Original Article

Screening Rates for Primary Aldosteronism in Resistant Hypertension

A Cohort Study

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Abstract—Resistant hypertension is associated with higher rates of cardiovascular disease, kidney disease, and death than primary hypertension. Although clinical practice guidelines recommend screening for primary aldosteronism among persons with resistant hypertension, rates of screening are unknown. We identified 145 670 persons with hypertension and excluded persons with congestive heart failure or advanced chronic kidney disease. Among this cohort, we studied 4660 persons ages 18 to <90 from the years 2008 to 2014 with resistant hypertension and available laboratory tests within the following 24 months. The screening rate for primary aldosteronism in persons with resistant hypertension was 2.1%. Screened persons were younger (55.9±13.3 versus 65.5±11.6 years; $P<0.0001$) and had higher systolic (145.1±24.3 versus 139.6±20.5 mm Hg; $P=0.04$) and diastolic blood pressure (81.8±13.6 versus 74.4±13.8 mm Hg; $P<0.0001$), lower rates of coronary artery disease (5.2% versus 14.2%; $P=0.01$), and lower serum potassium concentrations (3.9±0.6 versus 4.1±0.5 mmol/L; $P=0.04$) than unscreened persons. Screened persons had significantly higher rates of prescription for calcium channel blockers, mixed α/β-adrenergic receptor antagonists, sympatholytics, and vasodilators, and lower rates of prescription for loop, thiazide, and thiazide-type diuretics. The prescription of mineralocorticoid receptor antagonists or other potassium-sparing diuretics was not significantly different between groups ($P=0.20$). In conclusion, only 2.1% of eligible persons received a screening test within 2 years of meeting criteria for resistant hypertension. Low rates of screening were not due to the prescription of antihypertensive medications that may potentially interfere with interpretation of the screening test. Efforts to highlight guideline-recommended screening and targeted therapy are warranted. **(*Hypertension*. 2020;75:00-00. DOI: 10.1161/HYPERTENSIONAHA.119.14359.)**

Key Words: aldosterone ■ cardiovascular diseases ■ hypertension ■ renin

Hypertension is a common condition that affects ≈75 to 100 million adults (≈33% of the general population) in the United States.[1] With the publication of the 2017 American Heart Association/American College of Cardiology hypertension guidelines[2] recommending more intensive blood pressure control than prior Joint National Commission 7 and 8 guidelines,[3,4] many more persons will be classified with hypertension.[5] In concert, the 2017 guidelines have lowered the blood pressure threshold for classification of resistant hypertension (130/80 mm Hg, in contrast to 140/90 mm Hg in the Joint National Committee 7 and 8 reports[3,4]) such that the number of persons classified with resistant hypertension will also increase.[6]

Clinical studies suggest that the prevalence of resistant hypertension ranges from 8.9% to 33% of all persons with hypertension.[6–12] Resistant hypertension is associated with heightened risks of death, major cardiovascular events, left ventricular hypertrophy, progressive kidney disease, and cognitive impairment.[6–8,10,13,14] Rates of secondary, potentially reversible causes of hypertension are also higher among persons with resistant hypertension.[6]

Primary aldosteronism accounts for ≈20% of cases of resistant hypertension,[6,15–19] and its prevalence is estimated to be 5% to 10% among all persons with hypertension.[6,20–22] There is evidence to suggest that persons with primary aldosteronism have 4 to 12× higher rates of myocardial infarction, stroke, coronary artery disease, and arrhythmias[23,24] and poorer health-related quality of life[25–27] than persons with primary hypertension, independent of blood pressure. Persons with primary aldosteronism most commonly present with hypertension without classical hypokalemia, and for this reason, the diagnosis may be overlooked.[28,29] Thus, multiple national and international medical societies, including the American Heart Association, the American College of Cardiology, the Endocrine Society, the European Society of Hypertension, the French Society of Hypertension, Hypertension Canada, the Japan Endocrine Society, and the National Heart Foundation of Australia, recommend screening persons with resistant

Received November 11, 2019; first decision November 22, 2019; revision accepted December 23, 2019.

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hypertension for primary aldosteronism by obtaining a ratio of plasma aldosterone-to-plasma renin activity.[2,15,30–34] However, the rate of screening for primary aldosteronism in real-world practice is not known.

We sought to quantify screening rates for primary aldosteronism among persons with resistant hypertension within an academic health system and to determine factors associated with screening.

Methods

Consistent with Transparency and Openness Promotion Guidelines for authors publishing in an American Heart Association Journal, the data that support the findings of this study, including the algorithms to identify persons with resistant hypertension, are available from the corresponding author upon request.

Study Design and Participants

We assembled our electronic health registry using the Stanford Translational Research Integrated Database Environment, a research and development project at Stanford University to create a standards-based informatics platform supporting clinical and translational research.[35] We identified all persons aged 18 to <90 years from 2008 to 2014 with an *International Classification of Diseases, Ninth Revision* (*ICD-9*) code for hypertension (N=145 670; Figure). From this cohort, we excluded persons with a history of congestive heart failure (*ICD-9* codes: 428 525), who are often prescribed agents dually effective for the management of heart failure and hypertension (eg, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, β-adrenergic receptor antagonists, mixed α/β-adrenergic receptor antagonists, diuretics, nitrates, or vasodilators). We also excluded persons with chronic kidney disease stages 4 or 5, including persons with end-stage kidney disease (*ICD-9* codes: 585.4, 585.5, and 585.6). We then selected persons (N=5160) who met one of 2 criteria for the diagnosis of resistant hypertension[6]: (1) Blood pressure that remained above goal (>140/90 mm Hg) despite prescription orders for 3 antihypertensive drug classes, one of which was a diuretic. We imposed a requirement that the recorded blood pressure measurement >140/90 mm Hg must have occurred on at least 2 separate occasions, measured at least one week after the start of the third drug (N=2337); (2) Prescription orders for 4 or more antihypertensive drug classes, regardless of blood pressure control (N=2823).

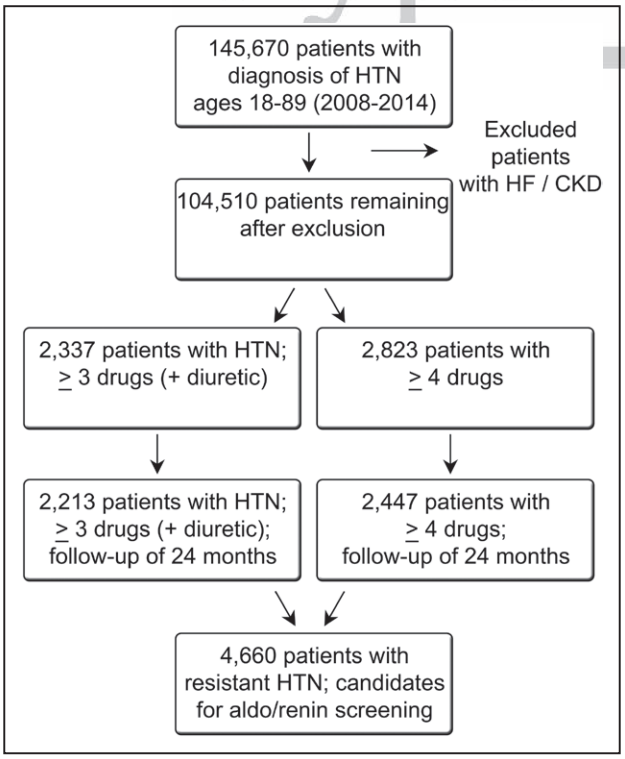

Figure. Cohort definition. CKD indicates chronic kidney disease stages 4, 5, or end-stage kidney disease; HF, heart failure; and HTN, hypertension.

We ascertained antihypertensive medication use data through the EpiC Clarity database.[36] We consolidated antihypertensive medications into the following drug classes: angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, loop diuretics, and thiazide (ie, hydrochlorothiazide) or thiazide-type (ie, chlorthalidone, indapamide, or metolazone) diuretics. Additional classes included potassium-sparing diuretics such as mineralocorticoid receptor antagonists and epithelial sodium channel inhibitors, α and β-adrenergic receptor antagonists, direct renin inhibitors, sympatholytics, and vasodilators. To ensure that persons were prescribed 3 or more antihypertensive drug classes simultaneously, we designed and programmed a novel crossover algorithm. Using this algorithm, we searched for an overlap of at least 21 days during which persons were on 3 or more antihypertensive drug classes. We treated combination antihypertensive drugs as 2 separate classes. To program this algorithm, we obtained start and end dates for each drug class and then collapsed each class revealing overlapping periods of drug usage.

To ensure that we captured all persons with resistant hypertension who also had the opportunity to be screened for primary aldosteronism, we excluded persons without a laboratory blood draw within 24 months following inclusion in the cohort. In the remaining persons (N=4660), we analyzed rates of screening, a laboratory order for plasma aldosterone, as well as demographic and clinical data. We also performed systematic chart review of 100 persons randomly chosen and evenly distributed among those who met a 3-drug or 4-drug criteria and were screened or unscreened. We accurately identified screen-eligible resistant hypertension and antihypertensive prescription data in 82% and 94% of persons using the 3-drug and 4-drug criteria, respectively. We performed a series of companion analyses in which we excluded persons who were: (1) not seen by a primary care provider within our health system; (2) treated with potassium-sparing diuretics; or (3) given a diagnosis of primary hyperaldosteronism.

We deidentified all data sets generated for this study according to the Health Insurance Portability and Accountability Act and did not contact any patients for the study. The Institutional Review Board at Stanford University approved the study protocol, including a waiver of informed consent for this study.

Descriptive Analyses of Patient Characteristics

We tabulated patient factors, including age, sex, race/ethnicity, insurance status (private, public, unknown), and systolic and diastolic blood pressure. We also identified diagnoses for secondary causes of hypertension by *ICD-9* code(s): artery stenosis (403, 405.91, and 440.1), fibromuscular dysplasia (447.3), obstructive sleep apnea (327.23), Conn syndrome (255.12), hyperaldosteronism (255.1), Cushing syndrome (255.0), and pheochromocytoma (227). It should be noted that the *ICD* codes for these secondary causes of hypertension are observations from individuals before they met resistant hypertension criteria and do not represent outcomes after screening. We measured comorbidities using qualitative and quantitative variables: smoking status (never, smoker, missing), alcoholism (*ICD-9* code: 303), polysubstance abuse (*ICD-9* code: 305.9), type 2 diabetes mellitus (*ICD-9* codes: 250.X0, 250.X2 or abnormal laboratory values according to American Diabetes Association guidelines [any 2 of the following: hemoglobin A1c >6.5% ever, fasting blood glucose >126 mg/dL, random blood glucose >200 mg/dL, or oral glucose tolerance test >200 mg/dL]),[37] Quetélet (body mass) index (in kg/m^2), coronary artery disease or myocardial infarction (*ICD-9* codes: 410.4, 410.7, 410.71, 410.9, and 414.01), percutaneous coronary intervention (V45.82), cerebrovascular accident or transient ischemic attack (*ICD-9* codes: 434.11, 435.9, and 437.9), or peripheral vascular disease (*ICD-9* codes: 443.9 and 440.2).

Statistical Analysis

For continuous variables, we present means and SDs or medians with 25th, 75th percentile ranges and compared groups by Student *t* test or the Wilcoxon rank-sum test, respectively. For categorical variables, we present frequencies and proportions and compared groups by the χ^2 test. We defined significance as a 2-tailed $P<0.05$. We performed statistical analysis using R version 3.4.3 and SAS 9.4 (SAS Institute Inc, Cary, NC).

Role of the Funding Source

The funder for this study had no role in the study design, data collection, data analysis, data interpretation, or writing of this article. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Of the 145 670 persons ages 18 to <90 from the years 2008 to 2014 with an *ICD-9* diagnosis of hypertension, 5160 persons (3.7%) met stringently defined criteria for resistant hypertension, of which 4660 persons also had the opportunity to obtain a screening lab within the following 24 months. Of the 4660, 97 (2.1%) were screened for primary aldosteronism in accordance with recommendations from clinical practice guidelines. Individuals that met the 4-drug rather than 3-drug criteria were more likely to be screened (2.8% versus 1.3%, $P=0.005$). The median time to screening was 145 days (25th, 75th percentile range, [24, 346]).

As depicted in Table 1, screened persons were on average younger than unscreened persons (55.9±13.3 versus 65.6±11.6 years; $P<0.0001$). There were no differences in screening rates by sex or race/ethnicity. Additionally, screened persons had a higher mean systolic (145.1±24.3 versus 139.6±20.5 mm Hg; $P=0.04$) and diastolic blood pressure (81.8±13.6 versus 74.4±13.8 mm Hg; $P<0.0001$) and more often had private health insurance (40.2% versus 24.8%; $P<0.0001$) than unscreened persons. Among secondary causes of hypertension, screened persons had higher prevalence of an ICD-9 code for renal artery stenosis (12.4% versus 7.0%; $P=0.04$), hyperaldosteronism (11.3% versus 0.1%; $P<0.0001$), and pheochromocytoma (5.2% versus 0.4%; $P<0.0001$) but not fibromuscular dysplasia or Cushing syndrome. With respect to comorbidities, unscreened persons had a higher prevalence of *ICD-9* codes for coronary artery disease (14.2% versus 5.2%; $P=0.01$) and peripheral arterial disease (5.3% versus 0.0%; $P=0.006$). There were no differences in rates of smoking, alcohol use, or polysubstance abuse and no difference in diabetes mellitus or obesity among screened and unscreened persons. Regarding clinical parameters, screened persons had significantly lower serum potassium concentrations (3.9±0.6 versus 4.1±0.5 mmol/L; $P=0.04$) than unscreened persons.

Screened persons were significantly more likely to have a visit with a primary care provider within the integrated health network in the 24-month follow-up period than persons who were unscreened (50.5% versus 39.6%; $P=0.03$). However, when we restricted the analysis to persons who visited their primary care physician within this 24-month period, only 2.6% of persons (49/1858) were screened.

With respect to antihypertensive drug classes (Table 2), screened persons were more frequently prescribed calcium channel blockers (71.1% versus 57.2%; $P=0.006$), mixed α and β-adrenergic receptor antagonists (15.5% versus 9.2%; $P=0.03$), sympatholytics (26.8% versus 11.0%; $P<0.0001$), and systemic vasodilators (11.3% versus 5.2%; $P=0.008$). Conversely, unscreened persons had a higher prescription rate for loop (18.2% versus 9.3%; $P=0.02$) and thiazide and thiazide-type diuretics (75.8% versus 61.9%; $P=0.002$), but there was no difference in the use of potassium-sparing diuretics (28.1% versus 34.0%; $P=0.20$). Among persons who met criteria for screening (N=4660), 28.3% were ordered a potassium-sparing diuretic. Of those persons with resistant hypertension prescribed 4 or more drug classes, 30.1% had medication orders for a potassium-sparing diuretic.

We also examined screening rates by excluding specific subgroups for whom the screening test would not be interpretable or who may have been screened before cohort entry. When we eliminated persons with an *ICD-9* code for primary aldosteronism (Conn syndrome or hyperaldosteronism; N=14) and were prescribed a potassium-sparing diuretic (N=1654), 69 persons (1.7%) were screened.

Discussion

We assessed adherence to established clinical practice guidelines addressing the diagnostic approach for persons with resistant hypertension. A survey of general practitioners in Europe noted that the diagnosis of primary aldosteronism did not match estimates of disease prevalence, but screening rates were not assessed.[29] Screening for primary aldosteronism can lead to higher rates of diagnosis at specialty centers,[38] but our study found a profoundly low rate of screening (2.1%) in a broad-based academic medical center- and community-based health system. This rate is substantially lower than conventional screening rates (eg, for common cancers (50% to 80%).[39]

Primary aldosteronism is reported to be present in 5% to 10% of persons with hypertension and is more common among patients with resistant hypertension.[6,15,16] In view of the most recent guidelines that recommend significantly lower blood pressure targets (ie, <130/80 mm Hg),[2] it is essential that we consider evaluation, diagnosis, and treatment of primary aldosteronism for persons with hypertension, in particular, those with resistant hypertension. Biochemical testing with the plasma aldosterone-to-plasma renin activity ratio and identification of the subtype of primary aldosteronism are critical to provide appropriate treatment options.[15] Patients with primary aldosteronism have markedly worse clinical outcomes than patients with primary hypertension when matched for blood pressure, including a multi-fold higher risk of major cardiovascular events, including ischemia, heart failure, and arrhythmia.[23,24]

There is evidence that screening and further workup to diagnose aldosterone-producing adenomas is fruitful. Results from the Prevention And Treatment of Hypertension With Algorithm based therapY-2 (PATHWAY-2) trial indicate that persons with resistant hypertension are most sensitive to inhibitors of aldosterone action.[40,41] However, performing adrenalectomy in those with appropriate indications (as opposed to empirical medical treatment with mineralocorticoid receptor antagonists or other potassium-sparing diuretics) is associated with significantly lower rates of all-cause mortality (hazard ratio =0.23),[42]

Table 1. Descriptive analysis of persons with resistant hypertension.

Variable	Description	All (N=4660)	Unscreened (N=4563)	Screened (N=97)	p-value
DEMOGRAPHICS					
Age		65.3 (11.7)	65.5 (11.6)	55.9 (13.3)	<0.0001
Sex	Female	2410 (51.7%)	2354 (51.6%)	56 (57.7%)	0.23
	Male	2250 (48.3%)	2209 (48.4%)	41 (42.3%)	
Race / Ethnicity	Asian	657 (14.1%)	644 (14.1%)	13 (13.4%)	0.83
	Black	371 (8.0%)	361 (7.9%)	10 (10.3%)	
	Other	805 (17.3%)	786 (17.2%)	19 (19.6%)	
	Unknown	139 (3.0%)	137 (3.0%)	2 (2.1%)	
	White	2688 (57.7%)	2635 (57.7%)	53 (54.6%)	
Insurance Status	Private	1171 (25.1%)	1132 (24.8%)	39 (40.2%)	<0.0001
	Public	2155 (46.2%)	2129 (46.7%)	26 (26.8%)	
	Unknown	1334 (28.6%)	1302 (28.5%)	32 (33.0%)	
Systolic Blood Pressure		139.7 (20.6)	139.6 (20.5)	145.1 (24.3)	0.04
	Missing	210 (4.5%)	204 (4.5%)	6 (6.2%)	
Diastolic Blood Pressure		74.6 (13.9)	74.4 (13.8)	81.8 (13.6)	<0.0001
	Missing	210 (4.5%)	204 (4.5%)	6 (6.2%)	
SECONDARY CAUSES of HTN					
Renal Artery Stenosis	N	4246 (91.1%)	4164 (91.3%)	82 (84.5%)	0.04
	Y	331 (7.1%)	319 (7.0%)	12 (12.4%)	
	Missing	83 (1.8%)	80 (1.8%)	3 (3.1%)	
Fibromuscular Dysplasia	N	4574 (98.2%)	4480 (98.2%)	94 (96.9%)	0.94
	Y	3 (0.1%)	3 (0.1%)	0	
	Missing	83 (1.8%)	80 (1.8%)	3 (3.1%)	
Obstructive Sleep Apnea	N	4115 (88.3%)	4027 (88.3%)	88 (90.7%)	0.23
	Y	462 (9.9%)	456 (10.0%)	6 (6.2%)	
	Missing	83 (1.8%)	80 (1.8%)	3 (3.1%)	
Conn's syndrome	N	4576 (98.2%)	4482 (98.2%)	94 (96.9%)	0.97
	Y	1 (0.0%)	1 (0.0%)	0	
	Missing	83 (1.8%)	80 (1.8%)	3 (3.1%)	
Hyperaldosteronism	N	4563 (97.9%)	4480 (98.2%)	83 (85.6%)	<0.0001
	Y	14 (0.3%)	3 (0.1%)	11 (11.3%)	
	Missing	83 (1.8%)	80 (1.8%)	3 (3.1%)	
Cushing's Syndrome	N	4566 (98.0%)	4472 (98.0%)	94 (96.9%)	0.8
	Y	11 (0.2%)	11 (0.2%)	0	
	Missing	83 (1.8%)	80 (1.8%)	3 (3.1%)	
Pheochromocytoma	N	4553 (97.7%)	4464 (97.8%)	89 (91.8%)	<0.0001
	Y	24 (0.5%)	19 (0.4%)	5 (5.2%)	
	Missing	83 (1.8%)	80 (1.8%)	3 (3.1%)	
CO-MORBIDITIES					
Smoking	Never	2061 (44.2%)	2024 (44.4%)	37 (38.1%)	0.40
	Smoker	1522 (32.7%)	1489 (32.6%)	33 (34.0%)	
	Missing	1077 (23.1%)	1050 (23.0%)	27 (27.8%)	
Alcoholism	N	4492 (96.4%)	4399 (96.4%)	93 (95.9%)	0.31

(*Continued*)

Table 1. Continued

Variable	Description	All (N=4660)	Unscreened (N=4563)	Screened (N=97)	p-value
	Y	85 (1.8%)	84 (1.8%)	1 (1.0%)	
	Missing	83 (1.8%)	80 (1.8%)	3 (3.1%)	
Polysubstance Abuse	N	4545 (97.5%)	4451 (97.5%)	94 (96.9%)	0.51
	Y	32 (0.7%)	32 (0.7%)	0	
	Missing	83 (1.8%)	80 (1.8%)	3 (3.1%)	
Diabetes Mellitus	N	3560 (76.4%)	3478 (76.2%)	82 (84.5%)	0.06
	Y	1100 (23.6%)	1085 (23.8%)	15 (15.5%)	
Body Mass Index		29.0 (25.0, 34.0)	29.0 (25.0, 34.0)	29.0 (25.0, 33.0)	0.87
Coronary Artery Disease	N	3922 (84.2%)	3833 (84.0%)	89 (91.8%)	0.01
	Y	655 (14.1%)	650 (14.2%)	5 (5.2%)	
	Missing	83 (1.8%)	80 (1.8%)	3 (3.1%)	
Percutaneous Coronary Intervention	N	4375 (93.9%)	4281 (93.8%)	94 (96.9%)	0.04
	Y	202 (4.3%)	202 (4.4%)	0	
	Missing	83 (1.8%)	80 (1.8%)	3 (3.1%)	
Cerebrovascular Accident /	N	4402 (94.5%)	4312 (94.5%)	90 (92.8%)	0.19
Transient Ischemic Attack	Y	175 (3.8%)	171 (3.7%)	4 (4.1%)	
	Missing	83 (1.8%)	80 (1.8%)	3 (3.1%)	
Peripheral Vascular Disease	N	4337 (93.1%)	4243 (93.0%)	94 (96.9%)	0.006
	Y	240 (5.2%)	240 (5.3%)	0	
	Missing	83 (1.8%)	80 (1.8%)	3 (3.1%)	
CLINICAL DATA					
Estimated Glomerular Filtration Rate (mL/min/1.73m^2)		73.3 (22.5)	73.2 (22.5)	77.9 (23.4)	0.09
	Missing	843 (18.1%)	824 (18.1%)	19 (19.6%)	
Serum creatinine (mg/dL)		1.1 (0.4)	1.1 (0.4)	1.1 (0.4)	0.94
	Missing	843 (18.1%)	824 (18.1%)	19 (19.6%)	
Serum potassium (mmol/L)		4.0 (0.5)	4.1 (0.5)	3.9 (0.6)	0.04
	Missing	865 (18.6%)	847 (18.6%)	18 (18.6%)	

For continuous variables means and standard deviations are presented. Since body mass index was skewed we presented the median and interquartile range. For categorical variables, frequencies and percentages are presented.

HTN, hypertension

prolongation of freedom from atrial fibrillation,[43] and reduced incidence of chronic kidney disease.[44] Adrenalectomy (relative to empirical medical therapy) is cost-effective and associated with a significant increase in quality-adjusted life-years saved.[45] Older age at diagnosis and longer duration of hypertension in persons with surgically correctable primary aldosteronism has been associated with worse clinical outcomes after unilateral adrenalectomy,[46–48] including higher blood pressure and the ongoing need for antihypertensive medications. These data suggest that delays in diagnosis may result in an attenuated response to surgical therapy. Therefore, early diagnosis of patients—in particular, those with surgically correctable disease—has the potential to save and improve lives.

If we conservatively estimate that only 5% of patients with diagnosed hypertension have resistant hypertension, 20% of those with resistant hypertension have primary aldosteronism, and ≈33% of patients with primary aldosteronism have unilateral hypersecretion of aldosterone, then over 300 000 persons in the United States have the potential to be cured of their hypertension by surgery.[1,15,49] This estimate does not include additional patients with unilateral aldosterone-producing adenoma who present rather with hypertension and hypokalemia, hypertension with an adrenal nodule or hypertension and obstructive sleep apnea—3 other overlapping cohorts for whom screening for primary aldosteronism is recommended.[15] Despite these data and numerous guideline recommendations, our study shows that there may be insufficient screening for primary aldosteronism.

Screening persons with resistant hypertension is also valuable for other secondary causes of hypertension. In addition to primary aldosteronism (high aldosterone and low renin), persons with normal aldosterone and low renin may be candidates for empirical mineralocorticoid receptor antagonists on epithelial sodium channel inhibitors as demonstrated in the PATHWAY-2 trial.[40,41] For persons with low aldosterone and low renin with Liddle syndrome or a Liddle-like phenotype, an epithelial sodium channel inhibitor, for example, amiloride,

Table 2. Antihypertensive drug classes in Unscreened and Screened persons

Drug Class	All (N=4660)	Unscreened (N=4563)	Screened (N=97)	p-value
Primary Antihypertensives				
Angiotensin Converting Enzyme Inhibitors	2122 (45.5%)	2082 (45.6%)	40 (41.2%)	0.39
Angiotensin II Receptor Blockers	1926 (41.3%)	1884 (41.3%)	42 (43.3%)	0.69
Calcium Channel Blockers	2677 (57.5%)	2608 (57.2%)	69 (71.1%)	0.006
Loop Diuretics	839 (18.0%)	830 (18.2%)	9 (9.3%)	0.02
Thiazide and Thiazide-type Diuretics	3518 (75.5%)	3458 (75.8%)	60 (61.9%)	0.002
Secondary Antihypertensives				
Potassium Sparing Diuretics	1317 (28.3%)	1284 (28.1%)	33 (34.0%)	0.20
Alpha Adrenergic Receptor Antagonists	341 (7.3%)	334 (7.3%)	7 (7.2%)	0.97
Beta Adrenergic Receptor Antagonists	2616 (56.1%)	2557 (56.0%)	59 (60.8%)	0.35
Alpha/Beta Adrenergic Receptor Antagonists	433 (9.3%)	418 (9.2%)	15 (15.5%)	0.03
Direct Renin Inhibitors	58 (1.2%)	55 (1.2%)	3 (3.1%)	0.09
Sympatholytics	526 (11.3%)	500 (11.0%)	26 (26.8%)	<0.0001
Systemic Vasodilators	248 (5.3%)	237 (5.2%)	11 (11.3%)	0.008
Coronary Vasodilators	207 (4.4%)	206 (4.5%)	1 (1.0%)	0.05

may represent a superior, targeted therapy.[50–54] Genetic causes of hypertension are enriched in blacks and more common than previously appreciated.[54,55] Moreover, screening may reveal renovascular disease or renin-producing tumors (high aldosterone, high renin) and guide therapy.[6,54]

We examined factors associated with screening among persons with resistant hypertension. These data suggest that providers may be more suspicious of secondary causes of hypertension in persons who are younger, more hypertensive, have a lower serum potassium and an *ICD-9* code for endocrine causes of hypertension (hyperaldosteronism or pheochromocytoma). Persons with substantial comorbid disease, such as coronary or peripheral artery disease, were less likely to be screened. This observation may suggest that providers are more willing to consider diagnostic tests to tailor medical versus surgical therapies in persons who have lower surgical risk or could represent therapeutic nihilism.

Several guidelines recommend withdrawal of potassium-sparing diuretics before screening.[6,15,56] Interpretation of the screening plasma aldosterone-to-plasma renin activity ratio may be confounded if the patient is taking one of several drug classes.[57,58] Thus, it is reasonable to consider that many providers may have deferred screening due to interfering medications or confusion regarding the optimal approach to screening in the setting of select medication use. First, we considered whether the lack of screening was due to the use of specific antihypertensive drug classes that may empirically treat primary aldosteronism. Empirical treatment involves the use of potassium-sparing diuretics—either mineralocorticoid receptor antagonists (spironolactone or eplerenone) or epithelial sodium channel inhibitors (specifically amiloride, as triamterene carries a higher risk of kidney injury[59])—which are effective for controlling hypertension in this disorder.[40,41] In our cohort, 28.3% of persons with resistant hypertension were prescribed these drug classes, and this prescription rate is higher than estimates from national epidemiological studies.[60] However, we found no significant difference in the prescription of potassium-sparing diuretics between persons who were screened versus unscreened. When we excluded persons prescribed these medications, the screening rate was similar to that in the overall cohort.

Second, interpretation of the aldosterone-to-renin ratio while concurrently using an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker can increase the false-negative rate by limiting aldosterone secretion. In our study, 86.7% of persons with resistant hypertension were prescribed one of these drug classes; however, rates of screening in these persons were not significantly different (Table 2). Third, use of loop, thiazide, or thiazide-type diuretics can invoke hypokalemia, another criterion for screening for primary aldosteronism.[15] Conversely, these diuretics can increase the false-negative rate by raising plasma renin activity. Prescription for loop and thiazide-type diuretics were significantly higher among unscreened persons. Fourth, β or mixed α/β-adrenergic receptor antagonists and sympatholytics can increase the false positive rate by suppressing renin secretion.[57] However, these drug classes were prescribed similarly or more frequently in screened persons. Taken together, medication use is an insufficient explanation for these exceptionally low screening rates. Notably, this study allowed for screening up to 2 years after meeting resistant hypertension criteria. We think this is a reasonable amount of time to withdraw drugs to undergo screening should the practitioner have believed that the patient could safely have one or more agents held short-term. In practice, most agents need not be withdrawn, the screening test can be interpreted within the context of medication use, and concern over false positive or negative results may be overstated.

We note several limitations to our study. First, we analyzed data from an integrated, academic healthcare system with affiliated community-based practices. There may be some ascertainment bias related to persons with resistant hypertension who might have been seen for tertiary care/second

opinions and may have already received screening by a primary care provider or specialist outside of the purview of our electronic health record. However, the rate of screening in persons with primary care visits within our healthcare system was only 2.6%. Also, when we excluded persons who were more likely to have received screening tests before cohort entry, that is, those with prescriptions for potassium-sparing diuretics or an *ICD-9* code for primary aldosteronism, screening rates remained low. We also used an order for plasma aldosterone, rather than a completed laboratory test, to account for persons who have their blood work performed at a local laboratory not affiliated with our electronic health record. Second, we did not have access to medication adherence data. However, even if a substantial number of those that we classified as having resistant hypertension were non-adherent[61,62] and were thus removed from the cohort, the fraction of those who were screened remains unacceptable. For example, if only 10% of individuals were adherent to medications and thus only 466 individuals met criteria for resistant hypertension, this would result in a screening rate of only 21%. Third, the definitions for resistant hypertension,[6] includes maximum tolerable doses of medications. While there are many reasons to escalate therapy with an additional class of antihypertensive medication due to a dose-limiting side effect with current therapy (eg, peripheral edema with calcium channel blockers; hyponatremia or hyperuricemia/gout with thiazide-type diuretics; or bradycardia with β-adrenergic receptor antagonists), we cannot know for certain. Fourth, our use of *ICD-9* codes for the diagnosis of hypertension has previously been validated[11,63,64]; however, clinic blood pressures may be influenced by poor measurement techniques[65] and the use of over-the-counter drugs (ie, nonsteroidal anti-inflammatory drugs, decongestants), caffeine, and certain illicit drugs (ie, methamphetamines and cocaine) which we could not assess. Fifth, we cannot determine the rates of screening in persons with heart failure or advanced chronic kidney disease as we excluded them from the analysis. We acknowledge these limitations but they are unlikely to materially change the conclusions of this study.

We detected a lower rate of resistant hypertension (3.7%) among persons with hypertension than in other published cohorts.[6–12] To avoid misclassification bias, we used a more stringent definition of resistant hypertension that excluded persons who may be taking antihypertensive drugs for heart failure or advanced chronic kidney disease. In doing so, we may have reduced our sensitivity, as there are likely persons who developed heart failure or advanced chronic kidney disease secondary to hypertension that was resistant to conventional 3-drug therapy. We also required a 21-consecutive day prescription to exclude the classification of resistant hypertension due to acute emergency room visits or hospitalizations. We devised and validated our search algorithms based on *ICD-9* codes, blood pressure readings, and conventional definitions of resistant hypertension with rigorous exclusion of conditions that would confound screening. Notably, despite fewer persons with resistant hypertension, as noted above, the prescription of potassium-sparing diuretics at this primary and tertiary medical center exceeded national averages,[60] suggesting that physicians were actively managing these persons with severe hypertension.

We quantified screening rates in persons with resistant hypertension, but screening for primary aldosteronism is also recommended in persons with severe hypertension, hypertension with sporadic or diuretic-induced hypokalemia, hypertension with an incidental adrenal mass, and hypertension with sleep apnea.[15] Low screening rates have been found in individuals with hypertension and hypokalemia.[66] Increased use of screening has been shown to improve detection of primary aldosteronism across 5 continents.[38] These data highlight an opportunity to implement on-screen alerts to primary care providers and selected specialists through the electronic health record similar to those used to remind providers about breast or colorectal cancer screening or, for example, the provision of aspirin after acute myocardial infarction. The criteria for resistant hypertension are objective, and we demonstrate and validate an algorithm to identify appropriate persons for screening. On-screen alerts for the recognition of resistant hypertension could also encourage the use of empirical mineralocorticoid receptor antagonists or epithelial sodium channel inhibitors per guideline recommendations.[6] These findings also present an educational opportunity for the interpretation of this ratio and referral to a hypertension specialty practice.

Perspectives

The recommendation to screen persons with resistant hypertension using a plasma aldosterone-to-plasma renin activity ratio is recognized and endorsed by the American Heart Association and the American College of Cardiology as well as other national and international societies of Endocrinology, Cardiology, and Hypertension.[2,15,30–34] After the release of the 2017 American Heart Association hypertension guidelines that emphasize lower blood pressure targets[2] and lower blood pressure criteria to classify resistant hypertension,[6] the proper workup and identification of secondary causes of hypertension, notably primary aldosteronism, is more relevant than ever. Our study suggests substantial underscreening for primary aldosteronism, one of the most common causes of secondary hypertension and a condition associated with cardiovascular morbidity and mortality. Unidentified primary aldosteronism is associated with premature death, preventable strokes, and other consequential cardiovascular events along with poorer health-related quality of life. While there are many possible explanations for the underscreening of appropriate persons, this study represents an opportunity to implement screening practices in accordance with standard of care.

Acknowledgments

G. Jaffe, Z. Gray, M. Stedman, and Y. Zheng received support from the Division of Nephrology and the Department of Medicine in the Stanford University School of Medicine. G. Krishnan received support from the National Institutes of Health (NIH) UL1 TR001085. G.M. Chertow receives support from the NIH (1K24 DK085446). J.T. Leppert received support from the NIH (1K23 DK089086). V. Bhalla receives support from the Division of Nephrology and Stanford Health Care. The project described was supported by the National Center for Research Resources and the National Center for Advancing Translational Sciences, NIH, through grant UL1 TR001085. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. We thank Drs Tara Chang,

Robert Isom, and Joy Wu for helpful discussions and Dr Pablo Garcia for assistance with the graphical abstract.

Sources of Funding

This work was supported by the Department of Medicine, Stanford University School of Medicine; National Institutes of Health.

Disclosures

None.

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Novelty and Significance

What Is New?

- We quantify rates of screening and factors associated with screening in patients with resistant hypertension. In a large electronic health registry, we detected a profoundly low rate of screening; one in 50 eligible patients received a screening test within 2 years of meeting criteria for resistant hypertension.

What Is Relevant?

- Resistant hypertension is present in a substantial number of persons with hypertension and is associated with high rates of heart disease, stroke, kidney disease, and death. Despite guideline-based recommendations to screen for primary aldosteronism, screening rates in the community and factors associated with screening are unknown. We found that persons screened for primary aldosteronism were younger, had higher blood pressure, a lower serum potassium, and a lower rate of diagnosis of coronary artery disease. Low rates of screening were not due to a higher prescription rate of antihypertensive medications that may potentially interfere with interpretation of the screening test. In particular, although we detected a high prescription rate of potassium-sparing diuretics compared with other community cohorts, in companion analyses, screening rates did not differ even if we excluded this subgroup.

Summary

Our study suggests substantial underscreening for primary aldosteronism, one of the most common causes of secondary hypertension and a condition associated with cardiovascular morbidity and mortality. Unidentified primary aldosteronism is associated with premature death, preventable strokes, and other consequential cardiovascular events along with poorer health-related quality of life. Although there are many possible explanations for the underscreening of appropriate persons, this study represents an opportunity to implement screening practices in accordance with standard of care.