Title

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Journal

Nephrology Dialysis Transplantation, 37(9)

ISSN

0931-0509

Authors

Ascher, Simon B
Scherzer, Rebecca
Estrella, Michelle M
et al.

Publication Date

2022-08-22

DOI

10.1093/ndt/gfab255

Peer reviewed

Nephrol Dial Transplant (2022) 37: 1637–1646
doi: 10.1093/ndt/gfab255
Advance Access publication 2 September 2021

ORIGINAL ARTICLE

Kidney tubule health, mineral metabolism and adverse events in persons with CKD in SPRINT

Simon B. Ascher[1,2], Rebecca Scherzer[1], Michelle M. Estrella[1], Jarett D. Berry[3], James A. de Lemos[3], Vasantha K. Jotwani[1], Pranav S. Garimella[4], Rakesh Malhotra[4], Alexander L. Bullen[4,5], Ronit Katz[6], Walter T. Ambrosius[7], Alfred K. Cheung[8,9], Michel Chonchol[10], Anthony A. Killeen [11], Joachim H. Ix[4,5,*] and Michael G. Shlipak[1,*], for the SPRINT Research Group

[1]Department of Medicine, Kidney Health Research Collaborative, San Francisco Veterans Affairs Health Care System and University of California San Francisco, San Francisco, CA, USA, [2]Division of Hospital Medicine, University of California Davis, Sacramento, CA, USA, [3]Divison of Cardiology, University of Texas Southwestern Medical Center, Dallas, TX, USA, [4]Division of Nephrology-Hypertension, University of California San Diego, San Diego, CA, USA, [5]Nephrology Section, Veterans Affairs San Diego Healthcare System, San Diego, CA, USA, [6]Department of Obstetrics and Gynecology, University of Washington, Seattle, WA, USA, [7]Department of Biostatistics and Data Science, Wake Forest School of Medicine, Winston-Salem, NC, USA, [8]Division of Nephrology and Hypertension, University of Utah Health, Salt Lake City, UT, USA, [9]Department of Medical Service, Veterans Affairs Salt Lake City Health Care System, Salt Lake City, UT, USA, [10]Division of Renal Diseases and Hypertension, University of Colorado Denver, Aurora, CO, USA and [11]Department of Laboratory Medicine and Pathology, University of Minnesota, Minneapolis, MN, USA

*These authors contributed equally to this work.
Correspondence to: Michael G. Shlipak; E-mail: michael.shlipak@ucsf.edu

ABSTRACT

Background. Measures of kidney tubule health are risk markers for acute kidney injury (AKI) in persons with chronic kidney disease (CKD) during hypertension treatment, but their associations with other adverse events (AEs) are unknown.

Methods. Among 2377 Systolic Blood Pressure Intervention Trial (SPRINT) participants with CKD, we measured at baseline eight urine biomarkers of kidney tubule health and two serum biomarkers of mineral metabolism pathways that act on the kidney tubules. Cox proportional hazards models were used to evaluate biomarker associations with risk of a composite of prespecified serious AEs (hypotension, syncope, electrolyte abnormalities, AKI, bradycardia and injurious falls) and outpatient AEs (hyperkalemia and hypokalemia).

Results. At baseline, the mean age was 73 ± 9 years and mean estimated glomerular filtration rate (eGFR) was 46 ± 11 mL/min/1.73 m^2. During a median follow-up of 3.8 years, 716 (30%) participants experienced the composite AE. Higher urine interleukin-18, kidney injury molecule-1, neutrophil gelatinase-associated lipocalin (NGAL) and monocyte chemoattractant protein-1 (MCP-1), lower urine uromodulin (UMOD) and higher serum fibroblast growth factor-23 were individually associated with higher risk of the composite AE outcome in multivariable-adjusted models including eGFR and albuminuria. When modeling biomarkers in combination, higher NGAL [hazard ratio (HR) = 1.08 per 2-fold higher biomarker level, 95% confidence interval (CI) 1.03–1.13], higher MCP-1 (HR = 1.11, 95% CI 1.03–1.19) and lower UMOD (HR = 0.91, 95% CI 0.85–0.97) were each associated with higher composite AE risk. Biomarker associations did not vary by intervention arm ($P > 0.10$ for all interactions).

Conclusions. Among persons with CKD, several kidney tubule biomarkers are associated with higher risk of AEs during hypertension treatment, independent of eGFR and albuminuria.

Keywords: adverse events, biomarkers, chronic kidney disease, hypertension, kidney tubule

INTRODUCTION

Hypertension is the single largest contributor to cardiovascular disease (CVD) and the most common comorbidity affecting persons with chronic kidney disease (CKD), with a prevalence ranging from 67% to 92% depending on CKD stage [1, 2]. The Systolic Blood Pressure Intervention Trial (SPRINT) demonstrated in individuals with hypertension and high CVD risk that a systolic blood pressure (SBP) target of <120 mm Hg compared with <140 mm Hg significantly reduced CVD events and all-cause deaths, but also increased the risk of hypotension, syncope, electrolyte abnormalities and acute kidney injury (AKI) [3]. Intensive BP lowering appeared to have a similar risk reduction for CVD and mortality and increased the risk of AKI, hyperkalemia and hypokalemia in the 28% of SPRINT participants with a baseline estimated glomerular filtration rate (eGFR) of 20–59 mL/min/1.73 m^2 [4]. Ongoing debate remains

KEY LEARNING POINTS

What is already known about this subject?

- Hypertension is the single largest contributor to cardiovascular disease (CVD) and the most common comorbidity affecting individuals with chronic kidney disease (CKD).
- Identifying risk markers for adverse events (AEs) during hypertension treatment may be useful for achieving blood pressure (BP) goals safely.
- Subclinical measures of kidney tubule health and mineral metabolism are associated with higher risk of CVD, mortality, longitudinal estimated glomerular filtration rate (eGFR) decline and acute kidney injury, but their relationships with common antihypertensive-related AEs are unknown.

What this study adds?

- Several biomarkers reflecting kidney tubule dysfunction, injury, inflammation and disordered mineral metabolism are associated with higher risk of AEs during hypertension treatment, independent of eGFR and albuminuria.
- Urine neutrophil gelatinase-associated lipocalin, monocyte chemoattractant protein-1 and uromodulin were selected from a panel of 10 biomarkers as having the strongest associations with risk of AEs when modeled in combination.

What impact this may have on practice or policy?

- The kidney tubules are an underappreciated dimension of kidney health and may be an important determinant of AEs during hypertension treatment.
- In the context of prior work, kidney tubule biomarkers provide prognostic information about both the benefits and harms of intensive BP lowering in individuals with CKD.

about the evidence for lower BP targets in persons with CKD, resulting in differing guideline recommendations and added emphasis on individualizing BP targets [5–7]. Thus, there is a pressing need to identify risk factors that provide information about both the benefits and harms of intensive BP lowering in persons with CKD.

The kidney tubules comprise >90% of the kidney's cortical mass and have a central role in BP regulation, electrolyte balance and drug secretion [8]. However, neither eGFR nor albuminuria, which define and stage CKD, adequately capture kidney tubule health. We previously found that biomarkers reflecting pathophysiological processes specific to the kidney tubules have independent associations with AKI in SPRINT participants with CKD [9]. Whether measures of kidney tubule health or mineral metabolism pathways that act on the kidney tubules are associated with risk of other adverse events (AEs) during antihypertensive treatment is unknown.

Our study had three objectives. First, we evaluated the associations of baseline clinical characteristics with risk of a composite of AEs of interest among SPRINT participants with CKD. We hypothesized that clinical characteristics, eGFR and albuminuria would be independently associated with risk of the composite AE. Second, we evaluated the associations of 10 biomarkers reflecting kidney tubule health and mineral metabolism pathways that act on the kidney tubules with risk of both the composite AE and individual AEs of interest. Finally, we evaluated whether biomarker associations varied by randomization to intensive versus standard BP lowering. We hypothesized that biomarker levels indicating compromised kidney tubule health or disordered mineral metabolism would be associated with increased risk of the composite AE, independent of eGFR, albuminuria and randomized BP treatment arm.

MATERIALS AND METHODS

Study design

The design and protocol of SPRINT have been reported previously [3, 10]. In brief, SPRINT was an open-label clinical trial that randomized participants with hypertension to an 'intensive' SBP target of <120 mmHg versus a 'standard' SBP target of <140 mmHg. Inclusion criteria were age ≥50 years; SBP 130–180 mmHg; and high CVD risk [defined as prior clinical or subclinical CVD other than stroke, CKD (eGFR 20–59 mL/min/1.73 m^2), age ≥75 years or 10-year CVD risk >15% based on the Framingham risk score]. Key exclusion criteria included diabetes mellitus, eGFR <20 mL/min/1.73 m^2 and proteinuria >1 g/day. A total of 9361 participants were enrolled between November 2010 and March 2013 across 102 sites in the USA and Puerto Rico. The SPRINT protocol comprised a baseline visit and follow-up visits monthly for the first 3 months, then every 3 months thereafter. The trial was stopped early after a median follow-up of 3.26 years due to interim CVD and mortality results that favored the intensive arm.

For this ancillary study, we measured eight urine biomarkers and two serum biomarkers at baseline among 2514 SPRINT participants with CKD, defined as a baseline eGFR <60 mL/min/1.73 m^2 according to the chronic kidney disease epidemiology collaboration (CKD-EPI) combined creatinine and cystatin C estimating equation [11]. The biomarkers included measures reflecting tubule function [urine α-1 microglobulin (α1m), β-2 microglobulin (β2m) and uromodulin (UMOD)], tubule injury

[urine interleukin-18 (IL-18), kidney injury molecule-1 (KIM-1) and neutrophil gelatinase-associated lipocaline (NGAL)], tubule inflammation and repair [urine monocyte chemoattractant protein-1 (MCP-1) and chitinase 3-like protein 1 (YKL-40)] and mineral metabolism pathways that act on the kidney tubules [serum intact fibroblast growth factor-23 (FGF-23) and intact parathyroid hormone (PTH)]. We excluded 78 participants due to unavailable urine specimens, 8 participants due to invalid urine biomarker measurements and 51 participants due to missing covariate data, resulting in a final study sample of 2377 participants. This study was approved by the committees on human research at the University of California, San Francisco, the San Francisco Veterans Affairs Health Care System and the Veterans Affairs San Diego Healthcare System.

Exposures

All blood and urine specimens were processed immediately, shipped overnight on dry ice and stored at −80°C until biomarker measurement without prior thaw. Urine biomarkers were measured at the Laboratory for Clinical Biochemistry Research at the University of Vermont by personnel blinded to clinical information. Serum biomarkers were measured at the SPRINT Central Laboratory (University of Minnesota, Minneapolis, MN, USA) in 2015. Biomarker analytic ranges, inter-assay coefficients of variation and assays are shown in Supplementary data, Table S1. Urine biomarkers were measured in duplicate and averaged.

Outcomes

The primary outcome was a composite of AEs of interest pre-specified in SPRINT's protocol, including six events identified as a serious adverse event (SAE) or reported during an emergency department (ED) visit (hypotension, syncope, electrolyte abnormalities, AKI, bradycardia and injurious fall) and two laboratory monitoring events identified on routine testing at SPRINT clinic visits [ambulatory hyperkalemia (serum potassium >5.5 mEq/L) and hypokalemia (serum potassium <3.0 mEq/L)] [3, 10]. Secondary outcomes included the AEs of interest separated into six groups: (i) hypotension or syncope; (ii) electrolyte abnormality; (iii) AKI; (iv) other (bradycardia or injurious fall); (v) ambulatory hyperkalemia; and (vi) ambulatory hypokalemia. This analysis focused on time to the first event for each AE of interest. Participants who experienced multiple different AEs could have more than one first event included as secondary outcomes.

SAEs in SPRINT were defined as safety events meeting any of the following criteria: fatal or life-threatening, resulting in significant or persistent disability, requiring or prolonging hospitalization, or judged by the investigator to represent significant hazard or harm to the participant that might require medical or surgical intervention. SAEs were ascertained at study visits every 3 months using structured interviews, and between visits if study staff received notification of SAEs by trial participants, trial investigators involved in participant care or electronic medical records. SPRINT safety officers at the Coordinating Center reviewed medical records from hospitalizations, ED visits and SAE reports, and used the Medical Dictionary for Regulatory Activities (MedDRA) version 14.0 to classify the SAEs. Up to three MedDRA codes were assigned to each event. Hypotension was coded when symptomatic low BP, without specific BP cut-offs, was mentioned in the admission history and physical or discharge summary as a reason for admission. Syncope was coded with report of a sudden temporary loss of consciousness. Injurious fall was coded with report of a sudden, unintentional change in position in which the participant came to rest on the ground, floor or a lower level not as the result of syncope or overwhelming external force. A fall due to syncope was not counted as an injurious fall because syncope was captured separately. Bradycardia was coded with report of a symptomatic heart rate <40 beats per minute. Electrolyte abnormality was coded with serum sodium <132 or >150 mEq/L, or with serum potassium <3.0 or >5.5 mEq/L. AKI was coded if the diagnosis was noted in an ED visit without subsequent hospitalization, or if the diagnosis was listed in the hospital discharge summary and was believed by the safety officer to be one of the top three reasons for admission or continued hospitalization.

We included ambulatory hyperkalemia and hypokalemia monitoring events given their associations with intensive BP lowering in SPRINT participants with CKD and the possibility that these events may prompt treatment discontinuation [4]. Laboratory monitoring events were detected from SPRINT protocol-driven labs or from as-needed SPRINT labs. Protocol-driven labs were performed at 1 month, then quarterly during the first year, then every 6 months during follow-up.

Covariates

Age, gender, race, past medical history and smoking status were obtained by questionnaire. Trained study coordinators measured BP using a standardized protocol, and recorded BP as the mean of three seated BP measurements taken 1 min apart after a 5-min rest period using an automated oscillometric device (Model 907; Omron Healthcare) [12]. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Fasting serum total cholesterol (T Chol), high-density lipoprotein (HDL) cholesterol and triglycerides (TGs); serum creatinine and cystatin C; and urine albumin and creatinine were measured at the SPRINT Central Laboratory.

Both serum and urine creatinine were measured with assays using an enzymatic creatinine method traceable to isotope dilute mass spectrometry (Roche, Indianapolis, IN, USA). Serum cystatin C was measured by immunoassay (Gentian, Moss, Norway). eGFR was calculated according to the CKD-EPI combined creatinine and cystatin C estimating equation [11]. Urine albumin was measured by a nephelometric method using the Siemens ProSpec nephelometer (Siemens, Tarrytown, NY, USA).

Statistical analyses

We tested for differences in baseline characteristics among those who did and did not develop an AE of interest using the chi-squared test for categorical variables and the Wilcoxon rank sum test for continuous variables. We used Poisson regression to estimate annual event rates and 95% confidence intervals (CIs) for each AE of interest across intervention arms.

Biomarkers were $\log_2$-transformed to correct their right-skewed distributions. Because 14% of urine α1m values were below the limit of detection, undetectable values were estimated using a Tobit regression model [13]. For other biomarkers, values below the limit of detection were assigned a value equivalent to the lower limit of detection divided by the square root of two. All urine biomarker analyses adjusted for urine creatinine to control for tonicity.

We used restricted cubic splines to assess whether each biomarker had an approximately linear association with the composite AE. In our primary analyses, we modeled biomarkers as continuous, linear predictors. We evaluated associations of clinical risk factors and the kidney tubule biomarkers with risk of the composite AE using Cox proportional hazards models. SPRINT participants were censored at death or the last available follow-up when the trial stopped administratively in August 2015. For our analysis of the AE subgroups, we considered that it was possible participants experienced multiple different AEs of interest, and that analyzing AE subgroups using separate Cox proportional hazards models does not account for the possible relationship between events. Therefore, we applied the marginal approach of Wei–Lin–Weissfeld (WLW) to Cox proportional hazards model to evaluate kidney biomarker associations with each AE subgroup. The WLW model is a marginal model that assumes participants are simultaneously at risk for all AEs of interest and remain at risk for each event until it occurs [14]. We evaluated biomarker associations with models adjusted for urine creatinine only (for urine biomarker analyses) and with models that also adjusted for demographics, intervention arm, clinical characteristics, urine albumin and eGFR. There was no evidence that the proportional hazards were violated. We also evaluated for interactions by intervention arm, baseline angiotensin-converting enzyme inhibitor (ACEi) or angiotensin II receptor blocker (ARB) use, and baseline diuretic use in multivariable adjusted models using a likelihood ratio test.

We next modeled all 10 biomarkers in combination using the adaptive least absolute shrinkage and selection operator (LASSO) in order to identify a parsimonious set of biomarkers that were jointly associated with risk of the composite AE. Adaptive LASSO is a method of penalized regression that can perform simultaneous coefficient estimation and variable selection in the setting of high dimensional data [15]. We used cross-validation to determine the number of included biomarkers and the degree of coefficient shrinkage to avoid overfitting. We included the parsimonious set of biomarkers together in a multivariable adjusted model to determine if they were jointly associated with risk of the composite AE outcome.

Adaptive LASSO was conducted using the R package *ncvreg* [16]. All other analyses were conducted using the SAS system, version 9.4 (SAS Institute, Inc., Cary, NC, USA).

RESULTS

Among the 2377 SPRINT participants with baseline CKD, the mean age was 73 ± 9 years, 40% were women, and the median [interquartile range (IQR)] eGFR and urine albumin-to-creatinine ratio (ACR) were 48 mL/min/1.73 m^2 (IQR 39–55) and 14 mg/g (IQR 7–46), respectively. During a median follow-up of 3.8 years (IQR 3.2–4.4), 716 (30%) SPRINT participants with CKD experienced one or more AE of interest. Participants who experienced an AE of interest were older and more likely to have prevalent CVD and heart failure (HF), lower diastolic BP (DBP), lower BMI, higher serum HDL cholesterol, lower eGFR and higher urine ACR. Those who experienced an AE of interest also had higher urine α1m, higher urine NGAL, lower urine UMOD, higher serum FGF-23 and higher serum PTH (Table 1). The annual event rates of the composite AE in the intensive and standard BP arms were 11.4 (95% CI 10.3–12.5) and 10.4 (95% CI 19.4–11.5) events per 100 persons per year, respectively. Annual event rates and the proportion of participants experiencing each AE of interest are shown in Supplementary data, Table S2.

In multivariable adjusted models, older age, higher serum HDL cholesterol, prevalent CVD or HF, lower eGFR and higher urine ACR were independently associated with a higher risk of the composite AE, and statin use was associated with a lower risk (Figure 1). Each 10 mL/min lower baseline eGFR was associated with an 18% relative increase in the risk of the composite AE, and each 2-fold higher urine ACR level was associated with an 11% increase. When stratified by intervention arm, statin use was associated with a lower risk of the composite AE in the standard arm, but showed no association in the intensive arm ($P = 0.025$ for interaction). In contrast, older age was associated with a higher risk of the composite AE in the standard arm, but showed no association in the intensive arm ($P = 0.002$ for interaction). All other clinical risk factors appeared similarly associated with the composite AE irrespective of randomization arm (Supplementary data, Table S3).

We next modeled individual kidney tubule biomarker associations with the composite AE. In multivariable models adjusting for demographics, intervention arm, clinical characteristics, urine albumin and eGFR, higher urine IL-18, KIM-1, NGAL and MCP-1, lower urine UMOD and higher serum FGF-23 were associated with a higher risk of the composite AE (Table 2). Associations of each biomarker with the composite AE were also evaluated stratified by intervention arm, baseline ACEi or ARB use and baseline diuretic use; none of the interactions tested reached statistical significance (Supplementary data, Tables S4 and S5, $P > 0.10$ for all).

Biomarker associations with AE subgroups were also evaluated (Table 3). In multivariable adjusted models, higher urine α1m, higher urine KIM-1, lower urine UMOD and higher serum PTH were individually associated with an increased risk of AKI. Higher urine IL-18, KIM-1, NGAL, MCP-1 and YKL-40 and higher serum FGF-23 associated with an increased risk of electrolyte abnormalities. None of the biomarkers was associated with hypotension or syncope, and only one biomarker was associated with bradycardia or injurious falls. Higher urine IL-18 and MCP-1, lower urine UMOD and higher serum FGF-23 associated with an increased risk of ambulatory hyperkalemia, and higher urine YKL-40 associated with an increased risk of ambulatory hypokalemia.

Finally, we modeled the 10 kidney tubule biomarkers in combination and used adaptive LASSO to identify a parsimonious set that jointly associated with the composite AE outcome.

Table 1. Baseline characteristics of SPRINT participants with CKD by development of AEs of interest during follow-up

Characteristic	No AE of interest[a] during follow-up ($n = 1661$), n (%)	≥1 AE of interest during follow-up ($n = 716$), n (%)	P-value
Intensive BP arm	836 (50)	381 (53)	0.20
Age, years	74 (66–79)	77 (69–81)	<0.001
Female	669 (40)	292 (41)	0.82
Race			
White	1190 (72)	537 (75)	0.064
African American	439 (26)	173 (24)	
Other	32 (2)	6 (1)	
Hispanic	121 (7)	42 (6)	0.21
Smoking			
Current	140 (8)	71 (10)	0.32
Former	742 (45)	329 (46)	
Never	779 (47)	316 (44)	
Prevalent CVD	434 (26)	240 (34)	<0.001
Prevalent HF	86 (5)	62 (9)	0.001
SBP, mmHg	138 (129–148)	140 (129–151)	0.040
DBP, mmHg	74 (66–83)	73 (64–81)	0.008
No. of antihypertensive meds	2.0 (1.0–3.0)	2.0 (1.0–3.0)	0.41
Antihypertensive med class			
Beta blocker	761 (46)	356 (50)	0.080
Diuretic	928 (56)	373 (52)	0.090
Calcium channel blocker	659 (40)	308 (43)	0.13
ARB	380 (23)	182 (25)	0.18
ACEi	658 (40)	278 (39)	0.72
BMI, kg/m^2	29 (26–33)	28 (25–32)	0.003
T Chol, mg/dL	180 (156–206)	175 (153–206)	0.099
HDL cholesterol, mg/dL	49 (42–60)	51 (43–62)	0.009
Statin use	872 (52)	364 (51)	0.46
eGFR, mL/min/1.73 m^2	50 (40–55)	45 (35–53)	<0.001
eGFR categories			
45–59 mL/min/1.73 m^2	1070 (64)	350 (49)	<0.001
30–44 mL/min/1.73 m^2	475 (29)	267 (37)	<0.001
<30 mL/min/1.73 m^2	116 (7)	99 (14)	<0.001
Urine ACR, mg/g	12.5 (6.5–37.1)	20.0 (8.3–81.3)	<0.001
Urine α1m, mg/dL	12.9 (6.9–24.4)	13.9 (7.5–26.9)	0.041
Urine β2m, ng/mL	94 (35–295)	100 (29–366)	0.62
Urine IL-18, pg/mL	32 (17–56)	28 (15–58)	0.060
Urine KIM-1, pg/mL	873 (387–1568)	801 (380–1643)	0.75
Urine MCP-1, pg/mL	185 (93–333)	171 (83–318)	0.23
Urine NGAL, ng/mL	26 (15–54)	30 (15–69)	0.033
Urine YKL-40, ng/mL	544 (225–1182)	528 (197–1381)	0.72
Urine UMOD, ng/mL	6950 (4618–10 381)	5730 (3748–8982)	<0.001
Serum FGF-23, pg/mL	65 (51–86)	70 (54–92)	<0.001
Serum PTH, pg/mL	46 (35–64)	50 (36–73)	<0.001

Data displayed are n (%) or median (IQR). P-values calculated from Chi-squared tests for categorical variables and Wilcoxon rank sum tests for continuous variables.
[a]AEs of interest include hypotension, syncope, bradycardia, electrolyte abnormalities, injurious fall or AKI that were either documented in an ED visit or were reported in a serious AE, defined as a fatal or life threatening event, resulting in significant or persistent disability, requiring or prolonging hospitalization or judged important medical event. AEs of interest also included hyperkalemia and hypokalemia on routine laboratory monitoring at clinic visits.

In multivariable models, higher urine MCP-1 [hazard ratio (HR) 1.11 per 2-fold higher level, 95% CI 1.03–1.19], higher urine NGAL (HR = 1.08, 95% CI 1.03–1.13) and lower urine UMOD (HR = 0.91, 95% CI 0.85–0.97) were jointly associated with an increased risk of the composite AE outcome. In the combined biomarker model, lower eGFR (HR = 1.19 per 10 mL/min/1.73 m^2 lower eGFR, 95% CI 1.10–1.28) and higher urine albumin (HR = 1.07 per 2-fold higher level, 95% CI 1.03–1.11) were also jointly associated with increased risk of the composite AE outcome (Figure 2).

DISCUSSION

The kidney tubules play a central role in BP regulation, electrolyte homeostasis and drug elimination, suggesting that impaired kidney tubule health could predispose individuals to AEs during antihypertensive treatment [8, 17]. In this ancillary study of SPRINT participants with CKD, higher levels of urine MCP-1 and NGAL and lower levels of urine UMOD were associated with higher risk of the composite AE independent of demographics, clinical characteristics, eGFR, albuminuria and one another. In addition, the kidney tubule biomarkers

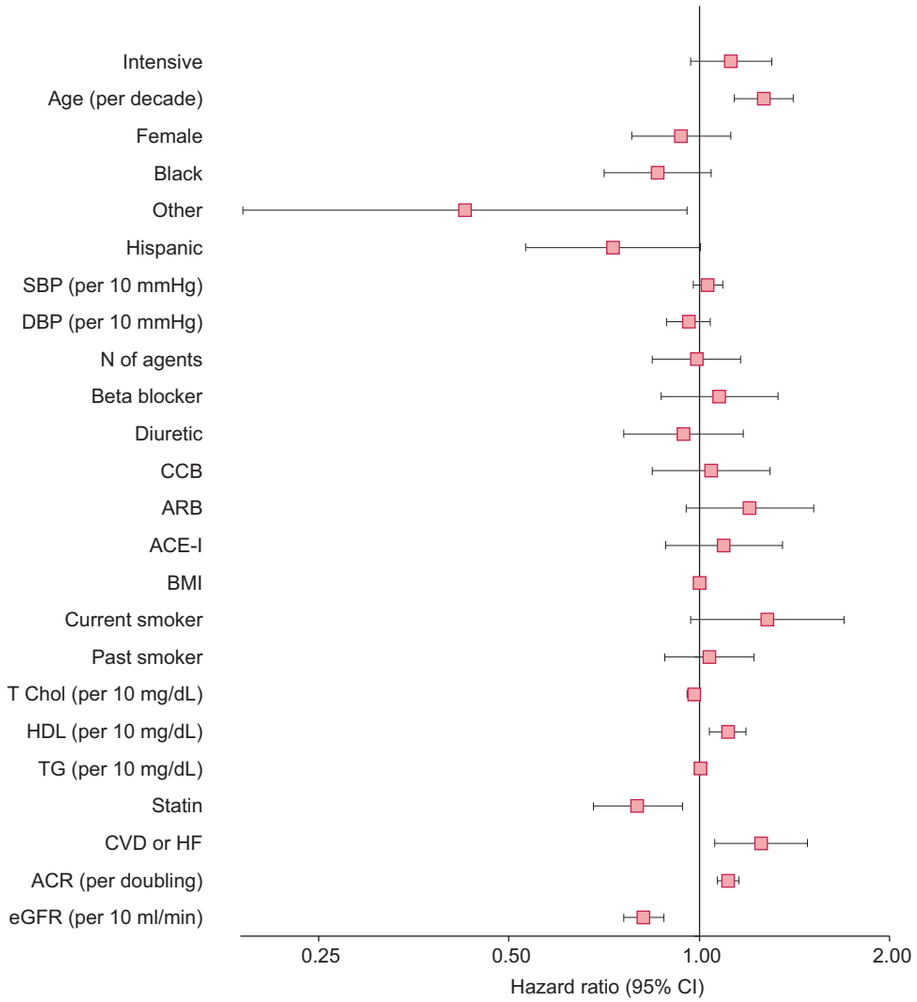

FIGURE 1: Multivariable-adjusted associations of clinical characteristics with risk of a composite of AEs of interest in SPRINT participants with CKD. HRs with 95% CIs obtained from multivariable Cox proportional hazards models that included demographics (age, sex and race), intervention arm, clinical characteristics (SBP, DBP, number of antihypertensive medications at baseline, antihypertensive medication class at baseline, BMI, smoking, T Chol, HDL cholesterol, TGs, statin use, history of CVD and history of HF), eGFR and urine ACR. CCB, calcium channel blocker.

conferred a similar AE risk as albuminuria. Randomization to the intensive versus standard BP arms of the trial did not appreciably modify the kidney tubule biomarker associations with the composite AE. These results suggest that, among persons with CKD, biomarkers reflecting impaired kidney tubule health provide additional information about the risk of AEs during antihypertensive treatment above and beyond eGFR and albuminuria, and regardless of the intensity of BP lowering.

We also observed several clinical risk factors, including older age, statin use, history of CVD or HF, lower eGFR and higher urine ACR, were independently associated with risk of the composite AE. Our results are difficult to compare to other BP target trials due to heterogeneity in AE definitions, documentation and reporting [18]. Previous studies in the overall SPRINT population, of which 72% of participants had a baseline eGFR $\geq$60 mL/min/1.73 m^2, reported a similar combination of risk factors associated with SAEs, including: older age, female gender, current smoking, statin use, TG levels, elevated pulse pressure, high visit-to-visit DBP variability, lower eGFR and albuminuria [19–24].

We have previously shown in SPRINT CKD participants that measures of kidney tubule health are associated with higher risk of CVD, mortality, longitudinal eGFR decline and AKI, but their relationships with other common antihypertensive-related AEs were unknown [9, 25–28]. Similar to our previous work, we reported that higher urine α1m and lower urine UMOD levels were associated with higher risk of AKI independent of eGFR, albuminuria or shared risk factors [9]. In this analysis, we also find that kidney tubule biomarkers relate to global AE risk, which appears to be driven more by electrolyte abnormalities and AKI than systemic BP-related AEs, such as hypotension or syncope.

Impaired kidney tubule health may compromise the response to electrolyte disturbances and renal blood flow perturbations that can occur with antihypertensive medications or during acute illness. This may have been captured in part by the

Table 2. Associations of biomarkers of kidney tubule health and mineral metabolism with risk of a composite of AEs of interest in SPRINT participants with CKD

Biomarker	HR (95% CI) per 2-fold higher biomarker level	
	Model 1[a]	Model 2[b]
Tubule function		
Urine α1m	**1.11 (1.07–1.16)**	0.99 (0.95–1.04)
Urine β2m	1.02 (0.99–1.05)	0.98 (0.95–1.00)
Urine UMOD	**0.88 (0.83–0.92)**	**0.94 (0.88–1.00)**
Tubule injury		
Urine IL-18	**1.10 (1.03–1.17)**	**1.10 (1.03–1.18)**
Urine KIM-1	**1.19 (1.12–1.27)**	**1.08 (1.01–1.16)**
Urine NGAL	**1.10 (1.05–1.14)**	**1.07 (1.02–1.12)**
Tubule inflammation and repair		
Urine MCP-1	**1.21 (1.13–1.29)**	**1.13 (1.05–1.21)**
Urine YKL-40	**1.05 (1.01–1.09)**	1.03 (1.00–1.07)
Mineral metabolism		
Serum FGF-23	**1.34 (1.20–1.50)**	**1.15 (1.01–1.32)**
Serum PTH	**1.22 (1.10–1.36)**	1.10 (0.98–1.24)

Bolded estimates with $P < 0.05$. Biomarkers are modeled individually, not jointly.
[a]Model 1: adjusted for urine creatinine (for urine biomarkers only).
[b]Model 2: adjusted for Model 1 plus demographics (age, sex and race), intervention arm, clinical risk factors (SBP, DBP, number of antihypertensive medications at baseline, antihypertensive medication class at baseline, BMI, smoking, T Chol, HDL cholesterol, TGs, statin use, history of CVD and history of HF), baseline urine albumin and eGFR.

biomarkers in our study, which represent an array of pathophysiologic mechanisms specific to the kidney tubules. Urine IL-18, KIM-1 and NGAL are produced by kidney tubule epithelial cells in response to various injuries [29–31]. Urine MCP-1 is a chemotactic cytokine produced by kidney tubule epithelial cells and mediates monocyte and macrophage responses to the site of kidney injury [32]. Urine UMOD is exclusively produced in the thick ascending limb and early distal convoluted tubule, and higher levels correlate with increased tubular mass and function [33]. Serum FGF-23 is a phosphaturic hormone that acts on the kidney tubules, has strong associations with CVD risk, and is commonly elevated in CKD [34]. Higher serum FGF-23 may, in part, reflect kidney tubule resistance to mineral metabolism hormonal regulation [35]. Alternatively, the FGF-23 association with AE risk may be through cardiovascular-related mechanisms [36]. The overall pattern of our findings suggests that multiple pathophysiologic processes in the kidney tubules—impaired function, injury and inflammation—reflect susceptibility to AEs during antihypertensive treatment. Our findings warrant validation in other studies of hypertensive persons with CKD and further investigations into the mechanisms of kidney tubule-mediated AEs during antihypertensive treatment.

Table 3. Associations of biomarkers of kidney tubule health and mineral metabolism with risk of specific AEs of interest in SPRINT participants with CKDBradycardia or injurious fall

Biomarker[b]	HR (95% CI) per 2-fold higher biomarker level[a]		
	Hypotension or syncope	Electrolyte abnormality	AKI
Tubule function			
Urine α1m	0.94 (0.87–1.02)	1.02 (0.93–1.11)	**1.10 (1.01–1.20)**
Urine β2m	0.96 (0.91–1.01)	1.00 (0.95–1.06)	0.98 (0.94–1.03)
Urine UMOD	1.05 (0.92–1.20)	1.00 (0.88–1.14)	**0.87 (0.80–0.93)**
Tubule injury			
Urine IL-18	1.07 (0.92–1.23)	**1.24 (1.09–1.41)**	1.12 (0.99–1.27)
Urine KIM-1	1.07 (0.94–1.23)	**1.28 (1.12–1.47)**	**1.18 (1.03–1.34)**
Urine NGAL	1.00 (0.91–1.10)	**1.12 (1.02–1.23)**	1.06 (0.99–1.14)
Tubule inflammation and repair			
Urine MCP-1	1.07 (0.92–1.24)	**1.23 (1.07–1.43)**	1.14 (1.00–1.31)
Urine YKL-40	1.06 (0.98–1.13)	**1.10 (1.02–1.19)**	1.06 (1.00–1.13)
Mineral metabolism			
Serum FGF-23	0.92 (0.73–1.17)	**1.36 (1.01–1.84)**	1.09 (0.88–1.34)
Serum PTH	0.89 (0.71–1.10)	1.15 (0.90–1.46)	**1.48 (1.21–1.82)**
	Bradycardia or injurious fall	Ambulatory hyperkalemia	Ambulatory hypokalemia
Tubule function			
Urine α1m	0.99 (0.93–1.05)	1.04 (0.95–1.13)	1.00 (0.85–1.16)
Urine β2m	0.99 (0.95–1.02)	0.97 (0.92–1.03)	1.02 (0.91–1.14)
Urine UMOD	0.98 (0.89–1.09)	**0.84 (0.77–0.92)**	0.86 (0.72–1.02)
Tubule injury			
Urine IL-18	1.06 (0.97–1.16)	**1.17 (1.02–1.34)**	1.19 (0.94–1.51)
Urine KIM-1	1.08 (0.97–1.21)	1.07 (0.95–1.21)	1.04 (0.77–1.40)
Urine NGAL	1.06 (0.99–1.12)	1.04 (0.95–1.13)	0.91 (0.72–1.15)
Tubule inflammation and repair			
Urine MCP-1	1.05 (0.94–1.18)	**1.24 (1.06–1.44)**	1.06 (0.77–1.46)
Urine YKL-40	1.03 (0.98–1.08)	1.01 (0.94–1.09)	**1.17 (1.06–1.30)**
Mineral metabolism			
Serum FGF-23	**1.22 (1.01–1.46)**	**1.43 (1.17–1.77)**	0.75 (0.47–1.18)
Serum PTH	1.02 (0.87–1.18)	1.18 (0.95–1.48)	1.41 (0.96–2.09)

Bolded estimates with $P < 0.05$. Biomarkers are modeled individually, not jointly.
Models are adjusted for demographics (age, sex and race), intervention arm and clinical risk factors (SBP, DBP, number of antihypertensive medications at baseline, antihypertensive medication class at baseline, BMI, smoking, T Chol, HDL cholesterol, TGs, statin use, history of CVD and history of HF), urine albumin and eGFR.
[a]HRs estimated using marginal WLW Cox models for multiple events data.
[b]Urine biomarkers adjusted additionally for urine creatinine.

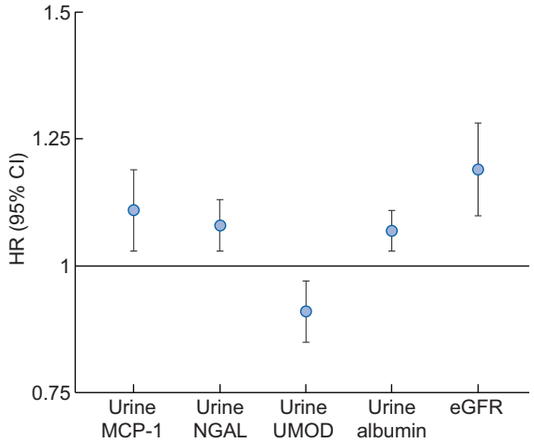

FIGURE 2: Comparison of multivariable-adjusted associations between selected kidney tubule biomarkers, albuminuria and eGFR with risk of a composite of AEs of interest in SPRINT participants with CKD. The figure compares the HRs for the composite AE outcome per 2-fold higher baseline levels of the three kidney tubule biomarkers and albuminuria and per 10 mL/min/1.73 m^2 lower baseline eGFR. HRs and 95% CIs were obtained from a multivariable Cox proportional hazards model that included all three kidney tubule biomarkers, albuminuria and eGFR in the same model and adjusted for all the variables listed in Model 2 in the preceding tables and text.

Developing approaches that facilitate safe BP lowering is particularly important for persons with CKD. CVD is the leading cause of death among persons with CKD, and the relative benefits from intensive BP lowering on CVD and mortality risks in the overall SPRINT population appear to be similar in SPRINT participants with CKD, a particularly important finding given that persons with CKD have much higher absolute risk of these adverse outcomes [4, 37]. With only half of persons with CKD and hypertension in the USA achieving a BP of <130/80 mmHg, novel approaches are needed to close this quality gap in CKD care [38–40]. However, the high burden of adverse drug events, multimorbidity, frailty and polypharmacy in the CKD population make BP control challenging [41, 42]. This study and our previous work suggest kidney tubule biomarkers may warrant evaluation in prospective studies that integrate the benefits and harms of intensive BP lowering into hypertension treatment decisions.

As an ancillary study of SPRINT, this analysis benefited from including men and women across the USA who represent the largest CKD population in a randomized trial comparing BP targets to date. AEs were defined according to National Heart, Lung and Blood Institute guidelines and the Office for Human Resources Policy, centrally adjudicated, monitored at quarterly clinic visits with structured interviews and evaluated using ED, hospital admission and discharge summary records.

There are also several important limitations. First, because of the SPRINT design, our findings may not be generalizable to persons with CKD who have severe albuminuria, advanced CKD or diabetes mellitus. Second, participants were not blinded to treatment assignment and those in the intensive arm had 30% more study visits; this may have led to differential ascertainment bias due to over-reporting of AEs among participants receiving intensive BP lowering. However, this was unlikely to affect biomarker associations with AEs, which broadly did not vary by intervention arm. Third, AEs were prospectively identified and not blinded to investigators, which may have led to detection bias. Fourth, although we studied multiple kidney tubule biomarkers, we did not include formal adjustments for multiple comparisons. We hypothesized *a priori* that the intercorrelated biomarkers associate with AEs in a mutually reinforcing pattern that should not be viewed exclusively as a series of independent tests. To reduce the possibility of false discovery, we used penalized regression to produce a parsimonious set of biomarkers. However, chance findings are still possible.

In summary, we demonstrated that lower eGFR, higher albuminuria and six kidney tubule biomarkers are independently associated with risk of AEs in SPRINT participants with CKD. Among the kidney tubule biomarkers, higher urine NGAL and MCP-1 and lower urine UMOD appear to provide the most information about AE risk. In the context of our prior work, this study provides evidence that measures of kidney tubule health have associations with CVD, mortality, longitudinal eGFR decline, AKI and additional adverse outcomes in SPRINT participants with CKD, independent of eGFR and albuminuria. Additional studies are warranted to validate these findings in other hypertensive CKD populations, and to evaluate the potential clinical role of kidney tubule biomarkers in the management of hypertension in persons with CKD.

SUPPLEMENTARY DATA

Supplementary data are available at ndt online.

ACKNOWLEDGEMENTS

The authors thank the participants and staff members of the SPRINT, which is sponsored by the National Institutes of Health (NIH), including the National Heart, Lung, and Blood Institute, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), the National Institute on Aging and the National Institute of Neurological Disorders and Stroke, under Contract Numbers HHSN268200900040C, HHSN268200900046C, HHSN268200900047C, HHSN268200900048C, HHSN268200900049C and Inter-Agency Agreement Number A-HL-13-002-001. It was also supported in part with resources and use of facilities through the Department of Veterans Affairs. The SPRINT investigators acknowledge the contribution of study medications (azilsartan and azilsartan combined with chlorthalidone) from Takeda Pharmaceuticals International, Inc. All components of the SPRINT study protocol were designed and implemented by the investigators. The investigative team collected, analyzed and interpreted the data. All aspects of manuscript writing and revision were carried out by the coauthors. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH, the US Department of Veterans Affairs or the US Government. For a full list of contributors to SPRINT, please see the

supplementary acknowledgement list: https://www.sprinttrial.org/public/dspScience.cfm.

We also acknowledge the support from the following CTSAs funded by NCATS: CWRU: UL1TR000439, OSU: UL1RR025755, U Penn: UL1RR024134 and UL1TR000003, Boston: UL1RR025771, Stanford: UL1TR000093, Tufts: UL1RR025752, UL1TR000073 and UL1TR001064, University of Illinois: UL1TR000050, University of Pittsburgh: UL1TR000005, UT Southwestern: 9U54TR000017-06, University of Utah: UL1TR000105-05, Vanderbilt University: UL1 TR000445, George Washington University: UL1TR000075, University of CA, Davis: UL1 TR000002, University of Florida: UL1 TR000064, University of Michigan: UL1TR000433, Tulane University: P30GM103337 COBRE Award NIGMS and Wake Forest University: UL1TR001420.

FUNDING

This ancillary study was supported by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) (R01DK098234 for M.G.S./J.H.I. and K24DK110427 for J.H.I.) and the American Heart Association (14EIA18560026 for J.H.I.).

AUTHORS' CONTRIBUTIONS

Research idea and study design were carried out by S.B.A., R.S., J.H.I. and M.G.S.; data acquisition by J.H.I. and M.G.S.; data analysis/interpretation by S.B.A., R.S., J.H.I., M.G.S., M.M.E., J.D.B., J.A.d.L., V.K.J., P.S.G., R.M., A.L.B., R.K., W.T.A., A.K.C., M.C. and A.A.K.; statistical analyses by R.S.; and supervision or mentorship by M.G.S. Each author contributed important intellectual content during manuscript drafting or revision, accepts personal accountability for the author's own contributions and agrees to ensure that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

CONFLICT OF INTEREST STATEMENT

The results presented in this article have not been published previously in whole or part, except in abstract format. M.G.S. has received consulting income from Cricket Health, Inc. and Intercept Pharmaceuticals. J.H.I. holds an investigator initiated research grant from Baxter International Inc., serves as a member of a data safety monitoring board for Sanifit Therapeutics, is a member of the scientific advisory board for Alpha Young, and has served on advisory boards for AstraZeneca and Ardelyx. J.A.d.L. has received grant support from Roche Diagnostics and Abbott Diagnostics, and consulting income from Siemen's Health Care Diagnostics, Ortho Clinical Diagnostics and Quidel, unrelated to the present research.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the National Heart, Lung, and Blood Institute (NHLBI) Biologic Specimen and Data Repositories upon request.

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Received: 19.5.2021; Editorial decision: 3.8.2021