Predicting timing of clinical outcomes in patients with chronic kidney disease and severely decreased glomerular filtration rate

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Patients with chronic kidney disease and severely decreased glomerular filtration rate (GFR) are at high risk for kidney failure, cardiovascular disease (CVD) and death. Accurate estimates of risk and timing of these clinical outcomes could guide patient counseling and therapy. Therefore, we developed models using data of 264,296 individuals in 30 countries participating in the international Chronic Kidney Disease Prognosis Consortium with estimated GFR (eGFR)s under 30 ml/min/1.73m^2. Median participant eGFR and urine albumin-to-creatinine ratio were 24 ml/min/1.73m^2 and 168 mg/g, respectively. Using competing-risk regression, random-effect meta-analysis, and Markov processes with Monte Carlo simulations, we developed two- and four-year models of the probability and timing of kidney failure requiring kidney replacement therapy (KRT), a non-fatal CVD event, and death according to age, sex, race, eGFR, albumin-to-creatinine ratio, systolic blood pressure, smoking status, diabetes mellitus, and history of CVD. Hypothetically applied to a 60-year-old white male with a history of CVD, a systolic blood pressure of 140 mmHg, an eGFR of 25 ml/min/1.73m^2 and a urine albumin-to-creatinine ratio of 1000 mg/g, the four-year model predicted a 17% chance of survival after KRT, a 17% chance of survival after a CVD event, a 4% chance of survival after both, and a 28% chance of death (9% as a first event, and 19% after another CVD event or KRT). Risk predictions for KRT showed good overall agreement with the published kidney failure risk equation, and both models were well calibrated with observed risk. Thus, commonly-measured clinical characteristics can predict the timing and occurrence of clinical outcomes in patients with severely decreased GFR.

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KEYWORDS: albuminuria; cardiovascular disease; chronic kidney disease

Chronic kidney disease (CKD) is an increasingly common problem globally.[1] In the developing world, disease burden is shifting from communicable to noncommunicable causes, and the prevalence of CKD has grown with the rise of hypertension, obesity, and diabetes.[2] In the developed world, the prevalence of CKD has increased with improvements in life expectancy.[3] The implications of

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CKD include morbidity, mortality, and reduction in quality of life at the individual level and high costs at the societal level.[4] Patients with severely decreased glomerular filtration rate (GFR) in particular are at high risk for adverse outcomes, including kidney failure, cardiovascular disease (CVD) events, and death.[5,6] Accurate prediction of whether and when clinical outcomes will occur in patients with severely decreased estimated GFR (eGFR <30 ml/min per 1.73 m^2, subsequently designated stage G4+) will help target efforts to treat and prevent worsening of disease.

There are a few existing tools to predict the onset of kidney failure treated with kidney replacement therapy (KRT; also frequently referred to as end-stage kidney disease), one of the most costly outcomes of CKD.[4] Tangri *et al.*[7] developed an absolute risk prediction tool for patients with stages G3 to G5 CKD (eGFR <60 ml/min per 1.73 m^2) in two Canadian cohorts, and this kidney failure risk equation (KFRE) was subsequently validated in 31 global cohorts.[8] Other prediction tools exist, but they have not undergone robust validation.[9–11] None of the tools was developed specifically for a population with stage G4+ CKD, nor do they predict other potentially more common events, such as pre-KRT death and nonfatal CVD events.

Using 29 cohorts of patients with stage G4+ CKD participating in the international CKD Prognosis Consortium, we simultaneously assessed the risks of KRT, nonfatal CVD events, and death, applying competing risk, meta-analysis with random effects models, and Markov process methodology. The goal was to develop a 2- and 4-year calculator to predict both the probability and the order of clinical events according to nine demographic and clinical characteristics.

RESULTS

Baseline characteristics

In total, there were 264,296 participants with eGFR <30 ml/min per 1.73 m^2 from 29 cohorts in 30 countries for use in model development (Table 1; Supplementary Table S1). Twenty cohorts had data for nonfatal CVD events, KRT, and death; and 9 had data for KRT and death only. Average age ranged from 47 years old (Nanjing CKD, China) to 82 years old (Parcours de Soins des Personnes Agées [PSPA], France). The distribution of eGFR and albuminuria varied by cohort but was often skewed toward the higher end of eGFR <30 ml/min per 1.73 m^2 and the lower end of urine albumin-to-creatinine ratio (ACR) (Supplementary Figures S1 to S2). Cause of CKD included diabetes, hypertension, glomerulonephritis, polycystic kidney disease, and interstitial nephritis but was unknown in most of the cohorts (Supplementary Table S2).

Rates, risk factors, and adjusted absolute risk of adverse outcomes

Overall, there were 123,985 deaths, 31,541 events of kidney failure treated with KRT, and 70,394 CVD events identified over a mean follow-up of 3.5 years. Events were categorized not only by their occurrence but also by their timing relative to KRT and CVD events and modeled as a function of age, sex, race, history of CVD, current smoking status, systolic blood pressure, diabetes mellitus, eGFR, and urine ACR (Figure 1). Strong risk factors for developing KRT as a first event included younger age, black race, higher systolic blood pressure, lower eGFR, and higher urine ACR (Supplementary Table S3). In contrast, strong risk factors for developing a CVD event prior to KRT included older age, previous history of CVD, and diabetes. Older age and smoking were the strongest risk factors for death prior to KRT or CVD. There was some quantitative heterogeneity across cohorts, but risk associations were qualitatively consistent (Supplementary Figures S3 and S4). The adjusted cumulative incidence of each event over time varied across cohorts, particularly by cohort type (Figure 2). The adjusted absolute risk of KRT as a first event was generally highest among the CKD research cohorts, whereas the risk of a CVD event or death prior to KRT was highest among the administrative cohorts. Second and third events were quantified in a similar manner (Supplementary Table S4 and S6 and Supplementary Figures S5 and S7).

Risk prediction model: 2- and 4-year outcomes

Risk factors and adjusted absolute risk were combined using a Markov process and simulations to create a prediction model for the probability and timing of clinical events and were approximated using a multinomial model (median R^2 = 0.99; Supplementary Table S7; http://ckdpcrisk.org/lowgfrevents/). In hypothetical scenarios, the probability of adverse events increased with longer follow-up and higher albuminuria. For example, a 60-year-old white man with a history of CVD, systolic blood pressure of 140 mm Hg, eGFR of 25 ml/min per 1.73 m^2, and urine ACR of 30 mg/g but no current smoking or diabetes mellitus was predicted to have a 74% chance of remaining event-free at 2 years, along with a 9% chance of death and a 5% chance of KRT (Figure 3a). In contrast, a similar scenario but for urine ACR of 1,000 mg/g and assessment at 4 years resulted in a prediction of event-free survival of 34%, with a 28% chance of death, a 17% chance of survival with KRT, a 17% chance of survival with CVD, and a 4% chance of both (Figure 3b). Other scenarios that dramatically affected the probability of adverse events included lower eGFR (higher risk of KRT), the presence of diabetes mellitus (higher risk of CVD events) and older age (higher risk of death) (Supplementary Figures S8 to S13).

Comparison with the KFRE and observed risk of kidney failure treated with KRT

We compared absolute risk projections from the developed risk prediction model with the previously developed 2-year and 4-variable KFRE for a set of scenarios holding constant the overlapping risk characteristics (age, sex, eGFR, and albuminuria) but varying others that were included only in our model (race, systolic blood pressure, diabetes mellitus, smoking status, and history of CVD), demonstrating good

Table 1 | Outcomes and baseline characteristics of included cohorts

Study	*N*	Death	Kidney failure treated with KRT	CVD event after baseline	Mean follow-up, yr	Age, yr	Systolic blood pressure, mm Hg	eGFR, ml/min per 1.73 m^2	Urine ACR, mg/g	Male sex	Black race	History of CVD	Diabetes mellitus
AASK (USA)[c]	622	135	286	38	4 (3)	56 (12)	135 (21)	25 (4)	130 (34, 488)	60%	100%	53%	1%
BC CKD (Canada)	9672	4717	3036	NA	5 (3)	71 (13)	137 (23)	24 (5)	225 (42, 1233)	55%	0.41%	16%	50%
CanPREDDICT (Canada)[b]	1739	452	435	334	3 (2)	69 (13)	134 (20)	23 (5)	188 (37, 929)	62%	1.6%	38%	52%
CCF (USA)[b]	9256	3000	1115	NA	2 (1)	73 (13)	130 (22)	24 (5)	51 (13, 346)	46%	17%	24%	30%
CRIB (UK)[c]	315	133	185	NA	6 (3)	62 (14)	152 (23)	18 (7)	589 (118, 1345)	61%	5.1%	45%	17%
CRIC (USA)[c]	1764	473	834	475	5 (3)	60 (11)	131 (24)	25 (4)	267 (48, 1066)	54%	45%	45%	60%
CRISIS (UK)[b]	1717	710	461	NA	3 (3)	66 (14)	140 (22)	20 (6)	150 (55, 466)	62%	0.64%	48%	36%
GCKD (Germany)[c]	504	34	33	34	2 (0)	64 (11)	140 (22)	26 (4)	130 (23, 877)	61%	0%	43%	44%
Geisinger (USA)[a]	19,293	10,039	1802	6292	4 (4)	73 (14)	127 (22)	24 (5)	48 (15, 232)	41%	0.99%	56%	43%
GLOMMS2 (UK)[b]	6384	3283	265	NA	3 (2)	79 (11)	NA	25 (5)	44 (10, 189)	38%	<5%[e]	26%	12%
Gonryo (Japan)[b]	729	57	354	48	2 (2)	67 (13)	135 (17)	19 (7)	666 (318, 1401)	59%	0%	27%	38%
Hong Kong CKD (China)[c]	502	191	270	NA	6 (3)	61 (12)	138 (19)	17 (7)	60 (21, 150)	56%	0%	27%	46%
ICES-KDT (Canada)[a]	79,272	42,006	9240	25,993	4 (3)	76 (13)	NA	25 (5)	53 (13, 360)	43%	<5%[e]	34%	48%
Maccabi (Israel)[a]	12,576	7531	1693	3480	4 (3)	76 (13)	135 (22)	25 (5)	70 (10, 301)	49%	0%	64%	46%
MASTERPLAN (Netherlands)[c]	437	93	142	32	4 (1)	61 (12)	138 (22)	24 (5)	185 (53, 666)	69%	0%	32%	32%
MDRD (USA)[c]	851	474	724	NA	14 (7)	51 (13)	134 (19)	22 (6)	335 (64, 1002)	60%	10%	17%	9%
Nanjing CKD (China)[c]	1584	116	1003	108	4 (3)	47 (14)	141 (22)	21 (6)	1008 (550, 1839)	54%	0%	12%	21%
NephroTest (France)[c]	740	213	372	NA	6 (4)	61 (14)	139 (22)	22 (6)	277 (69, 820)	67%	11%	24%	36%
NRHP-URU (Uruguay)[b]	2090	658	512	385	3 (2)	72 (13)	135 (22)	21 (5)	83 (0, 655)	49%	0.14%	36%	32%
NZDCS (New Zealand)[b]	1372	919	438	620	6 (3)	71 (12)	138 (21)	23 (6)	13 (2, 93)	43%	0.073%	47%	100%
PSP CKD (UK)[b]	3522	1251	141	688	2 (1)	80 (12)	131 (19)	24 (5)	48 (18, 151)	43%	0.51%	47%	30%
PSPA (France)[c]	573	437	294	NA	3 (2)	82 (5)	145 (22)	13 (4)	463 (174, 1015)	57%	0%	55%	39%
RCAV (USA)[a]	78,114	30,012	4148	21,672	3 (2)	69 (11)	125 (24)	24 (5)	38 (10, 220)	97%	21.6%	61%	58%
RENAAL (Multi)[c,d]	1078	234	327	400	3 (1)	60 (7)	151 (21)	26 (3)	1604 (690, 3133)	59%	12.5%	28%	100%
SCREAM (Sweden)[a]	18,486	12,370	1132	7882	3 (2)	70 (12)	NA	25 (5)	112 (27, 787)	45%	<5%[e]	54%	25%
SMART (Netherlands)[c]	137	79	31	29	6 (4)	65 (11)	152 (25)	21 (8)	187 (47, 523)	70%	0%	52%	29%
SRR CKD (Sweden)[b]	2555	778	770	932	3 (2)	69 (14)	142 (23)	21 (6)	211 (43, 953)	66%	<5%[e]	33%	38%
Sunnybrook (Canada)[b]	1592	636	362	533	3 (2)	72 (14)	136 (22)	23 (6)	236 (62, 807)	54%	0%	17%	41%
West of Scotland CKD (UK)[b]	6820	2954	1136	419	5 (3)	68 (13)	143 (24)	24 (6)	151 (34, 800)	49%	0.088%[e]	25%	21%
Total	264,296	123,985	31,541	70,394									

ACR, urine albumin-to-creatinine ratio; CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; KRT, kidney replacement therapy; *N*, number of participants; NA, not available. Numbers are means (SD) or medians (1st quartile, 3rd quartile).

[a]Administrative cohort (general population cohort from a clinical or health system database; covariates and outcomes generally from International Classification of Diseases codes).

[b]Referred CKD cohort (similar design to Administrative but restricted to patients under the care of a nephrologist or in a CKD registry).

[c]CKD research cohort (designed as a research study with planned study visits and active outcome ascertainment; patients may be similar to those in the referred CKD type).

[d]RENAAL contains participants from 28 countries: Argentina, Austria, Brazil, Canada, Chile, China, Costa Rica, Czech Republic, Denmark, France, Germany, Hungary, Israel, Italy, Japan, Malaysia, Mexico, Netherlands, New Zealand, Peru, Portugal, Russia, Singapore, Spain, Slovakia, United Kingdom, United States, and Venezuela.

[e]See analytic notes in Appendix S1 for the cohort in regards to the race variable.

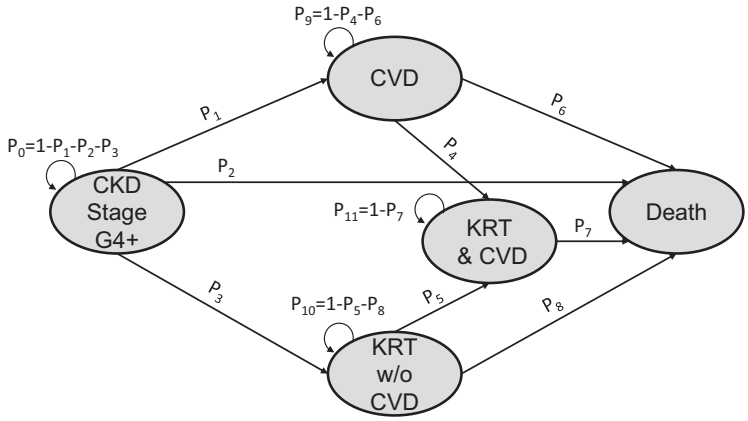


Figure 1 | Diagram of states and transitions included in the 5-state Markov model. States are shown in gray ovals and include chronic kidney disease (CKD) stage G4+, cardiovascular disease (CVD), kidney replacement therapy (KRT) without CVD, KRT and CVD, and death. The state transition probabilities are denoted by P_1 through P_8, where P is a function of age, x (a vector of covariates), and time. This vector includes baseline sex, race, history of CVD, current smoking, systolic blood pressure, diabetes status, albuminuria (P_1 to P_4 and P_6), estimated glomerular filtration rate (baseline for P_1 to P_3, time updated for P_4 and P_6), and transplantation status (for P_5, P_7, and P_8). The probabilities of remaining in a state are denoted by P_0, and P_9 to P_{11}.

agreement (within-cohort R^2 ranging from 0.89 to 0.97; median within-study C statistic of 0.814 (range, 0.680 to 0.972) and 0.817 (range, 0.666 to 0.929), respectively (Supplementary Figures S14 to S19). Calibration to observed risk using clinically relevant categories was also good for both the developed risk prediction model as well as the KFRE (Supplementary Figure S20). Within cohorts, the prevalence of 2-year predicted KRT risk of >40% (potentially an actionable threshold) was approximately 10% in most cohorts, by using the KFRE and slightly higher by using our Markov model; but many participants had >50% predicted probability of remaining event-free at 4 years (Supplementary Figures S21 and S22).

Alternative risk prediction model: assessment of variation by cohort type

Alternate versions of the risk model that incorporated adjusted absolute risk estimates from the 3 types of cohort (CKD research, administrative, and referred CKD) showed an approximately 2-fold variation in the predicted risk of clinical events between models (Supplementary Figure S23; Figure 4). The predicted probability of KRT was higher and probability of death was lower in the CKD research cohort-based prediction model than in the overall prediction model; the opposite was true in the administrative cohort-based prediction model (Supplementary Figures S24 to S26). Variation in adjusted absolute risk over time was less consistent by region or cause of disease (Supplementary Figures S27 and S28).

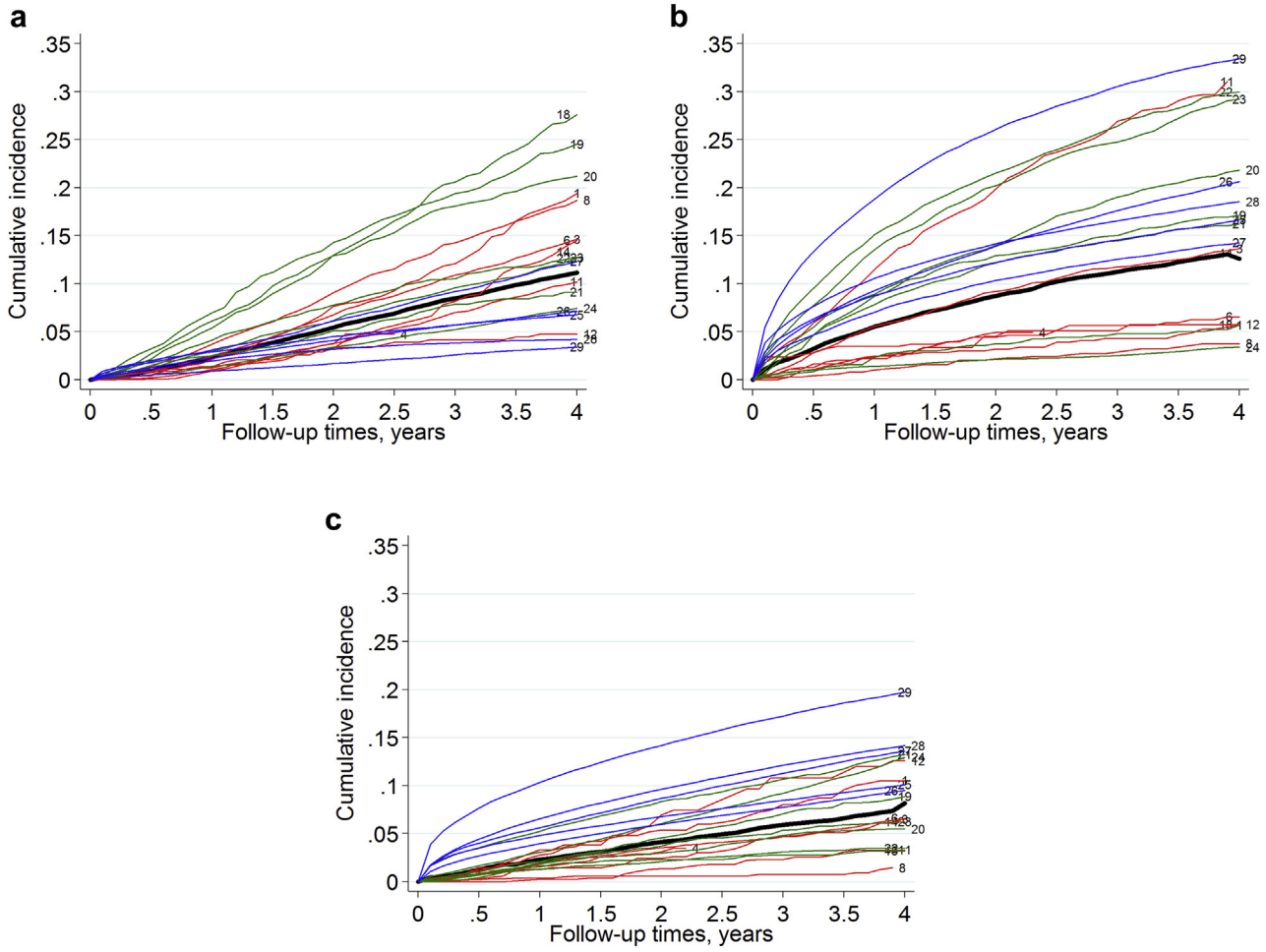
Alternative risk prediction model: three-state Markov model

In sensitivity analysis, we compared the predicted probability of KRT and death from the 5-state Markov model derived from data from the 20 cohorts with all 3 outcomes to the predicted probability of KRT and death from a 3-state Markov model (CKD G4+, KRT, and death) derived from data from all 29 cohorts with available KRT and death (Supplementary Figure S29). Risk projections were similar (Supplementary Figure S30).

DISCUSSION

In this global consortium of 264,296 patients with eGFR of <30 ml/min per 1.73 m^2, we developed and tested a model to predict the absolute risk and relative order of KRT, nonfatal CVD events, and death in 2- and 4-year periods. The risk calculator has been made publicly available (http://ckdpcrisk.org/lowgfrevents/) and may aid in patient counseling, including referral recommendations for transplantation or vascular access surgery. With the caveat that many of our cohorts represent incident stage G4+ CKD patients, we found that occurrence of events (KRT, nonfatal CVD events, or death) was not uniformly high, with nearly 50% of the participants expected to be event-free at the end of 4 years.

Our study provides evidence that clinical characteristics at eGFR of <30 ml/min per 1.73m^2 have strong relationships with subsequent events, even in individuals with severely decreased GFR.[12] Both lower eGFR and higher albuminuria were strong risk factors for kidney failure treated with KRT. However, the absolute risks varied substantially according to age, with the predicted 4-year risk of KRT declining from 33% in a 35-year-old patient to 5% in an 85-year-old patient in a scenario with baseline eGFR of 25 ml/min per 1.73 m^2 and urine ACR of 100 mg/g. Not surprisingly, a history of CVD was an exceptionally strong risk factor for the occurrence of a CVD event among patients with stage G4+ CKD, supporting the potential importance of cardiovascular risk factor reduction in these patients despite their advanced kidney disease. Interestingly, in the included cohorts, many of the participants were predicted to remain event-free in the subsequent four years. This may be in part due to selection: there was a significant subset of participants with relatively low albuminuria, which may or may not be generalizable to the greater population.



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CKD Research Cohort	AASK	CRIB	CRIC	GCKD	Hong Kong-CKD	MASTERPLAN	MDRD	Nanjing-CKD	NephroTest	PSPA	RENAAL	SMART
	1	2	3	4	5	6	7	8	9	10	11	12

Referred CKD	BC2016	CanPREDDICT	CCF	CRISIS	GLOMMS2	Gonryo	NRHP-URU	NZDCS	PSP-CKD	SRR-CKD	Sunnybrook	WestScot-CKD
	13	14	15	16	17	18	19	20	21	22	23	24

Administrative Cohorts	Geisinger	ICES-KDT	Maccabi	RCAV	SCREAM
	25	26	27	28	29

Figure 2 | Adjusted* cumulative incidence of (a) kidney failure requiring kidney replacement therapy, (b) cardiovascular event, and (c) death as first event from Markov model. Color coding of the lines is described in (**d**). The black bold line indicates the equal weighted mean. *Adjusted to 60 years of age, half male, nonblack, half history of cardiovascular disease, half smoker, systolic blood pressure 140 mm Hg, half diabetes, estimated glomerular filtration rate 25 ml/min per 1.73 m^2 and urine albumin-to-creatinine ratio 100 mg/g. Gray shaded cohorts (**d**) did not have cardiovascular events and were not included in panels **a** to **c**. CKD, chronic kidney disease. Study acronyms and abbreviations are listed in Appendix S2.

A well-validated risk equation for kidney failure requiring KRT in stage G3+ CKD already exists.[7,8] Our study adds to the published findings by simultaneously accounting for and estimating rates of competing events, particularly death. We confirm the accuracy of the KFRE in a population with lower GFR than the cohorts in which it was originally developed and validated, and we compared the KFRE to our own model, finding similar results. We suggest that health providers and systems use the KFRE in persons with GFR of <60 ml/min per 1.73 m^2, in whom kidney failure treated with KRT is the primary event of interest and when a limited number of covariates are available. For patients with eGFR of <30 ml/min per 1.73 m^2 in whom there is interest in incident CVD events or death or the sequence of such events in relation to KRT, we suggest our newly developed equation, which uses additional covariates to produce a more refined estimate.

Strengths of our study include a large number of patients with stage G4+ CKD from a broad range of countries. Models were developed and rigorously tested with many different sensitivity analyses. Prediction tools incorporated 9 different clinical and demographic variables and explained approximately 40-fold of the variation in explained risk, but there remained approximately 5-fold variation between cohorts

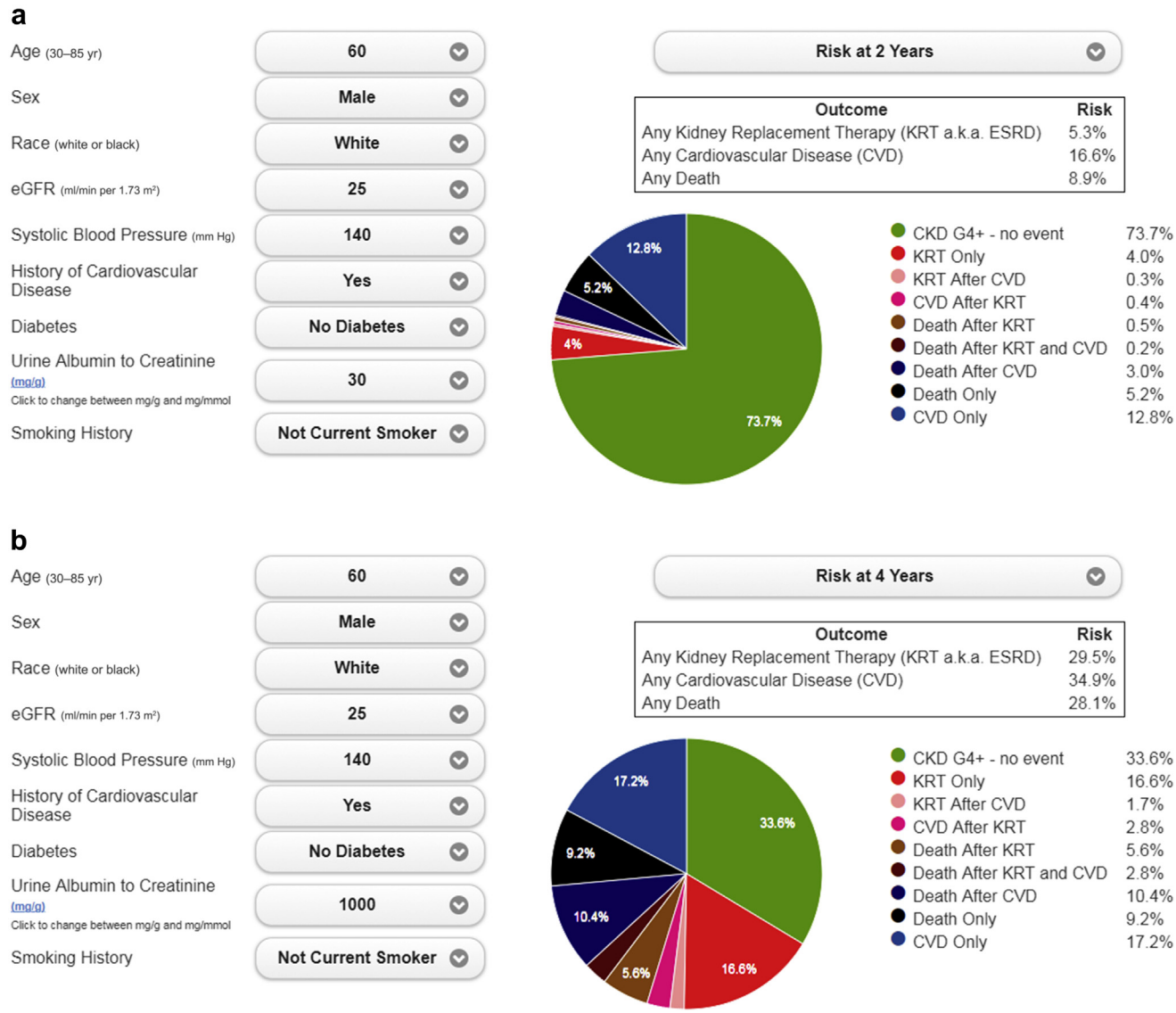

Figure 3 | Probability and timing of clinical events at 2 and 4 years with increasing level of albuminuria. (**a**) Two years and urine albumin-to-creatinine ratio (ACR) of 30 mg/g; (**b**) 4 years and urine ACR of 1000 mg/g. In these models, the scenario was set at 60 years of age, male, white, history of CVD, not a current smoker, systolic blood pressure of 140 mm Hg, no diabetes, and an estimated glomerular filtration rate of 25 ml/min per 1.73 m^2. ESRD, end-stage renal disease; KRT, kidney replacement therapy.

that was unexplained. Type of cohort did seem to be an important contributor in risk variation, with research cohorts having markedly higher KRT risk than others, even adjusted for baseline covariates. In those cohorts for which we had data, cause of CKD was not a major contributor to variation between cohorts. Although region has previously been found to play an important role in KRT risk, we did not see consistent differences between North America and non-North American regions, perhaps due to the relatively small number of cohorts from each region.[8] We had limited data with which to evaluate whether differences in therapeutic interventions such as renin-angiotensin system inhibition or statin use might partially explain variation across cohorts.[13]

As with all models, there were certain assumptions. Relative risks were modeled as constant over time. The cumulative incidence of competing events was scaled to the cumulative incidence of the composite event derived from Cox regression. Initiation of KRT, which we and others used as an operational definition for the major adverse kidney disease endpoint, is a treatment decision which may be influenced by factors other than kidney function. For example, our observation of older age conferring lower risk for KRT may reflect preferences for conservative care rather than a slower progression of CKD or fewer symptoms. Fatal CVD events were simply counted as death, and not CVD.

In conclusion, our model predicts the occurrence and order of nonfatal CVD events, kidney failure treated with KRT, and death in patients with eGFR of <30 ml/min per 1.73 m^2, based on parameters that are readily available in routine clinical practice. This tool may be a useful supplement

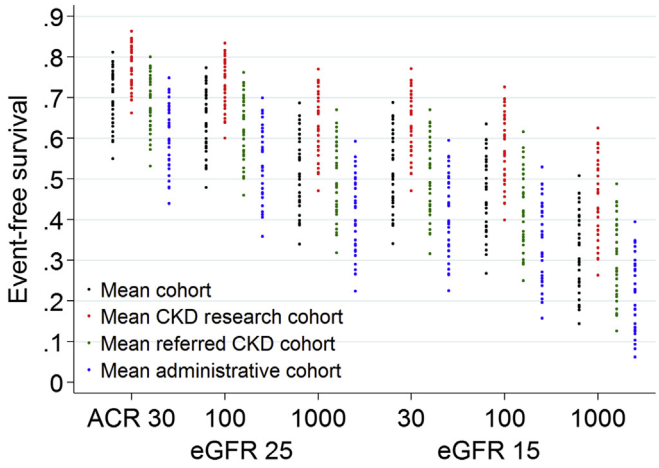

Figure 4 | Markov model predicted 2-year survival without kidney failure treated with kidney replacement therapy or cardiovascular events for a range of scenarios (varying systolic blood pressure, race, diabetes, history of cardiovascular disease, and smoking status) for a 60-year-old man, comparing estimates using overall mean with cohort type-specific means for the baseline hazards and subhazards. ACR, urine albumin-to-creatinine ratio; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

to existing risk calculators when refined estimates that take into account competing events and patterns of events are required. Additional work is needed to further characterize sources of unexplained variation between cohorts, with the ultimate goal of identifying treatment strategies and practice patterns that can prevent or forestall adverse outcomes in patients with severely decreased GFR.

METHODS

Study population

Cohorts were identified from the CKD Prognosis Consortium (CKD-PC) as well as through an open call by the Kidney Disease: Improving Global Outcomes (KDIGO) entity. The CKD-PC has been described previously and in more detail in Appendices S1 and S2.[14–17] Cohorts were considered eligible for the current study if they contained at least 500 patients with eGFR <30 ml/min per 1.73 m^2, data for albuminuria, and at least 50 events each of kidney failure requiring KRT and death. There were 29 cohorts included in analyses using a 3-state Markov model, and 20 cohorts using a 5-state Markov model. Thirteen cohorts were classified as CKD research cohorts (designed as a research study with planned study visits and active outcome ascertainment), 5 were classified as administrative cohorts (captured from a clinical or health system database covering an entire patient population), and 11 were classified as referred CKD cohorts (similar design as the administrative cohorts, but restricted to patients under the care of a nephrologist or in a CKD registry). This study was approved by the institutional review board at the Johns Hopkins Bloomberg School of Public Health (Baltimore, Maryland).

Covariates and outcomes

Serum creatinine was standardized to isotope dilution mass spectrometry and converted to eGFR, using the CKD-EPI 2009 creatinine equation.[18] Measurements of albuminuria included the urine albumin-to-creatinine ratio, urine albumin excretion rate, and urine protein-to-creatinine ratio, with conversion to ACR as needed.[7] In analyses, urine ACR was log-transformed and scaled to ln(10), so that coefficients were interpreted reflecting differences per 10-fold higher ACR. Diabetes was defined by individual cohorts as fasting glucose ≥7.0 mmol/l (126 mg/dl), nonfasting glucose ≥11.1 mmol/l (200 mg/dl), hemoglobin A_{1c} ≥6.5%, use of glucose-lowering drugs, or self-reported diabetes. History of CVD was defined as a history of myocardial infarction, coronary revascularization, heart failure, or stroke. Smoking was categorized as current smoker versus former or never-smoker. Systolic blood pressure was reported by the cohorts and treated as a linear spline in regression models, with a knot at 140 mm Hg. Cause of disease was classified by individual cohorts. Outcomes included KRT, cardiovascular events, and death, and were defined using cohort-specific definitions (Appendix S1). Missing covariates (except for age, sex, race, and eGFR) were estimated using multiple imputation chained equations.[19–21]

Competing risk analyses

The associations between baseline covariates and first outcome were determined using competing risk regression, using the method of Fine and Gray, and treating first KRT, first nonfatal CVD event, and pre-KRT, precardiovascular death as competing events.[22] This was repeated for all participants who reached KRT first, treating post-KRT CVD events and death as competing events, and for all participants who had a CVD event first, treating post-CVD event KRT and death as competing events. Only the first nonfatal CVD event after the onset of eGFR <30 ml/min per 1.73 m^2 was captured. At each step, a composite endpoint was also evaluated in the same manner using Cox regression. For the first event, the composite endpoint consisted of first KRT, first CVD event or death pre-KRT and pre-CVD event. For the second event after KRT, the composite endpoint consisted of post-KRT CVD events or post-KRT death. For the second event after a CVD event, the composite endpoint consisted of post-CVD event KRT or post-CVD event death. For the outcome of death after a participant had developed both KRT and a CVD event, Cox regression was used to estimate associations, as there was no competing event.

Meta-analysis and estimation of baseline subhazards

Fine and Gray subhazard ratios derived in each cohort were pooled using random effects meta-analysis. Heterogeneity was evaluated using forest plots and I^2 statistics.[23–25] Cohort-specific adjusted baseline subhazards were estimated in each cohort by using competing risk regression, holding subhazard ratios constant and equal to the meta-analyzed subhazard ratios but allowing the baseline subhazard to vary between cohorts. The baseline subhazards were then used to calculate the adjusted cumulative incidence of each event over time. Baseline subhazards (i.e., the adjusted absolute risk over time) were displayed graphically to evaluate heterogeneity and summarized as the equally weighted mean over cohorts and, for cohort type-specific analysis, the equally weighted mean within cohort type. Note that, for the composite endpoints as well as event of death after KRT and a CVD event (where there is no competing event), Cox regression and baseline hazards were used, but the procedure was otherwise the same. A Weibull model was then fitted on the equal-weighted mean adjusted subhazard (or hazard) in order to allow a smooth, parametric estimate for use in the Markov process.

Markov process and simulations of absolute risks

The combination of parameters from the Weibull model and the meta-analyzed subhazard ratios were used to predict time-varying

state transition probabilities (e.g., the probability of moving from stage G4+ to first KRT) for a given set of baseline covariates (age, sex, race, history of CVD, smoking status, diabetes mellitus, systolic blood pressure, eGFR, and urine ACR). In order to ensure that the probabilities for each state summed to 1, we scaled the cumulative probability of the events (for the first state transition, first KRT, first CVD event, and first death) to the cumulative probability of a composite endpoint ascertained using Cox proportional hazards model, as done previously.[26] These state transition probabilities thus varied by time, age, and baseline covariates and were incorporated in a heterogeneous Markov process, using a cycle length of 1 month and time horizons of 2- and 4-years. Outcomes were estimated using 10,000 simulations for each scenario, where a scenario corresponded to a set of covariates. In other words, each iteration corresponded to 1 hypothetical person with the given set of covariates, and variation in the results of the iteration represented the stochastic natures in which persons traversed the Markov model. In order to assess the sensitivity of risk prediction to cohort type, we repeated the procedures using cohort-type-specific parameters for the baseline subhazards. We also repeated analyses in a 3-state model (CKD stage G4+, KRT, and death) (Supplementary Figure S29) to compare the results. To evaluate sources of unexplained variation, we examined the distribution of cumulative incidence of events by type of cohort, region, and prevalence of different causes of CKD.

Development of a web calculator

In order to implement the Markov process as a Web tool, we developed an estimating equation on simulated estimates for 3,702 baseline scenarios (every combination of age [35, 45, 55, 60, 65, 75, 80, and 85 years of age], sex, race [black and nonblack], diabetes status, history of CVD status, smoking status [current smoker and never- or former smoker], systolic blood pressure [180 and 140 mm Hg], eGFR [15 and 25 ml/min per 1.73 m^2], and ACR [30, 100, and 1,000 mg/g]). To do this, we fitted multinomial models and weighted them by the inverse probability of each outcome from simulations (e.g., KRT only, CVD only, death only; KRT followed by CVD, CVD followed by KRT, and so forth). Multinomial models incorporated all the available covariates and two-way interactions significant for any of the outcomes. Calibration of the multinomial model to the simulated outcomes was assessed using R^2 and root-mean-squared errors for each outcome. Functional forms of covariates were the same as those used in the competing risk regression. For the purposes of this manuscript, predicted probabilities in the figures and text stem from the multinomial model.

Comparison of our developed risk model with the KFRE and observed risk

We compared absolute risk estimates of the probability of KRT from our newly developed risk model to that calculated in the absence of competing events using the previously published KFRE.[7,8] To do this, we held shared variables constant (age, sex, eGFR, and ACR) and varied the covariates unique to our model (race, systolic blood pressure, diabetes mellitus, smoking status, and history of CVD), and we assessed R^2 within cohorts. We also compared risk predictions from our developed risk model as well as the KFRE to observed KRT risk. To do this, we divided predicted risk categories into <20%, 20% to 40%, >40% probability of KRT in the subsequent 2 years (clinically meaningful thresholds), using our developed risk model and the KFRE, and then we plotted the mean risk estimate against the observed risk within each category by cohort. Discrimination was assessed using the C statistic. All analyses were done using Stata 14 MP software (College Station, TX).

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Study acronyms/abbreviations are listed in Appendix S2. AASK: Brad Astor, Lawrence Appel; BC CKD: Adeera Levin, Ognjenka Djurdjev; CanPREDDICT: Adeera Levin, Mila Tang, Ognjenka Djurdjev; CCF: Sankar D. Navaneethan, Stacey E. Jolly, Jesse D. Schold, Joseph V. Nally Jr.; CRIB: David C. Wheeler, Jonathan Emberson, John Townend, Martin Landray; CRIC: Harold I. Feldman, Chi-yuan Hsu, James Lash, Lawrence Appel; CRISIS: Philip A. Kalra, James Ritchie, Raman Maharajan, Rachel Middleton, Donal J. O'Donoghue; GCKD: Kai-Uwe Eckardt, Markus P. Schneider, Anna Köttgen, Florian Kronenberg, Barbara Bärthlein; Geisinger: Alex R. Chang, Jamie Green, H. Lester Kirchner, Kevin Ho; GLOMMS2: Angharad Marks, Corri Black, Gordon Prescott, Nick Fluck; Gonryo: Masaaki Nakayama, Mariko Miyazaki, Tae Yamamoto, Gen Yamada; Hong Kong CKD: Angela Yee Moon Wang, Sharon Cheung, Sharon Wong, Jessie Chu, Henry Wu; ICES-KDT: Amit X. Garg, Eric McArthur, Danielle M. Nash; Maccabi: Varda Shalev, Gabriel Chodick; MASTERPLAN: Peter J Blankestijn, Jack Wetzels, Arjan van Zuilen, Jan van den Brand; MDRD: Andrew S. Levey, Lesley A. Inker, Mark Sarnak, Hocine Tighiouart; Nanjing CKD: Haitao Zhang; NephroTest: Benedicte Stengel, Marie Metzger, Martin Flamant, Pascal Houillier, Jean-Philippe Haymann; NRHP-URU: Pablo Rios, Nelson Mazzuchi, Liliana Gadola, Verónica Lamadrid, Laura Sola; NZDCS: John Collins, C. Raina Elley, Timothy Kenealy; PSPA: Olivier Moranne, Cecile Couchoud, Cecile Vigneau; PSP CKD: Nigel J. Brunskill, Rupert Major, David Shepherd, James Medcalf; RCAV: Csaba P. Kovesdy, Kamyar Kalantar-Zadeh, Miklos Z. Molnar, Keiichi Sumida, Praveen Potukuchi; RENAAL: Hiddo J.L. Heerspink, Dick de Zeeuw, Barry Brenner; SCREAM: Juan Jesus Carrero, Alessandro Gasparini, Abdul Rashid Qureshi, Carl Gustaf Elinder; SMART: Frank L.J. Visseren, Yolanda van der Graaf; SRR CKD: Marie Evans, Maria Stendahl, Staffan Schön, Mårten Segelmark, Karl-Göran Prütz; Sunnybrook: David Naimark, Navdeep Tangri; West of Scotland CKD: Patrick B. Mark, Jamie P. Traynor, Colin C. Geddes, Peter C. Thomson

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KIDNEY DISEASE: IMPROVING GLOBAL OUTCOMES FOUNDATION CONTROVERSIES CONFERENCE ON PROGNOSIS AND OPTIMAL MANAGEMENT OF PATIENTS WITH ADVANCED CKD

Kai-Uwe Eckardt (Conference Co-Chair), Brenda Hemmelgarn (Conference Co-Chair), David C. Wheeler (KDIGO Co-Chair), Wolfgang Winkelmayer (KDIGO Co-Chair), John Davis (CEO), Danielle Green (Managing Director), Michael Cheung (Chief Scientific Officer), Tanya Green (Communications Director), Melissa McMahan (Programs Director).

DISCLOSURE

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Some of the data reported here have been supplied by the United States Renal Data System. The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy or interpretation of the US government.

SUPPLEMENTARY MATERIAL

Appendix S1. Data analysis overview and analytic notes for some of individual studies.

Appendix S2. Acronyms or abbreviations for studies included in the current report and their key references linked to the web references.

Appendix S3. Acknowledgements and funding for collaborating cohorts.

Table S1. Underlying data selection by cohort.

Table S2. Cause of chronic kidney disease.

Table S3. Random effects meta-analysis of subhazard ratios for KRT, nonfatal CVD, or death as the first event after eGFR <30 ml/min per 1.73 m^2, 20 cohorts with information on all three outcomes.

Table S4. Random effects meta-analysis of subhazard ratios for nonfatal CVD or death as the second event after KRT, 20 cohorts with information on all three outcomes.

Table S5. Random effects meta-analysis of subhazard ratios for KRT or death as the second event after nonfatal CVD, 20 cohorts with information on all three outcomes.

Table S6. Random effects meta-analysis of subhazard ratios for death as the third event after KRT and CVD, 20 cohorts with information on all three outcomes.

Table S7. Multinomial coefficients from the model approximating the Markov chain results, 2 (**A**) and 4 (**B**) years.

Figure S1. Distribution of eGFR by cohort, color-coded by cohort type.

Figure S2. Distribution of ACR by cohort, color-coded by cohort type.

Figure S3. Forest plot of the subhazard ratio associated with 5 ml/min per 1.73 m^2 lower eGFR for risk of first KRT, across 20 cohorts with data on KRT, CVD and death.

Figure S4. Forest plot of the subhazard ratio associated with 10-fold higher urine albumin-to-creatinine ratio for risk of first KRT, across 20 cohorts with data on KRT, CVD, and death.

Figure S5. Adjusted* cumulative incidence of (**A**) CVD after first KRT and (**B**) death after first KRT from Markov model. Color coding of the lines is described in (**C**).

Figure S6. Adjusted* cumulative incidence of (**A**) KRT after first nonfatal CVD and (**B**) death after first nonfatal CVD from Markov model. Color coding of the lines is described in (**C**).

Figure S7. Adjusted* cumulative incidence of (**A**) death after having experienced both KRT and CVD from Markov model. Color coding of the lines is described in (**B**).

Figure S8. The probability and timing of clinical outcomes at 2 and 4 years with increasing level of ACR.

Figure S9. The probability and timing of clinical outcomes at 4 years, varied by diabetes status.

Figure S10. The probability and timing of clinical outcomes at 4 years, varied by SBP level.

Figure S11. The probability and timing of clinical outcomes at 4 years, varied by history of CVD.

Figure S12. The probability and timing of clinical outcomes at 4 years, varied by age.

Figure S13. The probability and timing of clinical outcomes at 4 years, with further subdivision by age.

Figure S14. Absolute risk projections for KRT at 2-years for a set of scenarios for a 35-year old man (**A**) or woman (**B**).

Figure S15. Absolute risk projections for KRT at 2-years for a set of scenarios for a 45-year old man (**A**) or woman (**B**).

Figure S16. Absolute risk projections for KRT at 2-years for a set of scenarios for a 55-year old man (**A**) or woman (**B**).

Figure S17. Absolute risk projections for KRT at 2-years for a set of scenarios for a 65-year old man (A) or woman (B).

Figure S18. Absolute risk projections for KRT at 2-years for a set of scenarios for a 75-year old man (**A**) or woman (**B**).

Figure S19. Absolute risk projections for KRT at 2 years for a set of scenarios for an 85-year old man (**A**) or woman (**B**).

Figure S20. Calibration of the predicted versus observed 2-year risk of KRT for the (**A**) kidney failure risk equation (KFRE) and (**B**) MCMC model.

Figure S21. Prevalence of 2-year predicted KRT risk for the (**A**) kidney failure risk equation (KFRE) and (**B**) MCMC model.
Figure S22. Distribution of 4-year event free survival.
Figure S23. Equal-weighted mean of the adjusted cumulative incidence curves for first KRT (**A**), first CVD (**B**), and death as a first event (**C**) within the three types of cohort (CKD research, administrative, and referred CKD).
Figure S24. The probability and timing of clinical outcomes at 4 years overall and by type of cohort.
Figure S25. The probability and timing of clinical outcomes at 4 years overall and by type of cohort.
Figure S26. The probability and timing of clinical outcomes at 4 years overall and by type of cohort.
Figure S27. Cumulative incidence of first KRT (**A**), first CVD (**B**), and death as a first event (**C**) by region.
Figure S28. Adjusted absolute risk of KRT by cause of CKD in cohorts with available data (Supplementary Table S2).
Figure S29. Diagram of states and transitions included in the 3-state Markov model.
Figure S30. Absolute KRT (**A**) or death (**B**) risk projections at 2-years for a set of scenarios for a 60-year old man from a 5-state Markov model compared to a 3-state Markov model.
Supplementary material is linked to the online version of the paper at www.kidney-international.org.

REFERENCES

1. Levin A, Tonelli M, Bonventre J, et al. Global kidney health 2017 and beyond: a roadmap for closing gaps in care, research, and policy. *Lancet*. 2017.
2. Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012;380:2095–2128.
3. Grams ME, Chow EK, Segev DL, et al. Lifetime incidence of CKD stages 3-5 in the United States. *Am J Kidney Dis*. 2013;62:245–252.
4. United States Renal Data System: 2016 USRDS annual data report: epidemiology of kidney disease in the United States. Bethesda, MD: National Institutes of Health; 2016.
5. Astor BC, Matsushita K, Gansevoort RT, et al. Lower estimated glomerular filtration rate and higher albuminuria are associated with mortality and end-stage renal disease. A collaborative meta-analysis of kidney disease population cohorts. *Kidney Int*. 2011;79:1331–1340.
6. Chronic Kidney Disease Prognosis, Matsushita K, van der Velde M, et al. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. *Lancet*. 2010;375:2073–2081.
7. Tangri N, Stevens LA, Griffith J, et al. A predictive model for progression of chronic kidney disease to kidney failure. *JAMA*. 2011;305:1553–1559.
8. Tangri N, Grams ME, Levey AS, et al. Multinational assessment of accuracy of equations for predicting risk of kidney failure: a meta-analysis. *JAMA*. 2016;315:164–174.
9. Schroeder EB, Yang X, Thorp ML, et al. Predicting 5-year risk of RRT in stage 3 or 4 CKD: development and external validation. *Clin J Am Soc Nephrol*. 2017;12:87–94.
10. Weiss JW, Platt RW, Thorp ML, et al. Predicting mortality in older adults with kidney disease: a pragmatic prediction model. *J Am Geriatr Soc*. 2015;63:508–515.
11. Johnson ES, Thorp ML, Yang X, et al. Predicting renal replacement therapy and mortality in CKD. *Am J Kidney Dis*. 2007;50:559–565.
12. Evans M, Grams ME, Sang Y, et al. Risk factors for prognosis in patients with severely decreased GFR. *Kidney Int Rep*. https://doi.org/10.1016/j.ekir.2018.01.002.
13. Schmidt M, Mansfield KE, Bhaskaran K, et al. Adherence to guidelines for creatinine and potassium monitoring and discontinuation following renin-angiotensin system blockade: a UK general practice-based cohort study. *BMJ Open*. 2017;7:e012818.
14. Matsushita K, Coresh J, Sang Y, et al. Estimated glomerular filtration rate and albuminuria for prediction of cardiovascular outcomes: a collaborative meta-analysis of individual participant data. *Lancet Diabetes Endocrinol*. 2015;3:514–525.
15. Coresh J, Turin TC, Matsushita K, et al. Decline in estimated glomerular filtration rate and subsequent risk of end-stage renal disease and mortality. *JAMA*. 2014;311:2518–2531.
16. Kovesdy CP, Coresh J, Ballew SH, et al. Past decline versus current eGFR and subsequent ESRD risk. *J Am Soc Nephrol*. 2016;27:2447–2455.
17. Matsushita K, Ballew SH, Astor BC, et al. Cohort profile: the chronic kidney disease prognosis consortium. *Int J Epidemiol*. 2013;42:1660–1668.
18. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150:604–612.
19. Moons KG, Donders RA, Stijnen T, et al. Using the outcome for imputation of missing predictor values was preferred. *J Clin Epidemiol*. 2006;59:1092–1101.
20. White IR, Royston P. Imputing missing covariate values for the Cox model. *Stat Med*. 2009;28:1982–1998.
21. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. *Stat Med*. 2011;30:377–399.
22. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc*. 1999;94:496–509.
23. Borenstein M, Hedges LV, Higgins JP, et al. *Introduction to Meta-analysis*. Chichester, UK: John Wiley and Sons; 2009.
24. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327:557–560.
25. Riley RD, Higgins JP, Deeks JJ. Interpretation of random effects meta-analyses. *BMJ*. 2011;342:d549.
26. Grams ME, Yang W, Rebholz CM, et al. Risks of adverse events in advanced CKD: the Chronic Renal Insufficiency Cohort (CRIC) study. *Am J Kidney Dis*. 2017;70:337–346.