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Kidney Damage Biomarkers and Incident CKD During Blood Pressure Reduction: A Case-Control Study within SPRINT

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Abstract

Background: It is unknown whether the increased incidence of chronic kidney disease (CKD) during intensive systolic blood pressure (SBP) lowering is accompanied by intrinsic kidney injury.

Objective: To compare changes in kidney damage biomarkers among matched incident CKD cases and controls and among incident CKD cases in the intensive (<120 mmHg) vs. standard (<140 mmHg) SBP management arms of SPRINT.

Design: Nested case-control study within SPRINT.

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Reproducible Research Statement
Study protocol: Available as Supplementary Material.
Statistical code: Available from Mr. Craven (tcraven@wakehealth.edu)
Data set: Available from SPRINT Coordinating Center (pnance@wakehealth.edu)

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Setting: Adults with hypertension without baseline kidney disease.

Participants: Cases (N=162) developed incident CKD during trial follow-up (128 in the intensive arm and 34 in the standard arm). Controls (N=162) without incident CKD were matched on age, sex, race, baseline estimated glomerular filtration rate (eGFR), and randomization arm.

Measurements: Nine urinary biomarkers of kidney damage were measured at baseline and 1 year. Linear mixed-effects models were used to estimate 1-year biomarker changes.

Results: Higher concentrations of baseline albumin-creatinine ratio (ACR), kidney injury molecule-1, and monocyte chemoattractant protein-1 were each significantly associated with higher odds of incident CKD (adjusted OR per doubling [95% CI]: 1.50 [1.14,1.98], 1.51 [1.05, 2.17], and 1.70 [1.13, 2.56], respectively). After 1 year of blood pressure intervention, incident CKD cases in the intensive arm had significantly larger declines in ACR, interleukin-18, anti-chitinase-3-like protein 1 (YKL-40), and uromodulin, compared with matched controls. When compared with CKD cases in the standard arm, cases in the intensive arm had significantly larger declines in ACR, β2-microglobulin, α1-microglobulin, YKL-40, and uromodulin.

Limitations: Biomarker measurements were only available at baseline and 1 year.

Conclusion: Incident CKD in the setting of intensive SBP lowering was not accompanied by elevations, but rather declines, of kidney damage biomarkers and thus may reflect benign changes in renal blood flow rather than intrinsic injury.

Introduction

It has been well established that lower blood pressures are associated with substantial cardiovascular and mortality benefit.(1–3) The Systolic Blood Pressure Intervention Trial (SPRINT) was a pivotal randomized controlled trial that demonstrated that intensive systolic blood pressure [SBP] management to <120 mmHg reduced rates of major cardiovascular events and all-cause mortality, compared to standard management to <140 mmHg.(4) Despite these benefits, one notable harm was a more than 3-fold incidence of chronic kidney disease (CKD) in the intensive vs. standard arms. Nonetheless, recent guidelines by the American College of Cardiology and American Heart Association have lowered blood pressure targets for hypertension diagnosis and management.(5) These policy changes may dramatically increase the incidence of CKD at the population level and pose an important public health concern. However, in the setting of intensive blood pressure lowering, kidney function decline measured by creatinine may be a benign manifestation of reduced renal blood flow. Thus, there remains uncertainty regarding whether incident CKD that develops during intensive blood pressure lowering is accompanied by intrinsic kidney injury or instead reflects hemodynamic changes.

To address this question, we designed a nested case-control study of incident CKD cases and matched controls within SPRINT. We used a panel of urinary biomarkers of kidney damage measured at baseline and at 1-year of follow-up. Our aims were to determine whether (1) baseline biomarker concentrations were associated with incident CKD; (2) changes in urinary biomarkers were associated with risk of incident CKD; and (3) the extent of biomarker changes differed between cases of incident CKD that arose during intensive vs.

standard SBP management. We hypothesized that biomarker changes among incident CKD cases in the intensive arm would represent benign changes in renal blood flow rather than intrinsic tissue injury.

Methods

Study design and population

SPRINT was a randomized, controlled, open-label trial of intensive (targeting <120 mmHg) vs. standard (targeting < 140 mmHg) SBP therapy among individuals at high cardiovascular risk and without diabetes.(4) A total of 9,361 participants were enrolled between November 2010 and March 2013 at 102 sites in the U.S. and Puerto Rico. Among these, 2,646 participants (28%) had baseline CKD, defined as an eGFR <60 ml/min/1.73m^2 by the Modification of Diet in Renal Disease (MDRD) equation. Full details of the study protocols are published elsewhere.(6)

Among participants without CKD at baseline, the SPRINT protocol defined incident CKD as ≥ 30% reduction from baseline in eGFR defined by the MDRD equation and eGFR <60 ml/min/1.73m^2 confirmed on two serial eGFR measurements at least 3 months apart. Over SPRINT follow-up of a median of 3.26 years, there were 162 participants who developed incident CKD: 128 in the intensive arm and 34 in the standard arm. Among these 162 incident CKD cases, 26.5% (N=43) had been diagnosed by the 1-year follow-up visit, whereas the remaining cases were diagnosed subsequently. In the SPRINT Kidney Tubule Health ancillary project, we defined baseline CKD using the CKD Epidemiology Collaboration (CKD-EPI) equation with both cystatin C and creatinine (resulting in 2,503 cases of baseline CKD), which accounts for the modest difference between the number of incident CKD cases in our study (N=162) relative to the original publication (N=154). For each incident CKD case, we used prevalent control sampling to select one matched control that had not developed CKD at the end of follow-up. We used a hierarchical matching scheme prioritizing the following factors in order: randomization arm, age (within 5 years), sex, race, and baseline eGFR (within 5 ml/min/1.73m^2) to account for these potential confounders. There was 1 control in which race could not be matched following matching on randomization arm, eGFR, and age. The SPRINT Research Group approved the study protocol, which was adherent to the Declaration of Helsinki.

Urinary kidney damage biomarker measurements

Our biomarker panel included the following nine urinary biomarkers: albumin-creatinine ratio (ACR), interleukin-18 (IL-18), kidney injury molecule-1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL), monocyte chemoattractant protein-1 (MCP-1), anti-chitinase-3-like protein 1 (YKL-40), beta-2 microglobulin (β2M), alpha-1 microglobulin (α1M), and uromodulin (UMOD). These proteins have been well-studied in kidney disease as direct markers of kidney damage, particularly in the settings of drug nephrotoxocity(7, 8) and acute kidney injury.(9–11) Broadly, the biomarkers reflect glomerular injury (ACR), tubular injury and fibrosis (IL-18, KIM-1, NGAL, MCP-1), tubular injury repair (YKL-40), proximal tubular dysfunction (β2M, α1m), and loop of Henle protein production (uromodulin).

We used urine specimens that were collected from cases and controls at randomization (baseline) and at the 1-year follow-up visit. All specimens were in continuous storage at −80°C without previous freeze-thaw until measurement. Biomarkers were measured at the University of Vermont Laboratory for Clinical Biochemistry Research. Urinary biomarkers from both baseline and 1 year were measured contemporaneously to minimize influence of laboratory drift. Most biomarkers were measured simultaneously using multiplex immunoassays from Meso Scale Discovery (MSD, Gaithersburg, MD), except for α1m, which was measured using the BN II Nephelometer assay (Siemens, Newark, DE). Urine creatinine was measured using a Cobas c311 clinical analyzer (Roche Diagnostics, Indianapolis, IN). Details regarding assay methods are shown in Appendix Tables 1a **and** 1b. Biomarker concentrations below the lower limit of detection were imputed with a value calculated from subtracting a small number from the limit of detection. Laboratory personnel were blinded to clinical information about the participants, and specimens were evaluated in random order. With the exception of urinary ACR and α1m, all biomarkers were measured in duplicate and results were averaged to improve precision.

Covariates

In addition to matching factors, covariates examined included baseline and 1-year SBP and diastolic blood pressure (DBP); number of anti-hypertensive medications; angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use; and baseline total cholesterol and high-density lipoprotein cholesterol concentrations, body mass index, history of clinical cardiovascular disease, history of chronic heart failure, and smoking status. Covariates were selected based on evidence from prior studies(12) and were collected as part of the parent trial. Our pre-specified analytic plan included statistical adjustments for baseline covariates that differed between cases and controls within each intervention arm.

Statistical Methods

We first summarized baseline characteristics in cases and matched controls, stratified by intervention arm, and tested for differences using univariate conditional logistic regression models. We next compared baseline biomarker concentrations between incident CKD cases and matched controls in our overall study sample, as well as stratified by intervention arm, by fitting separate conditional logistic regression models for each biomarker with adjustment for baseline SBP and urine creatinine. Due to their skewed distributions, biomarker concentrations were summarized using geometric mean and standard errors. All models except those for ACR were adjusted for $\log_2$-transformed urine creatinine concentrations to account for urine tonicity.

We assessed the potential for bias due to the choice of prevalent control sampling at the end of follow-up rather than incidence-density sampling. To account these potential control selection biases, we employed the semi-parametric weighted estimator proposed by Landsman and Graubard.(13) We then re-calculated associations between biomarkers at baseline and case-control status using the sample weights. Cases were assigned a weight of “1” since all incident CKD cases were included in the sample. Initial weights for controls were calculated at each distinct CKD onset time as the inverse probability of selection after inclusion of subsequent cases as potential controls to simulate incidence-density sampling.

After re-scaling these weights by dividing them by their mean value, we calibrated them to the predicted weights using the matching factors. This resulted in the model-adjusted weights for the logistic regression analyses.

We next compared 1-year changes in each biomarker between cases and controls, stratified by intervention arm. We also compared 1-year changes between incident CKD cases in the intensive and standard arms. Although comparing controls between intervention arms was not part of our pre-specified analytic plan, these data have been included for completeness. We examined 1-year changes by modeling the difference (1-year minus baseline) in $\log_2$-transformed biomarker concentrations using linear mixed-effect models, adjusting for baseline SBP and both linear and quadratic terms for $\log_2$-transformed urine creatinine concentrations. To account for the matched study design, we included case-control pair ID as a random effect and adjusted for the matching variables (age, race, sex, and eGFR). Only subjects with complete data for case-control pairs were used in these analyses, which resulted in varying samples sizes across the biomarkers. Predicted (least-squares) means of the change in biomarker and associated 95% confidence intervals were back-transformed to estimate the mean ratio of 1-year to baseline levels. Associated Wald tests for differences in the predicted mean changes were used to test significance. The mean changes in each biomarker and the comparisons between groups were presented graphically for ease of communication. We used an interaction term to evaluate whether relative biomarker changes between cases and controls were statistically different comparing the intervention and standard arms.

P-values <0.05 were considered statistically significant for all analyses without adjustment for multiple comparisons, as biomarkers were hypothesized to be mutually reinforcing rather than a series of independent tests.(14) All analyses were performed using SAS® version 9.4 software (SAS Institute, Cary, NC), in particular the LOGISTIC® procedure for conditional logistic regression analyses and the MIXED® procedure for linear mixed-effects models.

Results

Following matching controls to cases on age, gender, race, baseline eGFR and randomization arm, additional baseline characteristics and cardiovascular risk factors were well balanced between respective incident CKD cases and controls (Table 1). The only exception was baseline systolic blood pressure, which was significantly higher among incident CKD cases than among matched controls within both intervention arms. At 1 year after randomization, incident CKD cases in both intervention arms had significantly increased serum creatinine concentrations and decreased eGFRs, compared with respective controls. In addition, individuals in the intensive arm were prescribed greater numbers of anti-hypertensive medications, including angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, at 1 year than those in the standard arm. Within the intensive arm, incident CKD cases were prescribed significantly more antihypertensive medications and had significantly lower diastolic blood pressures at 1 year, compared with matched controls.

At baseline, the nine kidney biomarkers were only weakly inter-correlated (Appendix Table 2); moderate correlations were observed for only two biomarkers pairs (α1m and β2m, r=0.53; KIM-1 and MCP-1, r=0.49), whereas the other pairwise comparisons showed weak associations. We evaluated the association of baseline biomarker concentrations and incident CKD case status, adjusting for baseline SBP and urine creatinine (Table 2). Higher concentrations of ACR, KIM-1, and MCP-1 were each significantly associated with higher odds of incident CKD. These results were not impacted by re-weighting of the matched controls to the broader cohort of non-cases (Appendix Table 3). When stratified by intervention arm, we observed similar effect sizes in each group, although the associations were not statistically significant in the standard arm (Appendix Table 4).

The 1-year biomarker concentrations of cases and controls for each intervention arm are presented in Appendix Table 5. We compared the 1-year relative changes of each biomarker between cases and controls and found that incident CKD cases in the intensive arm had relative declines in ACR, IL-18, YKL-40, and uromodulin that significantly differed from the relative changes in matched controls (Figure 1). The 1-year relative changes in KIM-1, NGAL, β2M, and α1m did not differ significantly between intensive arm cases and controls, and MCP-1 relatively increased in intensive arm cases. In the standard arm, there were no significant differences between cases and controls in the 1-year relative changes for any biomarker. We tested for interactions comparing the case-control differences between the two intervention arms and found none to be statistically significant (Appendix Table 6).

At 1 year, the cases in the standard arm had higher concentrations of all nine biomarkers compared with cases in the intensive arm but was only statistically significant for YKL-40 (p=0.01) (Appendix Table 5). We compared the 1-year relative changes of each biomarker between incident CKD cases in the intensive vs. standard arms, adjusting for baseline SBP and urine creatinine, and found significant differences for ACR, β2M, α1m, YKL-40, and uromodulin (Figure 1). All five of these biomarkers were decreased at 1 year among cases in the intensive arm and either increased or remained unchanged among cases in the standard arm.

To determine whether use of renin-angiotensin-aldosterone system inhibitors influenced the ACR declines, we stratified the intensive arm cases by users (N=90) and non-users (N=19) of angiotensin converting enzyme inhibitors or angiotensin receptor blockers during follow-up until CKD diagnosis. The median (IQR) reduction in ACR was near unity among these two groups [−33% (−66% to +25%) vs. −46% (−86% to +41%), respectively]. Among standard arm cases, the change in ACR differed substantially by use of these medications: −16% (−68% to +44%) among the 23 users vs. +85% (+54% to +159%) among the 10 non-users.

Discussion

In this case-control study nested within a trial of hypertensive participants without CKD at baseline, we used a diverse panel of urinary biomarkers to characterize intrinsic kidney damage among incident CKD cases in the setting of intensive blood pressure reduction to SBP <120 mmHg. Our findings demonstrate that, despite their substantial eGFR declines in

the first year of SPRINT, incident CKD cases in the setting of intensive blood pressure lowering were not characterized by intrinsic kidney damage and rather had less injury overall than matched controls without CKD. In contrast, cases of incident CKD in the standard arm of the trial had relative elevations of 5 of the 9 biomarkers we evaluated, compared with intensive arm cases. These data support the notion that eGFR declines in the setting of intensive blood pressure lowering are generally manifestations of benign changes in renal blood flow.

Although participants did not have clinically diagnosed CKD at baseline, we found that baseline concentrations of urinary ACR, KIM-1 and MCP-1 were associated with the development of incident CKD during follow-up. Compared with their respective controls, baseline characteristics of the future incident CKD cases were otherwise distinguished only by higher SBP. These findings suggest that urinary biomarkers may identify individuals with sub-clinical kidney injury who may be at increased risk for subsequent eGFR changes. These findings are consistent with studies in other settings that reported associations of ACR, KIM-1, and MCP-1 with incident CKD and kidney function decline.(15–17)

Our comparisons of 1-year biomarker changes are also consistent with prior clinical trials reporting the distinct associations of eGFR declines from intensive vs. standard SBP management with cardiovascular disease and mortality.(18–22) For example, a *post hoc* analysis of the Secondary Prevention of Small Subcortical Strokes (SPS3) trial found that early eGFR declines within the intensive SBP reduction arm were not associated with adverse cardiovascular outcomes, in contrast to eGFR declines within the standard care arm, which portended higher cardiovascular risk.(23) Similarly, analyses of the MDRD and African American Study of Kidney Disease and Hypertension (AASK) trials found that participants randomized to more intensive SBP lowering had initial elevations in creatinine but lower long-term mortality risk, compared to those randomized to less intensive management.(24, 25) These investigators hypothesized that blood pressure treatment lowers renal blood flow and reduces hydrostatic pressure gradients across the glomerular capillaries, in turn benignly decreasing creatinine clearance and eGFR. Building upon these findings, our results suggest that blood pressure lowering may even alleviate hypertensive kidney injury, regardless of changes in serum creatinine.

Although we measured a panel of biomarkers to broadly characterize kidney damage, it is important to highlight the unique physiological domains that these biomarkers represent. For example, ACR, α1m, and β2m, systemic proteins that are freely filtered at the glomerulus and reabsorbed by the proximal tubules, significantly decreased in the intensive vs. standard arm cases at 1 year.(26–28) These relative declines among cases in the intensive arm may be a direct reflection of reduced renal blood flow and glomerular filtration in the setting of intensive blood pressure lowering, independent of renin-angiotensin-aldosterone system inhibitor use. In contrast, the relative elevations among standard arm cases may represent impaired tubular absorption of these proteins, a manifestation of true intrinsic kidney damage.

The other 6 biomarkers are largely produced within the kidney and released into urine, and two of these biomarkers differed significantly in the case vs. case comparisons: YKL-40 and

uromodulin decreased in the intensive arm cases and remained unaltered or increased in the standard arm cases. YKL-40 is largely produced by kidney tubular cells and signifies kidney tubular injury and repair.(29, 30) The relative declines of YKL-40 suggest that incident CKD cases in the setting of intensive blood pressure lowering have less tubular damage compared with matched controls and with cases in the standard arm. However, this pattern was not observed for other traditional markers of tubule injury (IL-18, KIM-1, NGAL, and MCP-1).

The relative declines of uromodulin among intensive arm cases that significantly differed from elevations among standard arm cases were unexpected. Uromodulin, which is produced in the thick ascending limb of Henle's loop and the distal tubule and is believed to protect against CKD. When measured at a single timepoint, higher uromodulin has been associated with less CKD progression in prior studies,(31) although baseline uromodulin was not associated with odds of incident CKD in this study. Thus, we expected to observe relative elevations in uromodulin among intensive arm cases. However, dynamic changes in uromodulin have not been evaluated in prior studies. It is possible that lower renal blood flow may lead to decreased requirement for uromodulin production and/or secretion. Nonetheless, we acknowledge that this finding may be discrepant with our overall hypotheses. Future studies are necessary to examine the dynamic changes of uromodulin in response to treatments that influence kidney health and its association with outcomes.

Strengths of this study include the matched case-control design in a randomized trial setting that minimized potential confounding. The SPRINT cohort involved 102 centers across the U.S. and Puerto Rico, had close follow-up of participants, and frequent creatinine measurements and longitudinal urine samples, which provided a unique opportunity to investigate kidney changes in the context of intensive blood pressure reduction.

We also acknowledge several important limitations. While the biomarker results exhibit an overall consistent pattern, we are unable to explain the biological mechanisms of some of the specific changes. For example, KIM-1 and NGAL were significantly increased in a similar magnitude in case versus control comparisons. We are uncertain why these biomarkers would increase during follow-up, and no prior study to our knowledge has measured them repeatedly in a similar cohort. In addition, our study lacked power to compare cases and controls within the standard arm, as only 34 incident CKD cases occurred in this arm. This may explain the absence of significant differences of baseline biomarkers with incident CKD in the standard arm and of significant differences in the 1-year changes between cases and controls in this arm. Because we measured biomarkers only at baseline and at year 1, we do not have biomarker concentrations from the precise time of CKD diagnosis. The majority of incident CKD endpoints occurred after the 1 year biomarker measurements; thus, concentrations may have been different if measured at the time of incident CKD diagnosis. However, the mean eGFR decline at 1 year was significantly larger among cases vs. controls in the intensive arm (20 vs. 4 mL/min/1.73m^2) and in the standard arm (16 vs. 0 mL/min/1.73m^2), so the eGFR had already declined substantially among the CKD cases at the time of biomarker measurement. If the substantial eGFR declines found among incident CKD cases in the intervention arm had been associated with intrinsic kidney injury, we should have detected elevations in biomarker concentrations at 1 year. Finally, our findings may not

be generalizable to all hypertensive persons, particularly to those with diabetes or proteinuria >1 gram/day, as such persons were excluded from SPRINT.

Two important and distinct roles for urinary biomarkers emerge from our findings: identifying persons susceptible to CKD using the baseline concentrations; and using changes in the biomarkers to evaluate longitudinal changes in kidney health. The biomarkers that provided baseline prediction of CKD, a potential proxy of kidney reserve, were not the same as those that reflect responses to blood pressure changes. An eventual biomarker panel in clinical care will warrant a collection of proteins that achieve both of these objectives. Future work should investigate whether urinary biomarkers can prognosticate and distinguish individuals with true tubular injury accompanying eGFR changes in CKD, similar to their use in acute kidney injury.(32, 33)

In conclusion, the perception of a trade-off between cardiovascular benefits and kidney harms during intensive blood pressure lowering may be misguided. We found that incident CKD cases in the setting of intensive SBP treatment did not have elevations in biomarkers of kidney damage in the first year of treatment and, instead, had relative declines in several biomarkers compared both with matched controls and with incident CKD cases in the standard arm. These findings suggest that eGFR declines observed in the setting of intensive blood pressure lowering are mostly hemodynamic in nature, even among patients who may be inappropriately labeled as having a new diagnosis of CKD. We also demonstrate the limitations of serum creatinine and the potential utility of urinary biomarkers for monitoring kidney health during hypertension treatment when changes in renal blood flow may confound the clinical interpretation of changes in serum creatinine. Ultimately, these findings, in conjunction with lower cardiovascular disease and mortality risk reported in SPRINT, should be reassuring for clinicians who embark on evidence-based intensive blood pressure lowering for their patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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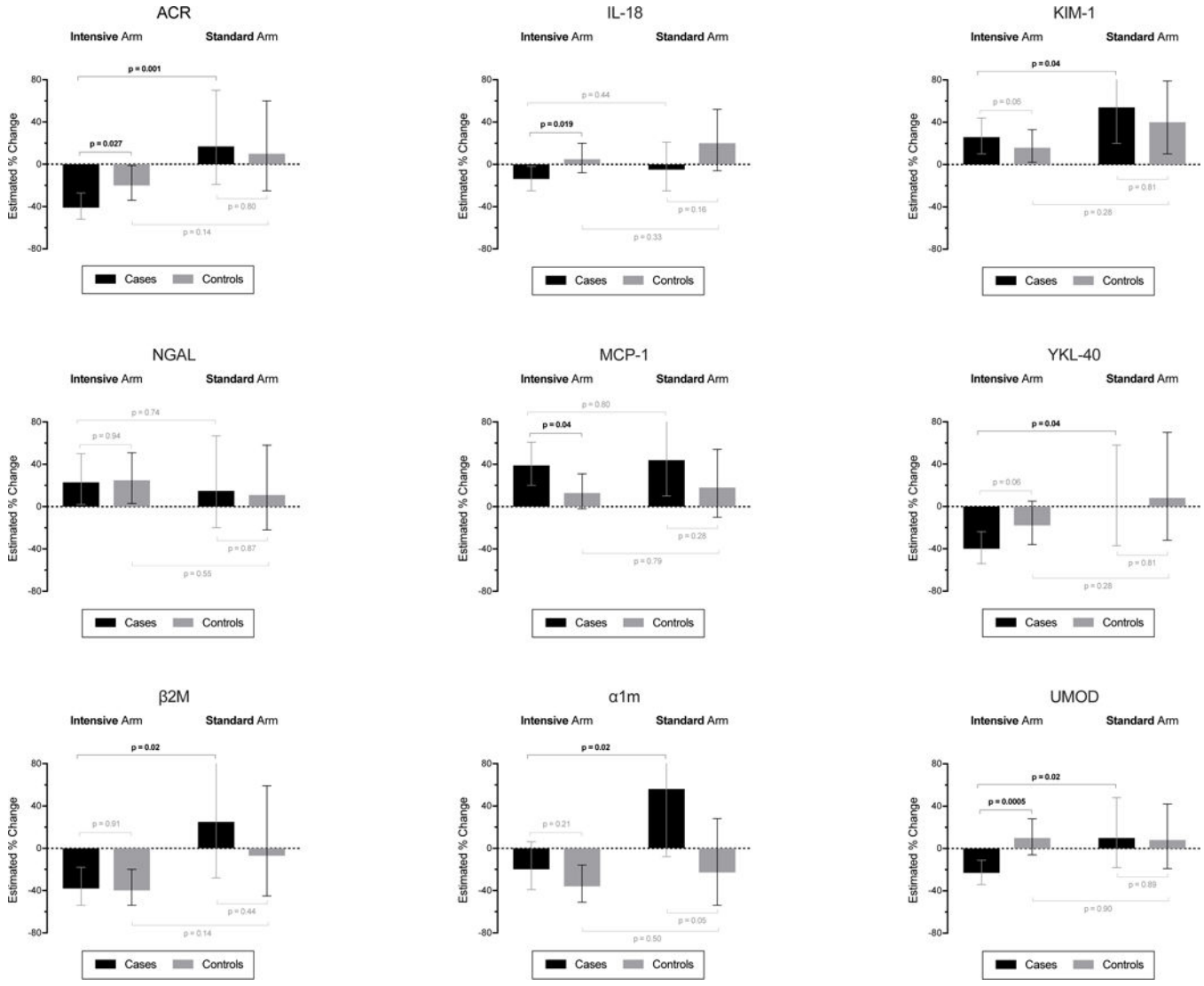

Figure 1.

The 1-year percent changes of nine urinary biomarkers among incident CKD cases and matched controls, stratified by randomization arm, in SPRINT. The black bars denote incident CKD cases, and the gray bars denote matched controls without CKD. There were 128 cases in the intensive arm and 34 in the standard arm; one control was matched per case within each intervention arm on age (within 5 years), sex, race, and baseline eGFR (within 5 ml/min/1.73m2). The 1-year changes were estimated from separate linear mixed models for each biomarker, adjusting for log2-transformed urine creatinine and systolic blood pressure. Error bars denote the 95% confidence intervals (CIs). The y-axes are truncated at +/− 80%. The 95% CI upper bounds for several biomarkers among cases in the standard arm were truncated: the 95% CI upper bounds of 1-year changes in KIM-1, MCP-1, β2M, and α1M extend to 97%, 89%, 114%, and 163%, respectively. Brackets with p-values represent comparisons of 1-year changes between respective groups at bracket tails. P-values <0.05 were considered statistically significant and have been bolded. The numerical values of the 1-year change and 95% CIs are presented in Appendix Table 6. Full names for each urinary

biomarker are as follows: albumin-creatinine ratio (ACR), interleukin-18 (IL-18), kidney injury molecule-1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL), monocyte chemoattractant protein-1 (MCP-1), anti-chitinase-3-like protein 1 (YKL-40), beta-2 microglobulin (β2M), α1microglobulin (α1M), and uromodulin (UMOD).

Table 1.

Baseline and year 1 characteristics among incident CKD cases and matched controls, stratified by randomization arm, in SPRINT

	Intensive Arm (N=128 pairs)			Standard Arm (N=34 pairs)		
	Cases	Controls	P-value*	Cases	Controls	P-value*
Baseline characteristics						
Age, *years*	67 ± 9	67 ± 9	†	68 ± 8	68 ± 9	†
Female, *N (%)*	45 (35)	45 (35)	†	14 (41)	14 (41)	†
Race, *N (%)*			†			†
African American	41 (32)	42 (33)		13 (38)	13 (38)	
Caucasian	71 (56)	67 (52)		18 (53)	18 (53)	
Hispanic/Other	16 (13)	19 (15)		3 (9)	3 (9)	
eGFR, *mL/min/1.73m²*						
MDRD	80 ± 15	79 ± 17	†	75 ± 9	74 ± 12	†
CKD-EPI (with CysC)	80 ± 14	80 ± 14		77 ± 12	77 ± 12	
SBP, *mmHg*	146 ± 19	140 ± 15	0.007	151 ± 14	140 ± 15	0.009
DBP, *mmHg*	80 ± 14	80 ± 11	0.92	80 ± 13	78 ± 11	0.34
Serum creatinine, *g/dL*	0.94 ± 0.18	0.95 ± 0.19	0.17	0.97 ± 0.16	0.99 ± 0.18	0.42
Total cholesterol, *mg/dL*	195 ± 47	192 ± 40	0.53	193 ± 44	195 ± 32	0.80
HDL cholesterol, *mg/dL*	54 ± 16	52 ± 14	0.26	57 ± 15	59 ± 14	0.67
Body mass index, *kg/m²*	30 ± 6	31 ± 6	0.66	28 ± 5	30 ± 6	0.40
History of clinical CVD, *N (%)*	24 (19)	24 (19)	1.00	7 (21)	5 (15)	0.57
History of CHF, *N (%)*	2 (1.6)	2 (1.6)	1.00	0 (0.0)	0 (0.0)	---
ACE-I or ARB use, *N (%)*	54 (42)	51 (40)	0.71	10 (29)	10 (29)	1.00
# anti-hypertensives, *N*	1.8 ± 1.1	1.7 ± 1.1	0.52	1.7 ± 1.0	1.8 ± 1.1	0.71
Current smoker, *N (%)*	18 (14)	15 (12)	0.58	7 (21)	3 (9)	0.18
Year 1‡ characteristics						
Serum creatinine, *g/dL*	1.25 ± 0.27	0.99 ± 0.20	<.0001	1.35 ± 0.83	0.99 ± 0.19	0.006
Change from baseline	0.31 ± 0.22	0.04 ± 0.12	<.0001	0.39 ± 0.83	0.01 ± 0.09	0.008
eGFR, *mL/min/1.73m²*						
MDRD	58 ± 12	75 ± 15	<.0001	59 ± 19	74 ± 15	0.004
SBP, *mmHg*	119 ± 14	121 ± 12	0.25	140 ± 15	133 ± 13	0.077
DBP, *mmHg*	66 ± 11	70 ± 10	0.002	76 ± 13	76 ± 9	0.74
ACE-I or ARB use, *N (%)*	114 (92)	92 (74)	0.0007	25 (74)	18 (53)	0.083
# anti-hypertensive, *N*	3.3 ± 1.2	2.7 ± 0.9	0.0001	2.3 ± 1.1	1.9 ± 1.4	0.19

Data are presented as mean ± standard deviation for continuous variables and frequency (%) for categorical variables.

*P-values from univariate conditional logistic regression model.

†Matching factor, no test performed.

[≠]Year 1 number of case/control pairs for Intensive Arm: serum creatinine, eGFR - N=123; SBP, DBP ACE-inhibitor use, number of anti-hypertensive meds - N=124. Standard Arm: serum creatinine, eGFR - N=33; SBP, DBP, ACE-inhibitor use, number of anti-hypertensive meds - N=34.

eGFR = estimated glomerular filtration rate; MDRD = Modification of Diet in Renal Disease study equation; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration equation; SBP = systolic blood pressure; DBP = diastolic blood pressure; HDL = high density lipoprotein; CVD = cardiovascular disease; CHF = congestive heart failure; ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker

Table 2.

Comparison of baseline biomarker concentrations among incident CKD cases and matched controls among SPRINT participants in both randomization arms combined

Biomarker	Baseline Biomarker Concentrations			OR* (95% CI)	P-value
	N (pairs)	Cases	Controls		
ACR, *mg/g*	150	18.2 ± 1.9	10.5 ± 0.85	1.50 (1.14, 1.98)	0.004
IL-18, *pg/mL*	158	36.9 ± 2.7	34.4 ± 2.5	1.30 (0.93, 1.79)	0.12
KIM-1, *pg/mL*	158	595.9 ± 59.7	546.2 ± 55.8	1.51 (1.05, 2.17)	0.027
NGAL, *ng/mL*	157	25.9 ± 2.5	28.1 ± 2.6	0.96 (0.71, 1.30)	0.80
MCP-1, *pg/mL*	158	160.2 ± 13.4	148.4 ± 13.5	1.70 (1.13, 2.56)	0.012
YKL-40, *pg/mL*	158	660.8 ± 68.8	590.8 ± 53.3	1.18 (0.90, 1.56)	0.23
β2M, *ng/mL*	154	78.3 ± 8.5	77.0 ± 7.3	0.95 (0.74, 1.22)	0.68
α1M, *mg/L*	157	4.98 ± 0.61	4.14 ± 0.52	1.18 (0.90, 1.56)	0.23
UMOD, *μg/mL*	157	9.95 ± 0.58	10.34 ± 0.67	1.04 (0.77, 1.40)	0.80

*Odds Ratio (OR) per standard deviation increase in $\log_2$-transformed biomarker concentrations. All models *except* for albumin-creatinine ratio adjust for $\log_2$-transformed urine creatinine concentrations. All models adjust for baseline systolic blood pressure.

Data presented as geometric means ± standard error of the mean (SEM). Full names for each urinary biomarker are as follows: albumin-creatinine ratio (ACR), interleukin-18 (IL-18), kidney injury molecule-1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL), monocyte chemoattractant protein-1 (MCP-1), anti-chitinase-3-like protein 1 (YKL-40), beta-2 microglobulin (β2M), α1microglobulin (α1M), and uromodulin (UMOD).