - Higher plasma and urinary aldosterone values
  - Younger patient age

(Primary Aldosteronism, 2024) (Lenders, Eisenhofer, & Reincke, 2017)

Genetics

- Causative somatic mutations in key proteins of adrenal glomerulosa cells detected in APAs
- KCNJ5 – younger, female > male
- ATPA1A1 and ARP2B3 – male > female
- CTNNB1 – female > male, older, shorter duration HTN, increased risk malignant transformation
- **Rarely seen in MEN**

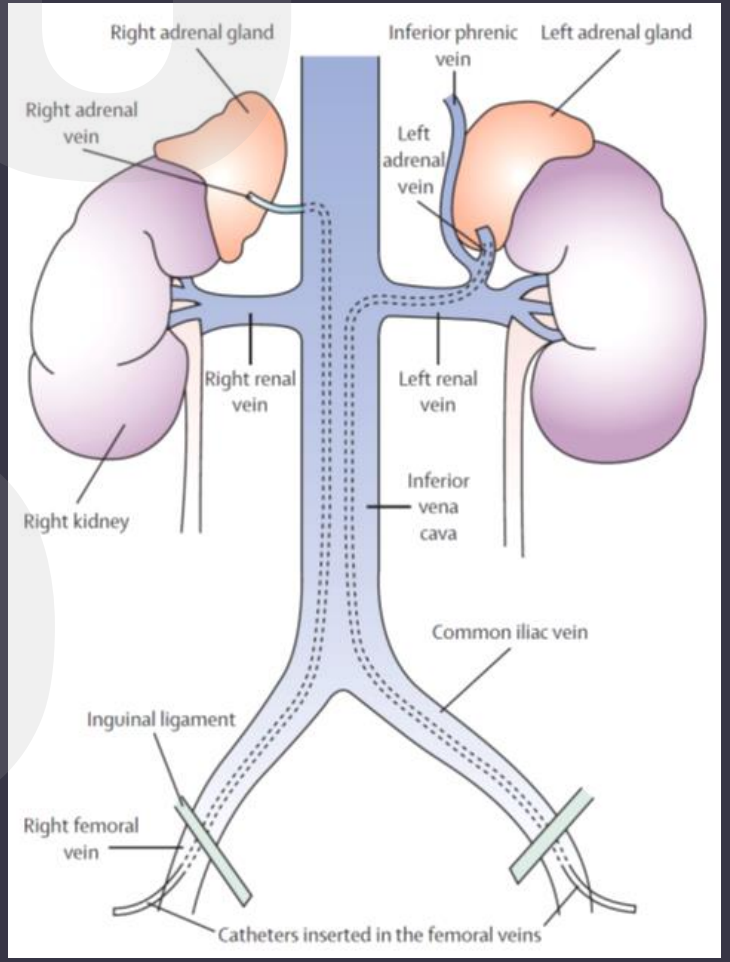


(Wang et al., 2017) (Funder 2016) (Kitamoto & Nishikawa, 2022) (Nanba et al., 2020)

Adrenal Venous Sampling (AVS)

- Procedure of sampling the adrenal glands to determine if excess aldosterone is coming from one or both glands
- *** **Only pursue this if patient is a surgical candidate willing to undergo surgery** ***
- Expensive, invasive, need expert hands
- Sensitivity 95% and specificity 100% in detecting APA
- 60-90 minute procedure

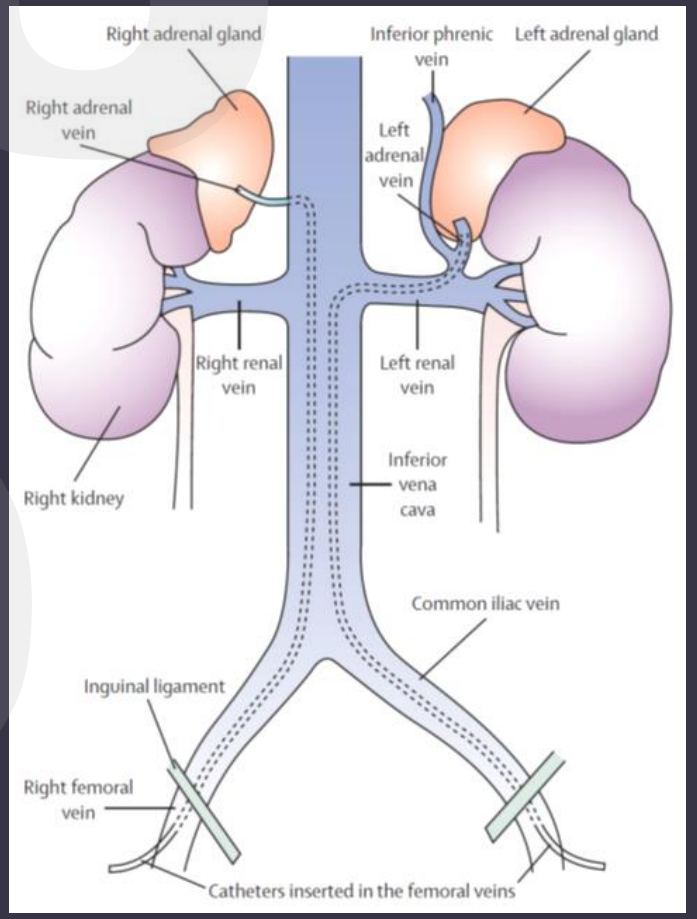
Primary Aldosteronism Foundation



(Ha 2023) (Monticone et al., 2015)

Adrenal Venous Sampling (AVS)

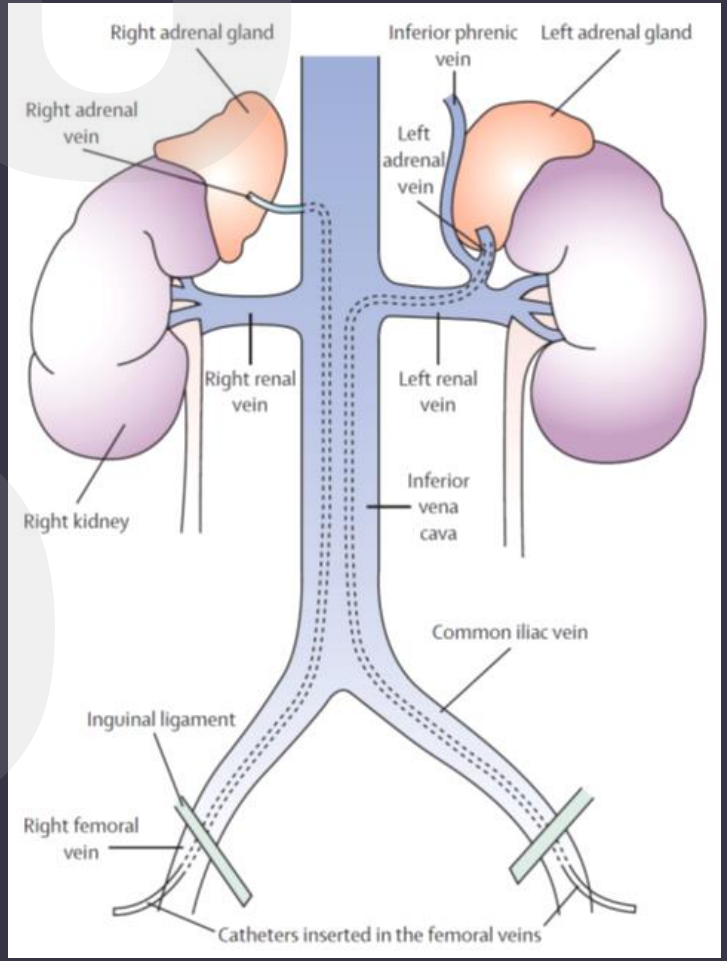
- May be able to skip AVS in clear cut cases ?
- In a study of 203 patients with PA evaluated with both CT and AVS, CT was accurate in 53%
  - 42 (22%) of patients would've been incorrectly excluded from surgery
  - 48 (25%) would have had unnecessary/inappropriate surgery



(Ha 2023) (Monticone et al., 2015) (Funder 2016) (Young et al., 2004)

Adrenal Venous Sampling

- Discontinue spironolactone, diuretics and amiloride **6 weeks** prior to test
  - a-blockers, calcium-channel blockers preferred
  - β-blockers, ACE inhibitors, ARBs can be used
- Expectation
  - Adrenal venous [cortisol] right > left
  - Adrenal vein: IVC ratio of 10:1
  - Contralateral suppression of aldosterone
- Complications uncommon (0.61%: groin hematoma adrenal hemorrhage, adrenal vein dissection



(Ha 2023) (Monticone et al., 2015)

Mr BP: AVS

	Peripheral	Right adrenal	Left adrenal	Notes
Cortisol	16	1385	561	
Aldosterone	55	14272	111	
Aldo/Cort	3.44	10.30	0.20	
lateralization index		52.08	0.02	Aldo:Cort of Adrenal vein/ Aldo:Cort of contralateral vein (LI>4 unilateral, L<3 bilateral, 3-4 indeterminant)
Selectivity index		86.56	35.06	Cortisol (Adrenal Vein/Peripheral) - adequacy of cannulation
Contralateral and Ipsilateral Ratio		3.00	0.06	ILR>2 , CLR<1 to diagnose unilateral PA (Aldo:Cort adrenal vein/ Aldo:Cort peripheral)
	Lateralization Result	Right APA	Right APA?	
	CI/IR Result	Right APA	Right APA?	

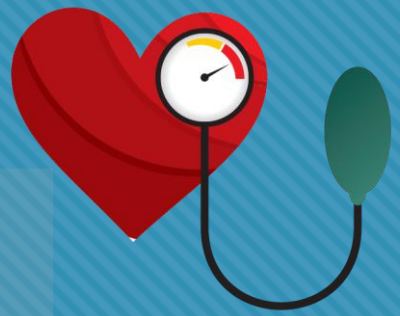
Monticone et al (2015) Adrenal vein sampling in aldersteronism: towards a standardised protocol. Lancet Diabetes Endocrinol 3:296-303

Laparoscopic Adrenalectomy

- Lower rates of clinical and surgical complications than open approach
- Avoid adrenal sparing approach (cortical sparing partial adrenalectomy)
- Normalize BP and potassium prior to surgery
- Monitor BP and potassium closely after surgery
  - 5% required fludrocortisone
  - Pre operative treatment with MRA can reduce risk of post op hypoaldosteronism

(Puar et al., 2024) (Ahmed & Hundemer, 2022) (Stowasser & Gordon, 2016) (Burrello, 2020) (Young, 2003) (Young, 2007) (Funder 2016) (Faconti 2024)

Post Operatively



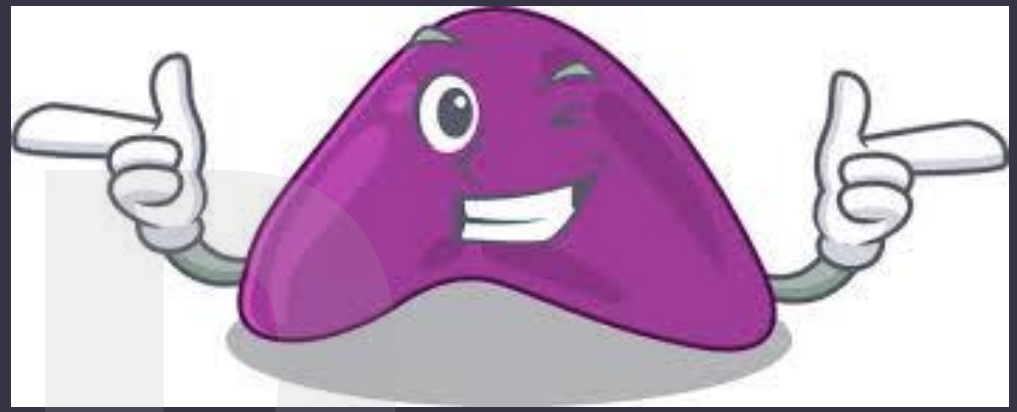
- Blood pressure improves over 1-6 months
- Reduction (47%) or withdrawal (37%) of blood pressure meds
- Normalization of potassium and ARR (94%)
- Superior to medical management in
  - controlling BP
  - reducing number BP meds
  - lowering risk of atrial fibrillation
  - lowering risk of CKD kidney disease
  - reversing left ventricular hypertrophy
  - lowering mortality
- Predicting cure HTN: young age, female sex, short history of HTN, high number antiHTN medications, absence of vascular remodeling, absence of CKD

(Puar et al., 2024) (Ahmed & Hundemer, 2022) (Stowasser & Gordon, 2016) (Burrello, 2020) (Young, 2003) (Young, 2007) (Funder 2016) (Faconti 2024)

Mr BP: Surgery

- Underwent robot assisted laparoscopic right adrenalectomy
- No intraoperative complications

- In hospital:
  - K 3.9 (3.5-5.0) mmol/L
  - Cr 0.9 (0.5-1.2) mg/dL



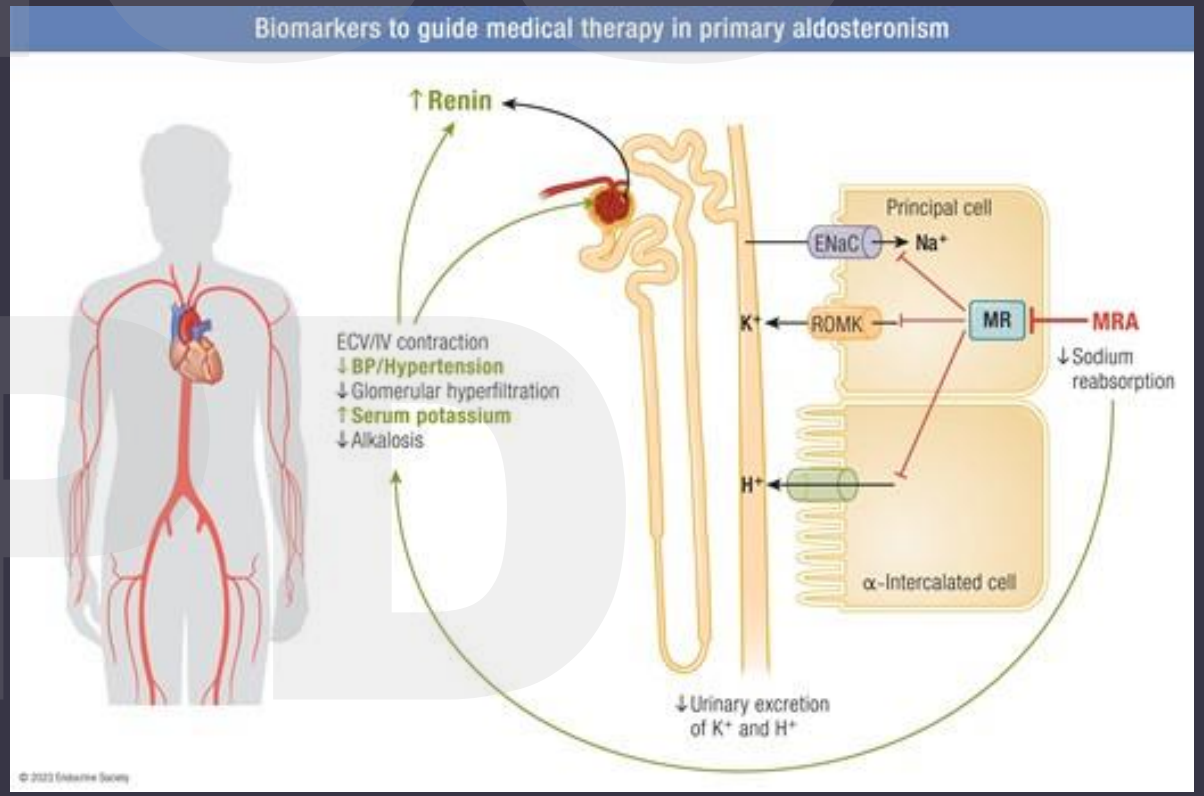
- On discharge
  - stopped amiloride and potassium
  - continued benazepril and amlodipine

- At home
  - potassium 4.4 (3.5-5.0) mmol/L
  - blood pressure 120/80

(Pappachan and Fernandez 2022)

Medical Management

- Bilateral disease
- Non surgical candidates
- Non curative adrenalectomy
- Goals
  - normalize BP
  - normalize K +
  - reduce cardiovascular risk
  - unsuppress renin



(Hundemer et al., 2024)

Medical Management

- Dietary sodium restriction
  - reduces urinary potassium excretion
  - 10% reduction in urinary sodium excretion associated with decline in LV mass index

(Hundemer et al., 2024)

Medical Management

- Spironolactone
  - 12.5-25 mg/day, max usually 100 mg/day
  - Adverse effects: gynecomastia (10-50%; dose dependent) and impotence in men, spotting in women
- Eplerenone
  - Steroid selective MRA
  - Lower side effect profile than spironolactone but only 50% antagonist potency of spironolactone
- Finerenone
  - Non steroidal MRA
  - No affinity for glucocorticoid or androgen receptor
  - Less hyperkalemia and reduction in eGFR
  - Approved for CKD associated with DM2

(Funder 2016) (Factoni 2024) (Cohen et al., 2023)

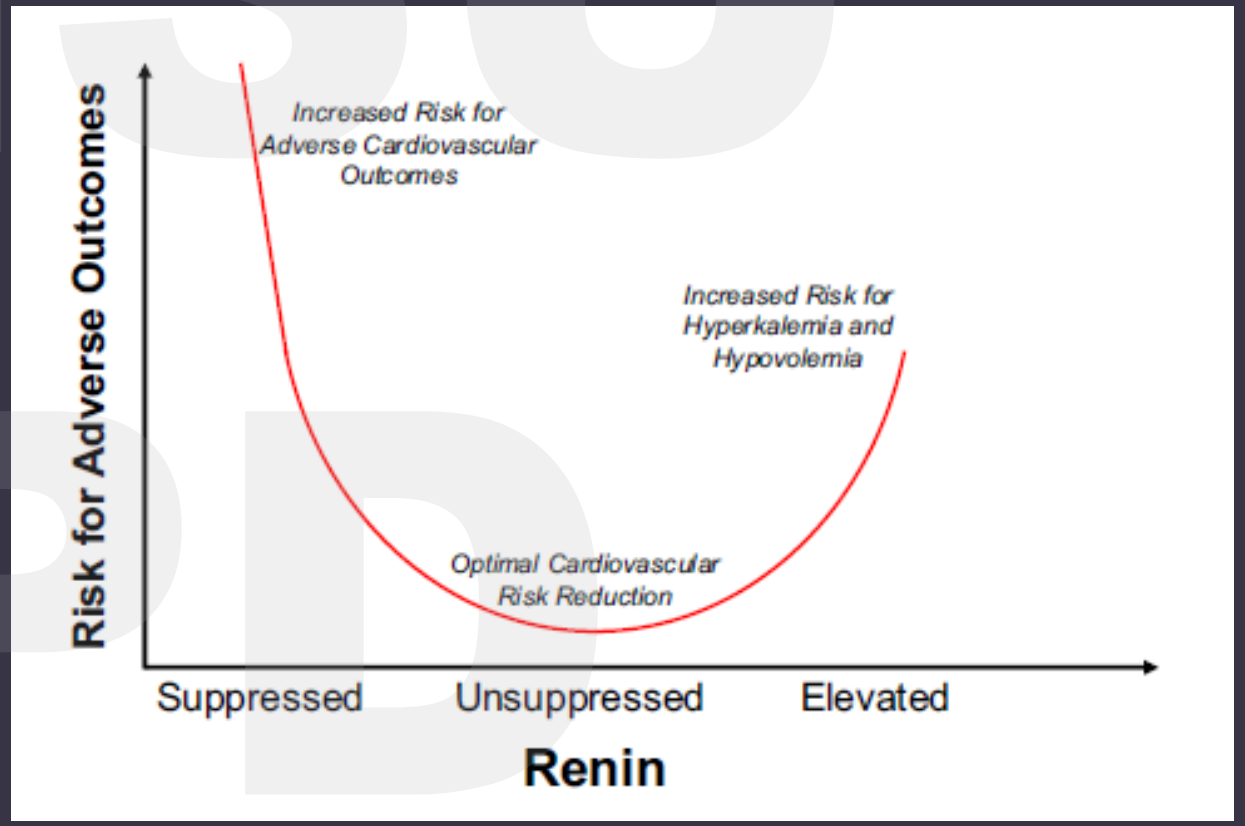
Medical Management

- Amiloride
  - Epithelial sodium channel antagonist
  - 5-40 mg/day
  - Lacks sex steroid related side effects
  - Doesn’t provide beneficial effects on endothelial function

(Hundemer et al., 2024)

Release The Renin

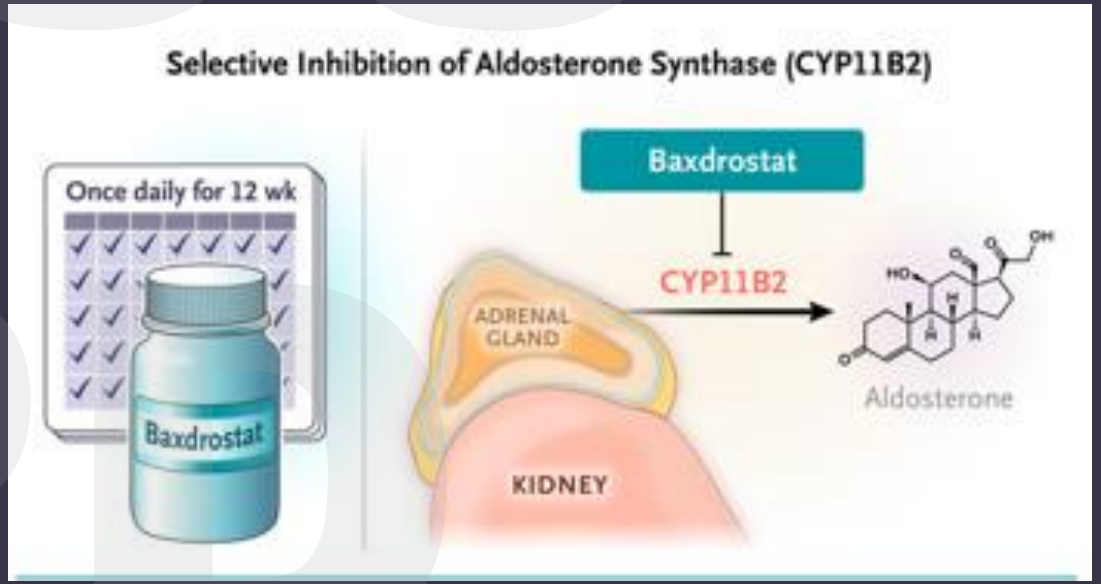
- Suppressed > unsuppressed renin associated with improved cardiovascular and kidney outcomes
- May not be possible due to effect of high doses of beta blocker and/or CKD
- Treat hyperkalemia with
  - diuretics
  - SGLT2 inhibitors
  - potassium binders (patriomer)
  - discontinue RAS inhibitors
- Can take several medication titrations spanning months to years



(Mansur, Vaidya, & Turchin, 2023) (Hundemer et al., 2024)

Medical Management: Future

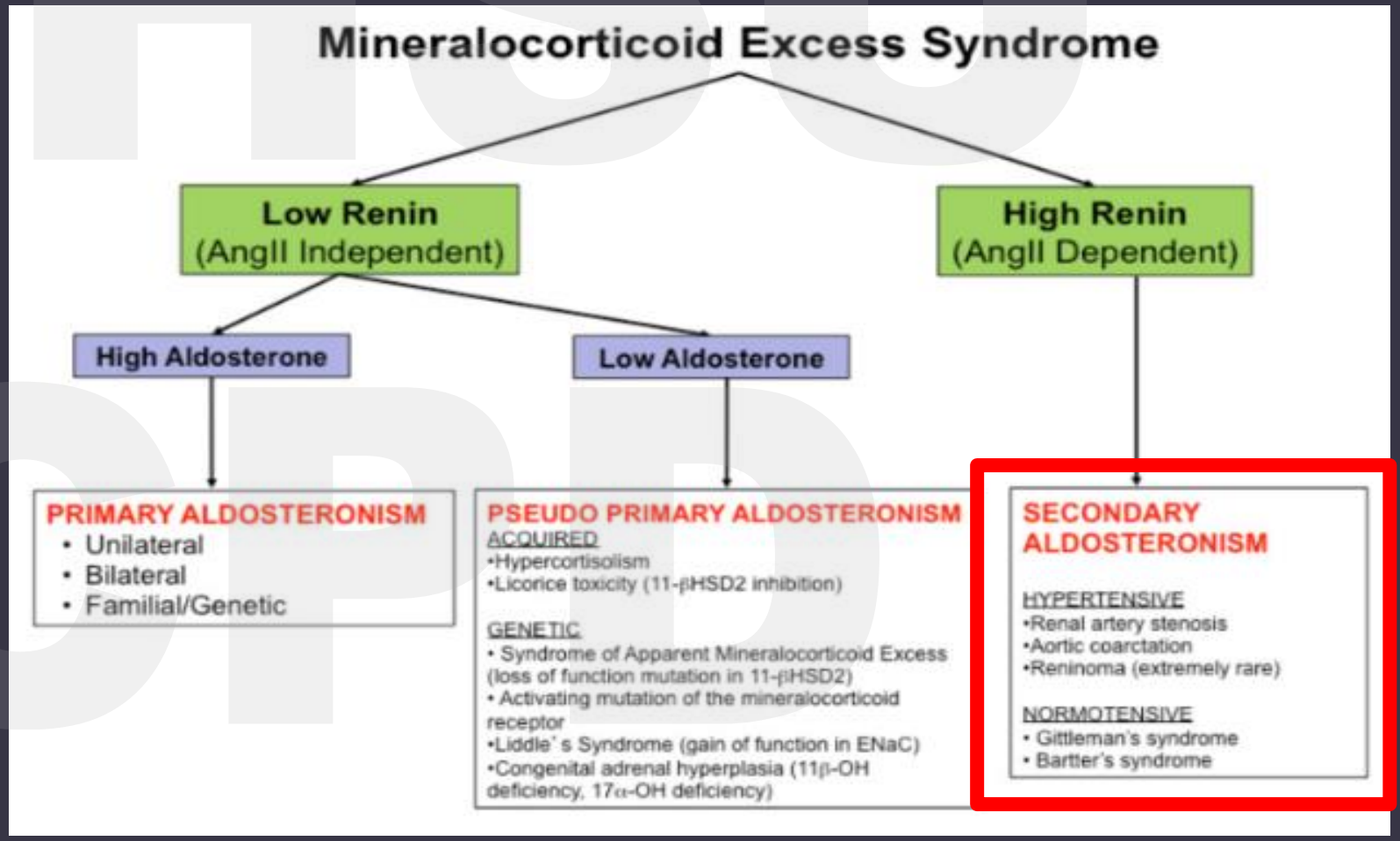
- **Aldosterone synthase inhibitors**
- Where as mineralocorticoid antagonists increase aldosterone concentration
- Osilodrostat – used for Cushing's syndrome
  - Lowered aldosterone and BP
  - Lack of specificity
  - Also blocks 11 B hydroxylase in cortisol synthesis
  - Increased production of 11 deoxycorticosterone (mineralocorticoid receptor agonist)
- Baxdrostat
  - 100:1 selectivity for enzyme inhibition
  - Adverse effects: hyperkalemia, hypotension, hyponatremia
- Lorundrostat (MLS-101) – Target-HTN
  - High selectivity for inhibition of human CYP11B2 vs CYP11B1
  - In clinical trials for those with resistant HTN and low renin
  - Adverse effects: hyperkalemia, decrease in eGFR



(Laffin et al., 2023) (Freeman et al., 2023)

Secondary Hyperaldosteronism

- States with low effective circulating blood volume (CHF, nephrotic syndrome, diuretic use) = increased aldosterone



(Williams et al., 2022)

Were You Paying Attention?

Linda is a 52 year old female

- Hypertension onset in 20s diagnosed during pregnancy and persisted after
- Hypokalemia and cramping
- On amlodipine, lisinopril, clonidine, potassium supplement
- Blood pressure 145/80
- Potassium 3.5 mmol/L (3.6-5.2)

Big Bob is a 72 year old male

- History MI, CABG, CVA
- Can't remember onset of HTN
- On amlodipine, lisinopril, clonidine
- Blood pressure 155/90
- Potassium 3.9 mmol/L (3.6-5.2)
- Left adrenal nodule found on lung cancer screening CT

(Hundemer et al., 2024) (Young, 2007)

Next Steps

Reference Range:
Aldosterone 0.00 -30 ng/dL
Renin 0.167 – 5.380 ng/mL/hr
Potassium 3.5-5.1 mmol/L

Linda

Big Bob

(Hundemer et al., 2024) (Young, 2007)

Next Steps

Reference Range:
Aldosterone 0.00 -30 ng/dL
Renin 0.167 – 5.380 ng/mL/hr
Potassium 3.5-5.1 mmol/L

Linda

- CT showed possible 0.5 cm LEFT adrenal nodule
- AVS lateralized aldosterone production to RIGHT adrenal
- Underwent RIGHT adrenalectomy
- Post op K 3.8 mmol/L
- In follow up blood pressure 130/80 on lisinopril alone

Big Bob

- He decides against surgery
- Started on spironolactone and up titrated to 100 mg a day
- Blood pressure 135/75
- Renin 0.5 ng/ml/hr
- Potassium 4.2 mmol/L (3.6-5.2)
- Able to stop clonidine

(Hundemer et al., 2024) (Young, 2007)

Future Work To Be Done

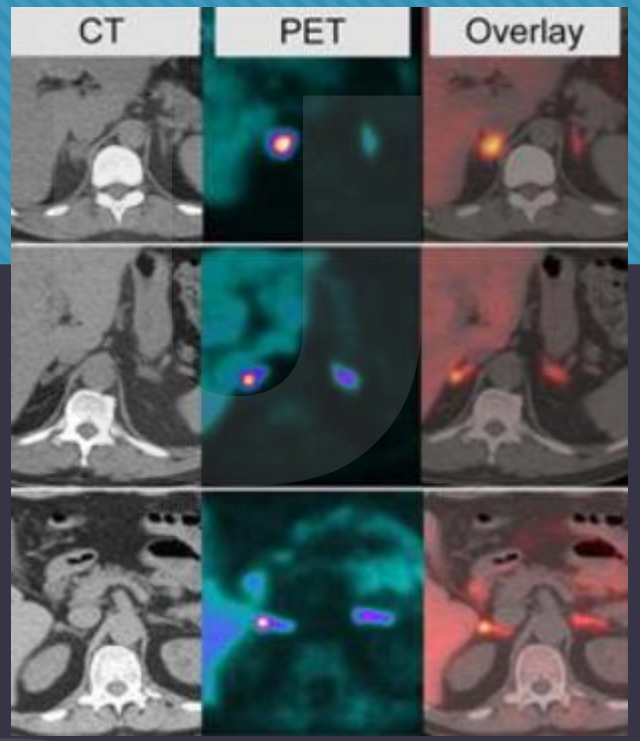
- Greater awareness (being done right here!)
- Identifying populations to screen other than classic high risk populations
- Less reliance on aldosterone-renin ratio
  - Consider skipping screening testing in high risk patients and go straight to confirmatory dynamic testing
- Looser screening cutoffs
- Consider repeat screening, especially those with low renin
- Looser confirmatory cutoffs
- New diagnostic tools – novel biomarkers of aldosterone excess and mineralocorticoid receptor activation (urinary exosomes and steroid metabolome profiling)
  - 18OHB, 18OHF and 18oxoF secreted at higher rates in those with APA than BAH
  - Combination of LC-MS based steroid profiling with machine learning algorithm (accuracy 78-97%)

(Mehdi, Rao, & Thomas, 2021) (Ha 2023)

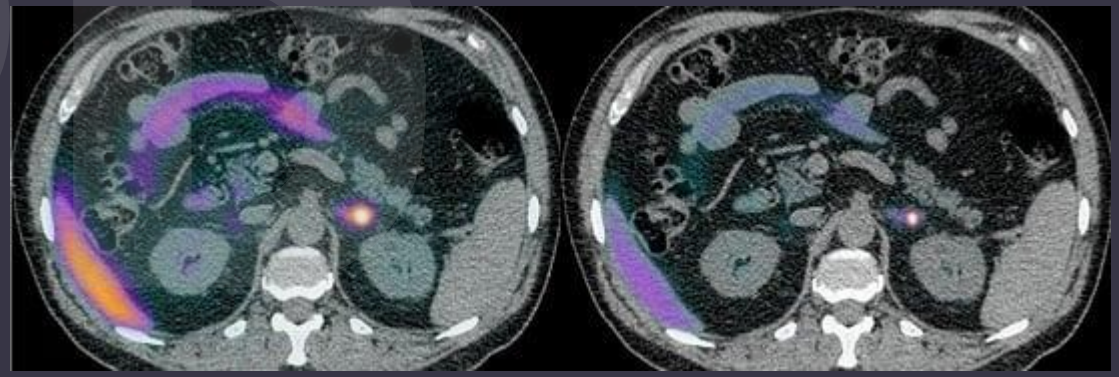
Conclusions

- PA is out there! (or maybe in here 👀)
- We need to screen for PA more
- Finding and treating PA early is important to prevent complications from unopposed mineralocorticoid action
- **Biochemical testing first! Then localization.**
- We at OHSU have the resources to lateralize aldosterone production (AVS)
- Can treat surgically if APA or medically if BAH
- Find a case of PA this month !

Functional Imaging?



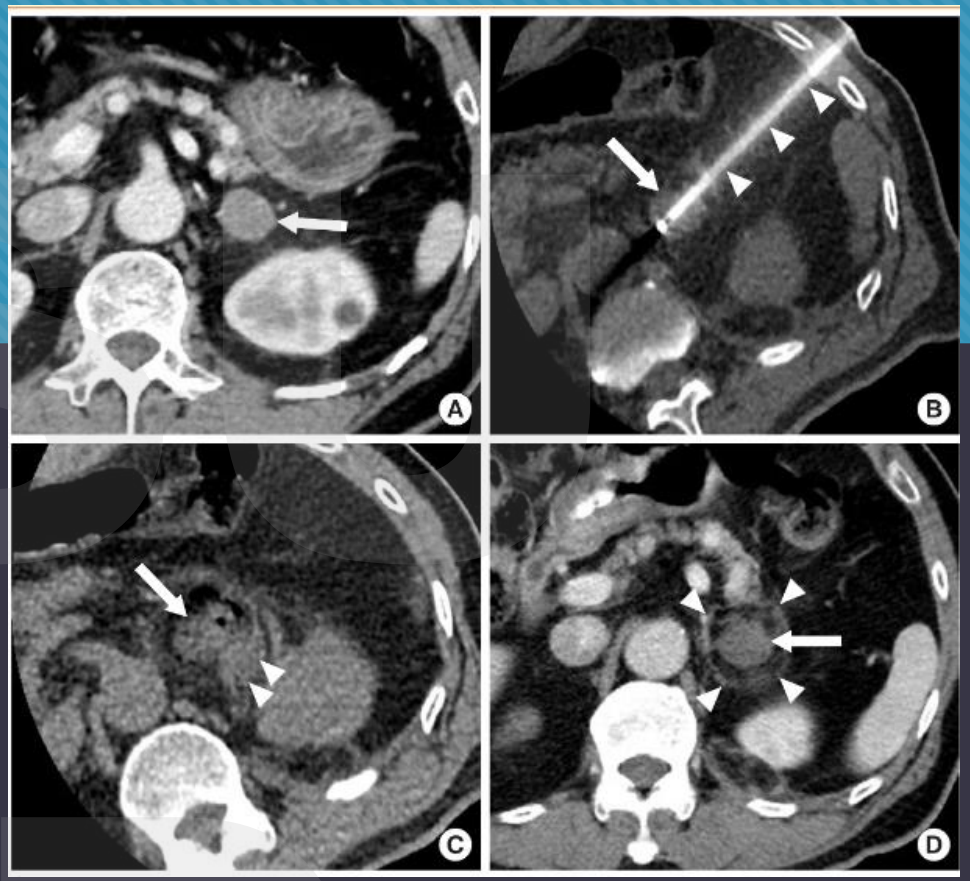
- ^{11}C-metomidate (PET)-CT scan
  - 76% sensitivity and 87% specificity in subtyping
  - Metomidate can inhibit crucial enzymes in cortisol and aldosterone synthesis
  - Pre-procedure dexamethasone administration can enhance the contrast between APA and normal adrenal tissue
  - Need for an on-site cyclotron
- ^{18}F-CDP2230
  - Highly selective aldosterone synthase inhibitor
  - Doesn't require dexamethasone pre treatment
- 68Ga-pentixafor PET/CT
  - sensitivity of 88% and a specificity of 100%,
  - based on the high expression of CXC chemokine receptor type 4 (CXCR4) in APAs (a factor associated with CYP11B2 expression)



(Ha 2023) (Funder 2016) (Mendichovszky et al., 2024) (Ding et al., 2020)

Radiofrequency Ablation

- Induces thermal damage by delivering electrical energy into target tissue resulting in coagulation necrosis
- Used for thyroid nodules, liver, kidney, lung
- There is also cryoablation, microwave ablation
- Poor surgical candidates for laparoscopic adrenalectomy
- Guided by CT
- Normalization of aldosterone, renin and ARR achieved in 90-100%
- Complications: hypertensive crisis (catecholamine release), bleeding, thermal damage to surrounding organs, adrenal insufficiency (rare)



Radiofrequency Ablation Outcomes of Functioning Adrenal Masses

Investigators	No. of cases	Clinical diagnoses	Mean FU period, mo	Biochemical resolution, %
Liu et al. [14]	36	Aldosteronoma (*n*=36)	74	100 (36/36)
Mendiratta-Lala et al. [16]	13	Aldosteronoma (*n*=10) etc.	21.2	100 (13/13)
Szejnfeld et al. [17]	11	Aldosteronoma (*n*=9) etc.	3	100 (11/11)
Nunes et al. [20]	11	Aldosteronoma (*n*=9) etc.	Not reported	90 (9/10)

(Ha 2023)

Surgery for Bilateral Hyperaldosteronism?

- Goal of attenuating disease severity rather than cure
- 56 patients found to have bilateral primary aldosteronism from AVS
- Surgery recommended for asymmetrical aldosterone production or suspected aldosterone producing adenoma (from disease severity and adrenal CT scans)
- Treated with either unilateral surgery (n=43) or bilateral adrenal surgery (n=13)

Clinical and biochemical outcomes of patients with bilateral primary aldosteronism treated with adrenal surgery

	Unilateral surgery (n=43)	Bilateral surgery (n=13)	Total (n=56)	95% CI	p value
Outcomes at 6–12 months of follow-up					
Clinical					
Complete	7/37 (19%)	6/13 (46%)	13/50 (26%)	0·32–16·23	0·197
Partial	23/37 (62%)	6/13 (46%)	29/50 (58%)	..	..
Absent	7/37 (19%)	1/13 (8%)	8/50 (16%)	..	..
Biochemical					
Complete	24/37 (65%)	11/13 (85%)	35/50 (70%)	0·29–9·27	0·264
Partial	10/37 (27%)	1/13 (8%)	11/50 (22%)	..	..
Absent	3/37 (8%)	1/13 (8%)	4/50 (8%)	..	..
Outcomes at >12 months of follow-up					
Clinical					
Complete	5/28 (18%)	5/12 (42%)	10/40 (25%)	0·27–14·55	0·217
Partial	17/28 (61%)	4/12 (33%)	21/40 (53%)	..	..
Absent	6/28 (21%)	3/12 (25%)	9/40 (23%)	..	..
Biochemical					
Complete	13/27 (48%)	10/12 (83%)	23/39 (59%)	1·91–12·99	0·098
Partial	7/27 (26%)	2/12 (17%)	9/39 (23%)	..	..
Absent	7/27 (26%)	0	7/39 (18%)	..	..

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Papers to Add

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Adrenal nodule