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Hypertension Management:

Risks of Uncontrolled Disease and the Role of Aldosterone

Categories of Blood Pressure in Adults[1]

	Normal	Elevated	Stage 1	Stage 2	Severe
SBP (mm Hg)	<120 *AND*	120–129 *AND*	130–139 *OR*	≥140 *OR*	>180 *OR*
DBP (mm Hg)	<80	<80	80–89	≥90	>120

HTN

The Burden of Uncontrolled Hypertension

~1 in 2 US Adults

taking ≥2 antihypertensive medications of different classes **may not be controlled**[2a]

Uncontrolled HTN Is Associated With Increased Risks[3,4]

Among patients taking **≥2 antihypertensives, uncontrolled HTN**[b] compared with controlled HTN[b] was **associated with a higher risk of**[c]**:**

ALL-CAUSE MORTALITY	MI	Stroke	ESRD
~1.3× (aHR: 1.25; 95% CI, 1.06–1.47)	~1.8× (aHR: 1.78; 95% CI, 1.48–2.12)	~2.2× (aHR: 2.17; 95% CI, 1.79–2.64)	~2.5× (aHR: 2.54; 95% CI, 1.79–3.59)

EnligHTN study in US patients[3b,d]

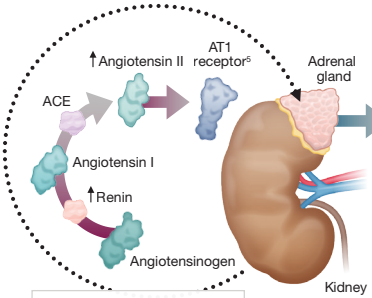
Patients with **midlife HTN** had a **higher risk of dementia**[e]

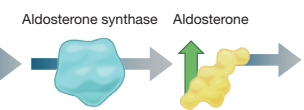
Dementia
~1.4× (aHR: 1.39; 95% CI, 1.22–1.59)

ARIC study in US patients[4f]

[a]Based on an analysis of data from the 2009–2014 US NHANES from participants aged ≥20 years who self-reported taking antihypertensive medication, had ≥1 class of antihypertensive medication identified during a pill bottle review conducted as part of the NHANES examination, and had ≥3 BP measurements obtained during their study exam (N=4158). Uncontrolled HTN was defined as BP ≥130/80 mm Hg from the 2018 AHA Scientific Statement[2]; [b]In US patients (N=41,994), controlled HTN (n=12,864; 31%) was defined as BP <130/80 mm Hg and inadequately controlled HTN (n=29,130; 69%) was defined as BP >130/80 mm Hg[3]; [c]Evaluated by multivariable Cox proportional hazards model adjusted for disease risk score. aHR >1 corresponds with a higher risk of the adverse outcome in patients with icHTN vs cHTN[3]; [d]EnligHTN is an observational, longitudinal, multinational, cohort study of over 240,000 patients with HTN that assessed clinical characteristics and real-world disease burden in patients with controlled or inadequately controlled HTN using secondary de-identified claims and EMR data of patients with HTN, including IQVIA Ambulatory EMR-US linked with IQVIA PharMetrics® Plus claims. Patient characteristics were summarized by country. Patients were included if they were ≥18 years, diagnosed with HTN between 2018 and 2023, treated with ≥2 antihypertensive medications for ≥30 days, and had ≥1 day of follow-up[3]; [e]Evaluated by Cox proportional hazards regression models and a discrete time analysis binary model with a complementary log-log link[4]; [f]ARIC (Atherosclerosis Risk in Communities) is a prospective cohort study of over 15,000 patients recruited from 1987 to 1989 that evaluated the associations between midlife vascular risk factors and 25-year incidence of dementia. Analysis dates were from April 2015 to August 2016. Participants from 4 ARIC US field communities aged 44–66 years were included. Patient demographics, vascular risk factors (obesity, smoking, diabetes, pre-HTN, HTN, and hypercholesterolemia), and APOE ε4 genotype were measured at baseline. Dementia was assessed from longitudinal cognitive evaluations (visits 2, 4, and 5), complete neuropsychological battery (visit 5), informant interviews, and computer algorithmic diagnoses generated standardized definitions of dementia.[4]

The Role of Aldosterone in Blood Pressure





2 Increased aldosterone production[5,6]

3 Water and sodium reabsorption leading to plasma volume expansion and increased BP[6-8]

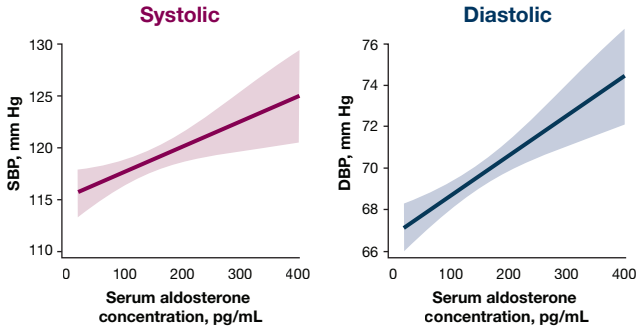
Feedback loop[6,7]
Elevations in BP and sodium lead to:
4
- Inhibition of renin release
- Decreased RAAS activation
- Reduced aldosterone production

1 Activation of RAAS in response to low Na^+, low BP, and low renal perfusion[5,6]

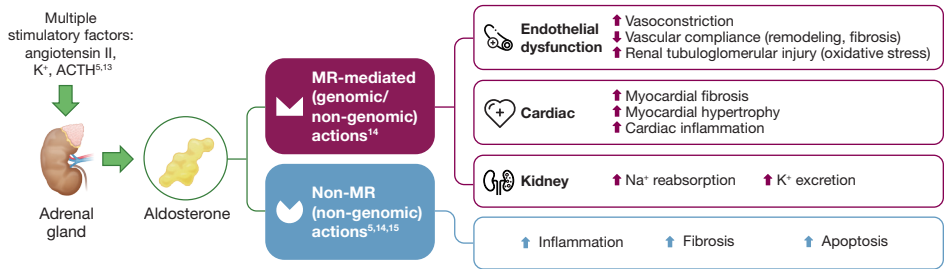
Abnormal aldosterone production, occurring despite sodium retention and volume expansion, may be a **key driver** of the pathophysiology of **HTN**[5-11]

There Is a Positive Correlation Between Aldosterone and BP[12]

Association between serum aldosterone concentrations and BP at baseline[a,b]



Aldosterone Exhibits Effects Through Multiple Pathways[5,9]



Therapies targeting only MR[16]**:**

May leave some of aldosterone's harmful effects unaddressed

Have been shown to increase aldosterone levels, which may exacerbate non–MR-mediated actions

[a]Study included 948 US adults (46–88 years of age) from the multicenter longitudinal cohort Multi-Ethnic Study of Atherosclerosis (MESA), recruited between July 2000 and August 2002, with follow-up through July 2015. Participants had measurements of serum aldosterone collected and had not taken antihypertensive medications. Results displayed represented the cohort of 700 participants who had follow-up coronary computed tomography scans[12]; [b]Adjusted for age, sex, CAC at exam 2 or 3, race, education, insurance status, income, smoking status, alcohol intake, physical activity, statin prescription, BMI, LDL, serum and urinary potassium, serum and urinary sodium, and plasma renin activity.[12]

Aldosterone May Contribute to End-Organ Damage Independent of Blood Pressure[17]

Aldosterone:

Can drive **vascular remodeling and lead to CV damage**[15,17,18]

Can impact **LV cardiac remodeling and cardiac function,** leading to CV morbidity[18-20]

May induce **fibrotic and inflammatory changes in the kidneys,** leading to damage[15,21]

Higher Aldosterone Is Associated With an Increased Risk of Mortality in Patients With CAD[22]

CV Mortality in Patients With CAD[22a]

Aldosterone quartile[b]	CV mortality HR (95% CI)[c]
1	Reference
2	1.63 (1.20–2.20)
3	1.39 (1.01–1.90)
4	1.58 (1.15–2.16)

58%

Higher risk of CV mortality in highest vs lowest quartile of aldosterone[c]

Existing Therapies Fail to Address Aldosterone Production[23-27d]

Effect on aldosterone levels

ACEis and ARBs	CCBs	Thiazide diuretics	MRAs
↓ ~3% to ~16%[23e]	↓ ~15%[24f]	↑ ~55%[23e]	↑ ~25%-120%[25,26,28,29,30,g]

Aldosterone breakthrough can occur with long-term treatment of HTN with ACEis/ARBs, with a reported incidence between 10% and 53%[27]

[a]Results depicted are from a prospective cohort study of 3153 patients undergoing coronary angiography[22]; [b]Q1: ≤48 pg/mL, Q2: 49–78 pg/mL, Q3: 79-123 pg/mL, Q4: ≥124 pg/mL[22]; [c]Results adjusted for age, sex, BMI, fibrinogen, high-sensitivity C-reactive protein, HbA1c, plasminogen-activator-inhibitor type1, current smoking, creatinine, daily physical activity, NT-proBNP, dyslipidemia, 1,25-dihydroxyvitamin D, free fatty acids, asymmetric dimethylarginine, serum sodium, serum potassium, CAD, systolic aortic pressure, and the use of ACEi, ARB, beta-blocker, calcium channel blocker, or diuretic[22]; [d]This list represents selected antihypertensive medications for educational purposes and does not represent a comprehensive treatment list; [e]Based on a randomized, open-label trial that assessed aldosterone escape in patients with mild to moderate HTN (n=63) treated for 12 weeks with antihypertensives, including an ACEi, an ARB, a diuretic, or an ACEi+ARB combination. From Week 0 to Week 12, quinapril (20 mg/day) lowered plasma aldosterone by 15.8% (7.6–6.4) and irbesartan (150 mg/day) lowered aldosterone by 2.5% (8.0–7.8), while aldosterone levels increased by 54.9% with a hydrochlorothiazide diuretic (25 mg/day; 9.1–14.1)[23]; [f]In a randomized study of patients with HTN and suspected PA (n=230) that evaluated the effects of single antihypertensive therapies prescribed for at least 2 months on ARR, amlodipine (10 mg/day) reduced PAC by 14.72% (29.2–24.9)[24]; [g]In a study of healthy volunteers who received eplerenone (100 mg/day) for 10 days, a 120% increase in serum aldosterone AUC was observed.[26] In a separate study that evaluated the effects of spironolactone (25 mg/day) on PAC in patients with resistant HTN (n=39), PAC increased by 24.67% (15.4–19.2) after 6 months of therapy.[25] Increases in aldosterone were observed within this range in other studies, including a retrospective study of patients with HTN treated with MRAs (n=146; 62% of whom were diagnosed with PA), a separate randomized controlled dose-ranging trial in Japanese patients with essential HTN (n=193), and another randomized study using the subset cohort of patients from the EPHESUS trial (n=453).[28–30]

Summary

~1 in 2 US adults taking ≥2 antihypertensive medications of different classes **may not be controlled**[2]

Abnormal aldosterone production may be a **key driver** of the pathophysiology **of hypertension** and may contribute to end-organ damage independent of BP[5-11,17]

Aldosterone exhibits effects through **multiple pathways.** Therapies targeting only MR may leave the harmful effects of aldosterone unaddressed[5,9,16]

Could directly targeting aldosterone change how you think about treating hypertension?

ACE=angiotensin-converting enzyme; ACEi=angiotensin-converting enzyme inhibitor; ACTH=adrenocorticotropic hormone; AHA=American Heart Association; aHR=adjusted hazard ratio; APOE=apolipoprotein E; ARB=angiotensin receptor blocker; ARR=aldosterone-renin ratio; AT1=angiotensin II receptor type 1; AUC=area under the curve; BMI=body-mass index; BP=blood pressure; CAC=coronary artery calcium; CAD=coronary artery disease; CCB=calcium channel blocker; cHTN=controlled hypertension; CI=confidence interval; CV=cardiovascular; DBP=diastolic blood pressure; EMR=electronic medical record; EPHESUS=Eplerenone Post–Acute Myocardial Infarction Heart Failure Efficacy and Survival Study; ESRD=end-stage renal disease; HbA1c=glycated hemoglobin; HR=hazard ratio; HTN=hypertension; icHTN=inadequately controlled hypertension; K^+=potassium; LDL=low-density lipoprotein; LV=left ventricular; MI=myocardial infarction; MR=mineralocorticoid receptor; MRA=mineralocorticoid receptor antagonist; Na^+=sodium; NHANES=National Health and Nutrition Examination Survey; NT-proBNP=N-terminal pro–B-type natriuretic peptide; PA=primary aldosteronism; PAC=plasma aldosterone concentration; Q=quartile; RAAS=renin–angiotensin–aldosterone system; SBP=systolic blood pressure.

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References:

1. Jones DW, et al. *J Am Coll Cardiol*. 2025;86(18):1567-1678; 2. Carey RM, et al. *Hypertension*. 2019;73(2)(incl. Suppl):424-431; 3. McCormack T, et al. Poster presented at: European Society of Cardiology (ESC) Congress; August 29–September 1, 2025; Madrid, Spain; 4. Gottesman RF, et al. *JAMA Neurol*. 2017;74(10):1246-1254; 5. Crompton M, et al. *Biomolecules*. 2023;13(6):1004; 6. Scott JH, et al. Physiology, aldosterone. In: *StatPearls*. [Internet] Treasure Island (FL): StatPearls Publishing; Updated May 1, 2023. Accessed May 6, 2026. https://www.ncbi.nlm.nih.gov/books/NBK470339; 7. Papadopoulou-Marketou N, et al. Hyperaldosteronism. In: *Endotext* [Internet]. South Dartmouth (MA): MDText.com, Inc. Updated February 16, 2026. Accessed May 6, 2026. https://www.ncbi.nlm.nih.gov/books/NBK279065; 8. Triebel H, et al. *Pflugers Arch*. 2024;476(5):705-713; 9. Hargovan M, Ferro A. *JRSM Cardiovasc Dis*. 2014;3:2048004014522440; 10. Brown JM, et al. *Ann Intern Med*. 2020;173(1):10-20; 11. Yuan YE, et al. *J Clin Endocrinol Metab*. 2024;109(2):e773-e779; 12. Inoue K, et al. *Hypertension*. 2020;76(1):113-120; 13. Kritis AA, et al. *J Physiol Pharmacol*. 2016;67(1):21-30; 14. Fioretti F, et al. *J Am Coll Cardiol*. 2025;86(5):354-373; 15. Muñoz-Durango N, et al. *Int J Mol Sci*. 2016;17(7):797; 16. Mazzieri A, et al. *Kidney Blood Press Res*. 2024;49(1):1041-1056; 17. Verhovez A, et al. *Curr Signal Transduct Ther*. 2012;7(2):132-141; 18. Buffolo F, et al. *Hypertension*. 2022;79(9):1899-1911; 19. Monzo L, et al. *Eur J Heart Fail*. 2023;25(10):1742-1752; 20. Varadarajan V, et al. *Am J Hypertens*. 2023;36(9):517-523; 21. Brem AS, et al. *Am J Kidney Dis*. 2011;58(3):471-479; 22. Tomaschitz A, et al. *Eur Heart J*. 2010;31(10):1237-1247; 23. Ubaid-Girioli S, et al. *J Clin Hypertens (Greenwich)*. 2007;9(10):770-774; 24. Mulatero P, et al. *Hypertension*. 2002;40(6):897-902; 25. Ubaid-Girioli S, et al. *J Clin Hypertens (Greenwich)*. 2009;11(5):245-252; 26. Eudy RJ, et al. *J Transl Med*. 2011;9:180; 27. Bomback AS, et al. *Nat Clin Pract Nephrol*. 2007;3(9):486-492; 28. Tezuka Y, et al. *Endocr Pract*. 2020;26(12):1416-1424; 29. Saruta T, et al. *J Clin Hypertens (Greenwich)*. 2004;6(4):175-185; 30. Kobayashi M, et al. *JACC Heart Fail*. 2025;13(8):102479.