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Apparent Treatment-Resistant Hypertension Assessed by Office and Ambulatory Blood Pressure in Chronic Kidney Disease—A Report from the Chronic Renal Insufficiency Cohort Study

George Thomas,[1] Jesse Felts,[2] Carolyn S. Brecklin,[3] Jing Chen,[4] Paul E. Drawz,[5] Eva Lustigova,[6] Rupal Mehta,[7,8] Edgar R. Miller III,[9] Stephen M. Sozio,[9] Matthew R. Weir,[10] Dawei Xie,[11] Xue Wang,[11] and Mahboob Rahman,[2] on behalf of the CRIC Study Investigators[*]

Abstract

Background Apparent treatment-resistant hypertension is common in patients with CKD. Whether measurement of 24-hour ambulatory BP monitoring is valuable for risk-stratifying patients with resistant hypertension and CKD is unclear.

Methods We analyzed data from the Chronic Renal Insufficiency Cohort study, a prospective study of participants (n=1186) with CKD. Office BP was measured using standardized protocols; ambulatory BP was measured using Spacelabs monitors. Apparent treatment-resistant hypertension was defined on the basis of office BP, ambulatory BP monitoring, and use of more than three antihypertensive medications. Outcomes were composite cardiovascular disease, kidney outcomes, and mortality. Groups were compared using Cox regression analyses with a control group of participants without apparent treatment-resistant hypertension.

Results Of 475 participants with apparent treatment-resistant hypertension on the basis of office BP, 91.6% had apparent treatment-resistant hypertension confirmed by ambulatory BP monitoring. Unadjusted event rates of composite cardiovascular disease, kidney outcomes, and mortality were higher in participants with ambulatory BP monitoring–defined apparent treatment-resistant hypertension compared with participants without apparent treatment-resistant hypertension. In adjusted analyses, the risks of composite cardiovascular disease (hazard ratio, 1.27; 95% confidence interval [95% CI], 0.59 to 2.7), kidney outcomes (hazard ratio, 1.68; 95% CI, 0.88 to 3.21), and mortality (hazard ratio, 1.27; 95% CI, 0.5 to 3.25) were not statistically significantly higher in participants with ambulatory BP monitoring–defined apparent treatment-resistant hypertension compared with participants without apparent treatment-resistant hypertension.

Conclusions In our study population with CKD, most patients with apparent treatment-resistant hypertension defined on the basis of office BP have apparent treatment-resistant hypertension confirmed by ambulatory BP monitoring. Although ABPM-defined apparent treatment-resistant hypertension was not independently associated with clinical outcomes, it identified participants at high risk for adverse clinical outcomes.

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Introduction

Resistant hypertension is defined as BP that remains above goal despite the concurrent use of three different antihypertensive medication classes at maximum or maximally tolerated doses, commonly including a calcium channel blocker, a blocker of the renin-angiotensin system, and a diuretic; or BP at goal on four or more antihypertensive medication classes (1).

[1]Department of Nephrology and Hypertension, Cleveland Clinic, Cleveland, Ohio
[2]Department of Medicine, University Hospitals Cleveland Medical Center, Louis Stokes Cleveland Veterans Affairs Medical Center, Case Western Reserve University, Cleveland, Ohio
[3]Deparment of Medicine, University of Illinois, Chicago, Illinois
[4]Department of Medicine, Tulane School of Medicine, New Orleans, Louisiana
[5]Department of Medicine, University of Minnesota, Minneapolis, Minnesota
[6]Kaiser Permanente Medical Group, Pasadena, California
[7]Department of Medicine, Feinberg School of Medicine, Northwestern University, Chicago, Illinois
[8]Jesse Brown Veterans Affairs Medical Center, Chicago, Illinois
[9]Department of Medicine, Johns Hopkins University, Baltimore, Maryland
[10]Department of Medicine, University of Maryland School of Medicine, Baltimore, Maryland
[11]Department of Biostatistics, Epidemiology and Informatics, Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania

Correspondence: Mahboob Rahman, Case Western Reserve University, 11100 Euclid Avenue, Cleveland, OH 44106. Email: Mahboob.Rahman@uhhospitals.org

Resistant hypertension is associated with high risk of adverse renal and cardiovascular outcomes (2−4). Resistant hypertension is a particularly important clinical problem in patients with CKD (5,6). In the Chronic Renal Insufficiency Cohort (CRIC) study, we previously showed that resistant hypertension is common in CKD and associated with higher cardiovascular and renal risk and mortality (7).

The term apparent treatment-resistant hypertension (ATRH) is commonly used in epidemiologic studies because the definition is on the basis of office readings, and individuals with pseudoresistance cannot be definitively identified and excluded (8,9). One such factor may be the white coat effect, where BP is high in the office but not in the ambulatory setting (10). Ambulatory BP monitoring (ABPM) provides a broader measure of the burden of hypertension, including estimates of 24-hour, daytime, and nighttime BP along with information about diurnal changes in BP. Abnormal ambulatory BP profiles are more prevalent in patients with CKD, and they are also associated with higher risk for adverse clinical outcomes, independent of office BP (11). Therefore, there has been interest in using ABPM to further characterize patients with resistant hypertension (12). Resistant hypertension confirmed by ABPM is associated with high cardiovascular risk in the general population (13−15). Few previous studies have evaluated the role of ABPM in patients with ATRH and CKD (16).

The purpose of this study is to determine the prevalence and factors associated with ATRH incorporating both office BP measurement and ABPM in a large cohort of participants with CKD and to evaluate the association of ATRH with long-term clinical outcomes. We hypothesized that the presence of ATRH confirmed by ABPM would be associated with higher risk of adverse renal and cardiovascular outcomes compared with individuals without ATRH in a population with CKD.

Materials and Methods

The CRIC study is a multicenter, prospective, observational cohort study of participants with CKD. The study design and baseline characteristics of participants have been described previously (17,18). Between 2003 and 2008, 3939 participants aged 21–74 years with eGFR between 20 and 70 ml/min per 1.73 m^2 were enrolled for participation in the study. Exclusion criteria included a diagnosis of polycystic kidney disease and active immunosuppression for GN as well as cirrhosis, class 3 or 4 heart failure, HIV infection, cancer, and pregnancy. The study protocol was approved by the institutional review board of each participating site, and written informed consent was obtained from all participants.

At study visits, demographic and physical measures, medical history, medication use, and serum and urine for laboratory assessments were collected. Participants were followed annually with in-person clinic visits and also contacted by telephone calls approximately 6 months apart. Diabetes was determined as at least one of the following: self-reported insulin or oral hypoglycemic medication, fasting blood glucose ≥126 mg/dl or a nonfasting level ≥200 mg/dl, or hemoglobin A1c ≥6.5%. The GFR was estimated using the CRIC study equation (19).

BP was measured three times while seated during a clinic visit by trained study staff following standardized protocols recommended by the American Heart Association (AHA) using aneroid sphygmomanometers; the average of these three measurements was used to define office BP. ABPM was obtained in 1502 participants. The exclusion criteria for ABPM, derivation of the ABPM cohort from the overall CRIC cohort, and details of ABPM measurement protocol have been previously published (20). Briefly, ABPM measures were obtained during the second phase of the CRIC study. The first phase of the CRIC study was between 2003 and 2007, in which 3939 participants were recruited to participate in the study. ABPM was conducted between 2008 and 2012 during the second phase of the CRIC study; therefore, participants who had died, were lost to follow-up, or did not reconsent for the second phase were not available for measurement of ABPM. Of patients enrolled in phase 2, participants were chosen randomly for measurement of ABPM. Selection of participants was stratified by clinical site. The coordinating center notified the sites if a participant was chosen for ABPM, and the site approached the participant to further evaluate for exclusion criteria and obtained the ABPM measurement. Details of reasons for exclusion have been previously published (20). The average time from the CRIC enrollment visit to ABPM was 5.1 years. For the purposes of this manuscript, baseline was defined as the measurements and clinic visit closest to the measurement of ABPM. The ABPM monitor was placed the same day as the measurement of office BP in 75% of participants and within 2 weeks in 90% of participants. The ABPM monitor (Spacelabs 90207 or 90217) recorded BP every 30 minutes throughout the day and night; the recording was considered valid if there were at least 14 readings between 6:00 AM and midnight and at least 6 readings between midnight and 6:00 AM. Nighttime ambulatory BP was defined by the average of readings between midnight and 6:00 AM.

We further excluded 316 individuals from this analyses if they met the following criteria: mean office systolic BP <140 mm Hg and diastolic BP <90 mm Hg not taking antihypertensive medication, mean office systolic BP ≥140 mm Hg and diastolic BP ≥90 mm Hg on fewer than three medications, and mean office systolic BP <140 and <90 mm Hg and average ABPM daytime systolic BP ≥135 mm Hg or diastolic BP ≥85 mm Hg (because masked hypertension is the subject of a separate manuscript) (Supplemental Figure 1). The primary definitions and BP goals used for this analysis are on the basis of guidelines for office BP and ABPM in effect at the time when ABPM was done (between 2008 and 2012) (21). Our total analytic population included 1186 participants who met these criteria.

ABPM ATRH (ATRH by ABPM and Office BP Criteria)

ABPM ATRH is defined as mean office systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg and average ABPM daytime systolic BP ≥135 mm Hg or diastolic BP ≥85 mm Hg in patients taking three or more antihypertensive medications. ATRH on the basis of the use of more than three antihypertensive medications is mean office systolic BP <140 mm Hg and diastolic BP <90 mm Hg and average ABPM daytime systolic BP <135 mm Hg and diastolic BP <85 mm Hg in patients taking more than three antihypertensive medications.

White Coat ATRH (ATRH by Office BP but Not by ABPM Criteria)

White coat ATRH is defined as mean office systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg and average ABPM daytime systolic BP <135 mm Hg and diastolic BP <85 mm Hg in patients taking three or more antihypertensive medications.

No ATRH

No ATRH is defined as mean office systolic BP <140 mm Hg and diastolic BP <90 mm Hg and average ABPM daytime systolic BP <135 mm Hg and diastolic BP <85 mm Hg in patients taking three or fewer antihypertensive medications.

Sensitivity analyses were conducted using alternate definitions for hypertension on the basis of the 2017 American College of Cardiology (ACC)/AHA guidelines (22). Given the higher frequency of nocturnal hypertension in patients with CKD, additional sensitivity analyses were done using average 24-hour BP thresholds to define ATRH on the basis of ABPM data.

Cardiovascular events were ascertained during the course of the study by asking participants about hospitalizations during the clinic or phone visit. Hospital records were then obtained and were adjudicated using event-specific guidelines by two clinicians. Cardiovascular events evaluated during follow-up included myocardial infarction, stroke, heart failure, and peripheral arterial disease. In addition to participant report, ESKD was also ascertained through the US Renal Data System. Mortality was ascertained through report from next of kin, retrieval of death certificates or obituaries, review of hospital records, and linkage with the Social Security Mortality Master File.

Statistical Analyses

Baseline characteristics are reported as mean and SD or median and interquartile range for continuous variables and frequency and percentage for categorical variables. *P* values were calculated using ANOVA, Kruskal–Wallis rank sum test, or Pearson chi-squared test as appropriate according to ATRH group.

Logistic regression models were used to examine the cross-sectional association of clinical and demographic factors with the ATRH groups; these included age, sex, race, eGFR, 24-hour urine protein excretion, body mass index, and diabetes. Cox proportional hazard regression models were used to estimate the association between the ATRH groups and cardiovascular disease, kidney, and death outcomes.

Outcomes included the cardiovascular composite outcomes (composite of myocardial infarction, stroke, peripheral arterial disease, and heart failure), kidney outcomes (composite of ESKD or halving of eGFR), and all-cause mortality. Components of the cardiovascular outcomes and a combination of the composite cardiovascular outcomes and mortality were also evaluated. The no ATRH group served as the reference category. For each outcome, we fitted four models—the first model was unadjusted. Model A was adjusted for demographic factors (age, sex, and race/ethnicity) and clinical center. Model B was additionally adjusted for traditional cardiovascular risk factors, such as diabetes, smoking status, history of cardiovascular disease, body mass index, and hemoglobin. Model C added eGFR and 24-hour urine protein excretion. We checked the proportional hazard assumption in the Cox regression models; there are several variables, such as the center and body mass index, violating this assumption in different models. We then compared the hazard ratios (HRs) for the main exposure with and without taking into account the proportional hazards assumption violation and found similar results (data not shown). The models presented are without taking into account the proportional hazard assumption violation. All *P* values are two sided, and statistical significance is defined as $P=0.05$. All statistical analyses were conducted with SAS, version 9.4 (Cary, NC).

Results

Of the 1502 CRIC participants with available ABPM measures, 1186 participants formed the basis for the primary analyses in this paper (Supplemental Figure 1). ATRH on the basis of office BP readings was present in 475 (40%) participants. Of these participants, 8.4% had white coat ATRH, and 91.6% had ABPM ATRH (34.1% by ABPM criteria and 57.5% by use of more than three antihypertensive medications). Participants with ABPM ATRH were older; were more likely to be men, non-Hispanic black, diabetic, and obese; and were more likely to have less than high school education than participants with no ATRH (Table 1).

In cross-sectional analyses, participants who were older (adjusted odds ratio [OR], 1.14; 95% confidence interval [95% CI], 1.06 to 1.24), were men (adjusted OR, 1.75; 95% CI, 1.28 to 2.38), were non-Hispanic black (adjusted OR, 3.19; 95% CI, 2.31 to 4.40), were obese (adjusted OR, 2.04; 95% CI, 1.20 to 3.46), were diabetic (adjusted OR, 1.93; 95% CI, 1.43 to 2.61), had lower eGFR (adjusted OR, 1.07; 95% CI, 1.02 to 1.12), and had higher proteinuria (adjusted OR, 2.01; 95% CI, 1.53 to 2.63) were more likely to have ABPM ATRH (Table 2). Hispanic (adjusted OR, 5.12; 95% CI, 2.02 to 12.92) and non-Hispanic black participants (adjusted OR, 2.47; 95% CI, 1.01 to 6.03) were more likely to have white coat ATRH compared with non-Hispanic white participants.

After a mean duration of follow-up of 4.84 years, unadjusted event rates of composite cardiovascular disease outcomes and kidney outcomes were higher in participants with ABPM ATRH compared with the participants without ATRH (Table 3). In participants with ABPM ATRH, the risks of composite cardiovascular outcomes (HR, 1.48; 95% CI, 1.09 to 2.0), kidney outcomes (HR, 2.43; 95% CI, 1.81 to 3.26), and mortality (HR, 1.42; 95% CI, 1.01 to 1.99) were higher than in participants without ATRH when adjusted for clinical and demographic factors (Table 4). However, adjustment for GFR and proteinuria attenuated the risk, and the association was not statistically significant. Results were consistent for combined composite cardiovascular outcomes and mortality as well as heart failure (Supplemental Table 1).

Similar results were seen in a sensitivity analysis where ATRH was defined using average 24-hour BP thresholds to define ATRH on the basis of ABPM data (Supplemental Table 2). In another sensitivity analysis conducted using the 2017 ACC/AHA guidelines for definition of hypertension,

Table 1. Characteristics of Chronic Renal Insufficiency Cohort participants by hypertension category

Variable	Apparent Treatment-Resistant Hypertension by Office Blood Pressure Criteria, n=475			No Apparent Treatment-Resistant Hypertension by Office Blood Pressure Criteria, n=711	P Value
	White Coat Apparent Treatment-Resistant Hypertension, n=40	Ambulatory Blood Pressure Monitoring Apparent Treatment-Resistant Hypertension, n=435			
		Apparent Treatment-Resistant Hypertension by Ambulatory Blood Pressure Monitoring Criteria, n=162	Apparent Treatment-Resistant Hypertension by Use of >3 Antihypertensive Medications, n=273		
Age, yr, mean ± SD	65.8 (±7.9)	66.3 (±8.2)	64.7 (±9)	63.0 (±10.4)	<0.001
Women, *n* (%)	25 (62.5%)	68 (42.0%)	92 (33.7%)	315 (44.3%)	0.001
Race, *n* (%)					<0.001
Non-Hispanic white	10 (25%)	31 (19.1%)	113 (41.4%)	386 (54.3%)	
Non-Hispanic black	15 (37.5%)	95 (58.6%)	130 (47.6%)	222 (31.2%)	
Hispanic or other	15 (37.5%)	36 (22.2%)	30 (11.0%)	103 (14.5%)	
Education category, *n* (%)					<0.001
Less than high school	11 (27.5%)	40 (24.7%)	53 (19.4%)	86 (12.1%)	
High school graduate	9 (22.5%)	45 (27.8%)	47 (17.2%)	115 (16.2%)	
Some college	10 (25%)	42 (25.9%)	101 (37.0%)	228 (32.1%)	
College graduate or higher	10 (25%)	35 (21.6%)	72 (26.4%)	282 (39.7%)	
Household income, *n* (%)					<0.001
$20,000 or under	20 (50%)	56 (34.6%)	89 (32.6%)	147 (20.7%)	
$20,001–$50,000	12 (30%)	53 (32.7%)	72 (26.4%)	182 (25.6%)	
$50,000–$100,000	2 (5%)	14 (8.6%)	43 (15.7%)	194 (27.3%)	
>$100,000	1 (2.5%)	8 (4.9%)	31 (11.3%)	89 (12.5%)	
Do not wish to answer	5 (12.5%)	31 (19.1%)	38 (13.9%)	99 (13.9%)	
Health insurance status, *n* (%)					<0.001
None	4 (10%)	18 (11.1%)	22 (8.0%)	46 (6.5%)	
Medicaid/public aid	7 (17.5%)	28 (17.3%)	36 (13.2%)	79 (11.1%)	
Any Medicare	15 (37.5%)	68 (42.0%)	101 (37.0%)	240 (33.7%)	
VA/military/champus	0 (0%)	14 (8.6%)	29 (10.6%)	40 (5.6%)	
Private/commercial	7 (17.5%)	13 (8.0%)	28 (10.2%)	130 (18.3%)	
Unknown/incomplete information	7 (17.5%)	21 (13.0%)	57 (20.89)	176 (24.7%)	
Nephrology care, *n* (%)	31 (77.5%)	134 (82.7%)	246 (90.1%)	598 (84.1%)	0.04
MI/prior revascularization, *n* (%)	15 (37.5%)	63 (38.9%)	133 (48.7%)	156 (22.0%)	<0.001
Stroke, *n* (%)	6 (15%)	25 (15.4%)	44 (16.1%)	70 (9.8%)	0.02
Heart failure, *n* (%)	4 (10%)	22 (13.6%)	62 (22.7%)	48 (6.7%)	<0.001
Peripheral vascular disease, *n* (%)	0 (0%)	13 (8.02%)	35 (12.8%)	37 (5.2%)	<0.001
Diabetes, *n* (%)	27 (67.5%)	110 (67.9%)	184 (67.4%)	316 (44.4%)	<0.001
BMI, kg/m^2, mean ± SD	33.4 (±8.1)	33.1 (±7.0)	33.2 (±6.4)	31.2 (±6.9)	<0.001
Current smoker, *n* (%)	1 (2.5%)	17 (10.5%)	24 (±8.8%)	51 (7.2%)	0.11
eGFR, ml/min per 1.73 m^2, mean ± SD	39.8 (±17.4)	40.0 (±20.0)	38.5 (±17.1)	47.7 (±18.6)	<0.001
Urine protein-creatinine ratio[a]	0.8 (1.7)	1.4 (1.994)	0.735 (1.321)	0.406 (0.828)	<0.001
Office systolic BP, mm Hg, mean ± SD	149.0 (±13.5)	155.0 (±20.0)	120.0 (±13.5)	117.9 (±11.9)	<0.001
Office diastolic BP, mm Hg, mean ± SD	75.45 (±12.5)	75.0 (±15.1)	64.0 (±10.7)	67.0 (±10.3)	<0.001
24-h mean systolic BP, mm Hg, mean ± SD	124.1 (±8.1)	148.5 (±13.5)	127.3 (±13.2)	122.3 (±12.0)	<0.001
24-h mean diastolic BP, mm Hg, mean ± SD	68.8 (±8.4)	77.4 (±10.8)	69.3 (±8.1)	70.2 (±7.9)	<0.001
Daytime mean systolic BP, mm Hg, mean ± SD	126.3 (±7.4)	150.6 (±12.7)	128.9 (±12.7)	124.8 (±11.8)	<0.001
Daytime mean diastolic BP, mm Hg, mean ± SD	70.7 (±8.5)	79.0 (±10.8)	70.7 (±8.1)	72.2 (±8.2)	<0.001
Nighttime mean systolic BP, mm Hg, mean ± SD	117.8 (±13.4)	142.4 (±18.9)	122.4 (±16.9)	114.5 (±14.8)	<0.001
Nighttime mean diastolic BP, mm Hg, mean ± SD	63.2 (±10.2)	72.6 (±12.56)	64.9 (±10.0)	64.1 (±8.7)	<0.001
Mean no. of antihypertensive medications, mean ± SD	3.5(±0.6)	3.8(±0.9)	4.5(±0.7)	2.1(±0.8)	<0.001
β-Blockers, *n* (%)	30 (75%)	122 (75.3%)	257 (94.1%)	295 (41.5%)	<0.001
Calcium channel blockers, *n* (%)	29 (72.5%)	106 (65.4%)	194 (71.1%)	247 (34.7%)	<0.001
ACE inhibitors, *n* (%)	17 (42.5%)	68 (42.0%)	146 (53.5%)	341 (48.0%)	0.10
Angiotensin receptor blockers, *n* (%)	13 (32.5%)	61 (37.6%)	111 (40.7%)	186 (26.2%)	<0.001

Table 1. (Continued)

Variable	Apparent Treatment-Resistant Hypertension by Office Blood Pressure Criteria, n=475			No Apparent Treatment-Resistant Hypertension by Office Blood Pressure Criteria, n=711	P Value
	White Coat Apparent Treatment-Resistant Hypertension, n=40	Ambulatory Blood Pressure Monitoring Apparent Treatment-Resistant Hypertension, n=435			
		Apparent Treatment-Resistant Hypertension by Ambulatory Blood Pressure Monitoring Criteria, n=162	Apparent Treatment-Resistant Hypertension by Use of >3 Antihypertensive Medications, n=273		
Vasodilators, n (%)	8 (20%)	60 (37.0%)	92 (33.7%)	30 (4.2%)	<0.001
α-Blockers, n (%)	9 (22.5%)	61 (37.7%)	134 (49.1%)	69 (9.7%)	<0.001
α2-Agonists, n (%)	2 (5%)	16 (9.9%)	40 (14.6%)	11 (1.5%)	<0.001
Diuretics (any), n (%)	33 (82.5%)	127 (78.4%)	244 (89.3%)	315 (44.3%)	<0.001

VA, Veterans Affairs; champus, Civilian Health and Medical Program of the Uniformed Services; MI, myocardial infarction; BMI, body mass index; ACE, angiotensin converting enzyme.
[a]ABPM-ATRH, apparent treatment resistant hypertension by ABPM criteria or use of more than 3 antihypertensive medications; white coat-ATRH, apparent treatment resistant hypertension by office BP but not by ABPM criteria.

of study participants who had ATRH by office BP, 86.5% had ABPM ATRH. Participants with ATRH using this definition were at higher risk of mortality (HR, 1.93; 95% CI, 1.12 to 3.35) but not the composite cardiovascular outcomes and kidney outcomes compared with participants with no ATRH in a fully adjusted model (Supplemental Table 3). Analysis limited to participants with ATRH on the basis of the use of more than three antihypertensive medications showed similar results (data not shown).

In participants with white coat ATRH, the risk of composite cardiovascular outcomes and mortality was not significantly different compared with in participants with no ATRH. The risk of kidney outcomes was higher in participants with white coat ATRH compared with participants with no ATRH when adjusted for clinical and demographic factors; however, the risk was attenuated and not statistically significant when adjusted for GFR and proteinuria (Table 4). Similar results were seen in sensitivity analyses on the basis of hypertension defined by the 2017 ACC/AHA guidelines (Supplemental Table 3). Participants with white coat ATRH (when defined using average 24-hour BP thresholds on the basis of ABPM data) were at higher risk for kidney outcomes (HR, 3.30; 95% CI, 1.58 to 6.86) compared with participants with no ATRH.

Discussion

In this cohort of participants with CKD, most patients with ATRH on the basis of office measurement also had ATRH when defined by ABPM or the number of antihypertensive medications. A small proportion (<10%) of patients with ATRH defined by office readings had normal readings on ABPM, suggesting a white coat effect. Older age, men, black race, lower GFR, higher proteinuria, obesity, and diabetes were independently associated with ATRH. Although the presence of ATRH was not an independent risk factor for adverse outcomes when adjusted for other risk factors, specifically GFR and proteinuria, the high event rates experienced by these participants suggest that it is a marker of high risk.

Population-based studies show high rates of hypertension in patients with CKD (23). Resistant hypertension is also common in these patients; these estimates are derived on the basis of BP measured in the office (5). Our prior analysis of the CRIC cohort using office BP measurement alone noted that 40% of study participants had ATRH (7). By applying ABPM criteria to further stratify participants who are resistant to treatment on the basis of office BP, our analysis confirms that most patients have ATRH, and a very small proportion had white coat effect underlying the diagnosis of ATRH. The high prevalence of ATRH in the CRIC cohort is likely due to the presence of CKD as well as the inclusion of a larger proportion of blacks, both of which are associated with resistant hypertension (1). We demonstrate that event rates of important clinical outcomes are higher in participants with ATRH when defined by ABPM or the number of antihypertensive medications. The presence of ATRH was associated with higher risk of adverse composite cardiovascular (48% increase in risk) and kidney outcomes (more than twofold risk) when adjusted for clinical and demographic characteristics; the association was, however, statistically nonsignificant when additionally adjusted for GFR and proteinuria. This suggests that low GFR and proteinuria, at least in part, explain the high risk of clinical outcomes seen with ATRH. Our results are qualitatively similar to other studies in the general population and patients with CKD that show that resistant hypertension identified by ABPM is associated with high risk of cardiovascular and renal disease outcomes (14,16). Although the study by De Nicola *et al.* (16) in Italy showed similar findings, our study expands the

Table 2. Factors associated with ambulatory blood pressure monitoring apparent treatment-resistant hypertension and white coat apparent treatment-resistant hypertension

Variable	Adjusted Odds Ratio (95% Confidence Interval)	
	White Coat Apparent Treatment-Resistant Hypertension Compared with No Apparent Treatment-Resistant Hypertension	Ambulatory Blood Pressure Monitoring Apparent Treatment-Resistant Hypertension Compared with No Apparent Treatment-Resistant Hypertension
Age, per 5-yr increase	1.15 (0.95 to 1.41)	1.14 (1.06 to 1.24)
Sex, men versus women	0.58 (0.28 to 1.21)	1.75 (1.28 to 2.38)
Race: Hispanic or other versus non-Hispanic white	5.12 (2.02 to 12.92)	1.41 (0.91 to 2.18)
Race: non-Hispanic black versus non-Hispanic white	2.47 (1.01 to 6.03)	3.19 (2.31 to 4.40)
eGFR per SD	1.05 (0.94 to 1.18)	1.07 (1.02 to 1.12)
Urine protein-creatinine ratio (log) per SD	1.28 (0.70 to 2.34)	2.01 (1.53 to 2.63)
BMI: 25 to <30 (overweight) versus <25 (normal)	0.87 (0.29 to 2.62)	1.56 (0.90 to 2.71)
BMI: 30 to <40 (obese) versus <25 (normal)	0.65 (0.22 to 1.90)	2.04 (1.20 to 3.46)
BMI: >40 (morbidly obese) versus <25 (normal)	1.37 (0.40 to 4.74)	2.62 (1.39 to 4.96)
Diabetes mellitus (yes versus no)	2.09 (0.96 to 4.57)	1.93 (1.43 to 2.61)

Ambulatory BP monitoring apparent treatment-resistant hypertension indicates apparent treatment-resistant hypertension by ambulatory BP monitoring criteria or use of more than three antihypertensive medications; white coat apparent treatment-resistant hypertension indicates apparent treatment-resistant hypertension by office BP but not by ambulatory BP monitoring criteria. BMI, body mass index.

findings in a larger cohort including a significant proportion of black patients in whom resistant hypertension is more common than in other racial ethnic groups. A recent study in patients with diabetes showed that ABPM ATRH was associated with twofold increased risk of cardiovascular mortality and 38% higher risk of adverse renal outcomes (15).

ATRH using alternate definitions of hypertension on the basis of the 2017 ACC/AHA guidelines was associated with an almost twofold higher risk of mortality in a fully adjusted model, reinforcing the prognostic significance of ATRH. Studies in the resistant hypertension literature have used different criteria to define BP phenotypes using ABPM—some studies have used average daytime BP thresholds, and others have used average 24-hour BP thresholds (13−16). Because nighttime BP is often elevated in patients with CKD, we conducted a sensitivity analysis using the average 24-hour BP threshold to include nighttime BP, which showed similar results.

We demonstrate that a small proportion (<10%) of patients with office-based ATRH had a white coat effect. This is in contrast to an Argentinian study of diabetic patients without CKD where 41% of those initially classified

Table 3. Number of events and unadjusted event rates (per 100 patient years) by hypertension category

Outcome	No. of Events (Event Rate per 100 patient-years)			
	White Coat Apparent Treatment-Resistant Hypertension	Ambulatory Blood Pressure Monitoring Apparent Treatment-Resistant Hypertension		No Apparent Treatment-Resistant Hypertension
		By Ambulatory Blood Pressure Monitoring Criteria	By Use of >3 Antihypertensive Medications	
Composite cardiovascular outcomes	8 (4.68)	52 (8.19)	68 (6.43)	90 (2.77)
Kidney outcomes	13 (8.74)	67 (12.75)	65 (6.81)	88 (2.97)
Mortality	2 (1.04)	38 (4.93)	54 (4.32)	76 (2.18)

Ambulatory BP monitoring apparent treatment-resistant hypertension indicates apparent treatment-resistant hypertension by ambulatory BP monitoring criteria or use of more than three antihypertensive medications; white coat apparent treatment-resistant hypertension indicates apparent treatment-resistant hypertension by office BP but not by ambulatory BP monitoring criteria. Composite cardiovascular outcomes are myocardial infarction, stroke, peripheral arterial disease, and heart failure. Kidney outcomes are 50% decrease in eGFR or ESKD defined as renal transplantation or start of long-term renal dialysis.

Table 4. Hazard ratios for clinical outcomes in participants with ambulatory blood pressure monitoring-apparent treatment resistant hypertension and white coat-apparent treatment resistant hypertension compared to no apparent treatment resistant hypertension

Outcome	Hazard Ratio (95% Confidence Interval)			
	Unadjusted	Model A	Model B	Model C
Composite of myocardial infarction, stroke, peripheral arterial disease, and heart failure				
Ambulatory BP monitoring apparent treatment-resistant hypertension	2.55 (1.94 to 3.35)	2.22 (1.67 to 2.96)	1.48 (1.09 to 2.0)	1.11 (0.8 to 1.55)
White coat apparent treatment-resistant hypertension	1.68 (0.82 to 3.47)	1.38 (0.66 to 2.87)	0.94 (0.44 to 1.99)	0.82 (0.37 to 1.84)
Kidney outcomes				
Ambulatory BP monitoring apparent treatment-resistant hypertension	3.04 (2.32 to 3.98)	2.94 (2.22 to 3.9)	2.43 (1.81 to 3.26)	1.35 (0.96 to 1.9)
White coat apparent treatment-resistant hypertension	2.97 (1.66 to 5.32)	2.59 (1.43 to 4.72)	2.01 (1.1 to 3.67)	1.37 (0.68 to 2.76)
All-cause mortality				
Ambulatory BP monitoring apparent treatment-resistant hypertension	2.1 (1.55 to 2.84)	1.8 (1.31 to 2.48)	1.42 (1.01 to 1.99)	1.16 (0.78 to 1.71)
White coat apparent treatment-resistant hypertension	0.48 (0.12 to 1.97)	0.43 (0.1 to 1.76)	0.34 (0.08 to 1.4)	0.43 (0.1 to 1.77)

Model A: adjusted for age, sex, race, and clinical center. Model B: adjusted for model A plus diabetes, smoking status, history of cardiovascular disease, body mass index (BMI), and hemoglobin. Model C: adjusted for model B plus eGFR and urine protein-creatinine ratio, 24-hour and spot measures combined adding spline terms of log urine protein-creatinine ratio. Kidney outcomes: 50% decrease in eGFR or ESKD defined as renal transplantation or start of long-term renal dialysis. Ambulatory BP monitoring apparent treatment-resistant hypertension indicates apparent treatment-resistant hypertension by ambulatory BP monitoring criteria or use of more than three antihypertensive medications; white coat apparent treatment-resistant hypertension indicates apparent treatment-resistant hypertension by office BP but not by ambulatory BP monitoring criteria.

as having ATRH by office BP levels had white coat hypertension (15). Similarly, the prevalence of white coat hypertension contributing to ATRH was 39% in a Spanish study (24). This is consistent with previously reported differences in white coat hypertension across different countries and racial-ethnic groups in patients with CKD (25). The reasons underlying these differences remain unclear and require further study. In our study, participants have been followed for several years, and are familiar with study staff and visit procedures; this may contribute to the lower rates of white coat hypertension seen. Although there was no association between the presence of white coat ATRH and cardiovascular outcomes, the risk of adverse renal outcomes was high in some analyses. However, given the small number of patients and events along with wide confidence intervals in those with white coat ATRH, these findings have to be interpreted with caution. On the basis of these findings, it would seem reasonable that ABPM is not essential in the risk assessment of most patients with CKD and ATRH. This may be especially appropriate in resource-limited settings where ABPM is unavailable. However, in selected patients without clinical risk factors for ABPM-confirmed ATRH, ABPM may be considered.

Our study has a number of strengths; these include the large sample size, long duration of follow-up, and careful ascertainment and adjudication of clinical outcomes. However, important limitations of this study need to be considered. This is an observational study, and the reported associations do not imply causation. Additionally, assessment of office BP and ABPM at a single time does not take into account possible changes in BP during follow-up. ABPM was conducted only during the second phase of the CRIC; therefore, events prior to this may have been missed. Although the BP measurement technique (average of three seated measurements) used in the CRIC study is recommended, it may not be followed in the real-world setting. Thus, the rate of white coat ATRH may be higher in the community setting than noted in the research setting. A comprehensive evaluation of resistant hypertension was not done in the CRIC study; therefore, although the white coat component has been addressed in our study, pseudoresistance due to nonadherence to medications and other reasons cannot be not excluded (26).

In summary, resistant hypertension is a common and important condition in patients with CKD. ABPM confirms the diagnosis of resistant hypertension in most patients and therefore, may not be needed for routine evaluation of patients with CKD and resistant hypertension if BP in the office is taken according to recommended guidelines. Given the high risk of cardiovascular and kidney disease in patients with CKD and resistant hypertension, future research should target novel and innovative techniques to improve resistant hypertension in this population.

Disclosures

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Author Contributions

M. Rahman and G. Thomas conceptualized the study; C.S. Brecklin, J. Chen, P.E. Drawz, E. Lustigova, R. Mehta, E.R. Miller, M. Rahman, S.M. Sozio, G. Thomas, and M.R. Weir were responsible for investigation; J. Chen, J. Felts, M. Rahman, and G. Thomas were responsible for methodology; P.E. Drawz, M. Rahman, X. Wang, and D. Xie were responsible for data curation; X. Wang and D. Xie were responsible for formal analysis; M. Rahman was responsible for project administration; M. Rahman provided supervision; J. Felts, M. Rahman, G. Thomas, X. Wang, and D. Xie wrote the original draft; and C.S. Brecklin, J. Chen, P.E. Drawz, J. Felts, E. Lustigova, R. Mehta, E.R. Miller, M. Rahman, S.M. Sozio, G. Thomas, X. Wang, M.R. Weir, and D. Xie reviewed and edited the manuscript.

Supplemental Material

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Supplemental Figure 1. Flow diagram of exclusion criteria.

Supplemental Table 1. Hazard ratios for clinical outcomes in participants with ABPM-ATRH and White coat-ATRH compared to No ATRH.

Supplemental Table 2. Sensitivity analysis-ATRH definition based on average 24 hour blood pressure thresholds by ABPM: Hazard ratios for clinical outcomes in participants with ABPM-ATRH and White coat-ATRH compared to No ATRH.

Supplemental Table 3. Sensitivity analysis-hypertension defined by the 2017 ACC/AHA guidelines: Hazard ratios for clinical outcomes in participants with ABPM-ATRH and white coat-ATRH compared to participants with no ATRH.

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*The CRIC Study Investigators include Lawrence J. Appel, Harold I. Feldman, Alan S. Go, Jiang He, James P. Lash, Robert G. Nelson, Vallabh O. Shah, Raymond R. Townsend, and Mark L. Unruh.