Resistant Hypertension and Primary Hyperaldosteronism

DATE: April 11,2025

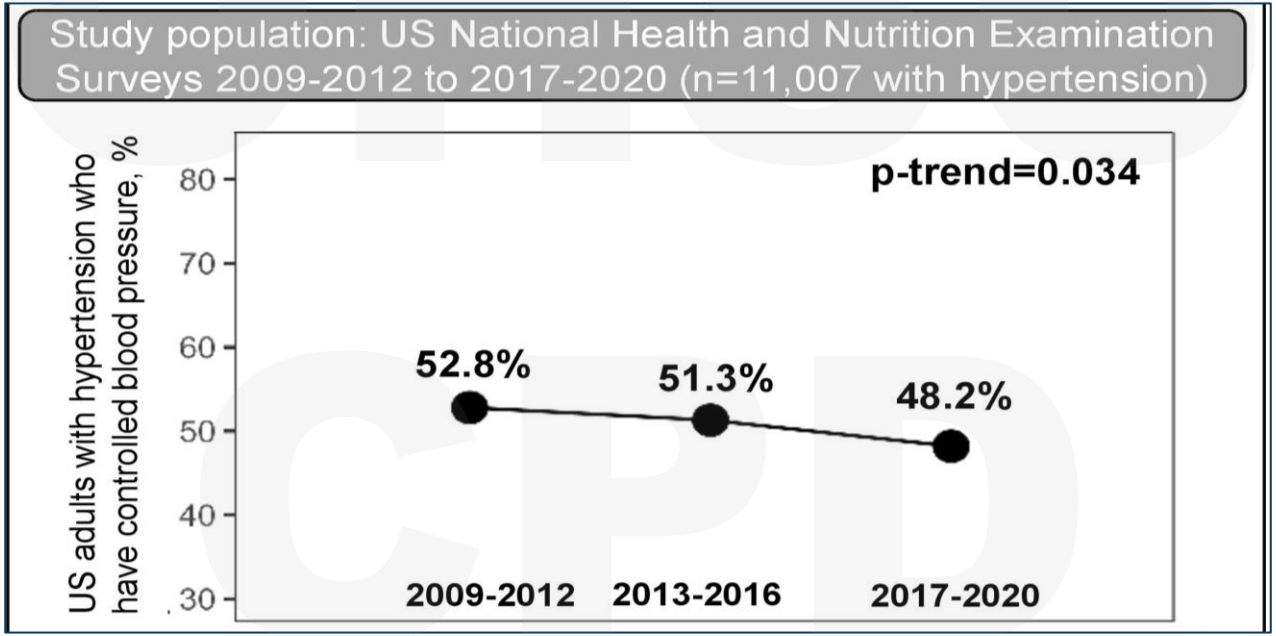
PRESENTED BY: Nupur Mistry, MD
Assistant Professor
Director of Comprehensive Hypertension Program
OHSU Division of Nephrology & Hypertension

No Disclosures

Objectives

- Review current anti-hypertensive medication guidelines
- Define resistant hypertension
- Review epidemiology and diagnosis of Primary Hyperaldosteronism
- Review management of Primary Hyperaldosteronism
- Futures of Management

Rate of Blood Pressure Control

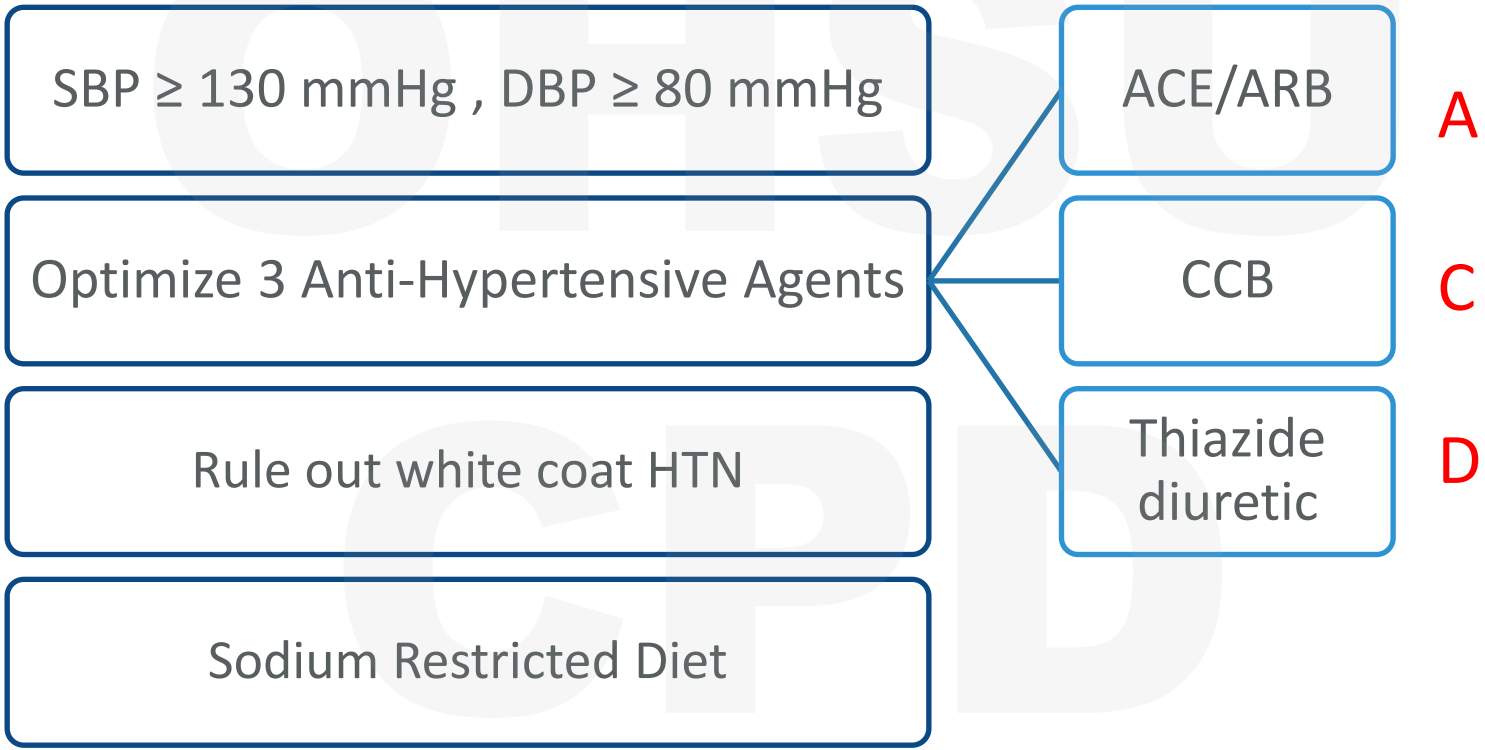


Muntner. *Hypertension*. 2022

Barriers to Blood Pressure Control

- Lack of access to care
- Therapeutic inertia
- Poor adherence to treatments
- Inadequate education
- Resistant hypertension

Resistant Hypertension



Life-Style Modifications in Hypertension Management

Modification	SBP Reduction
Weight Reduction – BMI 18.5-24.9	5-20 mmHg/10 kg
Adopt DASH diet	8-14 mmHg
Dietary Sodium Reduction	2-8 mmHg
Physical Activity	4-9 mmHg
Moderation of Alcohol consumption	2-4 mmHg

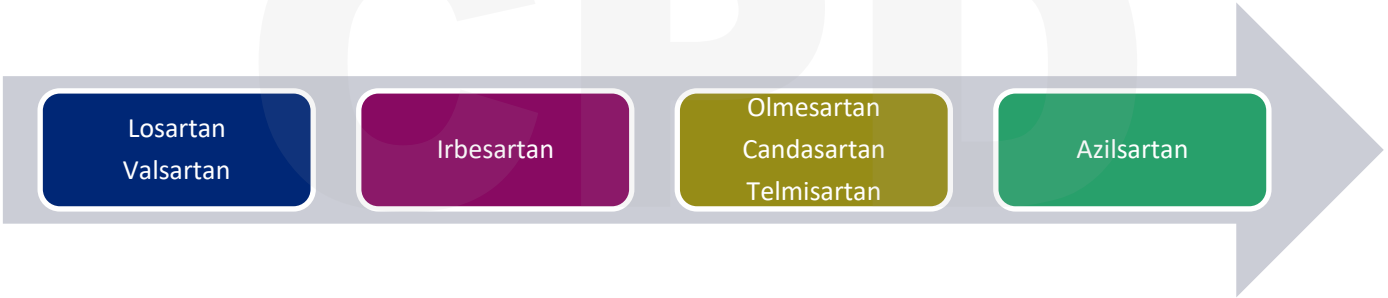
Adapted from Sayarlioglu, *Kidney Int Suppl.* 2013

Initial 3 Drug Regimen

Ensure adequate dosing of medications based on half life

Ex. HCTZ and lisinopril

Note strength of agents within drug class



Initial 3 Drug Regimen

Ensure adequate dosing of medications based on half life

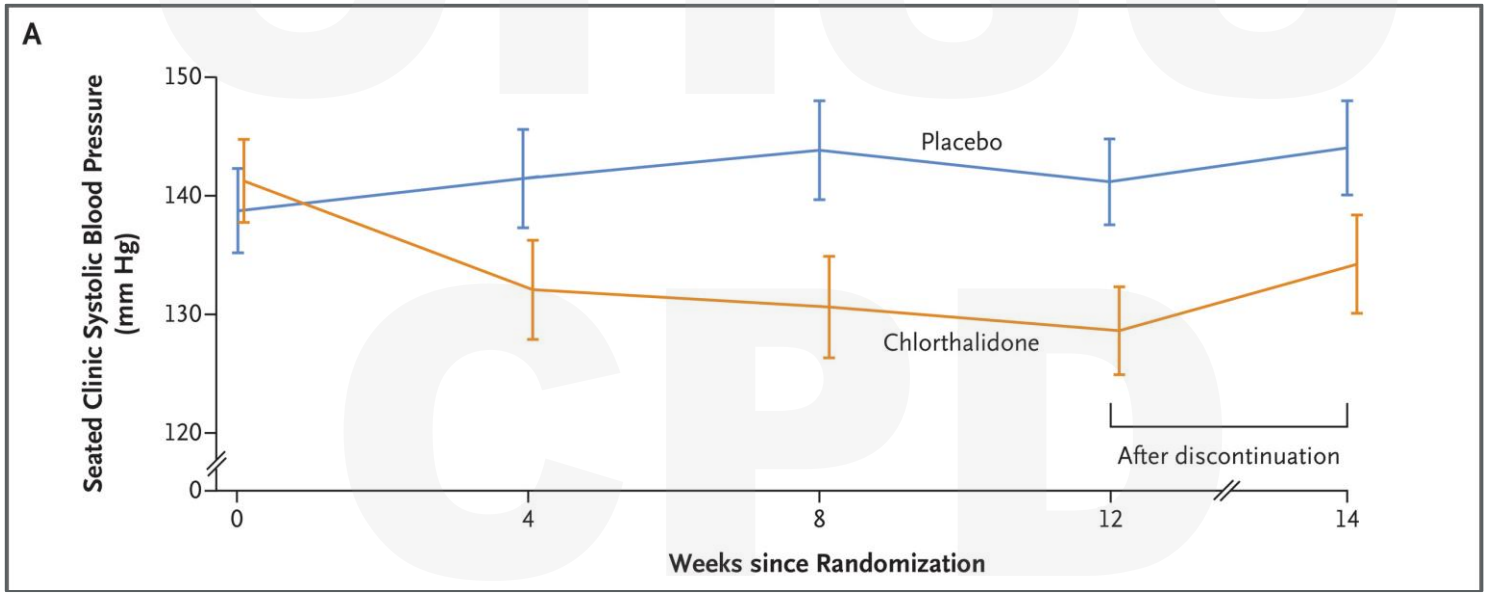
Ex. HCTZ and lisinopril

Note strength of agents within drug class

Ensure selected diuretics are appropriate for eGFR

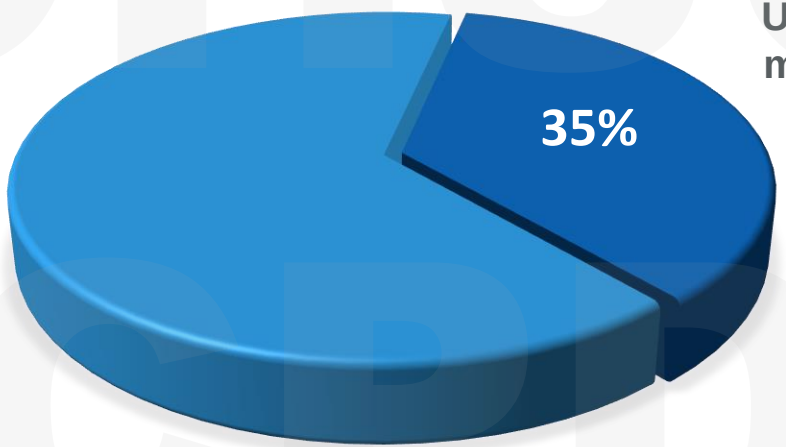
CLICK Trial

Patients with CKD4 randomized 1:1 Chlorthalidone vs Placebo



Agarwal, *NEJM* 2021

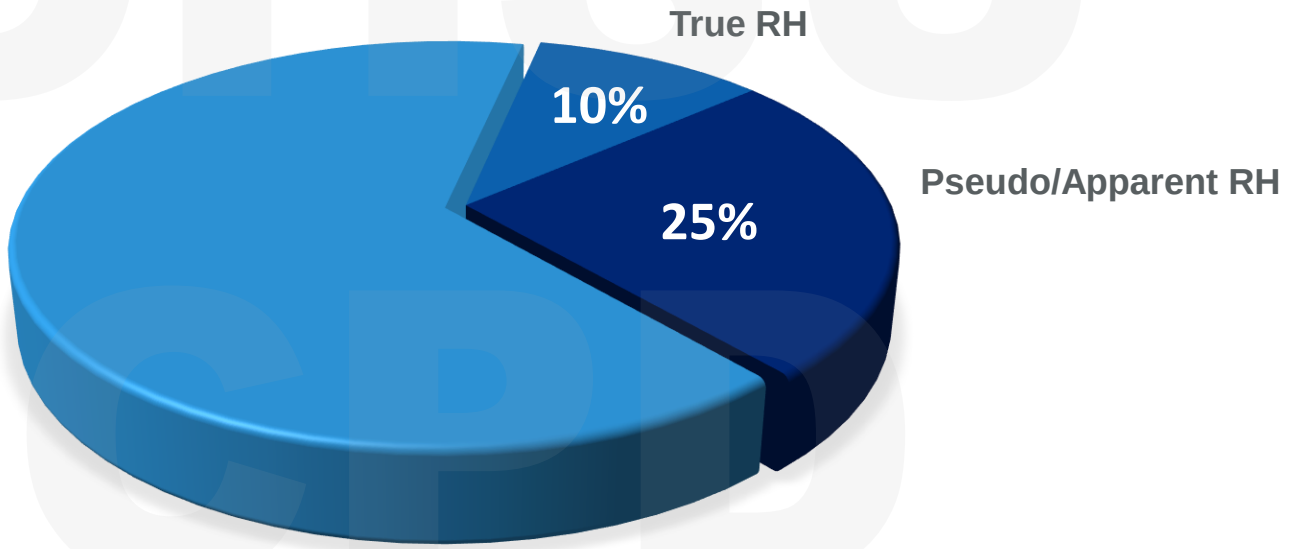
POPULATION WITH HYPERTENSION



Uncontrolled on 3 meds/Requiring 4 meds

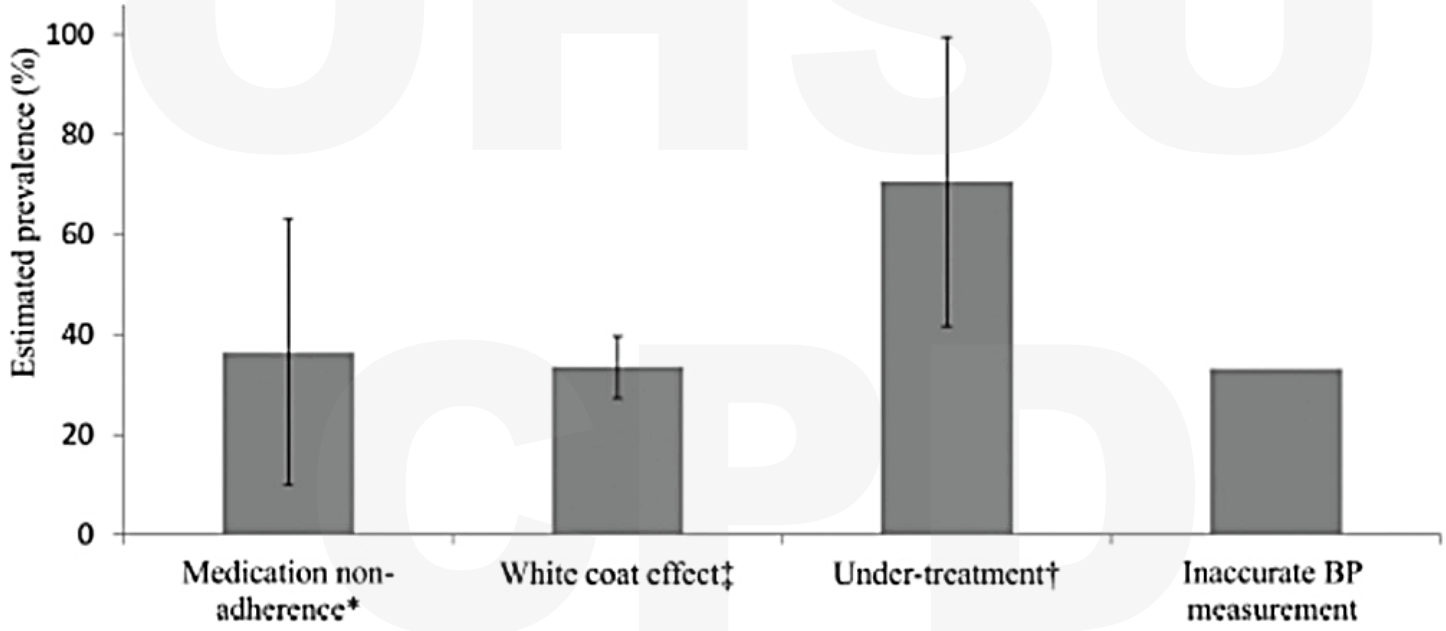
Adapted from Noubiapp, *Heart* 2019

POPULATION WITH HYPERTENSION



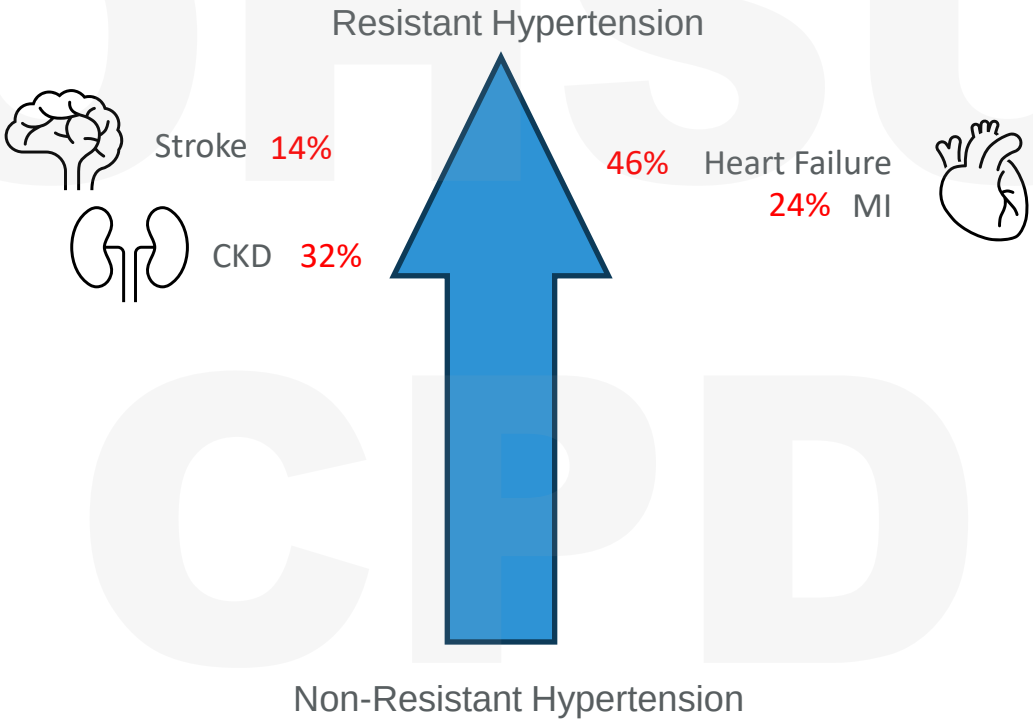
Adapted from Noubiapp, Heart 2019

Pseudo-Resistant Hypertension



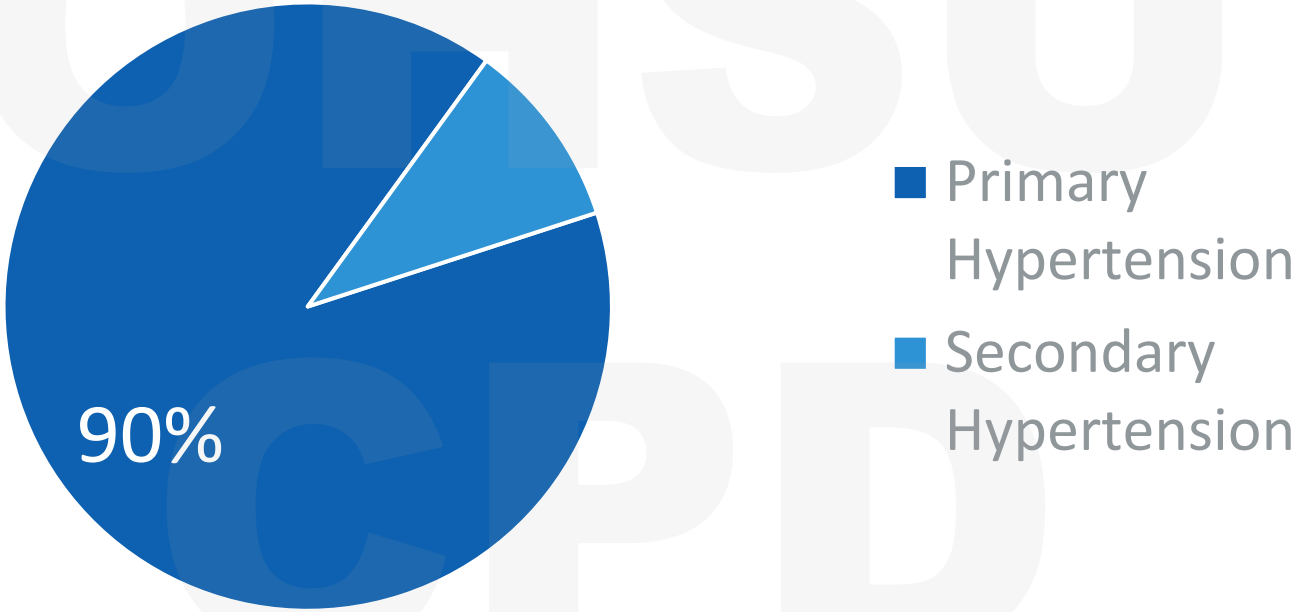
Carey, *Hypertension* 2018

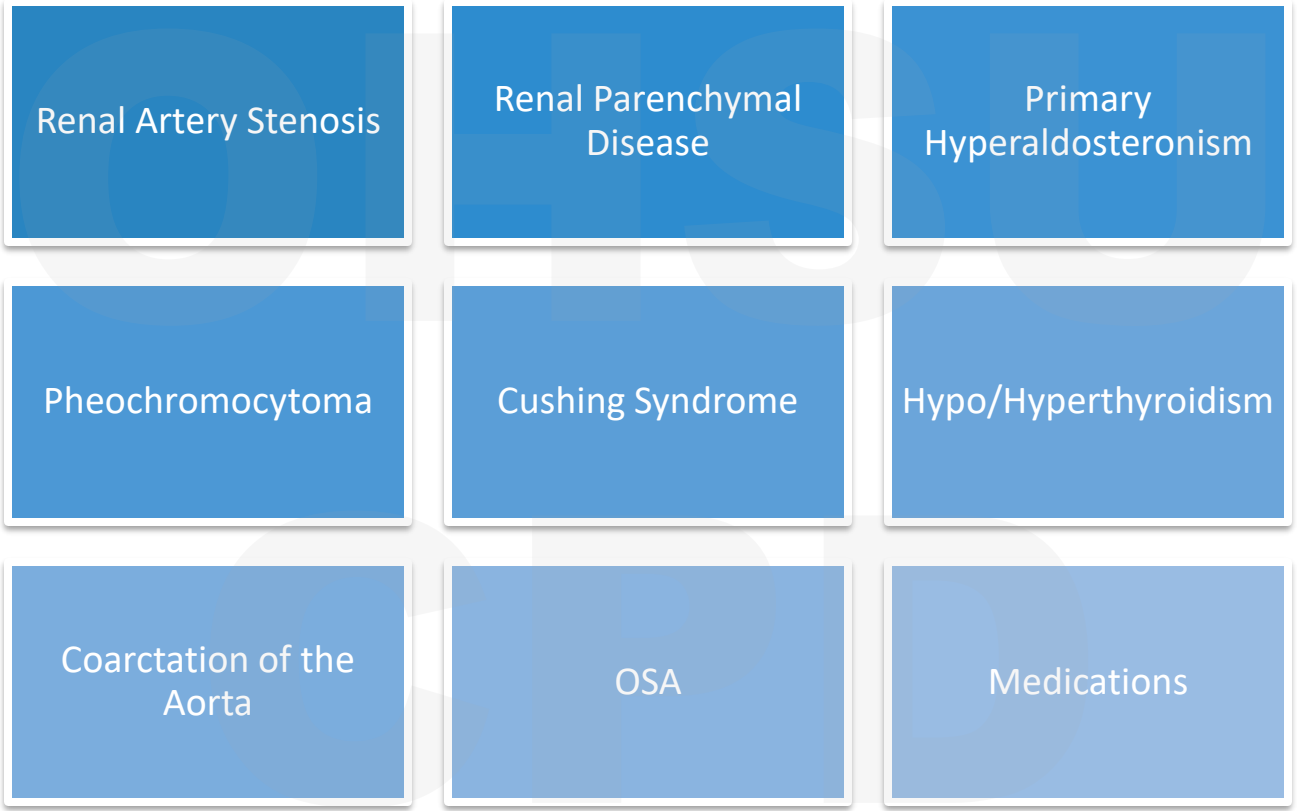
Prognosis for Individuals with RH



Sim, *Kidney Int* 2015

All Patients with Hypertension




Renal Artery Stenosis
Renal Parenchymal Disease
Primary Hyperaldosteronism
Pheochromocytoma
Cushing Syndrome
Hypo/Hyperthyroidism
Coarctation of the Aorta
OSA
Medications

Case Presentation #1

- Mr. N is a 47 yo M, referred due to concern of primary hyperaldosteronism
- HTN diagnosed 2 years ago
- Home Medications:
  - Diltiazem 300mg
  - Spironolactone 50mg
- Prior Medications
  - Hydrochlorothiazide - discontinued

History

Additional Past Medical Hx

- OSA using CPAP
- Pre-Diabetes

Family Hx

- Mother diagnosed with HTN at age 65

Social Hx

- Non-smoker
- Social Alcohol Use

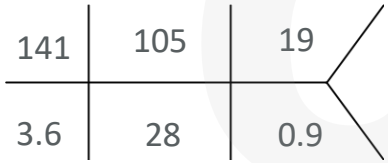
Physical Exam

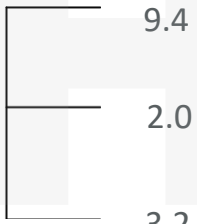
Vitals:

BP: 149/82 HR: 67 Home BPs: 137-148/84-93

Physical Exam: Unremarkable

Lab Studies





A1c: 5.9

Urinalysis: No protein, no blood

Why Primary Hyperaldosteronism?

Primary Hyperaldosteronism

~20-25% of resistant hypertension

30-60 years of age

Unprovoked hypokalemia (30-35%)

Will commonly see hypokalemia in presence of diuretic therapy

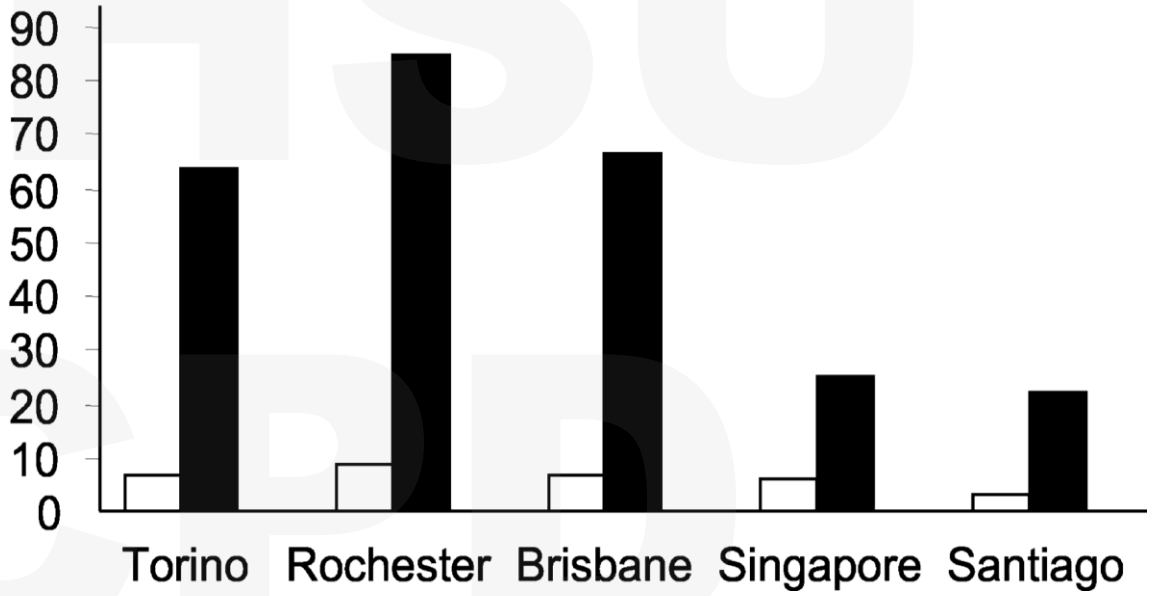
Who Should Be Tested?

- Patients with Hypertension and Hypokalemia
- Treatment-Resistant Hypertension
- Severe Hypertension
- Hypertension and Incidental Adrenal Mass
- Early Onset of Hypertension
- Family Hx of Primary Hyperaldosteronism

Number of Cases of Primary Hyperaldosteronism Diagnosed

Testing for clinical suspicion

Testing for anyone with BP >160/100



Mulatero, *JCEM*. 2004

Initial Testing – PAC and PRA

Ideally performed in AM

Seated patient

Can be performed in setting of most antihypertensive medications

- Do not need to discontinue ACE/ARB, BB
- MRA/potassium-sparing diuretic medications
  - Spironolactone: discontinued for 4-6 weeks
  - Eplerenone, amiloride, triamterene: discontinued for 2 weeks

Normokalemia

Primary Hyperaldosteronism - ARR

No consensus on ARR threshold

Ranges from 12-30

Confirmatory Testing

- Oral Salt Load
- Saline Suppression Test
- Fludrocortisone suppression Test
- Captopril Challenge Test

Oral Salt Load

Procedure:	Results	Advantage	Disadvantage
6g/day sodium chloride intake for 3 days Supplement KCl Check 24 hr U-Aldo, Una, UCr starting on day 3	Ualdo > 12 confirms primary hyperaldo Must have UNa >200 mEq	Inexpensive Perform in outpatient	Need accurate urine collection Risky in severe HTN, CKD, HF, or arrhythmia

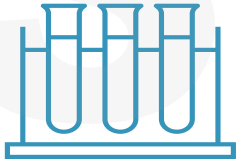
Our Patient's Labs

Medication Regimen

Discontinue spironolactone and diltiazem

Started on amlodipine-olmesartan 5-40mg qd

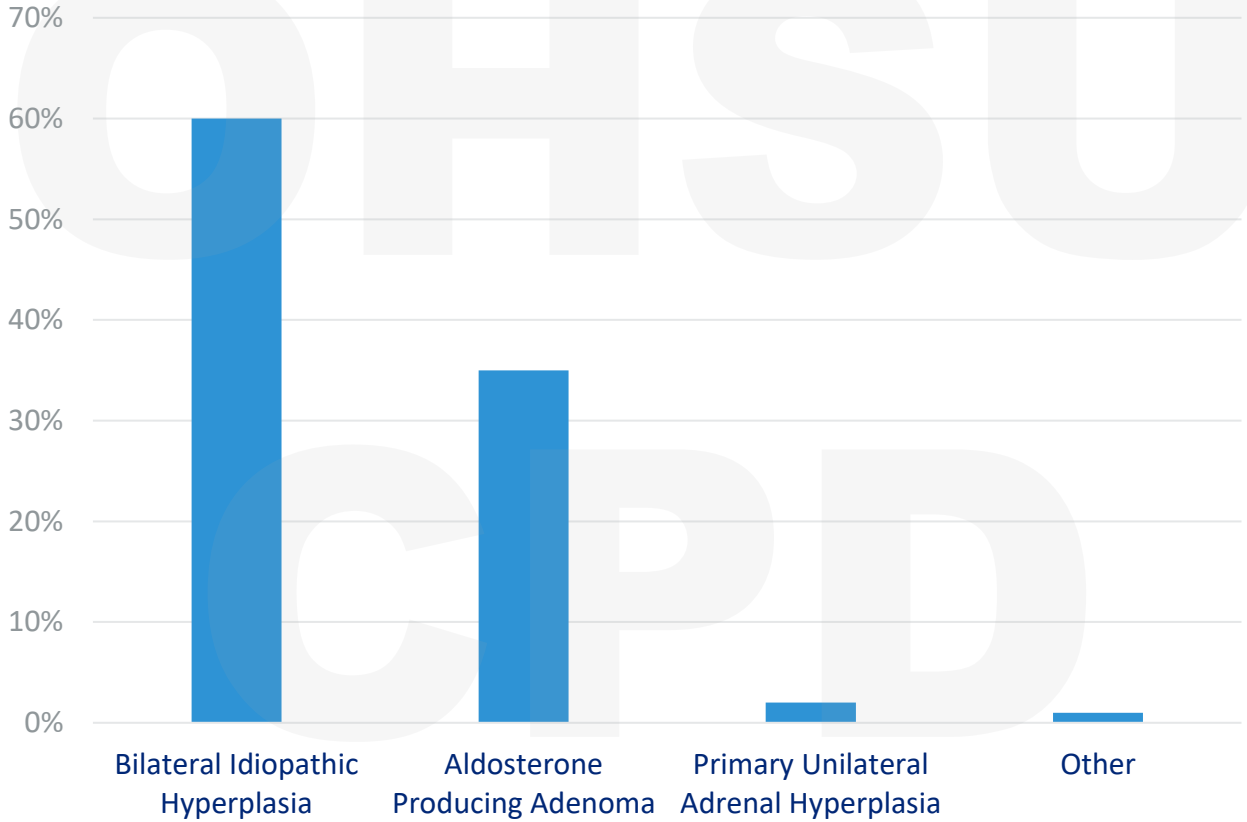
KCl 20mEq BID



Lab results 30 days later

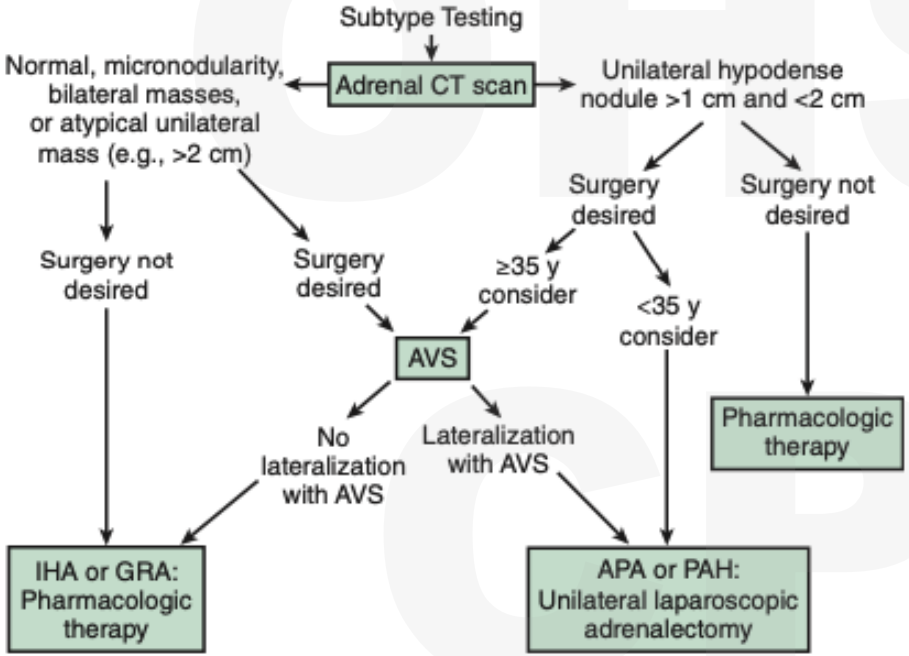
Aldosterone	53
Renin	0.98
ARR	54

Subtypes of Primary Hyperaldosteronsim



Adapted from Fagugli, *Int J Hypertens.* 2011

Imaging


Subtype Testing
Adrenal CT scan
Normal, micronodularity, bilateral masses, or atypical unilateral mass (e.g., >2 cm)
Unilateral hypodense nodule >1 cm and <2 cm
Surgery not desired
Surgery desired
Surgery desired
Surgery not desired
≥35 y consider
<35 y consider
AVS
No lateralization with AVS
Lateralization with AVS
Pharmacologic therapy
IHA or GRA: Pharmacologic therapy
APA or PAH: Unilateral laparoscopic adrenalectomy


10/23/48
10cm

Adrenal Vein Sampling - Interpreting the Results

Selectivity Index	• Adrenal vein cortisol/IVC Cortisol ≥ 5:1 • Indicates successful adrenal vein catheterization
Lateralization Index	• [High side A/C ratio]/ [Low side A/C ratio] ≥ 4 • Indicates lateralization of aldosterone secretion
Suppression Index	• Low side A/C ratio/ IVC A/C ratio < 1.0 • Indicates suppression of aldo from low side

Our Patient

- Selectivity Index:
  - L: 509/28 = 18
  - R: 526/28 = 18
- Lateralization Index
  - 8.25/0.14 = 58
- Suppression Index
  - 0.14/1.8 = 0.07

> 5 ✓

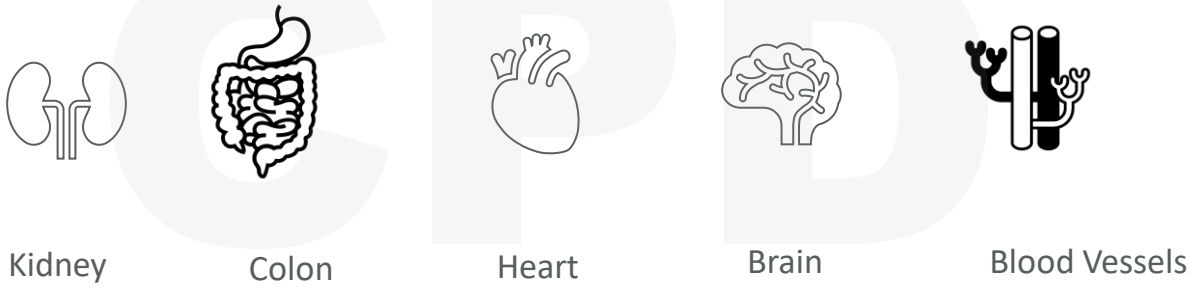
> 4 ✓

< 1 ✓

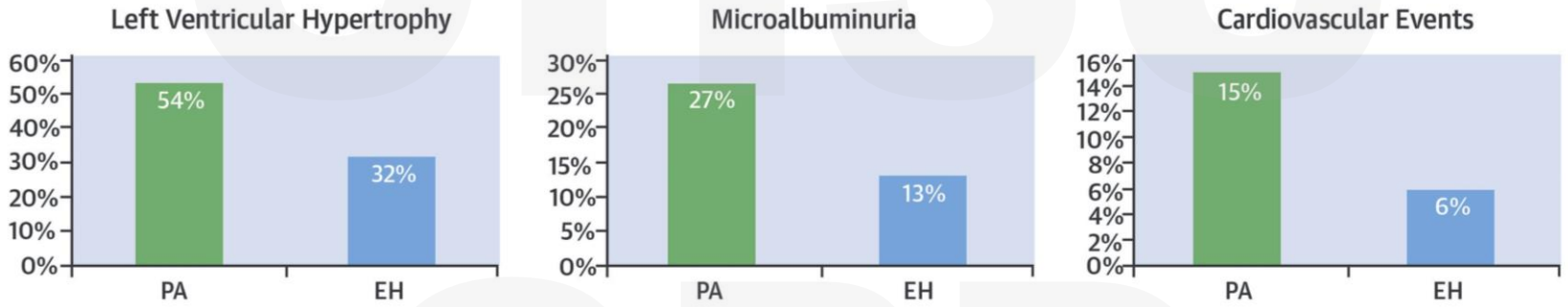
Venous Site	Aldosterone	Cortisol	A/C Ratio
L Adrenal Vein	4200	509	8.25
R Adrenal Vein	74	526	0.14
IVC	52	28	1.8

Treatment

- Goal
  - Not just BP management
  - Aldosterone receptors are located in:



B. Target Organ Damage and Cardiovascular Events



Monticone. *J am Coll Cardiol.* 2017

All Cause Mortality

Adrenalectomy

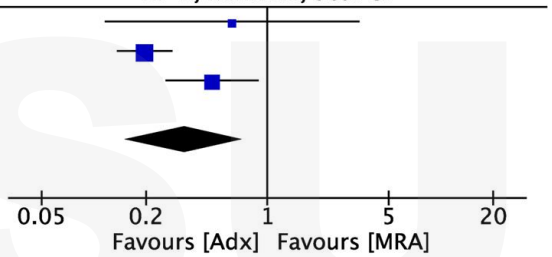
MRA

A

Study or Subgroup	Adx Events	Adx Total	MRA Events	MRA Total	Weight	Odds Ratio M-H, Random, 95% CI
Rossi 2018	2	41	5	66	15.2%	0.63 [0.12, 3.39]
Wu 2016	32	846	420	2516	45.9%	0.20 [0.14, 0.28]
Wu 2021	20	545	23	313	38.9%	0.48 [0.26, 0.89]
Total (95% CI)		**1432**		**2895**	**100.0%**	**0.33 [0.15, 0.73]**
Total events	54		448			

Heterogeneity: $Tau^2 = 0.31$; $Chi^2 = 7.33$, df = 2 (P = 0.03); $I^2 = 73\%$

Test for overall effect: Z = 2.76 (P = 0.006)

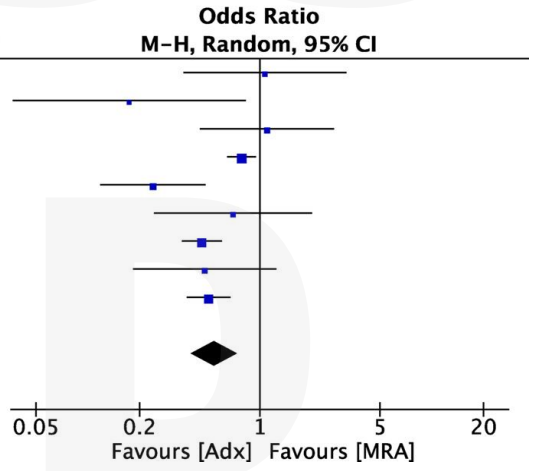


B MACE

Study or Subgroup	Adx Events	Adx Total	MRA Events	MRA Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Catena 2008	10	24	12	30	5.8%	1.07 [0.36, 3.19]	2008
Kunzel 2012	2	49	11	56	3.3%	0.17 [0.04, 0.83]	2012
Mulatero 2013	7	57	24	213	7.7%	1.10 [0.45, 2.71]	2013
Wu 2016	163	846	587	2516	21.0%	0.78 [0.65, 0.95]	2016
Hundemer 2018	11	201	38	195	10.4%	0.24 [0.12, 0.48]	2018
Rossi 2018	6	41	13	66	6.1%	0.70 [0.24, 2.01]	2018
Chang 2020	70	799	409	2368	19.6%	0.46 [0.35, 0.60]	2020
Puar 2021	8	86	12	68	7.0%	0.48 [0.18, 1.25]	2021
Wu 2021	155	545	138	313	19.0%	0.50 [0.38, 0.67]	2021
Total (95% CI)		**2648**		**5825**	**100.0%**	**0.55 [0.40, 0.74]**	
Total events	432		1244				

Heterogeneity: $Tau^2 = 0.11$; $Chi^2 = 24.65$, df = 8 (P = 0.002); $I^2 = 68\%$

Test for overall effect: Z = 3.86 (P = 0.0001)



Chen, *Eur J Endocrinol.* 2022

Adrenalectomy Outcomes

BP Control improves in almost 100% of patients

Hypertension Cure Rate ≈ 30% to 60%

Persistent hypertension:

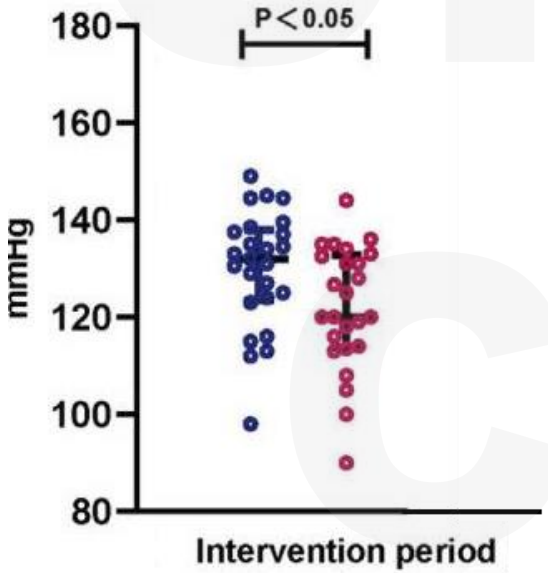
Male Gender	Family Hx	Number of BP meds	Older age	CKD	Duration of hypertension

Medical Management

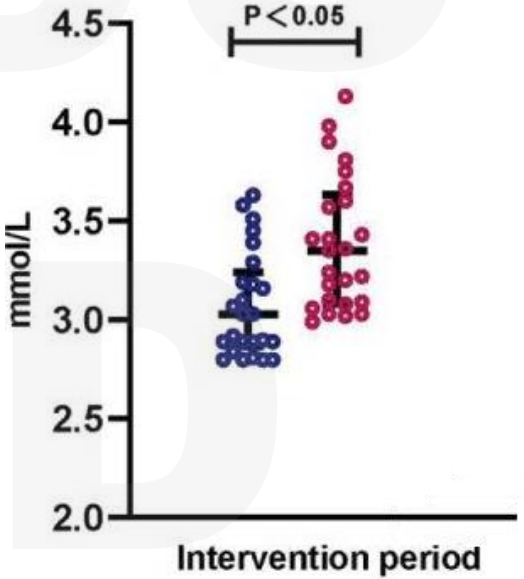
A Sodium restricted diet (<100 mEq of sodium per day)

Impact of Low Sodium Diet

Systolic Blood Pressure



Serum Potassium Levels



Zhou, *Front Endocrinol.* 2023

Medical Management

A Sodium restricted diet (<100 mEq of sodium per day)

MRA treatment

Spironolactone

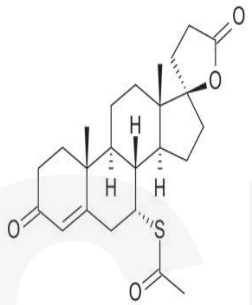
Eplerenone

Mineralocorticoid Receptor Antagonists

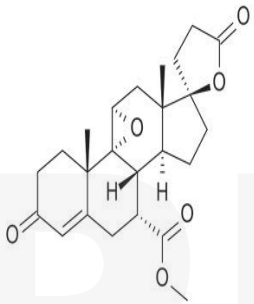
Steroidal MRAs
(aldosterone antagonists)

Higher affinity to MR receptor

Higher selectivity to MR receptor



Spironolactone



Eplerenone

Higher incidence of:
- Gynecomastia
- Impotence

Kolkhof, *Pharm Research* 2021

Medical Management

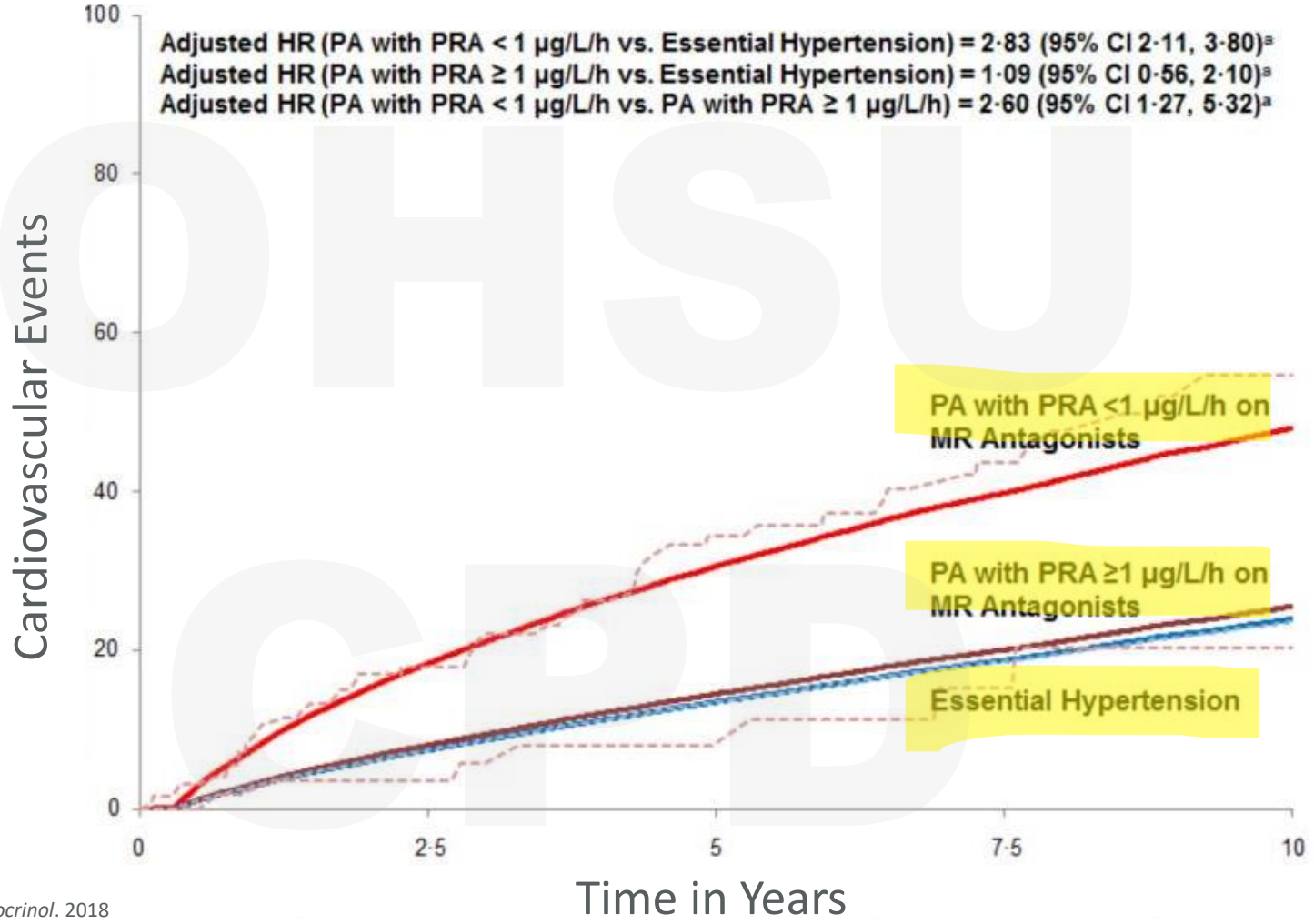
A Sodium restricted diet (<100 mEq of sodium per day)

MRA treatment

Spironolactone

Eplerenone

Goal of Renin > 1



Hundemer, *Lancet Diabetes Endocrinol*. 2018

Our Patient

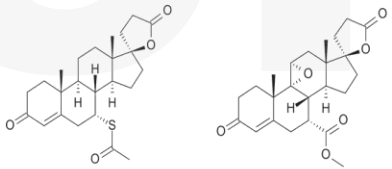
- Received an adrenalectomy
- On follow up, was off all antihypertensive therapies with BPs 130/75
- No further hypokalemia

Future Directions

- Non-steroidal MRA
- Aldosterone Synthetase Inhibitors
- Imaging vs AVS

Mineralocorticoid Receptor Antagonists

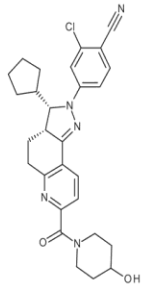
Steroidal MRAs
(aldosterone antagonists)



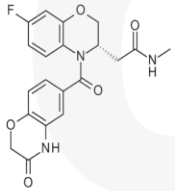
Spironolactone

Eplerenone

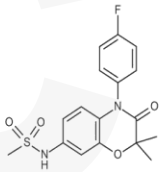
Non-steroidal MRAs



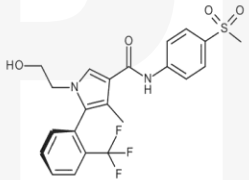
KBP-5074
(Phase II)



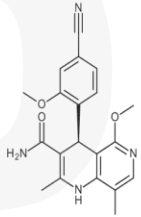
AZD9977
(Phase II)



Apararenone
MT-3995
(Phase II)



Esaxerenone
CS-3150
(launched in Japan)



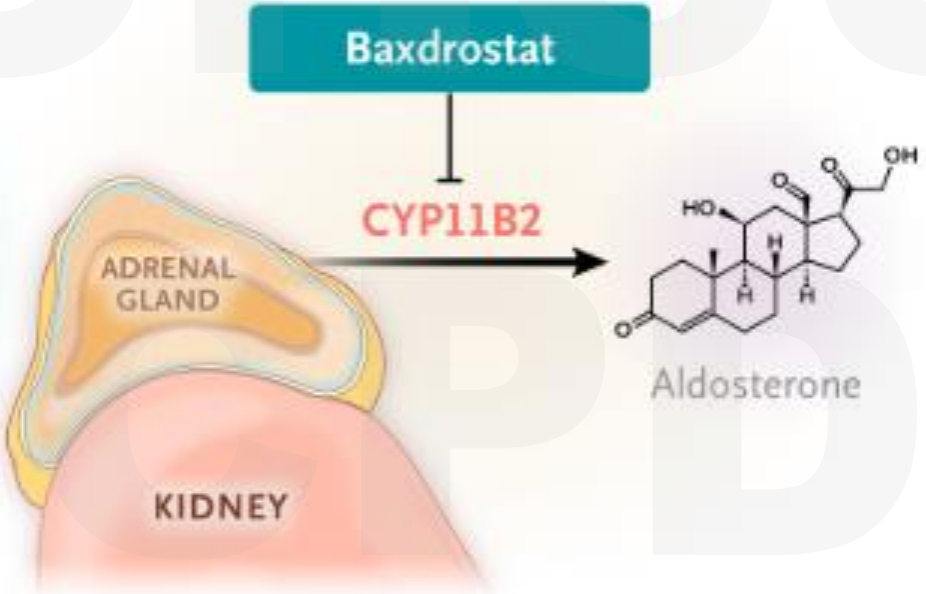
Finerenone
BAY 94-8862
(launched in the United States)

Kolkhof, *Pharm Research* 2021

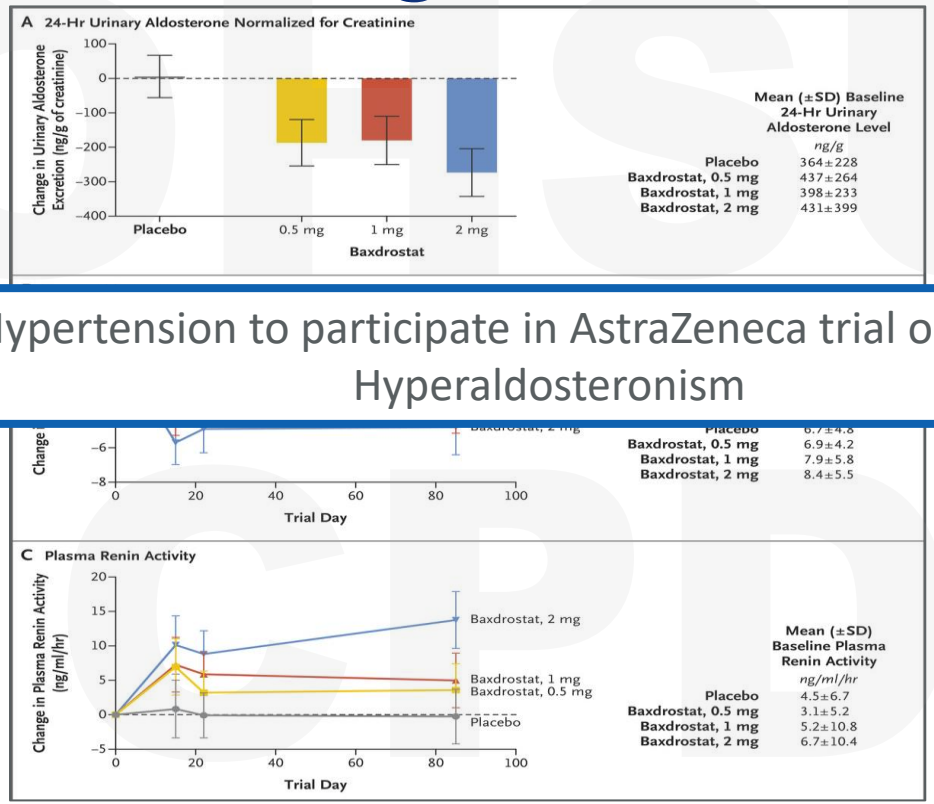
Finerenone vs Spironolactone in Primary Hyperaldosteronism

	Finerenone (n=30)			Spironolactone (n=29)			
	Baseline	**Final visit**	**Change from baseline**	**Baseline**	**Final visit**	**Change from baseline**	**Mean difference (95% CI)**
Daytime SBP, mm Hg	143.2±12.8	133.3±16.2	−9.9±13.0	142.5±12.4	134.7±13.6	−7.8±10.2	−2.1 (−8.2 to 4.0)
Daytime DBP, mm Hg	90.2±9.9	85.3±12.2	−4.9±7.9	89.2±8.3	84.2±10.8	−5.0±8.4	0.1 (−4.1 to 4.3)
24-h SBP, mm Hg	141.8±12.5	130.9±15.7	−10.9±12.5	141.8±12.1	134.1±13.5	−7.8±9.5	−3.1 (−8.9 to 2.7)
24-h DBP, mm Hg	88.6±9.8	82.7±11.7	−5.9±7.4	87.8±8.1	83.2±9.5	−4.7±6.7	−1.2 (−4.9 to 2.4)
Office SBP, mm Hg	151.5±16.7	133.8±13.6	−17.7±19.7	154.2±24.2	137.1±18.9	−17.1±19.0	−0.6 (−10.7 to 9.5)
Office DBP, mm Hg	95.0±10.0	85.9±11.0	−9.1±8.3	94.0±12.9	87.2±11.7	−6.8±11.9	−2.3 (−7.6 to 3.1)
Serum potassium, mmol/L	3.9±0.4	4.1±0.4	0.2±0.4	3.7±0.4	4.2±0.4	0.5±0.4	−0.3 (−0.5 to −0.1)*
eGFR, mL·min^{-1}·1.73 m^{-2}	86.3 (72.5 to 99.8)	79.5 (70.5 to 95.8)	−2.3 (−5.9 to 2.0)	88.5 (79.9 to 91.8)	76.2 (70.0 to 87.8)	−6.4 (−11.7 to 1.2)	3.9 (−3.6 to 10.8)
Upright PAC, pg/mL	190.5 (164.0 to 226.0)	287.5 (228.5 to 345.0)	79.5 (35.5 to 145.0)	177.0 (159.0 to 229.0)	233.0 (190.0 to 302.0)	22.0 (−3.0 to 91.4)	36.6 (−19.0 to 88.0)
Upright PRC, μIU/mL	3.4 (2.6 to 5.4)	7.9 (5.0 to 17.1)	3.4 (1.4 to 7.0)	2.7 (1.3 to 5.4)	8.1 (3.4 to 21.3)	5.0 (1.3 to 12.8)	−0.8 (−6.2 to 2.2)
Office BP control rate, n (%)†	...	20 (66.7)	...	...	14(48.3)	...	...

Baxdrostat – Aldosterone Synthetase Inhibitor



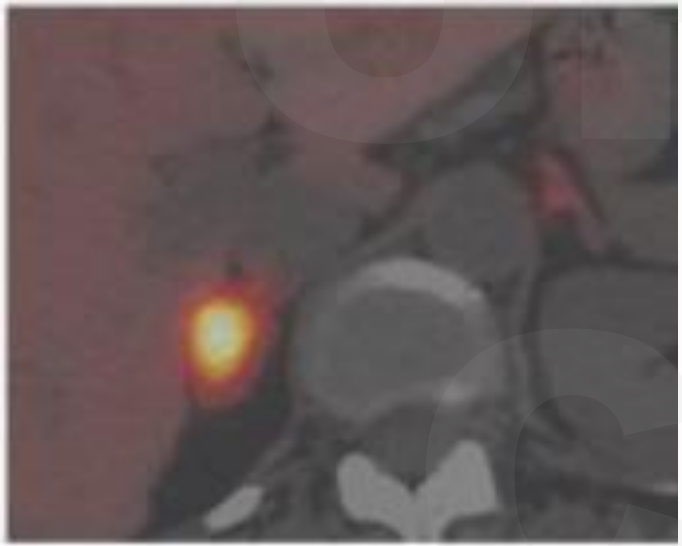
Baxdrostat – BrigHTN Trial

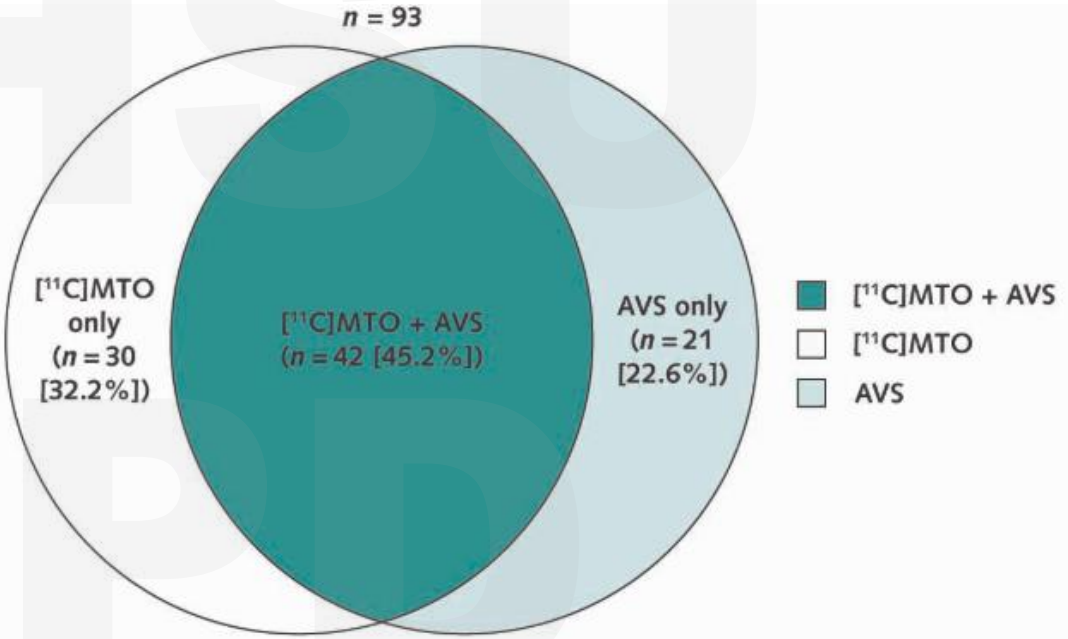


OHSU Hypertension to participate in AstraZeneca trial on use in Primary Hyperaldosteronism

MW Freeman et al. N Engl J Med 2023.

NM PET Scan vs AVS





Take Aways

- Primary aldosteronism is a condition that should be recognized and appropriately diagnosed in patients with RH
- Medical management targeted to un-suppressed renin may be equivalent to surgery
- New methods for diagnosis and treatment may further improve outcomes

Thank You