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PREVALENCE AND PROGNOSTIC SIGNIFICANCE OF APPARENT TREATMENT RESISTANT HYPERTENSION IN CHRONIC KIDNEY DISEASE: A REPORT FROM THE CRIC STUDY

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Abstract

The association between apparent treatment resistant hypertension (ATRH) and clinical outcomes is not well studied in chronic kidney disease (CKD). We analyzed data on 3367 hypertensive participants in the Chronic Renal Insufficiency Cohort (CRIC) to determine prevalence, associations, and clinical outcomes of ATRH in non-dialysis CKD patients. ATRH was defined as blood pressure (BP) ≥140/90 mm Hg on ≥3 antihypertensives, or use of ≥4 antihypertensives with BP at goal at baseline visit. Prevalence of ATRH was 40.4%. Older age, male gender, black race, diabetes, and higher BMI were independently associated with higher odds of having ATRH. Participants with ATRH had a higher risk of clinical events compared to participants without ATRH - composite of myocardial infarction (MI), stroke, peripheral arterial disease (PAD), congestive heart failure (CHF), and all-cause mortality HR [95% CI]: (1.38 [1.22,1.56]); renal

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Conflict(s) of Interest/Disclosure(s)

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events (1.28 [1.11, 1.46]); CHF (1.66 [1.38, 2.00]); and all-cause mortality (1.24 [1.06,1.45]). The subset of participants with ATRH and BP at goal on ≥4 medications also had higher risk for composite of MI, stroke, PAD, CHF, and all-cause mortality HR [95% CI] (1.30 [1.12, 1.51]) and CHF (1.59 [1.28, 1.99]) compared to those without ATRH. ATRH was associated with significantly higher risk for CHF and renal events only among those with eGFR ≥30 ml/min/1.73 m^2. Our findings show that ATRH is common and associated with high risk of adverse outcomes in a cohort of patients with CKD. This underscores the need for early identification and management of patients with ATRH and CKD.

Keywords

hypertension; resistant hypertension; chronic kidney disease; chronic renal insufficiency cohort

Introduction

The American Heart Association (AHA), in a Scientific Committee Statement in 2008, defined treatment resistant hypertension as blood pressure (BP) that remains above goal despite the concurrent use of 3 different antihypertensive medication classes, or controlled BP while being treated with ≥4 antihypertensive medication classes (1). The reported prevalence of treatment resistant hypertension in the literature has varied from 3 to 30% of patients with hypertension (HTN) (2–4), with an increase in prevalence noted in analysis of data from the 1998 to 2008 US National Health and Nutrition Examination Survey (NHANES) (2). The term “Apparent Treatment Resistant Hypertension” (ATRH) is commonly used in epidemiologic studies to estimate prevalence and assess outcomes, as individuals with pseudo-resistance (including white coat effect, measurement errors, or medication non-compliance) cannot be definitively identified and excluded (5–8). Recent evidence suggests that the presence of ATRH is associated with a higher risk of adverse renal and cardiovascular outcomes (3, 6–10).

Resistant hypertension is an especially important clinical problem in patients with chronic kidney disease (CKD). Good control of BP is important in lowering the high risk of cardiovascular disease in this population (11–16). While the prevalence of HTN has been consistently reported to be high in CKD patients (17–19), ATRH is not well studied in this population. In addition, most studies evaluating the long term prognosis of ATRH are in the general population or in populations with established cardiovascular disease, with a relatively low prevalence of patients with CKD (3, 6, 9).

We analyzed data from the Chronic Renal Insufficiency Cohort (CRIC) study, which is an observational cohort study of patients with CKD. Previous analyses from CRIC have reported that the prevalence of HTN was 85%, and despite high rates of HTN awareness and treatment among CRIC participants, the rates of HTN control were suboptimal (20). We sought to determine the prevalence and factors associated with ATRH in a large cohort of non-dialysis CKD patients, and to evaluate the association of ATRH with long-term clinical outcomes. We hypothesized that ATRH is associated with various clinical and demographic

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characteristics of CKD patients, and that the presence of ATRH is associated with a higher risk of renal and cardiovascular outcomes and mortality in this population.

Methods

Patient population

The CRIC study is a multicenter, prospective, observational study of risk factors for progression of CKD. The design, rationale, and baseline patient characteristics of CRIC have been described in detail previously (21, 22). In brief, the CRIC study includes a racially diverse group of adults aged 21 – 74 years with estimated glomerular filtration rates (eGFR) of 20 to 70 ml/min/1.73 m^2. The CRIC study recruited 3939 patients between June 2003 and December 2008 from 13 sites in 7 centers in the United States (Baltimore, MD; Philadelphia, PA; Cleveland, OH; Detroit, MI; Chicago, IL; New Orleans, LA; and Oakland, CA). After exclusion of patients without BP information, medication information, or a diagnosis of HTN (systolic blood pressure (SBP) < 140 mm Hg and diastolic blood pressure (DBP) < 90 mm Hg and not taking anti-hypertensive medications at baseline), 3367 patients were included in these analyses (Figure 1). The study protocol was approved by the Institutional Review Boards of all participating centers and conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent.

Data Collection

During the baseline study visit, all CRIC data were collected by trained study staff using questionnaires, anthropometric measures, collection of blood specimens, and a 24 hour urine sample. Current cigarette smoking was defined as currently smoking cigarettes and having smoked at least 100 cigarettes during an individual's lifetime. Alcohol drinking was defined as the consumption of one or more beverages containing alcohol over the previous year. Body weight and height were each measured twice and averaged for analysis. Body-mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Waist circumference was measured at the uppermost lateral border of the iliac crest with a Gulick II tape and repeated until two measures agreed within 1 centimeter. Participants reporting a prior diagnosis of HTN were asked whether they were using lifestyle modifications (i.e., salt reduction, weight loss, exercise, or alcohol reduction) to lower BP.

BP Measurements

BP measurements in the CRIC study followed a standardized protocol - 3 BP measurements were obtained in the sitting position after at least 5 minutes of quiet rest by trained staff according to the protocol. An aneroid sphygmomanometer was used with 1 of 4 cuff sizes (pediatric, regular adult, large adult, or thigh) based on the participant's arm circumference. Participants were advised to refrain from coffee, tea, or alcohol intake, cigarette smoking, and vigorous exercise for at least 30 minutes before their examination. All BP observers successfully completed training sessions on the use of the BP measurement protocol. Requirements for certification as a CRIC BP observer consisted of satisfactory performance on a written test assessing knowledge of preparation of study participants for BP measurement, selection of an appropriate cuff size, standard BP measurement techniques, a standardized videotape examination, and concordant live BP measurements with an

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instructor using a Y-tube stethoscope. Based on the average of all 3 BP measurements in participants, HTN was defined as SBP ≥140 mm Hg and/or DBP ≥90 mm Hg and/or current antihypertensive medication use if they responded affirmatively to the question "Do you currently take prescribed medication for your HTN or high BP? " on the baseline study questionnaire.

Definition of ATRH

We defined ATRH as mean SBP ≥140 mm Hg and/or mean DBP ≥90 mm Hg while taking ≥3 anti-hypertensive medications, OR taking ≥4 anti-hypertensive medications with mean SBP < 140 mm Hg and mean DBP < 90 mm Hg (1). We did not specify the use of a diuretic as a requirement for our primary analysis, but used an alternative definition specifying the use of a diuretic in sensitivity analysis. The BP goal of < 140/90 mm Hg used for this analysis is consistent with the recommended BP goal for CKD patients in recent guidelines (23, 24).

Outcome measures

The following incident outcomes were defined a priori for this analysis: 1) composite of MI (myocardial infarction), stroke, and PAD (peripheral arterial disease) – which comprised atherosclerotic cardiovascular events; 2) composite of MI, stroke, PAD, and congestive heart failure (CHF); 3) composite of MI, stroke, PAD, CHF, and all-cause mortality; 4) CHF; 5) stroke; 6) renal events; and 7) all-cause mortality. Renal events were defined as a 50% decline in eGFR and/or end stage renal disease (ESRD - start of long-term dialysis or renal transplantation). Cardiovascular events were adjudicated by blinded reviewers using predefined criteria. Deaths were ascertained from reports by next of kin, death certificates, hospital records, and linkage with the Social Security Death Master File. Details of the process of event ascertainment and adjudication in the CRIC study has been previously published (21). Participants were followed up until the occurrence of death, withdrawal from the study, or when the database was locked for analysis.

Statistical methods

Summary statistics by ATRH status were performed for basic demographic and clinical characteristics. The chi-square test was used to compare categorical variables and t-test or Wilcoxon rank sum test were used for continuous variables. We then explored the factors associated with ATRH with logistic regression models. This was done in two steps: Step 1, unadjusted associations between ATRH and each of the factors including age, gender, race, eGFR, 24 hour urine protein, BMI, and diabetes were modeled. Step 2, all these factors entered a multivariable model. Due to non-normal distribution, 24 hour urine protein was log transformed. For the relationship between ATRH and outcomes, the outcomes were first analyzed by ATRH status using the Kaplan Meier method. Cox regression models were then used. For each outcome, we fit four models in a tiered fashion. The first model only included ATRH as the predictor (i.e., the unadjusted model); model A adjusted for age, gender, race, and clinical center; model B further adjusted for diabetes, smoking status, history of cardiovascular disease, BMI, hemoglobin, and low-density lipoprotein (LDL) cholesterol; model C further adjusted for eGFR and 24 hour urine protein. To find whether the associations were consistent across subgroups, we also did stratified analyses in subgroups

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which were defined by age (below or above mean), gender, race, eGFR (<30, 30–60, and >60 ml/min/1.73m^2), and 24 hour urine protein (below or above median). As a sensitivity analysis, we modeled ATRH using three more definitions: 1) Mean SBP ≥140 mm Hg and/or mean DBP ≥90 mm Hg while taking ≥3 anti-hypertensive medications; 2) Mean SBP ≥140 mm Hg and/or mean DBP ≥90 mm Hg while taking ≥3 anti-hypertensive medications including a diuretic; and 3) taking ≥4 anti-hypertensive medications with mean SBP < 140 mm Hg and mean DBP < 90 mm Hg. In the sensitivity analyses for (1) and (3) above, the "No ATRH" comparison group stays the same which includes patients who are adequately treated and at goal on ≤3 medications, and also those with BP not at goal but on fewer than 3 medications. In sensitivity analysis for (2), the "No ATRH" comparison group includes patients who are adequately treated and at goal on ≤3 medications and those with BP not at goal but on fewer than 3 medications or not on a diuretic. Additional sensitivity analysis was done defining ATRH as mean SBP ≥140 mm Hg and/or DBP ≥90 mm Hg while taking ≥3 anti-hypertensive medications, OR taking ≥4 anti-hypertensive medications with mean SBP < 140 mm Hg and mean DBP < 90 mm Hg at baseline enrollment and at year 1 of follow-up. All analyses were conducted using SAS v9.4 (Cary, NC). All p-values were two-sided and statistical significance was defined as $p<0.05$.

Results

Of the 3939 CRIC participants, 3367 were hypertensive, had baseline BP and medication information, and are included in these analyses. The prevalence of ATRH in the hypertensive participants in this cohort was 40.4% (n = 1359), of which 52.5% (n = 713) had BP that was not at goal on ≥3 medications, and 47.5% (n = 646) had BP that was at goal on ≥4 medications. The baseline characteristics of patients with and without ATRH are detailed in Table 1. Those with ATRH were older, male, black, more likely to have an annual household income of < $20,000, and have history of cardiovascular disease (MI, stroke, CHF, PAD), and diabetes. On average, patients with ATRH had higher BMI and larger waist circumference, higher SBP, and lower total and LDL cholesterol levels than those without ATRH. Patients with ATRH were more likely to be under the care of a nephrologist, and to report at least 1 lifestyle modification for hypertension. Supplemental Table S1 shows baseline characteristics of patients with ATRH separated by component definitions (BP not at goal on ≥3 medications, and BP at goal on ≥4 medications). Renin-angiotensin system (RAS) blockers and diuretics were the most commonly used antihypertensive medications in all groups. There were no major differences in baseline characteristics of patients within the No ATRH group (BP at goal on ≤3 medications and BP not at goal on less than 3 medications) (Supplemental Table S2).

ATRH was more common in patients with lower eGFR; the prevalence was 22.3% in those with eGFR > 60 ml/min/1.73 m^2, 39.4% in those with eGFR between 30 – 60 ml/min/1.73m^2, and 54.2 % in those with eGFR < 30 ml/min/1.73 m^2 (Figure 2). The association between clinical and demographic factors and ATRH are shown in Table 2. Older age, male gender, black race, presence of diabetes, and higher BMI were independently associated with significantly higher odds of having ATRH. In addition, every 5 ml/min/1.73 m^2 decrease in GFR was associated with a 14% higher odds of ATRH (adjusted OR (95% CI)

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1.14 (1.10–1.17)), and doubling of proteinuria was associated with a higher odds of ATRH (adjusted OR (95% CI) 1.28 (1.16–1.42)).

The incidence rate of all clinical outcomes studied was higher in participants with ATRH, compared to those without ATRH (Figures 3A and 3B shows cardiovascular and renal outcomes, other outcomes are shown in Supplemental Figures S6 – S10). Median follow-up for the various outcomes are as indicated in Tables 3 and 4. The presence of ATRH was associated with higher risk of all outcomes in unadjusted models, and also when adjusted for demographic and cardiovascular risk factors (Table 3). Although attenuated after full multivariable adjustment, the HR for each outcome except stroke remained statistically significant in ATRH - HR (95% CI) 1.26 (1.05, 1.53) for composite of MI, stroke, PAD; 1.48 (1.28, 1.72) for composite of MI, stroke, PAD, CHF; 1.38 (1.22, 1.56) for composite of MI, stroke, PAD, CHF, all-cause mortality; 1.66 (1.38, 2.00) for CHF; 1.40 (0.97, 2.02) for stroke; 1.28 (1.11, 1.46) for renal events; and 1.24 (1.06, 1.45) for all-cause mortality (Table 3).

The association between ATRH and clinical outcomes was consistent when stratified by subgroups of age, gender, race/ethnicity, and proteinuria (shown in Supplemental Figures S1 – S5). However, there was significant interaction between the differences between ATRH and No ATRH groups for CHF (interaction p value 0.0001) and renal (interaction p value 0.02) events when stratified by baseline eGFR (Figures 4A and 4B). ATRH was significantly associated with CHF in individuals with eGFR > 60 ml/min/1.73 m^2 (HR (95% CI) 2.28 (1.13, 4.58)), and 30–60 ml/min/1.73 m^2 (HR (95% CI) 2.18 (1.72, 2.75)) but not in participants with eGFR < 30 ml/min/1.73 m^2 (HR (95% CI) 1.00 (0.74, 1.35)). Similarly ATRH was significantly associated with renal events in individuals with eGFR > 60 ml/min/1.73 m^2 (HR (95% CI) 2.29 (1.15, 4.57)), and 30–60 ml/min/1.73 m^2 (HR (95% CI) 1.47 (1.23, 1.75)) but not in participants with eGFR < 30 ml/min/1.73 m^2 (HR (95% CI) 1.09 (0.89, 1.33)).

Additional analyses explored the components of the definition of ATRH. Individuals with ATRH and whose BP was at goal on ≥4 medications had significantly increased HR for composite of MI, stroke, PAD, CHF, all-cause mortality (HR (95% CI) 1.30 (1.12, 1.51)), composite of MI, stroke, PAD, CHF (HR (95% CI) 1.42 (1.18, 1.70)), and CHF (HR (95% CI) 1.59 (1.28, 1.99)), but not if CHF was excluded from the composite outcomes, or for individual components of the composite outcomes other than CHF - composite of MI, stroke, and PAD (HR (95% CI) 1.18 (0.93, 1.48)); all-cause mortality (HR (95% CI) 1.11 (0.91, 1.36)); stroke (HR (95% CI) 1.11 (0.70, 1.75)); and renal events (HR (95% CI) 1.05 (0.88, 1.25)) (Table 4). The point estimates of the hazard ratios of risk were lower in participants with controlled BP on ≥4 medications compared with participants whose BP was not at goal on 3 or more medications (Table 4).

In sensitivity analysis, the outcomes were similar in those with ATRH whose BP was not at goal on 3 or more medications with or without use of diuretics, compared to those with no ATRH (Table 4). Additional sensitivity analysis defining ATRH at baseline and at 1 year of follow-up showed similar results (Supplemental Table S3).

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Discussion

This is the largest cohort of patients to study the prognostic significance of ATRH in CKD. In this cohort of patients with CKD, the prevalence of ATRH was high, and patients with lower levels of eGFR were more likely to have ATRH. As in non-CKD populations, older age, male gender, black race, proteinuria, diabetes, and higher BMI were independently associated with ATRH. The presence of ATRH independently predicted a higher risk of mortality and adverse cardiovascular and renal outcomes. The increased risk for these outcomes was consistent in subgroups defined by age, gender, race, and urine protein excretion. ATRH was associated with higher risk of renal outcomes and CHF in participants with earlier stages (eGFR ≥30 ml/min/1.73 m^2), but not in those with more advanced stages of CKD (eGFR < 30 ml/min/1.73 m^2).

Population-based studies show high rates of HTN in patients with CKD (17–19). A previous analysis of the CRIC cohort noted high rates of awareness and treatment of HTN in adult CKD patients, but showed that control rates were suboptimal (20). The prevalence rates of ATRH in the literature have varied, related in part to the differences in definitions used for ATRH. The 40% prevalence of ATRH in this cohort is higher than other studies which report prevalence of 12.7% to 21.7% in the general population (3, 7, 10); and 11.1% to 22.9% in patients with established cardiovascular disease (6, 9). While one clinic-based study which was limited to CKD patients reported an ATRH prevalence of 23%, this was a small study that was limited to a Caucasian population (8). The high prevalence of ATRH in the CRIC cohort may be due to the presence of CKD, and the inclusion of a large proportion of African Americans, both predictors of resistant hypertension (1, 25).

Our finding of increasing ATRH prevalence with decreasing eGFR confirms a similar trend noted in the REGARDS study analysis (25). There was a 14% higher risk of ATRH with every 5 ml/min/1.73 m^2 decrease in eGFR in our study. While the mechanisms that contribute to resistant hypertension in CKD are not well defined, it may be speculated that increased salt and water retention, excessive activation of the renin-angiotensin-aldosterone system, and higher levels of sympathetic activation with decreasing eGFR would contribute to uncontrolled BP (26). Decreased eGFR and both moderately and severely increased albuminuria have been shown to be independently associated with lesser longitudinal SBP and DBP reductions in hypertensive patients, strongly inferring that these variables are physiological mediators of resistance to pharmacologic BP lowering (27).

The association between ATRH and adverse cardiovascular and renal outcomes has been reported mostly in patients without CKD (3, 6, 9). We demonstrate that ATRH is an independent predictor of adverse cardiovascular and renal outcomes in patients with CKD. While the magnitude of risk for outcomes is different, our results are similar to other studies in that there is a clear increased risk for most adverse cardiovascular and renal outcomes with the presence of ATRH (38% increase in risk for composite of MI, stroke, PAD, CHF and all-cause mortality; and 28% increase in risk for 50% decrease in eGFR or incident ESRD). The risk of stroke was not statistically significant in the fully adjusted model in this analysis – the number of stroke events, however, was low in this cohort. Importantly, ATRH was associated with a 66% increased risk for CHF. Given the increasing recognition of heart

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failure as a major cause of morbidity in patients with CKD (28, 29, 30), our findings point toward a potential reversible factor contributing to the risk of heart failure. The findings were consistent in subgroups of age, race, gender, and proteinuria. Coupled with the high prevalence of ATRH shown in this cohort, our data highlight the importance of recognition of ATRH in patients with CKD. Whether a targeted intervention to lower BP in patients with ATRH results in improved cardiovascular and renal outcomes needs to be established in prospective studies and should be a high priority for future research.

The definition of resistant hypertension has been the subject of some debate in this field (31). While the traditional definition has been uncontrolled BP on at least 3 antihypertensive medications classes (32), the AHA definition also added a new group of patients, those with controlled BP on 4 or more antihypertensive medication classes (1). To our knowledge, the prognostic implication of this new component of the definition of resistant hypertension has not been previously studied in patients with CKD. A recent study of hypertensive patients followed in a large healthcare system showed that the risk of ESRD and stroke were significantly higher in patients whose BP was not at goal on 3 or more medications compared to controlled BP requiring 4 or more medications, while the risks for ischemic heart events, CHF, and mortality were similar (33). We demonstrate that while the magnitude of risk for most clinical outcomes was lower in CKD patients with controlled BP on 4 or more medications than those with uncontrolled hypertension on 3 or more medications, the risk (especially for CHF and composite outcomes that included CHF) was still higher than those without ATRH. This supports the inclusion of this group of patients in the ATRH definition since it does help in risk stratification. These data also suggest that optimization of drug therapy and achievement of BP goal may lower the risk of outcomes. Our sensitivity analyses showed increased risk of adverse outcomes regardless of whether a diuretic was part of the antihypertensive regimen.

The association between ATRH and clinical outcomes differed based on level of eGFR; ATRH was associated with higher risk of renal outcomes and CHF in patients with eGFR > 60 ml/min/1.73 m^2 and eGFR 30–60 ml/min/1.73 m^2, but not eGFR < 30 ml/min/1.73 m^2. This underscores the importance of early recognition and systematic evaluation of underlying factors that may be contributing to ATRH in patients with relatively preserved renal function. It is also consistent with the concept that some risk factors can be detected in early, but not late CKD; for example, fibroblast growth factor (FGF) 23 was associated with progression of kidney disease only in patients with eGFR > 30 ml/min/1.73 m^2, but not in eGFR < 30 ml/min/1.73 m^2 (34). It is also known that lower eGFR and higher albuminuria are associated with higher risk of all-cause mortality and cardiovascular mortality, independent of traditional cardiovascular risk factors including HTN (35).

Our study has a number of strengths; these include the large sample size (including subgroups to allow robust subgroup analyses), long duration of follow up, and careful ascertainment and adjudication of clinical outcomes. In addition, sensitivity analyses with alternate definitions are consistent with the overall results reported. However, important limitations of this study need to be considered; this is an observational study, and the reported associations do not prove causation. A comprehensive evaluation of resistant hypertension was not done in the CRIC study; therefore, pseudo-resistance is not excluded.

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Heart rate variability was not examined in our analysis, but this has previously been shown to be a predictor of mortality in the CRIC cohort (36). The 'No ATRH' comparison group in this study includes patients who are adequately treated and at goal on ≤3 medications, and also those with BP not at goal but on less than 3 medications – the latter could potentially be due to physician or patient inertia, but could also be due to inability to tolerate more medications due to side effects. Studies in the resistant hypertension literature have addressed this issue in different ways. Most studies have compared ATRH with no ATRH as in our analyses (3, 6, 9). Other studies (7, 10) excluded patients who were uncontrolled on less than 3 medications in primary analysis, or included them in a secondary analysis. We examined the baseline characteristics of patients within the No ATRH group (BP at goal on ≤3 medications and BP not at goal on less than 3 medications) and did not find major differences. Additionally, defining ATRH at 2 time points - baseline and at 1 year one of follow-up - did not change results.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Perspectives

The association of ATRH with adverse cardiovascular and renal outcomes is compelling and has important clinical implications for patients with CKD. Our findings underscore the need for early identification, and systematic evaluation and management of patients with ATRH and CKD. In addition, these data support the need for novel therapeutic strategies to improve BP control in patients with CKD.

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Novelty and Significance

1) What Is New?

- Apparent treatment resistant hypertension is associated with an increased risk of adverse cardiovascular and renal outcomes in patients with CKD.
- Individuals with apparent treatment resistant hypertension who have BP at goal but on ≥4 medications have significantly increased risk for many adverse cardiovascular outcomes
- The increased risk for heart failure and adverse renal outcomes was present in subgroups defined by eGFR (estimated glomerular filtration rate) > 60 ml/min/1.73 m^2 and eGFR 30–60 ml/min/1.73 m^2, but not eGFR <30 ml/min/1.73 m^2

2) What Is Relevant?

- Varying prevalence of apparent treatment resistant hypertension in the general population and in patients with established cardiovascular disease
- Few studies have investigated the prevalence and prognostic significance of apparent treatment resistant hypertension in patients with CKD.

3) Summary

There is a strong association between apparent treatment resistant hypertension and adverse cardiovascular and renal outcomes in patients with CKD. The current study underscores the need for early identification, and systematic evaluation and management of patients with apparent treatment resistant hypertension and CKD. These data support the need for novel therapeutic strategies to improve BP control in patients with CKD.

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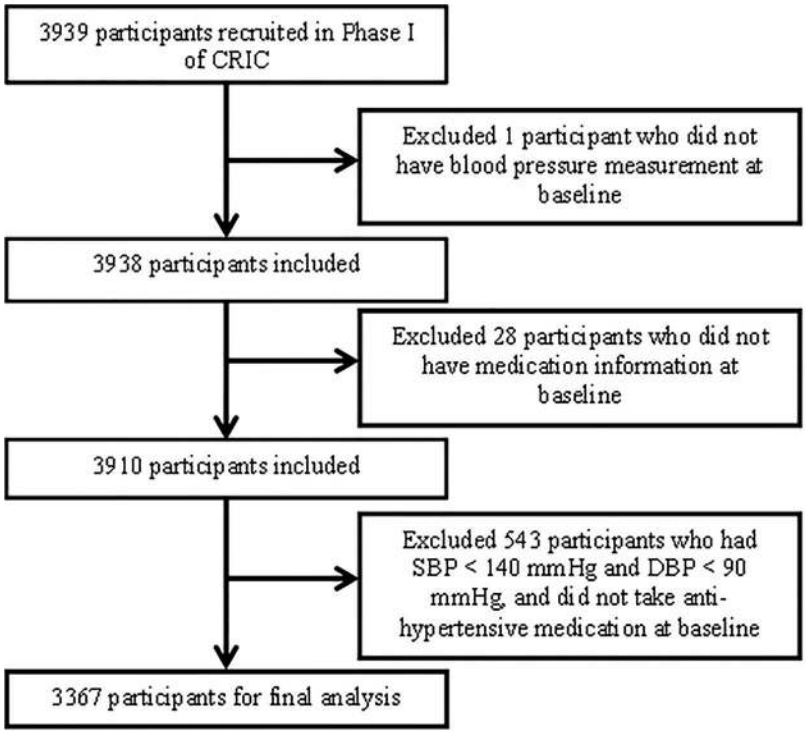

Figure 1.
Flow diagram of exclusion criteria applied to determine study population for final analysis

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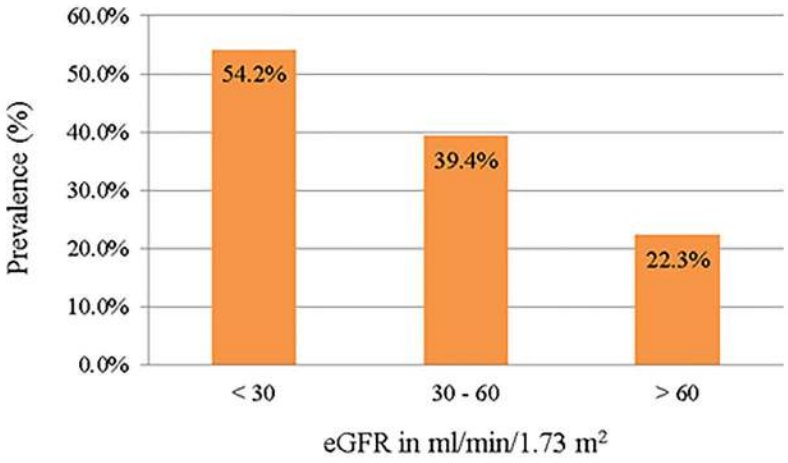

Figure 2.
Prevalence of apparent treatment resistant hypertension (ATRH) by eGFR status

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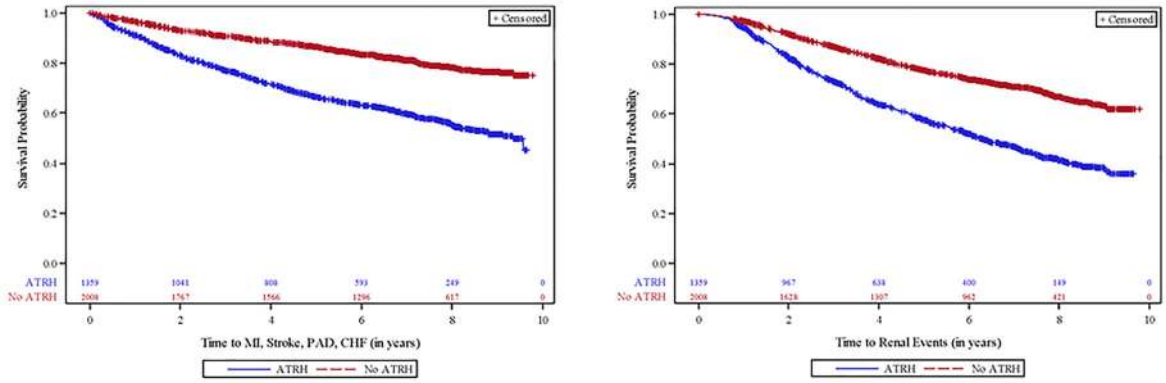

Figure 3.

Figure 3A. Cumulative incidence of composite cardiovascular outcomes (Composite of MI, stroke, PAD, CHF) between patients with and without ATRH

Figure 3B. Cumulative incidence of renal outcomes between patients with and without ATRH

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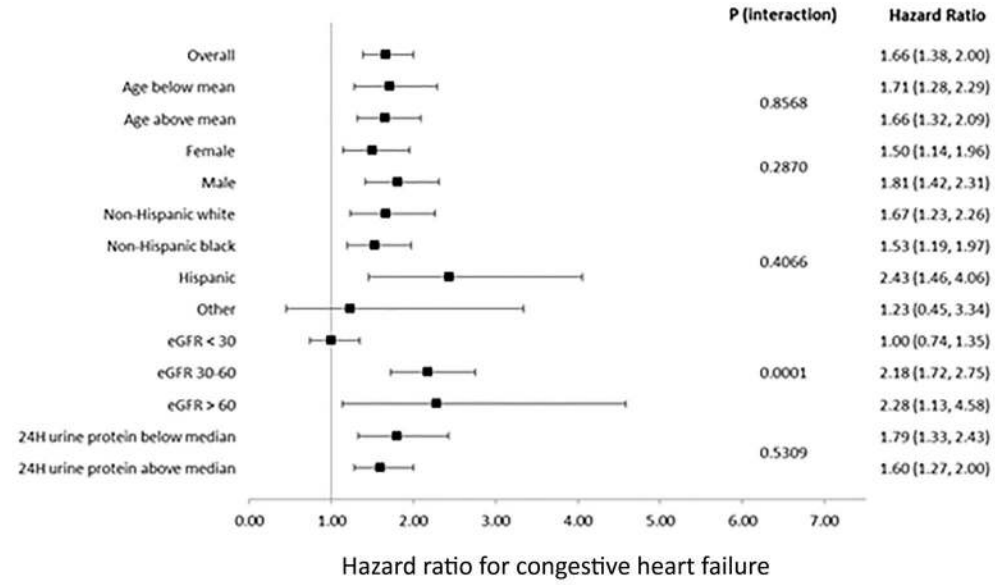

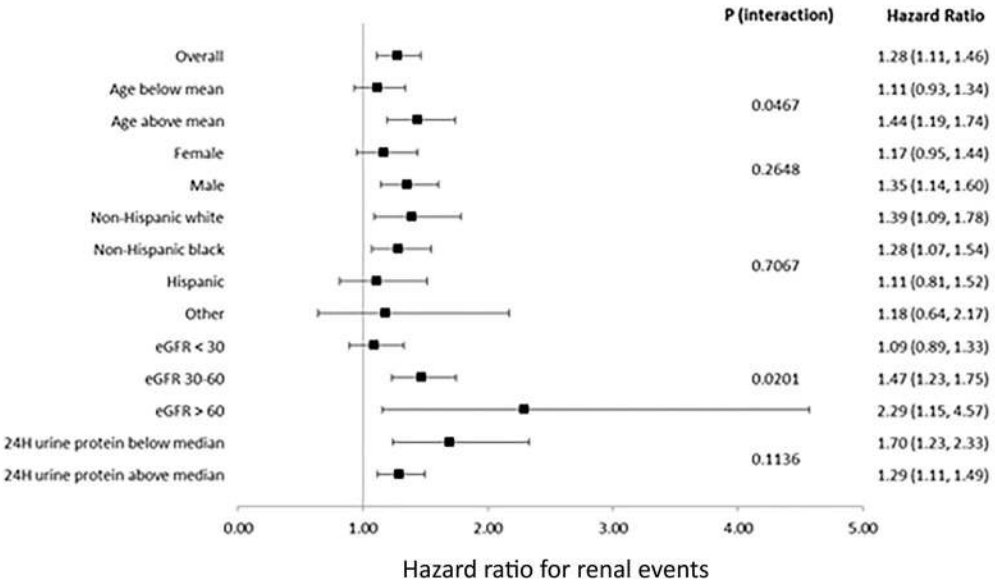

Figure 4.

Figure 4A. Hazard ratios (confidence intervals) for congestive heart failure in participants with or without ATRH in subgroups

Figure 4B. Hazard ratios (confidence intervals) for renal outcomes in participants with or without ATRH in subgroups

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Table 1

Characteristics of CRIC participants by ATRH Status at baseline visit.

Characteristics	Overall population (n = 3367)		
	No ATRH* (n=2008)	ATRH* (n=1359)	P value†
Age, years (mean ± SD)	57.9 ± 11.2	60.6 ± 9.2	<.0001
Female, n (%)	926 (46.1)	561 (41.3)	0.0056
Race, n (%)			<.0001
Non-Hispanic white	896 (44.6)	388 (28.6)	
Non-Hispanic black	776 (38.6)	747 (55)	
Hispanic	266 (13.2)	173 (12.7)	
Other	70 (3.5)	51 (3.8)	
Education, n (%)			<.0001
Less than high school	411 (20.5)	362 (26.6)	
High school graduate	381 (19)	293 (21.6)	
Some college	571 (28.4)	418 (30.8)	
College graduate or higher	645 (32.1)	286 (21)	
Household income, n (%)			<.0001
$20,000 or under	603 (30)	520 (38.3)	
$20,001 – $50,000	492 (24.5)	351 (25.8)	
$50,001 – $100,000	394 (19.6)	190 (14)	
More than $100,000	200 (10)	88 (6.5)	
Don't wish to answer	319 (15.9)	210 (15.5)	
Health insurance, n (%)			<.0001
None	156 (8.6)	91 (7.8)	
Medicaid/Public aid	271 (14.9)	198 (17)	
Any Medicare	604 (33.2)	482 (41.4)	
VA/Military/Champus	100 (5.5)	73 (6.3)	
Private/Commercial	306 (16.8)	126 (10.8)	
Unknown/Incomplete information	383 (21)	195 (16.7)	
Nephrology care, n (%)	1292 (64.3)	984 (72.4)	<.0001
Myocardial infarction, n (%)	313 (15.6)	467 (34.4)	<.0001
Stroke, n (%)	156 (7.8)	206 (15.2)	<.0001
Congestive heart failure, n (%)	110 (5.5)	235 (17.3)	<.0001
Peripheral arterial disease, n (%)	107 (5.3)	135 (9.9)	<.0001
Diabetes, n (%)	863 (43)	889 (65.4)	<.0001
BMI, kg/m^2 (mean ± SD)	31.6 ± 7.7	33.9 ± 7.9	<.0001
Waist circumference, cm (mean ± SD)	104.5± 17.2	110.4 ± 17.2	<.0001
Smoking status, n (%)			0.0142
Never	911 (45.4)	567 (41.7)	
Past	819 (40.8)	623 (45.8)	
Current	278 (13.8)	169 (12.4)	
Any lifestyle modification, n (%)	1949 (97.1)	1345 (99)	0.0002

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Characteristics	Overall population (n = 3367)		
	No ATRH* (n=2008)	ATRH* (n=1359)	P value†
Weight loss, n (%)	1449 (72.5)	1043 (76.9)	0.0044
Exercise, n (%)	1273 (63.7)	835 (61.6)	0.2160
Alcohol reduction, n (%)	1191 (59.6)	880 (64.9)	0.0019
Salt reduction, n (%)	1653 (82.7)	1245 (91.8)	<.0001
Alcohol use, n (%)	1323 (65.9)	731 (53.8)	<.0001
NSAID use, n (%)	1000 (49.8)	785 (57.8)	<.0001
eGFR, ml/min/1.73m^2 (mean ± SD)	45.8 ± 15.6	38.9 ± 13.7	<.0001
eGFR category, n (%)			<.0001
< 30 ml/min/1.73m^2	341 (17)	404 (29.7)	
30–60 ml/min/1.73m^2	1311 (65.3)	853 (62.8)	
> 60 ml/min/1.73m^2	356 (17.7)	102 (7.5)	
24 hour urine protein, g/24h, median (q1, q3)	0.14 (0.07, 0.70)		<.0001
Total cholesterol, mg/dl (mean ± SD)	185.8 ± 45.9	178.9 ± 45.9	<.0001
LDL, mg/dl (mean ± SD)	104 ± 34.9	98.7 ± 35.8	<.0001
HDL, mg/dl (mean ± SD)	48.3 ± 15.9	45.3 ± 14.2	<.0001
24 hour urine sodium, mmol/24h (mean ± SD)	161.7 ± 77.6	165 ± 77.8	0.2344
Systolic blood pressure, mmHg (mean ± SD)	125.3 ± 18.7	139.5 ± 24.0	<.0001
Diastolic blood pressure, mmHg (mean ± SD)	71.9 ± 12.1	72.4 ± 14.5	0.2927
Beta Blockers, n (%)	720 (35.9)	1114 (82)	<.0001
Calcium channel blockers, n (%)	618 (30.8)	939 (69.1)	<.0001
ACE inhibitors, n (%)	978 (48.7)	814 (59.9)	<.0001
Angiotensin receptor blockers, n (%)	447 (22.3)	493 (36.3)	<.0001
Renin-angiotensin system blockers, n (%)	1361 (67.8)	1153 (84.8)	<.0001
Vasodilators, n (%)	77 (3.8)	435 (32.0)	<.0001
Alpha blockers, n (%)	115 (5.7)	405 (29.8)	<.0001
Alpha-2 agonists, n (%)	50 (2.5)	291 (21.4)	<.0001
Potassium sparing diuretics, n (%)	198 (9.9)	165 (12.1)	0.0363
Thiazide diuretics, n (%)	585 (29.1)	481 (35.4)	0.0001
Loop diuretics, n (%)	531 (26.4)	865 (63.6)	<.0001
Diuretics, n (%)	994 (49.5)	1215 (89.4)	<.0001
Not on any diuretics or calcium channel blockers, n (%)	681 (33.9)	27 (2)	<.0001

ATRH = apparent treatment resistant hypertension; BMI = Body Mass Index; eGFR = estimated glomerular filtration rate; LDL = low density lipoprotein; HDL = high density lipoprotein; ACE = angiotensin converting enzyme

*ATRH defined as: mean SBP ≥140 mm Hg and/or DBP ≥90 mm Hg while taking ≥3 anti-hypertensive medications, OR taking ≥4 anti-hypertensive medications with mean SBP < 140 mm Hg and mean DBP < 90 mm Hg

†For continuous variables, the p values are generated using the Student's t test or the Wilcoxon rank sum test; for categorical variables, the p values are generated using the χ^2 test.

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Table 2

Factors associated with apparent treatment resistant hypertension (ATRH)*

Variable	Unadjusted† Odds Ratio (95% CI)	Adjusted‡ Odds Ratio (95% CI)
Age (per 5 year increase)	**1.14 (1.10, 1.18)**	**1.18 (1.13, 1.23)**
Male (ref=Female)	**1.22 (1.06, 1.40)**	**1.61 (1.36, 1.91)**
Race (ref=Non-Hispanic white)		
Non-Hispanic black	**2.22 (1.90, 2.60)**	**2.18 (1.83, 2.59)**
Hispanic	1.50 (1.20, 1.88)	1.08 (0.83, 1.40)
Other	1.68 (1.15, 2.46)	2.20 (1.44, 3.37)
eGFR (per 5 ml/min/1.73m^2 decrease)	**1.17 (1.14, 1.20)**	**1.14 (1.10, 1.17)**
24 hour urine protein (g/24h; doubling)§	**1.45 (1.34, 1.57)**	**1.28 (1.16, 1.42)**
BMI categories (ref=18.5 to less than 25 kg/m^2)		
Less than 18.5 kg/m^2	1.50 (0.62, 3.67)	1.47 (0.55, 3.93)
25 to less than 30 kg/m^2	1.44 (1.13, 1.85)	1.23 (0.94, 1.62)
30 to less than 35 kg/m^2	**1.83 (1.43, 2.34)**	**1.53 (1.16, 2.01)**
35 to less than 40 kg/m^2	**2.47 (1.89, 3.21)**	**2.03 (1.51, 2.73)**
Greater than or equal to 40 kg/m^2	**2.73 (2.08, 3.58)**	**2.26 (1.66, 3.08)**
Diabetes (ref=No)	**2.51 (2.18, 2.89)**	**1.84 (1.56, 2.17)**

BMI = Body Mass Index; eGFR = estimated glomerular filtration rate; ref = reference

*ATRH defined as: mean SBP ≥140 mm Hg and/or DBP ≥90 mm Hg while taking ≥3 anti-hypertensive medications, OR taking ≥4 anti-hypertensive medications with mean SBP < 140 mm Hg and mean DBP < 90 mm Hg

†Logistic regression with ATRH (yes/no) as the outcome variable and each one of the variables as the predictor variable.

‡Logistic regression with ATRH (yes/no) as the outcome variable and all of the variables as the predictor variables.

§24 hour urine protein has a non-normal distribution, and thus log transformation is applied on it.

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Table 3

Hazard ratios for outcomes comparing individuals with and without apparent treatment resistant hypertension (ATRH)*

Outcome	Unadjusted HR (95% CI) (n=3367)	Model A† HR (95% CI) (n=3367)	Model B† HR (95% CI) (n=3332)	Model C† HR (95% CI) (n=3166)
Composite of MI, stroke, PAD n: No ATRH=248, ATRH=296; Median follow-up: 6.8 years	2.03 (1.72, 2.41)	1.84 (1.54, 2.18)	1.41 (1.17, 1.70)	1.26 (1.05, 1.53)
Composite of MI, stroke, PAD, CHF n: No ATRH=380, ATRH=518; Median follow-up: 6.5 years	2.50 (2.19, 2.85)	2.25 (1.96, 2.58)	1.65 (1.43, 1.90)	1.48 (1.28, 1.72)
Composite of MI, stroke, PAD, CHF, all-cause mortality n: No ATRH=581, ATRH=719; Median follow-up: 6.5 years	2.31 (2.07, 2.58)	2.01 (1.80, 2.25)	1.56 (1.38, 1.75)	1.38 (1.22, 1.56)
CHF n: No ATRH=222, ATRH=375; Median follow-up: 6.8 years	3.01 (2.55, 3.55)	2.73 (2.30, 3.23)	1.92 (1.60, 2.29)	1.66 (1.38, 2.00)
Stroke n: No ATRH=68, ATRH=89; Median follow-up: 7.1 years	2.14 (1.56, 2.93)	1.85 (1.33, 2.55)	1.53 (1.08, 2.17)	1.40 (0.97, 2.02)
Renal: 50% decrease in eGFR or end stage renal disease defined as renal transplantation or start of long-term renal dialysis n: No ATRH=522, ATRH=601; Median follow-up: 5.0 years	2.19 (1.95, 2.47)	2.11 (1.87, 2.38)	1.84 (1.61, 2.09)	1.28 (1.11, 1.46)
All-cause mortality n: No ATRH=345, ATRH=440; Median follow-up: 7.4 years	2.10 (1.82, 2.41)	1.79 (1.55, 2.07)	1.44 (1.23, 1.68)	1.24 (1.06, 1.45)

*ATRH defined as: mean SBP ≥140 mm Hg and/or DBP ≥90 mm Hg while taking ≥3 anti-hypertensive medications, OR taking ≥4 anti-hypertensive medications with mean SBP < 140 mm Hg and mean DBP < 90 mm Hg

n = number of events

†Cox regression model for each outcome variable with ATRH (yes/no) as the main predictor variable.

Model A: adjusted for age (years), gender (male/female), race (non-Hispanic white, non-Hispanic black, Hispanic, other), and center (7 categories).

Model B: adjusted for model A plus diabetes (yes/no), smoking status (never/past/current), cardiovascular disease (yes/not yes), BMI (kg/m^2), hemoglobin (g/dl), and LDL (mg/dl)

Model C: adjusted for model B plus eGFR ($ml/min/1.73m^2$) and 24 hour urine protein§ (g/24h)

§24 hour urine protein has a non-normal distribution, and thus log transformation is applied on it.

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Table 4

Hazard ratios for clinical outcomes comparing participants with and without apparent treatment resistant hypertension (ATRH) by definitions based on BP Control Status and use of diuretic

Outcome	Adjusted HR (95% CI) in those with BP not at goal on ≥3 medications*	Adjusted HR (95% CI) in those with BP not at goal on ≥3 medications including a diuretic†	Adjusted HR (95% CI) in those with BP at goal on ≥4 medications*
Composite of MI, stroke, PAD	1.29 (1.02, 1.62) n: No ATRH=248, ATRH=160; median follow up: 6.9 years	1.26 (0.99, 1.59) n: No ATRH=272, ATRH=136; median follow up: 6.9 years	1.18 (0.93, 1.48) n: No ATRH=248, ATRH=136; median follow up: 7 years
Composite of MI, stroke, PAD, CHF	1.49 (1.25, 1.79) n: No ATRH=380, ATRH=275; median follow up: 6.7 years	1.50 (1.25, 1.80) n: No ATRH=415, ATRH=240; median follow up: 6.7 years	1.42 (1.18, 1.70) n: No ATRH=380, ATRH=243; median follow up: 6.8 years
Composite of MI, stroke, PAD, CHF, all-cause mortality	1.41 (1.21, 1.63) n: No ATRH=581, ATRH=391; median follow up: 6.7 years	1.45 (1.24, 1.68) n: No ATRH=628, ATRH=344; median follow up: 6.7 years	1.30 (1.12, 1.51) n: No ATRH=581, ATRH=328; median follow up: 6.8 years
CHF	1.62 (1.29, 2.02) n: No ATRH=222, ATRH=194; median follow up: 6.9 years	1.65 (1.32, 2.06) n: No ATRH=241, ATRH=175; median follow up: 6.9 years	1.59 (1.28, 1.99) n: No ATRH=222, ATRH=181; median follow up: 7 years
Stroke	1.45 (0.95, 2.23) n: No ATRH=68, ATRH=53; median follow up: 7.1 years	1.23 (0.80, 1.90) n: No ATRH=80, ATRH=41; median follow up: 7.1 years	1.11 (0.70, 1.75) n: No ATRH=68, ATRH=36; median follow up: 7.3 years
Renal: 50% decrease in eGFR or end stage renal disease defined as renal transplantation or start of long-term renal dialysis	1.46 (1.25, 1.71) n: No ATRH=522, ATRH=372; median follow up: 5 years	1.49 (1.27, 1.75) n: No ATRH=565, ATRH=329; median follow up: 5 years	1.05 (0.88, 1.25) n: No ATRH=522, ATRH=229; median follow up: 5.7 years
All-cause mortality	1.24 (1.02, 1.50) n: No ATRH=345, ATRH=244; median follow up: 7.5 years	1.32 (1.09, 1.60) n: No ATRH=371, ATRH=218; median follow up: 7.5 years	1.11 (0.91, 1.36) n: No ATRH=345, ATRH=196; median follow up: 7.5 years

Adjusted for age (years), gender (male/female), race non-Hispanic white, non-Hispanic black, Hispanic, other), center (7 categories), diabetes (yes/no), smoking status (never/past/current), cardiovascular disease (yes/not yes), BMI (kg/m^2), hemoglobin (g/dl), LDL (mg/dl), eGFR (ml/min/1.73m^2) and 24 hour urine protein § (g/24h)

n = number of events

*compared to ATRH, No ATRH defined as patients who are adequately treated and at goal on ≤3 medications, and also those with BP not at goal but on fewer than 3 medications

†compared to ATRH, No ATRH defined as patients who are adequately treated and at goal on ≤3 medications and those with BP not at goal but on fewer than 3 medications or not on a diuretic

§24 hour urine protein has a non-normal distribution, and thus log transformation is applied on it