MRAs (Steroidal and Non-Steroidal) and Aldosterone Synthase Inhibitors in Hypertension and Renal Disease

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Disclosure

I have no financial interests or relationships to disclose.

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Remembering Dr. George Bakris (1952-2024)

"George Bakris was the most prolific researcher, teacher, and clinician in the history of hypertension...He will live on through his great work."

—Prof. Michael Davidson

https://biologicalsciences.uchicago.edu/news/george-bakris-obituary

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OBJECTIVES

1. Understand the role of aldosterone in cardiovascular and kidney disease
2. Compare steroidal vs. non-steroidal MRAs
3. Review evidence for MRAs in hypertension and CKD
4. Introduce aldosterone synthase inhibitors (ASIs)

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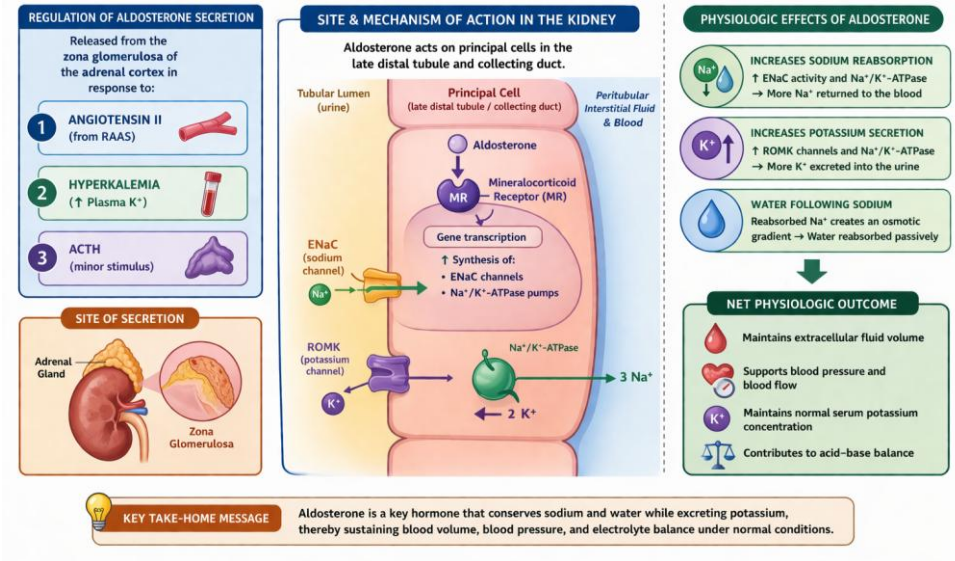
WHY ALDOSTERONE MATTERS



Brown, JAHA 2024

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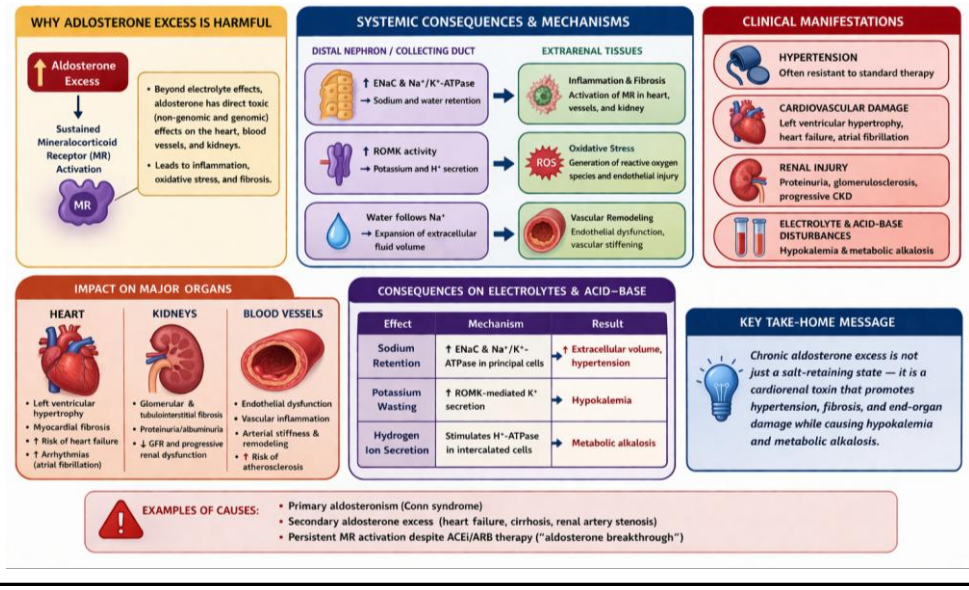
DANGERS OF ALDOSTERONE EXCESS



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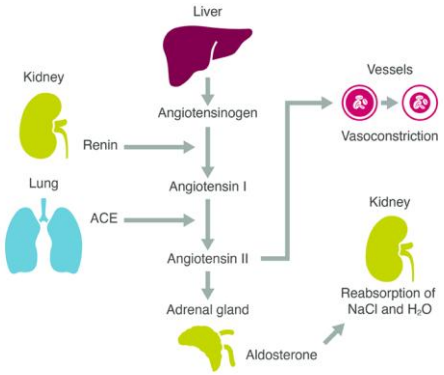
ALDOSTERONE BREAKTHROUGH

ACEi/ARBs suppress aldosterone secretion…why is this often not enough?

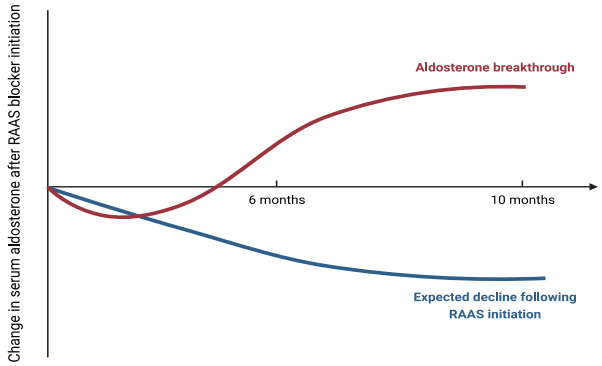


Mogi, Hypertens Res 2022

7

ALDOSTERONE BREAKTHROUGH

Aldosterone levels often “breakthrough” over time leading to persistent MR activation despite RAAS blockade.



Mogi, Hypertens Res 2022

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MEDICATIONS TARGETING ALDOSTERONE

Steroidal MRAs
- Spironolactone
- Eplerenone

Non-Steroidal MRAs
- Finerenone

Aldosterone Synthase Inhibitors
- Baxdrostat
- Lorundrostat
- Vicadrostat

Helmeczi and Hundemer, Curr Opin Neph HTN 2025

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SPIRONOLACTONE

- Non-selective steroidal MR antagonist
- Initially approved by the FDA in 1960

- Pros:
  - Inexpensive and widely available
  - ~2x as potent as eplerenone
  - Dosed once daily due to long-acting metabolites

- Cons:
  - Breast tenderness
  - Gynecomastia
  - Menstrual irregularities
  - Reduced libido
  - Hyperkalemia (particularly in those with CKD)

Helmeczi and Hundemer, Curr Opin Neph HTN 2025

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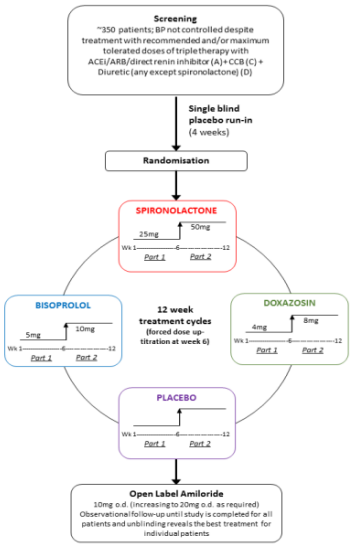
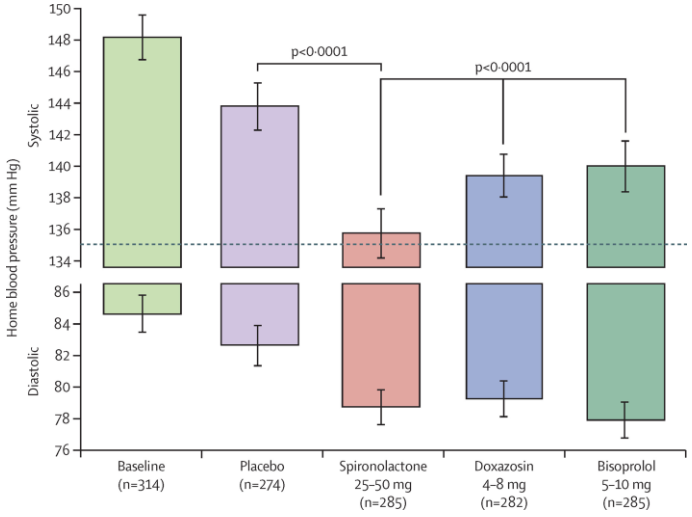
PATHWAY-2





Williams et al., Lancet 2015

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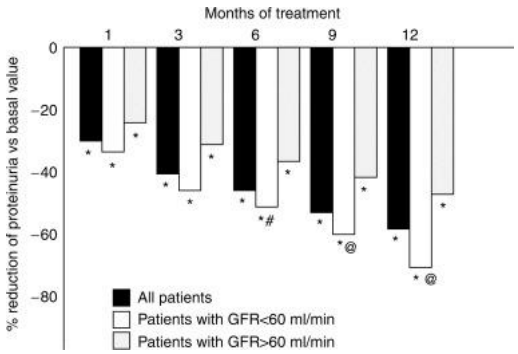
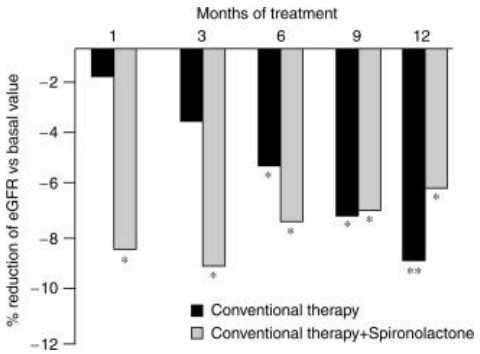
SPIRONOLACTONE AND KIDNEY HEALTH

Proteinuria



eGFR Decline



Bianchi et al., Kidney Int 2006

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EPLERENONE

- Selective steroidal MR antagonist
- Pros:
  - Greater selectivity for the MR so anti-androgen effects are far less common
- Cons:
  - Half as potent as spironolactone
  - Shorter acting so should be dosed BID
  - More expensive
  - Hyperkalemia (particularly in those with CKD)

Helmeczi and Hundemer, Curr Opin Neph HTN 2025

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SPIRONOLACTONE VS. EPLERENONE

Why Spironolactone?

- Cheaper
- 2x as potent
- Once daily dosing

Why Eplerenone?

- Less side effects (especially for men)

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LIMITATIONS OF STEROIDAL MRAs

- Hyperkalemia, particularly in CKD
- Endocrine side effects
- Under-utilization in clinical practice

Helmeczi and Hundemer, Curr Opin Neph HTN 2025

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FINERENONE

- Selective non-steroidal MR antagonist
- Different tissue distribution
- Pros:
  - Less off-target effects
  - Less hyperkalemia???
  - Well proven anti-fibrotic effects
  - Well proven organ protection
- Cons:
  - Can be expensive
  - Less BP reduction

Helmeczi and Hundemer, Curr Opin Neph HTN 2025

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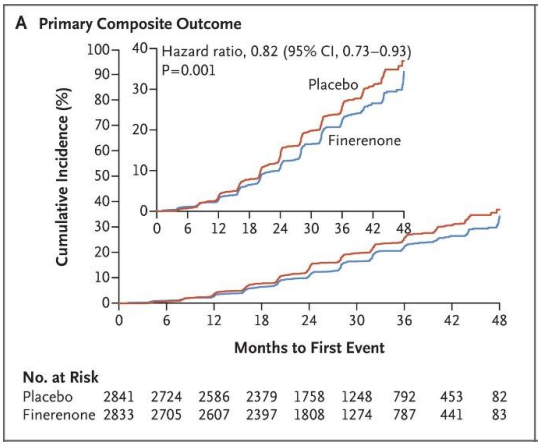
FIDELIO-DKD

Effect of Finerenone on Chronic Kidney Disease Outcomes in Type 2 Diabetes

George L. Bakris, M.D., Rajiv Agarwal, M.D., Stefan D. Anker, M.D., Ph.D., Bertram Pitt, M.D., Luis M. Ruilope, M.D., Peter Rossing, M.D., Peter Kolkhof, Ph.D., Christina Nowack, M.D., Patrick Schloemer, Ph.D., Amer Joseph, M.B., B.S., and Gerasimos Filippatos, M.D., for the FIDELIO-DKD Investigators*



Bakris et al., NEJM 2020

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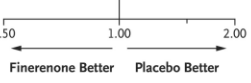
FIDELIO-DKD

Outcome	Finerenone (N=2833) no. of patients with event (%)	Placebo (N=2841) no. of patients with event (%)	Finerenone (N=2833) per 100 patient-yr	Placebo (N=2841) per 100 patient-yr	Hazard Ratio (95% CI)	P Value
Primary composite outcome	504 (17.8)	600 (21.1)	7.59	9.08	0.82 (0.73–0.93)	0.001
Kidney failure	208 (7.3)	235 (8.3)	2.99	3.39	0.87 (0.72–1.05)	—
End-stage kidney disease	119 (4.2)	139 (4.9)	1.60	1.87	0.86 (0.67–1.10)	—
Sustained decrease in eGFR to <15 ml/min/1.73 m²	167 (5.9)	199 (7.0)	2.40	2.87	0.82 (0.67–1.01)	—
Sustained decrease of ≥40% in eGFR from baseline	479 (16.9)	577 (20.3)	7.21	8.73	0.81 (0.72–0.92)	—
Death from renal causes	2 (<0.1)	2 (<0.1)	—	—	—	—
Key secondary composite outcome	367 (13.0)	420 (14.8)	5.11	5.92	0.86 (0.75–0.99)	0.03
Death from cardiovascular causes	128 (4.5)	150 (5.3)	1.69	1.99	0.86 (0.68–1.08)	—
Nonfatal myocardial infarction	70 (2.5)	87 (3.1)	0.94	1.17	0.80 (0.58–1.09)	—
Nonfatal stroke	90 (3.2)	87 (3.1)	1.21	1.18	1.03 (0.76–1.38)	—
Hospitalization for heart failure	139 (4.9)	162 (5.7)	1.89	2.21	0.86 (0.68–1.08)	—
Death from any cause	219 (7.7)	244 (8.6)	2.90	3.23	0.90 (0.75–1.07)	—
Hospitalization for any cause	1263 (44.6)	1321 (46.5)	22.56	23.87	0.95 (0.88–1.02)	—
Secondary composite kidney outcome	252 (8.9)	326 (11.5)	3.64	4.74	0.76 (0.65–0.90)	—
Sustained decrease of ≥57% in eGFR from baseline	167 (5.9)	245 (8.6)	2.41	3.54	0.68 (0.55–0.82)	—



Bakris et al., NEJM 2020

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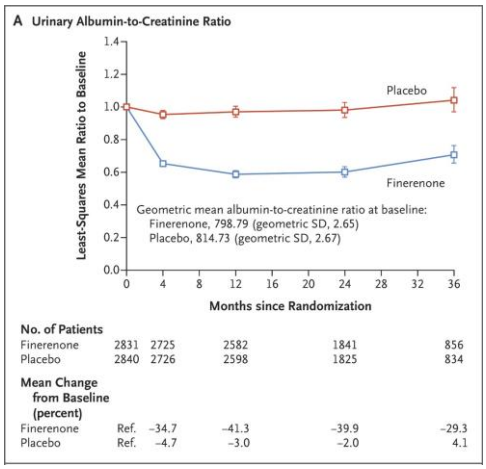
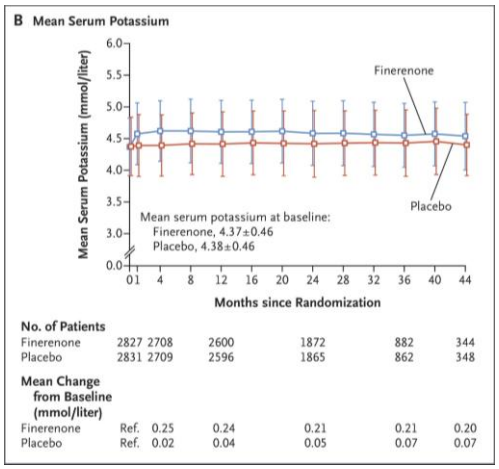
FIDELIO-DKD





***Note:* Effects on systolic BP with finerenone were quite modest (~2-4 mmHg reduction)**

Bakris et al., NEJM 2020

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FIDELIO-DKD

Event	Finerenone (N=2827)	Placebo (N=2831)
	no. of patients (%)	
Any adverse event	2468 (87.3)	2478 (87.5)
Adverse event related to trial regimen	646 (22.9)	449 (15.9)
Adverse event leading to discontinuation of trial regimen	207 (7.3)	168 (5.9)
Any serious adverse event†	902 (31.9)	971 (34.3)
Serious adverse event related to trial regimen†	48 (1.7)	34 (1.2)
Serious adverse event leading to discontinuation of trial regimen†	75 (2.7)	78 (2.8)
Investigator-reported hyperkalemia‡	516 (18.3)	255 (9.0)
Hyperkalemia related to trial regimen	333 (11.8)	135 (4.8)
Serious hyperkalemia†	44 (1.6)	12 (0.4)
Hospitalization due to hyperkalemia	40 (1.4)	8 (0.3)
Permanent discontinuation of trial regimen due to hyperkalemia	64 (2.3)	25 (0.9)
Investigator-reported hypokalemia	28 (1.0)	61 (2.2)
Investigator-reported renal-related adverse events		
Acute kidney injury§	129 (4.6)	136 (4.8)
Hospitalization due to acute kidney injury§	53 (1.9)	47 (1.7)
Discontinuation of trial regimen due to acute kidney injury§	5 (0.2)	7 (0.2)
Hospitalization due to acute renal failure¶	70 (2.5)	71 (2.5)
Discontinuation of trial regimen due to acute renal failure¶	31 (1.1)	36 (1.3)

Bakris et al., NEJM 2020

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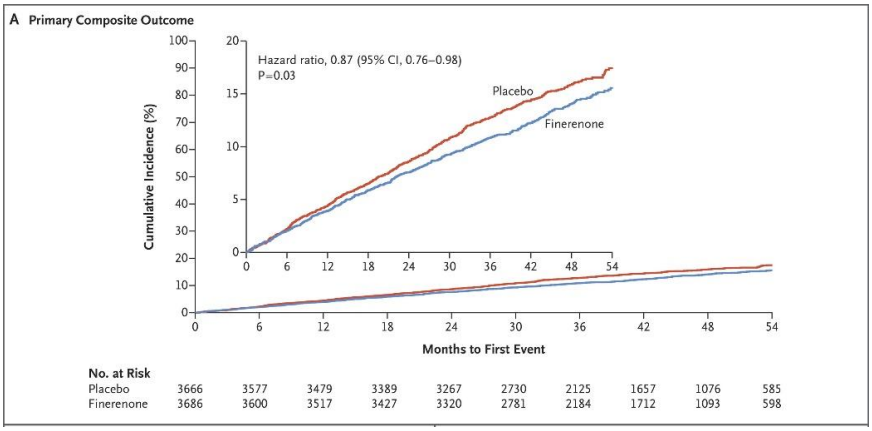
FIGARO-DKD

Cardiovascular Events with Finerenone in Kidney Disease and Type 2 Diabetes

B. Pitt, G. Filippatos, R. Agarwal, S.D. Anker, G.L. Bakris, P. Rossing, A. Joseph, P. Kolkhof, C. Nowack, P. Schloemer, and L.M. Ruilope, for the FIGARO-DKD Investigators*



Pitt et al., NEJM 2021

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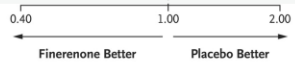
FIGARO-DKD

Outcome	Finerenone (N=3686)	Placebo (N=3666)	Finerenone (N=3686)	Placebo (N=3666)	Hazard Ratio (95% CI)	P Value
	no. of patients with event (%)		*no. of patients with event per 100 patient-yr*			
Primary composite outcome	458 (12.4)	519 (14.2)	3.87	4.45	0.87 (0.76–0.98)	0.03
Death from cardiovascular causes	194 (5.3)	214 (5.8)	1.56	1.74	0.90 (0.74–1.09)	—
Nonfatal myocardial infarction	103 (2.8)	102 (2.8)	0.85	0.85	0.99 (0.76–1.31)	—
Nonfatal stroke	108 (2.9)	111 (3.0)	0.89	0.92	0.97 (0.74–1.26)	—
Hospitalization for heart failure	117 (3.2)	163 (4.4)	0.96	1.36	0.71 (0.56–0.90)	—
Kidney composite outcome with ≥40% decrease in eGFR	350 (9.5)	395 (10.8)	3.15	3.58	0.87 (0.76–1.01)	—
Kidney failure	46 (1.2)	62 (1.7)	0.40	0.54	0.72 (0.49–1.05)	—
End-stage kidney disease	32 (0.9)	49 (1.3)	0.26	0.40	0.64 (0.41–0.995)	—
Sustained decrease in eGFR of <15 ml/min/1.73 m²	28 (0.8)	38 (1.0)	0.24	0.33	0.71 (0.43–1.16)	—
Sustained ≥40% decrease in eGFR from baseline	338 (9.2)	385 (10.5)	3.04	3.49	0.87 (0.75–1.00)	—
Death from renal causes	0	2 (0.1)	—	—	—	—
Hospitalization for any cause	1573 (42.7)	1605 (43.8)	16.9	17.5	0.97 (0.90–1.04)	—
Death from any cause	333 (9.0)	370 (10.1)	2.68	3.01	0.89 (0.77–1.04)	—
Kidney composite outcome with ≥57% decrease in eGFR	108 (2.9)	139 (3.8)	0.95	1.23	0.77 (0.60–0.99)	—
Sustained ≥57% decrease in eGFR from baseline	90 (2.4)	116 (3.2)	0.79	1.02	0.76 (0.58–1.00)	—



***Note:* Effects on systolic BP with finerenone were quite modest (~2-4 mmHg reduction)**

Pitt et al., NEJM 2021

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FIGARO-DKD

Event	Finerenone (N=3683)	Placebo (N=3658)
Investigator-reported adverse events — no. (%)		
Any adverse event	3134 (85.1)	3129 (85.5)
Adverse event related to finerenone or placebo	560 (15.2)	413 (11.3)
Adverse event leading to discontinuation of trial regimen	207 (5.6)	183 (5.0)
Any serious adverse event	1158 (31.4)	1215 (33.2)
Serious adverse event related to finerenone or placebo	35 (1.0)	27 (0.7)
Serious adverse event leading to discontinuation of trial regimen	70 (1.9)	76 (2.1)
Adverse event with outcome of death	79 (2.1)	100 (2.7)
Hyperkalemia†	396 (10.8)	193 (5.3)
Hyperkalemia related to finerenone or placebo	240 (6.5)	114 (3.1)
Serious hyperkalemia	25 (0.7)	4 (0.1)
Hospitalization due to hyperkalemia	21 (0.6)	2 (0.1)
Permanent discontinuation of trial regimen due to hyperkalemia	46 (1.2)	13 (0.4)
Hypokalemia	42 (1.1)	88 (2.4)
Renal-related adverse events		
Acute kidney injury‡	91 (2.5)	98 (2.7)
Hospitalization due to acute kidney injury‡	32 (0.9)	39 (1.1)
Discontinuation of trial regimen due to acute kidney injury‡	9 (0.2)	3 (0.1)
Hospitalization due to acute renal failure§	45 (1.2)	49 (1.3)
Discontinuation of trial regimen due to acute renal failure§	26 (0.7)	12 (0.3)

Pitt et al., NEJM 2021

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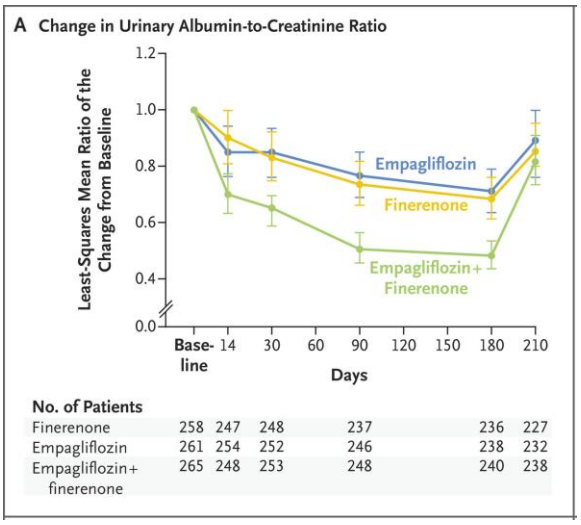
CONFIDENCE

Finerenone with Empagliflozin in Chronic Kidney Disease and Type 2 Diabetes

Rajiv Agarwal, M.D.,[1,2] Jennifer B. Green, M.D.,[3] Hiddo J.L. Heerspink, Ph.D.,[4] Johannes F.E. Mann, M.D.,[5,6] Janet B. McGill, M.D.,[7] Amy K. Mottl, M.D.,[8] Julio Rosenstock, M.D.,[9] Peter Rossing, M.D.,[10,11] Muthiah Vaduganathan, M.D., M.P.H.,[12] Meike Brinker, M.D.,[13] Robert Edfors, M.D., Ph.D.,[14] Na Li, M.D., Ph.D.,[15] Markus F. Scheerer, Ph.D.,[16] Charlie Scott, M.Sc.,[17] and Masaomi Nangaku, M.D., Ph.D.,[18] for the CONFIDENCE Investigators*



Agarwal et al., NEJM 2025

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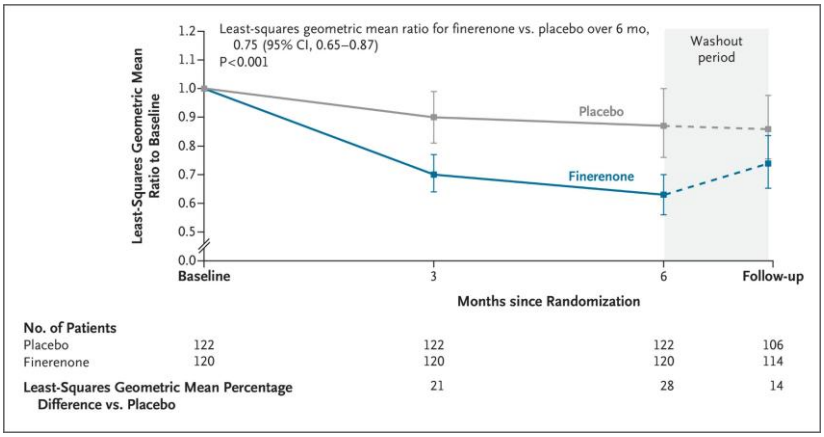
FINE-ONE

Finerenone in Type 1 Diabetes and Chronic Kidney Disease

Hiddo J.L. Heerspink, Ph.D.,[1,2] Andreas L. Birkenfeld, M.D.,[3,5] David Z.I. Cherney, M.D., Ph.D.,[6] Helen M. Colhoun, M.D.,[7] Per-Henrik Groop, M.D.,[8] Linong Ji, M.D.,[9] Niels Jongs, Ph.D.,[2] Chantal Mathieu, M.D.,[10] Richard E. Pratley, M.D.,[11] Sylvia E. Rosas, M.D., M.S.C.E.,[12] Peter Rossing, M.D.,[13,14] Jay S. Skyler, M.D.,[15] Katherine R. Tuttle, M.D.,[16] Robert Lawatscheck, M.D.,[17] Meike Brinker, M.D.,[18] Markus F. Scheerer, Ph.D.,[19] Julie Russell, M.Sc.,[20] Patrick Schloemer, Ph.D.,[21] and Janet B. McGill, M.D.,[22] for the FINE-ONE Investigators*



No. of Patients				
Placebo	122	122	122	106
Finerenone	120	120	120	114
Least-Squares Geometric Mean Percentage Difference vs. Placebo		21	28	14

Heerspink et al., NEJM 2026

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FINE-ONE

Subgroup	No. of Patients		Least-Squares Geometeric Mean Ratio to Baseline		Least-Squares Geometeric Mean Ratio for Finerenone vs. Placebo
	Finerenone (N=120)	Placebo (N=122)	Finerenone (N=120)	Placebo (N=122)	
Estimated GFR					
<45 ml/min/1.73 m²	32	29	0.77	1.04	0.74 (0.57–0.97)
45 to <60 ml/min/1.73 m²	32	27	0.63	0.93	0.67 (0.51–0.89)
≥60 ml/min/1.73 m²	54	59	0.63	0.77	0.82 (0.67–1.00)
Urinary ACR					
<300	29	33	0.62	0.87	0.71 (0.54–0.93)
300 to 1000	55	50	0.63	0.87	0.72 (0.58–0.89)
>1000	34	32	0.77	0.85	0.91 (0.70–1.18)
Age					
<65 yr	92	94	0.69	0.89	0.78 (0.67–0.92)
≥65 yr	26	21	0.57	0.78	0.73 (0.54–1.00)
Sex					
Female	40	36	0.69	0.93	0.74 (0.58–0.94)
Male	78	79	0.65	0.84	0.78 (0.65–0.92)
Geographic region					
North America	36	40	0.73	0.89	0.82 (0.64–1.04)
Asia	16	23	0.90	1.02	0.88 (0.63–1.23)
Europe	66	52	0.59	0.79	0.74 (0.61–0.90)
Race or ethnic group					
White	84	84	0.61	0.85	0.72 (0.61–0.85)
Black	8	5	0.71	0.83	0.86 (0.47–1.59)
Asian	23	25	0.82	0.97	0.85 (0.63–1.14)
Other	3	1	1.23	0.53	2.32 (0.69–7.78)
Serum potassium					
<4.0 mmol/liter	10	7	0.60	0.58	1.04 (0.62–1.73)
4.0 to 4.8 mmol/liter	76	82	0.68	0.88	0.78 (0.65–0.92)
>4.8 mmol/liter	32	26	0.65	0.95	0.69 (0.52–0.91)
Systolic blood pressure					
<130 mm Hg	39	42	0.77	1.03	0.75 (0.59–0.94)
≥130 mm Hg	79	73	0.62	0.79	0.78 (0.66–0.93)
Glycated hemoglobin					
≤7.5%	53	67	0.74	0.92	0.80 (0.66–0.98)
>7.5%	65	46	0.61	0.80	0.76 (0.62–0.93)

Heerspink et al., NEJM 2026

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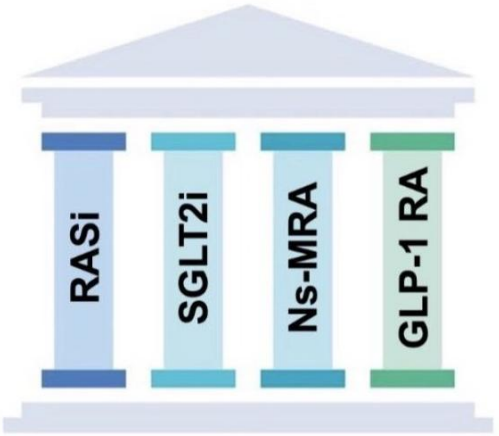
FINERENONE – BOTTOM LINE

- Target patient population: Diabetes + CKD + Albuminuria
- To be used as one of the 4 pillars of treatment for these patients along with ACEi/ARB, SGLT2i, and GLP1RA
- Well-proven benefits in regard to hard cardiovascular and kidney health outcomes
- BP effects are modest
- Hyperkalemia does occur though rates of discontinuation because of this are low



Helmeczi and Hundemer, Curr Opin Neph HTN 2025

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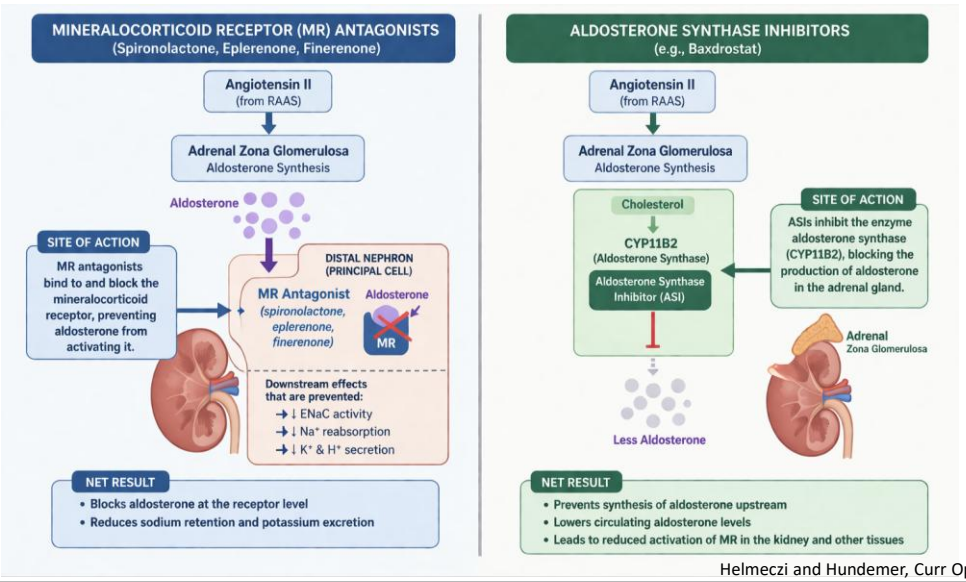
ALDOSTERONE SYNTHASE INHIBITORS



Helmeczi and Hundemer, Curr Opin Neph HTN 2025

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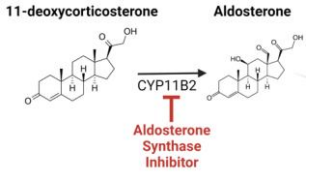
HISTORY OF ALDOSTERONE SYNTHASE INHIBITORS



- Have been developed for over a decade
- Target enzyme CYP11B2 (aldosterone synthase)
- CYP11B2 is >90% homologous with CYP11B1 (11β-hydroxylase [final step in cortisol synthesis])…this led to the failure of many 1st-generation ASIs as they inadvertently led to adrenal insufficiency
  - This has been the biggest holdup with ASI development
- However, several highly selective 2nd-generation CYP11B2 inhibitors have been developed in recent years and look highly promising for future clinical practice
  - Baxdrostat
  - Lorundrostat
  - Vicadrostat

Helmeczi and Hundemer, Curr Opin Neph HTN 2025

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BAXDROSTAT

- CYP11B2 inhibitor with >100-fold selectivity over CYP11B1 so adrenal insufficiency is unlikely
- Has been predominantly studied in uncontrolled and resistant hypertension
- However, is now also being studied for use in a number of other conditions including:
  - CKD progression (in combination with dapagliflozin)
  - Primary aldosteronism (to be discussed later today)

Helmeczi and Hundemer, Curr Opin Neph HTN 2025

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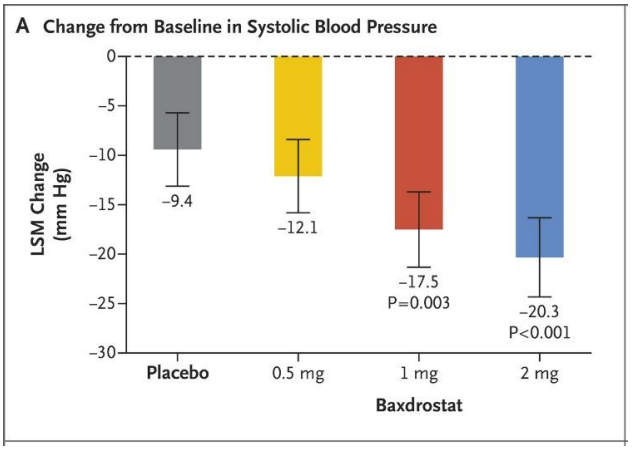
BrigHTN (Phase 2)

Phase 2 Trial of Baxdrostat for Treatment-Resistant Hypertension

Mason W. Freeman, M.D., Yuan-Di Halvorsen, Ph.D., William Marshall, M.D., Mackenzie Pater, Ph.D., Jon Isaacsohn, M.D., Catherine Pearce, D.H.Sc., Brian Murphy, M.D., M.P.H., Nicholas Alp, M.D., Ajay Srivastava, M.D., Deepak L. Bhatt, M.D., M.P.H., and Morris J. Brown, M.D., for the BrigHTN Investigators*



Freeman et al., NEJM 2023

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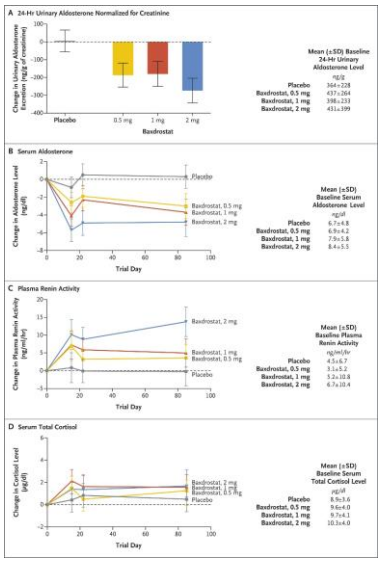
BrigHTN (Phase 2)



Freeman et al., NEJM 2023

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HALO (Phase 2, Unpublished)

Efficacy and Safety of Baxdrostat in Patients With Uncontrolled Hypertension - HALO

Principal Findings:

The primary outcome, change in mean seated SBP for baxdrostat 0.5 mg, 1 mg, 2 mg, or placebo, was: -17.0 vs. -16.0 vs. -19.8 vs. -16.6 mm Hg ($p > 0.05$).

- Placebo-corrected change in mean seated SBP for baxdrostat 0.5 mg: -0.5 mm Hg ($p = 0.83$), baxdrostat 1 mg: 0.6 mm Hg ($p = 0.79$), and baxdrostat 2 mg: -3.2 mm Hg ($p = 0.15$)

Interpretation:

The results of this phase 2 trial indicate that baxdrostat at the doses studied did not significantly reduce SBP or DBP compared with placebo among patients with uncontrolled HTN. A larger than anticipated placebo effect was noted; there was also low adherence with study medication at a few sites. Baxdrostat is an aldosterone synthase inhibitor and reduces aldosterone but not cortisol levels. In BrigHTN (also a phase 2 trial), the highest (2 mg) dose was superior to placebo in reducing BP at 12 weeks among patients with treatment-resistant HTN.

Presented by Dr. Deepak Bhatt at the 2023 ACC Scientific Session

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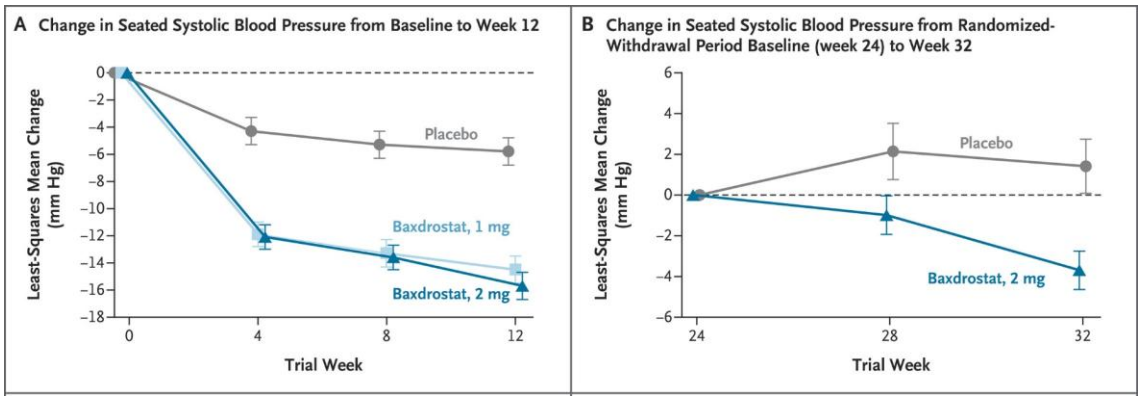
BaxHTN (Phase 3)

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*



Flack et al., NEJM 2025

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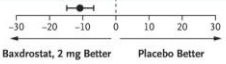
BaxHTN (Phase 3)

Subgroup	Baxdrostat, 2 mg	Placebo	Least-Squares Mean Difference in Seated Systolic Blood Pressure (95% CI)
	no. of patients		*mm Hg*
All patients	266	263	−9.8 (−12.6 to −7.0)
Age			
<65 yr	145	138	−11.4 (−15.5 to −7.4)
≥65 to <75 yr	88	91	−7.9 (−12.6 to −3.2)
≥75 yr	33	34	−7.7 (−14.0 to −1.4)
Sex			
Female	103	102	−11.6 (−16.4 to −6.7)
Male	163	161	−9.0 (−12.4 to −5.6)
Race or ethnicity			
Black	21	15	−9.5 (−21.1 to 2.1)
Asian	72	72	−8.9 (−14.1 to −3.6)
White	168	166	−9.6 (−13.1 to −6.2)
Hispanic or Latino	39	38	−12.7 (−19.8 to −5.6)
Not Hispanic or Latino	216	215	−9.1 (−12.3 to −6.0)
Geographic region			
Asia Pacific, Middle East, and Africa	80	80	−10.7 (−15.8 to −5.6)
Americas	68	74	−10.9 (−16.2 to −5.6)
Europe	118	109	−8.5 (−12.8 to −4.1)
Hypertension at baseline			
Uncontrolled	67	71	−10.1 (−15.3 to −4.9)
Resistant	199	192	−9.8 (−13.1 to −6.4)
Systolic blood pressure at baseline			
<145 mm Hg	92	92	−8.3 (−13.3 to −3.3)
≥145 mm Hg	174	171	−10.7 (−14.1 to −7.3)
eGFR at baseline			
<60 ml/min/1.73 m²	30	29	−8.4 (−17.6 to 0.8)
≥60 ml/min/1.73 m²	236	234	−10.1 (−13.0 to −7.1)
Body-mass index at baseline			
<30	126	128	−8.7 (−12.6 to −4.7)
≥30	140	135	−10.8 (−14.8 to −6.7)



Flack et al., NEJM 2025

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BaxHTN (Phase 3)

Adverse Events	Baxdrostat, 1 mg (N=264)	Baxdrostat, 2 mg (N=266)	Placebo (N=264)
Any serious adverse event — no. (%)*	5 (1.9)	9 (3.4)	7 (2.7)
Death — no. (%)	0	0	1 (0.4)
Any adverse event — no. (%)	125 (47.3)	119 (44.7)	109 (41.3)
Moderate or severe event	27 (10.2)	37 (13.9)	23 (8.7)
Severe event	3 (1.1)	7 (2.6)	5 (1.9)
Adverse event leading to discontinuation — no. (%)			
Any	7 (2.7)	12 (4.5)	5 (1.9)
Hyperkalemia	2 (0.8)	4 (1.5)	0
Adverse event of special interest — no. (%)†			
Hyperkalemia	7 (2.7)	21 (7.9)	0
Hyponatremia	2 (0.8)	6 (2.3)	1 (0.4)
Hypotension	5 (1.9)	6 (2.3)	2 (0.8)
Serum potassium — no./total no. (%)‡			
>5.5 mmol/liter	16/262 (6.1)	29/261 (11.1)	1/260 (0.4)
>6.0 mmol/liter	6/262 (2.3)	8/263 (3.0)	1/262 (0.4)
>6.5 mmol/liter	5/262 (1.9)	1/263 (0.4)	1/263 (0.4)

***Note:* No instances of adrenal insufficiency occurred.**

Flack et al., NEJM 2025

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BAXDROSTAT – BOTTOM LINE

- Highly effective in uncontrolled and resistant hypertension
  - Lower systolic BP by ~9-10 mmHg in this population relative to placebo
- Effectively lowers aldosterone levels which did not fully return to baseline even after drug discontinuation - Prolonged beneficial reset of the RAAS system?
- Hyperkalemia does occur though rates of discontinuation because of this are low
- Adrenal insufficiency did not occur in clinical trials

Helmeczi and Hundemer, Curr Opin Neph HTN 2025

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BAXDROSTAT FDA APPROVAL

Baxdrostat New Drug Application accepted under FDA Priority Review in the US for patients with hard-to-control hypertension

PUBLISHED
2 December 2025

Regulatory decision is expected in the second quarter of 2026.

https://www.astrazeneca.com/media-centre/press-releases/2025/baxdrostat-new-drug-application-accepted-under-fda-priority-review-in-the-us-for-patients-with-hard-to-control-hypertension.html

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LORUNDROSTAT

- Another highly selective CYP11B2 inhibitor which is a competitor to Baxdrostat
- Similarly, has been predominantly studied in uncontrolled hypertension
- Also being studied for use in proteinuric CKD as add-on therapy to ACEi/ARB + SGLT2i

Helmeczi and Hundemer, Curr Opin Neph HTN 2025

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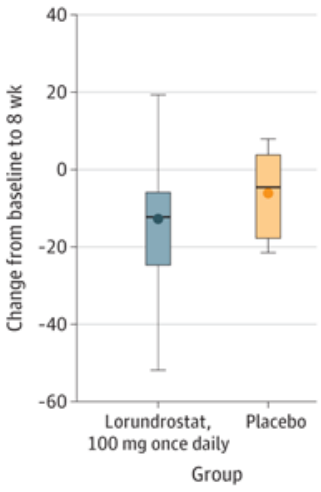
Target-HTN (Phase 2)

JAMA | Original Investigation

Aldosterone Synthase Inhibition With Lorundrostat for Uncontrolled Hypertension
The Target-HTN Randomized Clinical Trial

Luke J. Laffin, MD; David Rodman, MD; James M. Luther, MD; Anand Vaidya, MD; Matthew R. Weir, MD; Natasa Rajicic, ScD; B. T. Slingsby, MD, PhD; Steven E. Nissen, MD; for the Target-HTN Investigators

Systolic BP was reduced by ~8-10 mmHg with lorundrostat relative to placebo



Laffin et al., JAMA 2023

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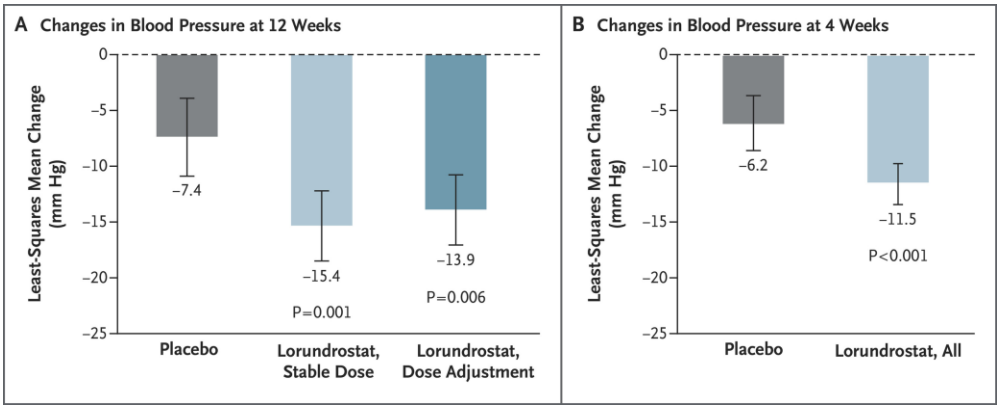
Advance-HTN (Phase 2)

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 et al., NEJM 2025

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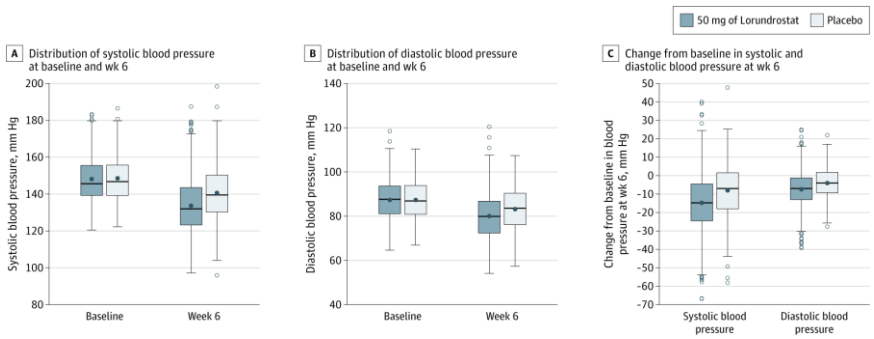
Launch-HTN (Phase 3)

JAMA | Original Investigation

Lorundrostat in Participants With Uncontrolled Hypertension and Treatment-Resistant Hypertension
The Launch-HTN Randomized Clinical Trial

Manish Saxena, MBBS; Luke Laffin, MD; Claudio Borghi, MD; Beatriz Fernandez Fernandez, MD, PhD; Jalal K. Ghali, MD; Branko Kopjar, MD, PhD; Krishna Polu, MD; Simon D. Roger, MD; B. T. Slingsby, MD, PhD; Frank Strutz, MD; Liffert Vogt, MD, PhD; Matthew R. Weir, MD; David Rodman, MD; for the Launch-HTN Investigators



Systolic BP was reduced by ~9 mmHg with lorundrostat vs. placebo

Saxena et al., JAMA 2025

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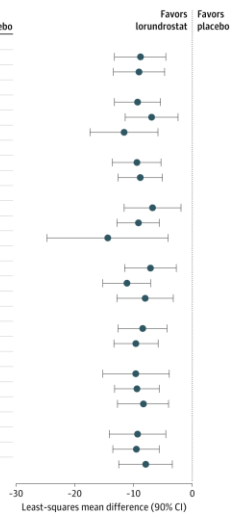
Launch-HTN (Phase 3)

Baseline characteristics	No. of participants: 50 mg of Lorundrostat[a]	Placebo
No. of antihypertensive therapies		
2	318	112
≥3	490	158
Age group, y		
<65	471	161
65-74	265	80
≥75	72	29
Sex		
Female	374	132
Male	434	138
Race		
Black or African American	223	87
White	554	175
Other[b]	31	8
Systolic blood pressure, mm Hg		
<140	218	73
140-159	445	144
≥160	145	53
Body mass index[c]		
<30	293	103
≥30	515	167
Waist-to-hip ratio		
Healthy	97	42
Obese	473	149
High risk	238	79
Estimated glomerular filtration rate, mL/min/1.73 m^2		
<60	173	49
60-89	401	150
≥90	234	71



Saxena et al., JAMA 2025

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Launch-HTN (Phase 3)

Table 3. Summary of Adverse Events

	No. (%)		
	Lorundrostat		
	50 mg and then 100 mg (n = 270)[a]	50 mg (n = 538)	Placebo (n = 270)
Died	0	0	1 (0.4)
Serious adverse event	2 (0.7)	12 (2.2)	8 (3.0)
Treatment-emergent adverse event			
Severe	6 (2.2)	9 (1.7)	8 (3.0)
Moderate	30 (11.1)	100 (18.6)	31 (11.5)
Mild	115 (42.6)	180 (33.5)	59 (21.9)
Special interest adverse event			
Severely elevated blood pressure[b]	2 (0.7)	10 (1.9)	11 (4.1)
Hypotension with symptoms	5 (1.9)	11 (2.0)	1 (0.4)
Hyperkalemia[c]	7 (2.6)	11 (2.0)	1 (0.4)
Hyponatremia[c]	28 (10.4)	37 (6.9)	9 (3.3)
Glucocorticoid deficiency[d]	0	0	3 (1.1)
Reduction in estimated glomerular filtration rate[c]	9 (3.3)	16 (3.0)	2 (0.7)

Saxena et al., JAMA 2025

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LORUNDROSTAT – BOTTOM LINE

- Highly effective in uncontrolled hypertension
  - Lower systolic BP by ~9 mmHg in this population (comparable to baxdrostat)
- Hyperkalemia does occur though rates of discontinuation because of this are low
- Adrenal insufficiency did not occur in clinical trials

Helmeczi and Hundemer, Curr Opin Neph HTN 2025

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LORUNDROSTAT FDA APPROVAL

Mineralys Therapeutics Announces FDA Acceptance of NDA for Lorundrostat for Treatment of Adults with Hypertension

Regulatory decision is expected in late 2026.

https://ir.mineralystx.com/news-events/press-releases/detail/93/mineralys-therapeutics-announces-fda-acceptance-of-nda-for

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VICADROSTAT

- Another highly selective CYP11B2 inhibitor
- Previously known as BI 690517
- Has been predominantly studies in slowing CKD progression in those with proteinuric CKD

Helmeczi and Hundemer, Curr Opin Neph HTN 2025

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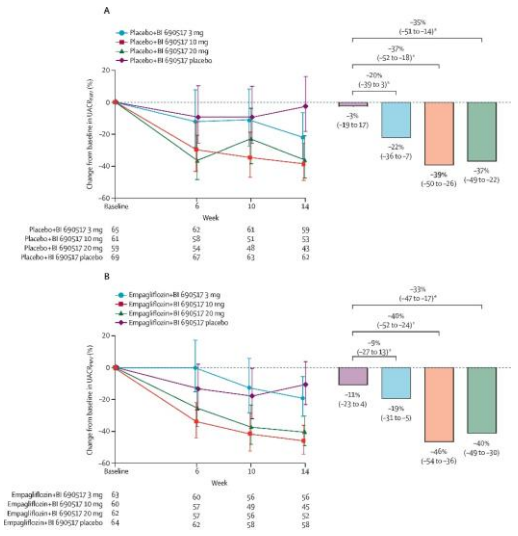
VICADROSTAT

Efficacy and safety of aldosterone synthase inhibition with and without empagliflozin for chronic kidney disease: a randomised, controlled, phase 2 trial

Katherine R Tuttle, Sibylle J Hauske*, Maria Eugenia Canziani, Maria Luiza Caramori, David Cherney, Lisa Cronin, Hiddo J L Heerspink, Christian Hugo, Masaomi Nangaku, Ricardo Correa Rotter, Arnold Silva, Shimoli V Shah, Zhichao Sun, Dorothea Urbach, Dick de Zeeuw, Peter Rossing*, on behalf of the ASi in CKD group†*



Systolic BP was reduced by ~2-6 mmHg with vicadrostat monotherapy and ~7-8 mmHg with vicadrostat/empagliflozin combination therapy vs. placebo

Tuttle et al., Lancet 2024

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VICADROSTAT

	Pooled BI 690517, placebo (N=147)	Pooled BI 690517, 3 mg (N=146)	Pooled BI 690517, 10 mg (N=144)	Pooled BI 690517, 20 mg (N=146)
Any adverse event	79 (54%)	80 (55%)	88 (61%)	91 (62%)
Any serious adverse event	10 (7%)	7 (5%)	11 (8%)	11 (8%)
Adverse event of special interest	1 (1%)	1 (1%)	4 (3%)	4 (3%)
Adrenal insufficiency	1 (1%)	1 (1%)	3 (2%)	3 (2%)
Cushing's syndrome	0	0	0	0
Ketoacidosis	0	0	1 (1%)	0
Events leading to lower limb amputation	0	0	0	1 (1%)
Other important adverse events				
Investigator-reported hyperkalaemia	9 (6%)	14 (10%)	22 (15%)	26 (18%)
Hypotension	1 (1%)	1 (1%)	4 (3%)	2 (1%)
Orthostatic hypotension	1 (1%)	0	0	0
Acute kidney injury	1 (1%)	0	2 (1%)	4 (3%)

Pooled groups include participants who received BI 690517 either as monotherapy or in combination with empagliflozin.

Table 3: **Adverse events summary**

Tuttle et al., Lancet 2024

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VICADROSTAT – BOTTOM LINE

- Highly effective in reducing albuminuria with concurrent ACEi/ARB and SGLT2i use – additive efficacy
- Favorable safety profile
- EASi-KIDNEY (Phase 3 Trial) underway
  - Aims to enroll ~11,000 CKD patients worldwide
  - CKD patients on maximally tolerated ACEi/ARB randomized to vicadrostat/empagliflozin vs. empagliflozin
  - Studying whether vicadrostat reduces CKD progression, cardiovascular death, and heart failure hospitalization

Helmeczi and Hundemer, Curr Opin Neph HTN 2025

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Role of ASIs vs. MRAs in the Future???

- Will ASIs compete with or replace MRAs?
- Cost will likely be an issue in the short-term
- Ultimately need head-to-head studies to compare
- Could we think of the dynamic of these 2 medication classes similarly to how we currently think of ACEi/ARBs in regard to being largely interchangeable? Time will tell…

$$\frac{\text{ARB}}{\text{ACEI}} \approx \frac{\text{MRA}}{\text{ASI}}$$

Helmeczi and Hundemer, Curr Opin Neph HTN 2025

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Clinical Case

A 62-year-old female with type 2 diabetes, CKD (eGFR 38 mL/min/1.73 m2), and UACR 1000 mg/g. They are prescribed maximally tolerated doses of an ACEi, CCB, thiazide, and SGLT2i. BP is 132/81 mmHg, and serum K+ is 4.8 mmol/L.

What Is the Next Best Therapy?

A. Spironolactone
B. Eplerenone
C. Finerenone
D. Aldosterone Synthase Inhibitor?