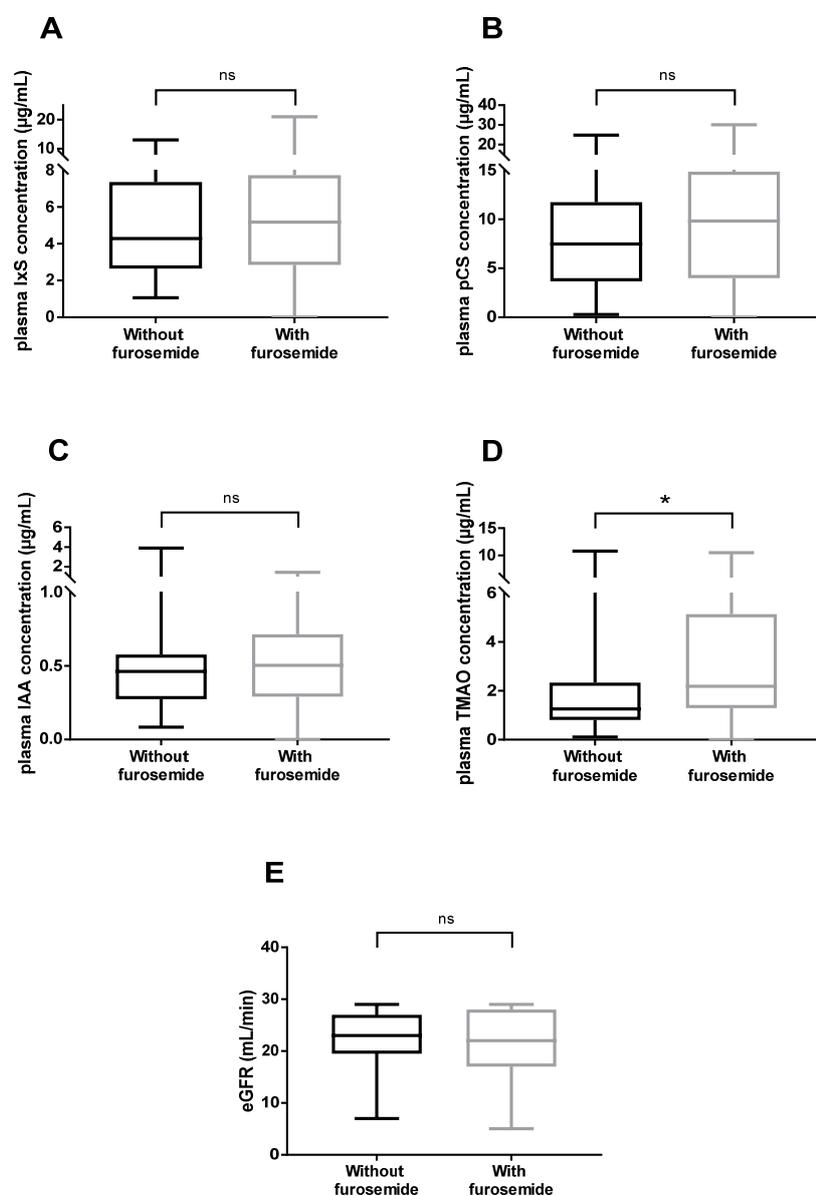


## Supplementary Materials: The Prescription of Drugs that Inhibit Organic Anion Transporters 1 or 3 is Associated with the Plasma Accumulation of Uremic Toxins in Kidney Transplant Recipients

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**Figure S1.** Plasma accumulation of IxS (A), pCS (B), IAA (C) and TMAO (D), and the eGFR (E) in CKD stage 4/5 patients treated ( $n=37$ ) or not ( $n=57$ ) with furosemide. \* $p<0.05$

**Table S1.** Characteristics of the study population, as a function of the median plasma pCS concentration.

|  | All patients<br>(n=403) | pCS<4.32 µg/mL<br>(n=202) | pCS > 4.32<br>µg/mL (n=201) | p-Value  |
|--|-------------------------|---------------------------|-----------------------------|----------|
| <b>Demographic characteristics</b>       |                         |                           |                             |          |
| Age (years)                              | 56 (48-66)              | 53 (44-63)                | 59 (51-69)                  | < 0.0001 |
| Males                                    | 250 (62.03)             | 120 (59.41)               | 130 (64.68)                 | 0.3234   |
| BMI (kg/m <sup>2</sup> )                 | 26.5 (23.4-29.7)        | 25.6 (22.9-29.8)          | 26.8 (24.1-29.5)            | 0.1834   |
| <b>Clinical characteristics</b>          |                         |                           |                             |          |
| Time since transplantation (months)      | 78.0 (40.0-158.5)       | 74.0 (36.0-149.8)         | 82.0 (43.0-167.0)           | 0.1171   |
| CKD stage                                |                         |                           |                             |          |
| 1  | 13 (3.23)               | 12 (5.94)                 | 1 (0.5)                     |          |
| 2  | 68 (16.87)              | 46 (22.77)                | 22 (10.95)                  |          |
| 3A + 3B                                  | 228 (56.58)             | 118 (58.42)               | 110 (54.73)                 | < 0.0001 |
| 4  | 84 (20.84)              | 25 (12.38)                | 59 (29.35)                  |          |
| 5  | 10 (2.48)               | 1 (0.5)                   | 9 (4.48)                    |          |
| Cause of CKD                             |                         |                           |                             |          |
| Diabetes                                 | 20 (4.96)               | 7 (3.47)                  | 13 (6.47)                   |          |
| Vascular disease                         | 26 (6.45)               | 13 (6.44)                 | 13 (6.47)                   |          |
| Chronic glomerulonephritis               | 38 (9.43)               | 20 (9.90)                 | 18 (8.96)                   |          |
| Polycystic kidney disease                | 62 (15.38)              | 29 (14.36)                | 33 (16.42)                  |          |
| Interstitial nephritis                   | 5 (1.24)                | 2 (0.99)                  | 3 (1.49)                    | 0.9323   |
| Autoimmune disorder                      | 72 (17.87)              | 36 (17.82)                | 36 (17.91)                  |          |
| Genetic disorder                         | 45 (11.17)              | 23 (11.39)                | 22 (10.95)                  |          |
| Other causes                             | 106 (26.30)             | 56 (27.72)                | 50 (24.8)                   |          |
| More than one cause                      | 29 (7.20)               | 16 (7.92)                 | 13 (6.47)                   |          |
| SBP (mmHg)                               | 142 (132-158)           | 141 (131-155)             | 142.5 (133-160)             | 0.2681   |
| DBP (mmHg)                               | 80 (72-87)              | 80 (72-87)                | 80 (73-87)                  | 0.7741   |
| PP (mmHg)                                | 64 (54-75)              | 62 (53-75)                | 66 (54-75)                  | 0.2668   |
| Hypertension                             | 392 (97.30)             | 194 (96.04)               | 197 (98.01)                 | 0.3804   |
| Liver disease                            | 1 (0.25)                | 0 (0)                     | 1 (0.50)                    | 0.4988   |
| <b>Laboratory data</b>                   |                         |                           |                             |          |
| eGFR (MDRD) (ml/min/1.73m <sup>2</sup> ) | 41 (30-57)              | 49 (34.3-61)              | 36 (27-47)                  | < 0.0001 |
| Creatinine (µmol/L)                      | 146 (116-187)           | 126 (99-161)              | 166 (127-214)               | < 0.0001 |
| Calcium (mmol/L)                         | 2.41 (2.32-2.49)        | 2.42 (2.33-2.49)          | 2.40 (2.30-2.48)            | 0.1245   |
| Phosphate (mmol/L)                       | 1.05 (0.91-1.20)        | 1.00 (0.87-1.14)          | 1.09 (0.97-1.24)            | < 0.0001 |
| Uric acid (µmol/L)                       | 471 (390-565)           | 453 (387-550)             | 485 (392-577)               | 0.1305   |
| CRP (mg/L)                               | 3.70 (0.60-9.00)        | 3.45 (0.96-9.65)          | 3.77 (0.55-8.90)            | 0.9376   |
| Protein (g/L)                            | 67 (64-70)              | 67 (65-70)                | 66 (63-70)                  | 0.1262   |
| Albumin (g/L)                            | 38.9 (36.7-41.1)        | 39.2 (37.5-41.4)          | 38.7 (36.4-40.9)            | 0.0311   |
| Glucose (mmol/L)                         | 5.4 (4.8-6.3)           | 5.4 (4.8-6.3)             | 5.4 (4.9-6.3)               | 0.9392   |
| <b>OAT1/OAT3 inhibitors</b>              |                         |                           |                             |          |
| Number of OAT1/OAT3 inhibitors           |                         |                           |                             |          |
| 0  | 92                      | 60                        | 32                          |          |
| 1  | 145                     | 68                        | 77                          |          |
| 2  | 129                     | 64                        | 65                          | 0.0011   |
| 3  | 34                      | 9                         | 25                          |          |
| 4  | 3                       | 1                         | 2                           |          |
| at least one OAT inhibitor               | 311                     | 142                       | 169                         | 0.0015   |

The data are quoted as the median (interquartile range) or the frequency (percentage). BMI, body mass index; CKD, chronic kidney disease; CRP, C-reactive protein; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; pCS, para-cresyl sulfate; PP, pulse pressure; SBP, systolic blood pressure.

**Table S2.** Characteristics of the study population, as a function of the median plasma IxS concentration.

|  | All patients<br>(n=403) | pCS<4.32 µg/mL<br>(n=202) | pCS > 4.32<br>µg/mL (n=201) | p-Value  |
|--|-------------------------|---------------------------|-----------------------------|----------|
| <b>Demographic characteristics</b>       |                         |                           |                             |          |
| Age (years)                              | 56 (48-66)              | 54 (44-65)                | 58 (50-68)                  | 0.0039   |
| Males                                    | 250 (62.03)             | 130 (64.36)               | 120 (59.70)                 | 0.3897   |
| BMI (kg/m <sup>2</sup> )                 | 26.5 (23.4-29.7)        | 25.6 (22.8-29.0)          | 27.3 (23.9-30.7)            | 0.0066   |
| <b>Clinical characteristics</b>          |                         |                           |                             |          |
| Time since transplantation (months)      | 78.0 (40.0-158.5)       | 69.5 (32.0-144.8)         | 87.0 (48.0-168.0)           | 0.0088   |
| CKD stage                                |                         |                           |                             |          |
| 1  | 13 (3.23)               | 13 (6.44)                 | 0 (0)                       |          |
| 2  | 68 (16.87)              | 60 (29.70)                | 8 (3.98)                    |          |
| 3A + 3B                                  | 228 (56.58)             | 116 (57.43)               | 112 (55.72)                 | < 0.0001 |
| 4  | 84 (20.84)              | 13 (6.44)                 | 71 (35.32)                  |          |
| 5  | 10 (2.48)               | 0 (0)                     | 10 (4.98)                   |          |
| Cause of CKD                             |                         |                           |                             |          |
| Diabetes                                 | 20 (4.96)               | 10 (4.95)                 | 10 (4.98)                   |          |
| Vascular disease                         | 26 (6.45)               | 10 (4.95)                 | 16 (7.96)                   |          |
| Chronic glomerulonephritis               | 38 (9.43)               | 17(8.42)                  | 21 (10.45)                  |          |
| Polycystic kidney disease                | 62 (15.38)              | 31 (15.35)                | 31 (15.42)                  |          |
| Interstitial nephritis                   | 5 (1.24)                | 2 (0.99)                  | 3(1.49)                     | 0.9405   |
| Autoimmune disorder                      | 72 (17.87)              | 39(19.31)                 | 33 (16.42)                  |          |
| Genetic disorder                         | 45 (11.17)              | 23 (11.39)                | 22 (10.95)                  |          |
| Other causes                             | 106 (26.30)             | 56 (27.72)                | 50 (24.88)                  |          |
| More than one cause                      | 29 (7.20)               | 14 (6.93)                 | 15 (7.46)                   |          |
| SBP (mmHg)                               | 142 (132-158)           | 140 (131-154)             | 144 (133-160)               | 0.0836   |
| DBP (mmHg)                               | 80 (72-87)              | 80 (72-87)                | 80 (72-87)                  | 0.4387   |
| PP (mmHg)                                | 64 (54-75)              | 62 (52-70)                | 66 (55-79.8)                | 0.0169   |
| Hypertension                             | 392 (97.30)             | 195 (96.53)               | 196 (97.51)                 | 0.7710   |
| Liver disease                            | 1 (0.25)                | 0 (0)                     | 1 (0.50)                    | 0.4988   |
| <b>Laboratory data</b>                   |                         |                           |                             |          |
| eGFR (MDRD) (ml/min/1.73m <sup>2</sup> ) | 41 (30-57)              | 55 (41-64)                | 33 (24-40)                  | < 0.0001 |
| Creatinine (µmol/L)                      | 146 (116-187)           | 121 (98-148)              | 177 (146-228)               | < 0.0001 |
| Calcium (mmol/L)                         | 2.41 (2.32-2.49)        | 2.43 (2.34-2.49)          | 2.39 (2.30-2.49)            | 0.1342   |
| Phosphate (mmol/L)                       | 1.05 (0.91-1.20)        | 1.00 (0.87-1.12)          | 1.12 (0.98-1.29)            | < 0.0001 |
| Uric acid (µmol/L)                       | 471 (390-565)           | 450 (370-531)             | 499 (406-597)               | 0.0008   |
| CRP (mg/L)                               | 3.70 (0.60-9.00)        | 2.34 (0.44-10.82)         | 4.39 (0.68-8.68)            | 0.2193   |
| Protein (g/L)                            | 67 (64-70)              | 67 (65-70)                | 66 (63-70)                  | 0.1958   |
| Albumin (g/L)                            | 38.9 (36.7-41.1)        | 39.3 (37.5-41.6)          | 38.6 (36.3-40.8)            | 0.0010   |
| Glucose (mmol/L)                         | 5.4 (4.8-6.3)           | 5.4 (4.8-6.1)             | 5.4 (4.9-6.3)               | 0.6105   |
| <b>OAT1/OAT3 inhibitors</b>              |                         |                           |                             |          |
| Number of OAT1/OAT3 inhibitors           |                         |                           |                             |          |
| 0  | 92                      | 54                        | 38                          |          |
| 1  | 145                     | 76                        | 69                          |          |
| 2  | 129                     | 62                        | 67                          |          |
| 3  | 34                      | 10                        | 24                          | 0.0146   |
| 4  | 3                       | 0                         | 3                           |          |
| at least one OAT inhibitor               | 311                     | 148                       | 163                         | 0.0796   |

The data are quoted as the median (interquartile range) or the frequency (percentage). BMI, body mass index; CKD, chronic kidney disease; CRP, C-reactive protein; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; IxS, indoxyl sulfate; MDRD, Modification of Diet in Renal Disease; PP, pulse pressure; SBP, systolic blood pressure.

**Table S3.** Characteristics of the study population, as a function of the median plasma IAA concentration.

|  | All patients<br>(n=403) | pCS<4.32 µg/mL<br>(n=202) | pCS > 4.32<br>µg/mL (n=201) | p-Value  |
|--|-------------------------|---------------------------|-----------------------------|----------|
| <b>Demographic characteristics</b>       |                         |                           |                             |          |
| Age (years)                              | 56 (48-66)              | 54 (46-64)                | 58 (49-68)                  | 0.0148   |
| Males                                    | 250 (62.03)             | 114 (56.44)               | 136 (67.66)                 | 0.0265   |
| BMI (kg/m <sup>2</sup> )                 | 26.5 (23.4-29.7)        | 26.2 (22.8-29.7)          | 26.5 (23.8-29.7)            | 0.2869   |
| <b>Clinical characteristics</b>          |                         |                           |                             |          |
| Time since transplantation (months)      | 78.0 (40.0-158.5)       | 75.0 (34.5-159.8)         | 79.0 (43.0-157.0)           | 0.6069   |
| CKD stage                                |                         |                           |                             |          |
| 1  | 13 (3.23)               | 10 (4.95)                 | 3 (1.49)                    |          |
| 2  | 68 (16.87)              | 40 (19.80)                | 28 (13.93)                  |          |
| 3A + 3B                                  | 228 (56.58)             | 119 (58.91)               | 109 (54.23)                 | 0.0035   |
| 4  | 84 (20.84)              | 31 (15.35)                | 53 (26.37)                  |          |
| 5  | 10 (2.48)               | 2 (0.99)                  | 8 (3.98)                    |          |
| Cause of CKD                             |                         |                           |                             |          |
| Diabetes                                 | 20 (4.96)               | 9 (4.46)                  | 11 (5.47)                   |          |
| Vascular disease                         | 26 (6.45)               | 11 (5.45)                 | 15 (7.46)                   |          |
| Chronic glomerulonephritis               | 38 (9.43)               | 21 (10.40)                | 17(8.46)                    |          |
| Polycystic kidney disease                | 62 (15.38)              | 27 (13.37)                | 35 (17.41)                  |          |
| Interstitial nephritis                   | 5 (1.24)                | 3 (1.49)                  | 2 (1.00)                    | 0.9306   |
| Autoimmune disorder                      | 72 (17.87)              | 38 (18.81)                | 34 (16.92)                  |          |
| Genetic disorder                         | 45 (11.17)              | 23 (11.39)                | 22 (10.95)                  |          |
| Other causes                             | 106 (26.30)             | 54 (26.73)                | 52 (25.87)                  |          |
| More than one cause                      | 29 (7.20)               | 16 (7.92)                 | 13 (6.47)                   |          |
| SBP (mmHg)                               | 142 (132-158)           | 143 (134-155)             | 141 (130-159)               | 0.7565   |
| DBP (mmHg)                               | 80 (72-87)              | 80 (74-88)                | 80.0 (71-87)                | 0.4087   |
| PP (mmHg)                                | 64 (54-75)              | 63 (55-74)                | 64 (52-76)                  | 0.9621   |
| Hypertension                             | 391 (97.30)             | 198 (98.02)               | 193 (96.02)                 | 0.2590   |
| Liver disease                            | 1 (0.25)                | 1 (0.50)                  | 0 (0)                       | 1.0000   |
| <b>Laboratory data</b>                   |                         |                           |                             |          |
| eGFR (MDRD) (ml/min/1.73m <sup>2</sup> ) | 41 (30-57)              | 46 (37-59)                | 37 (28-52)                  | < 0.0001 |
| Creatinine (µmol/L)                      | 146 (116-187)           | 134 (108-171)             | 159 (125-206)               | < 0.0001 |
| Calcium (mmol/L)                         | 2.41 (2.32-2.49)        | 2.42 (2.33-2.49)          | 2.40 (2.31-2.49)            | 0.1476   |
| Phosphate (mmol/L)                       | 1.05 (0.91-1.20)        | 1.03 (0.90-1.17)          | 1.07 (0.93-1.24)            | 0.0382   |
| Uric acid (µmol/L)                       | 471 (390-565)           | 456 (374-547)             | 485 (397-579)               | 0.0678   |
| CRP (mg/L)                               | 3.70 (0.60-9.00)        | 3.38 (0.55-7.90)          | 3.97 (0.63-10.99)           | 0.3693   |
| Protein (g/L)                            | 67 (64-70)              | 67 (64-70)                | 67 (64-70)                  | 0.7404   |
| Albumin (g/L)                            | 38.9 (36.7-41.1)        | 38.9 (36.6-41.0)          | 39.0 (36.8-41.2)            | 0.6791   |
| Glucose (mmol/L)                         | 5.4 (4.8-6.3)           | 5.3 (4.8-6.3)             | 5.5 (4.9-6.3)               | 0.4898   |
| <b>OAT1/OAT3 inhibitors</b>              |                         |                           |                             |          |
| Number of OAT1/OAT3 inhibitors           |                         |                           |                             |          |
| 0  | 92                      | 54                        | 38                          |          |
| 1  | 145                     | 71                        | 74                          |          |
| 2  | 129                     | 60                        | 69                          | 0.3587   |
| 3  | 34                      | 15                        | 19                          |          |
| 4  | 3                       | 2                         | 1                           |          |
| at least one OAT inhibitor               | 311                     | 148                       | 163                         | 0.0796   |

The data are quoted as the median (interquartile range) or the frequency (percentage). BMI, body mass index; CKD, chronic kidney disease; CRP, C-reactive protein; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; IxS, indoxyl sulfate; MDRD, Modification of Diet in Renal Disease; PP, pulse pressure; SBP, systolic blood pressure.

**Table S4.** Drugs with an IC<sub>50</sub>s for OAT1 (A) or OAT3 (B) above the therapeutic range, as prescribed to patients in the present study.

| <b>A</b>            |                          |  |
|---------------------|--------------------------|--|
| OAT1                |                          |  |
| Drug                | IC <sub>50</sub> (µg/mL) | Plasma therapeutic concentration range (µg/mL) |
| Bumetanide          | 2.7                      | 0.03-0.40 [40,41]                              |
| Candesartan         | 7.4                      | 0.08-0.18 [42]                                 |
| Fluvastatin         | 10.8                     | 0.05-0.40 [42]                                 |
| Hydrochlorothiazide | 20.03                    | 0.04-2.00 [42]                                 |
| Ketoconazole        | 169.5                    | 1-6 [42]                                       |
| Losartan            | 5.07                     | 0.20-0.65 [42,55]                              |
| Pantoprazole        | 24.2                     | 4.6 [42]                                       |
| Paracetamol         | 96.1                     | 5-25 [42]                                      |
| Pravastatin         | 173.2                    | 0.05-0.15 [43]                                 |
| Rifampicin          | 65.1                     | 0.1-10 [42]                                    |
| Simvastatin         | 30.8                     | 0.005-0.015 [42]                               |

| <b>B</b>            |                          |  |
|---------------------|--------------------------|--|
| OAT3                |                          |  |
| Drug                | IC <sub>50</sub> (µg/mL) | Plasma therapeutic concentration range (µg/mL) |
| Candesartan         | 1.3                      | 0.08-0.18 [42]                                 |
| Cimetidine          | 43.6                     | 0.25-3.00 [42]                                 |
| Hydrochlorothiazide | 280.4                    | 0.04-2.00 [42]                                 |
| Indapamide          | 4.02                     | 0.17-0.27 [44]                                 |
| Pravastatin         | 5.8                      | 0.05-0.15 [43]                                 |
| Simvastatin         | 13.5                     | 0.005-0.015 [42]                               |
| Sitagliptin         | 65.1                     | 0.05-0.38 [42]                                 |