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The Unrecognized Prevalence of Primary Aldosteronism

A Cross-sectional Study

Jenifer M. Brown, MD; Mohammed Siddiqui, MD; David A. Calhoun, MD; Robert M. Carey, MD; Paul N. Hopkins, MD, MSPH; Gordon H. Williams, MD; and Anand Vaidya, MD, MMSc

Background: Primary aldosteronism is a nonsuppressible renin-independent aldosterone production that causes hypertension and cardiovascular disease.

Objective: To characterize the prevalence of nonsuppressible renin-independent aldosterone production, as well as biochemically overt primary aldosteronism, in relation to blood pressure.

Design: Cross-sectional study.

Setting: 4 U.S. academic medical centers.

Participants: Participants with normotension (n = 289), stage 1 hypertension (n = 115), stage 2 hypertension (n = 203), and resistant hypertension (n = 408).

Measurements: Participants completed an oral sodium suppression test, regardless of aldosterone or renin levels, as a confirmatory diagnostic for primary aldosteronism and to quantify the magnitude of renin-independent aldosterone production. Urinary aldosterone was measured in participants in high sodium balance with suppressed renin activity. Biochemically overt primary aldosteronism was diagnosed when urinary aldosterone levels were higher than 12 μg/24 h.

Results: Every blood pressure category had a continuum of renin-independent aldosterone production, where greater severity of production was associated with higher blood pressure, kaliuresis, and lower serum potassium levels. Mean adjusted levels of urinary aldosterone were 6.5 μg/24 h (95% CI, 5.2 to 7.7 μg/24 h) in normotension, 7.3 μg/24 h (CI, 5.6 to 8.9 μg/24 h) in stage 1 hypertension, 9.5 μg/24 h (CI, 8.2 to 10.8 μg/24 h) in stage 2 hypertension, and 14.6 μg/24 h (CI, 12.9 to 16.2 μg/24 h) in resistant hypertension; corresponding adjusted prevalence estimates for biochemically overt primary aldosteronism were 11.3% (CI, 5.9% to 16.8%), 15.7% (CI, 8.6% to 22.9%), 21.6% (CI, 16.1% to 27.0%), and 22.0% (CI, 17.2% to 26.8%). The aldosterone–renin ratio had poor sensitivity and negative predictive value for detecting biochemically overt primary aldosteronism.

Limitation: Prevalence estimates rely on arbitrary and conventional thresholds, and the study population may not represent nationwide demographics.

Conclusion: The prevalence of primary aldosteronism is high and largely unrecognized. Beyond this categorical definition of primary aldosteronism, there is a prevalent continuum of renin-independent aldosterone production that parallels the severity of hypertension. These findings redefine the primary aldosteronism syndrome and implicate it in the pathogenesis of "essential" hypertension.

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For author affiliations, see end of text.
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Hypertension is a highly prevalent chronic disease affecting more than 1 billion people worldwide (1). Most hypertension is considered idiopathic, and the approach for antihypertensive treatment is rarely directed toward a primary underlying mechanism.

Primary aldosteronism is caused by renin-independent aldosterone production, wherein aldosterone is produced despite the suppression of renin and angiotensin II and is not adequately suppressed by sodium loading or extracellular volume expansion. This renin-independent aldosterone production can cause hypertension, but interactions with the mineralocorticoid receptor also cause hypokalemia and increased risk for adverse cardiovascular outcomes (2, 3). Despite the availability of targeted treatments that can mitigate cardiovascular disease in primary aldosteronism (3), primary aldosteronism is grossly underdiagnosed, even among high-risk patients with hypertension who clearly meet indications for diagnostic testing (4–6).

Current guidelines recommend screening for primary aldosteronism by measuring the aldosterone–renin ratio (ARR) in patients with severe hypertension or hypertension accompanied by hypokalemia, sleep apnea, or an adrenal mass (7). Patients with an elevated ARR and aldosterone level are considered to have positive screening results for primary aldosteronism and can then undergo more definitive confirmation of the diagnosis via gold-standard dynamic testing (such as oral sodium or intravenous saline loading, fludrocortisone suppression, or captopril challenge) (7). Although primary aldosteronism is often considered an uncommon cause of hypertension, it is frequently identified when hypertensive persons undergo systematic screening for a high ARR and aldosterone level (6, 8–12). However, accumulating evidence indicates that a much larger and clinically relevant spectrum of renin-independent aldosterone production may exist, even among persons who do not have an arbitrarily "high" ARR and are not hypertensive or hypokalemic (13–17). Recognizing the scope of abnormal renin-independent aldosterone production in the general population could better define the prevalence of primary aldosteronism and inform the understanding of the pathogenesis and treatment of hypertension.

We systematically evaluated for the presence of abnormal and nonsuppressible renin-independent al-

See also:

Editorial comment 1

Web-Only
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dosterone production and biochemically overt primary aldosteronism using dynamic confirmatory testing, regardless of the ARR, in participants recruited to represent the entire blood pressure spectrum. The severity spectrum of renin-independent aldosterone production was assessed using an oral sodium suppression test, an established and recommended method to confirm a diagnosis of primary aldosteronism (7).

METHODS

Design Overview

The current study was designed to evaluate the results of a gold-standard confirmatory diagnostic for primary aldosteronism across the spectrum of hypertension severity by pooling 5 study protocols from 4 distinct sites across the United States (Birmingham, Alabama; Boston, Massachusetts; Charlottesville, Virginia; and Salt Lake City, Utah) that recruited participants with specific blood pressure phenotypes to investigate hormonal mechanisms of blood pressure. Every participant completed an oral sodium loading protocol regardless of circulating aldosterone, renin, and ARR values. The individual study populations, inclusion and exclusion criteria, study protocols, and laboratory assays for each site are described briefly below and in more detail in the **Supplement** (available at Annals.org).

Setting and Participants

In the Salt Sensitivity of Blood Pressure protocol, healthy adult volunteers with normotension or hypertension were recruited from the greater Charlottesville area to the University of Virginia to study salt sensitivity of blood pressure (18). Inclusion criteria specified age 18 to 70 years and body mass index of 18 to 30 kg/m^2. Patients with known severe or secondary hypertension, renal or cardiovascular disease, or pregnancy were excluded.

The Prospective Phenotyping of Autonomous Aldosterone Secretion protocol recruited overweight normotensive volunteers from the greater Boston area to Brigham and Women's Hospital to study subclinical aldosterone dysregulation. Inclusion criteria were an untreated systolic blood pressure on screening of 120 to 135 mm Hg, an untreated diastolic blood pressure on screening of 75 to 85 mm Hg, a body mass index of at least 25 kg/m^2, and a first-degree relative with hypertension before age 60 years. The study excluded patients with morbid obesity, poorly controlled diabetes, renal or cardiovascular disease, active cancer, use of opioids or glucocorticoids, or pregnancy.

Adult volunteers with normotension or hypertension were recruited from the greater Boston and Salt Lake City areas to study mechanisms of hypertension in the Hypertensive Pathotype Consortium. Normotension was defined by both blood pressure and an absence of family history of hypertension in a first-degree relative before age 60 years. Hypertension was defined by blood pressure or use of antihypertensive drugs. Persons with known or suspected secondary hypertension or established renal or cardiovascular disease were excluded.

Patients referred to the University of Alabama at Birmingham Resistant Hypertension Clinic were recruited to study hormonal mechanisms of resistant hypertension (19), defined as uncontrolled blood pressure despite use of 3 or more antihypertensive medications (including a diuretic) or controlled blood pressure requiring 4 or more antihypertensive medications. The study excluded patients with known congestive heart failure, chronic kidney disease, primary aldosteronism or another secondary form of hypertension, or long-term glucocorticoid use.

All study participants provided informed consent, and the studies were approved by the institutional review boards at participating sites.

Measures

If applicable, antihypertensive medications were systematically withdrawn over 2 to 12 weeks (**Supplement**) to minimize confounding of renin and aldosterone measurements, such that all study assessments were done in an untreated state. The exception to this was the Resistant Hypertension Clinic protocol, where participants stopped receiving mineralocorticoid receptor antagonists and epithelial sodium-channel inhibitors 6 weeks before study assessments, but other antihypertensive medications were continued for safety.

In the research volunteer protocols (Charlottesville, Boston, and Salt Lake City), all participants were prescribed a high-sodium diet and standardized potassium intake for 5 to 7 days before completing a 24-hour urine collection and measurement of blood pressure and circulating levels of renin, aldosterone, and electrolytes. In the patient protocol of the Resistant Hypertension Clinic (Birmingham), rather than a standardized diet, potassium was supplemented to correct hypokalemia to a serum potassium level greater than 3.5 mmol/L. Sodium was supplemented for 3 days only if 24-hour urinary sodium excretion was less than 200 mmol without supplementation, after which 24-hour urine collection was repeated.

For each participant, 24-hour urine collections were used to measure urinary excretion of aldosterone, sodium, and potassium. Blood pressure, plasma renin activity, serum aldosterone, and serum potassium were measured in either the seated or supine position, depending on the protocol. The **Supplement** and **Supplement Table 1** (available at Annals.org) give specific details of individual laboratory assays. The rate of urinary aldosterone excretion in 24 hours, the primary measure of interest, was measured by immunoassay at a centralized laboratory at Brigham and Women's Hospital (Boston) for all participants except those from the Resistant Hypertension Clinic (Birmingham), where it was measured by liquid chromatography tandem mass spectrometry (Mayo Clinic laboratory).

The oral sodium suppression test consists of an oral sodium load, with the goal of achieving a 24-hour urinary sodium balance of at least 180 to 200 mmol, to induce expansion of intravascular volume and physiologic suppression of renin and angiotensin II. Given the

unreliability of single measurements of circulating aldosterone due to variable (20–23) and pulsatile secretion in primary aldosteronism and high-sodium states (20, 24, 25), 24-hour urinary aldosterone excretion was used as a consistent and integrated measurement of renin-independent aldosterone production.

Aldosterone production in the context of a high sodium balance and renin suppression was quantified as "renin-independent" aldosterone production. Renin-independent aldosterone production is categorized as "biochemically overt primary aldosteronism" when it exceeds the international diagnostic threshold, an aldosterone excretion rate of at least 12 μg/24 h in the context of both high sodium balance and suppressed renin activity (7). The estimated prevalence of biochemically overt primary aldosteronism was calculated by dividing the number of such cases by the total population in adequate sodium balance regardless of renin activity (n = 1015); this prevalence was also determined within the subset with suppressed renin activity (n = 691) (Figure 1).

We used blood pressure, measured on the day of urinary and blood measurements (Supplement and Supplement Table 1), to classify untreated participants on the basis of the 2017 hypertension guidelines from the American College of Cardiology and American Heart Association (26) as normotensive (<130/80 mm Hg), stage 1 hypertensive (130-139/80–89 mm Hg), or stage 2 hypertensive (≥140/90 mm Hg); treated participants with resistant hypertension were kept in their own category.

Statistical Analysis

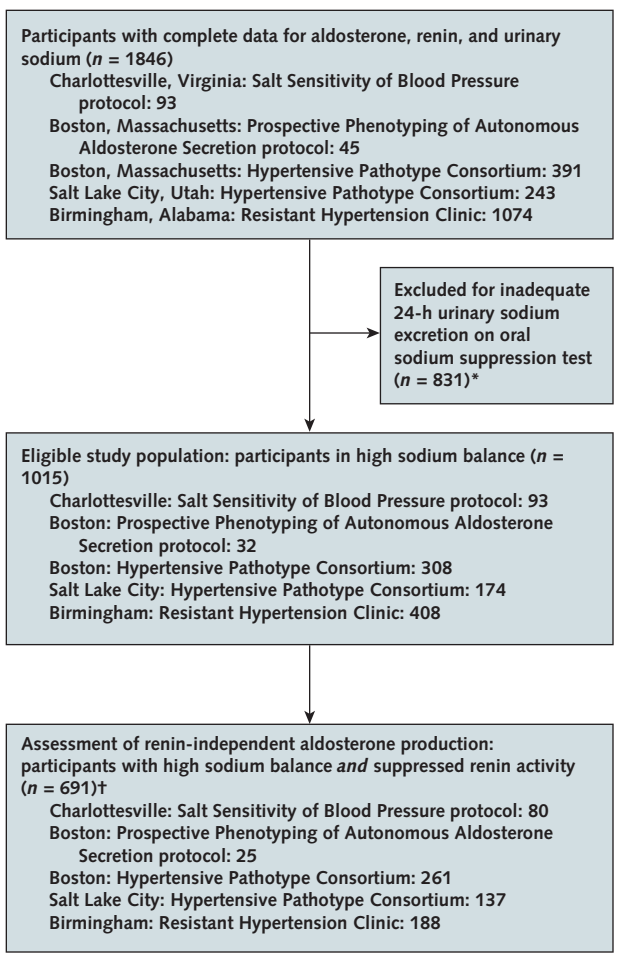
We did cross-sectional analyses from the combined multisite study population to examine the distribution of renin-independent aldosterone production and prevalence of biochemically overt primary aldosteronism across categories of blood pressure.

Participants were required to have complete data for aldosterone and renin activity, as well as a 24-hour rate of urinary sodium excretion reflective of high sodium balance (≥190 mmol/24 h). Renin-independent aldosterone production was then assessed among those with suppression of renin activity (<1.0 μg/L per hour seated or <0.6 μg/L per hour supine). Participants with 24-hour urinary sodium excretion less than 190 mmol were excluded because physiologic aldosterone suppressibility could not be adequately assessed. Participants who had unsuppressed renin activity despite achieving a high sodium balance had a physiology that was incompatible with renin-independent aldosteronism and instead exhibited renin-*dependent* aldosterone production; these participants could not have primary aldosteronism but were still included in the denominator of prevalence estimates (Figure 1; Supplement Figures 1 to 4, available at Annals.org).

Primary analyses describe the distribution of renin-independent aldosterone production by presenting the 24-hour rate of urinary aldosterone excretion among participants who were in adequate sodium balance and had suppression of renin and by presenting the prevalence estimates of biochemically overt primary aldosteronism. Mean adjusted rates of aldosterone excretion and adjusted estimates of prevalence were calculated using the PROC GLM procedure and LSMEANS statement in SAS, version 9.4 (SAS Institute). In secondary analyses, the continuous relationships between urinary aldosterone excretion and biomarkers of mineralocorticoid receptor activation (blood pressure, ratio of urinary potassium–sodium excretion, and serum potassium) were assessed using adjusted linear regression (PROC REG in SAS).

Fewer than 1% of data points were missing, with no missing values for the primary analyses by design. Five other continuous descriptive and demographic variables had less than 5% random missing data, which was imputed using the MICE package in R, version 3.8.0 (R Project for Statistical Computing). All other analyses were done using SAS, version 9.4.

Figure 1. Overall pooled study population.



The eligible study population consisted of all participants in high sodium balance. Renin-independent aldosterone production could be assessed only in the subset in whom renin was suppressed.
* Adequate oral sodium suppression with a high sodium balance is defined as 24-h urinary sodium excretion ≥190 mmol.
† Suppressed renin activity is defined as seated plasma renin activity <1.0 μg/L per hour or supine plasma renin activity <0.6 μg/L per hour.

Table 1. Characteristics of the Eligible Study Population, by Blood Pressure Category*

Characteristic	Untreated Normotension (*n* = 289)	Untreated Stage 1 Hypertension (*n* = 115)	Untreated Stage 2 Hypertension (*n* = 203)	Treated Resistant Hypertension (*n* = 408)
Mean age (SD), *y*	41.0 (13.1)	47.5 (10.4)	51.5 (7.8)	54.0 (11.1)
Mean BMI (SD), *kg/m²*	26.1 (4.6)	29.1 (4.4)	29.3 (4.2)	35.4 (7.1)
Female sex, *n (%)*	147 (50.9)	34 (29.6)	79 (38.9)	165 (40.4)
Race, *n (%)*				
White	224 (77.5)	89 (77.4)	151 (74.4)	162 (39.7)
Black	32 (11.1)	19 (16.5)	41 (20.2)	242 (59.3)
Other/unknown	33 (11.4)	7 (6.1)	11 (5.4)	4 (1.0)
Diabetes, *n (%)*	25 (8.7)	19 (16.5)	24 (11.8)	100 (24.5)
Antihypertensive medications at study assessment, *n (%)*				
Total	0 (0)	0 (0)	0 (0)	408 (100)
ACEI/ARB	–	–	–	338 (82.8)
Calcium-channel blocker	–	–	–	292 (71.6)
Thiazide diuretic	–	–	–	309 (75.7)
$\beta/\alpha\beta$-Blocker	–	–	–	253 (62.0)
Loop diuretic	–	–	–	39 (9.6)
α-Blocker	–	–	–	34 (8.3)
Other†	–	–	–	138 (33.8)
MRA/ENaC inhibitor	–	–	–	0 (0)
Study site, *n (%)*				
Salt Sensitivity of Blood Pressure (Charlottesville, Virginia)	75 (26.0)	11 (9.6)	7 (3.4)	0 (0)
Prospective Phenotyping of Autonomous Aldosterone Secretion (Boston, Massachusetts)	27 (9.3)	4 (3.5)	1 (0.5)	0 (0)
Hypertensive Pathotype Consortium (Boston, Massachusetts)	123 (42.6)	66 (57.4)	119 (58.6)	0 (0)
Hypertensive Pathotype Consortium (Salt Lake City, Utah)	64 (22.1)	34 (29.6)	76 (37.4)	0 (0)
Resistant Hypertension Clinic (Birmingham, Alabama)	0 (0)	0 (0)	0 (0)	408 (100)
Mean high-salt SBP (SD), *mm Hg*	112.3 (9.9)	131.3 (7.1)	154.8 (13.9)	156.7 (27.3)
Mean high-salt DBP (SD), *mm Hg*	68.4 (6.8)	81.0 (6.2)	89.7 (9.4)	88.9 (15.7)
Mean urinary sodium excretion (SD), *mmol/24 h*	276.8 (67.3)	278.3 (65.1)	272.4 (63.6)	265.0 (69.3)
Mean urinary potassium excretion (SD), *mmol/24 h*	77.7 (29.6)	81.0 (31.8)	79.0 (25.4)	72.8 (29.0)
Mean urinary potassium–sodium ratio (SD)	0.29 (0.11)	0.30 (0.11)	0.30 (0.10)	0.29 (0.12)
Mean serum potassium level (SD), *mmol/L*	4.07 (0.38)	4.14 (0.39)	4.06 (0.39)	3.87 (0.48)

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker; BMI = body mass index; DBP = diastolic blood pressure; ENaC = epithelial sodium channel; MRA = mineralocorticoid receptor antagonist; SBP = systolic blood pressure.
* Percentages may not sum to 100 due to rounding.
† Included α2-agonists, nitric oxide–mediated vasodilators, and potassium-channel agonists.

Role of the Funding Source

The National Institutes of Health had no role in the design, conduct, or analysis of this work.

RESULTS

Of the 1846 participants with complete data for aldosterone, renin, and urinary sodium, 1015 had a rate of urinary sodium excretion of at least 190 mmol/24 h (Figure 1). A subset of 691 had suppressed renin activity and were eligible for the assessment of the magnitude of renin-independent aldosterone production (Figure 1).

The study population included 289 untreated normotensive participants, 115 with untreated stage 1 hypertension, 203 with untreated stage 2 hypertension, and 408 with resistant hypertension who were receiving antihypertensive treatment (Table 1). As expected, participants with more severe hypertension were older, had higher body mass index, and were more predominantly black and diabetic. Demographic characteristics are shown by study site in Supplement Table 2 (available at Annals.org) and by eligibility criteria in Supplement Table 3 (available at Annals.org).

A continuum of renin-independent aldosterone production was observed to parallel the severity of hypertension, whereby despite a high sodium balance and suppression of renin, 24-hour rates of urinary aldosterone excretion ranged from the lower bounds of detection to values exceeding the diagnostic threshold for primary aldosteronism (Figure 2). Findings were similar by study site (Supplement Figure 5, available at Annals.org). Although the categorical diagnostic threshold of 12 μg/24 h is recommended to designate those with and without primary aldosteronism (7), the magnitude of renin-independent aldosterone production was progressively higher across blood pressure categories, regardless of this arbitrary designation (Figure 2).

The adjusted prevalence of biochemically overt primary aldosteronism ranged from 11.3% (95% CI, 5.9% to 16.8%) in normotension to 22.0% (CI, 17.2% to 26.8%) in resistant hypertension (Table 2). This prevalence could be substantially modulated with the application of more liberal or conservative diagnostic thresholds (7). Among the subset of participants with suppressed renin activity in high sodium balance, the prevalence of biochemically overt primary aldosteronism was further enriched (Table 2).

Among participants confirmed to have biochemically overt primary aldosteronism, the sensitivity and negative predictive value of the ARR were poor, which

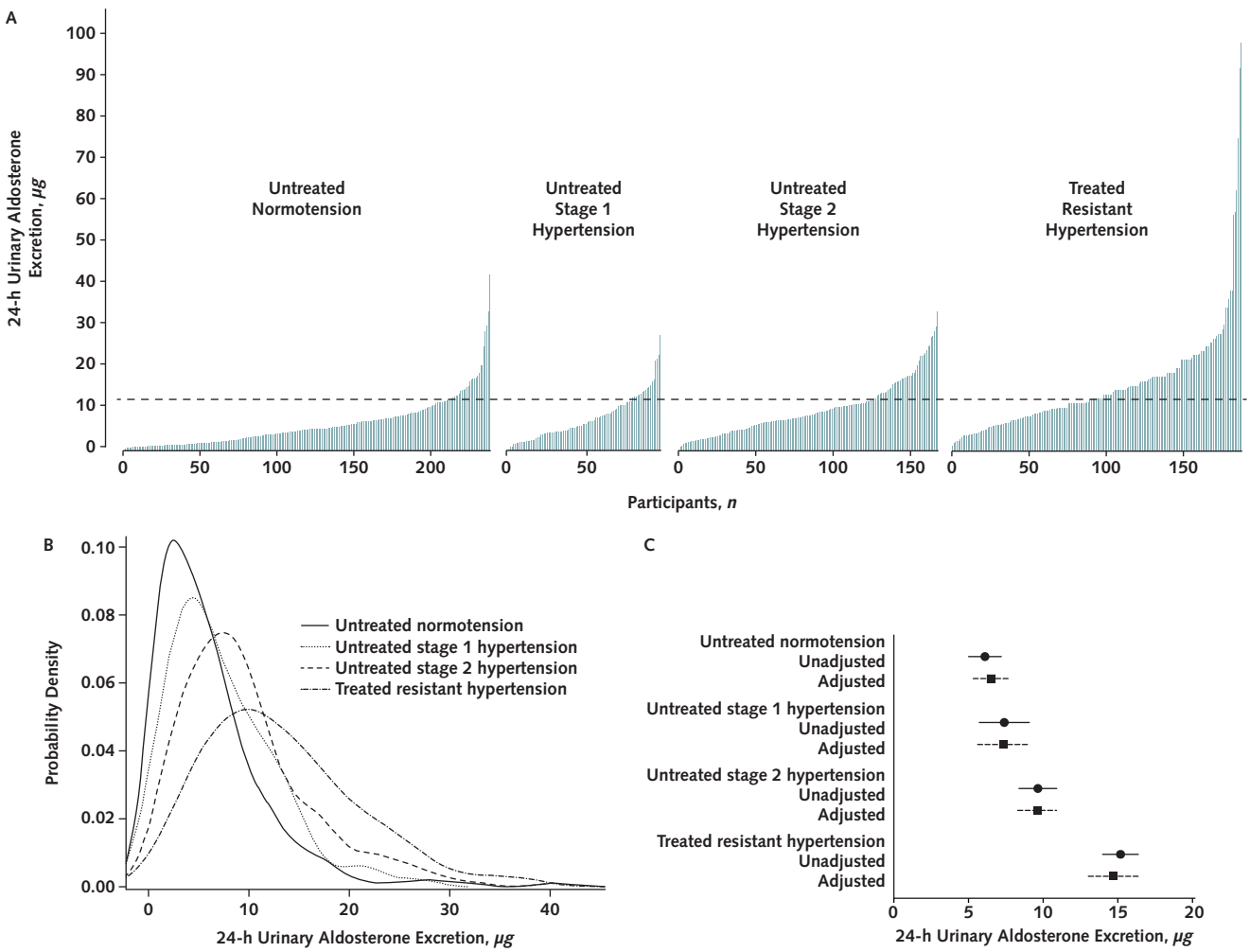
highlights the limitations of this diagnostic ratio in screening for–and excluding–true cases of primary aldosteronism (Table 3; Supplement Table 4, available at Annals.org). Similarly, among participants with resistant hypertension, where the pretest probability of primary aldosteronism is high, 24.5% of confirmed case patients (24 of 98) had a serum aldosterone concentration less than 277 pmol/L (10 ng/dL), a threshold below which the diagnosis of primary aldosteronism is almost never entertained (7, 12, 27).

There was a continuous relationship between the severity of renin-independent aldosterone production and biomarkers of mineralocorticoid activity and serum aldosterone (Table 4; Supplement Figure 6, available at Annals.org).

Discussion

We show a pervasive spectrum of renin-independent aldosterone production that parallels the severity of human hypertension and correlates with biomarkers of mineralocorticoid receptor activation. These findings indicate a highly prevalent pathologic continuum of renin-independent aldosteronism that extends, or redefines, the classic concept of primary aldosteronism as a "secondary" cause of hypertension. By applying established diagnostic thresholds to this continuum, we found the estimated prevalence of primary aldosteronism to be much higher than conventionally considered in every blood pressure category, providing a stark contrast to the fact that primary aldosteronism is currently rarely diagnosed, even among high-risk populations with resistant hyper-

Figure 2. Distribution of renin-independent aldosterone production, by blood pressure category.



A. The unadjusted urinary aldosterone excretion rate in the context of high sodium balance and renin suppression. Vertical bars represent the unadjusted renin-independent aldosterone excretion rate (*y*-axis) for each individual participant, ordered from lowest to highest (*x*-axes). The dashed horizontal line represents the conventional 12 μg/24 h threshold for the diagnosis of biochemically overt primary aldosteronism. **B.** Unadjusted overlaid density plots depicting the distribution of renin-independent aldosterone production, by blood pressure category (truncated at 45 μg/24 h). The *x*-axis shows the 24-h urinary aldosterone excretion rate. The *y*-axis shows the probability density function (smoothed using a kernel density estimation) per unit on the *x*-axis. **C.** Mean (95% CI) urinary aldosterone excretion rates for each blood pressure category, unadjusted (*solid lines with circles*) and adjusted (*dotted lines with squares*) for age, body mass index, race, sex, history of diabetes, and 24-h urinary sodium excretion.

Table 2. Prevalence of Biochemically Overt Primary Aldosteronism*

Prevalence	Liberal Definition (Aldosterone Excretion Rate ≥10 μg/24 h)	Conventional Definition (Aldosterone Excretion Rate ≥12 μg/24 h)	Conservative Definition (Aldosterone Excretion Rate ≥15 μg/24 h)
Within total study population (*n* = 1015)†			
Untreated normotension (*n* = 289)			
Crude prevalence	13.8 (8.9 to 18.8)	9.0 (4.6 to 13.4)	4.8 (1.1 to 8.6)
Adjusted prevalence‡	18.5 (12.4 to 24.6)	11.3 (5.9 to 16.8)	6.1 (1.5 to 10.7)
Untreated stage 1 hypertension (*n* = 115)			
Crude prevalence	23.5 (15.7 to 31.3)	15.7 (8.7 to 22.6)	6.1 (0.2 to 12.0)
Adjusted prevalence‡	24.3 (16.3 to 32.3)	15.7 (8.6 to 22.9)	6.1 (0.0 to 12.1)
Untreated stage 2 hypertension (*n* = 203)			
Crude prevalence	33.0 (27.1 to 38.9)	20.7 (15.4 to 25.9)	14.8 (10.3 to 19.2)
Adjusted prevalence‡	34.0 (27.9 to 40.0)	21.6 (16.1 to 27.0)	15.2 (10.6 to 19.8)
Treated resistant hypertension (*n* = 408)			
Crude prevalence	28.4 (24.3 to 32.6)	24.0 (20.3 to 27.7)	17.6 (14.5 to 20.8)
Adjusted prevalence‡	24.5 (19.2 to 29.9)	22.0 (17.2 to 26.8)	16.6 (12.5 to 20.7)
Prevalence within subset with suppressed renin (*n* = 691)§			
Untreated normotension (*n* = 239)			
Crude prevalence	16.7 (11.1 to 22.4)	10.9 (5.7 to 16.1)	5.9 (1.3 to 10.4)
Adjusted prevalence‡	19.9 (13.0 to 26.7)	11.6 (5.3 to 17.8)	5.8 (0.3 to 11.3)
Untreated stage 1 hypertension (*n* = 96)			
Crude prevalence	28.1 (19.2 to 37.1)	18.8 (10.5 to 27.0)	7.3 (0.1 to 14.5)
Adjusted prevalence‡	27.4 (18.3 to 36.5)	17.4 (9.0 to 25.8)	6.1 (−1.2 to 13.5)
Untreated stage 2 hypertension (*n* = 168)			
Crude prevalence	39.9 (33.1 to 46.7)	25.0 (18.8 to 31.2)	17.9 (12.4 to 23.3)
Adjusted prevalence‡	40.0 (33.1 to 46.9)	25.4 (19.0 to 31.7)	17.9 (12.3 to 23.5)
Treated resistant hypertension (*n* = 188)			
Crude prevalence	61.7 (55.3 to 68.1)	52.1 (46.2 to 58.0)	38.3 (33.2 to 43.4)
Adjusted prevalence‡	58.0 (49.3 to 66.7)	51.6 (43.6 to 59.6)	38.9 (31.9 to 45.9)

* Values are percentages (95% CIs). Biochemically overt primary aldosteronism is diagnosed when the 24-h rate of urinary aldosterone excretion is ≥10 μg (liberal definition), ≥12 μg (conventional definition), or ≥15 μg (conservative definition) in the context of a high sodium balance and suppressed plasma renin activity.
† The prevalence of primary aldosteronism is described as a proportion of the entire eligible study population in high sodium balance (*n* = 1015).
‡ Adjusted for age, body mass index, race, sex, history of diabetes mellitus, and 24-h urinary sodium excretion.
§ The prevalence of primary aldosteronism is described as a proportion of only those participants who also had suppressed renin activity when in high sodium balance (*n* = 691).

tension or hypokalemia (4–7). Our results also highlight the fact that the conventional approach of requiring an arbitrarily "high" ARR and circulating aldosterone level to screen for potential cases of primary aldosteronism is insensitive and likely contributes to underdiagnosis. Collectively, these findings show that primary aldosteronism may be a common and unrecognized "primary" cause of hypertensive disease and progression.

An unrecognized spectrum of primary aldosteronism has been suggested previously. After discovering primary aldosteronism, Jerome Conn and others proposed that it could be a prevalent cause of hypertension with origins as a phenotype of renin-independent aldosteronism in normotension (28, 29). As early as 1972, Carey and Liddle recognized that spironolactone could normalize blood pressure in patients with suppressed renin activity but not in those with higher renin activity (30). Many prior investigations have characterized the "low-renin" phenotype in essential hypertension (31–35); however, the application of arbitrary thresholds of "high," "normal," and "low" circulating levels of aldosterone may have limited the identification of primary aldosteronism cases to only the most severe. Support for this theory was seen in PATHWAY-2 (Prevention And Treatment of Hypertension With Algorithm-based therapy number 2), a trial of add-on therapy for uncontrolled resistant hypertension wherein participants were randomly assigned to sequential crossover treatment with spironolactone, bisoprolol, doxazosin, and placebo and were included only after a specialist had excluded primary aldosteronism (15). Despite this presumptive exclusion, the efficacy of spironolactone directly correlated with the combination of lower renin levels, higher aldosterone levels within the "normal" range, and higher ARR values (15, 16), thereby demonstrating that the efficacy of mineralocorticoid receptor antagonists in lowering blood pressure was dependent on the magnitude of unrecognized renin-independent aldosterone production. The current study provides mechanistic support for the findings of PATHWAY-2 and suggests that primary aldosteronism may be better considered to be a severity spectrum of renin-independent aldosterone production.

In a prior demonstration of the prevalence of primary aldosteronism, Monticone and colleagues (12) systematically screened consecutive hypertensive patients. They reported a prevalence of biochemically overt primary aldosteronism ranging from 3.9% to 11.8% across the range of mild to severe hypertension (12). However, these estimates were determined by doing gold-standard confirmatory testing only in patients with an ARR greater than 832 pmol/L per μg/L per hour (30 ng/dL per ng/mL per hour) and an absolute aldosterone level higher than 277 pmol/L (10 ng/dL). Al-

Table 3. Circulating Renin and Aldosterone Measurements and Test Characteristics of the ARR Using a Cutoff of 832 pmol/L per µg/L per hour (30 ng/dL per ng/mL per hour)*

Characteristic	Untreated Normotension	Untreated Stage 1 Hypertension	Untreated Stage 2 Hypertension	Treated Resistant Hypertension
Crude prevalence of biochemically overt primary aldosteronism by oral sodium suppression test with urinary aldosterone excretion ≥12 µg/24 h	9.0 (26/289)	15.7 (18/115)	20.7 (42/203)	24.0 (98/408)
Percentage of total population with ARR >832 pmol/L per µg/L per hour	7.6 (22/289)	9.6 (11/115)	22.2 (45/203)	8.8 (36/408)
Crude prevalence of biochemically overt primary aldosteronism using screening ARR >832 pmol/L per µg/L per hour	2.4 (7/289)	3.5 (4/115)	10.3 (21/203)	6.6 (27/408)
Sensitivity of ARR >832 pmol/L per µg/L per hour	26.9 (7/26)	22.2 (4/18)	50.0 (21/42)	27.6 (27/98)
Specificity of ARR >832 pmol/L per µg/L per hour	94.3 (248/263)	92.8 (90/97)	85.1 (137/161)	97.1 (301/310)
Positive predictive value of ARR >832 pmol/L per µg/L per hour	31.8 (7/22)	36.4 (4/11)	46.7 (21/45)	75.0 (27/36)
Negative predictive value of ARR >832 pmol/L per µg/L per hour	92.9 (248/267)	86.5 (90/104)	86.7 (137/158)	80.9 (301/372)
ARR, *pmol/L per µg/L per hour*				
Mean (SD)	368.7 (317.3)	430.1 (411.7)	658.6 (649.8)	312.9 (355.8)
Median (IQR)	257.0 (138.7–462.3)	289.2 (173.5–694.0)	446.9 (231.3–721.2)	190.8 (65.4–447.0)
Serum aldosterone level, *pmol/L*				
Mean (SD)	136.8 (142.3)	114.6 (82.4)	147.3 (105.5)	304.4 (222.2)
Median (IQR)	83.2 (69.4–149.8)	77.1 (69.4–121.2)	105.4 (69.4–185.9)	249.7 (141.5–388.4)
PRA, *µg/L per hour*				
Mean (SD)	0.56 (0.60)	0.43 (0.34)	0.39 (0.43)	5.11 (13.49)
Median (IQR)	0.50 (0.20–0.60)	0.32 (0.14–0.60)	0.30 (0.10–0.50)	1.10 (0.60–3.10)

ARR = aldosterone–renin ratio; IQR = interquartile range; PRA = plasma renin activity.
* Values are percentages (n/N) unless otherwise specified. An ARR threshold of 832 pmol/L per µg/L per hour (30 ng/dL per ng/mL per hour) is shown. For the purposes of standardization, supine aldosterone values below the assay limit of <69.4 pmol/L (2.5 ng/dL) were set at 69.4 pmol/L and supine PRA values below the assay limit of <0.1 µg/L per hour were set at 0.1 µg/L per hour; seated aldosterone values below the assay limit of <83.2 pmol/L (3.0 ng/dL) were set at 83.2 pmol/L and seated PRA values below the assay limit of <0.6 µg/L per hour were set at 0.6 µg/L per hour.

though this approach to screening is recommended and has been used in nearly all prior studies focused on primary aldosteronism prevalence (8–11), the requirement for a "high" circulating level of aldosterone and "high" ARR likely limited detection to only a fraction of true cases. Had we required a "high" ARR to screen for these potential cases, we would have reported an underestimation of prevalence similar to that found by Monticone and colleagues (3.5% to 10.3%) (Table 3). Similarly, had we required a circulating aldosterone concentration of at least 277 pmol/L (10 ng/dL) to be considered "high" enough to be primary aldosteronism, as is usually recommended (10, 16, 25), we would have missed 25% of true diagnoses in resistant hypertension. These findings underscore the fact that a focus on "high" circulating aldosterone or ARR is insensitive for detecting primary aldosteronism and, more important, that excessive focus on binary diagnostic thresholds overlooks the continuum of renin-independent aldosterone production that transcends these categorizations. The insensitivity of a single ARR, compared with dynamic suppression testing, may be due to the variable and pulsatile production of aldosterone (20–25).

Our findings also extend the results of prior studies implicating primary aldosteronism in the pathogenesis of a substantial proportion of hypertension and downstream cardiovascular risk. Continuous associations between nonphysiologic aldosterone production and higher blood pressure and risk for cardiovascular disease have been observed in hypertensive persons (36–38). However, primary aldosteronism can be detected

Table 4. Change in Continuous Markers of Mineralocorticoid Receptor Activity Associated With a 5-µg Increase in 24-Hour Urinary Aldosterone Excretion

Marker	Unadjusted		Adjusted	
	Point Estimate (95% CI)	*P* Value	Point Estimate (95% CI)	*P* Value
Serum aldosterone level, *pmol/L*	53.1 (46.7 to 59.5)	<0.001	43.7 (37.8 to 49.6)*	<0.001
Urinary potassium–sodium ratio	0.018 (0.014 to 0.023)	<0.001	0.018 (0.013 to 0.022)*	<0.001
Serum potassium level, *mmol/L*	−0.049 (−0.066 to −0.031)	<0.001	−0.040 (−0.059 to −0.021)*	<0.001
Systolic blood pressure, *mm Hg*†	5.2 (3.7 to 6.7)	<0.001	3.1 (1.6 to 4.5)‡	<0.001
Diastolic blood pressure, *mm Hg*†	2.6 (1.7 to 3.5)	<0.001	1.5 (0.7 to 2.4)‡	<0.001

* Multivariable model covariates were age, body mass index, race, sex, history of diabetes mellitus, study site, and 24-h urinary sodium excretion.
† Analyses were done in participants who were assessed while not receiving any antihypertensive medications; the treated resistant hypertensive subpopulation was not included in these analyses.
‡ Multivariable model covariates were age, body mass index, race, sex, history of diabetes mellitus, study site, and urinary potassium–sodium ratio.

even among apparently healthy normotensive persons, and higher aldosterone levels in the context of suppressed renin are independently associated with higher risk for future blood pressure elevations and incident hypertension (13, 14, 39–41). Our current findings provide the mechanistic underpinnings to refine these epidemiologic observations and suggest that the distinction between "biochemically overt primary aldosteronism" and "renin-independent aldosterone production" is an arbitrary construct limited to identifying the most severe primary aldosteronism. Because primary aldosteronism and mineralocorticoid receptor activation are modifiable mechanisms of cardiovascular risk (3, 42, 43), reframing the terminology to indicate that primary aldosteronism is a syndrome of renin-independent aldosterone production that is prevalent across the entire continuum of human blood pressure may be necessary to raise awareness, increase diagnosis rates, and promote targeted treatment interventions.

Our findings have practical clinical implications. First, the classic stereotype of severe hypertension or hypokalemia is not the sine qua non for primary aldosteronism; primary aldosteronism can frequently be detected in normokalemic hypertensive persons of all blood pressure categories, and even among normotensive persons. Consequently, clinicians should consider screening for primary aldosteronism much more frequently, especially in the general hypertensive population (44, 45). Second, although the ARR can be a simple and useful screening method, circulating levels in patients with primary aldosteronism can vary and are not always apparently "high" (20–25); therefore, reliance on a single ARR is insensitive, even among patients with resistant hypertension. Further, although aldosterone values less than 277 pmol/L (10 ng/dL) start approaching the lower limit of detection of most modern assays, they may still correlate with evidence of mineralocorticoid receptor activation and thus be "inappropriate" relative to renin activity. In contrast, suppressed renin is a biomarker that identifies patients who are more likely to have primary aldosteronism and may especially benefit from mineralocorticoid receptor antagonists (15, 16). For these patients, clinicians should first strongly emphasize the importance of dietary sodium restriction, not only as a general intervention to improve blood pressure (46) but also as a targeted maneuver to minimize the fuel that feeds primary aldosteronism pathophysiology (47, 48). In addition, and when resources permit, more definitive (and laborious) physiologic testing may be done to confirm the diagnosis and to consider whether a surgical intervention might be warranted. At minimum, clinicians should consider prescribing mineralocorticoid receptor antagonists more liberally for hypertensive patients with suppressed renin.

This study has several limitations. First, the study population was not a representative nationwide cohort; therefore, the generalizability of our findings to the U.S. population is uncertain. Second, the heterogeneity of the site-specific protocols, recruitment of geographically and physically disparate participants, sampling in different postures, and use of multiple laboratory assays may all have imparted bias and variability to our results. Future studies that focus on representative nationwide participants may provide more refined point estimates for primary aldosteronism prevalence. Third, the cross-sectional design of the study means that causality cannot be determined. However, the observation of greater renin-independent aldosterone production in parallel with increasing hypertension severity and biomarkers of mineralocorticoid receptor activity recapitulates a known causal phenomenon; reverse causality can be considered, but clinical trials have already demonstrated the efficacy of mineralocorticoid receptor antagonists in lowering blood pressure preferentially when renin-independent aldosterone production is present (15, 16). Fourth, most participants were evaluated while not receiving antihypertensive medications, but patients with resistant hypertension were studied while receiving treatment. Although this factor probably did not meaningfully change the results, potential misclassification due to these medications would likely cause underestimation, rather than overestimation, of the true prevalence given that the typical effect of renin–angiotensin–aldosterone system inhibitors and diuretics is to raise renin levels (27, 49).

In addition, our ability to control only some of the many regulators of aldosterone production may have influenced our findings. For example, we used protocolized diets to standardize potassium intake and prevent hypokalemia during sodium loading. Although raising extracellular potassium levels can stimulate aldosterone production, we observed renin-independent aldosterone production that was associated with higher blood pressure and kaliuresis despite lower serum potassium concentrations within the normal range, supporting aldosterone production independent of potassium (50, 51). Similarly, adrenocorticotropic hormone, which we did not directly investigate, could have played a role. In fact, some patients with primary aldosteronism have been shown to have adrenocorticotropic hormone sensitivity (52–54). Further, although we have here highlighted the notable frequency of renin-independent aldosterone production, not all secondary hypertension is explained by primary aldosteronism. Alternative causes, such as sympathetic overactivity and renovascular hypertension, may have been operative in participants with a phenotype of renin-dependent aldosterone production, but these causes were not comprehensively evaluated in the current study. Finally, our study was not designed to determine the underlying cause of the prevalent phenotype of renin-independent aldosterone production. However, prior studies have implicated body weight or adiposity (55), somatic mutations that result in autonomous aldosterone production (17, 56, 57), and autoimmune factors (58, 59).

In summary, our findings show a high prevalence of unrecognized yet biochemically overt primary aldosteronism using current confirmatory diagnostic thresholds. They highlight the inadequacy of the current diagnostic approach that heavily relies on the ARR and,

most important, show the existence of a pathologic continuum of nonsuppressible renin-independent aldosterone production that parallels the severity of hypertension. These findings support the need to redefine primary aldosteronism from a rare and categorical disease to, instead, a common syndrome that manifests across a broad severity spectrum and may be a primary contributor to hypertension pathogenesis.

From Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts (J.M.B., G.H.W., A.V.); University of Alabama at Birmingham, Birmingham, Alabama (M.S., D.A.C.); University of Virginia Health System, Charlottesville, Virginia (R.M.C.); and University of Utah School of Medicine, Salt Lake City, Utah (P.N.H.).

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Corresponding Author: Anand Vaidya, MD, MMSc, Center for Adrenal Disorders, Division of Endocrinology, Diabetes, and Hypertension, Brigham and Women's Hospital, Harvard Medical School, 221 Longwood Avenue, RFB, Boston, MA 02115; e-mail, anandvaidya@bwh.harvard.edu.

Current author addresses and author contributions are available at Annals.org.

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Current Author Addresses: Dr. Brown: Division of Cardiovascular Medicine, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115.
Dr. Siddiqui: University of Alabama at Birmingham, 933 19th Street South, Room 115 Community Health Service Building, Birmingham, AL 35209.
Dr. Calhoun: University of Alabama at Birmingham, Division of Cardiology, BMR2 430, Birmingham, AL 35294.
Dr. Carey: PO Box 801414, University of Virginia Health System, Charlottesville, VA 22908.
Dr. Hopkins: Division of Cardiovascular Genetics, University of Utah School of Medicine, 50 North Medical Drive, Room 1160, Salt Lake City, UT 84132.
Drs. Williams and Vaidya: Center for Adrenal Disorders, Division of Endocrinology, Diabetes, and Hypertension, Brigham and Women's Hospital, Harvard Medical School, 221 Longwood Avenue, RFB, Boston, MA 02115.

Author Contributions: Conception and design: J.M. Brown, D.A. Calhoun, R.M. Carey, G.H. Williams, A. Vaidya.
Analysis and interpretation of the data: J.M. Brown, M. Siddiqui, D.A. Calhoun, R.M. Carey, A. Vaidya.
Drafting of the article: J.M. Brown, M. Siddiqui, A. Vaidya.
Critical revision of the article for important intellectual content: J.M. Brown, M. Siddiqui, R.M. Carey, P.N. Hopkins, G.H. Williams, A. Vaidya.
Final approval of the article: J.M. Brown, M. Siddiqui, D.A. Calhoun, R.M. Carey, P.N. Hopkins, G.H. Williams, A. Vaidya.
Provision of study materials or patients: M. Siddiqui, R.M. Carey, G.H. Williams, A. Vaidya.
Statistical expertise: P.N. Hopkins, A. Vaidya.
Obtaining of funding: D.A. Calhoun, R.M. Carey, A. Vaidya.
Administrative, technical, or logistic support: P.N. Hopkins, G.H. Williams, A. Vaidya.
Collection and assembly of data: J.M. Brown, M. Siddiqui, D.A. Calhoun, R.M. Carey, P.N. Hopkins, A. Vaidya.