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Characteristics in the Electronic Medical Record Associated with Blood Pressure Response to Spironolactone in Patients with Resistant Hypertension

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ABSTRACT

Objective: Identify blood pressure (BP) response to spironolactone in patients with resistant hypertension using electronic medical records (EMRs) in order to estimate response in a real-world clinical setting.

Design: Developed an algorithm to determine BP and electrolyte response to spironolactone.

Setting: An academic medical center in Nashville, Tennessee

Population: Patients with resistant hypertension prescribed spironolactone.

Main Outcome Measures: Baseline BP and BP response, determined as the change in mean systolic and diastolic BP (SBP and DBP, respectively) following spironolactone initiation. Additional response measures were serum sodium, potassium, and creatinine, estimated glomerular filtration rate, hemoglobin A1c (HbA1c), glucose, high density lipoprotein, low density lipoprotein, triglycerides. Demographic characteristics included race, age, gender, body mass index (BMI), diabetes mellitus, chronic kidney disease stage three, ischemic heart disease, and smoking.

Results: The mean decreases in SBP and DBP were 8.1 and 3.4 mmHg, consistent with clinical trial data. Using a mean decrease in SBP of five mmHg or in DBP of two mmHg to define "responders," 30.3% of patients did not respond. In univariable analyses, responders had higher BMI, baseline SBP, DBP, sodium, and HbA1c, and lower creatinine. In multivariable analysis, responders were older and had significantly higher BMI and baseline SBP and DBP, and lower potassium. Increases in potassium and creatinine following spironolactone were larger in responders than in nonresponders. When BP was evaluated as a continuous variable, decreases in SBP and DBP correlated

with baseline BP, decrease in sodium, and increases in potassium and creatinine following spironolactone. Decreasing SBP was associated with decreasing glucose in European Americans.

Conclusions: We developed an algorithm to assess BP response to spironolactone, a commonly prescribed medication in patients with resistant hypertension. Electrolyte changes associated with the BP response are consistent with its mechanism of action of blocking the mineralocorticoid receptor and decreasing epithelial sodium channel activity.

ARTICLE SUMMARY

Strengths and Limitations of this study:

- This study defined the blood pressure response to spironolactone in a large number of patients with resistant hypertension using the electronic health record. The accuracy of algorithms for the identifying patients with resistant hypertension who were initiated on spironolactone were validated by manual review..
- The availability of clinical electrolyte measurements, in addition to blood pressure measurements, provides data supporting the mechanism of MR antagonism in responders to spironolactone.
- This study provides methodology which can be applied in future pharmacogenetic studies using electronic health records. The algorithm can be adapted for use in other large-scale electronic health record systems with linked genetic data.
- Limitations of this study include the inability to confirm medication adherence, a lack of ambulatory blood pressure measurements, and a lack of some laboratory measures, such HbA1c and lipids, for the entire population.

Keywords: spironolactone; mineralocorticoid receptor antagonist; blood pressure response; resistant hypertension; electronic medical record

INTRODUCTION

The mineralocorticoid receptor (MR) antagonist spironolactone has been identified as effective add-on therapy for blood pressure (BP) control in patients with resistant hypertension in clinical trials, including the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA) and the Prevention and Treatment of Hypertension with Algorithm Based Therapy-2 (PATHWAY-2).[1-4] In the PATHWAY-2 trial, addition of spironolactone at a dose of 25-50 mg/day to a therapeutic regimen containing an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB), calcium channel blocker (CCB), and thiazide-like diuretic significantly decreased home systolic blood pressure (SBP) by a mean of 8.7 mmHg.[1] In prior clinical studies the SBP/diastolic blood pressure (DBP) responses to spironolactone have ranged from a mean decrease of 4.6/1.8 mmHg to a mean decrease of 25/12 mmHg.[1-5]

Clinical trials often assess homogenous groups of patients limiting the applicability in a real-world clinical setting. We hypothesized that we could use electronic medical records (EMR) to assess the BP response to the addition of spironolactone in resistant hypertensive patients who were on a stable anti-hypertensive regimen of at least three medications including a thiazide diuretic or dihydropyridine CCB. We used a previously published algorithm for the identification of patients with resistant hypertension.[6] To evaluate the BP response to spironolactone we developed an additional algorithm to identify patients who were prescribed spironolactone during a period of stable medication use from up to six months before the start of spironolactone

to six months after. The accuracy of the algorithm was validated by electronic record review.

We collected all outpatient BPs and laboratory measurements during the period of stable medication use before and after initial spironolactone prescription. We assessed BP response as a continuous variable and as a dichotomized variable (responders vs non-responders). We also assessed electrolyte measurements relevant to the mechanism of action of spironolactone, MR antagonism.

METHODS

Electronic Medical Record

We obtained Institutional Review Board approval to access the Vanderbilt University Medical Center (VUMC) Synthetic Derivative (SD). The SD is a de-identified copy of the VUMC EMR with Health Insurance Portability and Accountability Act of 1996 (HIPAA) identifiers removed by established de-identification software as well as custom techniques.[7] The SD contains almost all available clinical data including basic demographics, such as race and sex; text from clinical care notes; laboratory values; inpatient and outpatient medication data; international classification of disease (ICD) and current procedural terminology (CPT) codes; and other diagnostic reports.[7] To date, the SD contains approximately 2.8 million records, approximately one million of which contain detailed longitudinal data.

Spironolactone Response Algorithm Development

Patients within the SD were identified as having resistant hypertension using a previously published algorithm.[6] Patients were defined as having resistant hypertension if their BP was greater than or equal to 140/90 mmHg, despite concurrent use of three antihypertensives including a thiazide diuretic or dihydropyridine CCB, or if they were taking four or more antihypertensive medications, including a thiazide diuretic or dihydropyridine CCB. Patients with secondary hypertension, chronic kidney disease (CKD) stages four and five, heart failure with reduced ejection fraction less than 35 percent, thyroid and parathyroid disorders, nephrotic syndrome, chronic

glomerulonephritis, anomalies of the bulbus cordis, coarctation of the aorta, adrenal gland neoplasms and disorders (excluding adrenal insufficiencies), chronic pulmonary heart disease, thyrotoxicosis, disorders of thyrocalcitonin secretion, and obstructive uropathy were excluded by the resistant hypertension algorithm (**Supplemental Table 2**).

All drug exposures to antihypertensive medications including spironolactone were identified from the SD by electronic-prescribing tools and MedEx.[8] The utility of these tools for extracting medication data from the EMR has been shown previously.[9, 10] For a medication exposure to be considered valid at least one of the following identifiers- dose, route, frequency, or duration- was required.

We developed an algorithm to identify patients in the SD who were prescribed spironolactone and in whom BP was measured within a stable window of time before and after initiation of spironolactone. Using electronic prescribing tools and MedEx,[8] the novel start date (NSD) for a spironolactone prescription was determined by the earliest mention of spironolactone, aldactone, or aldactazide in a patient's record after the patient met the resistant hypertension case definition. In addition, spironolactone, aldactone, or aldactazide prescription had to have been listed at least twice, at least one month apart, during the subsequent six-month period. Patients who were initiated on aldactazide (aldactone/hydrochlorothiazide combination therapy) were required to have been using a thiazide diuretic immediately prior to the NSD for aldactazide. Patients who were not prescribed a thiazide prior to the start of aldactazide were excluded as having been started on spironolactone and hydrochlorothiazide (HCTZ) concurrently. Use of the MR antagonist eplerenone was not included in the study as it was prescribed to only 2% of the resistant hypertensive population.

Patients prescribed spironolactone without an outpatient BP measurement in the six months before or after the NSD were excluded. Patients who were diagnosed with other indications for spironolactone including heart failure, hepatic cirrhosis, hyperandrogenism, acne, or polycystic ovarian syndrome within a year of the NSD were also excluded. Using the algorithm, we identified sliding time windows up to six months before (baseline) and six months after the NSD (response) when there were no changes to each patient's prescribed antihypertensive medications, including dose (when available), the number of medications, and class type (**Figure 1**).

Once the baseline and response periods were defined, all outpatient BP measurements taken during these periods were identified. Any patient without at least two BP measurements during the baseline and response periods was excluded. The SBP and DBP responses were calculated as the difference between the mean SBP or DBP in the stable post-treatment window minus the mean SBP or DBP in the pre-treatment window (e.g. $\Delta SBP = \overline{SBPpost} - \overline{SBPpre}$). Any SBP and DBP responses that were more than two standard deviations from the mean were reviewed manually to confirm accuracy.

We also defined patients as responders versus non-responders based on a review of BP responses reported in clinical trials of spironolactone in European (EA) and African Americans (AA).[1-5] We defined responders as those who had a decrease in mean SBP of at least five mmHg or a decrease in mean DBP of at least two mmHg, corresponding to the smallest SBP and DBP responses to spironolactone reported among the studies reviewed.[5]

All patient characteristics, including age, gender, race, body mass index (BMI), outpatient BP measurements, serum potassium, creatinine, and sodium, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, glucose, hemoglobin A1C (HbA1c), and history of CKD stage three, ischemic heart disease (IHD), type two diabetes mellitus (T2DM), and smoking, were extracted from the SD using a combination of ICD-9 and -10 codes, CPT codes, laboratory measurements, and natural-language processing (**Supplemental Table 1**). Aldosterone, renin, renin activity, and aldosterone-renin-ratio (ARR) were not evaluated due to the small numbers of patients with data. For each patient, age and BMI at NSD or the date closest to NSD was used. The estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease (MDRD) formula.[11] CKD stage three was defined as an eGFR $\geq$30 mL/min/1.73m^2 and $\leq$60 mL/min/1.73m^2 or equivalent ICD-9 or -10 code at any point before NSD. Patient race was administratively assigned in the SD based on either physician or patient report. Previous work has shown that self-identified race is highly correlated with genetic ancestry[12, 13] and administratively assigned race in the VUMC SD is sufficient for genetic association analyses[14] and correlates tightly with genetic ancestry.[13]

After the algorithms were iteratively refined, blinded chart reviews of randomly chosen, never overlapping, charts were performed to determine algorithm efficacy. Based on a population size of 17,082, review of 138 charts would allow detection of a misclassification rate of 10% with a margin of error of 5%. We therefore reviewed 150 charts to determine algorithm efficacy. The review consisted of 75 charts from resistant hypertensive patients that were included by the algorithm and 75 that were excluded. The

algorithm was refined until a negative predictive value (NPV), positive predictive value (PPV), sensitivity, and specificity greater than 90% was achieved based on the review of 150 charts. The final version of the algorithm will be made available at Phenotype KnowledgeBase (PheKB).[15]

Statistical Methods

Data are presented as frequencies for categorical variables and mean ± standard deviations for continuous variables. Univariable analysis for binary BP response was performed using Pearson's chi-squared test for categorical variables and the Wilcoxon rank-sum test for continuous variables. A multivariable logistic regression model or multivariable linear regression model was fitted for binary BP response and continuous BP change on all variables available in more than 70% of the population. Missing values were not imputed. HDL cholesterol, LDL cholesterol, triglycerides, and HbA1c were excluded from multivariable regression models due to large amounts of missing values. The method of complete-case analysis was used and a linear relationship was assumed for all the continuous variables. All statistical analyses were conducted using the SPSS software version 24 (SPSS, Chicago, IL, USA) or R 3.3.0.[16]

Patient and Public Involvement

Because this study involved the use of the VUMC SD, patients were not recruited and there was no intervention. While patients were not involved in the development of the specific research question or study design, there has been extensive patient and community engagement in the establishment of the SD. Further, a community advisory

board within the Vanderbilt Institute for Clinical and Translational Research (VICTR) reviews programs including the SD. Dissemination of study results will occur through local reporting of study results.

RESULTS

Algorithm validation

NPV, PPV, sensitivity, and specificity of the algorithm for spironolactone response were determined after the blinded review of 150 electronic records. All but one excluded record were excluded appropriately. That record was excluded by the algorithm due to an erroneous ascertainment that a medication other than spironolactone had been added during the response periods. Five of the 75 records included in the algorithm should have been excluded. Four of these patients had inconsistencies in their medication history during the baseline or response period. In another patient, spironolactone was listed as a potential therapy in several notes but was not apparently prescribed. Based on this review, the NPV was 98.7%, PPV was 93.3%, sensitivity was 98.6%, and specificity was 93.7%.

Identification of spironolactone response population

Among EA and AA patients with resistant hypertension in the SD 3,405 EA and 1,054 AA were prescribed spironolactone. After applying exclusion and inclusion criteria, 1,114 EA patients and 369 AA patients were included in the study for evaluation of spironolactone response, 32.7% and 35.0% of the original number of patients prescribed spironolactone, respectively (**Figure 2**). The median dose of spironolactone was 25 mg and ranged from 5 to 200 mg. The majority of patients included in the study, 1,043 (70.3%), were prescribed 25 mg of spironolactone. The average number of

outpatient BPs measured during the baseline and response periods were 4 and 4.8, respectively.

Characteristics of spironolactone responders and non-responders

Defining spironolactone response as a reduction in SBP of at least five mmHg or in DBP of at least two mmHg, we identified 1,034 responders (69.7%) and 449 non-responders (30.3%) in the total population. Of the responders, 15.8% met the criteria for a DBP response, 19.4% for a SBP response, and 64.8% for both a DBP and SBP response. Patient characteristics appear in **Table 1**. In univariable analyses, patients who responded to spironolactone were heavier and less likely to have a history of IHD. Responders had significantly higher baseline SBP, DBP, serum sodium, and HbA1c, and significantly lower baseline creatinine than nonresponders (**Table 1**). Responders also had greater decreases in serum sodium and eGFR as well as greater increases in serum potassium and creatinine after starting spironolactone than nonresponders (**Table 1**). HbA1c did not change in responders whereas it declined over time in non-responders. In a multivariable model adjusting for all variables present in at least 1000 patients, responders were older and heavier, had higher baseline SBP and DBP, had lower baseline serum potassium and had a greater increase in serum potassium and creatinine after starting spironolactone than non-responders (**Table 2**).

Table 1. Characteristics of spironolactone responders and nonresponders in the total population.

Variable	N	Nonresponders (n=449)	Responders (n=1,034)	p-value
Age, years	1483	63.67 ± 13.18	64.28 ± 12.63	0.33
Female, n (%)	1483	215 (47.9%)	532 (51.5%)	0.21
Black Race, n (%)	1483	106 (23.6%)	263 (25.4%)	0.46
BMI, kg/m^2	1358	32.2 ± 8.0	33.5 ± 8.3	0.004
Diagnostic History				
T2DM, n (%)	1483	236 (52.6%)	566 (54.7%)	0.44
CKD3, n (%)	1483	163 (36.3%)	398 (38.5%)	0.43
IHD, n (%)	1483	179 (39.9%)	351 (33.9%)	0.03
Smoking, n (%)	1483	96 (21.4%)	211 (20.4%)	0.67
Baseline measurements				
SBP, mmHg	1483	133.20 ± 17.40	147.59 ± 18.70	< 0.001
DBP, mmHg	1483	71.66 ± 11.74	79.00 ± 13.08	< 0.001

Serum sodium, mmol/L	1176	138.67 ± 3.22	139.25 ± 2.98	0.004
Serum potassium, mmol/L	1177	3.95 ± 0.47	3.91 ± 0.43	0.15
Creatinine, mg/dL	1184	1.12 ± 0.36	1.09 ± 0.42	0.03
eGFR, mL/min/1.73m^2	1382	76.73 ± 23.78	77.38 ± 20.95	0.51
Glucose, mg/dL	1179	125.56 ± 58.56	126.98 ± 50.61	0.80
HbA1c, %	538	6.91 ± 1.81	7.23 ± 3.06	0.02
HDL cholesterol, mg/dL	575	47.48 ± 17.97	45.53 ± 15.31	0.44
LDL cholesterol, mg/dL	537	95.65 ± 39.74	98.54 ± 34.72	0.41
Triglycerides, mg/dL	578	163.98 ± 111.71	169.39 ± 121.20	0.85
Difference from baseline following initial spironolactone prescription				
Serum sodium, mmol/L	1101	-0.49 ± 2.63	-0.95 ± 2.70	0.006
Serum potassium, mmol/L	1104	0.13 ± 0.48	0.25 ± 0.42	< 0.001

Creatinine, mg/dL	1108	0.02 ± 0.23	0.134 ± 0.30	< 0.001
eGFR, mL/min/1.73m^2	1254	-5.22 ± 15.73	-9.09 ± 15.10	< 0.001
Glucose, mg/dL	1101	-0.27 ± 47.82	-0.37 ± 40.62	0.88
HbA1c, %	284	-0.25 ± 1.23	0.02 ± 1.05	0.02
HDL cholesterol, mg/dL	214	0.70 ± 11.51	-1.36 ± 9.35	0.23
LDL cholesterol, mg/dL	197	-5.74 ± 32.54	-7.48 ± 34.94	0.77
Triglycerides, mg/dL	220	-17.86 ± 107.95	-19.43 ± 107.16	0.91

Abbreviations: BMI, body mass index; CKD3, chronic kidney disease stage three; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; IHD, ischemic heart disease; LDL, low-density lipoprotein; N, number of individuals with the specific measure; SBP, systolic blood pressure; T2DM, type 2 diabetes mellitus.

Data are presented as mean ± standard deviation for continuous variables and count (%) for categorical variables

Table 2. Multivariable logistic regression model for responder versus non-responder in the total population without missing data (N=1019).

	Odds Ratio*	95% Confidence Interval	p-value
Age, years	1.034	1.017-1.052	< 0.001
Gender, Male: Female	0.897	0.603-1.323	0.59
Race, White: Black	1.217	0.800-1.849	0.36
Mean BMI, kg/m^2	1.030	1.008-1.054	0.01
Diagnostic history			
T2DM, Yes: No	1.132	0.794-1.615	0.49
CKD3, Yes: No	0.932	0.654-1.330	0.70
IHD, Yes: No	1.256	0.905-1.749	0.18
Smoking, Yes: No	1.074	0.745-1.559	0.71
Baseline measurements			
SBP, mmHg	1.034	1.023-1.046	< 0.001
DBP, mmHg	1.043	1.025-1.062	< 0.001

Serum sodium, mmol/L	1.013	0.957-1.071	0.66
Serum potassium, mmol/L	1.686	1.106-2.588	0.02
Creatinine, mg/dL	1.266	0.603-2.995	0.57
eGFR, mL/min/1.73m^2	1.007	0.993-1.021	0.32
Glucose, mg/dL	0.999	0.996-1.003	0.80
Difference from baseline following initial spironolactone prescription			
Serum sodium, mmol/L	0.946	0.888-1.007	0.08
Serum potassium, mmol/L	1.968	1.290-3.030	0.002
Creatinine, mg/dL	3.570	1.610-9.131	0.004
eGFR, mL/min/1.73m^2	1.001	0.987-1.015	0.92
Glucose, mg/dL	0.997	0.992-1.001	0.12

Abbreviations: BMI, body mass index; CKD 3, chronic kidney disease stage three; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; IHD, ischemic heart disease; N, number of individuals included in the analysis; SBP, systolic blood pressure.

*For continuous variables, the odds ratio reflects the effect of a one-unit increase. For example, a one mmHg increase in baseline SBP increases the odds ratio for responder versus non-responder 0.03.

Among EA patients, 343 (30.8%) did not respond to spironolactone. EA responders were heavier and less likely to have IHD. They had higher baseline SBP, DBP, and serum sodium than nonresponders (**Supplemental Table 3**). EA responders also had a greater decrease in serum sodium and eGFR and a greater increase in serum potassium and creatinine after starting spironolactone (**Supplemental Table 3**).

Among AA patients, 106 (28.7%) did not respond to spironolactone. Like EA responders, AA responders had significantly higher baseline SBP and DBP and a greater decrease in serum sodium and increase in creatinine after starting spironolactone than nonresponders (**Supplemental Table 4**).

Blood pressure response to spironolactone as a continuous variable

For the entire group, the mean decrease in SBP following initiation of spironolactone was 8.1 mmHg and the mean decrease in DBP was 3.4 mmHg following initial spironolactone prescription. Analyses of BP change as a continuous variable were performed using a multivariable model that included all variables except for HbA1c, HDL cholesterol, LDL cholesterol, and triglycerides, as data were not available in the majority of patients.

In the total population, patients with higher baseline SBP, lower baseline creatinine, and a greater decrease in serum sodium, increase in serum potassium, or increase in creatinine after starting spironolactone had greater reductions in SBP (**Table 3** and **Figure 3**). Patients with higher baseline SBP and DBP and a greater decrease in serum sodium, increase in serum potassium, or increase in creatinine after spironolactone

had greater reductions in DBP (**Table 3**). Older patients and female patients also had significantly greater reductions in DBP (**Table 3**).

Table 3. Significant coefficients in multivariable models for change in systolic and diastolic blood pressures.

	Associated Variable	Coefficient	95% Confidence Interval	p-value
Total population (N=1019)				
Change in SBP	Baseline SBP	-0.415	-0.475, -0.356	< 0.001
	Baseline creatinine	3.628	0.202, 7.054	0.04
	Change in serum sodium	0.701	0.338, 1.064	< 0.001
	Change in serum potassium	-3.483	-5.834, -1.131	0.004
	Change in creatinine	-5.039	-8.704, -1.374	0.01
Change in DBP	Age	-0.141	-0.196, -0.086	< 0.001
	Gender- Male: Female	1.390	0.170, 2.610	0.03

	Baseline SBP	-0.045	-0.080, -0.011	0.01
	Baseline DBP	-0.379	-0.436, -0.321	< 0.001
	Change in serum sodium	0.274	0.063, 0.485	0.01
	Change in serum potassium	-2.042	-3.413, -0.671	0.004
	Change in creatinine	-3.979	-6.116, -1.841	< 0.001
European Americans (N=753)				
Change in SBP	Baseline SBP	-0.401	-0.470, -0.333	< 0.001
	Change in serum sodium	0.525	0.117, 0.933	0.01
	Change in serum potassium	-3.074	-5.766, -0.381	0.03
	Change in glucose	0.031	0.003, 0.059	0.03

Change in DBP	Age	-0.135	-0.200, -0.070	< 0.001
	Gender, Male: Female	1.669	0.230, 3.108	0.02
	Baseline SBP	-0.045	-0.084, -0.005	0.03
	Baseline DBP	-0.370	-0.436, -0.303	< 0.001
	Change in serum potassium	-1.809	-3.385, -0.232	0.03
	Change in creatinine	-3.328	-5.772, -0.884	0.01
African Americans (N=266)				
Change in SBP	Baseline SBP	-0.445	-0.571, -0.319	< 0.001
	Baseline creatinine	5.572	0.017, 11.127	0.05
	Change in serum sodium	1.338	0.517, 2.159	0.002
	Change in potassium	-5.206	-10.205, -0.207	0.04

	Change in creatinine	-10.923	-19.456, -2.391	0.01
Change in DBP	Age	-0.156	-0.265, -0.046	0.01
	Baseline DBP	-0.407	-0.512, -0.278	< 0.001
	Change in sodium	0.530	0.053-1.007	0.03
	Change in potassium	-2.864	-5.768, 0.039	0.05
	Change in creatinine	-7.370	-12.326, -2.413	0.004

Abbreviations: DBP, diastolic blood pressure; N, number of individuals included in the analysis; SBP, systolic blood pressure.

In EA alone, a greater decrease in either SBP or DBP was significantly associated with baseline SBP, as well as increase in serum potassium (**Table 3**). A greater reductions in SBP was further associated with greater decreases in serum sodium and glucose (**Table 3**). The change in DBP was also significantly associated with age, sex, and creatinine (**Table 3**).

In AA, greater reductions in SBP and DBP were significantly associated with greater decreases in serum sodium and increases in serum potassium and creatinine (**Table 3**). Patients with higher baseline SBP and baseline creatinine had a greater reduction in SBP, while patients with higher baseline DBP and older age had a greater reduction in DBP (**Table 3**).

DISCUSSION

We developed a highly accurate algorithm to define the BP response to spironolactone in patients with resistant hypertension using the EMR. The mean decreases in SBP and DBP for the total study population, 8.1 mmHg and 3.4 mmHg, respectively, are consistent with responses reported in prior clinical trials, such as the PATHWAY-2 trial.[1] In total, 30.3% of patients prescribed spironolactone did not achieve a five mmHg decrease in SBP or two mmHg decrease in DBP in the six months following spironolactone initiation. Higher pretreatment SBP and DBP predicted a greater therapeutic response to spironolactone, measured either as a dichotomous or continuous variable. Response to spironolactone was associated with a greater decrease in serum sodium and greater increase in serum potassium, consistent with effective MR blockade.

By blocking the MR, spironolactone inhibits the aldosterone-stimulated increase in serum and glucocorticoid receptor kinase (SGK1) expression. This results in a decrease in the phosphorylation of neural precursor cell-expressed

developmentally downregulated (gene 4) protein (NEDD4-2) resulting in NEDD4-2-dependent downregulation of the epithelial sodium channel (ENaC). We found that BP decrease after spironolactone correlated significantly with an increase in serum sodium and a decrease in serum potassium, consistent with a decrease in ENaC activity. These results suggest that individuals exhibiting smaller decreases in BP may have relatively increased residual ENaC activity during spironolactone. In the present study, we are unable to determine if this inadequate BP response is due to inadequate spironolactone dose, spironolactone noncompliance, or non-MR mediated ENaC activation.

We found a significant correlation between decreasing BP and increasing creatinine after starting spironolactone in all groups. An increase in creatinine can result from hemodynamic effects of BP medications and especially from blocking the renin-angiotensin-aldosterone system (RAAS).[1] Clinical trials of ACEis and ARBs also demonstrate an initial decrease in eGFR or increase in serum creatinine with RAAS blockade even as these drugs slow the rate of renal decline.[17, 18] Nevertheless National Kidney Foundations-Kidney Disease

Outcomes Quality Initiative (NKF-KDOQI) guidelines, recommend decreasing ACEi and ARB dose and monitoring eGFR frequently in patients in whom serum creatinine increases more than 30% after initiation of one of these drugs.[19] Similar conservative measures may be warranted in patients in whom creatinine increases significantly after initiation of spironolactone.

In the present study, we also observed a significant correlation between the SBP response and decreasing glucose in EA, whereas among those in whom it was measured before and after therapy, HbA1c declined in nonresponders but not responders. The latter observation may reflect the fact that responders had a higher baseline HbA1c than non-responders. The impact of spironolactone on glucose homeostasis is of particular interest in patients with resistant hypertension because T2DM is a common comorbidity. In fact, in our study population, 566 patients (56%) had a history of T2DM prior to the initiation of spironolactone. The potential for spironolactone to improve glucose is supported by a murine study of diet-induced metabolic dysfunction that identified an improvement in glucose levels after initiation of spironolactone *in vivo*.[20] Further,

in another rodent study investigating the role of low-dose spironolactone on oxidative stress and insulin-stimulated glucose transport spironolactone treatment significantly improved in insulin signaling and insulin-stimulated glucose uptake in skeletal muscle.[21]

While these findings may suggest a potential benefit to glucose management from MR antagonism it is important to note that the exact relationship between MR antagonism and glucose is not perfectly understood. Contrary to the aforementioned murine studies and our results, clinical trials in patients with T2DM and heart failure have reported increases in glucose and HbA1c after starting spironolactone.[2, 22] One potential explanation for the inconsistency between the observed relationship between BP response and change in SBP in EA patients and those reported in previous clinical trials is that clinical glucose measurements are often not made while patients are fasting. Because glucose management is an important aspect of health in the majority of patients with resistant hypertension and because our findings, as well as others,

suggest an association between spironolactone use and glucose levels additional studies to better characterize this relationship are warranted.

A lack of BP response to spironolactone in some patients could result from non-adherence. A limitation of this study and many other studies of resistant hypertension is the inability to measure adherence directly in the patients prescribed spironolactone without measuring drug levels, which is not routinely done in clinical practice. Nonadherence alone does not likely explain the lack of BP response in nonresponders, however. First, patients nonadherent to spironolactone would likely be nonadherent to other medications. Nonadherent patients, therefore, would be expected to have higher baseline BPs than adherent patients. To the contrary, we found that nonresponders had lower baseline SBP and DBP than responders and baseline SBP and DBP significantly predicted BP response. In addition, initiation of spironolactone resulted in an increase in serum potassium and decrease in serum sodium in non-responders as well as responders, albeit to a lesser degree. Taken together these findings

suggest that nonadherence is not the predominant driver of the lack of BP response in non-responders.

Another way to assess adequacy of spironolactone dose is to assess whether renin activity remains suppressed. Unfortunately, an insufficient number of patients had renin measured during the baseline and response periods to assess change in renin concentration or activity. The limited number of renin measurements in the EMR is reflective of poor screening rates for primary aldosteronism.[23] Previous studies have reported limited value in the addition of aldosterone levels or the ARR to prediction models of BP response to MR antagonism in resistant hypertension, however.[24, 25]

Other limitations of the study include the exclusion of a significant number of patients with resistant hypertension due to inadequate documentation of pre- and post-treatment BPs. The relatively small number of AA limits the power to detect predictors of response to spironolactone in this group.

In conclusion, we have developed a highly accurate algorithm for the assessment of BP response to spironolactone, a commonly prescribed medication, in patients with

resistant hypertension using EMR. Electrolyte changes associated with the BP response to spironolactone are consistent with its mechanism of action to block the MR and decrease activity of ENaC. The finding that the response to spironolactone correlated with a decrease in glucose in EA could be consistent with a beneficial effect of spironolactone on insulin sensitivity or insulin secretory capacity.

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DISCLOSURES

None

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FIGURE LEGENDS

Figure 1. Schematic of the spironolactone response algorithm and identification of the baseline and response periods for patients. The earliest date a patient was prescribed spironolactone is indicated by the novel start date (NSD). The baseline period is determined by identifying all visits in which same three medication classes as prescribed to the patient as on the NSD. If the visit date for the start of the baseline period occurred more than six months before the NSD a baseline period of six months was used. The determination of the response period is not shown in the schematic above. Similar logic was applied to the selection of this period.

Figure 2. Diagram of the algorithm for the identification of patients with resistant hypertension in the VUMC Synthetic Derivative (SD) prescribed spironolactone during a period of stable medication use for the evaluation of blood pressure response.

Figure 3. The significant correlations with systolic blood pressure change in the total population. Correlation between the change in systolic blood pressure (SBP) after starting spironolactone and baseline A) SBP [correlation coefficient (CC)= -0.415, p<0.001], and the change in B) creatinine (CC= -5.039, p=0.01), C) serum sodium (CC= 0.701, p<0.001), and D) serum potassium (CC= -3.483, p= 0.004).

AUTHOR STATEMENT

Contributorship

MMS and NJB contributed to the design of the study; MMS, BP, HN, CY, JML, and NJB contributed to the analysis and interpretation of the results; MMS and NJB contributed to the drafting of the manuscript; MMS, BP, HN, CY, JML, and NJB contributed to the editing of the manuscript and final approval for submission

Competing Interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: Dr Brown reports consulting for Shire HGT, Novartis Pharmaceuticals, Viamet Pharmaceuticals and serving on

the Scientific Advisory Board of Alnylam Pharmaceuticals. Dr. Brown also sits on the Joint Scientific Committee for the Vanderbilt Bayer Alliance. All authors report no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Patient Consent

No identifiable patient data was used in the study.

Ethical Approval

The study was approved by the Vanderbilt University Medical Center Institutional Review Board (#130848).

Transparency Declaration

M. Shuey affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Data Sharing

The full data set is available upon request to the corresponding author.

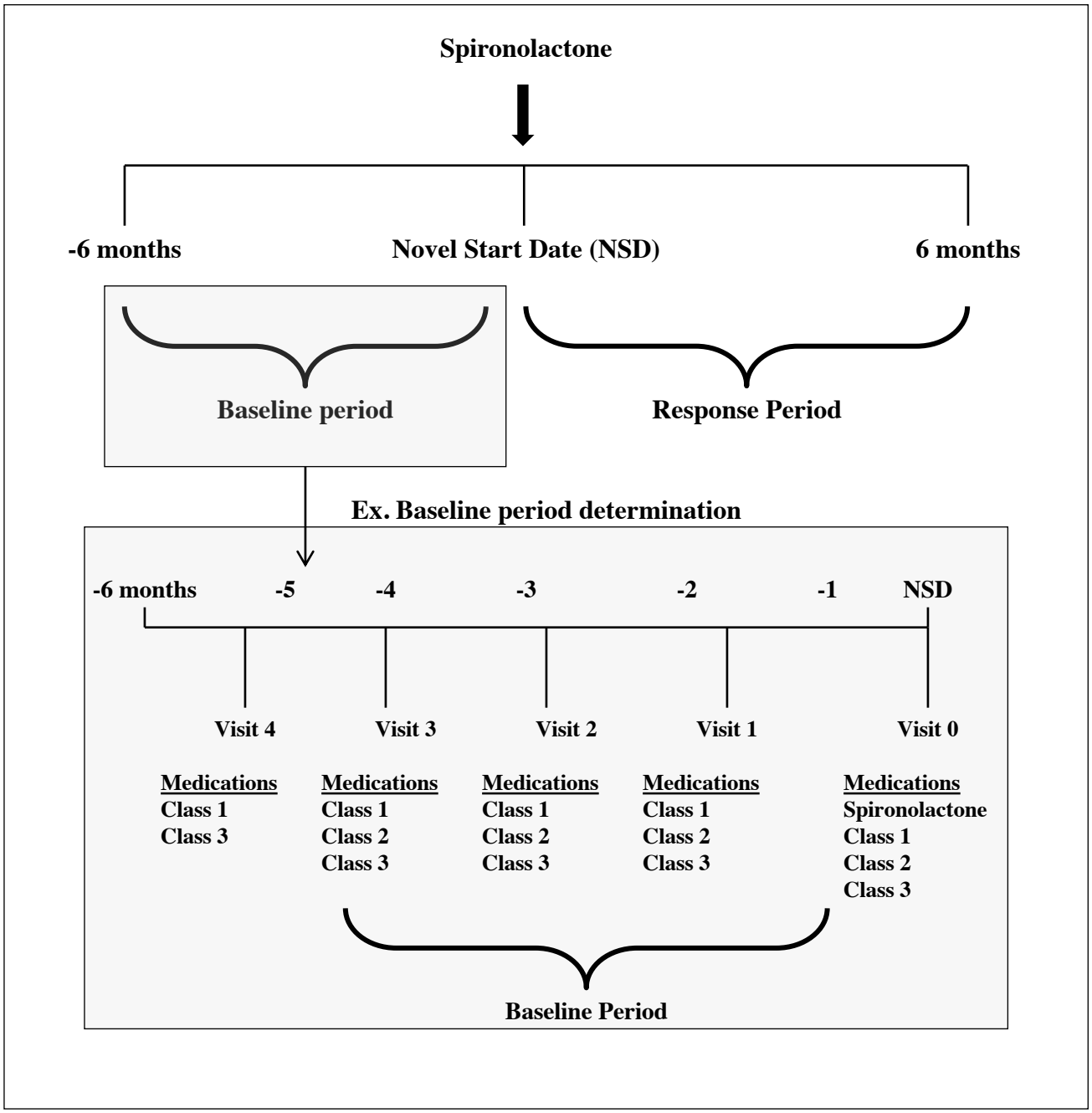
WHAT THIS PAPER ADDS

What is already known on this subject

Patients with resistant hypertension represent a subset of hypertensive patients with difficult to control hypertension despite adequate medication prescription. Spironolactone, a MR antagonist, has been identified by numerous clinical trials as the preferred add-on therapy for BP control in patients with resistant hypertension

What this study adds

Using a large clinical cohort derived from the EMR we determined that 30.3% of the patients prescribed spironolactone did not achieve a mean decrease in either SBP or DBP of at least 5 mmHg or 2 mmHg, respectively. Consistent with spironolactone's mechanism of action we demonstrate that the decrease in BP was significantly associated with changes in serum sodium and potassium. We also demonstrate that decreasing BP is associated with a decrease in eGFR and increase in creatinine similar to that observed following RAAS antagonism by ACEis or ARBs. Finally, the association between change in BP and glucose homeostasis warrants further scrutiny.


Spironolactone
-6 months
Novel Start Date (NSD)
6 months
Baseline period
Response Period
Ex. Baseline period determination
-6 months
-5
-4
-3
-2
-1
NSD
Visit 4
Visit 3
Visit 2
Visit 1
Visit 0
Medications
Class 1
Class 3
Medications
Class 1
Class 2
Class 3
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Spironolactone
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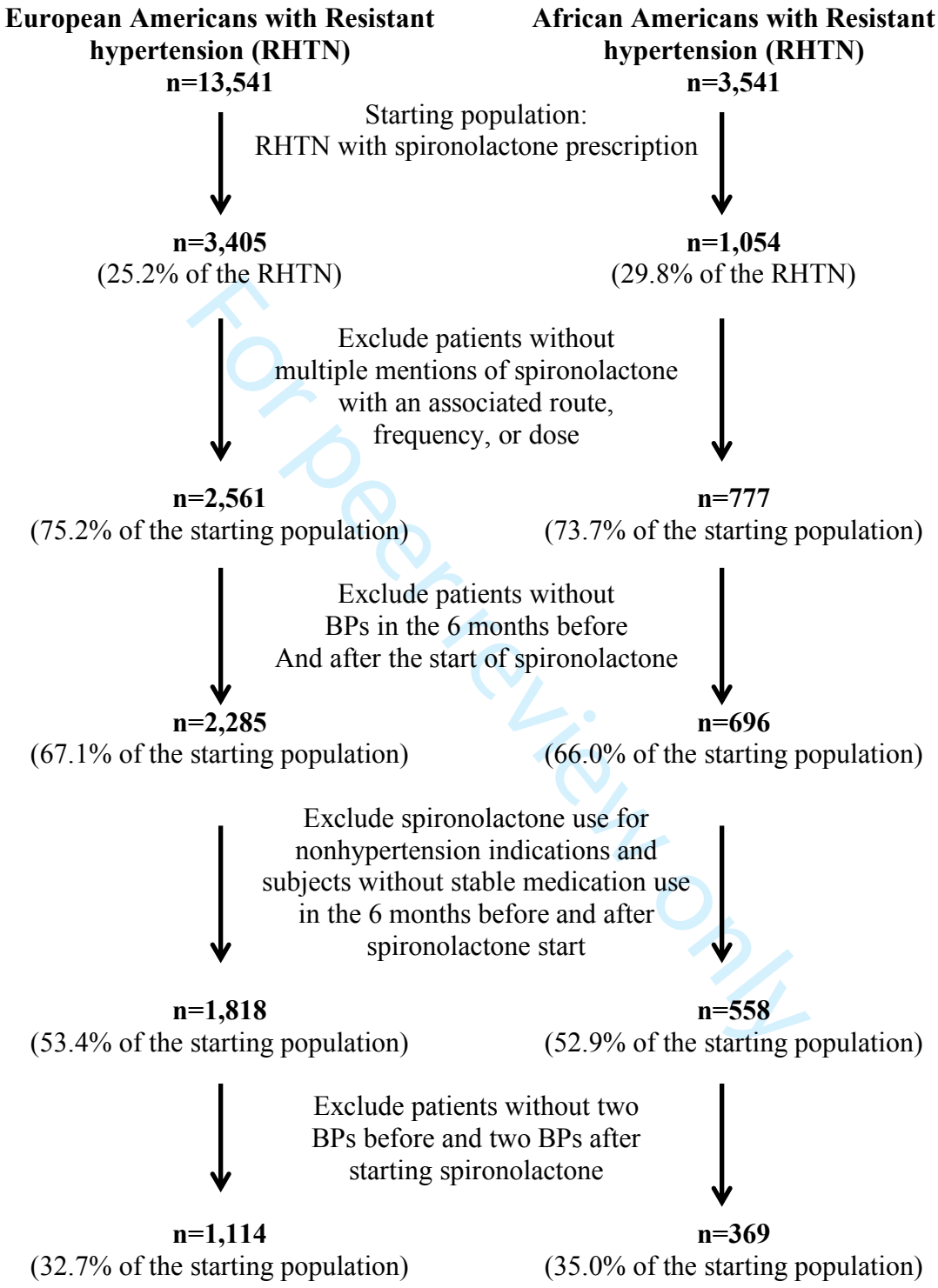
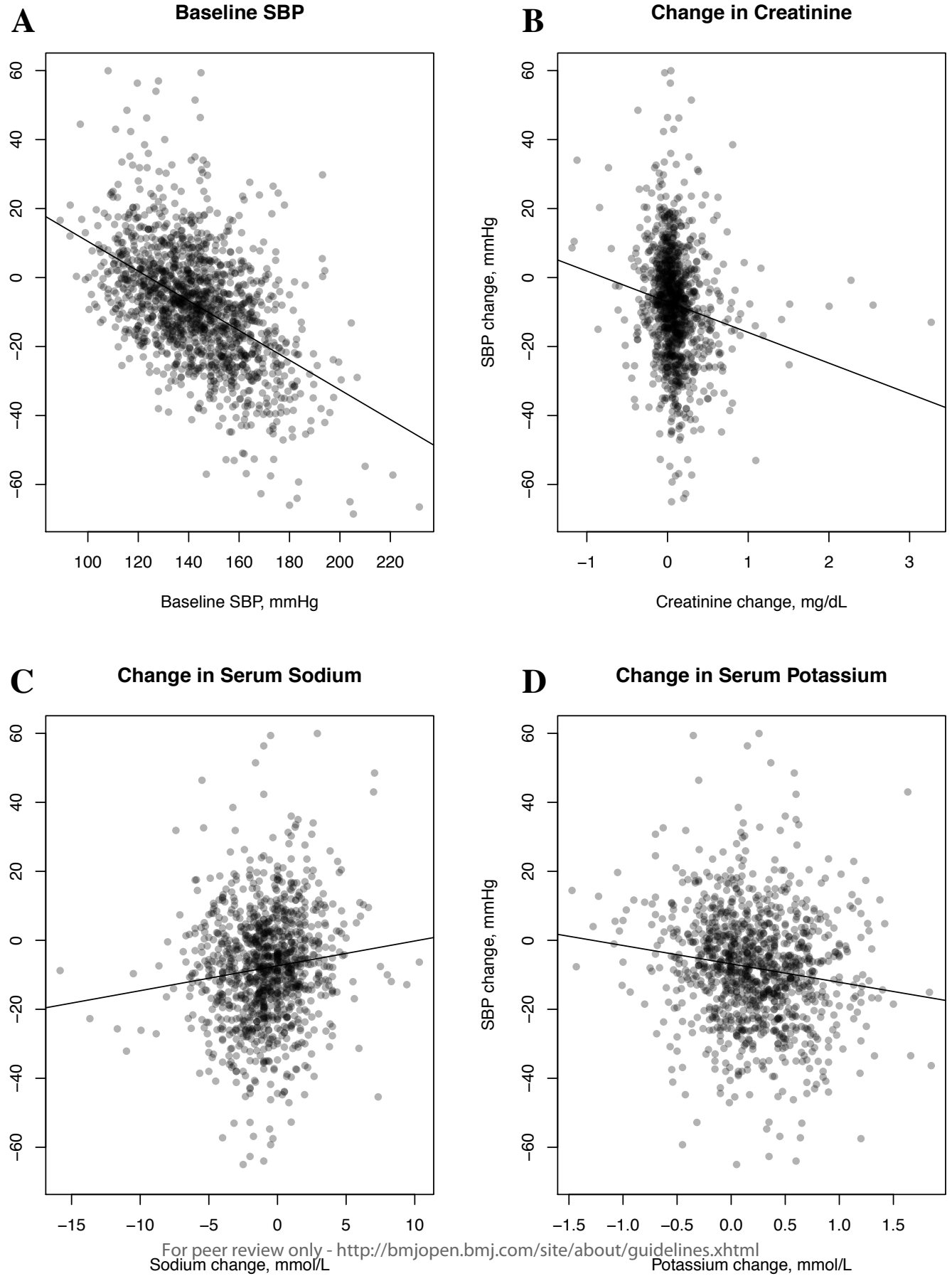
Class 2
Class 3
Baseline Period





DATA SUPPLEMENT

Supplemental Table 1. International Classifiers of Disease (ICD)-9 and ICD-10 codes used for history of diagnosis

Diagnosis	ICD-9 codes	ICD-10 codes	Other
Chronic kidney disease	585.1	N18.1	eGFR > 30 mL/min/1.73
stage 3	585.2	N18.2	m^2 but < 60 mL/min/1.73
			m^2
Ischemic heart disease	410.*	I20.*	
	411.*	I22.*	
	413.*	I24.*	
	414.*	125.*	
Type 2 diabetes mellitus	250	E11	
	250.*	E11.*	
	327.2*	G47.3*	
Smoking	305.1	F17.*	
	V15.82	Z87.891	

Abbreviations: eGFR, estimated glomerular filtration rate

Supplemental Table 2. International Classifiers of Disease (ICD)-9 and -10 exclusions for resistant hypertensive subjects

Description	ICD-9-CM codes	ICD-10-CM-codes
Exclusion for Case Type I, Case Type II, and Control if ever present in a patient record		
Malignant neoplasm of unspecified adrenal gland	194.0	C74.9
Benign neoplasm of unspecified adrenal gland	227.0	D35.00
Disorders of the adrenal gland (excluding adrenal insufficiencies)	255.0, 255.1*, 255.2, 255.3, 255.6, 255.8, 255.9	E24.*, E26.*, E25.*, E27.0, E27.5, E27.8, E27.9
Secondary Hypertension	405.*	I15.0, I15.8
Chronic pulmonary heart disease	416.*	I27. *
Nephrotic syndrome	581.*	N04.*, N08
Chronic glomerulonephritis	582.*	N03.*, N08
Bulbus cordis anomalies	745.*	Q20.*, Q21.*
Coarctation of aorta	747.1*	Q25.1, Q25.2
Exclusion for Case Type I and Case Type II if present in a patient record 5 years before or 1 year after identification as a Case		
Thyrotoxicosis	242.*	E05.*
Disorder of thyrocalcitonin secretion	246.0	E07.0
Disorders of the thyroid NEC	246.8	E03.4, E07.89
Disorders of the thyroid NOS	246.9	E07.9
Parathyroid disorder NEC	252.8	E21.4
Parathyroid disorder NOS	252.9	E21.5
Obstructive uropathy	599.6*	N13.9

Abbreviations: NEC, not elsewhere classified; NOS, not otherwise classified

Supplemental Table 3. Characteristics of spironolactone responders and nonresponders in European Americans.

Variable	N	Nonresponders (n=343)	Responders (n=771)	p-value*
Age, years	1,114	65.66 ± 13.09	66.21 ± 12.04	0.50
Female, n (%)	1,114	151 (44.0%)	368 (47.7%)	0.25
BMI, kg/m^2	1,023	31.3 ± 7.2	32.5 ± 7.7	0.01
Diagnostic History				
T2DM, n (%)	1,114	173 (50.4%)	393 (51.0%)	0.87
CKD3, n (%)	1,114	124 (36.2%)	296 (38.4%)	0.48
IHD, n (%)	1,114	149 (43.4%)	280 (36.3%)	0.02
Smoking, n (%)	1,114	75 (21.9%)	157 (20.4%)	0.57
Baseline measures				
SBP, mmHg	1,114	131.37 ± 16.99	145.91 ± 18.52	< 0.001
DBP, mmHg	1,114	69.46 ± 10.88	76.78 ± 12.52	< 0.001
Serum sodium, mmol/L	872	138.45 ± 3.26	139.04 ± 3.00	0.01
Serum potassium, mmol/L	871	3.99 ± 0.46	3.93 ± 0.43	0.07
Creatinine, mg/dL	878	1.11 ± 0.37	1.07 ± 0.37	0.11
eGFR, mL/min/1.73m^2	1,029	75.16 ± 24.47	75.23 ± 19.83	0.96

Glucose, mg/dL	875	124.46 ± 56.69	126.59 ± 48.81	0.57
HbA1c, %	383	6.76 ± 1.67	7.24 ± 3.54	0.10
HDL cholesterol, mg/dL	420	46.96 ± 18.89	44.11 ± 14.83	0.10
LDL cholesterol, mg/dL	390	92.09 ± 37.86	95.30 ± 34.75	0.43
Triglycerides, mg/dL	426	167.8 ± 117.0	182.5 ± 129.4	0.27
Difference from baseline following initial spironolactone prescription				
Serum sodium, mmol/L	810	-0.70 ± 2.63	-1.12 ± 2.71	0.04
Serum potassium, mmol/L	812	0.12 ± 0.48	0.27 ± 0.43	< 0.001
Creatinine, mg/dL	816	0.01 ± 0.23	0.13 ± 0.32	< 0.001
eGFR, mL/min/1.73m^2	924	-4.82 ± 15.68	-8.76 ± 14.51	< 0.001
Glucose, mg/dL	810	1.44 ± 47.52	0.01 ± 39.03	0.65
HbA1c, %	181	-0.13 ± 1.31	-0.05 ± 0.92	0.63
HDL cholesterol, mg/dL	156	0.03 ± 9.35	-0.94 ± 8.62	0.54
LDL cholesterol, mg/dL	142	-7.29 ± 35.21	-8.63 ± 35.09	0.86
Triglycerides, mg/dL	162	-11.99 ± 107.79	-22.93 ± 121.66	0.59

Abbreviations: BMI, body mass index; CKD 3, chronic kidney disease stage three; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; IHD, ischemic heart disease; LDL, low-density

lipoprotein; N, number of individuals with the specific measure; SBP, systolic blood pressure.

Data are presented as mean ± standard deviation for continuous variables and count (%) for categorical variables.

* P-values from the multivariable regression model are provided for all variables except HbA1c, HDL cholesterol, LDL cholesterol, and triglycerides. Univariate p-values are provided for these variables.

Supplemental Table 4. Characteristics of spironolactone responders and nonresponders in African Americans.

Variable	N	Nonresponders (n=106)	Responders (n=263)	p-value*
Age, years	369	57.23 ± 11.30	58.65 ± 12.64	0.32
Female, n (%)	369	64 (60.3%)	164 (62.4%)	0.72
BMI, kg/m^2	335	35.3 ± 9.7	37.3 ± 9.2	0.40
Diagnostic History				
T2DM, n (%)	369	63 (59.4%)	173 (65.7%)	0.25
CKD3, n (%)	369	39 (36.8%)	102 (38.8%)	0.72
IHD, n (%)	369	30 (28.3%)	71 (27.0%)	0.80
Smoking, n (%)	369	21 (19.8%)	211 (20.5%)	0.87
Baseline measures				
SBP, mmHg	369	139.15 ± 17.46	152.51 ± 18.40	< 0.001
DBP, mmHg	369	78.78 ± 11.67	85.50 ± 12.53	< 0.001
Serum sodium, mmol/L	304	139.37 ± 3.00	139.81 ± 2.85	0.23
Serum potassium, mmol/L	304	3.81 ± 0.50	3.84 ± 0.44	0.58
Creatinine, mg/dL	306	1.14 ± 0.33	1.16 ± 0.54	0.73
eGFR, mL/min/1.73m^2	353	81.69 + 20.78	83.42 + 22.80	0.51

Glucose, mg/dL	304	129.05 ± 64.32	128.05 ± 55.37	0.89
HbA1c, %	155	7.45 ± 2.17	7.22 ± 1.65	0.50
HDL cholesterol, mg/dL	155	49.07 ± 14.93	49.21 ± 15.95	0.56
LDL cholesterol, mg/dL	147	106.51 ± 43.81	106.70 ± 33.43	0.98
Triglycerides, mg/dL	152	151.35 ± 92.16	135.01 ± 88.22	0.34
Difference from baseline following initial spironolactone prescription				
Serum sodium, mmol/L	291	0.17 ± 2.52	-0.52 ± 2.63	0.05
Serum potassium, mmol/L	292	0.16 ± 0.50	0.19 ± 0.39	0.57
Creatinine, mg/dL	292	0.06 ± 0.23	0.14 ± 0.26	0.01
eGFR, mL/min/1.73m^2	330	-6.50 ± 15.89	-9.99 ± 16.61	0.09
Glucose, mg/dL	291	-5.56 ± 48.63	-1.37 ± 44.65	0.48
HbA1c, %	103	-0.54 ± 0.97	0.02 ± 1.23	0.09
HDL cholesterol, mg/dL	58	3.17 ± 17.66	-1.67 ± 10.92	0.24
LDL cholesterol, mg/dL	55	0.04 ± 19.86	-4.82 ± 34.85	0.65
Triglycerides, mg/dL	58	-43.47 ± 109.99	-11.64 ± 61.01	0.21

Abbreviations: BMI, body mass index; CKD 3, chronic kidney disease stage three; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; IHD, ischemic heart disease; LDL, low-density

lipoprotein; N, number of individuals with the specific measure; SBP, systolic blood pressure.

Data are presented as mean ± standard deviation for continuous variables and count (%) for categorical variables.

* P-values from the multivariable regression model are provided for all variables except HbA1c, HDL cholesterol, LDL cholesterol, and triglycerides. Univariate p-values are provided for these variables.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1,2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2,3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5-6, 7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7-11
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-11
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-11, Supplemental Table 1
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	7-9, 13, Figure 2
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9, 11
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	11
		(*b*) Describe any methods used to examine subgroups and interactions	11
		(*c*) Explain how missing data were addressed	11
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	10-11
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	13, Figure 2
		(b) Give reasons for non-participation at each stage	Figure 2
		(c) Consider use of a flow diagram	Figure 2
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	14, Tables 1 and 2
		(b) Indicate number of participants with missing data for each variable of interest	Tables 1 and 2
		(c) Summarise follow-up time (eg, average and total amount)	13, Figure 2
Outcome data	15*	Report numbers of outcome events or summary measures over time	13-19
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	14-20, Table 1, 2, and 3
		(*b*) Report category boundaries when continuous variables were categorized	13
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Table 3, Supplemental tables 3 and 4
Discussion			
Key results	18	Summarise key results with reference to study objectives	24-27
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	4, 26-27
Generalisability	21	Discuss the generalisability (external validity) of the study results	4, 26-27
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	29

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Development of an Electronic Algorithm to Determine and Characterize the Blood Pressure Response to Spironolactone in Patients with Apparent Therapy-resistant Hypertension in an Electronic Medical Record

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Development of an Electronic Algorithm to Determine and Characterize the Blood Pressure Response to Spironolactone in Patients with Apparent Therapy-resistant Hypertension in an Electronic Medical Record

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ABSTRACT

Objective: Identify blood pressure (BP) response to spironolactone in patients with apparent therapy-resistant hypertension (aTRH) using electronic medical records (EMRs) in order to estimate response in a real-world clinical setting.

Design: Developed an algorithm to determine BP and electrolyte response to spironolactone.

Setting: An academic medical center in Nashville, Tennessee

Population: Patients with aTRH prescribed spironolactone.

Main Outcome Measures: Baseline BP and BP response, determined as the change in mean systolic and diastolic BP (SBP and DBP, respectively) following spironolactone initiation. Additional response measures were serum sodium, potassium, and creatinine, estimated glomerular filtration rate, hemoglobin A1c (HbA1c), glucose, high density lipoprotein, low density lipoprotein, triglycerides. Demographic characteristics included race, age, gender, body mass index (BMI), diabetes mellitus, chronic kidney disease stage three, ischemic heart disease, and smoking.

Results: The mean decreases in SBP and DBP were 8.1 and 3.4 mmHg, consistent with clinical trial data. Using a mean decrease in SBP of five mmHg or in DBP of two mmHg to define "responders," 30.3% of patients did not respond. In univariable analyses, responders had higher BMI, baseline SBP, DBP, sodium, and HbA1c, and lower creatinine. In multivariable analysis, responders were older and had significantly higher BMI and baseline SBP and DBP, and lower potassium. Increases in potassium and creatinine following spironolactone were larger in responders. When BP was evaluated as a continuous variable, decreases in SBP and DBP correlated with baseline BP, decrease

in sodium, and increases in potassium and creatinine following spironolactone. The decrease in SBP was associated with decreasing glucose in European Americans.

Conclusions: We developed an algorithm to assess BP response to a commonly prescribed medication for aTRH using EMRs. Electrolyte changes associated with the BP response to spironolactone are consistent with its mechanism of action of blocking the mineralocorticoid receptor and decreasing epithelial sodium channel activity.

Strengths and Limitations of this study:

- This study defined the blood pressure response to spironolactone in a large number of patients with apparent therapy-resistant hypertension (aTRH) using the electronic medical record. The accuracy of algorithms for the identifying patients with aTRH who were initiated on spironolactone were validated by manual review.
- The availability of clinical electrolyte measurements, in addition to blood pressure measurements, provides data supporting the mechanism of mineralocorticoid receptor (MR) antagonism in responders to spironolactone.
- This study provides methodology which can be applied in future pharmacogenetic studies using electronic health records. The algorithm can be adapted for use in other large-scale electronic medical record systems with linked genetic data.
- Limitations of this study include the inability to confirm medication adherence, a lack of ambulatory blood pressure measurements, and a lack of some laboratory measures, such hemoglobin A1c (HbA1c) and lipids, for the entire population.

Keywords: spironolactone; mineralocorticoid receptor antagonist; blood pressure response; apparent therapy-resistant hypertension; electronic medical record

INTRODUCTION

The mineralocorticoid receptor (MR) antagonist spironolactone has been identified as effective add-on therapy for blood pressure (BP) control in patients with apparent therapy-resistant hypertension (aTRH) in clinical trials, including the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA) and the Prevention and Treatment of Hypertension with Algorithm Based Therapy-2 (PATHWAY-2).[1-4] In the PATHWAY-2 trial, addition of spironolactone at a dose of 25-50 mg/day to a therapeutic regimen containing an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB), calcium channel blocker (CCB), and thiazide-like diuretic significantly decreased home systolic blood pressure (SBP) by a mean of 8.7 mmHg.[1] In prior clinical studies the SBP/diastolic blood pressure (DBP) responses to spironolactone have ranged from a mean decrease of 4.6/1.8 mmHg to a mean decrease of 25/12 mmHg.[1-5]

Clinical trials often assess homogenous groups of patients limiting the applicability in a real-world clinical setting. We hypothesized that we could use electronic medical records (EMR) to assess the BP response to the addition of spironolactone in resistant hypertensive patients who were on a stable anti-hypertensive regimen of at least three medications including a thiazide diuretic or dihydropyridine CCB. We used a previously published algorithm for the identification of patients with aTRH.[6] To evaluate the BP response to spironolactone we developed an additional algorithm to identify patients who were prescribed spironolactone during a period of

stable medication use from up to six months before the start of spironolactone to six months after. The accuracy of the algorithm was validated by electronic record review.

We collected all outpatient BPs and laboratory measurements during the period of stable medication use before and after initial spironolactone prescription. We assessed BP response as a continuous variable and as a dichotomized variable (responders vs non-responders). We also assessed electrolyte measurements relevant to the mechanism of action of spironolactone, MR antagonism.

METHODS

Electronic Medical Record

We obtained Institutional Review Board approval to access the Vanderbilt University Medical Center (VUMC) Synthetic Derivative (SD). The SD is a de-identified copy of the VUMC EMR with Health Insurance Portability and Accountability Act of 1996 (HIPAA) identifiers removed by established de-identification software as well as custom techniques.[7] The SD contains almost all available clinical data including basic demographics, such as race and sex; text from clinical care notes; laboratory values; inpatient and outpatient medication data; international classification of disease (ICD) and current procedural terminology (CPT) codes; and other diagnostic reports.[7] To date, the SD contains approximately 2.8 million records, approximately one million of which contain detailed longitudinal data.

Spironolactone Response Algorithm Development

Patients within the SD were identified as having aTRH using a previously published algorithm.[6] Patients were defined as having aTRH if their BP was greater than or equal to 140/90 mmHg, despite concurrent use of three antihypertensives including a thiazide diuretic or dihydropyridine CCB, or if they were taking four or more antihypertensive medications, including a thiazide diuretic or dihydropyridine CCB. Patients with secondary hypertension, chronic kidney disease (CKD) stages four and five, heart failure with reduced ejection fraction less than 35 percent, thyroid and parathyroid disorders, nephrotic syndrome, chronic glomerulonephritis, anomalies of the bulbus

cordis, coarctation of the aorta, adrenal gland neoplasms and disorders (excluding adrenal insufficiencies), chronic pulmonary heart disease, thyrotoxicosis, disorders of thyrocalcitonin secretion, and obstructive uropathy were excluded by the aTRH algorithm (**Supplemental Table 1**).

All drug exposures to antihypertensive medications including spironolactone were identified from the SD by electronic-prescribing tools and MedEx.[8] The utility of these tools for extracting medication data from the EMR has been shown previously.[9, 10] For a medication exposure to be considered valid at least one of the following identifiers- dose, route, frequency, or duration- was required.

We developed an algorithm to identify patients in the SD who were prescribed spironolactone and in whom BP was measured within a stable window of time before and after initiation of spironolactone. Using electronic prescribing tools and MedEx,[8] the novel start date (NSD) for a spironolactone prescription was determined by the earliest mention of spironolactone, aldactone, or aldactazide in a patient's record after the patient met the aTRH case definition. In addition, spironolactone, aldactone, or aldactazide prescription had to have been listed at least twice, at least one month apart, during the subsequent six-month period. Patients who were initiated on aldactazide (aldactone/hydrochlorothiazide combination therapy) were required to have been using a thiazide diuretic immediately prior to the NSD for aldactazide. Patients who were not prescribed a thiazide prior to the start of aldactazide were excluded as having been started on spironolactone and hydrochlorothiazide (HCTZ) concurrently. Use of the MR antagonist eplerenone was not included in the study as it was prescribed to only 2% of the resistant hypertensive population.

Patients prescribed spironolactone without an outpatient BP measurement in the six months before or after the NSD were excluded. Patients who were diagnosed with other indications for spironolactone including heart failure, hepatic cirrhosis, hyperandrogenism, acne, or polycystic ovarian syndrome within a year of the NSD were also excluded. Using the algorithm, we identified sliding time windows up to six months before (baseline) and six months after the NSD (response) when there were no changes to each patient's prescribed antihypertensive medications, including dose (when available), the number of medications, and class type (**Figure 1**).

Once the baseline and response periods were defined, all outpatient BP measurements taken during these periods were identified. Any patient without at least two BP measurements during the baseline and response periods was excluded. The SBP and DBP responses were calculated as the difference between the mean SBP or DBP in the stable post-treatment window minus the mean SBP or DBP in the pre-treatment window (e.g. $\Delta SBP = \overline{SBPpost} - \overline{SBPpre}$). Any SBP and DBP responses that were more than two standard deviations from the mean were reviewed manually to confirm accuracy.

We also defined patients as responders versus non-responders based on a review of BP responses reported in clinical trials of spironolactone in European (EA) and African Americans (AA).[1-5] We defined responders as those who had a decrease in mean SBP of at least five mmHg or a decrease in mean DBP of at least two mmHg, corresponding to the smallest SBP and DBP responses to spironolactone reported among the studies reviewed.[5]

All patient characteristics, including age, gender, race, body mass index (BMI), outpatient BP measurements, serum potassium, creatinine, and sodium, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, glucose, hemoglobin A1C (HbA1c), and history of CKD stage three, ischemic heart disease (IHD), type two diabetes mellitus (T2DM), and smoking, were extracted from the SD using a combination of ICD-9 and -10 codes, CPT codes, laboratory measurements, and natural-language processing (**Supplemental Table 2**). Aldosterone, renin, renin activity, and aldosterone-renin-ratio (ARR) were not evaluated due to the small numbers of patients with data. For each patient, age and BMI at NSD or the date closest to NSD was used. The estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease (MDRD) formula.[11] CKD stage three was defined as an eGFR $\geq$30 mL/min/1.73m^2 and $\leq$60 mL/min/1.73m^2 or equivalent ICD-9 or -10 code at any point before NSD. Patient race was administratively assigned in the SD based on either physician or patient report. Previous work has shown that self-identified race is highly correlated with genetic ancestry[12, 13] and administratively assigned race in the VUMC SD is sufficient for genetic association analyses[14] and correlates tightly with genetic ancestry.[13]

After the algorithms were iteratively refined, blinded chart reviews of randomly chosen, never overlapping, charts were performed to determine algorithm efficacy. Based on a population size of 17,082, review of 138 charts would allow detection of a misclassification rate of 10% with a margin of error of 5%. We therefore reviewed 150 charts to determine algorithm efficacy. The review consisted of 75 charts from resistant hypertensive patients that were included by the algorithm and 75 that were excluded. The

algorithm was refined until a negative predictive value (NPV), positive predictive value (PPV), sensitivity, and specificity greater than 90% was achieved based on the review of 150 charts. The final version of the algorithm will be made available at Phenotype KnowledgeBase (PheKB).[15]

Statistical Methods

Data are presented as frequencies for categorical variables and mean ± standard deviations for continuous variables. Univariable analysis for binary BP response was performed using Pearson's chi-squared test for categorical variables and the Wilcoxon rank-sum test for continuous variables. A multivariable logistic regression model or multivariable linear regression model was fitted for binary BP response and continuous BP change on all variables available in more than 70% of the population. Missing values were not imputed. HDL cholesterol, LDL cholesterol, triglycerides, and HbA1c were excluded from multivariable regression models due to large amounts of missing values. The method of complete-case analysis was used and a linear relationship was assumed for all the continuous variables. All statistical analyses were conducted using the SPSS software version 24 (SPSS, Chicago, IL, USA) or R 3.3.0.[16]

Patient and Public Involvement

Because this study involved the use of the VUMC SD, patients were not recruited and there was no intervention. While patients were not involved in the development of the specific research question or study design, there has been extensive patient and community engagement in the establishment of the SD. Further, a community advisory

board within the Vanderbilt Institute for Clinical and Translational Research (VICTR) reviews programs including the SD. Dissemination of study results will occur through local reporting of study results.

RESULTS

Algorithm validation

NPV, PPV, sensitivity, and specificity of the algorithm for spironolactone response were determined after the blinded review of 150 electronic records. All but one excluded record were excluded appropriately. That record was excluded by the algorithm due to an erroneous ascertainment that a medication other than spironolactone had been added during the response periods. Five of the 75 records included in the algorithm should have been excluded. Four of these patients had inconsistencies in their medication history during the baseline or response period. In another patient, spironolactone was listed as a potential therapy in several notes but was not apparently prescribed. Based on this review, the NPV was 98.7%, PPV was 93.3%, sensitivity was 98.6%, and specificity was 93.7%.

Identification of spironolactone response population

Among EA and AA patients with aTRH in the SD 3,405 EA and 1,054 AA were prescribed spironolactone. Consistent with the aTRH definition, in addition to other antihypertensive medications, patients were prescribed a thiazide diuretic or a dihydropyridine CCB prior to spironolactone initiation. The median daily dose of thiazide diuretic was 25 mg with a range from 12.5 mg to 50 mg (**Supplemental Table 3**). The predominant dihydropyridine CCBs prescribed were amlodipine and nifedipine. The median daily dose of amlodipine and nifedipine were 10 mg with a range from 2.5 mg to 10 mg and 90 mg with a range from 30 mg to 120 mg, respectively (**Supplemental Table 3**). For a subset of these patients the thiazide or dihydropyridine CCB dose at

spironolactone initiation, e.g. dose of the medication identified in the month preceding or following spironolactone prescription, could not be determined. From the patients with confirmed doses 566 (80.6%) were prescribed a 25 mg thiazide, 312 (73.9%) were prescribed 10 mg amlodipine, and 110 (40.3%) were prescribed 90 mg nifedipine.

After applying exclusion and inclusion criteria, 1,114 EA patients and 369 AA patients were included in the study for evaluation of spironolactone response, 32.7% and 35.0% of the original number of patients prescribed spironolactone, respectively (**Figure 2**). The median dose of spironolactone was 25 mg and ranged from 12.5 to 200 mg. The majority of patients included in the study, 1,050 (70.8%), were prescribed 25 mg of spironolactone. 107 patients were prescribed spironolactone at a dose of 12.5mg and one at a dose of 200 mg. In total, 261 patients (17.6%) patients were prescribed a 50 mg or greater dose of spironolactone. The average number of outpatient BPs measured during the baseline and response periods were 4 and 4.8, respectively.

Characteristics of spironolactone responders and non-responders

Defining spironolactone response as a reduction in SBP of at least five mmHg or in DBP of at least two mmHg, we identified 1,034 responders (69.7%) and 449 non-responders (30.3%) in the total population. Of the responders, 15.8% met the criteria for a DBP response, 19.4% for a SBP response, and 64.8% for both a DBP and SBP response. Patient characteristics appear in **Table 1**. In univariable analyses, patients who responded to spironolactone were heavier and less likely to have a history of IHD. Responders had significantly higher baseline SBP, DBP, serum sodium, and HbA1c, and significantly lower baseline creatinine than nonresponders (**Table 1**). Responders also

had greater decreases in serum sodium and eGFR as well as greater increases in serum potassium and creatinine after starting spironolactone than nonresponders (**Table 1**). HbA1c did not change in responders whereas it declined over time in non-responders. In a multivariable model adjusting for all variables present in at least 1000 patients, responders were older and heavier, had higher baseline SBP and DBP, had lower baseline serum potassium and had a greater increase in serum potassium and creatinine after starting spironolactone than non-responders (**Table 2**).

Table 1. Characteristics of spironolactone responders and nonresponders in the total population.

Variable	N	Nonresponders (n=449)	Responders (n=1,034)	p-value
Age, years	1483	63.67 ± 13.18	64.28 ± 12.63	0.33
Female, n (%)	1483	215 (47.9%)	532 (51.5%)	0.21
Black Race, n (%)	1483	106 (23.6%)	263 (25.4%)	0.46
BMI, kg/m^2	1358	32.2 ± 8.0	33.5 ± 8.3	0.004
Diagnostic History				
T2DM, n (%)	1483	236 (52.6%)	566 (54.7%)	0.44
CKD3, n (%)	1483	163 (36.3%)	398 (38.5%)	0.43
IHD, n (%)	1483	179 (39.9%)	351 (33.9%)	0.03
Smoking, n (%)	1483	96 (21.4%)	211 (20.4%)	0.67
Baseline measurements				
SBP, mmHg	1483	133.20 ± 17.40	147.59 ± 18.70	< 0.001
DBP, mmHg	1483	71.66 ± 11.74	79.00 ± 13.08	< 0.001
Serum sodium, mmol/L	1176	138.67 ± 3.22	139.25 ± 2.98	0.004
Serum potassium, mmol/L	1177	3.95 ± 0.47	3.91 ± 0.43	0.15
Creatinine, mg/dL	1184	1.12 ± 0.36	1.09 ± 0.42	0.03
eGFR, mL/min/1.73m^2	1382	76.73 ± 23.78	77.38 ± 20.95	0.51
Glucose, mg/dL	1179	125.56 ± 58.56	126.98 ± 50.61	0.80
HbA1c, %	538	6.91 ± 1.81	7.23 ± 3.06	0.02
HDL cholesterol, mg/dL	575	47.48 ± 17.97	45.53 ± 15.31	0.44

LDL cholesterol, mg/dL	537	95.65 ± 39.74	98.54 ± 34.72	0.41
Triglycerides, mg/dL	578	163.98 ± 111.71	169.39 ± 121.20	0.85
Difference from baseline following initial spironolactone prescription				
Serum sodium, mmol/L	1101	-0.49 ± 2.63	-0.95 ± 2.70	0.006
Serum potassium, mmol/L	1104	0.13 ± 0.48	0.25 ± 0.42	< 0.001
Creatinine, mg/dL	1108	0.02 ± 0.23	0.134 ± 0.30	< 0.001
eGFR, mL/min/1.73m^2	1254	-5.22 ± 15.73	-9.09 ± 15.10	< 0.001
Glucose, mg/dL	1101	-0.27 ± 47.82	-0.37 ± 40.62	0.88
HbA1c, %	284	-0.25 ± 1.23	0.02 ± 1.05	0.02
HDL cholesterol, mg/dL	214	0.70 ± 11.51	-1.36 ± 9.35	0.23
LDL cholesterol, mg/dL	197	-5.74 ± 32.54	-7.48 ± 34.94	0.77
Triglycerides, mg/dL	220	-17.86 ± 107.95	-19.43 ± 107.16	0.91

Abbreviations: BMI, body mass index; CKD3, chronic kidney disease stage three; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; IHD, ischemic heart disease; LDL, low-density lipoprotein; N, number of individuals with the specific measure; SBP, systolic blood pressure; T2DM, type 2 diabetes mellitus.

Data are presented as mean ± standard deviation for continuous variables and count (%) for categorical variables

Table 2. Multivariable logistic regression model for responder versus non-responder in the total population without missing data (N=1019).

	Odds Ratio*	95% Confidence Interval	p-value
Age, years	1.034	1.017-1.052	< 0.001
Gender, Male: Female	0.897	0.603-1.323	0.59
Race, White: Black	1.217	0.800-1.849	0.36
Mean BMI, kg/m^2	1.030	1.008-1.054	0.01
Diagnostic history			
T2DM, Yes: No	1.132	0.794-1.615	0.49
CKD3, Yes: No	0.932	0.654-1.330	0.70
IHD, Yes: No	1.256	0.905-1.749	0.18
Smoking, Yes: No	1.074	0.745-1.559	0.71
Baseline measurements			
SBP, mmHg	1.034	1.023-1.046	< 0.001
DBP, mmHg	1.043	1.025-1.062	< 0.001
Serum sodium, mmol/L	1.013	0.957-1.071	0.66
Serum potassium, mmol/L	1.686	1.106-2.588	0.02
Creatinine, mg/dL	1.266	0.603-2.995	0.57
eGFR, mL/min/1.73m^2	1.007	0.993-1.021	0.32
Glucose, mg/dL	0.999	0.996-1.003	0.80
Difference from baseline following initial spironolactone prescription			
Serum sodium, mmol/L	0.946	0.888-1.007	0.08

Serum potassium, mmol/L	1.968	1.290-3.030	0.002
Creatinine, mg/dL	3.570	1.610-9.131	0.004
eGFR, mL/min/1.73m^2	1.001	0.987-1.015	0.92
Glucose, mg/dL	0.997	0.992-1.001	0.12

Abbreviations: BMI, body mass index; CKD 3, chronic kidney disease stage three; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; IHD, ischemic heart disease; N, number of individuals included in the analysis; SBP, systolic blood pressure.

*For continuous variables, the odds ratio reflects the effect of a one-unit increase. For example, a one mmHg increase in baseline SBP increases the odds ratio for responder versus non-responder 0.03.

Among EA patients, 343 (30.8%) did not respond to spironolactone. EA responders were heavier and less likely to have IHD. They had higher baseline SBP, DBP, and serum sodium than nonresponders (**Supplemental Table 4**). EA responders also had a greater decrease in serum sodium and eGFR and a greater increase in serum potassium and creatinine after starting spironolactone (**Supplemental Table 4**).

Among AA patients, 106 (28.7%) did not respond to spironolactone. Like EA responders, AA responders had significantly higher baseline SBP and DBP and a greater decrease in serum sodium and increase in creatinine after starting spironolactone than nonresponders (**Supplemental Table 5**).

Blood pressure response to spironolactone as a continuous variable

For the entire group, the mean decrease in SBP following initiation of spironolactone was 8.1 mmHg and the mean decrease in DBP was 3.4 mmHg following initial spironolactone prescription. In total, 933 patients (62.9%) achieved a decrease in BP to ≤ 140/90 mmHg, the pressure goal recommended in guidelines at the time.[17] An additional 23 patients achieved a decrease in SBP but not DBP to guideline recommendation and 262 patients achieved DBP but not SBP control. Analyses of BP change as a continuous variable were performed using a multivariable model that included all variables except for HbA1c, HDL cholesterol, LDL cholesterol, and triglycerides, as data were not available in the majority of patients.

In the total population, patients with higher baseline SBP, lower baseline creatinine, and a greater decrease in serum sodium, increase in serum potassium, or increase in creatinine after starting spironolactone had greater reductions in SBP (**Table 3**

and **Figure 3**). Patients with higher baseline SBP and DBP and a greater decrease in serum sodium, increase in serum potassium, or increase in creatinine after spironolactone had greater reductions in DBP (**Table 3**). Older patients and female patients also had significantly greater reductions in DBP (**Table 3**).

Table 3. Significant coefficients in multivariable models for change in systolic and diastolic blood pressures.

	Associated Variable	Coefficient	95% Confidence Interval	p-value
Total population (N=1019)				
Change in SBP	Baseline SBP	-0.415	-0.475, -0.356	< 0.001
	Baseline creatinine	3.628	0.202, 7.054	0.04
	Change in serum sodium	0.701	0.338, 1.064	< 0.001
	Change in serum potassium	-3.483	-5.834, -1.131	0.004
	Change in creatinine	-5.039	-8.704, -1.374	0.01
Change in DBP	Age	-0.141	-0.196, -0.086	< 0.001
	Gender- Male: Female	1.390	0.170, 2.610	0.03
	Baseline SBP	-0.045	-0.080, -0.011	0.01
	Baseline DBP	-0.379	-0.436, -0.321	< 0.001
	Change in serum sodium	0.274	0.063, 0.485	0.01
	Change in serum potassium	-2.042	-3.413, -0.671	0.004
	Change in creatinine	-3.979	-6.116, -1.841	< 0.001
European Americans (N=753)				
Change in SBP	Baseline SBP	-0.401	-0.470, -0.333	< 0.001
	Change in serum sodium	0.525	0.117, 0.933	0.01
	Change in serum potassium	-3.074	-5.766, -0.381	0.03
	Change in glucose	0.031	0.003, 0.059	0.03
Change in DBP	Age	-0.135	-0.200, -0.070	< 0.001
	Gender, Male: Female	1.669	0.230, 3.108	0.02

	Baseline SBP	-0.045	-0.084, -0.005	0.03
	Baseline DBP	-0.370	-0.436, -0.303	< 0.001
	Change in serum potassium	-1.809	-3.385, -0.232	0.03
	Change in creatinine	-3.328	-5.772, -0.884	0.01
African Americans (N=266)				
Change in SBP	Baseline SBP	-0.445	-0.571, -0.319	< 0.001
	Baseline creatinine	5.572	0.017, 11.127	0.05
	Change in serum sodium	1.338	0.517, 2.159	0.002
	Change in potassium	-5.206	-10.205, -0.207	0.04
	Change in creatinine	-10.923	-19.456, -2.391	0.01
Change in DBP	Age	-0.156	-0.265, -0.046	0.01
	Baseline DBP	-0.407	-0.512, -0.278	< 0.001
	Change in sodium	0.530	0.053-1.007	0.03
	Change in potassium	-2.864	-5.768, 0.039	0.05
	Change in creatinine	-7.370	-12.326, -2.413	0.004

Abbreviations: DBP, diastolic blood pressure; N, number of individuals included in the analysis; SBP, systolic blood pressure.

In EA alone, a greater decrease in either SBP or DBP was significantly associated with baseline SBP, as well as increase in serum potassium (**Table 3**). A greater reductions in SBP was further associated with greater decreases in serum sodium and glucose (**Table 3**). The change in DBP was also significantly associated with age, sex, and creatinine (**Table 3**).

In AA, greater reductions in SBP and DBP were significantly associated with greater decreases in serum sodium and increases in serum potassium and creatinine (**Table 3**). Patients with higher baseline SBP and baseline creatinine had a greater reduction in SBP, while patients with higher baseline DBP and older age had a greater reduction in DBP (**Table 3**).

DISCUSSION

We developed a highly accurate algorithm to define the BP response to spironolactone in patients with aTRH using the EMR. The mean decreases in SBP and DBP for the total study population, 8.1 mmHg and 3.4 mmHg, respectively, are consistent with responses reported in prior clinical trials, such as the PATHWAY-2 trial.[1] In total, 30.3% of patients prescribed spironolactone did not achieve a five mmHg decrease in SBP or two mmHg decrease in DBP in the six months following spironolactone initiation. Higher pretreatment SBP and DBP predicted a greater therapeutic response to spironolactone, measured either as a dichotomous or continuous variable.

In addition using the electronic algorithm, we were able to detect not only the BP response, but also changes in serum sodium, potassium, and creatinine after spironolactone initiation. Regardless of race, the response to spironolactone was associated with a greater decrease in serum sodium and greater increase in serum potassium, consistent with MR antagonism. These changes are also consistent with a decrease in epithelial sodium channel (ENaC) activity. In the present study, however, we are unable to determine if this inadequate BP response is due to inadequate spironolactone dose, spironolactone noncompliance, or non-MR mediated ENaC activation. Further, we found a significant correlation between decreasing BP and increasing creatinine after starting spironolactone in all groups. This correlation is likely a result from hemodynamic effects of BP medications and especially from blocking the renin-angiotensin-aldosterone system (RAAS).[1]

Race was not significantly associated with BP response to spironolactone nor electrolyte changes which suggests spironolactone exerts a consistent BP lowering effect regardless of race. These findings are supported by those of Nishizaka, et al. who determined that low-dose spironolactone provided a significant decrease in BP in AA and EA with resistant hypertension with and without primary aldosteronism.[4]

In EA, we also observed a significant correlation between the SBP response and decreasing glucose; whereas, among those in whom HbA1c was measured before and after therapy, HbA1c declined in nonresponders but not responders. The latter observation may reflect the fact that responders had a higher baseline HbA1c than non-responders. While these findings may suggest a potential benefit to glucose management from MR antagonism it is important to note that the exact relationship between MR antagonism and glucose is not perfectly understood. Because our findings, as well as others, suggest an association between spironolactone use and glucose levels, additional studies to better characterize this relationship are warranted.

A limitation of this study and many other studies of aTRH is the inability to measure adherence directly in the patients prescribed spironolactone without measuring drug levels, which is not routinely done in clinical practice. Nonadherence alone does not likely explain the lack of BP response in nonresponders, however. First, patients nonadherent to spironolactone would likely be nonadherent to other medications. Nonadherent patients, therefore, would be expected to have higher baseline BPs than adherent patients. To the contrary, we found that nonresponders had lower baseline SBP and DBP than responders and baseline SBP and DBP significantly predicted BP response. In addition, initiation of spironolactone resulted in an increase in serum

potassium and decrease in serum sodium in non-responders as well as responders, albeit to a lesser degree. Taken together these findings suggest that nonadherence is not the predominant driver of the lack of BP response in non-responders.

Another way to assess adequacy of spironolactone dose is to assess whether renin activity remains suppressed. Unfortunately, an insufficient number of patients had renin measured during the baseline and response periods to assess change in renin concentration or activity. The limited number of renin measurements in the EMR is reflective of poor screening rates for primary aldosteronism.[18] Previous studies have reported limited value in the addition of aldosterone levels or the ARR to prediction models of BP response to MR antagonism in aTRH, however.[19,20]

Other limitations of the study include the exclusion of a significant number of patients with aTRH due to inadequate documentation of pre- and post-treatment BPs, which limits our power of detection for some responses. The relatively small number of AA, for example, limits the power to detect predictors of response to spironolactone in this group.

In conclusion, we have developed a highly accurate algorithm for the assessment of BP response to spironolactone, a commonly prescribed medication, in patients with aTRH using EMR. Electrolyte changes associated with the BP response to spironolactone are consistent with its mechanism of action to block the MR and decrease activity of ENaC. A strength of this algorithm is its applicability to evaluate BP and electrolyte responses to medications other than spironolactone as well as its utility to evaluate the long-term clinical consequences of medication use. Further, this electronic algorithm could be amended for use in other EMR systems.

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DISCLOSURES

None

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FIGURE LEGENDS

Figure 1. Schematic of the spironolactone response algorithm and identification of the baseline and response periods for patients. The earliest date a patient was prescribed spironolactone is indicated by the novel start date (NSD). The baseline period is determined by identifying all visits in which same three medication classes as prescribed to the patient as on the NSD. If the visit date for the start of the baseline period occurred more than six months before the NSD a baseline period of six months was used. The determination of the response period is not shown in the schematic above. Similar logic was applied to the selection of this period.

Figure 2. Diagram of the algorithm for the identification of patients with apparent therapy-resistant hypertension (aTRH) in the VUMC Synthetic Derivative (SD) prescribed spironolactone during a period of stable medication use for the evaluation of blood pressure response.

Figure 3. The significant correlations with systolic blood pressure change in the total population. Correlation between the change in systolic blood pressure (SBP) after starting spironolactone and baseline A) SBP [correlation coefficient (CC)= -0.415, $p<0.001$], and the change in B) creatinine (CC= -5.039, p=0.01), C) serum sodium (CC= 0.701, $p<0.001$), and D) serum potassium (CC= -3.483, p= 0.004).

STATEMENTS

Contributorship

MMS and NJB contributed to the design of the study; MMS, BP, HN, CY, JML, and NJB contributed to the analysis and interpretation of the results; MMS and NJB contributed to the drafting of the manuscript; MMS, BP, HN, CY, JML, and NJB contributed to the editing of the manuscript and final approval for submission

Competing Interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: Dr Brown reports consulting for Shire HGT, Novartis Pharmaceuticals, Viamet Pharmaceuticals and serving on the Scientific Advisory Board of Alnylam Pharmaceuticals. Dr. Brown also sits on the Joint Scientific Committee for the Vanderbilt Bayer Alliance. All authors report no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Patient Consent

No identifiable patient data was used in the study.

Ethical Approval

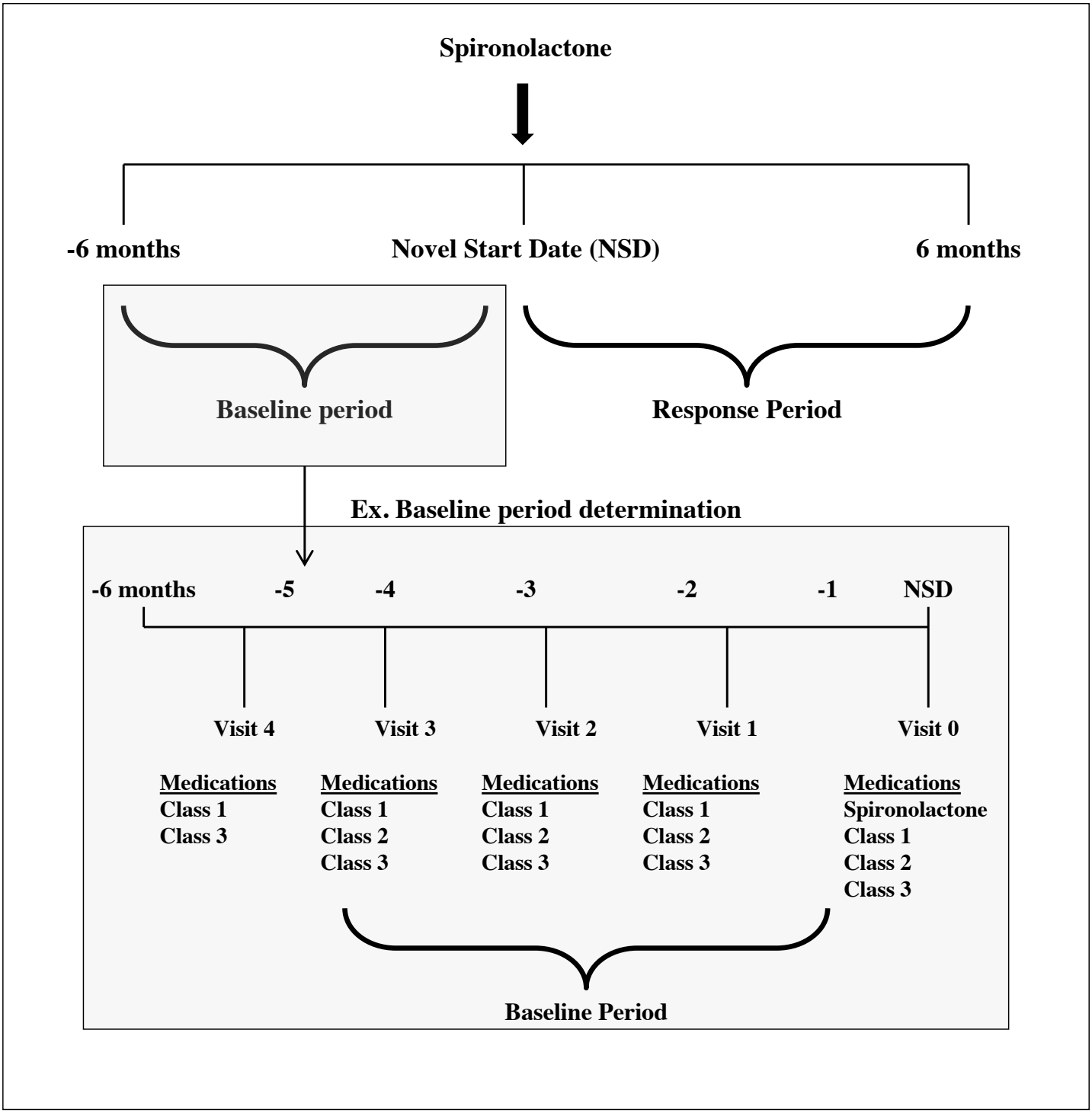
The study was approved by the Vanderbilt University Medical Center Institutional Review Board (#130848).

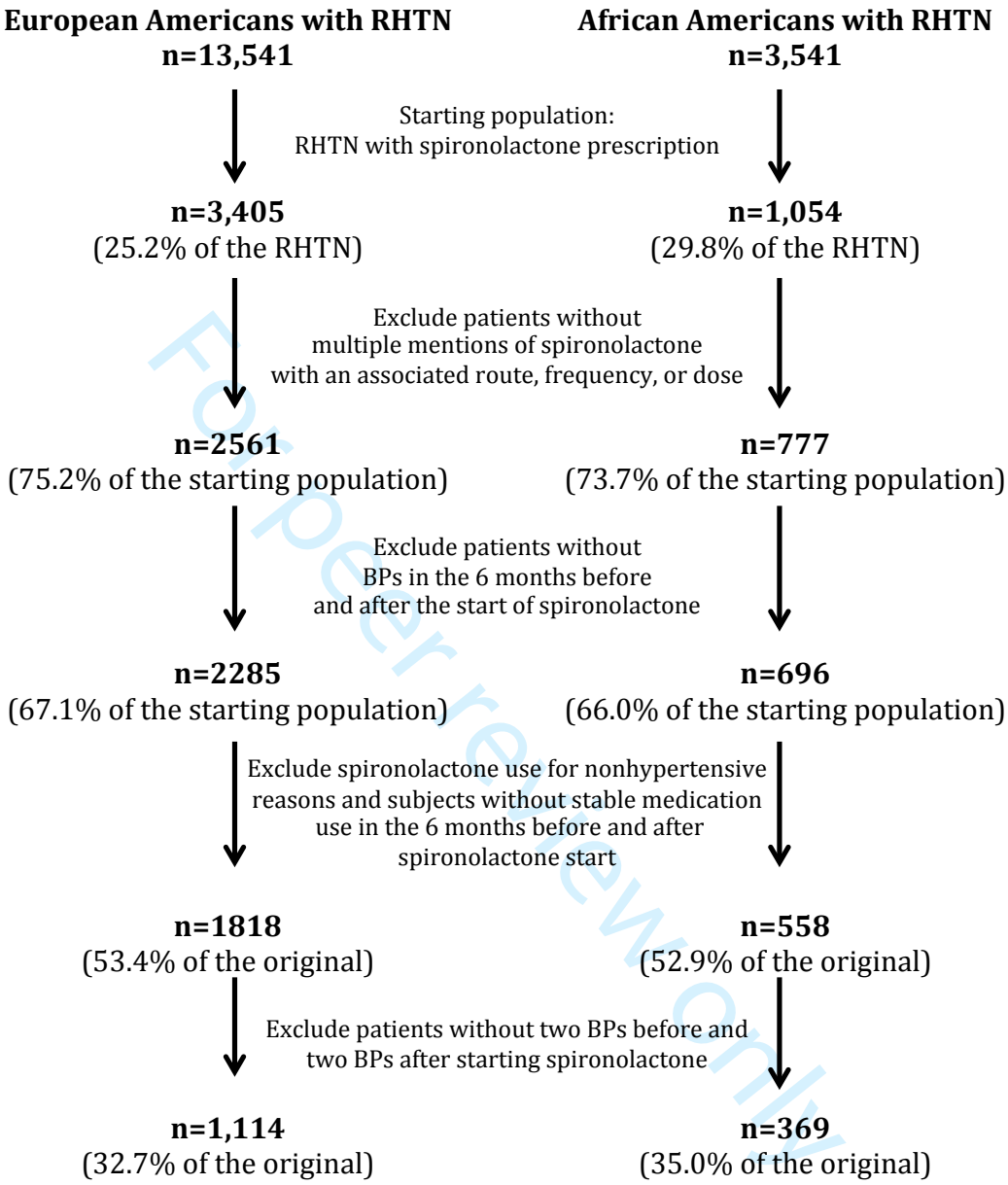
Transparency Declaration

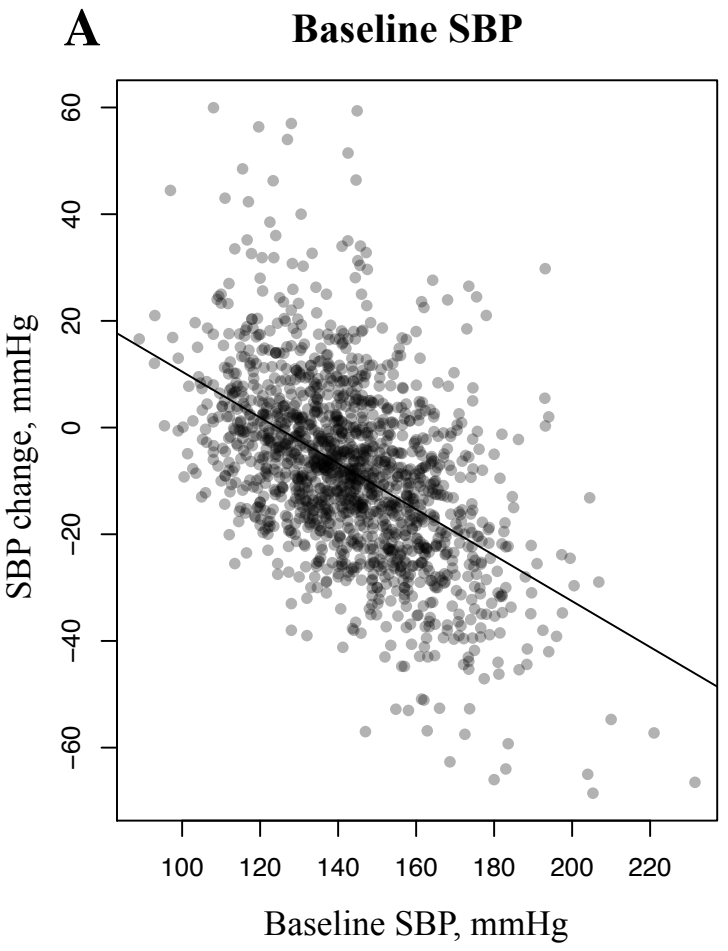
M. Shuey affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

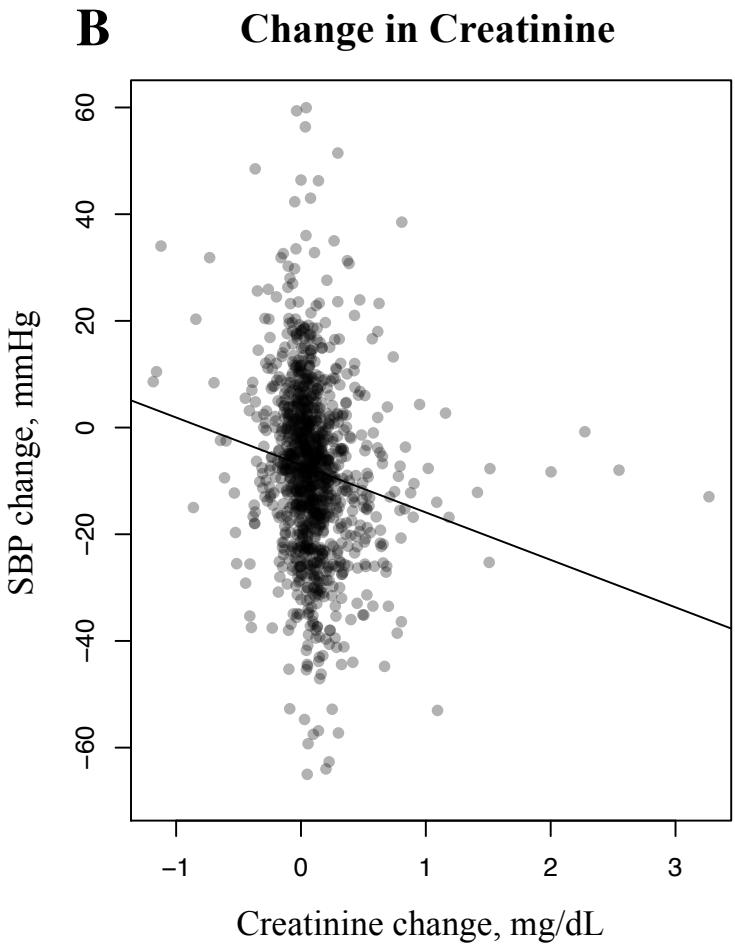
Data Sharing

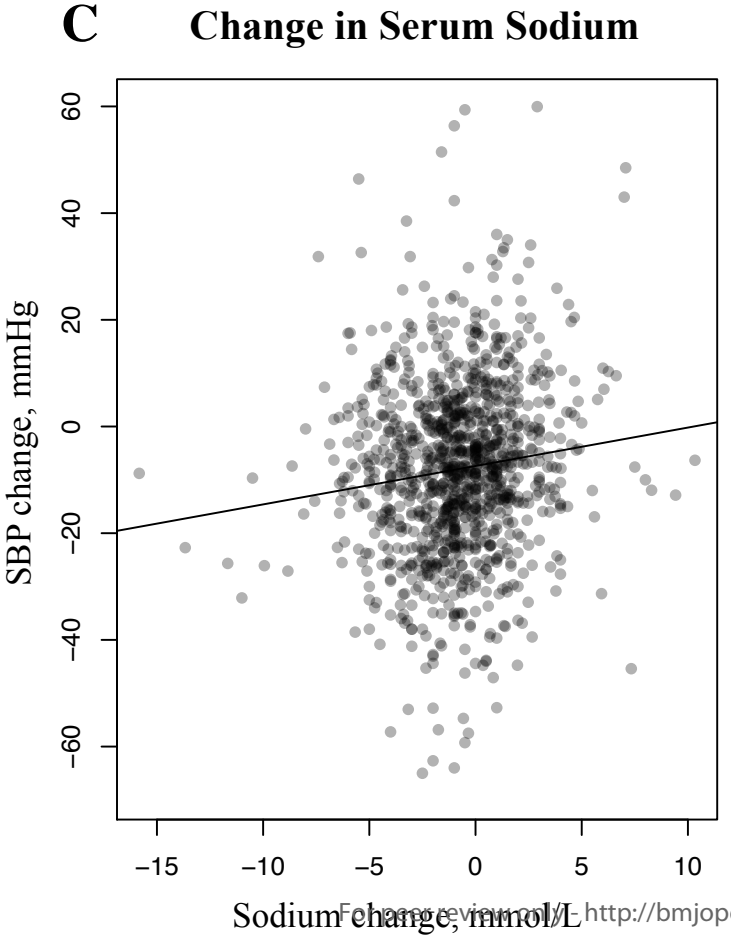
The full data set is available upon request to the corresponding author.

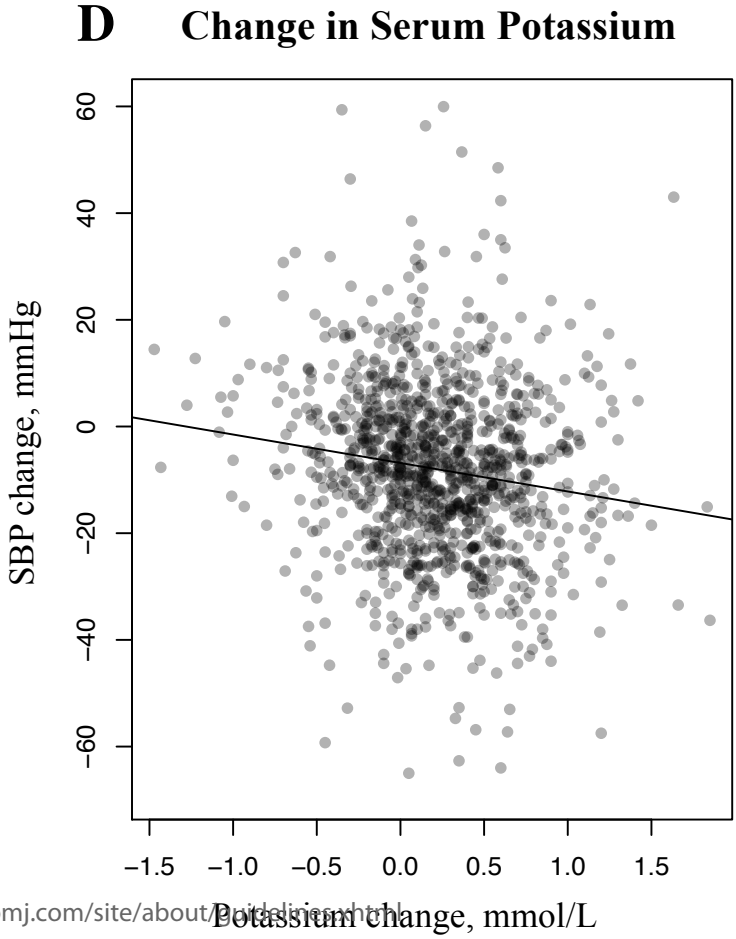












DATA SUPPLEMENT

Supplemental Table 1. International Classifiers of Disease (ICD)-9 and -10 exclusions for resistant hypertensive subjects

Description	ICD-9-CM codes	ICD-10-CM-codes
Exclusion for Case Type I, Case Type II, and Control if ever present in a patient record		
Malignant neoplasm of unspecified adrenal gland	194.0	C74.9
Benign neoplasm of unspecified adrenal gland	227.0	D35.00
Disorders of the adrenal gland (excluding adrenal insufficiencies)	255.0, 255.1*, 255.2, 255.3, 255.6, 255.8, 255.9	E24.*, E26.*, E25.*, E27.0, E27.5, E27.8, E27.9
Secondary Hypertension	405.*	I15.0, I15.8
Chronic pulmonary heart disease	416.*	I27. *
Nephrotic syndrome	581.*	N04.*, N08
Chronic glomerulonephritis	582.*	N03.*, N08
Bulbus cordis anomalies	745.*	Q20.*, Q21.*
Coarctation of aorta	747.1*	Q25.1, Q25.2
Exclusion for Case Type I and Case Type II if present in a patient record 5 years before or 1 year after identification as a Case		
Thyrotoxicosis	242.*	E05.*
Disorder of thyrocalcitonin secretion	246.0	E07.0
Disorders of the thyroid NEC	246.8	E03.4, E07.89
Disorders of the thyroid NOS	246.9	E07.9
Parathyroid disorder NEC	252.8	E21.4
Parathyroid disorder NOS	252.9	E21.5
Obstructive uropathy	599.6*	N13.9

Abbreviations: NEC, not elsewhere classified; NOS, not otherwise classified

Supplemental Table 2. International Classifiers of Disease (ICD)-9 and ICD-10 codes used for history of diagnosis

Diagnosis	ICD-9 codes	ICD-10 codes	Other
Chronic kidney disease stage 3	585.1	N18.1	eGFR > 30 mL/min/1.73 m^2
	585.2	N18.2	but < 60 mL/min/1.73 m^2
Ischemic heart disease	410.*	I20.*	
	411.*	I22.*	
	413.*	I24.*	
	414.*	125.*	
Type 2 diabetes mellitus	250	E11	
	250.*	E11.*	
	327.2*	G47.3*	
Smoking	305.1	F17.*	
	V15.82	Z87.891	

Abbreviations: eGFR, estimated glomerular filtration rate

Supplemental Table 3. The daily dose and frequency of thiazide diuretic and dihydropyridine calcium channel blocker prescription in patients with apparent treatment-resistant hypertension prior to spironolactone prescription

Medication	Daily dose	Patients prescribed, n (%)*
Thiazide diuretic		884
	12.5 mg	86 (9.7)
	25 mg	566 (64.0)
	50 mg	78 (8.8)
	unknown	154 (17.4)
Dihydropyridine calcium channel blocker		980
Amlodipine		
	2.5 mg	8 (0.8)
	5 mg	99 (10.1)
	7.5 mg	3 (0.3)
	10 mg	312 (31.8)
	unknown	52 (5.3)
Nifedipine		
	30 mg	38 (3.9)
	60 mg	100 (10.2)
	90 mg	110 (11.2)
	120 mg	25 (2.6)
	unknown	233 (23.8)

*The frequency of medication dose based on medication type, e.g. thiazide diuretic or dihydropyridine calcium channel blocker.

Supplemental Table 4. Characteristics of spironolactone responders and nonresponders in European Americans.

Variable	N	Nonresponders (n=343)	Responders (n=771)	p-value*
Age, years	1,114	65.66 ± 13.09	66.21 ± 12.04	0.50
Female, n (%)	1,114	151 (44.0%)	368 (47.7%)	0.25
BMI, kg/m^2	1,023	31.3 ± 7.2	32.5 ± 7.7	0.01
Diagnostic History				
T2DM, n (%)	1,114	173 (50.4%)	393 (51.0%)	0.87
CKD3, n (%)	1,114	124 (36.2%)	296 (38.4%)	0.48
IHD, n (%)	1,114	149 (43.4%)	280 (36.3%)	0.02
Smoking, n (%)	1,114	75 (21.9%)	157 (20.4%)	0.57
Baseline measures				
SBP, mmHg	1,114	131.37 ± 16.99	145.91 ± 18.52	< 0.001
DBP, mmHg	1,114	69.46 ± 10.88	76.78 ± 12.52	< 0.001
Serum sodium, mmol/L	872	138.45 ± 3.26	139.04 ± 3.00	0.01
Serum potassium, mmol/L	871	3.99 ± 0.46	3.93 ± 0.43	0.07
Creatinine, mg/dL	878	1.11 ± 0.37	1.07 ± 0.37	0.11
eGFR, mL/min/1.73m^2	1,029	75.16 ± 24.47	75.23 ± 19.83	0.96
Glucose, mg/dL	875	124.46 ± 56.69	126.59 ± 48.81	0.57
HbA1c, %	383	6.76 ± 1.67	7.24 ± 3.54	0.10
HDL cholesterol, mg/dL	420	46.96 ± 18.89	44.11 ± 14.83	0.10
LDL cholesterol, mg/dL	390	92.09 ± 37.86	95.30 ± 34.75	0.43
Triglycerides, mg/dL	426	167.8 ± 117.0	182.5 ± 129.4	0.27
Difference from baseline following initial spironolactone prescription				
Serum sodium, mmol/L	810	-0.70 ± 2.63	-1.12 ± 2.71	0.04

Serum potassium, mmol/L	812	0.12 ± 0.48	0.27 ± 0.43	< 0.001
Creatinine, mg/dL	816	0.01 ± 0.23	0.13 ± 0.32	< 0.001
eGFR, mL/min/1.73m^2	924	-4.82 ± 15.68	-8.76 ± 14.51	< 0.001
Glucose, mg/dL	810	1.44 ± 47.52	0.01 ± 39.03	0.65
HbA1c, %	181	-0.13 ± 1.31	-0.05 ± 0.92	0.63
HDL cholesterol, mg/dL	156	0.03 ± 9.35	-0.94 ± 8.62	0.54
LDL cholesterol, mg/dL	142	-7.29 ± 35.21	-8.63 ± 35.09	0.86
Triglycerides, mg/dL	162	-11.99 ± 107.79	-22.93 ± 121.66	0.59

Abbreviations: BMI, body mass index; CKD 3, chronic kidney disease stage three; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; IHD, ischemic heart disease; LDL, low-density lipoprotein; N, number of individuals with the specific measure; SBP, systolic blood pressure.

Data are presented as mean ± standard deviation for continuous variables and count (%) for categorical variables.

* P-values from the multivariable regression model are provided for all variables except HbA1c, HDL cholesterol, LDL cholesterol, and triglycerides. Univariate p-values are provided for these variables.

Supplemental Table 5. Characteristics of spironolactone responders and nonresponders in African Americans.

Variable	N	Nonresponders (n=106)	Responders (n=263)	p-value*
Age, years	369	57.23 ± 11.30	58.65 ± 12.64	0.32
Female, n (%)	369	64 (60.3%)	164 (62.4%)	0.72
BMI, kg/m^2	335	35.3 ± 9.7	37.3 ± 9.2	0.40
Diagnostic History				
T2DM, n (%)	369	63 (59.4%)	173 (65.7%)	0.25
CKD3, n (%)	369	39 (36.8%)	102 (38.8%)	0.72
IHD, n (%)	369	30 (28.3%)	71 (27.0%)	0.80
Smoking, n (%)	369	21 (19.8%)	211 (20.5%)	0.87
Baseline measures				
SBP, mmHg	369	139.15 ± 17.46	152.51 ± 18.40	< 0.001
DBP, mmHg	369	78.78 ± 11.67	85.50 ± 12.53	< 0.001
Serum sodium, mmol/L	304	139.37 ± 3.00	139.81 ± 2.85	0.23
Serum potassium, mmol/L	304	3.81 ± 0.50	3.84 ± 0.44	0.58
Creatinine, mg/dL	306	1.14 ± 0.33	1.16 ± 0.54	0.73
eGFR, mL/min/1.73m^2	353	81.69 + 20.78	83.42 + 22.80	0.51
Glucose, mg/dL	304	129.05 ± 64.32	128.05 ± 55.37	0.89
HbA1c, %	155	7.45 ± 2.17	7.22 ± 1.65	0.50
HDL cholesterol, mg/dL	155	49.07 ± 14.93	49.21 ± 15.95	0.56
LDL cholesterol, mg/dL	147	106.51 ± 43.81	106.70 ± 33.43	0.98

Triglycerides, mg/dL	152	151.35 ± 92.16	135.01 ± 88.22	0.34
Difference from baseline following initial spironolactone prescription				
Serum sodium, mmol/L	291	0.17 ± 2.52	-0.52 ± 2.63	0.05
Serum potassium, mmol/L	292	0.16 ± 0.50	0.19 ± 0.39	0.57
Creatinine, mg/dL	292	0.06 ± 0.23	0.14 ± 0.26	0.01
eGFR, mL/min/1.73m^2	330	-6.50 ± 15.89	-9.99 ± 16.61	0.09
Glucose, mg/dL	291	-5.56 ± 48.63	-1.37 ± 44.65	0.48
HbA1c, %	103	-0.54 ± 0.97	0.02 ± 1.23	0.09
HDL cholesterol, mg/dL	58	3.17 ± 17.66	-1.67 ± 10.92	0.24
LDL cholesterol, mg/dL	55	0.04 ± 19.86	-4.82 ± 34.85	0.65
Triglycerides, mg/dL	58	-43.47 ± 109.99	-11.64 ± 61.01	0.21

Abbreviations: BMI, body mass index; CKD 3, chronic kidney disease stage three; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; IHD, ischemic heart disease; LDL, low-density lipoprotein; N, number of individuals with the specific measure; SBP, systolic blood pressure.

Data are presented as mean ± standard deviation for continuous variables and count (%) for categorical variables.

* P-values from the multivariable regression model are provided for all variables except HbA1c, HDL cholesterol, LDL cholesterol, and triglycerides. Univariate p-values are provided for these variables.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1,2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2,3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5-6, 7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7-11
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-11
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-11, Supplemental Table 1
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	7-9, 13, Figure 2
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9, 11
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	11
		(*b*) Describe any methods used to examine subgroups and interactions	11
		(*c*) Explain how missing data were addressed	11
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	10-11
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	13, Figure 2
		(b) Give reasons for non-participation at each stage	Figure 2
		(c) Consider use of a flow diagram	Figure 2
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	14, Tables 1 and 2
		(b) Indicate number of participants with missing data for each variable of interest	Tables 1 and 2
		(c) Summarise follow-up time (eg, average and total amount)	13, Figure 2
Outcome data	15*	Report numbers of outcome events or summary measures over time	13-19
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	14-20, Table 1, 2, and 3
		(*b*) Report category boundaries when continuous variables were categorized	13
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Table 3, Supplemental tables 3 and 4
Discussion			
Key results	18	Summarise key results with reference to study objectives	24-27
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	4, 26-27
Generalisability	21	Discuss the generalisability (external validity) of the study results	4, 26-27
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	29

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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A Retrospective Cohort Study to Characterize the Blood Pressure Response to Spironolactone in Patients with Apparent Therapy-resistant Hypertension using Electronic Medical Record Data

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A Retrospective Cohort Study to Characterize the Blood Pressure Response to Spironolactone in Patients with Apparent Therapy-resistant Hypertension using Electronic Medical Record Data

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ABSTRACT

Objective: Identify blood pressure (BP) response to spironolactone in patients with apparent therapy-resistant hypertension (aTRH) using electronic medical records (EMRs) in order to estimate response in a real-world clinical setting.

Design: Developed an algorithm to determine BP and electrolyte response to spironolactone.

Setting: An academic medical center in Nashville, Tennessee

Population: Patients with aTRH prescribed spironolactone.

Main Outcome Measures: Baseline BP and BP response, determined as the change in mean systolic BP (SBP) and diastolic BP (DBP) following spironolactone initiation. Additional response measures were serum sodium, potassium, and creatinine, estimated glomerular filtration rate, hemoglobin A1c (HbA1c), glucose, high density lipoprotein, low density lipoprotein, triglycerides. Demographic characteristics included race, age, gender, body mass index (BMI), diabetes mellitus, chronic kidney disease stage three, ischemic heart disease, and smoking.

Results: The mean decreases in SBP and DBP were 8.1 and 3.4 mmHg, consistent with clinical trial data. Using a mean decrease in SBP of five mmHg or in DBP of two mmHg to define "responders," 30.3% of patients did not respond. In univariable analyses, responders had higher BMI, baseline SBP, DBP, sodium, and HbA1c, and lower creatinine. In multivariable analysis, responders were older and had significantly higher BMI and baseline SBP and DBP, and lower potassium. Increases in potassium and creatinine following spironolactone were larger in responders. When BP was evaluated as a continuous variable, decreases in SBP and DBP correlated with baseline BP, decrease

in sodium, and increases in potassium and creatinine following spironolactone. The decrease in SBP was associated with decreasing glucose in European Americans.

Conclusions: We developed an algorithm to assess BP response to a commonly prescribed medication for aTRH using EMRs. Electrolyte changes associated with the BP response to spironolactone are consistent with its mechanism of action of blocking the mineralocorticoid receptor and decreasing epithelial sodium channel activity.

Strengths and Limitations of this study:

- A strength of this study is the accuracy of the algorithm developed to determine blood pressure response to spironolactone in a large number of patients with apparent therapy-resistant hypertension (aTRH).
- The availability of clinical electrolyte measurements, in addition to blood pressure measurements, is another strength as it provides data supporting the mechanism of mineralocorticoid receptor (MR) antagonism in responders to spironolactone.
- Additional strengths are that this study provides methodology which can be applied in future pharmacogenetic studies using electronic health records, and that the algorithm can be adapted for use with other medications or in other large-scale electronic medical record systems with linked genetic data.
- Limitations of this study include the inability to confirm medication adherence, a lack of ambulatory blood pressure measurements, and a lack of some laboratory measures, such hemoglobin A1c (HbA1c) and lipids, for the entire population.

Keywords: spironolactone; mineralocorticoid receptor antagonist; blood pressure response; apparent therapy-resistant hypertension; electronic medical record

INTRODUCTION

The mineralocorticoid receptor (MR) antagonist spironolactone has been identified as effective add-on therapy for blood pressure (BP) control in patients with apparent therapy-resistant hypertension (aTRH) in clinical trials, including the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA) and the Prevention and Treatment of Hypertension with Algorithm Based Therapy-2 (PATHWAY-2).[1-4] In the PATHWAY-2 trial, addition of spironolactone at a dose of 25-50 mg/day to a therapeutic regimen containing an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB), calcium channel blocker (CCB), and thiazide-like diuretic significantly decreased home systolic blood pressure (SBP) by a mean of 8.7 mmHg.[1] In prior clinical studies the SBP/diastolic blood pressure (DBP) responses to spironolactone have ranged from a mean decrease of 4.6/1.8 mmHg to a mean decrease of 25/12 mmHg.[1-5]

Clinical trials often assess homogenous groups of patients limiting the applicability in a real-world clinical setting. We hypothesized that we could use electronic medical records (EMR) to assess the BP response to the addition of spironolactone in resistant hypertensive patients who were on a stable anti-hypertensive regimen of at least three medications including a thiazide diuretic or dihydropyridine CCB. We used a previously published algorithm for the identification of patients with aTRH.[6] To evaluate the BP response to spironolactone we developed an additional algorithm to identify patients who were prescribed spironolactone during a period of

stable medication use from up to six months before the start of spironolactone to six months after. The accuracy of the algorithm was validated by electronic record review.

We collected all outpatient BPs and laboratory measurements during the period of stable medication use before and after initial spironolactone prescription. We assessed BP response as a continuous variable and as a dichotomized variable (responders vs non-responders). We also assessed electrolyte measurements relevant to the mechanism of action of spironolactone, MR antagonism.

METHODS

Electronic Medical Record

We obtained Institutional Review Board approval to access the Vanderbilt University Medical Center (VUMC) Synthetic Derivative (SD). The SD is a de-identified copy of the VUMC EMR with Health Insurance Portability and Accountability Act of 1996 (HIPAA) identifiers removed by established de-identification software as well as custom techniques.[7] The SD contains almost all available clinical data including basic demographics, such as race and sex; text from clinical care notes; laboratory values; inpatient and outpatient medication data; international classification of disease (ICD) and current procedural terminology (CPT) codes; and other diagnostic reports.[7] To date, the SD contains approximately 2.8 million records, approximately one million of which contain detailed longitudinal data.

Spironolactone Response Algorithm Development

Patients within the SD were identified as having aTRH using a previously published algorithm.[6] Patients were defined as having aTRH if their BP was greater than or equal to 140/90 mmHg, despite concurrent use of three antihypertensives including a thiazide diuretic or dihydropyridine CCB, or if they were taking four or more antihypertensive medications, including a thiazide diuretic or dihydropyridine CCB. Patients with secondary hypertension, chronic kidney disease (CKD) stages four and five, heart failure with reduced ejection fraction less than 35 percent, thyroid and parathyroid disorders, nephrotic syndrome, chronic glomerulonephritis, anomalies of the bulbus

cordis, coarctation of the aorta, adrenal gland neoplasms and disorders (excluding adrenal insufficiencies), chronic pulmonary heart disease, thyrotoxicosis, disorders of thyrocalcitonin secretion, and obstructive uropathy were excluded by the aTRH algorithm (**Supplemental Table 1**).

All drug exposures to antihypertensive medications including spironolactone were identified from the SD by electronic-prescribing tools and MedEx.[8] The utility of these tools for extracting medication data from the EMR has been shown previously.[9, 10] For a medication exposure to be considered valid at least one of the following identifiers- dose, route, frequency, or duration- was required.

We developed an algorithm to identify patients in the SD who were prescribed spironolactone and in whom BP was measured within a stable window of time before and after initiation of spironolactone. Using electronic prescribing tools and MedEx,[8] the novel start date (NSD) for a spironolactone prescription was determined by the earliest mention of spironolactone, aldactone, or aldactazide in a patient's record after the patient met the aTRH case definition. In addition, spironolactone, aldactone, or aldactazide prescription had to have been listed at least twice, at least one month apart, during the subsequent six-month period. Patients who were initiated on aldactazide (aldactone/hydrochlorothiazide combination therapy) were required to have been using a thiazide diuretic immediately prior to the NSD for aldactazide. Patients who were not prescribed a thiazide prior to the start of aldactazide were excluded as having been started on spironolactone and hydrochlorothiazide (HCTZ) concurrently. Use of the MR antagonist eplerenone was not included in the study as it was prescribed to only 2% of the resistant hypertensive population.

Patients prescribed spironolactone without an outpatient BP measurement in the six months before or after the NSD were excluded. Patients who were diagnosed with other indications for spironolactone including heart failure, hepatic cirrhosis, hyperandrogenism, acne, or polycystic ovarian syndrome within a year of the NSD were also excluded. Using the algorithm, we identified sliding time windows up to six months before (baseline) and six months after the NSD (response) when there were no changes to each patient's prescribed antihypertensive medications, including dose (when available), the number of medications, and class type (**Figure 1**).

Once the baseline and response periods were defined, all outpatient BP measurements taken during these periods were identified. Any patient without at least two BP measurements during the baseline and response periods was excluded. The SBP and DBP responses were calculated as the difference between the mean SBP or DBP in the stable post-treatment window minus the mean SBP or DBP in the pre-treatment window (e.g. $\Delta SBP = \overline{SBPpost} - \overline{SBPpre}$). Any SBP and DBP responses that were more than two standard deviations from the mean were reviewed manually to confirm accuracy.

We also defined patients as responders versus non-responders based on a review of BP responses reported in clinical trials of spironolactone in European (EA) and African Americans (AA).[1-5] We defined responders as those who had a decrease in mean SBP of at least five mmHg or a decrease in mean DBP of at least two mmHg, corresponding to the smallest SBP and DBP responses to spironolactone reported among the studies reviewed.[5]

All patient characteristics, including age, gender, race, body mass index (BMI), outpatient BP measurements, serum potassium, creatinine, and sodium, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, glucose, hemoglobin A1C (HbA1c), and history of CKD stage three, ischemic heart disease (IHD), type two diabetes mellitus (T2DM), and smoking, were extracted from the SD using a combination of ICD-9 and -10 codes, CPT codes, laboratory measurements, and natural-language processing (**Supplemental Table 2**). Aldosterone, renin, renin activity, and aldosterone-renin-ratio (ARR) were not evaluated due to the small numbers of patients with data. For each patient, age and BMI at NSD or the date closest to NSD was used. The estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease (MDRD) formula.[11] CKD stage three was defined as an eGFR $\geq$30 mL/min/1.73m^2 and $\leq$60 mL/min/1.73m^2 or equivalent ICD-9 or -10 code at any point before NSD. Patient race was administratively assigned in the SD based on either physician or patient report. Previous work has shown that self-identified race is highly correlated with genetic ancestry[12, 13] and administratively assigned race in the VUMC SD is sufficient for genetic association analyses[14] and correlates tightly with genetic ancestry.[13]

After the algorithms were iteratively refined, blinded chart reviews of randomly chosen, never overlapping, charts were performed to determine algorithm efficacy. Based on a population size of 17,082, review of 138 charts would allow detection of a misclassification rate of 10% with a margin of error of 5%. We therefore reviewed 150 charts to determine algorithm efficacy. The review consisted of 75 charts from resistant hypertensive patients that were included by the algorithm and 75 that were excluded. The

algorithm was refined until a negative predictive value (NPV), positive predictive value (PPV), sensitivity, and specificity greater than 90% was achieved based on the review of 150 charts. The final version of the algorithm will be made available at Phenotype KnowledgeBase (PheKB).[15]

Statistical Methods

Data are presented as frequencies for categorical variables and mean ± standard deviations for continuous variables. Univariable analysis for binary BP response was performed using Pearson's chi-squared test for categorical variables and the Wilcoxon rank-sum test for continuous variables. A multivariable logistic regression model or multivariable linear regression model was fitted for binary BP response and continuous BP change on all variables available in more than 70% of the population. Missing values were not imputed. HDL cholesterol, LDL cholesterol, triglycerides, and HbA1c were excluded from multivariable regression models due to large amounts of missing values. The method of complete-case analysis was used and a linear relationship was assumed for all the continuous variables. All statistical analyses were conducted using the SPSS software version 24 (SPSS, Chicago, IL, USA) or R 3.3.0.[16]

Patient and Public Involvement

Because this study involved the use of the VUMC SD, patients were not recruited and there was no intervention. While patients were not involved in the development of the specific research question or study design, there has been extensive patient and community engagement in the establishment of the SD. Further, a community advisory

board within the Vanderbilt Institute for Clinical and Translational Research (VICTR) reviews programs including the SD. Dissemination of study results will occur through local reporting of study results.

RESULTS

Algorithm validation

NPV, PPV, sensitivity, and specificity of the algorithm for spironolactone response were determined after the blinded review of 150 electronic records. All but one excluded record were excluded appropriately. That record was excluded by the algorithm due to an erroneous ascertainment that a medication other than spironolactone had been added during the response periods. Five of the 75 records included in the algorithm should have been excluded. Four of these patients had inconsistencies in their medication history during the baseline or response period. In another patient, spironolactone was listed as a potential therapy in several notes but was not apparently prescribed. Based on this review, the NPV was 98.7%, PPV was 93.3%, sensitivity was 98.6%, and specificity was 93.7%.

Identification of spironolactone response population

Among EA and AA patients with aTRH in the SD 3,405 EA and 1,054 AA were prescribed spironolactone. Consistent with the aTRH definition, in addition to other antihypertensive medications, patients were prescribed a thiazide diuretic or a dihydropyridine CCB prior to spironolactone initiation. The median daily dose of thiazide diuretic was 25 mg with a range from 12.5 mg to 50 mg (**Supplemental Table 3**). The predominant dihydropyridine CCBs prescribed were amlodipine and nifedipine. The median daily dose of amlodipine and nifedipine were 10 mg with a range from 2.5 mg to 10 mg and 90 mg with a range from 30 mg to 120 mg, respectively (**Supplemental Table 3**). For a subset of these patients the thiazide or dihydropyridine CCB dose at

spironolactone initiation, e.g. dose of the medication identified in the month preceding or following spironolactone prescription, could not be determined. From the patients with confirmed doses 566 (80.6%) were prescribed a 25 mg thiazide, 312 (73.9%) were prescribed 10 mg amlodipine, and 110 (40.3%) were prescribed 90 mg nifedipine.

After applying exclusion and inclusion criteria, 1,114 EA patients and 369 AA patients were included in the study for evaluation of spironolactone response, 32.7% and 35.0% of the original number of patients prescribed spironolactone, respectively (**Figure 2**). The median dose of spironolactone was 25 mg and ranged from 12.5 to 200 mg. The majority of patients included in the study, 1,050 (70.8%), were prescribed 25 mg of spironolactone. 107 patients were prescribed spironolactone at a dose of 12.5mg and one at a dose of 200 mg. In total, 261 patients (17.6%) patients were prescribed a 50 mg or greater dose of spironolactone. The average number of outpatient BPs measured during the baseline and response periods were 4 and 4.8, respectively.

Characteristics of spironolactone responders and non-responders

Defining spironolactone response as a reduction in SBP of at least five mmHg or in DBP of at least two mmHg, we identified 1,034 responders (69.7%) and 449 non-responders (30.3%) in the total population. Of the responders, 15.8% met the criteria for a DBP response, 19.4% for a SBP response, and 64.8% for both a DBP and SBP response. Patient characteristics appear in **Table 1**. In univariable analyses, patients who responded to spironolactone were heavier and less likely to have a history of IHD. Responders had significantly higher baseline SBP, DBP, serum sodium, and HbA1c, and significantly lower baseline creatinine than nonresponders (**Table 1**). Responders also

had greater decreases in serum sodium and eGFR as well as greater increases in serum potassium and creatinine after starting spironolactone than nonresponders (**Table 1**). HbA1c did not change in responders whereas it declined over time in non-responders. In a multivariable model adjusting for all variables present in at least 1000 patients, responders were older and heavier, had higher baseline SBP and DBP, had lower baseline serum potassium and had a greater increase in serum potassium and creatinine after starting spironolactone than non-responders (**Table 2**).

Table 1. Characteristics of spironolactone responders and nonresponders in the total population.

Variable	N	Nonresponders (n=449)	Responders (n=1,034)	p-value
Age, years	1483	63.67 ± 13.18	64.28 ± 12.63	0.33
Female, n (%)	1483	215 (47.9%)	532 (51.5%)	0.21
Black Race, n (%)	1483	106 (23.6%)	263 (25.4%)	0.46
BMI, kg/m^2	1358	32.2 ± 8.0	33.5 ± 8.3	0.004
Diagnostic History				
T2DM, n (%)	1483	236 (52.6%)	566 (54.7%)	0.44
CKD3, n (%)	1483	163 (36.3%)	398 (38.5%)	0.43
IHD, n (%)	1483	179 (39.9%)	351 (33.9%)	0.03
Smoking, n (%)	1483	96 (21.4%)	211 (20.4%)	0.67
Baseline measurements				
SBP, mmHg	1483	133.20 ± 17.40	147.59 ± 18.70	< 0.001
DBP, mmHg	1483	71.66 ± 11.74	79.00 ± 13.08	< 0.001
Serum sodium, mmol/L	1176	138.67 ± 3.22	139.25 ± 2.98	0.004
Serum potassium, mmol/L	1177	3.95 ± 0.47	3.91 ± 0.43	0.15
Creatinine, mg/dL	1184	1.12 ± 0.36	1.09 ± 0.42	0.03
eGFR, mL/min/1.73m^2	1382	76.73 ± 23.78	77.38 ± 20.95	0.51
Glucose, mg/dL	1179	125.56 ± 58.56	126.98 ± 50.61	0.80
HbA1c, %	538	6.91 ± 1.81	7.23 ± 3.06	0.02
HDL cholesterol, mg/dL	575	47.48 ± 17.97	45.53 ± 15.31	0.44

LDL cholesterol, mg/dL	537	95.65 ± 39.74	98.54 ± 34.72	0.41
Triglycerides, mg/dL	578	163.98 ± 111.71	169.39 ± 121.20	0.85
Difference from baseline following initial spironolactone prescription				
Serum sodium, mmol/L	1101	-0.49 ± 2.63	-0.95 ± 2.70	0.006
Serum potassium, mmol/L	1104	0.13 ± 0.48	0.25 ± 0.42	< 0.001
Creatinine, mg/dL	1108	0.02 ± 0.23	0.134 ± 0.30	< 0.001
eGFR, mL/min/1.73m^2	1254	-5.22 ± 15.73	-9.09 ± 15.10	< 0.001
Glucose, mg/dL	1101	-0.27 ± 47.82	-0.37 ± 40.62	0.88
HbA1c, %	284	-0.25 ± 1.23	0.02 ± 1.05	0.02
HDL cholesterol, mg/dL	214	0.70 ± 11.51	-1.36 ± 9.35	0.23
LDL cholesterol, mg/dL	197	-5.74 ± 32.54	-7.48 ± 34.94	0.77
Triglycerides, mg/dL	220	-17.86 ± 107.95	-19.43 ± 107.16	0.91

Abbreviations: BMI, body mass index; CKD3, chronic kidney disease stage three; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; IHD, ischemic heart disease; LDL, low-density lipoprotein; N, number of individuals with the specific measure; SBP, systolic blood pressure; T2DM, type 2 diabetes mellitus.

Data are presented as mean ± standard deviation for continuous variables and count (%) for categorical variables

Table 2. Multivariable logistic regression model for responder versus non-responder in the total population without missing data (N=1019).

	Odds Ratio*	95% Confidence Interval	p-value
Age, years	1.034	1.017-1.052	< 0.001
Gender, Male: Female	0.897	0.603-1.323	0.59
Race, White: Black	1.217	0.800-1.849	0.36
Mean BMI, kg/m^2	1.030	1.008-1.054	0.01
Diagnostic history			
T2DM, Yes: No	1.132	0.794-1.615	0.49
CKD3, Yes: No	0.932	0.654-1.330	0.70
IHD, Yes: No	1.256	0.905-1.749	0.18
Smoking, Yes: No	1.074	0.745-1.559	0.71
Baseline measurements			
SBP, mmHg	1.034	1.023-1.046	< 0.001
DBP, mmHg	1.043	1.025-1.062	< 0.001
Serum sodium, mmol/L	1.013	0.957-1.071	0.66
Serum potassium, mmol/L	1.686	1.106-2.588	0.02
Creatinine, mg/dL	1.266	0.603-2.995	0.57
eGFR, mL/min/1.73m^2	1.007	0.993-1.021	0.32
Glucose, mg/dL	0.999	0.996-1.003	0.80
Difference from baseline following initial spironolactone prescription			
Serum sodium, mmol/L	0.946	0.888-1.007	0.08

Serum potassium, mmol/L	1.968	1.290-3.030	0.002
Creatinine, mg/dL	3.570	1.610-9.131	0.004
eGFR, mL/min/1.73m^2	1.001	0.987-1.015	0.92
Glucose, mg/dL	0.997	0.992-1.001	0.12

Abbreviations: BMI, body mass index; CKD 3, chronic kidney disease stage three; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; IHD, ischemic heart disease; N, number of individuals included in the analysis; SBP, systolic blood pressure.

*For continuous variables, the odds ratio reflects the effect of a one-unit increase. For example, a one mmHg increase in baseline SBP increases the odds ratio for responder versus non-responder 0.03.

Among EA patients, 343 (30.8%) did not respond to spironolactone. EA responders were heavier and less likely to have IHD. They had higher baseline SBP, DBP, and serum sodium than nonresponders (**Supplemental Table 4**). EA responders also had a greater decrease in serum sodium and eGFR and a greater increase in serum potassium and creatinine after starting spironolactone (**Supplemental Table 4**).

Among AA patients, 106 (28.7%) did not respond to spironolactone. Like EA responders, AA responders had significantly higher baseline SBP and DBP and a greater decrease in serum sodium and increase in creatinine after starting spironolactone than nonresponders (**Supplemental Table 5**).

Blood pressure response to spironolactone as a continuous variable

For the entire group, the mean decrease in SBP following initiation of spironolactone was 8.1 mmHg and the mean decrease in DBP was 3.4 mmHg following initial spironolactone prescription. In total, 933 patients (62.9%) achieved a decrease in BP to ≤ 140/90 mmHg, the pressure goal recommended in guidelines at the time.[17] An additional 23 patients achieved a decrease in SBP but not DBP to guideline recommendation and 262 patients achieved DBP but not SBP control. Analyses of BP change as a continuous variable were performed using a multivariable model that included all variables except for HbA1c, HDL cholesterol, LDL cholesterol, and triglycerides, as data were not available in the majority of patients.

In the total population, patients with higher baseline SBP, lower baseline creatinine, and a greater decrease in serum sodium, increase in serum potassium, or increase in creatinine after starting spironolactone had greater reductions in SBP (**Table 3**

and **Figure 3**). Patients with higher baseline SBP and DBP and a greater decrease in serum sodium, increase in serum potassium, or increase in creatinine after spironolactone had greater reductions in DBP (**Table 3**). Older patients and female patients also had significantly greater reductions in DBP (**Table 3**).

Table 3. Significant coefficients in multivariable models for change in systolic and diastolic blood pressures.

	Associated Variable	Coefficient	95% Confidence Interval	p-value
Total population (N=1019)				
Change in SBP	Baseline SBP	-0.415	-0.475, -0.356	< 0.001
	Baseline creatinine	3.628	0.202, 7.054	0.04
	Change in serum sodium	0.701	0.338, 1.064	< 0.001
	Change in serum potassium	-3.483	-5.834, -1.131	0.004
	Change in creatinine	-5.039	-8.704, -1.374	0.01
Change in DBP	Age	-0.141	-0.196, -0.086	< 0.001
	Gender- Male: Female	1.390	0.170, 2.610	0.03
	Baseline SBP	-0.045	-0.080, -0.011	0.01
	Baseline DBP	-0.379	-0.436, -0.321	< 0.001
	Change in serum sodium	0.274	0.063, 0.485	0.01
	Change in serum potassium	-2.042	-3.413, -0.671	0.004
	Change in creatinine	-3.979	-6.116, -1.841	< 0.001
European Americans (N=753)				
Change in SBP	Baseline SBP	-0.401	-0.470, -0.333	< 0.001
	Change in serum sodium	0.525	0.117, 0.933	0.01
	Change in serum potassium	-3.074	-5.766, -0.381	0.03
	Change in glucose	0.031	0.003, 0.059	0.03
Change in DBP	Age	-0.135	-0.200, -0.070	< 0.001
	Gender, Male: Female	1.669	0.230, 3.108	0.02

	Baseline SBP	-0.045	-0.084, -0.005	0.03
	Baseline DBP	-0.370	-0.436, -0.303	< 0.001
	Change in serum potassium	-1.809	-3.385, -0.232	0.03
	Change in creatinine	-3.328	-5.772, -0.884	0.01
African Americans (N=266)				
Change in SBP	Baseline SBP	-0.445	-0.571, -0.319	< 0.001
	Baseline creatinine	5.572	0.017, 11.127	0.05
	Change in serum sodium	1.338	0.517, 2.159	0.002
	Change in potassium	-5.206	-10.205, -0.207	0.04
	Change in creatinine	-10.923	-19.456, -2.391	0.01
Change in DBP	Age	-0.156	-0.265, -0.046	0.01
	Baseline DBP	-0.407	-0.512, -0.278	< 0.001
	Change in sodium	0.530	0.053-1.007	0.03
	Change in potassium	-2.864	-5.768, 0.039	0.05
	Change in creatinine	-7.370	-12.326, -2.413	0.004

Abbreviations: DBP, diastolic blood pressure; N, number of individuals included in the analysis; SBP, systolic blood pressure.

In EA alone, a greater decrease in either SBP or DBP was significantly associated with baseline SBP, as well as increase in serum potassium (**Table 3**). A greater reduction in SBP was further associated with greater decreases in serum sodium and glucose (**Table 3**). The change in DBP was also significantly associated with age, sex, and creatinine (**Table 3**).

In AA, greater reductions in SBP and DBP were significantly associated with greater decreases in serum sodium and increases in serum potassium and creatinine (**Table 3**). Patients with higher baseline SBP and baseline creatinine had a greater reduction in SBP, while patients with higher baseline DBP and older age had a greater reduction in DBP (**Table 3**).

DISCUSSION

We developed a highly accurate algorithm to define the BP response to spironolactone in patients with aTRH using the EMR. The mean decreases in SBP and DBP for the total study population, 8.1 mmHg and 3.4 mmHg, respectively, are consistent with responses reported in prior clinical trials, such as the PATHWAY-2 trial.[1] In total, 30.3% of patients prescribed spironolactone did not achieve a five mmHg decrease in SBP or two mmHg decrease in DBP in the six months following spironolactone initiation. Higher pretreatment SBP and DBP predicted a greater therapeutic response to spironolactone, measured either as a dichotomous or continuous variable.

In addition, using the electronic algorithm, we were able to detect not only the BP response, but also changes in serum sodium, potassium, and creatinine after spironolactone initiation. Regardless of race, the response to spironolactone was associated with a greater decrease in serum sodium and greater increase in serum potassium, consistent with MR antagonism. These changes are also consistent with a decrease in epithelial sodium channel (ENaC) activity. In the present study, however, we are unable to determine if this inadequate BP response is due to inadequate spironolactone dose, spironolactone noncompliance, or non-MR mediated ENaC activation. Further, we found a significant correlation between decreasing BP and increasing creatinine after starting spironolactone in all groups. This correlation is likely a result from hemodynamic effects of BP medications and especially from blocking the renin-angiotensin-aldosterone system (RAAS).[1]

Race was not significantly associated with BP response to spironolactone nor electrolyte changes which suggests spironolactone exerts a consistent BP lowering effect regardless of race. These findings are supported by those of Nishizaka, et al. who determined that low-dose spironolactone provided a significant decrease in BP in AA and EA with resistant hypertension with and without primary aldosteronism.[4]

In EA, we also observed a significant correlation between the SBP response and decreasing glucose; whereas, among those in whom HbA1c was measured before and after therapy, HbA1c declined in nonresponders but not responders. The latter observation may reflect the fact that responders had a higher baseline HbA1c than non-responders. While these findings may suggest a potential benefit to glucose management from MR antagonism it is important to note that the exact relationship between MR antagonism and glucose is not perfectly understood. Because our findings, as well as others, suggest an association between spironolactone use and glucose levels, additional studies to better characterize this relationship are warranted.

A limitation of this study and many other studies of aTRH is the inability to measure adherence directly in the patients prescribed spironolactone without measuring drug levels, which is not routinely done in clinical practice. Nonadherence alone does not likely explain the lack of BP response in nonresponders, however. First, patients nonadherent to spironolactone would likely be nonadherent to other medications. Nonadherent patients, therefore, would be expected to have higher baseline BPs than adherent patients. To the contrary, we found that nonresponders had lower baseline SBP and DBP than responders and baseline SBP and DBP significantly predicted BP response. In addition, initiation of spironolactone resulted in an increase in serum

potassium and decrease in serum sodium in non-responders as well as responders, albeit to a lesser degree. Taken together these findings suggest that nonadherence is not the predominant driver of the lack of BP response in non-responders.

Another way to assess adequacy of spironolactone dose is to assess whether renin activity remains suppressed. Unfortunately, an insufficient number of patients had renin measured during the baseline and response periods to assess change in renin concentration or activity. The limited number of renin measurements in the EMR is reflective of poor screening rates for primary aldosteronism.[18] Previous studies have reported limited value in the addition of aldosterone levels or the ARR to prediction models of BP response to MR antagonism in aTRH, however.[19,20]

Other limitations of the study include the exclusion of a significant number of patients with aTRH due to inadequate documentation of pre- and post-treatment BPs, which limits our power of detection for some responses. The relatively small number of AA, for example, limits the power to detect predictors of response to spironolactone in this group.

The advantage of this approach is that it is an accurate, rapid, high throughput, and inexpensive approach for quantifying clinical response to medications and determine responders and nonresponders. The identified population can then be used as a research cohort to investigate other relevant topics including pharmacogenetic inquiries, long term outcome and event studies, as well as evaluate medication levels to determine compliance or the presence of rapid or insufficient metabolizers. Further, the method can easily be adapted for use with other medication types and in other EMR systems. These adaptations could also allow for inquires related to personnel and infrastructure

performance, e.g. when the algorithm is adapted for evaluation of a response for a medication used exclusively in-hospital.

In conclusion, we have developed a highly accurate algorithm for the assessment of BP response to spironolactone, a commonly prescribed medication, in patients with aTRH using EMR. Electrolyte changes associated with the BP response to spironolactone are consistent with its mechanism of action to block the MR and decrease activity of ENaC. A strength of this algorithm is its applicability to evaluate BP and electrolyte responses to medications other than spironolactone as well as its utility to evaluate the long-term clinical consequences of medication use. Further, this electronic algorithm could be amended for use in other EMR systems.

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DISCLOSURES

None

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FIGURE LEGENDS

Figure 1. Schematic of the spironolactone response algorithm and identification of the baseline and response periods for patients. The earliest date a patient was prescribed spironolactone is indicated by the novel start date (NSD). The baseline period is determined by identifying all visits in which same three medication classes as prescribed to the patient as on the NSD. If the visit date for the start of the baseline period occurred more than six months before the NSD a baseline period of six months was used. The determination of the response period is not shown in the schematic above. Similar logic was applied to the selection of this period.

Figure 2. Diagram of the algorithm for the identification of patients with apparent therapy-resistant hypertension (aTRH) in the VUMC Synthetic Derivative (SD) prescribed spironolactone during a period of stable medication use for the evaluation of blood pressure response.

Figure 3. The significant correlations with systolic blood pressure change in the total population. Correlation between the change in systolic blood pressure (SBP) after starting spironolactone and baseline A) SBP [correlation coefficient (CC)= -0.415, $p<0.001$], and the change in B) creatinine (CC= -5.039, p=0.01), C) serum sodium (CC= 0.701, $p<0.001$), and D) serum potassium (CC= -3.483, p= 0.004).

STATEMENTS

Contributorship

MMS and NJB contributed to the design of the study; MMS, BP, HN, CY, JML, and NJB contributed to the analysis and interpretation of the results; MMS and NJB contributed to the drafting of the manuscript; MMS, BP, HN, CY, JML, and NJB contributed to the editing of the manuscript and final approval for submission

Competing Interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: Dr Brown reports consulting for Shire HGT, Novartis Pharmaceuticals, Viamet Pharmaceuticals and serving on the Scientific Advisory Board of Alnylam Pharmaceuticals. Dr. Brown also sits on the Joint Scientific Committee for the Vanderbilt Bayer Alliance. All authors report no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Patient Consent

No identifiable patient data was used in the study.

Ethical Approval

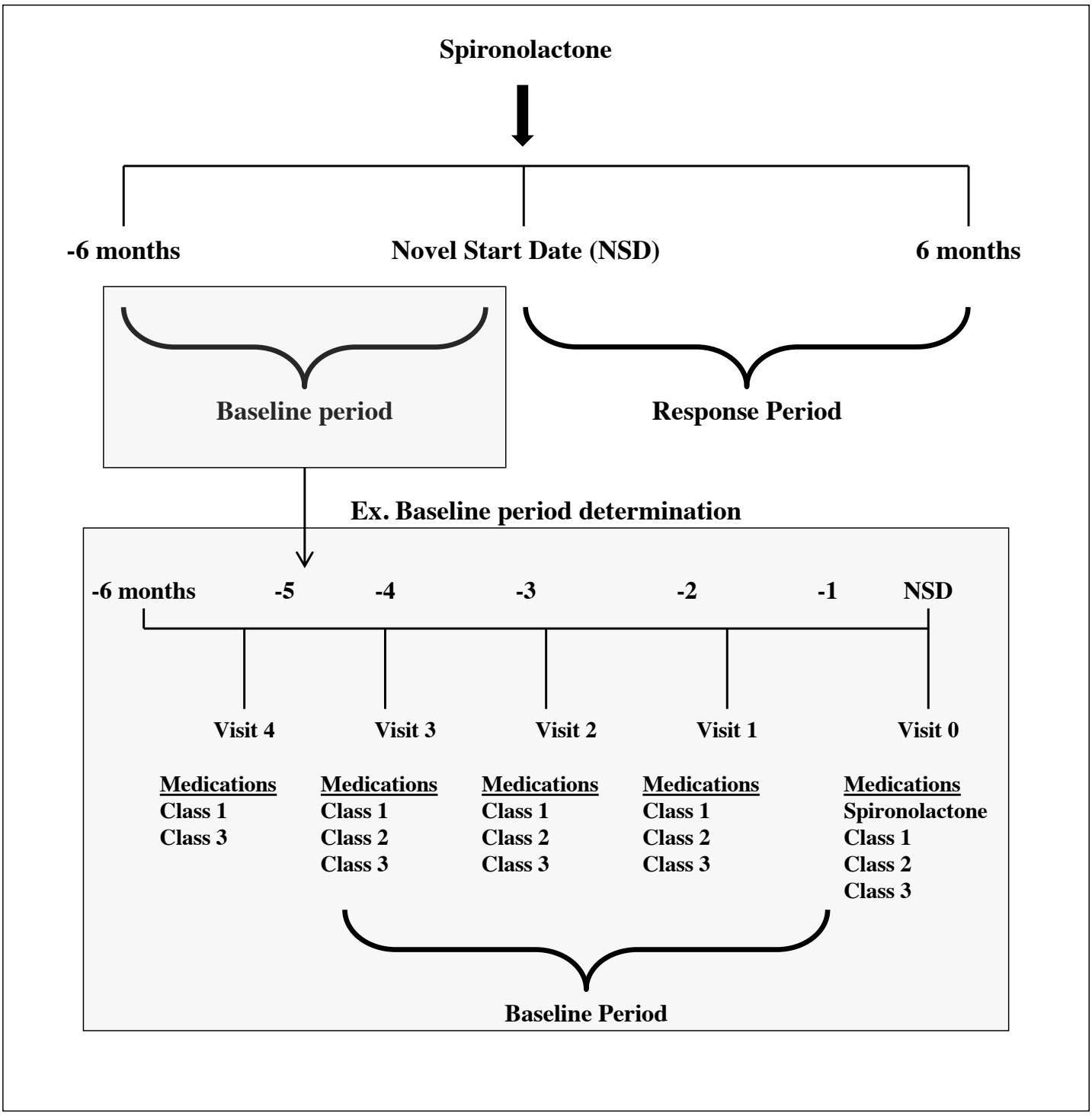
The study was approved by the Vanderbilt University Medical Center Institutional Review Board (#130848).

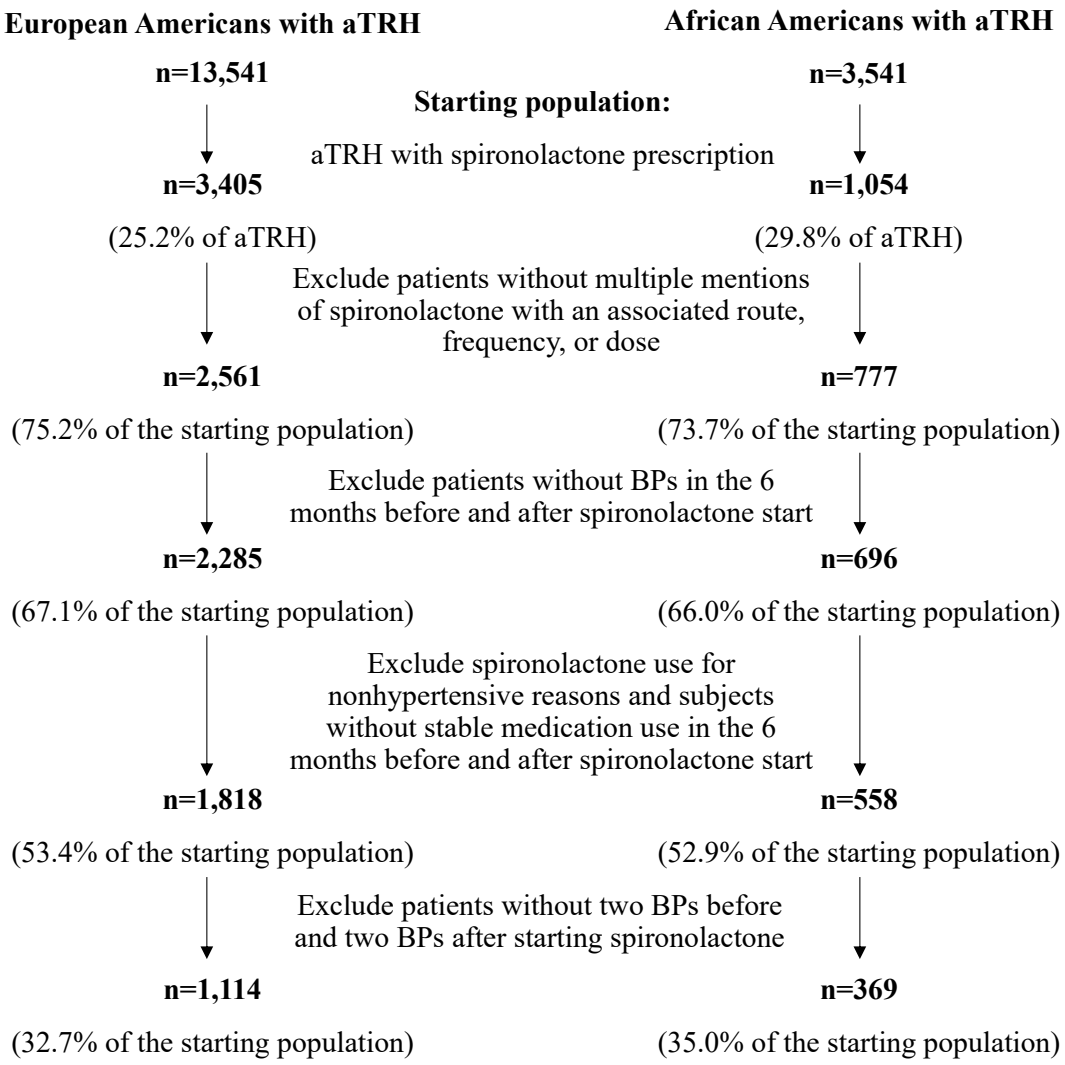
Transparency Declaration

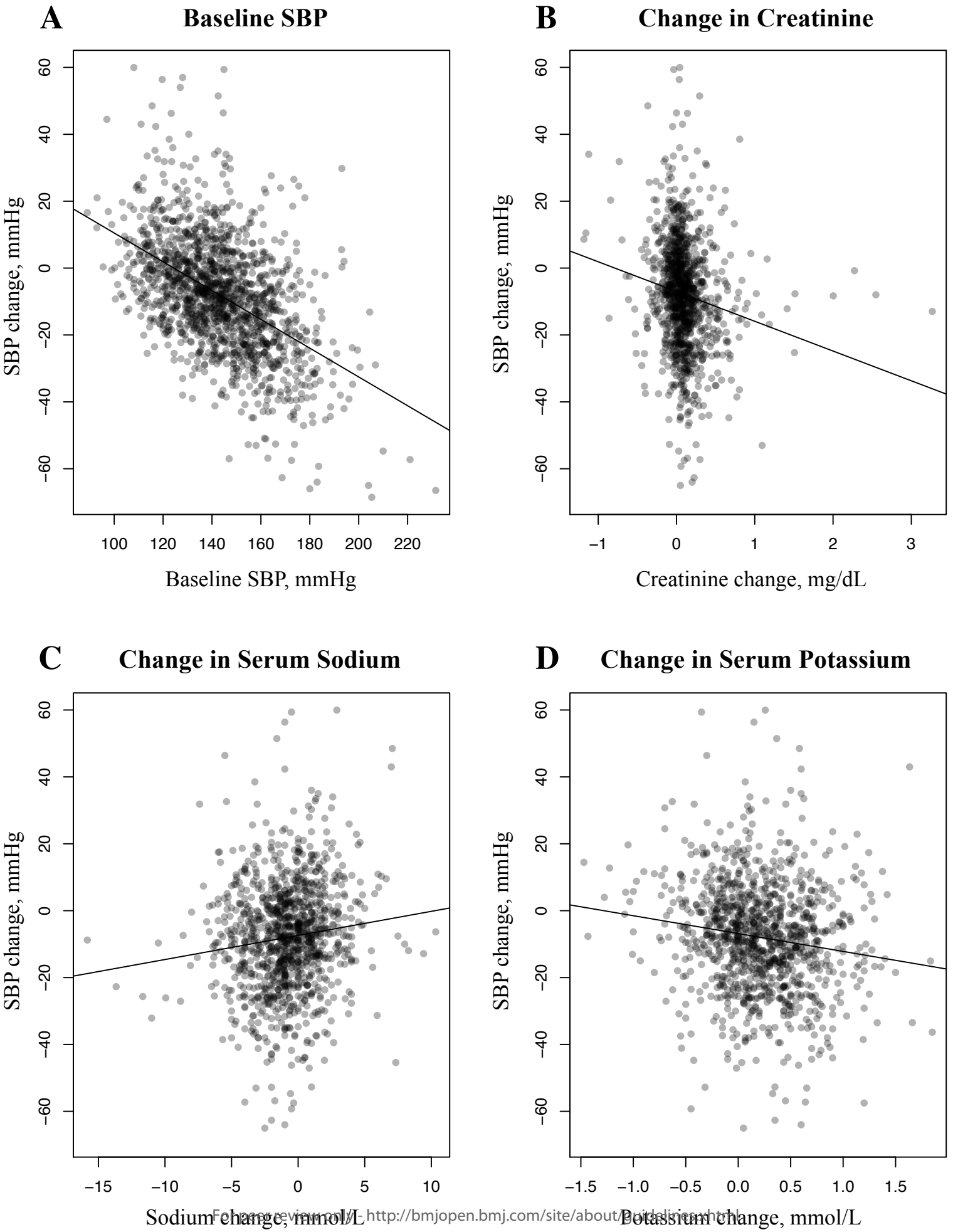
M. Shuey affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Data Sharing

The full data set is available upon request to the corresponding author.







DATA SUPPLEMENT

Supplemental Table 1. International Classifiers of Disease (ICD)-9 and -10 exclusions for resistant hypertensive subjects

Description	ICD-9-CM codes	ICD-10-CM-codes
Exclusion for Case Type I, Case Type II, and Control if ever present in a patient record		
Malignant neoplasm of unspecified adrenal gland	194.0	C74.9
Benign neoplasm of unspecified adrenal gland	227.0	D35.00
Disorders of the adrenal gland (excluding adrenal insufficiencies)	255.0, 255.1*, 255.2, 255.3, 255.6, 255.8, 255.9	E24.*, E26.*, E25.*, E27.0, E27.5, E27.8, E27.9
Secondary Hypertension	405.*	I15.0, I15.8
Chronic pulmonary heart disease	416.*	I27. *
Nephrotic syndrome	581.*	N04.*, N08
Chronic glomerulonephritis	582.*	N03.*, N08
Bulbus cordis anomalies	745.*	Q20.*, Q21.*
Coarctation of aorta	747.1*	Q25.1, Q25.2
Exclusion for Case Type I and Case Type II if present in a patient record 5 years before or 1 year after identification as a Case		
Thyrotoxicosis	242.*	E05.*
Disorder of thyrocalcitonin secretion	246.0	E07.0
Disorders of the thyroid NEC	246.8	E03.4, E07.89
Disorders of the thyroid NOS	246.9	E07.9
Parathyroid disorder NEC	252.8	E21.4
Parathyroid disorder NOS	252.9	E21.5
Obstructive uropathy	599.6*	N13.9

Abbreviations: NEC, not elsewhere classified; NOS, not otherwise classified

Supplemental Table 2. International Classifiers of Disease (ICD)-9 and ICD-10 codes used for history of diagnosis

Diagnosis	ICD-9 codes	ICD-10 codes	Other
Chronic kidney disease stage 3	585.1	N18.1	eGFR > 30 mL/min/1.73 m^2
	585.2	N18.2	but < 60 mL/min/1.73 m^2
Ischemic heart disease	410.*	I20.*	
	411.*	I22.*	
	413.*	I24.*	
	414.*	125.*	
Type 2 diabetes mellitus	250	E11	
	250.*	E11.*	
	327.2*	G47.3*	
Smoking	305.1	F17.*	
	V15.82	Z87.891	

Abbreviations: eGFR, estimated glomerular filtration rate

Supplemental Table 3. The daily dose and frequency of thiazide diuretic and dihydropyridine calcium channel blocker prescription in patients with apparent treatment-resistant hypertension prior to spironolactone prescription

Medication	Daily dose	Patients prescribed, n (%)*
Thiazide diuretic		884
	12.5 mg	86 (9.7)
	25 mg	566 (64.0)
	50 mg	78 (8.8)
	unknown	154 (17.4)
Dihydropyridine calcium channel blocker		980
Amlodipine		
	2.5 mg	8 (0.8)
	5 mg	99 (10.1)
	7.5 mg	3 (0.3)
	10 mg	312 (31.8)
	unknown	52 (5.3)
Nifedipine		
	30 mg	38 (3.9)
	60 mg	100 (10.2)
	90 mg	110 (11.2)
	120 mg	25 (2.6)
	unknown	233 (23.8)

*The frequency of medication dose based on medication type, e.g. thiazide diuretic or dihydropyridine calcium channel blocker.

Supplemental Table 4. Characteristics of spironolactone responders and nonresponders in European Americans.

Variable	N	Nonresponders (n=343)	Responders (n=771)	p-value*
Age, years	1,114	65.66 ± 13.09	66.21 ± 12.04	0.50
Female, n (%)	1,114	151 (44.0%)	368 (47.7%)	0.25
BMI, kg/m^2	1,023	31.3 ± 7.2	32.5 ± 7.7	0.01
Diagnostic History				
T2DM, n (%)	1,114	173 (50.4%)	393 (51.0%)	0.87
CKD3, n (%)	1,114	124 (36.2%)	296 (38.4%)	0.48
IHD, n (%)	1,114	149 (43.4%)	280 (36.3%)	0.02
Smoking, n (%)	1,114	75 (21.9%)	157 (20.4%)	0.57
Baseline measures				
SBP, mmHg	1,114	131.37 ± 16.99	145.91 ± 18.52	< 0.001
DBP, mmHg	1,114	69.46 ± 10.88	76.78 ± 12.52	< 0.001
Serum sodium, mmol/L	872	138.45 ± 3.26	139.04 ± 3.00	0.01
Serum potassium, mmol/L	871	3.99 ± 0.46	3.93 ± 0.43	0.07
Creatinine, mg/dL	878	1.11 ± 0.37	1.07 ± 0.37	0.11
eGFR, mL/min/1.73m^2	1,029	75.16 ± 24.47	75.23 ± 19.83	0.96
Glucose, mg/dL	875	124.46 ± 56.69	126.59 ± 48.81	0.57
HbA1c, %	383	6.76 ± 1.67	7.24 ± 3.54	0.10
HDL cholesterol, mg/dL	420	46.96 ± 18.89	44.11 ± 14.83	0.10
LDL cholesterol, mg/dL	390	92.09 ± 37.86	95.30 ± 34.75	0.43
Triglycerides, mg/dL	426	167.8 ± 117.0	182.5 ± 129.4	0.27
Difference from baseline following initial spironolactone prescription				
Serum sodium, mmol/L	810	-0.70 ± 2.63	-1.12 ± 2.71	0.04

Serum potassium, mmol/L	812	0.12 ± 0.48	0.27 ± 0.43	< 0.001
Creatinine, mg/dL	816	0.01 ± 0.23	0.13 ± 0.32	< 0.001
eGFR, mL/min/1.73m^2	924	-4.82 ± 15.68	-8.76 ± 14.51	< 0.001
Glucose, mg/dL	810	1.44 ± 47.52	0.01 ± 39.03	0.65
HbA1c, %	181	-0.13 ± 1.31	-0.05 ± 0.92	0.63
HDL cholesterol, mg/dL	156	0.03 ± 9.35	-0.94 ± 8.62	0.54
LDL cholesterol, mg/dL	142	-7.29 ± 35.21	-8.63 ± 35.09	0.86
Triglycerides, mg/dL	162	-11.99 ± 107.79	-22.93 ± 121.66	0.59

Abbreviations: BMI, body mass index; CKD 3, chronic kidney disease stage three; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; IHD, ischemic heart disease; LDL, low-density lipoprotein; N, number of individuals with the specific measure; SBP, systolic blood pressure.

Data are presented as mean ± standard deviation for continuous variables and count (%) for categorical variables.

* P-values from the multivariable regression model are provided for all variables except HbA1c, HDL cholesterol, LDL cholesterol, and triglycerides. Univariate p-values are provided for these variables.

Supplemental Table 5. Characteristics of spironolactone responders and nonresponders in African Americans.

Variable	N	Nonresponders (n=106)	Responders (n=263)	p-value*
Age, years	369	57.23 ± 11.30	58.65 ± 12.64	0.32
Female, n (%)	369	64 (60.3%)	164 (62.4%)	0.72
BMI, kg/m^2	335	35.3 ± 9.7	37.3 ± 9.2	0.40
Diagnostic History				
T2DM, n (%)	369	63 (59.4%)	173 (65.7%)	0.25
CKD3, n (%)	369	39 (36.8%)	102 (38.8%)	0.72
IHD, n (%)	369	30 (28.3%)	71 (27.0%)	0.80
Smoking, n (%)	369	21 (19.8%)	211 (20.5%)	0.87
Baseline measures				
SBP, mmHg	369	139.15 ± 17.46	152.51 ± 18.40	< 0.001
DBP, mmHg	369	78.78 ± 11.67	85.50 ± 12.53	< 0.001
Serum sodium, mmol/L	304	139.37 ± 3.00	139.81 ± 2.85	0.23
Serum potassium, mmol/L	304	3.81 ± 0.50	3.84 ± 0.44	0.58
Creatinine, mg/dL	306	1.14 ± 0.33	1.16 ± 0.54	0.73
eGFR, mL/min/1.73m^2	353	81.69 + 20.78	83.42 + 22.80	0.51
Glucose, mg/dL	304	129.05 ± 64.32	128.05 ± 55.37	0.89
HbA1c, %	155	7.45 ± 2.17	7.22 ± 1.65	0.50
HDL cholesterol, mg/dL	155	49.07 ± 14.93	49.21 ± 15.95	0.56
LDL cholesterol, mg/dL	147	106.51 ± 43.81	106.70 ± 33.43	0.98

Triglycerides, mg/dL	152	151.35 ± 92.16	135.01 ± 88.22	0.34
Difference from baseline following initial spironolactone prescription				
Serum sodium, mmol/L	291	0.17 ± 2.52	-0.52 ± 2.63	0.05
Serum potassium, mmol/L	292	0.16 ± 0.50	0.19 ± 0.39	0.57
Creatinine, mg/dL	292	0.06 ± 0.23	0.14 ± 0.26	0.01
eGFR, mL/min/1.73m^2	330	-6.50 ± 15.89	-9.99 ± 16.61	0.09
Glucose, mg/dL	291	-5.56 ± 48.63	-1.37 ± 44.65	0.48
HbA1c, %	103	-0.54 ± 0.97	0.02 ± 1.23	0.09
HDL cholesterol, mg/dL	58	3.17 ± 17.66	-1.67 ± 10.92	0.24
LDL cholesterol, mg/dL	55	0.04 ± 19.86	-4.82 ± 34.85	0.65
Triglycerides, mg/dL	58	-43.47 ± 109.99	-11.64 ± 61.01	0.21

Abbreviations: BMI, body mass index; CKD 3, chronic kidney disease stage three; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; IHD, ischemic heart disease; LDL, low-density lipoprotein; N, number of individuals with the specific measure; SBP, systolic blood pressure.

Data are presented as mean ± standard deviation for continuous variables and count (%) for categorical variables.

* P-values from the multivariable regression model are provided for all variables except HbA1c, HDL cholesterol, LDL cholesterol, and triglycerides. Univariate p-values are provided for these variables.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1,2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2,3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5-6, 7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7-11
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-11
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-11, Supplemental Table 1
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	7-9, 13, Figure 2
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9, 11
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	11
		(*b*) Describe any methods used to examine subgroups and interactions	11
		(*c*) Explain how missing data were addressed	11
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	10-11
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	13, Figure 2
		(b) Give reasons for non-participation at each stage	Figure 2
		(c) Consider use of a flow diagram	Figure 2
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	14, Tables 1 and 2
		(b) Indicate number of participants with missing data for each variable of interest	Tables 1 and 2
		(c) Summarise follow-up time (eg, average and total amount)	13, Figure 2
Outcome data	15*	Report numbers of outcome events or summary measures over time	13-19
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	14-20, Table 1, 2, and 3
		(*b*) Report category boundaries when continuous variables were categorized	13
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Table 3, Supplemental tables 3 and 4
Discussion			
Key results	18	Summarise key results with reference to study objectives	24-27
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	4, 26-27
Generalisability	21	Discuss the generalisability (external validity) of the study results	4, 26-27
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	29

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.