

Update in Internal Medicine 2022

Hyperaldosteronism: Diagnostic Dilemmas and Future Directions

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Hyperaldosteronism: Misconceptions

1. “Primary Aldosteronism (PA) is rare”
 - Actually, PA prevalence is ~5% in all HTN, up to 20% in resistant HTN¹
2. “I only need to test for PA if hypokalemia is present”
 - Hypokalemia is only seen in 25% of PA pts²
3. “Hypertensive pts are appropriately screened for PA”
 - In the US, only ~1 in 550 pts with PA are dx’ed and treated³



¹Byrd B, et al. Circulation. 2018;138:823–835

²Burello J, et al. Hypertension. 2020 Apr;75(4):1025-1033

³Funder J, et al. Hypertension. 2022.Apr;79(4):726-735

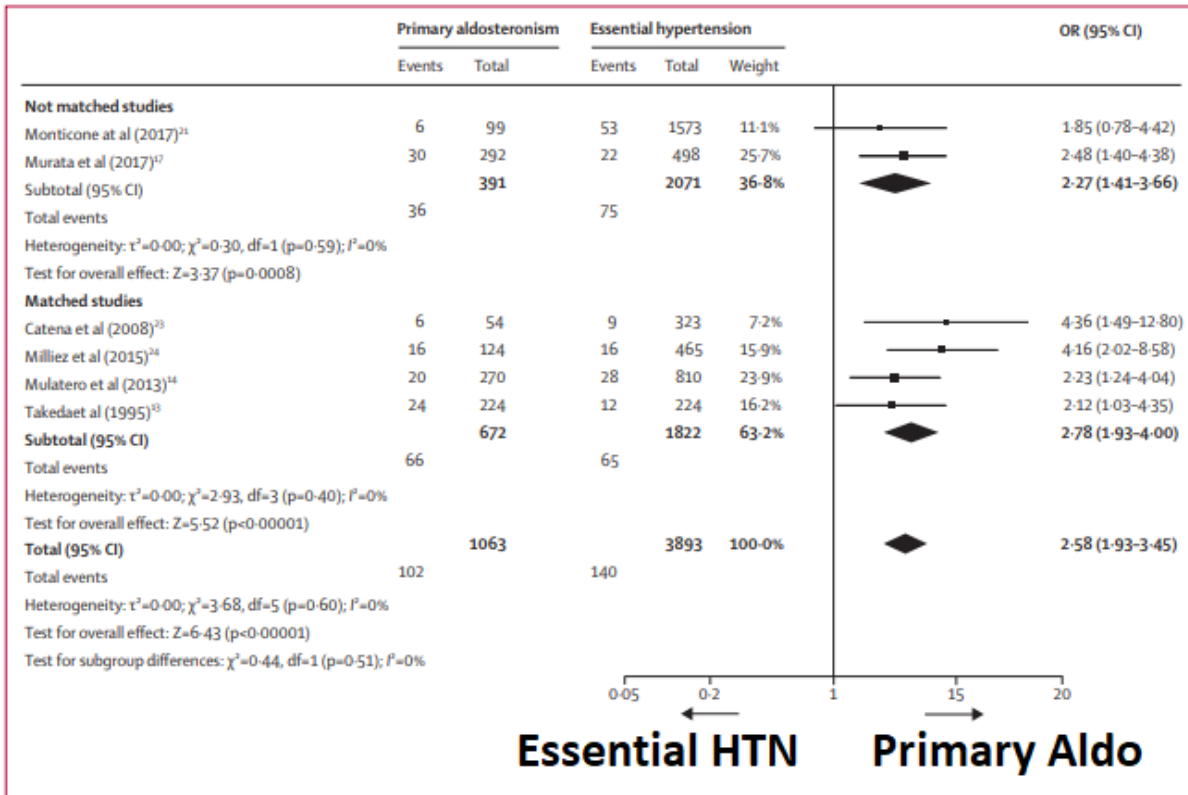
Hyperaldosteronism: Case 1

45 y/o female with longstanding HTN

- Currently on 4-drug antihypertensive therapy with good BP control
 - Chlorthalidone, lisinopril, amlodipine, and hydralazine
- Screening for PA performed
 - PAC (aldosterone) 21 ng/dL, PRA (renin) < 0.6 ng/mL/h, Serum [K] 3.6
- Pt not interested in surgical evaluation
 - “My BP is great, and I don’t mind taking a few pills.”
- It is reasonable to continue the pt’s antihypertensives since BP at target?

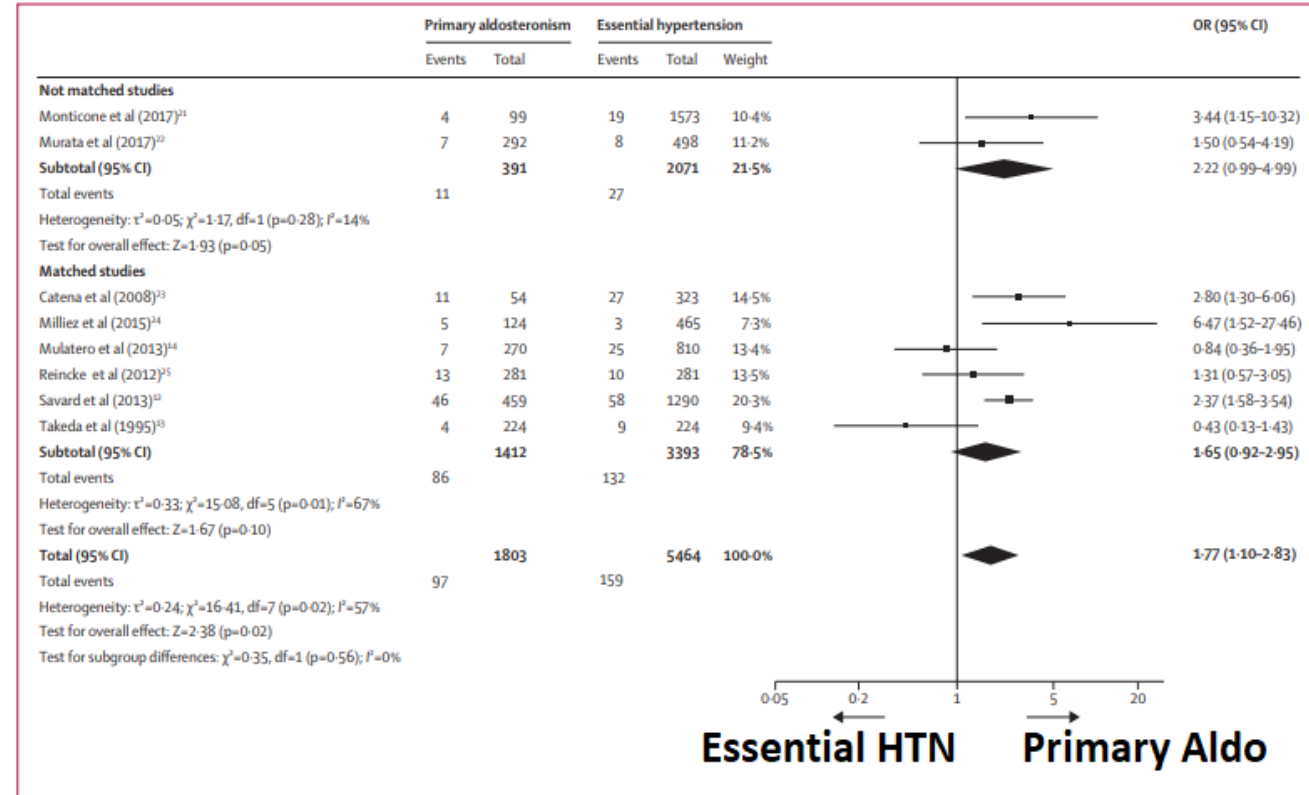
Hyperaldosteronism: Target Organ Damage

Stroke



OR 2.58 (1.93-3.45)

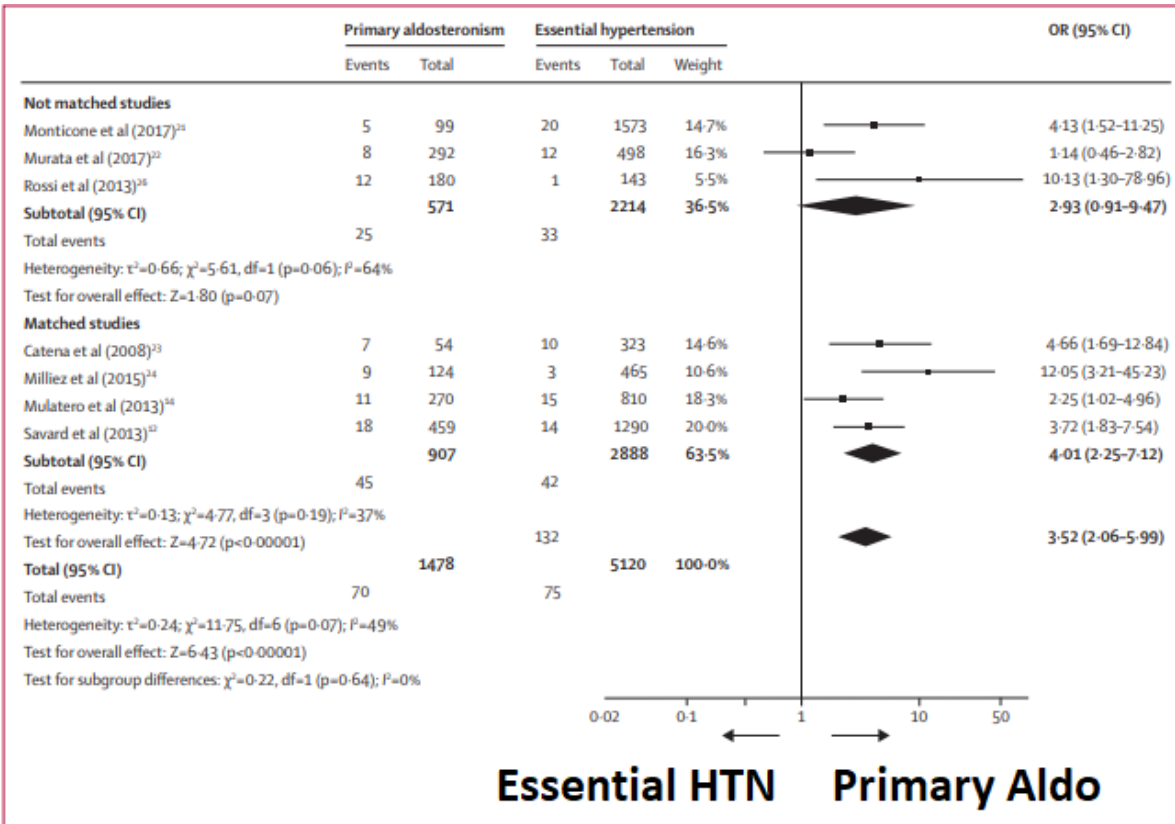
CAD



OR 1.77 (1.1-2.83)

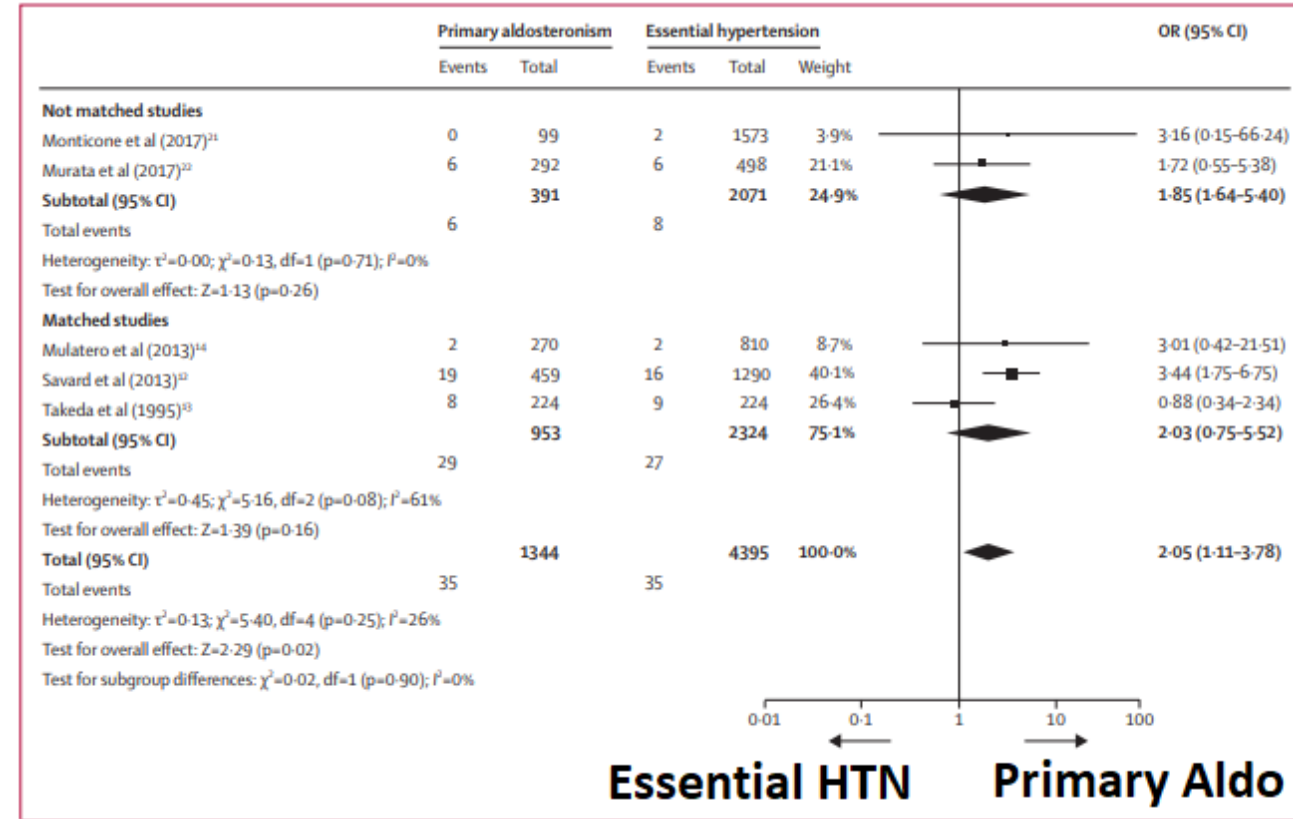
Hyperaldosteronism: Target Organ Damage

Atrial fibrillation



OR 3.52 (2.06-5.99)

Heart Failure



OR 2.05 (1.11-3.78)

Hyperaldosteronism: Case 1, Revisited

45 y/o female with longstanding HTN

- Currently on 4-drug antihypertensive therapy with good BP control
 - Chlorthalidone, lisinopril, amlodipine, and hydralazine
- Positive PA screen
- Pt not interested in surgical evaluation
 - “My BP is great, and I don’t mind taking a few pills.”
- It is reasonable to continue the pt’s antihypertensives since BP at target?

No. Risk of CV events and organ damage increased in PA independent of BP

Hyperaldosteronism: Case 2

- 39 y/o man on 4-drug antihypertensive therapy with appropriate control
- Is screening for PA necessary?

Hyperaldosteronism: Whom to Screen?

Patients with sustained blood pressure above 150/100 mmHg, grade 2 and grade 3 hypertension

Patients with resistant hypertension (blood pressure not controlled by three conventional drugs including a diuretic) or controlled BP (<140/90 mmHg) on four or more antihypertensive drugs

Patients with hypertension and spontaneous or diuretic induced hypokalemia

Patients with hypertension and an adrenal incidentaloma

Patients with hypertension and sleep apnea

Patients with hypertension and a family history of early-onset hypertension or cerebrovascular accident at a young age (<40 years)

All first-degree relatives of patients with PA

VS

When to Consider Testing for Primary Aldosteronism:

- All patients with hypertension should be tested at least once

↓

$\text{PAC} \geq 10 \text{ ng dL}^{-1}$
and
↓ $\text{PRA} (< 1 \text{ ng mL}^{-1} \text{ h}^{-1})$

Endocrine Society Guidelines, 2016

Young, WF. Diagnosis and treatment of primary aldosteronism. *J Intern Med* 2019; 285: 126–148.

The Time has Come for Systematic Screening for Primary Aldosteronism in All Hypertensives*

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JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

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PUBLISHED BY ELSEVIER

VOL. 69, NO. 14, 2017

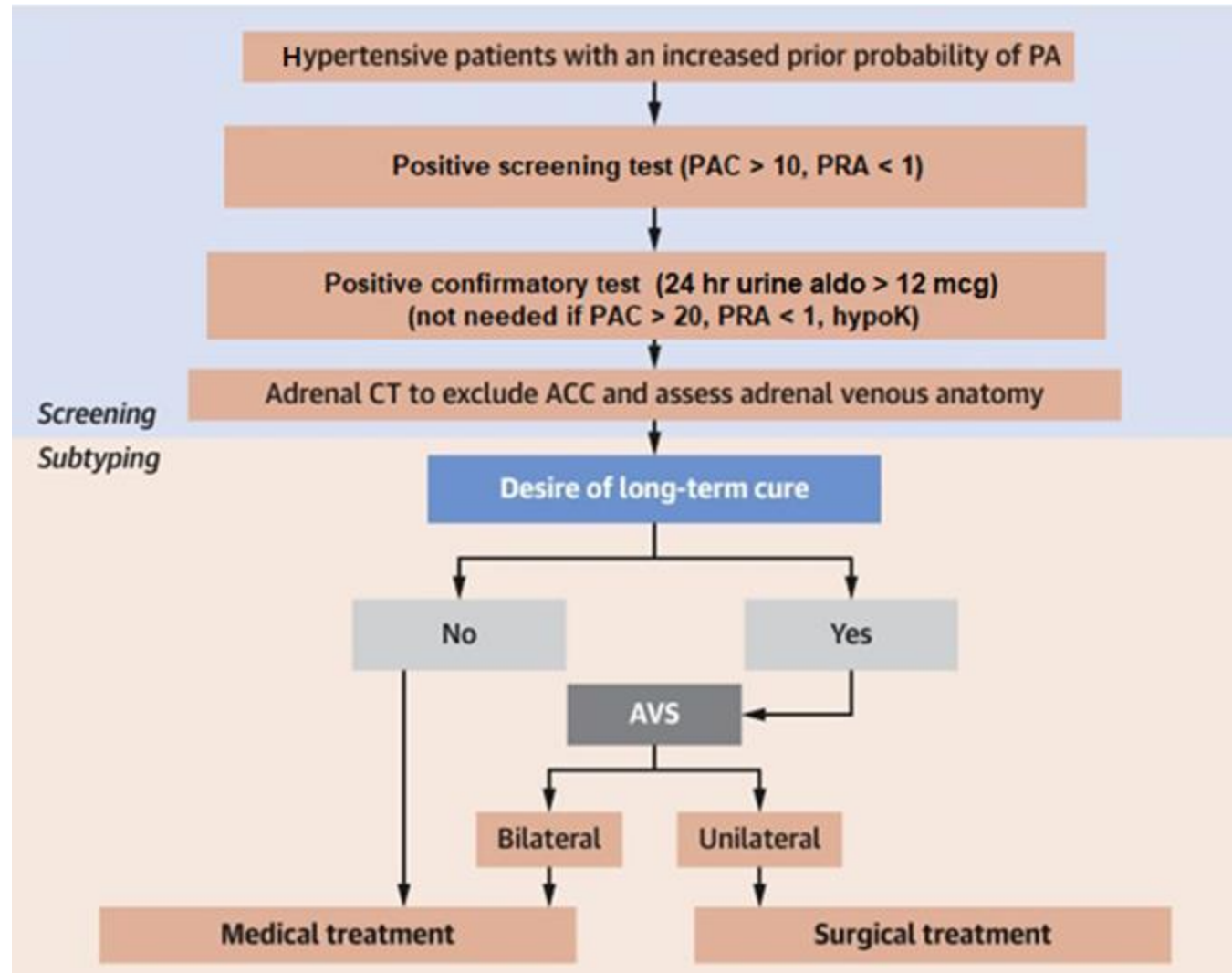
ISSN 0735-1097/\$36.00

<http://dx.doi.org/10.1016/j.jacc.2017.02.041>

Hyperaldosteronism: Case 2, revisited

- 39 y/o man on 4-drug antihypertensive therapy with good BP control
- Is screening for PA necessary? Yes
- Aldosterone 11 (16:30), renin < 0.6, serum [K] 3.1
- After KCl supplementation and change to 09:00 collection
 - Aldosterone 16, renin < 0.6, serum [K] 3.9

Hyperaldosteronism: Simplified Algorithm

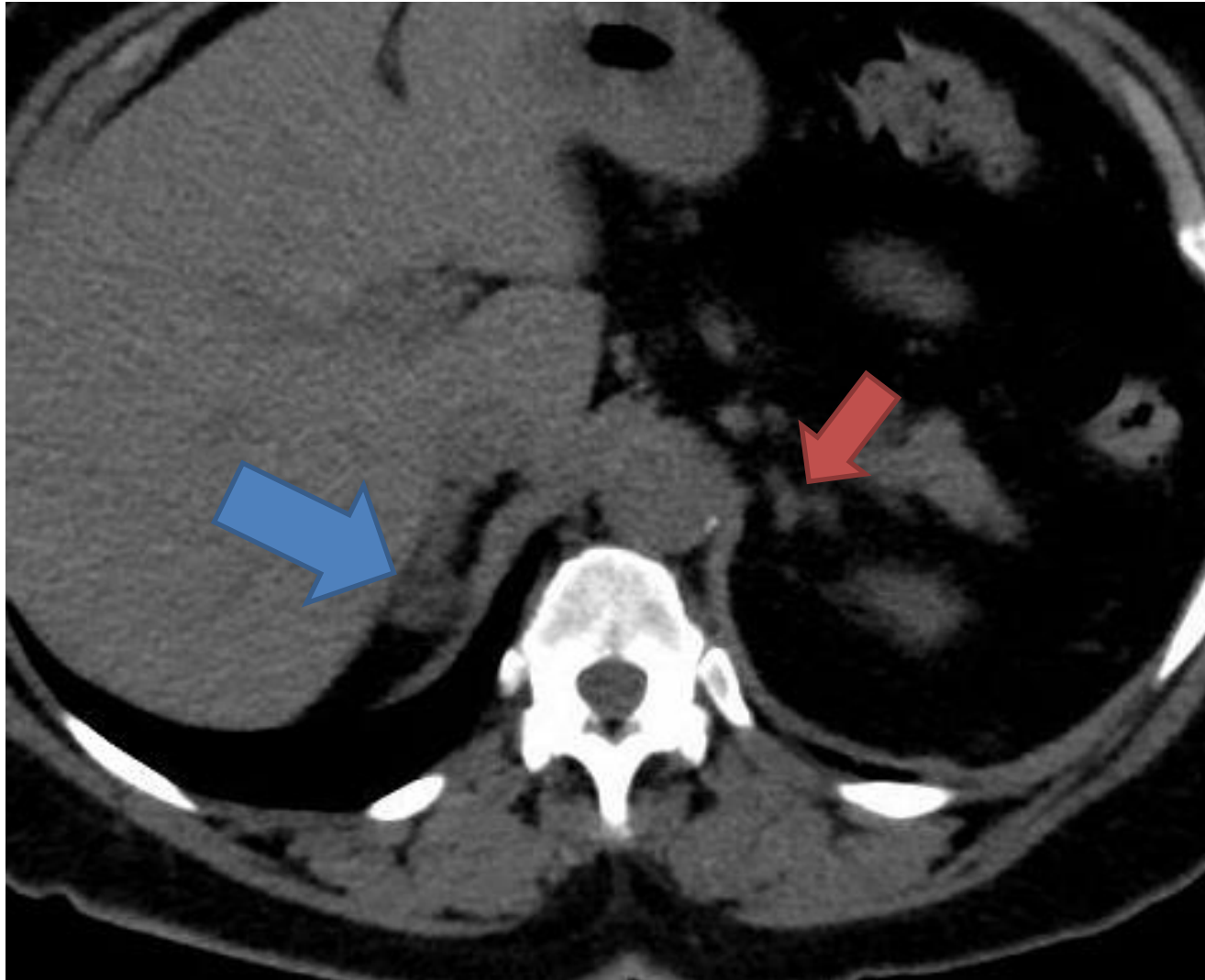


Hyperaldosteronism: Case 2, revisited

39 y/o man on 4-drug antihypertensive therapy

- Positive biochemical screen for PA
- 24 hr urine: Na 240 mmol, aldosterone 13.4 mcg, creat 1.5

Hyperaldosteronism: Case 2, revisited



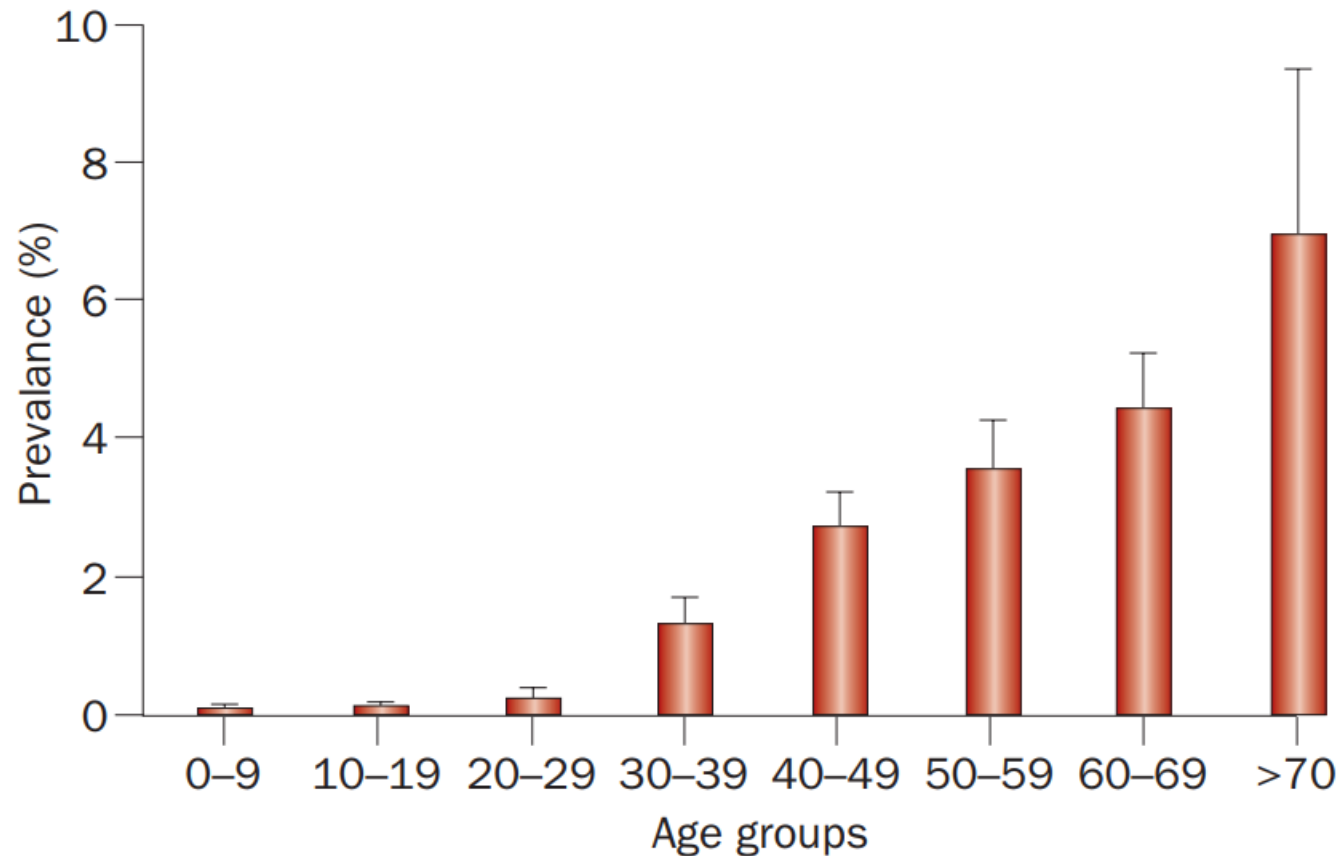
Hyperaldosteronism: Case 2, revisited

39 y/o man on 4-drug antihypertensive therapy

- Positive biochemical screen for PA
- CT abd/pelvis with right-sided 1.5 cm adenoma
- Is AVS needed?

Hyperaldosteronism: Limitation of CT Abd

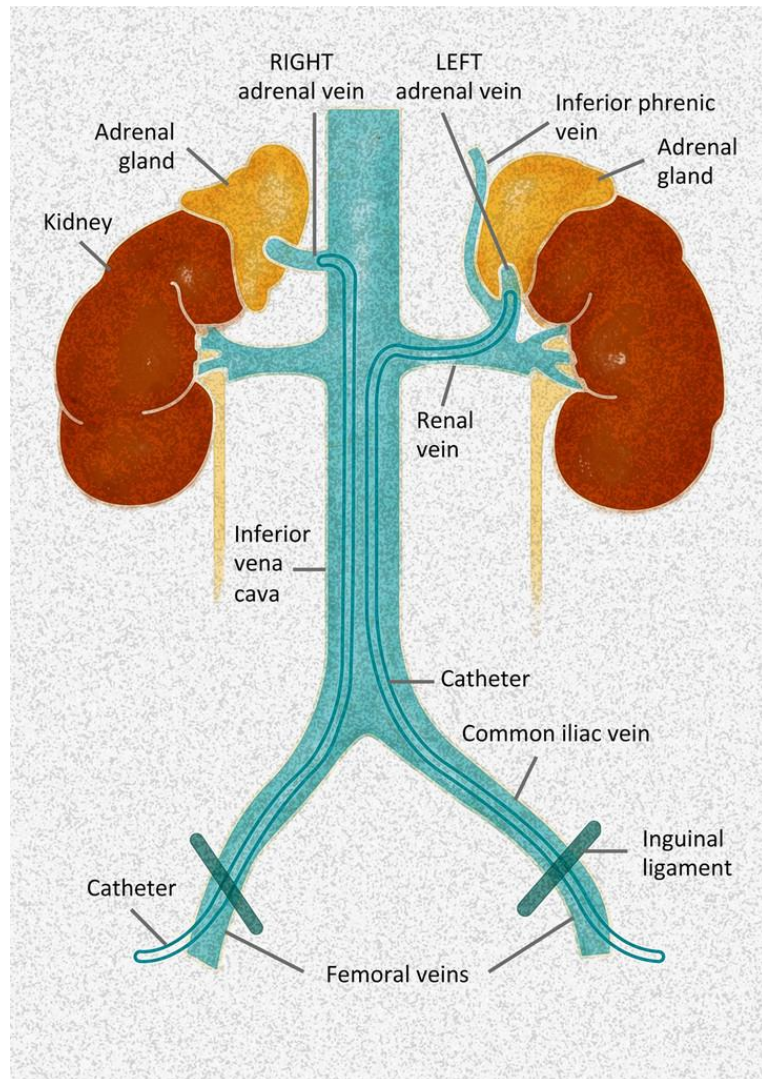
- High Prevalence of Adrenal Incidentaloma in General Population



Hyperaldosteronism: Poor CT Abd Performance

Study	Number of Subjects	Accuracy of CT for Aldo Hypersecretion
Young WF, et al (2004)	194	53%
Nwariaku FE, et al (2006)	48	54%
Lim V, et al (2014)	143	59%
Ladurner R, et al (2017)	152	61%

Hyperaldosteronism: Adrenal Venous Sampling



- Adrenal veins cannulated by IR sequentially
- Aldosterone and cortisol levels are measured simultaneously from L + R adrenal veins and IVC

“Are catheters in correct position?” – Selectivity Index (SI)

- **Adrenal:IVC cortisol ≥ 3** shows correct catheterization

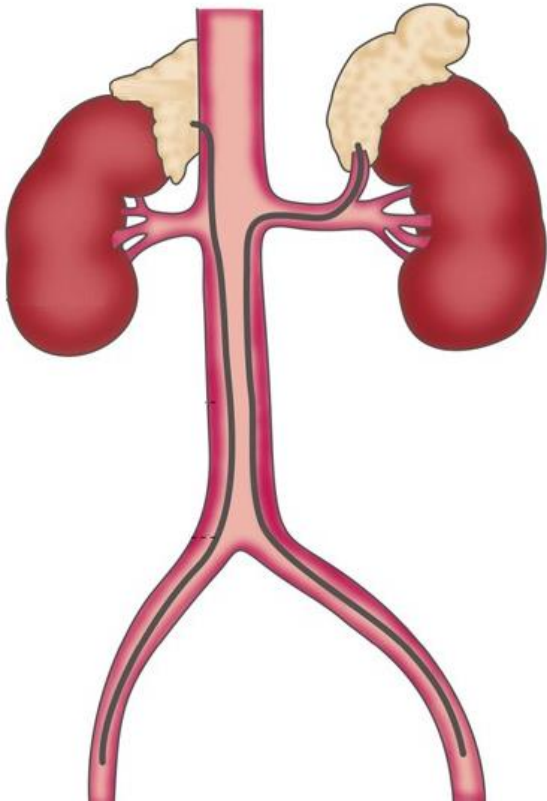
“Does aldo production lateralize?” – Lateralization Index (LI)

- **Dominant Aldo:cortisol/Non-dominant aldo:cortisol ≥ 4**

Hyperaldosteronism: Case 2, revisited

- 39 y/o man with primary aldosteronism
- CT abd/pelvis with right-sided 1.5 cm adenoma
- AVS performed...

“Are catheters in correct position?”
Adrenal:IVC cortisol ≥ 3 shows correct catheterization



Cortisol	(mcg/dL)	
IVC	L adrenal vein	R adrenal vein
36.1	581.2	840

Aldo/Cortisol		
IVC	L adrenal vein	R adrenal vein
0.64	5.85	0.43

“Does aldo production lateralize?”
Dominant aldo:cortisol/Non-dominant aldo:cortisol ≥ 4



Aldosterone	(ng/dL)	
IVC	L adrenal vein	R adrenal vein
23.2	3400	362

Hyperaldosteronism: Case 2, revisited

Pt underwent L adrenalectomy

- Post-operatively, potassium supplements and ACE-I held

One week later

- HTN improved (4 BP drugs -> amlodipine monotherapy)
- Hyperkalemia to 6.1 -> treated with fludrocortisone x 6 wks

Hyperaldosteronism: Case 3

56 y/o man with HTN

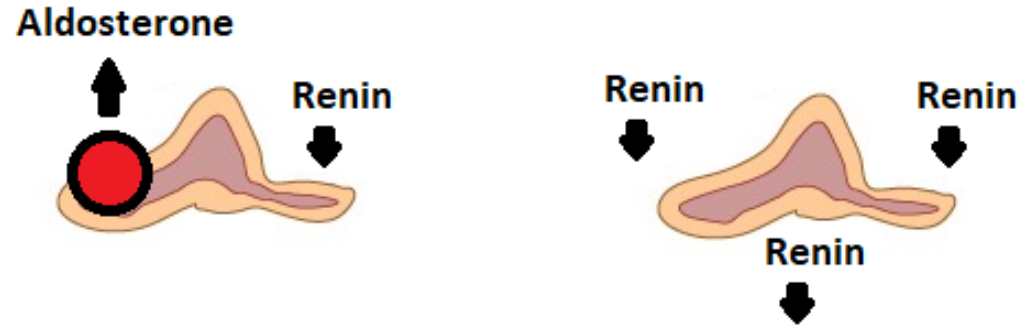
- BP controlled while on spironolactone 50 mg daily, amlodipine 10 mg daily
- Screening for PA performed
 - PAC 21 ng/dL, PRA < 0.6 ng/mL/h, [K] 3.4
- Can these results be interpreted while on BP meds?
 - Yes! No BP med will cause false positive testing for PA
 - But if PAC elevated and PRA not suppressed, hold BP meds (or switch to alpha blocker or CCB) and repeat testing in 2 wks

Hyperaldosteronism: Med Effect on Aldo/Renin

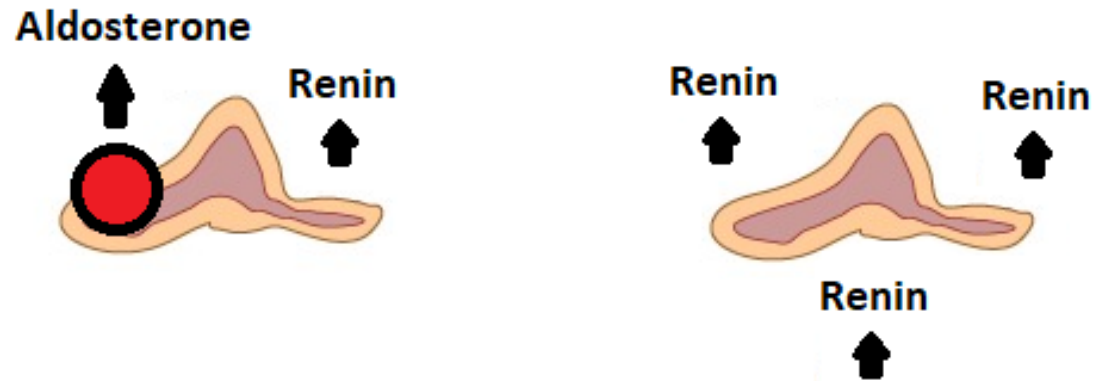
	Aldosterone	Renin
β -Blockers	↓	↓
ACEi, ARBs	↓	↑
K ⁺ -sparing diuretics	↑	↑
K ⁺ -wasting diuretics	↕	↑
CCBs (DHP only)	↕	↑

Aldo Interpretation Based on Renin Levels

Adenoma with suppressed renin

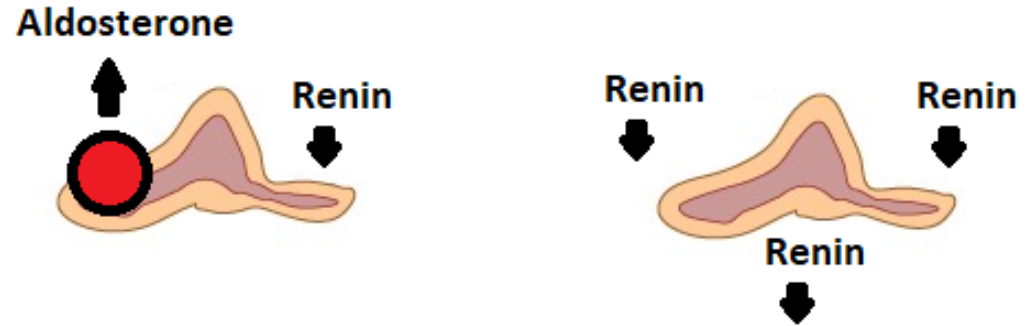


Adenoma without suppressed renin



Aldo Interpretation Based on Renin Levels

Adenoma with suppressed renin



Adenoma without suppressed renin



Hyperaldosteronism: Case 4

65 y/o man with longstanding HTN

- Positive testing for PA
- CT abdomen unremarkable
- AVS discussed with the patient, but he is concerned about complications
- He asks, “Could this be managed with a medication instead?”

Hyperaldosteronism: Challenges

1. Spironolactone Tolerability

- Incidence of gynecomastia
 - 10% with 25 mg daily¹
 - 30% with 100 mg daily²
 - 62% with 200 mg daily²

¹Pitt B, et al. NEJM, 1999 Sep 2;341(10):709-17 ²Huffman D, et al. Clin Pharmacol Ther. 1978 Oct;24(4):465-73.

Hyperaldosteronism: Goals of Therapy

1. Spironolactone Tolerability

- Incidence of gynecomastia
 - 10% with 25 mg daily¹
 - 30% with 100 mg daily²
 - 62% with 200 mg daily²

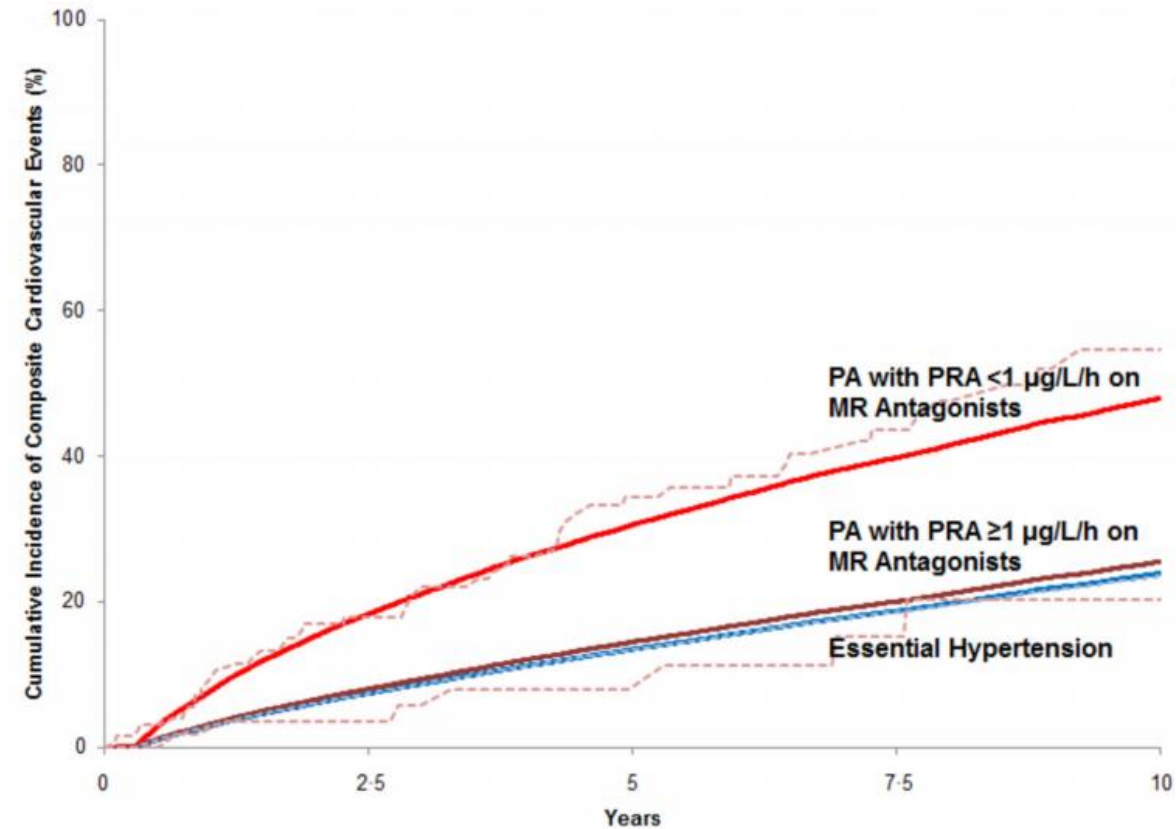
2. Goals of therapy not entirely straightforward

- BP control not enough, need adequate MR blockade
- Serum [K] > 4.5, PRA > 1

¹Pitt B, et al. NEJM, 1999 Sep 2;341(10):709-17. ²Huffman D, et al. Clin Pharmacol Ther. 1978 Oct;24(4):465-73.

Hyperaldosteronism: Treat to Renin > 1

- 602 PA pts treated with MR antagonists
- 41,853 age-matched pts with essential HTN
- 1^o outcome – incident CV event
 - MI, revascularization, CHF admit, CVA
- Found 2x risk in PA vs essential HTN
- UNLESS treated to PRA > 1 (no diff)



Hyperaldosteronism: Pearls of Med Therapy

1. High doses of spironolactone generally not needed
 - MR blockade achieved in > 90% of PA pts with 50 mg spironolactone¹
2. In case of antiandrogenic side effects, switch to eplerenone
 - Eplerenone must be given twice daily (3-6hr half life)
 - So, if pt intolerant of spironolactone 50 mg daily, use eplerenone 50 mg bid
3. PA is a hyperfiltration state: eGFR will decrease with MRA therapy²
 - Mean decrease in eGFR of 15 ml/min per 1.73 m²

¹Lechner B, et al. Euro J of Endocrinology 181, R147-153 (2019) ²Ribstein J, et al. J Am Soc Nephrol 16: 1320 –1325 (2005)

Hyperaldosteronism: Not Just a Salt Problem

1. Spironolactone Tolerability

- Incidence of gynecomastia
 - 10% with 25 mg daily¹
 - 30% with 100 mg daily²
 - 62% with 200 mg daily²

2. Goals of therapy not entirely straightforward

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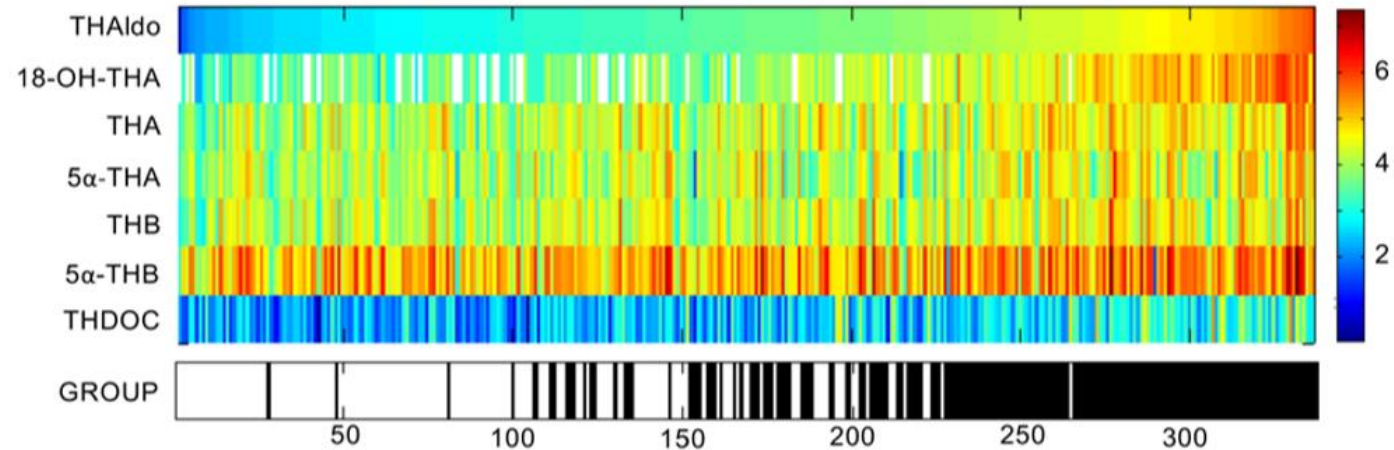
3. Is MR blockade enough?

- How do we deal with glucocorticoid excess in PA?

¹Pitt B, et al. NEJM, 1999 Sep 2;341(10):709-17. ²Huffman D, et al. Clin Pharmacol Ther. 1978 Oct;24(4):465-73.

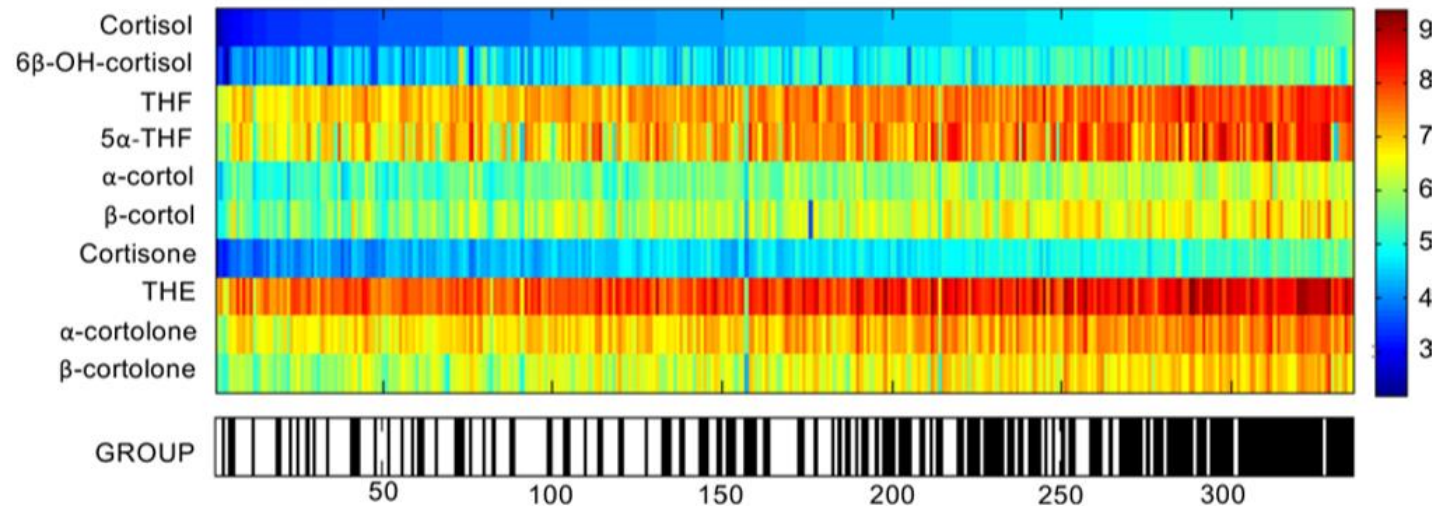
Hyperaldosteronism: Not Just Salt

Mineralocorticoid

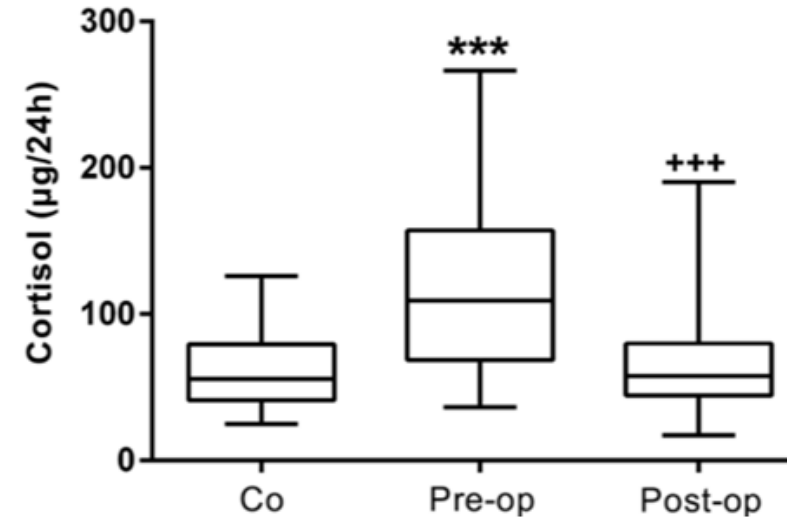
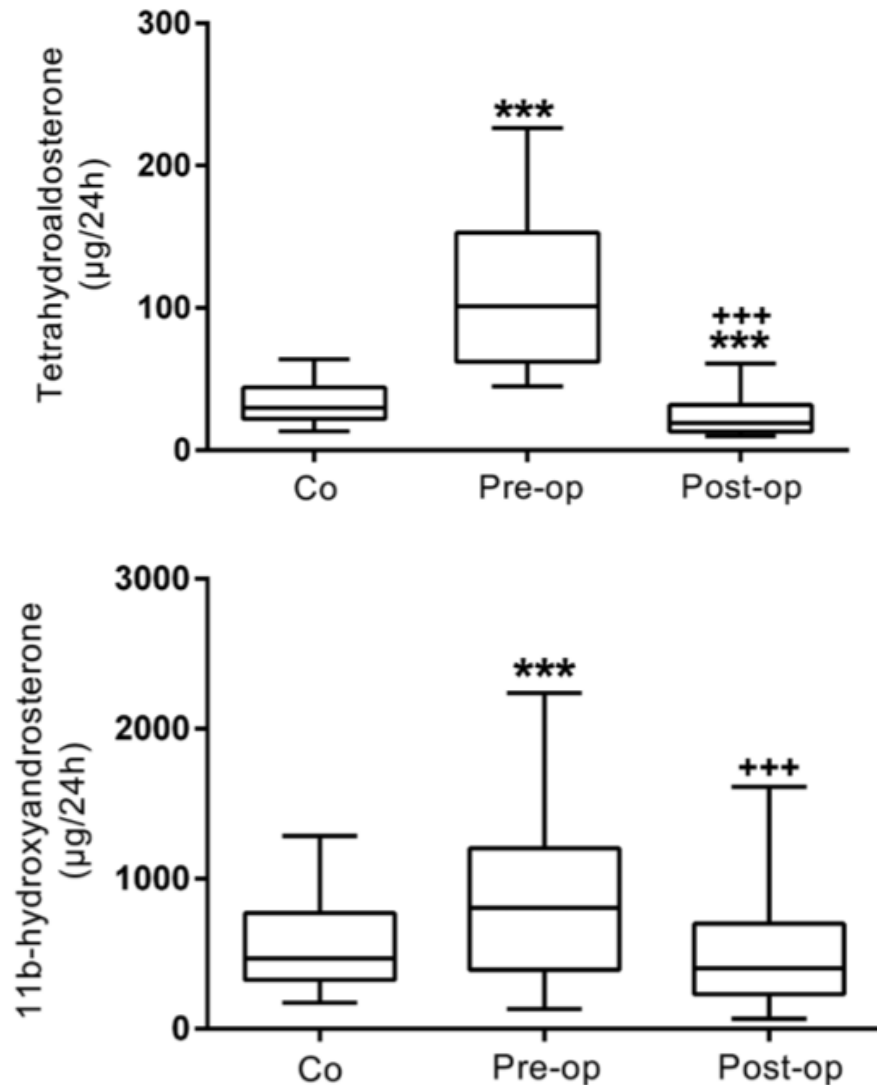


■ PA Subject
□ Healthy Control

Glucocorticoid



Hyperaldosteronism: Not Just Salt

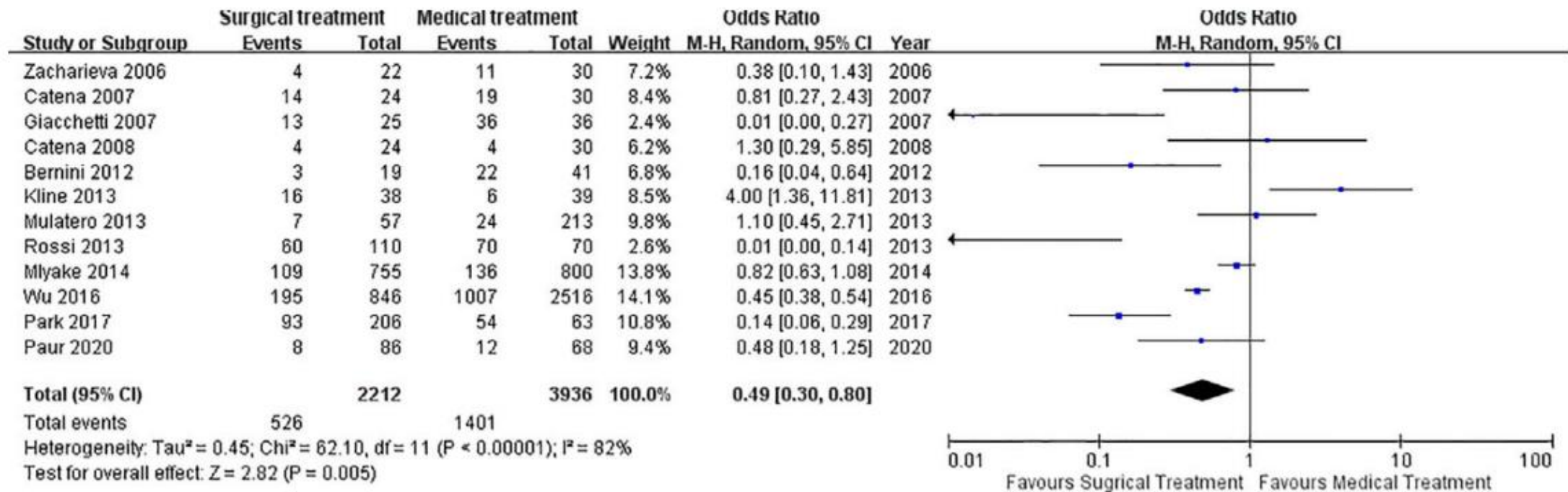


- Is MRA therapy enough?

Hyperaldosteronism: Medical vs Surgical Rx

12 studies including 6148 PA pts

- Surgery (versus medical therapy)
 - Lower incidence of composite CV outcomes
 - Less persistence of HTN



Hyperaldosteronism: Future Directions

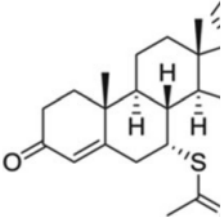
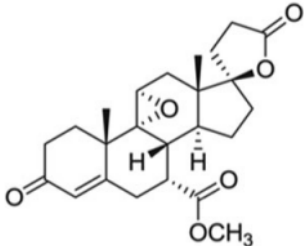
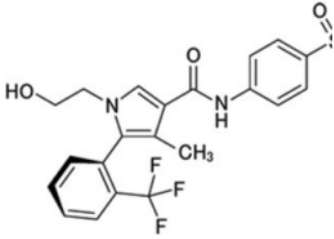
High Affinity, Selective, MRAs

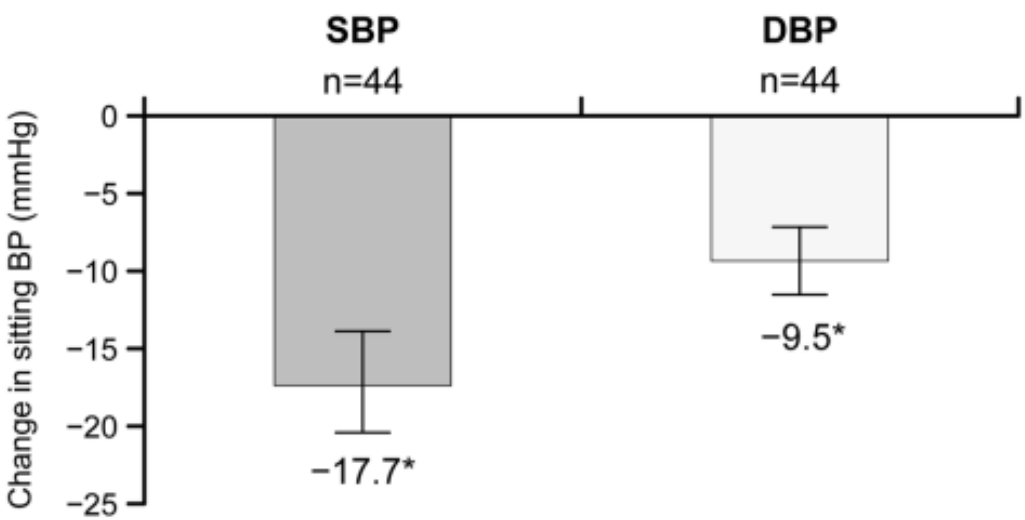
- Esaxerenone

Future Subtype Studies for PA

- Peripheral “hybrid” steroids (18-Oxocortisol)
- Nuclear Imaging (68Ga-Pentixafor)

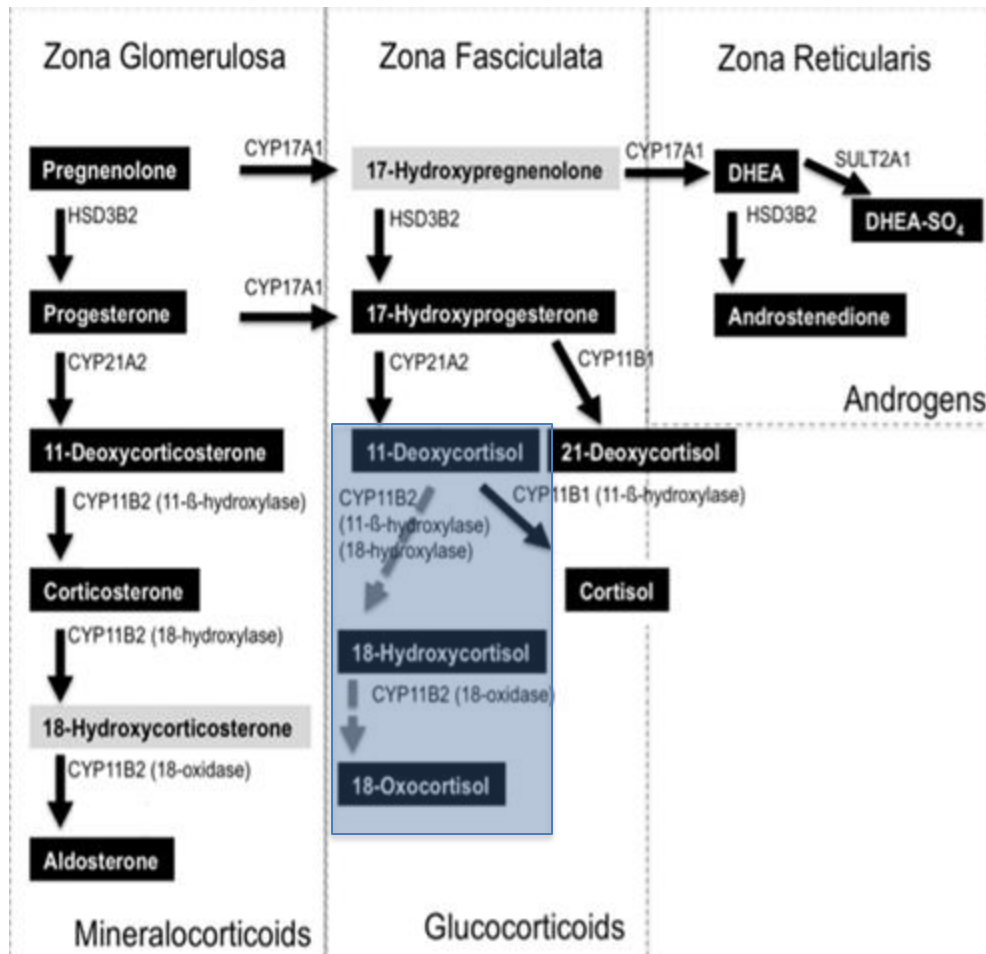
Hyperaldosteronism: Esaxerenone

	Spironolactone	Eplerenone	Esaxerenone
Chemical structure			
Molecular formula	C ₂₄ H ₃₂ O ₄ S	C ₂₄ H ₃₀ O ₆	C ₂₂ H ₂₁ F ₃ N ₂ O ₄ S
Oral bioavailability	60–90%	69%	90%
EC ₅₀ or IC ₅₀ (nM) (rats or rabbits)			
MR	36	713	9.4
GR	764	3060	>10,000
AR	133	>100,000	>10,000
PR	1200	>100,000	>10,000
T _{1/2}	Human: >12 h	Human: 3–5 h	Human: 18.6–25.1 h Monkey: 10–13 h



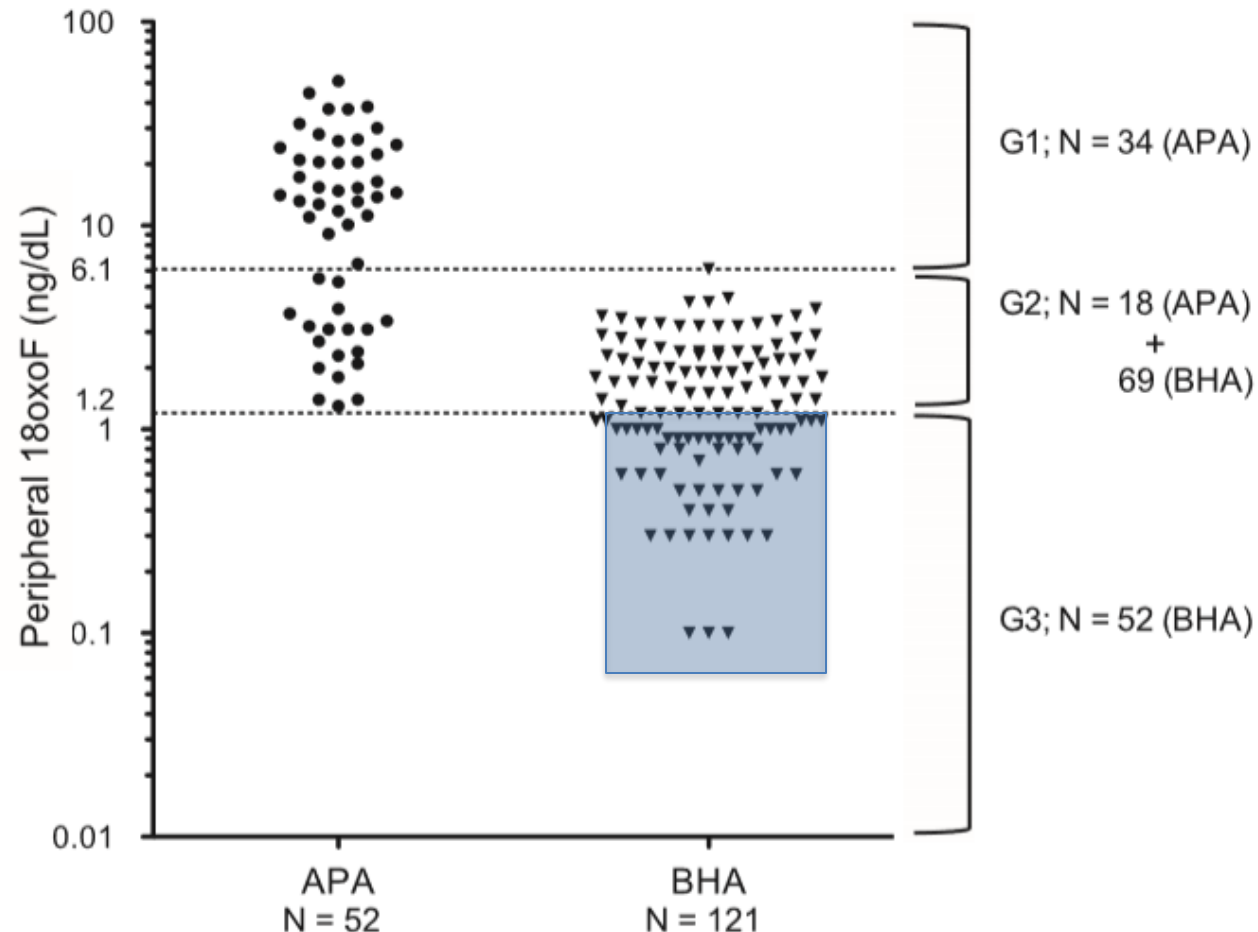
Hyperaldosteronism: 18-Oxocortisol

Peripheral 18-Oxocortisol to Distinguish APA from BHA



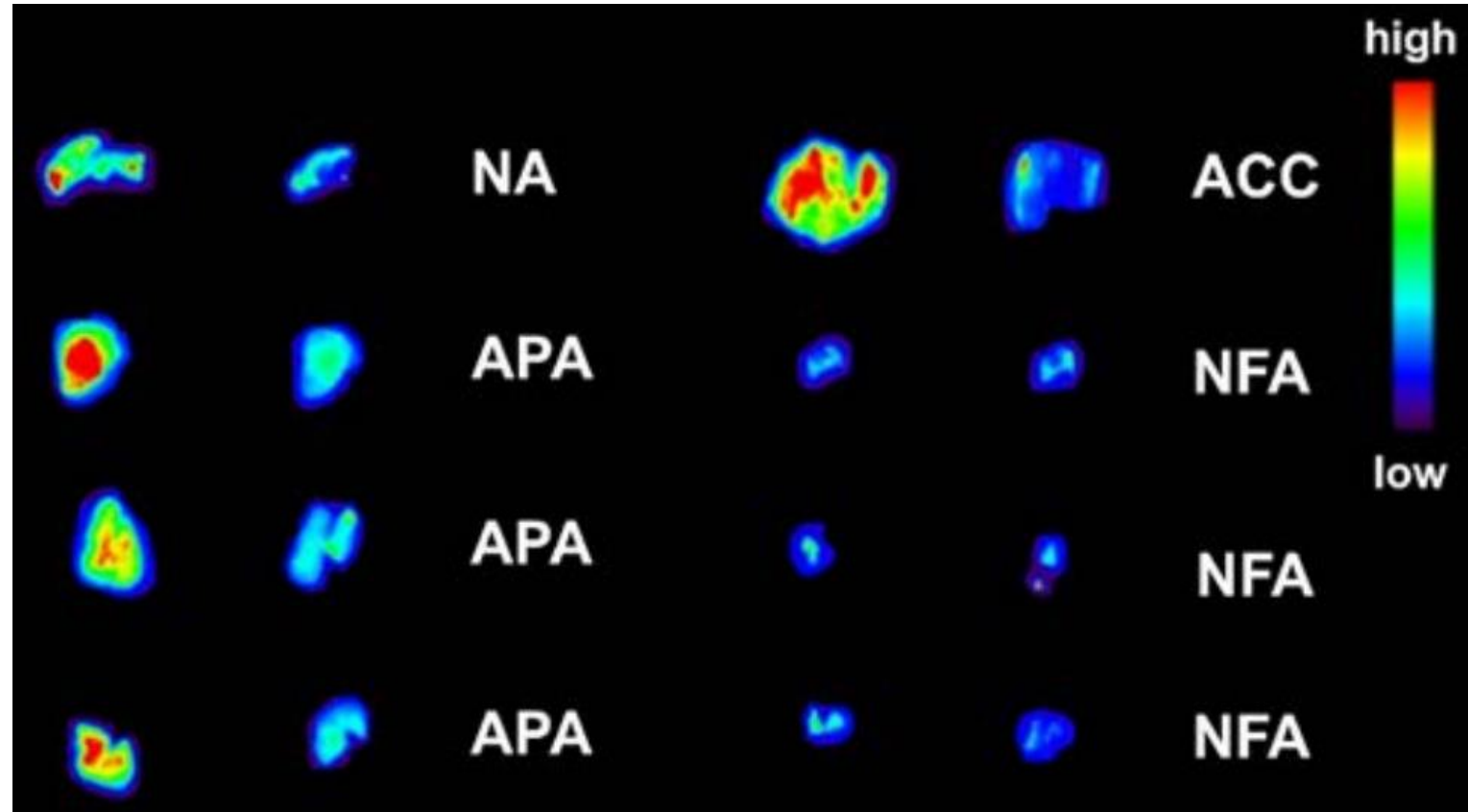
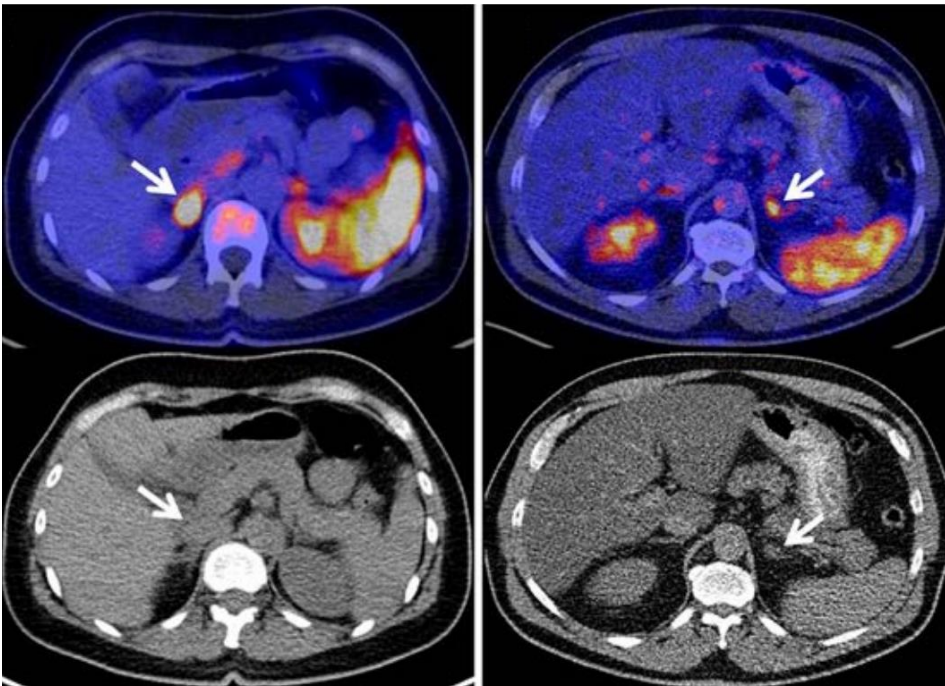
Hyperaldosteronism: 18-Oxocortisol

Peripheral 18-Oxocortisol to Distinguish APA from BHA



Hyperaldosteronism: Functional Imaging

^{68}Ga -Pentixafor Targets CXCR4 in Aldo-Producing Adenomas



Hyperaldosteronism: Summary

- PA associated with cardiac/renal injury if aldosterone excess not addressed
 - EVEN if BP controlled with other antihypertensives
- When screening hypertensive pts for PA
 - Positive screen is aldo > 10 ng/dL and PRA < 1 (early morning collection)
 - If aldo > 10 but PRA > 1,
 - Hold other BP meds (can use α - or CCB) and recheck aldo:renin in 2 wks
 - Within 6 weeks, renin should fall if PA present
- Can do screening, confirmatory, and AVS testing for PA if spironolactone used
 - BUT ONLY if renin is suppressed (i.e., PRA < 1)
- Most effective tx for APA is adrenalectomy; if bilateral, use MR antag.
- If treating medically, must have adequate MR blockade
 - Target serum [K] of ~4.5, PRA > 1