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.

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).
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 m² 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 (Space-labs 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.

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                                      | White Coat Apparent Treatment-Resistant Hypertension, n=40 | Ambulatory Blood Pressure Monitoring Apparent Treatment-Resistant Hypertension, n=162 | No Apparent Treatment-Resistant Hypertension by Office Blood Pressure Criteria, n=711 | P Value |
|-----------------------------------------------|-----------------------------------------------------------|------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|---------|
| Age, yr, mean ± SD                           | 65.8 (±7.9)                                               | 66.3 (±8.2)                                                                         | 64.7 (±9)                                                                            | <0.001 |
| Women, n (%)                                  | 25 (62.5%)                                                | 68 (42.0%)                                                                          | 92 (33.7%)                                                                          | <0.001 |
| Race, n (%)                                   |                                                          |                                                                                     |                                                                                     |         |
| Non-Hispanic white                            | 10 (25%)                                                  | 31 (19.1%)                                                                          | 113 (41.4%)                                                                         | <0.001 |
| Non-Hispanic black                            | 15 (37.5%)                                                | 95 (58.6%)                                                                          | 130 (47.6%)                                                                         |         |
| Hispanic or other                             | 15 (37.5%)                                                | 36 (22.2%)                                                                          | 30 (11.0%)                                                                          |         |
| Education category, n (%)                    |                                                          |                                                                                     |                                                                                     |         |
| Less than high school                         | 11 (27.5%)                                                | 40 (24.7%)                                                                          | 53 (19.4%)                                                                          | <0.001 |
| High school graduate                          | 9 (22.5%)                                                 | 45 (27.8%)                                                                          | 47 (17.2%)                                                                          |         |
| Some college                                  | 10 (25%)                                                  | 42 (25.9%)                                                                          | 101 (37.0%)                                                                         |         |
| College graduate or higher                    | 10 (25%)                                                  | 35 (21.6%)                                                                          | 72 (26.4%)                                                                          |         |
| Household income, n (%)                       |                                                          |                                                                                     |                                                                                     | <0.001 |
| <$20,000 or under                             | 7 (17.5%)                                                 | 13 (8.0%)                                                                           | 21 (13.0%)                                                                          |         |
| <$20,001–$50,000                              | 15 (37.5%)                                                | 63 (38.9%)                                                                          | 133 (48.7%)                                                                         | <0.001 |
| <$50,000–$100,000                             | 15 (37.5%)                                                | 68 (42.0%)                                                                          | 101 (37.0%)                                                                         |         |
| >$100,000                                     | 2 (5%)                                                    | 14 (8.6%)                                                                           | 43 (15.7%)                                                                          | <0.001 |
| Do not wish to answer                         | 5 (12.5%)                                                 | 21 (13.0%)                                                                          | 38 (13.9%)                                                                          |         |
| Health insurance status, n (%)                |                                                          |                                                                                     |                                                                                     | <0.001 |
| None                                          | 4 (10%)                                                   | 18 (11.1%)                                                                          | 22 (8.0%)                                                                           |         |
| Medicaid/public aid                           | 7 (17.5%)                                                 | 28 (17.3%)                                                                          | 36 (13.2%)                                                                          |         |
| Any Medicare                                  | 15 (37.5%)                                                | 68 (42.0%)                                                                          | 101 (37.0%)                                                                         | <0.001 |
| VA/military/champus                           | 0 (0%)                                                    | 14 (8.6%)                                                                           | 29 (10.6%)                                                                          |         |
| Private/commercial                             | 7 (17.5%)                                                 | 13 (8.0%)                                                                           | 28 (10.2%)                                                                          |         |
| Unknown/incomplete information                 | 7 (17.5%)                                                 | 21 (13.0%)                                                                          | 57 (20.8%)                                                                          |         |
| Nephropathy, n (%)                             | 31 (77.5%)                                                | 134 (82.7%)                                                                         | 246 (90.1%)                                                                         |         |
| MI prior revascularization, n (%)             | 15 (37.5%)                                                | 63 (38.9%)                                                                          | 133 (48.7%)                                                                         | <0.001 |
| Stroke, n (%)                                 | 6 (15%)                                                   | 25 (15.4%)                                                                          | 44 (16.1%)                                                                          | 0.02    |
| Heart failure, n (%)                           | 4 (10%)                                                   | 22 (13.6%)                                                                          | 62 (22.7%)                                                                          | <0.001 |
| Peripheral vascular disease, n (%)            | 0 (0%)                                                    | 13 (8.0%)                                                                           | 35 (12.8%)                                                                          | <0.001 |
| Diabetes, n (%)                               | 27 (67.5%)                                                | 110 (67.9%)                                                                         | 184 (67.4%)                                                                         | <0.001 |
| BMI, kg/m², mean ± SD                         | 33.4 ± 8.1                                                | 33.1 ± 7.0                                                                           | 33.2 ± 6.4                                                                          | <0.001 |
| Current smoker, n (%)                          | 1 (2.5%)                                                  | 17 (10.5%)                                                                          | 24 (8.8%)                                                                           | 0.11    |
| eGFR, ml/min per 1.73 m², mean ± SD           | 39.8 ± 17.4                                               | 40.0 ± 20.0                                                                          | 38.5 ± 17.1                                                                         | <0.001 |
| Urine protein-creatinine ratio#               | 0.8 (1.7)                                                 | 1.4 (1.994)                                                                          | 0.735 (1.321)                                                                       | <0.001 |
| Office systolic BP, mm Hg, mean ± SD          | 149.0 ± 13.5                                              | 155.0 ± 20.0                                                                         | 120.0 ± 13.5                                                                        | <0.001 |
| Office diastolic BP, mm Hg, mean ± SD         | 75.45 ± 12.5                                              | 75.0 ± 15.1                                                                          | 64.0 ± 10.7                                                                         | <0.001 |
| 24-h mean systolic BP, mm Hg, mean ± SD       | 124.1 ± 8.1                                               | 148.5 ± 13.5                                                                         | 127.3 ± 13.2                                                                        | <0.001 |
| 24-h mean diastolic BP, mm Hg, mean ± SD      | 68.8 ± 8.4                                                | 77.4 ± 10.8                                                                          | 69.3 ± 8.1                                                                          | <0.001 |
| Daytime mean systolic BP, mm Hg, mean ± SD    | 126.3 ± 7.4                                               | 150.6 ± 12.7                                                                         | 128.9 ± 12.7                                                                        | <0.001 |
| Nighttime mean systolic BP, mm Hg, mean ± SD  | 70.7 ± 5.8                                                | 79.0 ± 10.8                                                                          | 70.7 ± 8.1                                                                          | <0.001 |
| Nighttime mean diastolic BP, mm Hg, mean ± SD | 117.8 ± 13.4                                              | 142.4 ± 18.9                                                                         | 122.4 ± 16.9                                                                        | <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%)                                                                         | <0.001 |
| Calcium channel blockers, n (%)               | 29 (72.5%)                                                | 106 (65.4%)                                                                          | 194 (71.1%)                                                                         | <0.001 |
| ACE inhibitors, n (%)                          | 17 (42.5%)                                                | 68 (42.0%)                                                                          | 146 (53.5%)                                                                         | 0.10    |
| Angiotensin receptor blockers, n (%)           | 13 (32.5%)                                                | 61 (37.6%)                                                                          | 111 (40.7%)                                                                         | <0.001 |
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 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...
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 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)** | **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.

| 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)** | **Ambulatory Blood Pressure Monitoring Apparent Treatment-Resistant Hypertension** | **By Ambulatory Blood Pressure Monitoring Criteria** | **By Use of >3 Antihypertensive Medications** | **No Apparent Treatment-Resistant Hypertension** |
| 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.
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
M.R. Weir reports acting as a scientific advisor to AstraZeneca, Boehringer-Ingelheim, Boston Scientific, Janssen, Otsuka, Relypsa, and Vifor. All remaining authors have nothing to disclose.

Funding
Funding for the CRIC Study was obtained under a cooperative agreement from Health and Human Services, National Institutes of Health (NIH), National Institute of Diabetes and Digestive and Kidney Diseases grants U01DK060990, U01DK060984, U01DK061022, U01DK060994, and U01DK061029.
U01DK061021, U01DK061028, U01DK060980, U01DK060963, U01DK060902, and U24DK060990. In addition, this work was supported in part by Perelman School of Medicine, University of Pennsylvania Clinical and Translational Science Award NIH/National Center for Advancing Translational Sciences UL1TR000003; Johns Hopkins University grant UL1 TR-000424; University of Maryland grant GCRC M01 RR-16500; Clinical and Translational Science Collaborative of Cleveland grant UL1TR000439 from the National Center for Advancing Translational Sciences component of the NIH and NIH roadmap for Medical Research; Michigan Institute for Clinical and Health Research grant UL1TR000433; Center for Clinical and Translational Science, University of Illinois at Chicago grant UL1RR029879; Tulane Center of Biomedical Research Excellence for Clinical and Translational Research in Cardiometabolic Diseases grant P20 GM109036; Kaiser Permanente NIH/National Center for Research Resources grant UCSF-CTSI U11 RR-24131; Department of Internal Medicine, University of New Mexico School of Medicine Albuquerque grant NM R01DK191999; the Leonard C. Rosenberg Foundation; and the HHS, NIH, National Center for Advancing Translational Sciences.

Acknowledgments

Dr. Rupal Mehta reports other from Abbott Laboratories, other from AbbVie Inc., other from Teva Pharmaceuticals, and personal fees from Akebia/Oksuba, outside the submitted work. Dr. Mahboob Rahman reports grants from Bayer, grants from Duke Clinical Research Institute, personal fees from Reata, and personal fees from Relypsa, outside the submitted work.

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

This article contains supplemental material online at http://kidyney360.asnjournals.org/lookup/suppl/doi:10.34067/KID.0002072020/-/DCSupplemental.

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.

References

1. Carey RM, Calhoun DA, Bakris GL, Brook RD, Daugherty SL, Dennison-Himmelfarb CR, Egan BM, Flack JM, Gridding SS, Judd E, Lackland DT, Laifer CL, Newton-Cheh C, Smith SM, Taler SJ, Textor SC, Turan TN, White WB; American Heart Association Professional/Public Education and Publications Committee of the Council on Hypertension; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; Council on Genomic and Precision Medicine; Council on Peripheral Vascular Disease; Council on Quality of Care and Outcomes Research; and Stroke Council: Resistant hypertension: Detection, evaluation, and management: A scientific statement from the American Heart Association. Hypertension 72: e53–e90, 2018

2. Daugherty SL, Powers JD, Magid DJ, Tavel HM, Masoudi FA, Margolis KL, O’Connor PJ, Selhy JV, Ho PM: Incidence and prognosis of resistant hypertension in hypertensive patients. Circulation 125: 1635–1642, 2012

3. Muntner P, Davis BR, Cushman WC, Bangalore S, Calhoun DA, Pressel SL, Black HR, Kostis JB, Probstfield JF, Whelton PK, Rahman M; ALLHAT Collaborative Research Group: Treatment-resistant hypertension and the incidence of cardiovascular disease and end-stage renal disease: Results from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). Hypertension 64: 1012–1021, 2014

4. Bangalore S, Fayyad R, Laskey R, Demico PA, Deedwania P, Kostis JB, Messerli FH; Treating to New Targets Steering Committee and Investigators: Prevalence, predictors, and outcomes in treatment-resistant hypertension in patients with coronary disease. Am J Med 127: 71–81.e1, 2014

5. Tanner RA, Calhoun DA, Bell EK, Bowling CB, Gutierrez OM, Irvin MR, Lackland DT, Oparil S, Warnock D, Muntner P: Prevalence of apparent treatment-resistant hypertension among individuals with CKD. Clin J Am Soc Nephrol 8: 1583–1590, 2013

6. de Beus E, Bots ML, van Zuielen AD, Wetzels JF, Blankstijn PJ; MASTERPLAN Study Group: Prevalence of apparent therapy-resistant hypertension and its effect on outcome in patients with chronic kidney disease. Hypertension 66: 998–1005, 2015

7. Thomas G, Xie D, Chen HY, Anderson AH, Appel LJ, Bodana S, Brecklin CS, Drawz P, Flack JM, Miller ER 3rd, Steigerwald SP, Townsend RR, Weir MR, Wright JT Jr, Rahman M; CRIC Study Investigators: Prevalence and prognostic significance of apparent treatment resistant hypertension in chronic kidney disease: Report from the chronic renal insufficiency cohort study. Hypertension 67: 387–396, 2016

8. Howard VJ, Tanner RM, Anderson A, Irvin MR, Calhoun DA, Lackland DT, Oparil S, Muntner P: Apparent treatment-resistant hypertension among individuals with history of stroke or transient ischemic attack. Am J Med 128: 505–512.e1, 2015

9. Tanaka S, Ninomiya T, Hiyamuta H, Taniguchi M, Tsuchiya H, Masunari K, Ooboshi H, Nakano T, Tsuyura K, Kitazono T: Apparent treatment-resistant hypertension and cardiovascular risk in hemodialysis patients: Ten-year outcomes of the Q-cohort study. Sci Rep 9: 10439, 2019

10. de la Sierra A, Segura J, Banegas JR, Gorostidi M, de la Cruz JJ, Armario P, Oliveras A, Ruijloop LM: Clinical features of 8295 patients with resistant hypertension classified on the basis of ambulatory blood pressure monitoring. Hypertension 57: 898–902, 2011

11. Gabbari FB, Rahman M, Hu B, Appel LJ, Charleston J, Contreras G, Faulkner ML, Hiremath L, Jamerson KA, Lea JP, Lipkowitz MS, Pogue VA, Rostand SG, Smogorzewski MJ, Wright JT, Greene T, Gassman J, Wang X, Phillips RA; African American Study of Kidney Disease and Hypertension (AASK) Study Group: Relationship between ambulatory BP and clinical outcomes in patients with hypertensive CKD. Clin J Am Soc Nephrol 7: 1770–1776, 2012

12. Judd E, Calhoun DA: Apparent and true resistant hypertension: Definition, prevalence and outcomes. J Hum Hypertens 28: 463–468, 2014

13. Salles GF, Cardoso CR, Muxfeldt ES: Prognostic influence of office and ambulatory blood pressures in resistant hypertension. Arch Intern Med 168: 2340–2346, 2008

14. Pierdomenico SD, Lapenna D, Bucci A, Di Tommaso R, Di Mascio R, Manente BM, Caldarella MP, Neri M, Ciccurello F, Mezzetti A: Cardiovascular outcome in treated hypertensive
patients with responder, masked, false resistant, and true resistant hypertension. *Am J Hypertens* 18: 1422–1428, 2005

15. Cardoso CRL, Leite NC, Bacan G, Ataíde DS, Gorgonio LKC, Salles GF: Prognostic importance of resistant hypertension in patients with type 2 diabetes: The Rio de Janeiro type 2 diabetes cohort study. *Diabetes Care* 43: 219–227, 2020

16. De Nicola L, Gabbai FB, Agarwal R, Chiiodoni P, Borrelli S, Bellizzi V, Nappi F, Conte G, Minutolo R: Prevalence and prognostic role of resistant hypertension in chronic kidney disease patients. *J Am Coll Cardiol* 61: 2461–2467, 2013

17. Feldman HI, Appel LJ, Chertow GM, Cifelli D, Cizman B, Daugirdas J, Fink JC, Franklin-Becker ED, Go AS, Hamm LL, He J, Hostetter T, Hsu CY, Jamerson K, Joffe M, Kusek JW, Landis JR, Lash JP, Miller ER, Mohler ER 3rd, Munter P, Ojo AO, Rahman M, Townsend RR, Wright JT; Chronic Renal Insufficiency Cohort (CRIC) Study Investigators: The chronic renal insufficiency cohort (CRIC) study: Design and methods. *J Am Soc Nephrol* 14[Suppl 2]: S148–S153, 2003

18. Lash JP, Go AS, Appel LJ, He J, Ojo A, Rahman M, Townsend RR, Xie D, Cifelli D, Cohan J, Fink JC, Fischer MJ, Gadebekcu E, Hamm LL, Kusek JW, Landis JR, Narva A, Robinson N, Teal V, Feldman HI; Chronic Renal Insufficiency Cohort (CRIC) Study Group: Chronic Renal Insufficiency Cohort (CRIC) study: Baseline characteristics and associations with kidney function. *Clin J Am Soc Nephrol* 4: 1302–1311, 2009

19. Anderson AH, Yang W, Hsu CY, Joffe MM, Leonard MB, Xie D, Chen J, Greene T, Jaar BG, Kao P, Kusek JW, Landis JR, Lash JP, Townsend RR, Weir MR, Feldman HI; CRIC Study Investigators: Estimating GFR among participants in the Chronic Renal Insufficiency Cohort (CRIC) study. *Am J Kidney Dis* 60: 250–261, 2012

20. Drawz PE, Alper AB, Anderson AH, Brecklin CS, Charleston J, Chen J, Dee R, Fischer MJ, He J, Hsu CY, Huan Y, Keane MG, Kusek JW, Makos GK, Miller ER 3rd, Solman EZ, Steigerwalt SP, Taliercio J, Townsend RR, Weir MR, Wright JT Jr., Xie D, Rahman M; Chronic Renal Insufficiency Cohort Study Investigators: Masked hypertension and elevated nighttime blood pressure in CKD: Prevalence and association with target organ damage. *Clin J Am Soc Nephrol* 11: 642–652, 2016

21. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr., Jones DW, Materson BJ, Oparil S, Wright JT Jr., Roccella EJ; Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. National Heart, Lung, and Blood Institute; National High Blood Pressure Education Program Coordinating Committee: Seventh report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. *Hypertension* 42: 1206–1252, 2003

22. Whelton PK, Carey RM, Aronow WS, Casey DE Jr., Collins KJ, Dennison Himmelfarb C, DePalma SM, Gidding S, Jamerson KA, Jones DW, MacLaughlin EF, Munter P, Oviabgele B, Smith SC Jr., Spencer CC, Stafford RS, Talor SJ, Thomas RJ, Williams KA Sr., Williamson JD, Wright JT Jr.; 2017 ACC/AHA/ABC/ACPW/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: A report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines [published correction appears in *Hypertension* 71: e136–e139, 2018]. *Hypertension* 71: e13–e115, 2018

23. Peralta CA, Hicks LS, Chertow GM, Ayanian JZ, Vittinghoff E, Lin F, Shlipak MG: Control of hypertension in adults with chronic kidney disease in the United States. *Hypertension* 45: 1119–1124, 2005

24. Poveda García MI, Del Pino Y Pino MD, Alarcón Rodríguez R, Rodelo-Haad C, Parrón Carreño T: The value of ABPM and subclinical target organ damage parameters in diagnosis of resistant hypertension. *Nefrología* 39: 67–72, 2019

25. Drawz PE, Brown R, De Nicola L, Fuji N, Gabbai FB, Gassman J, He J, Imuno S, Lash J, Minutolo R, Phillips RA, Rudser K, Ruilope L, Steigerwalt S, Townsend RR, Xie D, Rahman M; CRIC Study Investigators: Variations in 24-hour BP profiles in cohorts of patients with kidney disease around the world: The I-DARE study. *Clin J Am Soc Nephrol* 13: 1348–1357, 2018

26. Hamdilouche I, Gosse P, Cremer A, Lorthioir A, Delsart P, Courand PY, Denolle T, Halimi JM, Girerd X, Ormezzano O, Rossignol P, Pereira H, Azizi M; DENERHTN Investigators: Clinic versus ambulatory blood pressure in resistant hypertension: Impact of antihypertensive medication nonadherence: A post hoc analysis the DENERHTN study. *Hypertension* 74: 1096–1103, 2019

Received: April 14, 2020 Accepted: June 24, 2020

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