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Association of Urinary Dickkopf-3 Levels with Cardiovascular Events and Kidney Disease Progression in Systolic Blood Pressure Intervention Trial.

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Abstract:	Background: Urinary Dickkopf-3 (uDKK3) is a tubular epithelial-derived profibrotic protein secreted into the urine under tubular stress. It is associated with kidney disease progression in persons with chronic kidney disease (CKD) and diabetes, and post-operative and contrast-associated acute kidney injury (AKI). We explored associations

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Association of Urinary Dickkopf-3 Levels with Cardiovascular Events and Kidney Disease Progression in Systolic Blood Pressure Intervention Trial

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Abstract:

Background: Urinary Dickkopf-3 (uDKK3) is a tubular epithelial-derived profibrotic protein secreted into the urine under tubular stress. It is associated with kidney disease progression in persons with chronic kidney disease (CKD) and diabetes, and post-operative and contrast-associated acute kidney injury (AKI). We explored associations of uDKK3 with cardiovascular disease (CVD), kidney and mortality outcomes within the subset of Systolic Blood Pressure Intervention Trial (SPRINT) participants with non-diabetic CKD.

Methods: We included 2,344 participants with estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2 at baseline. We used Cox proportional hazards models to evaluate associations of uDKK3 with CVD (acute decompensated heart failure, myocardial infarction, acute coronary syndrome, stroke or CVD death), kidney outcomes (incident end stage kidney disease [ESKD], incident AKI, and eGFR decline ≥30%), and all-cause mortality. We used linear mixed models to examine the association of uDKK3 with annual percentage change in eGFR. Models were adjusted for demographic and clinical characteristics, eGFR and albuminuria.

Results: Over a median follow up of 3.5 years, there were 292 CVD, 73 ESKD, 183 AKI, 471 eGFR decline, and 228 mortality events. In multivariable models without adjustment for eGFR and albuminuria, uDKK3 was strongly associated with CVD, ESKD, AKI, eGFR decline ≥30%, and mortality. However, after further adjustment for eGFR and albuminuria, uDKK3 was no longer associated with risks for composite CVD (hazard ratio [HR] 1.07, 95% confidence interval [CI] 0.92-1.23), ESKD (0.80; 0.62-1.02), AKI (1.01; 0.85-1.21), eGFR decline >30% (0.88; 0.79-0.99) or mortality (1.02; 0.87-1.20). For the linear eGFR change outcome, higher uDKK3 also had no association in the fully adjusted model (-0.03; -0.41-0.36).

Conclusions: Among individuals with hypertension and non-diabetic CKD, higher uDKK3 appeared to have associations with a greater risk of CVD events, incident ESKD, incident AKI, eGFR decline ≥30%, and mortality, but was not independent of eGFR and albuminuria.

Introduction:

Over the past decades, the development of serum and urine kidney biomarkers has progressed substantially, offering valuable insight into disease progression.[1-3] Consequently, the exploration of novel biomarkers holds the potential for quantifying the extent of kidney disease involvement non-invasively and for expanding the understanding of the underlying pathophysiology of chronic kidney disease (CKD) and cardiovascular disease (CVD).[4,5] Urine is an easily accessible specimen source, making it potentially ideal for measuring biomarkers in the clinical setting. Prior studies conducted in participants with CKD within the Systolic Blood Pressure Intervention Trial (SPRINT) revealed strong associations of urine kidney tubular biomarkers with CVD and CKD outcomes, independent of traditional risk factors and above and beyond the glomerular markers, estimated glomerular filtration rate (eGFR) and urine albumin-to-creatinine ratio (ACR). Specifically, higher levels of urine alpha-1-microglobulin (A1M), kidney injury molecule 1 (KIM-1), interleukin 18 (IL-18) and monocyte chemoattractant protein 1 (MCP-1) were independently associated with increased risk of CKD progression and CVD events, whereas higher urine concentrations of the protective factor, uromodulin (UMOD), were associated with slower decline in estimated glomerular filtration rate (eGFR) and decreased risk of CVD events.[6-8]

Markers that reflect distinct physiologic mechanisms remain of great interest to prognostic information gained from the most established biomarkers, eGFR and albuminuria. Among the recently studied biomarkers is urinary Dickkopf-3 (uDKK3), a tubular epithelial–derived profibrotic protein secreted into the urine under tubular stress.[9-11] Prior studies have demonstrated that uDKK3 is associated with tubular dysfunction and tubulointerstitial fibrosis,[11-13] and have also established uDKK3 as an independent predictor of post-operative and contrast-induced acute kidney injury (AKI).[14,15] Furthermore, uDKK3 has been associated with risk of rapid eGFR decline, end-stage kidney disease (ESKD) and mortality, independently of albuminuria.[16] These prospective findings derived from European general population cohorts without CKD, persons with CKD mainly due to diabetic kidney disease, and trial participants with IgA nephropathy.[16,17] These associations have not been previously evaluated in persons with non-diabetic CKD, and the association between uDKK3 and CVD remains

unknown in persons with CKD.

As previous studies on other kidney tubule biomarkers have provided novel insights into the strong relationship between kidney tubule disease and CVD, we aimed in this study to explore associations of uDKK3 with CVD outcomes, and to confirm its relationships with CKD progression and AKI. We evaluated this unique research question in the SPRINT trial participants with hypertension and non-diabetic CKD, all of whom had adjudicated CVD endpoints.

Methods:

Study Design and Participants:

SPRINT was an open-label clinical trial where participants with hypertension and elevated risk of CVD events were randomized to intensive versus standard systolic blood pressure (BP) targets for a primary CVD composite outcome. A total of 9,361 participants were enrolled between November 2010 and March 2013. Details on the trial design have previously been published.[18] Briefly, SPRINT inclusion criteria were age ≥50 years, systolic BP 130-180 mmHg and high CVD risk, which was defined by prior clinical or subclinical CVD other than stroke, 10-year risk of ≥15% for CVD on the Framingham risk score, eGFR 20–59 ml/min/1.73m^2, or age ≥75 years.[19] Major exclusion criteria included diabetes mellitus, proteinuria >1 gram/day, polycystic kidney disease, prior stroke, symptomatic heart failure (HF), or a left ventricular ejection fraction <35%. 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, the San Francisco Veterans Affairs Health Care System and the San Diego Veterans Affairs Health Care System.

We measured baseline uDKK3 among participants in the SPRINT-Kidney ancillary study sub-cohort of 2,514 participants with eGFR < 60 ml/min/1.73 m^2, as defined by the 2012 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation that

uses both serum creatinine and cystatin C.[20] Of these, we excluded 170 due to missing urine specimens or invalid measurements, resulting in a final analytic sample of 2,344 participants.

Urinary DKK-3 measurement:

Urinary specimens from the baseline SPRINT visit were collected and stored at -80^0 C until thawing for measurement. uDKK3 was measured using singleplex assays on the Meso Scale Discovery platform with a detectable range from 8.0 to 220,000 pg/mL. Each specimen was measured twice, and results were averaged for improved precision. Intra-assay and inter-assay coefficients of variation were 1.009 and 0.788, respectively. Urine creatinine was measured using an enzymatic procedure (Roche, Indianapolis, IN, USA) and urine albumin using a nephelometric method (Siemens, Tarrytown, NY, USA). All urine biomarker analyses were adjusted for urine creatinine to account for differences in urine tonicity.[21]

Cardiovascular outcomes:

We used the SPRINT primary composite CVD endpoint that included acute decompensated HF, myocardial infarction (MI), acute coronary syndrome (ACS) not resulting in MI, stroke or CVD death. We also evaluated individual components of the primary composite, with the exception of ACS not resulting in MI, and all-cause mortality. All these endpoints were centrally adjudicated by members of the Morbidity and Mortality subcommittee blinded to treatment assignment as previously described.[18]

Kidney outcomes:

Serum creatinine was measured by the SPRINT Central Laboratory (University of Minnesota) at baseline, 1 month, 3 months, 6 months and every 6 months thereafter. eGFR was estimated using the 2021 race-free CKD-EPI equation for creatinine.[22] We considered the following kidney outcomes: (1) incident ESKD requiring dialysis or kidney transplantation, ascertained through year 6 after trial enrollment and via the United States Renal Data System database; (2) incident AKI requiring hospitalization, derived from the serious adverse events reported during the trial duration; and (3) eGFR decline ≥ 30% from study baseline. Finally, we assessed annualized eGFR slope, based

on serial serum creatinine measurements.

Covariates:

All included covariates were taken from the baseline study visit. Demographic, clinical, and laboratory data included age, sex, race, ethnicity, body mass index (BMI), smoking (current/former/never), systolic BP, number of anti-hypertensive medications, class of antihypertensive medication, statin use, total and high-density lipoprotein (HDL) cholesterol and history of CVD or HF. Race and ethnicity were self-reported and obtained by questionnaires. Additionally, we adjusted for randomization assignment to control for any potential confounding effects that might arise due to the differences in treatment strategies between the standard and intensive BP control groups. Finally, we adjusted for clinical measures of kidney health including eGFR and albuminuria, and all models were adjusted for urine creatinine to account for differences in urine concentration at the time of urine specimen collection.

Statistical Analysis:

We summarized baseline characteristics, event numbers and incident rates by quartiles of uDKK3. The incidence rates were tabulated by indexing urinary DKK3 to urinary creatinine levels (uDKK3/uCr). As uDKK3 levels were right-skewed, we log-transformed uDKK3 to achieve a more normal distribution. We used Cox proportional hazard models to evaluate the associations of uDKK3 with CVD, mortality, and kidney outcomes, treating uDKK3 as a continuous variable (per 1 standard deviation [SD] increase) and as quartiles. Proportional hazards assumptions were assessed using Schoenfeld residuals. For the kidney outcome of eGFR decline ≥30%, we employed interval-censored Cox models, where exact dates were unknown. The time to event was measured up to the last study visit. Incident ESKD was assessed up to December 31, 2019. To address the competing risk of death, we employed the Fine and Gray method to evaluate the association between uDKK3 and incident ESKD, reporting the sub-distribution hazard ratio.[23] For each outcome, we constructed two successive nested models. In Model 1, adjusted for intervention arm, and urine creatinine, in addition to demographic and clinical risk factors listed as covariates above. In Model 2, further

adjusted for baseline eGFR and urine albumin.

Linear mixed models with random intercepts, random slopes, and an unstructured covariance structure were used to evaluate uDKK3 associations with annualized eGFR slope. Estimated GFR was log-transformed in analyses of eGFR slope to allow interpretation of the slope as annualized percent change. Model covariates were the same as for our Cox models, except that we did not control for baseline eGFR. These models included uDKK3-by-time and covariate-by-time interactions.

Because eGFR trajectories differed by randomization arm, we stratified the analyses by randomization arm. To assess whether the associations of uDKK3 with outcomes differed by CKD severity, analyses were additional stratified by baseline eGFR (<45 vs. ≥45 ml/min/1.73m^2) and urine ACR (≤30 vs. >30 mg/g). Finally, interaction analyses were performed with stratification by randomization arm, baseline eGFR, and urine ACR.

Analyses were conducted using the SAS version 9.4 (SAS Institute, Inc, Cary, NC) and Stata version 17.0 (College Station, TX).

Results:

Baseline characteristics

Among the 2,344 participants with CKD included in this analysis, mean ±SD age was 73 ±9 years, 41% were women, 73% self-identified as White, and 7% self-identified as Hispanic. Median baseline eGFR and urine ACR were 50 ml/min/1.73m^2 (interquartile range [IQR] 40, 57) and 14 mg/g (IQR 7, 45), respectively. The mean ±SD uDKK3 was 1.23 ± 3.56 ng/mL. The baseline characteristics stratified by quartile of uDKK3 levels measured at study baseline are shown in **Table 1**. Compared to participants with lower uDKK3 levels, those in the highest quartile were on average older and, less often female and, had more prevalent CVD, lower BMI, higher systolic BP, lower total cholesterol, lower eGFR, and higher urine ACR. Additionally, participants with higher uDKK3 levels had less frequent diuretic use compared to those in the lower quartiles.

Cardiovascular and mortality outcomes

Over a median follow up of 3.5 years, there were 292 composite CVD and 228 mortality events. The incidence rates of the composite CVD endpoint and all-cause mortality increased with higher uDKK3/uCr quartiles (**Figure 1**); quartiles 3 and 4 had higher event rates compared to quartiles 1 and 2 for all CVD outcomes (**Table 2**). Each 1 SD higher uDKK3 was associated with a 26% higher risk of the primary composite CVD outcome in models that adjusted for demographics and CVD risk factors. However, this association was attenuated and no longer statistically significant after additional adjustment for baseline eGFR and urine albumin. Likewise, each 1 SD higher baseline uDKK3 was associated with a 32% higher risk of all-cause mortality in adjusted models before inclusion of eGFR and urine albumin, but these associations were again attenuated after adjustment for these two covariates (**Table 2**). Similar findings were observed when uDKK3 was analyzed categorically across quartiles.

Kidney outcomes

Over a median follow up of 3.5 years, 73 developed ESKD, 183 had incident AKI, and 471 had a ≥30% decline in baseline eGFR. The incidence rates of ESKD, AKI and decline in eGFR≥30% from baseline were lower in those in quartiles 1 and 2 compared with participants in quartile 4 of baseline uDKK3/uCr (**Figure 2 and Table 3).** In multivariable models that were not adjusted for eGFR and urine albumin, uDKK3 as a continuous variable was associated with significantly higher risk of incident ESKD and AKI, but not with eGFR decline ≥30%. These associations were completely attenuated after additional adjustment for baseline eGFR and urine albumin. Results were similar when evaluating uDKK3 as quartiles. (**Table 3**).

Participants had a mean of 8.9±2.5 eGFR measures, including baseline, over a median follow-up of 3.5 years (IQR 2.5, 4.0). In multivariable adjusted analysis, each 1 SD higher uDKK3 was associated with an 0.71% faster annual decline in eGFR (95%CI: -1.09, -0.32). Once more, this association was completely attenuated after further adjustment for urine albumin (-0.03%, 95%CI: -0.41, +0.36). (**Table 4**)

We found no significant interactions of the associations of uDKK3 with CVD and CKD outcomes by urine albumin, eGFR category or randomization arm (all p-interactions > 0.05).

Discussion:

This study investigated the association of uDKK3 concentrations with CVD and kidney outcomes in a well-characterized, high-cardiovascular risk cohort of hypertensive trial participants with non-diabetic CKD. Higher uDKK3 levels were consistently associated with increased risk of CVD and kidney outcomes after adjustment for demographic characteristics and CVD risk factors. However, all of these associations weakened after adjustment for baseline eGFR and albuminuria. These findings were similar when stratified by randomization arm, baseline eGFR, and urine albumin levels.

Few studies have explored the association of uDKK3 and CVD. A single study conducted in a European cohort of community-dwelling individuals found that plasma DKK3 levels were associated with CVD risk factors, but not independently associated with prevalent and new-onset CVD.[9] To our knowledge, this is the first study to explore the association of uDKK3 and CVD in a cohort with CKD. In this relatively large CKD cohort with adjudicated CVD events, we found that, unlike other tubule markers of kidney health, uDKK3 was not associated with CVD events independently of eGFR and albuminuria.

Our findings add to the growing body of research evaluating the association of uDKK3 in persons with CKD. DKK3 is a secreted glycoprotein derived from tubular epithelial cells that has been implicated in the canonical WNT-Catenin signaling pathway, suggesting a potentially important role in kidney fibrosis.[8,11-13] The value of uDKK3 as a biomarker arises from its secretion into urine under conditions of tubular stress, and its correlation with the extent of tubulointerstitial fibrosis observed in kidney biopsy pathology.[17,24] Prior studies have shown the potential of uDKK3 to offer insights into

disease mechanisms, distinguish among CKD etiologies, and estimate risk of disease progression.[14,16,17] Although some studies have investigated its properties as a plasma biomarker, plasma DKK3 has had less consistent associations with kidney outcomes.[9,10,25] Among persons with CKD secondary to diabetes or other heterogenous etiologies, higher urine concentrations of DKK3 were independently associated with eGFR decline, incident ESKD and death.[16,17] Furthermore, uDKK3 has been associated with post-operative AKI after cardiac surgery in persons without CKD and with contrast-associated AKI after coronary angiography in persons with and without CKD.[14,15] In contrast to these prior studies, we found no independent association of uDKK3 with similar kidney outcomes. Our study population differed from prior studies, as we evaluated ambulatory hypertensive individuals without diabetes and with low grade albuminuria, thus representing a distinct subgroup within CKD, which could explain our results.

Another potential explanation may be that uDKK3 may have stronger associations with kidney outcomes among populations with greater albuminuria[10]; for example, the mean ±SD albuminuria was 322 ±1,930 mg/g among 575 participants with CKD in the CARE FOR HOMe cohort.[17] Wong *et al*. demonstrated that prolonged albuminuria could lead to increased expression of DKK3 in rodent models.[12] In our study, participants were overwhelmingly non-albuminuric; even in the highest uDKK3 quartile, the median urine ACR was 33 mg/g with IQR (13,199). Thus, the uDKK3 concentrations that we studied in SPRINT may have been below the threshold for elevated risk for kidney outcomes.

Strengths of this study include its substantial sample size of 2,344 participants, comprehensive assessments of clinically relevant CVD and kidney outcomes, and focus on a high-risk hypertensive population without diabetes. Further, assessment within a clinical trial provided protocolized measurements of eGFR for all participants at pre-specified study visits. All CVD events were also adjudicated, as they served as the primary endpoint for the SPRINT trial.

The study also has important limitations. As stated, the degree of albuminuria was

limited by inclusion criteria. Our study design was observational, and although we made efforts to adjust for potential confounders, residual confounding cannot be ruled out. We evaluated only a single measurement of uDKK3 at baseline, whereas longitudinal measurements could potentially provide further insights into their associations with CVD and kidney outcomes.

In conclusion, among individuals with hypertension and mild-to-moderate, non-diabetic CKD, baseline uDKK3 levels do not provide a unique contribution to prognosis beyond the current clinical measures of eGFR and urine albumin. These findings suggest that tubule stress may not be a major factor leading to CVD, and that use of uDKK3 as a prognostic biomarker for CKD progression may be limited to specific patient populations.

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Table 1: Baseline characteristics of SPRINT participants with chronic kidney disease by urine DKK3 quartiles

		Urine DKK3, ng/mL			
Characteristic	**Total**	**Quartile 1**	**Quartile 2**	**Quartile 3**	**Quartile 4**
Range		**N= 586**	**N= 586**	**N= 586**	**N= 586**
		0.01-0.29	**0.29-0.57**	**0.57-1.19**	**1.19-121.67**
Age, y	73 (65, 79)	74 (67, 79)	76 (68, 80)	75 (67, 81)	
Female	325 (55%)	274 (47%)	210 (36%)	155 (26%)	
Race and Ethnicity					
Black	178 (30%)	148 (25%)	115 (20%)	142 (24%)	
Hispanic	28 (5%)	44 (8%)	47 (8%)	44 (8%)	
White	404 (69%)	430 (73%)	459 (78%)	431 (74%)	
Intensive arm	311 (53%)	304 (52%)	283 (48%)	295 (50%)	
Prevalent CVD	158 (27%)	149 (25%)	172 (29%)	177 (30%)	
Prevalent heart failure	38 (6%)	27 (5%)	39 (7%)	41 (7%)	
Smoking					
Current	63 (11%)	41 (7%)	42 (7%)	55 (9%)	
Former	271 (46%)	247 (42%)	270 (46%)	259 (44%)	
Never	252 (43%)	298 (51%)	274 (47%)	272 (46%)	
BMI, kg/m^2	30 (26, 34)	29 (26, 34)	28 (25, 32)	27 (25, 31)	
Systolic BP, mm Hg	136 (127, 147)	139 (128, 149)	139 (130, 150)	141 (131, 151)	
HDL cholesterol, mg/dL	51 (43, 61)	50 (42, 60)	50 (42, 60)	50 (42, 60)	
Total cholesterol, mg/dL	183 (159, 212)	179 (154, 203)	176 (154, 206)	175 (151, 203)	
eGFR, mL/min/1.73m^2	52 (43, 57)	51 (42, 58)	50 (41, 58)	46 (35, 55)	
Urine ACR, mg/g	10 (5, 23)	11 (6, 31)	15 (7, 49)	33 (13, 119)	
No. antihypertensive medications	2.0 (2.0, 3.0)	2.0 (1.0, 3.0)	2.0 (1.0, 3.0)	2.0 (1.0, 3.0)	
Antihypertensive class					
Diuretic	432 (74%)	328 (56%)	292 (50%)	225 (38%)	
ACE inhibitor/ ARB	371 (63%)	379 (65%)	366 (62%)	343 (59%)	
Beta-blocker	301 (51%)	266 (45%)	256 (44%)	271 (46%)	
Statin use	283 (49%)	308 (53%)	311 (53%)	307 (53%)	

Data displayed as N (%) or median [interquartile range]

Abbreviations: ACE, angiotensin-converting enzyme; ACR, albumin-to-creatinine ratio; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate by creatinine and cystatin C; HDL, high-density lipoprotein; HF, heart failure; SPRINT, Systolic Blood Pressure Intervention Trial; DKK3, Dickkopf-3

Table 2: Associations of urine DKK3 with cardiovascular outcomes in multivariable models among SPRINT participants with chronic kidney disease

	Hazard Ratios (95% confidence intervals)				
Outcome	**Per 1 SD increase** Urine DKK3 Range (ng/mL)	**Quartile 1** 0.01-0.29	**Quartile 2** 0.29-0.57	**Quartile 3** 0.57-1.19	**Quartile 4** 1.19-121.67
Composite CVD					
Events (%)	-	59 (10.1%)	48 (8.2%)	90 (15.4%)	95 (16.2%)
Model 1	1.26 (1.11, 1.44)	1.00 (ref)	0.97 (0.65, 1.46)	1.80 (1.25, 2.59)	1.84 (1.26, 2.67)
Model 2	1.07 (0.92, 1.23)	1.00 (ref)	0.85 (0.56, 1.28)	1.42 (0.98, 2.07)	1.24 (0.83, 1.85)
HF					
Events (%)	-	30 (5.1%)	21 (3.6%)	34 (5.8%)	33 (5.6%)
Model 1	1.16 (0.94, 1.41)	1.00 (ref)	1.09 (0.59, 2.02)	1.70 (0.97, 2.98)	1.61 (0.90, 2.87)
Model 2	0.87 (0.69, 1.10)	1.00 (ref)	0.90 (0.49, 1.67)	1.20 (0.67, 2.16)	0.88 (0.47, 1.63)
Stroke					
Events (%)	-	13 (2.2%)	8 (1.4%)	21 (3.6%)	22 (3.8%)
Model 1	1.30 (0.99, 1.70)	1.00 (ref)	0.50 (0.19, 1.32)	1.40 (0.65, 3.03)	1.37 (0.62, 3.03)
Model 2	1.23 (0.91, 1.66)	1.00 (ref)	0.47 (0.18, 1.25)	1.27 (0.58, 2.80)	1.15 (0.49, 2.69)
MI					
Events (%)	-	18 (3.1%)	21 (3.6%)	37 (6.3%)	29 (4.9%)
Model 1	1.08 (0.86, 1.36)	1.00 (ref)	1.13 (0.58, 2.21)	1.89 (1.02, 3.49)	1.36 (0.70, 2.62)
Model 2	0.97 (0.75, 1.24)	1.00 (ref)	1.03 (0.53, 2.03)	1.65 (0.88, 3.10)	1.07 (0.53, 2.16)
CVD death					
Events (%)	-	9 (1.5%)	12 (2.0%)	17 (2.9%)	32 (5.5%)
Model 1	1.63 (1.27, 2.09)	1.00 (ref)	1.86 (0.73, 4.73)	2.64 (1.10, 6.35)	4.34 (1.86, 10.1)
Model 2	1.23 (0.93, 1.62)	1.00 (ref)	1.40 (0.55, 3.59)	1.77 (0.72, 4.33)	2.09 (0.86, 5.05)
All-cause mortality					
Events (%)	-	38 (6.5%)	44 (7.5%)	61 (10.4%)	85 (14.5%)
Model 1	1.32 (1.14, 1.53)	1.00 (ref)	1.23 (0.77, 1.95)	1.59 (1.02, 2.49)	2.03 (1.31, 3.16)

	Model 2	1.02 (0.87, 1.20)	1.00 (ref)	0.94 (0.59, 1.50)	1.10 (0.69, 1.73)	1.07 (0.67, 1.72)

Abbreviations: DKK3, Dickkopf-3; HF, heart failure; MI, myocardial infarction; CVD, cardiovascular disease; SD, standard deviation; ref, reference.

Model 1: intervention arm, age, sex, log urine creatinine, race, smoking, body mass index, systolic blood pressure, number of anti-hypertensive medications at baseline, type of antihypertensive medication, history of CVD, HF, HDL cholesterol, total cholesterol and statin use
Model 2: model 1 plus eGFR and urine albumin

Table 3: Associations of urine DKK3 with kidney outcomes in multivariable models among SPRINT participants with chronic kidney disease

		Hazard Ratios (95% confidence intervals)				
Outcome		**Per 1 SD increase** Urine DKK3 Range (ng/mL)	**Quartile 1** 0.01-0.29	**Quartile 2** 0.29-0.57	**Quartile 3** 0.57-1.19	**Quartile 4** 1.19-121.67
Incident ESKD[‡]						
	Events (%)	-	16 (2.7%)	10 (1.7%)	15 (2.6%)	32 (5.5%)
	Model 1	1.65 (1.33, 2.04)	1.00 (ref)	1.31 (0.54, 3.21)	2.54 (1.14, 5.68)	5.52 (2.36, 12.88)
	Model 2	0.80 (0.62, 1.02)	1.00 (ref)	0.71 (0.31, 1.62)	0.67 (0.30, 1.50)	0.64 (0.30, 1.35)
Incident AKI						
	Events (%)	-	38 (6.5%)	42 (7.2%)	32 (5.5%)	71 (12.1%)
	Model 1	1.32 (1.13, 1.54)	1.00 (ref)	1.35 (0.84, 2.17)	1.02 (0.61, 1.70)	2.23 (1.40, 3.53)
	Model 2	1.01 (0.85, 1.21)	1.00 (ref)	1.04 (0.65, 1.68)	0.68 (0.40, 1.15)	1.12 (0.68, 1.85)
Decline in eGFR ≥30% from baseline						
	Events (%)*	-	123 (21.3%)	112 (19.5%)	96 (16.6%)	140 (24.2%)
	Model 1	1.10 (0.99, 1.21)	1.00 (ref)	0.99 (0.75, 1.31)	0.84 (0.63, 1.14),	1.28 (0.96, 1.71)
	Model 2	0.88 (0.79, 0.99)	1.00 (ref)	0.84 (0.64, 1.12)	0.64 (0.48, 0.87)	0.76 (0.56, 1.04)

*The denominators for the number of events for each quartile of urine DKK3 are respectively 577; 575; 578 and 579.

[‡] Sub-hazard ratios from multivariable Fine-Gray proportional hazards models to account for competing risk of death.

Abbreviations: DKK3, Dickkopf-3; ESKD, end stage kidney disease; AKI, acute kidney disease; eGFR, estimated glomerular filtration rate; SD, standard deviation; ref, reference.

Model 1: intervention arm, age, sex, log urine creatinine, race, smoking, body mass index, systolic blood pressure, number of anti-hypertensive medications at baseline, type of antihypertensive medication, history of CVD, HF, HDL cholesterol, total cholesterol and statin use
Model 2: model 1 plus eGFR and urine albumin

Table 4: Associations of urine DKK3 with annual percentage change in eGFR among SPRINT participants with chronic kidney disease

	Urine DKK3, ng/mL				
	Hazard Ratios (95% confidence intervals)				
Outcome	**Per 1 SD increase**	**Quartile 1** 0.01-0.29	**Quartile 2** 0.29-0.57	**Quartile 3** 0.57-1.19	**Quartile 4** 1.19-121.67
Annual % change in eGFR					
Model 1	-0.71 (-1.09, -0.32)	1.00 (ref)	-0.56 (-1.39, 0.26)	-0.80 (-1.62, 0.03)	-2.04 (-3.10, -0.98)
Model 2	-0.03 (-0.41, 0.36)	1.00 (ref)	-0.07 (-0.88, 0.75)	0.09 (-0.73, 0.92)	-0.45 (-1.46, 0.57)

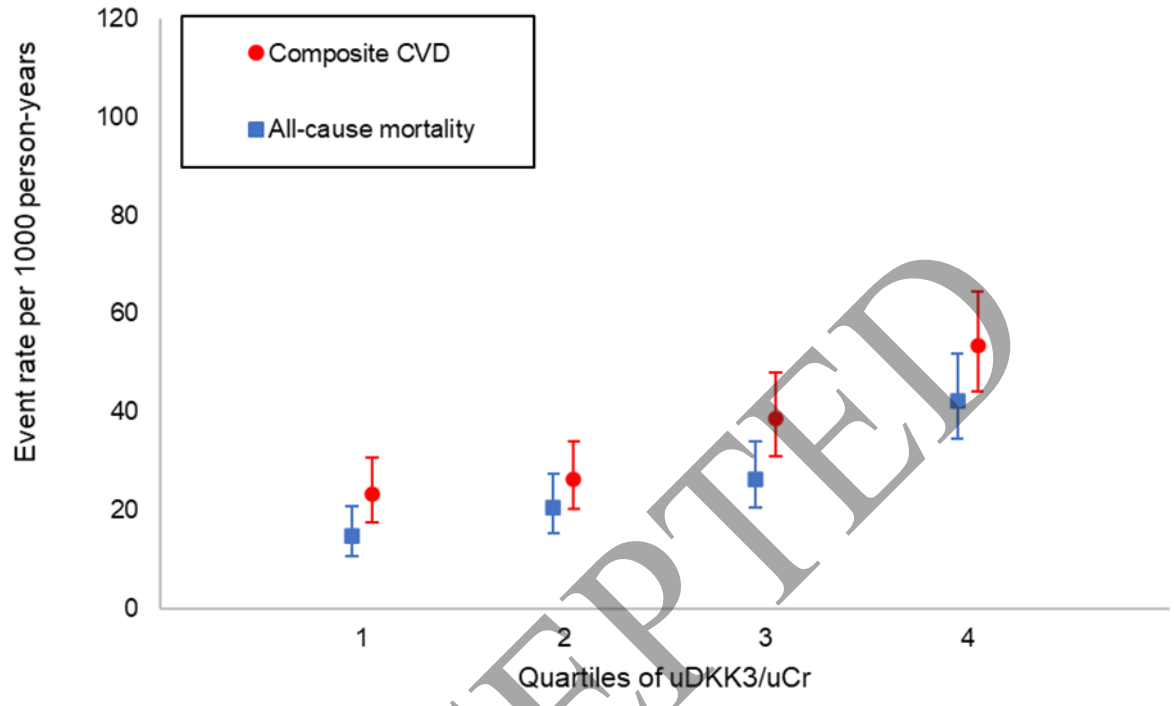
All results are from linear mixed models with random intercepts and slopes, using time x biomarker interactions to test associations with changes in eGFR over time

Abbreviations: DKK3, Dickkopf-3; eGFR, estimated glomerular filtration rate; HR, hazard ratio; ref, reference; SD, standard deviation

Model 1: intervention arm, age, sex, log urine creatinine, race, smoking, body mass index, systolic blood pressure, number of anti-hypertensive medications at baseline, type of antihypertensive medication, history of CVD, HF, HDL cholesterol, total cholesterol and statin use
Model 2: model 1 plus urine albumin

Figure Legends

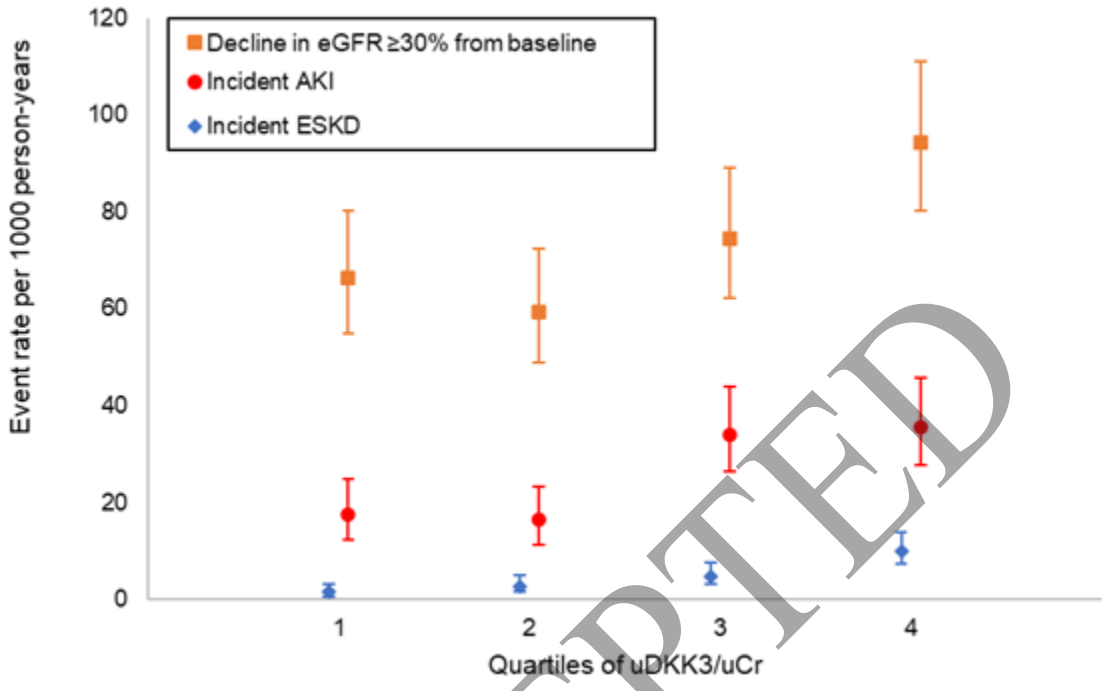
Figure 1: Unadjusted incidence rates of cardiovascular outcomes across uDKK3/uCr quartiles



Error bars denote 95% confidence intervals

Abbreviations: CVD, cardiovascular disease; uDKK3, urinary Dickkopf-3; uCr, urine creatinine

Figure 2: Unadjusted incidence rates of kidney outcomes across uDKK3/uCr quartiles



Error bars denote 95% confidence intervals

Abbreviations: ESKD, end stage kidney disease; AKI, acute kidney disease; eGFR, estimated glomerular filtration rate; uDKK3, urinary Dickkopf-3; uCr, urine creatinine

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Date of Completion: January 29, 2024
Disclosure Updated Date: January 29, 2024

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V. Peschard reports the following:
Employer: University of California, San Francisco (UCSF)

I understand that the information above will be published within the journal article, if accepted, and that failure to comply and/or to accurately and completely report the potential financial conflicts of interest could lead to the following: 1) Prior to publication, article rejection, or 2) Post-publication, sanctions ranging from, but not limited to, issuing a correction, reporting the inaccurate information to the authors' institution, banning authors from submitting work to ASN journals for varying lengths of time, and/or retraction of the published work.

Name: Vanessa-Giselle Peschard
Manuscript ID: K360-2024-000056
Manuscript Title: Association of urinary Dickkopf-3 with cardiovascular events and kidney disease progression in the Systolic Blood Pressure Intervention Trial
Date of Completion: January 29, 2024
Disclosure Updated Date: January 29, 2024

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R. Scherzer reports the following:
Employer: UCSF; and Advisory or Leadership Role: Editorial board of journals: CJASN, Kidney360 and JAIDS.

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Name: Rebecca Scherzer
Manuscript ID: K360-2024-000056
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M. Shlipak reports the following:
Research Funding: Bayer Pharmaceuticals; Honoraria: Bayer; AstraZeneca; Boeringer Ingelheim;; Patents or Royalties: Kidney Health Monitoring in Hypertension Patients; Advisory or Leadership Role: American Journal of Kidney Disease; Journal of the American Society of Nephrology; Circulation; Board Member, Northern California Institute for Research and Education; and Other Interests or Relationships: Committee Member - KDIGO Guidelines Committee.

I understand that the information above will be published within the journal article, if accepted, and that failure to comply and/or to accurately and completely report the potential financial conflicts of interest could lead to the following: 1) Prior to publication, article rejection, or 2) Post-publication, sanctions ranging from, but not limited to, issuing a correction, reporting the inaccurate information to the authors' institution, banning authors from submitting work to ASN journals for varying lengths of time, and/or retraction of the published work.

Name: Michael Shlipak
Manuscript ID: K360-2024-000056
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