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Obesity, African American race, chronic kidney disease, and resistant hypertension: the step beyond observed risk

Eric Judd, MD[1] and **David A. Calhoun, MD**[1]

[1]University of Alabama at Birmingham

The risk surrounding individuals with blood pressure (BP) that is difficult-to-control has now been characterized in many different populations in the United States. Prospective cohort studies[1,2], retrospective analyses of large clinical registries[3,4], and subgroup analyses of clinical trials[5,6] have consistently identified a higher prevalence of obesity, African American race, chronic kidney disease, and diabetes mellitus among individuals with apparent treatment resistant hypertension (ATRH). Despite subtle differences in defining ATRH between studies, individuals with difficult-to-control BP are at increased risk for cardiovascular and kidney events compared to individuals with hypertension being treated with less than 3 antihypertensive medications.[1,2,5,7,8] In this issue of *Hypertension*, Thomas *et al.* expand these risk associations into the chronic kidney disease (CKD) population by examining ATRH in the Chronic Renal Insufficiency Cohort (CRIC).

The CRIC study included an ethnically diverse group of adults from across the United States with an estimated glomerular filtration rate (eGFR) 20–70 mL/min/1.73m^2. Hypertension was present in 85.7% of the cohort, highlighting the strong, interdependent relationship between kidney disease and hypertension. Adhering to the American Heart Association definition of resistant hypertension[9], Thomas *et al.* reported a prevalence of ATRH of 40.4% among CRIC study participants with hypertension. While much higher than prevalence estimates for ATRH in general hypertensive populations (12.8 – 21.5%), it is no surprise that ATRH is more common in CKD populations. In a cross-sectional analysis of the Kaiser Permanente Southern California health system, CKD had the strongest association with resistant hypertension with an adjusted odds ratio of 1.84 (1.78–1.90, 95% CI).[3] When evaluated, CKD is inevitably associated with resistant hypertension.[1,3,4]

The analyses by Thomas *et al.* are well suited to characterize the relationship between CKD and ATRH. Overall, late stages of CKD and ATRH commonly coexist. Over half of CRIC study participants with an eGFR < 30 mL/min/1.73m^2 met criteria for ATRH. In an adjusted model, every 5 mL/min/1.73m^2 decrease in eGFR was associated with a 14% higher odds of ATRH and a doubling of proteinuria was associated with a 28% higher odds of ATRH. Many risk factors for developing CKD and hypertension overlap, and certain comorbidities like diabetes mellitus are also dependent on shared conditions like obesity or socioeconomic

Correspondence: Eric Judd, MD, Vascular Biology and Hypertension Program, CH19 Room 115, 1720 2nd Ave South, Birmingham, AL 35294-2041 Tel: 205 934-9281; fax: 205 934-1302; ejudd@uab.edu.

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status. Notably, kidney function and proteinuria were independently associated with ATRH after adjusting for age, gender, race, body mass index, and diabetes mellitus.

Besides kidney function and proteinuria, the strongest risk factors associated with ATRH in the CRIC were non-Hispanic black race [adjusted OR 2.18 (1.83–2.59, 95% CI)] and body mass index ≥ 40 kg/m^2 [adjusted OR 2.26 (1.66–3.08, 95% CI)]. These findings are consistent with those seen in the Reasons for Geographic And Racial Differences in Stroke (REGARDS) prospective study where African Americans were oversampled and comprised a similar proportion of the cohort (42% of REGARDS and 45% of CRIC).[2,10] In REGARDS participants with a history of stroke or transient ischemic attack, multivariable adjusted analysis revealed Black race, CKD, albuminuria, and waist circumference as the primary factors independently associated with ATRH.[10] While findings from observational studies are limited by design in their ability to identify causal relationships, the repeated and consistent associations between resistant hypertension and CKD, African American race, and obesity throughout United States study populations implies a shared pathophysiology.

Resistant hypertension, in general, portends worse cardiovascular and kidney disease. Compared to hypertensive individuals without ATRH, individuals with ATRH start dialysis at a rate 6 times higher [HR 6.32 (4.3–9.3, 95% CI)][8], have 24% higher risk for ischemic heart events [HR 1.24 (1.20–1.28, 95% CI)][7], have 46% higher risk of developing congestive heart failure [HR 1.46 (1.40–1.52, 95% CI)][7], and with an uncontrolled BP have 36% higher risk of all-cause mortality [HR 1.36 (1.18–1.57, 95% CI)].[1] Outcome assessment comparing individuals with and without ATRH in the CRIC population reveals similar risks. After adjusting for demographics and comorbidities, individuals with ATRH are at 48% higher risk for combined cardiovascular events of myocardial infarction, stroke, peripheral arterial disease, or heart failure; 28% higher risk for halving of eGFR or end-stage kidney disease; and 24% higher risk for all-cause mortality.[2]

When comparing risk between groups, the composition of the ATRH group may differ between studies. For example, the hazard ratio for all-cause mortality in the REGARDS cohort is 1.14 (0.93–1.40, 95% CI) for individuals receiving ≥ 4 antihypertensive medications and who have a controlled BP when compared to individuals without ATRH, which differs from the 1.36 HR (1.18–1.57, 95% CI) seen when the ATRH group is composed of individuals with an uncontrolled BP receiving ≥ 3 antihypertensive medications.[1] In order to address any potential discrepancies, Thomas *et al.* performed Cox regression modeling for 3 separate ATRH groups in a sensitivity analysis. Hazard ratios for composite cardiovascular outcomes were similar regardless of how ATRH was defined (uncontrolled BP on ≥ 3 medications, uncontrolled BP on ≥ 3 medications including a diuretic, or controlled BP on ≥ 4 medications). However, ATRH defined by an uncontrolled BP with or without a diuretic was associated with a significant increase in risk of the composite renal outcome and all-cause mortality, which was not seen in the ATRH group defined by controlled BP on ≥ 4 medications. Although not definitive, results from this sensitivity analysis support a potential benefit in up titrating antihypertensive medication in patients with CKD to achieve BP control.

The findings reported by Thomas *et al*. fit in nicely with existing data that together identify key risk factors associated with major non-communicable diseases in the United States. Data gathered by the Institute for Health Metrics and Evaluation show that non-communicable diseases now dominate as the cause of years of healthy life lost, measured by disability-adjusted life years (DALYs), in developed countries. Some of this can be explained by an aging population that is accumulating comorbidities. However, in the United States age-standardized rates of CKD and diabetes mellitus are rising and can be attributed to metabolic risk factors.

Examining risk factors associated with known high risk groups like ATRH, illuminates the high impact areas for risk modification. Obesity, African American race, and CKD are consistent independent predictors of ATRH. Note, the association between ATRH and diabetes mellitus is also evident but diminished by the shared comorbidities of obesity and CKD. The aim of controlling BP is to reduce the risk of cardiovascular and kidney disease. Certainly, prescribing antihypertensive regimens that are effective for each individual, evaluating for secondary causes of hypertension, identifying confounding medications, and encouraging patient adherence to their regimen is critical in achieving BP control. However, studies like the one by Thomas *et al.* have identified new targets for BP management and research. The greatest impact in reducing cardiovascular and kidney disease may be through prevention of risk factor development and early identification of high risk groups.

In an analysis of 6 healthy lifestyle factors among patients with ATRH in the REGARDS cohort, self-reported exercise ≥ 4 times per week and not smoking were associated with reduced cardiovascular risk [adjusted HR 0.67 (0.50–0.91, 95% CI) and 0.54 (0.41–0.72, 95% CI), respectively].[11] Closely following the Dietary Approaches to Stop Hypertension (DASH) diet or having a low sodium-to-potassium intake were not associated with reduced risk. However, nutritional assessment of the diet was performed on a self-administered food frequency questionnaire.

A low sodium diet has been shown to improve BP control among patients with resistant hypertension and is recommended in salt-sensitive hypertension, which is more common in both African Americans and individuals with CKD. However, effectively intervening on dietary salt intake at the individual level is challenging. A large proportion of CRIC participants reported attempts to reduce dietary sodium. The reported prevalence of sodium restriction was significantly higher among individuals with ATRH compared with those without ATRH (91.8% vs. 82.7%, $p < 0.0001$). However, no difference was seen in the 24-hour urine sodium content between the ATRH and no ATRH groups (165 ± 77.8 mmol vs. 161.7 ± 77.6 mmol, p 0.23).[2] Despite a high self-report of dietary sodium restriction, CRIC participants consumed an average of 1.4 grams more sodium than the recommended 2.3 grams/day.

In conclusion, the findings reported by Thomas *et al*. advance the risk characterization associated with ATRH, and along with other observational studies, we can now say that the risk of ATRH has been observed. In addition to continued efforts in developing strategies to improve BP control, the next major step in reducing cardiovascular disease, kidney disease, and DALYs may be risk factor prevention and targeted interventions in high risk groups like

African Americans. Preventing development of obesity and CKD has the potential to improve BP control.

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