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.**

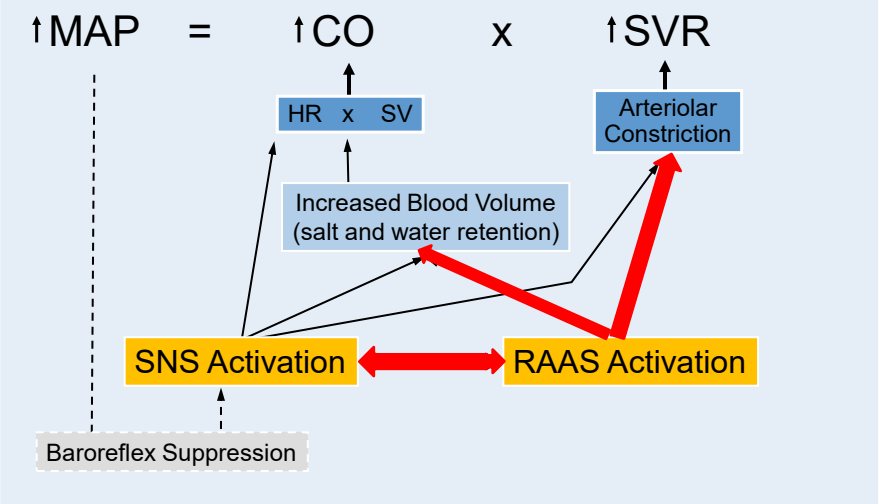
3

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.**

4

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

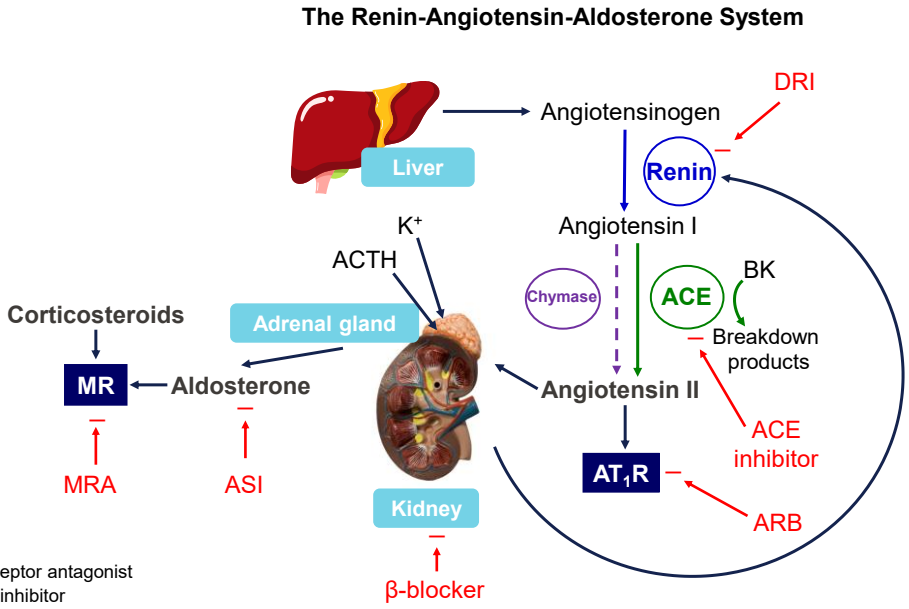
University of Michigan
First Division Chief Endocrinology & Metabolism from 1943-1973

Jerome W. Conn, MD

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

6

Blockade of the Renin-Angiotensin-Aldosterone System



MRA, mineralocorticoid receptor antagonist
ASI, aldosterone synthase inhibitor

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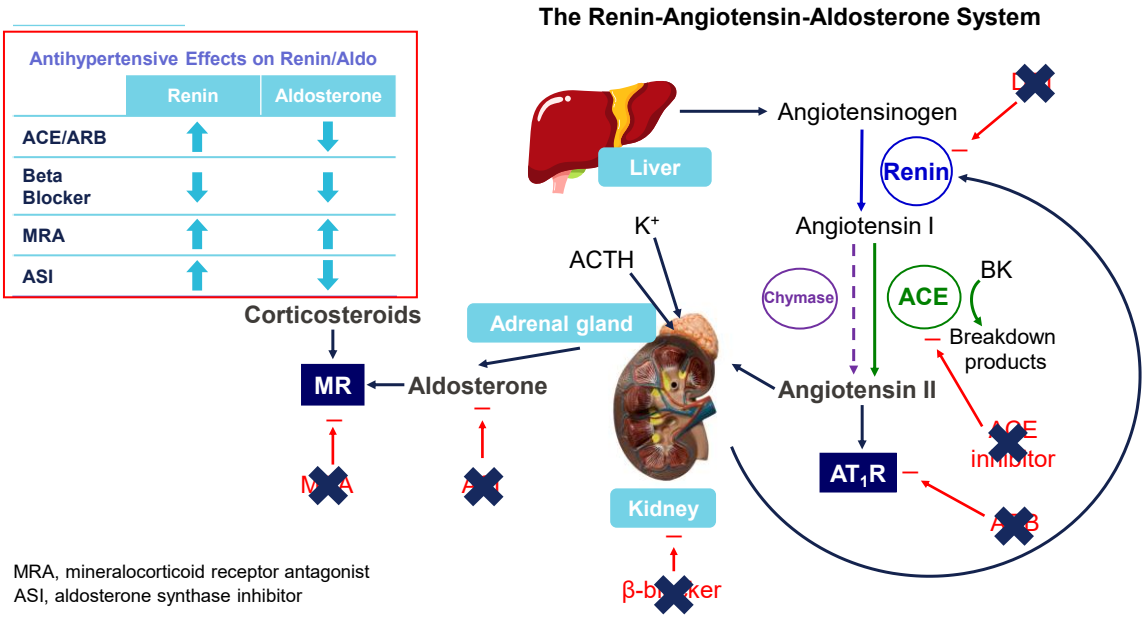
Blockade of the Renin-Angiotensin-Aldosterone System



MRA, mineralocorticoid receptor antagonist
ASI, aldosterone synthase inhibitor

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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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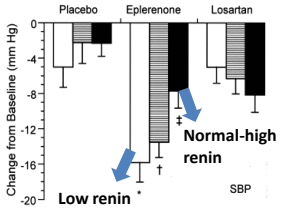
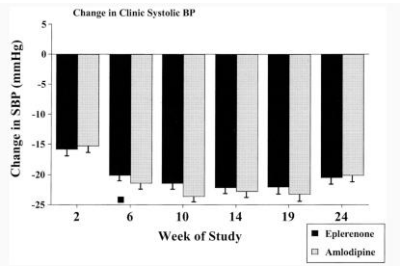
MRA Monotherapy in Essential HTN

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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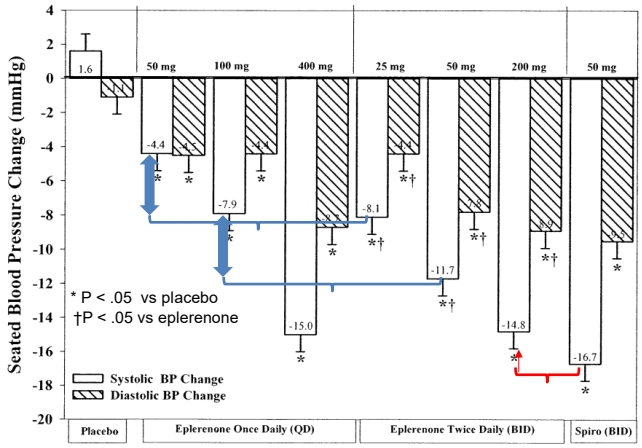
MR Antagonist Monotherapy in Essential HTN

Eplerenone 50 mg to 400 mg vs. Spironolactone 50 mg



	Placebo	Eplerenone Once Daily 50 mg	Eplerenone Once Daily 100 mg	Eplerenone Once Daily 400 mg	Eplerenone Twice Daily 25 mg	Eplerenone Twice Daily 50 mg	Eplerenone Twice Daily 200 mg	Spironolactone Twice Daily 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)
Sinusitus	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)

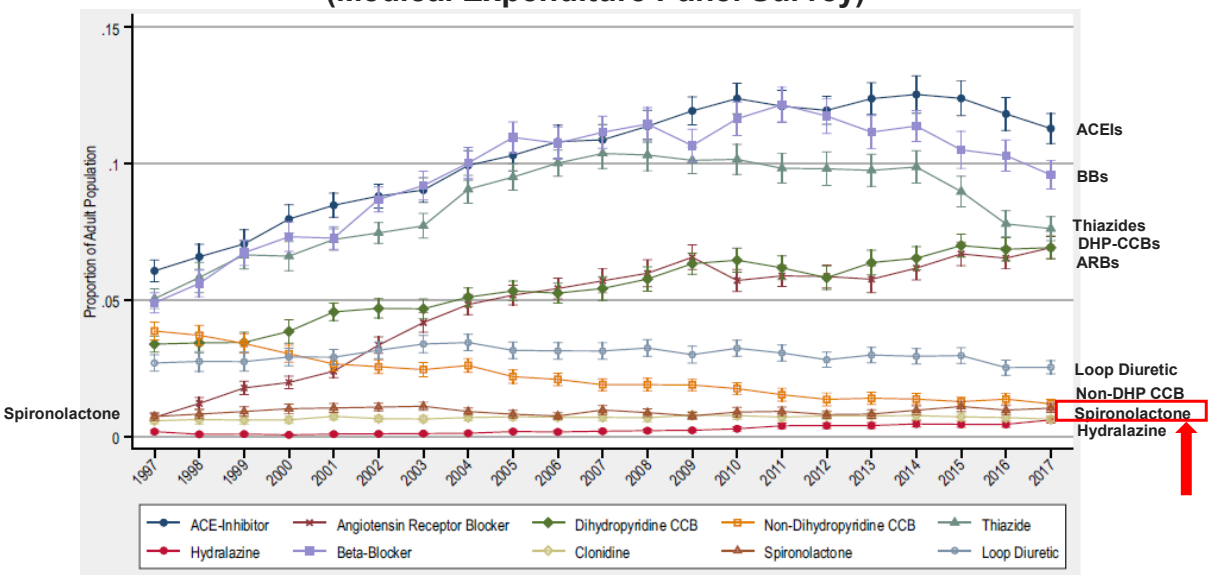

Figure 2. Johansen M.E. et al. *J. Gen. Int. Med.*. 2020 36(3):699-704

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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, thiazide-type diuretics, long-acting dihydropyridine CCB, and ACEi or ARB 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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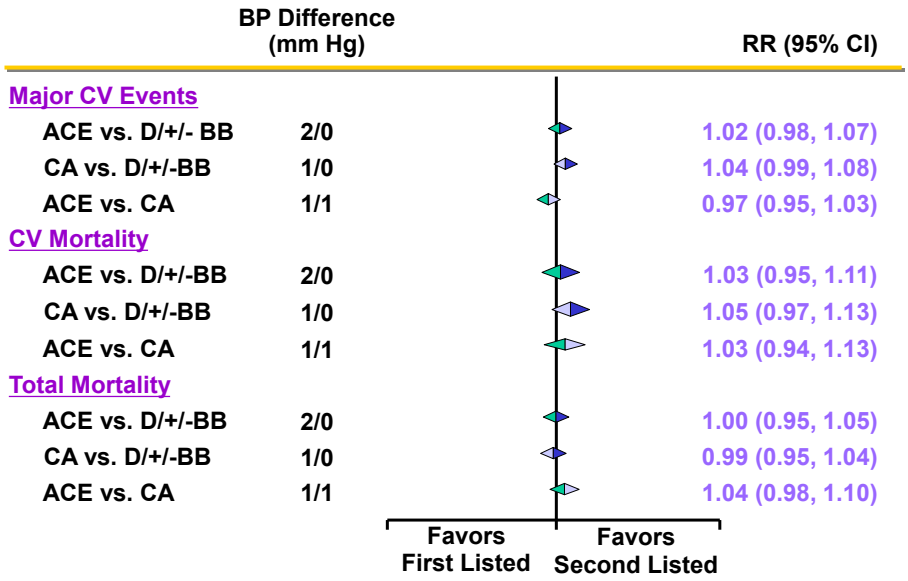
BP-Lowering Treatment Trialists Group

Comparisons of Different Active Treatments



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

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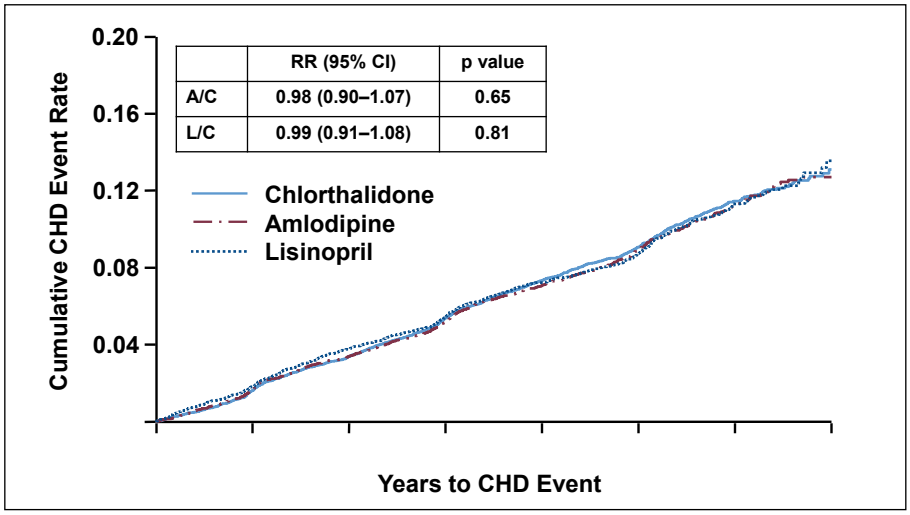
Cumulative Event Rates for the Primary Outcome (Fatal CHD or Non-fatal MI) by ALLHAT Treatment Group



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

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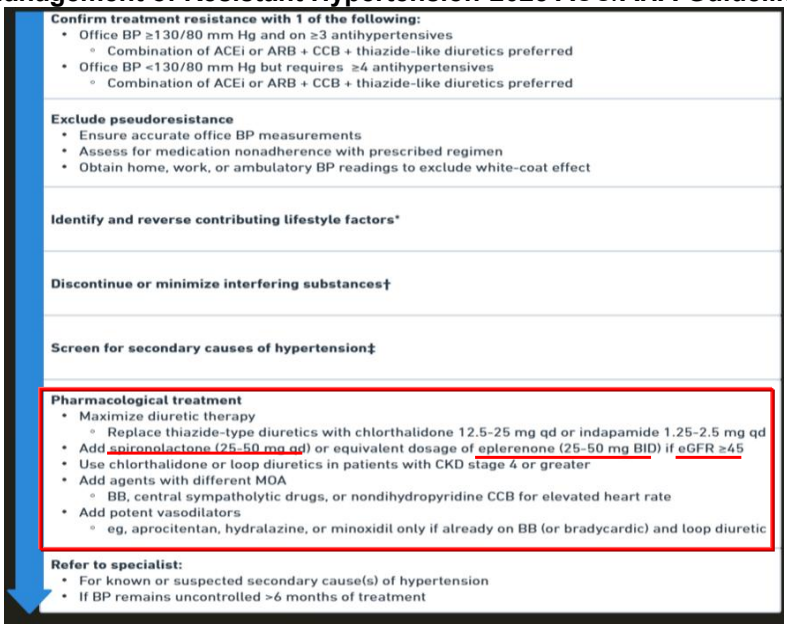
Management of Resistant Hypertension-2025 ACC/AHA Guideline



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

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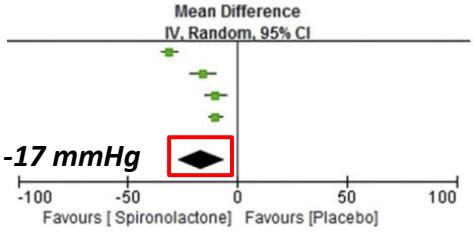
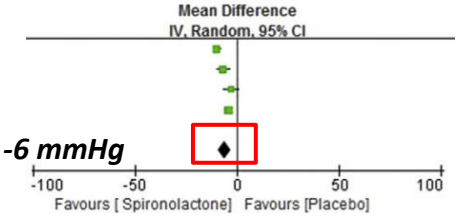
Spironolactone as Add-On in Resistant HTN

Meta-analysis: 4 trials (n=869)

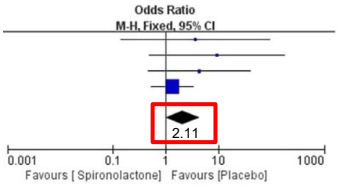
SBP reduction vs. placebo



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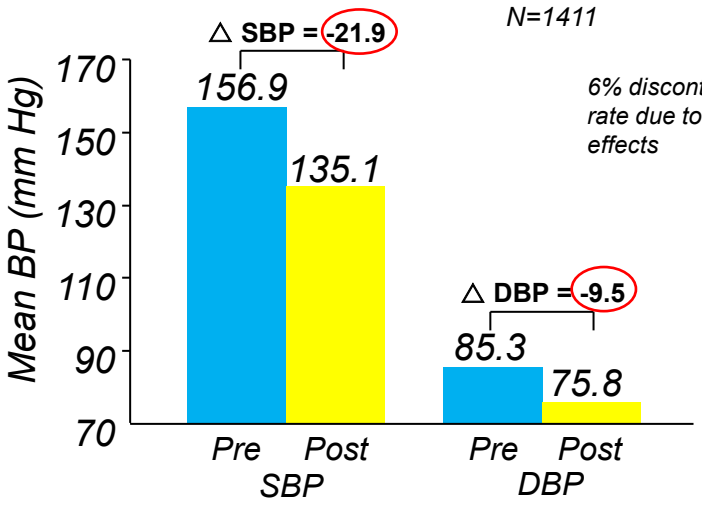
BP Response with Spironolactone 25-50 mg as 4th Drug: ASCOT* Results



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

**Anglo-Scandanavian Cardiovascular Outcomes Trial*

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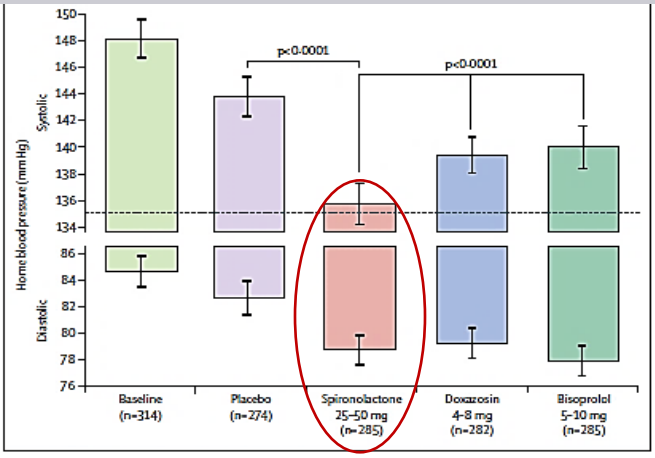
Spironolactone versus Placebo, Bisoprolol, and Doxazosin for Drug Resistant Hypertension (PATHWAY-2)

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]	Steroidal	Low	Medium	No active metabolites	Higher in kidney	▪ ↓ Sexual ▪ ↑ Hyperkalemia ▪ Less BP Reduction

[a]Based 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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Eplerenone[b]	Steroidal	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

[a]Based 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; Dhillon 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/m^2)
  - 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	Other medications
Losartan/HCTZ 100 mg/25 QD	Atorvastatin 40 mg
Nebivolol 10 mg QD	E/C ASA 81 mg
KCL 40 meq for past 6 months	

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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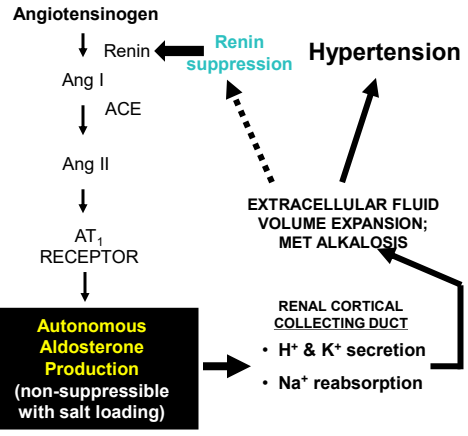
AUTONOMOUS ALDOSTERONE PRODUCTION IN PRIMARY ALDOSTERONISM

⇧Aldo ⇩Renin

Renin-Independent
Aldosterone-Induced Hypertension



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/11β-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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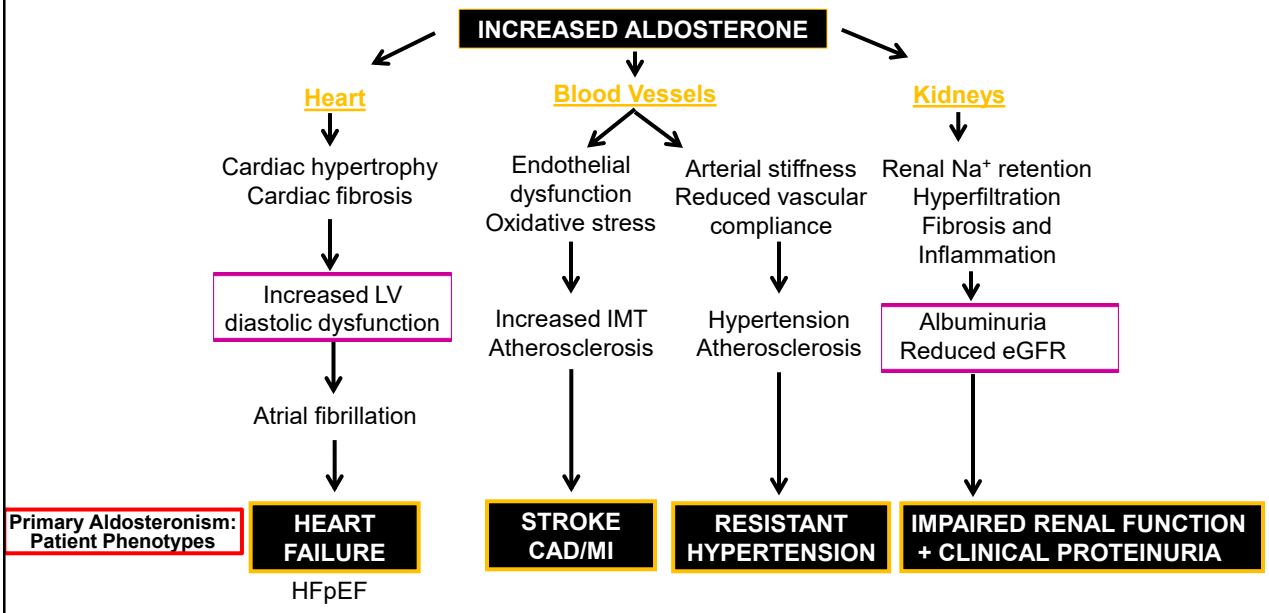
CARDIOVASCULAR and RENAL BURDEN OF PRIMARY ALDOSTERONISM

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

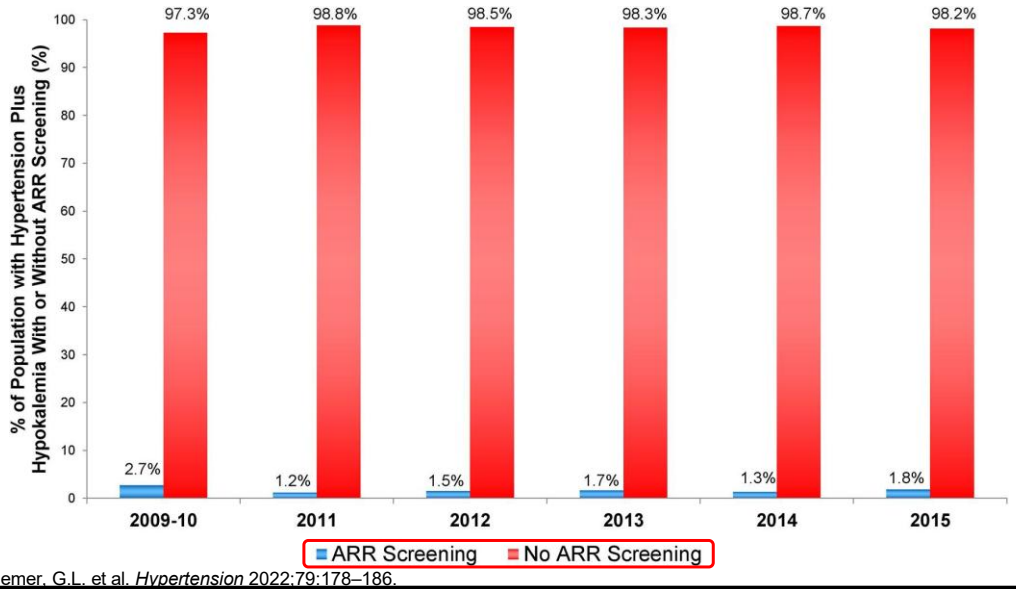

Fig 2. Hundemer, G.L. et al. *Hypertension* 2022;79:178–186.

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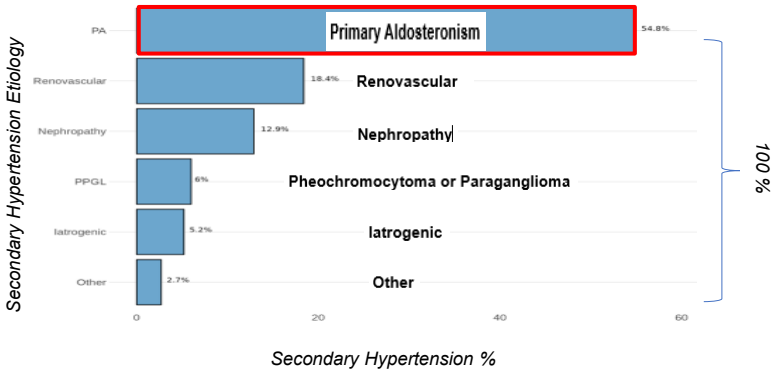
ORIGINAL ARTICLE

Prevalence and Risk Factors for Secondary Hypertension in Young Adults

Jean-Baptiste de 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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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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Secondary Forms of Hypertension

Recommendations for Secondary Forms of Hypertension References that support recommendations are summarized in the evidence table.		
COR	**LOE**	**Recommendations**
1	**B-NR**	**2. In adults with resistant hypertension, screening for primary aldosteronism is recommended regardless of whether hypokalemia is present to increase rates of detection, diagnosis, and specific targeted therapy.**

Only in Resistant HTN

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

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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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, screening for primary aldosteronism is recommended in the presence of any of the following conditions to increase rates of detection, diagnosis, and specific targeted therapy: resistant hypertension (regardless of whether hypokalemia is present), hypokalemia (spontaneous or diuretic induced), OSA, incidentally discovered adrenal mass, family history of early-onset hypertension, or stroke at a young age (<40 years).**
2b	**C-EO**	**2. In adults with stage 2 hypertension, screening for primary aldosteronism may be considered 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 Hypertension[1]
- -In all Patients Suspected of Secondary Hypertension[2]
- -In all Young Patients < 40 years of age with HTN[3]
- -In All Patients with HTN?-Europeans say YES![4]
- -Suggested in All Patients with Hypertension[5]

[1]Jones, D.W. et al *Circulation*. August 14, 2025 DOI:10.1161/CIR.0000000000001356.
[2]Carey 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
[4]McEvoy JW, et al; ESC Scientific Document Group. *Eur Heart J*. 2024:ehae178.
[5]Adler, 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 !!

37

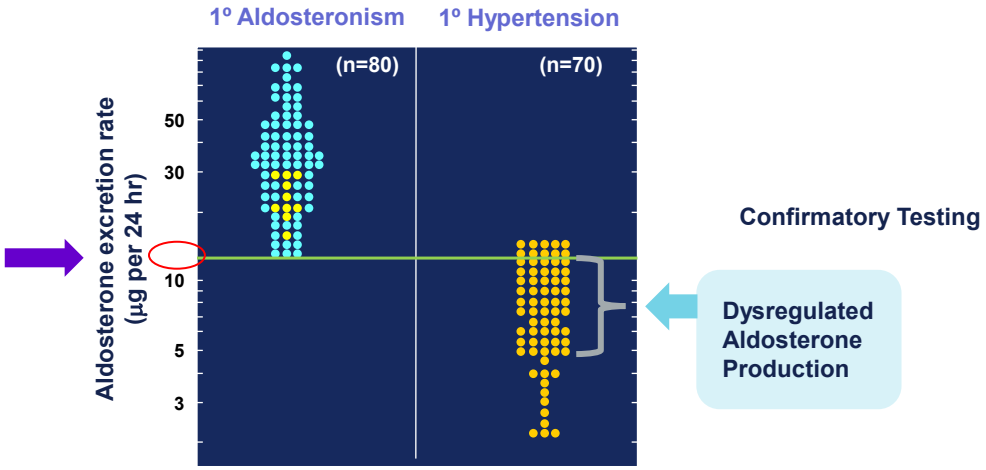
Primary Aldosteronism

What's New!!

The Concept of Aldosterone Dysregulation Paralleling Hypertension Severity

38

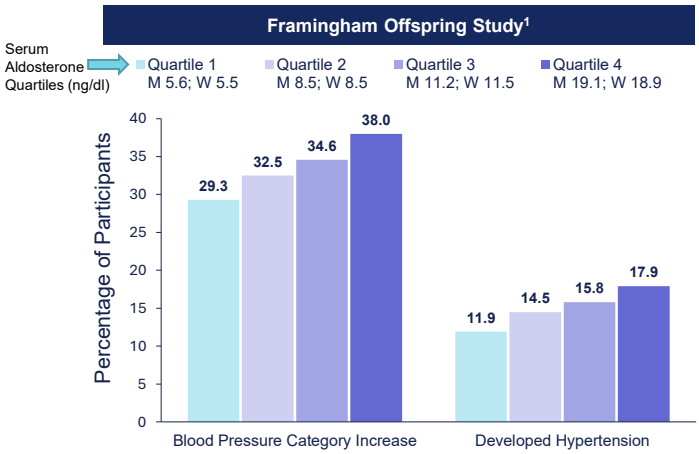
Aldosterone Dysregulation After Three Days of Oral Sodium Loading (250 mEq Na in Urine per 24 hr)



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

39

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 years[1]
- Age- and sex-adjusted BP outcomes stratified by baseline serum aldosterone level quartiles[1] (mean age 55, 58% women)
- An increase in BP was defined as an increment of ≥1 BP category[2]

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

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

1. Vasan, Ramachadran 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.

40

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.

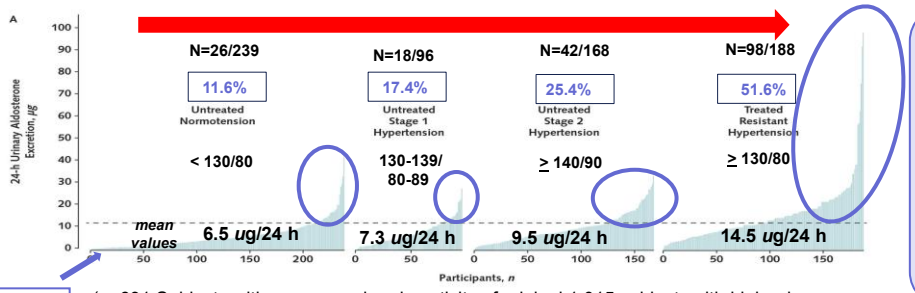
Cross-sectional study of 1,015 hypertensive subjects at 4 U.S. academic medical centers. (Birmingham, Boston, Charlottesville, Salt Lake City).

All given an Oral Sodium Suppression Test

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

41

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



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

PA > 12 *ug*/24 hrs

(n=691 Subjects with suppressed renin activity of original 1,015 subjects with high urinary sodium)

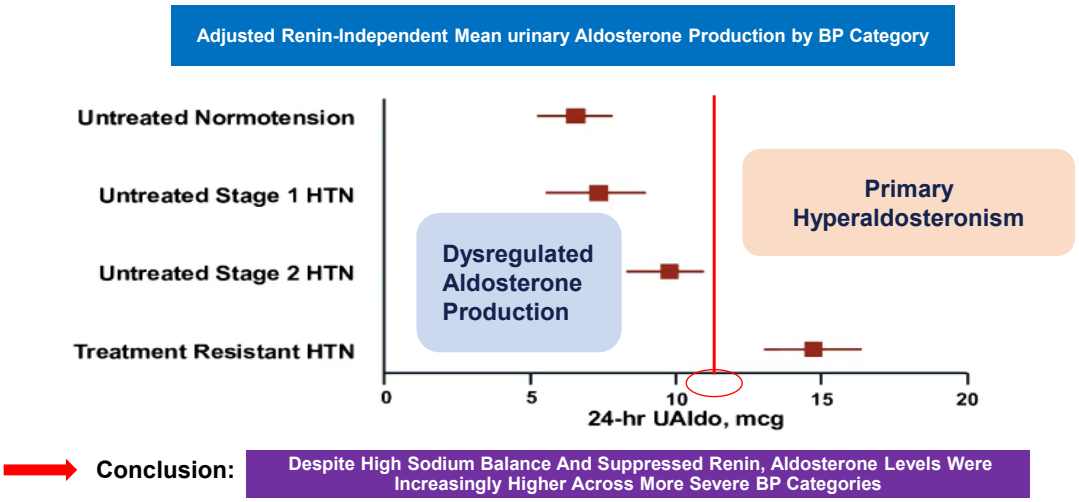
Conclusions:

- 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.

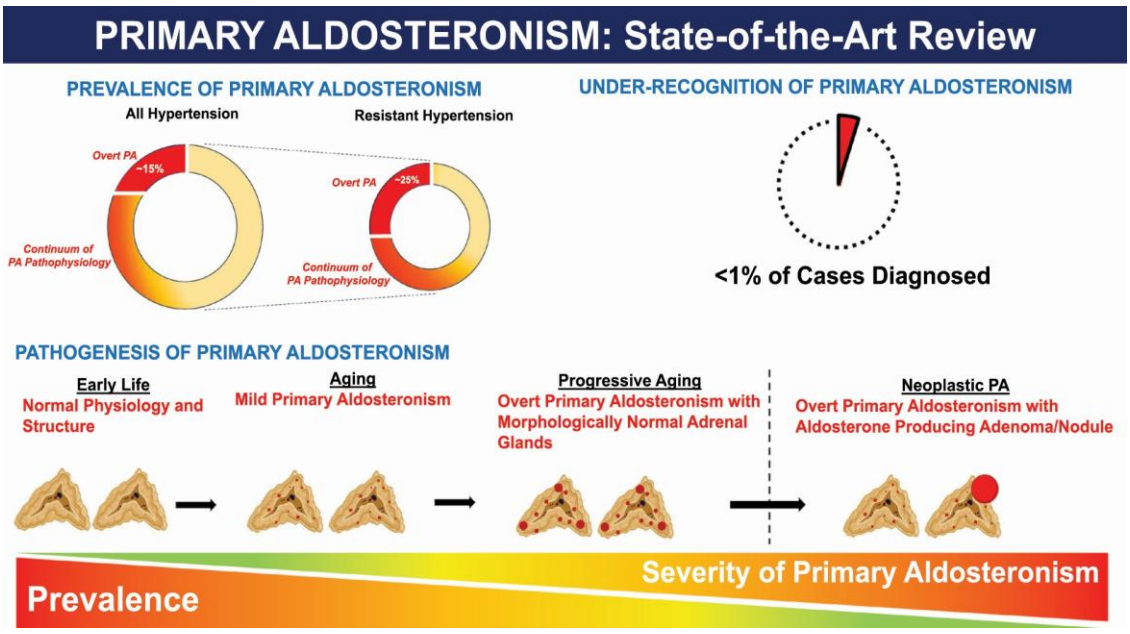
42

The Severity of Aldosterone Dysregulation Parallels Hypertension Severity



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

43

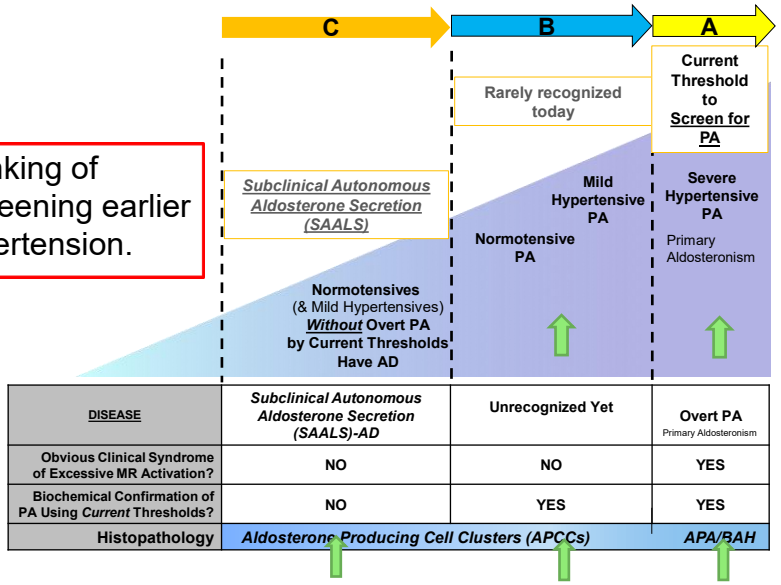


Vaidya A et al. Am J Hypertens. Dec 2022. Volume 35, Issue 12, 2022, Pages 967–988

44

THE SPECTRUM OF ALDOSTERONE DYSREGULATION (AD) AND PRIMARY ALDOSTERONISM (PA) IS OFTEN NOT RECOGNIZED

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

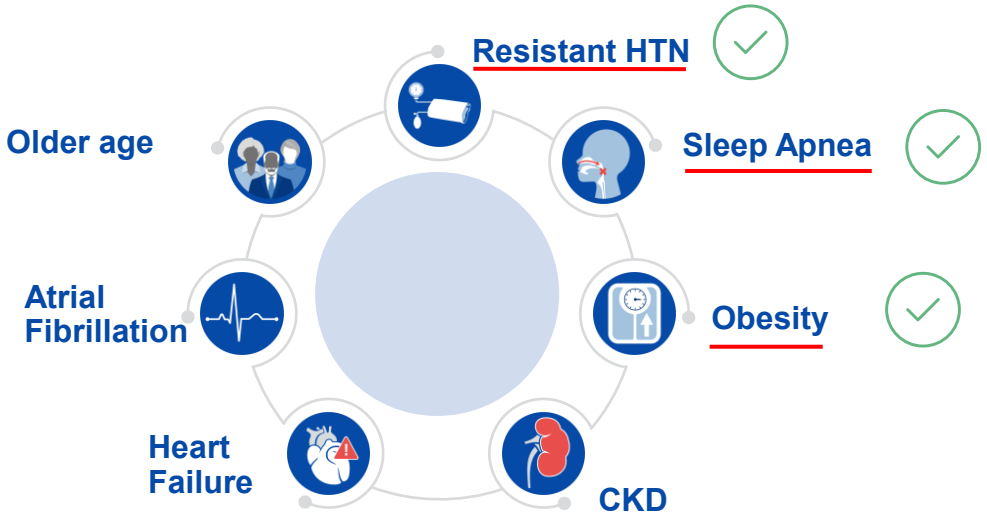


DISEASE	Subclinical Autonomous Aldosterone Secretion (SAALS)-AD	Unrecognized Yet	Overt PA (Primary Aldosteronism)
Obvious Clinical Syndrome of Excessive MR Activation?	NO	NO	YES
Biochemical Confirmation of PA Using *Current* Thresholds?	NO	YES	YES
Histopathology	*Aldosterone Producing Cell Clusters (APCCs)*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

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

45

High Prevalence of Aldosterone-Mediated HTN in Multiple Patient Populations

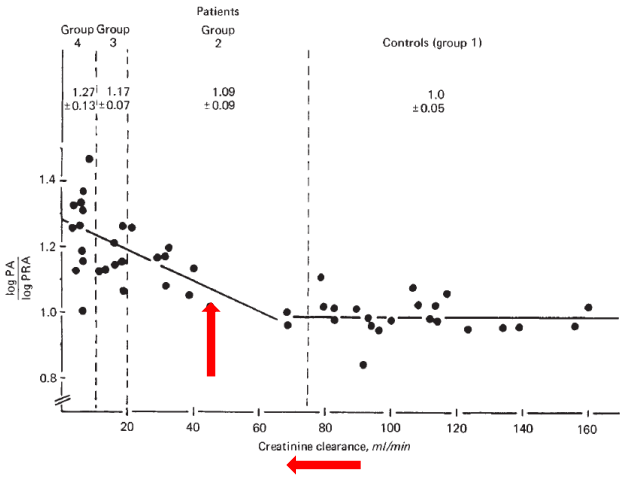


Wannachalee T, et al. Curr Hypertens Rep. 2022;24:123-132.

46

Aldosterone Dysregulation Occurs in CKD

Plasma Aldosterone Rises as GFR Falls

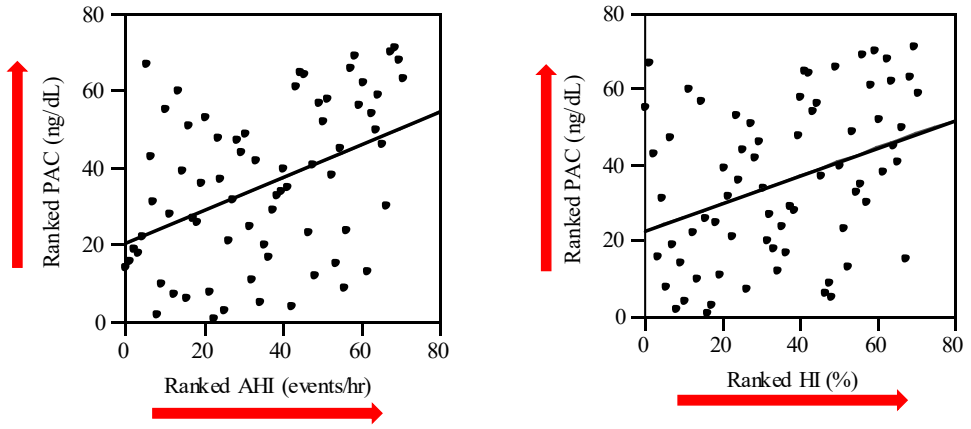


Hené RJ et al, Kidney Int. 1982 Jan;21(1):98-101.

47

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

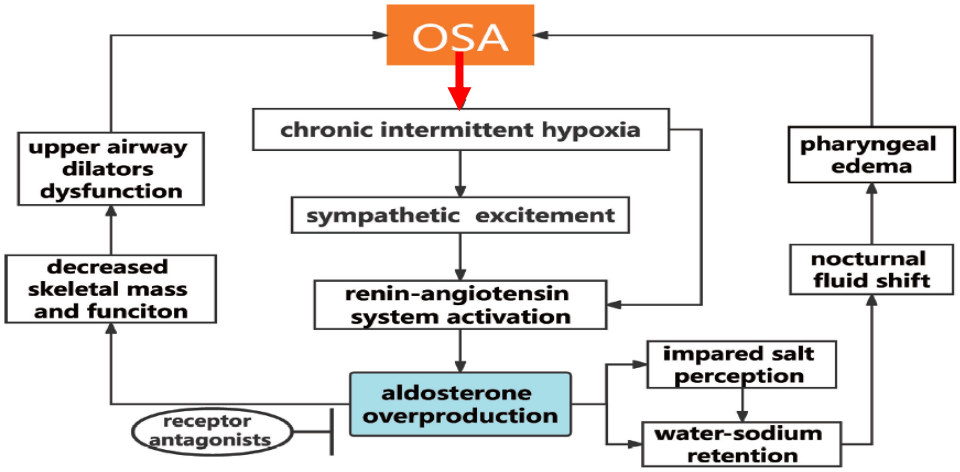
Figure 1



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

48

Aldosterone Dysregulation Occurs in OSA



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

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

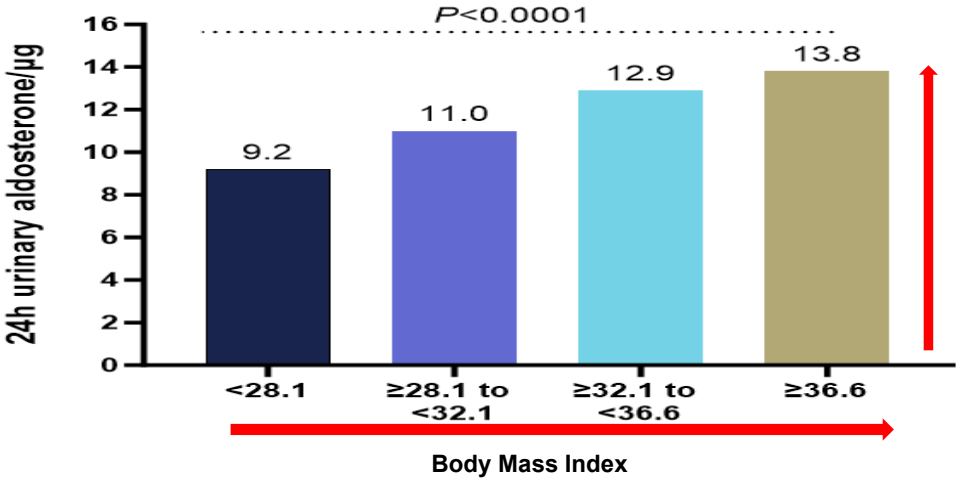

Fig 1 D. Dudenbostel T. et al. *Hypertension*. 2016;68(4):995-1003.

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

50

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	Non-steroidal MRA
Spironolactone	Finerenone
Eplerenone	Ocedurenone

Aldosterone Synthase Inhibitors (ASI)
Baxdrostat
Lorundrostat
BI 690517 (Vicadrostat)

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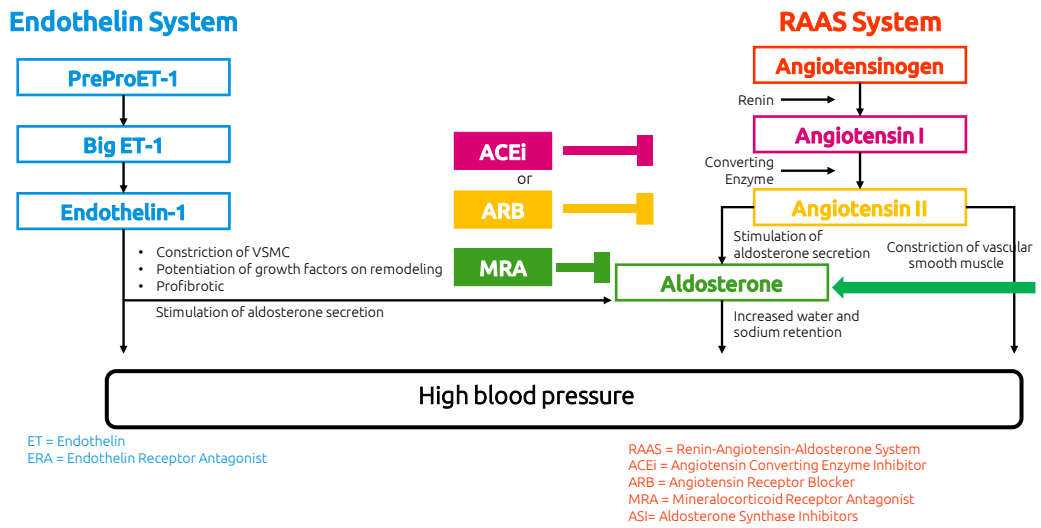
Old Targets and New Pathways in Hypertension



ET = Endothelin
ERA = Endothelin Receptor Antagonist

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.

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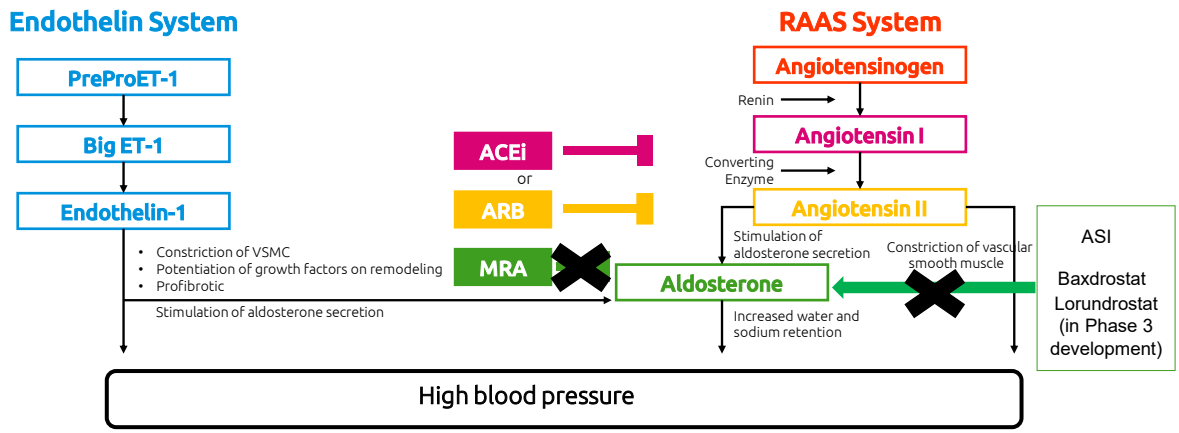
Old Targets and New Pathways in Hypertension



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

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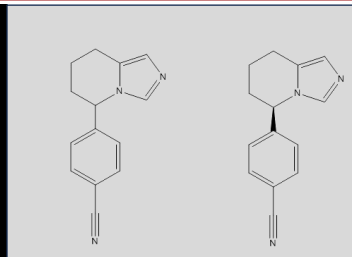
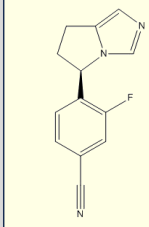
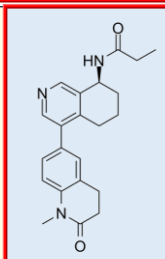
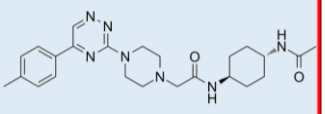
Aldosterone Synthase Inhibitors

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%)

Characteristic	Placebo (n=264)	Baxdrostat, 1 mg (n=264)	Baxdrostat, 2 mg (n=266)
Age, mean ± SD, yrs	61.9 ± 11.6	59.8 ± 11.8	61.8 ± 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)

*Reported by the participant.
HTN, hypertension; 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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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/1.73m^2

Characteristic	Placebo (n=264)	Baxdrostat, 1 mg (n=264)	Baxdrostat, 2 mg (n=266)
Seated BP, mmHg*			
Systolic, mean ± SD	149.0 ± 8.7	149.7 ± 10.1	149.1 ± 9.1
Diastolic, mean ± SD	85.8 ± 10.5	88.0 ± 10.5	85.8 ± 10.5
eGFR, mL/min/1.73m^2			
Mean	84.1 ± 18.0	86.6 ± 18.5	84.3 ± 17.9
<60, n (%)	29 (11.0)	27 (10.2)	30 (11.3)
Serum sodium, mmol/L			
Mean ± SD	139.6 ± 2.5	139.9 ± 2.6	139.8 ± 2.5
Serum potassium, mmol/L			
Mean ± SD	4.2 ± 0.5	4.2 ± 0.4	4.2 ± 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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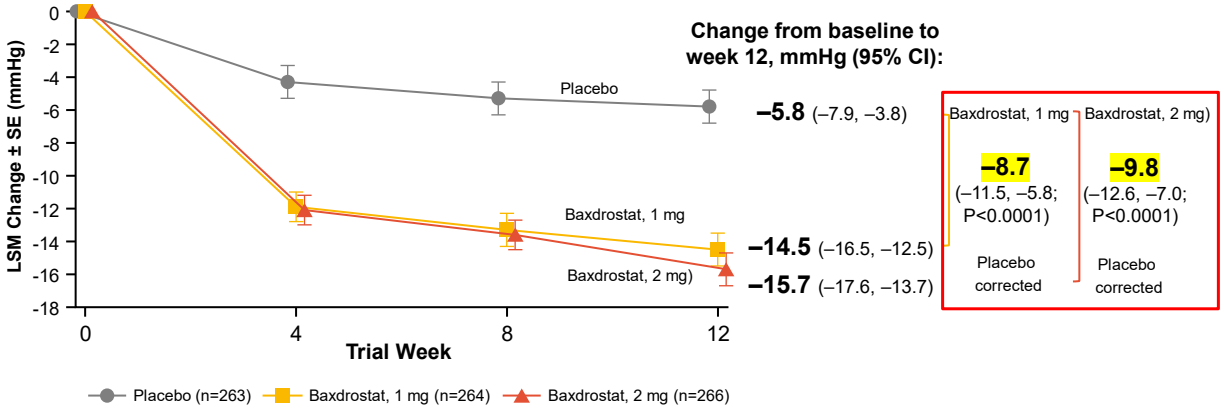
Primary Outcome-Bax HTN

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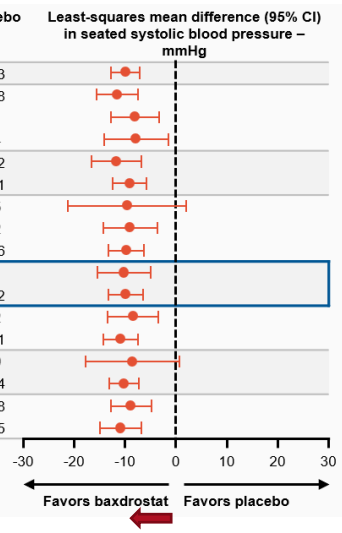
Changes in Seated SBP at Week 12 Were Consistent Across All Pre-specified Subgroups with Baxdrostat 2 mg vs Placebo

Subgroup		Baxdrostat 2 mg n	Placebo n
Overall		266	263
Age – years	<65	145	138
	≥65 to <75	88	91
	≥75	33	34
Sex	Female	103	102
	Male	163	161
Race	Black or African American	21	15
	Asian	72	72
	White	168	166
Baseline hypertension	Uncontrolled hypertension	67	71
	Resistant hypertension	199	192
Baseline SBP – mmHg	<145	92	92
	≥145	174	171
Baseline eGFR – mL/min/1.73m²	<60	30	29
	≥60	236	234
Baseline body mass index – kg/m²	<30	126	128
	≥30	140	135



CI, confidence interval, eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure.

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 hyperkalaemia (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 in systolic AOBP at week 4	2025

AOPB, 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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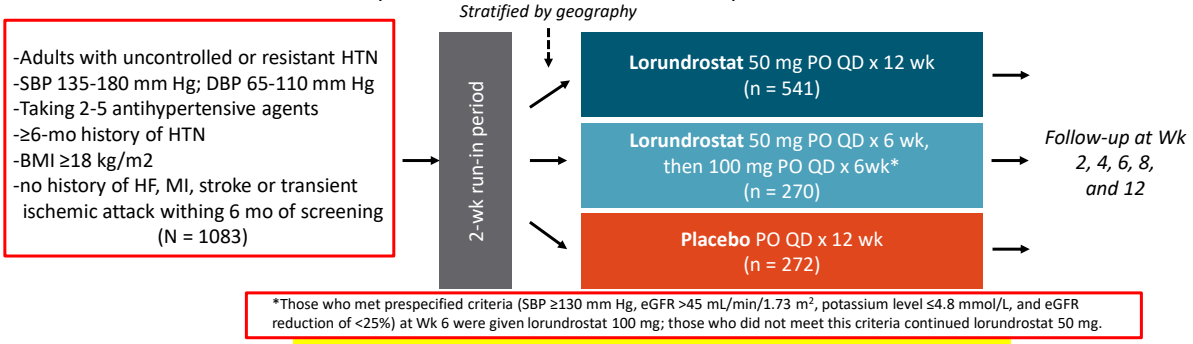
Launch-HTN:
Lorundrostat in Patients with Uncontrolled or Treatment-Resistant HTN

- 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 m 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

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

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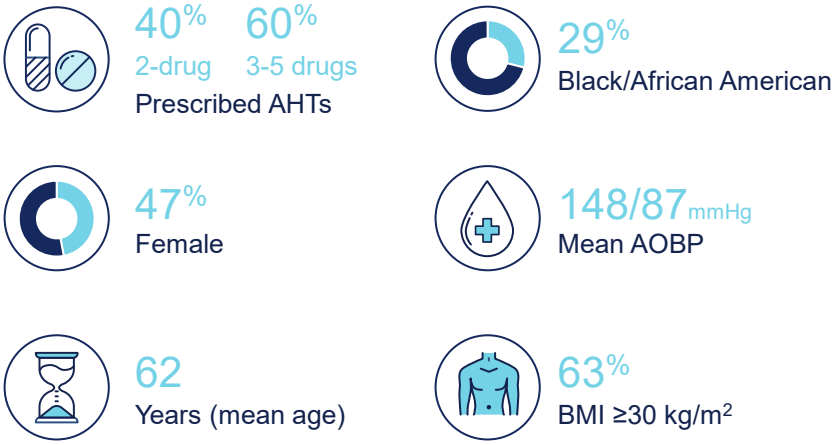
Launch-HTN Trial: Participant Baseline Characteristics

N = 1083 Randomized



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

AOBP, automated office blood pressure.

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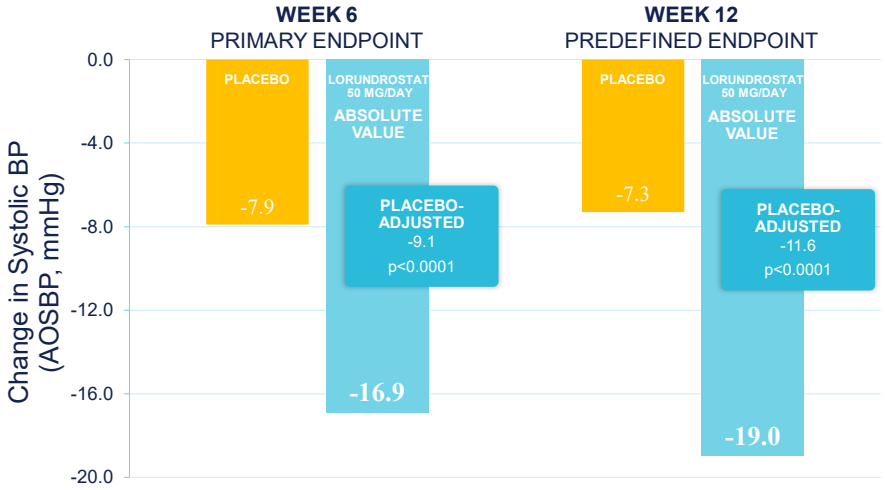
Launch-HTN Trial: Lorundrostat 50 mg/day Efficacy in Reducing BP



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.

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

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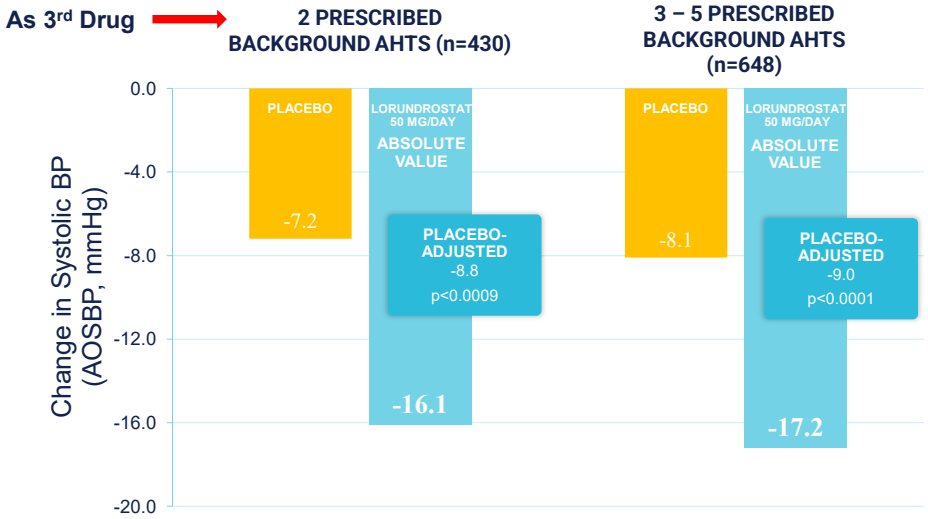
Launch-HTN Trial: Lorundrostat 50 mg/day Efficacy in Reducing BP



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

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

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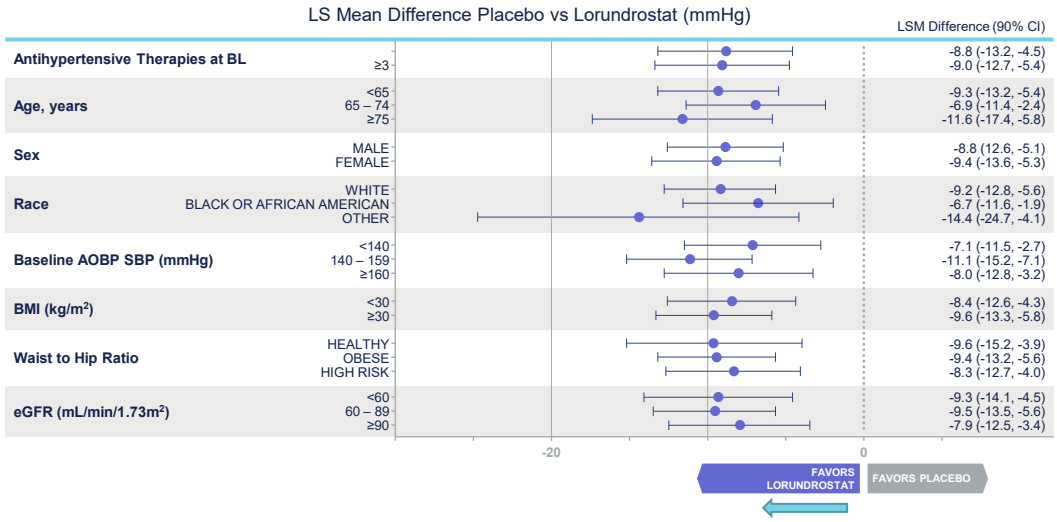
Lorundrostat 50 mg at Week 6 (Pooled): Efficacy Was Consistent Across Subgroups



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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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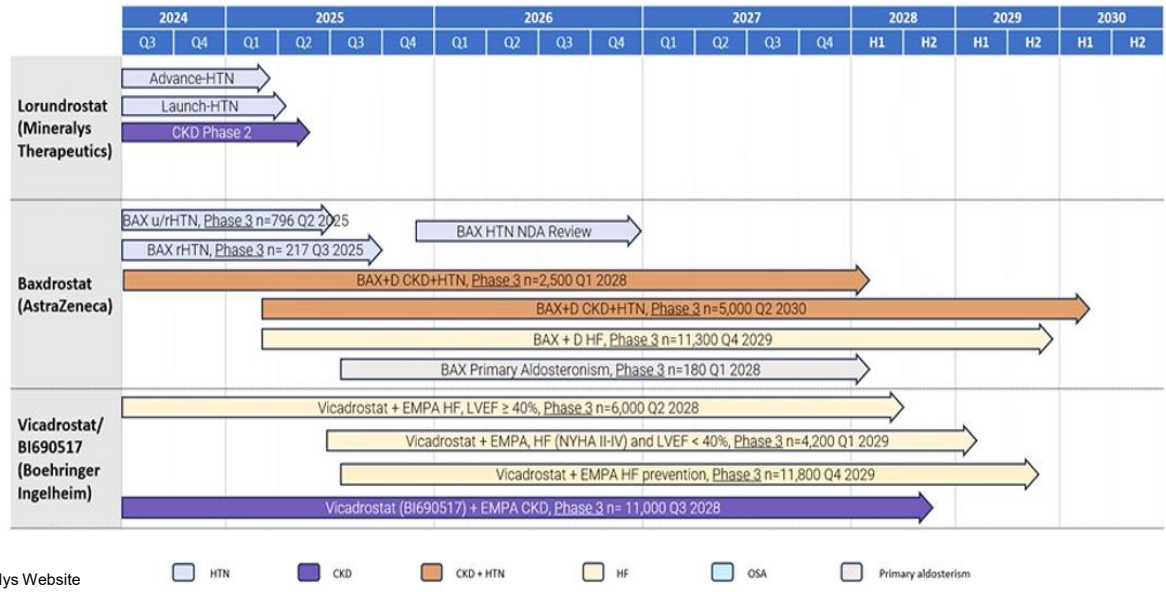
Late-Stage ASI: Development Timelines and Indications



Mineralys Website
AstraZeneca Website
Boehringer Ingelheim Website

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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.

CONTINUING EDUCATION COMPANY

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