

Aldosterone: The Forgotten Hormone in Hypertension

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Disclosure

Consultant: Alnylam (Hypertension); Blue Earth Diagnostics; Corcept; Eli Lilly (SURPASS-CVOT); Idorsia (Hypertension); Mineralys; Novo Nordisk; ReCor; UpToDate (Hypertension Section)

Research Grant: Corcept; Eli Lilly (TRIUMPH); Sonivie – THRIVE Study

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Today's Objectives

- **Discuss the History of the R-A-A System and the observation that MRAs have been reserved mostly for patients with resistant hypertension and are not used as often as they should be.**
- **Discuss the resurgence of interest in primary aldosteronism and specific phenotypes where aldosterone dysregulation is involved in BP control.**
- **Contrast the Mineralocorticoid Receptor Antagonists (MRAs) with the Aldosterone Synthase Inhibitors (ASIs), both of which may play a larger role in the future treatment of aldosterone dysregulation and hypertension.**

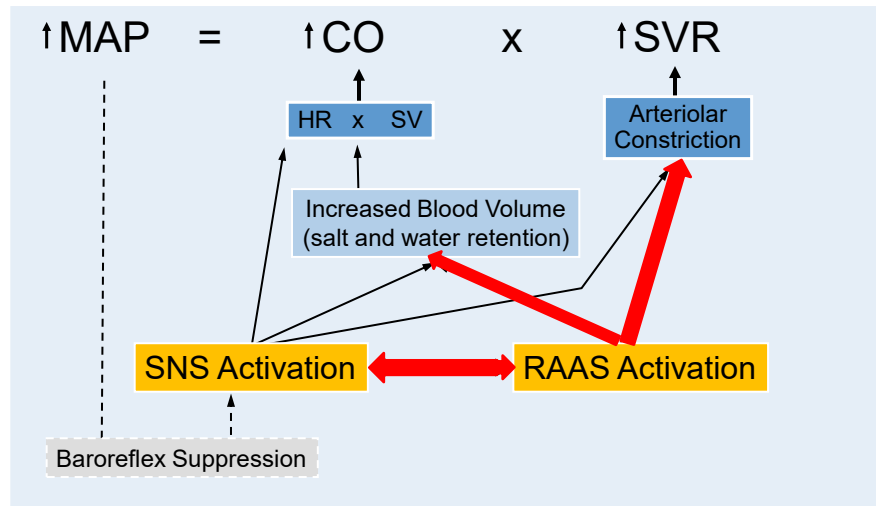
3

Today's Objectives

- **Discuss the History of the R-A-A System and the observation that MRAs have been reserved mostly for patients with resistant hypertension and are not used as often as they should be.**

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Systemic Hemodynamics



Izzo J.L. et al. editors *Hypertension Primer* 4th edition 2008; 126-132, 443-450, 455-464.

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History of the Renin-Angiotensin-Aldosterone Axis

- 1898: Tigerstadt and Bergman first described a pressor substance known as **renin**.
- 1936 to 1958-work first by Harry Goldblatt, and then Eduardo Menendez in Buenos Aires and Irvine Page of the Cleveland Clinic naming another pressor substance **angiotensin**.
- 1953: **Aldosterone** first discovered as a sodium retaining and potassium wasting hormone.
- 1954: Jerome Conn: reported the successful removal of an aldosterone overproducing adrenal gland in a patient with HTN and hypokalemia (Conn syndrome) and found suppressed renin, volume expansion, and non-suppressible aldosterone (Renin-Independent aldosterone excess).
- 1960: Spironolactone was first FDA approved and marketed as a potassium-sparing diuretic but mostly used in patients with hyper-aldosteronism (primary and secondary, e.g., in liver failure).
 - ➔ Progesterone-like and anti-androgen side effects at high doses limited its use.
- 2003: Eplerenone marketed as a “cleaner” spironolactone

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



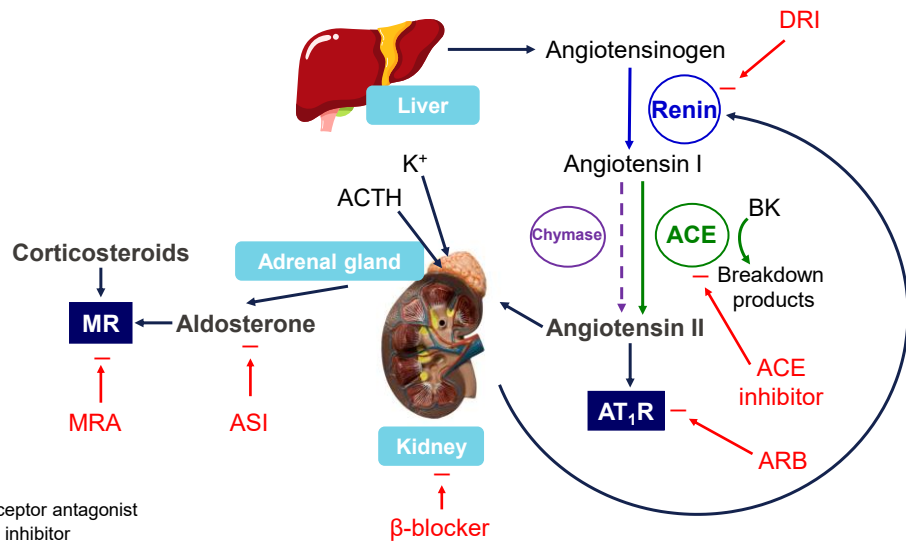
Jerome W. Conn, MD

Basso N and Terragno M. A. *Hypertension* 2001;38(6):1246-9..

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Blockade of the Renin-Angiotensin-Aldosterone System

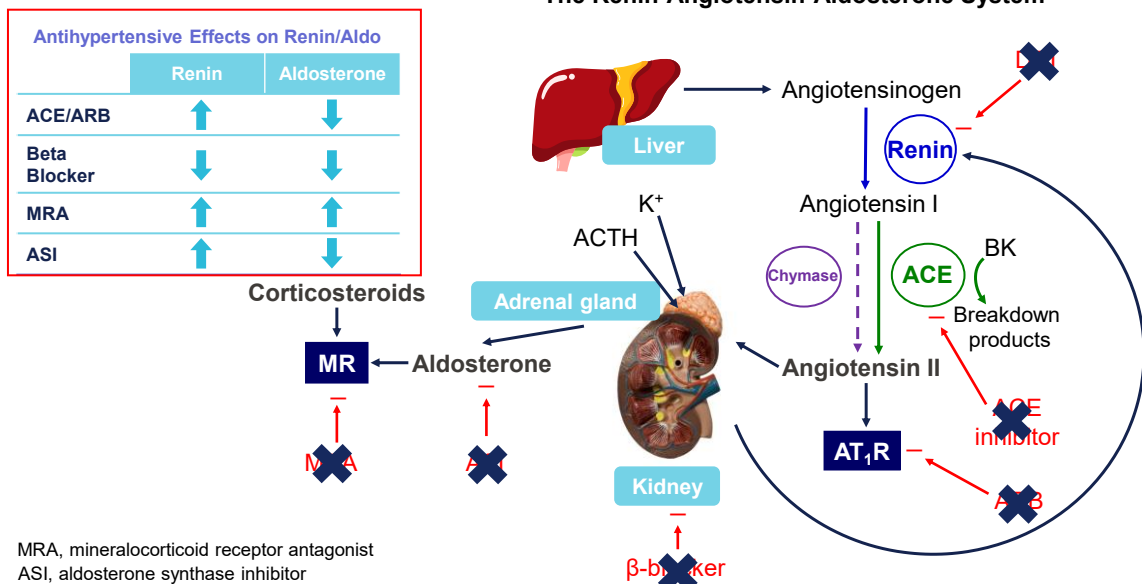
The Renin-Angiotensin-Aldosterone System



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Blockade of the Renin-Angiotensin-Aldosterone System

The Renin-Angiotensin-Aldosterone System



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Of Note:

-In Hypertension, Spironolactone (and Eplerenone) Have Been Held Mostly in Reserve for Resistant Hypertension perhaps because of their Side Effect Profile.

-While They Were Never Marketed for Earlier Use in the Treatment of Essential Hypertension, They Have Been Studied

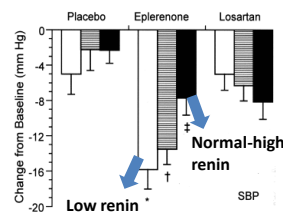
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MRA Monotherapy in Essential HTN

Eplerenone 50 mg vs. Losartan 50 mg

-10.3 vs. -6.9, $P < .0001$

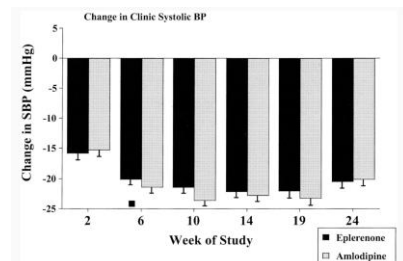
- More effective in low-renin patients
- Equally effective in black vs. white patients



Eplerenone 50 – 200 mg vs. amlodipine 2.5 - 10 mg

-20.5 mm Hg vs. -20.1, $p = NS$

- Equally effective
- Better reduction in urine albumin w Eplerenone
- AEs similar, no gynecomastia reported, potassium elevation was more frequent with eplerenone

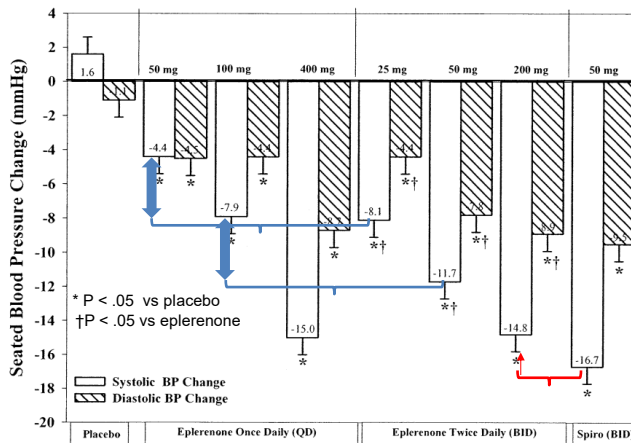


Flack JM et al. J Am Coll Cardiol. 2003 Apr 2;41(7):1148-55
White WB,... Weber MA. Hypertension. 2003 May;41(5):1021-6

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MR Antagonist Monotherapy in Essential HTN

Eplerenone 50 mg to 400 mg vs. Spironolactone 50 mg



	Placebo	Eplerenone Once Daily			Eplerenone Twice Daily			Spirolactone Twice Daily
		50 mg	100 mg	400 mg	25 mg	50 mg	200 mg	50 mg
No. of patients	53	54	49	56	55	54	48	48
Discontinued due to AE	(2)	4 (7)	1 (2)	0	1 (2)	1 (2)	1 (2)	2 (4)
Any adverse event	23 (43)	23 (43)	28 (57)	27 (48)	24 (44)	21 (39)	27 (56)	17 (35)
Arthralgia	0	0	0	0	0	1 (2)	3 (6)	0
Dizziness	0	2 (4)	2 (4)	1 (2)	2 (4)	1 (2)	3 (6)	3 (6)
Headache	9 (17)	5 (3)	9 (18)	9 (16)	5 (9)	9 (17)	6 (13)	4 (8)
Leg cramps	0	0	1 (2)	0	0	0	3 (6)	0
Nausea	1 (2)	1 (2)	1 (2)	3 (5)	0	0	2 (4)	0
Respiratory infection	2 (4)	2 (4)	1 (2)	1 (2)	5 (9)	3 (6)	6 (13)	1 (2)
Sinusitis	0	0	4 (8)	0	1 (2)	3 (6)	1 (2)	1 (2)

- Eplerenone (E) is significantly more effective for BP reduction when given bid than qd.
- Spiro (S) has similar BP Reduction to E at ¼ of the dose when both given bid.
- S is felt to be a better BP-lowering agent at doses required for use.

Weinberger MH et al *Am Jnl Hypertension* 2002; 15:709–716

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Percentage of US Adults Using Specific Antihypertensive Classes 1997-2017 (Medical Expenditure Panel Survey)

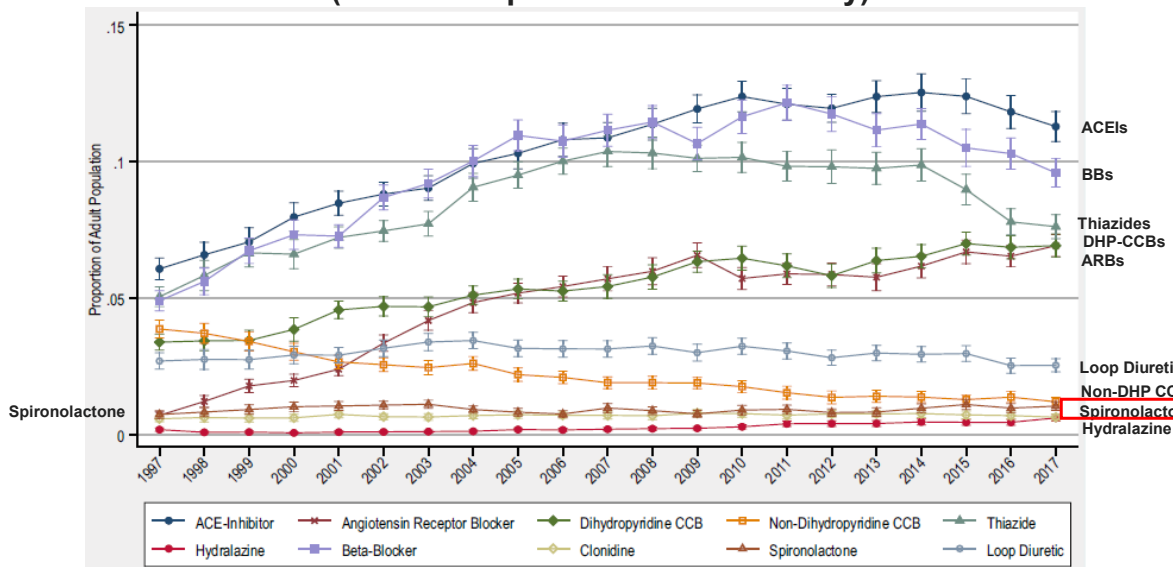


Figure 2. Johansen M.E. et al. *J. Gen. Int. Med.* 2020 36(3):699-704

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2025 AHA/ACC Guideline:



Initial Medication Selection for Those with Primary HTN

Recommendation for Initial Medication Selection for Treatment of Primary Hypertension		
Referenced studies that support the recommendation are summarized in the evidence table.		
COR	LOE	Recommendation
1	A	1. For adults initiating antihypertensive drug therapy, <u>thiazide-type diuretics</u>, <u>long-acting dihydropyridine CCB</u>, and <u>ACEi or ARB</u> are recommended as first-line therapy to prevent CVD.

Jones, D. et al. 2025 AHA/ACC/AANP/AAPA/ABC/ACCP/ACPM/AGS/AMA/ASPC/NMA/PCNA/SGIM Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults. Published ahead of print August 14, 2025, available at Circulation: <https://www.ahajournals.org/doi/10.1161/CIR.0000000000001356>

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Initial Medications for the Management of Hypertension-2025

Lifestyle Modification—Especially Diet and Exercise

Thiazide-Like Diuretics

**ACE Inhibitors
or
ARBs**

DHP-CCBs

2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults: Report From the Panel Members Appointed to the Eighth Joint National Committee (JNC 8). JAMA 2014; 311(5): 507-520. Feb 5, 2014

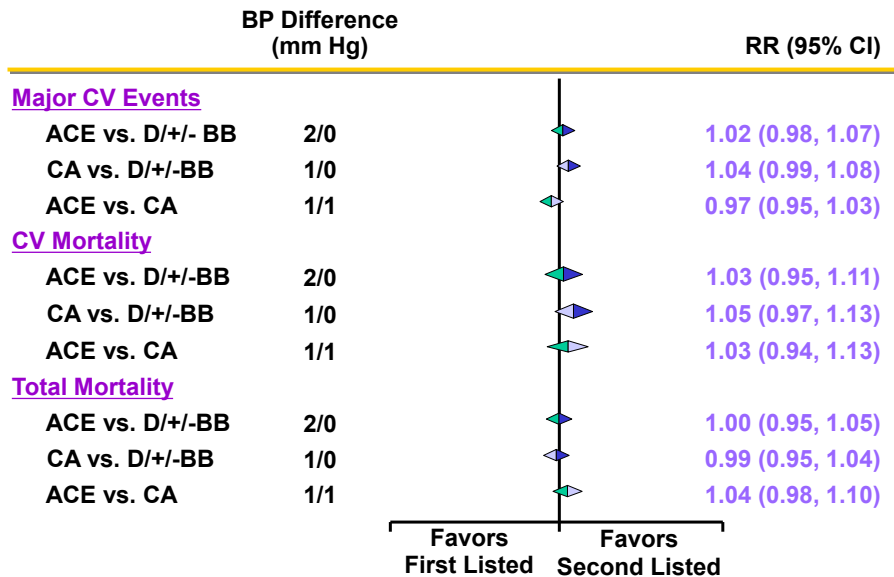
2017 ACC-AHA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults. Whelton PK, Carey RM et al. Hypertension 2018; 71:e13-e115.

2025 AHA/ACC/AANP/AAPA/ABC/ACCP/ACPM/AGS/AMA/ASPC/NMA/PCNA/SGIM Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults. Published ahead of print August 14, 2025, available at: Circulation. <https://www.ahajournals.org/doi/10.1161/CIR.0000000000001356> And Journal of the American College of Cardiology, published online ahead of print August 14, 2025. J Am Coll Cardiol. <https://www.jacc.org/doi/10.1016/j.jacc.2025.05.007>

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BP-Lowering Treatment Trialists Group

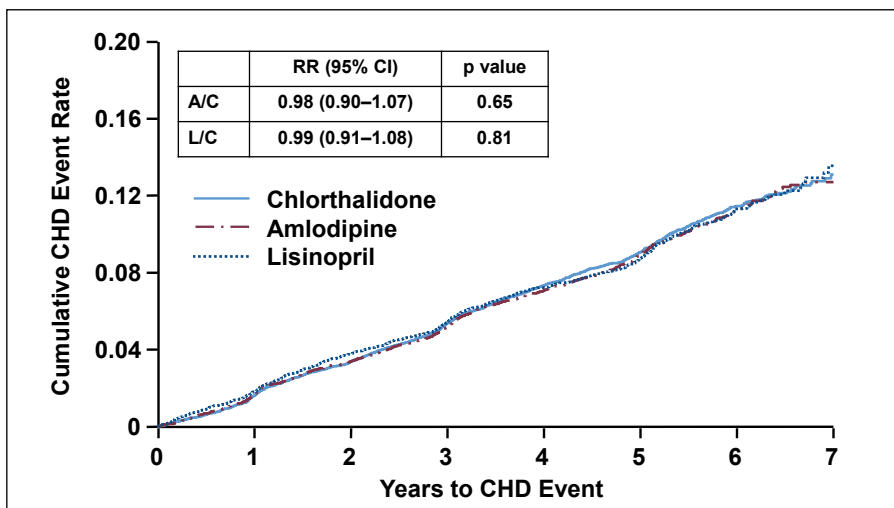
Comparisons of Different Active Treatments



Adapted from Lancet 2000; Vol 356, Issue 9246, pgs 1955-1964.

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Cumulative Event Rates for the Primary Outcome (Fatal CHD or Non-fatal MI) by ALLHAT Treatment Group



Adapted with permission from ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. *JAMA*. 2002;288:2981–2997.

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Management of Resistant Hypertension-2025 ACC/AHA Guideline

- Confirm treatment resistance with 1 of the following:**
- Office BP $\geq 130/80$ mm Hg and on ≥ 3 antihypertensives
 - Combination of ACEi or ARB + CCB + thiazide-like diuretics preferred
 - Office BP $< 130/80$ mm Hg but requires ≥ 4 antihypertensives
 - Combination of ACEi or ARB + CCB + thiazide-like diuretics preferred
- Exclude pseudoresistance**
- Ensure accurate office BP measurements
 - Assess for medication nonadherence with prescribed regimen
 - Obtain home, work, or ambulatory BP readings to exclude white-coat effect
- Identify and reverse contributing lifestyle factors***
- Discontinue or minimize interfering substances†**
- Screen for secondary causes of hypertension‡**
- Pharmacological treatment**
- Maximize diuretic therapy
 - Replace thiazide-type diuretics with chlorthalidone 12.5-25 mg qd or indapamide 1.25-2.5 mg qd
 - Add spironolactone (25-50 mg qd) or equivalent dosage of eplerenone (25-50 mg BID) if eGFR ≥ 45
 - Use chlorthalidone or loop diuretics in patients with CKD stage 4 or greater
 - Add agents with different MOA
 - BB, central sympatholytic drugs, or nondihydropyridine CCB for elevated heart rate
 - Add potent vasodilators
 - eg, aprocritentan, hydralazine, or minoxidil only if already on BB (or bradycardic) and loop diuretic
- Refer to specialist:**
- For known or suspected secondary cause(s) of hypertension
 - If BP remains uncontrolled > 6 months of treatment

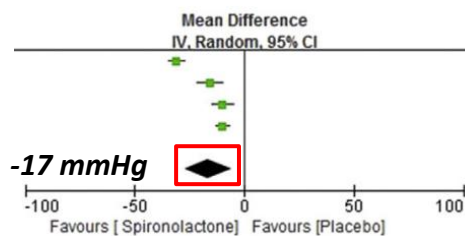
Jones, D.W. et al 2025 ACC AHA HTN Guideline *Circulation*. August 14, 2025 DOI:10.1161/CIR.0000000000001356..

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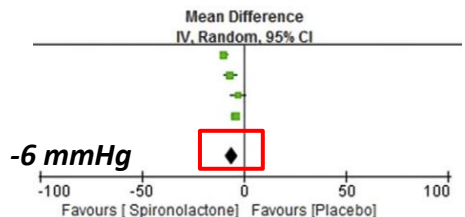
Spironolactone as Add-on in Resistant HTN

Meta-analysis: 4 trials (n=869)

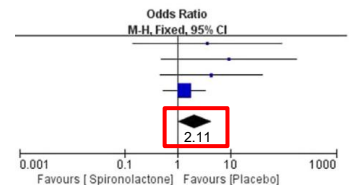
SBP
reduction vs.
placebo



DBP
reduction vs.
placebo



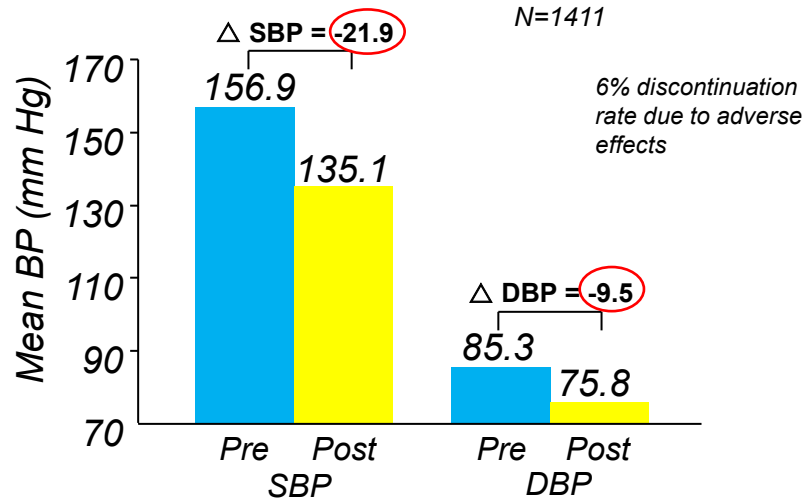
But also: 2.1x greater adverse
event rate compared to placebo



Colussi et al. *Journal of Hypertension* 2013, 31:3-15

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BP Response with Spironolactone 25-50 mg as 4th Drug: ASCOT* Results



Chapman et al. Hypertension. 2007;49:839.

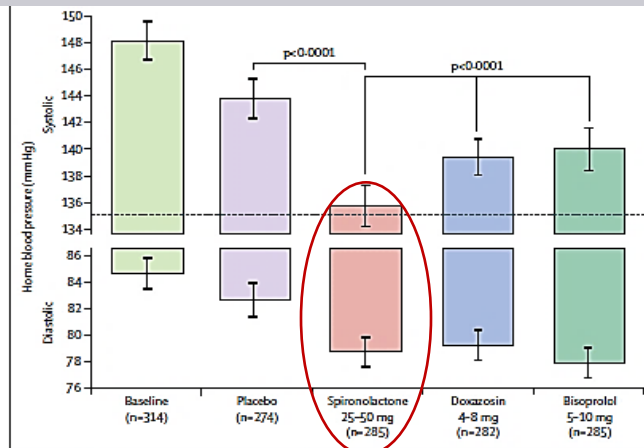
*Anglo-Scandinavian Cardiovascular Outcomes Trial

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Spironolactone versus Placebo, Bisoprolol, and Doxazosin for Drug Resistant Hypertension (PATHWAY-2)

Trial design: Patients (n=285, 230 completed all cycles) with Resistant Hypertension were randomized to each of four different add-on study medications, each for a 6 (lower dose) and then 12-week (Higher dose) period; spironolactone 25-50 mg daily, doxazosin 4-8 mg daily, bisoprolol 5-10 mg daily, or placebo.

- Spironolactone superior to other agents, had largest added effect
- 58% achieved BP target with spironolactone (3x greater vs other agents)
- Discontinuations due to renal impairment, hyperkalemia or gynecomastia not increased with spironolactone



Williams B. Lancet 2015; 386: 2059-2068

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Potency and Selectivity of MRAs

		Potency For BP Reduction	Selectivity	Metabolites	Tissue Distribution ^a (Kidney/Heart)	Adverse Effects
Spironolactone ^b	Steroidal	High	Low	Multiple, active	Higher in kidney	↑ Sexual (eg, gynecomastia) ↑ Hyperkalemia ↑ BP reduction
Eplerenone ^b		Low	Medium	No active metabolites	Higher in kidney	↓ Sexual ↑ Hyperkalemia - Less BP Reduction

^aBased on standard whole-body quantitative analysis in healthy rats; b. FDA/EMA approved treatment of hypertension and HFrEF; Kolkhof P, et al. Handb Exp Pharmacol. 2017;243:271-305; Agarwal R, et al. Eur Heart J. 2021;42:152-161; Dhillon S. Drugs. 2013;73:1451-62.

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Spironolactone (MRA)

- A potent, long-acting, antihypertensive agent dosed once daily.
- With its metabolites its effects can last up to a week.
- Comes in 12.5, 25, 50, and 100 mg tablets.
- Dose Titration is done every 4-8 weeks.
- A slight decrease in eGFR after starting therapy may indicate treatment efficacy rather than a side effect.
- Dietary salt restriction increases its efficacy.
- Adverse Effects: +androgen and progesterone receptor blockade:
 - Gynecomastia (dose dependent 6.9% at doses < 50 mg/day, 52% at doses > 150 mg/day)
 - Decreased libido, ED
 - Menstrual irregularities-spotting (progesterone)-20%, breast tenderness

Up to Date 2026

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Eplerenone (MRA)

- A more selective MRA with no metabolites.
- Less Effective BP Reducing Agent than spironolactone.
- Comes in 25 and 50 mg tablets.
- Short t_{1/2}-dosed bid at 25 mg, 50 mg, 100, then 200 mg all bid.
- Titration every 1-2 weeks.
- Although generic, more expensive than spironolactone.
- Low affinity for both androgen (0.1%) and progesterone (1.0%) receptors.
- Adverse effects: dizziness, headache, fatigue, diarrhea, hypertriglyceridemia and elevated liver function tests.

Up to Date 2026

23

Potency and Selectivity of MRAs

		Potency	Selectivity	Metabolites	Tissue Distribution ^a (Kidney/Heart)	Adverse Effects
Spironolactone ^b	Steroidal	High	Low	Multiple, active	Higher in kidney	▪ ↑ Sexual (eg, gynecomastia) ▪ ↑ Hyperkalemia ▪ ↑ BP reduction
Eplerenone ^b		Low	Medium	No active metabolites	Higher in kidney	▪ ↓ Sexual ▪ ↑ Hyperkalemia
Finerenone ^c	Nonsteroidal	High	High	No active metabolites	Balanced in heart and kidney	▪ Sexual (rare) ▪ ↓ Hyperkalemia ▪ ↓ BP reduction thought to be less than Spiro

^aBased on standard whole-body quantitative analysis in healthy rats; b. FDA/EMA approved treatment of hypertension and HFrEF; c. FDA/EMA approved for the treatment of CKD associated with T2D. BP, blood pressure; CKD, chronic kidney disease; EMA, European Medicines Agency; FDA, US Food and Drug Administration; T2D, type 2 diabetes. Kolkhof P, et al. Handb Exp Pharmacol. 2017;243:271-305; Agarwal R, et al. Eur Heart J. 2021;42:152-161; Dhillion S. Drugs. 2013;73:1451-62.

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Bottom Line

- **There are no head-to-head studies comparing Finerenone to Spironolactone specifically for BP control.**
- **Spironolactone is felt to be the best BP-Lowering MRA (steroidal or non-steroidal) but its side-effect profile has sometimes limited its use.**

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2nd Objective

- **Discuss the resurgence of interest in primary aldosteronism and specific phenotypes where aldosterone dysregulation is involved in BP control.**

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There Has Been a Resurgence of Interest in Aldosterone

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Patient With Recent Worsening of Hypertension



65-year-old
White Male lawyer referred to me in 2018

• History of:

- Hypertension x 20 years
- S/p Uvulopalatopharyngoplasty (UPPP) for sleep apnea in 2014 and no longer snores
- No hx of stroke, MI, CKD, HF, or diabetes
- Obesity (BMI 32.0 kg/m²)
- Stopped smoking in 1982, rare alcohol, low salt and reads labels
- BP easily controlled over many years until 3 years ago
- But control has gotten really bad over the past 6 months, now requiring 3 medicines and KCL tablets

• BPs in the office (average x 3)

- AOBP = 168/96 mmHg (average x3) without orthostasis
- Home BP = (average 1 week, 2 in am and pm) 166/94

• P exam-no significant findings of secondary HTN

• Labs

– Sodium 141, Potassium 3.3, Chloride 101, CO2 29, Anion Gap 11, BUN 17, Glucose 104, Creatinine 0.86, eGFR >60, Ca++ 9.1, Urine for microalbumin 24 mg/g creatinine

Antihypertensive medications

Losartan/HCTZ 100 mg/25 QD

Nebivolol 10 mg QD

KCL 40 meq for past 6 months

Other medications

Atorvastatin 40 mg

E/C ASA 81 mg

AOBP, automated office blood pressure.

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PRIMARY ALDOSTERONISM

Definition

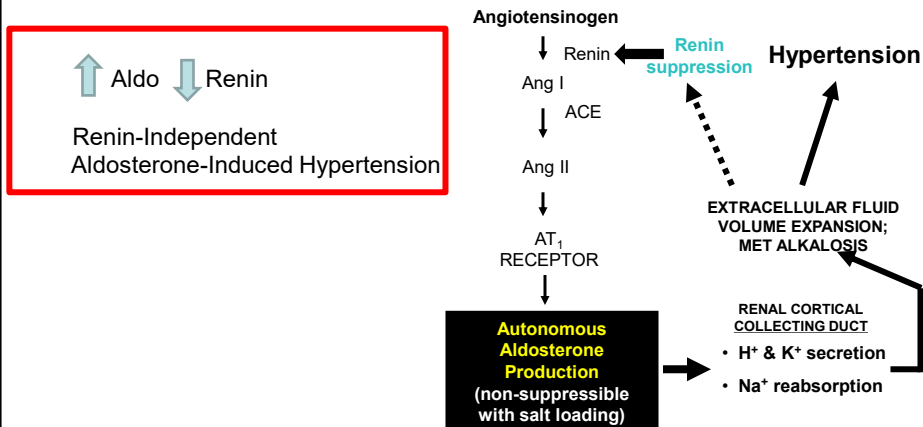
A group of disorders in which aldosterone production is inappropriately **high**, relatively **autonomous** and independent of the renin-angiotensin system (**RAS**), in which aldosterone secretion is **not suppressed by sodium loading**.

↑ 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 PRODUCTION IN PRIMARY ALDOSTERONISM



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

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CAUSES OF SECONDARY HYPERTENSION

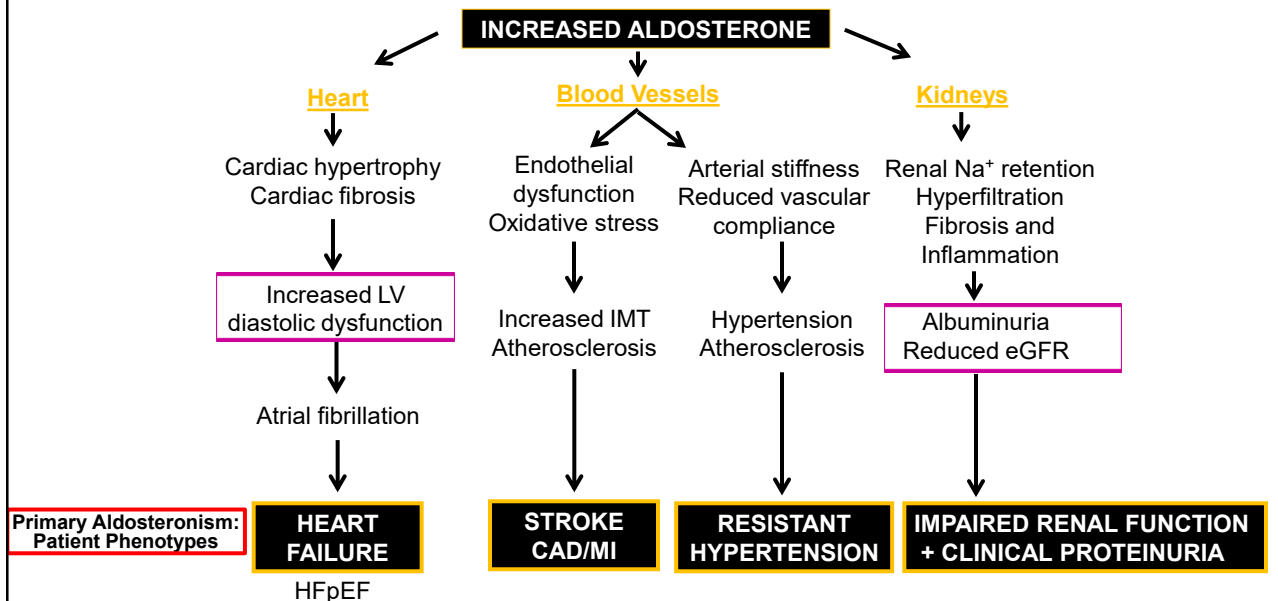
Relatively Common	% of ALL with Hypertension
•Primary aldosteronism	10-15%? (20-25% in resistant HT)
•Renal vascular hypertension	~3%
•Renal parenchymal disease	~1%
•Drug or alcohol-induced	~1%
•Sleep Apnea	common but rarely responsible alone for the degree of BP elevation seen in RH
Rare	<1%
•Pheochromocytoma	
•Cushing's syndrome	
•Hypo- or hyper-thyroidism	
•Primary hyperparathyroidism	
•Acromegaly	
•Apparent mineralocorticoid excess/11 β -OHase deficiency	
•Hyperdeoxycorticosteronism (congenital adrenal hyperplasia, primary cortisol resistance, DOC-producing tumor)	
Remaining ~ 87% have primary (essential) hypertension.	

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

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CARDIOVASCULAR and RENAL BURDEN OF PRIMARY ALDOSTERONISM

HOW DOES IT PRESENT?



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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

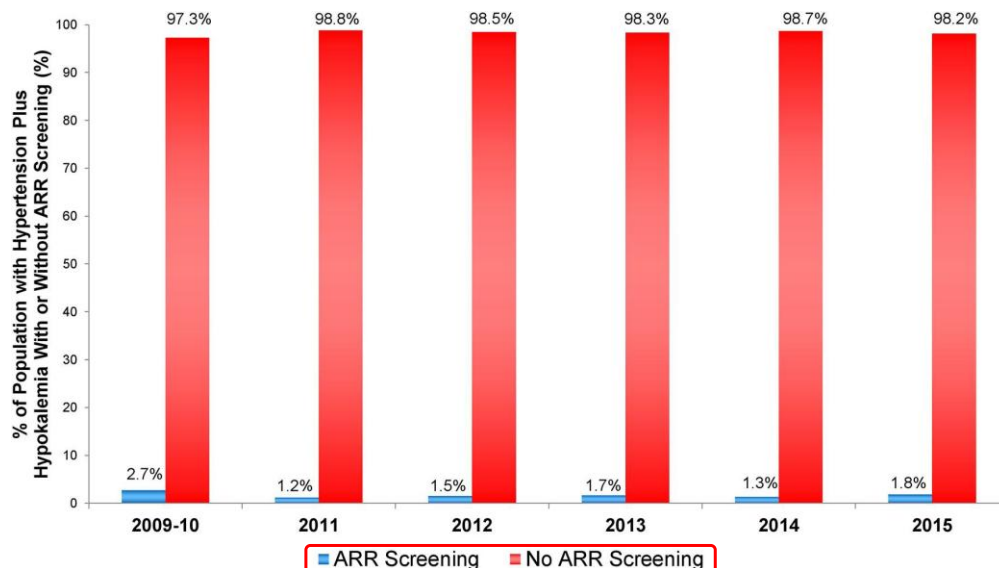


Fig 2. Hundemer, G.L. et al. *Hypertension* 2022;79:178–186.

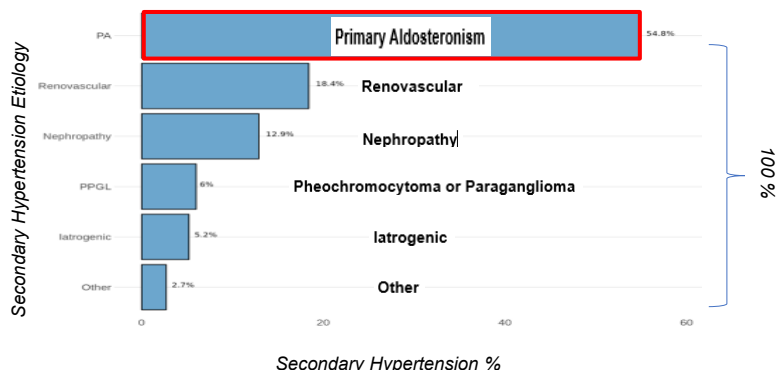
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ORIGINAL ARTICLE

Prevalence and Risk Factors for Secondary Hypertension in Young Adults

Jean-Baptiste de Fremerville¹, Margherita Gardini², Antoine Cremer, Scarlett Camelli, Stephanie Baron³, Guillaume Bobrie, Philippe Gosse⁴, Romain Boulestreau⁵, Nicole Gebara⁶, Julien Doublet, Thomas Dussartre, Christine Grataloup, Aurélien Lorthioir⁷, Christine Massien, Anne-Marie Madjalian, Julien Riancho⁸, Gilles Soulat⁹, Nicolas Postel-Vinay, Michel Azizi¹⁰, Bastien Rance¹¹, Laurence Amar¹²

- 2090 pts with confirmed HTN
- Aged 18 to 40
- Full w/up for 2° HTN
- 30% had 2° HTN
- Prevalence of 2° 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



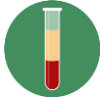
BOTTOM LINE: Screen all adults under 40 for 2° HTN

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

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2024 ESC Guidelines for Managing Elevated BP and HTN

Screening: This Is New



- Renin and aldosterone should be measured in all patients with HTN:

-Primary aldosteronism and Hyperaldosteronism is common not only in secondary HTN but in early forms of hypertension.

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

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The Endocrine Society 2025: Screen All with Hypertension for Primary Aldosteronism

1. PA screening is suggested in all individuals with hypertension.

Adler, G.K.et al. Endocrine Society Guideline *Journal Clin. Endocrine and Metab.* July 14 2025; <https://doi.org/10.1210/clinem/dgaf284>.

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Primary Aldosteronism

1: Strong (Benefit >>> Risk)

2a: Moderate (Benefit >> Risk) certainty is reasonable/useful/effective

2b: Weak (Benefit > Risk), may/might be considered, may/might be reasonable

Recommendations for Primary Aldosteronism

COR	LOE	Recommendations
1	C-EO	1. In adults with hypertension, <u>screening for primary aldosteronism</u> is recommended in the presence of any of the following conditions to increase rates of detection, diagnosis, and specific targeted therapy: <u>resistant hypertension (regardless of whether hypokalemia is present)</u> , <u>hypokalemia (spontaneous or diuretic induced)</u> , <u>OSA</u> , <u>incidentally discovered adrenal mass</u> , <u>family history of early-onset hypertension</u> , or <u>stroke at a young age (<40 years)</u> .
2b	C-EO	2. In adults with <u>stage 2 hypertension</u> , screening for primary aldosteronism <u>may be considered</u> to increase rates of detection, diagnosis, and specific targeted therapy.

2025 AHA/ACC/AANP/AAPA/ABC/ACCP/ACPM/AGS/AMA/ASPC/NMA/PCNA/SGIM Guideline for the Prevention, Detection, Evaluation, and Management of High BP in Adults. Published ahead of print August 14, 2025. available at Circulation: <https://www.ahajournals.org/doi/10.1161/CIR.0000000000001356>

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

- In all patients with Resistant Hypertension¹
- In all Patients Suspected of Secondary Hypertension²
- In all Young Patients < 40 years of age with HTN³
- In All Patients with HTN?-Europeans say YES!⁴
- Suggested in All Patients with Hypertension⁵

¹Jones, D.W. et al *Circulation*. August 14, 2025 DOI:10.1161/CIR.0000000000001356.

²Carey R M et.al. *Hypertension* 2018; 72:e53-e90. November 2018

³*Hypertension* 2024;81:00-00. Nov 2024. DOI 10.1161/HypertensionAHA.124.22753

⁴McEvoy JW, et al; ESC Scientific Document Group. *Eur Heart J*. 2024;ehae178.

⁵Adler, G.K.et al. Endocrine Society Guideline *Journal Clin. Endocrine and Metab*. July 14 2025; <https://doi.org/10.1210/clinem/dgaf284>.

But the ACC/AHA 2025 Guideline Fell Short !!

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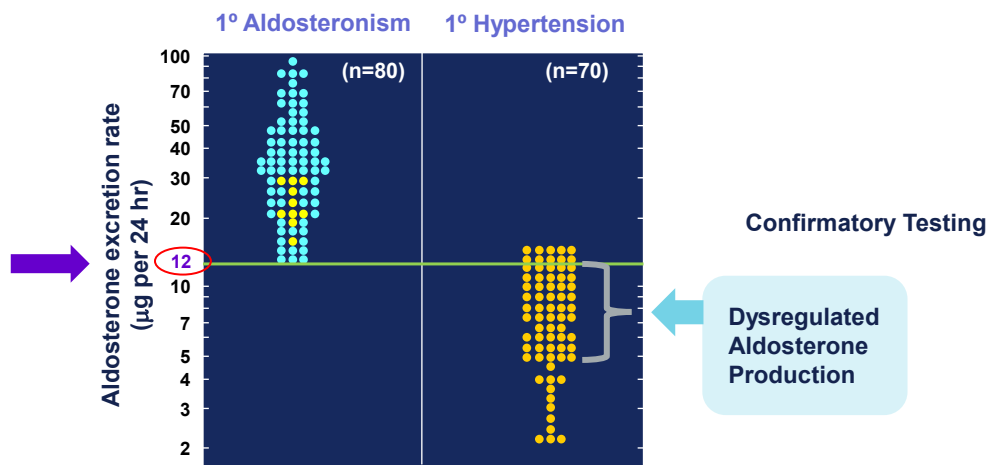
Primary Aldosteronism

What's New!!

The Concept of Aldosterone Dysregulation Paralleling Hypertension Severity

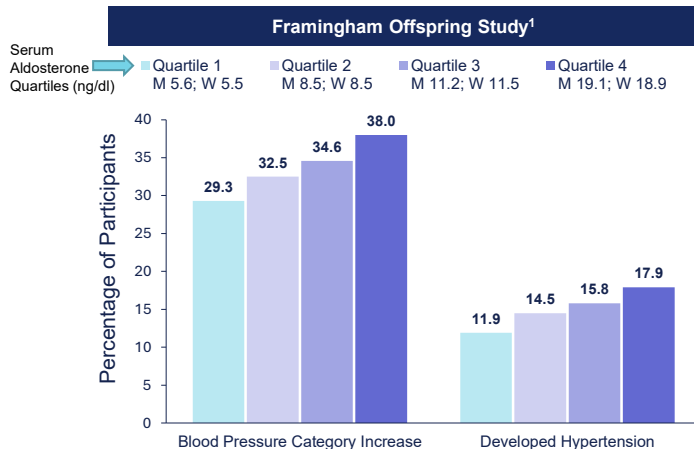
39

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

Bravo EL, et al. *Am Journal Med.* 1983;April:641-651.

40

Dysregulated Aldosterone in Previously Normotensive Individuals Is Associated with an Increased Incidence of Hypertension Over Time



- Cohort study of 1,688 normotensive participants at baseline with follow-up at 4 years¹
- Age- and sex-adjusted BP outcomes stratified by baseline serum aldosterone level quartiles¹ (mean age 55, 58% women)
- An increase in BP was defined as an increment of ≥ 1 BP category²

CONCLUSIONS

In our community-based sample, increased aldosterone levels within the physiologic range predisposed persons to the development of hypertension.

BP Categories	Optimal	Normal	High-Normal	Stage 1 HTN	Stage 2 HTN	Stage 3 HTN
	<120/80	120-129/80-84	130-139/85-89	140-159/90-99	160-179/100-109	$\geq 180 / \geq 110$

1. Vasan, Ramachandran S, et al. *N Engl J Med*. 2004;351(1):33-41.

2. The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Arch Intern Med*. 1997;157:2413-46.

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Continuous Spectrum of the Primary Aldosterone Syndrome

Primary aldosteronism diagnosed if urinary aldosterone $> 12 \mu\text{g}/24 \text{ h}$ 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).



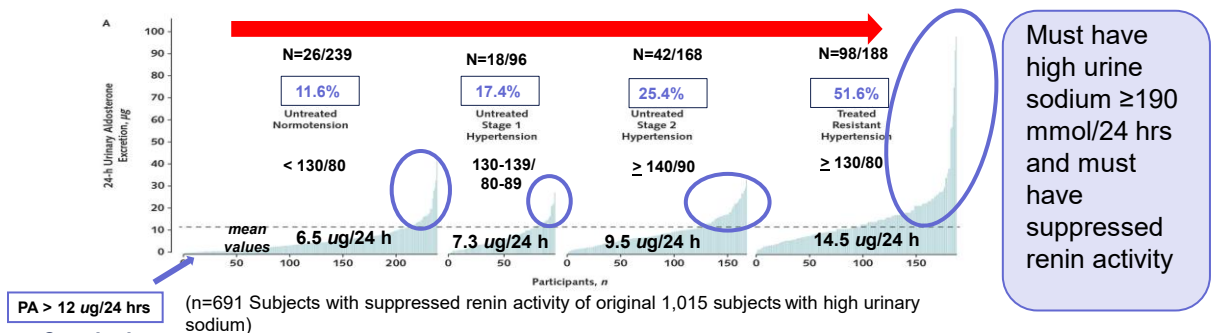
All given an Oral Sodium Suppression Test



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

42

Dysregulated Aldosterone Occurs as a Spectrum (Here in 691/1015 on a High Sodium Load **and** with Suppressed Renin)



Conclusions:

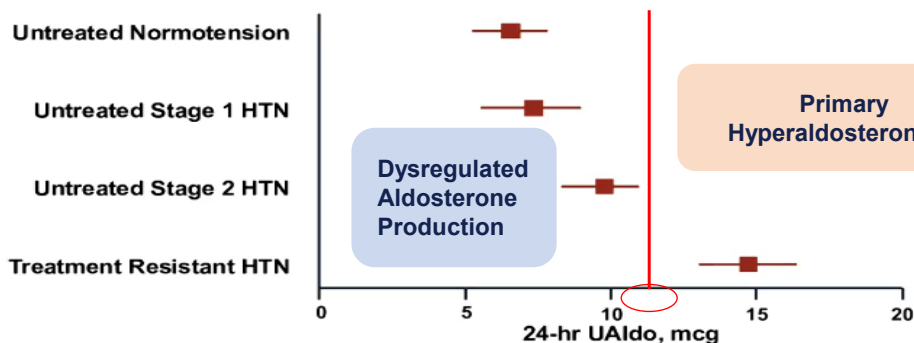
- There is a spectrum of renin-independent aldosterone production that occurs in “healthy” untreated normotensives and increases with the severity of hypertension.
- This suggests aldosterone dysregulation with suppressed renin plays a role in untreated primary “essential” hypertension to the more often recognized patient with treatment-resistant hypertension.
- Perhaps mineralocorticoid-receptor-antagonists should be used more often, and perhaps earlier, in treatment of hypertension. (They were FDA approved in 1960)
- The role of aldosterone synthase inhibitors awaits further evaluation in the treatment of these patients.

Adapted from Table 2 Lower Panel in Brown JM, et.al. *Annals Int Med.* 2020;173(1):10-20.

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The Severity of Aldosterone Dysregulation Parallels Hypertension Severity

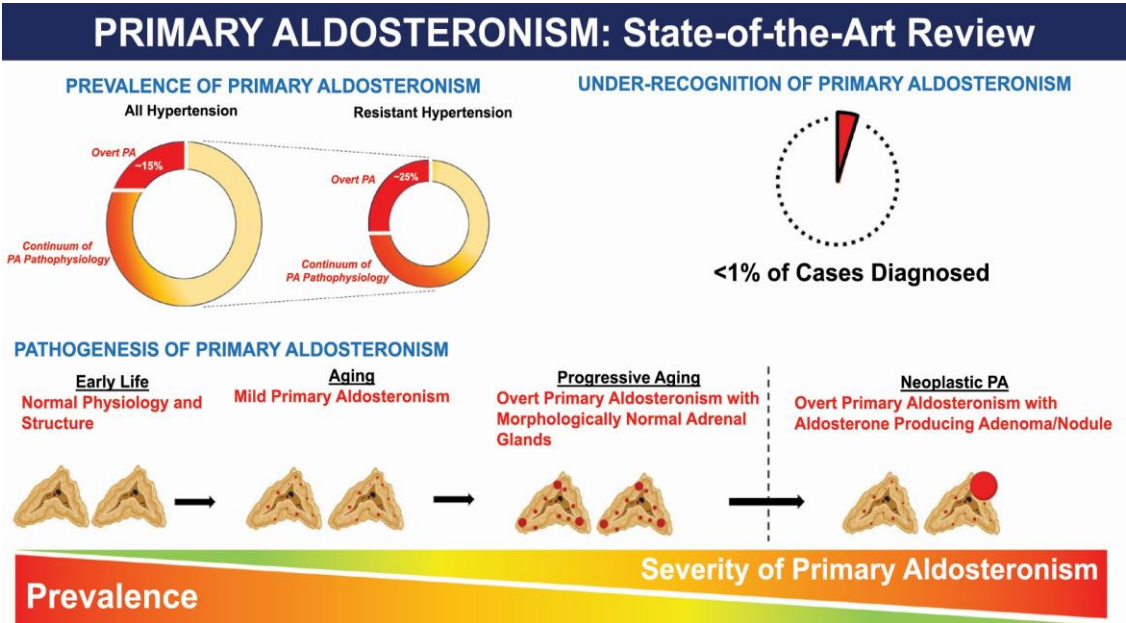
Adjusted Renin-Independent Mean urinary Aldosterone Production by BP Category



➔ **Conclusion:** Despite High Sodium Balance And Suppressed Renin, Aldosterone Levels Were Increasingly Higher Across More Severe BP Categories

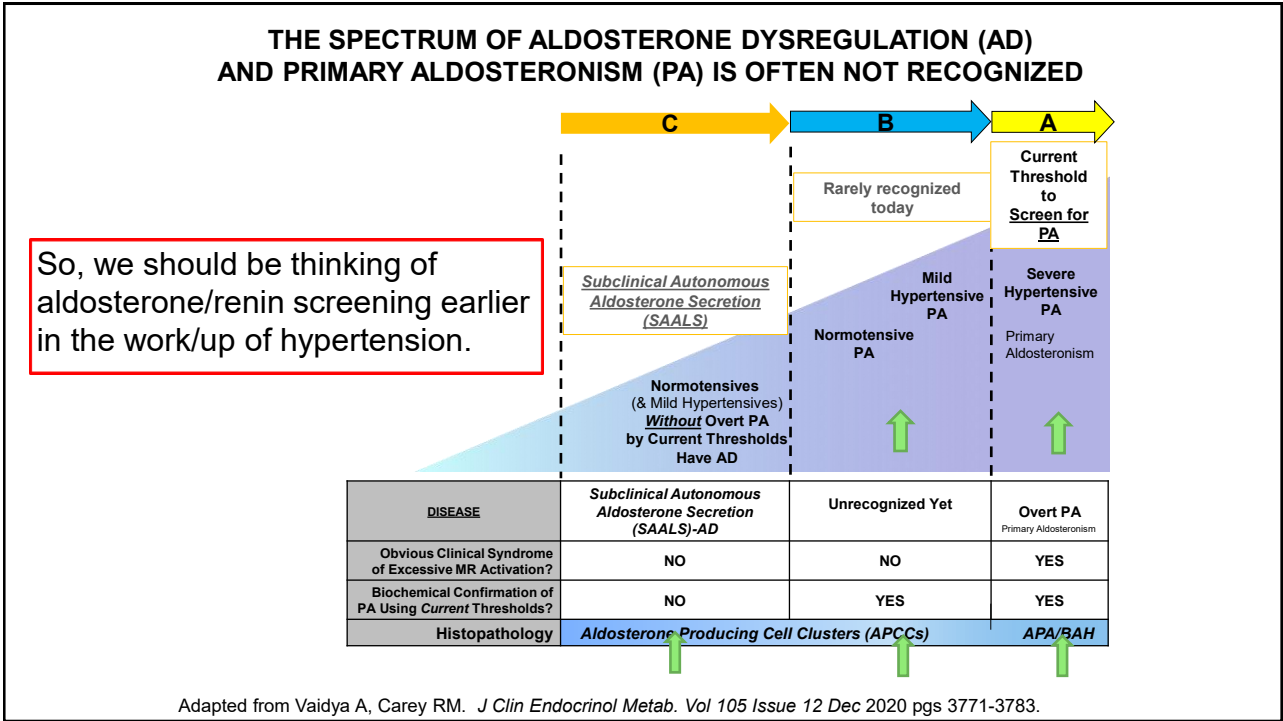
Adapted from Figure 2A Brown JM et.al. *Annals Int Med* July 7 2020; 173 (1):pg 10-20.

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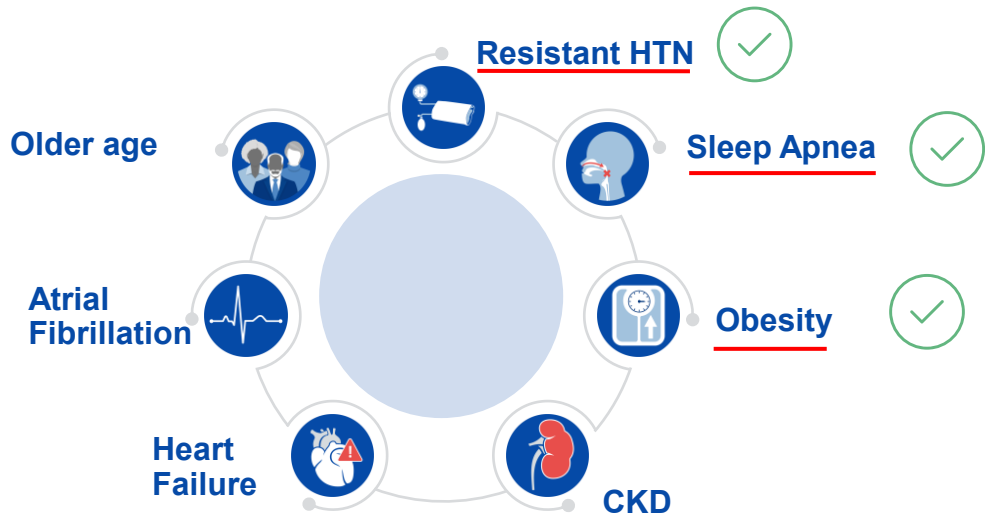
Vaidya A et al. Am J Hypertens. Dec 2022. Volume 35, Issue 12, 2022, Pages 967–988

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High Prevalence of Aldosterone-Mediated HTN in Multiple Patient Populations



Wannachalee T, et al. Curr Hypertens Rep. 2022;24:123-132.

47

The Forgotten Hormone: Role of Mineralocorticoid Receptor Antagonists (MRA's) in Specific Groups with Hypertension:

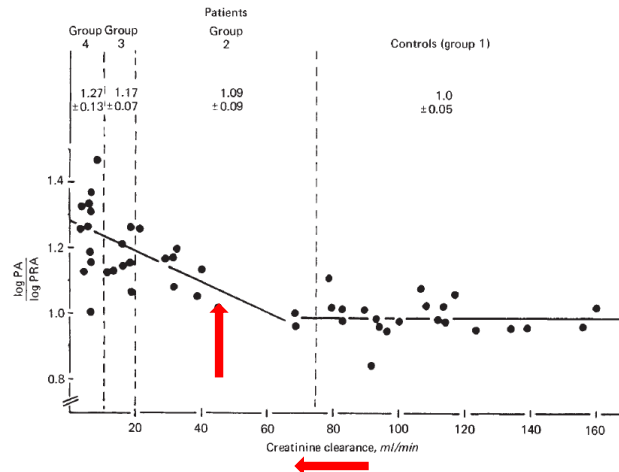
1. CKD
2. OSA
3. Obesity

Mineralocorticoid Receptor Antagonists should be considered for the control of BP in these situations.

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Aldosterone Dysregulation Occurs in CKD

Plasma Aldosterone Rises as GFR Falls

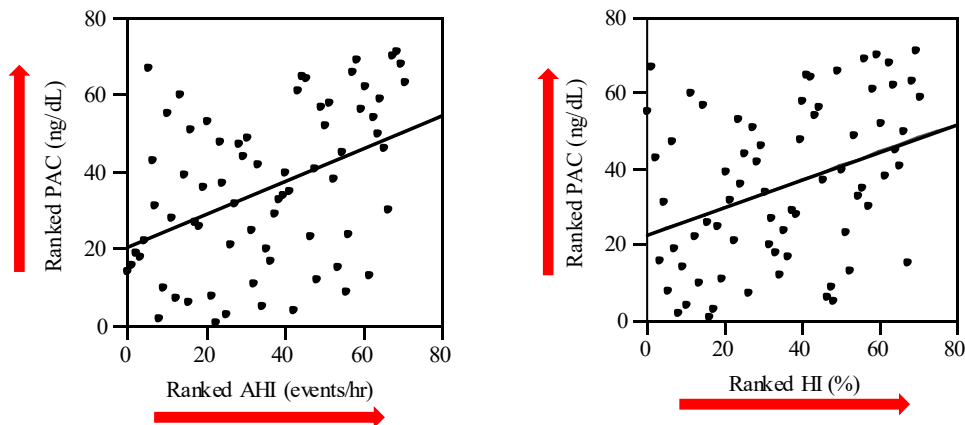


Hené RJ et al, *Kidney Int.* 1982 Jan;21(1):98-101.

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

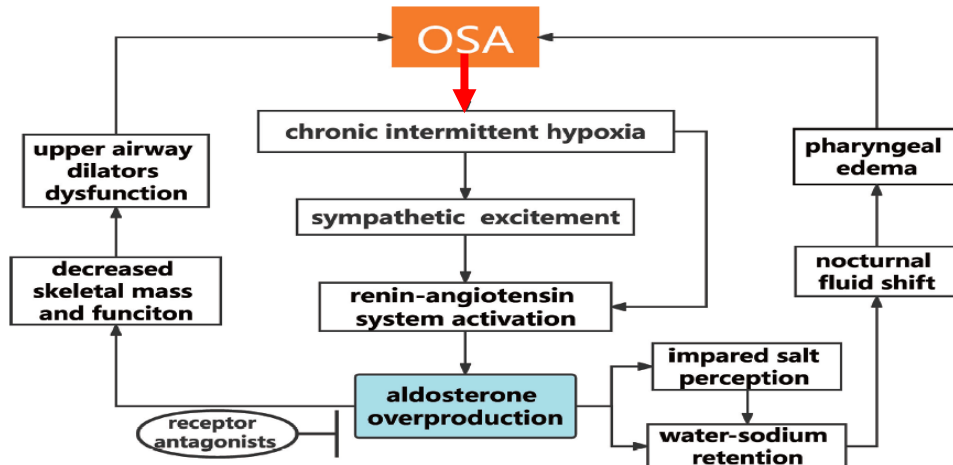
Figure 1



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

50

Aldosterone Dysregulation Occurs in OSA



Wang et al. *Frontiers in Endocrinol.* January 2022;Vol 12:801689.

51

Obesity Is a Driver of Increasing Aldosterone Production in Patients with Treatment-Resistant HTN

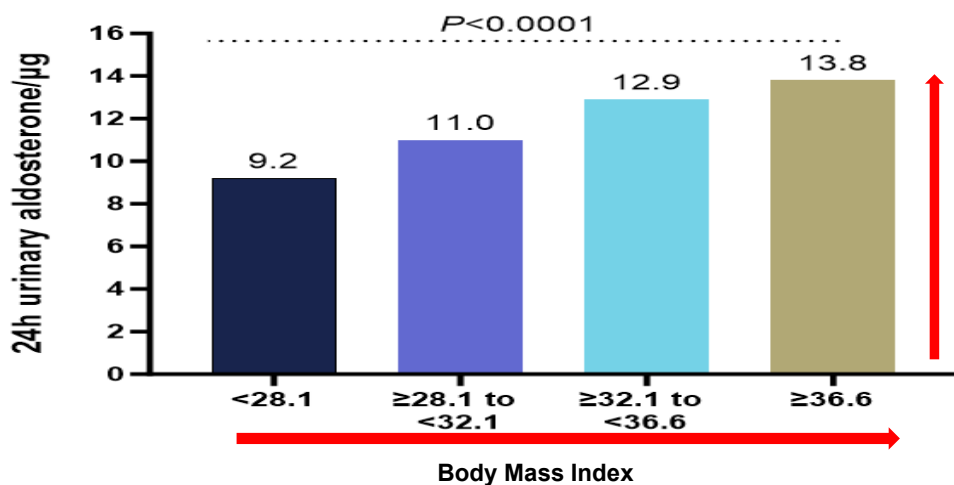


Fig 1 D. Dudenbostel T. et al. *Hypertension*. 2016;68(4):995-1003.

Acelajado MC et al. *Circ Res*. 2019;14:1061-1070.

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Today's Objectives

- Contrast the Mineralocorticoid Receptor Antagonists (MRAs) with the Aldosterone Synthase Inhibitors (ASIs), both of which may play a larger role in the future treatment of aldosterone dysregulation and hypertension.

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MR Antagonists and Aldosterone Synthase Inhibitors (ASI)

Steroidal MRA

Spironolactone

Eplerenone

Non-steroidal MRA

Finerenone

Ocedurenone

Aldosterone Synthase Inhibitors (ASI)

Baxdrostat

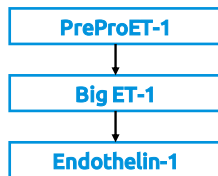
Lorundrostat

BI 690517 (Vica drostat)

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Old Targets and New Pathways in Hypertension

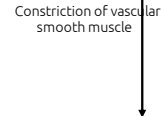
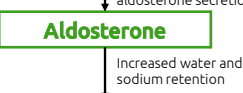
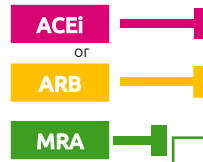
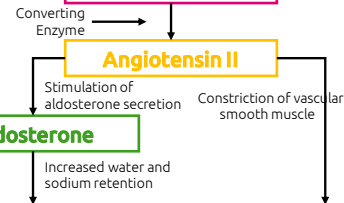
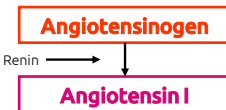
Endothelin System



- Constriction of VSMC
 - Potentiation of growth factors on remodeling
 - Profibrotic
- Stimulation of aldosterone secretion

ET = Endothelin
ERA = Endothelin Receptor Antagonist

RAAS System



High blood pressure

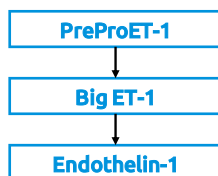
RAAS = Renin-Angiotensin-Aldosterone System
ACEi = Angiotensin Converting Enzyme Inhibitor
ARB = Angiotensin Receptor Blocker
MRA = Mineralocorticoid Receptor Antagonist
ASI = Aldosterone Synthase Inhibitors

1. Ojha U. et al. *Am J Cardiovasc Drugs*,2022;22(3):271-285.

55

Old Targets and New Pathways in Hypertension

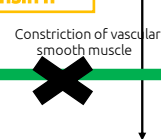
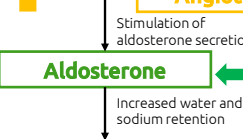
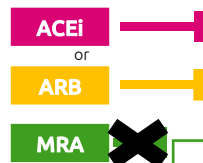
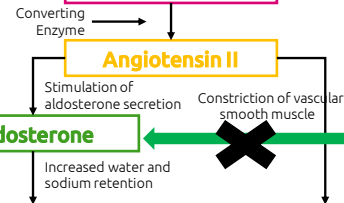
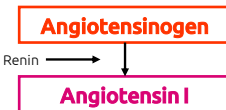
Endothelin System



- Constriction of VSMC
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- Stimulation of aldosterone secretion

ET = Endothelin
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RAAS System



High blood pressure

ASI
Baxdrostat
Lorundrostat
(in Phase 3 development)

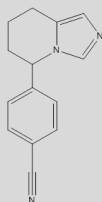
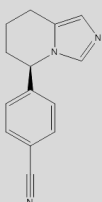
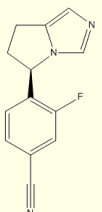
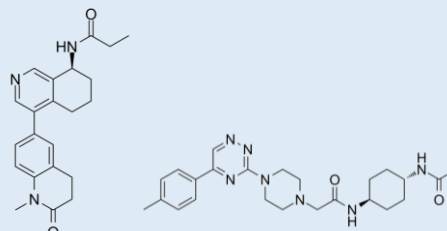
RAAS = Renin-Angiotensin-Aldosterone System
ACEi = Angiotensin Converting Enzyme Inhibitor
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MRA = Mineralocorticoid Receptor Antagonist
ASI = Aldosterone Synthase Inhibitors

1. Ojha U. et al. *Am J Cardiovasc Drugs*,2022;22(3):271-285.

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Aldosterone Synthase Inhibitors

Aldosterone synthase CYP 11B2 shares 93% sequence identity to CYP11B1 (cortisol synthesis)

Structure					
Drug	Fadrozole	(R)-Fadrozole	Osilodrostat	Baxdrostat (qd)	Lorundrostat(qd)
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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Select Published / Ongoing Baxdrostat Trials

ClinicalTrials.gov ID	Phase	Study Name	Projected Enrollment (n)	Background Therapy	Comparators	Primary Outcome	Estimate Completion (ClinicalTrials.gov)
NCT06034743 ^[1]	Phase 3	BaxHTN	794	Stable regimen of 2 or more BP agents, one of which is a diuretic	Placebo 1 mg 2 mg	Change from baseline in seated SBP at week 12	Published NEJM Aug 13, 2025
NCT06344104 ^[2]	Phase 3	BaxAsia	300	Stable regimen of 2 or more BP agents, one of which is a diuretic	Placebo 1 mg 2 mg	Change from baseline in seated SBP at week 12	2026-05-20
NCT06168409 ^[3]	Phase 3	Bax24	212	Stable regimen of 3 or more BP agents, one of which is a diuretic	Placebo 2 mg	Change from baseline in ambulatory 24-h average SBP	Presented at ASN October 2025
NCT06268873 ^[4]	Phase 3	-	2500	Dapagliflozin ACE or ARB (eGFR 30-90) (UACR 200-5000)	Placebo 2 mg	Change from baseline in eGFR to post-treatment	2027-12-10

1. ClinicalTrials.gov. NCT06034743. Accessed March 30, 2025;

2. ClinicalTrials.gov. NCT06344104. Accessed March 30, 2025;

3. ClinicalTrials.gov. NCT06168409. Accessed March 30, 2025;

4. ClinicalTrials.gov. NCT06268873. Accessed March 30, 2025.

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Efficacy and Safety of Baxdrostat in Uncontrolled and Resistant Hypertension

John M. Flack, M.D.,¹ Michel Azizi, M.D.,^{2,3} Jenifer M. Brown, M.D.,⁴
 Jamie P. Dwyer, M.D.,⁵ Jakub Fronczek, M.D.,⁶ Erika S.W. Jones, M.D.,⁷
 Daniel S. Olsson, M.D.,⁸ Shira Perl, M.D.,⁹ Hirotaka Shibata, M.D., Ph.D.,¹⁰
 Ji-Guang Wang, M.D.,¹¹ Ulrica Wilderäng, Ph.D.,⁸ Janet Wittes, Ph.D.,¹²
 and Bryan Williams, M.D.,¹³ for the BaxHTN Investigators*

ABSTRACT

Flack J. et al. *N Engl. J. Med* Aug 30 2025 DOI: 10.1056/NEJMoa2507109.

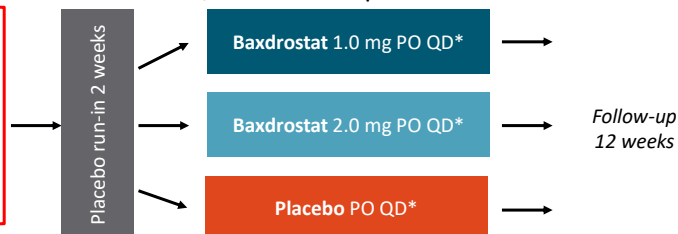
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BaxHTN: Baxdrostat in Patients with Uncontrolled or Resistant HTN

Part 1 lasted 12 weeks

- Multicenter, double-blind, placebo-controlled, randomized phase III trial

-Adults with uncontrolled or resistant HTN
 -Sitting SBP ≥ 140 to < 170 mm Hg
 -Taking 2 antihypertensive agent regimen if uncontrolled or ≥ 3 antihypertensives if resistant, with 1 being a diuretic for ≥ 4 wks
 -eGFR ≥ 45 mL/min/1.73 m²
 -Potassium level 3.5 to < 5.0 mmol/L
 (N = 796)



*Patients to be treated in double-blind period for 12 wk, followed by a rerandomization to treatment arms for 12-wk open-label period, an 8-wk withdrawal period randomized to baxdrostat 2.0 mg or placebo, and then a final 20-wk open-label period.

- Co-primary endpoints:** change in seated Office SBP for both baxdrostat arms at 12 wk
- Key secondary endpoints:** change in seated Office SBP for baxdrostat 2.0 mg at 32 wk; change in seated Office SBP, seated office DBP, patients who achieved seated office SBP < 130 mm Hg for both baxdrostat arms; and safety

Flack J. et al. *N Engl. J. Med*. Aug 30 2025 DOI: 10.1056/NEJMoa2507109.

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Bax HTN: Baseline Participant Characteristics



794 participants
27% uncontrolled HTN
73% resistant HTN

- Participants were 62% male and 63% White
 - 26% Asian; 7% Black
- Mean (SD) age was 61 (12) years
- Participants were from:
 - The Americas (27%)
 - Europe (43%)
 - Asia Pacific, Middle East, and Africa (30%)

*Reported by the participant.
 HTN, hypertension; SD, standard deviation.

Characteristic	Placebo (n=264)	Baxdrostat, 1 mg (n=264)	Baxdrostat, 2 mg (n=266)
Age, mean $\pm$ SD, yrs	61.9 $\pm$ 11.6	59.8 $\pm$ 11.8	61.8 $\pm$ 11.7
Male sex, n (%)	162 (61.4)	169 (64.0)	163 (61.3)
Race, n (%)*			
White	167 (63.3)	165 (62.5)	168 (63.2)
Black	15 (5.7)	23 (8.7)	21 (7.9)
Asian	72 (27.3)	65 (24.6)	72 (27.1)
Native Hawaiian or Pacific Islander	1 (0.4)	1 (0.4)	0 (0.0)
Other	9 (3.4)	10 (3.8)	5 (1.9)

Adapted from Table 1. Flack J. et al. *N Engl. J. Med* Aug 30 2025 DOI: 10.1056/NEJMoa2507109.

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Baseline Participant Characteristics (Con't)-Bax HTN

- Clinical characteristics at baseline were similar across treatment arms
- Baseline BP: 149/87 mmHg**
- Median number of background AHT medications: 3 (for each treatment group)
 - Almost all on a diuretic (99.6%)
 - 90% on an ACEi or ARB
 - 70% on a calcium channel blocker
 - 34% on a beta blocker
- 52% had obesity, 38% had diabetes
- Baseline potassium: 4.2 mmol/L
- Baseline eGFR: 85.0 mL/min/1.73m²

Characteristic	Placebo (n=264)	Baxdrostat, 1 mg (n=264)	Baxdrostat, 2 mg (n=266)
Seated BP, mmHg*			
Systolic, mean $\pm$ SD	149.0 $\pm$ 8.7	149.7 $\pm$ 10.1	149.1 $\pm$ 9.1
Diastolic, mean $\pm$ SD	85.8 $\pm$ 10.5	88.0 $\pm$ 10.5	85.8 $\pm$ 10.5
eGFR, mL/min/1.73m²			
Mean	84.1 $\pm$ 18.0	86.6 $\pm$ 18.5	84.3 $\pm$ 17.9
<60, n (%)	29 (11.0)	27 (10.2)	30 (11.3)
Serum sodium, mmol/L			
Mean $\pm$ SD	139.6 $\pm$ 2.5	139.9 $\pm$ 2.6	139.8 $\pm$ 2.5
Serum potassium, mmol/L			
Mean $\pm$ SD	4.2 $\pm$ 0.5	4.2 $\pm$ 0.4	4.2 $\pm$ 0.4
Serum aldosterone, ng/dL†			
Median (IQR)	7.5 (4.2, 10.3)	7.9 (4.7, 10.8)	7.2 (4.5, 10.9)
PRA, ng/mL/h‡			
Median (IQR)	1.4 (0.6, 4.0)	1.8 (0.7, 4.7)	1.5 (0.6, 5.0)

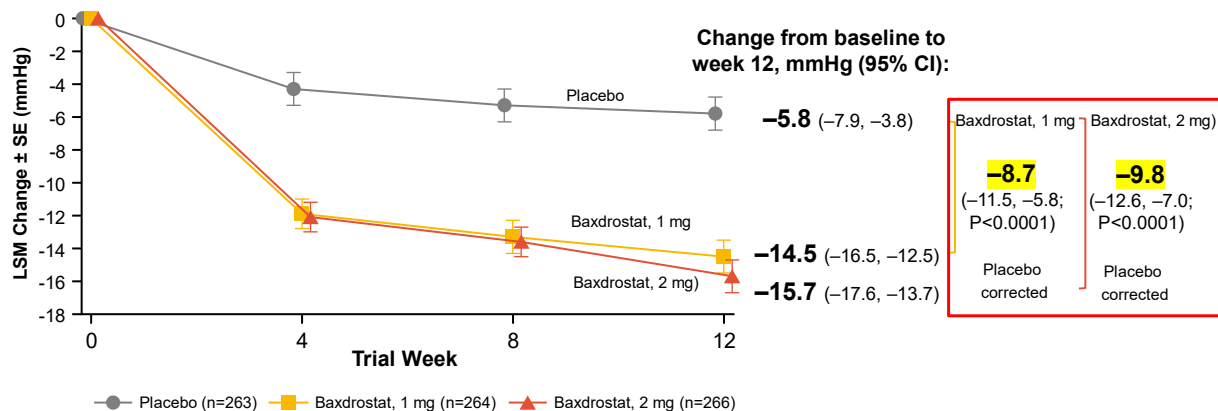
*n=1 placebo had a missing SBP value at baseline; †placebo: n=224; baxdrostat 1 mg: n=228; baxdrostat 2 mg: n=227; ‡placebo: n=178; baxdrostat 1 mg: n=197; baxdrostat 2 mg: n=179.
 ACEi, angiotensin-converting enzyme inhibitor; AHT, antihypertensive treatments; ARB, angiotensin-receptor blocker; BP, blood pressure; eGFR, estimated glomerular filtration rate; IQR, interquartile range; PRA, plasma renin activity; SD, standard deviation.

Adapted from Table 1. Flack J. et al. *N Engl. J. Med* Aug 30 2025 DOI: 10.1056/NEJMoa2507109.

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Primary Outcome-Bax HTN

Change in Seated-SBP: Baxdrostat versus Placebo; Baseline to Week 12

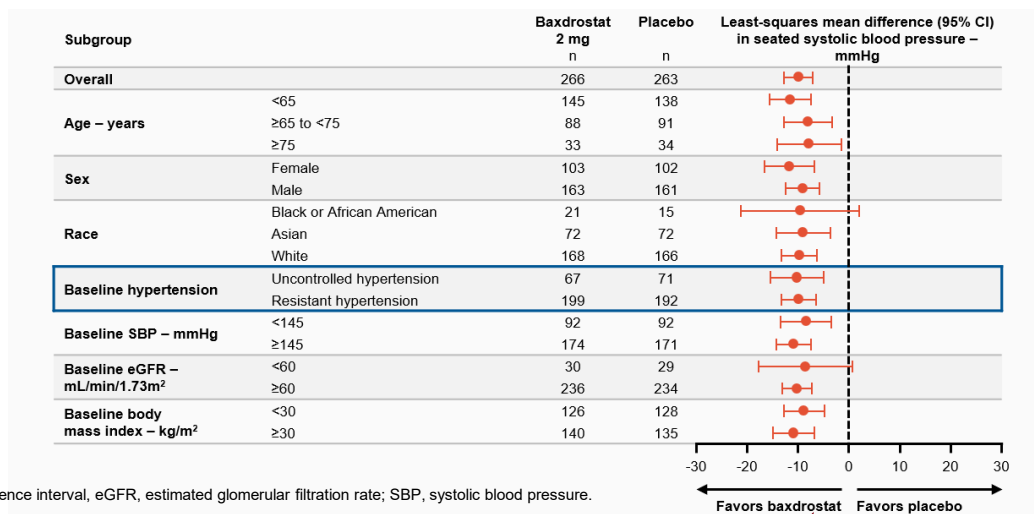


CI, confidence interval; LSM, least-squares mean; SBP, systolic blood pressure; SE, standard error.

Adapted from Fig 1. Flack J. et al. *N Engl. J. Med* Aug 30 2025 DOI: 10.1056/NEJMoa2507109.

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Changes in Seated SBP at Week 12 Were Consistent Across All Pre-specified Subgroups with Baxdrostat 2 mg vs Placebo



Adapted from Fig 2. Flack J. et al. *N Engl. J. Med* Aug 30 2025 DOI: 10.1056/NEJMoa2507109.

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Adverse Events During the 12-Week Double Blind Treatment Period: Bax HTN

- AEs were mostly mild
- One death in the placebo group
- No reports of adrenal insufficiency
- Most common AEs – numerically higher for baxdrostat versus placebo:
 - Hyperkalemia
 - Hyponatremia
 - Hypotension
 - Muscle spasms
 - Dizziness
- There were low rates of:
 - Confirmed serum potassium >6.0 mmol/L
 - Hyperkalemia leading to discontinuation

Event, n (%)	Placebo (N=264)	Baxdrostat, 1 mg (N=264)	Baxdrostat, 2 mg (N=266)
Any adverse event	109 (41.3)	125 (47.3)	119 (44.7)
Moderate/severe	23 (8.7)	27 (10.2)	37 (13.9)
Severe	5 (1.9)	3 (1.1)	7 (2.6)
Any adverse event leading to discontinuation	5 (1.9)	7 (2.7)	12 (4.5)
Hyperkalemia leading to discontinuation	0 (0.0)	2 (0.8)	4 (1.5)
Any serious adverse event*	7 (2.7)	5 (1.9)	9 (3.4)
Death	1 (0.4)	0 (0.0)	0 (0.0)
Adverse event of special interest†			
Hyperkalemia	0 (0.0)	7 (2.7)	21 (7.9)
Hyponatremia	1 (0.4)	2 (0.8)	6 (2.3)
Hypotension	2 (0.8)	5 (1.9)	6 (2.3)
Serum potassium – mmol/L			
>5.5 mmol/L	1/260 (0.4)	16/262 (6.1)	29/261 (11.1)
>6.0 mmol/L	1/262 (0.4)	6/262 (2.3)	8/263 (3.0)
Confirmed >6.0 mmol/L‡	0/262 (0.0)	3/262 (1.1)	3/263 (1.1)

*One case of hyperkalemia (baxdrostat, 1 mg) and two cases of hyponatremia (baxdrostat, 1 mg and 2 mg) were deemed by investigators to be possibly related to study drug. †Elevated potassium levels, low sodium levels, and low blood pressure were adverse events of special interest if they required clinical intervention.

‡Central laboratory measurement >6.0 mmol/L confirmed with a local laboratory potassium measurement from the same day. AE, adverse event.

Adapted from Table 3. Flack J. et al. *N Engl. J. Med* Aug 30 2025 DOI: 10.1056/NEJMoa2507109.

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Select Future / Ongoing Lorundrostat Clinical Trials

ClinicalTrials.gov ID	Phase	Study Name	Projected Enrollment (n)	Background Therapy	Comparators	Primary Outcome	Estimate Completion (ClinicalTrials.gov)
NCT06153693 ^[1]	Phase 3	Launch-HTN	1000	Stable regimen of 2-5 BP agents	Placebo 50 mg 50-100 mg	Change from baseline in systolic AOBP at week 6	Published in JAMA online June 30, 2025
NCT05769608 ^[2]	Phase 2b	ADVANCE-HTN	261	Olmesartan 40 mg Indapamide 2.5 mg +/- Amlodipine 10 mg	Placebo 50 mg 50-100 mg	Change from baseline in ambulatory 24-h average SBP at week 12	Published in NEJM April 25, 2025
NCT06150924 ^[3]	Phase 2	Explore-CKD	60	Dapagliflozin or pt's regularly prescribed SGLT2i, ACE, or ARB	Placebo 25 mg	Change from baseline in systolic AOBP at week 4	2025

AOBP, automated office BP.

1. ClinicalTrials.gov. NCT06153693. Accessed March 30, 2025;

2. ClinicalTrials.gov. NCT05769608. Accessed March 30, 2025;

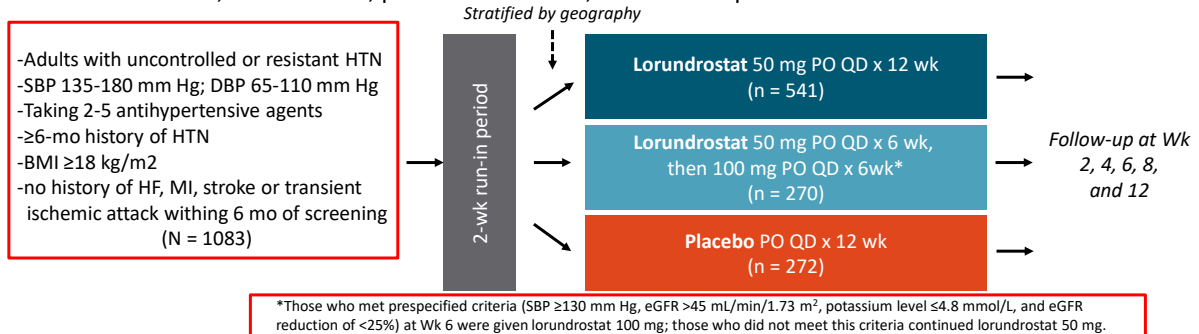
3. ClinicalTrials.gov. NCT06150924. Accessed March 30, 2025.

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Launch-HTN:

Lorundrostat in Patients with Uncontrolled or Treatment-Resistant HTN

- Multicenter, double-blind, placebo-controlled, randomized phase III trial in 13 countries



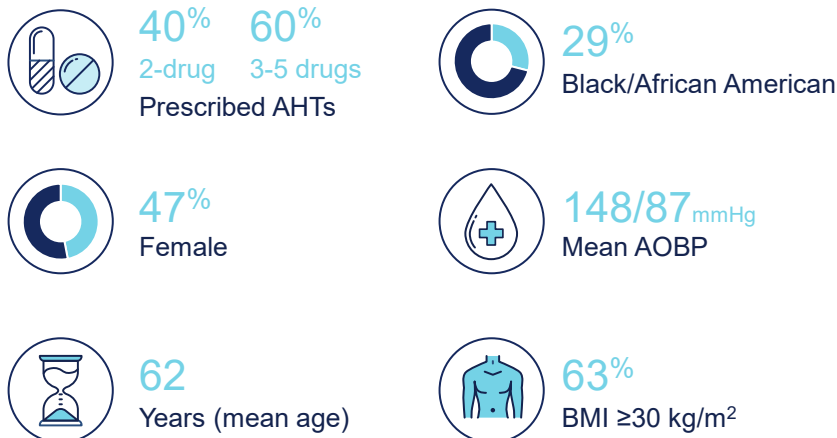
- Primary endpoint:** change in office SBP in lorundrostat 50 mg arm vs placebo at Wk 6
- Key secondary endpoints:** patients with office SBP <130 mm Hg in lorundrostat 50 mg vs placebo at Wk 6, change in office SBP in participants taking 2 or ≥3 antihypertensive agents at Wk 6, safety

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Launch-HTN Trial: Participant Baseline Characteristics

N = 1083 Randomized

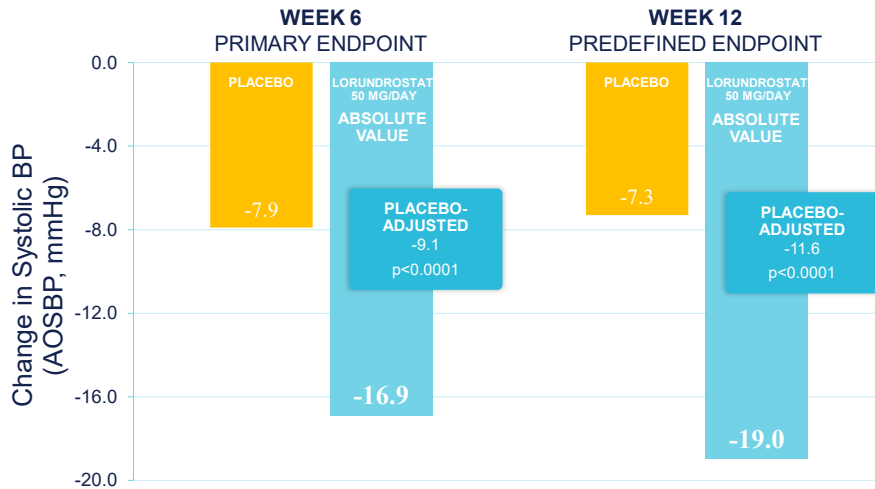


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AOBP, automated office blood pressure.

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Launch-HTN Trial: Lorundrostat 50 mg/day Efficacy in Reducing BP

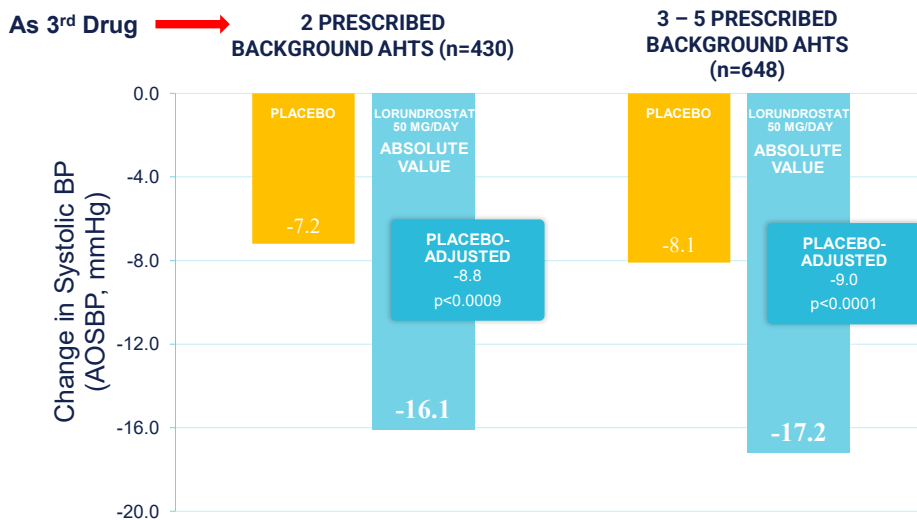


AOSBP, automated office systolic blood pressure. Week 6 primary endpoint pooled lorundrostat 50 mg/day $n=808$. Week 12 predefined endpoint lorundrostat 50 mg/day group $n=538$. Modified from Supplement eFigure 4.

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Launch-HTN Trial: Lorundrostat 50 mg/day Efficacy in Reducing BP



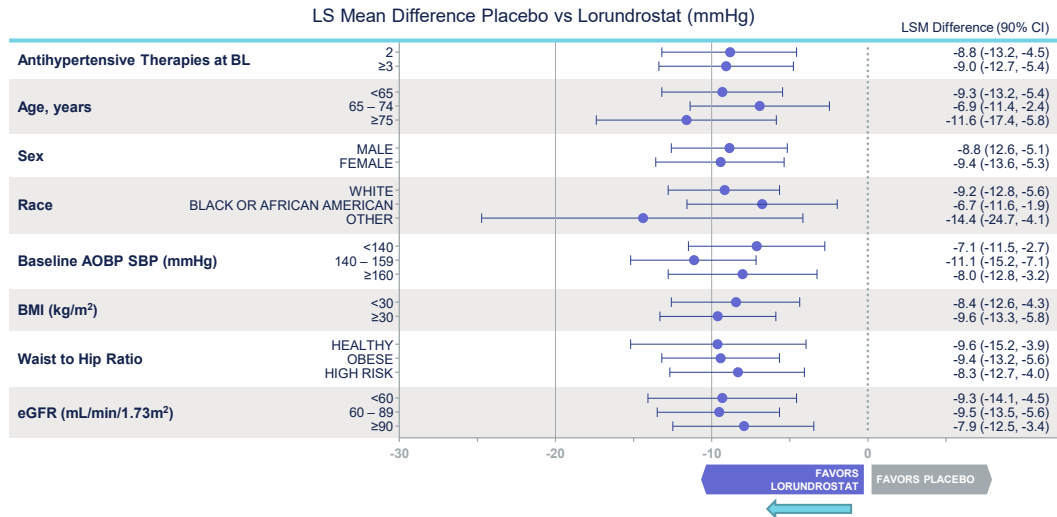
Secondary endpoint. Week 6, pooled lorundrostat 50 mg/day.

AHTs, antihypertensive treatments; AOSBP, automated office systolic blood pressure.

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Lorundrostat 50 mg at Week 6 (Pooled): Efficacy Was Consistent Across Subgroups



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Launch-HTN Trial Safety: Serum Potassium

Potassium at Study Visit Repeat Test*

SERUM POTASSIUM (mmol/L)	PLACEBO (N=270)	LORUNDROSTAT 50 mg/day (N=538)
≤5.5	267 (98.9)	504 (93.7)
>5.5	3 (1.1)	34 (6.3)
>6.0	1 (0.4)	3 (0.6)
>6.5	0 (0.0)	0 (0.0)

In the lorundrostat 50 mg/day group:

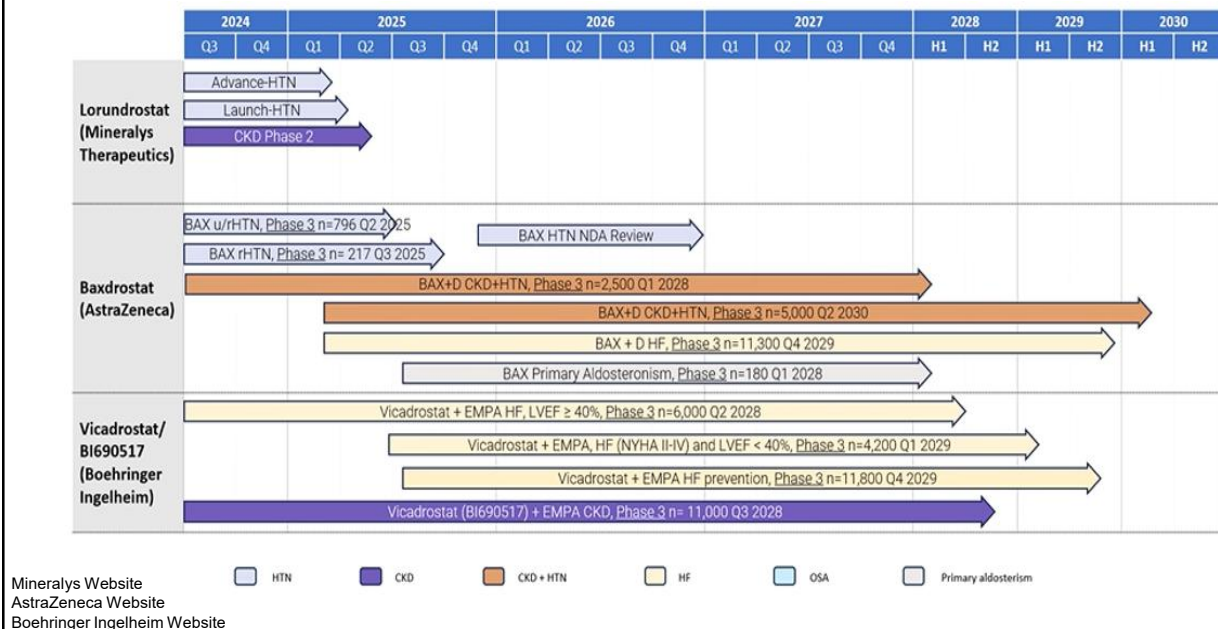
- An increase in serum potassium typically occurred within 2 weeks and then stabilized
- Incidence of confirmed serum potassium >6.0 mmol/L was low (0.6%)

*Includes repeat blood draws within 48-72 hours when participant is in double-blind treatment period and continues to take study medication.

Saxena M. et al. *JAMA*. Published online June 30, 2025;334(5):409-418 and supplement eFigure 5.

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Late-Stage ASI: Development Timelines and Indications



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Summary on Aldosterone: The Forgotten Hormone in HTN

1. Think about Aldosteronism in all patients with HTN but especially in certain phenotypes with hypertension.
2. Dysregulated aldosterone can occur in the normotensive population but more commonly occurs in stage I and stage II hypertension, and most commonly in treatment-resistant hypertension.
3. Primary aldosteronism (PA) is a 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 essential hypertension, likely due to the direct toxic actions of unrecognized aldosterone excess.
4. At present, Baxdrostat and Lorundrostat seem to have more in common with each other than difference from one another.
5. In the future, with additional favorable research with ASI's, it is anticipated that aldosterone dysregulation in all its forms will be more often addressed and more effectively treated with either MRAs or ASIs. Stay Tuned!

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I Will Screen a Patient for Primary Aldosteronism/Aldosterone Dysregulation with a Plasma Aldo/Renin Level:

- A. When the Initial diagnosis of hypertension is made.
- B. When they are < 40 years of age with hypertension.
- C. When they have resistant hypertension or are thought to have secondary hypertension.
- D. (B) & (C)
- E. Before I refer them to a specialist in hypertension.



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