RESEARCH LETTERS

Sodium Excretion and Cardiovascular Outcomes in African American Patients With CKD: Findings From the African American Study of Kidney Disease and Hypertension

To the Editor:

Patients with chronic kidney disease (CKD) are advised to reduce sodium intake, but some studies show higher risks for death and cardiovascular events at lower levels of sodium intake.[1-3] However, many previous studies used a single 24-hour urine collection to estimate sodium intake,[4] and studies in CKD were conducted in relatively homogenous European or Australian cohorts.[3,5-8] In contrast, the African American Study of Kidney Disease and Hypertension (AASK) was comprised of self-identified African Americans with significant CKD and ascertained serial 24-hour urine collections.[9] We used data from AASK to evaluate the association of sodium excretion with blood pressure (BP), left ventricular mass, and cardiovascular events among African Americans with hypertensive CKD.

For the outcomes of systolic and diastolic BP, we used average values ascertained by 24-hour ambulatory BP monitoring (ABPM) during the cohort phase. Left ventricular mass was measured using 2-dimensional and M-mode imaging from a limited transthoracic echocardiogram during the cohort phase. We examined the cardiovascular composite end point of hospitalization for myocardial infarction, heart failure, stroke, cardiovascular death, or death from any cause.

During the AASK trial phase (1995-1998), 24-hour urine collections were ascertained at baseline and every 6 months thereafter. During the AASK cohort phase (2002-2007), 24-hour urine collections were ascertained at baseline and annually thereafter. We describe baseline characteristics by quintile of mean calibrated 24-hour urinary sodium excretion collected during the first 18 months of the trial phase (median number of urine collections, 3; interquartile range, 2-4). To correct for potential incomplete 24-hour samples, we calibrated urine sodium excretion to mean sex-specific creatinine excretion[10]: 1,745 mg/24 h for men and 1,194 mg/24 h for women.

We used the %SPECI SAS Macro[11] (SAS Institute Inc) to determine the form of sodium excretion that provided the best combination of model fit and clinical applicability for each of our outcomes. To examine the association of sodium excretion with BP and left ventricular mass, we used linear regression, using the mean of all available 24-hour urine collections from randomization up to (but not after) the date of the ABPM or echocardiogram (median number of urine collections, 10; interquartile range, 8-12), respectively. We report the β coefficient for each 1-g increase in urinary sodium excretion and 95% confidence intervals.

To examine the association of sodium excretion with the cardiovascular composite end point, we used proportional hazards regression models and report hazard ratios and 95% confidence intervals. We modeled sodium excretion as a time-varying continuous variable, calculating the cumulative mean urinary sodium excretion using all available 24-hour urine sodium measurements. Follow-up time began at the start of the trial phase. To account for multiple records per patient, we used robust sandwich covariance estimates. Because only 4% of patients were missing 1 or more variables, we performed a complete-case analysis.

All analyses were done using SAS Enterprise Guide 7.15 (SAS Institute Inc). The Institutional Review Board at Stanford University determined that use of the publicly available AASK data set for research did not require further review. This research was conducted under data use agreement 20629 with the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Central Database Repository.

Of the 1,094 participants in AASK, 1,061 had at least one 24-hour urine collection during the first 18 months of the trial phase and were included in the analysis. Overall, mean sodium excretion was 3.7 ± 1.5 g/d (Table 1). Of the 691 participants from the AASK trial phase who enrolled in the cohort phase, 647 had ABPM available. Each 1-g increase in 24-hour sodium excretion was associated with a 1.3/0.9 mm Hg increase in systolic/diastolic BP (Table 2). Higher urinary sodium excretion was associated with higher left ventricular mass (Table 2). During a total of 7,792 person-years of follow-up, there were 354 cardiovascular composite end points (event rate, 4.5/100 person-years). We found no significant association of sodium excretion with the cardiovascular composite end point (Table 2).

In conclusion, using multiple 24-hour urine collections collected in African American patients with hypertensive CKD, we found a modest association between sodium excretion and BP. Although we found an association between sodium excretion and left ventricular mass, we found no significant association of sodium excretion with the cardiovascular composite end point. However, AASK was not originally powered to detect differences in cardiovascular outcomes. Well-designed studies with optimal sodium assessment methodology are needed to determine its relation with cardiovascular and other important clinical outcomes, particularly in patients with CKD.

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Table 1. Baseline Characteristics by Quintile of 24-Hour Sodium Excretion During the First 18 Months of the AASK Trial Phase

	Q1	Q2	Q3	Q4	Q5	*P*-Trend
Urine sodium, mg/24 h	2,079.4 ± 429.3	2,886.2 ± 154.5	3,430.0 ± 189.3	4,160.5 ± 235.9	5,937.5 ± 1,345.3	<0.001
Demographics						
Age, y	54.9 ± 11.0	54.7 ± 10.6	54.5 ± 11.2	53.5 ± 10.8	55.0 ± 10.1	0.70
Female sex	131 (61.8%)	96 (45.3%)	84 (39.4%)	56 (26.4%)	51 (24.1%)	<0.001
Employed	69 (32.5%)	84 (39.6%)	97 (45.5%)	82 (38.7%)	70 (33.0%)	>0.99
Lives alone	50 (23.6%)	43 (20.3%)	42 (19.7%)	43 (20.3%)	57 (26.9%)	0.46
<High school education	80 (37.7%)	86 (40.6%)	83 (39.0%)	88 (41.5%)	91 (42.9%)	0.29
<$15,000 annual income	109 (51.4%)	96 (45.3%)	96 (45.1%)	100 (47.2%)	104 (49.1%)	0.79
Insurance status						
Private	87 (41.0%)	96 (45.3%)	99 (46.5%)	82 (38.7%)	84 (39.6%)	0.38
Medicare/Medicaid	52 (24.5%)	46 (21.7%)	52 (24.4%)	51 (24.1%)	54 (25.5%)	0.65
None	73 (34.4%)	70 (33.0%)	62 (29.1%)	79 (37.3%)	74 (34.9%)	0.61
Family history of end-stage renal disease	26 (12.3%)	22 (10.4%)	34 (16.0%)	25 (11.8%)	31 (14.6%)	0.40
Left ventricular hypertrophy	68 (32.1%)	73 (34.4%)	77 (36.2%)	95 (44.8%)	91 (42.9%)	0.002
History of heart disease	108 (50.9%)	97 (45.8%)	101 (47.4%)	116 (54.7%)	121 (57.1%)	0.05
Current smoker	48 (22.6%)	55 (25.9%)	62 (29.1%)	69 (32.5%)	73 (34.4%)	0.002
Exercises	105 (49.5%)	85 (40.1%)	104 (48.8%)	84 (39.6%)	85 (40.1%)	0.07
Drinks alcohol	41 (19.3%)	49 (23.1%)	67 (31.5%)	77 (36.3%)	61 (28.8%)	0.001
Measured glomerular filtration rate, mL/min/1.73 m^2						
>60	38 (17.9%)	42 (19.8%)	36 (16.9%)	39 (18.4%)	43 (20.3%)	0.70
45-59	82 (38.7%)	88 (41.5%)	81 (38.0%)	86 (40.6%)	72 (34.0%)	0.33
30-44	62 (29.2%)	50 (23.6%)	62 (29.1%)	51 (24.1%)	61 (28.8%)	0.96
<30	30 (14.2%)	32 (15.1%)	34 (16.0%)	36 (17.0%)	36 (17.0%)	0.34
Mean ± SD	46.6 ± 13.4	47.4 ± 13.4	46.2 ± 14.0	46.9 ± 13.8	45.9 ± 13.6	0.52
Albumin, g/dL	4.2 ± 0.3	4.2 ± 0.3	4.3 ± 0.3	4.2 ± 0.3	4.2 ± 0.4	0.04
Body mass index, kg/m^2	30.0 ± 6.4	30.9 ± 6.7	30.5 ± 6.4	31.0 ± 6.5	30.7 ± 6.8	0.32
Systolic blood pressure, mm Hg	148.5 ± 23.9	147.7 ± 24.9	148.7 ± 22.8	152.2 ± 23.1	153.8 ± 24.1	0.004
Diastolic blood pressure, mm Hg	94.0 ± 13.1	94.5 ± 15.1	94.0 ± 13.7	97.3 ± 15.3	97.7 ± 13.7	<0.001
Baseline diuretic use	113 (53.3%)	135 (63.7%)	137 (64.3%)	128 (60.4%)	148 (69.8%)	0.005

Note: Categorical variables are given as number (percent); continuous variables are given as mean ± SD. N = 212 for quartiles 1, 2, 4 and 5. N = 213 for quartile 3.
Abbreviation: AASK, African American Study of Kidney Disease and Hypertension; Q, quartile; SD, standard deviation.

Table 2. Association of 1,000-mg Increase in 24-Hour Sodium Excretion With Specified Outcomes

	N	Unadjusted	Adjusted[a]
Systolic blood pressure, mm Hg	647	β, 1.23; 95% CI, 0.19 to 2.27	β, 1.31; 95% CI, 0.21 to 2.42
Diastolic blood pressure, mm Hg	647	β, 1.01; 95% CI, 0.36 to 1.67	β, 0.88; 95% CI, 0.21 to 1.56
Left ventricular mass (2D), g	613	β, 18.79; 95% CI, 13.59 to 23.98	β, 8.81; 95% CI, 3.70 to 13.93
Left ventricular mass (M-mode), g	621	β, 14.43; 95% CI, 8.75 to 20.11	β, 3.31; 95% CI, −2.32 to 8.93
Death or cardiovascular events	1021	HR, 1.09; 95% CI, 1.02 to 1.15	HR, 1.03; 95% CI, 0.96 to 1.11

Note: Values shown are the β coefficient or HR as indicated and 95% CIs.
Abbreviations: 2D, 2-dimensional; CI, confidence interval; HR, hazard ratio.
[a]Models were adjusted for age, sex, employment status, income, education, insurance status, family history of end-stage renal disease, exercise, drinks alcohol, current smoking, chronic kidney disease stage, history of heart disease, evidence of left ventricular hypertrophy on electrocardiogram, body mass index, serum albumin level, baseline diuretic use, and randomly assigned blood pressure and antihypertensive medication intervention groups.

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REFERENCES

1. O'Donnell M, Mente A, Rangarajan S, et al. Urinary sodium and potassium excretion, mortality, and cardiovascular events. *N Engl J Med*. 2014;371:612-623.
2. Stolarz-Skrzypek K, Kuznetsova T, Thijs L, et al. Fatal and nonfatal outcomes, incidence of hypertension, and blood pressure changes in relation to urinary sodium excretion. *JAMA*. 2011;305:1777-1785.
3. Thomas MC, Moran J, Forsblom C, et al. The association between dietary sodium intake, ESRD, and all-cause mortality in patients with type 1 diabetes. *Diabetes Care*. 2011;34:861-866.
4. Cobb LK, Anderson CAM, Elliott P, et al. Methodological issues in cohort studies that relate sodium intake to cardiovascular disease outcomes: a science advisory from the American Heart Association. *Circulation*. 2014;129(10):1173-1186.
5. Cianciaruso B, Bellizzi V, Minutolo R, et al. Salt intake and renal outcome in patients with progressive renal disease. *Miner Electrolyte Metab*. 1998;24:296-301.
6. McMahon EJ, Bauer JD, Hawley CM, et al. A randomized trial of dietary sodium restriction in CKD. *J Am Soc Nephrol*. 2013;24:2096-2103.
7. Smyth A, Dunkler D, Gao P, et al. The relationship between estimated sodium and potassium excretion and subsequent renal outcomes. *Kidney Int*. 2014;86(6):1205-1212.
8. Vegter S, Perna A, Postma MJ, Navis G, Remuzzi G, Ruggenenti P. Sodium intake, ACE inhibition, and progression to ESRD. *J Am Soc Nephrol*. 2012;23:165-173.
9. Wright JT Jr, Bakris G, Greene T, et al. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial. *JAMA*. 2002;288:2421-2431.
10. Mills KT, Chen J, Yang W, et al. Sodium excretion and the risk of cardiovascular disease in patients with chronic kidney disease. *JAMA*. 2016;315:2200-2210.
11. Liu S, Stedman M. A SAS Macro for Covariate Specification in Linear, Logistic, and Survival Regression: Paper 1223-2017. *Proceedings of the SAS Global 2017 Conference*. Cary, NC: SAS Institute Inc; 2017.

Physician Attitudes on Kidney Biopsies for Research: A Survey Study

To the Editor:

Kidney biopsy is the gold standard for diagnosing many kidney diseases, but only a minute fraction of patients undergoes this invasive procedure.[1] Severe bleeding is a major complication associated with biopsy.[2,3] Recent interest in kidney biopsies for research purposes has raised the question of safety for participants.[4] To understand how physicians perceive the risks of kidney biopsy, we sent an institutional review board–approved anonymous online survey to 60 hospitalists at 1 academic hospital in Boston and 98 nephrologists at 3 academic hospitals in Boston. Survey participants were asked about their clinical experience, their perceived risk of kidney biopsies, and the likelihood that they would support biopsies being obtained from their patients for research purposes.

The overall response rate was 46% (15/60 hospitalists and 57/98 nephrologists). Twenty-nine (51%) nephrologists had mixed clinical, research, and administrative roles. Twelve (21%) identified as clinicians, and 16 (28%), as researchers. Twenty-eight (47%) were in practice for more than 10 years. All but 1 of the hospitalists had a patient who had undergone a kidney biopsy in the previous 5 years. Three (5%) nephrologists had never done a biopsy, 12 (21%) had performed 10 or fewer, 25 (44%) had performed 11 to 50, and 17 (30%) had performed more than 50 biopsies.

Participants were asked to estimate the likelihood of a variety of postbiopsy complications, including hematoma formation, need for transfusion, need for angiographic or surgical intervention, kidney loss, and death (Table 1). Hospitalists were more likely to underestimate the risk for hematoma complicating a biopsy compared with nephrologists. There were no significant differences between respondents' assessments of kidney biopsy risk when comparing researchers versus clinicians or stratifying by years of experience or number of biopsies performed. The current literature suggests that the risks for hematoma,