ASSOCIATION OF BLOOD PRESSURE PHENOTYPES WITH KIDNEY DISEASE

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EPIDEMIOLOGY

ABSTRACT

Kidney disease is common, with recent estimates indicating a prevalence of 13% among US adults. Furthermore, the vast majority of individuals with kidney disease have hypertension. Apparent treatment-resistant hypertension (aTRH), 24-hour blood pressure (BP) variability, and inter-arm differences (IADs) in BP have been identified as risk factors for cardiovascular disease, and there is increasing evidence that these phenotypes provide prognostic information above and beyond mean clinic BP. However, these phenotypes have not been extensively studied among individuals with kidney disease. The goal of this dissertation was to determine the association of kidney disease with BP phenotypes in the context of three studies, namely, the REasons for Geographic And Racial Differences in Stroke (REGARDS) study, the Jackson Heart Study, and the Hypertension Genetic Epidemiology Network (HyperGEN) study. We observed a high prevalence of aTRH in the REGARDS study and demonstrated that lower estimated glomerular filtration rate (eGFR), higher albumin-to-creatinine ratio (ACR), and lower eGFR and higher ACR considered jointly were associated with higher prevalence ratios for aTRH. Additionally, individuals with aTRH had a higher risk of developing ESRD than their counterparts without aTRH. Using data from the Jackson Heart Study, we found that kidney disease was associated with higher 24-hour BP variability, but the association was explained by the higher mean BP among those with kidney disease. Finally, through analysis of HyperGEN data, we identified small IADs in BP among participants with and without kidney disease. Notably, 18% of those with kidney disease

had IADs in systolic BP in excess of 10 mmHg. In conclusion, this dissertation examines the association between unconventional BP phenotypes with kidney disease and identifies correlates of these phenotypes among individuals with kidney disease. Evaluating these phenotypes may help define the need for screening and their routine clinical evaluation among patients with kidney disease.

Keywords: chronic kidney disease, end-stage renal disease, blood pressure, apparent treatment-resistant hypertension, blood pressure variability, inter-arm differences

DEDICATION

For Dagney

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INCIDENT ESRD AND APPARENT TREATMENT-RESISTANT HYPERTENSION: RESULTS FROM THE REGARDS STUDY

LIST OF ABBREVIATIONS

ABPM	ambulatory blood pressure monitoring
ACR	albumin-to-creatinine ratio
ARV	average real variability
aTRH	apparent treatment-resistant hypertension
BP	blood pressure
CI	confidence interval
CKD	chronic kidney disease
CVD	cardiovascular disease
DBP	diastolic blood pressure
eGFR	estimated glomerular filtration rate
ESRD	end-stage renal disease
HyperGEN	Hypertension Genetic Epidemiology Network
IAD	inter-arm difference
JHS	Jackson Heart Study
REGARDS	REasons for Geographic And Racial Differences in Stroke
SBP	systolic blood pressure
SD_{dn}	day-night standard deviation

INTRODUCTION

Over 19 million American adults have chronic kidney disease (CKD),[1] evidenced by low estimated glomerular filtration rate (eGFR) and/or high albumin-to-creatinine ratio (ACR). CKD is a significant public health challenge given its high prevalence and association with adverse outcomes, including cardiovascular disease (CVD) incidence, end-stage renal disease (ESRD) and mortality.[2,3] Hypertension is the most prevalent comorbidity among individuals with CKD,[4] with prior studies suggesting a prevalence exceeding 80%.[5-7] Since hypertension is both a cause and a consequence of CKD[8] and CKD is associated with adverse outcomes, hypertensive individuals might be expected to have a higher risk for mortality than those who are not hypertensive. However, a recent meta-analysis reported that, among individuals with CKD, individuals with hypertension do not have a higher risk for mortality than their counterparts without hypertension and, in fact, those without hypertension may have the higher mortality risk.[4] This finding perhaps underlines the importance of evaluating the associations of unconventional blood pressure (BP) phenotypes, rather than mean clinic BP, among individuals with CKD. Some unconventional BP phenotypes, namely, apparent treatment-resistant hypertension (aTRH), 24-hour BP variability, and inter-arm differences (IADs) in BP have been identified as risk factors for CVD in the general population, and there is increasing evidence that these phenotypes may provide prognostic information above and beyond mean BP;[9,10] however, they have not been extensively studied in the context of CKD.

CKD and aTRH

Although the majority of people with CKD are treated with multiple classes of antihypertensive medication, a substantial proportion still have uncontrolled hypertension.[2,11] aTRH is defined as BP that remains above goal despite concurrent use of ≥ 3 antihypertensive medications from different classes or use of ≥ 4 antihypertensive medication classes regardless of BP level.[12] Studies suggest that aTRH is common and its prevalence is increasing among US adults. Based on data from the 2005-2008 National Health and Nutrition Examination Surveys (NHANES), Egan, et al. estimated the prevalence of aTRH to be 11.8% among hypertensive adults, an increase from 5.5% in the period 1988-1994.[13] To date, the association between aTRH and CKD has been examined in at least two small clinic-based studies. Abdel-Kader, et al. reported a 30% prevalence of aTRH among 88 CKD participants in the Pittsburgh-based Sleep-SCORE study.[14] In another clinic-based study of 300 patients with CKD, the prevalence of aTRH was 26% at study enrollment and 38% after 6 months of follow-up. Furthermore, in this latter study, aTRH was associated with increased risk of the pooled outcome of dialysis, transplantation, or death over a median of 37.6 months of follow-up [HR (95% CI): 1.85 (1.13 – 3.03)].[15] Egan, et al. previously reported eGFR < 60 mL/min/1.73m^2 and ACR > 300 mg/g to be associated with an increased odds ratio for aTRH.[13] However, the prevalence of aTRH by level of eGFR and albuminuria was not reported, nor were correlates of aTRH among individuals with CKD evaluated. This dissertation extends these findings by investigating the association between level of eGFR and albuminuria with the prevalence of aTRH and the correlates of aTRH among individuals with CKD in a large, population-based sample of US adults. Furthermore, identifying an increased

prevalence of aTRH with reduced eGFR and increased ACR may help raise awareness of aTRH and define the need for screening and routine clinical evaluation of aTRH among patients with CKD.

CKD and 24-hour BP Variability

ABPM yields a better estimate of mean BP than a single clinic BP measure and can enrich office BP measurement by quantifying out-of-office BP parameters such as 24-hour BP variability. Twenty-four hour BP variability has been associated with adverse outcomes and my represent a novel CVD risk factor.[16-18] A meta-analysis by Hansen, et al. reported an association between ambulatory BP variability and incident cardiovascular mortality and stroke [adjusted hazard ratios of 1.17 (95% CI: 1.07 – 1.28) and 1.25 (95% CI: 1.13 – 1.39), respectively, per standard deviation higher BP variability].[16] Individuals with CKD are at increased risk for CVD and mortality and there is a need to identify modifiable risk factors to reduce this risk.[19] Furthermore, factors associated with high 24-hour BP variability (e.g. older age and higher mean SBP) are common among individuals with CKD.[6,20] Prior research has demonstrated that African Americans have higher ambulatory BP variability than whites,[21] suggesting a potentially larger clinical impact among African Americans with CKD. However, despite higher rates of ESRD[22] and some cardiovascular outcomes[23] and a higher prevalence of hypertension among African Americans,[24,25] few ABPM studies to date have included non-whites.

CKD and IADs in BP

The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7) recommends that BP be measured in both arms at the initial assessment for hypertension and in the arm with the higher BP at subsequent visits.[26] Prior studies, such as HyperGEN, have reported large IADs in BP. HyperGEN is a study in which genetic and environmental determinants of hypertension were investigated in 2,395 hypertensive siblings and 854 volunteers in five geographical field centers. Arnett, et al. reported that up to 14.2% of HyperGEN participants had IADs in excess of 10 mmHg when three BP measurements per arm were analyzed.[27] Furthermore, some,[28,29] but not all,[30] small clinic-based studies have demonstrated that IADs in BP are reproducible and carry prognostic information. For example, in a study of 230 patients treated for hypertension, Clark, et al. reported that mean IADs of 10 mmHg and 15 mmHg were associated with an increased risk of all-cause mortality [adjusted hazard ratio 3.6 (95% CI: 2.0 – 6.5) and 3.1 (95% CI: 1.6 – 6.0), respectively].[29] However, to our knowledge, data have not been published on the association of IADs in BP with CKD or on correlates of IADs in BP by CKD status.

Implications for Current Research

Few data are available on the aforementioned BP phenotypes in the CKD population. Most studies that have been conducted in the CKD population have been small clinic-based studies. Evaluating these risk factors may help define the need for screening and their routine clinical evaluation among patients with CKD. Furthermore, this research may help identify new therapeutic targets, as well as individuals who could

benefit from intensive BP monitoring and early therapeutic interventions for renal protection. Accordingly, we sought to evaluate the association between aTRH and CKD in the REasons for Geographic And Racial Differences in Stroke (REGARDS) study and further, to determine whether individuals with aTRH have an increased risk for incident ESRD, to evaluate the association between 24-hour BP variability and CKD among African Americans in the Jackson Heart Study (JHS), and to determine the association between IADs in BP and CKD and identify correlates of high IADs among individuals with and without CKD in the Hypertension Genetic Epidemiology Network (HyperGEN) study.

PREVALENCE OF APPARENT TREATMENT-RESISTANT HYPERTENSION AMONG INDIVIDUALS WITH CHRONIC KIDNEY DISEASE: RESULTS FROM THE REGARDS STUDY

by

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ABSTRACT

Background

Apparent treatment-resistant hypertension (aTRH) is defined as systolic/diastolic blood pressure (BP) ≥ 140/90 mmHg with concurrent use of ≥ 3 antihypertensive medication classes or use of ≥ 4 antihypertensive medication classes regardless of BP level.

Methods

We determined the prevalence of aTRH among REasons for Geographic And Racial Differences in Stroke (REGARDS) study participants treated for hypertension (n=10,700) by level of estimated glomerular filtration rate (eGFR) and albumin-to-creatinine ratio (ACR) and evaluated correlates of aTRH among those with CKD. CKD was defined as an ACR ≥ 30 mg/g or eGFR < 60 mL/min/1.73m^2.

Results

The prevalence of aTRH was 15.8%, 24.9%, and 33.4% for those with eGFR ≥ 60, 45-59, and < 45 mL/min/1.73m^2, respectively and 12.1%, 20.8%, 27.7%, and 48.3% for ACR < 10, 10-29, 30-299, and ≥ 300 mg/g, respectively. The multivariable adjusted prevalence ratios (95% CI) for aTRH were 1.25 (1.11 – 1.41) and 1.20 (1.04 – 1.37) for eGFR levels of 45-59 and < 45 mL/min/1.73m^2, respectively, versus ≥ 60 mL/min/1.73m^2, and 1.54 (1.39 – 1.71), 1.76 (1.57 – 1.97), and 2.44 (2.12 – 2.81) for ACR levels of 10-29, 30-299, and ≥ 300 mg/g, respectively, versus ACR < 10 mg/g. After multivariable adjustment,

male gender, black race, larger waist circumference, diabetes, a history of myocardial infarction or stroke, statin use, and lower eGFR and higher ACR levels were associated with aTRH among individuals with CKD.

Conclusions

This study highlights the high prevalence of aTRH among individuals with CKD.

Introduction

Hypertension is common among individuals with chronic kidney disease (CKD), with previous studies suggesting a prevalence exceeding 80%.[1-3] Although the majority of people with CKD are treated with multiple classes of antihypertensive medication, a substantial proportion still have uncontrolled hypertension.[3] Apparent treatment-resistant hypertension (aTRH) is defined as blood pressure (BP) that remains above goal despite concurrent use of ≥ 3 antihypertensive medications from different classes or use of ≥ 4 antihypertensive medication classes regardless of BP level.[4] Studies suggest that aTRH is common and its prevalence is increasing among US adults. Based on data from the 2005-2008 National Health and Nutrition Examination Surveys (NHANES), Egan, et al. estimated the prevalence of aTRH to be 11.8% among hypertensive adults.[5] Furthermore, in recent studies, aTRH has been associated with an increased risk of cardiovascular disease (CVD) outcomes and the pooled outcome of dialysis, transplantation, or death. [6,7]

Egan, et al. previously reported estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m^2 and albumin-to-creatinine ratio (ACR) > 300 mg/g to be associated with an increased odds ratio for aTRH. However, the prevalence of aTRH by level of eGFR and albuminuria was not reported. Identifying an increased prevalence of aTRH with reduced eGFR and increased ACR may help raise awareness of aTRH and define the need for screening and routine clinical evaluation of aTRH among patients with CKD. Therefore, the goal of the current analysis was to determine the association between level of eGFR and ACR and the prevalence of aTRH. Additionally, we sought to identify clinical and demographic correlates of aTRH in individuals with CKD. To address these

aims, we analyzed data from a large, population-based sample of adults participating in the REasons for Geographic And Racial Differences in Stroke (REGARDS) study.

Methods

Study Participants

The REGARDS study is a population-based cohort study of 30,239 black and white US adults ≥ 45 years of age enrolled between June 2003 and October 2007.[8] Participants were recruited from the 48 contiguous US states and the District of Columbia. The present analysis was restricted to 15,227 individuals with hypertension who were taking ≥ 1 classes of antihypertensive medication. Those missing serum creatinine, urine albumin or urine creatinine, BP data, or information from the pill-bottle review (n=1,721) were also excluded. Additionally, participants who reported being on dialysis at baseline or who were missing information on dialysis status (n=122) were excluded. Finally, we excluded participants with uncontrolled BP on 1 or 2 antihypertensive medication classes (n=2,684) from the main analyses as we were unable to determine whether these participants had aTRH. As described below, these participants were included in secondary analyses. After these exclusion criteria were applied, data from 10,700 participants were analyzed (Figure 1). The REGARDS study protocol was approved by the Institutional Review Boards governing research in human subjects at the participating centers and all participants provided written consent.

Data Collection

Of relevance to the current analysis, information on the following demographic, behavioral and medical history characteristics were collected during a telephone interview: age, sex, race, education, annual household income, smoking status, alcohol consumption, frequency of physical activity, and a history of diabetes, stroke, or myocardial infarction. Medication adherence was assessed using the 4-item Morisky Medication Adherence Scale (MMAS). Scores on this scale can range from 0 to 4 with higher scores indicating worse adherence. During the in-home examination, standardized protocols were followed to obtain two BP measurements. Also, an electrocardiogram was obtained, waist circumference was measured, and blood and urine samples were collected. A pill-bottle review was conducted to record information for all medications participants reported taking during the 2 weeks preceding the in-home study visit. Medication doses were not recorded. Total and high-density lipoprotein (HDL) cholesterol were measured by colorimetric reflectance spectrophotometry and high sensitivity C-reactive protein was measured using a high-sensitivity particle-enhanced immunonephelometric assay. Diabetes was defined as a fasting serum glucose $\geq$ 126 mg/dL, non-fasting serum glucose $\geq$ 200 mg/dL, or use of antidiabetes medication.

Definition of eGFR and ACR

Using the blood sample collected during the in-home examination, serum creatinine was measured using an isotope-dilution mass spectrometry (IDMS) traceable method. eGFR was calculated via the Chronic Kidney Disease Epidemiology

Collaboration (CKD-EPI) equation[9] and categorized as ≥ 60, 45-59, and < 45 mL/min/1.73m^2. Using spot urine samples collected during the in-home examination, urinary albumin was measured with the BN ProSpec Nephelometer from Dade Behring (Marburg, Germany). Urinary creatinine was measured with a rate-blanked Jaffé procedure, using the Modular-P analyzer (Roche/Hitachi; Indianapolis, IN). ACR was categorized as < 10, 10-29, 30-299, and ≥ 300 mg/g. CKD was defined as an ACR ≥ 30 mg/g or an eGFR < 60 mL/min/1.73m^2.

Definition of aTRH

During the in-home examination, BP was measured twice by trained technicians following a standardized protocol using aneroid sphygmomanometers. Participants were asked to sit quietly for 3 minutes with both feet on the floor prior to the BP measurements. Measurements were taken in the left arm when possible, using an appropriately sized cuff. The cuff was inflated to 20 mmHg above the pulse obliteration level and slowly deflated. After a 30 second rest period, this process was repeated on the same arm to obtain the second BP measurement. Quality control for BP measurement in REGARDS was monitored by central examination of digit preference and technicians were retrained as necessary.[8,10] The two BP measurements were averaged for analysis. Uncontrolled BP was defined as systolic BP ≥ 140 mmHg and/or diastolic BP ≥ 90 mmHg. aTRH was defined as uncontrolled BP with concurrent use of ≥ 3 antihypertensive medication classes or use of ≥ 4 antihypertensive medication classes, regardless of BP level. Antihypertensive medication classes were defined using the

Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7).[11] One-pill combinations were classified into multiple medication classes.

Statistical Analysis

Characteristics of REGARDS participants were calculated by CKD and aTRH status. We calculated the prevalence of aTRH by levels of eGFR (≥ 60, 45-59, and < 45 mL/min/1.73m^2) and ACR (< 10, 10-29, 30-299, and ≥ 300 mg/g). We used Poisson regression models to obtain crude and multivariable adjusted prevalence ratios of aTRH associated with eGFR and ACR. Prevalence ratios are recommended, instead of odds ratios, for cross-sectional studies with common outcomes.[12] Initial multivariable adjustment included age, race, and sex. A subsequent model included additional adjustment for geographic region of residence, income, education, physical activity, current smoking, alcohol use, waist circumference, diabetes, total cholesterol, HDL-C, statin use, c-reactive protein, history of myocardial infarction, history of stroke, ACR (in analyses investigating the prevalence ratio for aTRH associated with eGFR), and eGFR (in analyses investigating the prevalence ratio for aTRH associated with ACR). In sensitivity analyses, we conducted the above analyses limited to individuals with perfect medication adherence, defined by appropriate medication taking behaviors on each item on the MMAS and using a secondary definition of aTRH requiring the use of a diuretic. Next, we calculated the prevalence of aTRH by the cross-tabulation of eGFR level and ACR level and multivariable adjusted prevalence ratios for aTRH associated with levels

of eGFR and ACR jointly, using REGARDS participants with eGFR ≥ 60 ml/min/1.73 m^2 and ACR < 10 mg/g as the reference category. Finally, for individuals with CKD, we calculated prevalence ratios for aTRH associated with the study covariates included in the full multivariable adjusted model described above. We repeated the above analyses including the 2,684 individuals with uncontrolled BP on 1 or 2 classes of antihypertensive medication categorized as not having aTRH. All analyses were conducted using SAS 9.2 (SAS Institute, Cary, North Carolina).

Results

Participant Characteristics

After excluding individuals with uncontrolled BP on 1 or 2 classes of antihypertensive medication, 17.9% of REGARDS study participants with hypertension had aTRH. Individuals with both CKD and aTRH were more likely to have diabetes or a history of myocardial infarction or stroke than those with neither CKD nor aTRH, CKD alone, or aTRH alone. Those with aTRH, regardless of CKD status, were more likely to be black, have larger waist circumferences, and use statins (Table 1).

Prevalence of aTRH by eGFR and ACR

The prevalence of aTRH was 15.8%, 24.9%, and 33.4% for REGARDS participants with an eGFR ≥ 60, 45-59, and < 45 mL/min/1.73m^2, respectively (Figure 2) and 12.1%, 20.8%, 27.7%, and 48.3% for ACR < 10, 10-29, 30-299, and ≥ 300 mg/g,

respectively (Figure 3). The prevalence of aTRH was 28.0% and 32.1% among participants with eGFR < 60 and ACR ≥ 30 mg/g, respectively. Also, 28.1% of those with CKD, versus 13.6% of their counterparts without CKD had aTRH. Lower eGFR and higher ACR were associated with higher prevalence ratios for aTRH in crude and multivariable adjusted models (Table 2). Results were similar when limited to individuals with perfect medication adherence (Table 3) and when using a secondary definition of aTRH requiring the use of a diuretic (Table 4).

Cross-tabulation of eGFR and ACR on aTRH

The prevalence of aTRH was 11.2% among individuals with eGFR ≥ 60 mL/min/1.73m^2 and ACR < 10 mg/g. Within each eGFR level, the prevalence of aTRH increased at higher ACR levels. Similarly, for ACR < 10 mg/g or ≥ 300 mg/g there was a higher prevalence of aTRH at lower eGFR levels (Figure 4). However, for ACR 10-29 mg/g or 30-299 mg/g, the prevalence of aTRH was higher for individuals with an eGFR of 45 - 59 mL/min/1.73m^2, but not < 45 mL/min/1.73m^2, as compared to an eGFR ≥ 60 mL/min/1.73m^2. The prevalence of aTRH among individuals with eGFR < 45 mL/min/1.73m^2 and ACR ≥ 300 mg/g was 56.4%. Similar patterns were present after multivariable adjustment (Table 5).

Correlates of aTRH Among Hypertensive Individuals with CKD

After age and race adjustment, female gender was associated with a lower prevalence ratio for aTRH and after age and sex adjustment, black race was associated with a higher prevalence ratio of aTRH (Table 6). After age, race, sex-adjustment, income < $20,000, a larger waist circumference, diabetes, history of myocardial infarction or stroke, statin use, eGFR < 45 mL/min/1.73m^2, and higher ACR were associated with a higher prevalence ratio of aTRH. Physical activity 4+ times per week versus none, higher total and HDL-cholesterol were associated with a lower prevalence ratio for aTRH. After multivariable adjustment, female gender was associated with a lower prevalence ratio for aTRH. Black race, a larger waist circumference, diabetes, history of myocardial infarction or stroke, statin use, lower eGFR, and higher ACR were associated with a higher prevalence ratio for aTRH.

Antihypertensive Medication Use

The median number of antihypertensive medication classes being taken was 2.0 (25th, 75th percentile: 1.0, 2.0) for individuals without aTRH, compared to 4.0 (25th, 75th percentile: 3.0, 4.0) for those with aTRH (Table 7). Over half of the study participants with aTRH were taking diuretics (86.8%), beta blockers (73.4%), calcium channel blockers (72.1%), and angiotensin converting enzyme (ACE) inhibitors (62.0%).

Sensitivity Analysis Including Individuals with Uncontrolled BP on 1 or 2 Classes of Antihypertensive Medication

Among individuals on 1 or 2 classes of antihypertensive medication, the prevalence of uncontrolled BP was 28.0%, compared to 33.2% among those on ≥ 3 classes of antihypertensive medication. When including individuals with uncontrolled BP on 1 or 2 classes of antihypertensive medication, 14.3% of study participants with hypertension had aTRH. The prevalence of aTRH was 12.5%, 20.4%, and 28.3% for REGARDS participants with eGFR ≥ 60, 45-59, and < 45 mL/min/1.73 m^2, respectively and 10.1%, 15.9%, 20.8%, and 34.7% for those with ACR < 10, 10-29, 30-299 and ≥ 300 mg/g, respectively. The prevalence of aTRH was 22.0% for individuals with CKD and 11.0% for individuals without CKD. Additionally, 23.2% and 12.5% of participants with and without eGFR < 60 mL/min/1.73m^2 and 23.9% and 11.9% with and without ACR ≥ 30 mg/g had aTRH, respectively.

Discussion

Using data from a large, population-based sample of black and white adults, we found a strong, graded association between lower eGFR and higher ACR with a higher prevalence of aTRH. The prevalence of aTRH was high and exceeded 50% among individuals with both eGFR < 45 ml/min/1.73 m^2 and ACR ≥ 300 mg/g. Among individuals with CKD, black race, larger waist circumference, diabetes, history of myocardial infarction and stroke and lower eGFR and higher ACR were associated with a higher prevalence ratio for aTRH.

Hypertension is common among individuals with CKD. Furthermore, most

people with CKD and hypertension take multiple classes of antihypertensive medication.[3,13] In an analysis of 3,612 participants in the Chronic Renal Insufficiency (CRIC) study, 83% of individuals with hypertension were taking at least two classes of antihypertensive medication, with 26% and 32% of participants taking antihypertensive medications from 3 and ≥ 4 classes, respectively.[3] Consistent with this finding, 87% of 238 pre-dialysis CKD patients in a recent study were taking at least two antihypertensive medications, with 34% of patients taking 3 antihypertensive medications and 33% taking four or more antihypertensive medications.[13] However, the prevalence of aTRH was not evaluated in these prior studies.

The association between aTRH and CKD has been examined in at least two small clinic-based studies. Abdel-Kader, et al. reported a 30% prevalence of aTRH among 88 CKD participants in the Pittsburgh-based Sleep-SCORE study.[14] In another clinic-based study of 300 patients with CKD, the prevalence of aTRH was 26% at study enrollment and 38% after 6 months of follow-up. Furthermore, in this latter study, aTRH was associated with increased risk of the pooled outcome of dialysis, transplantation, or death over a median of 37.6 months of follow-up [HR (95% CI): 1.85 (1.13 – 3.03)].[7] Also, Egan, et al. previously identified an association between aTRH and CKD prevalence using NHANES data.[5] The current analysis extends these findings by investigating the association between level of eGFR and albuminuria, separately and jointly, and the prevalence of aTRH and the correlates of aTRH among individuals with CKD in a large population-based sample of US adults.

Data from the REGARDS study indicate that aTRH is a common condition among individuals with CKD, suggesting the need for greater awareness of this

comorbidity among clinicians. Among those with CKD, in particular men, blacks, individuals with large waist circumferences, and those with a history of diabetes, stroke, or myocardial infarction had a higher prevalence of aTRH. The identification of individuals at high risk of developing aTRH who may benefit from intensive BP monitoring and early therapeutic interventions (e.g. treatment for secondary hypertension, referral to a hypertension specialist, and cessation of medications that increase BP) should be a high priority. Furthermore, the American Heart Association (AHA) scientific statement on aTRH diagnosis, evaluation, and treatment recommends diuretics as first-line therapy for patients with hypertension, with the subsequent addition of an ACE inhibitor or angiotensin receptor blocker (ARB) and then a calcium channel blocker, as needed to achieve BP control.[4] In the current study, 86.8% of participants with aTRH were taking a diuretic. However, only 7.6% were taking an aldosterone antagonist. Although careful monitoring for hyperkalemia is necessary in CKD patients taking aldosterone antagonists, studies have demonstrated that they provide significant antihypertensive and anti-proteinuric benefits when added to existing multidrug treatment regimens.[15,16] This is especially important since prior studies suggest that BP control can be achieved and maintained even in difficult to control populations.[17,18] Furthermore, the results of this study emphasize the need for the development and dissemination of appropriate therapeutic regimens for CKD patients with aTRH.

The causal pathway between albuminuria and aTRH is not known and may be bidirectional. aTRH may result in microalbuminuria through prolonged increases in glomerular pressure and subsequent renal damage.[19] Further, sodium retention and excessive activation of the renin-angiotensin-aldosterone system have been linked to

uncontrolled BP in individuals with CKD.[20,21] Also, albuminuria is thought to be preceded by systemic endothelial dysfunction.[22] While endothelial dysfunction is associated with incident hypertension, the presence of uncontrolled blood pressure has also been associated with worsening endothelial function.[23,24] Several therapies (e.g., smoking cessation, ACE-inhibitor use) that improve endothelial function also reduce albuminuria.[25] Given the cross-sectional study design used for the current analysis, we could not assess the direction of the albuminuria – aTRH association. Future studies with longitudinal assessments of albuminuria, endothelial function and blood pressure are warranted to investigate this further.

The findings of the current study should be considered in the context of certain limitations. Most importantly, the analysis used a cross-sectional study design. CKD is both a common cause and complication of hypertension, and it is unknown whether aTRH preceded the development of CKD or whether CKD resulted in the incidence of aTRH.[26] Also, BP, eGFR, and albuminuria were only assessed at a single time point, making misclassification of CKD and aTRH status possible. An additional limitation is the lack of medication dosing information. Some individuals may have been on an inadequate treatment regimen and not truly treatment resistant. We do not have data on potential secondary causes of aTRH or whether participants took antihypertensive medication on the day of their study visit prior to the BP measurement.[4] Our study minimizes misclassification of the aTRH phenotype through the use of a pill-bottle review to identify the number of antihypertensive medication classes being taken, consideration of medication adherence, and standardized in-home BP measurement, which limits potential white-coat effects. Additional studies may be warranted to

determine whether the use of home BP monitoring is a potentially useful strategy for diagnosis and management of aTRH in difficult to control populations. Other strengths include the large, population-based sample of blacks and whites and the availability of both albuminuria and eGFR measurements.

In conclusion, data from the current study demonstrate a strong, graded association between lower eGFR and higher ACR with a higher aTRH prevalence. A very high prevalence of aTRH was present among people with both lower eGFR and higher ACR when they were considered jointly. Strategies are needed to improve BP control and better manage aTRH in people with CKD.

Acknowledgement

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Table 1. Characteristics of REasons for Geographic And Racial Differences in Stroke (REGARDS) study participants with and without chronic kidney disease (CKD) by apparent treatment-resistant hypertension (aTRH) status.

	CKD			No CKD		
	aTRH (n=880)	No aTRH (n=2,254)	p-value	aTRH (n=1,032)	No aTRH (n=6,534)	p-value
Age, years	69.1 (8.9)	69.6 (9.2)	0.14	66.3 (8.1)	64.5 (8.5)	<0.001
Female gender, %	48.3	56.3	<0.001	51.4	58.9	<0.001
Black race, %	60.3	46.4	<0.001	58.9	46.0	<0.001
Region, %						
Non-belt	45.9	45.0	0.86	43.5	42.1	0.49
Belt	33.0	33.1		36.1	35.9	
Buckle	21.1	21.9		20.4	22.0	
Income <$20,000, %	28.3	23.5	0.10	22.5	17.5	<0.001
Less than high school education, %	21.0	17.7	0.01	18.2	12.2	<0.001
Waist circumference, cm	104.5 (16.7)	99.6 (15.9)	<0.001	103.7 (16.0)	97.5 (14.6)	<0.001
Diabetes, %	52.7	38.1	<0.001	36.3	22.6	<0.001
Current smoking, %	13.2	12.9	0.69	10.4	12.9	0.05
Current alcohol use, %	28.1	29.9	0.34	33.8	35.4	0.31
Physical activity, %						
4+ times per week	20.3	24.5	0.02	26.5	28.5	0.08
1 to 3 times per week	32.1	32.1		35.0	36.7	
None	47.6	43.4		38.5	34.9	
History of MI, %	27.9	20.4	<0.001	23.0	13.1	<0.001
History of stroke, %	16.8	12.5	0.001	9.7	6.5	<0.001
Statin use, %	58.2	45.8	<0.001	47.9	41.3	<0.001
Total cholesterol, mg/dL	178.9 (39.8)	185.5 (40.3)	<0.001	181.4 (37.5)	186.7 (38.7)	<0.001
HDL-cholesterol, mg/dL	46.5 (14.8)	49.5 (15.8)	<0.001	49.7 (14.6)	51.2 (15.7)	0.004
C-reactive protein, mg/L	3.1 (1.4, 6.9)	3.0 (1.3, 6.7)	0.13	2.6 (1.2, 5.7)	2.4 (1.1, 5.5)	0.07
Systolic BP, mmHg	143.7 (19.4)	124.1 (10.0)	<0.001	140.9 (17.1)	123.0 (9.9)	<0.001
Diastolic BP, mmHg	79.1 (12.1)	73.7 (8.2)	<0.001	80.8 (11.1)	75.1 (7.5)	<0.001

eGFR, mL/min/1.73m^2	60.8 (23.5)	64.7 (24.3)	<0.001	87.3 (15.6)	88.6 (15.3)	0.01
ACR, mg/g	64.1 (21.0, 256.3)	36.1 (9.0, 88.9)	<0.001	8.3 (5.3, 14.1)	6.5 (4.5, 10.3)	<0.001

Numbers in table are mean (standard deviation) or percent except for c-reactive protein and albumin-to-creatinine ratio which are presented as median (25th percentile, 75th percentile).

HDL= high-density lipoprotein; eGFR= estimated glomerular filtration rate; ACR= albumin-to-creatinine ratio

CKD defined as an ACR ≥30 mg/g or an eGFR <60 mL/min/1.73m^2.

Table 2. Prevalence ratios for apparent treatment-resistant hypertension (aTRH) associated with estimated glomerular filtration rate (eGFR) and albumin-to-creatinine ratio (ACR) among REasons for Geographic And Racial Differences in Stroke (REGARDS) study participants.

	n	Crude prevalence ratio (95% CI)	Age-, race-, sex-adjusted prevalence ratio (95% CI)	Multivariable* adjusted prevalence ratio (95% CI)
eGFR, mL/min/1.73m^2				
≥60	8,876	1 (ref)	1 (ref)	1 (ref)
45-59	1,166	1.57 (1.41, 1.76)	1.49 (1.33, 1.67)	1.25 (1.11, 1.41)
<45	658	2.12 (1.88, 2.38)	1.90 (1.68, 2.15)	1.20 (1.04, 1.37)
ACR, mg/g				
<10	6,166	1 (ref)	1 (ref)	1 (ref)
10-29	2,580	1.72 (1.55,1.90)	1.68 (1.52, 1.86)	1.54 (1.39, 1.71)
30-299	1,536	2.29 (2.06, 2.54)	2.09 (1.88, 2.33)	1.76 (1.57, 1.97)
≥300	418	3.99 (3.54, 4.50)	3.48 (3.08, 3.93)	2.44 (2.12, 2.81)

CI= confidence interval

*Adjusted for age, race, sex, geographic region, income, education, physical activity, current smoking, alcohol use, waist circumference, diabetes, total cholesterol, high-density lipoprotein cholesterol, statin use, c-reactive protein, history of myocardial infarction, history of stroke, ACR (log transformed, in eGFR analyses), and eGFR (in ACR analyses)

Table 3. Prevalence ratios for apparent treatment-resistant hypertension (aTRH) associated with estimated glomerular filtration rate (eGFR) and albumin-to-creatinine ratio (ACR) among REasons for Geographic And Racial Differences in Stroke (REGARDS) study participants, limited to those with perfect medication adherence.

	eGFR level, mL/min/1.73m^2		
	≥60 (n=6,061)	45-59 (n=823)	<45 (n=439)
n with aTRH	909	196	140
Crude	1 (ref)	1.59 (1.39, 1.82)	2.13 (1.83, 2.47)
Age-, race-, sex-adjusted	1 (ref)	1.52 (1.32, 1.75)	1.92 (1.65, 2.25)
Multivariable* adjusted	1 (ref)	1.28 (1.10, 1.48)	1.23 (1.04, 1.46)

	ACR level, mg/g			
	<10 (n=4,233)	10-29 (n=1,771)	30-299 (n=1,046)	≥300 (n=273)
n with aTRH	501	351	269	124
Crude	1 (ref)	1.67 (1.48, 1.90)	2.17 (1.90, 2.48)	3.84 (3.29, 4.48)
Age-, race-, sex-adjusted	1 (ref)	1.66 (1.46, 1.88)	2.00 (1.75, 2.28)	3.30 (2.83, 3.86)
Multivariable* adjusted	1 (ref)	1.49 (1.31, 1.70)	1.70 (1.48, 1.96)	2.25 (1.88, 2.69)

Perfect medication adherence was defined as a score of 0 on the 4-item Morisky Medication Adherence Scale.

Numbers in table are prevalence ratio (95% confidence interval)

Prevalence ratios adjusted for age, race, sex, geographic region, income, education, physical activity, current smoking, alcohol use, waist circumference, diabetes, total cholesterol, high-density lipoprotein cholesterol, statin use, c-reactive protein, history of myocardial infarction, history of stroke, albumin-to-creatinine ratio (log transformed, in eGFR analyses), and eGFR (in ACR analyses)

Table 4. Prevalence ratios for secondary definition of apparent treatment-resistant hypertension (aTRH) associated with estimated glomerular filtration rate (eGFR) and albumin-to-creatinine ratio (ACR) among REasons for Geographic And Racial Differences in Stroke (REGARDS) study participants.

	Crude prevalence ratio (95% CI)	Age-, race-, sex-adjusted prevalence ratio (95% CI)	Multivariable** adjusted prevalence ratio (95% CI)
eGFR, mL/min/1.73m^2			
≥60	1 (ref)	1 (ref)	1 (ref)
45-59	1.62 (1.44, 1.82)	1.56 (1.37, 1.76)	1.33 (1.17, 1.51)
<45	2.04 (1.79, 2.33)	1.88 (1.64, 2.15)	1.25 (1.08, 1.46)
ACR, mg/g			
<10	1 (ref)	1 (ref)	1 (ref)
10-29	1.68 (1.51, 1.87)	1.64 (1.48, 1.83)	1.49 (1.33, 1.66)
30-299	2.14 (1.90, 2.39)	1.98 (1.76, 2.22)	1.64 (1.45, 1.85)
≥300	3.41 (2.97, 3.92)	3.03 (2.63, 3.48)	2.03 (1.73, 2.39)

CI= confidence interval

Secondary definition requiring the use of a diuretic.

**Adjusted for age, race, sex, geographic region, income, education, physical activity, current smoking, alcohol use, waist circumference, diabetes, total cholesterol, high-density lipoprotein cholesterol, statin use, c-reactive protein, history of myocardial infarction, history of stroke, ACR (log transformed, in eGFR analyses), and eGFR (in ACR analyses)

Table 5. Multivariable adjusted prevalence ratios for apparent treatment-resistant hypertension (aTRH) associated with cross-tabulation of albumin-to-creatinine ratio (ACR) level and estimated glomerular filtration rate (eGFR) level among REasons for Geographic And Racial Differences in Stroke (REGARDS) study participants.

ACR, mg/g	eGFR, mL/min/1.73m^2		
	≥60	45-59	<45
<10	1 (ref)	1.36 (1.11, 1.67)	1.73 (1.30, 2.30)
10-29	1.59 (1.41, 1.79)	1.99 (1.62, 2.45)	1.62 (1.15, 2.29)
30-299	1.88 (1.65, 2.14)	2.22 (1.79, 2.75)	2.02 (1.59, 2.57)
≥300	2.73 (2.25, 3.31)	3.13 (2.44, 4.03)	3.44 (2.88, 4.10)

Numbers in table are prevalence ratio (95% confidence interval)

Prevalence ratios adjusted for age, race, sex, geographic region, income, education, physical activity, current smoking,alcohol use, waist circumference, diabetes, total cholesterol, high-density lipoprotein cholesterol (HDL-C), statin use, c-reactive protein, history of myocardial infarction, and history of stroke

Table 6. Prevalence ratios for apparent treatment-resistant hypertension (aTRH) associated with study covariates among REasons for Geographic And Racial Differences in Stroke (REGARDS) study participants with chronic kidney disease.

	Age-, race, sex-adjusted	Multivariable adjusted*
Age, per 10 years	0.99 (0.93, 1.05)	1.05 (0.98, 1.13)
Female gender	0.75 (0.67, 0.84)	0.87 (0.76, 0.99)
Black race	1.56 (1.38, 1.75)	1.49 (1.31, 1.68)
Region		
Non-belt	1 (ref)	1 (ref)
Belt	1.03 (0.91, 1.17)	1.04 (0.92, 1.19)
Buckle	1.04 (0.90, 1.20)	1.05 (0.91, 1.22)
Income <$20,000	1.18 (1.04, 1.33)	1.08 (0.94, 1.23)
Less than high school education	1.07 (0.93, 1.23)	0.99 (0.85, 1.15)
Waist circumference, per 15 cm	1.19 (1.13, 1.25)	1.13 (1.07, 1.20)
Diabetes	1.44 (1.29, 1.62)	1.13 (1.00, 1.28)
Current smoking	0.98 (0.83, 1.16)	1.01 (0.85, 1.20)
Alcohol use	0.95 (0.83, 1.07)	1.02 (0.90, 1.17)
Physical activity		
None	1 (ref)	1 (ref)
1 to 3 times per week	0.91 (0.80, 1.04)	1.00 (0.88, 1.14)
4+ times per week	0.79 (0.68, 0.92)	0.90 (0.77, 1.05)
History of myocardial infarction	1.34 (1.19, 1.51)	1.20 (1.06, 1.36)
History of stroke	1.23 (1.07, 1.42)	1.15 (1.00, 1.33)
Statin use	1.44 (1.29, 1.62)	1.29 (1.14, 1.46)
Total cholesterol, per 40 mg/dL	0.90 (0.84, 0.95)	0.97 (0.91, 1.04)
HDL-cholesterol, per 15 mg/dL	0.86 (0.81, 0.92)	0.95 (0.88, 1.02)
C-reactive protein >3 mg/L	1.07 (0.96, 1.20)	0.96 (0.86, 1.08)
eGFR, mL/min/1.73m^2		
≥60	1 (ref)	1 (ref)
45-59	0.95 (0.83, 1.09)	1.18 (1.00, 1.40)
<45	1.25 (1.08, 1.44)	1.22 (1.05, 1.43)
ACR, mg/g		
<10	1 (ref)	1 (ref)
10-29	1.44 (1.16, 1.79)	1.32 (1.06, 1.65)
30-299	1.43 (1.20, 1.70)	1.50 (1.22, 1.83)
≥300	2.37 (1.97, 2.85)	2.24 (1.83, 2.76)

Chronic kidney disease was defined as an ACR ≥30 mg/g or an eGFR <60 mL/min/1.73m^2.

Numbers in table are prevalence ratio (95% confidence interval)

HDL= high-density lipoprotein; eGFR= estimated glomerular filtration rate; ACR= albumin-to-creatinine ratio

Prevalence ratios adjusted for age, race, sex, geographic region, income, education, physical activity, current smoking, alcohol use, waist circumference, diabetes, total cholesterol, high-density lipoprotein cholesterol, statin use, c-reactive protein, history of myocardial infarction, history of stroke, ACR, and eGFR

Table 7. Number of antihypertensive medication classes being taken and percent of REasons for Geographic And Racial Differences in Stroke (REGARDS) participants taking each class of medication

	no aTRH (n=8,788)	aTRH (n=1,912)
Antihypertensive medication classes Mean (SD) Median (25^{th}, 75^{th} percentile)	 1.9 (0.7) 2.0 (1.0, 2.0)	 3.6 (0.7) 4.0 (3.0, 4.0)
Aldosterone antagonist, %	1.3	7.6
Alpha blocker, %	4.3	16.3
Angiotensin converting enzyme (ACE) inhibitor, %	39.3	62.0
Angiotensin receptor blocker (ARB), %	24.6	40.1
Beta blocker, %	31.6	73.4
Calcium channel blocker, %	32.4	72.1
Central acting agent, %	0.3	1.1
Diuretic, %	51.4	86.8
Vasodilator, %	0.2	3.3

aTRH: apparent treatment-resistant hypertension

Figure 1. Exclusion criteria

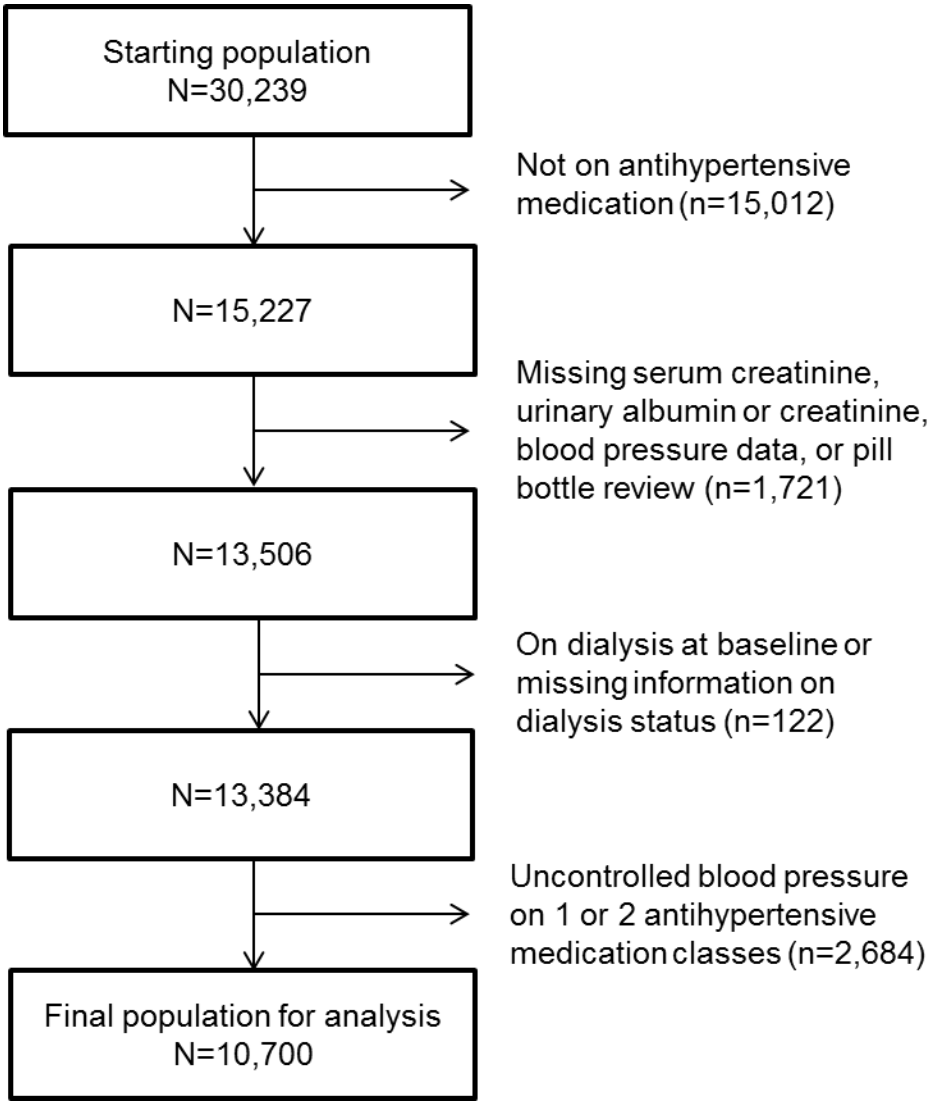


Figure 2. Prevalence of apparent treatment-resistant hypertension (aTRH) by estimated glomerular filtration rate (eGFR) among REasons for Geographic And Racial Differences in Stroke (REGARDS) study participants.

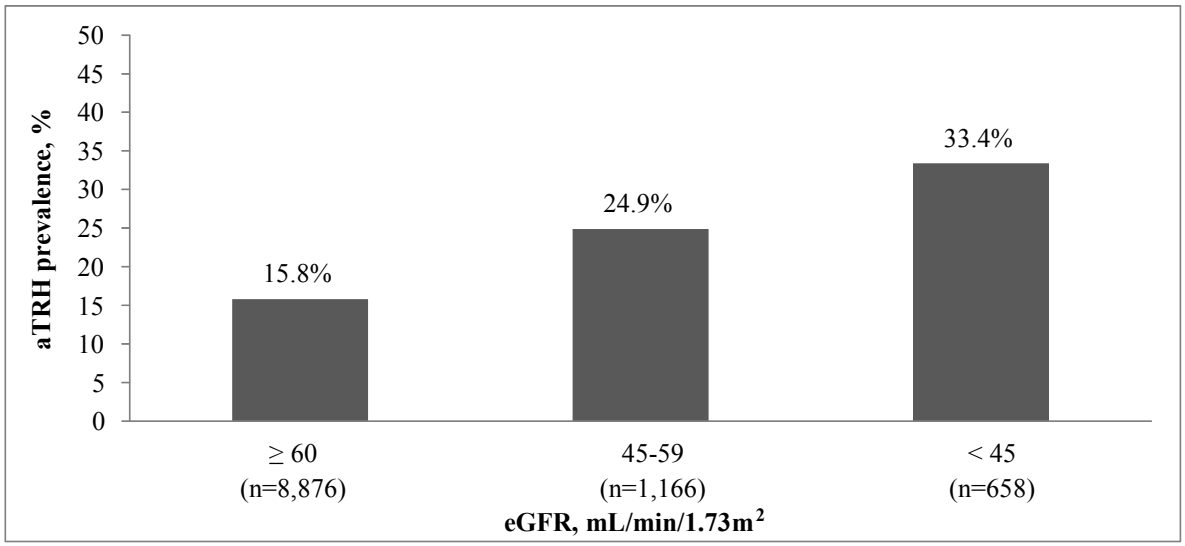


Figure 3. Prevalence of apparent treatment -esistant hypertension (aTRH) by albumin-to-creatinine ratio (ACR) among REasons for Geographic And Racial Differences in Stroke (REGARDS) study participants

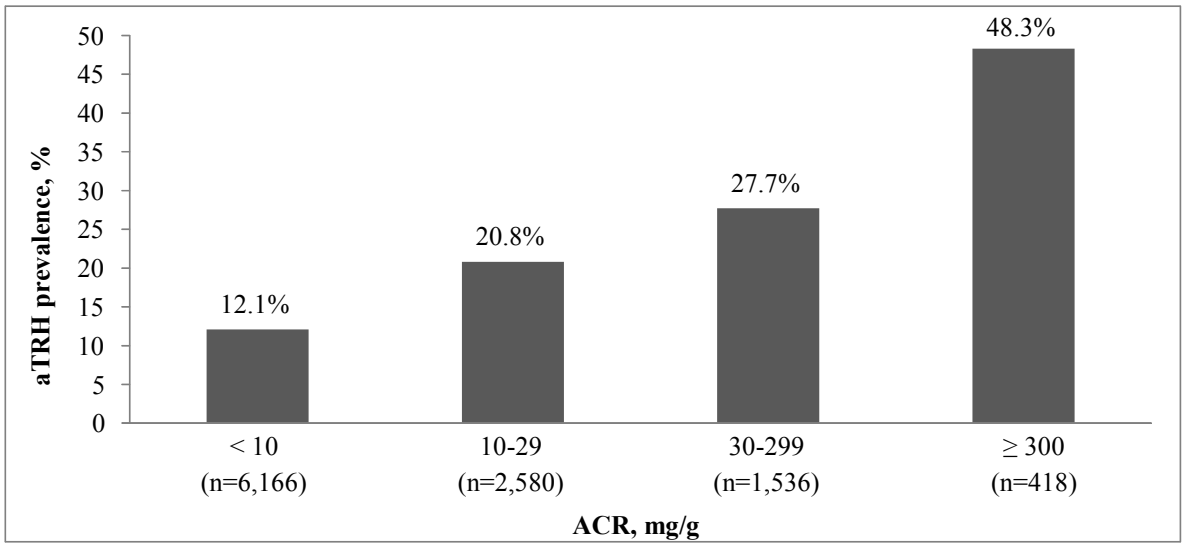
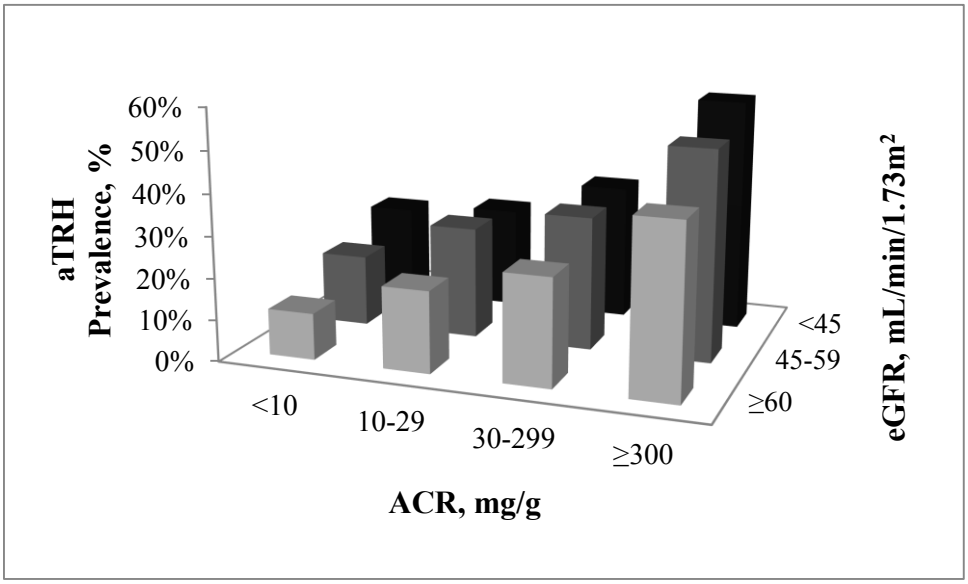


Figure 4. Prevalence of apparent treatment-resistant hypertension (aTRH) by the cross-tabulation of albumin-to-creatinine ratio (ACR) and estimated glomerular filtration rate (eGFR) among REasons for Geographic And Racial Differences in Stroke (REGARDS) study participants.



INCIDENT ESRD AND APPARENT TREATMENT-RESISTANT HYPERTENSION: RESULTS FROM THE REASONS FOR GEOGRAPHIC AND RACIAL DIFFERENCES IN STROKE (REGARDS) STUDY

by

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ABSTRACT

Background

Studies suggest that apparent treatment-resistant hypertension (aTRH) is common and increasing in prevalence among US adults. While hypertension is a risk factor for end-stage renal disease (ESRD), few data are available on the association between aTRH and ESRD risk.

Methods

We analyzed data from 9,974 REasons for Geographic And Racial Differences in Stroke (REGARDS) study participants treated for hypertension without ESRD at baseline. aTRH was defined as uncontrolled blood pressure (BP) with concurrent use of 3 antihypertensive medication classes including a diuretic or use of ≥ 4 antihypertensive medication classes including a diuretic, regardless of BP level. Incident ESRD was identified through linkage of REGARDS study participants with the United States Renal Data System. During a baseline in-home study visit, BP was measured twice and classes of antihypertensive medication being taken were determined by pill bottle inspection.

Results

Over a median follow-up of 6.4 years, there were 152 incident cases of ESRD (110 ESRD cases among 2,147 with aTRH and 42 ESRD cases among 7,827 without aTRH). The incidence of ESRD per 1,000 person-years for hypertensive participants with and without aTRH was 8.86 (95% CI: 7.35, 10.68) and 0.88 (95% CI: 0.65, 1.19),

respectively. After multivariable adjustment, the hazard ratio for ESRD comparing hypertensive participants with versus without aTRH was 6.32 (95% CI: 4.30, 9.30). Of the participants who developed incident ESRD during follow-up, 72% had aTRH at baseline.

Conclusions

Individuals with aTRH are at increased risk for ESRD. Appropriate clinical management strategies are needed to treat aTRH in order to preserve renal function in this high risk group.

Introduction

Apparent treatment-resistant hypertension (aTRH) is defined as uncontrolled blood pressure (BP) with concurrent use of ≥ 3 antihypertensive medication classes or use of ≥ 4 antihypertensive medication classes, regardless of BP level. Ideally, one of these antihypertensive medication classes should be a diuretic and all agents should be prescribed at optimal dosages.[1] Based on data from the 2005-2008 National Health and Nutrition Examination Surveys (NHANES), Egan, et al. estimated the prevalence of aTRH to be 11.8% among hypertensive adults.[2]

End-stage renal disease (ESRD) is associated with a heavy economic burden and excess risk of mortality.[3] Hypertension affects the majority of individuals with chronic kidney disease (CKD) and is a major risk factor for ESRD.[4-6] Further, recent studies have reported a high prevalence of aTRH among individuals with CKD.[7-9] aTRH has been associated with increased risk of coronary heart disease, stroke, all-cause mortality and, in small clinic-based samples, ESRD. [9,10] However, few data are available on ESRD risk in a large, population-based sample of persons with aTRH. The goal of the current analysis was to determine whether individuals with aTRH have an increased risk for ESRD. To do so, we analyzed data from adults participating in the REasons for Geographic And Racial Differences in Stroke (REGARDS) study.

Methods

Study Participants

The REGARDS study enrolled a population-based sample of black and white US adults ≥ 45 years of age.[11] Between June 2003 and October 2007, 30,239 black and white US adults ≥ 45 years of age were enrolled from the 48 contiguous US states and the

District of Columbia.[11] Participants with hypertension who were taking ≥ 1 class of antihypertensive medication and did not have prevalent ESRD at baseline (n=14,734) formed the base population for the present analysis. Prevalent ESRD was defined by self-report of receipt of dialysis or an ESRD incidence date in the USRDS prior to REGARDS in-home visit date. Those missing BP data, serum creatinine, albumin-to-creatinine ratio (ACR), or information on medications they were taking (n=1,295) were excluded from all analyses. We also excluded participants with uncontrolled BP on 1 or 2 antihypertensive medication classes (n=3,465) from the main analyses, as we were unable to determine whether these participants had aTRH. As described below, these participants were included in sensitivity analyses. After these exclusion criteria were applied, data from 9,974 hypertensive participants were included in the main analyses. The REGARDS study protocol was approved by the institutional review boards governing research in human subjects at the participating centers and all participants provided written consent.

Data Collection

Baseline REGARDS study data were collected through a computer-assisted telephone interview, an in-home examination conducted in the morning, and self-administered questionnaires. Of relevance to the current analysis, information on the following demographic, behavioral and medical history characteristics was collected during the telephone interview: age, sex, race, region of residence, education, annual household income, smoking status, alcohol consumption, frequency of physical activity, and a history of diabetes, stroke, or myocardial infarction (MI). Medication adherence

was assessed using the 4-item Morisky Medication Adherence Scale (MMAS).

During the in-home examination, two BP measurements were made by trained personnel using standardized protocols. Also, an electrocardiogram was obtained, waist circumference was measured, and blood and urine samples were collected and sent to a central laboratory for analysis. A pill bottle review was conducted to record the names of all prescription and over-the-counter medications participants reported taking during the 2 weeks preceding the in-home study visit. Total and high-density lipoprotein (HDL) cholesterol were measured by colorimetric reflectance spectrophotometry and high sensitivity C-reactive protein was measured using a high-sensitivity particle-enhanced immunonephelometric assay. Serum glucose was measured by colorimetric reflectance spectrophotometry on the Ortho Vitros 950 IRC Clinical Analyzer (Johnson & Johnson Clinical Diagnostics), and diabetes was defined as a fasting serum glucose ≥ 126 mg/dL, non-fasting serum glucose ≥ 200 mg/dL, or use of antidiabetes medication. Serum creatinine was measured using an isotope-dilution mass spectrometry (IDMS) traceable method. Estimated glomerular filtration rate (eGFR) was calculated via the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation[12] and categorized as ≥ 60, 45-59, or < 45 mL/min/1.73 m^2. Urinary albumin was measured with the BN ProSpec Nephelometer from Dade Behring (Marburg, Germany) and urinary creatinine was measured with a rate-blanked Jaffé procedure, using the Modular-P analyzer (Roche/Hitachi; Indianapolis, IN). ACR was categorized as < 30 or ≥ 30 mg/g.

Definition of aTRH

During the in-home examination, BP was measured twice by trained technicians following a standardized protocol using aneroid sphygmomanometers. Participants were asked to sit quietly for 5 minutes with both feet on the floor prior to the BP measurements. Measurements were taken using an appropriately sized cuff, which was inflated to 20 mmHg above the pulse obliteration level and slowly deflated. After a 30 second rest period, this process was repeated on the same arm to obtain the second BP measurement.[13] Quality control for BP measurement in REGARDS was monitored by central examination of digit preference and technicians were retrained as necessary.[11] The two BP measurements were averaged for analysis. Uncontrolled BP was defined as systolic BP ≥ 140 mmHg and/or diastolic BP ≥ 90 mmHg except for individuals with an ACR ≥ 30 mg/g wherein uncontrolled BP was defined as systolic BP ≥ 130 mmHg and/or diastolic BP ≥ 80 mmHg.[14] Medication names recorded during the pill bottle review were coded into generic drug names and subsequently grouped into drug classes. One-pill combinations were classified into multiple medication classes. Each generic drug name was counted in only one class. Drug dose was not recorded. Antihypertensive medication classes were defined using the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7).[15] aTRH was defined as uncontrolled BP with concurrent use of 3 antihypertensive medication classes including a diuretic or use of ≥ 4 antihypertensive medication classes including a diuretic, regardless of BP level. In the main analyses, the comparison group (i.e. "no aTRH") was comprised of participants with controlled BP on 3 or fewer classes of antihypertensive medication. In sensitivity analyses, the comparison

group also included participants with uncontrolled BP on 1 or 2 classes of antihypertensive medication.

Definition of ESRD

Incident cases of ESRD were identified through linkage of REGARDS study participants with the USRDS, which records virtually all incident ESRD cases in the United States. A finder file with unique individual identifiers (name, social security number, and date of birth) was submitted for linkage with the USRDS. Different configurations of full and partial individual identifiers were then sequentially matched. For participants with a partial match to the USRDS, the nonmatching variables were visually inspected to confirm a valid match could not be made. Data from the USRDS included all incident ESRD cases, regardless of treatment modality, through September 30, 2011. For participants not developing ESRD, follow up time ended on their date of death (ascertained through death certificates, National Death Index data, or Social Security Death Index) or, for those who remained alive, September 30, 2011.

Statistical Analysis

Baseline characteristics of REGARDS participants were calculated by aTRH status. The cumulative incidence of ESRD was calculated using the Kaplan-Meier method for participants with and without aTRH. Next, using Cox proportional hazards regression models, the crude; age, race-, sex-adjusted; and multivariable adjusted hazard ratios for ESRD associated with aTRH were calculated for the overall population and for subgroups defined by age, race, sex, history of diabetes, MI, and stroke. Multivariable

adjustment included age, race, sex, region of residence, education, income, physical activity, current smoking, alcohol use, statin use, waist circumference, diabetes, total cholesterol, high-density lipoprotein cholesterol, c-reactive protein, and history of MI and stroke.

We did not adjust for ACR or eGFR in the main analyses, since they may be in the causal pathway between aTRH and ESRD.[16-18] Instead, we calculated multivariable adjusted hazard ratios for ESRD associated with aTRH stratified by level of baseline ACR (< 30 or ≥ 30 mg/g) and baseline eGFR (≥ 60, 45 – 59, and < 45 mL/min/1.73 m^2). To reduce model over-fitting in these stratified analyses, we calculated each participant's propensity (i.e. predicted probability) for having aTRH based on variables in the multivariable adjusted model described above. We then adjusted for this propensity in the regression model rather than adjusting for each covariate individually. In sensitivity analyses, we calculated the incidence rates and hazard ratios for ESRD associated with aTRH (1) limited to participants with perfect medication adherence, defined by appropriate medication-taking behaviors on all four MMAS items, (2) including the 3,465 participants with uncontrolled BP on 1 or 2 classes of antihypertensive medication in the analysis and categorizing this group as not having aTRH, and (3) including adjustment for ACR and eGFR in a final multivariable model. Also, we calculated incidence rates and hazard ratios for ESRD comparing participants with aTRH and controlled BP and, separately, with uncontrolled BP to participants without aTRH. Hazard ratios for ESRD were also calculated for those with aTRH comparing participants with uncontrolled versus controlled BP. All analyses were conducted using SAS version 9.2 (SAS Institute, Cary, NC).

Results

Participant Characteristics

After excluding participants with uncontrolled BP on 1 or 2 classes of antihypertensive medication, 21.5% of REGARDS study participants with hypertension had aTRH. Participants with aTRH were older on average than their counterparts without aTRH and more likely to be black, have an annual household income < $20,000, less than a high school education, use statins, and have diabetes or a history of MI or stroke (Table 1). Those with aTRH were less likely to be female, to consume alcohol or to participate in physical activity. On average, participants with aTRH had a larger waist circumference and higher systolic and diastolic BP and ACR and lower total cholesterol, HDL cholesterol, and eGFR than those without aTRH. Details on the number and classes of antihypertensive medications being taken by participants with and without aTRH are provided in Table 2.

ATRH and Incident ESRD

Over a median follow-up of 6.4 years (maximum: 8.6 years), 152 participants developed ESRD. Of the 152 cases of incident ESRD, 110 (72%) had aTRH at the baseline study visit. The cumulative incidence of ESRD was higher for participants with versus without aTRH (Figure 1). The incidence of ESRD was 8.86 (95% CI: 7.35, 10.68) per 1,000 person-years and 0.88 (95% CI: 0.65, 1.19) per 1,000 person-years among participants with and without aTRH, respectively (Table 3). This association was present after age, race, sex and multivariable adjustment and in sub-groups defined by age, race,

gender, and a history of diabetes, MI, or stroke (Figure 2). Results were similar when analyses were limited to participants with perfect medication adherence and when participants with uncontrolled BP on 1 or 2 classes of antihypertensive medication were included in the analysis as not having aTRH; however, aTRH was not associated with ESRD after multivariable adjustment including ACR and eGFR [hazard ratio 1.39 (95% CI: 0.92, 2.11); Table 4].

For both participants with and without aTRH, ESRD incidence increased as level of ACR increased and eGFR decreased (Table 5). Additionally, within each ACR and eGFR category, the crude ESRD incidence rate was higher among participants with versus without aTRH. The propensity adjusted hazard ratios for ESRD associated with aTRH among those with ACR levels < 30 and ≥ 30 mg/g were 1.55 (95% CI: 0.61, 3.94) and 2.54 (95% CI: 1.61, 4.00), respectively. The propensity adjusted hazard ratios for ESRD comparing participants with and without aTRH were 3.57 (95% CI: 1.58, 8.07), 6.53 (95% CI: 1.86, 22.96), and 3.22 (95% CI: 2.01, 5.15) for participants with eGFR ≥ 60, 45 – 59, and < 45 mL/min/1.73m^2, respectively.

ESRD Associated with Controlled and Uncontrolled BP

Characteristics of the study population with aTRH by BP control are shown in Table 6. Participants with aTRH and controlled BP and aTRH with uncontrolled BP each had a higher risk of ESRD when compared to participants without aTRH (Table 7). After multivariable adjustment and compared to those without aTRH, the hazard ratios (95% CI) for ESRD were 2.89 (1.52, 5.47) and 7.68 (5.18, 11.40) for those with aTRH and controlled and uncontrolled BP, respectively. After multivariable adjustment and

compared to those with aTRH and controlled BP, the hazard ratio for ESRD was 2.69 (95% CI: 1.49, 4.86) for participants with aTRH and uncontrolled BP (Table 8).

Discussion

Using data from a large, population-based sample of black and white adults, we found a strong association between aTRH and incident ESRD, which persisted after multivariable adjustment. The incidence rate of ESRD among people with aTRH in this population-based study (8.86 per 1,000 person-years) is over two times higher than USRDS estimates for blacks with diabetes (4.0 per 1,000 population), a population which has historically been considered at especially high risk of ESRD.[3] Additionally, although 22% of REGARDS participants had aTRH at baseline, 72% of those who went on to develop ESRD during follow-up had aTRH at their baseline study visit. These data suggest that aTRH may be an important marker for increased ESRD risk.

The association between aTRH and ESRD has been examined in clinic-based studies.[7,9] De Nicola and colleagues reported aTRH to be associated with increased risk of the composite outcome of dialysis, transplantation, or death over a median 37.6 months of follow-up [hazard ratio: 1.85 (95% CI: 1.13, 3.03)] among 300 patients with CKD.[7] More recently, the same group reported an increased risk for cardiovascular events and renal events among 436 clinic patients with aTRH over 57 months of follow-up [hazard ratio (95% CI): 1.98 (1.14, 3.43) and 2.66 (1.62, 4.37), respectively].[9] Also, in a study of individuals enrolled in the international REduction of Atherothrombosis for Continued Health (REACH) registry, aTRH versus no aTRH was associated with a multivariable adjusted hazard ratio of 1.11 (95% CI: 1.02, 1.20) for the composite

outcome of cardiovascular death, MI, or stroke.[19]

In the current study, aTRH, regardless of BP control, was associated with an increased risk for ESRD. Furthermore, aTRH with uncontrolled BP was associated with an increased risk for ESRD compared to aTRH with controlled BP, suggesting that, among individuals with CKD, prevention of aTRH and achieving BP control among those with aTRH are important. Achieving BP control is a major challenge in the management of individuals with CKD;[20] however, prior studies suggest that, with appropriate interventions, BP control can be achieved and maintained even in difficult to control populations.[21-24] Additionally, randomized controlled trials have demonstrated that, among individuals with aTRH, catheter-based renal denervation can reduce BP in individuals without major adverse effects or changes in renal function.[25,26] However, the optimal BP goal for reducing cardiovascular disease and renal outcomes is unclear and whether renal denervation slows the progression of CKD is not known. A small randomized trial demonstrated that reductions in dietary sodium are associated with lower BP among individuals with aTRH.[27] Data from randomized trials are needed to assess the benefits of reducing dietary sodium intake on cardiovascular outcomes among individuals with aTRH.

The findings of the current study emphasize the need for appropriate clinical management strategies to lower BP among individuals with aTRH. The American Heart Association (AHA) scientific statement on aTRH diagnosis, evaluation, and treatment recommends diuretics as first-line therapy for persons with hypertension, with the subsequent addition of an ACE inhibitor or angiotensin receptor blocker (ARB) and then a calcium channel blocker, as needed to achieve BP control.[1] Furthermore, among

individuals with aTRH, clinical trials indicate that the addition of an aldosterone antagonist lowers systolic BP by 20 to 25 mm Hg and diastolic BP by 10 to 15 mmHg.[28,29] However, in the current study, less than 10% of individuals with aTRH were taking an aldosterone antagonist. Ineffective antihypertensive therapy, including sub-optimal drug combination strategies, constitutes a barrier to BP control. Comparative effectiveness studies are needed to test the effects of different multi-drug medication regimens on BP, cardiovascular and renal disease outcomes in individuals with aTRH.

Our study minimizes misclassification of the aTRH phenotype through the use of a pill-bottle review to identify the number of antihypertensive medication classes being taken, standardized in-home BP measurement, and assessment of medication adherence. Other strengths include the large, population-based sample of blacks and whites and the availability of linkage with the USRDS which captures virtually all incident ESRD cases in the US. However, the findings of the current study should be considered in the context of certain limitations. BP, eGFR, and albuminuria were assessed at a single time point, making misclassification of CKD and aTRH status possible. An additional limitation is the lack of medication dosing information. Some individuals may have been on an inadequate treatment regimen and not truly treatment-resistant. Ambulatory BP monitoring was not available to rule out white-coat hypertension. Also, we do not have data on potential secondary causes of aTRH or genetic data to investigate the potential contribution of disease-promoting haplotypes. In the current study, the association between aTRH and ESRD was attenuated by adjustment for ACR and reduced eGFR, suggesting that these are either confounders or mediators between aTRH and ESRD risk. Given the strong association between hypertension, reduced eGFR, and albuminuria, it is

possible that albuminuria and reduced eGFR may be in the causal pathway between aTRH and ESRD risk.[30] However, given the data currently available in the REGARDS study, we cannot exclude the possibility that they are confounders.

In conclusion, data from the current study demonstrate an increased risk for ESRD among individuals with aTRH. Additionally, a substantial proportion of participants who developed ESRD had aTRH at baseline. Strategies are needed to prevent and treat aTRH in an effort to reduce the incidence of ESRD.

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Table 1. Characteristics of REasons for Geographic And Racial Differences in Stroke (REGARDS) study participants with and without apparent treatment-resistant hypertension (aTRH).

	No aTRH (n=7,827)	aTRH (n=2,147)	p-value
Age, years	65.4 (8.9)	67.5 (8.6)	<0.001
Female gender, %	58.9	50.3	<0.001
Black race, %	45.3	59.1	<0.001
Region, % Non-belt Belt Buckle	 42.4 35.2 22.4	 44.7 34.5 20.9	0.137
Income <$20,000, %	18.2	25.0	<0.001
Less than high school education, %	13.0	19.7	<0.001
Current smoking, %	12.8	11.9	0.275
Current alcohol use, %	34.5	31.0	0.003
Perfect medication adherence, %	70.6	67.1	0.001
Physical activity, % 4+ times per week 1 to 3 times per week None	 27.8 35.9 36.3	 23.9 33.3 42.8	<0.001
Waist circumference, cm	97.6 (14.8)	104.2 (16.2)	<0.001
Statin use, %	42.2	52.5	<0.001
Diabetes, %	24.7	45.6	<0.001
History of MI, %	14.4	25.1	<0.001
History of stroke, %	7.5	13.4	<0.001
Total cholesterol, mg/dL	186.0 (38.7)	180.4 (38.8)	<0.001
HDL-cholesterol, mg/dL	50.9 (15.8)	48.2 (15.0)	<0.001
C-reactive protein, mg/L	2.5 (1.1, 5.7)	2.9 (1.3, 6.5)	0.001
Systolic BP, mmHg	122.4 (9.8)	141.0 (17.7)	<0.001
Diastolic BP, mmHg	74.3 (7.7)	79.8 (11.3)	<0.001
eGFR, mL/min/1.73m^2	84.2 (19.5)	74.8 (23.9)	<0.001
ACR, mg/g	7.0 (4.6, 12.5)	17.4 (7.1, 74.7)	<0.001

MI: myocardial infarction; HDL: high-density lipoprotein; eGFR: estimated glomerular filtration rate; ACR: albumin-to-creatinine ratio

Numbers in table are mean (standard deviation) or percent, except c-reactive protein and ACR, which are presented as median (25th percentile, 75th percentile).

Table 2. Number of antihypertensive medication classes being taken and percent of REasons for Geographic And Racial Differences in Stroke (REGARDS) participants taking each class of medication

	No aTRH (n=7,827)	aTRH (n=2,147)
Antihypertensive medication classes Mean (SD)	1.8 (0.7)	3.6 (0.6)
Aldosterone antagonist, %	1.3	7.2
Alpha blocker, %	4.2	15.2
Angiotensin converting enzyme (ACE) inhibitor, %	39.2	61.4
Angiotensin receptor blocker (ARB), %	24.8	39.8
Beta blocker, %	31.4	71.0
Calcium channel blocker, %	31.6	71.1
Central acting agent, %	0.2	1.1
Diuretic, %	51.2	86.2
Vasodilator, %	0.3	2.8

aTRH: apparent treatment-resistant hypertension

Table 3. Incidence rates and hazard ratios for end-stage renal disease associated with apparent treatment-resistant hypertension (aTRH) among REasons for Geographic And Racial Differences in Stroke (REGARDS) study participants

	No aTRH	aTRH
N (at risk)	7,827	2,147
ESRD events, N (%)	42 (0.54)	110 (5.12)
ESRD incidence rate (95% CI)	0.88 (0.65, 1.19)	8.86 (7.35, 10.68)
Hazard ratio (95% CI) for ESRD		
Crude	1 (ref)	10.06 (7.05, 14.36)
Age, race, sex-adjusted	1 (ref)	8.34 (5.82, 11.96)
Multivariable adjusted[1]	1 (ref)	6.32 (4.30, 9.30)

ESRD: end-stage renal disease

[1]Adjusted for age, race, sex, region of residence, education, income, physical activity, current smoking, alcohol use, statin use, waist circumference, diabetes, total cholesterol, high-density lipoprotein cholesterol, c-reactive protein, history of myocardial infarction, and history of stroke.

Incidence rates are per 1,000 person-years.

Table 4. Sensitivity analyses on the incidence rates and hazard ratios for end-stage renal disease associated with apparent treatment-resistant hypertension (aTRH) among REasons for Geographic And Racial Differences in Stroke (REGARDS) study participants

	No aTRH	aTRH
Limited to individuals with perfect medication adherence[†]		
N (at risk)	5,395	1,412
ESRD events, N (%)	29 (0.54)	67 (4.75)
ESRD incidence rate (per 1,000 person-years)	0.88 (0.61, 1.27)	8.21 (6.46, 10.43)
Hazard ratio (95% CI) for ESRD		
Crude	1 (ref)	9.36 (6.05, 14.47)
Age, race, sex-adjusted	1 (ref)	7.49 (4.81, 11.64)
Multivariable adjusted[1]	1 (ref)	5.50 (3.43, 8.80)
Including individuals with uncontrolled BP on 1 or 2 classes of antihypertensive medication		
N (at risk)	11,292	2,147
ESRD events, N (%)	129 (1.14)	110 (5.12)
ESRD incidence rate (per 1,000 person-years)	1.88 (1.58, 2.23)	8.86 (7.35, 10.68)
Hazard ratio (95% CI) for ESRD		
Crude	1 (ref)	4.73 (3.67, 6.10)
Age, race, sex-adjusted	1 (ref)	4.09 (3.16, 5.29)
Multivariable adjusted[1]	1 (ref)	3.15 (2.39, 4.15)
Including adjustment for albumin-to-creatinine ratio and estimated glomerular filtration rate		
N (at risk)	7,827	2,147
ESRD events, N (%)	42 (0.54)	110 (5.12)
ESRD incidence rate (per 1,000 person-years)	0.88 (0.65, 1.19)	8.86 (7.35, 10.68)
Hazard ratio (95% CI) for ESRD		
Crude	1 (ref)	10.06 (7.05, 14.36)
Age, race, sex-adjusted	1 (ref)	8.34 (5.82, 11.96)
Multivariable adjusted[2]	1 (ref)	1.39 (0.92, 2.11)

ESRD: end-stage renal disease

[†]Defined as a score of 0 on the 4-item Morisky medication adherence scale

[‡]Defined as systolic or diastolic BP that remains above goal despite concurrent use of ≥ 2 antihypertensive medication classes plus a diuretic or use of ≥ 3 antihypertensive medication classes plus a diuretic, regardless of BP level

[1]Adjusted for age, race, sex, region of residence, education, income, physical activity, current smoking, alcohol use, statin use, waist circumference, diabetes, total cholesterol, high-density lipoprotein cholesterol, c-reactive protein, history of myocardial infarction, and history of stroke.

[2]Adjusted for model 1 plus albumin-to-creatinine ratio (log transformed) and estimated glomerular filtration rate

Table 5. Incidence rates and hazard ratios for end-stage renal disease associated with apparent treatment-resistant hypertension (aTRH) among REasons for Geographic And Racial Differences in Stroke (REGARDS) study participants, stratified by level of albumin-to-creatinine ratio and estimated glomerular filtration rate

	No aTRH		aTRH		
	N events/ N at risk	Incidence rate (95%CI)	N events/ N at risk	Incidence rate (95% CI)	Propensity adjusted[†] hazard ratio (95% CI)
ACR, mg/g					
< 30	14/7,222	0.32 (0.19, 0.53)	9/1,289	1.14 (0.59, 2.19)	1.55 (0.61, 3.94)
≥ 30	28/605	8.20 (5.66, 11.88)	101/858	22.28 (18.33, 27.08)	2.54 (1.61, 4.00)
eGFR, mL/min/1.73m^2					
≥ 60	12/6,987	0.28 (0.16, 0.49)	16/1,549	1.70 (1.04, 2.78)	3.57 (1.58, 8.07)
45 – 59	3/564	0.91 (0.29, 2.82)	15/337	8.13 (4.90, 13.48)	6.53 (1.86, 22.96)
< 45	27/276	18.96 (13.00, 27.64)	79/261	66.66 (53.47, 83.10)	3.22 (2.01, 5.15)

ACR: albumin-to-creatinine ratio; eGFR: estimated glomerular filtration rate

Incidence rates are per 1,000 person-years

[†]Adjusted for predicted probability of treatment-resistant hypertension based on age, race, sex, region of residence, education, income, physical activity, current smoking, alcohol use, statin use, waist circumference, diabetes, total cholesterol, high-density lipoprotein cholesterol, c-reactive protein, history of myocardial infarction, and history of stroke.

Table 6. Characteristics of REasons for Geographic And Racial Differences in Stroke (REGARDS) study participants without apparent treatment-resistant hypertension (aTRH) and with controlled versus uncontrolled aTRH

	No aTRH (n=7,827)	aTRH with controlled BP (n=564)	aTRH with uncontrolled BP (n=1,583)
Age, years	65.4 (8.9)	67.4 (8.5)	67.6 (8.6)
Female gender, %	58.9	48.9	50.7
Black race, %	45.3	54.1	60.8
Region, %			
Non-belt	42.4	43.6	45.0
Belt	35.2	33.0	35.0
Buckle	22.4	23.4	20.0
Income <$20,000, %	18.2	20.6	26.5
Less than high school education, %	13.0	16.7	20.8
Current smoking, %	12.8	10.7	12.4
Current alcohol use, %	34.5	33.0	30.3
Perfect medication adherence, %	70.6	69.6	66.2
Physical activity, %			
4+ times per week	27.8	24.2	23.8
1 to 3 times per week	35.9	32.7	33.5
None	36.3	43.1	42.7
Waist circumference, cm	97.6 (14.8)	104.1 (16.0)	104.2 (16.3)
Statin use, %	42.2	56.9	51.0
Diabetes, %	24.7	44.2	46.1
History of MI, %	14.4	28.0	24.1
History of stroke, %	7.5	12.6	13.7
Total cholesterol, mg/dL	186.0 (38.7)	172.5 (36.9)	183.3 (39.1)
HDL-cholesterol, mg/dL	50.9 (15.8)	47.2 (15.1)	48.6 (15.0)
C-reactive protein, mg/L	2.5 (1.1, 5.7)	2.7 (1.2, 5.9)	3.1 (1.3, 6.7)
Systolic BP, mmHg	122.4 (9.8)	122.7 (10.6)	147.5 (14.9)
Diastolic BP, mmHg	74.3 (7.7)	72.2 (8.6)	82.5 (10.9)
eGFR, mL/min/1.73m^2	84.2 (19.5)	73.8 (22.6)	75.1 (24.3)
ACR, mg/g	7.0 (4.6, 12.5)	8.7 (4.9, 17.1)	27.7 (8.9, 109.0)

MI: myocardial infarction; HDL: high-density lipoprotein; eGFR: estimated glomerular filtration rate; ACR: albumin-to-creatinine ratio

Numbers in table are mean (standard deviation) or percent, except c-reactive protein and ACR, which are presented as median (25th percentile, 75th percentile).

Table 7. Incidence rates and hazard ratios for end-stage renal disease associated with controlled and uncontrolled blood pressure among REasons for Geographic And Racial Differences in Stroke (REGARDS) study participants with apparent treatment-resistant hypertension (aTRH)

	No aTRH	aTRH with controlled BP	aTRH with uncontrolled BP
N (at risk)	7,827	564	1,583
ESRD events, N (%)	42 (0.54)	13 (2.30)	97 (6.13)
ESRD incidence rate	0.88 (0.65, 1.19)	3.89 (2.26, 6.70)	10.68 (8.75, 13.04)
Hazard ratio (95% CI) for ESRD			
Crude	1 (ref)	4.42 (2.37, 8.23)	12.15 (8.46, 17.45)
Age, race, sex-adjusted	1 (ref)	3.83 (2.05, 7.15)	9.94 (6.88, 14.36)
Multivariable adjusted[1]	1 (ref)	2.89 (1.52, 5.47)	7.68 (5.18, 11.40)

ESRD: end-stage renal disease; BP: blood pressure

[1]Adjusted for age, race, sex, region of residence, education, income, physical activity, current smoking, alcohol use, statin use, waist circumference, diabetes, total cholesterol, high-density lipoprotein cholesterol, c-reactive protein, history of myocardial infarction, and history of stroke

Incidence rates are per 1,000 person-years

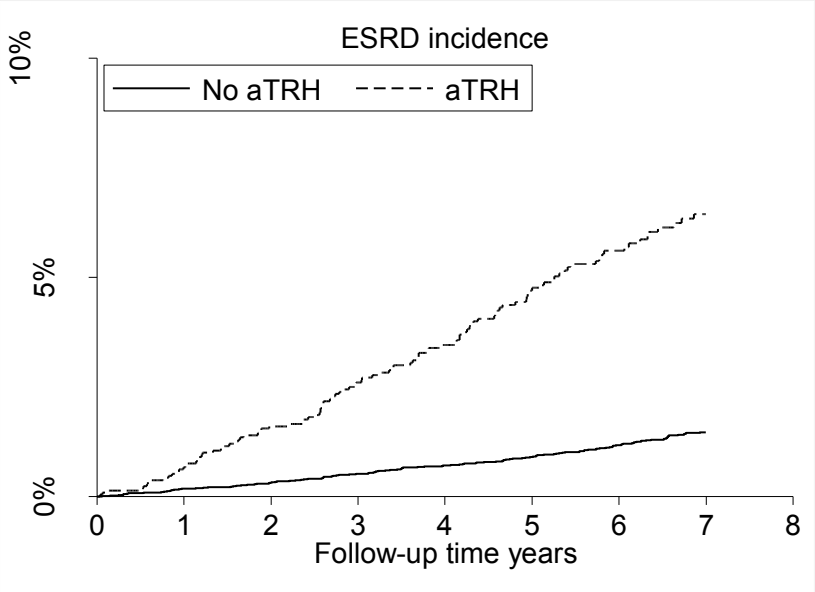
Table 8. Hazard ratios for incident end-stage renal disease associated with uncontrolled blood pressure among REasons for Geographic And Racial Differences in Stroke (REGARDS) study participants with apparent treatment-resistant hypertension (aTRH)

	aTRH with controlled BP	aTRH with uncontrolled BP
N (at risk)	564	1,583
ESRD events, N (%)	13 (2.30)	97 (6.13)
ESRD incidence rate (per 1,000 person-years)	3.89 (2.26, 6.70)	10.68 (8.75, 13.04)
Hazard ratio (95% CI) for ESRD		
Crude	1 (ref)	2.75 (1.54, 4.90)
Age, race, sex-adjusted	1 (ref)	2.59 (1.45, 4.63)
Multivariable adjusted[1]	1 (ref)	2.69 (1.49, 4.86)

ESRD: end-stage renal disease; BP: blood pressure

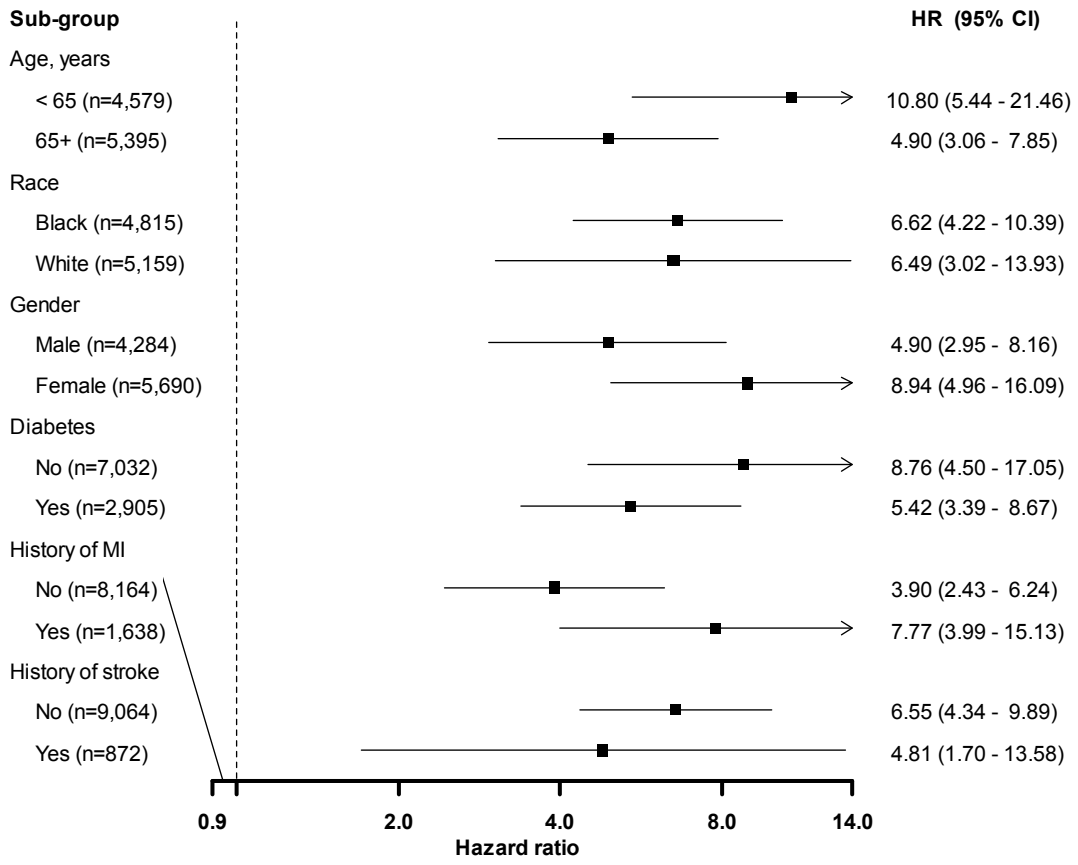
[†]Adjusted for age, race, sex, region of residence, education, income, physical activity, current smoking, alcohol use, waist circumference, diabetes, total cholesterol, high-density lipoprotein cholesterol, c-reactive protein, history of myocardial infarction, and history of stroke.

Figure 1. Cumulative incidence of end-stage renal disease associated with apparent treatment-resistant hypertension (aTRH)



ESRD: end-stage renal disease

Figure 2. Multivariable adjusted hazard ratios for incident end-stage renal disease associated with apparent treatment-resistant hypertension (aTRH) among REasons for Geographic And Racial Differences in Stroke (REGARDS) study participants, in subgroups



Hazard ratios adjusted for age, race, sex, region of residence, education, income, physical activity, current smoking, alcohol use, statin use, waist circumference, diabetes, total cholesterol, high-density lipoprotein cholesterol, c-reactive protein, history of myocardial infarction, and history of stroke.

ASSOCIATION BETWEEN 24-HOUR BLOOD PRESSURE VARIABILITY AND CHRONIC KIDNEY DISEASE AMONG AFRICAN AMERICANS PARTICIPATING IN THE JACKSON HEART STUDY

by

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ABSTRACT

Background

Prior studies suggest 24-hour blood pressure (BP) variability has prognostic value for cardiovascular disease. Several factors associated with high 24-hour BP variability are common among individuals with chronic kidney disease (CKD). We hypothesized 24-hour BP variability would be higher for individuals with versus without CKD.

Methods

We analyzed 1,022 Jackson Heart Study participants who underwent 24-hour ambulatory blood pressure monitoring (ABPM). BP variability was defined by two metrics: day-night standard deviation (SD_{dn}) and average real variability (ARV). CKD was defined as ACR ≥30 mg/g or eGFR <60 mL/min/1.73m^2.

Results

The mean SD_{dn} of SBP was 10.2 ± 0.2 mmHg and 9.1 ± 0.1 mmHg and the mean ARV of SBP was 9.2 ± 0.2 mmHg and 8.6 ± 0.1 mmHg for those with and without CKD, respectively (each p≤0.001). After adjustment for age and sex, SD_{dn} and ARV were 0.98 mmHg (95% CI 0.59, 1.38) and 0.52 mmHg (95% CI 0.18, 0.86), respectively, higher among participants with versus without CKD. These differences were not statistically significant after further multivariable adjustment including 24-hour mean SBP. Older age, larger waist circumference, and higher 24-hour mean SBP were associated with higher SD_{dn} and ARV of SBP among participants with CKD. Mean SD_{dn} and ARV of

DBP were higher for participants with versus without CKD but these associations were not present after multivariable adjustment.

Conclusions

Data from the current study suggest that CKD is associated with higher BP variability, but the association is explained by the higher mean BP among those with CKD.

Introduction

Over 19 million American adults have chronic kidney disease (CKD)[1], evidenced by estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m^2 or albumin-to-creatinine ratio (ACR) ≥ 30 mg/g. CKD is a significant public health challenge given its high prevalence and association with adverse outcomes, including cardiovascular disease (CVD) incidence and all-cause mortality.[2,3] Identifying factors that explain this increased risk may provide guidance on the development of interventions to reduce it.

Ambulatory blood pressure monitoring (ABPM) is useful for the identification of phenotypes that cannot be ascertained by blood pressure (BP) measurements in the clinic setting. This includes the identification of white coat hypertension, masked hypertension, circadian BP patterns, and 24-hour BP variability. Recent data have suggested that 24-hour BP variability has prognostic value for CVD and mortality independent of mean BP.[4-6] For example, Hansen, et. al. reported an association between higher 24-hour BP variability and increased risk for cardiovascular mortality and stroke in a pooled analysis of 11 studies.[4] Autonomic dysfunction has been proposed as a key factor underlying higher 24-hour BP variability.[7] Many individuals with CKD have autonomic dysfunction and other factors associated with high 24-hour BP variability including older age, higher mean systolic BP (SBP), and higher levels of inflammation are more common among individuals with CKD. [8-10] Therefore, we hypothesized that individuals with CKD would have higher 24-hour BP variability compared to their counterparts without CKD. To test this hypothesis, we conducted an analysis of African-American adults participating in the Jackson Heart Study.

Methods

Study Participants

The Jackson Heart Study is a community-based observational study of 5,301 African American adults recruited from urban and rural areas of 3 counties (Hinds, Madison, and Rankin) that comprise the Jackson, Mississippi metropolitan area. Baseline data collection occurred between September 2000 and March 2004. Details of the study design and recruitment have been published previously.[11-13] In brief, the study was designed to identify risk factors for CVD in African Americans. Individuals were selected for enrollment through a combination of drivers' license registries and commercially available lists. The final cohort includes 5,301 African American adults ≥ 21 years of age. The study protocol was approved by the Institutional Review Boards governing research in human subjects at the participating centers and all participants provided written consent.

Data Collection

Data used for the current analysis were collected through an in-home interview, a study examination after an overnight fast, and 24-hour ABPM. Information on age, sex, education, income, cigarette smoking, and a history of diabetes, stroke, or myocardial infarction were collected during the study interview. During the clinic visit, a standardized protocol was followed to obtain two BP measurements, waist circumference was measured, and blood and urine samples were collected. Information was recorded on all medications, vitamins, mineral supplements, and herbal or home remedies used within the two weeks prior to the participant's interview.[12]

Using the blood and urine samples collected during the clinic visit, total and high-density lipoprotein (HDL) cholesterol were assayed by the cholesterol oxidase method supplied by Boehringer Mannheim Diagnostics on a Roche COBAS Fara analyzer (Indianapolis, IN). Serum c-reactive protein was measured with a high-sensitivity immunoturbidimetric CRP-Latex assay (Kamiya Biomedical Company, Washington) and levels > 3 mg/L were defined as elevated. Urinary albumin was measured with the Dade Behring BN II nephelometer (Newark, Delaware). Serum and urine creatinine were measured using a multi-point enzymatic spectrophotometric assay on a Vitros 950 Ortho-Clinical Diagnostics analyzer (Raritan, New Jersey). Creatinine values were biochemically calibrated to Cleveland Clinic-equivalent Minnesota Beckman CX3 assay for analysis purposes.[14] eGFR was calculated via the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation,[15] and CKD was defined as ACR $\geq$ 30 mg/g or eGFR < 60 mL/min/1.73m^2.

During the clinic visit, BP was measured after a 5-minute rest with a Hawksley random zero sphygmomanometer equipped with one of four cuff sizes selected following measurement of each participant's arm circumference (Hawksley and Sons Ltd). The average of the 2 measures taken 1 minute apart was used to define clinic BP. Upon completion of the study visit, participants were asked to complete an ABPM over the next 24 hours. ABPM measurements were obtained with a portable, noninvasive oscillometric device (Spacelabs 90207; Medifacts International Ltd, Rockville, MD) with a cuff fitted to the participant's non-dominant arm. Trained technicians instructed participants in the proper use of the ABPM device. With the participant in the seated position, 3-5 simultaneous ABPM and office sphygmomanometer BP readings were

taken to calibrate the ABPM device. The device was programmed to measure BP every 20 minutes for 24 hours, and participants were instructed to proceed with their normal daily activities but keep their arm still and extended at their side during each BP reading. Participants returned to the clinic after 24 hours for the removal of the device. The monitor was connected to a computer and the BP readings were downloaded with commercially available software (Medicom, version 3.41; Medifacts Ltd). Quality control was assured by technician recertification, procedural checklists, and data review.[12,16-18]

Assessment of BP Variability

All BP readings were reviewed to eliminate out-of-range readings and errors due to motion artifacts or equipment problems, relying on predetermined acceptable ranges of SBP and DBP.[18] BP variability was defined by two metrics: day-night standard deviation (SD_{dn}) and average real variability (ARV). SD_{dn} was calculated as a weighted average of the daytime and nighttime standard deviation of SBP and diastolic BP (DBP), separately, during the ABPM period. The ARV was calculated for SBP and DBP, separately, as the mean of the absolute difference of consecutive BP measurements during the ABPM period.

Statistical Analysis

The current analysis was restricted to participants with valid ABPM data based on the International Database of Ambulatory Blood Pressure in relation to Cardiovascular Outcome (IDACO) criteria, which requires 10 daytime (defined as 10a-8p) and 5 nighttime (defined as 12p-6a) SBP and DBP measurements (N=1,046). Participants

missing clinic SBP (n=5), with ESRD at baseline (n=9), and without a serum creatinine measurement at baseline (n=10) were excluded. We used multiple imputation (n=10 data sets) and chained equations to impute ACR and other variables with missing data. Table 1 summarizes the percentage of participants with missing data prior to imputation. We included 1,022 Jackson Heart Study participants in the current analysis.

Participant characteristics and SD_{dn} and ARV of SBP and DBP were calculated for those with and without CKD, separately. The statistical significance of differences across groups were calculated using t-tests and chi-square tests, as appropriate. Next, using linear regression, we calculated the adjusted differences in SD_{dn} and ARV of SBP and DBP for participants with, versus without, CKD. Three levels of adjustment were performed. Initial models included adjustment for age and sex. A second model included age, sex, education, income, smoking status, waist circumference, diabetes, history of stroke, history of myocardial infarction, total cholesterol, HDL-cholesterol, c-reactive protein, statin use, and antihypertensive medication use. The full multivariable adjusted model included the variables in the second model and mean 24-hour SBP, in analyses of SD_{dn} and ARV of SBP, and mean 24-hour DBP, in analyses of SD_{dn} and ARV of DBP. Analyses were repeated comparing SD_{dn} and ARV of SBP and DBP between participants with eGFR less than versus greater than or equal to 60 ml/min/1.73 m^2 and ACR greater than or equal to versus less than 30 mg/g. Finally, for individuals with CKD, we calculated differences in SD_{dn} and ARV of SBP and DBP associated with each study covariate included in full multivariable adjusted models. All analyses were conducted using Stata Version 13 (Stata Corp. College Station, TX).

Results

Participant Characteristics

On average, compared to their counterparts without CKD, participants with CKD were older, had a larger waist circumference, and higher mean clinic and 24-hour SBP and DBP (Table 2). Also, participants with CKD had lower HDL-cholesterol compared to those without CKD. Those with CKD were more likely to have less than a high school education, diabetes, and a history of stroke.

CKD and SD_{dn} and ARV of SBP

SD_{dn} of SBP was higher among participants with versus without CKD (Table 3, top panel). After age and sex-adjustment and further adjustment for education, income, smoking status, waist circumference, diabetes, history of stroke, history of myocardial infarction, total cholesterol, HDL-cholesterol, c-reactive protein, statin use, and antihypertensive medication use, SD_{dn} of SBP was higher for participants with versus without CKD. The difference in SD_{dn} of SBP for those with, versus without, CKD was attenuated and not statistically significant after further adjustment for mean 24-hour SBP. ARV of SBP was higher for those with versus without CKD after age and sex adjustment, but this difference was attenuated and no longer statistically significant after further multivariable adjustment.

SD_{dn} and ARV of SBP were higher among participants with ACR $\geq$ 30 mg/g versus their counterparts with ACR < 30 mg/g (Table 3, middle panel). These associations were attenuated and no longer statistically significant after multivariable adjustment including mean 24-hour SBP. SD_{dn} and ARV of SBP were higher for

participants with eGFR < 60 mL/min/1.73m^2 compared to their counterparts with eGFR ≥ 60 mL/min/1.73m^2 (Table 3, bottom panel). These differences were attenuated and no longer statistically significant after adjustment for age and sex or further multivariable adjustment.

Among participants with CKD, older age, larger waist circumference, and higher 24-hour SBP were associated with higher SD_{dn} and ARV of SBP (Table 4). Total cholesterol was associated with higher SD_{dn} of SBP but not ARV of SBP. Higher HDL-cholesterol was associated with lower ARV of SBP among those with CKD.

CKD and SD_{dn} and ARV of DBP

SD_{dn} and ARV of DBP were higher for participants with versus without CKD (Table 5, top panel). SD_{dn} of DBP was higher for participants with versus without CKD after age, sex-adjustment and after further adjustment for education, income, smoking status, waist circumference, diabetes, history of stroke, history of myocardial infarction, total and HDL-cholesterol, c-reactive protein, statin use, and antihypertensive medication use. However, this association was attenuated and not statistically significant after adjustment for mean 24-hour DBP. The age and sex-adjusted mean difference in ARV of DBP was higher for individuals with CKD compared to those without CKD, but this association was no longer statistically significant after further multivariable adjustment. Compared to those with ACR < 30 mg/g, participants with ACR ≥ 30 mg/g had higher SD_{dn} of DBP and ARV of DBP (Table 5, middle panel). This association was no longer statistically significant after multivariable adjustment including mean 24-hour DBP. Differences in SD_{dn} of DBP and ARV of DBP between participants with eGFR < and ≥

60 mL/min/1.73m^2 were small and not statistically significant before or after multivariable adjustment (Table 5, bottom panel).

Among participants with CKD, larger waist circumference and higher 24-hour DBP were associated with higher SD_{dn} and ARV of DBP (Table 6). Female gender was associated with lower ARV of DBP among those with CKD.

Discussion

In this population-based sample of African American adults, CKD was associated with higher SD_{dn} of BP and ARV of DBP. However, these associations were explained by the higher mean 24-hour BP among participants with CKD. Older age, larger waist circumference, and higher mean 24-hour SBP were associated with higher SBP variability. Female gender, larger waist circumference, and higher mean 24-hour DBP were associated with higher DBP variability.

Twenty-four hour BP variability has been associated with adverse outcomes and may represent a novel CVD risk factor. In a pooled analysis of 11 studies, Hansen, et al. reported that ARV of BP was associated with total and cardiovascular mortality (hazard ratio [HR] for ARV of SBP: 1.11 (95% confidence interval [CI]: 1.04 – 1.18) and 1.17 (95% CI: 1.07 – 1.28), respectively; hazard ratio for ARV of DBP: 1.13 (95% CI: 1.07 – 1.19) and 1.21 (95% CI: 1.12 – 1.31), respectively).[4] Additionally, Eguchi, et al. reported SD of nighttime SBP to be an independent risk factor for the composite outcome of stroke, myocardial infarction, or sudden cardiac death (HR: 2.21; 95% CI 1.08 – 4.53).[19]

Long-term BP variability (i.e. "visit-to-visit" variability) has been associated with adverse outcomes among individuals with CKD in several studies.[20-23] For example, in

an analysis of 374 elderly patients with CKD, DiIorio, et al. reported that each 1% increase in BP variability was associated with a higher risk for all-cause mortality (hazard ratio: 1.05 (95% CI: 1.02 – 1.09).[20] In an analysis of the African American Study of Kidney Disease (AASK) trial, McMullan, et al. found an association between tertile of BP variability with all-cause mortality and cardiovascular mortality (hazard ratio comparing highest with lowest tertile of BP variability: 2.82 (95% CI: 1.14 – 6.95) and 4.91 (95% CI: 1.12 – 21.50), respectively).[21] Though not extensively studied, 24-hour BP variability has been associated with target organ damage among individuals with CKD in at least one study. Ryu, et al. reported that ARV of SBP was associated with left ventricular hypertrophy (odds ratio: 1.05 (95% CI: 1.02 – 1.09)), but not kidney injury (defined as eGFR <30 mL/min/1.73m^2 and proteinuria) in a large sample of hypertensive CKD patients in Korea.[24]

In the current analysis, CKD was associated with higher 24-hour BP variability, but this association was no longer present after adjustment for mean 24-hour BP. The direction of the association between mean BP and BP variability is unclear. For example, higher mean BP and its associated sequelae (e.g., arterial stiffness) could lead to higher BP variability. Alternatively, higher BP variability could cause vascular injury, making BP harder to control. Given the cross-sectional nature of our analysis, future studies with longitudinal ABPM assessments could prove helpful for characterizing this association. Autonomic imbalance is a characteristic of BP variability which has also been associated with CKD progression[25] and may suggest a potential physiologic mechanism for the association between 24-hour variability and CKD. Sympathetic nerve terminals innervate the kidneys directly, potentially affecting tubular function by enhancing solute and fluid

resorption and modifying renal microvascular function by enhancing the effects of angiotensin.[25-27] Additionally, several CVD risk factors which adversely affect the glomerulus (e.g. endothelial dysfunction, dyslipidemia, insulin resistance, and oxidative stress) are also associated with high sympathetic and low parasympathetic tone, suggesting a potential mechanism involving the nervous system's role in regulating hemodynamics, vascular tone, metabolism, and inflammation.[25]

Our study maintains several strengths, most notably the large sample size of African American adults with available ABPM data and the availability of comprehensive data which allowed us to adjust for potential confounders. However, the current findings should be considered in the context of certain limitations. The analysis employed a cross-sectional study design. CKD is potentially a cause and a consequence of BP variability, and it is unknown whether BP variability preceded the development of CKD or whether CKD resulted in increased BP variability. Also, eGFR and albuminuria were only assessed at a single time point; misclassification of CKD status may be present. Finally, the applicability of our results to other race/ethnic groups needs to be assessed in other studies.

In conclusion, data from the current study suggest that CKD is associated with higher SD_{dn} of SBP and DBP and ARV of DBP. However, these associations were no longer present after adjustment for 24-hour mean BP. Further studies with repeated measurements of 24-hour BP variability and mean BP are needed to determine the direction of the association. Such data may be useful in identifying new therapeutic targets in an effort to improve health outcomes for individuals with CKD.

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Table 1. Summary of missing data prior to multiple imputation.

Characteristics	N (%) missing
Age, years	0 (0%)
Female gender, %	0 (0%)
Less than high school education, %	4 (0.4%)
Low income, %	117 (11.4%)
Diabetes, %	1 (0.1%)
History of stroke, %	0 (0%)
History of myocardial infarction, %	0 (0%)
Current smoking, %	0 (0%)
Waist circumference, cm	2 (0.2%)
Total cholesterol, mg/dL	67 (6.6%)
HDL-cholesterol, mg/dL	68 (6.7%)
C-reactive protein > 3 mg/L, %	2 (0.2%)
Mean clinic SBP, mmHg	0 (0%)
Mean clinic DBP, mmHg	0 (0%)
Mean 24-hour SBP, mmHg	0 (0%)
Mean 24-hour DBP, mmHg	0 (0%)
eGFR, mL/min/1.73m^2	0 (0%)
Albumin-to-creatinine ratio, mg/g	243 (23.8%)

HDL: high-density lipoprotein; SBP: systolic blood pressure; DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate

Table 2. Characteristics of Jackson Heart Study participants with and without chronic kidney disease

	No CKD (n=849)	CKD (n=173)	p-value
Age, years	58.9 (0.4)	60.8 (0.9)	0.041
Female gender, %	68.3	65.1	0.452
Less than high school education, %	18.1	26.7	0.022
Low income, %	10.8	15.6	0.142
Diabetes, %	21.2	40.6	<0.001
History of stroke, %	2.9	8.8	0.002
History of myocardial infarction, %	4.1	7.5	0.074
Current smoking, %	5.3	7.4	0.329
Waist circumference, cm	99.1 (0.5)	104.5 (1.3)	<0.001
Total cholesterol, mg/dL	200.7 (1.4)	205.0 (3.5)	0.242
HDL-cholesterol, mg/dL	54.1 (0.5)	51.5 (1.0)	0.043
C-reactive protein > 3 mg/L, %	46.7	52.1	0.213
Mean clinic SBP, mmHg	126.0 (0.6)	132.9 (1.6)	<0.001
Mean clinic DBP, mmHg	77.3 (0.4)	77.1 (0.9)	0.781
Mean 24-hour SBP, mmHg	125.0 (0.4)	132.7 (1.4)	<0.001
Mean 24-hour DBP, mmHg	73.8 (0.3)	76.2 (0.9)	0.004
eGFR, mL/min/1.73m^2	94.4 (0.6)	77.7 (2.4)	<0.001
Albumin-to-creatinine ratio, mg/g	5.5 (3.7, 9.4)	55.3 (22.9, 125.5)	<0.001

CKD: chronic kidney disease, defined as an estimated glomerular filtration rate < 60 mL/min/1.73m^2 or an albumin-to-creatinine ratio ≥ 30 mg/g; HDL: high-density lipoprotein; SBP: systolic blood pressure; DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate

Numbers in table are presented as mean (standard error) or percent except albumin-to-creatinine ratio, which is presented as median (interquartile range).

Table 3. Association of chronic kidney disease status, albumin-to-creatinine ratio, and estimated glomerular filtration rate with measures of systolic blood pressure variability

Chronic kidney disease status			
Blood pressure variability measure	No CKD (n=849)	CKD (n=173)	p-value
Day-night standard deviation			
Mean ± standard error	9.1 ± 0.1	10.2 ± 0.2	<0.001
Age, sex adjusted	0 (ref)	0.98 (0.59, 1.38)	<0.001
Multivariable adjusted 1†	0 (ref)	0.64 (0.19, 1.09)	0.005
Multivariable adjusted 2‡	0 (ref)	0.31 (-0.12, 0.74)	0.162
Average real variability			
Mean ± standard error	8.6 ± 0.1	9.2 ± 0.2	0.001
Age, sex adjusted	0 (ref)	0.52 (0.18, 0.86)	0.003
Multivariable adjusted 1†	0 (ref)	0.32 (-0.09, 0.72)	0.125
Multivariable adjusted 2‡	0 (ref)	0.08 (-0.31, 0.46)	0.695
Albumin-to-creatinine ratio, mg/g			
Blood pressure variability measure	ACR < 30 (n=885)	ACR ≥ 30 (n=137)	p-value
Day-night standard deviation			
Mean ± standard error	9.2 ± 0.1	10.2 ± 0.3	<0.001
Age, sex adjusted	0 (ref)	1.09 (0.65, 1.53)	<0.001
Multivariable adjusted 1†	0 (ref)	0.85 (0.33, 1.37)	0.001
Multivariable adjusted 2‡	0 (ref)	0.35 (-0.16, 0.85)	0.179
Average real variability			
Mean ± standard error	8.7 ± 0.1	9.2 ± 0.2	0.01
Age, sex adjusted	0 (ref)	0.57 (0.18, 0.95)	0.004
Multivariable adjusted 1†	0 (ref)	0.41 (-0.06, 0.89)	0.085
Multivariable adjusted 2‡	0 (ref)	0.05 (-0.41, 0.50)	0.844
Estimated glomerular filtration rate, mL/min/1.73m^2			
Blood pressure variability measure	eGFR ≥ 60 (n=960)	eGFR < 60 (n=62)	p-value
Day-night standard deviation			
Mean ± standard error	9.3 ± 0.1	10.4 ± 0.4	<0.001
Age, sex adjusted	0 (ref)	0.58 (-0.04, 1.20)	0.066
Multivariable adjusted 1†	0 (ref)	0.24 (-0.39, 0.86)	0.455
Multivariable adjusted 2‡	0 (ref)	0.17 (-0.42, 0.77)	0.565
Average real variability			
Mean ± standard error	8.7 ± 0.1	9.5 ± 0.2	0.004
Age, sex adjusted	0 (ref)	0.27 (-0.24, 0.78)	0.296
Multivariable adjusted 1†	0 (ref)	-0.01 (-0.54, 0.52)	0.981
Multivariable adjusted 2‡	0 (ref)	-0.05 (-0.56, 0.46)	0.842

†Adjusted for age, sex, education, income, smoking status, waist circumference, diabetes, history of stroke, history of myocardial infarction, total cholesterol, high-density lipoprotein cholesterol, c-reactive protein, statin use, and antihypertensive medication use.

‡Adjusted for above model 1 plus mean 24-hour systolic blood pressure.

CKD: chronic kidney disease, ACR: albumin-to-creatinine ratio, eGFR: estimated glomerular filtration rate

Table 4. Association of study covariates with systolic blood pressure variability among individuals with chronic kidney disease

Characteristic	Day-night standard deviation β-coefficient (95% CI)	Average real variability β-coefficient (95% CI)
Age, per 10 years	0.35 (0.19, 0.51)	0.40 (0.26, 0.53)
Female gender	-0.30 (-0.65, 0.05)	-0.23 (-0.53, 0.07)
Less than high school education	0.16 (-0.23, 0.54)	0.00 (-0.34, 0.33)
Low income	0.13 (-0.35, 0.61)	0.27 (-0.15, 0.69)
Current smoking	0.20 (-0.46, 0.85)	0.40 (-0.17, 0.97)
Waist circumference, per 15 cm	0.16 (0.01, 0.31)	0.20 (0.06, 0.33)
Diabetes	0.00 (-0.36, 0.36)	0.19 (-0.12, 0.50)
History of stroke	0.19 (-0.55, 0.92)	0.22 (-0.41, 0.85)
History of myocardial infarction	0.48 (-0.21, 1.16)	0.10 (-0.50, 0.69)
Total cholesterol, per 40 mg/dL	0.19 (0.03, 0.34)	0.10 (-0.03, 0.23)
HDL-cholesterol, per 15 mg/dL	-0.06 (-0.22, 0.10)	-0.14 (-0.29, 0.00)
C-reactive protein > 3 mg/L	-0.04 (-0.35, 0.27)	-0.18 (-0.28, 0.25)
Statin use	0.29 (-0.14, 0.72)	0.02 (-0.35, 0.39)
Antihypertensive medication use	0.18 (-0.14, 0.51)	0.05 (-0.24, 0.34)
24-hour systolic blood pressure, per 15 mmHg	0.84 (0.66, 1.01)	0.60 (0.45, 0.75)

CI: confidence interval

For each column above, all variables were included in a single multivariable model. Units for continuous variables represent one standard deviation.

Table 5. Association of chronic kidney disease status, albumin-to-creatinine ratio, and estimated glomerular filtration rate with measures of diastolic blood pressure variability

Chronic kidney disease status			
Blood pressure variability measure	No CKD (n=849)	CKD (n=173)	p-value
Day-night standard deviation			
Mean ± standard error	8.0 ± 0.1	8.5 ± 0.2	0.004
Age, sex adjusted	0 (ref)	0.54 (0.17, 0.90)	0.004
Multivariable adjusted 1†	0 (ref)	0.43 (0.00, 0.85)	0.049
Multivariable adjusted 2‡	0 (ref)	0.25 (-0.16, 0.66)	0.231
Average real variability			
Mean ± standard error	7.5 ± 0.1	7.9 ± 0.2	0.043
Age, sex adjusted	0 (ref)	0.37 (0.01, 0.72)	0.041
Multivariable adjusted 1†	0 (ref)	0.32 (-0.09, 0.72)	0.128
Multivariable adjusted 2‡	0 (ref)	0.19 (-0.21, 0.59)	0.351
Albumin-to-creatinine ratio, mg/g			
Blood pressure variability measure	ACR < 30 (n=885)	ACR ≥ 30 (n=137)	p-value
Day-night standard deviation			
Mean ± standard error	8.0 ± 0.1	8.6 ± 0.2	0.002
Age, sex adjusted	0 (ref)	0.64 (0.23, 1.06)	0.002
Multivariable adjusted 1†	0 (ref)	0.63 (0.13, 1.13)	0.013
Multivariable adjusted 2‡	0 (ref)	0.39 (-0.10, 0.87)	0.122
Average real variability			
Mean ± standard error	7.5 ± 0.1	8.1 ± 0.2	0.011
Age, sex adjusted	0 (ref)	0.53 (0.13, 0.93)	0.010
Multivariable adjusted 1†	0 (ref)	0.57 (0.09, 1.05)	0.021
Multivariable adjusted 2‡	0 (ref)	0.39 (-0.09, 0.87)	0.108
Estimated glomerular filtration rate, mL/min/1.73m^2			
Blood pressure variability measure	eGFR ≥ 60 (n=960)	eGFR < 60 (n=62)	p-value
Day-night standard deviation			
Mean ± standard error	8.1 ± 0.1	8.2 ± 0.3	0.572
Age, sex adjusted	0 (ref)	0.17 (-0.39, 0.72)	0.551
Multivariable adjusted 1†	0 (ref)	0.07 (-0.50, 0.64)	0.805
Multivariable adjusted 2‡	0 (ref)	0.01 (-0.55, 0.56)	0.977
Average real variability			
Mean ± standard error	7.6 ± 0.1	7.5 ± 0.2	0.655
Age, sex adjusted	0 (ref)	-0.13 (-0.66, 0.41)	0.641
Multivariable adjusted 1†	0 (ref)	-0.19 (-0.75, 0.36)	0.487
Multivariable adjusted 2‡	0 (ref)	-0.24 (-0.78, 0.30)	0.384

†Adjusted for age, sex, education, income, smoking status, waist circumference, diabetes, history of stroke, history of myocardial infarction, total cholesterol, high-density lipoprotein cholesterol, c-reactive protein, statin use, and antihypertensive medication use.

‡Adjusted for above model 1 plus mean 24-hour diastolic blood pressure.

CKD: chronic kidney disease, ACR: albumin-to-creatinine ratio, eGFR: estimated glomerular filtration rate

Table 6. Association of study covariates with diastolic blood pressure variability among individuals with chronic kidney disease

Characteristic	Day-night standard deviation β-coefficient (95% CI)	Average real variability β-coefficient (95% CI)
Age, per 10 years	0.10 (-0.5, 0.24)	0.14 (-0.01, 0.28)
Female gender	-0.32 (-0.66, 0.02)	-0.37 (-0.70, -0.03)
Less than high school education	-0.14 (-0.51, 0.22)	-0.25 (-0.61, 0.11)
Low income	0.36 (-0.11, 0.83)	0.36 (-0.10, 0.83)
Current smoking	0.25 (-0.37, 0.86)	0.32 (-0.28, 0.93)
Waist circumference, per 15 cm	0.43 (0.29, 0.57)	0.42 (0.28, 0.56)
Diabetes	-0.11 (-0.44, 0.22)	0.05 (-0.27, 0.38)
History of stroke	-0.13 (-0.81, 0.56)	-0.34 (-1.01, 0.33)
History of myocardial infarction	-0.04 (-0.68, 0.60)	-0.41 (-1.04, 0.22)
Total cholesterol, per 40 mg/dL	0.05 (-0.10, 0.19)	0.03 (-0.11, 0.17)
HDL-cholesterol, per 15 mg/dL	-0.02 (-0.17, 0.13)	-0.08 (-0.23, 0.06)
C-reactive protein > 3 mg/L	0.03 (-0.26, 0.32)	0.13 (-0.16, 0.41)
Statin use	-0.12 (-0.53, 0.28)	-0.17 (-0.56, 0.22)
Antihypertensive medication use	-0.08 (-0.39, 0.23)	-0.28 (-0.58, 0.03)
24-hour diastolic blood pressure, per 10 mmHg	0.54 (0.38, 0.71)	0.39 (0.23, 0.55)

CI: confidence interval

For each column above, all variables were included in a single multivariable model. Units for continuous variables represent one standard deviation.

INTER-ARM DIFFERENCES IN SEATED SYSTOLIC AND DIASTOLIC BLOOD PRESSURE AMONG ADULTS WITH CHRONIC KIDNEY DISEASE: THE HYPERTENSION GENETIC EPIDEMIOLOGY NETWORK (HYPERGEN) STUDY

by

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ABSTRACT

Background

Large inter-arm differences (IADs) in blood pressure (BP) are reproducible and associated with peripheral vascular disease and mortality. Furthermore, there is a high prevalence of peripheral vascular disease among individuals with chronic kidney disease (CKD). We hypothesized that individuals with CKD may have larger IADs in BP compared to those without CKD.

Methods

We included 4,324 participants in the population-based Hypertension Genetic Epidemiology Network (HyperGEN) study. Data were collected through an interview followed by a physical examination. A standardized protocol was used to obtain three BP measurements in each arm. Albuminuria was defined as albumin excretion rate ≥ 300 mg/day and reduced eGFR was defined as an eGFR < 60 mL/min/1.73m^2. CKD was defined as presence of albuminuria or reduced eGFR.

Results

When all three BP measurements were averaged, the absolute IADs in SBP were 9.4 mmHg and 8.7 mmHg among participants with and without CKD, respectively. The absolute IADs in DBP were 5.4 mmHg and 5.1 mmHg, respectively. Results were

consistent by albuminuria status and reduced eGFR status. Among those with CKD, the prevalence of IADs <10 mmHg, 10-20 mmHg, and ≥20 mmHg was 82.1%, 16.8%, and 1.2%, respectively, for SBP and 95.5%, 4.0%, and 0.5%, respectively, for DBP. After full multivariable adjustment, use of 3 or more antihypertensive medications was associated with a lower prevalence ratio for IADs in SBP ≥10 mmHg (prevalence ratio 0.13; 95% CI: 0.02, 0.94).

Conclusions

In conclusion, we observed small but insignificant IADs among individuals with CKD in a large, population-based sample of whites and African-Americans. Future studies are needed to explore the relationship between IADs in BP and CKD using standardized BP measurement protocols.

Introduction

Over 19 million American adults have chronic kidney disease (CKD)[1], evidenced by reduced estimated glomerular filtration rate (eGFR) or albuminuria. CKD is a significant public health challenge given its high prevalence and association with adverse outcomes, including cardiovascular disease (CVD), end-stage renal disease (ESRD), and all-cause mortality.[2,3] Identifying factors that explain this increased risk may provide guidance on the development of interventions to reduce it.

Large inter-arm differences (IADs) in blood pressure (BP) have been reported during routine physical examinations as early as 1920.[4] Now thought to be the result of subclavian stenosis, large IADs in BP have been shown in recent studies to be reproducible and associated with peripheral vascular disease and mortality.[5,6] Furthermore, there is a high prevalence of peripheral vascular disease among individuals with CKD.[7] Individuals with CKD may have larger IADs in BP compared to those without CKD and large IADs in BP may partially explain the excess mortality risk associated with CKD. To test this hypothesis, we conducted an analysis of data from the Hypertension Genetic Epidemiology Network (HyperGEN) study.

Methods

Study Participants

The HyperGEN study is a population-based multicenter study designed to investigate genetic and environmental determinants of hypertension in black and white adults. Details of the study design and recruitment have been published previously.[8] In brief, African American and non-Hispanic white participants were recruited from five field centers (Forsyth County, North Carolina; Minneapolis, Minnesota; Framingham,

Massachusetts; Salt Lake City, Utah; and Birmingham, Alabama). Participants were hypertensive (defined as BP ≥ 140/90 mmHg or use of antihypertensive medication) sibling pairs identified through population-based cohorts (Atherosclerosis Risk in Communities Study, NHLBI Family Heart Study, Utah Family Tree Study, and the Framingham Heart Study) and local hypertension clinics. A comparison group of unrelated subjects was also randomly selected from the source cohorts that generated the hypertensive siblings. Participants with type 1 diabetes or advanced renal disease (defined as serum creatinine level >2 mg/dL) were excluded from the study. In total, the HyperGEN study enrolled 2,407 hypertensive individuals from 917 sibships between September 1996 and August 1999.

Data Collection

Data were collected through an interview followed by a physical examination. Of relevance to the current study, the following data were collected during the interview: age, race, sex, smoking status, and medical history. During the examination, a standardized protocol was used to obtain three BP measurements in each arm. Also, blood and urine samples were collected and medication data were recorded for each participant.

Definition of CKD

Using the blood and urine samples collected during the physical exam, urinary albumin was measured by immunoterbidimetry using the DiaSorin antibody.[9] Serum

creatinine was measured by a thin-film adaptation of the amidohydrolase enzymatic method using the Vitros analyzer (Johnson & Johnson Clinical Diagnostics, Raritan, NJ).[10] eGFR was calculated via the CKD-EPI equation.[11] Albuminuria was defined as albumin excretion rate ≥ 300 mg/day and reduced eGFR was defined as an eGFR < 60 mL/min/1.73m^2. CKD was defined as presence of albuminuria or reduced eGFR.

BP Measurement

During the examination, BP was measured by certified technicians following a standardized protocol using an oscillometric blood pressure monitor (Dinamap 1846 SX/P; GE Healthcare, Waukesha, Wisconsin, USA). Prior to the measurements, subjects were seated alone in a quiet room for 5 minutes. Cuff size was chosen for each individual's right and left arm according to their mid-arm circumference, and the appropriate size cuff was used for each arm. Three BP readings were recorded in each arm with a 30 second rest interval between readings. The first arm tested was determined based on the birth date of the participant (e.g. for an odd date of birth, BP was measured in the left arm first). The order of measurement was determined by two different protocols, depending on the clinical center. In the first protocol, executed in four of the five centers, the order of measurements was as follows: if the first BP was measured in the right arm, the cuff tubing was switched to the left arm for two measurements, switched back to the right arm for the second and third right arm measurements, and then switched back to the left arm for the third left arm measurement. The second protocol, executed only in the Birmingham center, involved three BP measurements taken

consecutively in the first arm, followed by three consecutive measurements in the second arm. The BP measurement processes were regularly monitored to assure protocol adherence.[8,12,13]

Statistical Analysis

We excluded individuals missing demographic data or reporting a race other than white or black (n=11), missing urinary albumin or serum creatinine (n=337), and missing BP measurements (n=120), leaving 4,324 HyperGEN participants for the current analysis. IADs in BP were calculated as follows for both systolic BP (SBP) and diastolic BP (DBP): |(1^{st} right measure)-(1^{st} left measure)|, |(2^{nd} right measure)-(2^{nd} left measure)|, |(3^{rd} right measure)-(3^{rd} left measure)|, |(mean of right measures 1,2, and 3)-(mean of left measures 1,2, and 3)|, and |(mean of right measures 2 and 3)-(mean of left measures 2 and 3)|.[12] Mean values of continuous covariates and percentages of categorical covariates were calculated for the overall population by CKD status. Next, for participants with and without CKD, separately, we calculated mean IADs and their standard deviations. We determined the distribution of participants within each category of IADs (< 10 mm Hg, 10-20 mmHg, and ≥ 20 mmHg) by CKD status. Finally, among individuals with CKD, we calculated prevalence ratios for IADs in SBP ≥ 10 mmHg associated with study covariates. In secondary analyses, we repeated the above steps by albuminuria status and by reduced eGFR status. All analyses were conducted using SAS 9.2 (SAS Institute, Cary, North Carolina).

Results

Participant Characteristics

On average, HyperGEN participants with CKD were older, less likely to be male and African-American, and more likely to have a history of myocardial infarction, stroke, diabetes, or hypertension compared to those without CKD (Table 1). Those with CKD also had higher mean SBP and used more antihypertensive medications than their counterparts without CKD.

IADs in BP

When all three BP measurements were averaged, the absolute IADs in SBP were 9.4 mmHg and 8.7 mmHg among participants with and without CKD, respectively (Table 2). The absolute IADs in DBP were 5.4 mmHg and 5.1 mmHg, respectively. Individuals with CKD had higher mean SBP and DBP and slightly larger IADs in BP than their counterparts without CKD, regardless of the number or timing of BP measurements averaged; however, these differences were not significant. Results were consistent by albuminuria status (Table 3) and reduced eGFR status (Table 4).

Distribution of IADs in BP

Among those with CKD, the prevalence of IADs < 10 mmHg, 10-20 mmHg, and ≥ 20 mmHg was 82.1%, 16.8%, and 1.2%, respectively, for SBP and 95.5%, 4.0%, and 0.5%, respectively, for DBP (Table 5). Among those without CKD, the prevalence was

84.1%, 13.8%, and 2.1%, respectively, for SBP and 96.3%, 3.5%, and 0.2%, respectively, for DBP.

Correlates of IADs in SBP ≥ 10 mmHg Among Participants with CKD

After adjustment for age, race, and sex, DBP ≥ 90 mmHg (versus < 80 mmHg) was associated with a higher prevalence ratio for IADs in SBP ≥ 10 mmHg (prevalence ratio 1.94; 95% confidence interval [CI]: 1.02, 3.68; Table 6). Use of 3 or more antihypertensive medications was associated with a lower prevalence ratio for IADs in SBP ≥ 10 mmHg after age, race, sex adjustment and full multivariable adjustment (prevalence ratio 0.14; 95% CI: 0.02, 0.97 and 0.13; 95% CI: 0.02, 0.94, respectively).

Discussion

In the current study, we observed small and insignificant IADs in BP by CKD status. Notably, however, 18% of participants with CKD had IADs in SBP ≥ 10 mmHg. Of the study covariates investigated, only use of 3 or more antihypertensive medications was associated with IADs in SBP ≥ 10 mmHg.

IADs in BP have been reported in some,[12,14,15] but not all,[16] studies. Several historic studies reported a high prevalence of large IADs. For example, in 1943 Amsterdam and Amsterdam observed IADs in SBP ≥ 20 mmHg among 51% and 8% of individuals with and without hypertension, respectively.[17] A 1951 study of a clinic-based population found IADs in SBP ≥ 10 mmHg in about 50% of patients seen in an office

practice.[18] In the current study, we observed a smaller prevalence of large IADs (18%) among individuals with CKD, consistent with more recent studies which report prevalences of large IADs in BP of 10-15% in the general population.[12,14,19] One reason for this variability in prevalence estimates is that studies of IADs in BP differ significantly in their BP measurement protocols. In a recent meta-analysis, Verberk, et al. reported that measurement methodology has a major influence on IAD results. For example, the relative risk of obtaining an IAD in SBP ≥ 10 mmHg was 2.2 (95% CI: 1.4, 3.6) when measuring sequentially instead of simultaneously, 2.1 (95% CI: 1.1, 3.9) when using a manual instead of an automated device, and 2.0 (95% CI: 1.1, 3.8) when performing one BP measurement instead of multiple measurements.[20]

Data are limited on IADs in BP in large population-based studies, and even more so among individuals with CKD. At least one prior study examined IADs in BP among individuals with diabetes.[21] Clark, et al. reported that the prevalence of IADs in SBP ≥ 10 mmHg was higher among people with diabetes compared to those without (8.6% versus 2.9%, respectively). Also, among those with diabetes, IADs in SBP ≥ 10 mmHg were associated with peripheral arterial disease (odds ratio 3.4; 95% CI: 1.2, 9.3) while IADs in SBP ≥ 15 mmHg were associated with diabetic retinopathy (odds ratio 5.7; 95% CI: 1.5, 21.6) and CKD (odds ratio 7.0; 95% CI: 1.7, 29.8).

Peripheral arterial disease, an established risk factor for CVD events and mortality, is thought to be the pathological basis for IADs in BP.[22] A potential biological mechanism for large IADs involves unevenly distributed stiffening in the large arteries as a result of structural changes due to prolonged hypertension.[21] Su, et al. recently reported that IADs in SBP ≥ 10 mmHg are associated with elevated brachial-ankle pulse wave

velocity, suggesting increased arterial stiffness.[23] Furthermore, increased blood pressure variability has been identified as a potential confounder of IADs in BP and is associated with increased arterial stiffness.[21,24] Although peripheral arterial disease and uncontrolled hypertension are common among individuals with CKD, whether these comorbidities mediate larger IADs in BP among those with CKD remains to be seen, and additional studies of IADs in BP in this population are warranted.

The current study should be considered in the context of certain limitations. Heart rate variability may partially explain the IADs we observed since BP measurements were not taken simultaneously in both arms. However, the potential impact of this variability was minimized by averaging multiple BP measures per arm. Other strengths include a large, population-based sample of white and African-American adults and the availability of multiple BP measurements collected using rigorous study protocols.

In conclusion, we observed small but insignificant IADs among individuals with CKD in a large, population-based sample of whites and African-Americans. Nonetheless, 18% of those with CKD had IADs in SBP in excess of 10 mmHg when three BP measures per arm were analyzed. Recent literature suggests that BP measurement methodology is crucial to identifying IADs in BP. Future studies are needed to determine the appropriate methodology and then to explore the relationship between IADs in BP and CKD using standardized BP protocols.

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Table 1. Baseline characteristics of Hypertension Genetic Epidemiologic Network (HyperGEN) study participants by chronic kidney disease status

	No CKD (n=3,900)	CKD (n=424)	p-value
Age, years	48.2 (13.6)	61.2 (10.6)	<0.001
Male, %	44.0	36.6	0.003
African-American, %	49.5	40.0	<0.001
Current smoker, %	19.0	17.5	0.45
History of myocardial infarction, %	4.8	14.7	<0.001
History of stroke, %	3.3	10.0	<0.001
Diabetes, %	11.4	27.1	<0.001
Hypertension, %	61.7	90.1	<0.001
Mean systolic blood pressure, mmHg	123.8 (20.1)	132.9 (25.8)	<0.001
Mean diastolic blood pressure, mmHg	71.2 (11.2)	71.1 (12.5)	0.89
Age at hypertension onset, years†	39.2 (11.9)	41.8 (12.7)	<0.001
Hypertension duration, years†	14.6 (11.2)	19.6 (12.2)	<0.001
Number of antihypertensive medications 0 1 2 3 or more	 57.0 30.9 10.0 2.1	 23.6 45.5 24.1 6.8	<0.001
Writing hand Right Left Either	 90.5 8.3 1.2	 92.9 6.8 0.2	0.12
Protocol Switched arms, % Consecutive arms, %	 62.5 37.5	 73.1 26.9	<0.001

†Limited to those with hypertension

Numbers in table are presented as mean (standard deviation) or percent.

CKD: chronic kidney disease, defined as an estimated glomerular filtration rate < 60 mL/min/1.73m^2 or an albumin excretion rate ≥ 300 mg/day.

Table 2. Mean systolic blood pressure, mean diastolic blood pressure and the absolute inter-arm differences in blood pressure among Hypertension Genetic Epidemiologic Network (HyperGEN) participants by chronic kidney disease status

	No CKD (n=3,900)	CKD (n=424)
Mean of first, second, and third BP measurements, mmHg		
Mean right SBP	122.6 (20.0)	130.9 (25.6)
Mean left SBP	122.3 (19.9)	131.4 (25.3)
Absolute IAD in SBP	8.7 (8.8)	9.4 (9.3)
Mean right DBP	71.1 (11.1)	71.2 (12.5)
Mean left DBP	71.2 (11.1)	70.8 (12.6)
Absolute IAD in DBP	5.1 (4.6)	5.4 (5.7)
Mean of second and third BP measurements, mmHg		
Mean right SBP	122.2 (20.2)	130.5 (26.0)
Mean left SBP	121.9 (20.2)	130.9 (25.7)
Absolute IAD in SBP	5.3 (5.9)	5.6 (4.7)
Mean right DBP	70.9 (11.1)	70.7 (12.6)
Mean left DBP	71.0 (11.2)	70.5 (12.5)
Absolute IAD in DBP	3.1 (2.9)	3.3 (3.3)
First BP measurement, mmHg		
Right SBP	123.5 (20.4)	131.8 (25.8)
Left SBP	123.1 (20.2)	132.3 (25.5)
Absolute IAD in SBP	6.5 (6.0)	7.8 (6.9)
Right DBP	71.7 (11.6)	72.1 (12.9)
Left DBP	71.5 (11.6)	71.5 (13.3)
Absolute IAD in DBP	4.0 (3.4)	4.3 (3.5)
Second BP measurement, mmHg		
Right SBP	122.5 (21.0)	131.3 (26.3)
Left SBP	122.2 (20.5)	131.3 (26.1)
Absolute IAD in SBP	6.7 (6.8)	7.0 (6.6)

Right DBP	71.0 (11.4)	70.8 (13.0)
Left DBP	71.2 (11.5)	71.0 (12.6)
Absolute IAD in DBP	4.1 (3.6)	4.1 (3.8)
Third BP measurement, mmHg		
Right SBP	122.0 (20.5)	129.8 (26.6)
Left SBP	121.6 (20.6)	130.5 (26.3)
Absolute IAD in SBP	6.6 (6.2)	7.3 (6.9)
Right DBP	70.7 (11.4)	70.6 (12.9)
Left DBP	70.7 (11.5)	69.9 (13.0)
Absolute IAD in DBP	3.9 (3.5)	4.3 (4.2)

Numbers in table are presented as mean (standard deviation).

CKD: chronic kidney disease, defined as an estimated glomerular filtration rate < 60 mL/min/1.73m^2 or an albumin excretion rate ≥ 300 mg/day; BP: blood pressure; SBP: systolic BP; DBP: diastolic BP; IAD: inter-arm difference

Table 3. Mean systolic blood pressure, mean diastolic blood pressure, and the absolute inter-arm differences in blood pressure among Hypertension Genetic Epidemiologic Network (HyperGEN) participants by albuminuria status

	No albuminuria (n=4,207)	Albuminuria (n=117)
Mean of first, second, and third BP measurements, mmHg		
Mean right SBP	122.8 (20.1)	147.6 (26.4)
Mean left SBP	122.5 (20.0)	147.9 (26.9)
Absolute IAD in SBP	8.8 (8.7)	9.9 (12.4)
Mean right DBP	70.9 (11.1)	78.9 (13.6)
Mean left DBP	70.9 (11.2)	78.1 (13.8)
Absolute IAD in DBP	5.1 (4.6)	6.1 (7.9)
Mean of second and third BP measurements, mmHg		
Mean right SBP	122.3 (20.4)	147.7 (26.8)
Mean left SBP	122.1 (20.3)	147.7 (27.1)
Absolute IAD in SBP	5.3 (5.9)	5.7 (4.9)
Mean right DBP	70.6 (11.2)	78.4 (13.5)
Mean left DBP	70.7 (11.2)	77.5 (13.7)
Absolute IAD in DBP	3.1 (2.9)	3.4 (2.9)
First BP measurement, mmHg		
Right SBP	123.7 (20.6)	147.4 (26.6)
Left SBP	123.3 (20.3)	148.4 (27.3)
Absolute IAD in SBP	6.6 (6.0)	8.6 (7.6)
Right DBP	71.5 (11.6)	79.8 (14.2)
Left DBP	71.3 (11.6)	79.2 (14.5)
Absolute IAD in DBP	4.0 (3.4)	4.4 (3.9)
Second BP measurement, mmHg		
Right SBP	122.6 (21.2)	147.7 (27.3)
Left SBP	122.4 (20.7)	148.2 (27.1)
Absolute IAD in SBP	6.7 (6.8)	7.5 (7.2)

Right DBP	70.8 (11.4)	78.6 (14.3)
Left DBP	71.0 (11.5)	77.8 (13.6)
Absolute IAD in DBP	4.1 (3.5)	4.7 (5.0)
Third BP measurement, mmHg		
Right SBP	122.0 (20.6)	147.8 (27.3)
Left SBP	121.8 (20.8)	147.2 (28.3)
Absolute IAD in SBP	6.6 (6.2)	7.7 (8.1)
Right DBP	70.5 (11.4)	78.3 (13.6)
Left DBP	70.5 (11.5)	77.2 (14.3)
Absolute IAD in DBP	3.9 (3.5)	4.8 (4.5)

Numbers in table are presented as mean (standard deviation).

Albuminuria defined as an albumin excretion rate ≥ 300 mg/day.

Table 4. Mean systolic blood pressure, mean diastolic blood pressure, and the absolute inter-arm differences in blood pressure among Hypertension Genetic Epidemiologic Network (HyperGEN) participants by reduced estimated glomerular filtration rate (eGFR) status

	No reduced eGFR (n=3,978)	Reduced eGFR (n=346)
Mean of first, second, and third BP measurements, mmHg		
Mean right SBP	123.1 (20.4)	127.7 (24.1)
Mean left SBP	122.7 (20.3)	128.2 (23.6)
Absolute IAD in SBP	8.8 (9.0)	9.3 (7.8)
Mean right DBP	71.3 (11.2)	69.3 (11.4)
Mean left DBP	71.3 (11.2)	69.2 (11.6)
Absolute IAD in DBP	5.2	5.1 (4.6)
Mean of second and third BP measurements, mmHg		
Mean right SBP	122.7 (20.6)	127.2 (24.5)
Mean left SBP	122.4 (20.6)	127.7 (24.0)
Absolute IAD in SBP	5.3 (5.9)	5.7 (4.7)
Mean right DBP	71.0 (11.3)	68.8 (11.6)
Mean left DBP	71.1 (11.3)	68.9 (11.6)
Absolute IAD in DBP	3.1 (2.9)	3.2 (3.3)
First BP measurement, mmHg		
Right SBP	124.0 (20.8)	128.6 (24.5
Left SBP	123.5 (20.6)	129.2 (23.9)
Absolute IAD in SBP	6.6 (6.0)	7.7 (6.7)
Right DBP	71.8 (11.7)	70.3 (11.8)
Left DBP	71.7 (11.7)	69.6 (12.1)
Absolute IAD in DBP	4.0 (3.4)	4.2 (3.4)
Second BP measurement, mmHg		
Right SBP	122.9 (21.4)	128.2 (24.8)
Left SBP	122.7 (21.0)	127.9 (24.5)
Absolute IAD in SBP	6.7 (6.8)	6.8 (6.1)

Right DBP	71.2 (11.5)	68.9 (11.8)
Left DBP	71.3 (11.5)	69.4 (11.7)
Absolute IAD in DBP	4.1 (3.6)	3.9 (3.2)
Third BP measurement, mmHg		
Right SBP	122.4 (20.9)	126.2 (25.1)
Left SBP	122.0 (21.1)	127.5 (24.5)
Absolute IAD in SBP	6.6 (6.3)	7.2 (6.4)
Right DBP	70.9 (11.5)	68.7 (11.8)
Left DBP	70.9 (11.6)	68.4 (12.1)
Absolute IAD in DBP	3.9 (3.5)	4.1 (4.0)

Numbers in table are presented as mean (standard deviation).

Reduced eGFR defined as eGFR < 60 mL/min/1.73m^2

Table 5. Distribution of participants within each category of inter-arm difference in blood pressure, by chronic kidney disease status

	No CKD N (%)	CKD N (%)
SBP		
IAD < 10 mmHg	3,281 (84.1%)	348 (82.1%)
10 ≤ IAD < 20 mmHg	537 (13.8%)	71 (16.8%)
IAD ≥ 20 mmHg	82 (2.1%)	5 (1.2%)
DBP		
IAD < 10 mmHg	3,757 (96.3%)	405 (95.5%)
10 ≤ IAD < 20 mmHg	135 (3.5%)	17 (4.0%)
IAD ≥ 20 mmHg	8 (0.2%)	2 (0.5%)

CKD: chronic kidney disease, defined as an estimated glomerular filtration rate < 60 mL/min/1.73m^2 or an albumin excretion rate ≥ 300 mg/day; IAD: inter-arm difference, calculated as the mean of the second and third blood pressure measurements; BP: blood pressure; SBP: systolic BP; DBP: diastolic BP

Table 6. Prevalence ratios for inter-arm differences in systolic blood pressure ≥ 10 mmHg associated with study covariates among participants with chronic kidney disease.

	Age, race, sex adjusted prevalence ratio (95% CI)	Multivariable adjusted prevalence ratio[†] (95% CI)
Age ≥ 60 years	1.34 (0.85, 2.11)	1.42 (0.83, 2.44)
Male gender	1.35 (0.90, 2.03)	1.23 (0.79, 1.94)
African-American race	1.46 (0.96, 2.24)	1.52 (0.93, 2.48)
History of myocardial infarction	0.96 (0.54, 1.70)	1.06 (0.57, 1.97)
History of stroke	1.56 (0.92, 2.66)	1.61 (0.91, 2.86)
Hypertension	1.16 (0.53, 2.53)	1.02 (0.33, 3.09)
Systolic blood pressure, mmHg		
< 140	1 (ref)	1 (ref)
140-149	0.66 (0.31, 1.40)	0.61 (0.27, 1.39)
≥ 150	1.21 (0.76, 1.91)	1.21 (0.66, 2.23)
Diastolic blood pressure, mmHg		
< 80	1 (ref)	1 (ref)
80-89	1.27 (0.72, 2.24)	1.23 (0.63, 2.39)
≥ 90	1.94 (1.02, 3.68)	1.48 (0.65, 3.40)
Hypertension duration, years		
< 5	1 (ref)	1 (ref)
5-10	1.50 (0.69, 3.24)	1.49 (0.59, 3.80)
10-20	1.30 (0.68, 2.48)	1.41 (0.63, 3.16)
≥ 20	0.96 (0.50, 1.85)	1.03 (0.46, 2.34)
Number of antihypertensive medications		
0	1 (ref)	1 (ref)
1	1.00 (0.63, 1.61)	1.00 (0.57, 1.75)
2	0.63 (0.34, 1.18)	0.59 (0.30, 1.14)
3 or more	0.14 (0.02, 0.97)	0.13 (0.02, 0.94)

Chronic kidney disease defined as an estimated glomerular filtration rate < 60 mL/min/1.73m^2 or an albumin excretion rate ≥ 300 mg/day.

[†]For this column, all variables were included in a single multivariable model.

SUMMARY

Kidney disease is common, with recent estimates indicating a prevalence of 13% among US adults. Furthermore, the vast majority of individuals with kidney disease have hypertension. Apparent treatment-resistant hypertension (aTRH), 24-hour blood pressure (BP) variability, and inter-arm differences (IADs) in BP have been identified as risk factors for cardiovascular disease, and there is increasing evidence that these phenotypes provide prognostic information above and beyond mean clinic BP. The goal of this dissertation was to determine the association of kidney disease with BP phenotypes in the context of three studies, namely, the REasons for Geographic And Racial Differences in Stroke (REGARDS) study, the Jackson Heart Study, and the Hypertension Genetic Epidemiology Network (HyperGEN) study.

In a cross-sectional analysis of REGARDS data, we showed an increased prevalence of aTRH among study participants with hypertension with lower estimated glomerular filtration rate (eGFR) and higher albumin-to-creatinine ratio (ACR). We found that male gender, black race, larger waist circumference, diabetes, a history of myocardial infarction or stroke, statin use, and lower eGFR and higher ACE levels were associated with aTRH among individuals with kidney disease.

In a longitudinal analysis of REGARDS data, we reported incidence rates of end-stage renal disease (ESRD) of 8.86 per 1,000 person-years and 0.88 per 1,000 person years for hypertensive participants with and without kidney disease, respectively, over a

median 6.4 years follow-up. The multivariable adjusted hazard ratio for ESRD comparing hypertensive participants with versus without aTRH was 6.32 (95% confidence interval: 4.30, 9.30).

In a cross-sectional analysis of 1,022 African American Jackson Heart Study participants who underwent ambulatory BP monitoring, we found small differences in 24-hour blood pressure variability which were not statistically significant after multivariable adjustment including 24-hour mean BP. Older age, larger waist circumference, and higher 24-hour mean systolic BP were associated with higher day-night standard deviation and average real variability of systolic BP among participants with kidney disease.

Finally, in a cross-sectional analysis of HyperGEN data, we reported small differences in IADs which were not significant. Nonetheless, 18% of study participants with kidney disease had IADs in systolic BP in excess of 10 mmHg. After multivariable adjustment, use of 3 or more antihypertensive medications was associated with a lower prevalence ratio for IADs in SBP ≥ 10 mmHg (prevalence ratio 0.13; 95% CI: 0.02, 0.94).

In conclusion, this work highlights the high prevalence of aTRH among individuals with kidney disease and suggests that individuals with aTRH are at increased risk for ESRD. Additionally, our data suggest that kidney disease is associated with higher BP variability, but this association is mostly explained by the higher mean BP among those with kidney disease. Further research is needed to develop clinical management strategies to minimize the ESRD risk associated with aTRH and to

determine whether there is an increased risk of adverse outcomes associated with BP variability and IADs in BP among those with kidney disease.

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