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Urinary biomarkers of tubular damage are associated with mortality but not cardiovascular risk among SPRINT participants with chronic kidney disease

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Abstract

Background: Kidney tubulo-interstitial fibrosis on biopsy is a strong predictor of chronic kidney disease (CKD) progression, and CKD is associated with elevated risk of cardiovascular disease (CVD). Tubular health is poorly quantified by traditional kidney function measures, including estimated glomerular filtration rate (eGFR) and albuminuria. We hypothesized that urinary

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biomarkers of tubular injury, inflammation and repair would be associated with higher risk of CVD and mortality in persons with CKD.

Methods: We measured urinary concentrations of interleukin-18 (IL-18), kidney injury molecule-1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL), monocyte chemoattractant protein-1 (MCP-1), and chitinase-3-like protein-1 (YKL-40) at baseline among 2,377 participants of the Systolic Blood Pressure Intervention Trial who had an eGFR <60 ml/min/1.73m^2. We used Cox proportional hazards models to evaluate biomarker associations with CVD events and all-cause mortality.

Results: At baseline, the mean age of participants was 72±9 years and eGFR was 48±11 ml/min/1.73m^2 Over a median follow-up of 3.8 years, 305 CVD events (3.6% per year) and 233 all-cause deaths (2.6% per year) occurred. After multivariable adjustment including eGFR, albuminuria, and urinary creatinine, none of the biomarkers showed statistically significant associations with CVD risk. Urinary IL-18 (HR per 2-fold higher value, 1.14; 95% CI: 1.01, 1.29) and YKL-40 (HR per 2-fold higher value, 1.08; 95% CI: 1.02, 1.14) concentrations were each incrementally associated with higher mortality risk. Associations were similar when stratified by randomized blood pressure arm.

Conclusions: Among hypertensive trial participants with CKD, higher urinary IL-18 and YKL-40 were associated with higher risk of mortality, but not CVD.

Keywords

Introduction

Chronic kidney disease (CKD), when assessed by decreased estimated glomerular filtration rate (eGFR) or higher albuminuria, is associated with increased risk of cardiovascular disease (CVD).[1–3] Advanced tubular damage, characterized by tubular atrophy and interstitial fibrosis on kidney biopsy, is a strong predictor of CKD progression,[4,5] but tubular damage is inadequately captured by eGFR and albuminuria, which primarily mark glomerular function and injury.[6,7] Several urinary biomarkers have been investigated for detection of kidney tubular injury, inflammation and repair in persons with and without CKD. Whether or not these novel dimensions of kidney tubular health prognosticate CKD complications, including CVD and mortality, is uncertain.

Interleukin-18 (IL-18), kidney injury molecule-1 (KIM-1), and neutrophil gelatinase-associated lipocalin (NGAL) have been studied extensively as markers of tubular injury, with urine levels rising several-fold in response to ischemic or inflammatory acute kidney injury.[8–14] Monocyte chemoattractant protein-1 (MCP-1) is a chemokine that attracts macrophages to the site of injury,[15–17] whereas chitinase-3-like protein-1 (YKL-40) functions as a mediator of the reparative response to tubular injury.[18,19] Some studies have demonstrated that urinary markers of tubular damage are associated with higher cardiovascular and mortality risks,[17,20–22] whereas other studies found no significant associations.[23,24] Few of the existing studies included large numbers of participants with CKD who may have more extensive tubule damage and higher risk for CVD and death. In

addition, no prior study, to our knowledge, has evaluated urinary YKL-40, a marker of renal tubular repair, as a predictor of cardiovascular complications in CKD.

The objective of this study was to evaluate the associations of urinary markers of tubular injury (IL-18, KIM-1, and NGAL) and tubular inflammation and repair (MCP-1 and YKL-40) with the risks of CVD and mortality among participants of the Systolic Blood Pressure Intervention Trial (SPRINT) who had CKD at baseline. We hypothesized that these urinary markers would be associated with higher risk of CVD events and mortality, independent of eGFR and albuminuria.

Methods

Study Design and Participants

SPRINT was an open-label clinical trial that randomized persons with systolic blood pressure (SBP) >130 mm Hg and elevated risk for CVD events to an SBP target of <120 mm Hg ("intensive") vs. <140 mm Hg ("standard").[25] Trial results were published previously.[26,27] Participants were recruited from 102 centers in the United States and Puerto Rico, and were required to meet the following inclusion criteria: age 50 years, SBP 130 to 180 mm Hg, and increased risk for CVD events (defined by: prior clinical or subclinical CVD other than stroke, 10-year risk of CVD of 15% or greater based on the Framingham risk score,[28] CKD defined as eGFR 20–59 ml/min/1.73m^2, or age 75 years). Major exclusion criteria included: diabetes mellitus, proteinuria >1 gram/day, polycystic kidney disease, prior stroke or transient ischemic attack, symptomatic heart failure, or a left ventricular ejection fraction <35%. A total of 9,361 participants were enrolled between November 2010 and March 2013. Efforts to increase recruitment of participants with CKD resulted in the enrollment of 2,646 (28%) participants with eGFR <60 ml/min/1.73m^2 at baseline, based on the Modification of Diet in Renal Disease equation. SPRINT randomly assigned participants in a 1:1 ratio to the intensive or standard blood pressure arm. The antihypertensive regimens were adjusted to maintain SBP according to the randomized treatment target. Participants attended visits monthly for the first 3 months and every 3 months thereafter; clinical data were obtained at serial visits. Venous blood and urine specimens were processed immediately, shipped overnight on dry ice, and stored at −80°C at a central laboratory. All participants provided written informed consent, and Institutional Review Boards of all participating institutions approved the study. The present study was conducted in accordance with the Declaration of Helsinki and was also approved by the committees on human research at the University of California, San Francisco and the San Francisco and San Diego Veterans Affairs Health Care Systems.

We measured urinary biomarkers at the baseline visit among persons with CKD, defined by the CKD-EPI equation that combines serum creatinine and cystatin C.[29] Among the 2,514 SPRINT participants who had an eGFR <60 ml/min/1.73m^2 by this equation, 86 participants were excluded due to unavailable urine specimens or invalid urinary biomarker measurements and 51 participants were excluded due to missing covariate data, resulting in a final analytic sample of 2,377 participants.

Predictors

Urinary IL-18, KIM-1, NGAL, MCP-1 and YKL-40 were measured at the Laboratory for Clinical Biochemistry Research at the University of Vermont. All urine specimens were in continuous storage at −80°C until biomarker measurement without prior thaw. Laboratory personnel performing the biomarker assays were blinded to clinical information about the participants. Biomarker measurements were performed by multiplex assays (Meso Scale Diagnostics, Rockville, Maryland, USA). Inter-assay coefficients of variation for the urine measurements were: IL-18, 4.9–13.7%; KIM-1, 6.1–13.0%; NGAL, 12.9–16.2%; MCP-1, 7.1–12.0%; and YKL-40, 6.5–11.1%. Biomarkers were measured in duplicate and averaged to increase precision. Urine creatinine and albumin were measured by an enzymatic procedure (Roche, Indianapolis, IN) and by a nephelometric method (Siemens, Tarrytown, NY), respectively. Inter-assay coefficients of variation for urine creatinine and albumin measurements were 1.5–4.3% and 2.2–6.9%, respectively. Samples with biomarker values below the limit of detection were assigned a value equivalent to the lower limit of detection divided by the square root of two.[30]

Outcomes

The outcomes of this study included CVD events, the primary outcome of the SPRINT trial, and all-cause mortality. CVD events were defined as a composite of non-fatal myocardial infarction, acute coronary syndrome, non-fatal acute decompensated heart failure, non-fatal stroke, and death from CVD causes. Ascertainment and adjudication of these outcomes have been described previously.[25]

Statistical Analysis

Baseline characteristics of participants were compared across quartiles of each biomarker. Spearman coefficients were used to evaluate correlations among the urinary biomarkers, urine albumin, urine creatinine, and eGFR calculated by the CKD-EPI equation that combines serum creatinine and cystatin C.[29] We used Cox proportional hazards models to evaluate associations of each urinary biomarker with CVD events and all-cause mortality in separate models. Participants were censored at death or last available study follow-up. Covariates for multivariable models were selected based on biological plausibility, and included: age, sex, race (non-Hispanic white, non-Hispanic black, other), intervention arm, urine creatinine, eGFR (CKD-EPI equation for creatinine and cystatin C), urine albumin, smoking status (current, former, never), history of CVD or heart failure, number of antihypertensive medications, statin use, systolic blood pressure, diastolic blood pressure, body mass index (BMI), high-density lipoprotein, total cholesterol, and triglycerides. Baseline values were used for all covariates.

The optimal method for correcting biomarker concentrations for differences in urinary tonicity has not been established. Because urine creatinine is influenced by muscle mass and health status and may therefore influence the ratio of biomarkers to creatinine,[31] our primary analyses evaluated biomarker concentrations that adjusted for urine creatinine concentration in the multivariable models. In secondary analyses, the biomarkers were indexed to urine creatinine as biomarker/creatinine ratios. Due to their right-skewed distributions, biomarker levels (with or without indexing to creatinine) were analyzed as log base 2-transformed

continuous variables, with results presented per 2-fold higher value. We also evaluated biomarker levels by quartile, with participants in the lowest quartile comprising the reference group. Finally, we tested for interactions by randomization arm using a likelihood ratio test. The proportional hazards assumption was satisfied for all models by visual inspection of the log negative and log survival curves and by the Schoenfeld residuals. All analyses were conducted using Stata/MP Version 15.1 (StataCorp LCC, College Station, TX).

Results

Baseline characteristics of SPRINT CKD participants

Among the 2,377 participants included in this study, 1,222 participants were randomized to the intensive treatment arm and 1,155 participants were randomized to the standard treatment arm. The mean age was 72 years and 40% of participants were women. Non-Hispanic blacks comprised 26% of participants and 25% of participants had a history of CVD or heart failure. The median eGFR was 48 ml/min/1.73m^2 (IQR: 39, 55) and the median ACR was 14 mg/g (IQR: 7, 46). Compared to participants in the lowest quartile of urinary YKL-40 concentration, those in the highest quartile were older, more likely to be female or non-Hispanic black, and had lower prevalence of CVD or heart failure (Table 1). Compared to participants in the lowest quartile of urinary IL-18 concentration, those in the highest quartile were younger, more likely to be female or non-Hispanic black, and had higher body mass index (Supplemental Table 1). When we compared participants with and without subsequent CVD events (Supplemental Table 2) or mortality events (Supplemental Table 3) during follow-up, each type of event occurred more commonly in participants characterized by older age, male gender, prevalent CVD or heart failure at baseline, smoking history, lower eGFR, higher albuminuria, and randomization to the standard BP arm of the trial.

Correlations of urinary biomarkers and eGFR

Urinary concentrations of IL-18, KIM-1, NGAL, MCP-1 and YKL-40 showed moderately strong inter-correlations (Supplemental Table 4; r = 0.4 to 0.7, p<0.05) and each marker was positively correlated with urine albumin (r = 0.3 to 0.4; p<0.05) and urine creatinine (r = 0.3 to 0.7; p<0.05) concentrations. The urinary markers showed little correlation with eGFR (| r | < 0.1 for all five markers). After indexing to urine creatinine, correlations between the biomarkers were attenuated substantially (r =0.1 to 0.5; p<0.05).

Associations of urinary biomarkers with CVD events and all-cause mortality

Over a median follow-up of 3.8 years, there were 305 CVD events (3.6% per year) and 233 all-cause deaths (2.6% per year). In demographic-adjusted models, higher urine IL-18, NGAL, MCP-1, and YKL-40 concentrations were each associated with higher risk for CVD events (Table 2). However, after additional adjustment for eGFR, albuminuria, and traditional CVD risk factors, all associations were attenuated and none remained statistically significant. When the biomarkers were analyzed as quartiles (Figure 1), participants in the highest quartiles of IL-18 (HR 1.43; 95% CI: 0.95, 2.14) and YKL-40 (HR 1.41; 95% CI: 0.99, 2.00) had higher risk of CVD events than those in the lowest quartiles, but the

associations did not reach statistical significance. When the biomarkers were indexed to urine creatinine (Supplemental Table 5), participants in the highest versus lowest quartile of YKL-40/Cr had higher risk of CVD events (HR 1.41; 95% CI: 1.01, 1.99), but urinary YKL-40/Cr was not associated with CVD events when analyzed as a continuous variable. Urinary IL-18/Cr, KIM-1/Cr, NGAL/Cr, and MCP-1/Cr were not associated with CVD events in fully adjusted models.

In demographic-adjusted models, higher urinary IL-18, KIM-1, NGAL, MCP-1, and YKL-40 concentrations were each associated with higher mortality risk (Table 2). After additional adjustment for baseline eGFR, albuminuria, and traditional CVD risk factors, higher urinary IL-18 and YKL-40 remained significantly associated with higher mortality risk. By contrast, the associations of urinary KIM-1, NGAL and MCP-1 with mortality were substantially attenuated and were no longer statistically significant in fully adjusted models. When the biomarkers were analyzed as quartiles (Figure 2), participants in the highest vs lowest quartiles of urinary YKL-40 had significantly higher mortality risk in multivariable-adjusted models (HR 1.70; 95% CI: 1.12, 2.57). Findings were similar when the biomarkers were indexed to urine creatinine (Supplemental Table 6), with higher urinary IL-18/Cr (HR 1.20 per 2-fold higher value; 95% CI: 1.05, 1.36) and YKL-40/Cr (HR 1.08 per 2-fold higher value; 95% CI: 1.02, 1.14) each incrementally associated with higher mortality risk in multivariable models. Relative to participants in the lowest quartiles, those in the highest quartiles of urinary IL-18/Cr and YKL-40/Cr had higher CVD risk by 1.71-fold (95% CI: 1.15, 2.53) and 1.92-fold (95% CI: 1.27, 2.92), respectively. Urinary KIM-1/Cr, NGAL/Cr, and MCP-1/Cr showed no statistically significant associations with all-cause mortality in fully adjusted models.

There were no statistically significant interactions by intervention arm for the CVD outcome (p>0.1 for all biomarkers) or for all-cause mortality (p>0.3 for all biomarkers).

Discussion

Despite growing recognition of the adverse effects of kidney tubular damage on CKD progression, the prognostic significance of tubular damage for cardiovascular complications and mortality has been uncertain. We hypothesized that urinary markers of tubular injury (IL-18, KIM-1, and NGAL) and tubular inflammation and repair (MCP-1 and YKL-40) would be associated with cardiovascular events and death, independent of glomerular markers of kidney health: eGFR and albuminuria. We addressed this question in an ancillary study among the subset of SPRINT participants with CKD, as few prior studies have evaluated participants with established CKD in whom the risks of CVD and death are high. We found that higher urinary levels of IL-18 and YKL-40 were associated with increased mortality risk, after adjustment for baseline eGFR, albuminuria, and traditional cardiovascular risk factors. None of the urinary biomarkers were independently associated with risk of CVD events in primary analyses that adjusted for urine creatinine; however, in secondary analyses that indexed biomarkers to urine creatinine, the highest quartile of urinary YKL-40/cr was associated with higher CVD risk. These findings contribute to the growing literature on the associations of urinary markers of tubular health with risk of CKD complications.

As kidney diagnostics evolve to encompass multiple dimensions of kidney health, there has been considerable interest in determining whether markers that evaluate the health of kidney tubules can provide prognostic information beyond the established measures of glomerular health, eGFR and albuminuria. Kidney tubular health is necessary for numerous essential functions, including solute and water reabsorption, acid-base homeostasis, hormone production, and mineral metabolism.[32] Due to high metabolic demands, the kidney tubules are vulnerable to injury from ischemic, inflammatory, or toxic insults, and incomplete repair following injury can lead to the development of CKD.[32–36] However, tubular injury, inflammation and repair processes are poorly captured by eGFR and albuminuria. Our findings indicate that urinary biomarkers of kidney tubular injury and repair have independent associations with increased mortality risk in persons with CKD, but associations with CVD were weaker and generally absent. Further studies are needed to understand whether the associations with mortality represent a causal link or a shared pathogenesis.

Previous studies have examined urinary markers of tubular injury and clinical outcomes in ambulatory settings. In the Health, Aging and Body Composition (Health ABC) cohort of elders, who predominantly had preserved kidney function, higher urinary KIM-1 and NGAL were associated with higher risks of heart failure and cardiovascular disease, respectively, and both were associated with increased mortality risk over a median follow-up of 12.4 years.[21,23,37] Higher urinary IL-18 levels were also associated with increased mortality risk in a cohort of HIV-infected individuals with preserved kidney function.[22] Additionally, in the Chronic Renal Insufficiency Cohort (CRIC), a cohort of persons with CKD, higher urinary KIM-1 was associated with heart failure and ischemic atherosclerotic events and both urinary KIM-1 and NGAL were associated with higher risks of death over a median follow-up of 6.5 years.[20] In our study of SPRINT participants with CKD, higher urinary IL-18 and YKL-40 were each associated with higher mortality risk, but in contrast to the CRIC and Health ABC studies, none of the markers were associated with CVD risk. These discordant findings may be explained by the relatively short duration of follow-up in SPRINT or by differences in the study population, which was substantially older in SPRINT than in CRIC and excluded diabetes. Taken together with the existing literature, our findings suggest that more extensive kidney tubular injury is a risk factor for mortality, although the individual biomarker associations differ across cohorts. In future investigations, it will be necessary to develop methods for integrating information from inter-correlated biomarkers, which may reflect overlapping pathophysiology within the kidney.

Because biomarker concentrations are influenced by the tonicity of urine specimens, some prior studies have indexed biomarker concentrations to urine creatinine, similar to the albumin/creatinine ratio that is used in clinical practice. However, this approach may overestimate biomarker associations with adverse outcomes, due to the impact of worse overall health status and lower muscle mass on lower urine creatinine concentrations, which can increase the biomarker/creatinine ratio. Our primary analyses, therefore, evaluated urine creatinine-adjusted biomarker concentrations, and we evaluated creatinine- indexed biomarkers in secondary analyses to enable comparison with previous studies. Overall, we observed qualitatively similar effect sizes across the biomarkers for each outcome. However, in creatinine-indexed analyses, we found that the highest quartile of YKL-40/Cr was

significantly associated with higher risk for CVD. Although the preferred analytic method remains uncertain, our findings suggest that the interpretation of future urinary biomarker studies must take into consideration the approach for creatinine-standardization.

To our knowledge, the association of urinary YKL-40 with increased risk of mortality among persons with CKD has not been reported previously. Translational studies identified YKL-40 as a urinary marker of sepsis-induced acute kidney injury (AKI)[18] and as a critical component of the renal repair response following ischemia-reperfusion injury.[19] Among 249 hospitalized patients with AKI, higher urinary YKL-40 concentrations were associated with a composite outcome of AKI progression and/or death.[38] By contrast, the direction of association in a subsequent study of 1301 kidney donors was different. This study found that higher donor urinary YKL-40 concentrations were associated with reduced risk of delayed graft function, suggesting that YKL-40 may positively impact the response to acute tubular injury.[39] In the ambulatory setting, a nested case-control study within the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial found no association between urinary YKL-40 and kidney function decline during follow-up.[40] Our study builds upon the relatively sparse literature on urinary YKL-40 by demonstrating novel associations with mortality risk among persons with CKD.

There are several limitations of this study. First, because we evaluated a cohort of predominantly older non-diabetic individuals with CKD, our results may not be generalizable to younger populations or persons with diabetes or earlier stages of kidney damage. Second, although we did not observe statistically significant differences by randomization arm, our study was not designed to evaluate whether urinary biomarker levels will inform specific blood pressure treatment strategies. Third, urinary biomarkers were measured at baseline only and we did not have access to serum levels. Finally, although we adjusted for potential confounders in our multivariable models, we cannot exclude the possibility of residual confounding.

In this study of hypertensive individuals with CKD, higher urinary IL-18 and YKL-40 were associated with higher mortality risk, independent of eGFR and albuminuria, but not with CVD risk. Further studies are needed to validate these findings and to investigate the mechanisms underlying these associations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements & Funding Sources

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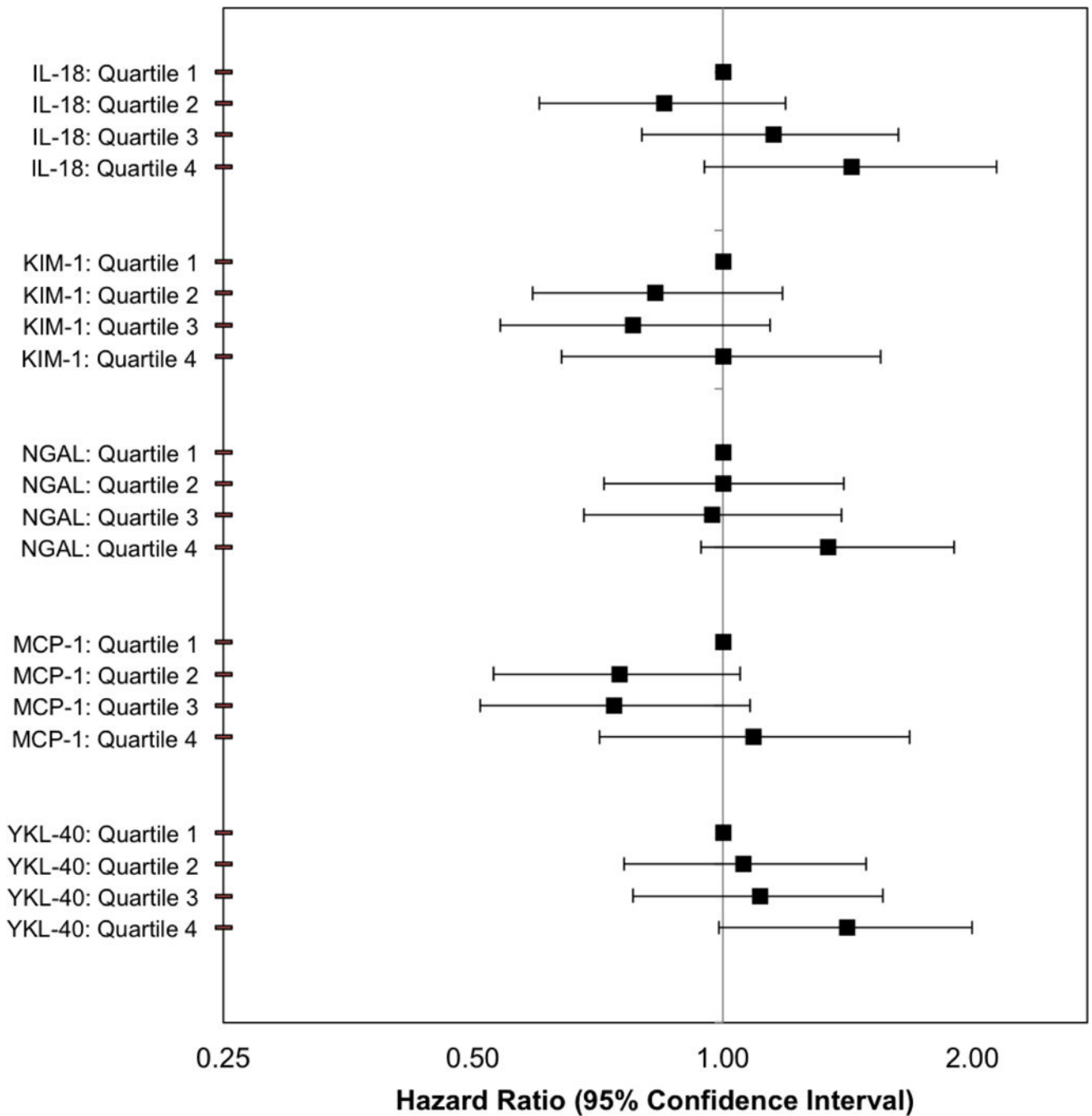
Figure 1: Multivariable adjusted associations of urinary biomarkers with CVD events among SPRINT participants with CKD (N=2,377).

Hazard ratios (95% confidence interval) displayed per quartile of baseline biomarker concentrations. Multivariable models adjust for age, sex, race, intervention arm, urine creatinine, baseline eGFR by combined CKD-EPI equation for serum creatinine and cystatin C, urine albumin, smoking status, history of cardiovascular disease or heart failure, number of antihypertensive medications, statin use, systolic blood pressure, diastolic blood pressure, body mass index, high-density lipoprotein, total cholesterol, and triglycerides.
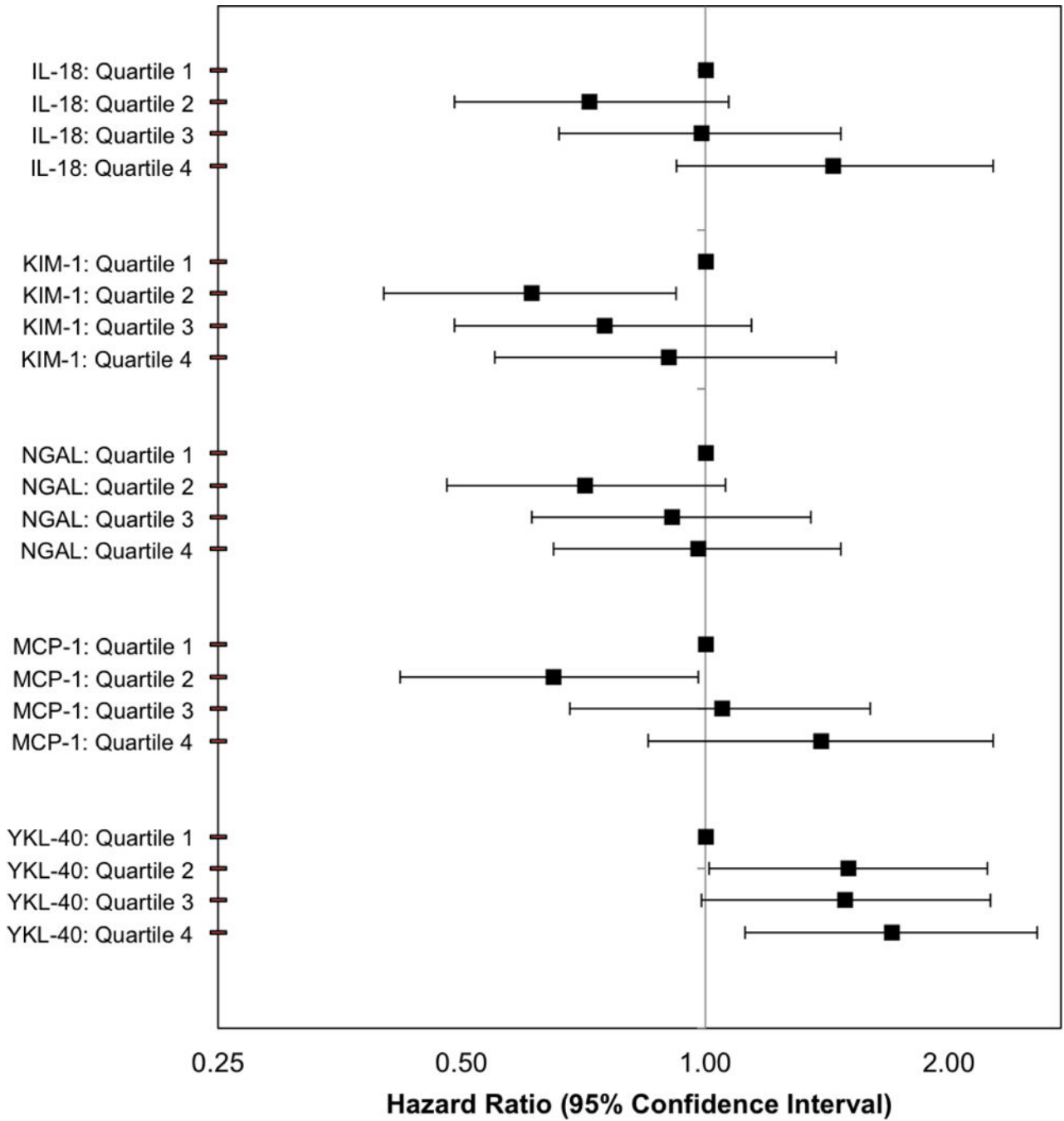
Figure 2: Multivariable adjusted associations of urinary biomarkers with all-cause mortality among SPRINT participants with CKD (N=2,377).
Hazard ratios (95% confidence interval) displayed per quartile of baseline biomarker concentrations. Multivariable models adjust for age, sex, race, intervention arm, urine creatinine, baseline eGFR by combined CKD-EPI equation for serum creatinine and cystatin C, urine albumin, smoking status, history of cardiovascular disease or heart failure, number of antihypertensive medications, statin use, systolic blood pressure, diastolic blood pressure, body mass index, high-density lipoprotein, total cholesterol, and triglycerides.

Table 1.

Baseline Characteristics of SPRINT Participants with CKD by Quartile of Urinary YKL-40 (N=2,377)

Range of YKL-40 (pg/mL) N	Q1 <214 595	Q2 214 – 542 594	Q3 543 – 1234 594	Q4 >1234 594
Age at randomization	71.9 (9.4)	73.5 (8.8)	73.5 (9.1)	73.5 (9.1)
Female	203 (34.1)	190 (32.0)	216 (36.4)	350 (58.9)
Race				
Non-Hispanic white	403 (67.7)	411 (69.2)	405 (68.2)	347 (58.4)
Non-Hispanic black	151 (25.4)	126 (21.2)	138 (23.2)	195 (32.8)
Hispanic and other	41 (6.9)	57 (9.6)	51 (8.6)	52 (8.8)
History of cardiovascular disease or heart failure [1]	165 (27.7)	142 (23.9)	147 (24.7)	145 (24.4)
Smoking Status				
Never	252 (42.4)	237 (39.9)	280 (47.1)	302 (50.8)
Former	286 (48.1)	306 (51.5)	262 (44.1)	241 (40.6)
Current	57 (9.6)	51 (8.6)	52 (8.8)	51 (8.6)
Systolic blood pressure (mm Hg)	139.2 (15.9)	138.8 (16.0)	139.4 (16.6)	140.6 (17.0)
Diastolic blood pressure (mm Hg)	73.2 (12.0)	73.6 (11.6)	74.7 (12.0)	75.5 (13.3)
Number of antihypertensive medications	2.3 (1.0)	2.1 (1.0)	2.1 (1.0)	2.2 (1.0)
ACE inhibitor use	255 (42.9)	234 (39.4)	219 (36.9)	225 (37.9)
ARB use	134 (22.5)	140 (23.6)	150 (25.3)	138 (23.2)
Calcium channel blocker use	227 (38.2)	215 (36.2)	248 (41.8)	275 (46.3)
Diuretic use	357 (60.0)	326 (54.9)	323 (54.4)	297 (50.0)
Beta blocker use	303 (50.9)	273 (46.0)	264 (44.4)	282 (47.5)
Alpha blocker use	55 (9.2)	56 (9.4)	35 (5.9)	27 (4.5)
Intensive blood pressure arm	317 (53.3)	296 (49.8)	302 (50.8)	307 (51.7)
Body mass index (kg/m²)	29.2 (5.7)	29.4 (5.7)	29.7 (5.9)	29.8 (6.2)
Statin use	310 (52.1)	317 (53.4)	310 (52.2)	302 (50.8)
Total cholesterol (mg/dL)	182.1 (40.1)	181.6 (40.7)	185.5 (40.4)	186.2 (42.4)
Low-density lipoprotein (mg/dL)	104.0 (33.5)	105.0 (34.6)	108.2 (34.9)	106.5 (34.7)
High-density lipoprotein (mg/dL)	52.1 (14.9)	51.7 (13.7)	51.9 (14.1)	53.4 (15.0)
Triglycerides (mg/dL)	114.0 [82.0, 147.0]	106.0 [78.0, 145.0]	113.0 [82.0, 162.0]	115.0 [84.0, 158.0]

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Range of YKL-40 (pg/mL) N	Q1 <214 595	Q2 214 – 542 594	Q3 543 – 1234 594	Q4 >1234 594
Serum creatinine (mg/dL)	1.5 (0.5)	1.4 (0.3)	1.4 (0.4)	1.4 (0.4)
Serum cystatin C (mg/L)	1.6 (0.5)	1.5 (0.3)	1.5 (0.4)	1.5 (0.4)
eGFR (ml/min/1.73m^2)	45.4 [35.1, 53.0]	49.0 [40.0, 54.9]	49.5 [40.6, 55.6]	48.3 [38.5, 55.0]
Urine creatinine	83.2 (48.6)	113.6 (57.4)	137.3 (63.5)	163.2 (94.9)
Albumin/creatinine ratio (mg/g)	16.5 [7.3, 56.0]	11.4 [6.0, 37.5]	12.5 [6.3, 36.0]	19.9 [9.8, 66.7]

Data are presented as median (interquartile range), mean ± standard deviation, or numbers (percent).

Abbreviations: ACE inhibitor, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate by combined CKD-EPI equation for serum creatinine and cystatin C; YKL-40, chitinase-3-like protein-1.

[1] Includes any one of the following: Previous myocardial infarction, percutaneous coronary intervention, coronary artery bypass surgery, carotid endarterectomy, carotid stenting, peripheral artery disease with revascularization, acute coronary syndrome with or without resting ECG change, ECG change on graded exercise test, or positive cardiac imaging study, at least a 50% diameter stenosis of a coronary, carotid, or lower extremity artery, abdominal aortic aneurysm >=5cm with or without repair, or self-reported heart failure.

Table 2.

Associations of urinary biomarkers with CVD events and all-cause mortality among SPRINT participants with CKD (N = 2,377)

	CVD events	All-cause mortality
	Hazard Ratio (95% CI)	**Hazard Ratio (95% CI)**
Urine IL-18		
Demographic-adjusted[1]	1.15 (1.04, 1.27)	1.22 (1.08, 1.37)
Multivariable-adjusted[2]	1.06 (0.96, 1.18)	1.14 (1.01, 1.29)
Urine KIM-1		
Demographic-adjusted[1]	1.06 (0.98, 1.16)	1.15 (1.03, 1.28)
Multivariable-adjusted[2]	0.93 (0.86, 1.02)	0.96 (0.86, 1.06)
Urine NGAL		
Demographic-adjusted[1]	1.09 (1.02, 1.17)	1.11 (1.02, 1.20)
Multivariable-adjusted[2]	1.03 (0.96, 1.11)	1.03 (0.95, 1.12)
Urine MCP-1		
Demographic-adjusted[1]	1.13 (1.02, 1.24)	1.13 (1.01, 1.27)
Multivariable-adjusted[2]	1.04 (0.94, 1.15)	1.03 (0.91, 1.17)
Urine YKL-40		
Demographic-adjusted[1]	1.07 (1.01, 1.13)	1.11 (1.05, 1.19)
Multivariable-adjusted[2]	1.04 (0.99, 1.10)	1.08 (1.02, 1.14)

Hazard ratios per doubling of baseline urinary biomarker concentration.

Abbreviations: CVD, cardiovascular disease; CI, confidence interval; IL-18, interleukin-18; KIM-1, kidney injury molecule-1; MCP-1, monocyte chemoattractant protein-1; NGAL, neutrophil gelatinase- associated lipocalin; YKL-40, chitinase-3-like protein-1.

[1] Adjusted for age, sex, race, intervention arm, and urine creatinine.

[2] Adjusted for age, sex, race, intervention arm, urine creatinine, baseline eGFR by combined CKD-EPI equation for serum creatinine and cystatin C, urine albumin, smoking status, history of cardiovascular disease or heart failure, number of antihypertensive medications, statin use, systolic blood pressure, diastolic blood pressure, body mass index, high-density lipoprotein, total cholesterol, and triglycerides.