Aldosterone: The Forgotten Hormone in Hypertension

Jan N. Basile, MD, FACP, FASH, FAHA
Professor of Medicine
Division of Cardiology
Medical University of South Carolina
Ralph H Johnson VA Medical Center
Previous Vice-Chair of Clinical Programs AHA Council of Hypertension
US National Leader SURPASS-CVOT
Charleston, SC
basilejn@musc.edu

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Disclosure

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

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

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2

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.**
- **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.**

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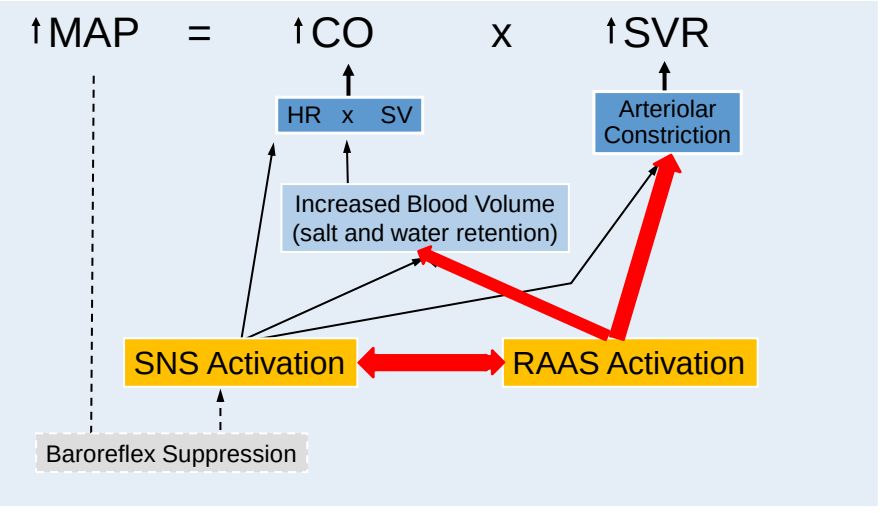
Systemic Hemodynamics



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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 effects at high doses limited its use.
- 2003: Eplerenone marketed.

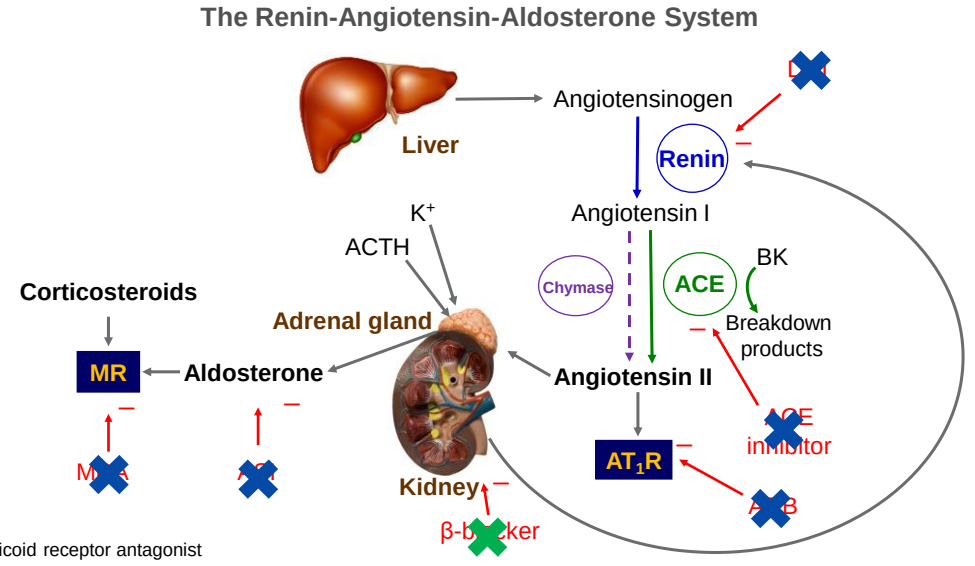
Jerome W. Conn, MD

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

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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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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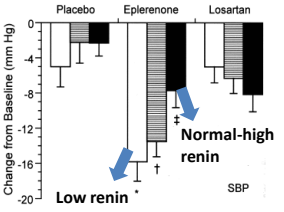
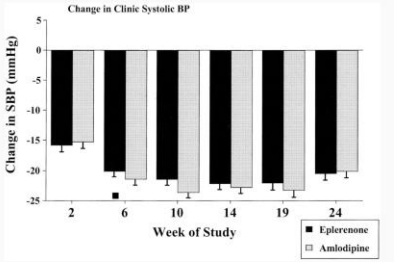
MRA Monotherapy in Essential HTN

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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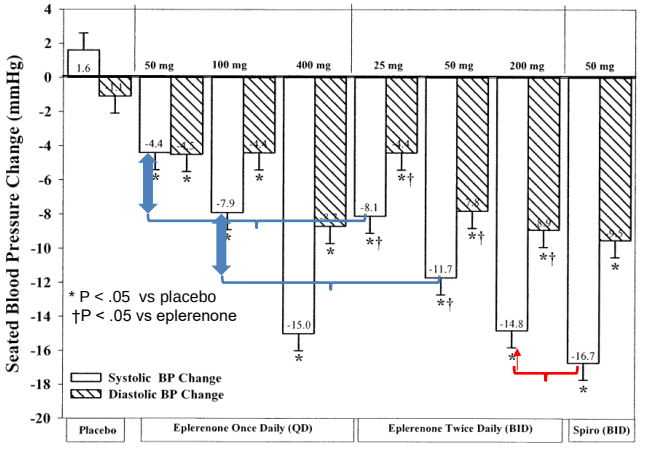
MR Antagonist Monotherapy in Essential HTN

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)	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 given bid than qd.**
- **Spiro (S) has similar BP Reduction to E at ¼ of the dose when both given bid.**

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)

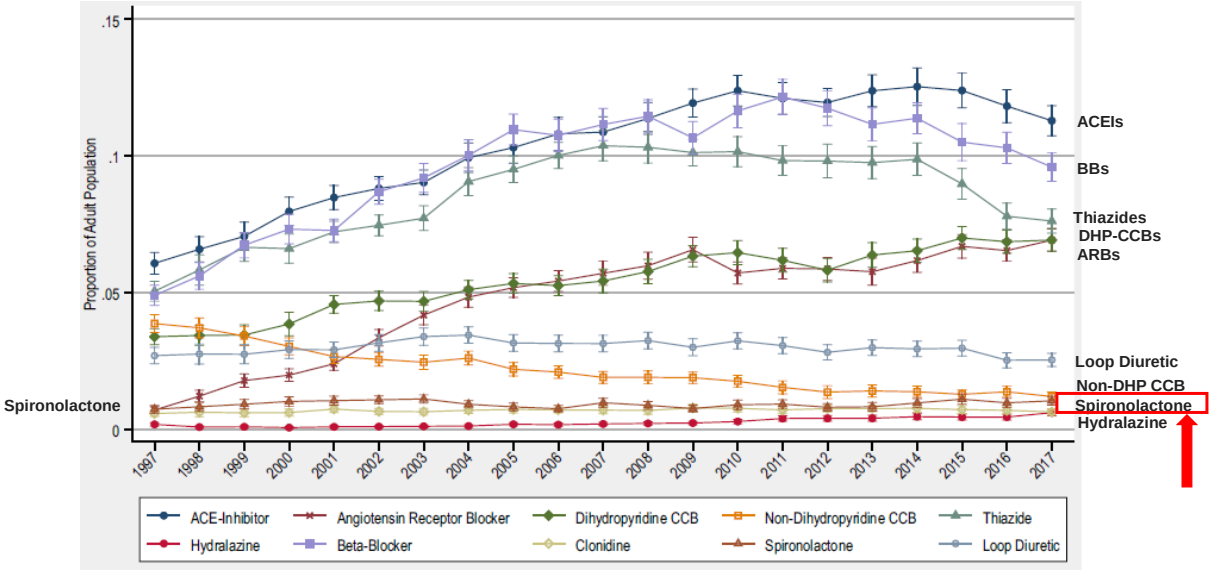

Figure 2. Johansen M.E. et al. *J. Gen. Int. Med*.. 2020 36(3):699-704

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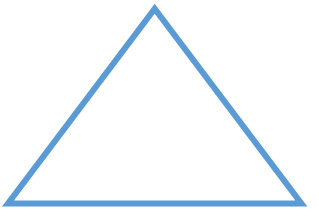
Initial Medications for the Management of Hypertension

Lifestyle Modification—Especially Diet and Exercise

Thiazide/Thiazide-Like Diuretics



ACE Inhibitors or ARBs

Calcium antagonists

Dihydropyridine preferred

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.

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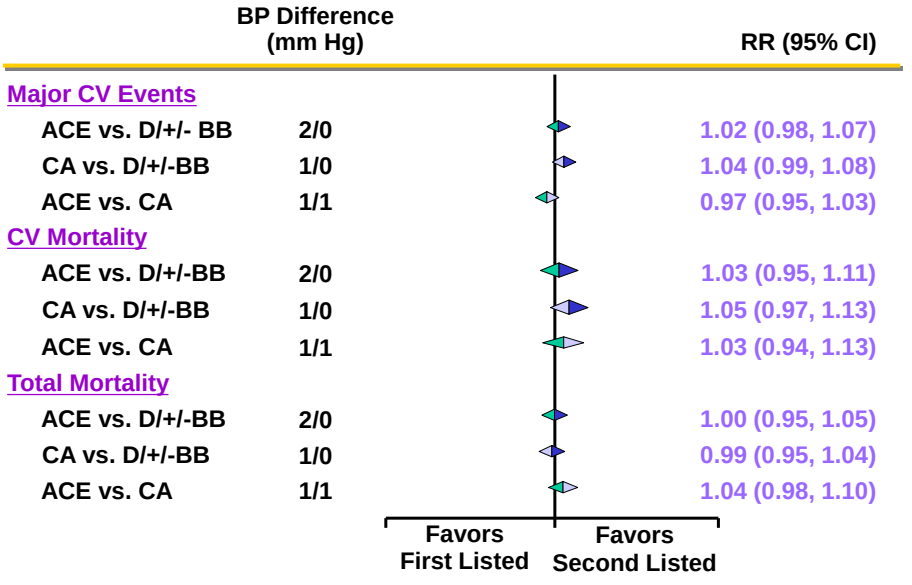
BP-Lowering Treatment Trialists Group

Comparisons of Different Active Treatments



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

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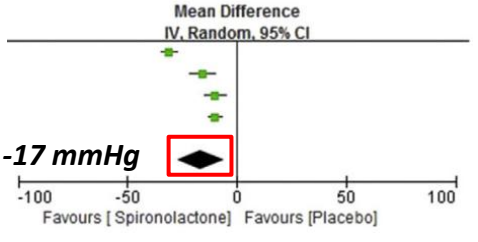
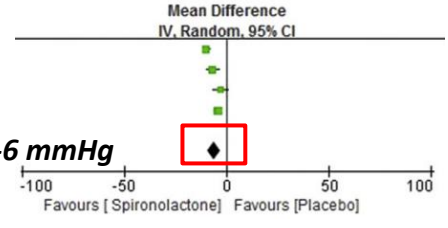
Spironolactone as Add-on in Resistant HTN

Meta-analysis: 4 trials (n=869)

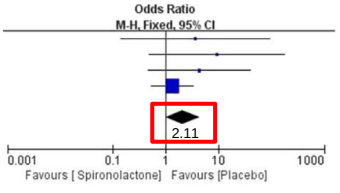
SBP reduction vs. placebo



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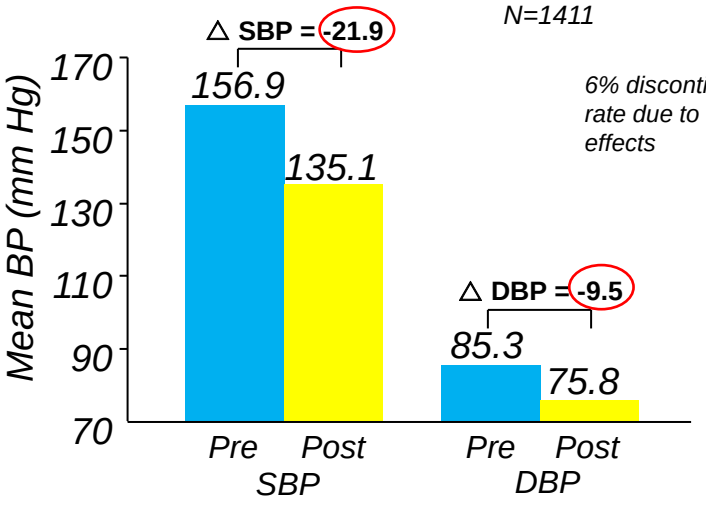
BP Response with Spironolactone 25-50 mg as 4th Drug: ASCOT* Results



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

**Anglo-Scandanavian Cardiovascular Outcomes Trial*

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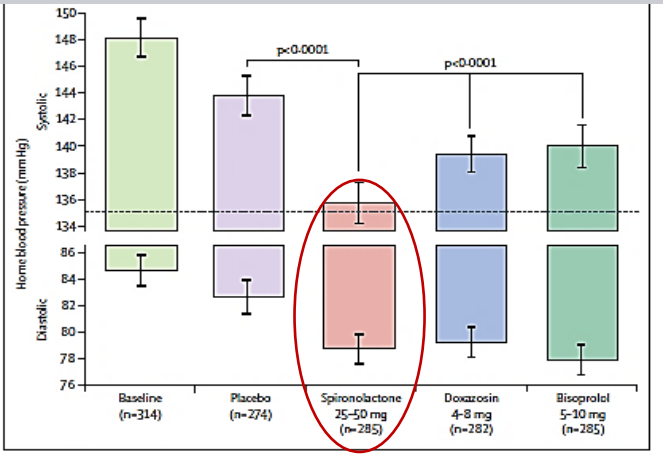
Spironolactone versus Placebo, Bisoprolol, and Doxazosin for Drug Resistant Hypertension (PATHWAY-2)

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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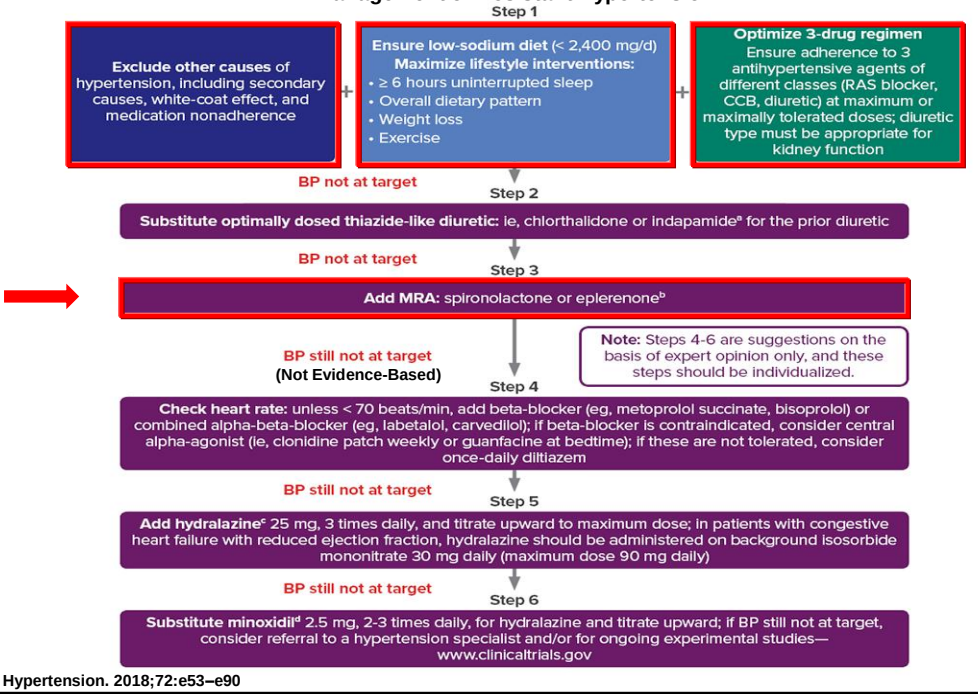
Management of Resistant Hypertension



Carey RM et al. Hypertension. 2018;72:e53–e90

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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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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
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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Designs of the Individual Finerenone Outcome Trials

	FIDELIO-DKD and FIGARO-DKD	FINEARTS-HF
Validly Randomized	12,990	6,001
Countries	48	37
Patient population	CKD and T2D	HFmrEF or HFpEF
Inclusion criteria	• Adults (≥18 years old) • T2D • UACR ≥ 30 mg/g • Maximally tolerated RASi	• Adults (≥40 years) • Symptomatic HF • LVEF ≥40% • Elevation natriuretic peptides • Structural heart disease • Recent diuretic use
Exclusion criteria	Potassium >4.8 mmol/L	Potassium >5.0 mmol/L
Dosage and titration	eGFR <60: 10 up to 20 mg eGFR ≥60: 20 mg (potentially down to 10 mg)	eGFR ≤60: 10 up to 20 mg eGFR >60: 20 up to 40 mg (potentially down to 10 mg)
Median follow-up	2.6 years (FIDELIO-DKD) 3.4 years (FIGARO-DKD)	2.6 years

Agarwal R, et al. *Eur Heart J*. 2022;43:474-484.

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FINEARTS-HF

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Finerenone in Heart Failure with Mildly Reduced or Preserved Ejection Fraction

S.D. Solomon, J.J.V. McMurray, M. Vaduganathan, B. Claggett, P.S. Jhund, A.S. Desai, A.D. Henderson, C.S.P. Lam, B. Pitt, M. Senni, S.J. Shah, A.A. Voors, F. Zannad, I.Z. Abidin, M.A. Alcocer-Gamba, J.J. Atherton, J. Bauersachs, M. Chang-Sheng, C.-E. Chiang, O. Chioncel, V. Chopra, J. Comin-Colet, G. Filippatos, C. Fonseca, G. Gajos, S. Goland, E. Goncalvesova, S. Kang, T. Katova, M.N. Kosiborod, G. Latkovskis, A.P.-W. Lee, G.C.M. Linssen, G. Llamas-Esperón, V. Mareev, F.A. Martinez, V. Melenovský, B. Merkely, S. Nodari, M.C. Petrie, C.I. Saldarriaga, J.F.K. Saraiva, N. Sato, M. Schou, K. Sharma, R. Troughton, J.A. Udell, H. Ukkonen, O. Vardeny, S. Verma, D. von Lewinski, L. Voronkov, M.B. Yilmaz, S. Zieroth, J. Lay-Flurrie, I. van Gameren, F. Amarante, P. Kolkhof, and P. Viswanathan, for the FINEARTS-HF Committees and Investigators*

Solomon SD, et al. N Engl J Med. 2024. doi:10.1056/NEJMoa2407107 [Epub ahead of print]

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Bottom Line

- **There are no head-to-head studies comparing Finerenone to Spironolactone specifically for BP control.**

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Today's Objectives

- **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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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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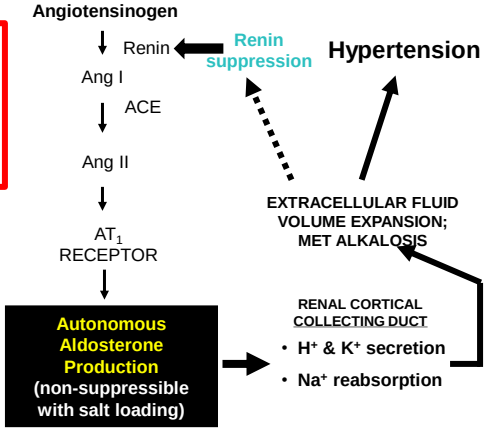
AUTONOMOUS ALDOSTERONE PRODUCTION IN PRIMARY ALDOSTERONISM

⇧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
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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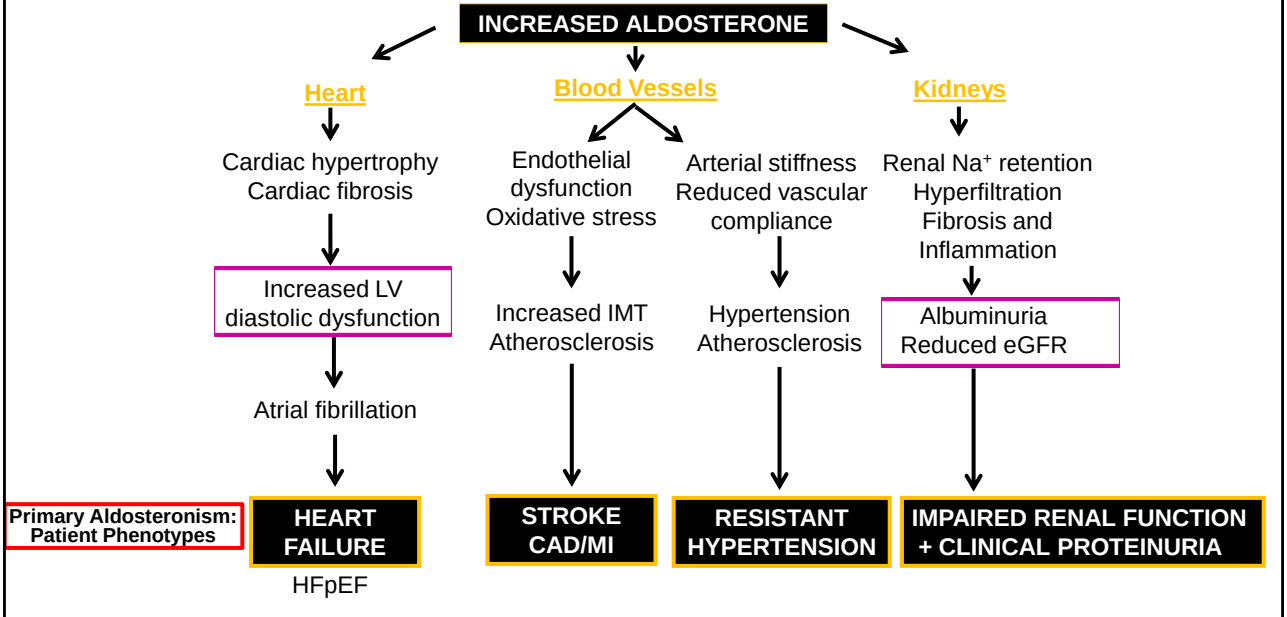
CARDIOVASCULAR and RENAL BURDEN OF PRIMARY ALDOSTERONISM
HOW DOES IT PRESENT?



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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

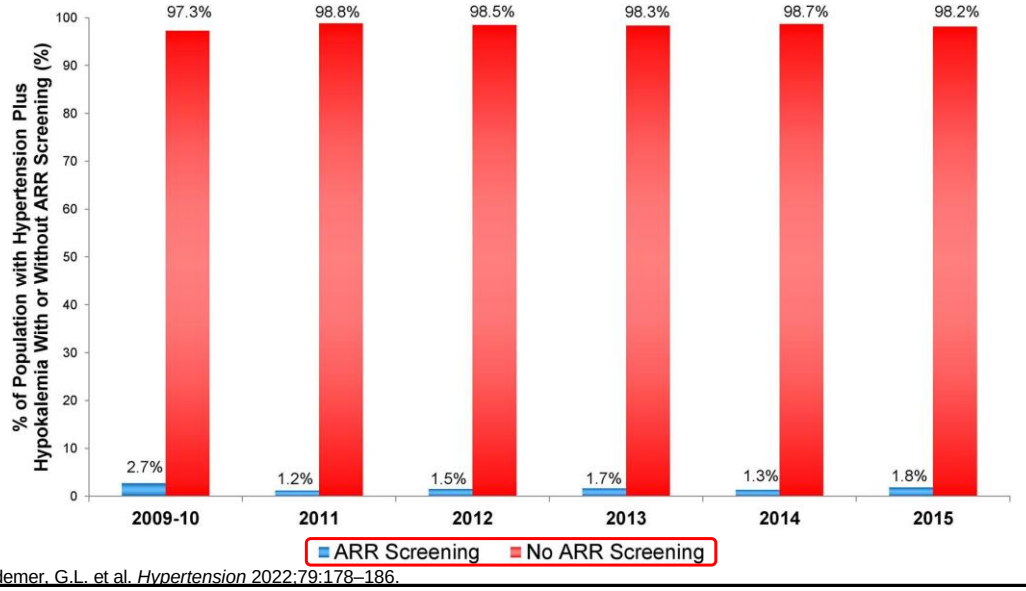

Fig 2. Hundemer, G.L. et al. *Hypertension* 2022;79:178–186.

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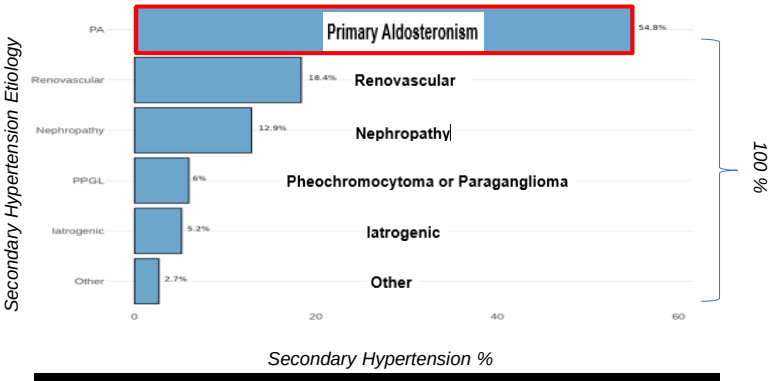
ORIGINAL ARTICLE

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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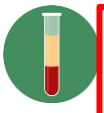
2024 ESC Guidelines for Managing Elevated BP and HTN

Screening for Secondary HTN

- **Patients with signs on physical exam or sxs on history suggestive of secondary HTN should be appropriately screened-Like the ACC/AHA 2017 Guideline**



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

This is new

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

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

We will have to See What the ACC/AHA 2025 Guideline Says!!

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

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

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

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Primary Aldosteronism

What's New!!

The Concept of Aldosterone Dysregulation Paralleling Hypertension Severity

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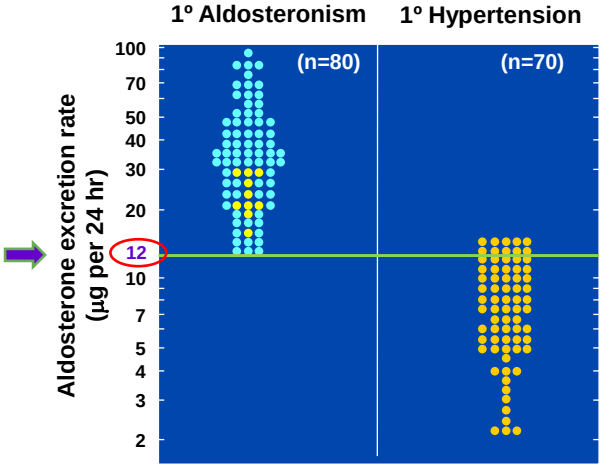
Aldosterone Excretion Rate After Three Days of Oral Sodium Loading (250 mEq Na in urine per 24 hr)



Confirmatory Testing

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

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Continuous Spectrum of the Primary Aldosterone Syndrome

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

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

All given an Oral Sodium Suppression Test

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

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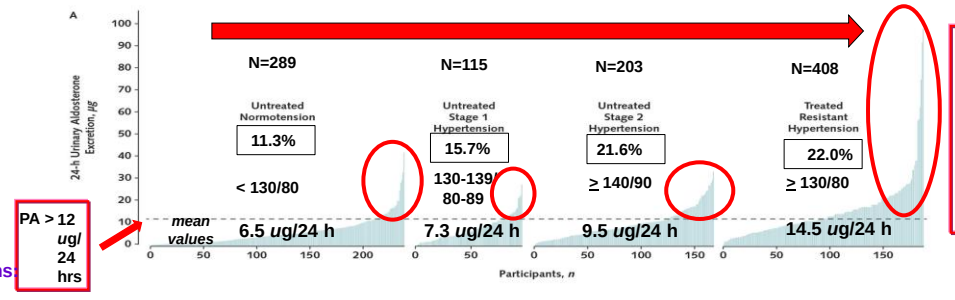
Primary Aldosteronism (PA) Occurs as a Spectrum (n=1,015 Subjects)



PA > 12 ug/ 24 hrs

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

Conclusions:

- The prevalence of primary aldosteronism is high and largely unrecognized.
- There is a spectrum of renin-independent aldosterone production (PA) that occurs in "healthy" untreated normotensives and increases with the severity of hypertension.
- This suggests aldosterone dysregulation 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 the future treatment of hypertension. (They were FDA approved in 1960)

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

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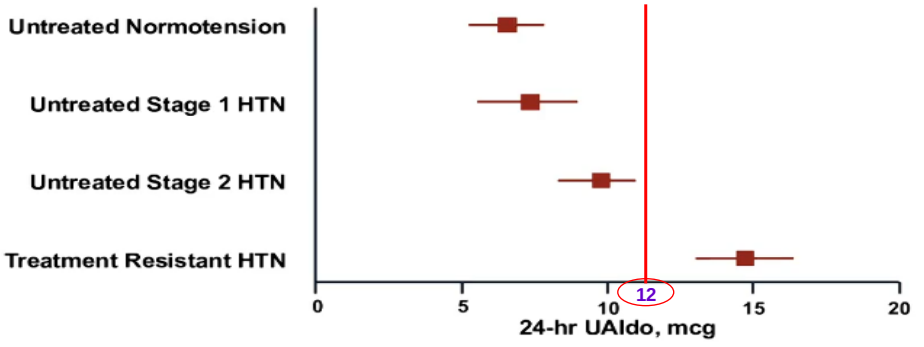
The Severity of Aldosterone Dysregulation Parallels Hypertension Severity

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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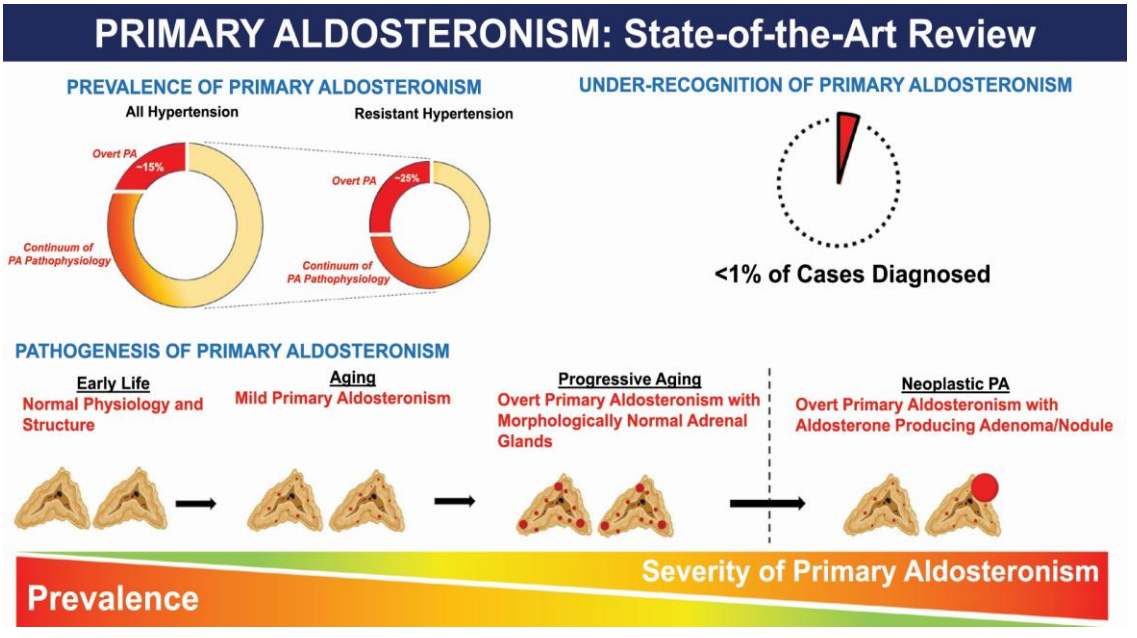

Vaidya A et al. Am J Hypertens. Dec 2022. Volume 35, Issue 12, 2022, Pages 967–988

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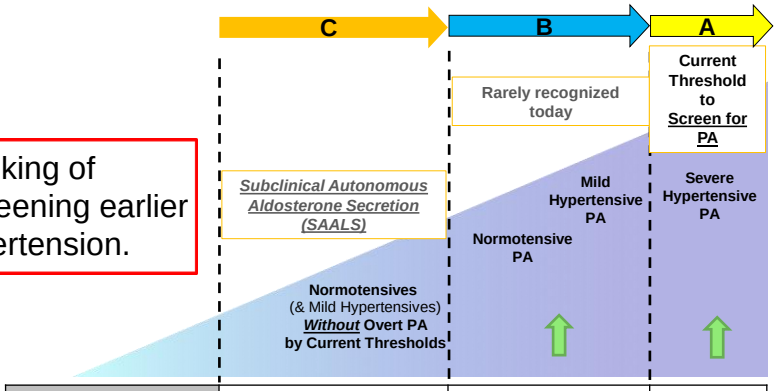
THE SPECTRUM OF PA EXTENDS BELOW CURRENT THRESHOLDS

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

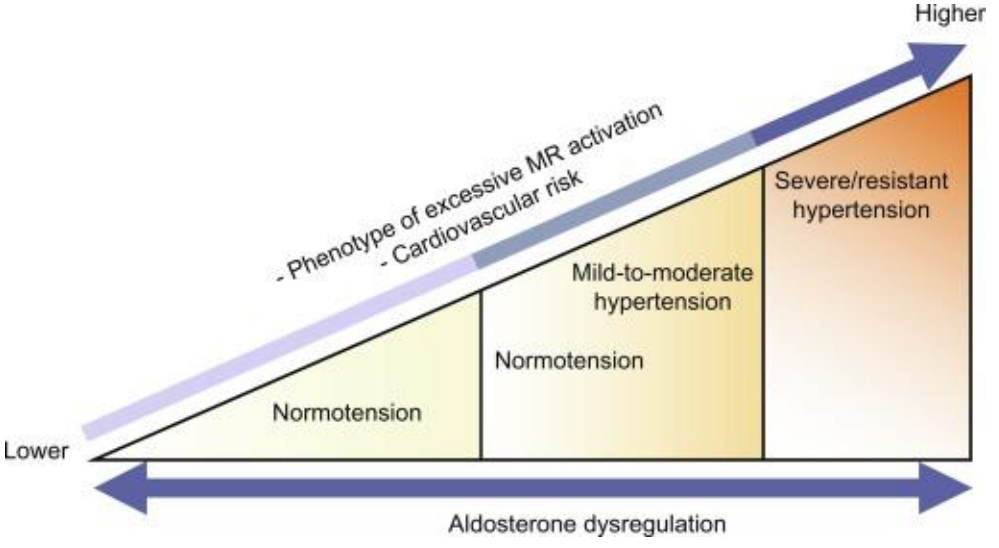


DISEASE	*Subclinical Autonomous Aldosterone Secretion (SAALS)*	Unrecognized Yet	Overt PA
Obvious Clinical Syndrome of Excessive MR Activation?	NO	NO	YES
Biochemical Confirmation of PA Using *Current* Thresholds?	NO	YES	YES
Histopathology	*Aldosterone Producing Cell Clusters (APCCs)*		*APA/BAH*

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

39

Spectrum of Aldosterone Dysregulation

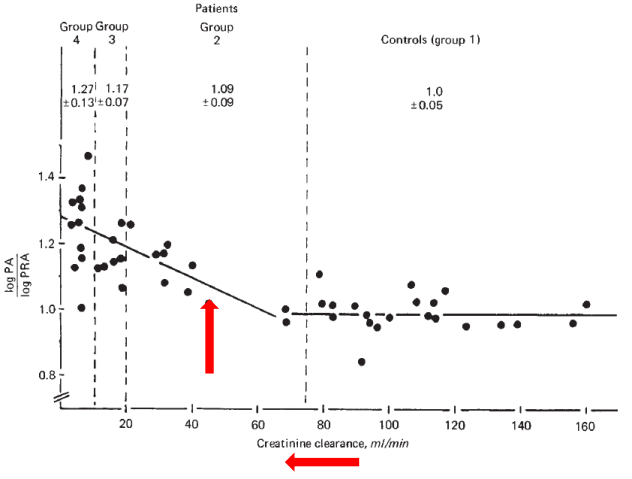


Wasita W, et al. In: Hypertension (Fourth Edition), A Companion to Braunwald's Heart Disease, 2024, Pages 274-284.

40

Aldosterone Dysregulation Occurs in CKD

Plasma Aldosterone Rises as GFR Falls

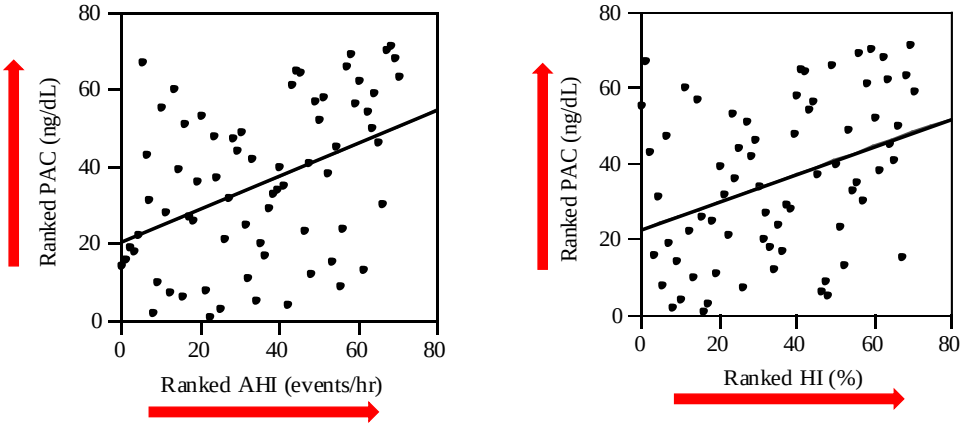


Hené RJ et al, Kidney Int. 1982 Jan;21(1):98-101.

41

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

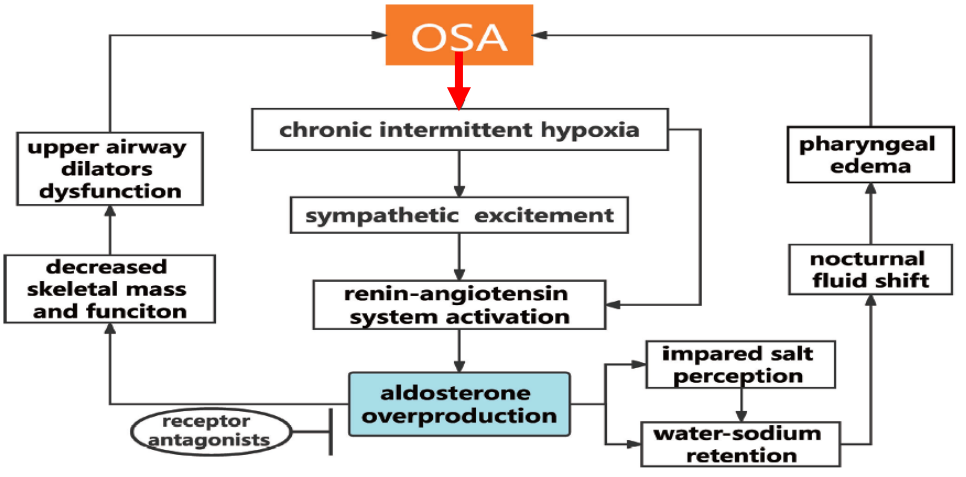
Figure 1



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

42

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

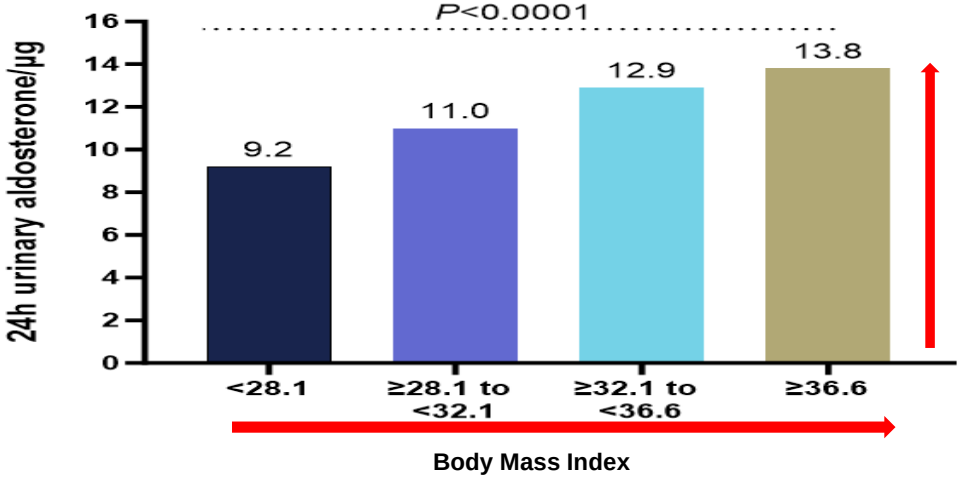
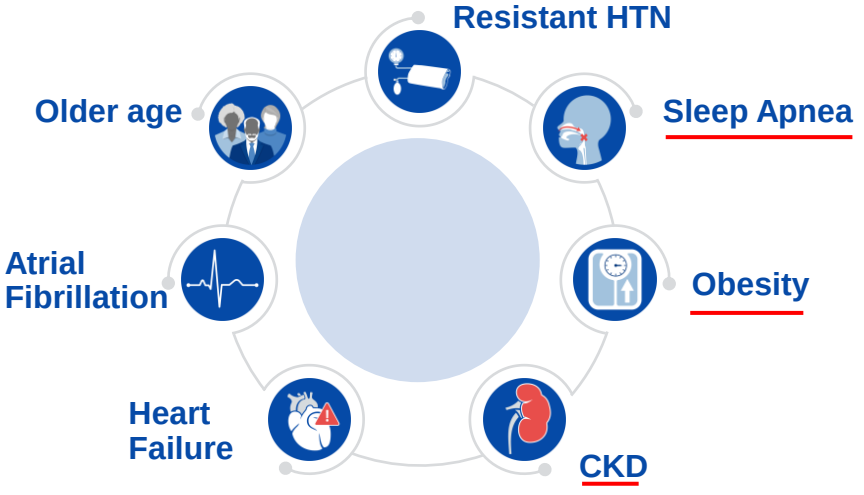


Fig 1 D. Dudenbostel T. et al. *Hypertension*. 2016;68(4):995-1003.

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

44

High Prevalence of Aldosterone-Mediated HTN in Multiple Patient Populations



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

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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	Non-steroidal MRA
Spironolactone	Finerenone
Eplerenone	Ocedurenone

Aldosterone Synthase Inhibitors
Baxdrostat
Lorundrostat
BI 690517 (Vicadrostat)

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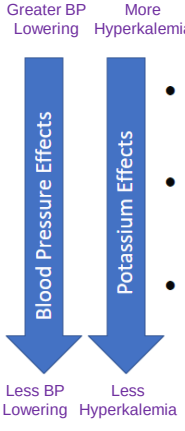
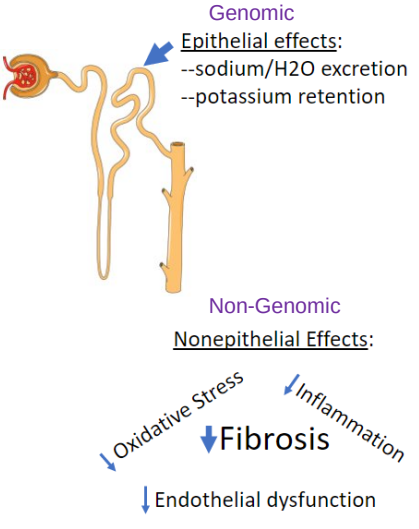
Mineralocorticoid Antagonists



- Spironolactone: Nonspecific steroidal MRA
- Eplerenone: Specific steroidal MRA
- Finerenone: Specific nonsteroidal MRA



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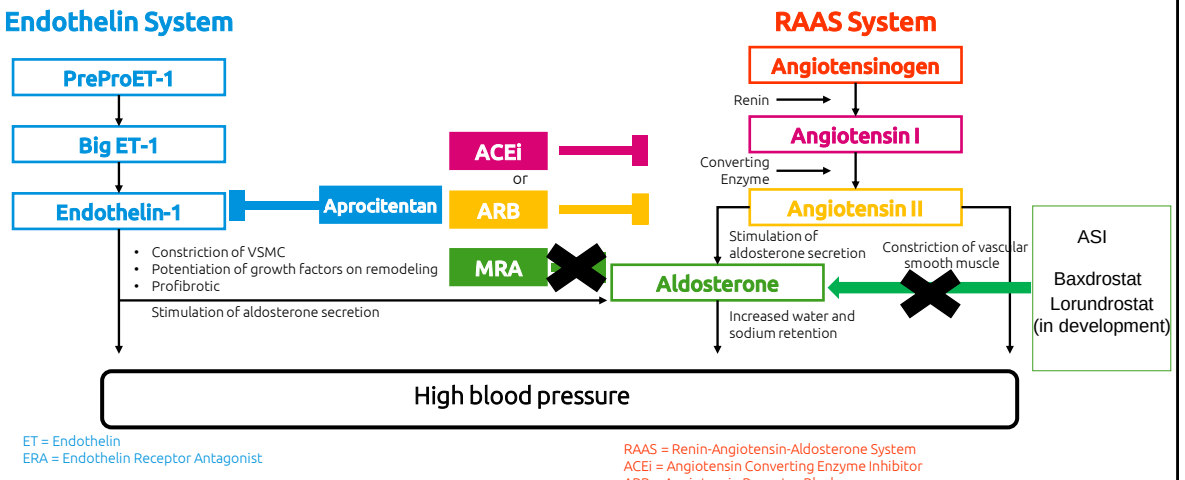
New Pathway Targets and New Ways to Target Old Pathways in Hypertension



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. Clozel M. *Can J Physiol. Pharmacol* 2022;100(7):573-583.
2. Ojha U. et al. *Am J Cardiovasc Drugs*,2022;22(3):271-285.

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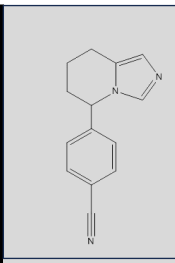
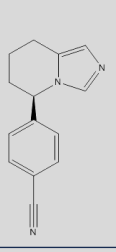
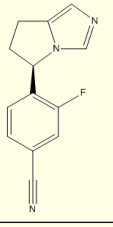
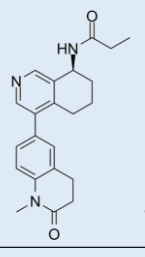
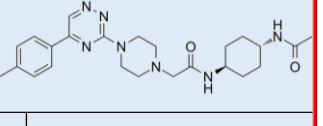
Aldosterone Synthase Inhibitors

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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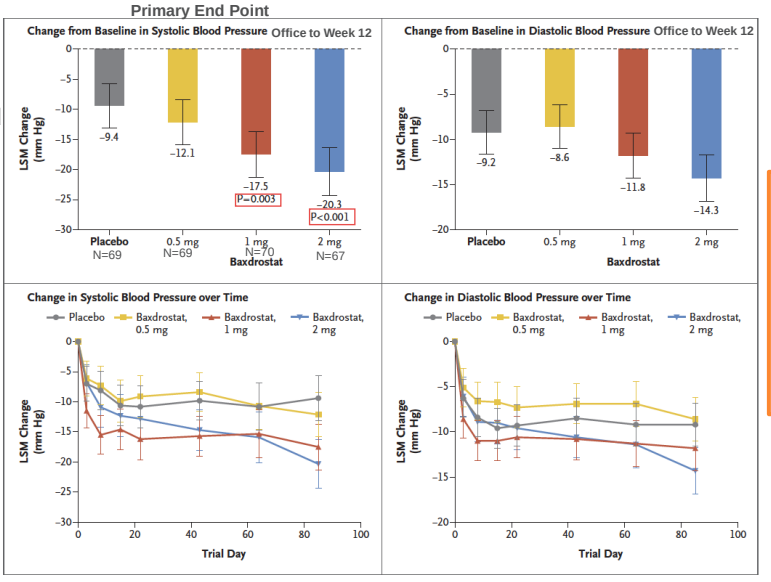
BrigHTN: Dose-Dependent Decreases in BP in Patients with Treatment-Resistant HTN Who Received Baxdrostat

- Phase 2
- Randomized
- Parallel group
- Dose-ranging
- 275 adults
- Seated BP ≥ 130/80 mmHg
- 3 AHT agents, including a diuretic
- 12 week results

Primary End Point



Primary End Point

Office BP at Week 12

Difference in SBP change between 2 mg and placebo: **−11.0 mm Hg** (95% CI, −16.4, −5.5; *P* < .001)

Difference in SBP change between the 1 mg and placebo: **−8.1 mm Hg** (95% CI, −13.5, −2.8; *P* = .003)

LSM, least squares mean.

Freeman MW, et al. N Engl J Med. 2023;388:395-405.

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Baxdrostat in Uncontrolled HTN-HALO Trial

Phase 2 – HALO Study

N enrollees = 249 US subjects
Mean age 60
Female 48%

Uncontrolled hypertension on a stable regimen of either 1 or 2 antihypertensives:
ACEi or ARB
ACEi/ARB + a thiazide diuretic, or
ACEi/ARB + CCB

8-week double-blind, placebo-controlled (baxdrostat 0.5 mg, 1 mg, or 2 mg or placebo), equal randomization

The primary endpoint was change in mean seated SBP at week 8

Primary End Point

	Change in Mean Seated SBP at Wk 8	Placebo-Corrected Change in Mean Seated SBP at Wk 8
0.5 mg baxdrostat	- 17.0 mm Hg	-0.5 mm Hg (*P* = .83)
1 mg baxdrostat	- 16.0 mm Hg	0.6 mm Hg (*P* = .79)
2 mg baxdrostat	- 19.8 mm Hg	-3.2 mm Hg (*P* = .15)
Placebo	- 16.6 mm Hg	-

- **The primary endpoint of placebo-corrected Mean Seated SBP change at 8 weeks was not met at any baxdrostat dose**
- **Adherence in patients, clustered at a few sites, was suboptimal, as assessed by measured drug levels < 1% expected.**

Bhatt D, et al. Presented at: the American College of Cardiology Annual Scientific Session (ACC.23/WCC), New Orleans, LA, March 4, 2023.

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Select Future / 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	720	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	2025-10-13
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	2025-04-25
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

Lorundrostat Efficacy and Safety in Patients with Uncontrolled Hypertension

L.J. Laffin,[1,2] B. Kopjar,[3] C. Melgaard,[2] K. Wolski,[2] J. Ibbitson,[4] S. Bhikam,[4] M.R. Weir,[5] E.O. Ofili,[6] R. Mehra,[7] J.M. Luther,[8] D.L. Cohen,[9] A. Sarraju,[1,2] M.J. Wilkinson,[10] J.M. Flack,[11] D. Rodman,[4] and S.E. Nissen,[1,2] for the Advance-HTN Investigators*

Laffin L. et al. *New Engl J Med*. April 25, 2025;392:1813-23.

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Objective

Assess the 24-hour blood pressure lowering effect of lorundrostat taken once daily in participants with uncontrolled and treatment-resistant hypertension on a standardized antihypertensive regimen

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Trial Design

- Multicenter (All 103 sites in the United States)
- Prospective
- Randomized
- Double-blind
- Placebo-controlled
- Parallel group
- Phase 2b trial

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Trial Design

2 weeks

Screening

2 - 5 BP medications

$Na^+ \geq 135$
$K^+ \leq 5.0$
eGFR ≥ 45

Office
SBP 140 to 180 mm Hg, or
DBP 90 to 110 mm Hg

57

Trial Design

2 weeks

Screening

2 - 5 BP medications

$Na^+ \geq 135$
$K^+ \leq 5.0$
eGFR ≥ 45

3 weeks

Single-blind run-in

Switch to standardized regimen:
Indapamide 2.5 mg daily or HCTZ 25 mg daily
Olmesartan 40 mg daily
+/- Amlodipine 10 mg daily

63% on 2 meds

37% on 3-5 meds

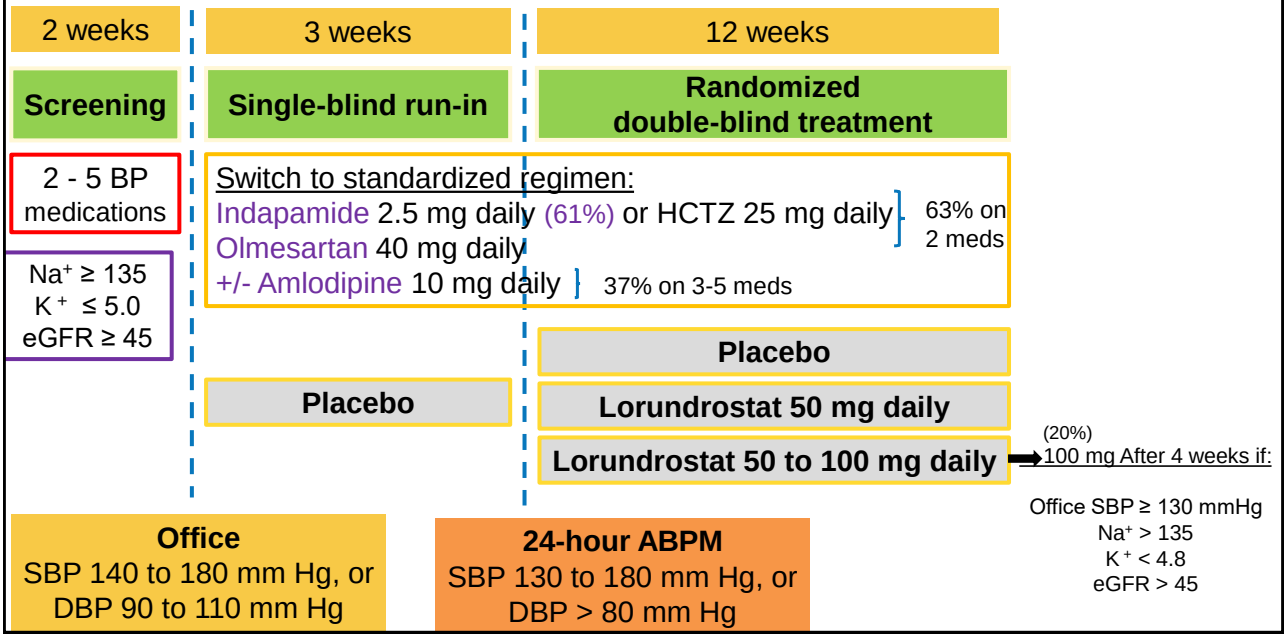
Placebo

Office
SBP 140 to 180 mm Hg, or
DBP 90 to 110 mm Hg

24-hour ABPM
SBP 130 to 180 mm Hg, or
DBP > 80 mm Hg

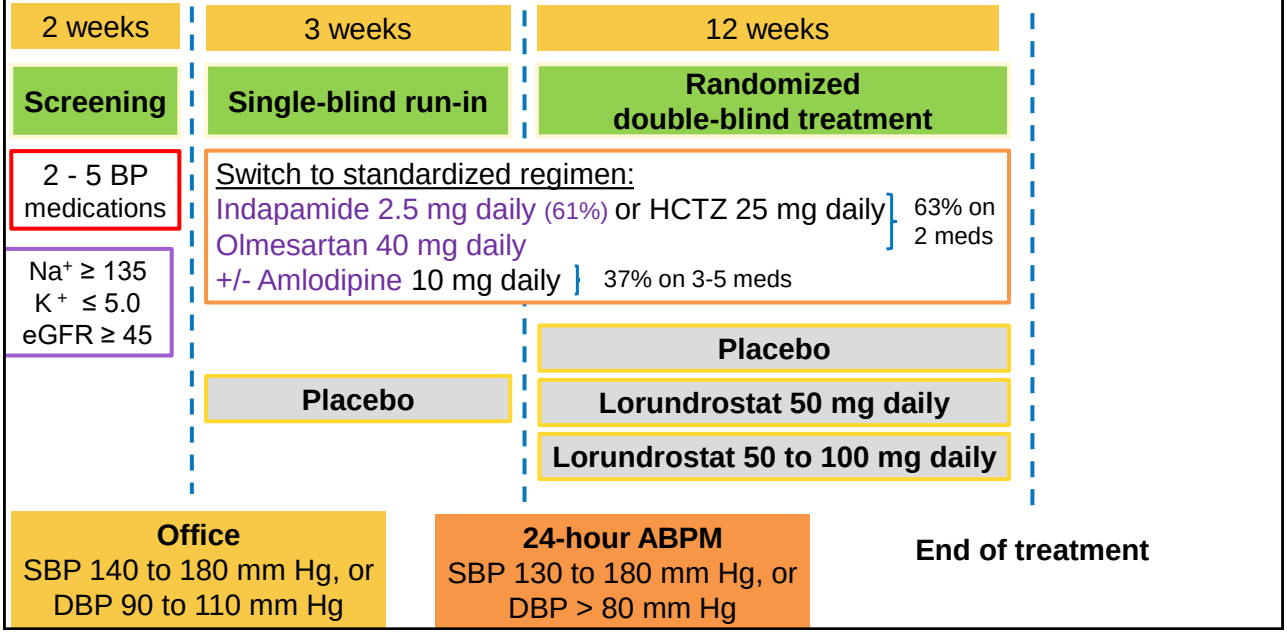
58

Trial Design



59

Trial Design



60

Participant Characteristics (mean)	Placebo	Lorundrostat 50 mg	Lorundrostat 50 to 100 mg
Age (60 years)	59	61	61
Women (40%)	35%	40%	44%
Black or African-American (53%)	46%	53%	58%
BMI (kg/m^2)	32	31	32
eGFR (Randomization)	74	77	76
Office BP (Screening)	155/91	153/88	152/89
24h ABPM (Randomization)	141/87	141/86	141/87

Adapted from Table 1. Laffin L. et al. *New Engl J Med*. April 25, 2025;392:1813-23.

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Lorundrostat for Uncontrolled Hypertension

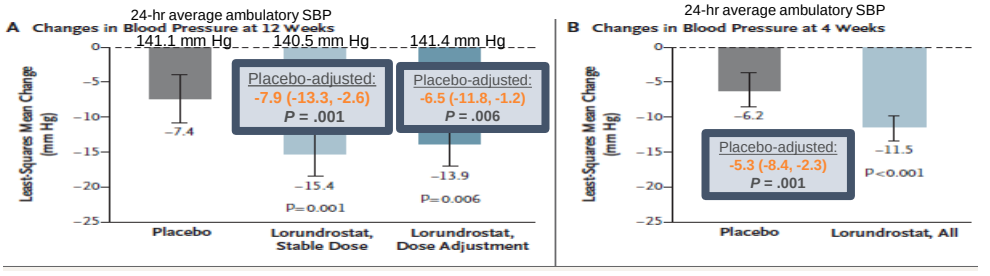

Table 2. Blood-Pressure Changes with Lorundrostat.*

End Point	Stable Dose (N=94)	Dose Adjustment (N=94)	Any Dose (N=188)†	With 2-Drug Standardized Regimen (N=117)‡	With 3-Drug Standardized Regimen (N=71)§	With Dose Increase at Week 4 (N=19)¶
Primary end point						
Placebo-adjusted change in 24-hr average ambulatory systolic BP at week 12 (97.5% CI) — mm Hg‖	−7.9 (−13.3 to −2.6)	−6.5 (−11.8 to −1.2)	—	—	—	—
P value	0.001	0.006	—	—	—	—
Key secondary end points						
Placebo adjusted change in 24-hr average ambulatory systolic BP at week 4 (98.75% CI) — mm Hg‖	—	—	−5.3 (−8.4 to −2.3)**	−6.1 (−10.8 to −1.4)	−4.6 (−10.6 to 1.5)	—
P value	—	—	<0.001	0.001	0.06	—
Mean change in office systolic BP at week 12 (99.58% CI) — mm Hg	—	—	—	—	—	−17.5 (−30.3 to −4.7)
P value	—	—	—	—	—	<0.001

Laffin L. et al. *New Engl J Med*. April 25, 2025;392:1813-23

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Adverse Events

Adverse Events	Placebo	Lorundrostat 50 mg	Lorundrostat 50 to 100 mg
Any serious AE	2%	6%	8%
Any study-drug related serious AE	0	2%	1%
Hypotension	3%	9%	8%
Hyponatremia	6%	9%	11%
Hyperkalemia (> 6.0 mmol / L) ▪ Single value	0	5%	7%
Hyperkalemia (> 6.0 mmol / L) ▪ Confirmed via per protocol repeat testing ▪ Spurious values (including suspected hemolysis) and values obtained following double-blind treatment period are excluded	0	2%	3%

AE, adverse event.

Adopted from Table 3. Laffin L. et al. *New Engl J Med*. April 25, 2025;392:1813-23.

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Advance-HTN Conclusions:

- Lorundrostat effectively lowered 24-hour BP among patients with well-treated uncontrolled and resistant hypertension.
- A dose escalation strategy from 50 to 100 mg did not lower BP more than 50 mg and was associated with numerically more adverse events.

Laffin L. et al. *New Engl J Med*. April 25, 2025;392:1813-23.

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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	Q2, 2025
NCT05769608[2]	Phase 2	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	Presented March 29, 2025 ACC Scientific Sessions
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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Summary on Aldosterone in HTN

1. Think about Aldosteronism in all patients with HTN but especially in certain phenotypes with hypertension.
2. Aldosterone Dysregulation plays a major role in the pathogenesis of hypertension, as well as CV and Kidney Disease.
3. Appreciate that Aldosterone Dysregulation spans a spectrum of severity from normotension to resistant hypertension but only about 30% of all patients with Primary Aldosteronism have hypokalemia.
4. Know that PA is associated with higher CV, Renal, and Metabolic risk compared to those with equivalent BP-associated essential HTN.
5. The role of Aldosterone Synthase Inhibitors remains to be proven on outcome, but they look promising in Phase 2 trials. Stay tuned.
6. Use Finerenone (ns-MRA), where evidence for their use is greatest; in HFmrEF and HFpEF (EF $\geq$ 40%) and in DKD.

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