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## Risks of Adverse Events in Advanced CKD: The Chronic Renal Insufficiency Cohort (CRIC) Study

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### Abstract

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\*A list of the CRIC Study Investigators appears in the Acknowledgements.

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**Background**—People with advanced chronic kidney disease (CKD) are at risk for the development of end-stage renal disease (ESRD), but also many other adverse outcomes, including cardiovascular disease (CVD) events and death. Determination of risk factors that explain the variability in prognosis and timing of these adverse outcomes can aid patient counseling and medical decision-making.

**Study Design**—Prospective research cohort.

**Setting & Participants**—1,798 participants with eGFR <30 ml/min/1.73 m<sup>2</sup> in the CRIC Study were followed up for a median of 5.5 years.

**Predictors**—Age, race, sex, eGFR, proteinuria, diabetes mellitus, body mass index, ejection fraction, systolic blood pressure, history of cardiovascular disease, and history.

**Outcomes**—ESRD, CVD (congestive heart failure, stroke, myocardial infarction, peripheral artery disease), and death.

**Results**—Baseline age of the cohort was 60 years; 46% were women, and 46% were African American. While 52.3% of participants progressed to ESRD during follow-up, the path by which this occurred was variable. For example, the predicted 1-year probabilities for a hypothetical 60-year-old white woman with eGFR 30 ml/min/1.73 m<sup>2</sup>, 1.8 g/d of proteinuria, and no diabetes or CVD (risk characteristics similar to the average participant), were 3.3%, 4.1%, and 0.3%, for first developing CVD, ESRD, and death, respectively. For a 40-year-old African-American man with similar characteristics but higher systolic blood pressure, the corresponding 1-year probabilities were 2.4%, 13.2%, and 0.1%. For all participants, the development of ESRD or CVD increased the risk of subsequent mortality, with no differences by patient race or body-mass index.

**Limitations**—The CRIC population was specifically recruited for kidney disease, and the vast majority had seen a nephrologist.

**Conclusions**—The prognosis and timing of adverse outcomes in CKD varies by patient characteristics. These results may help guide the development of personalized approaches for managing patients with advanced CKD.

### Index words

Chronic kidney disease (CKD); CKD progression; disease trajectory; end-stage renal disease (ESRD); cardiovascular disease (CVD); mortality; pre-ESRD death; incident ESRD; adverse event; advanced CKD; risk factor; prognosis; kidney function decline; CRIC (Chronic Renal Insufficiency Cohort)

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Patients with chronic kidney disease (CKD) are at high risk for adverse outcomes, including cardiovascular disease (CVD) events, end-stage renal disease (ESRD), and death.<sup>1–3</sup> More advanced kidney disease, as indicated by lower glomerular filtration rate (GFR) and/or higher albuminuria, generally portends higher risk.<sup>4</sup> However, the absolute risks of CVD, ESRD, and death in advanced CKD are ill-defined. Improved knowledge of the risk factors for and relative timing of individual adverse outcomes in patients with advanced CKD could enhance patient counseling and medical decision making. For example, arteriovenous fistula placement might be deferred in a person with a low likelihood of progression to ESRD or a high risk of pre-ESRD death.

Results of previous studies conflict regarding the absolute risk of adverse outcomes in advanced CKD: a clinical trial reported a preponderance of ESRD, whereas health system data demonstrated higher risk of pre-ESRD death.<sup>5-7</sup> These discrepancies may relate to differences in nephrology care or differences in patient characteristics between the study populations, such as age or racial distribution or the presence of heart failure, diabetes, or the level of proteinuria. For example, a higher representation of patients with significant proteinuria might result in higher rates of ESRD. Whether individual patients can be meaningfully risk-stratified for the short-term risks of ESRD, CVD, and death on the basis of demographic or health characteristics is unknown.

Using participants in the Chronic Renal Insufficiency Cohort (CRIC) with advanced CKD (defined as eGFR <30 ml/min/1.73 m<sup>2</sup>), the aim of this study was to evaluate the frequency, timing, and risk associations of adverse outcomes by baseline patient characteristics. We hypothesized that pre-ESRD outcomes of CVD and death would be common, and that the frequency and sequence of adverse events over a 1-year time horizon would vary by baseline patient characteristics. We also hypothesized that the development of ESRD or CVD would increase the risk for subsequent mortality.

## METHODS

### Study Population

Participants for the present study were selected from the CRIC study, a prospective cohort of people with CKD, which has been previously described.<sup>8</sup> In brief, eligibility for initial study enrollment into CRIC was determined by eGFR based on the best available estimating equation at the time, the MDRD (Modification of Diet in Renal Disease) Study equation: eGFR 20–70 ml/min/1.73 m<sup>2</sup> for participants aged 21–44 years, 20–60 ml/min/1.73 m<sup>2</sup> for participants aged 45–64 years, and 20–50 ml/min/1.73 m<sup>2</sup> for participants aged 65–74 years.<sup>8-10</sup> Participants were excluded for polycystic kidney disease, multiple myeloma, active glomerulonephritis, a previous dialysis requirement, recent immunotherapy for kidney disease and/or vasculitis, New York Heart Association class III or IV heart failure, and cirrhosis since these patients were expected to have very different natural history of disease than the target population.<sup>8</sup> Enrollment occurred at seven US clinical centers (13 enrollment sites in Philadelphia, Pennsylvania; Baltimore, Maryland (2 sites); Cleveland, Ohio (3 sites); Ann Arbor and Detroit, Michigan (2 sites); Chicago, Illinois; New Orleans, Louisiana; and San Francisco and Oakland, California) during May 2003-August 2008. A total of 3,939 participants completed a baseline visit; participants have since been followed up every 6 months by telephone contact and annually with clinical visits. Laboratory tests of kidney function (creatinine and cystatin C) were performed at each clinical visit. For the present study, only those participants with eGFR <30 ml/min/1.73 m<sup>2</sup> at baseline or observed during follow-up through the middle of 2013 were included (N=1,798). The threshold of eGFR 30 ml/min/1.73 m<sup>2</sup> (determined using the CRIC-specific equation for creatinine and cystatin C, which most accurately reflects measured GFR in the CRIC cohort) was selected based on guidelines for the definition of “severely decreased” kidney function (CKD stage G4).<sup>11-13</sup> The study protocol was approved by the institutional review boards of all participating

centers (protocol NA\_00044034 at Johns Hopkins University). All participants provided written informed consent.

## Outcomes

We defined three outcomes of interest: first CVD event after eGFR <30 ml/min/1.73 m<sup>2</sup>, ESRD, and death (through mid-2013). The CVD events included congestive heart failure, ischemic or hemorrhagic stroke (probable or definite), myocardial infarction (probable or definite), and peripheral artery disease (occlusive artery disease resulting in amputation or revascularization procedures), and were analyzed as a composite variable. Events were ascertained through alternating telephone and in-person contact every six months, through which participants were questioned about intervening hospitalizations, procedures, and the development of ESRD or CVD events. In addition, diagnostic codes from all hospitalizations were obtained, and those with codes indicating cardiovascular events were flagged for physician adjudication of the medical record. Criteria for definite and probable congestive heart failure, stroke, myocardial infarction, and peripheral artery disease have been published previously.<sup>14</sup> Incident ESRD was determined through self-report, review of medical records, and linkage to the US Renal Data System. Deaths were ascertained through contact with next of kin, review of medical records and death certificates, and search of the Social Security Death vital status and death certificate files, where possible.

## Covariates

Serum creatinine was initially calibrated to the Cleveland Clinic Research Laboratory (Cleveland, OH) and then to isotope-dilution mass spectrometry-traceable standards; cystatin C was measured using a Siemens BNII Machine and internally calibrated. Both biomarkers were converted to eGFR using a CRIC-specific equation.<sup>12,13</sup> Proteinuria was quantified as protein-creatinine ratio from 24-hour urine collections or, if that was not available, from random spot urine protein-creatinine ratio (n=166). If spot urine protein-creatinine ratio was also missing, proteinuria was imputed using the spot urine albumin-creatinine ratio (n=7).<sup>15,16</sup> Race/ethnicity, age, current smoking, and medication use were self-reported. Diabetes was assessed as any diabetes medication use, fasting plasma glucose level ≥126 mg/dL, or nonfasting plasma glucose level ≥200 mg/dL. Systolic blood pressure was measured at the clinic visit after 5 minutes of rest; the average of three measurements was taken.<sup>17</sup> Weight and height were measured twice and averaged before calculating body mass index (BMI). History of CVD was defined as self-report of coronary artery disease (myocardial infarction, angina, prior coronary revascularization), congestive heart failure, stroke or transient ischemic attack, or peripheral artery disease (claudication, amputation, or angioplasty). Ejection fraction was estimated using systolic and diastolic volumes of the left ventricle by the single-plane Simpson's rule method from echocardiography performed at each center in accordance with a centralized imaging protocol. Echocardiograms were then read by a single trained sonographer at the University of Pennsylvania. Echocardiograms were performed per CRIC protocol at year 1, year 4, eGFR <20 ml/min/1.73 m<sup>2</sup>, and after ESRD.<sup>18</sup> If an echocardiogram was not performed at the first visit in which a participant developed eGFR <30 ml/min/1.73 m<sup>2</sup>, ejection fraction from the most recent antecedent echocardiogram was used. Nephrology care was ascertained by the following question: "Have you ever seen a nephrologist or a kidney doctor?"

## Statistical Methods

Participant characteristics at the first visit in which eGFR  $<30$  ml/min/1.73 m<sup>2</sup> was observed were presented for the overall study population and according to the first outcome of interest (CVD event, ESRD, or death). Participants who withdrew before the end of the study (n=102) and those who survived to the end of follow-up without the development of an event of interest (n=384) were described separately. The cumulative incidence of first events was determined using competing risk regression using the user-written Stata command *stcompadj*. Results were adjusted to eGFR 30 ml/min/1.73 m<sup>2</sup> to account for differences in the first observed eGFR below the threshold of 30 ml/min/1.73 m<sup>2</sup>. Subsequent analyses of cumulative incidence of ESRD and death after CVD, and CVD and death after ESRD were not adjusted for eGFR and were performed using competing risk regression with the Stata command *stcompet*. The incidence of death after ESRD and CVD was estimated using standard Kaplan-Meier techniques since there was no competing event.

The adjusted associations between baseline characteristics and the first event of interest were assessed as sub-hazard ratios (HRs) from competing risk models, with the other two events treated as a composite competing event to the event of interest.<sup>19</sup> For comparison purposes, we also listed cause-specific HRs from Cox regression, censoring at the incidence of competing events (Table S1, available as online supplementary material). The difference between cause-specific HRs and sub-HRs for a particular risk factor will depend both on the risk factor's association with the competing event as well as the frequency of the competing event. Because cause-specific HRs do not directly correspond to cumulative incidence, they are less useful in the setting of an absolute risk prediction model. On the other hand, they may show stronger risk factor associations when a risk factor affects both the outcome of interest and the competing event.<sup>20–22</sup> For this study, risk factors were selected *a priori* from those previously reported to be associated with CVD, ESRD, and death in the literature.<sup>3,17,23–25</sup> Serum albumin was selected *a priori* for evaluation as a risk factor, but it was not significant in multivariable analysis and thus excluded from the final model. The BMI was evaluated as a categorical variable (BMI  $<25$ , 25–29.9, 30–35, and  $>35$  kg/m<sup>2</sup>) according to the National Heart, Lung, and Blood Institute's classification of normal weight, overweight, grade 1 obesity, and grade 2–3 obesity.<sup>26</sup> There were very few people with BMI  $<18.5$  kg/m<sup>2</sup>, hence they were included in the “normal weight” category. As per previous studies,<sup>4</sup> proteinuria was log-transformed and scaled to the natural log of 2, such that the coefficient for this variable represents the increase in risk associated with a doubling of urine protein levels. For the variables included in the ESRD as a first event competing risk model (Table 2), we evaluated the association with continuous eGFR decline (in ml/min/1.73 m<sup>2</sup> per year) using mixed models with the same covariates.

The probability (absolute risk) of having developed a first event of ESRD, CVD, and death at 1-year was estimated for several hypothetical patient scenarios using the baseline subhazard and sub-HRs estimated in the competing risk models. Because statistical software for multivariable competing risk regression can only estimate cumulative incidence in the setting of two competing events, the sum of the three probabilities was scaled to the 1-year probability of having any one of those events (i.e., a composite variable of ESRD, CVD, and

death) estimated using Cox regression with the same covariates. Scenarios were chosen to reflect common profiles of patients seen in nephrology clinical practice.

The adjusted associations of patient characteristics and all mortality events (i.e., both pre- and post-ESRD and CVD) were assessed using Cox proportional hazards with the same covariates as well as two time-varying variables indicating: (1) onset of ESRD, and (2) CVD event after eGFR  $30 \text{ ml/min/1.73 m}^2$ . *A priori*, we were interested in whether mortality risk associations between age, race, BMI and diabetes changed pre- and post-ESRD; this was assessed by including a product term for each of risk factor with time-varying ESRD. A positive finding would suggest that risk-relationships differed in the pre- and post-ESRD period (e.g., the often-cited “obesity paradox” suggests that higher BMI is a risk factor for death in CKD but protective in ESRD). We also assessed the interaction between baseline eGFR and proteinuria and ESRD, expecting the kidney function measurements to diminish in importance after the development of ESRD. All analyses were performed using Stata/MP 13.1 (College Station, TX).

## RESULTS

### Baseline Characteristics of Participants

There were 1,798 participants who enrolled in CRIC with eGFR  $<30 \text{ ml/min/1.73 m}^2$  (N=807) or who developed eGFR  $<30 \text{ ml/min/1.73 m}^2$  during the course of follow-up (N=991). At the first qualifying study visit (i.e., the first visit in which a participant had an observed eGFR  $<30 \text{ ml/min/1.73 m}^2$ ), mean age was 59.9 years and mean time since CRIC study enrollment was 1.6 years. Of these study participants, 45.8% were women, 46.2% were black, and 16.7% identified as Hispanic ethnicity (either black or white). The vast majority (90%) were under the care of a nephrologist. The average eGFR by the CRIC formula<sup>13</sup> was  $25 \text{ ml/min/1.73 m}^2$ , and mean proteinuria was 1.8 g/day. Nearly all had hypertension (95.0%), and 61.6% had diabetes mellitus. A minority of participants (18%) had an ejection fraction  $<45\%$ .

When classified by first event (CVD event, ESRD, or death), the 678 (37.7%) participants who first developed ESRD were younger, with higher blood pressure and proteinuria (Table 1). In contrast, the 455 (25.3%) participants who had a pre-ESRD CVD event were older, with higher BMI; they were also on more anti-hypertensive medications, had higher prevalence of CVD (particularly a history of myocardial infarction or coronary revascularization), and had lower ejection fraction on echocardiogram. The 162 (9.0%) participants who had death as a first event had the oldest mean age and were much more likely to be smokers. The 384 (21.4%) participants who survived to the end of follow-up event-free were also older (average age, 63.1 years), with lower systolic blood pressure (mean, 120 mmHg) and proteinuria (median, 0.2 g/day) than the other participants.

### Risk of ESRD, CVD, and Death as First Events in Participants With eGFR $<30 \text{ ml/min/1.73 m}^2$

Median time from the qualifying CRIC study visit (i.e., when eGFR was first observed to be  $<30 \text{ ml/min/1.73 m}^2$ ) to death or end of follow-up was 5.5 (interquartile range [IQR], 3.2–

7.3) years. Median time from the qualifying CRIC study visit to first event (CVD event, ESRD, death, or end-of-follow-up) was 2.6 (IQR, 1.1–4.7) years. At approximately 1.8 years of follow-up, ESRD surpassed CVD events as the most common first outcome in the overall population (Figure 1). This was similar in the 807 CRIC participants who enrolled with an eGFR <30 ml/min/1.73 m<sup>2</sup> as well as the 991 participants who developed eGFR <30 ml/min/1.73 m<sup>2</sup> during follow-up (Figure S1).

Patient characteristics at eGFR 30 ml/min/1.73 m<sup>2</sup> were significantly associated with first outcomes (Table 2). Risk factors for pre-ESRD CVD events included older age, higher systolic blood pressure, the presence of diabetes and pre-existing CVD, and lower ventricular ejection fraction. Risk factors for death as a first event included older age, black race, Hispanic ethnicity, and current smoking. In contrast, risk factors for first developing ESRD included younger age, male sex, lower eGFR, higher proteinuria, and the absence of prior CVD.

Further investigation of risk factors associated with eGFR decline confirmed much of the associations seen with first ESRD: there was a faster yearly decline with younger age (0.40 [95% CI, 0.21–0.58] ml/min/1.73 m<sup>2</sup> per year faster per 10 years younger), higher proteinuria (0.66 [95% CI, 0.57–0.75] ml/min/1.73 m<sup>2</sup> per year faster per two-fold higher), lower baseline eGFR (0.63 [95% CI, 0.37–0.88] ml/min/1.73 m<sup>2</sup> per year faster per 5 ml/min/1.73 m<sup>2</sup> lower), and higher systolic blood pressure (0.28 [95% CI, 0.19–0.37] ml/min/1.73 m<sup>2</sup> per year faster per 10 mmHg higher). In contrast, male sex and prior CVD were not associated with faster eGFR decline.

### 1-Year Probability of Events for Various Scenarios

Combining the sub-HRs and baseline subhazard of first events, we estimated the 1-year probability of first events for hypothetical scenarios. For a patient scenario close to the study mean (60-year-old white woman with eGFR of 30 ml/min/1.73 m<sup>2</sup>, proteinuria of 1.8 g/day, systolic blood pressure of 130 mmHg, no diabetes mellitus or history of CVD, an ejection fraction of 50%, BMI of 30 kg/m<sup>2</sup>, and no current smoking), the 1-year probability of remaining CVD-, ESRD-, and death-free was 92.3% (Table S2). The predicted probability of developing a first CVD event was similar to the 1-year predicted probability of first developing ESRD (3.3% versus 4.1%), and the probability of death was 0.3%. In contrast, a 40-year-old black man with similar risk factors but a systolic blood pressure of 150 mmHg had a predicted probability of remaining event-free of 84.3% at 1-year, with a much greater risk of first developing ESRD compared to a first CVD event (13.2% versus 2.4%).

### Subsequent Risks After First Events

After the initial adverse event, the incidence of subsequent adverse events increased. For example, both ESRD and pre-ESRD death after a first CVD event were high (Figure 2A). Four years after a first CVD event, over 50% of the participants had developed ESRD, and 20% had died prior to ESRD. Four years after ESRD as first event, nearly 40% of participants had developed either CVD or pre-CVD death (Figure 2B). Among those who had had a CVD event and then ESRD, the risk of a subsequent CVD event was higher still (Figure S2). Death after a participant had both ESRD and a CVD event was extremely high,



with 50% mortality by 6 years (Figure 2C). In analyses adjusting for baseline covariates, both the development of ESRD (HR, 3.68; 95% CI, 2.22–6.09) and CVD (HR, 2.43; 95% CI, 1.93–3.06) were significantly associated with higher risk of mortality (Table 3). Of note, there were no significant interactions of ESRD with age, sex, race, or BMI for mortality risk, suggesting that risk relationships between each characteristic and death were similar pre- and post-ESRD. There was a significant interaction between baseline eGFR and time-varying ESRD as well as diabetes and time-varying ESRD, with both measures having weaker, non-statistically significant associations with death in the post-ESRD period. The coefficient for proteinuria declined after ESRD onset, but the interaction was not statistically significant ( $p=0.5$ ).

## DISCUSSION

This study of 1,798 heterogeneous participants with advanced CKD demonstrates the variability in prognosis and timing of adverse outcomes. While the majority of participants progressed to ESRD during follow-up, the path by which this occurred differed by baseline characteristics. Older patients were more likely to develop CVD prior to ESRD; younger patients tended to have faster declines in eGFR without intervening CVD events. Once participants developed ESRD or CVD, the risk of subsequent adverse outcomes increased. For example, the risk of mortality was approximately 2-fold higher after an ESRD or CVD event. These results, and particularly their potential application to individual patients, can help guide patient counseling and therapy.

Knowledge of the range and sequence of adverse outcomes in CKD can inform patient care and counseling in several ways. Improving physician cognizance of the absolute risks not only of ESRD but also CVD and death may increase vigilance in prescribing traditionally cardiovascular-based therapies such as statins, aspirin, and smoking cessation.<sup>27</sup> Indeed, the high degree of overlap between ESRD and CVD – the risk of CVD was extremely high after ESRD, as was the risk of ESRD after CVD – supports assertions that CKD be considered a CVD risk equivalent.<sup>28</sup> Our study adds to the existing literature by quantifying the risk and sequence of individual adverse outcomes, as well as risk factor associations for their development.

Similar to the results of the African American Study of Kidney Disease and Hypertension (AASK),<sup>5</sup> the absolute risks of ESRD and CVD were higher than the risk of death in CRIC participants. Corresponding rates of ESRD and death have been shown in the MDRD Study as well as the Italian Target Blood Pressure Levels in CKD (TABLE-CKD) study.<sup>29,30</sup> Interestingly, studies in health care utilization datasets have reported opposite findings, with death being the most common first outcome in advanced CKD.<sup>6,7</sup> Heterogeneity in absolute risk of ESRD has also been reported by the CKD Prognosis Consortium, where it appeared to track with world region.<sup>31</sup> Our results capture adverse outcomes among volunteers in a longitudinal cohort study, which tend to represent patients who are relatively healthy, but suggest that some of these differences may relate to underlying patient characteristics, particularly the age, racial makeup, and prevalence of diabetes and CVD in the population. Others have hypothesized that referral to nephrology (which may vary widely by region) might explain differences.<sup>7</sup> In CRIC, the vast majority of participants had seen a

nephrologist at least once, but we have no information on the intensity of nephrology involvement in individual patient care. We note that CRIC participants have, on average, excellent blood pressure control with a mean systolic blood pressure of 130 mmHg; over 70% are receiving angiotensin-converting enzyme inhibitors or angiotensin receptor blockers.

Results from this study suggest that the best prognosis in advanced CKD is among participants with low levels of proteinuria and well-controlled blood pressure, with much of the risk relating to higher rates of CVD and ESRD. These findings are consistent with the long-term follow-up from historical clinical trials. For example, AASK participants with lower levels of proteinuria had slower progression of CKD. Among AASK participants with higher proteinuria, more intensive treatment of blood pressure resulted in slower progression of CKD, consistent with the MDRD Study, which showed a lower risk of kidney failure among those randomized to the lower blood pressure treatment arm.<sup>32,33</sup> They are also consistent with recent results from the Systolic Blood Pressure Intervention Trial (SPRINT), where intensive blood pressure control reduced all-cause mortality and a composite cardiovascular outcome in those with and without CKD (note that the mean eGFRs were 81 and 48 ml/min/1.73m<sup>2</sup> in the two groups, respectively).<sup>34</sup> Among SPRINT participants with CKD, there was a trend toward a lesser number of ESRD events in the intensive treatment arm (6 versus 10 events), although this difference was not statistically significant, likely due to a reduced sample size. Palit and colleagues also reported a strong relationship between systolic and diastolic blood pressure and the development of ESRD among patients with eGFR  $\geq$  30 ml/min/1.73 m<sup>2</sup>, with pulse pressure being a strong predictor of cardiovascular events.<sup>35</sup> Our data similarly suggests that high blood pressure is a risk factor, particularly for the development of CVD.

An interesting aspect of our study is the ability to follow participants from the development of eGFR  $<$ 30 ml/min/1.73 m<sup>2</sup> through death or end-of-follow-up, allowing evaluation of both pre- and post-ESRD risk associations. A traditional school of thought posits that blacks exhibit better survival on dialysis compared to whites, which has been suggested as a partial explanation for disparities in transplantation rates.<sup>36</sup> Similarly, higher BMI has been proposed as a protective factor for patients on dialysis.<sup>37</sup> However, these observations are limited in that they stem from a prevalent dialysis population, which by definition requires survival to dialysis. Our study adds to this literature by evaluating the risk of death in the pre- and post-dialysis periods. With the caveat that the population comprised volunteers in a research cohort, we found no difference in mortality risk between the pre- or post-ESRD period by race or BMI. The only risk factors that changed in importance after the development of ESRD were baseline eGFR and diabetes mellitus, both of which became non-significant after ESRD.

This study has strengths and limitations. Kidney function was estimated using a CRIC-specific equation that incorporates both creatinine and cystatin C, and thus likely closely corresponds to the measured GFR.<sup>38</sup> On the other hand, cystatin C and a study-specific equation are not routinely used in clinical practice, which may limit the generalizability of the data. Creatinine, cystatin C, and proteinuria were assessed according to research protocol, and presumably reflect values when a participant was in steady state rather than

acute illness. Participants were followed up closely for intervening events, and CVD and ESRD events were adjudicated by expert consensus. Few studies have echocardiogram data in advanced CKD, and ejection fraction proved to be an important risk factor.<sup>18</sup> On the contrary, the CRIC population was specifically recruited for kidney disease, and the vast majority had previously seen a nephrologist. This differs from the “real-world” setting, where many patients with advanced CKD have severe comorbidities, such as cancer or advanced heart failure, and are not necessarily receiving nephrology care. Conversely, the CRIC population may be fairly representative of a patient population seen in a nephrology practice in the United States. Additional work and validation of outcome prediction in patients with CKD may help inform delivery of “personalized medicine”; however, we acknowledge that the precision of such models will depend on the amount of variation explained by known covariates, and that such models may be much more accurate in the short-term.<sup>15,31,39</sup>

In summary, we report the clinical outcomes among CRIC participants with eGFR <30 ml/min/1.73 m<sup>2</sup>, demonstrating that while ESRD is the most common first event over the long-term, the risks of CVD and death are interrelated, with each adverse outcome increasing the risk for subsequent events. The work represents a novel approach to outcomes assessment in CKD as it focuses on advanced CKD, considering multiple end points at once, with evaluation not only of the occurrence of events but also the sequence. In clinical practice, an integrated approach to preventing CVD, ESRD, and death—potentially through the reduction of blood pressure and proteinuria—may provide optimal care in patients with advanced CKD. Additional work to individualize outcome prediction may inform a personalized approach that could help guide patient counseling and medical decision-making.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

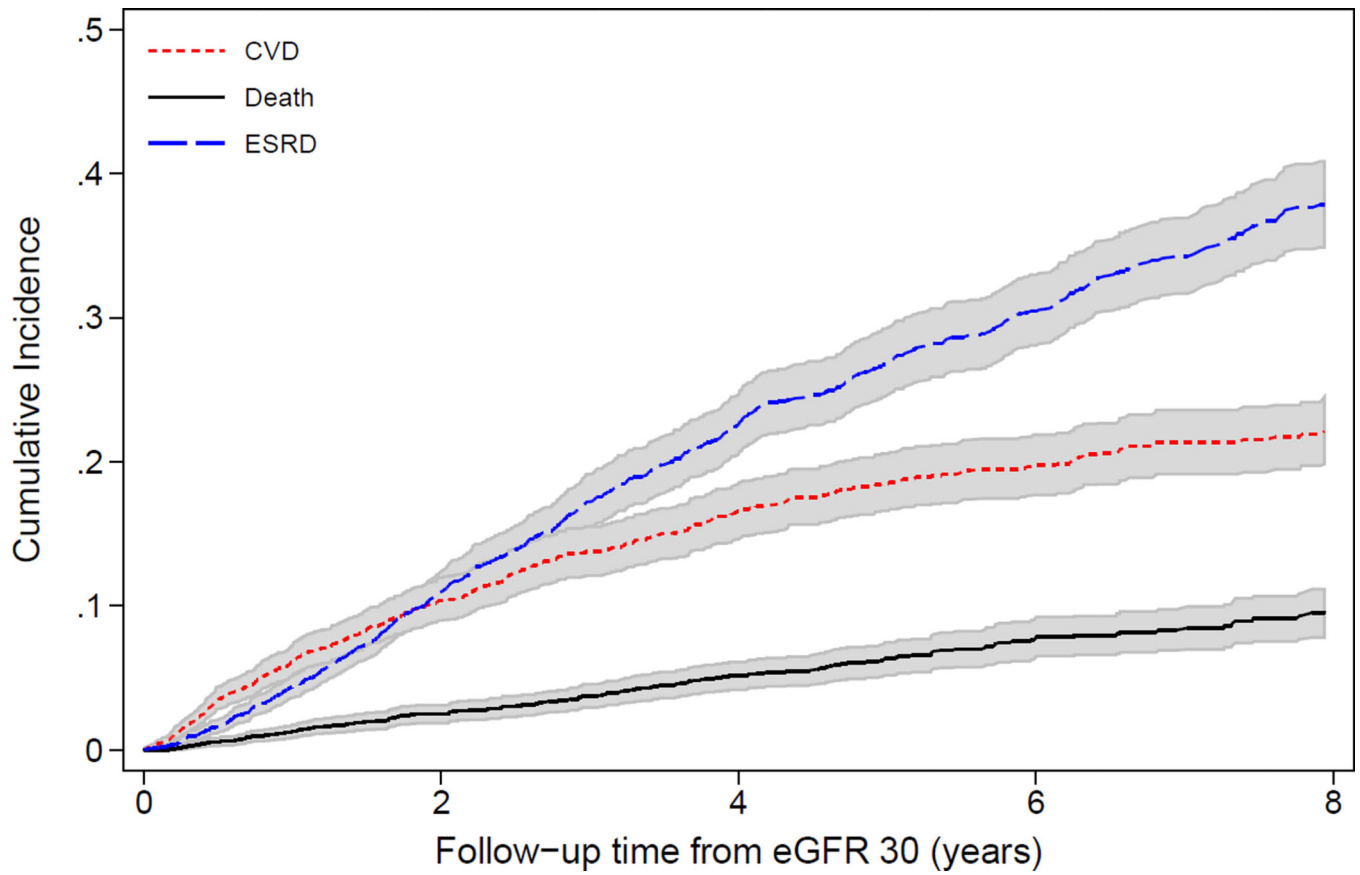
The CRIC Study Investigators are Harold I. Feldman, MD, MSCE, Alan S. Go, MD, John W. Kusek, PhD, James P. Lash, MD, Akinlolu Ojo, MD PhD, Mahboob Rahman, MD, and Raymond R. Townsend, MD.

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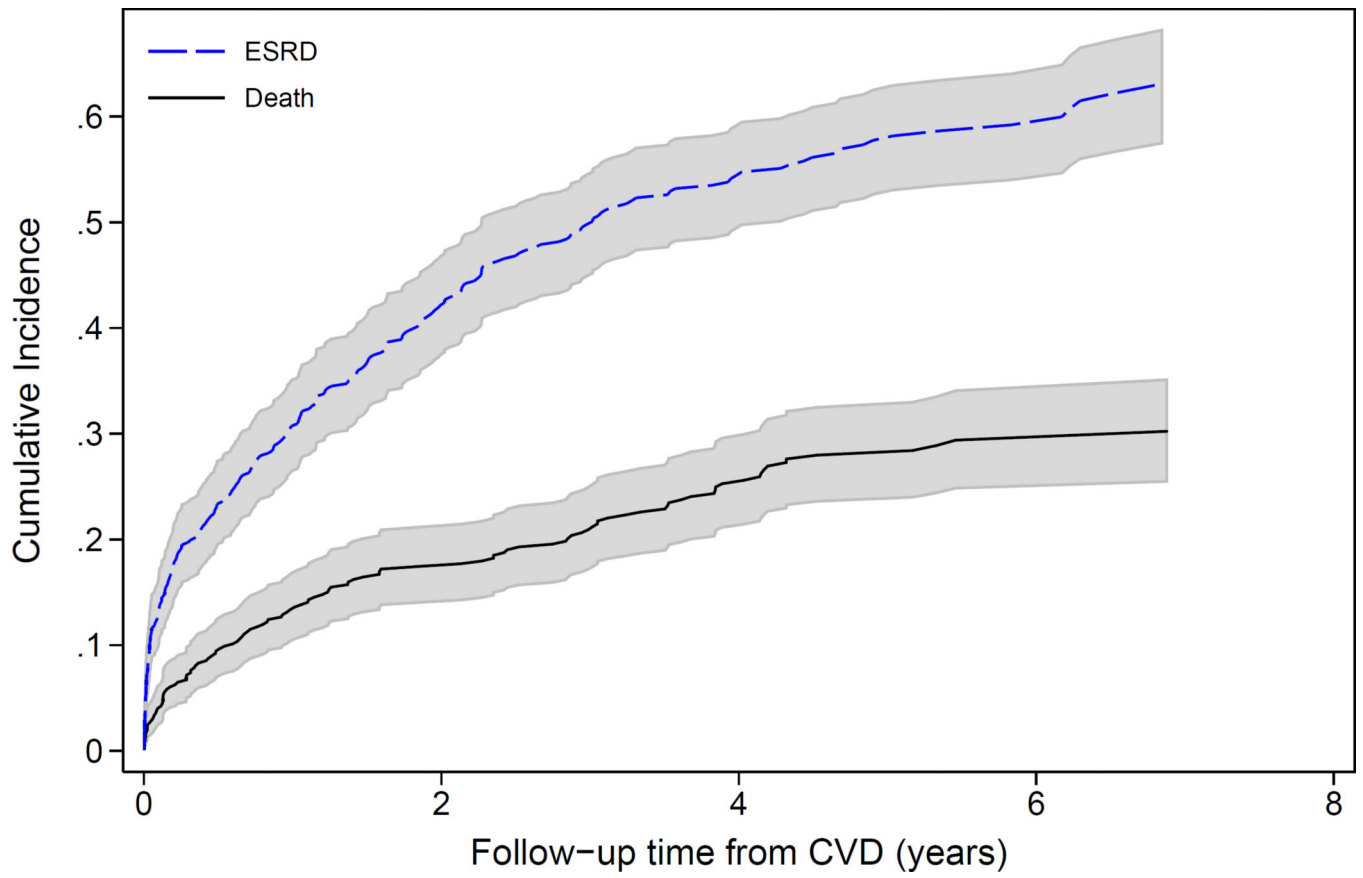
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**Figure 1.** Cumulative incidence of first events (ESRD, CVD, or death) over time among CRIC study participants from eGFR 30 ml/min/1.73 m<sup>2</sup> (N=1798).

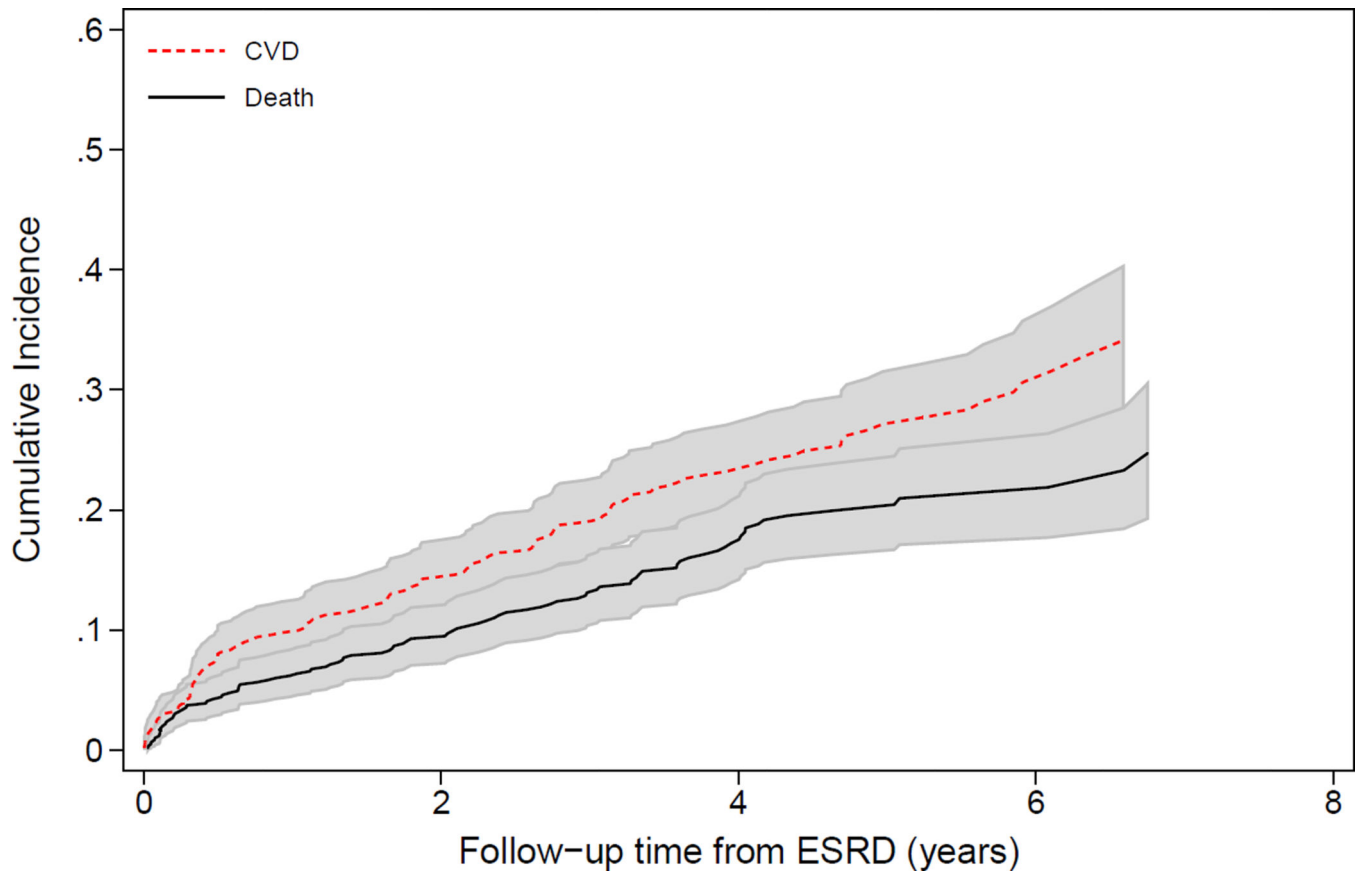


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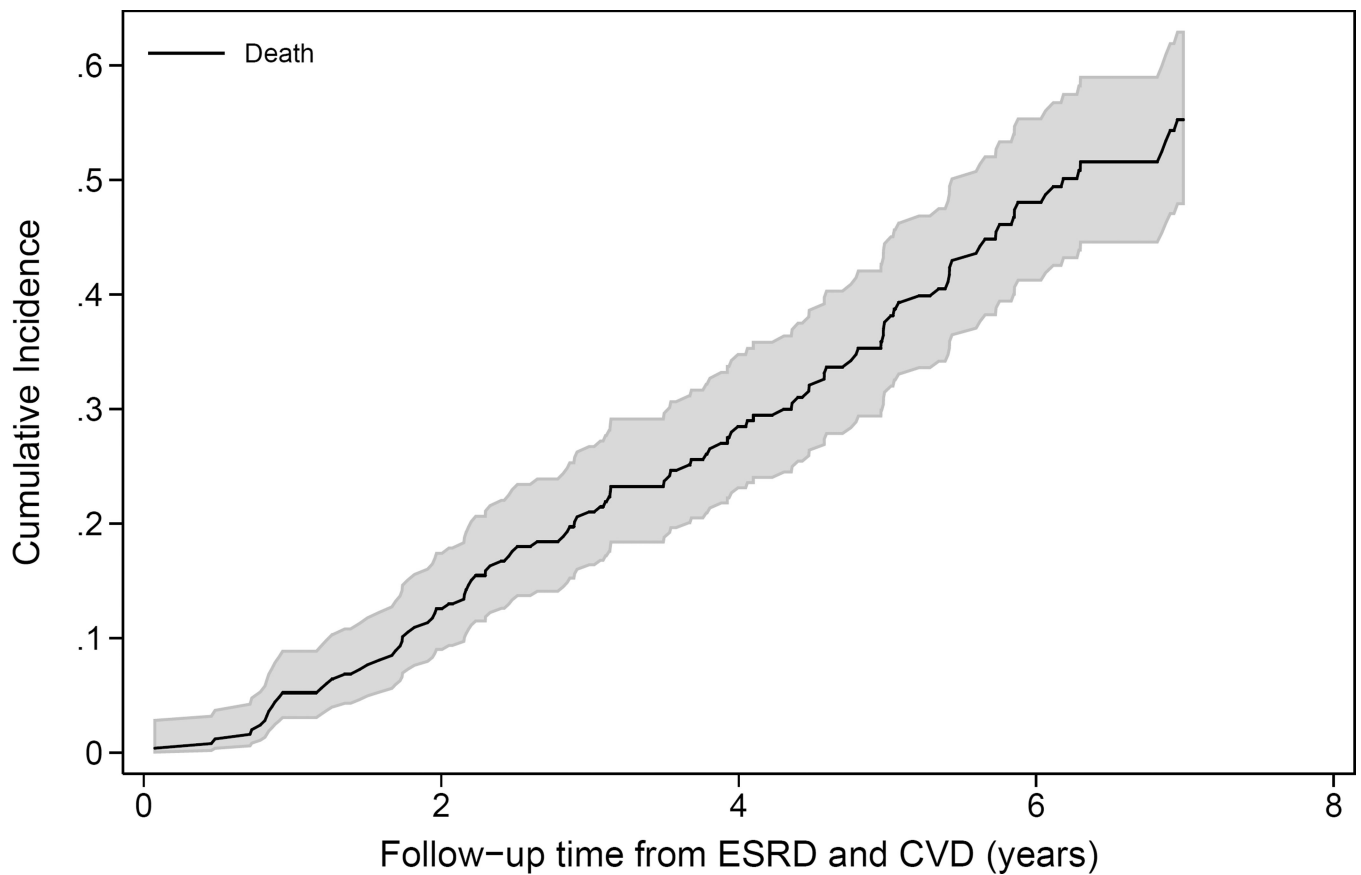
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**Figure 2.**

Cumulative incidence of subsequent events (ESRD, CVD, or death) over time among CRIC study participants. (A) reflects the incidence of ESRD and pre-ESRD death after the occurrence of a first CVD event (N=455); (B) reflects the occurrence of CVD or pre-CVD death after a first ESRD event (N=678); and (C) reflects the incidence of death after the occurrence of ESRD then CVD or CVD then ESRD, with time at risk accruing after the latter event (N=248).

**Table 1** Baseline characteristics of CRIC participants reaching eGFR <30 ml/min/1.73 m<sup>2</sup>, stratified by first outcome

	Overall (N=1,798)	Withdrawn (n=119 [6.6%])	Event-Free (n=384 [21.4%])	CVD Event (n=455 [25.3%])	ESRD Event (n=678 [37.7%])	Death Event (n=162 [9.0%])
Age, y	59.9 (11.3)	58.6 (12.5)	63.1 (10.2)	62.2 (9.3)	55.8 (12.1)	63.9 (8.3)
Female sex	45.8	51.3	52.3	44.6	42.2	44.4
Race						
White	41.0	41.2	50.5	39.6	37.5	37.7
Black	46.2	46.2	36.7	50.3	46.8	54.3
Other	12.8	12.6	12.8	10.1	15.8	8.0
Hispanic ethnicity	16.7	16.0	15.9	12.3	20.8	14.8
High school graduate	72.5	78.2	76.6	70.5	72.4	64.2
Under nephrology care	90.0	87.4	90.4	88.4	91.3	90.7
BMI, kg/m <sup>2</sup>	32.5 (8.1)	32.2 (7.2)	32.2(7.9)	33.9 (8.6)	31.9 (7.9)	32.6 (8.6)
BMI category						
<18.5 kg/m <sup>2</sup>	0.8	0	0.8	0.2	1	2.5
18.5–24.99 kg/m <sup>2</sup>	15.2	16	15.4	11.4	17.1	14.2
25–29.99 kg/m <sup>2</sup>	26.5	28.6	28.9	22.4	27	24.1
30–34.99 kg/m <sup>2</sup>	42.3	38.7	40.6	47	39.8	38.9
35 kg/m <sup>2</sup>	15.2	13.4	13	17.6	13.9	17.9
Systolic BP, mmHg	131.0 (23.8)	128.4 (20.4)	120.3 (20.6)	133.5 (23.2)	136.0 (23.6)	130.2 (27.0)
Diastolic BP, mmHg	69.1 (13.4)	69.1 (13.3)	65.3 (11.4)	67.3 (13.3)	73.1 (13.7)	66.9 (13.1)
Diabetes	61.6	53.8	49.2	74.3	61.5	61.1
History of CVD	45.8	27.7	40.9	67.7	34.8	54.9
History of CHF	16.3	9.2	9.1	32.1	9.7	21.6
History of MI/revasc	30.0	16	26.6	47.0	22.1	33.3
History of stroke	13.2	11.8	11.7	19.3	9.6	16.0
Current smoker	14.8	10.9	10.4	15.4	15.5	23.5
eGFR, mL/min/1.73 m <sup>2</sup>	24.9 (3.9)	25.5 (3.4)	26.5 (3.0)	24.7 (3.8)	23.9 (4.2)	24.7 (3.9)

	Overall (N=1,798)	Withdrew (n=119 [6.6%])	Event-Free (n=384 [21.4%])	CVD Event (n=455 [25.3%])	ESRD Event (n=678 [37.7%])	Death Event (n=162 [9.0%])
Proteinuria (g/d)	0.7 [0.1–2.2]	0.4 [0.1–1.5]	0.2 [0.1–0.5]	0.6 [0.1–2.3]	1.6 [0.6–3.5]	0.3 [0.1–1.3]
Serum albumin, g/dL	3.8 (0.5)	3.9 (0.5)	4.0 (0.4)	3.8 (0.5)	3.7 (0.5)	3.8 (0.5)
ACEi or ARB use	71.7	66.4	77.6	70.5	69.3	68.5
No. of BP drug classes	3.2 (1.5)	2.8 (1.4)	2.9 (1.4)	3.6 (1.3)	3.1 (1.5)	3.3 (1.3)
Statin use	64.1	48.7	65.9	69.0	61.9	61.1
Ejection Fraction, %	52.2 (9.3)	55.1 (8.5)	53.5 (7.9)	49.2 (11.5)	53.2 (7.7)	51.6 (10.9)
Ejection Fraction Category						
> 50%	71.3	58	70.6	53.2	69.5	56.2
46%–50%	10.7	6.7	10.2	10.3	9.6	7.4
36%–45%	12	5	10.7	13	11.1	7.4
35%	6	2.5	2.6	12.3	2.4	7.4

Note: Participant characteristics reflect values obtained from the first CRIC study visit in which eGFR <30 mL/min/1.73 m<sup>2</sup>. Values for categorical variables are given as percentages; values for continuous variables, as mean ± standard deviation or median [interquartile range]. All p-values for comparison <0.05 with the exception of ACEi/ARB use. All variables have complete data with the exception of BMI (n=1771), systolic and diastolic blood pressure (n=1794 and 1792, respectively), proteinuria (n=1580), medication use (n=1785), and ejection fraction (n=1605). Echocardiogram parameters were obtained at exams prior to the baseline visit for the majority of the participants (90%).

Abbreviations: BMI, body-mass index; BP, blood pressure; CRIC, Chronic Renal Insufficiency Cohort; CVD, cardiovascular disease; revas, revascularization; eGFR, estimated glomerular filtration rate calculated using the CRIC equation; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

**Table 2**

Subhazard ratios for first CVD, ESRD, and death event, among CRIC participants reaching eGFR <30 ml/min/1.73 m<sup>2</sup>

	<b>CVD Event</b>	<b>ESRD Event</b>	<b>Death Event</b>
Age, per 10-y older	<b>1.18 (1.04–1.32)</b>	<b>0.76 (0.70–0.83)</b>	<b>1.77 (1.41–2.24)</b>
Male sex	0.99 (0.78–1.25)	<b>1.22 (1.01–1.49)</b>	1.15 (0.77–1.71)
Race			
Black	0.90 (0.71–1.14)	1.16 (0.93–1.43)	<b>1.69 (1.09–2.62)</b>
Other	0.83 (0.54–1.28)	1.39 (0.99–1.96)	0.82 (0.38–1.76)
White	1.00 (reference)	1.00 (reference)	1.00 (reference)
Hispanic vs non-Hispanic ethnicity	0.89 (0.60–1.32)	0.80 (0.58–1.11)	<b>2.23 (1.20–4.15)</b>
eGFR, per 5-ml/min/1.73 m <sup>2</sup> higher	0.96 (0.83–1.11)	<b>0.76 (0.66–0.86)</b>	0.88 (0.69–1.12)
Urine PCR, per 2-fold higher	0.98 (0.92–1.03)	<b>1.34 (1.27–1.41)</b>	<b>0.89 (0.82–0.98)</b>
BMI category			
25–29.9 kg/m <sup>2</sup>	1.07 (0.73–1.58)	0.98 (0.74–1.29)	0.80 (0.43–1.50)
30–35 kg/m <sup>2</sup>	1.31 (0.90–1.90)	0.84 (0.62–1.14)	0.96 (0.53–1.73)
>35 kg/m <sup>2</sup>	1.33 (0.92–1.92)	0.76 (0.57–1.03)	1.01 (0.56–1.82)
25 kg/m <sup>2</sup>	1.00 (reference)	1.00 (reference)	1.00 (reference)
Diabetes	<b>1.69 (1.31–2.18)</b>	0.82 (0.67–1.01)	1.17 (0.77–1.78)
SBP, per 10-mm Hg higher	<b>1.08 (1.03–1.14)</b>	1.03 (0.99–1.08)	0.92 (0.82–1.02)
Any CVD History	<b>2.16 (1.70–2.75)</b>	<b>0.65 (0.52–0.82)</b>	1.04 (0.70–1.53)
Current smoking	1.16 (0.85–1.58)	0.84 (0.65–1.10)	<b>2.01 (1.25–3.25)</b>
Ejection fraction, per 5% greater	<b>0.85 (0.81–0.91)</b>	<b>1.06 (1.00–1.12)</b>	0.98 (0.88–1.10)

Note: Associations reflect sub-hazard ratios (95% confidence intervals) for each outcome, considering all other outcomes as competing risks, and adjusted for all variables shown in the table. Due to missing values detailed in Table 1, population size is 1384. Bold font indicates statistically significant values (p<0.05).

Abbreviations: eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; PCR, protein-creatinine ratio; BMI, body mass index; SBP, systolic blood pressure; CRIC, Chronic Renal Insufficiency Cohort; CVD, cardiovascular disease

**Table 3**

Multivariable associations between baseline characteristics and death, adjusted for time-varying ESRD and time-varying CVD

	<b>Death Event</b>
Age, per 10-y older	<b>1.54 (1.36–1.75)</b>
Male sex	1.07 (0.86–1.33)
Race	
Black	1.03 (0.81–1.30)
Other	1.03 (0.69–1.54)
White	1.00 (reference)
Hispanic vs non-Hispanic ethnicity	1.18 (0.83–1.70)
eGFR, per 5-ml/min/1.73 m <sup>2</sup> higher *	<b>0.79 (0.65–0.96)</b> ; 1.19(1.00–1.44)
Urine PCR, per 2-fold higher	1.02 (0.97–1.08)
BMI category	
25–30 kg/m <sup>2</sup>	0.85 (0.61–1.17)
30–35 kg/m <sup>2</sup>	0.91 (0.66–1.26)
>35 kg/m <sup>2</sup>	0.94 (0.68–1.30)
<25 kg/m <sup>2</sup>	1.00 (reference)
Diabetes *	<b>1.60 (1.15–2.21)</b> ; 0.94 (0.68–1.31)
SBP, per 10-mm Hg higher	0.99 (0.94–1.04)
Any CVD History	<b>1.60 (1.28–2.00)</b>
Current smoking	<b>1.74 (1.33–2.27)</b>
Ejection fraction, per 5% greater	<b>0.92 (0.87–0.97)</b>
Time-varying ESRD	<b>3.68 (2.22–6.09)</b>
Time-varying CVD	<b>2.43 (1.93–3.06)</b>

Note: Values are given as hazard ratio (95% confidence interval). Bold font indicates statistically significant relationships. There were no significant interactions between age, sex, race, proteinuria, BMI, and time-varying ESRD.

Abbreviations: eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; PCR, protein-creatinine ratio; BMI, body mass index; SBP, systolic blood pressure; CVD, cardiovascular disease

\* There were significant interactions between eGFR and time-varying ESRD and diabetes and time-varying ESRD. Coefficients shown reflect the pre-ESRD and post-ESRD relationship, respectively.