**Supplemental Table of Contents:**

Supplementary Table S1. Laboratory characteristics of endogenous secretory solutes measured in SPRINT participants with CKD

Supplementary Table S2. Baseline characteristics of SPRINT participants with baseline CKD stratified by secretion score quartiles

Supplementary Table S3. Correlation coefficients of the summary secretion score and individual markers of tubular secretion clearance

Supplementary Table S4. Associations of the summary secretion score with risk of AEs in SPRINT participants with CKD stratified by intervention arm

Supplementary Table S5. Correlation coefficients of the summary secretion score and individual markers of tubular secretion clearance

Supplementary Table S6. Associations of the summary secretion score with risk of AEs in SPRINT participants with CKD stratified by intervention arm

Supplementary Table S7. Epidemiologic studies of secretion biomarker associations with adverse outcomes in CKD

Supplementary Figure S1. Cumulative incidence of the composite adverse event (AE) outcome stratified by quartiles of the summary secretion score

**Supplementary Table S1. Laboratory characteristics of endogenous secretory solutes measured in SPRINT participants with CKD**

|  |  |  |
| --- | --- | --- |
|  | **Plasma** | **Urine** |
| **Endogenous secretory solute** | **Analytic range (µM)** | **Intra-assay CV (%)** | **Inter-assay CV (%)** | **Analytic range (µM)** | **Intra-assay CV (%)** | **Inter-assay CV (%)** |
| Adipic acid | 0.1-30 | 4.36 | 4.82 | 5-1500 | 2.75 | 3.33 |
| Cinnamoylglycine | 0.002-5 | 2.53 | 4.17 | 0.1-250 | 1.25 | 4.47 |
| P-cresol sulfate | 0.2-30 | 3.28 | 3.22 | 10-1500 | 2.32 | 3.55 |
| 1,7-dimethyluric acid | 0.1-30 | 2.63 | 5.15 | 5-1500 | 1.93 | 4.15 |
| 1,3,7-trimethyluric acid | 0.01-30 | 3.86 | 4.32 | 0.5-1500 | 4.61 | 4.10 |
| 2-furoylglycine | 0.02-30 | 2.46 | 3.58 | 1-1500 | 1.50 | 3.57 |
| Hippuric acid | 0.02-30 | 3.10 | 3.64 | 5-7500 | 2.55 | 4.52 |
| M-hydroxy hippurate | 0.02-30 | 2.85 | 3.97 | 1-1500 | 2.13 | 3.38 |
| Indoxyl sulfate | 0.1-30 | 2.94 | 4.82 | 5-1500 | 2.62 | 4.55 |
| Phenylacetylglutamine | 0.01-30 | 3.15 | 3.52 | 2.5-7500 | 2.10 | 4.79 |
| Tiglylglycine | 0.01-30 | 2.29 | 5.13 | 0.5-1500 | 1.82 | 3.77 |

Abbreviations: CKD, chronic kidney disease; CV, coefficient of variation; SPRINT, Systolic Blood Pressure Intervention Trial.

**Supplementary Table S2. Baseline secretion biomarker urine-to-plasma ratios of SPRINT participants with CKD stratified by development of adverse events of interest during follow-up**

|  |  |  |  |
| --- | --- | --- | --- |
| **Secretion marker** | **No AE of interest\* during follow-up** **(N =1462)** | **≥1 AE of interest during follow-up (N =627)** | ***P*** |
| Adipic Acid | 42 (23, 70) | 34 (19, 63) | <0.001 |
| Cinnamoylglycine | 140 (85, 211) | 111 (66, 176) | <0.001 |
| p-Cresol Sulfate | 16 (10, 24) | 13 (8, 21) | <0.001 |
| 1,7-Dimethyluric Acid  | 235 (147, 355) | 201 (111, 312) | <0.001 |
| 2-Furoylglycine | 356 (217, 580) | 296 (164, 507) | <0.001 |
| Hippuric Acid | 336 (220, 506) | 270 (167, 442) | <0.001 |
| m-Hydroxy Hippurate | 372 (229, 565) | 305 (173, 514) | <0.001 |
| Indoxyl Sulfate | 43 (26, 65) | 35 (21, 56) | <0.001 |
| Phenylacetylglutamine | 235 (154, 348) | 194 (119, 301) | <0.001 |
| Tiglylglycine | 293 (189, 435) | 239 (142, 370) | <0.001 |
| Summary score | 60.6 (55.9, 65.0) | 58.5 (53.3, 63.2) | <0.001 |

**Supplementary Table S3. Baseline secretion biomarker urine-to-plasma ratios of SPRINT participants with CKD stratified by treatment arm**

|  |  |  |  |
| --- | --- | --- | --- |
| **Secretion marker** | **Intensive arm****(N =1076)** | **Standard arm** **(N =1013)** | ***P*** |
| Adipic Acid | 39 (21, 67) | 41 (21, 70) | 0.40 |
| Cinnamoylglycine | 130 (78, 195) | 136 (80, 210) | 0.11 |
| p-Cresol Sulfate | 15 (10, 23) | 15 (9, 24) | 0.80 |
| 1,7-Dimethyluric Acid  | 224 (138, 334) | 229 (134, 346) | 0.75 |
| 2-Furoylglycine | 338 (198, 544) | 341 (194, 578) | 0.57 |
| Hippuric Acid | 318 (200, 474) | 325 (202, 500) | 0.52 |
| m-Hydroxy Hippurate | 350 (213, 542) | 353 (205, 554) | 0.81 |
| Indoxyl Sulfate | 41 (25, 61) | 40 (24, 64) | 0.97 |
| Phenylacetylglutamine | 223 (141, 335) | 226 (138, 338) | 0.70 |
| Tiglylglycine | 272 (177, 414) | 279 (175, 429) | 0.33 |
| Summary score | 59.9 (55.2, 64.1) | 60.3 (55.2, 64.7)  | 0.44 |

**Supplementary Table S4. Baseline characteristics of SPRINT participants with baseline CKD stratified by secretion score quartiles**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Characteristic** | **Quartile 1****(N=517)** | **Quartile 2****(N=530)** | **Quartile 3****(N=535)** | **Quartile 4****(N=507)** | **All****(N=2089)** |
| Secretion score |  |  |  |  |  |
|  Median [IQR] | 50 [46, 53] | 58 [56, 59] | 62 [61, 63] | 68 [66, 70] | 60 [55, 64] |
|  Range | 30.0 – 55.2 | 55.2 – 60.0 | 60.0 – 64.4 | 64.4 – 81.7 | 30.0 – 81.7 |
| Age, y | 73 (10) | 74 (9) | 74 (9) | 72 (8) | 73 (9) |
| Female | 238 (46) | 197 (37) | 201 (38) | 218 (43) | 854 (41) |
| Race |  |  |  |  |  |
|  Non-Hispanic White | 333 (64) | 356 (67) | 384 (72) | 328 (65) | 1401 (67) |
|  African American | 137 (27) | 133 (25) | 108 (20) | 131 (26) | 509 (24) |
|  Hispanic and Other | 47 (9) | 41 (8) | 43 (8) | 48 (10) | 179 (9) |
| BMI, kg/m2 | 29.3 (5.8) | 29.3 (6.0) | 29.9 (5.9) | 30.0 (5.7) | 29.6 (5.9) |
| Intensive BP arm | 266 (51) | 284 (54) | 281 (53) | 245 (48) | 1076 (52) |
| Prevalent CVD or HF | 146 (28) | 173 (33) | 137 (26) | 132 (26) | 588 (28) |
| Current smoker | 40 (8) | 55 (10) | 40 (8) | 45 (9) | 180 (9) |
| eGFR, mL/min/1.73m2 | 39 (12) | 44 (10) | 48 (9) | 51 (7) | 46 (11) |
| Urine ACR, mg/g | 31 [10, 144] | 15 [8, 56] | 12 [6, 29] | 10 [6, 27] | 15 [7, 48] |
| Systolic BP, mm Hg | 142 (17) | 139 (16) | 139 (16) | 138 (17) | 140 (16) |
| Diastolic BP, mm Hg | 74 (12) | 74 (12) | 74 (12) | 75 (13) | 74 (12) |
| No. of antihypertensive meds |  |  |  |  |  |
| Total cholesterol, mg/dL | 183 (41) | 182 (39) | 184 (41) | 185 (42) | 183 (41) |
| HDL cholesterol, mg/dL | 53 (15) | 52 (15) | 52 (14) | 52 (14) | 52 (14) |
| Triglycerides, mg/dL | 111 [79, 158] | 112 [80, 149] | 109 [81, 158] | 112 [85, 150] | 112 [82, 154] |
| Statin use | 77 (15) | 66 (13) | 76 (14) | 72 (14) | 291 (14) |

Data displayed are mean (SD), n (%), or median [interquartile range].

Abbreviations: ACR, albumin-to-creatinine ratio; BMI, body mass index; BP, blood pressure; CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate by creatinine and cystatin C; HDL, high-density lipoprotein cholesterol; HF, heart failure; IQR, interquartile range; SPRINT, Systolic Blood Pressure Intervention Trial.

**Supplementary Table S5. Correlation coefficients of the summary secretion score and individual markers of tubular secretion clearance**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Secretion score | U/P Adipic Acid | U/P Cinnamoylglycine  | U/P p-Cresol Sulfate | U/P 1,7-Dimethyluric Acid  | U/P 2-Furoylglycine |  U/P Hippuric Acid |  U/P m-Hydroxy Hippurate | U/P Indoxyl Sulfate | U/P Phenylacetylglutamine | U/P Tiglylglycine |
| Secretion score | 1.000 | .713\* | .878\* | .920\* | .918\* | .841\* | .862\* | .880\* | .932\* | .912\* | .946\* |
| U/P Adipic Acid |  | 1.000 | .576\* | .620\* | .592\* | .541\* | .515\* | .538\* | .615\* | .564\* | .625\* |
| U/P Cinnamoylglycine  |  |  | 1.000 | .793\* | .814\* | .702\* | .779\* | .754\* | .802\* | .801\* | .872\* |
| U/P p-Cresol Sulfate |  |  |  | 1.000 | .850\* | .725\* | .734\* | .779\* | .969\* | .848\* | .855\* |
| U/P 1,7-Dimethyluric Acid  |  |  |  |  | 1.000 | .770\* | .777\* | .824\* | .861\* | .834\* | .867\* |
| U/P 2-Furoylglycine |  |  |  |  |  | 1.000 | .732\* | .753\* | .740\* | .725\* | .782\* |
|  U/P Hippuric Acid |  |  |  |  |  |  | 1.000 | .804\* | .759\* | .872\* | .812\* |
|  U/P m-Hydroxy Hippurate |  |  |  |  |  |  |  | 1.000 | .806\* | .796\* | .846\* |
| U/P Indoxyl Sulfate |  |  |  |  |  |  |  |  | 1.000 | .859\* | .876\* |
| U/P Phenylacetylglutamine |  |  |  |  |  |  |  |  |  | 1.000 | .869\* |
| U/P Tiglylglycine |  |  |  |  |  |  |  |  |  |  | 1.000 |

\**P-value* <0.01

**Supplementary Table S6.** **Associations of the summary secretion score with risk of AEs in SPRINT participants with CKD stratified by intervention arm**

|  |  |  |
| --- | --- | --- |
|  | **HR (95% CI) per 1-SD lower secretion score** |  |
| **AEs of interest** | **Intensive BP arm** | **Standard BP arm** | **Pooled** | ***P* for interaction** |
| Composite adverse event | 1.20 (1.07, 1.34) | 1.12 (0.99, 1.27) | 1.16 (1.06, 1.27) | 0.40 |
| AE subtypes\* |  |  |  |  |
|  AKI | 1.21 (0.99, 1.49) | 1.20 (0.95, 1.50) | 1.21 (1.03, 1.41) | 0.92 |
|  Electrolyte abnormality | 1.15 (0.87, 1.51) | 1.51 (1.22, 1.86) | 1.31 (1.10, 1.56) | 0.12 |
|  Hypotension or syncope | 0.84 (0.65, 1.10) | 0.89 (0.71, 1.12) | 0.86 (0.72, 1.04) | 0.76 |
|  Bradycardia or injurious fall | 1.12 (0.96, 1.31) | 1.00 (0.82, 1.22) | 1.07 (0.94, 1.22) | 0.35 |
|  Ambulatory hyperkalemia | 1.74 (1.45, 2.10) | 1.48 (1.15, 1.91) | 1.63 (1.39, 1.91) | 0.28 |
|  Ambulatory hypokalemia | 1.71 (0.98, 2.96) | 0.90 (0.54, 1.50) | 1.33 (0.85, 2.07) | 0.096 |

\* Estimates are adjusted for demographics (age, sex, race), intervention arm, baseline prevalent CVD, EtOH use, smoking, frailty, BMI, SBP, DBP, heart rate; orthostatic hypotension at baseline visit; dizziness at baseline visit; # BP meds, total medication burden >=5, ACE use, ARB use, diuretic use, calcium channel blocker use, beta-blocker use, baseline eGFR, and urine ACR

\*AEs modeled with WLW approach to account for correlation between AE subtypes

**Supplementary Table S7. Epidemiologic studies of secretion biomarker associations with adverse outcomes in CKD**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Author. Title (journal year)** | **Cohort (N)** | **Secretion measure** | **Outcome** | **Results** |
| Suchy-Dicey AM, et al. Tubular Secretion in CKD (JASN 2017) | SKS (N=298) | 24-hour solute clearances of four markers:Hippurate (HA)Cinnamoylglycine (CMG)P-cresol sulfate (PCS) Indoxyl sulfate (IS) | CKD progression (incident dialysis)All-cause mortality | Lower clearance of HA, IS, CMG, and PCS was not significantly associated with CKD progression.Lower clearance of HA and PCS was significantly associated with mortality. |
| Chen Y, et al. Kidney Clearance of Secretory Solutes Is Associated with Progression of CKD: The CRIC Study (JASN 2020) | CRIC (N=3416) | 24-hour solute clearances of 11 markers:HAPyridoxic acidDimethyluric acidTrimethyluric acidIsovalerylglycineTiglyglycineKynurenic acidXanthosineCMGPCSISSummary secretion score averaged across the 11 secretory solutes  | CKD progression (≥50% eGFR decline, incident dialysis, or kidney transplantation)All-cause mortality | Lower clearance of six solutes and lower summary secretion score was significantly associated with CKD progressionLower clearance of four solutes and lower summary secretion score was significantly associated with mortality. |
| Chen Y, et al. Association of tubular solute clearances with the glomerular filtration rate and complications of chronic kidney disease: the Chronic Renal Insufficiency Cohort study (NDT 2020) | CRIC (N=1240) | 24-hour solute clearances of 11 markers:HAPyridoxic acidDimethyluric acidTrimethyluric acidIsovalerylglycineTiglyglycineKynurenic acidXanthosineCMGPCSISSummary secretion score averaged across the 11 secretory solutes | Measured GFRCKD complications (PTH, triglycerides, and serum uric acid, calcium, phosphate, hemoglobin, and bicarbonate) | Solute clearances were modestly correlated with measured GFRLower clearance of most solutes were significantly associated with higher PTH, triglycerides, and uric acid.  |
| Garimella PG, et al. Tubular Secretion of Creatinine and Risk of Kidney Failure: The Modification of Diet in Renal Disease (MDRD) Study (AJKD 2020) | MDRD (N=838) | Difference between measured creatinine clearance and measured GFR | CKD progression (initiation of kidney replacement therapy)All-cause mortalityCVD mortality | Lower tubular secretion of creatinine was significantly associated with CKD progression.Lower tubular secretion of creatinine was not significantly associated with mortality or CVD mortality. |
| Chen Y, et al. Association Between Kidney Clearance of Secretory Solutes and Cardiovascular Events: The Chronic Renal Insufficiency Cohort (CRIC) Study (AJKD 2021) | CRIC (N=3407) | 24-hour solute clearances of 11 markers:HAPyridoxic acidDimethyluric acidTrimethyluric acidIsovalerylglycineTiglyglycineKynurenic acidXanthosineCMGPCSISSummary secretion score averaged across the 11 secretory solutes | CVD events (heart failure, myocardial infarction, stroke) | Lower clearance of secretory solutes was not significantly associated with CVD events. |
| Garimella PG, et al. Kidney Tubulointerstitial Fibrosis and Tubular Secretion (AJKD 2021) | Boston Kidney Biopsy Cohort (N=418) | Spot urine-to-plasma ratios of nine markers:HAPyridoxic acidIsovalerylglycineTiglyglycineKynurenic acidXanthosineCMGPCSISSummary secretion score averaged across the nine secretory solutes | Histopathologic quantification of interstitial fibrosis and tubular atrophy (IFTA) | Greater IFTA severity was associated with lower secretion of seven solutes and lower summary secretion score. |
| Bhatraju PK, et al. Assessment of kidney proximal tubular secretion in critical illness (JCI insight, 2021) | Critical Illness Translational Research Cohort (N=170) and Healthy Kidney Study (N=70). | Spot urine-to-plasma ratios of seven markers:Kynurenic acidCinnamoylglycineIndoxyl sulfateIsovalerylglycinePyridoxic acidTiglyglycineXanthosineSummary secretion score averaged across the seven secretory solutes | Major adverse kidney events (doubling of serum creatinine, dialysis, and death) within 28 days | Higher summary secretion score was associated with lower risk of major adverse kidney events.  |

**Supplementary Figure S1. Cumulative incidence of the composite adverse event (AE) outcome stratified by quartiles of the summary secretion score**

