



Aldosterone Dysregulation in Essential Hypertension

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Aldosterone dysregulation is an important contributor to suboptimal blood pressure control in essential hypertension. A retrospective study was conducted using electronic health record data from Baylor Scott and White Health. Adults ≥ 18 years with essential hypertension who underwent at least 1 measurement of serum aldosterone and plasma renin between January 1, 2022 and October 31, 2024 were included. Aldosterone dysregulation was defined as aldosterone-to-renin ratio (ARR) >10 using plasma renin activity (PRA) or $ARR > 1$ using plasma renin concentration (PRC). Primary outcomes included uncontrolled hypertension (systolic blood pressure [SBP] ≥ 130 mmHg) and stage 2 hypertension (SBP ≥ 140 mmHg) based on office SBP obtained closest to and within 1 year following aldosterone measurement. Multivariable logistic regression models were adjusted for diabetes, encounter type, serum potassium, and aldosterone assay type. Among the 9,129 patients (age 58.7 [15.7] years; women 4,720 [51.7%]), aldosterone dysregulation was present in 39.4% patients, and was more prevalent among those with uncontrolled versus controlled hypertension (41.5% vs 31.9%, respectively). Aldosterone dysregulation was associated with uncontrolled hypertension (odds ratio [OR] 1.40, 95% confidence interval [CI] 1.26 to 1.56) and stage 2 hypertension (OR 1.38; 95% CI 1.26 to 1.50) in adjusted analysis. Aldosterone dysregulation was more common in those receiving multiple antihypertensives (44.2% on ≥ 4 agents, 40.8% on 3, 36.4% on 2, and 33.9% on 1). In conclusion, aldosterone dysregulation is common in patients with essential hypertension and is associated with suboptimal blood pressure control. Currently available treatments may not fully address aldosterone dysregulation.

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Hypertension remains a leading cause of preventable cardiovascular and kidney morbidity and mortality, accounting for more than 10 million cardiovascular deaths worldwide.¹ Nearly half of adults in the United States have hypertension and the majority of them remain uncontrolled, despite the availability of multiple antihypertensive medications.^{2,3} Aldosterone acts on the distal nephron to promote sodium retention and potassium excretion, contributing to blood volume expansion and elevated arterial pressure. Moreover, aldosterone acting via the mineralocorticoid receptors mediate adverse effects related to inflammation and fibrosis leading to multiple organ system dysfunction.⁴ Persistent hypertension can cause remodeling of resistance arteries and left ventricular hypertrophy (LVH), and is associated with adverse cardiovascular outcomes.⁵ In addition, aldosterone promotes myocardial fibrosis and LVH through mineralocorticoid receptor-mediated pathways. Aldosterone dysregulation exists as a continuum or spectrum from normotensives with inappropriate

aldosterone production all the way to primary aldosteronism. Aldosterone dysregulation is characterized by excess aldosterone production relative to renin levels and is increasingly recognized as a key biological factor in the pathophysiology of hypertension.^{6–8} The role of aldosterone dysregulation as an underlying driver of essential hypertension remains incompletely characterized in real-world settings. Herein, we aim to investigate the association between aldosterone dysregulation and uncontrolled hypertension in a large cohort of adults with essential hypertension in a real-world clinical setting.

Methods

Study population

A retrospective real-world cohort study (the Breakthrough Hypertension study) using electronic health record data from the Baylor Scott & White Health, a large integrated healthcare system in Texas with a diverse patient population and over 10 million patient encounters annually, was conducted. Eligible patients included adults

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age 18 years or older diagnosed with essential hypertension who underwent at least 1 laboratory assessment of aldosterone and renin levels between January 1, 2022, and October 31, 2024.

As part of a quality improvement initiative targeting resistant hypertension, best practice advisory alerts were sent to clinicians for patients with outpatient encounters who had a recorded blood pressure >140/90 mm Hg averaged over 3 consecutive encounters and were on at least 3 antihypertensive medications or had a recorded blood pressure >140/90 mm Hg averaged over 3 consecutive encounters and a serum potassium concentration of less than 3.5 mmol/dl on 2 or more occasions in the past year. Testing of serum aldosterone levels was, however, not limited to these clinical scenarios and clinicians could choose to order testing in patients who did not meet these criteria as well. All patients who underwent aldosterone and renin-based testing during the study period were included in the analytic cohort. Patients with diagnoses of adrenal adenomas or primary aldosteronism were excluded. Data on demographics, comorbidities, and medications were extracted from at least 1 year before the index aldosterone test, and laboratory parameters within 1 year before or after the index aldosterone test. The Institutional Review Board approved the study.

Laboratory assessment

Serum aldosterone measurements were obtained from 2 laboratory facilities, including the Baylor Scott & White Health Central Texas in house laboratory that utilizes immunoassay-based measurements and the Quest Diagnostics in North Texas that used liquid chromatography tandem mass spectrometry (LC-MS/MS). Comparing aldosterone measurements obtained from the 2 assay types, no significant differences were noted and results from both were combined for the analyses (Supplemental Figure 1). To account for variability in analysis, assay type was adjusted for in multivariable logistic regression models. Plasma renin levels were measured on the day of serum aldosterone measurement as either plasma renin activity (PRA) or plasma renin concentration (PRC).

Definition of aldosterone dysregulation

Since aldosterone dysregulation is a biological risk factor for hypertension that exists as a continuum or spectrum instead of a binary state, thresholds or cut-offs are somewhat arbitrary and contextual. For operational definition of aldosterone dysregulation, published literature was used to determine thresholds. Primary definition of aldosterone dysregulation was an elevated aldosterone-to-renin ratio (ARR) and was defined as $ARR \geq 10$ when PRA (ng/dL per ng/mL/h) or $ARR \geq 1$ when PRC (ng/dL per mU/L) was used.^{9,10} Secondary definitions for aldosterone dysregulation used for sensitivity analyses included (1) elevated aldosterone concentration (≥ 10 ng/dL) with $PRC \leq 10$ mU/L or elevated aldosterone concentration (≥ 10 ng/dL) with $PRA \leq 1$ ng/mL/h, and (2) the presence of any of the following: aldosterone ≥ 10 ng/dL, $PRA \leq 1$ ng/mL/h, or $PRC \leq 10$ mU/L.^{11–13}

Data collection and outcomes

Primary outcomes included the proportion of patients with uncontrolled hypertension, defined as systolic blood pressure (SBP) ≥ 130 mmHg and stage 2 hypertension, defined as SBP ≥ 140 mmHg. Outpatient office SBP readings obtained during routine clinic encounters closest to and within 1 year following aldosterone measurement were used for classification. Patients were also classified by the number of prescribed antihypertensive

drugs as monotherapy, dual therapy, or multidrug (≥ 3 classes). Multiple comorbidities including heart failure, myocardial infarction, stroke, type 2 diabetes, and obstructive sleep apnea were identified using ICD-10-CM diagnosis codes documented before or on the date of aldosterone measurement. Hypokalemia was defined as serum potassium in the bottom quartile of measurements (< 3.7 mEq/L). Cohort-specific lower quartile threshold was used to capture relative potassium suppression associated with aldosterone dysregulation. Patients were diagnosed with CKD when they had at least 2 eGFR measurements < 60 mL/min/1.73 m² within a 90-day window without an eGFR ≥ 60 mL/min/1.73 m² in between. Body mass index (BMI) was categorized into < 25 kg/m², 25 to 29.9 kg/m², 30 to 34.9 kg/m², and ≥ 35 kg/m². Patient residence zip codes were linked to the United States Department of Agriculture's Rural-Urban Commuting Area (RUCA) code classification scheme and were classified into urban (RUCA 1 to 3) or rural (RUCA 4 to 10). The primary insurance on file was classified into private, government, or self-pay.

Statistical analysis

Descriptive statistics were performed to compare baseline characteristics between patients with and without aldosterone dysregulation. Frequencies with percentages for categorical variables and means with standard deviations for continuous variables were calculated. χ^2 test or Fisher's exact test for categorical and Student's t-test for continuous variables were used to assess between-group comparisons. Multivariable logistic regression was used to evaluate the association between aldosterone dysregulation and uncontrolled and stage 2 hypertension. All models were adjusted for laboratory assay type (immunoassay vs LC-MS/MS), type-2 diabetes, serum potassium level, and encounter type (inpatient vs outpatients) at assay completion. Prespecified subgroup analyses included patients with suppressed renin ($PRA \leq 1$ or $PRC \leq 10$), baseline cardiovascular disease (heart failure, myocardial infarction, cerebrovascular disease, stroke, peripheral artery disease, coronary artery disease, or angina), and stratification by hypertension control status into controlled hypertension (SBP < 130 mmHg), uncontrolled HTN (SBP ≥ 130 mmHg), hard-to-control hypertension (SBP ≥ 130 mmHg on ≥ 2 classes), and resistant hypertension (SBP ≥ 130 mmHg on ≥ 3 classes). Odds ratios with 95% confidence intervals (CIs) were reported for all analyses. Two-tailed P values were used. All analyses were conducted using SAS software (v9.4).

Results

Study population

Between January 1, 2022, and October 31, 2024, a total of 10,892 patients were identified who had serum aldosterone measured. Of these, 42 had only urine aldosterone measurements and were excluded. Of the remaining, 5,283 patients had serum aldosterone measured by immunoassay and 5,567 by LC-MS/MS. After removing patients with primary aldosteronism (N = 173) or adrenal adenoma (N = 592) and without diagnosed hypertension (N = 956), a final cohort of 9,129 patients (4,555 from immunoassay and 4,574 from LC-MS/MS) were included in the analysis (Figure 1).

Baseline characteristics

The mean age of the patients was 58.7 ± 15.7 years, and 51.7% were women. The mean SBP was 144.7 (20.5). Overall, 62.1% had blood pressure measured on the day of aldosterone testing; 24.2% had measurement before and 13.7% after the day of testing. About 87.2% of SBP readings were performed within ± 7 days of aldosterone

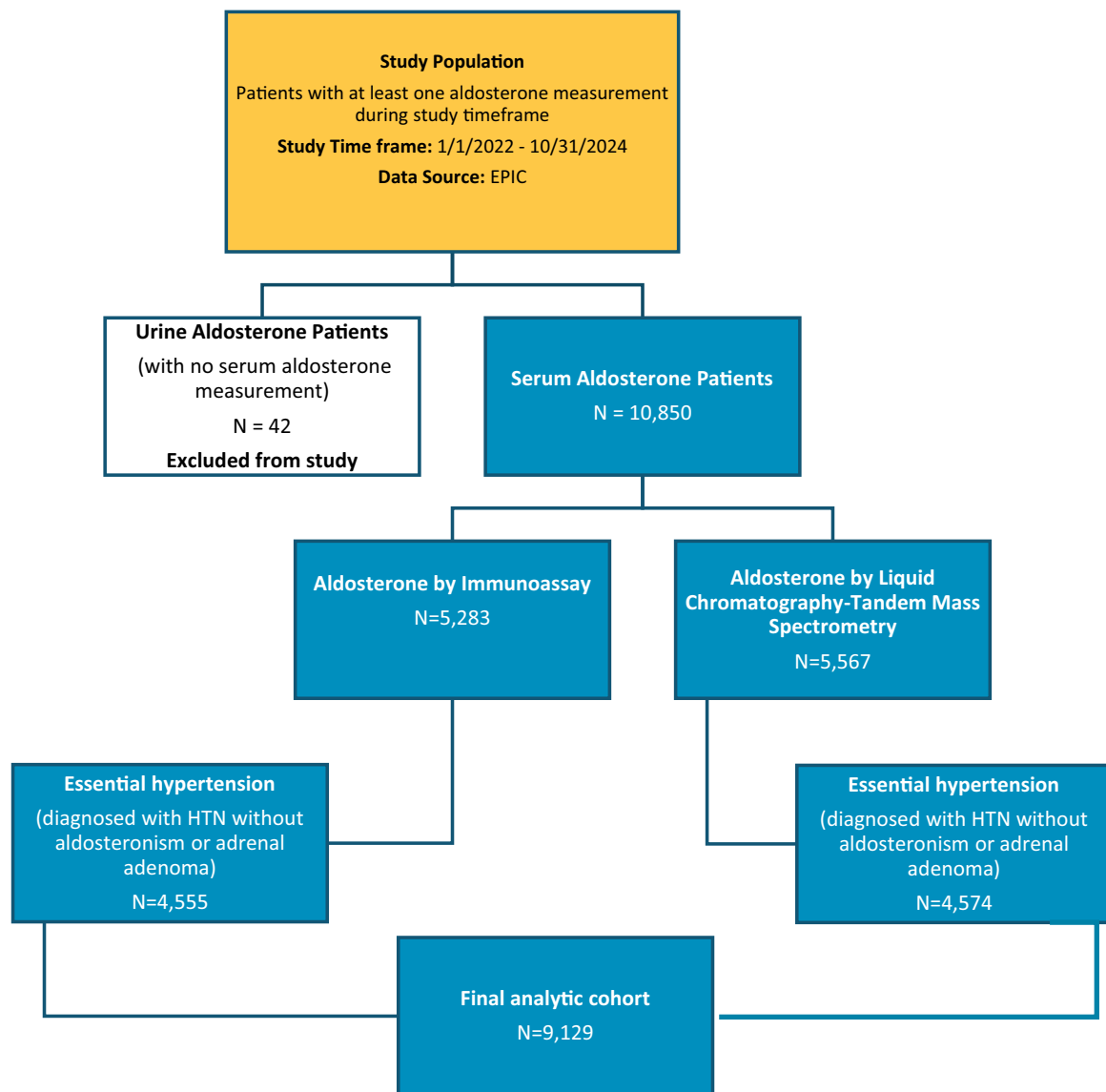


Figure 1. CONSORT flowchart. HTN = hypertension; LC-MS/MS = liquid chromatography–tandem mass spectrometry.

testing (62.1% on the same day). Overall, 1,960 (21.5%) of patients had controlled hypertension, 7,169 (78.5%) had uncontrolled hypertension, and 5,572 (61.0%) had resistant hypertension. The mean BMI of patients was 32.6 (7.9). Common comorbidities included cerebrovascular disease (n = 1,875; 20.5%), obstructive sleep apnea (n = 2,484; 27.2%), hypokalemia (n = 1,892; 21.1%), chronic kidney disease (n = 1,152; 12.6%), obesity (n = 5,339; 58.7%) and type 2 diabetes mellitus (n = 2,713; 29.7%). Overall, 72.8% of serum potassium levels were measured on the day of aldosterone measurement, 18.9% had potassium levels measured before and 8.2% after the date of aldosterone measurement.

Aldosterone dysregulation

A total of 3,601 (39.4%) patients met criteria for aldosterone dysregulation. Patients with aldosterone dysregulation were older (61.3 [50.1, 71.8] vs 59.2 [45.5, 70.2]), more often women (57.0% vs 48.3%), and Black (32.8% vs 21.4%); all $p < 0.01$. Inpatient index encounter was more common in the normal aldosterone regulation group (17.0% vs 11.0%; $p < 0.01$). Hypokalemia (23.4% vs 19.0%), obstructive sleep apnea (29.0% vs 26.1%), and history of stroke (14.7% vs 11.8%)

were more common in aldosterone dysregulation group (all $p < 0.05$). Beta-blockers (73.5% vs 59.9%), calcium channel blockers (83.3% vs 76.3%), and mineralocorticoid receptor antagonists (MRA; 26.8% vs 24.6%) were more frequently prescribed in the aldosterone dysregulation group (all $p < 0.05$). Baseline clinical and laboratory characteristics are summarized in [Tables 1 and 2](#).

Aldosterone dysregulation, hypertension, and number of medications

Aldosterone dysregulation was present in 31.9% of patients with controlled hypertension and 41.5% of patients with uncontrolled hypertension. Aldosterone dysregulation was associated with a higher likelihood of uncontrolled hypertension (OR 1.40; 95% CI: 1.26 to 1.56) and stage 2 hypertension (OR 1.38; 95% CI: 1.26 to 1.50). These results were consistent across subgroup based on age, sex, race, and serum potassium status and were consistent when patients with reported hypotension were excluded. When using secondary definitions of aldosterone dysregulation, the overall occurrence was lower but followed a similar trend ([Table 3 and Figure 2](#)).

Table 1
Baseline clinical characteristics

Characteristic	Overall	Aldosterone dysregulation		p-value
	N = 9,129	Yes (N = 3,601)	No (N = 5,528)	
Age, mean (SD)	58.73 (15.71)	60.51 (14.62)	57.56 (16.28)	<0.01
Female, n (%)	4721 (51.7%)	2051 (57.0%)	2670 (48.3%)	<0.01
Race/Ethnicity, n (%)				
Asian, non-Hispanic	303 (3.3%)	122 (3.4%)	181 (3.3%)	<0.01
Black	2363 (25.9%)	1182 (32.8%)	1181 (21.4%)	
Hispanic	1145 (12.5%)	395 (11.0%)	750 (13.6%)	
White	4895 (53.6%)	1759 (48.9%)	3136 (56.7%)	
Other Race	134 (1.5%)	54 (1.5%)	80 (1.5%)	
Unknown	289 (3.2%)	89 (2.5%)	200 (3.6%)	
Area codes, n (%)				
Rural	1043 (11.4%)	454 (12.6%)	589 (10.7%)	<0.01
Urban	8072 (88.4%)	3146 (87.4%)	4926 (89.1%)	
Unknown	14 (0.2%)	1 (0.1%)	13 (0.2%)	
Insurance, n (%)				
Government	3813 (41.8%)	1618 (44.9%)	2195 (39.7%)	<0.01
Private	4779 (52.4%)	1817 (50.5%)	2962 (53.6%)	
Self-pay	5 (0.1%)	1 (0.1%)	4 (0.1%)	
Unknown	532 (5.8%)	165 (4.6%)	367 (6.6%)	
Smoking status, n (%)				
Current	948 (10.4%)	396 (11.0%)	552 (10.0%)	<0.01
Former	2168 (23.8%)	807 (22.4%)	1361 (24.6%)	
Never	5594 (61.3%)	2263 (62.8%)	3331 (60.3%)	
Passive	4 (0.1%)	1 (0.1%)	3 (0.1%)	
Unknown	415 (4.6%)	134 (3.7%)	281 (5.1%)	
Systolic blood pressure, mmHg, mean (SD)	144.65 (20.46)	147.71 (20.72)	142.66 (20.04)	<0.01
Body mass index, n (%)				
Mean (SD)	32.60 (7.92)	32.53 (7.85)	32.64 (7.97)	0.51
Underweight (<25 kg/m ²)	76 (0.8%)	29 (0.81%)	47 (0.85%)	
Healthy (25–29.9 kg/m ²)	1270 (14.0%)	523 (14.56%)	747 (13.58%)	
Overweight (30–34.9 kg/m ²)	2407 (26.5%)	930 (25.90%)	1477 (26.85%)	
Obese (≥35 kg/m ²)	5339 (58.7%)	2109 (58.73%)	3230 (58.72%)	
Index encounter, n (%)				
Inpatient encounter	1336 (14.6%)	395 (11.0%)	941 (17.0%)	<0.01
Outpatient encounter	7793 (85.4%)	3206 (89.0%)	4587 (83.0%)	
Comorbidities, n (%)				
Angina	561 (6.2%)	237 (6.6%)	324 (5.9%)	0.16
Coronary artery disease	1951 (21.4%)	778 (21.6%)	1173 (21.2%)	0.66
Chronic kidney disease	1152 (12.6%)	485 (13.5%)	667 (12.1%)	0.05
Cerebrovascular disease	1875 (20.5%)	815 (22.6%)	1060 (19.2%)	<0.01
Heart failure	1323 (14.5%)	546 (15.2%)	777 (14.1%)	0.14
Hypokalemia	1892 (21.1%)	841 (23.4%)	1051 (19.0%)	<0.01
Myocardial infarction	613 (6.7%)	242 (6.7%)	371 (6.7%)	0.99
Nonalcoholic fatty liver disease	954 (10.5%)	341 (9.5%)	613 (11.1%)	0.01
Nonalcoholic steatohepatitis	81 (0.9%)	28 (0.8%)	53 (1.0%)	0.37
Obstructive sleep apnea	2484 (27.2%)	1044 (29.0%)	1440 (26.1%)	<0.01
Peripheral arterial disease	784 (8.6%)	285 (7.9%)	499 (9.0%)	0.06
Stroke	1178 (12.9%)	528 (14.7%)	650 (11.8%)	<0.01
Type 2 diabetes	2713 (29.7%)	1094 (30.4%)	1619 (29.3%)	0.26
Medications, n (%)				
Beta Blocker	5961 (65.3%)	2648 (73.5%)	3313 (59.9%)	<.01
Calcium Channel Blocker	7215 (79.0%)	3000 (83.3%)	4215 (76.3%)	<.01
Glucagon-like peptide-1 receptor agonist	1883 (20.6%)	727 (20.2%)	1156 (20.9%)	0.40
Lipid lowering	5089 (55.8%)	2059 (57.2%)	3030 (54.8%)	0.03
Loop Diuretics	1755 (19.2%)	716 (19.9%)	1039 (18.8%)	0.20
Renin-angiotensin system inhibitor	7716 (84.5%)	2991 (83.1%)	4725 (85.5%)	<0.01
Sodium-glucose co-transporter 2 inhibitor	769 (8.4%)	289 (8.0%)	480 (8.7%)	0.27
Other antihypertensives	4635 (50.8%)	1869 (51.9%)	2766 (50.0%)	0.08
Mineralocorticoid receptor antagonist	2324 (25.5%)	964 (26.8%)	1360 (24.6%)	0.02
Thiazide	5608 (61.4%)	2248 (62.4%)	3360 (60.8%)	0.11

In patients with uncontrolled hypertension, aldosterone dysregulation was more common among those receiving a greater number of antihypertensive drugs (44.2% in those on ≥4, 40.8% on 3, 36.4% on 2, and 33.9% on 1 antihypertensive medication). Distribution in those with controlled hypertension was more equally divided (34% on ≥4, 29.8% on 3, 30.5% on 2, and 29.1% on 1 antihypertensive medication) (Table 4). Additionally, aldosterone dysregulation was present in 42.4% of patients with hard-to-control hypertension (SBP ≥ 130 mmHg on ≥2 classes), 43.4% of patients with resistant hypertension

(SBP ≥ 130 mmHg on ≥3 classes), and 32.5% for patients with controlled HTN on ≥2 anti-HTN classes (Figure 3). Additional results are provided in Supplemental Figure 2.

Discussion

In this large cohort study utilizing real-world data on patients with essential hypertension, we report several key findings. Aldosterone dysregulation was common and existed across a spectrum of

Table 2
Baseline laboratory characteristics

Laboratory test within ± 1 year	Overall N = 9,129	Aldosterone dysregulation		
		Yes (N = 3,601)	No (N = 5,528)	p-value
A1c, % (N = 6,190)	5.8 (5.4, 6.6)	5.8 (5.4, 6.6)	5.8 (5.3, 6.6)	0.31
Albumin, g/dL (N = 8,773)	4.3 (4, 4.5)	4.2 (3.9, 4.4)	4.3 (4, 4.6)	<0.01
BNP, pg/mL (N = 1,883)	79 (26, 231)	78 (28, 222)	80 (25, 253)	0.99
CRP, mg/L (N = 1,480)	5.8 (2, 20.4)	4.8 (2, 14.3)	6 (2, 24)	<0.01
eGFR, mL/min/1.73 m ² (N = 8,983)	80.9 (63, 96)	79.6 (62.9, 93.3)	82.2 (63, 97.8)	<0.01
ESR, mm/hr (N = 1273)	20 (10, 40)	21 (10, 40)	20 (9, 41)	0.74
NT-proBNP, pg/mL (N = 912)	415.5 (120.5, 1530.5)	371 (121, 998)	440 (120, 1782)	0.05
Potassium, mEq/L (N = 8,955)	4.1 (3.7, 4.4)	4 (3.7, 4.3)	4.1 (3.8, 4.4)	<0.01
Potassium < 4 mEq/L [N (%)]	3656 (40.83%)	1612 (45.40%)	2044 (37.82%)	
Potassium < 3.5 mEq/L [N (%)]	1052 (11.75%)	449 (12.64%)	603 (11.16%)	
Sodium, mEq/L (N = 8,953)	139 (137, 141)	140 (138, 141)	139 (137, 141)	<0.01
Serum Creatinine, mg/dL (N = 8,983)	0.9 (0.8, 1.2)	0.9 (0.8, 1.2)	1 (0.8, 1.2)	0.03

BNP = B-type natriuretic peptide; CRP = C-reactive protein; eGFR = estimated glomerular filtration Rate; ESR = erythrocyte sedimentation rate; NT-proBNP = N-terminal pro B-type natriuretic peptide.

blood pressure control, in terms of both the number of baseline medications (ranging from 0 to ≥ 4) and blood pressure values (SBP < 130, SBP ≥ 130 , and SBP ≥ 140). Aldosterone dysregulation was independently associated with uncontrolled (SBP ≥ 130 mmHg) and stage 2 (SBP ≥ 140 mmHg) hypertension. These findings highlight the clinical relevance of aldosterone dysregulation in patients with hypertension and underscore the need to address aldosterone signaling in this population.

Among the 9,129 patients with essential hypertension included in our study, 39.4% met the criteria for aldosterone dysregulation by the primary definition. Notably, this was observed across the spectrum of blood pressure control in both patients with controlled and uncontrolled hypertension at rates of 32% and 42%, respectively. This finding challenges the notion that aldosterone dysregulation is confined only to those with overt or resistant hypertension and suggests that aldosterone dysregulation exists along a continuum and may be present even in individuals who appear well-controlled on antihypertensive therapy.⁷ The occurrence of aldosterone dysregulation increased

in parallel with treatment burden, such that among patients with uncontrolled hypertension, it rose from 30% in those not receiving antihypertensives to 44% in those on ≥ 4 medications. In addition, the occurrence of aldosterone dysregulation was the same in patients with hard-to-control hypertension in 2 or more classes (42%) and resistant hypertension (43%). This parity in proportion is compelling as it signals that patients may experience adverse biological effects of aldosterone dysregulation well before they reach the status of resistant hypertension. Waiting for resistant hypertension to develop as a clinical trigger for treatment intensification may miss a substantial opportunity for earlier intervention. This finding also indicates that aldosterone dysregulation may eventually contribute to treatment resistance and acts as a barrier to achieving targeted blood pressure goals in a broader population of patients with essential hypertension.^{14,15}

Notably, obstructive sleep apnea was more common among patients with aldosterone dysregulation than hypokalemia (29% vs 23%). Prior studies have demonstrated a robust association between

Table 3
Association between aldosterone dysregulation and hypertension

Aldosterone dysregulation	N (%)	OR (95% CI)	aOR (95% CI)*	p-value
Uncontrolled hypertension				
ARR (PRA) ≥ 10 or ARR (PRC) ≥ 1 (main result)				<0.01
Yes	3601 (39.4%)	1.52 (1.36, 1.69)	1.40 (1.26, 1.56)	
No	5528 (60.6%)	ref		
(Aldosterone ≥ 10 and PRA ≤ 1) or (Aldosterone ≥ 10 and PRC ≤ 10)				<0.01
Yes	1670 (18.3%)	1.57 (1.36, 1.81)	1.39 (1.20, 1.61)	
No	7459 (81.7%)	ref		
Aldosterone ≥ 10 or PRA ≤ 1 or PRC ≤ 10				<0.01
Yes	6326 (69.3%)	1.32 (1.19, 1.47)	1.23 (1.10, 1.37)	
No	2803 (30.7%)	ref		
Stage 2 hypertension				
ARR (PRA) ≥ 10 or ARR (PRC) ≥ 1 (main result)				<0.01
Yes	3601 (39.4%)	1.52 (1.36, 1.69)	1.38 (1.26, 1.50)	
No	5528 (60.6%)	ref		
(Aldosterone ≥ 10 and PRA ≤ 1) or (Aldosterone ≥ 10 and PRC ≤ 10)				<0.01
Yes	1670 (18.3%)	1.56 (1.35, 1.80)	1.34 (1.20, 1.50)	
No	7459 (81.7%)	ref		
Aldosterone ≥ 10 or PRA ≤ 1 or PRC ≤ 10				<0.01
Yes	6326 (69.3%)	1.33 (1.20, 1.48)	1.26 (1.15, 1.39)	
No	2803 (30.7%)	ref		

aOR = adjusted odds ratio; ARR = Aldosterone-to-Renin Ratio; CI = confidence interval; OR = odds ratio; PRA = plasma renin activity; PRC = plasma renin concentration; ref = reference category. Aldosterone > 10 = Serum aldosterone level > 10 ng/dL; PRA < 1 = Plasma renin activity < 1 ng/mL/h; PRC < 10 = Plasma renin concentration < 10 mU/L; ARR (PRA) > 10 = Ratio of aldosterone to PRA greater than 10; ARR (PRC) > 1 = Ratio of aldosterone to PRC greater than 1.

* models were adjusted for laboratory assay type (immunoassay vs LC-MS/MS), type-2 diabetes, serum potassium level, and encounter type (inpatient vs outpatients).

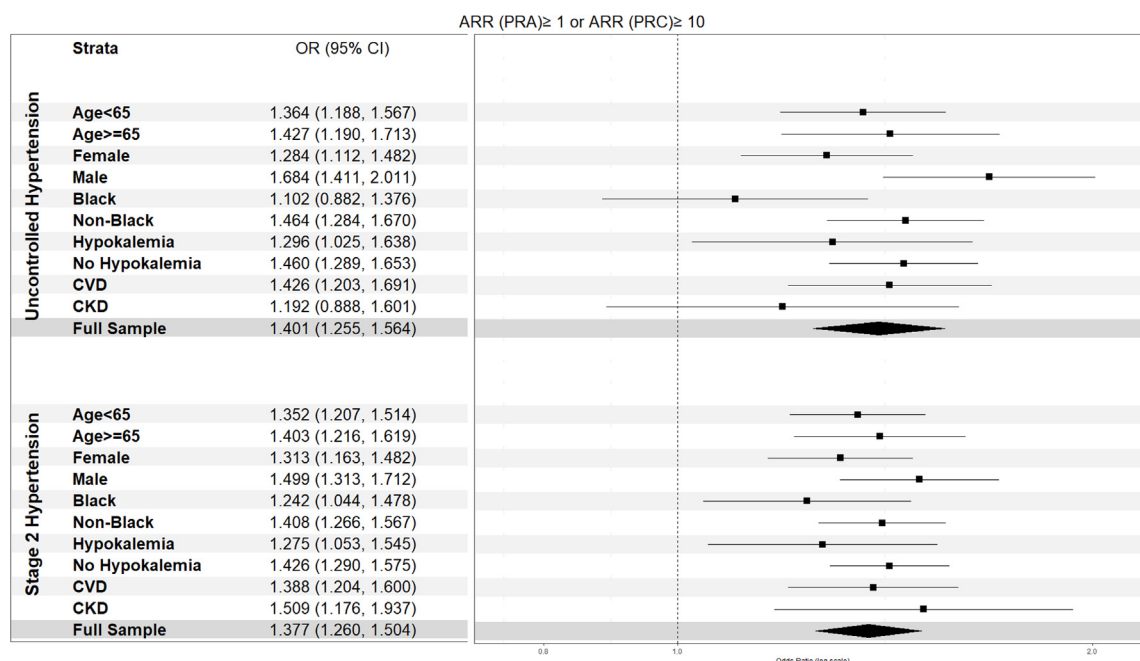


Figure 2. Forrest plot of association between aldosterone dysregulation and hypertension across subgroups. Odds ratios (ORs) with 95% confidence intervals (CIs) for the association between aldosterone dysregulation and uncontrolled or stage 2 hypertension across subgroups, Black squares represent point estimates, horizontal lines indicate 95% CIs, and diamonds indicate pooled estimates. ARR = aldosterone-to-renin ratio; CI = confidence interval; CKD = chronic kidney disease; CVD = cardiovascular disease; OR = odds ratio; PRA = plasma renin activity; PRC = plasma renin concentration.

aldosterone excess and obstructive sleep apnea, potentially mediated through sodium and fluid retention, overnight rostral fluid shift, and upper airway edema. This pattern suggests that the clinical manifestations of aldosterone dysregulation extend beyond its effects on kidneys alone. Although patients with aldosterone dysregulation were older than those without (mean age: 60.5 vs 57.6; $p < 0.01$), the association between aldosterone dysregulation and hypertension severity remained consistent across age subgroups. Whether age-related changes in renin-aldosterone physiology influence the occurrence and clinical impact of aldosterone dysregulation warrants further investigation. Aldosterone dysregulation was independently associated with an increased likelihood of uncontrolled and stage 2 hypertension, even after adjusting for multiple demographic and clinical factors. Aldosterone is a key pathophysiological driver contributing to poor blood pressure control and hypertension severity.¹⁶ Current hypertension treatments do not target directly aldosterone production and rely on medications that block the renin-angiotensin system (RAS), such as angiotensin converting enzyme (ACE) inhibitors and

angiotensin receptor blockers (ARB).^{17–19} Despite widespread use these agents, aldosterone “escape” or “breakthrough” has been observed in over half the patients due to alternative non-ACE pathways or compensatory feedback mechanisms.^{20–22} MRAs are effective in blocking aldosterone at the receptor level and are well established in the management of hypertension; however, they do not directly suppress aldosterone production, and their use may be limited in some patients due to concerns regarding hyperkalemia, particularly in those with chronic kidney disease, as well as dose-dependent endocrine adverse effects.^{23,24} In addition, circulating aldosterone levels may actually increase as a result of receptor blocking, enhancing adverse effects of aldosterone and leading to excess sympathetic activation, disrupted glucose homeostasis and negative vascular effects. These limitations represent an unmet therapeutic gap in patients with hard-to-control and resistant hypertension who experienced dysregulated aldosterone activity.

These findings reinforce the concept that aldosterone dysregulation is common and a clinically important biological risk factor

Table 4
Aldosterone dysregulation, hypertension, and number of medications

Aldosterone dysregulation	Uncontrolled hypertension (systolic blood pressure ≥130 mm Hg)					
	Overall	4+ drugs	3 drugs	2 drugs	1 drug	0 drugs
	N = 7169	N = 4264	N = 1308	N = 904	N = 554	N = 139
Yes	2976 (41.5%)	1885 (44.2%)	533 (40.8%)	329 (36.4%)	188 (33.9%)	41 (29.5%)
No	4193 (58.5%)	2379 (55.8%)	775 (59.3%)	575 (63.6%)	366 (66.1%)	98 (70.5%)
	Controlled hypertension (systolic blood pressure <130 mmHg)					
	Overall	4+ drugs	3 drugs	2 drugs	1 drug	0 drugs
	N = 1960	N = 1054	N = 383	N = 285	N = 179	N = 59
Yes	625 (31.9%)	358 (34.0%)	114 (29.8%)	87 (30.5%)	52 (29.1%)	14 (23.7%)
No	1335 (68.1%)	696 (66.0%)	269 (70.2%)	198 (69.5%)	127 (71.0%)	45 (76.3%)

Aldosterone dysregulation was defined as an elevated aldosterone-to-renin ratio (ARR) >10 with plasma renin activity (PRA) or >1 ARR with plasma renin concentration (PRC).

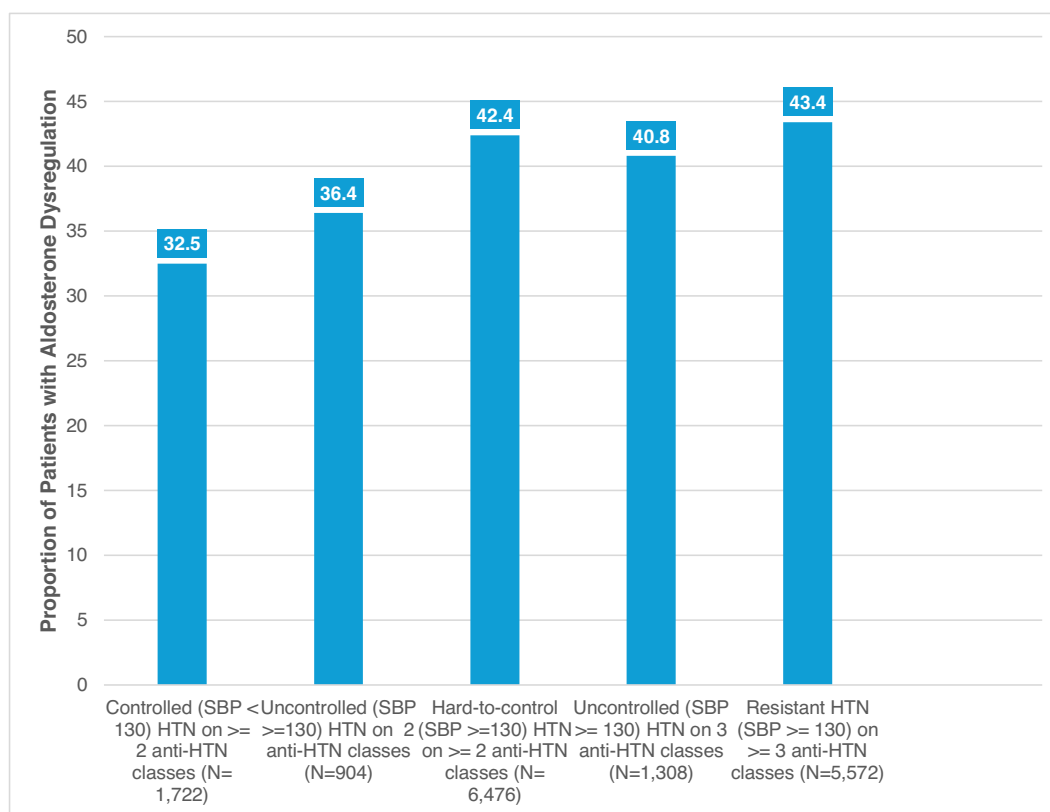


Figure 3. Proportion of patients with aldosterone dysregulation among those on 2 or more anti-hypertension drugs. Occurrence of aldosterone dysregulation across hypertension severity and treatment intensity. Proportions ranged from 32.5% among patients with controlled hypertension to 43.4% in those with resistant hypertension. HTN = hypertension; SBP = systolic blood pressure.

behind essential hypertension, which can exist regardless of blood pressure control or initial treatment intensity. The pervasiveness and the clinical potency of aldosterone as a driver of poor blood pressure control calls for a paradigm shift to address the root cause of hard to control hypertension. Aldosterone synthase inhibitors directly target the aldosterone signaling pathway and can effectively lower blood pressure through addressing aldosterone synthesis.²⁵ Aldosterone synthase inhibitors have shown promising results in recent Phase 2 trials, demonstrating significant reductions in systolic blood pressure.^{26,27} Phase 3 studies recently completed further clarified the role of aldosterone synthase inhibitors in hard to control hypertension population.^{28,29} Recent phase 2 trials including BrighTN, BLOCK-CKD, and Clarion-CKD further highlight the growing interest in targeted aldosterone pathway inhibition across populations with resistant hypertension and chronic kidney disease, demonstrating meaningful reductions in SBP with aldosterone synthase inhibitors while maintaining acceptable tolerability profiles. Because aldosterone synthase (CYP11B2) and 11 β -hydroxylase (CYP11B1) share substantial structural homology, there exists clinically important physiological and pharmacological overlap between aldosterone and cortisol regulation. Earlier aldosterone synthase inhibitors demonstrated nonselective CYP11B1 inhibition, raising concerns regarding iatrogenic cortisol insufficiency. In contrast, newer highly selective agents such as baxdrostat substantially exhibit greater selectivity for CYP11B2, enabling aldosterone suppression while preserving cortisol homeostasis. Currently, there is a growing momentum in recognizing the need for increased laboratory testing of aldosterone and renin for the diagnosis and management of primary aldosteronism. The 2025 American Heart Association and American College of Cardiology guideline on hypertension recommends screening for primary aldosteronism in all patients with resistant hypertension and indicate

that screening may be considered for all patients with stage 2 hypertension.¹⁹ While the guideline promotes the diagnosis and clinical management of primary aldosteronism, the guideline does not recommend the use of aldosterone and renin measurements as a screening strategy for the management of essential hypertension nor the management of the continuum of aldosterone dysregulation beyond primary aldosteronism.³⁰ It should also be acknowledged that the routine use of ARR testing in patients with resistant hypertension, particularly in the absence of hypokalemia, remains an area of ongoing debate. The cost-effectiveness of broader ARR testing in patients with resistant hypertension remains incompletely evaluated and warrants prospective evaluation. Given the high prevalence of aldosterone dysregulation documented in the present cohort, and the availability of emerging targeted therapies, the clinical and economic implications of systematic ARR screening merit careful consideration in future therapeutic development and guidelines.

Several limitations in this study should be noted. Variability in aldosterone measurement techniques (immunoassay vs LC-MS/MS) may have introduced measurement heterogeneity; however, our assessment of measurements from these 2 assay types did not reveal significant differences, and assay type was included as a covariate in multivariable models. Aldosterone and renin levels were not standardized to a fixed time relative to the index date, which might have introduced variations. Blood pressure measurements were obtained from routine outpatient office encounters rather than standardized ambulatory or serial home monitoring, which may have introduced some variability in blood pressure classification. Moreover, office blood pressure measurements were obtained during routine clinical care across multiple sites, and adherence to standardized measurement protocols could not be verified retrospectively. Additionally, assessments of treatment intensity, dose optimization, and therapy

duration were limited by the individualized nature of real-world hypertension management. Data on medication adherence, dietary sodium intake, and confirmatory testing for primary aldosteronism were unavailable. Relatively low proportion of patients with a diagnosis of primary aldosteronism likely reflects the well-documented underutilization of guideline-recommended screening and confirmatory testing in routine clinical practice. Accordingly, a subset of patients with biochemical evidence of aldosterone dysregulation may harbor undiagnosed primary aldosteronism. In addition, approximately 1 in 4 patients were receiving MRA, which may increase circulating aldosterone levels and represents a potential source of residual confounding. ARR has variable reproducibility, particularly when testing conditions are not standardized. Despite these limitations, the findings are derived from a large and diverse real-world cohort and remained consistent across multiple definitions and subgroup analyses, which strengthens the validity and relevance of the observed associations.

In conclusion, aldosterone dysregulation is common in patients with essential hypertension and is associated with sub-optimal blood pressure control and severity of hypertension. In addition, aldosterone dysregulation exists along a spectrum, including those with controlled hypertension. The current approach of introducing additional antihypertensive therapies does not change the status of aldosterone dysregulation and may lead to hypertension control not reaching target goal. There is an unmet need to address hypertension through targeted therapy for aldosterone dysregulation to improve outcomes.

Declaration of competing interest

AA and SL are employees and stockholders of AstraZeneca. MSK has received consulting fees from Bayer, Boehringer Ingelheim and Novartis, and has received research support from Merck. JB reports consultant activities for Abbott, Adaptix, Ameri-can Regent, Amgen, AskBio, AstraZeneca, Bayer, Boehringer Ingelheim, Boston Scientific, Bristol Myers Squibb, Cardiac Dimension, Cardior, CSLVifor, CVRx, Cytokinetics, Daxor, Diastol, Edwards, Element Sciences, Fara-day, Idorsia, Impulse Dynamics, Imbria, Innolife, Intellia, Inventiva, Levator, Lexicon, Eli Lilly, Mankind, Medtronic, Merck, New Amsterdam, Novartis, Novo Nordisk, Pfizer, Pharmacosmos, Pharmain, Prolaio, Pulnovo, Regen-eron, Renibus, Reprieve, Roche, Rycarma, Saillant, Salamandra, Salubris, SC Pharma, SQ Innovation, Secretome, Sequanna, Transmural, Tekkun-Lev, Tenex, Tricog, Ultromic, Vera, Zoll. FF, KH, MSA, MB, JE, EP and CS have no conflict of interest.

CRediT authorship contribution statement

Javed Butler: Writing – review & editing, Writing – original draft, Supervision, Resources, Methodology, Investigation, Funding acquisition, Conceptualization. **Kendall Hammonds:** Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation. **Muhammad Sameer Arshad:** Writing – review & editing, Writing – original draft. **Francesco Fioretti:** Writing – original draft. **Monica Bennett:** Writing – review & editing, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis. **Jason Ettlinger:** Writing – review & editing, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation. **Abiy Agiro:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization. **Shan Luan:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization. **Courtney Shaver:** Writing – review & editing, Supervision, Project administration, Investigation, Funding

acquisition. **Elisa Priest:** Writing – review & editing, Supervision, Resources, Project administration, Investigation, Funding acquisition. **Muhammad Shahzeb Khan:** Writing – review & editing, Writing – original draft, Visualization, Validation.

Supplementary materials

Supplementary material associated with this article can be found in the online version at <https://doi.org/10.1016/j.amjcard.2026.08.005>.

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