

## Supplemental material

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**Supplemental Table 1.** Correlation of urine-to-plasma urea ratio with clinical variables of the ADPKD patients from the DIPAK cohort (n=583)

	R	p-value
Age (years)	-0.40	<0.001
Sex, female	0.06	0.16
Body Mass Index (kg/m <sup>2</sup> )	0.03	0.46
Systolic BP (mmHg)	-0.12	0.004
Diastolic BP (mmHg)	-0.13	0.002
Antihypertensive therapy (% yes)	-0.31	<0.001
Diuretics (% yes)	-0.23	<0.001
<i>PKD</i> mutation		
<i>PKD1</i> T	-0.01	0.83
<i>PKD1</i> NT	0.009	0.86
htTKV (mL/m)	-0.33	<0.001
Mayo htTKV class		
1B + 1C	0.05	0.51
1D + 1E	-0.07	0.36
eGFR (mL/min/1.73m <sup>2</sup> )	0.66	<0.001
24h urine volume (L)	-0.31	<0.001
Estimated protein intake (g/24h)	0.10	0.02
Estimated salt intake (g/24h)	0.05	0.27

Assessed with use of Pearson's correlation statistics. Data logarithmically transformed if appropriate. Reference groups are *PKD2* and others (non-*PKD1* mutations) combined, and Mayo htTKV class 2 and 1A combined. Abbreviations: BP, blood pressure; eGFR, estimated glomerular filtration rate; htTKV, height adjusted total kidney volume; T, truncating, NT, non-truncating. Protein intake was estimated in grams with the following formula: (urine urea excretion in mmol per 24 hours x 0.4667 x 0.06 +(0.031 x weight)) x 6.25. Salt intake was estimated with the following equation: sodium excretion in mol x (sum of molecular mass of sodium and chloride in g/mol).

**Supplemental Table 2.** Associations of baseline urine-to-plasma urea ratio with rate of kidney function decline during follow-up in ADPKD patients from the DIPAK cohort (n=583)

	Model 1 n=583		Model 2 n=583		Model 3 n=573		Model 4 n=538	
	$\beta$	p-value	B	p-value	$\beta$	p-value	$\beta$	p-value
Urine-to-plasma urea ratio (per 1 unit)	0.97	<0.001	0.71	0.005	0.64	0.01	0.57	0.02
Age (per 10 year)	0.34	0.001	0.44	<0.001	0.28	0.03	-0.04	0.76
Sex (female vs. male)	0.59	0.003	0.57	0.006	0.67	0.001	0.43	0.04
eGFR (per 10 mL/min/1.73m <sup>2</sup> )			0.12	0.07	0.11	0.10	0.03	0.66
<i>PKD</i> mutation								
<i>PKD1</i> T					-1.05	<0.001	-0.90	0.001
<i>PKD1</i> NT					-0.81	0.002	-0.79	0.004
Mayo htTKV class								
1B+C							-0.59	0.13
1D+E							-1.77	<0.001

Associations tested with mixed model analysis. Urine-to-plasma urea ratio was ln transformed to attain normal distribution. Reference groups are PKD2 and other (non-PKD1 mutations) combined, and Mayo htTKV class 2 and 1A combined. Abbreviations; eGFR, estimated glomerular filtration rate; htTKV, height adjusted total kidney volume; NT, non-truncating; T, truncating.

**Supplemental Table 3.** Sensitivity analysis. Associations of baseline urine-to-plasma urea ratio corrected for plasma creatinine, with subsequent rate of kidney function decline in ADPKD patients from the DIPAK cohort (n=583)

	<b>Model 1</b> n=583		<b>Model 2</b> n=583		<b>Model 3</b> n=573		<b>Model 4</b> n=538	
	$\beta$	p-value	$\beta$	p-value	$\beta$	p-value	$\beta$	p-value
Urine-to-plasma urea ratio (per 10 mg/dL)	0.33	<0.001	0.28	<0.001	0.26	0.001	0.23	0.003
Age (per 10 year)	0.24	0.02	0.50	<0.001	0.33	0.01	0.01	0.94
Sex (female vs. male)	0.90	<0.001	0.77	0.001	0.87	<0.001	0.61	0.007
eGFR (per 10 mL/min/1.73m <sup>2</sup> )			0.21	<0.001	0.19	0.001	0.10	0.10
<i>PKD</i> mutation								
<i>PKD1</i> T					-1.02	<0.001	-0.87	0.001
<i>PKD1</i> NT					-0.78	0.003	-0.76	0.005
Mayo htTKV class								
1B+C							-0.59	0.12
1D+E							-1.74	<0.001

Associations tested with mixed model analysis. In these analyses, the urine-to-plasma urea ratio was not ln transformed. Reference groups are *PKD2* and others (non-*PKD1* mutations) combined, and Mayo htTKV class 2 and 1A combined. Abbreviations; eGFR, estimated glomerular filtration rate; htTKV, height adjusted total kidney volume; NT, non-truncating; T, truncating.

**Supplemental Table 4.** Baseline characteristics of the DIPAK cohort used for Cox regression analyses, both overall as well as divided into tertiles of the urine-to-plasma urea ratio (n=706)

	<b>overall</b>	<b>T1</b> <b>&lt; 19.7</b>	<b>T2</b> <b>19.7 – 31.6</b>	<b>T3</b> <b>&gt;31.6</b>	p-value
Number	706	236	235	235	
Age (years)	47 ± 11	52 ± 9 <sup>B</sup>	48 ± 8.9 <sup>B</sup>	41 ± 12	<0.001
Sex, male (%)	41	43	44	35	0.12
Body Mass Index (kg/m <sup>2</sup> )	26 ± 4.5	26 ± 4.0	27 ± 4.4	26 ± 5.0	0.39
Systolic BP (mmHg)	131 ± 14	132 ± 14 <sup>A</sup>	132 ± 14 <sup>A</sup>	129 ± 12	0.009
Diastolic BP(mmHg)	81 ± 9.4	81 ± 9.6 <sup>A</sup>	82 ± 9.2 <sup>A</sup>	79 ± 9.2	0.02
Antihypertensive therapy (% yes)	76	87 <sup>B</sup>	80 <sup>B</sup>	60	<0.001
Diuretics (% yes)	26	34 <sup>B</sup>	31 <sup>B</sup>	13	<0.001
<i>PKD</i> mutation (%)					
<i>PKD1</i> T	43	44	45	41	0.86
<i>PKD1</i> NT	25	25	25	25	
<i>PKD2</i>	22	21	24	21	
Other	7	8	6	9	
htTKV (mL/m)	913 [553 – 1357]	1105 <sup>B</sup> [709 – 1741]	1006 <sup>B</sup> [649 – 1478]	672 [427 – 956]	<0.001
Mayo htTKV class (%)					
1A	5	3	5	6	0.02
1B	19	14	18	24	
1C	33	32	33	32	
1D	22	23	26	17	
1E	12	13	12	11	
2	3	6	1	3	
Plasma creatinine (mg/dL)	1.23 [0.96 – 1.61]	1.61 <sup>B</sup> [1.23 – 2.01]	1.31 <sup>B</sup> [1.10 – 1.58]	0.94 [0.80 – 1.10]	<0.001
eGFR (mL/min/1.73m <sup>2</sup> )	63 ± 25	47 ± 19 <sup>B</sup>	58 ± 17 <sup>B</sup>	84 ± 22	<0.001
Plasma urea (mg/dL)	20.7 [16.0 – 26.9]	27.2 <sup>B</sup> [20.7 – 34.2]	22.4 <sup>B</sup> [17.6 – 26.6]	16.0 [13.4 – 19.9]	<0.001

**Supplemental Table 4.** Baseline characteristics – continued.

	overall	T1	T2	T3	p-value
		< 19.7	19.7 – 31.6	>31.6	
Copeptin (pmol/L)	7.8 [4.5 – 13.7]	9.1 <sup>B</sup> [4.9 – 16.5]	9.2 <sup>B</sup> [4.9 – 16.0]	5.9 [3.8 – 10.0]	<0.001
24h urine volume (L)	2.3 ± 0.79	2.5 ± 0.81 <sup>B</sup>	2.3 ± 0.73 <sup>B</sup>	2.0 ± 0.72	<0.001
Urine urea (mg/dL)	552 [409 – 697]	385 <sup>B</sup> [283 – 506]	540 <sup>B</sup> [448 – 641]	739 [619 – 910]	<0.001
Estimated protein intake (g/24h)	84 ± 25	81 ± 21	85 ± 26	86 ± 28	0.08
Sodium excretion (mmol/24h)	145 [107 – 190]	140 [104 – 182]	142 [113 – 198]	153 [106 – 198]	0.29
Urine-to-plasma urea ratio (mmol/L)	24 [17 – 36]	14.8 <sup>B</sup> [11.6 – 17.2]	24.2 <sup>B</sup> [22.0 – 27.8]	43.1 [35.8 – 55.1]	<0.001
Number of events	145	80 <sup>B</sup>	56 <sup>B</sup>	9	<0.001

Data presented as proportion of total population (%), mean ± SD or median [IQR] as appropriate. Differences between tertiles were assessed with Pearson's Chi-square for proportional data, one-way ANOVA for parametric data and Friedman's ANOVA for non-parametric data. Post-hoc comparisons with Bonferroni correction, where <sup>A</sup> signifies p<0.05, <sup>B</sup> p<0.001 compared to the third tertile. Abbreviations: BP, blood pressure; eGFR, estimated glomerular filtration rate; htTKV, height adjusted total kidney volume; NT, non-truncating; T, truncating. Urine urea was measured in an early morning fasting void. Protein intake was estimated in grams with the following formula: (urine urea excretion in 24 hours x 0.4667 x 0.06 + (0.031 x weight)) x 6.25.

**Supplemental Table 5.** Predictive value of the urine-to-plasma urea ratio as continuous variable and divided into tertiles for a combined kidney endpoint (n=706, N=145).

	As continuous variable		Tertile 3	Tertile 2	Tertile 1		
	Exp(B)	p-value	< 19.7	19.7 – 31.6	Exp(B)	p-value	
Model 1	0.43 (0.35 – 0.52)	<0.001	1.0	6.76 (3.35 – 13.7)	<0.001	13.1 (6.55 – 26.1)	<0.001
Model 2	0.40 (0.32 – 0.49)	<0.001	1.0	7.15 (3.48 – 14.7)	<0.001	14.4 (7.02 – 29.5)	<0.001
Model 3	0.69 (0.54 – 0.87)	0.002	1.0	2.29 (1.08 – 4.82)	0.03	2.93 (1.33 – 6.45)	0.008
Model 4	0.69 (0.54 – 0.88)	0.003	1.0	2.47 (1.13 – 5.40)	0.02	3.12 (1.37 – 7.14)	0.007
Model 5	0.70 (0.54 – 0.90)	0.006	1.0	2.56 (1.11 – 5.88)	0.03	3.29 (1.37 – 7.93)	0.008

Cox regression analysis. Reported are expected beta (Exp(B)) and (95% confidence interval for Exp(B)). The combined kidney endpoint defined as either start of kidney replacement therapy (dialysis or transplantation), reaching an eGFR below 15 mL/min/1.73m<sup>2</sup> or a decrease of eGFR of more than 40%. The exp(B) of the continuous urine-to-plasma urea ratio is presented per 10 units. Harrell's C statistic for model 5 was 0.8184 including, and 0.8108 excluding the continuous urine-to-plasma urea ratio (p = 0.03).

Model 1, crude

Model 2, adjustment for age and sex

Model 3, adjustment for age, sex and eGFR at baseline

Model 4, adjustment for age, sex, eGFR and *PKD* mutation (dummy 1: *PKD1* truncating, dummy 2 *PKD1* non-truncating, ref: *PKD2* and others),

Model 5, adjustment for age, sex, eGFR, *PKD* mutation and Mayo htTKV class (dummy 1: class 1B and 1C, dummy 2: class 1D and 1E, ref: class 1A and 2).

**Supplemental Figure 1.** Kidney function slopes of DIPAK cohort participants (n = 538) divided into risk groups according to Mayo htTKV class score (panel A), PKD mutation score (panel B) and urine-to-plasma urea ratio score (panel C). Dotted line indicates division between rapidly progressive disease and moderately progressive disease (respectively below or above -3.0 mL/min/1.73m<sup>2</sup> per year). Harrell's C-statistic of the total risk score was 0.72, which exceeded scores of A to C (A: 0.65, B: 0.63, C: 0.61, all p<0.05). A to C do not statistically differ from each other.

