Secondary Causes of Hypertension: An Update

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Disclosure

Consultant: Eli Lilly (SURPASS-CVOT); Idorsia – Hypertension; Medtronic; Novo Nordisk; ReCor (Renal Denervation); UpToDate (Hypertension Section)

Research Grant: Ablative Solutions; Eli Lilly (TRIUMPH); ReCor (Radiance I and II)

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LEARNING OBJECTIVES

After participating in this educational activity, clinicians should be better able to:

-Review the most common clinical situations that suggest a secondary cause of hypertension

-Recognize the screening tests to rule out secondary causes of hypertension and when to perform them.

-Be more familiar with the work up and treatment of the most important secondary causes of hypertension.

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THE VAST MAJORITY OF HYPERTENSION SEEN IN CLINICAL PRACTICE IS PRIMARY OR ESSENTIAL HYPERTENSION

- Pathogenesis of hypertension is complex:
  - Poly-genetic (multiple-genes) and environmental factors interact to cause hypertension.
  - Obesity, insulin resistance, diabetes, aging, sedentary lifestyle, family hx, and social determinants of health all contribute.
  - Pathophysiologically, activation of the R-A-A system, SNS, and Salt + Water Retention (Volume excess) elevates BP.
  -Mono-genetic (Single gene) hypertensive disorders can occur (ie Liddle's Syndrome), but these are extremely rare.

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The Worldwide Ranking of Modifiable Risk Factors for Population Attributable CV Death

Rank	Cause of Death	Number of Deaths in 2021 (95% UI)	Number of DALYs (95% UI)
1	High systolic blood pressure	10,800,000 (9,150,000-12,100,000)	209,000,000 (172,000,000-236,000,000)
2	Dietary risks	6,580,000 (2,270,000-9,520,000)	142,000,000 (45,300,000-200,000,000)
3	High low-density lipoprotein cholesterol	3,810,000 (2,170,000-5,420,000)	86,300,000 (54,100,000-115,000,000)
4	Ambient particulate matter pollution	3,130,000 (2,310,000-3,930,000)	62,500,000 (45,700,000-78,400,000)
5	Smoking	2,370,000 (498,000-4,410,000)	59,600,000 (13,100,000-107,000,000)
6	High fasting plasma glucose	2,300,000 (2,030,000-2,650,000)	41,200,000 (36,600,000-47,600,000)
7	High body mass index	1,950,000 (1,120,000-2,910,000)	43,900,000 (23,800,000-65,400,000)
8	Kidney dysfunction	1,870,000 (1,440,000-2,340,000)	38,200,000 (30,700,000-45,900,000)
9	Household air pollution from solid fuels	1,610,000 (904,000-2,820,000)	36,200,000 (21,200,000-61,100,000)
10	Lead exposure	1,570,000 (-139,000-3,170,000)	29,700,000 (-2,780,000-61,200,000)
11	Low temperature	1,020,000 (915,000-1,100,000)	17,700,000 (15,900,000-19,200,000)
12	Secondhand smoke	743,000 (297,000-1,070,000)	16,700,000 (6,870,000-24,300,000)
13	High alcohol use	407,000 (179,000-708,000)	9,260,000 (3,830,000-16,300,000)
14	Low physical activity	397,000 (122,000-684,000)	7,220,000 (2,870,000-11,500,000)
15	High temperature	164,000 (114,000-205,000)	3,440,000 (2,370,000-4,300,000)

Vaduganathan M. et al. *JACC* VOL. 80, NO. 25, pg 2361-2371 Dec 20/27 2022.

DALYs-Disability Adjusted Life Years

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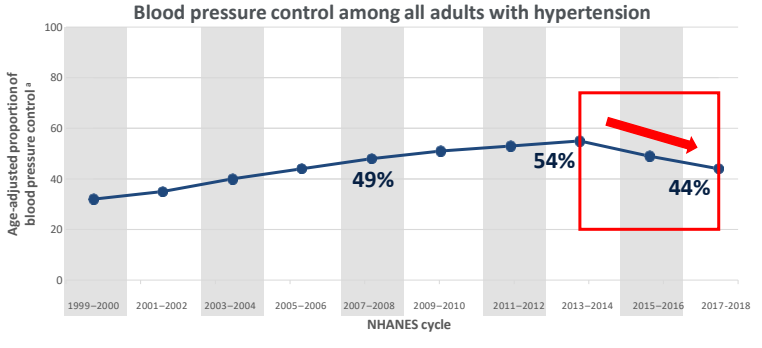
Hypertension Control Rates Have Most Recently Been Falling[1]

Age-Adjusted Trends in Blood Pressure Control (< 140/90 mm Hg)
Among US Adults 18 and Older With Hypertension,
NHANES 1999-2000 to 2017-2018 (N=18,262)



Why are BP Control Rates Falling

-10 % reduction in control rate observed from 2013 to 2018
-obesity and diabetes rates increased
-fewer patients received BP medication
-use of monotherapy increased
-access to care was unchanged

An overall decline in care quality.[2]

Despite our Best Efforts, hypertension control rates are not improving

1.Muntner et al. JAMA. 2020 Sep 22;324(12):1190-1200.
2.Egan B. and Myftari K. *Hypertension* VOL. 80, Issue 12, pg 2544-2546 Nov 15, 2023

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Hypertension Control Rates in US Adults (<130/80 mm Hg) Continue to Fall

Age-adjusted BP control among non-pregnant US adults who self-reported taking antihypertensive medication for hypertension

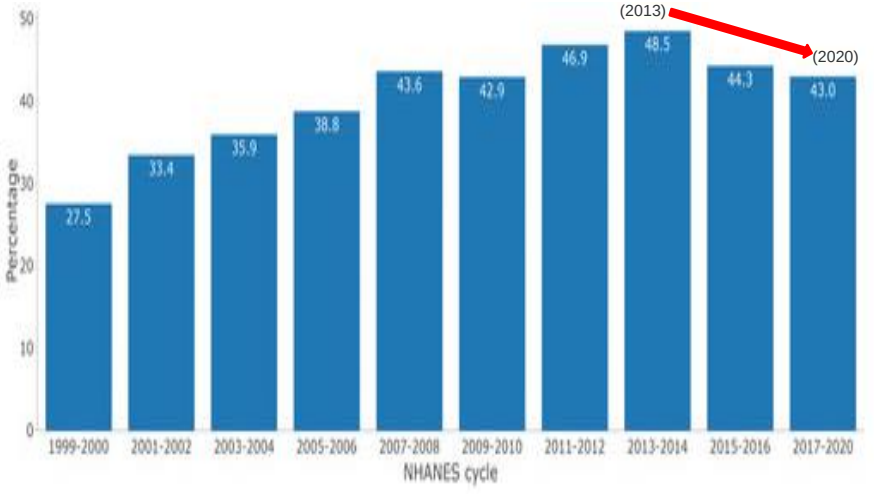

Fig 4. B. Jaeger B.C. et al. *Hypertension* June 2023 Vol 80, Issue 6: pages 1311-1320.

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But Sometimes You Have to Look Harder: Primary (Essential) vs Secondary Hypertension

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Secondary Forms of Hypertension

COR	LOE	Recommendations for Secondary Forms of Hypertension
I	C-EO	**Screening for specific form(s) of secondary hypertension is recommended when the clinical indications and physical examination findings are present or in all adults with resistant hypertension.**

2017 ACC-AHA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults; *Hypertension; JACC* Nov 2017

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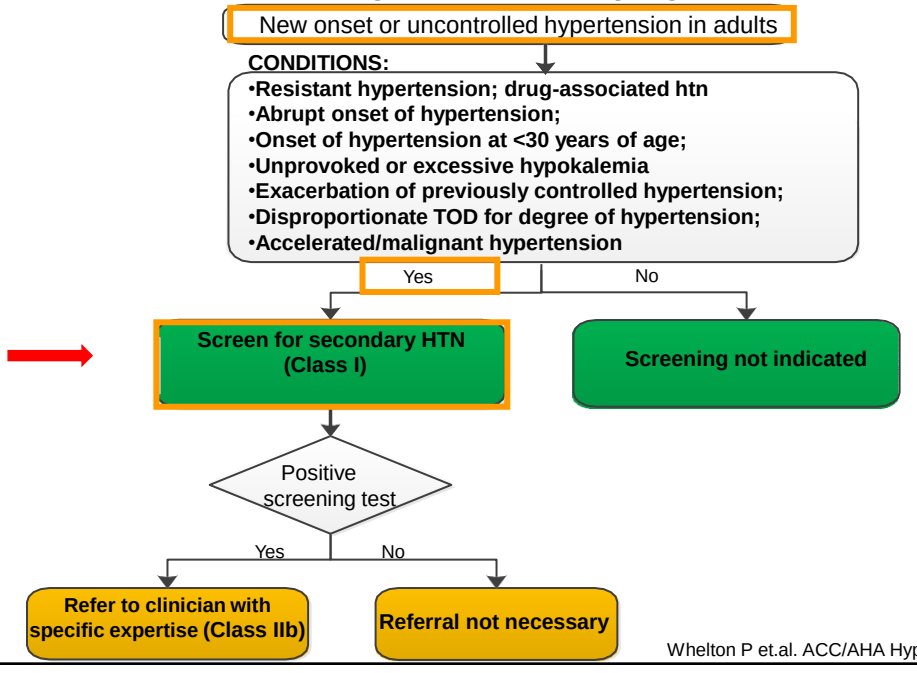
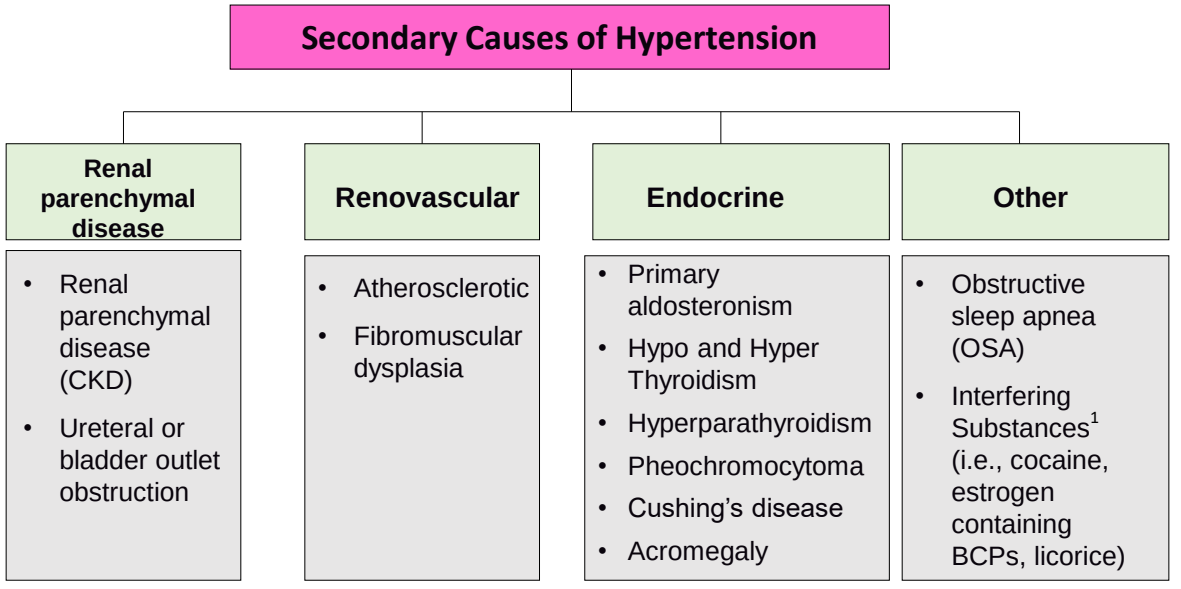
Screening for Secondary Hypertension



Whelton P et.al. ACC/AHA Hypertension 2017

10



[1]Carey R M et.al. Hypertension 2018; 72:e53-e90. November 2018

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CAUSES OF SECONDARY HYPERTENSION

Relatively Common	
•Primary aldosteronism	10% (20% in resistant HT)
•Renal vascular hypertension	~3%
•Renal parenchymal disease	~1%
•Drug or alcohol-induced	~1%
•Sleep Apnea	common but rarely responsible alone

Rare

•Pheochromocytoma
•Cushing's syndrome
•Hypo- or hyper-thyroidism
•Primary hyperparathyroidism
•Acromegaly
•Apparent mineralocorticoid excess/11β-OHase deficiency
•Hyperdeoxycorticosteronism (congenital adrenal hyperplasia, primary cortisol resistance, DOC-producing tumor)

Remaining ~ 85-90% have primary essential hypertension.

Carey R M et.al. Hypertension 2018; 72:e53-e90. November 2018

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Screening Tests for Common Causes of 2^{O} HTN

Condition	Screening Test	Routinely
• ↓, ↑ thyroid	TSH, (free T4)	*
• Pheochromocytoma	plasma free or 24-hr urinary fractionated metanephrines	*
• 1^{O} aldosteronism	↓ or nl K^{+}, ↑ plasma aldo with suppressed plasma renin	*
• Cushing's syndrome	Overnight Dex Suppression 24 hr urinary free cortisol	Hx PEx
• Hyperparathyroid	Ca^{++}, alb, Cl/P, iPTH	Ca++
• Renal artery stenosis	Duplex Ultrasound, Selective renal arteriogram	↑ Creat FPE*
• Sleep apnea	Hx*, polysomnography, overnight oximetry	Hx**

**Flash Pulmonary Edema*
***Positive Epworth Sleepiness Score*

Carey R M et.al. Hypertension 2018; 72:e53-e90. November 2018

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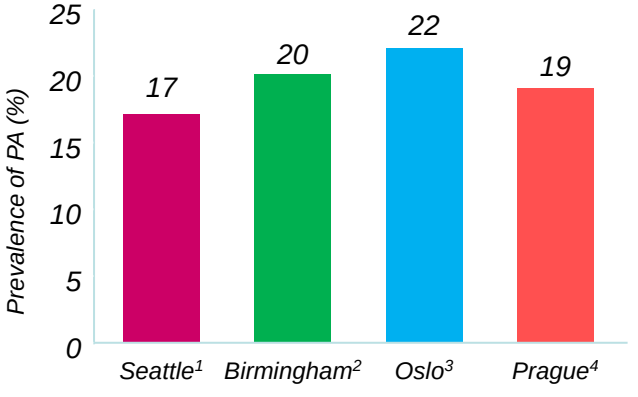
Prevalence of Primary Hyperaldosteronism in Subjects with Resistant Hypertension ~ 20%



PA = primary aldosteronism.
1. Gallay BJ, et al. Am J Kidney Dis. 2001;37:699-705.
2. Calhoun DA, et al. Hypertension. 2002;40:892-896.
3. Eide IK, et al. J Hypertens. 2004;22:2217-2226.
4. Strauch B, et al. J Hum Hypertens. 2003;17:349-352.

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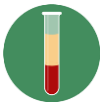
2024 ESC Guidelines for Managing Elevated BP and HTN

Screening for Secondary HTN

- **Patients with signs or history of secondary HTN should be appropriately screened**



- **Renin and aldosterone should be measured in <u>all</u> patients with HTN:**

  -Primary aldosteronism is a common form of secondary HTN

McEvoy JW, et al; ESC Scientific Document Group. Eur Heart J. 2024:ehae178.

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When to Screen for Lp(a)?

A Focused Update to the 2019 NLA Scientific Statement on Use of Lipoprotein(a) in Clinical Practice

Measure Lp(a) at least Once in all Adults and Selected High-Risk Children

Candidates for Lp(a) Screening

1. The adult population
2. The pediatric population (specifically, high-risk children and youth)
   - Clinically suspected or genetically confirmed familial hypercholesterolemia
   - First-degree relatives with a history of premature ASCVD
   - Ischemic stroke or unknown cause
   - First-degree relatives with elevated Lp(a)

Koschinsky M.L. et.al. *Journal of Clin. Lipidology* 2024; 18:e308-e319.

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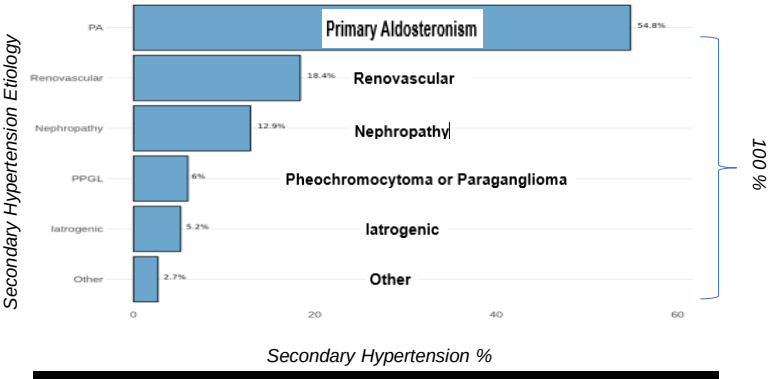
ORIGINAL ARTICLE

Prevalence and Risk Factors for Secondary Hypertension in Young Adults

Jean-Baptiste de Freminville, Margherita Gardini, Antoine Cremer, Scarlett Camelli, Stephanie Baron, Guillaume Bobrie, Philippe Gosse, Romain Boulestreau, Nicole Gebara, Julien Doublet, Thomas Dussartre, Christine Grataloup, Aurélien Lorthioir, Christine Massien, Anne-Marie Madjalian, Julien Riancho, Gilles Soulat, Nicolas Postel-Vinay, Michel Azizi, Bastien Rance, Laurence Amar

- 2090 pts with confirmed HTN
- Aged 18 to 40
- Full w/up for 2º HTN
- 30% had 2º HTN
- Prevalence of 2º HTN significantly greater for 30-40 compared to 18 to 30 year of age
- More likely if;
  -Female sex
  -Hypokalemic
  -Rx with at least 2 BP meds
  -no Family hx of HTN
  -BMI < 25
  -Have Diabetes



BOTTOM LINE: Screen all adults under 40 for 2º HTN

Hypertension 2024;81:00-00. Nov 2024. DOI 10.1161/HypertensionAHA.124.22753

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So, the Threshold for Screening for Primary Aldosteronism Seems to be Changing!

-In all patients with Resistant Hypertension[1]
-In all Patients Suspected of Secondary Hypertension[1]
-In all Young Patients < 40 years of age with HTN[2]
-In all Patients with HTN? [3]

[1]Carey R M et.al. *Hypertension* 2018; 72:e53-e90. November 2018

[2]*Hypertension* 2024;81:00-00. Nov 2024. DOI 10.1161/HypertensionAHA.124.22753

[3]McEvoy JW, et al; ESC Scientific Document Group. *Eur Heart J.* 2024:ehae178.

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What Is Primary Aldosteronism?

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PRIMARY ALDOSTERONISM
Definition

A group of disorders in which aldosterone production is inappropriately high, relatively autonomous and independent of the renin-angiotensin system (RAS), and in which aldosterone secretion is not suppressed by sodium loading. ⇧Aldo ⇩ Renin

Young WF. et al. AHA Screening for Endocrine Hypertension: An Endocrine Society Scientific Statement. *Endocrine Reviews* 38:103-122,2017.

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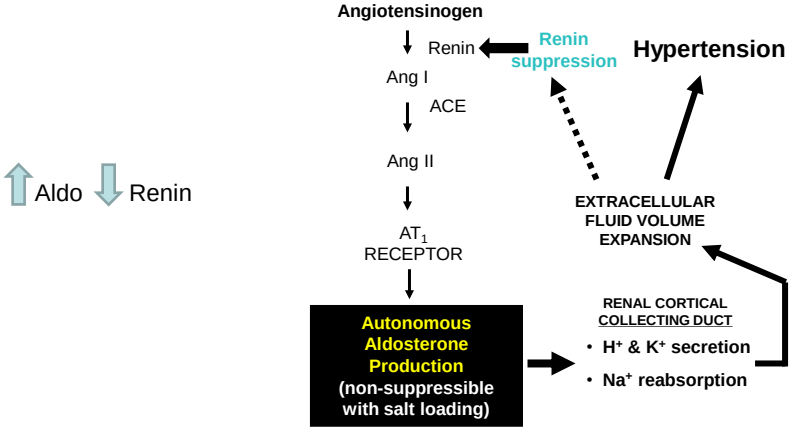
AUTONOMOUS ALDOSTERONE SECRETION INDEPENDANT OF RENIN OCCURS IN PRIMARY ALDOSTERONISM



Carey RM *et al.* *Circulation Research*. 2021;128:827-846.

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Primary Aldosteronism (PA)

Why is PA important for the clinician?

1. PA is more common than we have realized.
2. It is the most common endocrine cause of secondary hypertension.
3. It accounts for at least 10% of all people with high blood pressure and up to 20% of those with Resistant Hypertension.
4. The diagnosis of PA provides the clinician with a unique opportunity—to either cure hypertension with surgery or to use targeted pharmacotherapy and prevent end stage PA: with its associated renal, cerebral (stroke), and cardiac disease (LVH, MI, and AFib).

Mulatero P, et al. Increased diagnosis of primary aldosteronism, including surgically correctable forms, in centers from five continents. J Clin Endocrinol Metab. 2004 Mar;89(3):1045-50.

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

Silvia Monticone*, Fabrizio D'Ascenzo*, Claudio Moretti, Tracy Ann Williams, Franco Veglio, Fiorenzo Gaita, Paolo Mulatero

Findings We identified 31 studies including 3838 patients with primary aldosteronism and 9284 patients with essential hypertension. After a median of 8·8 years (IQR 6·2–10·7) from the diagnosis of hypertension, compared with patients with essential hypertension, patients with primary aldosteronism had an increased risk of stroke (odds ratio [OR] 2·58, 95% CI 1·93–3·45), coronary artery disease (1·77, 1·10–2·83), atrial fibrillation (3·52, 2·06–5·99), and heart failure (2·05, 1·11–3·78). These results were consistent for patients with aldosterone-producing adenoma and bilateral adrenal hyperplasia, with no difference between these subgroups. Similarly, primary aldosteronism increased the risk of diabetes (OR 1·33, 95% CI 1·01–1·74), metabolic syndrome (1·53, 1·22–1·91), and left ventricular hypertrophy (2·29, 1·65–3·17).

Interpretation Diagnosing primary aldosteronism in the early stages of disease, with early initiation of specific treatment, is important because affected patients display an increased cardiovascular risk compared with patients with essential hypertension.

www.thelancet.com/diabetes-endocrinology **Published online November 9, 2017**

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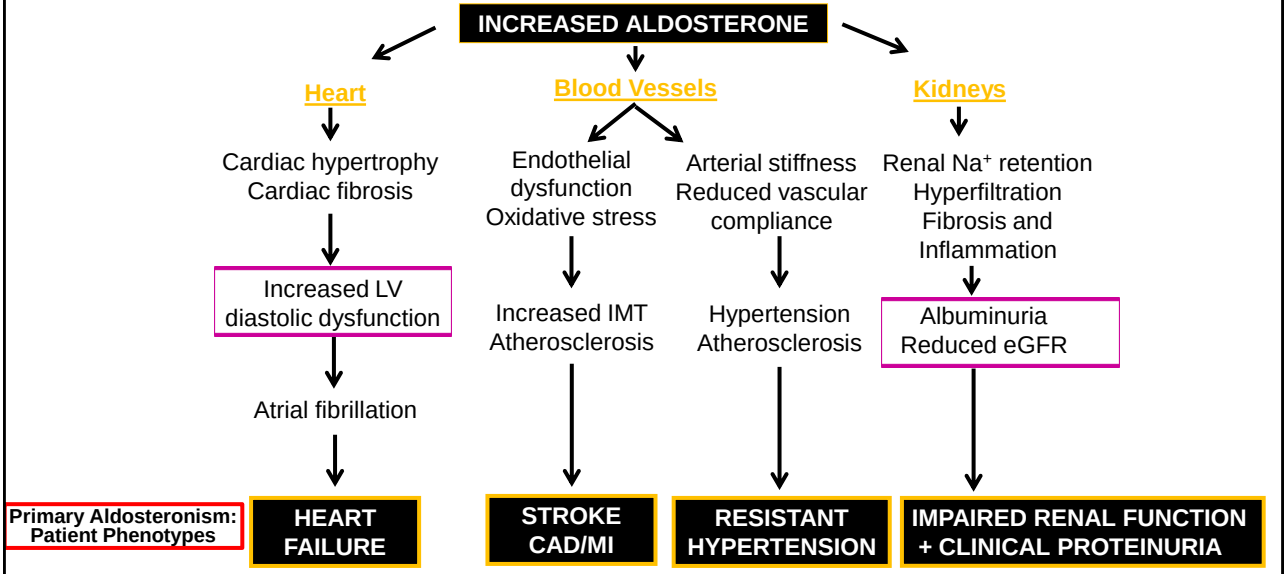
CARDIOVASCULAR and RENAL BURDEN OF PRIMARY ALDOSTERONISM

HOW DOES IT PRESENT?



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Primary Aldosteronism

Highly Prevalent
But Rarely Screened for

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Screening Rates for Primary Aldosteronism Among Individuals with HYPERTENSION PLUS HYPOKALEMIA (Serum K+ < 3.5 mEq/L by Year): A Population-Based Retrospective Cohort Study from Ontario Canada

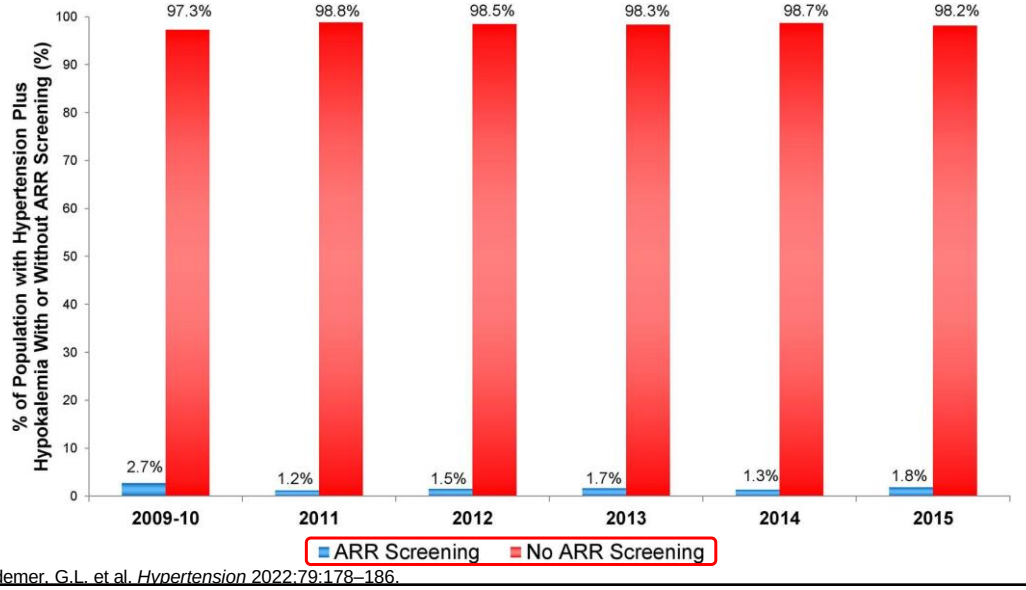

Fig 2. Hundemer, G.L. et al. *Hypertension* 2022;79:178–186.

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Testing for Primary Aldosteronism Is Rarely Done in Treatment Resistant Hypertension

Annals of Internal Medicine ORIGINAL RESEARCH

Testing for Primary Aldosteronism and Mineralocorticoid Receptor Antagonist Use Among U.S. Veterans

A Retrospective Cohort Study

Jordana B. Cohen, MD, MSCE; Debbie L. Cohen, MD; Daniel S. Herman, MD, PhD; John T. Leppert, MD, MS; James Brian Byrd, MD, MS*; and Vivek Bhalla, MD*

Background: Primary aldosteronism is a common cause of treatment-resistant hypertension. However, evidence from local health systems suggests low rates of testing for primary aldosteronism.

Objective: To evaluate testing rates for primary aldosteronism and evidence-based hypertension management in patients with treatment-resistant hypertension.

Design: Retrospective cohort study.

Setting: U.S. Veterans Health Administration.

Participants: Veterans with apparent treatment-resistant hypertension (*n* = 269 010) from 2000 to 2017, defined as either 2 blood pressures (BPs) of at least 140 mm Hg (systolic) or 90 mm Hg (diastolic) at least 1 month apart during use of 3 antihypertensive agents (including a diuretic), or hypertension requiring 4 antihypertensive classes.

Measurements: Rates of primary aldosteronism testing (plasma aldosterone-renin) and the association of testing with evidence-based treatment using a mineralocorticoid receptor antagonist (MRA) and with longitudinal systolic BP.

Results: 4277 (1.6%) patients who were tested for primary aldosteronism were identified. An index visit with a nephrologist (hazard ratio [HR], 2.05 [95% CI, 1.66 to 2.52]) or an endocrinologist (HR, 2.48 [CI, 1.69 to 3.63]) was associated with a higher likelihood of testing compared with primary care. Testing was associated with a 4-fold higher likelihood of initiating MRA therapy (HR, 4.10 [CI, 3.68 to 4.55]) and with better BP control over time.

Limitations: Predominantly male cohort, retrospective design, susceptibility of office BPs to misclassification, and lack of confirmatory testing for primary aldosteronism.

Conclusion: In a nationally distributed cohort of veterans with apparent treatment-resistant hypertension, testing for primary aldosteronism was rare and was associated with higher rates of evidence-based treatment with MRAs and better longitudinal BP control. The findings reinforce prior observations of low adherence to guideline-recommended practices in smaller health systems and underscore the urgent need for improved management of patients with treatment-resistant hypertension.

Primary Funding Source: National Institutes of Health.

Ann Intern Med. 2021;174:289-297. doi:10.7326/M20-4873 Annals.org
For author, article, and disclosure information, see end of text.
This article was published at Annals.org on 29 December 2020.
* Drs. Byrd and Bhalla contributed equally to this work.

Of 269,000 Veterans seen from 2000 to 2017 with apparent TRH, only 1.6% were tested for PA. If tested , 4X more likely to be treated with MRA.

Cohen J, et al. Testing for Primary Aldosteronism and Mineralocorticoid Receptor Antagonist Use Among US Veterans. *Ann Intern Med*. 2021;174:289-297.

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Step 1. Consider Testing for Primary Aldosteronism:

- Hypertension and hypokalemia
- Resistant hypertension (3 appropriate drugs and poor BP control)
- Adrenal incidentaloma and hypertension
- Sleep Apnea and Hypertension
- Onset of hypertension at a young age (<30 y)
- Marked persistent hypertension (≥150 mm Hg systolic or ≥100 mm Hg diastolic)
- Whenever considering secondary hypertension

NOTE: only 30% of patients with PA are hypokalemic!

UpToDate: Diagnosis of Primary Aldosteronism
WF Young.

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HYPOKALEMIA AND PRIMARY ALDOSTERONISM

- In the past, hypokalemia was the *sine qua non* for the diagnosis.
- Most studies now show that only a minority (9 – 37%) of patients with PA have hypokalemia.
- The presence of hypokalemia, in fact, has low sensitivity, specificity and low positive predictive value for the diagnosis of PA.
- Normokalemic hypertension is the most common presentation, with hypokalemia present only in the most severe cases.

Young WF. et al. AHA Screening for Endocrine Hypertension: An Endocrine Society Scientific Statement. *Endocrine Reviews* 38:103-122,2017.

29

Step 1. Consider Testing for Primary Aldosteronism:

- Hypertension and hypokalemia
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NOTE: only 30% of patients with PA are hypokalemic!

Step 2. Case Detection Testing:

Morning blood sample in ambulant patient, seated x 5 min

- Plasma aldosterone concentration (PAC)
- Plasma renin activity (PRA) or plasma renin concentration (PRC)

PAC (≥10 ng/dL; ≥277 pmol/L)

and

↓ PRA (<1.0 ng/mL/hr) or ↓ PRC (<8 mU/L)

NOTE: patients can be on any sodium diet and any BP meds INCLUDING SPL and EPL if plasma renin is suppressed

UpToDate: Diagnosis of Primary Aldosteronism
WF Young.

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Primary Aldosteronism

Can You Do Case Detection Screening on Spironolactone or Eplerenone?

Yes, If Plasma Renin Is Suppressed

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*Caveat on Spironolactone and Eplerenone

- **Mineralocorticoid receptor antagonists** – It may be difficult to interpret data obtained from patients treated with a mineralocorticoid receptor antagonist (spironolactone **and** eplerenone). These drugs prevent aldosterone from activating the receptor, resulting sequentially in sodium loss, a decrease in plasma volume, and an elevation in PRA, which will reduce the utility of the PAC/PRA ratio. For this reason, spironolactone and eplerenone should not be initiated until the evaluation is completed and the final decisions about treatment are made.

  However, there are exceptions to this rule. For example, if the patient is hypokalemic despite treatment with spironolactone or eplerenone, then the mineralocorticoid receptors are not fully blocked and PRA or PRC should be suppressed in such a patient with primary aldosteronism. In addition, most patients with primary aldosteronism who are treated with mineralocorticoid receptor antagonists are given subtherapeutic doses. Thus, PAC and PRA should be measured in patients treated with spironolactone or eplerenone, and if PRA is suppressed, these medications are not interfering. Thus, if PRA is suppressed, case-detection testing, confirmatory testing, and adrenal vein sampling (AVS) can be performed without discontinuing the mineralocorticoid receptor antagonists. However, if PRA is not suppressed, then the mineralocorticoid receptor antagonist should be discontinued for four to six weeks before retesting. Other potassium-sparing diuretics, such as amiloride and triamterene, usually do not interfere with testing unless the patient is on high doses.

*UpToDate: "Diagnosis of Primary Aldosteronism" WF Young. Accessed Sept 27, 2023.

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*Caveat on Spironolactone and Eplerenone

- **Mineralocorticoid receptor antagonists** – It may be difficult to interpret data obtained from patients treated with a mineralocorticoid receptor antagonist (spironolactone **and** eplerenone). These drugs prevent aldosterone from activating the receptor, resulting sequentially in sodium loss, a decrease in plasma volume, and an elevation in PRA, which will reduce the utility of the PAC/PRA ratio. For this reason, spironolactone and eplerenone should not be initiated until the evaluation is completed and the final decisions about treatment are made.

So, this is simply understanding physiology. If renin is suppressed in a patient taking SPL or EPL (or any medication), you can do case detection testing, confirmatory testing, and even AVS!

*UpToDate: "Diagnosis of Primary Aldosteronism" WF Young. Accessed Sept 27, 2023.

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PRIMARY ALDOSTERONISM: Antihypertensive Meds OK to Use for BP Control When Screening

Table 5. Medications with minimal effects on plasma aldosterone levels that can control hypertension during case finding and confirmatory testing for primary aldosteronism

Drug	Class	Usual Dose	Comments
Verapamil slow-release	Non-dihydropyridine slow-release antagonist calcium channel	90–120 mg twice daily	Use singly or in combination with the other agents listed in this table.
Hydralazine	Vasodilator	10–12.5 mg twice daily, increasing as required	Commence verapamil slow-release first to prevent reflex tachycardia. Commencement at low doses reduces risk of side effects (including headaches, flushing, and palpitations).
Prazosin hydrochloride	α-adrenergic blocker	0.5–1 mg twice daily or three times daily, increasing as required	Monitor for postural hypotension
Doxazosin mesylate	α-adrenergic blocker	1–2 mg once daily, increasing as required	Monitor for postural hypotension
Terazosin hydrochloride	α-adrenergic blocker	1–2 mg once daily, increasing as required	Monitor for postural hypotension

Endocrine Society Clinical Practice Guidelines for PA, *Jnl Clin Endocrine and Metabolism*, 2016

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Major Sources of Error in PA Screening

Factor	Effect on Aldosterone	Effect on Renin	Effect on ARR
MEDICATIONS			
K^+-wasting diuretics	↑/↔	↑↑	↓
K^+-sparing diuretics	↑	↑↑	↓
ACE inhibitors/ARBs	↓	↑↑	↓
Dihydroperidine Ca^{2+} channel blockers	↔/↓	↑	↓
β-adrenergic blockers	↓	↓↓	↑
Central agonists	↓	↓↓	↑
Renin inhibitors	↓	↓	↑
POTASSIUM STATUS			
Hypokalemia	↓	↔/↑	↓
DIETARY Na			
Na^+ restriction	↑	↑↑	↓
Na^+ loading	↓	↓↓	↑
OTHERS			
Advanced age	↓	↓↓	↑
Renal insufficiency	↔	↓	↑
Pregnancy	↑	↑↑	↓
Renovascular and malignant HTN	↑	↑↑	↓

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Major Sources of Error in PA Screening

Factor	Effect on Aldosterone	Effect on Renin	Effect on ARR
MEDICATIONS			
K^+-wasting diuretics	↑/↔	↑↑	↓
K^+-sparing diuretics	↑	↑↑	↓
ACE inhibitors/ARBs	↓	↑↑	↓
Dihydroperidine Ca^{2+} channel block	↔/↓	↑	↓
β-adrenergic block	↓	↓↓	↑
Central agonists			↑
Renin inhibitors			↑
POTASSIUM			
Hypokalemia			↓
DIETARY Na			
Na^+ restriction			↓
Na^+ loading	↓		↑
OTHERS			
Advanced age	↓	↓↓	↑
Renal insufficiency	↔	↓	↑
Pregnancy	↑	↑↑	↓
Renovascular and malignant HTN	↑	↑↑	↓

You may screen on any medications!
When ambiguous results are obtained, re-evaluate.

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Hypertension

ORIGINAL ARTICLE

Comparing ARR Versus Suppressed PRA as Screening Tests for Primary Aldosteronism

What Is New?

- We compared the efficiency of the aldosterone renin ratio (ARR) ≥20 or ≥30 versus plasma renin activity (PRA) <1 ng/mL per h as screening tests for primary aldosteronism (PA) in a cohort of 94 829 deidentified tests samples submitted at Quest Diagnostics for the measurement of the ARR.

Clinical/Pathophysiological Implications?

- Our data show that compared with PRA<1 ng/mL per h, the ARR screening tool set at 20 or 30 potentially misses many patients with PA. If future prospective studies confirm this finding, PRA<1 ng/mL per h should become the preferred screening tool for PA.

PRA < 1 ng/ml per hour will be the preferred screening test for PA

Marcelli M. et al. *Hypertension* Vol 81, Issue 10, October 2024;pg 2072-2081.

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Step 1. Consider Testing for Primary Aldosteronism:

- Hypertension and hypokalemia
- Resistant hypertension (3 appropriate drugs and poor BP control)
- Adrenal incidentaloma and hypertension
- Sleep Apnea and Hypertension
- Onset of hypertension at a young age (<30 y)
- Marked persistent hypertension (≥150 mm Hg systolic or ≥100 mm Hg diastolic)
- Whenever considering secondary hypertension

NOTE: only 30% of patients with PA are hypokalemic!

↓

Step 2. Case Detection Testing:

Morning blood sample in ambulant patient, seated x 5 min

- Plasma aldosterone concentration (PAC)
- Plasma renin activity (PRA) or plasma renin concentration (PRC)

NOTE: patients can be on any sodium diet and any BP meds INCLUDING SPL and EPL if plasma renin is suppressed

↓

PAC (≥10 ng/dL; ≥277 pmol/L)

and

↓ PRA (<1.0 ng/mL/hr) or ↓ PRC (<8 mU/L)

↓

Step 3. Confirmatory Testing

UpToDate: Diagnosis of Primary Aldosteronism
WF Young.

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Confirmatory Testing-Step 3

Oral Sodium Loading Test

- 6 gm NaCl/day x 3 days, assay 24-hour urine for Na^+, aldo
- Confirmatory if urinary aldo excretion >12 or 14 µg/day
- Not recommended for patients with heart failure, CKD, uncontrolled BP

IV Saline Suppression Test*

- 2 L of normal saline over 4 hours (8 AM to noon); assay plasma aldo
- Confirmatory if post-infusion plasma aldo >10 ng/dL
- Not recommended for patients with heart failure, CKD, uncontrolled BP

Fludrocortisone Suppression Test

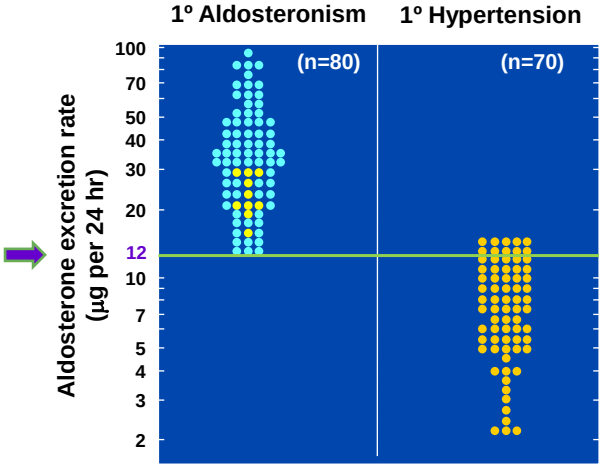
- 0.1 mg fludrocortisone q 6 hr x 4 days; assay plasma aldo while upright
- Confirmatory if plasma aldo >6 ng/dL (and PRA remains low on day 4)
- Difficult for outpatients who come from a distance

Captopril Challenge Test

- 25–50 mg of captopril p.o.; assay plasma aldo after 0, 1 - 2 hours
- Confirmatory (?) if plasma aldo remains elevated and renin is still suppressed
- Many false-negative or equivocal results, however

39

Aldosterone Excretion Rate After Three Days of Oral Sodium Loading (250 mEq Na in Urine per 24 hr)



Bravo EL and coworkers. *Am Journal Med* April 1983

40

Types of Primary Aldosteronism

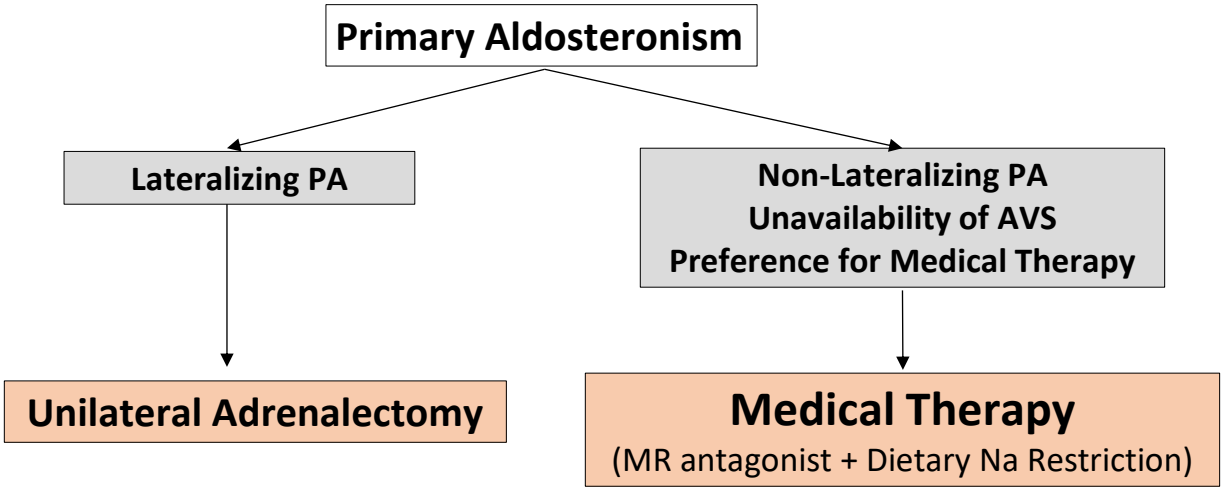
Type of primary aldosteronism	Cases
Aldosterone-producing adenoma (APA)	30%
Bilateral idiopathic hyperplasia (IHA)	60%
Primary (unilateral) adrenal hyperplasia	2%
Aldosterone-producing adrenocortical carcinoma	<1%
Familial hyperaldosteronism (FH)	
-Glucocorticoid-remediable aldosteronism (FH type I)	<1%
-FH type II (APA or IHA)	<6%
-FH type III (germline *KCNJ5* mutations)	<1%
-FH type IV (germline *CACNA1H* mutations)	<0.1%
-Ectopic aldosterone-producing adenoma or aldosterone-producing carcinoma	<0.1%

Genetic

Young WF Jr. *J Intern Med*. 2019;285(2):126-148.

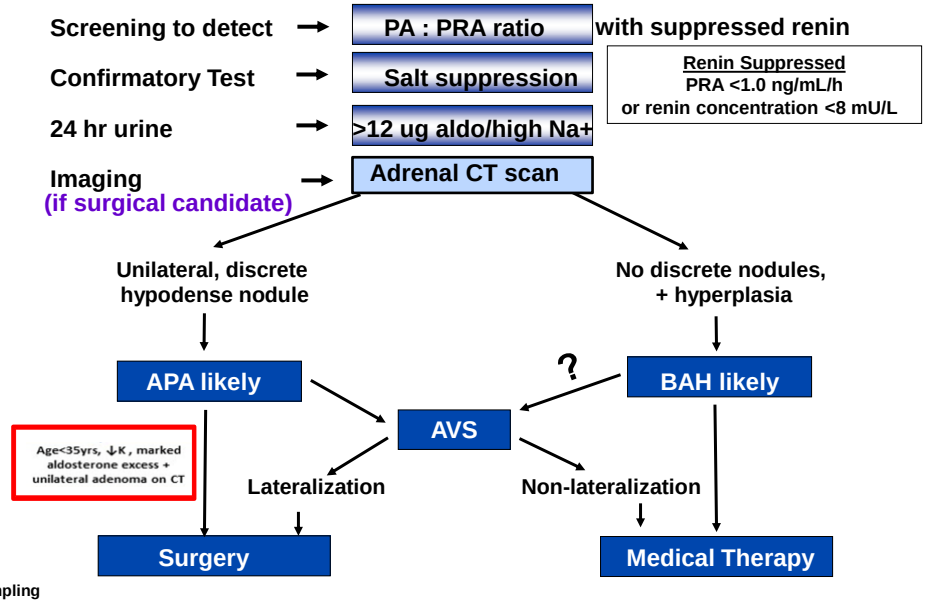
41

HISTORICAL TREATMENT APPROACH TO PRIMARY ALDOSTERONISM



42

The Older (Still Current) Approach to Patients at Risk for Primary Aldosteronism



AVS=adrenal vein sampling

43

History of Mineralocorticoid Receptor Antagonists (MRAs)

1953: Aldosterone as sodium retaining and potassium wasting hormone first discovered.

1954: Jerome Conn: suppressed renin, volume expansion, non-suppressible aldosterone; reported the successful removal of an aldosterone overproducing adrenal gland in a patient with HTN and hypokalemia (Conn syndrome).

1960: Spironolactone was first marketed as potassium-sparing diuretic but mostly used in patients with hyper-aldosteronism (primary and secondary, e.g., in liver failure).

➡ Progesterone-like and anti-androgen effects at high doses limited its use

2002: Eplerenone marketed.

University of Michigan
First Division Chief Endocrinology & Metabolism from 1943-1973

Jerome W. Conn, MD

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Medical Therapy for Hyperaldosteronism

- Give an adequate dose of MR antagonist (spironolactone or eplerenone) to reduce the CV and Renal effects of aldosterone excess:

An adequate dose of MRA:

- **Allows renin to no longer be suppressed**
- **Normalizes K+ without the need for K+ supplementation**
- **But you might have to add other anti-hypertensives as needed to control BP to < 130/80 mm Hg as some patients have primary aldosteronism on top of essential hypertension.**
- **And Don't forget the importance of a low sodium diet!**

-In the future but coming soon, it is hoped that Aldosterone Synthase Inhibitors (ASIs) will be utilized instead of MRA's

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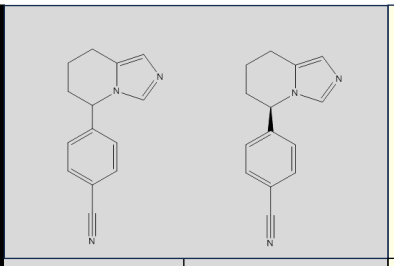
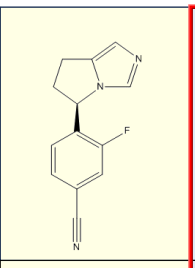
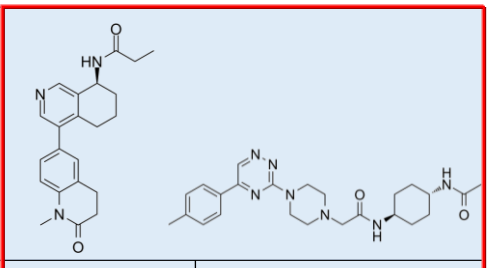
Aldosterone Synthase Inhibitors

Structure					
Drug	**Fadrozole**	**(R)-Fadrozole**	**Osilodrostat**	**Baxdrostat**	**Lorundrostat**
Alias	CGS16949A	FAD-286	LCI-699	RO6836191	MLS-101, MT-4129
Phase	Approved (Japan) as aromatase inhib.	NA	Approved (US) for Cushing's	Phase II/III	Phase II/III
CYP11B2:B1	8:1	40:1	8-10:1	100:1	374:1
ACTH cortisol	↓	↓	↓	↔	↔
Half-life	10.5 hrs	ND	4 hrs	25-31 hrs	10-12 hrs

CYP11B2:B1 calculated $IC_{50}B1/IC_{50}B2$

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The Unappreciated Prevalence of Primary Aldosteronism as a Spectrum of Disease: A New Concept

- Cross-sectional study of 1,015 hypertensive subjects at 4 U.S. academic medical centers.
- All participants completed an oral sodium suppression test for primary aldosteronism regardless of the aldosterone to renin ratio to quantify the magnitude of renin-independent aldosterone production.
- Urinary aldosterone was measured during high sodium balance and suppressed renin activity.
- Primary aldosteronism diagnosed if urinary aldosterone > 12 µg/24 h in the setting of high sodium balance and suppressed renin activity.

Brown JM et.al. *Annals Int Med* 2020; 173:10-20.

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Continuous Spectrum of the Primary Aldosterone Syndrome

Primary aldosteronism diagnosed if urinary aldosterone > 12 µg/24 h in the setting of high sodium balance and suppressed renin activity.

Cross-sectional study of 1,015 hypertensive subjects at 4 U.S. academic medical centers. (Birmingham, Boston, Charlottesville, Salt Lake City).

All given an Oral Sodium Suppression Test

Brown JM et.al. *Annals Int Med* 2020; 173:10-20.

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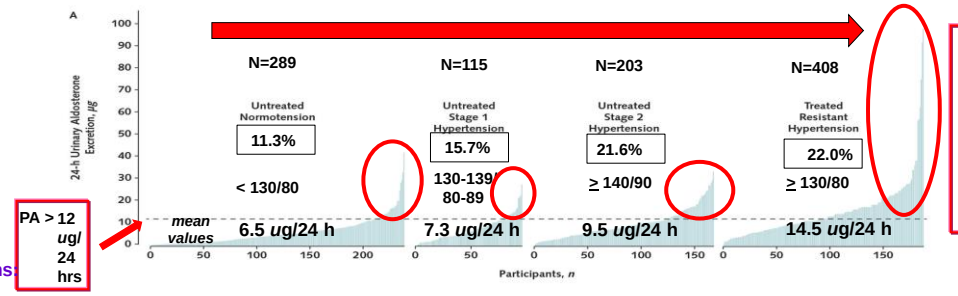
Primary Aldosteronism (PA) Occurs as a Spectrum (n=1,015 Subjects)



Must have suppressed renin and high urine sodium ≥190 mmol/24 hrs

PA > 12 ug/ 24 hrs

Conclusions:

- The prevalence of primary aldosteronism is high and largely unrecognized.
- There is a spectrum of renin-independent aldosterone production (PA) that occurs in "healthy" untreated normotensives and increases with the severity of hypertension.
- This suggests aldosterone excess plays a role in untreated primary "essential" hypertension to the more often recognized patient with treatment-resistant hypertension.
- This observation may be missed if only the ARR is performed as a screening test as it has low sensitivity and poor negative predictive value
- Perhaps mineralocorticoid-receptor-antagonists should be used more often, and perhaps earlier in the future treatment of hypertension. (They were FDA approved in 1960)

Figure 2A Brown JM et.al. *Annals Int Med July 7* 2020; 173 (1):pg 10-20.

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Have We Been Missing Primary Aldosteronism All These Years?

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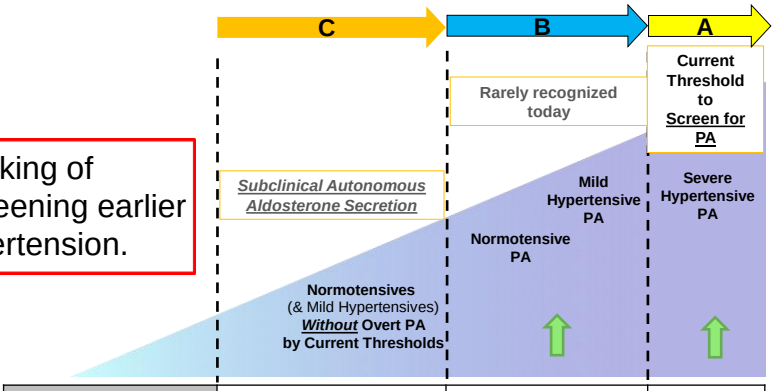
THE SPECTRUM OF PA EXTENDS BELOW CURRENT THRESHOLDS

So, should we be thinking of aldosterone/renin screening earlier in the work/up of hypertension.



DISEASE	*Subclinical Autonomous Aldosterone Secretion*	Unrecognized Yet	Overt PA
Obvious Clinical Syndrome of Excessive MR Activation?	NO	NO	YES
Biochemical Confirmation of PA Using *Current* Thresholds?	NO	YES	YES
Histopathology	*Aldosterone Producing Cell Clusters (APCCs)*		*APA/BAH*

Vaidya A, Carey RM. *J Clin Endocrinol Metab. Vol 105 Issue 12 Dec* 2020 pgs 3771-3783.

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Should it Be "Syndrome of Inappropriate Aldosterone Secretion (SIALDS)" Rather Than PA: A Common but Unrecognized Cause of Hypertension

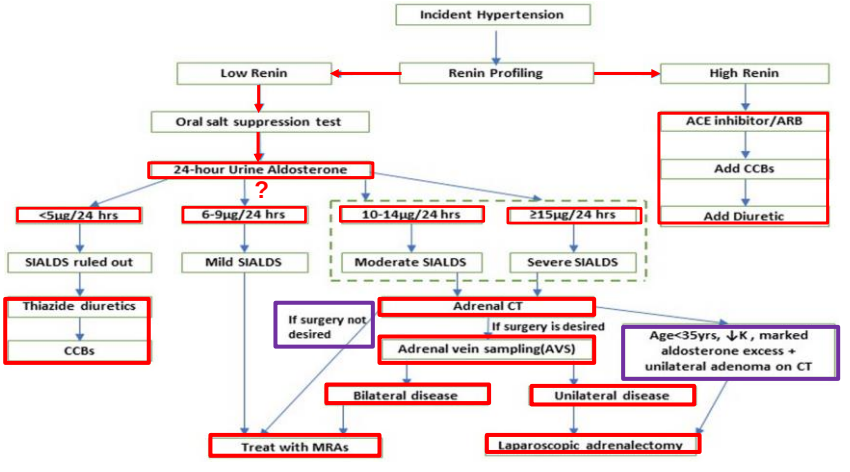

Fig 3.Lamda R. J of Clinical Hypertension, Volume: 25, Issue: 12, Pages: 1045-1052, First published: 25 October 2023, DOI: (10.1111/jch.14740)

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SUMMARY of Primary Aldosteronism (PA)

- Primary aldosteronism (PA) is the most common form of secondary hypertension and is associated with CV and Renal target organ damage and a mortality that is at least 3-fold greater than for primary hypertension, likely due to the direct toxic actions of aldosterone independent of BP.
- Yet, screening rates for PA are abysmal.
- Screen for PA, regardless of medications, but after K+ is normalized perhaps, in the future, in all hypertensives one time in their lifetime.
- Autonomous aldosterone secretion can occur in the normotensive population but more commonly occurs in stage I and stage II hypertension, and most commonly in treatment-resistant-hypertension.
- Future efforts should focus on guideline revision, simplification of the diagnostic process, and perhaps increased and earlier use of MR antagonists in the treatment of hypertension.
- Stay tuned as guideline revision is currently ongoing for PA and should be completed in 2025.

Funder J.W. and Carey R. M. *Hypertension.* 2022;79:00–00. DOI:10.1161/*HYPERTENSION* AHA.121.18761.April 2022

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CAUSES OF SECONDARY HYPERTENSION

Relatively Common	% of ALL with Hypertension
•Primary aldosteronism	8% (20% in resistant HT)
•Renal vascular hypertension	~3%
•Renal parenchymal disease	~1%
•Drug or alcohol-induced	~1%
•Sleep Apnea	common but rarely responsible alone for the degree of BP elevation seen
Rare	<1%
•Pheochromocytoma	
•Cushing's syndrome	
•Hypo- or hyper-thyroidism	
•Primary hyperparathyroidism	
•Acromegaly	
•Apparent mineralocorticoid excess/11β-OHase deficiency	
•Hyperdeoxycorticosteronism (congenital adrenal hyperplasia, primary cortisol resistance, DOC-producing tumor)	
Remaining ~ 87% have primary hypertension.	

Carey R M et.al. Hypertension 2018; 72:e53-e90. November 2018

54

Renovascular Hypertension Can Be Caused by Any Arterial Occlusion

- Atherosclerotic disease-85%
- Fibromuscular disease-14%

99%

- Renal artery embolism
- Dissection / thrombosis
- Post-traumatic injury
- Aortic stent graft occlusion
- Takayasu arteritis

1%

Budd JT. *Consultant.* 2021;61(3):e1-e8. doi:10.25270/con.2020.09.00006

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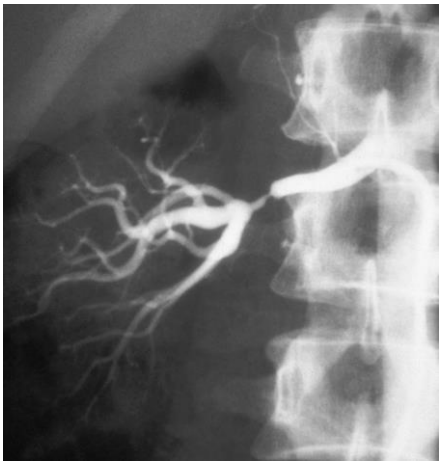
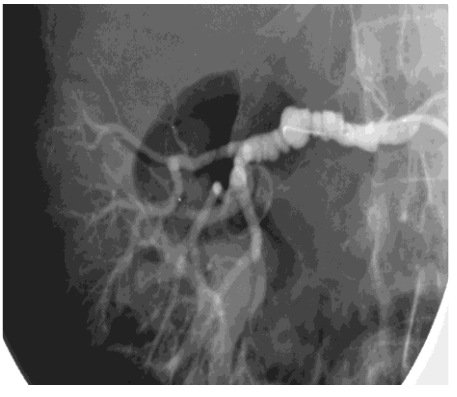
Renovascular Hypertension (RVH)



Atherosclerotic



Fibromuscular

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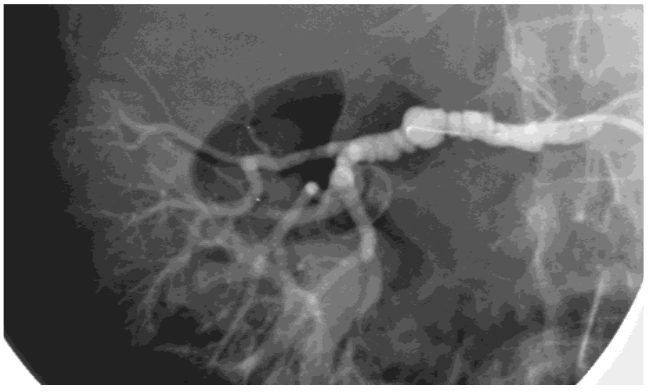
Fibromuscular Disease



- Early Onset (Mean age: 33 years)
- Non-ostial, medial to distal
- Female predominance: progresses with smoking
- Amenable to balloon dilation (angioplasty)

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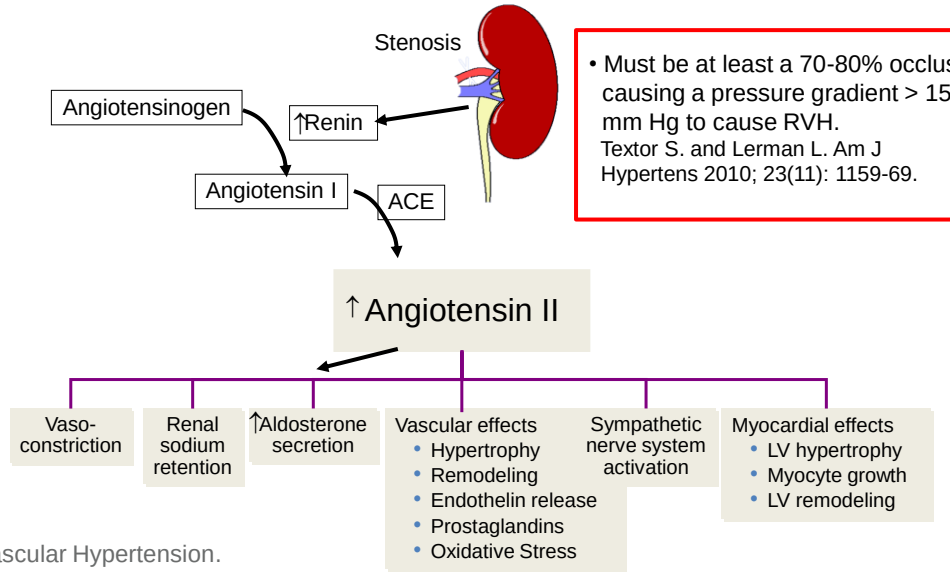
Consequences of Significant Renal Arterial Stenosis Causing RVH: Reduced Renal Perfusion and RAAS Activation



- Must be at least a 70-80% occlusion causing a pressure gradient > 15-25 mm Hg to cause RVH.
  Textor S. and Lerman L. Am J Hypertens 2010; 23(11): 1159-69.

RVH=Renal Vascular Hypertension.

58

Population at Risk for Renal Vascular HTN

- ***When to Suspect by Clinical history***

1. Recent onset of accelerated/malignant hypertension.
2. Resistant Hypertension.
3. Recent loss of previous BP control.
4. Recurrent "flash" pulmonary edema.
5. History of cigarette smoking, ↑ cholesterol, and underlying disease in other vascular beds.
6. Acute kidney failure in patients who are treated with an ACEI/ARB in a solitary functioning kidney or Bilateral RAS.
7. New onset hypertension at age ≥ 50.

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Population at Risk for Renal Vascular HTN

- **When to Suspect by Physical/laboratory clues**

1. Atherosclerotic disease in other vascular beds
2. Systolic/diastolic abdominal bruit.
3. Unilateral small kidney (asymmetric kidneys).
4. Elevated PRA with spontaneous hypokalemia.
   (⬆Renin ⬆Aldo)
5. Young female previously well controlled or with new onset severe hypertension-consider fibromuscular disease.

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The Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) Study:

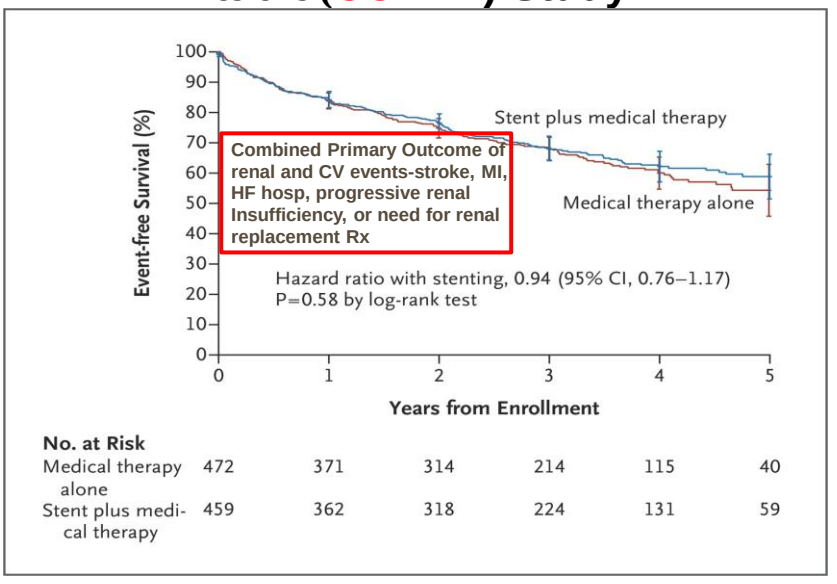

Figure 2 Cooper CJ et al. N Engl J Med 2014;370:13-22

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Many patients with Renal Artery Stenosis Can Be Treated for Years w/o Progressive Loss of Kidney Function

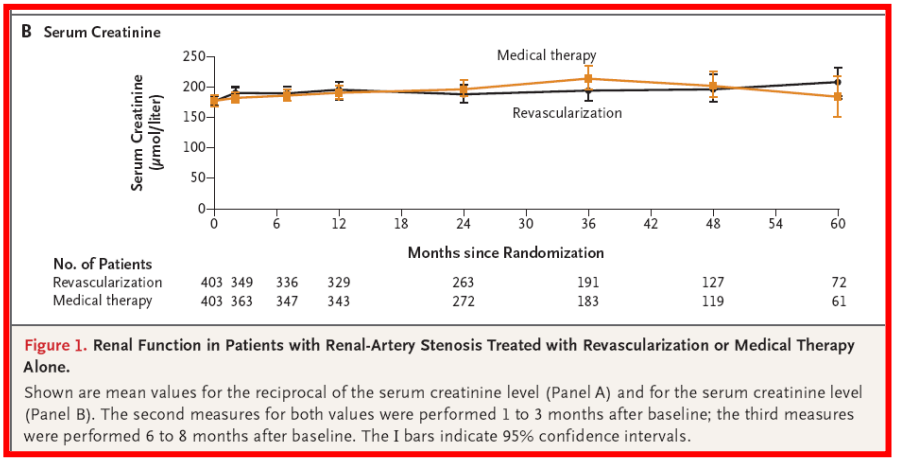

Figure 1. Renal Function in Patients with Renal-Artery Stenosis Treated with Revascularization or Medical Therapy Alone.

Shown are mean values for the reciprocal of the serum creatinine level (Panel A) and for the serum creatinine level (Panel B). The second measures for both values were performed 1 to 3 months after baseline; the third measures were performed 6 to 8 months after baseline. The I bars indicate 95% confidence intervals.

The ASTRAL Investigators: *N. Engl.J.Med:* 361: 1953-1962, 2009

62

SPECIFIC RECOMMENDATIONS FOR RENAL ARTERY STENOSIS

Recommendations for Renal Artery Stenosis		
COR	LOE	Recommendations
I	A	1. Medical therapy is recommended for adults with atherosclerotic renal artery stenosis .
IIb	C-EO	2. In adults with renal artery stenosis for whom medical management has failed (refractory hypertension, worsening renal function, and/or intractable HF) and those with non-atherosclerotic disease, including fibromuscular dysplasia, it may be reasonable to refer the patient for consideration of revascularization (percutaneous renal artery angioplasty and/or stent placement).

2017 ACC-AHA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults; *Hypertension; JACC* Nov 2017

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The Society for Vascular Medicine Recommends Against Screening for Renal Artery Stenosis Even If Known Atherosclerosis Is Present Unless Treatment Resistant Hypertension Is Present Along with Abnormal Renal Function or Flash Pulmonary Edema Because Intervention with Angioplasty, Stent, or Surgery Would Otherwise Not Be Indicated.

Society for Vascular Medicine. Feb 21, 2013. https://www.choosingwisely.org/wp-content

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SPECIFIC RECOMMENDATIONS FOR RENAL ARTERY STENOSIS

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2017 ACC-AHA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults; *Hypertension; JACC* Nov 2017

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WHEN CLINICALLY INDICATED, HOW SHOULD I SCREEN FOR RENAL VASCULAR DISEASE?

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RENAL VASCULAR DISEASE
Diagnostic Imaging

Technique	Sens	Spec
Renal Artery Duplex Ultrasound	85%	92%
Selective renal arteriogram	100%	100%
CTA	64%	92%
MRA (gadolinium-enhanced)	62%	84%

NOTE: Sens and spec to detect > 50% RAS in 356 patients.

BOTTOM LINE: CTA and MRA may fail to detect clinically important disease.

From Vasbinder et al., Ann Int Med 141:674-682, 2004

67

RENAL VASCULAR DISEASE
When Endovascular Treatment Is Indicated

Fibromuscular disease

- Fibromuscular Disease-Balloon Angioplasty.

Atherosclerotic Disease-Stent or Bypass when:

- Failed Multi-drug Rx for Sustained Hypertension
- Worsening Renal Function
- Intractable HF or Flash Pulmonary Edema

Budd JT. *Consultant.* 2021;61(3):e1-e8. doi:10.25270/con.2020.09.00006

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•Apparent mineralocorticoid excess/11β-OHase deficiency
•Hyperdeoxycorticosteronism (congenital adrenal hyperplasia, primary cortisol resistance, DOC-producing tumor)

We are left with ~ 87% with primary (essential) hypertension!

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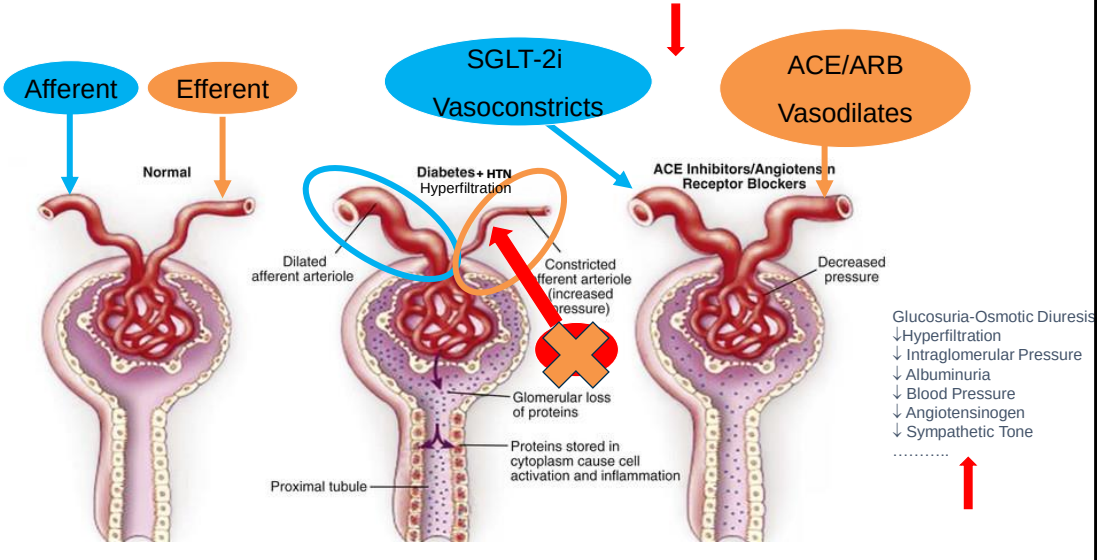
SGLT2 Inhibitors + ACE/ARB Provides Glomerular-Tubular Balance



Wolf G. Pathogenesis of DM. Abdominal Key. 2016

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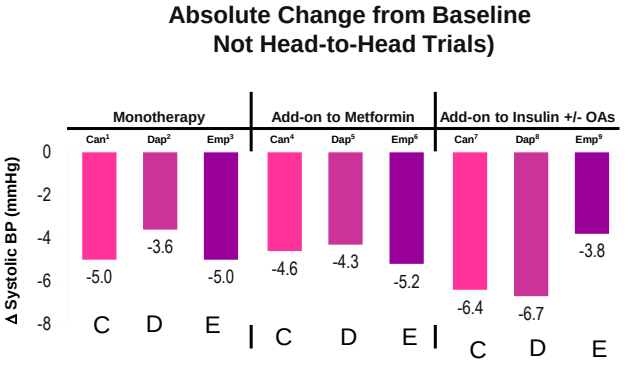
Additive BP Changes with SGLT2 Inhibitors



1.Stenlof K, et al. *Diabetes Obes Metab*. 2013;15:372-382.-Canagliflozin
2.Ferrannini E, et al. *Diabetes Care*. 2010;33:2217-2224.-Dapagliflozin
3. Roden M, et al. *Lancet Diabetes Endocrinol*. 2013;1:208-219-Empagliflozin.
4. Cefalu WT, et al. *Lancet*. 2013;382:941-950.- Canagliflozin
5. Nauck MA, et al. *Diabetes Care*. 2011;34:2015-2022 .-Dapagliflozin.
6. Haring HU, et al. *Diabetes Care*. 2014;37:1650-1659-Empagliflozin.
7. Yale J-F, et al. *Diabetes Obes Metab*. 2013;15:463-473.-Canagliflozin
8. Wilding JPH, et al. *Ann Intern Med*. 2012;156:405-415 .-Dapagliflozin.
9. Rosenstock J, et al. *Diabetes Care*. 2014;37:1815-1823-Empagliflozin.

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Drugs Used to Treat Hypertension (<130/80) in CKD

- ACEi or ARB
- SGLT2 inhibitors (Diabetic or Non-Diabetic, Empa-any eGFR, Dapa-eGFR $\geq$ 25; any degree of albuminuria)-some BP reduction
- Currently Finerenone and Semaglutide (FLOW) only for DKD
- Thiazide Diuretics (Chlorthalidone pref down to eGFR mean 23)
- Mineralocorticoid Receptor Antagonists (non-Diabetic CKD)
  -Spironolactone and Eplerenone for CKD when eGFR > 30 cc/min and K+ $\leq$ 5.0
- CCBs for BP control only

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•Cushing's syndrome
•Hypo- or hyperthyroidism
•Primary hyperparathyroidism
•Aortic Coarctation
•Acromegaly
•Apparent mineralocorticoid excess/11β-OHase deficiency
•Hyperdeoxycorticosteronism (congenital adrenal hyperplasia, primary cortisol resistance, DOC-producing tumor)

We are left with ~ 87% with primary (essential) hypertension!

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Drug-Induced (Medications) That Can Interfere with BP Control[1, 2]

- NSAIDs/COX-2 inhibitors
- Sodium-containing Antacids[2]
- Oral contraceptives (estrogen predominant)
- Sympathomimetic agents (decongestants, diet pills, cocaine)
- Stimulants (amphetamines, methylphenidate)
- Alcohol
- Anti-depressants (TCAs and SNRIs)
- Cyclosporine[1] or tacrolimus[2]
- Erythropoietin
- Natural licorice
- Herbal compounds (ephedra or ma huang)
- Tyrosine Kinase Inhibitors (VEGF inhibitors)-CardioOncology

[1] *Calhoun et al. AHA Scientific Statement: Hypertension 2008;51:1403-1419*
[2] 2017 ACC-AHA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults; *Hypertension; JACC* Nov 2017

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CAUSES OF SECONDARY HYPERTENSION

Relatively Common	% of ALL with HTN
•Primary aldosteronism	8% (20% in resistant HT)
•Renal vascular hypertension	~3%
•Renal parenchymal disease (CKD)	~1%
•Drug or alcohol-induced/Interfering Substances	~1%
Sleep Apnea	common but rarely responsible for the degree of BP elevation seen

Rare <1%

•Pheochromocytoma
•Cushing's syndrome
•Hypo- or hyperthyroidism
•Primary hyperparathyroidism
•Aortic Coarctation
•Acromegaly
•Apparent mineralocorticoid excess/11β-OHase deficiency
•Hyperdeoxycorticosteronism (congenital adrenal hyperplasia, primary cortisol resistance, DOC-producing tumor)

We are left with ~ 87% with primary (essential) hypertension!

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Sleep Apnea Patient

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PREVALENCE OF OSA and CV Disease

- Primary HTN: 35% prevalence of OSA
- Resistant HTN: 65 to 80% prevalence
  - Most common co-morbid association with hypertension
- Coronary Artery Disease: 30% prevalence
- Heart failure: 21-37% prevalence
- Atrial Fibrillation: OSA presence 5 X more likely
- Stroke: 60% prevalence

Kesai T. et al. *Circulation* 2012;126:1495-1510

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The Effect of CPAP on Resistant Hypertension Is Modest, at Best

HIPARCO Randomized Clinical Trial

Methods:

- **Spanish Study in 194 patients with resistant htn and OSA (AHI >15)**
- **CPAP vs no CPAP**
- **Primary Endpoint = Change in 24 hour mean BP as measured by ABPM**

Mean Change in BP with CPAP modest

- **Diastolic BP – 3.2 mm Hg**
- **Systolic BP – 3.1 mm Hg**
- **Greater prevalence of dipping (35.9% vs 21.6%)**

*** But important for concomitant conditions linked with sleep apnea including stroke, MI, HF, Atrial fib, CKD**

Martinez-Garcia et al.JAMA 2013; 310: 2407

** Molnar MZ et al. Thorazx 2015; DOI: 10.1136/thoraxjnl-2015-206790.*

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Screening Tests for Common Causes of 2^{O} HTN

Condition	Test	Routine
• ↓, ↑ thyroid	TSH, (free T4)	*
• Pheochromocytoma	plasma free or 24-hr urinary fractionated metanephrines	*
• 1^{O} aldosteronism	↓ or nl K^{+}, ↑ plasma aldo (> 10) with Aldo/PRA >20-30	*
• Cushing's disease	24 hr urinary free cortisol, Overnight dex supp	Hx PE
• Hyperparathyroid	Ca^{++}, alb, Cl/P, iPTH	Ca++
• Renal artery stenosis	Duplex Ultrasound, Selective renal arteriogram	↑ Creat FPE*
• Sleep apnea	Hx*, polysomnography, overnight oximetry	Hx**

*Flash Pulmonary Edema
**Positive Epworth Sleepiness Score

Carey R M et.al. Hypertension 2018; 72:e53-e90. November 2018*

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SPECIFIC RECOMMENDATION FOR OBSTRUCTIVE SLEEP APNEA

Recommendation for Obstructive Sleep Apnea		
COR	**LOE**	**Recommendation**
IIb	**B-R**	**1. In adults with hypertension and obstructive sleep apnea, the effectiveness of continuous positive airway pressure (CPAP) to reduce BP is not well established.**

2017 ACC-AHA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults; *Hypertension; JACC* Nov 2017

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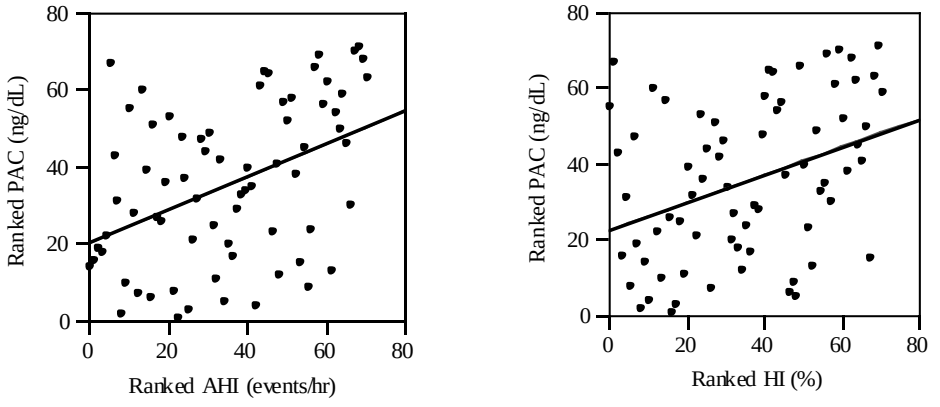
Apnea-hypopnea Index (AHI) and Hypoxic Index (HI) Correlates OSA with Plasma Aldosterone in Resistant Hypertension Subjects

Figure 1



Pratt-Ubunama MN et al. Plasma aldosterone is related to severity of OSA in subjects with Resistant Hypertension *Chest* 2007; 131: 453-458.

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Obstructive Sleep Apnea: Key Takeaways

1. CPAP treatment of OSA in patients with HTN provides symptomatic improvement in sleep quality and daytime alertness.
2. The individual patient benefit of CPAP treatment on BP varies, with greater benefit more likely to occur in patients with more severe OSA, higher BP levels, and better CPAP compliance.
3. Mineralocorticoid Receptor Antagonists should be considered for the control of BP in those with OSA.

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•Hyperdeoxycorticosteronism (congenital adrenal hyperplasia, primary cortisol resistance, DOC-producing tumor)	

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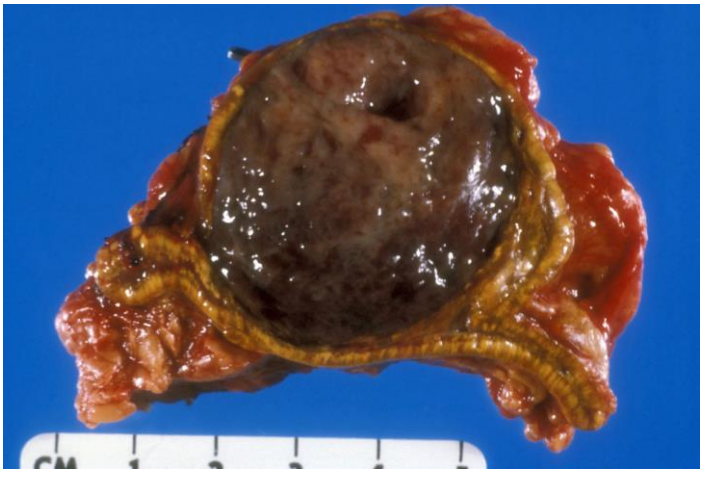
Pheochromocytoma-The "Great Masquerader"



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Pheochromocytoma

- A Catecholamine-secreting tumor that is usually localized to the adrenal gland.
- When outside the adrenal, it is called a paraganglioma.
- It is frequently sought but rarely found.
- When correctly diagnosed and properly treated, it is curable.
- When undiagnosed or improperly treated, it can be fatal.

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Pheo: Clinical Presentation

- **Prevalence** -- 0.01% to 0.2% of patients with HTN
- **Occurrence** -- equally in men and women, primarily in the 3rd through 5th decades.
- **Symptoms** – in 2024 symptoms are present <50% of patients; when present, typically paroxysmal.
- **Mode of Diagnosis** – has changed dramatically over the past 100 yrs—60% are currently discovered as adrenal incidentalomas*****

*****Gruber LM, et al. Pheochromocytoma Characteristics and Behavior Differ Depending on Method of Discovery. *J Clin Endocrinol Metab*. 2019; 104(5):1386-1393.

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**Flash Pulmonary Edema*
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Carey R M et.al. Hypertension 2018; 72:e53-e90. November 2018*

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Medications That May ↑ Measured Levels of NE & Normetanephrine

- Tricyclic antidepressants (including cyclobenzaprine [Flexeril®])
- Levodopa-DA (↑ 10-20 X) & NE & Normetanephrine—↑2-4 X
- Drugs containing adrenergic receptor agonists (e.g., decongestants)
- Amphetamines-variable effect
- Buspirone and Antipsychotic agents—↑3-10 X
- SNRIs may cause < 2-4 fold increase above upper limit of the reference range
- SSRIs do not interfere with the assay
- Prochlorperazine —variable
- Reserpine —↑3-10X
- Withdrawal from clonidine, benzodiazepines, and other drugs (eg, illicit drugs) —variable effect
- Ethanol and ethanol withdrawal — variable effect

Eisenhofer, G. *J Clinic Endocrinol Metab. 2003; 88:2656-2666.*

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Pheo: Summary Points

- Screening with early morning plasma free fractionated metanephrines is recommended. Typically, when a pheo is present, they are 2-3 times above the normal level.
- "All" false + testing for pheo is normetanephrine (NE). When metanephrine (EPI) is increased—pay attention!
- However, these biochemical tests may be normal in an asymptomatic pt presenting as an adrenal incidentaloma discovered in the "pre-biochemical phase"of the pheo—but the imaging phenotype will guide your management (Hounsefield Units)! Discuss with the Radiologist.

Lenders JW, et al. *J Clin Endocrinol Metab* 2014;99(6):1915-42
Carey RM, et al. *Hypertension* 2018; 72:e53-e90
Young WF Jr. N. Engl. J. Med 2007;356(6):601-610.

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Pheo: Summary Points

- Surgery is the recommended treatment with pre-operative alpha blockade used to prevent peri-operative labile BPs. *B*-Blockers are only used for symptomatic tachycardia and never in isolation.
- Patients are followed yearly with fractionated metanephrines to check for recurrence after surgery or if in the pre-biochemical phase.
- ^{123}I-metaiodobenzylguanidine (MIBG) scintigraphy is used to evaluate for a paraganglioma, metastases when additional tumors are detected on CT, or in those with recurrent disease.
- Finally, genetic testing is recommended in all pheo patients as germline mutations are found in 20-30% of patients.

Lenders JW, et al. *J Clin Endocrinol Metab* 2014;99(6):1915-42.
Schwartz G.L. *Endocrinol Metab Clin North America* 2011;40(2):279-294.

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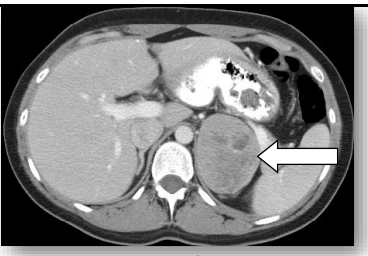
"Imaging Phenotype"

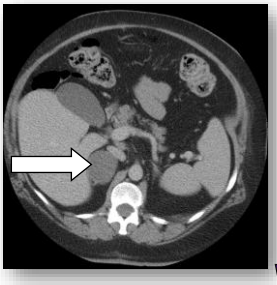
Radiodensity measured in Hounsfield Units (HU)



Slow contrast washout <50% at 10 min

+60 HU

Fast contrast washout >50% at 10 min



Lipid-poor
1)ACCarcinoma
2)Mets to adrenal
3)Pheo
4)Lipid-poor adenoma

Lipid-rich
Benign

-20 HU

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Summary

-Reviewed the most common clinical situations when a secondary cause of hypertension is suggested including in all patients with resistant hypertension.

-You are now familiar with the proper screening tests to rule out secondary causes of hypertension and when to use them.

-You are now familiar with the work up and treatment of the more common secondary causes of hypertension including the evolving workup of primary aldosteronism, when to workup renal vascular hypertension, the importance of sleep apnea for overall vascular health, and when to suspect the rare pheochromocytoma as a cause of hypertension.

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