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Marie Evans, MD, PhD, Morgan Grams, MD PhD, Yingying Sang, MS, Brad C. Astor, PhD, MPH, Peter J. Blankestijn, MD, PhD, Nigel J. Brunskill, MD, PhD, John F. Collins, MBChB, Philip A. Kalra, MD BChir, MD, Csaba P. Kovesdy, MD, Adeera Levin, MD, Patrick B. Mark, MBChB, PhD, Olivier Moranne, MD, PhD, Panduranga Rao, MD, Pablo G. Rios, MD, Markus P. Schneider, MD, Varda Shalev, MD, Haitao Zhang, MD, Alex R. Chang, MD, MS, Ron T. Gansevoort, MD, PhD, Kunihiro Matsushita, MD, PhD, Luxia Zhang, MD, MPH, Kai-Uwe Eckardt, MD, Brenda Hemmelgarn, MD, PhD, David C. Wheeler, MD

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Risk Factors for Prognosis in Patients with Severely Decreased Glomerular Filtration Rate

Marie Evans, MD, PhD¹, Morgan Grams, MD PhD², Yingying Sang, MS², Brad C Astor, PhD, MPH³, Peter J Blankestijn, MD, PhD⁴, Nigel J Brunskill, MD, PhD⁵, John F Collins, MBChB⁶, Philip A Kalra, MD BChir, MD⁷, Csaba P Kovesdy, MD⁸, Adeera Levin, MD⁹, Patrick B Mark, MBChB, PhD¹⁰, Olivier Moranne, MD, PhD¹¹, Panduranga Rao, MD¹², Pablo G Rios, MD¹³, Markus P Schneider, MD¹⁴, Varda Shalev, MD¹⁵, Haitao Zhang, MD¹⁶, Alex R Chang, MD, MS¹⁷, Ron T. Gansevoort, MD, PhD¹⁸, Kunihiro Matsushita, MD, PhD², Luxia Zhang, MD, MPH¹⁹, Kai-Uwe Eckardt, MD²⁰, Brenda Hemmelgarn, MD, PhD²¹, David C Wheeler, MD²² for the CKD Prognosis Consortium

¹Division of Renal Medicine, CLINTEC, Karolinska Institutet, Stockholm, Sweden and Swedish Renal Registry, Jönköping, Sweden; ²Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA; ³Departments of Medicine and Population Health Sciences, University of Wisconsin School of Medicine and Public Health, Madison, WI; ⁴Department of Nephrology, University Medical Center Utrecht, Utrecht, the Netherlands; ⁵Department of Infection Immunity and Inflammation, University of Leicester, UK; ⁶Department of Renal Medicine, Auckland City Hospital, Auckland, New Zealand; ⁷Institute of Cardiovascular Sciences, University of Manchester, Manchester Academic Health Sciences Centre, and Salford Royal NHS Foundation Trust, UK; ⁸University of Tennessee Health Science Center, Memphis, TN and Memphis Veterans Affairs Medical Center, Memphis, TN, USA; ⁹BC Provincial Renal Agency and University of British Columbia, Canada; ¹⁰Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, Scotland, UK; ¹¹Service de Néphrologie-Dialyses-Aphérèse, hopital Caremeau, CHU Nimes, France; EA2415, Université Montpellier-Nimes , France; ¹²Department of Internal Medicine, Division of Nephrology, University of Michigan Health System; ¹³National Renal Health
Care Program, Montevideo, Uruguay; 14Department of Nephrology and Hypertension, University Hospital of the Friedrich-Alexander-University Erlangen-Nürnberg, Erlangen, Germany; 15Medical Division, Maccabi Healthcare Services, and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel; 16National Clinical Research Center of Kidney Diseases, Jinling Hospital, Nanjing University School of Medicine, Nanjing, China; 17Division of Nephrology, Geisinger Health System, Danville, PA; 18Department of Nephrology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands; 19Peking University First Hospital, Beijing, China; 20Department of Nephrology and Medical Intensive Care, Charité – Universitätsmedizin Berlin, Berlin, Germany; 21Cumming School of Medicine, Division of Nephrology, and Department of Community Health Sciences, University of Calgary, Alberta, Canada; 22Centre for Nephrology, University College London, London, UK

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Correspondence to: Chronic Kidney Disease Prognosis Consortium Data Coordinating Center (Principal Investigator, Josef Coresh, MD, PhD), 2024 E. Monument Street, Baltimore, MD 21205; Tel: 410-955-9917, Fax: 410-955-8086, E-mail: ckdpc@jhmi.edu
ABSTRACT:

Introduction: Patients with chronic kidney disease (CKD) and estimated glomerular filtration rate (eGFR) <30 ml/min/1.73m² (corresponding to CKD stage G4+) comprise a minority of the overall CKD population but have the highest risk for adverse outcomes. Many CKD G4+ patients are older with multiple comorbidities, which may distort associations between risk factors and clinical outcomes.

Methods: We undertook a meta-analysis of risk factors for kidney failure treated with kidney replacement therapy (KRT), cardiovascular disease (CVD) events, and death in participants with CKD G4+ from 28 cohorts (n=185,024) across the world who were part of the CKD Prognosis Consortium.

Results: In the fully adjusted meta-analysis, risk factors associated with KRT were time-varying CVD, male sex, black race, diabetes, lower eGFR, and higher albuminuria and systolic blood pressure. Age was associated with a lower risk of KRT (adjusted HR 0.74, 95% CI 0.69-0.80) overall, and also in the subgroup of individuals below 65 years of age. The risk factors for CVD events included male sex, history of CVD, diabetes, lower eGFR, higher albuminuria, and the onset of KRT. Systolic blood pressure showed a U-shaped association with CVD events. Risk factors for mortality were similar to those for CVD events but also included smoking. Most risk factors had qualitatively consistent associations across cohorts.

Conclusion: Traditional CVD risk factors are of prognostic value in individuals with an eGFR <30 ml/min/1.73m², although the risk estimates vary for kidney and CVD outcomes. These results should encourage interventional studies on correcting risk factors in this high-risk population.
INTRODUCTION:

Chronic kidney disease (CKD) has a major impact on the affected individuals’ lives and carries an economic burden to societies.\(^1\) The prevalence of CKD Stage G3+ (estimated glomerular filtration rate [eGFR] <60 ml/min/1.73m\(^2\)) varies substantially across the world; in the USA, between 4.8% – 11.8,\(^2\) in China, 1.1% - 3.8%,\(^3\) and in Europe, 1.0 – 5.9%.\(^4\) Globally, the prevalence of CKD with severely decreased GFR (G4+, eGFR <30 ml/min/1.73m\(^2\)) is much lower (<0.5%). However, associated morbidity and mortality is higher among patients with CKD G4+,\(^5\) and less is known about relevant risk factors.

Patients with CKD have an elevated risk of progressing to kidney failure requiring kidney replacement therapy (KRT), cardiovascular disease (CVD) events, and mortality, with higher risk at higher CKD stage.\(^6,7\) Traditional cardiovascular risk factors such as older age and male sex are associated with CVD and mortality in CKD stage G3+.\(^8\) In addition, lower eGFR and higher albuminuria are important risk factors for progression to KRT, all-cause and cardiovascular mortality.\(^7\) However, risk factors for KRT, CVD events, and mortality may not be the same in a population which has already progressed to CKD G4+. For example, some believe that high blood pressure may be less of a risk factor in CKD with severely decreased GFR. In addition, it is not known whether risk factors vary by age – a characteristic of particular interest, given that the majority of patients with CKD G4+ are over the age of 65 years.\(^9\) A better understanding of factors associated with different outcomes may inform treatment strategies.

Using 28 cohorts from across the world, we investigated the relative risk associations between traditional risk factors and adverse outcomes in CKD G4+. We hypothesized that traditional risk factors would be important in CKD G4+ and that older age would not significantly modify the relationship between risk factors and outcomes.
MATERIALS AND METHODS:

Study population

This study followed a call for participation in the KDIGO controversies conference in Barcelona (December, 2016) for evaluation and management of CKD with severely decreased GFR. Study cohorts were part of the Chronic Kidney Disease Prognosis Consortium (CKD-PC), a worldwide, collaborative network consisting of CKD cohorts with information on eGFR and albuminuria.\textsuperscript{10,11} The underlying selection criteria are provided in the Supplement (Appendix 1 and Supplemental Table S1). For this specific project, 28 cohorts were selected, with inclusion criteria consisting of at least 500 individuals over the age of 18 years with an eGFR $\leq 30$ ml/min/1.73m$^2$ (CKD Stage G4+) at any visit. Furthermore, the cohorts had to have follow-up for both KRT and death pre and post ESRD and at least 50 events of each outcome. Time at risk began at the first visit in which eGFR was observed to be $<30$ ml/min/1.73 m$^2$.

Study variables

The study variables are listed in Table 1. eGFR was estimated by the CKD-EPI equation using age, sex, race, and serum creatinine standardized according to isotope dilution mass spectrometry traceable (IDMS) methods.\textsuperscript{12} For cohorts where serum creatinine was not standardized, we reduced the serum creatinine by 5%.\textsuperscript{13} Albuminuria was recorded as the urinary albumin/creatinine or protein/creatinine ratio and converted to ACR as done previously.\textsuperscript{14} If these measurements were not available, we used dipstick proteinuria information. Diabetes mellitus was defined as the use of glucose lowering drugs, a fasting glucose $\geq 7.0$ mmol/L or non-fasting glucose $\geq 11.1$ mmol/L, hemoglobin A1c $\geq 6.5\%$, or self-reported diabetes. Smoking status was recoded as current smoking versus not smoking. History of cardiovascular disease was defined as a previous diagnosis of myocardial infarction, percutaneous coronary intervention, bypass grafting, heart failure or stroke.
There were three major outcomes; kidney failure treated with KRT, CVD event and death. We also studied recurrent hospitalization events as a secondary outcome. The KRT outcome was defined as start of kidney replacement therapy and either actively ascertained or ascertained through linkages to registries or ICD-codes (Appendix 1). As for the CVD event, we accepted both fatal and non-fatal coronary heart disease, stroke and heart failure events occurring after enrollment in our cohort (Appendix 1). If fatal events were lacking, we did include non-fatal events. Note that any CVD event could occur also in individuals with a history of CVD at baseline, but only the first event after enrollment was quantified. A competing event such as death is treated as a censoring for both KRT and CVD.

Statistical analysis

Since the focus of our analysis was the risk relationship rather than the absolute risk of events, we used cause-specific hazards models for both KRT and CVD, and used Cox proportional hazards models for death. For the purpose of analyses, age was expressed per 10 years older, and eGFR per 5 ml/min/1.73m$^2$ lower. Albuminuria from the heterogeneous sources was referred to as urine ACR and log-transformed and scaled such that the coefficients reflect a 10-fold increase in ACR. Systolic blood pressure was modelled as a linear spline with a knot at 140 mmHg, based on review of the literature and exploratory data analysis in in-house cohorts, and expressed per 20 mmHg higher value. Race, sex, diabetes, smoking and history of CVD were dichotomized. In addition to serving as an outcome in some of the analyses, KRT and CVD were also modeled as time-varying variables during follow-up for analyses of the CVD and KRT, respectively, as well as for mortality for both. For analyses of hospitalizations, recurrent events were counted during follow-up. We started by analyzing the risk relationships in each cohort individually by time-varying Cox
proportional hazards models. For analyses of KRT and CVD as outcomes, death was treated as a censoring event. For hospitalization, we used negative binomial regression. Multiple imputation was used for any missing data except for demographic variables (age, sex, race), eGFR, and outcomes. Meta-analyses were conducted separately for studies with information on all three outcomes and those with information on only KRT and death. Adjusted risk ratios were pooled through meta-analysis using the random effects model.\textsuperscript{15} The random effects meta-analysis assumes that the observed estimates may vary across cohorts because of a real difference in effect of the variables in each study, but also because of chance. This type of analysis uses a more conservative approach, downplays larger studies, and produces confidence intervals that are generally larger than the corresponding fixed effects. Between-study heterogeneity was quantified by the $I^2$ statistic but also assessed through visual inspection of the individual coefficients and their corresponding 95\% intervals.\textsuperscript{16,17} All analyses were re-run stratified by age below or above 65 years. Meta-regressions were performed to explain any underlying heterogeneity of the risk factors, with investigated explanatory variables including region, cohort type, average cohort eGFR, average cohort ACR, proportion missing ACR, average cohort age, median follow-up time, average systolic blood pressure, and proportion of the cohort that were men, had diabetes, a history of CVD, and were current smokers. All analyses were done in Stata 14 MP (College Station, TX).

RESULTS

Study characteristics:

There were 28 cohorts included in this study, with 185,024 participants with eGFR <30 ml/min/1.73m\(^2\) from 30 different countries. There were 19 cohorts which had information on all three of the outcomes of interest (KRT, CVD events, and death), and 9 cohorts which only had information on KRT and death. The characteristics of all 28 cohorts are presented in
Table 1. Overall, average age was 70 years (standard deviation [SD], 13), 69% were men, 11% were black, 5.4% were Asian, 46% had diabetes, and 50% had a history of CVD. The mean eGFR was 24 ml/min/1.73 m$^2$ (SD, 6) and median urine ACR was 48 mg/g (interquartile range, 38 to 112). Inclusion criteria and extended description of the participating cohorts, covariates, and outcomes are found in the Appendix 1 and Supplemental Table S1. Mean follow-up for the 28 cohorts was 3.3 years (SD, 2.8).

Risk factors for kidney failure requiring KRT after eGFR 30 ml/min/1.73 m$^2$

The unadjusted incidence rates for KRT ranged from 17 to 302 events per 1000 person-years between the different cohorts (Supplemental Table S2). In total, there were 22,301 (12.1%) KRT events among 185,024 people. The meta-analyzed adjusted hazard ratios (HR) and 95% confidence intervals (CI) for the relationship between risk factors and onset of KRT in the 19 cohorts with outcome information on KRT, CVD events, and death are presented in Table 2, column 1. The risk factors most strongly associated with KRT were male sex (HR 1.44, 95% CI: 1.34-1.55), black race (HR 1.49, 95% CI: 1.29-1.72), lower eGFR (HR 1.73 per 5 ml/min/1.73 m$^2$ lower, 95% CI: 1.58-1.90), higher urine ACR (HR 2.15 per 10-fold higher, 95% CI: 1.87-2.48), and the occurrence of a CVD event during follow-up (HR 2.28, 95% CI: 2.02-2.57). Older age was associated with a lower risk of KRT (HR per 10 years older, 0.74, 95% CI 0.69-0.80). The direction and size of the age association was qualitatively consistent across most cohorts (Figure 1A). Men had higher risk of KRT in all of the participating 19 cohorts, although the point estimate varied to some degree (Figure 2A). The relationship between the presence of diabetes and KRT (excluding three cohorts that did not include persons with and without diabetes mellitus) was slightly weaker (HR 1.30, 95% CI: 1.14-1.47), with diabetes observed as an independent, statistically significant risk factor in only 8 of 16 cohorts (Supplemental Figure S1A). In meta-regression analyses, the heterogeneity in the association between diabetes and KRT was mainly explained by differences in cohorts.
with respect to urine ACR, with a stronger effect size in cohorts with less albuminuria testing and lower ACR levels, as well as to a lesser extent by differences in age, systolic blood pressure and history of CVD between the different cohorts (Supplemental Figure S2). In sensitivity analysis, we compared risk coefficients from the meta-analysis when the analyses were extended to the full 28 cohorts with information on KRT and death; results were similar (Supplemental Table S3, column 1 versus Table 2, column 1).

Risk factors for CVD events after eGFR 30 ml/min/1.73 m²

The unadjusted incidence rate of a CVD event was highly variable between the cohorts, both before and after KRT. In total, there were 44,401 (28.6%) CVD events that occurred among 155,014 people. In the fully adjusted model, the onset of KRT was among the most important risk factors for a subsequent CVD event (HR 1.39; 95% CI 1.15-1.68) (Table 2, column 2). Other important risk factors for a CVD event included a history of CVD, the presence of diabetes, as well as older age, male sex, higher ACR, and lower eGFR. Systolic blood pressure showed a U-shaped association with CVD event risk. Each 20 mmHg higher blood pressure above 140 mmHg was associated with a 9% higher risk of CVD events, whereas a systolic blood pressure of 140 mmHg relative to 120mmHg was associated with an 11% lower risk of CVD event. The association between age and CVD was consistent in direction across all cohorts but one (Figure 1B). Associations between sex and CVD events were also relatively similar across cohorts (Figure 2B), and meta-regression analyses did not identify any cohort-level factors that explained underlying heterogeneity (Supplemental Figure S3). The presence of diabetes was a strong risk factor for CVD in all cohorts but one (Supplemental Figure S1B).

Risk factors for mortality after eGFR 30 ml/min/1.73 m²
In total, there were 81,979 (44.3%) deaths among 185,024 people during follow-up. In the 19 cohorts with all outcomes present, the development of a CVD event and the onset of KRT were both exceedingly strong risk factors for subsequent death (Table 2, column 3). Other risk factors for mortality included lower eGFR and higher urine ACR, as well as older age, male sex, history of previous CVD, and the presence of diabetes. Similar to its association with CVD events, systolic blood pressure was associated with death in a non-linear fashion with lower blood pressure below 140 mmHg being associated with death, and no association for higher blood pressure with death above 140 mmHg. Smoking was significantly associated with death (HR 1.37; 95% CI 1.25-1.50). The association between age and mortality was qualitatively similar across cohorts (Figure 1C). The associations of male sex and diabetes with mortality were weaker and not always consistent in direction across cohorts and showed more heterogeneity between the different cohorts (Figure 2C and Supplemental Figure S1C). Meta-regression of the association between male sex and mortality as well as diabetes and mortality did not show any particular cohort-level factor that explained the variation (Supplemental Figures S4 and S5). The relationship between the risk factors and mortality remained similar in the analysis with all 28 cohorts included (Supplemental Table S3, column 2 versus Table 2, column 3).

Risk factors for hospitalization

Out of the 8 cohorts with information on hospitalization rates, the unadjusted incidence of recurrent hospitalization ranged from 12 to 1524 per 1000 person-years pre-onset of kidney failure treated with KRT, and 26 to 2293 hospitalizations per 1000 person-years after KRT (Supplemental Table S4). In all cohorts, hospitalizations rates were higher after KRT was initiated. Risk factors for recurrent hospitalizations included history of CVD, lower systolic blood pressure below 140 mmHg and higher systolic blood pressure above 140 mmHg, higher urine ACR and lower eGFR; history of CVD and higher systolic blood pressure above
140 mmHg were also risk factors post-KRT of similar magnitude both before and after KRT (Supplemental Table S5).

**Effect modification of risk factors by age**

In general, the associations between risk factors and outcomes (KRT, CVD event, and death) were similar in subgroups of participants with an age below or above 65 years (Figure 3). However, for both KRT and CVD events, diabetes was a slightly stronger risk factor in the younger subgroup. In contrast, male sex was a stronger risk factor for KRT in those >65 years of age. Notably, age demonstrated significant associations with each outcome within both age strata. For example, older age was associated with a lower risk of KRT even among those with an age <65 years.

**DISCUSSION**

In this large meta-analysis, we studied risk factors for KRT, CVD, and death in 185,244 people with stages 4-5 CKD. Traditional risk factors were of important prognostic value in this population, although associations varied by outcome of interest. Overall, the greatest explained variation was observed for KRT, mostly due to very strong risk relationships between eGFR, albuminuria and KRT. Lower eGFR and higher albuminuria were slightly weaker risk factors for CVD and mortality. Male sex, black race, presence of diabetes, and higher systolic blood pressure all increased the risk of KRT, while older age was associated with a lower risk of KRT. The risk factors for CVD and mortality were similar to those for KRT, although older age was also a risk factor and there was a non-linear association with systolic blood pressure. Smoking was significantly associated only with mortality. Importantly, we found that the onset of KRT or a CVD event in individuals with an eGFR <30 ml/min/1.73m² was strongly associated with subsequent mortality. Risk factor associations were fairly consistent across 28 cohorts as well as subgroups of age.
Although nephrologists know that those with severely decreased GFR represent a high-risk population for adverse outcomes, it has been difficult to assess the benefits of risk factor modification at this stage. The presence of multiple comorbidities in this population may distort relationships between risk factors such as hypertension and clinical outcomes. Most previous studies examining risk factors for CKD outcomes have recruited patients with a wide spectrum of kidney function and patients who survive to develop CKD stage G4+ may experience different risk associations when compared to those who never progress. Yet, studies in CKD stage G4+ are limited due to the relative rarity of disease and paucity of CKD stage G4+ disease registries. The results of our large, consortium-wide analysis including 185,244 individuals are consistent with the existing literature evaluating traditional risk factors in much smaller, local cohorts of patients with severely decreased GFR.

Age was one variable that showed differences in the direction of associations with different outcomes. The protective association between older age and KRT has been shown in some but not all previous studies. In our study, the age coefficient was consistently “protective” for the development of KRT across cohorts, as well as within subgroups of older and younger age. On the other hand, older age was a risk factor for CVD and death as would be expected. The apparent protective effect of age may be attributable to the competing event of death, but it may also be related to the rapidity of eGFR decline and the fact that starting KRT is a treatment option influenced by patient choice. Older adults may be more likely to choose conservative care or have negative attitudes toward dialysis treatment. Alternatively, age may influence the timing of dialysis.

Besides age, other demographic risk factors were also associated with adverse outcomes. Male sex was a risk factor for KRT, CVD events, and death in CKD stage G4+, similar to findings in the general population. Indeed, in contrast to reports that women have a higher prevalence of CKD stage G3, in our study population of CKD stage G4+, men were in the
majority. Mechanisms for a more rapid GFR decline in men could be related to underlying differences in glomerular hemo-dynamics, activity of local cytokines, or mediated by effects of sex hormones. Other reasons for the lower KRT incidence among women are also possible, such as later initiation of KRT, lower awareness, and lower rates of referral to nephrology care. Black race was a risk factor for KRT but not CVD events or death. This finding is consistent with previous work showing that African Americans have between 2-4-times higher incidence of KRT than people of other races and a higher odds of severely decreased GFR as compared to whites. Some of the risk for CKD progression may be attributable to the presence of Apolipoprotein-1 risk variants or sickle cell trait (inheritance of a single copy of the sickle mutation), both of which occur more often in people with African ancestry.

Traditional cardiovascular risk factors have been found to increase the risk of new onset CKD. In our analysis, the occurrence of a new CVD event during follow-up was associated with a more than two-fold increase in the risk of KRT. Similarly, after the initiation of KRT, the risk of both CVD events and death increased considerably. These results suggest that those who have a very high risk of CVD are likely to be the same individuals who also progress to require KRT and who are more likely to die.

Diabetes is an established risk factor for KRT, CVD, and all-cause mortality in the general population. In the kidney failure risk equation, a KRT prediction tool for people with CKD stage G3-G5, diabetes was not a significant risk factor once albuminuria had been taken into account. In contrast, our analysis found diabetes to be an independent risk factor for KRT in patients with CKD stage G4+. One reason for this difference could be that many of the participants in our study lacked ACR measurements. Although we used imputation to estimate ACR levels, we found that the effect of diabetes was stronger in cohorts with more missing ACR and lower ACR measurements – two correlated factors at the cohort level and
more indicative of an administrative cohort setting. Non-proteinuric CKD in the context of type 2 diabetes is a recognised risk factor for KRT, although the mechanisms of progressive kidney damage may be different when compared to patients who have albuminuria.\textsuperscript{42} Albuminuria itself remained an independent risk factor for all outcomes studied in this meta-analysis. Increases in albuminuria were recently shown to be associated with both the future initiation of KRT and mortality, whereas decreases were inversely correlated with KRT.\textsuperscript{43}

Smoking has been linked to new onset CKD and KRT in the general population.\textsuperscript{34,44} Our results are consistent with the recently published Study of Heart And Renal Protection (SHARP) sub-analysis, which showed that cigarette smoking was associated with risk of death, but not KRT in people with CKD G3+.\textsuperscript{45} Thus, even though the risk for KRT associated with smoking may change over the course of the disease, the elevated risk for death remains, reinforcing the importance of offering smoking cessation advice to people with severely decreased GFR. Elevated systolic blood pressure $>140$ mmHg has been demonstrated to be a risk factor for CVD and has also been associated with progression to KRT in CKD stage G3+ (eGFR $<30$ ml/min/1.73m$^3$).\textsuperscript{46} Our results show an independent association between systolic blood pressure and KRT after adjusting for albuminuria in people with more severely decreased GFR. This may indicate that achieving blood pressure targets are important also at later CKD stages. For CVD events and death, we observed a U-shaped risk association with higher risks both below 120 mmHg and above 140 mmHg. These results could be regarded as contradictory of some recent reports, suggesting better outcomes with intense blood pressure lowering medication.\textsuperscript{47} However, a more likely explanation is that our risk association for a low systolic blood pressure was confounded by comorbid factors, for example, patients with severe heart failure often having low, rather than high blood pressure.\textsuperscript{18} We did not include body mass index (BMI) and LDL cholesterol in our
analyses. For LDL in particular, there were many cohorts with missing information. Initial analyses of the data available indicated only weak relationships for both BMI and LDL.

This is the largest analysis of risk factors for adverse outcomes in people with severely decreased GFR conducted so far and complements projections of the probability and timing of events. We have included studies from many different regions of the world and, by doing so, have increased the generalizability of our results. There has been a concern that people progressing to later CKD stages have a different risk profile compared with people earlier in the course of the disease. By focusing on this specific group we have found that many of the traditional risk factors remain predictive, but that some risk factors, like age, behave differently for the different outcomes. One limitation of our analysis is that the selection of study participants differed between the individual cohorts; some research cohorts have specific inclusion and exclusion criteria (and two cohorts included only diabetics), while the large administrative databases do not. This may have affected the representativeness of study participants. In addition, in most cohorts, only a subset of the participants were selected (i.e., those with eGFR <30 ml/min/1.73 m²), a process designed to capture both people with prevalent disease as well as “progressors.” However, although the studies differed substantially in selection criteria and recruitment, the consistency in qualitative size and direction of our risk estimates throughout the different cohorts were reassuring. Other limitations included lack of data on LDL cholesterol in most cohorts. Although in preliminary analyses, LDL cholesterol was not a strong risk factor for any of the events of interest, the lack of association may be driven by survival bias and confounding by nutritional status. Lack of time-updated measurements prohibited us from analyzing any change in the direction of the risk factors closer to initiation of dialysis.

In summary, this large meta-analysis of people with severely decreased GFR shows that traditional risk factors such as male sex, black race, diabetes, lower eGFR, higher
albuminuria, smoking and higher systolic blood pressure remain important in CKD stage G4+. Furthermore, patients with CKD with severely decreased GFR who develop either CVD events or KRT have an even higher risk of mortality. These results should encourage healthcare professionals to assess traditional risk factors in individuals with stages 4-5 CKD and to offer interventions to reduce exposure to those that are modifiable. Future studies assessing the clinical benefits of such interventions should include this high-risk population.
Conflict of Interest Disclosures: All authors will complete and submit the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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Some of the data reported here have been supplied by the United States Renal Data System (USRDS). 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 U.S. government.
Supplementary Figure and Title Legends

**CKD-PC investigators/collaborators** (study acronyms/abbreviations are listed in appendix 3)

**Appendix 1.** Data analysis overview and analytic notes for some of individual studies

**Appendix 2.** Acronyms or abbreviations for studies included in the current report and their key references linked to the Web references

**Appendix 3.** Acknowledgements and funding for collaborating cohorts

**Supplemental Table S1.** Underlying data selection by cohort

**Supplemental Table S2.** Unadjusted incidence rates for KRT by participating cohort

**Supplemental Table S3.** Meta-analyzed hazard ratios of risk factors associated with KRT and mortality in all 28 cohorts

**Supplemental Table S4.** Unadjusted incidence rate of hospitalizations pre- and post-KRT by participating cohort.

**Supplemental Table S5.** Meta-analyzed hazard ratios of risk factors associated with hospitalizations pre- and post-KRT.

**Supplemental Figure S1.** Variation of the diabetes coefficient for KRT (A), CVD (B), and Death (C) across 19 cohorts in the main analysis.

**Supplemental Figure S2.** Meta-regression analyses for effect of diabetes on the risk of KRT according to various baseline characteristics

**Supplemental Figure S3.** Meta-regression analyses for effect of sex on the risk of CVD according to various baseline characteristics.
Supplemental Figure S4. Meta-regression analyses for effect of sex on the risk of mortality according to various baseline characteristics.

Supplemental Figure S5. Meta-regression analyses for effect of diabetes on the risk of mortality according to various baseline characteristics

Supplementary information is available at KI Report’s website
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<td>1%</td>
<td>29%</td>
</tr>
<tr>
<td>BC CKD (Canada)</td>
<td>9672</td>
<td>4717 (3305/1412)</td>
<td>3036</td>
<td>38 (38/0)</td>
<td>5 (3)</td>
<td>71 (13)</td>
<td>137 (23)</td>
<td>24 (5)</td>
<td>225 (42, 123)</td>
<td>55%</td>
<td>0.41%</td>
<td>16%</td>
<td>50%</td>
<td>11%</td>
</tr>
<tr>
<td>CanPREDDICT (Canada)</td>
<td>1739</td>
<td>452 (322/130)</td>
<td>435</td>
<td>334 (286/48)</td>
<td>3 (2)</td>
<td>69 (13)</td>
<td>134 (20)</td>
<td>23 (5)</td>
<td>188 (37, 929)</td>
<td>62%</td>
<td>1.6%</td>
<td>38%</td>
<td>52%</td>
<td></td>
</tr>
<tr>
<td>CCF (USA)</td>
<td>9256</td>
<td>3000 (2640/360)</td>
<td>1115</td>
<td>2 (1)</td>
<td>73 (13)</td>
<td>130 (22)</td>
<td>24 (5)</td>
<td>51 (13, 346)</td>
<td>46%</td>
<td>17%</td>
<td>24%</td>
<td>30%</td>
<td>9%</td>
<td></td>
</tr>
<tr>
<td>CRIB (UK)</td>
<td>315</td>
<td>133 (62/71)</td>
<td>185</td>
<td>6 (3)</td>
<td>62 (14)</td>
<td>152 (23)</td>
<td>18 (7)</td>
<td>589 (118, 1345)</td>
<td>61%</td>
<td>5.1%</td>
<td>45%</td>
<td>17%</td>
<td>12%</td>
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<tr>
<td>CRIC (USA)</td>
<td>1764</td>
<td>473 (235/238)</td>
<td>834</td>
<td>475 (346/129)</td>
<td>5 (3)</td>
<td>60 (11)</td>
<td>131 (24)</td>
<td>25 (4)</td>
<td>267 (48, 1066)</td>
<td>54%</td>
<td>45%</td>
<td>45%</td>
<td>60%</td>
<td>14%</td>
</tr>
<tr>
<td>CRISIS (UK)</td>
<td>1717</td>
<td>710 (553/157)</td>
<td>461</td>
<td>3 (3)</td>
<td>66 (14)</td>
<td>140 (22)</td>
<td>20 (6)</td>
<td>150 (55, 466)</td>
<td>62%</td>
<td>0.64%</td>
<td>48%</td>
<td>36%</td>
<td>14%</td>
<td></td>
</tr>
<tr>
<td>GCKD (Germany)</td>
<td>504</td>
<td>34 (30/4)</td>
<td>33</td>
<td>34 (32/2)</td>
<td>2 (0)</td>
<td>64 (11)</td>
<td>140 (22)</td>
<td>26 (4)</td>
<td>130 (23, 877)</td>
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<td>0%</td>
<td>43%</td>
<td>44%</td>
<td>15%</td>
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<td>Geisinger (USA)</td>
<td>19293</td>
<td>10039 (8953/1086)</td>
<td>1802</td>
<td>6292 (5822/470)</td>
<td>4 (4)</td>
<td>73 (14)</td>
<td>127 (22)</td>
<td>24 (5)</td>
<td>48 (15, 232)</td>
<td>41%</td>
<td>0.99%</td>
<td>56%</td>
<td>43%</td>
<td>6%</td>
</tr>
<tr>
<td>GLOMMS2 (UK)</td>
<td>6384</td>
<td>3283 (3175/108)</td>
<td>265</td>
<td>3 (2)</td>
<td>79 (11)</td>
<td>44 (10, 189)</td>
<td>38%</td>
<td>0%</td>
<td>26%</td>
<td>12%</td>
<td>1%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gonryo (Japan)</td>
<td>729</td>
<td>57 (57/0)</td>
<td>354</td>
<td>48 (43/5)</td>
<td>2 (2)</td>
<td>67 (13)</td>
<td>135 (17)</td>
<td>19 (7)</td>
<td>666 (318, 1401)</td>
<td>59%</td>
<td>0%</td>
<td>27%</td>
<td>38%</td>
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<td>Hong Kong CKD groups</td>
<td>502</td>
<td>191 (113/78)</td>
<td>270</td>
<td>6 (3)</td>
<td>61 (12)</td>
<td>138 (19, 17)</td>
<td>0%</td>
<td>60%</td>
<td>56%</td>
<td>0%</td>
<td>27%</td>
<td>46%</td>
<td>11%</td>
<td></td>
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<tr>
<td>Maccabi (Israel)</td>
<td>12576</td>
<td>7531 (6800/731)</td>
<td>1693</td>
<td>3480 (3338/142)</td>
<td>4 (3)</td>
<td>76 (13)</td>
<td>135 (22)</td>
<td>25 (5)</td>
<td>70 (10, 301)</td>
<td>49%</td>
<td>0%</td>
<td>64%</td>
<td>46%</td>
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<tr>
<td>MASTERPLAN (Netherlands)</td>
<td>437</td>
<td>93 (58/35)</td>
<td>142</td>
<td>32 (30/2)</td>
<td>4 (1)</td>
<td>61 (12)</td>
<td>138 (22)</td>
<td>24 (5)</td>
<td>185 (53, 666)</td>
<td>69%</td>
<td>0%</td>
<td>32%</td>
<td>32%</td>
<td>18%</td>
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<td>MDRD (USA)</td>
<td>851</td>
<td>474</td>
<td>724</td>
<td>14 (7)</td>
<td>51 (134)</td>
<td>22 (6)</td>
<td>335 (64)</td>
<td>10%</td>
<td>17%</td>
<td>9%</td>
<td>12%</td>
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<tr>
<td>Study</td>
<td>N</td>
<td>Age (years)</td>
<td>ACR (mg/g)</td>
<td>eGFR (ml/min/1.73m²)</td>
<td>Prevalence</td>
<td>Follow-up (years)</td>
<td></td>
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<tr>
<td>Nanjing CKD (China)</td>
<td>1584</td>
<td>(21/95)</td>
<td>1003</td>
<td>108 (44/64)</td>
<td>47 (14)</td>
<td>(22/16)</td>
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<td>NephroTest (France)</td>
<td>740</td>
<td>(100/113)</td>
<td>372</td>
<td>6 (4)</td>
<td>61 (14)</td>
<td>(22/22)</td>
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<td>NRHP-URU (Uruguay)</td>
<td>2090</td>
<td>(505/153)</td>
<td>512</td>
<td>385 (379/6)</td>
<td>72 (13)</td>
<td>(22/21)</td>
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<tr>
<td>NZDCS (New Zealand)</td>
<td>1372</td>
<td>(576/343)</td>
<td>438</td>
<td>620 (545/75)</td>
<td>71 (12)</td>
<td>(21/23)</td>
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<tr>
<td>PSP CKD (UK)</td>
<td>3522</td>
<td>(1224/27)</td>
<td>141</td>
<td>688 (675/13)</td>
<td>80 (12)</td>
<td>(19/24)</td>
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<tr>
<td>PSPA (France)</td>
<td>573</td>
<td>(238/199)</td>
<td>294</td>
<td>1251 (1224/27)</td>
<td>145 (22)</td>
<td>(13/4)</td>
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<td>RCAV (USA)</td>
<td>78114</td>
<td>(28014/1998)</td>
<td>4148</td>
<td>21672 (21063/609)</td>
<td>125 (11)</td>
<td>(24/24)</td>
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<tr>
<td>RENAAL (Multi*)</td>
<td>1078</td>
<td>(138/96)</td>
<td>327</td>
<td>400 (356/44)</td>
<td>60 (7)</td>
<td>(21/26)</td>
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<td>SCREAM (Sweden)</td>
<td>18486</td>
<td>(11841/529)</td>
<td>1132</td>
<td>7882 (7709/165)</td>
<td>70 (12)</td>
<td>(12/25)</td>
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<tr>
<td>SMART (Netherlands)</td>
<td>137</td>
<td>(55/24)</td>
<td>31</td>
<td>29 (23/6)</td>
<td>65 (11)</td>
<td>(25/21)</td>
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<tr>
<td>SRR CKD (Sweden)</td>
<td>2555</td>
<td>(532/246)</td>
<td>770</td>
<td>912 (807/105)</td>
<td>69 (14)</td>
<td>(23/21)</td>
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<tr>
<td>Sunnybrook (Canada)</td>
<td>1592</td>
<td>(457/179)</td>
<td>362</td>
<td>533 (438/95)</td>
<td>72 (14)</td>
<td>(22/23)</td>
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<td></td>
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<tr>
<td>West of Scotland CKD (UK)</td>
<td>6820</td>
<td>(2505/449)</td>
<td>1136</td>
<td>419 (304/115)</td>
<td>68 (13)</td>
<td>(24/24)</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
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<tr>
<td>Total</td>
<td>185024</td>
<td>81979</td>
<td>22301</td>
<td>44401</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

*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 of America, Venezuela.

All values are expressed as numbers unless other is indicated. Follow-up and age is presented in years (SD, standard deviation), Albumin creatinine ratio (ACR) in mg/g, estimated glomerular filtration rate (eGFR) by CKD-EPI equation in ml/min/1.73m², Interquartile range (IQR),
Systolic blood pressure (SBP) in mmHg, cardiovascular disease (CVD), Diabetes mellitus (DM), Kidney failure treated with kidney replacement therapy (KRT). The selection criteria and extended information about each cohort is given in Appendix 1 and Table S1.
Table 2. Meta-analyzed hazard ratios of risk factors associated with KRT, CVD and Death in the 19 cohorts

<table>
<thead>
<tr>
<th>Variables</th>
<th>Hazard ratio (95% CI)</th>
<th>KRT</th>
<th>CVD</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, 10 years</td>
<td>0.74 (0.69, 0.80)</td>
<td>1.30 (1.18, 1.44)</td>
<td>1.68 (1.61, 1.76)</td>
<td></td>
</tr>
<tr>
<td>Male sex</td>
<td>1.44 (1.34, 1.55)</td>
<td>1.14 (1.08, 1.21)</td>
<td>1.14 (1.08, 1.21)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>1.49 (1.29, 1.72)</td>
<td>1.02 (0.85, 1.23)</td>
<td>0.93 (0.82, 1.05)</td>
<td></td>
</tr>
<tr>
<td>History of CVD</td>
<td>0.91 (0.82, 1.02)</td>
<td>2.57 (2.27, 2.92)</td>
<td>1.27 (1.18, 1.36)</td>
<td></td>
</tr>
<tr>
<td>Smoker</td>
<td>1.02 (0.93, 1.11)</td>
<td>1.07 (0.99, 1.16)</td>
<td>1.37 (1.25, 1.50)</td>
<td></td>
</tr>
<tr>
<td>SBP&lt;140, 20mmHg</td>
<td>1.25 (1.10, 1.41)</td>
<td>0.90 (0.85, 0.95)</td>
<td>0.84 (0.81, 0.88)</td>
<td></td>
</tr>
<tr>
<td>SBP≥140, 20mmHg</td>
<td>1.17 (1.10, 1.24)</td>
<td>1.09 (1.04, 1.15)</td>
<td>1.02 (0.97, 1.07)</td>
<td></td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>1.30 (1.14, 1.47)</td>
<td>1.41 (1.30, 1.53)</td>
<td>1.12 (1.03, 1.22)</td>
<td></td>
</tr>
<tr>
<td>eGFR, -5 ml/min/1.73m²</td>
<td>1.73 (1.58, 1.90)</td>
<td>1.07 (1.05, 1.10)</td>
<td>1.12 (1.09, 1.15)</td>
<td></td>
</tr>
<tr>
<td>ACR, 2-fold increase</td>
<td>1.26 (1.21, 1.31)</td>
<td>1.05 (1.04, 1.07)</td>
<td>1.04 (1.02, 1.05)</td>
<td></td>
</tr>
<tr>
<td>Time-varying CVD</td>
<td>2.28 (2.02, 2.57)</td>
<td>2.87 (2.57, 3.20)</td>
<td>2.07 (1.80, 2.38)</td>
<td></td>
</tr>
<tr>
<td>Time-varying KRT</td>
<td></td>
<td>1.39 (1.15, 1.68)</td>
<td>207 (1.80, 2.38)</td>
<td></td>
</tr>
</tbody>
</table>

All values are expressed as pooled Hazard ratios with 95% confidence intervals. The HR for age is expressed for every 10 year increase in age at baseline, the HR for albumin to creatinine ratio (ACR) is expressed per two-fold increase in mg/g, the HR for estimated glomerular filtration rate (eGFR) is expressed for every 5 ml/min/1.73m² decrease, the HR for systolic blood pressure (SBP) is expressed as per 20 mmHg increase in blood pressure above and below 140 mmHg. Other abbreviations include cardiovascular disease (CVD), Kidney failure treated with kidney replacement therapy (KRT). The three cohorts that did not include persons with and without diabetes mellitus did not contribute to the meta-analyzed hazard ratio for Diabetes Mellitus.
Figure 1. Variation of the age coefficient for KRT (A), CVD (B), and Death (C) across 19 cohorts in the main analysis

The individual and average hazard ratios and 95% confidence interval from the adjusted cox regression model and expressed per 10 year higher age. Weights are from the random effects analysis. Heterogeneity between cohorts is assessed by $I^2$. Kidney failure treated with kidney replacement therapy (KRT), cardiovascular disease (CVD).
The individual and average hazard ratios and 95% confidence interval from the adjusted cox regression model. Weights are from the random effects analysis. Heterogeneity between cohorts is assessed by $I^2$. Kidney failure treated with kidney replacement therapy (KRT), cardiovascular disease (CVD).
Figure 3. Risk Factor Modification by Age for KRT (A), CVD (B), Death (C)

All values are expressed as hazard ratios (HR) and 95% confidence intervals unless otherwise indicated. The HR for age is expressed for every 10 year increase in age at baseline, the HR for albumin to creatinine ratio (ACR) is expressed per 2-fold increase in mg/g, the HR for estimated glomerular filtration rate (eGFR) is expressed for every 5 ml/min/1.73m^2 decrease, the HR for systolic blood pressure (SBP) is expressed as per 20 mmHg increase in blood pressure above and below 140 mmHg. Albumin creatinine ratio (ACR) in mg/g, estimated glomerular filtration rate (eGFR), Systolic blood pressure (SBP) in mmHg, cardiovascular disease (CVD), History of CVD (HxCVD), Kidney failure treated with kidney replacement therapy (KRT). InCVD is a CVD event after study inclusion, inKRT is incident KRT.