Supplemental data

Methods

Sample collection and creatinine determination

All blood and urine samples were collected in the morning during the same week patients were assessed. Creatinine determination was performed using the colorimetric Jaffe method with a Roche-Hitachi analyzer. We used the abbreviated Modification of Diet in Renal Disease (MDRD) equation to estimate glomerular filtration rate(1) throughout the study until 2002, when the laboratory switched to an isotope dilution mass spectroscopy (IDMS)-calibrated reference standard, at which point we used the IDMS-traceable MDRD study equation(2). We repeated all analyses using the six-variable MDRD formula after correcting serum creatinine values by 0.94 (175/186) for samples collected after 2002 and obtained the same results.

Quality assessment of the creatinine assay and reference values

Serum variability (human serum samples and laboratory products):

- Within-sample coefficient of variation (CV):
  - CV = 0.7% (Human serum);
  - CV = 0.6% (Precinorm);
  - CV = 0.6% (Precipath);
- Between-sample coefficient of variation:
  - CV = 2.3% (Human serum);
  - CV = 1.5% (Precinorm);
  - CV = 1.7% (Precipath);

Urine variability (human urine samples):

- Within-sample coefficient of variation (CV):
  - CV = 2.1% (Human urine I);
  - CV = 1.3% (Human urine II);
  - CV = 1.1% (Human urine III);
- Between-sample coefficient of variation:
  - CV = 2.2% (Human urine I);
  - CV = 1.7% (Human urine II);
  - CV = 1.2% (Human urine III);

Reference values for serum creatinine:

- Men: 62-106 micromol/L (0.7-1.2 mg/dL);
- Women: 44-80 micromol/L (0.5-0.9 mg/dL).

Reference values for urine creatinine:

- Men: 9-21 mmol/day (1040-2350 mg/day);
- Women: 7-14 mmol/day (740-1570 mg/day).

Accuracy of urine collection

Urine collection was considered inaccurate, discarded and repeated if measured creatinine excretion rate was outside the 60-140% range of the value estimated according to Dwyer and Kenler(3), who state:

> "[…] *A simple method to check for completeness of urine collection is to compare measured and calculated creatinine excretion rates. If the value is outside the 60 to 140% of calculated value, the sample should be discarded*."

Formulas for calculating creatinine excretion are:
Males: ratio %=100 (24-hr creatinine in mg)/24(wt in kg)
Females: ratio %=100 (24-hr creatinine in mg)/21(wt in kg)

Protein intake calculation

Dietary protein intake was estimated using daily urinary excretion of urea nitrogen(4):
[0.031 x body weight (kg) + urea (g/L)/2.13 x urine volume (L)] x 6.25

Urine protein determination

Determination of urine protein was performed using a colorimetric method based on pyrogallol red-molybdenum complex with a Cobas Integra Total Protein Urine/CSF (TPU-C) analyzer.

Reference value for 24-hour urine in adults: 28 to 141 mg/dl.

Reproducibility (data based on three human urine controls):

Within sample CV = 2.5% (urine I); 0.99% (urine II); 0.65% (urine III);
Between samples CV = 2.9% (urine I); 1.6% (urine II); 1.6% (urine III).

Results: Sensitivity analyses

Linear model

eTable 1: Predictors of baseline urine creatinine and rate of change of urine creatinine (UCr) over time in years (linear mixed model)

Sensitivity analysis: limited to observations between the 5th and 95th percentile of urine volume. Results of the main analysis are reported in Table 2 of the manuscript.

	Average effect on UCr	*95% Confidence Intervals*
Variables associated with baseline UCr (mg/day)		
Intercept* (CKD stage 3a)	1030	990 to 1070
CKD stage 3b vs. CKD stage 3a	-19	-59 to 21
CKD stage 4 vs. CKD stage 3a	-39	-79 to 6
CKD stage 5 vs. CKD stage 3a	-110	-164 to -56
Male sex (vs. female)	276	249 to 304
Diabetes (present vs. absent)	-37	-73 to -1
Age (10 years)	-59	-68 to -50
Protein intake (10 g/24 hours)	82	78 to 85
BMI (10 kg/m^2)	53	30 to 76
Variables associated with the rate of change of UCr (mg/day per year)		
Time (yearly change in CKD stage 3a to 4)	-17	-20 to -14
Time (yearly change in CKD stage 5)	3	-9 to 16

*The model intercept estimates the mean urine creatinine (UCr) excretion at baseline for a 57-year-old non-diabetic female with chronic kidney disease (CKD) stage 3a (reference category), a body mass index (BMI) of 26.5 kg/m2 and a protein intake of 65.6 g/day (mean values of continues covariates included in the models). Further details are in the footnote of Table 2.

Survival analysis

Main result

eTable 2. Predictors of dialysis initiation and death (dual-event survival model of Lunn-McNeil)

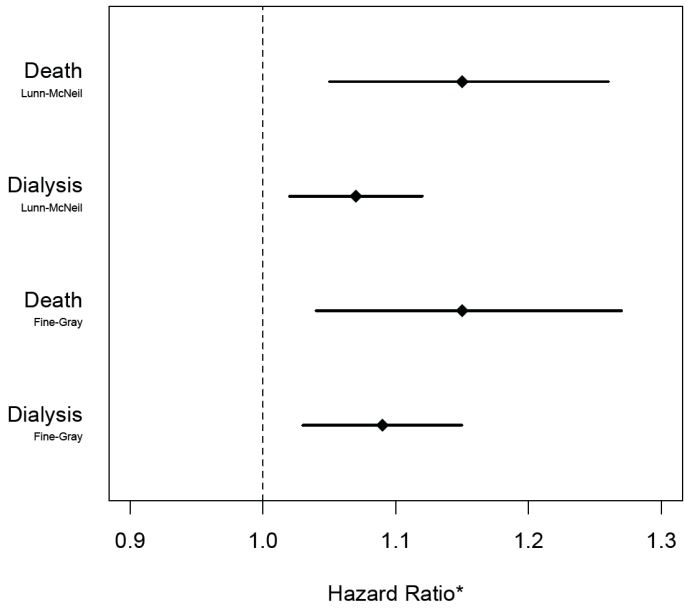
	HR (95% CI)
Predictors of dialysis initiation	
UCr (per 20 mg/day decline)*	1.02 (1.01, 1.03)
eGFR (per 2 ml/min/1.73 m^2 decline)*	1.13 (1.10, 1.16)
Proteinuria (per 1 g/24 h increase)	1.44 (1.32, 1.57)
Albumin (per 1 g/dl increase)	0.89 (0.62, 1.27)
Presence of diabetes	0.75 (0.51, 1.10)
Predictors of death	
UCr (per 20 mg/day decline)*	1.03 (1.01, 1.05)
eGFR (per 2 ml/min/1.73 m^2 decline)*	1.05 (1.01, 1.09)
Protein intake (10 g/day increase)	1.05 (0.92, 1.21)
Albumin (per 1 g/dl increase)	0.43 (0.27, 0.69)
Age (per year increase)	1.07 (1.05, 1.09)
Presence of diabetes	1.45 (0.95, 2.18)

Legend: UCr = urine creatinine; eGFR: estimated glomerular filtration rate; * the units chosen for UCr and eGFR approximate the average annual decline of UCr and eGFR in the present study cohort

Sensitivity analyses

In order to assess the appropriateness of standard survival analysis (i.e., censoring for death while studying the risk for dialysis and vice-versa), we conducted a sensitivity analysis using two competing risk approaches: the dual-event model of Lunn-McNeil for cause-specific hazards(5) which estimates both risks in the same model; and the sub-hazards model of Fine and Gray(6) with either dialysis as the outcome (with death as a competing risk) or death as the outcome (with dialysis start as a competing risk). The Lunn-McNeil model assumes independence of the competing risks; the Fine and Gray model relaxes this assumption and addresses the issue of potential informative censoring. Similarity of the sensitivity analysis results with those obtained by standard survival analysis is not consistent with informative censoring, supporting the validity of the Cox regression model reported in the main text.

eFigure 1: Urine creatinine decline (per 100 mg/day) and risk of dialysis and death



*Hazard ratios (Lunn-McNeil) and sub-hazard ratios (Fine and Gray) for dialysis and death associated with 100 mg/day decline in urinary creatinine (UCr) excretion.

eTable 3: The dual-event model of Lunn-McNeil and the Fine and Gray models:

	Lunn-McNeil model	Fine and Gray models
	Hazard Ratio (95% CI)	Sub-Hazard Ratio (95% CI)
Dialysis	1.07 (1.02, 1.12)	1.09 (1.03, 1.15)
Death	1.15 (1.05, 1.26)	1.15 (1.04, 1.27)

Both models are adjusted for levels of current (linear) eGFR, current proteinuria, current daily protein intake, current albumin, age and for diabetes. The dual-event model of Lunn-McNeil is stratified by event type: time to dialysis is censored for death; and time to death is censored for dialysis. In the renal survival model of Fine and Gray death is

treated as a competing risk; in the patient survival model of Fine and Gray dialysis is the competing risk.

Results of these models were the same using the following functions of eGFR and proteinuria: natural log, fractional polynomials and cubic splines. Also, results were the same adjusting for individual intercepts and slope predictions obtained respectively from the linear mixed model of proteinuria and from the linear mixed model of eGFR.

eTable 4: Reference models with additional adjustment for the *within-subject* percent change in UCr

	Lunn-McNeil	Fine and Gray
	Hazard Ratio (95% CI)	Sub-Hazard Ratio (95% CI)
Dialysis	1.08 (1.03, 1.13)	1.09 (1.04, 1.16)
Death	1.14 (1.03, 1.25)	1.14 (1.03, 1.27)

eTable 5: Survival results limited to observations between the 5^{th} and 95^{th} percentile of urine volume

	Lunn-McNeil	Fine and Gray
	Hazard Ratio (95% CI)	Sub-Hazard Ratio (95% CI)
Dialysis	1.08 (1.03, 1.14)	1.10 (1.04, 1.17)
Death	1.15 (1.03, 1.27)	1.13 (1.01, 1.26)

eTable 6. Survival results using baseline UCr as exposure (without updated UCr values)

	Lunn-McNeil	Fine and Gray
	Hazard Ratio (95% CI)	Sub-Hazard Ratio (95% CI)
Dialysis	1.05 (1.01, 1.09)	1.04 (1.01, 1.09)
Death	1.08 (1.01, 1.15)	1.08 (1.01, 1.16)

eTable 7. Survival results limited to study participants who survived at least 1 year (n=488), using change in UCr (individual slope of the linear mixed model) from baseline to year 1 as the exposure

	Lunn-McNeil	Fine and Gray
	Hazard Ratio (95% CI)	Sub-Hazard Ratio (95% CI)
Dialysis	1.12 (1.06, 1.19)	1.13 (1.07, 1.20)
Death	1.15 (1.04, 1.26)	1.14 (1.03, 1.27)

References

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3) Dwyer J and Kenler SR. Assessment of nutritional status in renal disease. In: Mitch WE and Klahr S. eds. *Nutrition and the Kidney*, 2nd edition, Little, Brown and Company 61–95, 1993

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6) Fine J, Gray RJ.: A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc 94: 496–509, 1999